STEREOSELECTIVE SYNTHESIS OF α-HYDROXY ACID DERIVATIVES AND β-LACTAMS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

BIDHAN A. SHINKRE

DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

NATIONAL CHEMICAL LABORATORY

PUNE - 411 008

DEDICATED TO
MY PARENTS AND
BROTHERS

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Stereoselective Synthesis of α-Hydroxy Acid Derivatives and β-Lactams"** submitted by Mr. Bidhan A. Shinkre was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date: 05.04.2004

National Chemical Laboratory — Dr. A. R. A. S. Deshmukh

Pune 411 008 — Research Guide

DECLARATION

I hereby declare that the work incorporated in the thesis entitled "**Stereoselective Synthesis of α-Hydroxy Acid Derivatives and β-Lactams"** 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. A. R. A. S. Deshmukh. The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other university.

Date: 05-04-2004

National Chemical Laboratory

Pune 411 008 Bidhan A. Shinkre

Acknowledgments

I take this opportunity to express my deep sense of gratitude to my research guide Dr. A. R. A. S. Deshmukh. His continuous inspiration and excellent guidance has helped me profoundly during the course of my work. The work presented in this thesis would not have been accomplished without his unfailing attention, constant encouragement, wise counsel and above all the freedom rendered to me for innovative thinking.

My special thanks are to Dr. Sunil V. Pansare for introducing me to the field of Asymmetric Synthesis and allowing me to include part of my work done under him in this thesis.

I am very thankful to Dr. B. M. Bhawal, Dr. Ganesh Pandey, Dr. N. P. Argade, Dr. A. Sarkar and Dr. Sanjayan for their advice, support and valuable suggestions throughout my research period in NCL. I would also like to thank Prof. Paknikar, Dr. Dinge and all my teachers from Goa University for teaching me the fundamentals of Chemistry.

Special thanks to Dr. Gumaste for his help and cheerful company. I thank my seniors Dr. R. P. Jain, Dr. Anand, Dr. Annyt and Dr. Krishnaswamy for their valuable suggestions and support. It is my pleasure to thank my colleagues of Lab 194, Dr. K. Thiagarajan, Dr. Arun, Govande, Jayanthi, Nilesh, Aarif, Kale, Tiwari, Pinak, Vinod, Rameshwar, Pooja, Saylee, Nazia and also Dr. D. Hazra, Suresh, Tarun, Dilip, Samanta and Anuradha for their help and cooperation during the entire research period. Thanks are due to Mr. Jadhav, for his help in lab maintenance.

My Special thanks to my friends Dr. Manoj P. Samant and Mr. Sanjay Raikar for their help on several occasions. I would also take this opportunity to thank my friends for their cheerful company and help namely: Anamitra, Prabal, Shrinivas, Devaraj, Nagendra S, Keshri, Kishore, Balakrishnan, Bhagwat, Mangaleswaran, Eshwar, Anirban, Santosh, Pasupathy, Murugan, Manmohan, Tiwari S, Subbu (S & U), Deendayal, Nandu, Yogesh B, Mahesh T, Patwa and many more. I also sincerely

thank my other friends from NCL and NCL GJ Hostel for their cheerful company and for making my stay at NCL a memorable one.

Help from Spectroscopic and Microanalytical groups are gratefully acknowledged. I would also like to thank Dr. Mrs. V. G. Puranik for her help in X-Ray crystallographic analysis. I thank all the staff members of OCS division, Library, Stores and Administration for their constant cooperation and help.

My special thanks are to Manas, Manali, Vibha maushi and bhauji for making my stay in Pune very comfortable. Special thanks are also to my cousin Samir and all my relatives for their constant encouragement and support.

Whatever I am and whatever I intend to be in future is because of the goodwill and unstinted support that I have received from my parents and two brothers Bipin and Biren. Their constant encouragement and freedom rendered to me has helped me in pursuing the Ph.D. study and no words are enough to acknowledge them. My successes are dedicated to them now and always.

I thank Dr. K. N. Ganesh, Head, Division of Organic Chemistry (Synthesis) for his critical and valuable suggestions during my assessment interviews and also for the divisional facilities. Finally I would like to thank the Director, NCL, for providing the infrastructure and CSIR, New Delhi for financial assistance.

(Bidhan A. Shinkre)

CONTENTS

CHAPTER III

CHAPTER IV

SYNTHESIS OF α-ALLYL-α-HYDROXY ACIDS BY TRIMETHYL PHOSPHITE INDUCED CLAISEN REARRANGEMENT

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded in chloroform or neat on Shimadzu FTIR-8400, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).
3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC-200, MSL-300 and Bruker DRX-500 instruments. Chemical shifts were recorded in parts per million (δ, ppm). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dq = doublet of quartet, bs = broad singlet and m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent for all the samples.
4. ^{13}C NMR spectra were recorded on Bruker AC-200, MSL-300 and Bruker DRX-500 instruments operating at 50 MHz, 75 MHz and 125 MHz respectively.
5. Elemental analyses (C, H, N, S) were obtained on a Carlo-Erba, CHNS-O EA 1108 Elemental analyzer.
6. Optical rotations were measured on a JASCO-181 digital Polarimeter and JASCO P-1020 Polarimeter using sodium D line (5893 Å). Concentration is expressed in g/100mL.
7. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system.
8. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX-102 spectrometer and JEOL JMS600 spectrometer.
9. The progress of the reaction was monitored by TLC using commercial, precoated silica gel (Merck 60F-254) plates.
10. Silica gel used for column chromatography was 60-120 mesh or 230-400 mesh size.
11. ^{1}H NMR & ^{13}C NMR spectra of the compounds are attached at the end of the corresponding chapters. For all the samples containing methylene and

quaternary carbons DEPT spectrum was scanned after scanning ^{13}C NMR spectra and then the assignment of the peaks in ^{13}C NMR was done.

12. Pet. ether (PE) refers to the petroleum fraction boiling between 60-80 °C.
13. Solvents for chromatography were distilled at their respective constant boiling points.
14. All reactions requiring anhydrous conditions were performed under a positive pressure of Argon using oven-dried glassware (120 °C) which was cooled under Argon.
15. Dichloromethane was dried over anhydrous P_2O_5 and stored over $4A^o$ molecular sieves. Ether, THF and dioxane were distilled over sodium benzophenone ketyl.
16. All other solvents were dried following the procedure given in the book 'Purification of Laboratory Chemicals' by Armarego and Perrin (third edition).

ABBREVIATIONS

Ac	Acetyl
Aq.	Aqueous
Bn	Benzyl
BOC	*tert*-butoxycarbonyl
Bu	Butyl
CAN	Ceric ammonium nitrate
Cbz	Benzyloxycarbonyl
CSI	*N*-Chlorosulfonyl isocyanate
m-CPBA	*meta*-Chloroperbenzoic acid
DCM	Dichloromethane
deg	Degree
DIBAL-H	Diisobutylaluminium hydride
de	Diastereomeric excess
ds	Diastereoselectivity
DMAP	*N*, *N*'-Dimethylaminopyridine
DME	1, 2 Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
ee	Enantiomeric excess
Equiv.	Equivalents
Et	Ethyl
EtOAc (EA)	Ethylacetate
g	Gram
HPLC	High performance liquid chromatography
h	Hour
LDH	Lactose dehydrogenase
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
MS	Mass spectrum

Me	Methyl
MTPA	α-Methoxy-α-(trifluoromethyl)phenylacetic acid
mL	Milli litre
mmol	Milli mole
min	minute
mp	Melting point
M	Molar
Pet. ether (PE)	Petroleum ether
PLE	Pig liver esterase
Ph	Phenyl
PhthN	Phthalimido
PMP	*p*-Methoxyphenyl
PNB	*p*-Nitrobenzyl
Pr	Propyl
PTSA	*p*-Toluenesulfonic acid
rt or RT	Room temperature
SAR	Structure activity relationship
TBDMS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Tetramethyl silane
TEA	Triethyl amine
Ts	*p*-Toluenesulfonyl

Name of student: **Mr. Bidhan A. Shinkre**
Name of Research Guide: **Dr. A. R. A. S. Deshmukh**

Abstract of thesis entitled: **"Stereoselective Synthesis of α-Hydroxy Acid Derivatives and β-Lactams"**

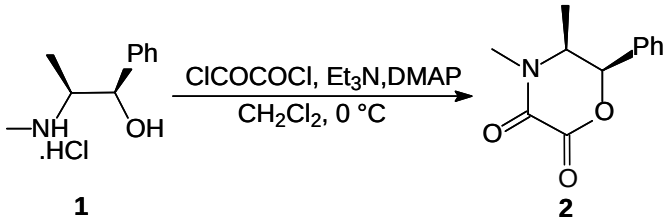
Chapter I

Asymmetric synthesis of α-hydroxy-γ-butyrolactones from an ephedrine-derived morpholine-dione

Enantiomerically pure 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 an ephedrine-derived morpholine-dione.

Reaction of ephedrine with oxalyl chloride gave morpholine-dione in 65% yield.

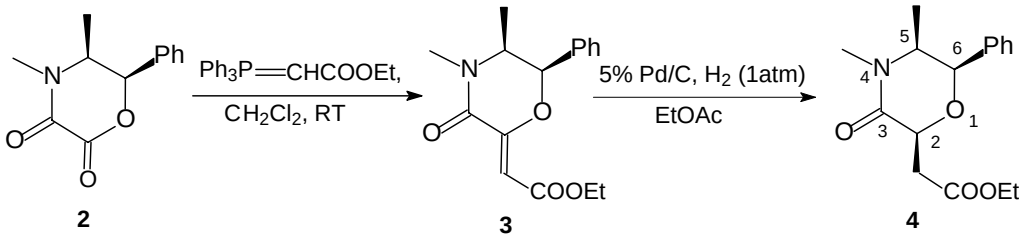
Scheme 1



1 **2**

The lactone carbonyl behaves as an isolated ketone and undergoes Wittig olefination and Grignard reactions. Treatment of **2** with (carbethoxymethylene)triphenyl phosphorane in dichloromethane at ambient temperature gives alkylidine morpholinone **3** (80%, Z/E= 20/1). Hydrogenation of the alkylidine ester **3**, gives ester **4** as a single diastereomer in quantitative yield.

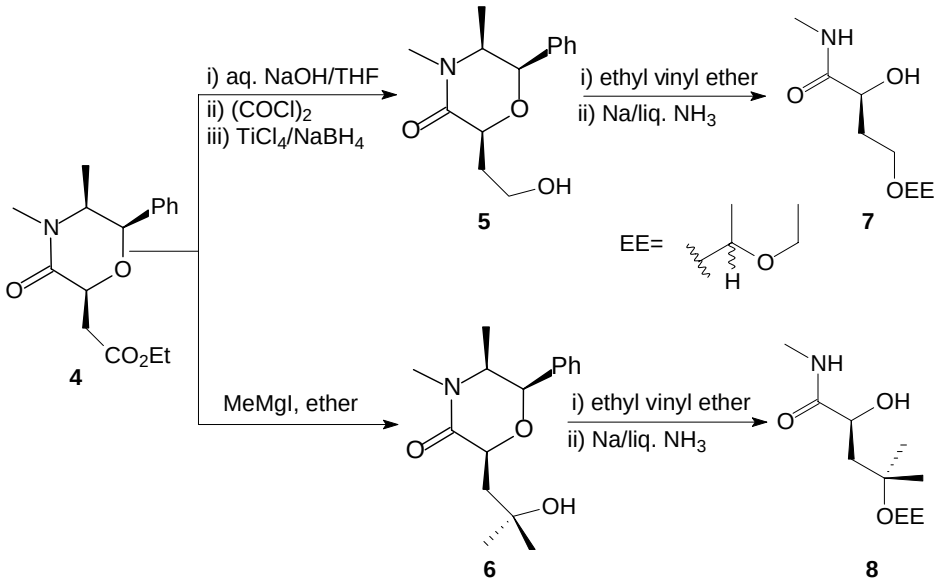
Scheme 2



Stereochemistry of reduction is governed by the C5 and C6 substituents and the addition of hydrogen molecule across the double bond takes place from the less hindered side giving the product with '*S*' stereochemistry. Further confirmation of the stereochemistry was done by NOESY experiment, which showed *syn* relationship of the C2, C5 and C6 hydrogens.

Hydrogenated ester **4** is a fully protected and chemically differentiated malic acid derivative, which is a valuable precursor to α-hydroxy-γ-butyrolactones. Hence, chemoselective transformations at the ester carbonyl in **4** were initiated.

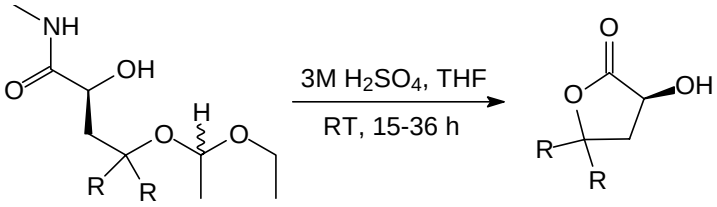
Scheme 3



Selective reduction of ester group in **4** proved to be unexpectedly difficult. Heating with excess LAH resulted in concomitant partial reduction of the amide carbonyl and reduction at ambient temperature gave poor yield of the alcohol **5**. Hence the ester **4** was hydrolyzed to acid (96%) and reduction of the acid chloride with a

combination of $TiCl_4/NaBH_4$ in dioxane was the procedure of choice and provided the alcohol **5** in 70% yield. Treatment of ester **4** with excess MeMgI provided the tertiary alcohol **6** in 75% yield. Subsequent protection of the alcohols **5** and **6** with ethyl vinyl ether followed by removal of the ephedrine portion by dissolving metal reduction (Na/liq. NH_3, -78 ^oC) gave the partially unmasked butyramides **7** and **8** (55-65% yield over 2 steps).

Scheme 4



7 (R= H)
8 (R= Me)

9 (R= H)
10 (R= Me)

Deprotection of **7** and **8** under mild acidic condition proceeded with concomitant lactonisation to generate α-hydroxy-γ-butyrolactones **9** (70%, 96%ee) and **10** (82%, 98%ee) respectively.

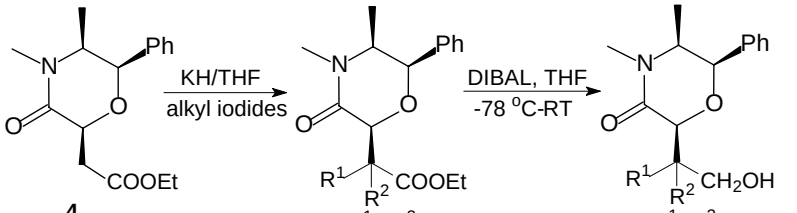
Chapter II

Studies on the Enantioselective synthesis of S-(+)-Pantolactone and its analogues

Pantolactone and its analogues constitute an important class of compounds due to their utility as a building block in the synthesis of natural products and their analogues. Pantolactone is also used as a chiral auxiliary in the asymmetric synthesis of natural products and is an important starting compound for: (a) pantothenic acid (a member of B-complex vitamins), (b) calcium pantothenate (enzyme co-factor vitamin), (c) (*R*)-panthenol (bactericide), (d) (*R*)-pantetheine (growth factor) and (e) (*R*)-pantoyl taurine (bacterial growth inhibitor). Pantolactone analogues are of interest due to their structural similarity to pantolactone and the potential for application as pantothenic acid analogues in biologically relevant molecules.

Ester **4** was used as the starting material for the synthesis of pantolactones. Preferential dialkylation at alpha position to the ester carbonyl was the key step in the synthesis. Different bases such as NaH, KOBu^t, KH and LDA were tried for selective dialkylation. Best results for dialkylation were obtained with KH in THF as a solvent and quenching the enolate with alkyl iodides gave the alkylated products **11-c** in 92-96% yields. Ester group was further reduced with DIBAL in THF as a solvent at –78 ^oC to give alcohols **12a-c** in good yields (76-80%).

Scheme 5



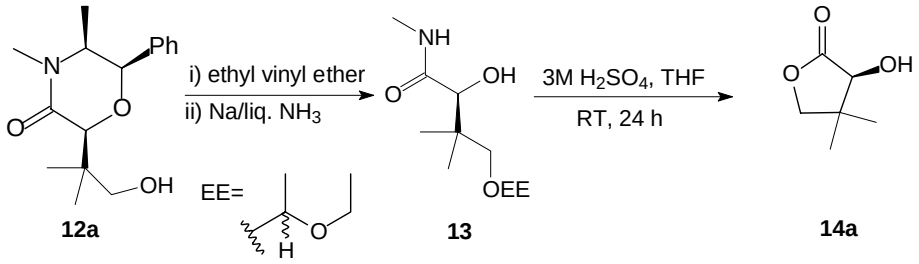
4

11a R^1= R^2= methyl
11b R^1= R^2= ethyl
11c R^1= R^2= allyl

12a R^1=R^2=methyl
12b R^1=R^2=ethyl
12c R^1=R^2=allyl

Hydroxy group in **12a** was protected as ethoxyethyl derivative and ephedrine portion was removed by Na/liq. NH_3 (-78 ^oC) to get the hydroxy butyramide **13** which was cyclised under mild acidic condition to give *S*-(+)-pantolactone **14a**.

Scheme 6



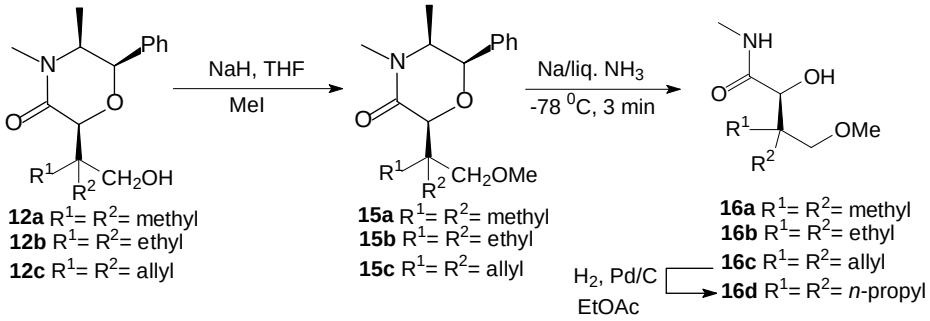
12a **13** **14a**

Observed rotation for *S*-(+)-pantolactone was +51.8 (*c* 2.0, H_2O) [Reported +50.1 (*c* 2, H_2O)].

In this study it was found that the ethoxyethyl protecting group was unstable and gave a low yield of the cleavage product **13** (30%). Hence the compounds were protected as methoxy derivatives **15a-c** in very good yields by using NaH in THF and MeI. In the next step the chiral auxiliary part from **15a-c** was removed by Birch reduction to give α-

hydroxy-γ-methoxy butyramides **16a-c** in good yields (Scheme 7). Furthermore, hydrogenation of **16c** gave the dipropyl hydroxy butyramide **16d** in good yields. The spectral data and optical rotation of compound **15a** matched exactly with that reported in literature.

Scheme 7



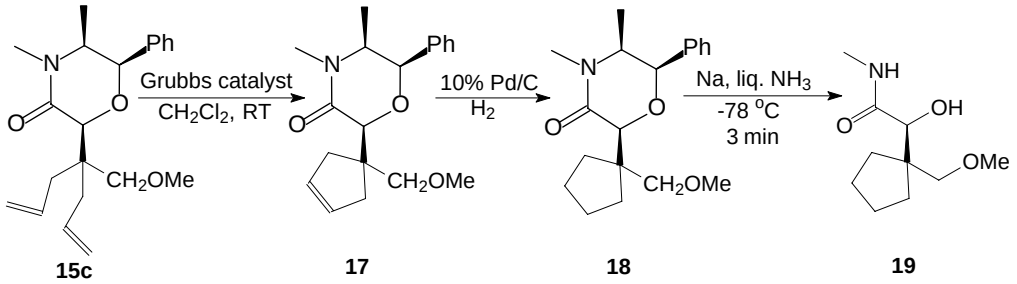
12a R^1= R^2= methyl
12b R^1= R^2= ethyl
12c R^1= R^2= allyl

15a R^1= R^2= methyl
15b R^1= R^2= ethyl
15c R^1= R^2= allyl

16a R^1= R^2= methyl
16b R^1= R^2= ethyl
16c R^1= R^2= allyl
16d R^1= R^2= *n*-propyl

The diallyl compound **15c** offered an advantage as manipulation of the double bonds is possible. One such conversion of **15c** to a 5-membered cyclic alkene **17** was achieved by ring closing metathesis (RCM) using Grubb's catalyst (Scheme 8). Hydrogenation of **17** gave cyclopentyl compound **18** and further the removal of chiral auxiliary part by Na/liq. NH_3 gave hydroxy butyramide **19**, which is a precursor to spirolactone.

Scheme 8

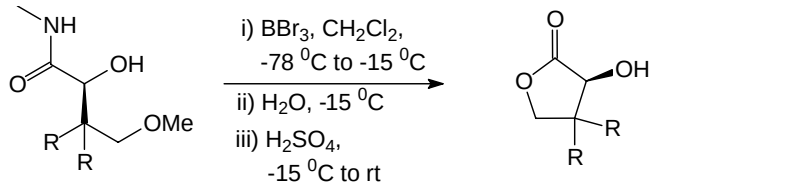


15c **17** **18** **19**

Conversion of the hydroxy butyramides **16a,b,d** and **19** to the target lactones **14a-d** was achieved in a one-pot reaction sequence. The primary hydroxyl group in butyramides was liberated by demethylation with BBr_3 in DCM at –78 ^oC. Subsequent acid catalysed lactonisation at –15 ^oC which involves a very facile intramolecular acyl

transfer from nitrogen to oxygen furnished *S*-(+)-pantolactone and its analogues **14a-d** in 70-97% yields with high enantiomeric excesses (Scheme 9).

Scheme 9



16a, R= Me
16b, R= Et
16d, R= *n*-propyl
19 R= R= cyclopentyl

14a, (*S*)-(+)-pantolactone, R= Me, 70%
14b, R= Et, 97%
14c, R= *n*-propyl, 88%
14d, R= R= cyclopentyl

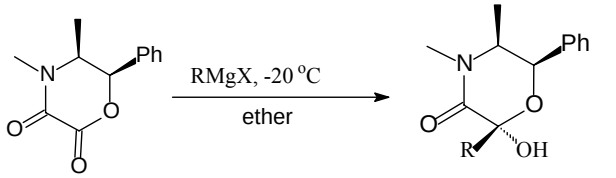
Chapter III

Section A: Diastereoselective synthesis of β-lactams using chiral acids derived from 1*R*, 2*S* ephedrine *via* Staudinger reaction

β-Lactams are used in the synthesis of variety of β-lactam antibiotics. Also the β-lactam skeleton has been recognized as a useful precursor to various non-β-lactam derivatives. Our objective in undertaking this study was to probe the effect of steric disposition on the stereoselectivity in β-lactam ring construction *via* Staudinger reaction using chiral acids derived from 1*R*, 2*S*-ephedrine.

Morpholine-dione **2** was prepared by the reaction of ephedrine with oxalyl chloride. Reaction of **2** with Grignard reagents provided the hemiketals **20a**/**20b** in 90-92% yield.

Scheme 10

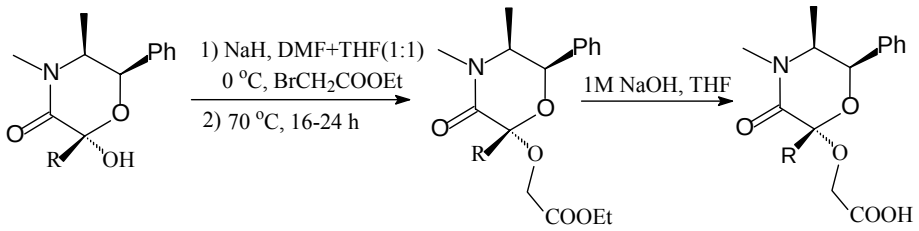


2

20a R= Me
20b R= isopropyl
ds> 10:1

Absolute configuration of the hemiketal carbon was assigned as '*S*' by comparison of the optical rotation and ^{1}H NMR of the hemiketals with the earlier reported hemiketals. Chiral acids were prepared from **20a**/**20b** by *O*-alkylation of the hemiketal OH group with ethylbromoacetate followed by hydrolysis.

Scheme 11



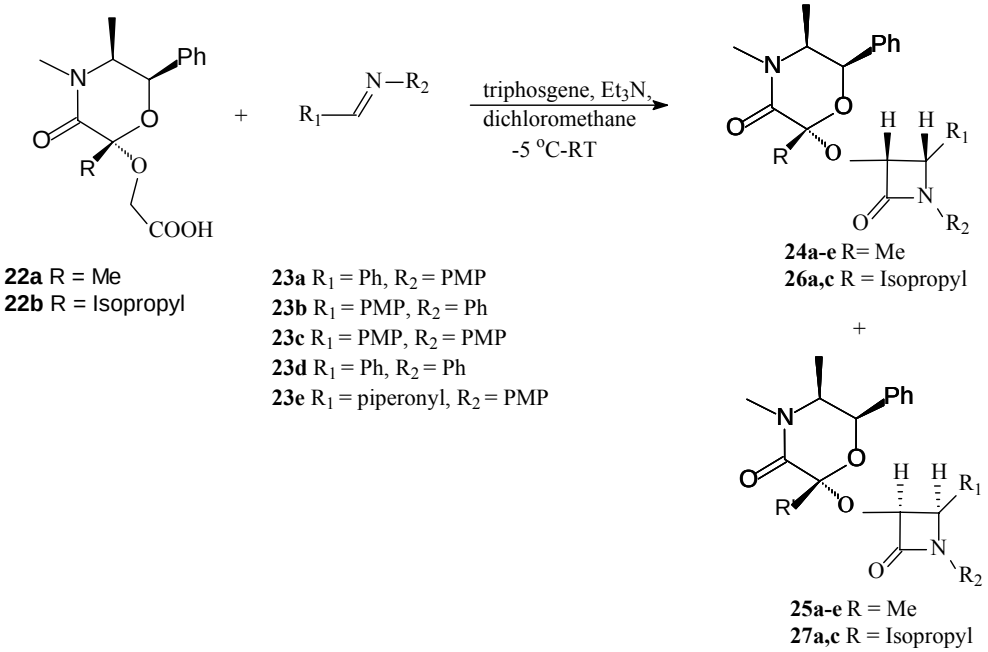
20a R= Me
20b R= isopropyl

21a R= Me
21b R= isopropyl

22a R= Me
22b R= isopropyl

These chiral acids **22a** and **22b** obtained from ephedrine were then subjected to Staudinger reaction. The chiral acids were *in situ* converted to acid chloride by triphosgene and triethyl amine in dichloromethane solvent and reacted with different imines **23a-e** at –5 °C to give β-lactams as a mixture of diastereomers (ds = 1:1 to 1.5:1, by ^{1}H NMR of crude β-lactams) in good yields.

Scheme 12



22a R = Me
22b R = Isopropyl

23a R_1 = Ph, R_2 = PMP
23b R_1 = PMP, R_2 = Ph
23c R_1 = PMP, R_2 = PMP
23d R_1 = Ph, R_2 = Ph
23e R_1 = piperonyl, R_2 = PMP

24a-e R= Me
26a,c R = Isopropyl

+

25a-e R = Me
27a,c R = Isopropyl

In most of the cases both the diastereomers (**24a-d**, **25a-e**, **26a,c** and **27a**) could be easily separated by careful flash column chromatography. One of the diastereomers **25b** could be crystallized and its single crystal X-ray data (Fig. 1) confirms the stereochemistry at the two β-lactam carbons and it is assigned as (3*S*, 4*R*).

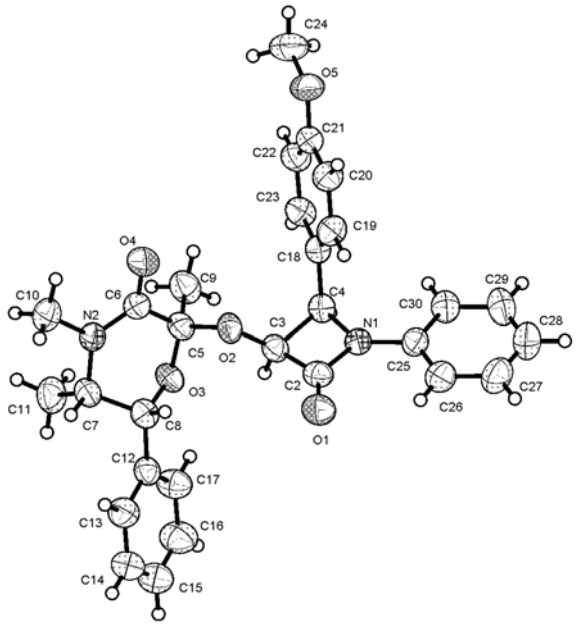


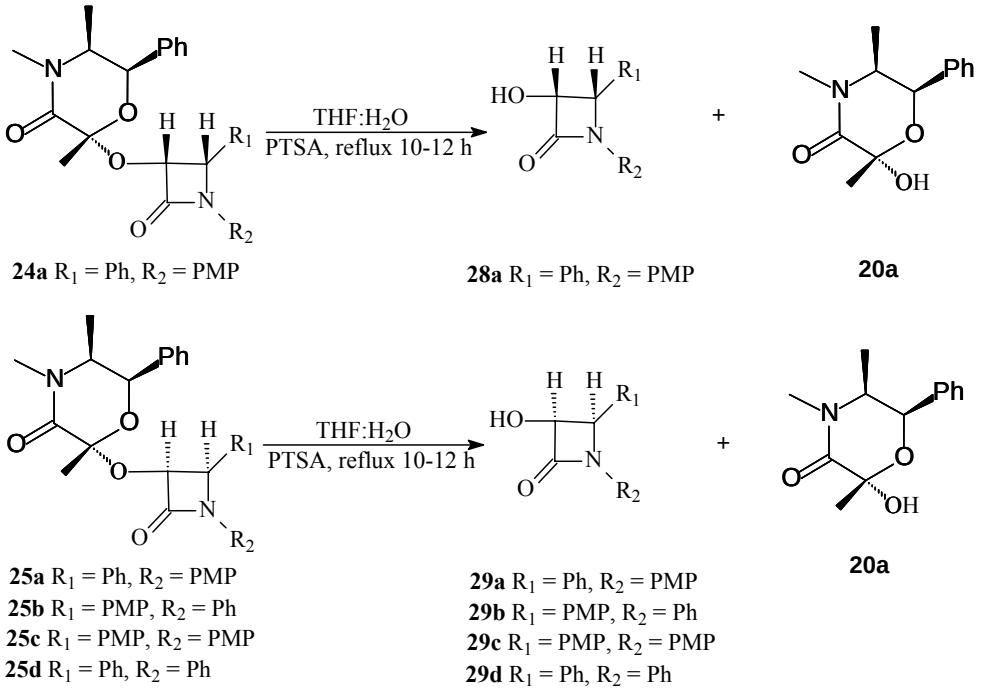
Fig. 1. X-ray structure of 25b

Section B: Synthesis of enantiopure 3-hydroxy-4-aryl-β-lactams

Enantiomerically pure 3-hydroxy-4-aryl-β-lactams constitute an important class of compounds. Suitably substituted 3-hydroxy-4-aryl-β-lactam can serve as a synthetic equivalent for the phenylisoserine side chain of taxol, an anticancer agent obtained from the bark of *Taxus brevifolia* or can be directly coupled with baccatin III (a precursor of taxol which is available in sufficient quantities from the leaves of the plant) to give taxol. They are also a source of enantiomerically pure α-hydroxy-β-amino acids, which are present in many biologically important compounds.

Cleavage of the chiral auxiliary in β-lactams **24a** and **25a-d** was investigated. Chiral auxiliary could be cleaved effectively from the β-lactam part by using PTSA in a mixture of THF and water (5:1) at reflux temperature for 10-12 h.

Scheme 13



24a R_1 = Ph, R_2 = PMP

28a R_1 = Ph, R_2 = PMP

20a

25a R_1 = Ph, R_2 = PMP
25b R_1 = PMP, R_2 = Ph
25c R_1 = PMP, R_2 = PMP
25d R_1 = Ph, R_2 = Ph

29a R_1 = Ph, R_2 = PMP
29b R_1 = PMP, R_2 = Ph
29c R_1 = PMP, R_2 = PMP
29d R_1 = Ph, R_2 = Ph

20a

On comparison of optical rotations of the product obtained in both the reactions with the reported value, the absolute configuration for **29a** was assigned as (3*S*, 4*R*) and for **28a** as (3*R*, 4*S*). The hemiketal **20a** formed during the hydrolysis of **24a** or **25a-d** was also isolated in quantitative yield by column chromatography and characterized by IR and ^{1}H NMR. There was no loss in enantiomeric purity of the recovered hemiketal **20a** as it showed exactly the same specific rotation as that of starting hemiketal.

Chapter IV

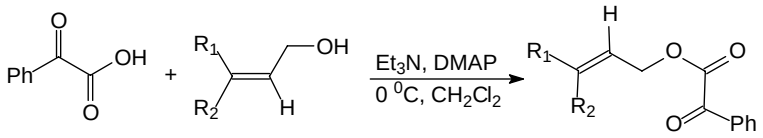
Synthesis of α-allyl-α-hydroxy acids by trimethyl phosphite induced Claisen rearrangement

α-allyl-α-hydroxy acids are attractive synthetic intermediates which are readily elaborated further by manipulation of the carbon-carbon double bond. Moreover, many methods are known in literature for the resolution of racemic α-allyl-α-hydroxy acids. Our objective was to synthesize α-allyl-α-hydroxy acids by trimethyl phosphite induced Claisen rearrangement. We anticipated that in case of allyl esters of α-keto acids after

complex formation with trimethyl phosphite it should undergo Claisen rearrangement, and the intermediate complex after hydrolysis should give us α-allyl-α-hydroxy acids.

Allyl phenyl glyoxylate **32a** was the starting material in the study, and it was easily prepared by the esterification of benzoylformic acid with allyl alcohol.

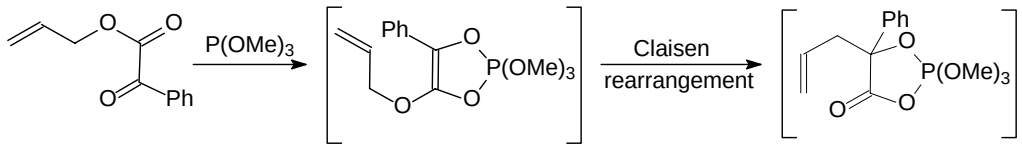
Scheme 14



30 **31a** $R_1 = R_2 = H$; **31b** $R_1 = R_2 = Me$ (70-75%) **32a** $R_1 = R_2 = H$; **32b** $R_1 = R_2 = Me$

The rearrangement study was done on **32a**. Reaction was done by mixing equimolar proportions of allyl ester **32a** with trimethyl phosphite under different conditions to give a 5-membered phosphite complex **33a**.

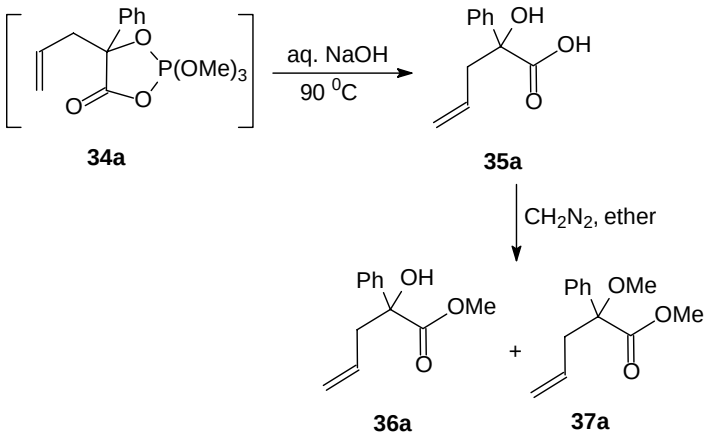
Scheme 15



32a **33a** **34a**

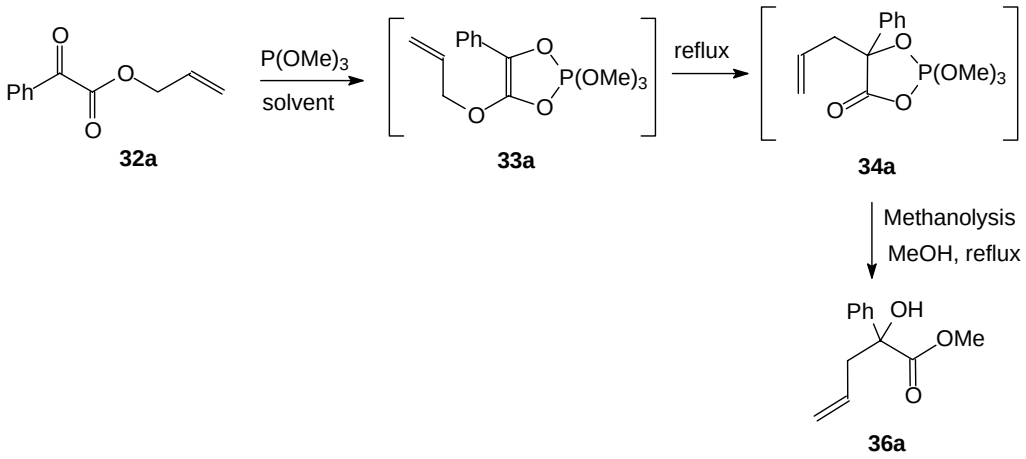
Different reaction conditions were tried for Claisen rearrangement. Both the phosphite complexes **33a** and **34a** were found to be unstable and hence the reaction was monitored by NMR of the aliquots taken during the reaction and noting the shift in the peak position of the allyl group. It was found that rearrangement requires longer reaction times at room temperature or heating in a suitable solvent. Rearrangement took place in polar aprotic solvents like acetonitrile, dioxane and THF and failed in non-polar solvents like benzene, toluene. Further, hydrolysis of the rearranged phosphite complex with aqueous NaOH gave the crude acid, which was purified by converting it to methyl ester by treatment with excess diazomethane.

Scheme 16



The yield of the reaction from **32a** to give **36a** was 20% (over 3 steps). Since excess diazomethane is used the benzylic hydroxyl group also gets methylated and is obtained as a side product **37a** (10%) in the reaction. To avoid this and to shorten the process, the rearranged complex was directly subjected to methanolysis by refluxing **34a** in methanol without subjecting it to basic hydrolysis.

Scheme 17



In this study, rearrangement was done in different solvents and the rearranged complex was subjected to methanolysis after removal of the solvent and refluxing the crude complex with methanol for 8-20 h. Maximum yield of 30% could be obtained by doing the rearrangement in acetonitrile solvent (2 h reflux) and refluxing the rearranged complex in methanol for 20 h.

Note: ***Compound numbers in the abstract are different from the numbers in the thesis.***

List of Publications:

1. Enantioselective synthesis of α-hydroxy-γ-butyrolactones from an ephedrine-derived morpholine-dione.

   Sunil V. Pansare, **Bidhan A. Shinkre** and Annyt Bhattacharyya. *Tetrahedron* **2002**, *58*, 8985.

2. Ephedrine derived reusable chiral auxiliary for the synthesis of optically pure 3-hydroxy-4-aryl-β-lactams.

   Bidhan A. Shinkre, Vedavati G. Puranik, B. M. Bhawal and A. R. A. S. Deshmukh. *Tetrahedron: Asymmetry* **2003**, *14*, 453.

3. Azetidin-2-ones, synthon for biologically important compounds.

   A. R. A. S. Deshmukh, B. M. Bhawal, D. Krishnaswamy, Vidyesh V. Govande, **Bidhan A. Shinkre** and A. Jayanthi. *Current Medicinal Chemistry* **2004**, in press.

4. The synthesis of (*S*)-(+)-pantolactone and its analogues from an ephedrine-derived morpholinone.

   Bidhan A. Shinkre and A. R. A. S. Deshmukh. *Tetrahedron: Asymmetry* **2004**, *15*, 1081.

5. A general route to the enantioselective synthesis of (*S*)-(+)-pantolactone and its analogues from an ephedrine-derived morpholinone.

   Bidhan A. Shinkre and A. R. A. S. Deshmukh. (Manuscript under preparation).

CHAPTER I

ASYMMETRIC SYNTHESIS OF α-HYDROXY-γ-BUTYROLACTONES FROM AN EPHEDRINE-DERIVED MORPHOLINE-DIONE

Part of this work was published in *Tetrahedron* **2002**, *58*, 8985.

CHAPTER II

STUDIES ON THE ENANTIOSELECTIVE SYNTHESIS OF *S*-(+)-PANTOLACTONE AND ITS ANALOGUES

Part of this work was published in *Tetrahedron: Asymmetry* **2004**, *15*, 1081.

CHAPTER III

SECTION A

DIASTEREOSELECTIVE SYNTHESIS OF β-LACTAMS USING CHIRAL ACIDS DERIVED FROM 1*R*, 2*S* EPHEDRINE VIA STAUDINGER REACTION

Part of this work was published in *Tetrahedron: Asymmetry* **2003**, *14*, 453.

CHAPTER III

SECTION B

SYNTHESIS OF ENANTIOPURE 3-HYDROXY-4-ARYL-β-LACTAMS

Part of this work was published in *Tetrahedron: Asymmetry* **2003**, *14*, 453.

CHAPTER IV

SYNTHESIS OF α-ALLYL-α-HYDROXY ACIDS BY TRIMETHYL PHOSPHITE INDUCED CLAISEN REARRANGEMENT

1.1: Introduction

The enantioselective synthesis of α-hydroxy-γ-butyrolactones[1] has been the subject of several recent investigations. Enantiomerically pure α-hydroxy-γ-butyrolactones constitute an important class of compounds[2] due to their utility as intermediates and chiral building blocks for the synthesis of natural products and biologically active molecules. A number of these lactones are natural products which has spurred interest in their total synthesis.[3]

Specifically, the α-hydroxy-γ-butyrolactone is a useful intermediate in the enantioselective synthesis of biologically most active isomer of CGA 80000 (Clozylacon),[4] a fungicide especially suited for soil application against Oomycetes. α-hydroxy-γ-butyrolactone is also an intermediate in the synthesis of Fluorocholecalciferol[5] and in the synthesis of polyhydroxylated pyrrolizidine alkaloids of the Alexine family (potent glycosidase inhibitors).[6] In addition, it also serves as a building block in the total synthesis of epothilones B and D (microtubule stabilizing antitumor drugs),[7] synthesis of polyether antibiotic-Monensin,[8] asymmetric total synthesis of Bacillariolide III[9] and in the synthesis of Iejimalides (potent antitumor compound).[2b]

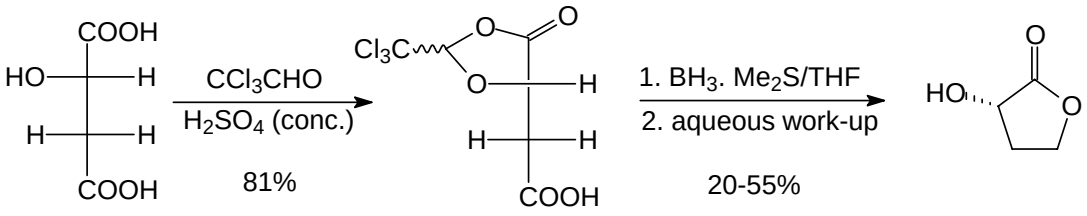
Moreover, α-hydroxy-γ-butyrolactones bearing an alkyl chain at the γ position are well identified hunger modulator substances.[10] (*S*)-γ,γ-dimethyl-α-hydroxy-γ-butyrolactone is a valuable intermediate in the synthesis of bark beetle pheromones.[11] Related γ,γ-dialkyl-α-hydroxy-γ-butyrolactones have been employed as components of chiral dopants in liquid crystals.[12]

1.2: Background for present work

There are two syntheses reported each for the α-hydroxy-γ-butyrolactone and (*S*)-γ,γ-dimethyl-α-hydroxy-γ-butyrolactone, which will be discussed in this section.

Buser *et. al.*[4] have reported a method for the preparation of α-hydroxy-γ-butyrolactone using L-malic acid as the chiral pool, which provides both the required absolute configuration and the correct number of C-atoms for the butyrolactone ring (Scheme 1).

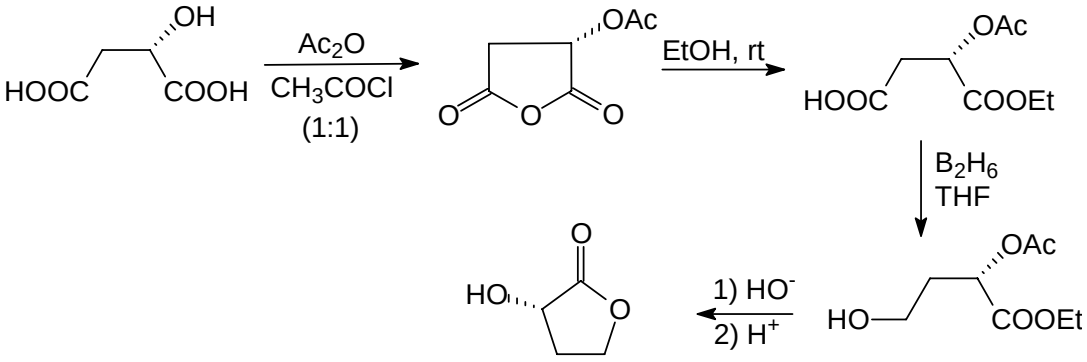
Scheme 1



The acid catalysed reaction of L-malic acid with chloral afforded the dioxolanone in good yield (81%) as a mixture of two diastereomers. Reduction of the carboxylic acid group with borane-dimethylsulfide complex in THF, followed by aqueous work-up, directly provided the (3*S*)-hydroxy butyrolactone. Unfortunately the yield in this step varied considerably and remained unsatisfactory (20-55%).

In another method, Shiuey *et. al.*[5] have also used the naturally occuring L-malic acid as starting material for the synthesis of (3*S*)-hydroxy butyrolactone (Scheme 2).

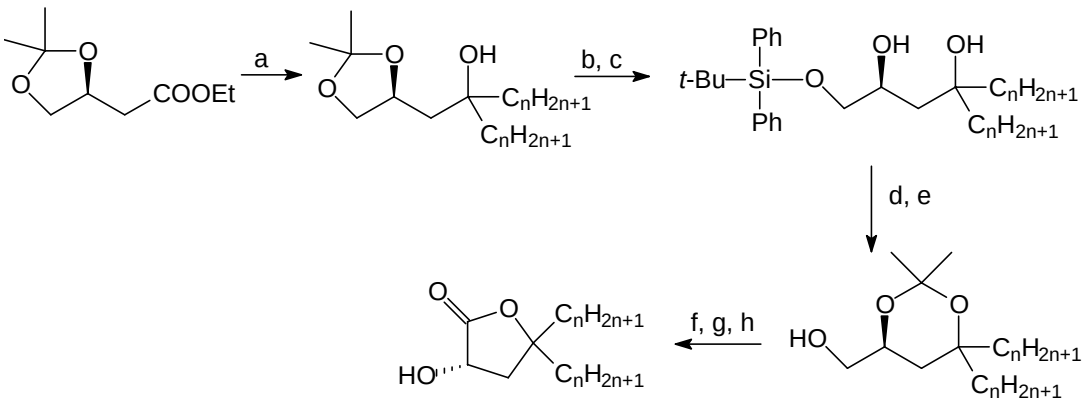
Scheme 2



Anhydride was obtained in 94% yield by treatment with (1:1) mixture of acetic anhydride and acetyl chloride. Regiospecific opening with ethanol afforded the crystalline acid ester (58%) which was reduced with diborane in tetrahydrofuran at 0 ^{o}C to give hydroxy ester in 99% yield. Hydrolysis followed by acidification produced the hydroxy lactone in 61% yield (ee >98%).

Ikemoto *et. al.*[12] have reported a method for the preparation of γ,γ-dialkyl-α-hydroxy-γ-butyrolactones (Scheme 3).

Scheme 3



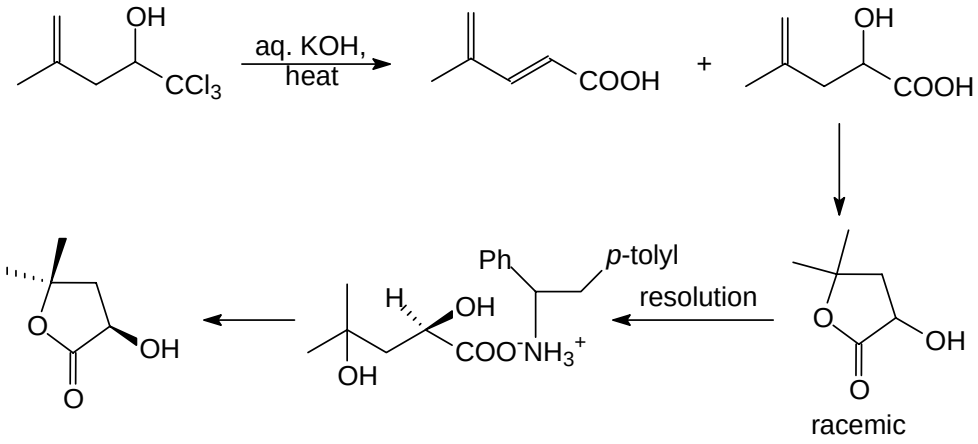
Reagents and Conditions:

a) $C_nH_{2n+1}MgBr$, Et_2O b) HCl, H_2O, THF c) *t*-$BuPh_2SiCl$, Imidazole, CH_2Cl_2 d) $Me_2C(OMe)_2$, PPTS e) *n*-Bu_4NF, THF f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 g) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O h) HCl, H_2O, THF

Commercially available (*S*)-(+)-2,2-dimethyl-4-ethoxycarbonylmethyl-1,3-dioxolane was added to a Grignard reagent prepared from *n*-alkyl bromide to give a tertiary alcohol. Deprotection of the acetonide followed by silylation of primary alcohol with *t*-butyldiphenylsilyl group gave a 1,3-diol. Diol was again protected as acetonide and the silyl group was deprotected. Further oxidation of the primary hydroxyl group followed by deprotection with hydrochloric acid gave the target lactones. The optical purities of the lactones were found to be very high (>90% ee) by analyzing the diastereomeric ratio of the corresponding (*S*)- α-methoxy-α-trifluoromethylphenyl acetate by HPLC.

Mori *et. al*.[11] has reported a method for the synthesis of racemic γ,γ-dialkyl-α-hydroxy-γ-butyrolactones which was then resolved (Scheme 4).

Scheme 4



The chloro alcohol, readily obtainable from chloral and isobutene, was heated with aqueous solution of KOH to give a mixture of two compounds. The later was lactonised to give a racemic lactone. The optical resolution was successfully carried out using (+)-α-phenyl-β-(*p*-tolyl)-ethylamine as the resolving agent to give a (+)-lactone, $[\alpha]_D^{21}$= +23.9 (MeOH). The high optical purity (>95%) was confirmed by converting it to the corresponding (*S*)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester.

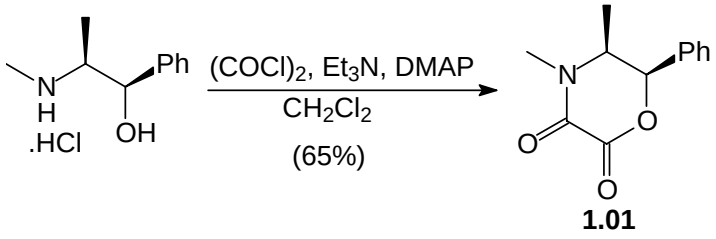
1.3: Present work

The objective of this study was to develop a general route for the asymmetric synthesis of α-hydroxy-γ-butyrolactones from an ephedrine-derived morpholine-dione.

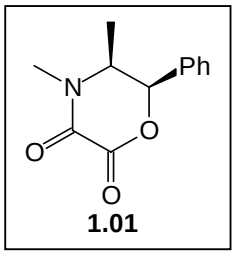
1.4: Results and discussion

The reaction of ephedrine hydrochloride with oxalyl chloride in the presence of triethylamine and catalytic DMAP in anhydrous dichloromethane gave morpholine-dione **1.01** as a crystalline white solid in 65% yield (Scheme 5).

Scheme 5



The structure of **1.01** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.01** showed strong bands at 1693 cm^{-1} and 1771 cm^{-1} corresponding to amide carbonyl and lactone carbonyls respectively.



The ^{1}H NMR spectrum of **1.01** showed a doublet at 1.12 ppm (J = 6.8 Hz) corresponding to the methyl group. Methyl group attached to nitrogen appeared as a singlet at 3.19 ppm. The characteristic doublet of quartet in the range 3.66-3.77 ppm is attributed to the proton on the methine carbon attached to nitrogen. Benzylic proton appeared as a doublet at 5.90 ppm (J = 2.9 Hz). All the aromatic protons appeared in the range 7.28-7.50 ppm.

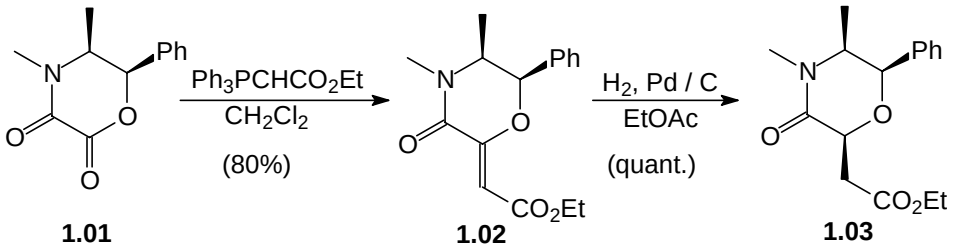
The ^{13}C NMR spectrum of **1.01** showed a peak at 156.4 ppm corresponding to lactone carbonyl and a peak at 153.0 ppm which corresponds to the amide carbonyl. The aromatic quaternary carbon appeared at 133.8 ppm. Other aromatic carbons appeared at 128.6, 128.0 and 125.3 ppm. The benzylic carbon appeared at 79.3 ppm. The two carbons attached to nitrogen appeared at 58.1 ppm (N*C*H) and 33.2 (N*C*H$_3$). Methyl group appeared in the aliphatic region at 11.8 ppm. This compound gave satisfactory elemental analysis.

Initial experiments resulted in low yields of **1.01**. The yield could be elevated upon dilution and control of reaction temperature. Addition of a dilute solution of oxalyl chloride over a prolonged period (4 hours) and further stirring at 0 ^{o}C for an hour had a beneficial effect. It should be noted that the dione **1.01** has been prepared earlier as a proof for the reactivity of an activated oxalic acid derivative but synthetic applications of **1.01** had not been reported prior to this study.[13]

The lactone carbonyl in **1.01** is akin to an isolated ketone as evidenced through Wittig olefination reaction and addition of organometallic reagents (discussed in Chapter 3). Treatment of **1.01** with (carbethoxymethylene) triphenylphosphorane in dichloromethane at ambient temperature gave the alkylidene morpholinone **1.02** (80%,

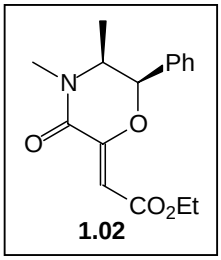
Z/*E* = 20/1, Scheme 6). The stereochemical assignment is based on the chemical shift of the olefinic methine proton (δ 6.22 in *Z*-**1.02**) as compared to the upfield shift[14] in the *E*-isomer (δ 5.83).

Scheme 6



1.01 **1.02** **1.03**

The structure of **1.02** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.02** showed a strong peak at 1701 cm^{-1} which indicated the conjugated carbonyl group of ester. The sharp peaks at 1637 cm^{-1} and 1668 cm^{-1} were assigned to the double bond and the amide carbonyl respectively.



1.02

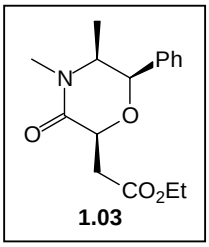
The ^{1}H NMR spectrum of **1.02** showed a doublet at 1.02 ppm (*J* = 6.6 Hz) and a triplet at 1.32 ppm (*J* = 7.3 Hz) which corresponds to methyl groups, attached to methine and methylene carbons respectively. A sharp singlet appeared at 3.15 ppm for methyl group attached to nitrogen. The characteristic doublet of quartet in the range 3.62-3.73 ppm (*J* = 2.9, 6.6 Hz) is attributed to C*H* attached to nitrogen. Multiplet in the range of 4.18-4.27 ppm corresponds to the methylene protons of ester group. The doublet at 5.47 ppm (*J* = 2.9 Hz) corresponds to benzylic proton. The characteristic singlet at 6.22 ppm is of the vinylic proton. Aromatic protons appeared in the range 7.30-7.55 ppm.

The ^{13}C NMR spectrum of **1.02** showed two peaks at 164.6 and 157.7 ppm corresponding to ester carbonyl and amide carbonyl respectively. The peak at 153.5 ppm corresponds to quaternary carbon of olefin. The aromatic quaternary carbon appeared at 135.5 ppm. Other aromatic carbons appeared at 128.4, 128.0 and 125.2 ppm. The vinylic carbon appeared at 101.0 ppm. The peak at 77.9 ppm is attributed to the benzylic carbon. The peak at 59.7 ppm corresponds to the methylene carbon attached to oxygen. The peaks at 57.9 ppm and 33.6 ppm are attributed to carbons attached to nitrogen (N*C*H and N*C*H$_3$ respectively). The methyl carbon in *C*H$_3$CH$_2$ and *C*H$_3$CH appeared in the aliphatic

region at 14.0 ppm and 11.4 ppm respectively. This compound gave satisfactory elemental analysis.

Hydrogenation of the alkylidene ester **1.02** (H_2, Pd/C, 1 atm) furnished **1.03** as a single diastereomer (^{1}H NMR) in quantitative yield (Scheme 6). The structure of **1.03** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

IR spectrum of **1.03** showed a strong band at 1738 cm^{-1} for the ester carbonyl and a band at 1653 cm^{-1} for the amide carbonyl.



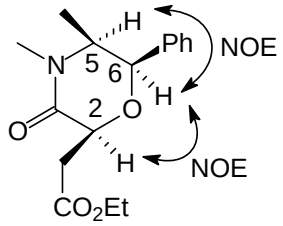
1.03

The ^{1}H NMR spectrum of **1.03** showed a doublet at 0.99 ppm (J = 6.4 Hz) and a triplet at 1.29 ppm (J = 6.8 Hz) which corresponds to the methyl groups, attached to methine and methylene carbons respectively. The sharp singlet at 3.04 ppm was attributed to the methyl group attached to nitrogen. The protons on the methylene carbon attached to ester carbonyl appeared as a multiplet in the range 2.88-3.15 ppm. The characteristic doublet of quartet for one methine proton of the chiral auxiliary appeared between 3.44 to 3.61 ppm. The methylene protons in the ester group appeared in the range 4.12-4.30 ppm (J = 6.8 Hz) as a quartet. The triplet at 4.66 ppm (J = 5.4 Hz) is for the proton on the methine carbon attached to the amide carbonyl. The characteristic doublet for the benzylic proton appeared at 5.06 ppm (J = 2.9 Hz). All the aromatic protons appeared in the range 7.22-7.46 ppm as a multiplet.

The ^{13}C NMR spectrum of **1.03** showed peaks at 170.0 ppm and 167.5 ppm corresponding to ester carbonyl and amide carbonyl respectively. The quaternary aromatic carbon appeared at 137.0 ppm. The other aromatic carbons appeared at 128.0, 127.3 and 125.1 ppm. The benzylic carbon appeared at 76.4 ppm. The methine carbon attached to amide carbonyl appeared at 74.6 ppm. The methylene carbon attached to oxygen appeared at 60.2 ppm. The methine carbon of ephedrine portion attached to nitrogen appeared at 58.4 ppm. The peak at 37.3 ppm corresponds to the methylene carbon attached to the ester carbonyl. The peak at 33.1 ppm corresponds to the methyl group attached to nitrogen. The peaks at 13.9 and 12.3 ppm are attributed to the methyl groups attached to the methylene and methine carbons respectively. The compound gave satisfactory elemental analysis.

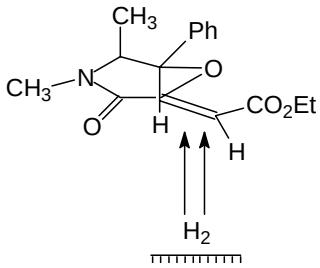
The stereochemistry of reduction is based on the observed diastereoselectivity for allylation and reduction on the ephedrine-derived template.[15,16] Further confirmation was done by NOESY experiment which indicated *cis* relationship of C_2, C_5 and C_6 hydrogens in the morpholinone ring (Figure 1).

Figure 1



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 2). The high stereoselectivity for hydrogenation emphasizes the strong, intrinsic stereochemical bias for reagent approach in the ephedrine-derived chiral template.

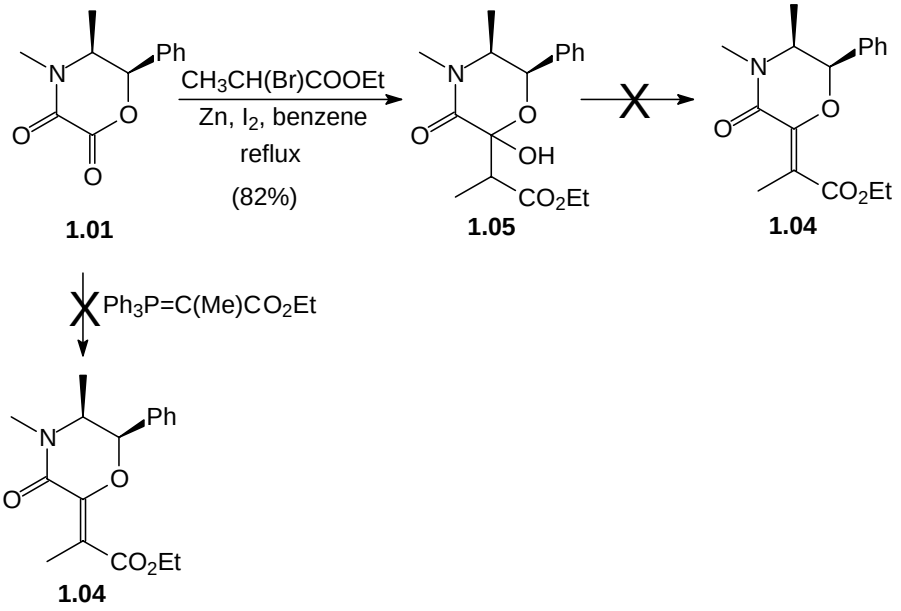
Figure 2



Due to the success of the Wittig reaction on **1.01**, we also tried a reaction of dione **1.01** with PPh_3=C(CH_3)COOEt. But it failed to give the ester **1.04** when reaction was done either in DCM at RT or in 1,2-dichloroethane at reflux temperature and only starting material was recovered.

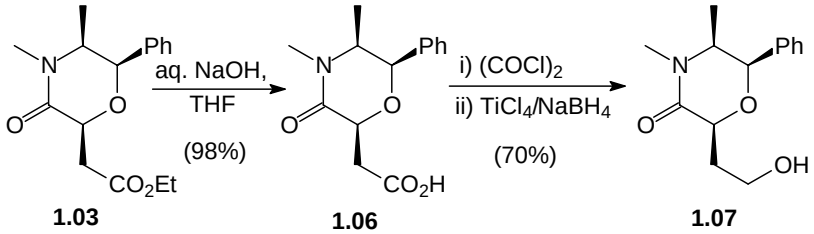
Hence the approach was slightly modified. Reformatsky reaction of **1.01** with ethyl-α-bromopropionate in benzene at reflux temperature afforded the hydroxy ester **1.05** as a mixture of diastereomers in 80% yield. Next, when dehydration of the tertiary hydroxyl group was tried with lewis acids such as trifluoroacetic acid and $TiCl_4$ at RT or at reflux temperature with solvents like DCM, 1,2-dichloroethane and methanol it failed to give the olefin **1.04** (Scheme 7).

Scheme 7

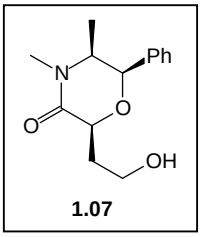


It is noteworthy that ester **1.03** is a fully protected and chemically differentiated malic acid derivative that is a valuable precursor to α-hydroxy butyrolactones. To this effect, chemoselective transformations at the ester carbonyl in **1.03** were investigated. Selective ester reduction in **1.03** to give alcohol **1.07** (Scheme 8) proved to be unexpectedly difficult. Heating **1.03** with excess LAH resulted in concomitant partial reduction of the amide carbonyl and reduction at ambient temperature was capricious, often giving poor yield of the alcohol. When ester was reduced with $Ca(BH_4)_2$, the yield of the alcohol **1.07** was only 35%. Hence an alternative way was chosen. Ester **1.03** was first hydrolysed to acid **1.06** with aqueous NaOH in a mixture of THF and water as a solvent. Although reduction of the acid **1.06** with BH_3 in THF was also inefficient, reduction of the acid chloride with a combination of $TiCl_4/NaBH_4$[17] in dioxane was the procedure of choice and furnished the alcohol **1.07** in 70% yield.

Scheme 8



The structure of **1.07** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.07** showed a broad band at 3401 cm^{-1} for the primary hydroxyl group and a sharp peak at 1641 cm^{-1} for the amide carbonyl.



1.07

The ^{1}H NMR spectrum of **1.07** showed a doublet at 1.0 ppm (J = 6.3 Hz) for three protons corresponding to the methyl group attached to a methine carbon. A multiplet in the range 2.10- 2.42 ppm corresponds to the methylene group attached to carbon on both sides. A sharp singlet at 3.05 ppm is for the methyl group in the chiral auxiliary attached to nitrogen. A characteristic doublet of quartet for one proton appeared in the range 3.43-3.58 ppm (J = 2.9, 6.3 Hz), which is attributed to the methine proton in the ephedrine part. A triplet at 3.89 ppm (J = 6.4 Hz) corresponds to the methylene protons attached to the hydroxyl group. The methine proton attached to the amide carbonyl appeared as a triplet at 4.47 ppm (J = 6.3 Hz). The characteristic doublet for benzylic proton appeared at 5.03 ppm (J = 2.9 Hz). The aromatic protons appeared in the range 7.20-7.55 ppm.

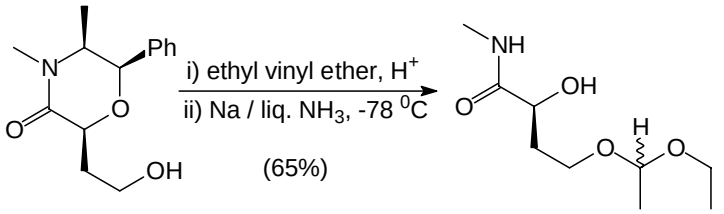
The ^{13}C NMR spectrum of **1.07** showed a peak at 169.9 ppm for the amide carbonyl. The quaternary aromatic carbon appeared at 137.1 ppm. The other aromatic carbons appeared at 127.7, 126.9 and 124.8 ppm. The benzylic carbon appeared at 75.8 ppm. The methine carbon attached to amide carbonyl appeared at 75.4 ppm. The methylene carbon attached to oxygen appeared at 58.4 ppm. The peak at 57.9 ppm corresponded to the methine carbon attached to nitrogen. The peak at 35.0 ppm is attributed to the methylene carbon, which is attached to the methine carbon. Methyl group attached to nitrogen appeared at 32.9 ppm. Other methyl group appeared at 12.2 ppm. The compound gave satisfactory elemental analysis.

Next we investigated the removal of chiral auxiliary in **1.07**. Removal of the ephedrine portion in **1.07** by dissolving metal reduction (Na, liq. NH_3, -78 ^{o}C) was problematic and resulted in a complex mixture, presumably due to the presence of free hydroxyl group. Conversion of **1.07** to the corresponding ethoxyethyl ether was beneficial.

Although the cleavage reaction worked after the protection of free hydroxyl group, the initial attempts gave a low yield of cleaved hydroxy amide **1.08**. It is noteworthy that the cleavage is dependant on the reaction time, amount of ammonia used, equivalents of sodium used for the reaction and the volume of THF used to dissolve the protected **1.07**. After optimizing the reaction conditions it was found that

quenching the reaction mixture with methanol after three minutes was ideal and gave a good yield of **1.08** (65%). However, quenching the reaction with methanol before three minutes gave incomplete reaction and the longer reaction time led to the formation of undesirable side products. The reduction of protected **1.07** proceeded smoothly at –78 ^{o}C (3 minutes) to generate α-hydroxy amide **1.08** in 65% yield over 2 steps (Scheme 9).

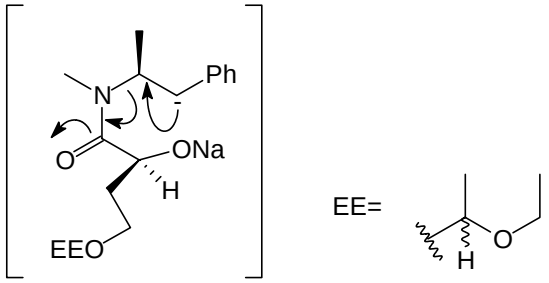
Scheme 9



1.07 **1.08**

We presume that the intermediate benzylic anion derived from ethoxyethyl protected compound **1.07** undergoes a facile β-elimination of the *N*-acyl moiety at lower temperature (Figure 3).

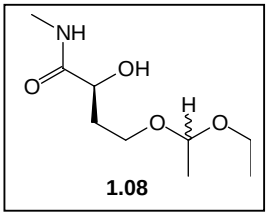
Figure 3



The ethoxyethyl ether **1.08** (mixture of diastereomers) was found to be unstable and hence was immediately characterized by IR and ^{1}H NMR and used further for cyclization (lactonization) reaction.

The structure of **1.08** was established by IR and ^{1}H NMR spectral data. IR spectrum of **1.08** showed a broad band at 3355 cm^{-1} for the hydroxyl group and a sharp peak at 1658 cm^{-1} for the amide carbonyl.

The ^{1}H NMR spectrum of **1.08** (major diastereomer) showed a doublet at 1.28 ppm (J = 5.3 Hz) and a triplet at 1.17 ppm (J = 7.0 Hz) respectively for the two methyl groups in the ethoxyethyl part. The two broad triplets at 2.25 ppm (J = 7.0 Hz) and 1.86 ppm (J = 7.3 ppm) are for the methylene group attached to carbons on either side. Methyl group attached to nitrogen appeared as a doublet at 2.81 ppm (J = 5.0 Hz). The multiplet in the range 3.36-3.90 ppm is for the two methylene groups attached to oxygen. A doublet of doublet appeared at 4.25 ppm (J = 2.9, 8.3 Hz), which is attributed to the methine proton alpha to the amide carbonyl. A multiplet in the range 4.60-4.70 ppm corresponds to the methine proton attached to two oxygens. The broad singlet at 6.95 ppm is for the proton of the amide N*H*.

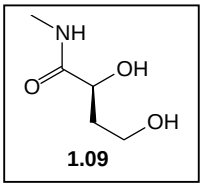


1.08

The following peaks for minor diastereomer of **1.08** are visible and appeared separately in ^{1}H NMR spectrum. Doublet for the methyl group at 1.25 ppm (J = 5.4 Hz) and a triplet for another methyl group at 1.16 ppm (J = 7.0 Hz), multiplet for the methylene protons in the range 1.79-1.98 ppm and 2.08-2.19 ppm, doublet for the methyl group attached to nitrogen at 2.76 ppm (J = 5.0 Hz) and a broad singlet at 6.00 ppm for the amide NH. Other peaks appeared in the same range as for the major diastereomer of **1.08**.

Dihydroxy amide **1.09** obtained by deprotection of the ethoxyethyl group in **1.08** was also characterized by ^{1}H NMR and HRMS data.

^{1}H NMR spectrum of **1.09** showed a multiplet separately for one proton each in the range 1.73-1.98 ppm and 2.0-2.23 ppm which is attributed to the protons on the methylene carbon. Methyl group attached to the nitrogen appeared as a doublet at 2.85 ppm (J = 5.4 Hz). The broad singlet at 3.25 ppm was attributed to the hydroxy group. Methylene group attached to the oxygen atom appeared as a multiplet in the range 3.84-3.95 ppm. The methine proton alpha to the carbonyl group appeared as a doublet of doublet in the range 4.25-4.38 ppm (J = 3.5, 7.9 Hz). The broad singlet at 4.58 ppm is attributed to the hydroxy group. The broad singlet at 7.03 ppm is typical of the amide NH group. HRMS data for **1.09** also matched with the calculated value.

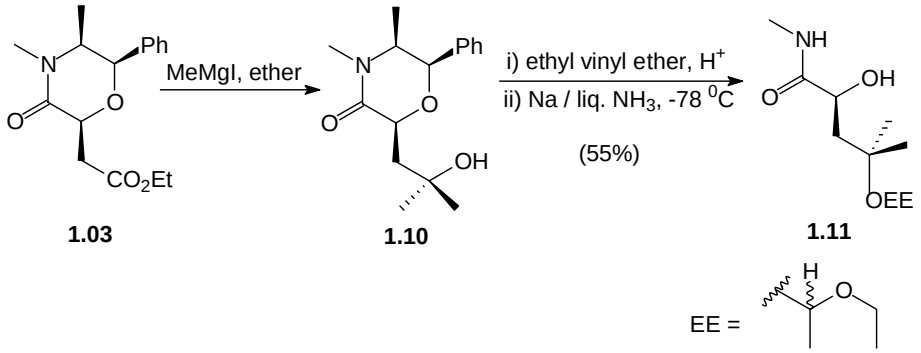


1.09

The ester group in **1.03** also serves as a useful tool for further functionalization of the embedded α-alkoxy succinate moiety. The potential of **1.03** as a common precursor

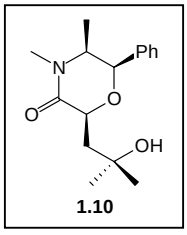
to the α-hydroxy butyrolactone scaffold was demonstrated with the synthesis of (*S*)-γ,γ-dimethyl-α-hydroxy-γ-butyrolactone. Treatment of **1.03** with excess MeMgI gave the tertiary alcohol **1.10** in 75% yield (Scheme 10).

Scheme 10



The structure of **1.10** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.10** showed a broad band at 3417 cm^{-1} for the tertiary hydroxyl group and a sharp peak at 1633 cm^{-1} for the amide carbonyl.

The ^{1}H NMR spectrum of **1.10** showed a doublet at 1.0 ppm (*J* = 6.3 Hz) for three protons corresponding to the methyl group attached to a methine carbon. A singlet at 1.33 ppm corresponds to the *gem*-dimethyl group. The methylene protons attached to the methine carbon appeared as doublet of doublets in the range 1.90-2.14 ppm (*J* = 7.8, 14.6 Hz) and 2.15-2.39 ppm (*J* = 4.9, 14.6 Hz). A sharp singlet at 3.04 ppm is for the methyl group in chiral auxiliary attached to nitrogen. The characteristic doublet of quartet for one proton appeared in the range 3.40-3.58 ppm (*J* = 2.5, 6.3 Hz) which is attributed to the methine proton in the ephedrine part. Broad singlet between 4.05-4.25 ppm corresponds to proton of hydroxy group. The proton on methine carbon attached to the amide carbonyl appeared as a doublet of doublet in the range 4.50-4.66 ppm (*J* = 4.9, 7.8 Hz). The characteristic doublet for benzylic proton appeared at 5.04 ppm (*J* = 2.5 Hz). The aromatic protons appeared in the range 7.17-7.45 ppm.



The ^{13}C NMR spectrum of **1.10** showed a peak at 169.6 ppm for the amide carbonyl. The quaternary aromatic carbon appeared at 137.2 ppm. The other aromatic carbons appeared at 128.4, 127.8 and 125.4 ppm. The benzylic carbon appeared at 77.2 ppm. The methine carbon attached to amide carbonyl appeared at 76.4 ppm. The

quaternary carbon attached to oxygen appeared at 69.4 ppm. The methine carbon attached to nitrogen appeared at 58.7 ppm. The methylene carbon attached to methine carbon appeared at 45.1 ppm. Methyl group attached to nitrogen appeared at 33.7 ppm. Methyl carbons of *gem*-dimethyl group appeared separately at 29.7 and 29.5 ppm. Other methyl group appeared at 13.0 ppm. The HRMS data of **1.10** matched with the calculated value.

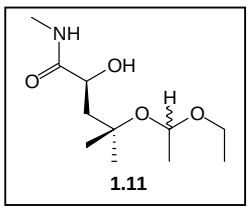
The conversion of **1.10** to the hydroxy amide **1.11** was achieved as described for the primary alcohol **1.07**. It is noteworthy that the crude ethoxyethyl ethers (of alcohols **1.07** and **1.10**) were unstable to column chromatography and therefore used without any purification for the reductive cleavage step.

Protection of **1.10** as the ethoxyethyl ether followed by reductive cleavage gave the hydroxy butyramide **1.11** (55% yield over two steps) (Scheme 10).

The ethoxyethyl ether **1.11** (mixture of diastereomers) was found to be unstable and characterized by IR and ^{1}H NMR and then used immediately for cyclization reaction.

IR spectrum of **1.11** showed a broad band at 3360 cm^{-1} for the hydroxyl group and a sharp peak at 1659 cm^{-1} is attributed to the amide carbonyl.

The ^{1}H NMR spectrum of **1.11** (major diastereomer) showed a multiplet between 1.05-1.50 ppm which is attributed to the four methyl groups. The methylene group appeared as a multiplet in the range 1.70-2.14 ppm. Methyl group attached to nitrogen appeared as a doublet at 2.84 ppm (J = 4.9 Hz). The methylene group attached to oxygen appeared in the range 3.37-3.77 ppm as a multiplet. The methine proton appeared in the range 4.28-4.46 ppm (J = 10.7 Hz) as a broad triplet. The proton on the methine carbon attached to two oxygen atoms appeared as a multiplet in the range 4.80-5.00 ppm. The broad singlet at 5.04 ppm is attributed to the hydroxy group and the broad singlet at 7.04 ppm typical of the amide NH.

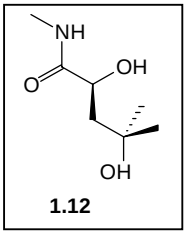


1.11

The following peaks for minor diastereomer of **1.11** appeared separately. A multiplet for the methylene protons in the range 2.25-2.60 ppm, doublet for the methyl group attached to nitrogen at 2.79 ppm (J = 4.8 Hz) and broad singlets at 5.70 ppm and 6.12 ppm for the hydroxy group and for the amide proton respectively. Other peaks appeared in the same range as for the major diastereomer of **1.11.**

Dihydroxy amide **1.12** obtained by deprotection of the ethoxyethyl group in **1.11** was also characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS data.

IR spectrum of **1.12** showed a broad band at 3340 cm^{-1} for the hydroxy group and a sharp peak at 1651 cm^{-1} for the amide carbonyl.



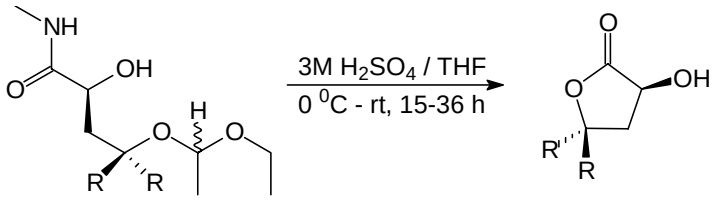
1.12

The ^{1}H NMR spectrum of **1.12** showed two separate singlets at 1.28 ppm and 1.34 ppm for the two methyl groups. The methylene protons appeared as two separate doublet of doublets integrating for one proton each in the range 1.93-2.10 ppm (J = 2.9, 14.7 Hz) and 1.62-1.84 ppm (J = 10.3, 14.7 Hz). The methyl group attached to nitrogen appeared as a doublet at 2.81 ppm (J = 4.9 Hz). The proton on the methine carbon alpha to the amide carbonyl, appeared as a doublet of doublet in the range 4.28-4.46 ppm (J = 2.9, 10.3 Hz). The broad singlet at 5.15 ppm was attributed to the hydroxy group. The broad singlet at 7.0 ppm is typical of the amide NH.

The ^{13}C NMR spectrum of **1.12** showed a peak at 174.9 ppm for the amide carbonyl. Methine carbon appeared at 72.1 ppm. Quaternary carbon attached to oxygen appeared at 70.5 ppm. The methylene carbon appeared at 44.8 ppm. Methyl group attached to nitrogen appeared at 31.4 ppm. The other two methyl groups appeared at 27.6 ppm and 25.7 ppm. HRMS data for **1.12** also matched with the calculated value.

The conversion of the α-hydroxy butyramides **1.08** and **1.11** to the target lactones **1.13** and **1.14** respectively was achieved under remarkably mild conditions. Unmasking of the protected alcohols in **1.08** and **1.11** was 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[18] to generate the desired lactones **1.13** (70%, 96%ee) and **1.14** (82%, 98%ee)[19] respectively (Scheme 11).

Scheme 11



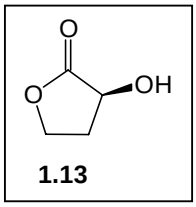
1.08, **1.11**

1.13 (R = H) 70%
1.14 (R = Me) 82%

The structure of **1.13** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.13** showed a broad band at 3441 cm^{-1} for the hydroxyl group. The

characteristic peak at 1776 cm^{-1} showed the presence of a 5-membered lactone carbonyl.

The ^1H NMR spectrum of **1.13** showed two separate multiplets in the range 2.16-2.43 ppm and 2.52-2.72 ppm for the methylene group attached to two carbons on either side. A broad singlet at 3.58 ppm is attributed to the proton of hydroxy group. The methine proton appeared at 4.25 ppm as a ddd (J = 6.0, 9.0, 10.0 Hz). The methylene group attached to oxygen appeared in the range 4.37-4.62 ppm as a multiplet.



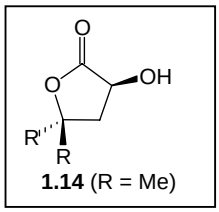
1.13

The ^{13}C NMR spectrum of **1.13** showed a peak at 177.7 ppm for the lactone carbonyl. The peaks at 67.4 ppm and 65.1 ppm correspond to the methine and methylene carbons attached to the oxygen respectively. The other methylene carbon appeared at 30.9 ppm.

The optical rotation $\{[\alpha]_D^{25} = -66.0$ (c 1.0, $CHCl_3)\}$ matched with the reported value $\{[\alpha]_D^{25} = -65.2$ (c 1.1, $CHCl_3)\}$[5] and the sign of the optical rotation confirmed the absolute stereochemistry at the chiral center.

The structure of **1.14** was established by IR, ^1H NMR and ^{13}C NMR spectral data. IR spectrum of **1.14** showed a broad band at 3431 cm^{-1} for the hydroxy group. The characteristic peak at 1770 cm^{-1} showed the presence of a 5-membered lactone.

The ^1H NMR spectrum of **1.14** showed two separate singlets for the methyl groups at 1.42 ppm and 1.52 ppm. Two separate doublet of doublets appeared in the range 1.90-2.20 ppm (J = 9.7, 12.7 Hz) and 2.40-2.60 ppm (J = 8.3, 12.7 Hz) for the methylene group. A broad signal appeared at 3.69 ppm for the proton of hydroxy group. The methine proton appeared in the range 4.60-4.80 ppm (J = 8.3, 9.7 Hz) as a doublet of doublet.



1.14 (R = Me)

The ^{13}C NMR spectrum of **1.14** showed a peak at 177.1 ppm for the lactone carbonyl. Quaternary carbon attached to oxygen appeared at 82.3 ppm. Methine carbon appeared at 68.8 ppm. Methylene carbon appeared at 42.9 ppm. The peaks at 29.1 ppm and 27.7 ppm corresponds to the two methyl groups. HRMS data for **1.14** matches with the calculated value.

The optical rotation $\{[\alpha]_D^{25} = -22.0$ (c 0.7, MeOH)$\}$ matched with the reported value {For R isomer $[\alpha]_D^{25} = +23.9$ (c 0.6, MeOH)}[11] and the sign of the optical rotation confirmed the absolute stereochemistry at the chiral center.

The absolute configuration of the lactones **1.13** and **1.14** are based on that of the precursor **1.03** since epimerization of the newly generated stereocenter in **1.03** during its conversion to the target lactones **1.13** and **1.14** is unlikely. Thus the lactones **1.13** and **1.14** are assigned the '*S*' configuration. The enantiomeric excess of the lactones was determined using chiral GC and found to be 96% and 98% respectively for the lactones **1.13** and **1.14**.

The overall conversion of morpholine-dione **1.01** to the target lactones **1.13** and **1.14** constitutes a new approach to these important intermediates. The results are summarized in Table 1.

Table 1. Conversion of morpholine dione **1.01** to α-hydroxy-γ-butyrolactones (**1.13**, **1.14**).

Alcohol (% yield)	**Hydroxy amide** (% yield)	**Butyrolactone** (% yield)	**% ee**[19]	**Configuration**
1.07 (70%)	**1.08** (65%)	**1.13** (70%)	96	*S*
1.10 (75%)	**1.11** (55%)	**1.14** (82%)	98	*S*

1.5: Conclusion

A general route for the asymmetric synthesis of α-hydroxy-γ-butyrolactones has been developed by functionalization of a readily available ephedrine-derived morpholine dione. The morpholinone **1.03** holds great potential as a common intermediate for a variety of functionalized α-hydroxy acids and α-hydroxy γ-butyrolactones. The potential of **1.03** as a common precursor to the α-hydroxy butyrolactone scaffold has been demonstrated with the synthesis of (*S*)-γ,γ-dimethyl-α-hydroxy-γ-butyrolactone. The (*R*) enantiomer of this lactone, which is a valuable intermediate in the synthesis of bark beetle pheromones, should also be readily available by the present methodology since 1*S*, 2*R* ephedrine is commercially available as well.

1.6: Experimental

(5*S*,6*R*)-4,5-Dimethyl-6-phenyl-morpholin-2,3-dione (1.01):

To a stirred suspension of ephedrine hydrochloride (2 g, 9.9 mmol) and DMAP (60 mg, 0.49 mmol) in dichloromethane (200 mL) at 0 ^{o}C was added triethylamine (5.5 mL, 39.6 mmol). The mixture was stirred for 10 minutes and a solution of oxalyl chloride (1.3 mL, 14.9 mmol) in dichloromethane (100 mL) was added dropwise over a period of 4 h at 0 ^{o}C. The mixture was further stirred at 0 ^{o}C for 1 h and ice was added. The mixture was warmed to ambient temperature and the biphase was separated. The dichloromethane layer was washed with water (70 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (3/1 ethyl acetate/petroleum ether) to furnish 1.42 g (65%) of **1.01** as a white solid.

mp: 182 ^{o}C

IR ($CHCl_3$):

1771, 1693 cm^{-1}.

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

δ 1.12 (d, 3H, *J* = 6.8 Hz, C*H*$_3$), 3.19 (s, 3H, NC*H*$_3$), 3.66-3.77 (dq, 1H, *J* = 2.9, 6.8 Hz, C*H*CH$_3$), 5.90 (d, 1H, *J* = 2.9 Hz, C*H*Ph), 7.28-7.50 (m, 5H, Ar*H*).

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

δ 11.8 (*C*H$_3$), 33.2 (N*C*H$_3$), 58.1 (CH$_3$*C*H), 79.3 (Ph*C*H), 125.3 (Ar*C*), 128.0 (Ar*C*), 128.6 (Ar*C*), 133.8 (Ar*Cipso*), 153.0 (N*C*=*O*), 156.4 (O*C*=*O*).

MS (EI, 70 ev):

m/z 219 (M^{+}).

Analysis for $C_{12}H_{13}NO_3$:

Calculated: C, 65.74; H, 5.97; N, 6.38; Obtained: C, 65.45; H, 6.09; N, 6.36.

Optical rotation:

$[\alpha]_D^{25}$ = –184.3 (*c* 0.8, $CHCl_3$).

***Z*-(5*S*,6*R*)-(4,5-Dimethyl-3-oxo-6-phenyl-morpholin-2-ylidine)-acetic acid ethyl ester (1.02):**

To a solution of **1.01** (219 mg, 1 mmol) in dichloromethane (3 mL) at room temperature was added carbethoxymethylene triphenylphosphorane (418 mg, 1.2 mmol) and the mixture was stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on

silica gel (2/3 ethyl acetate/petroleum ether) to furnish 231 mg (80%) of **1.02** as a white solid.

mp: 161-162 ^{o}C.

IR ($CHCl_3$):

1701, 1668, 1637 cm^{-1}.

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

δ 1.02 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH), 1.32 (t, 3H, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 3.15 (s, 3H, NC*H*$_3$), 3.62-3.73 (dq, 1H, *J* = 2.9, 6.6 Hz, CH$_3$C*H*), 4.18-4.27 (m, 2H, OC*H*$_2$C), 5.47 (d, 1H, *J* = 2.9 Hz, PhC*H*), 6.22 (s, 1H, *vinylic*), 7.55-7.30 (m, 5H, Ar*H*).

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

δ 11.4 (*C*H$_3$CH), 14.0 (CH$_2$*C*H$_3$), 33.6 (N*C*H$_3$), 57.9 (N*C*H), 59.7 (O*C*H$_2$), 77.9 (Ph*C*H), 101.0 (C=*C*H), 125.2 (Ar*C*), 128.0 (Ar*C*), 128.4 (Ar*C*), 135.5 (Ar*Cipso*), 153.5 (*C*=CH), 157.7 (N*C*=*O*), 164.6 (O*C*=*O*).

MS (EI, 70 ev):

m/z 289 (M^{+}).

Analysis for $C_{16}H_{19}NO_4$:

Calculated: C, 66.42; H, 6.62; N, 4.84; Obtained: C, 66.21; H, 6.75; N, 4.73.

Optical rotation:

$[\alpha]_D^{25} = -238.1$ (*c* 0.6, $CHCl_3$).

(2*S*,5*S*,6*R*)-(4,5-Dimethyl-3-oxo-6-phenyl-morpholin-2-yl)-acetic acid ethyl ester (1.03):

To a solution of **1.02** (289 mg, 1 mmol) in ethyl acetate (10 mL) was added Pd/C (5%, 25 mg) and the mixture was stirred under an atmosphere of hydrogen (1 atm.) for 12 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give 291 mg (100%) of **1.03** as a clear colorless gum.

IR ($CHCl_3$):

1738, 1653 cm^{-1}.

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

δ 0.99 (d, 3H, *J* = 6.4 Hz, CH$_3$C*H*), 1.29 (t, 3H, *J* = 6.8 Hz, C*H*$_3$CH$_2$), 3.04 (s, 3H, NC*H*$_3$), 2.88-3.15 (m, 2H, C*H*$_2$CO$_2$Et), 3.44-3.61 (dq, 1H, *J* = 2.9, 6.4 Hz,

CH_3CH), 4.12-4.30 (q, 2H, J = 6.8 Hz, OCH_2), 4.66 (t, 1H, J = 5.4 Hz, $CHCH_2$), 5.06 (d, 1H, J = 2.9 Hz, PhC*H*), 7.22-7.46 (m, 5H, Ar*H*).

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

δ 12.3 (CH_3CH), 13.9 (CH_2CH_3), 33.1 (NCH_3), 37.3 (CH_2CO_2Et), 58.4 (N-*C*H), 60.2 (OCH_2), 74.6 (*C*HCO), 76.4 (Ph*C*H), 125.1 (Ar*C*), 127.3 (Ar*C*), 128.0 (Ar*C*), 137.0 (Ar*Cipso*), 167.5 (N*C*=O), 170.0 (O*C*=O).

HRMS for $C_{16}H_{21}NO_4$:

Calculated: 291.1471; Obtained: 291.1474.

Optical rotation:

$[\alpha]_D^{25} = -114.0$ (*c* 1.1, $CHCl_3$).

(5*S*,6*R*)-2-(2-Hydroxy-4,5-dimethyl-3-oxo-6-phenyl-morpholin-2-yl)-propionic acid ethyl ester (1.05):

To activated Zn (1.492 g, 22.9 mmol) was added a crystal of iodine and warmed followed by the addition of benzene (15 mL). The resulting mixture was stirred for five minutes. To this was added 1.0 g of dione **1.01** in one portion followed by the addition of ethyl-2-bromopropionate (0.89 mL). The resulting mixture was stirred at room temperature for fifteen minutes and then refluxed for 2 h. To the reaction mixture was then added 2N HCl (20 mL) and stirred further for 12 h at room temperature. Ethyl acetate was then added and the organic layer was washed with water (2 x 15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated to give the crude compound which on purification by flash column chromatography with 3/2 EA/PE gave 1.202 g (82%) of **1.05** as a clear colorless gum.

IR ($CHCl_3$):

3400, 1738, 1650 cm^{-1}.

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

Major diastereomer:

δ 0.95 (d, 3H, J = 6.6 Hz, CH_3CH), 1.20-1.45 (m, 6H, CH_3CH, CH_3CH_2), 3.04 (s, 3H, NCH_3), 3.36 (q, 1H, J = 7.3 Hz, $CHCH_3$), 3.45-3.57 (m, 1H, NC*H*), 4.10-4.38 (m, 2H, OCH_2), 5.65 (d, 1H, J = 2.9 Hz, PhC*H*), 5.84 (bs, 1H, O*H*), 7.22-7.42 (m, 5H, Ar*H*).

Minor diastereomer:

δ 0.95 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH), 1.20-1.45 (m, 6H, C*H*$_3$CH, C*H*$_3$CH$_2$), 3.03 (s, 3H, NC*H*$_3$), 3.14 (q, 1H, *J* = 7.0 Hz, C*H*CH$_3$), 3.45-3.57 (m, 1H, NC*H*), 4.10-4.38 (m, 2H, OC*H*$_2$), 5.61 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.84 (bs, 1H, O*H*), 7.22-7.42 (m, 5H, Ar*H*).

(2*S*,5*S*,6*R*)-(4, 5-Dimethyl-3-oxo-6-phenyl-morpholin-2-yl)-acetic acid (1.06):

To the solution of **1.03** (580 mg, 2 mmol) in THF (8 mL) was added aqueous NaOH (1M, 8 mL) and the mixture was stirred at ambient temperature for 6-7 h. The aqueous layer was acidified with conc. HCl and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL). The bicarbonate extract was acidified with conc. HCl and the solution was extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated to give 502 mg (96%) of **1.06** as a white solid**.**

IR ($CHCl_3$):

2922, 1732, 1607 cm^{-1}.

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

δ 0.98 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 2.90-3.18 (m, 2H, C*H*$_2$COOH), 3.05 (s, 3H, NC*H*$_3$), 3.43-3.60 (dq, 1H, *J* = 2.4, 6.3 Hz, CH$_3$C*H*), 4.60-4.70 (m, 1H, C*H*CH$_2$), 5.05 (d, 1H, *J* = 2.4 Hz, PhC*H*), 7.20-7.43 (m, 5H, Ar*H*).

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

δ 12.6 (CH*C*H$_3$), 33.7 (N*C*H$_3$), 37.5 (*C*H$_2$CO$_2$H), 58.8 (N-*C*H), 74.4 (*C*HCO), 76.8 (Ph*C*H), 125.3 (Ar*C*), 127.6 (Ar*C*), 128.2 (Ar*C*), 137.1 (Ar*Cipso*), 168.5 (N*C*=O), 174.5 (O*C*=O).

MS (EI, 70 ev):

m/z 263 (M^+).

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

Calculated: C, 63.87; H, 6.5; N, 5.32; Obtained: C, 63.99; H, 6.72; N, 5.07.

Optical rotation:

$[\alpha]_D^{25} = -123.4$ (*c* 1.2, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(2-Hydroxyethyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (1.07):

To a solution of **1.06** (502 mg, 1.91 mmol) in dichloromethane (6 mL) was added oxalyl chloride (0.83 mL, 9.54 mmol) dropwise and the mixture was stirred at ambient temperature for 2 h. The solvent and excess oxalyl chloride were removed under reduced pressure and the residue was dissolved in dioxane (6 mL). The dioxane solution was added to a stirred suspension of sodium borohydride (722 mg, 19.1 mmol) in dioxane (6 mL) followed by addition of $TiCl_4$ (1.05 mL, 9.55 mmol). The resulting mixture was heated to 90 ^oC for 8 h and then cooled to 0 ^oC. Saturated aqueous bicarbonate was added and the resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate) to furnish 332 mg of **1.07** (70%) as a white solid.

mp: 135-136 ^oC.

IR ($CHCl_3$):

3404, 1641 cm^{-1}.

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

δ 1.00 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 2.10-2.42 (m, 2H, C*H*$_2$CH), 3.05 (s, 3H, NC*H*$_3$), 3.43-3.58 (dq, 1H, *J* = 2.9, 6.3 Hz, C*H*CH$_3$), 3.89 (t, 2H, *J* = 6.4 Hz, C*H*$_2$OH), 4.47 (t, 1H, *J* = 6.3 Hz, C*H*CO), 5.03 (d, 1H, *J* = 2.9 Hz, PhC*H*), 7.20-7.55 (m, 5H, Ar*H*).

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

δ 12.2 (*C*H$_3$CH), 32.9 (N*C*H$_3$), 35.0 (*C*H$_2$CH$_2$OH), 57.9 (N*C*H), 58.4 (*C*H$_2$OH), 75.4 (*C*HCO), 75.8 (Ph*C*H), 124.8 (Ar*C*), 126.9 (Ar*C*), 127.7 (Ar*C*), 137.1 (Ar*Cipso*), 169.9 (N*C*=O).

MS (EI, 70 ev):

m/z 249 (M^+).

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

Calculated: C, 67.45; H, 7.68; N, 5.62; Obtained: C, 67.50; H, 7.83; N, 5.24.

Optical rotation:

$[\alpha]_D^{25} = -177.7$ (*c* 0.5, $CHCl_3$).

(2*S*)-4-(1-Ethoxy-ethoxy)-2-hydroxy-*N*-methyl-butyramide (1.08):

To the solution of **1.07** (168 mg, 0.67 mmol) in chloroform (3 mL) was added ethyl vinyl ether (0.52 mL, 5.4 mmol) and trichloroacetic acid (a few crystals). The resulting mixture was stirred at ambient temperature for 12 h. Saturated aqueous $NaHCO_3$ was added and the organic layer was separated. The bicarbonate layer was extracted with chloroform (3 x 5 mL). Combined organic layers were dried (Na_2SO_4) and concentrated to give the ethoxyethyl derivative of **1.07** that was used further without purification.

The above derivative was dissolved in anhydrous THF (2 mL) and added to a mixture of anhydrous liquid ammonia (7 mL, distilled over sodium) and sodium (154 mg, 6.7 mmol) at –78 ^oC. The mixture was stirred at –78 ^oC for 3 minutes and methanol (6 mL) was added. The mixture was warmed to ambient temperature to remove ammonia and the methanol was removed under reduced pressure. The residue was taken up in water and the mixture was saturated with sodium chloride. The aqueous phase was extracted with ethyl acetate and the combined extracts were concentrated. The residue was purified by rapid filtration through a short silica gel column (ethyl acetate) to furnish 90 mg (65%) of **1.08** as a gum, which was immediately used further.

IR (neat):

3355, 1658 cm^{-1}.

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

Major diastereomer:

δ 1.17 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 1.28 (d, 3H, *J* = 5.3 Hz, $CHCH_3$), 1.86 (t, 1H, *J* = 7.3 Hz, CH_2), 2.25 (t, 1H, *J* = 7.0 Hz, CH_2), 2.81 (d, 3H, *J* = 5.0 Hz, NCH_3), 3.36-3.90 (m, 4H, 2xOCH_2), 4.25 (dd, 1H, *J* = 2.9, 8.3 Hz, CHOH), 4.60-4.70 (m, 1H, OCHO), 6.95 (bs, 1H, NH).

Minor diastereomer:

δ 1.16 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 1.25 (d, 3H, *J* = 5.4 Hz, $CHCH_3$), 1.79-1.98 (m, 1H, CH_2), 2.08-2.19 (m, 1H, CH_2), 2.76 (d, 3H, *J* = 5.0 Hz, NCH_3), 3.36-3.90 (m, 4H, 2xOCH_2), 4.25 (dd, 1H, CHOH), 4.60-4.70 (m, 1H, OCHO), 6.0 (bs, NH).

Dihydroxy amide **1.09** obtained by deprotection of the ethoxyethyl group in **1.08** was also characterized.

(2*S*)-2,4-Dihydroxy-*N*-methyl-butyramide (1.09):

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

δ 1.73-1.98 (m, 1H, C*H*$_2$CHOH), 2.0-2.23 (m, 1H, C*H*$_2$CHOH), 2.85 (d, 3H, *J* = 5.4 Hz, NHC*H*$_3$), 3.84-3.95 (m, 2H, C*H*$_2$OH), 4.25-4.38 (dd, 1H, *J*= 3.5, 7.9 Hz, C*H*OH), 4.58 (bs, 1H, O*H*), 7.03 (bs, 1H, N*H*).

HRMS for $C_5H_{11}NO_3$:

Calculated: 133.0925; Obtained: 133.0921.

Optical rotation:

$[\alpha]_D^{25} = -31.8$ (*c* 0.4, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(2-Hydroxy-2-methyl-propyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (1.10):

To a solution of **1.03** (160 mg, 0.55 mmol) in benzene (3 mL) was added MeMgI in ether (5.5 mmol) at 10-15 ^{0}C and the mixture was stirred for 2 h at ambient temperature. Saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (3/2 ethyl acetate/petroleum ether) to furnish 115 mg (75%) of **1.10** as a white solid.

mp: 104-105 ^{o}C.

IR (film):

3417, 1633 cm^{-1}.

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

δ 1.0 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 1.33 (s, 6H, (C*H*$_3$)$_2$C), 1.90-2.14 (dd, 1H, *J* = 7.8, 14.6 Hz, C*H*$_2$CH0), 2.15-2.39 (dd, 1H, *J* = 4.9, 14.6 Hz, C*H*$_2$CHO), 3.04 (s, 3H, NC*H*$_3$), 3.40-3.58 (dq, 1H, *J* = 2.5, 6.3 Hz, C*H*CH$_3$), 4.05-4.25 (bs, 1H, O*H*), 4.50-4.66 (dd, 1H, *J*= 4.9, 7.8 Hz, C*H*CO), 5.04 (d, 1H, *J* = 2.5 Hz, PhC*H*), 7.17-7.45 (m, 5H, Ar*H*).

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

δ 13.0 (*C*H$_3$CH), 29.5 ((*C*H$_3$)$_2$), 29.7 ((*C*H$_3$)$_2$C), 33.7 (N*C*H$_3$), 45.1 (*C*H$_2$CH), 58.7 (N*C*H), 69.4 (*C*-OH), 76.4 (*C*HCO), 77.2 (Ph*C*H), 125.4 (Ar*C*), 127.8 (Ar*C*), 128.4 (Ar*C*), 137.2 (Ar*Cipso*), 169.6 (N*C*=O).

MS (EI, 70 ev):

m/z 277 (M^+).

HRMS for $C_{16}H_{23}NO_3$:

Calculated: 277.1679; Obtained: 277.1680.

Optical rotation:

$[\alpha]_D^{25} = -163.2$ (*c* 0.6, $CHCl_3$).

(2*S*)-4-(1-Ethoxy-ethoxy)-2-hydroxy-4-methyl-pentanoic acid methyl amide (1.11):

To the solution of **1.10** (327 mg, 1.18 mmol) in chloroform (3 mL) was added ethyl vinyl ether (0.9 mL, 9.40 mmol) and trichloroacetic acid (a few crystals). The resulting mixture was stirred at ambient temperature for 18-20 h. Solid sodium bicarbonate was added and the chloroform was removed under reduced pressure. Attempted isolation of the product by conventional partitioning techniques results in decomposition to the starting material and the crude ethoxyethyl ether was therefore used further without any treatment or purification.

The crude ethoxyethyl ether was dissolved in THF (2 mL) and the solution was added to the mixture of anhydrous liquid ammonia (10 mL, distilled over sodium) and sodium (270 mg, 11.8 mmol) at –78 ^oC. The reaction mixture was stirred at -78 ^oC for 3 minutes, methanol was added and the mixture was warmed 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 solid NaCl and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by rapid filtration through a short silica gel column (ethyl acetate) to furnish 151 mg (55%) of **1.11** which was immediately used further.

IR (neat):

3360, 1659 cm^{-1}.

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

Major diastereomer:

δ 1.05-1.50 (m, 12H, $(CH_3)_2C$, CH_3CH, CH_3CH_2), 1.70-2.14 (m, 2H, CH_2CH), 2.84 (d, 3H, *J* = 4.9 Hz, NCH_3), 3.37-3.77 (m, 2H, OCH_2), 4.28-4.46 (t, 1H, *J* = 10.7 Hz, CHOH), 4.80-5.0 (m, 1H, OCHO), 5.04 (bs, 1H, OH), 7.04 (bs, 1H, NH).

Minor diastereomer:

δ 1.05-1.50 (m, 12H, $(CH_3)_2C$, CH_3CH, CH_3CH_2), 2.25-2.60 (m, 2H, CH_2CH), 2.79 (d, 3H, J = 4.8 Hz, NCH_3), 3.37-3.77 (m, 2H, OCH_2), 4.28-4.46 (t, 1H, J = 10.7 Hz, C*H*OH), 4.80-5.0 (m, 1H, OC*H*O), 5.70 (bs, 1H, O*H*), 6.12 (bs, 1H, N*H*).

Dihydroxy amide **1.12** obtained by deprotection of the ethoxyethyl group in **1.11** was also characterized.

(2*S*)-2,4-Dihydroxy-4-methyl-pentanoic acid methyl amide (1.12):

IR ($CHCl_3$):

3348, 1651 cm^{-1}.

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

δ 1.28 (s, 3H, CH_3C), 1.34 (s, 3H, CH_3C), 1.62-1.84 (dd, 1H, J = 10.3, 14.7 Hz, CH_2CH), 1.93-2.10 (dd, 1H, J = 2.9, 14.7 Hz, CH_2CH), 2.81 (d, 3H, J = 4.9 Hz, CH_3NH), 4.28-4.46 (dd, 1H, J = 2.9, 10.3 Hz, C*H*OH), 5.15 (bs, 1H, O*H*), 7.0 (bs, 1H, N*H*).

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

δ 25.7 (CH_3), 27.6 (*C*H3), 31.4 ($NHCH_3$), 44.8 (CH_2CH), 70.5 ($(CH_3)_2C$), 72.1 (*C*HOH), 174.9 (N*C*=O).

HRMS for $C_7H_{15}NO_3$:

Calculated: 161.1052; Found: 161.1051.

Optical rotation:

$[\alpha]_D^{25}$ = –25.9 (*c* 1.5, $CHCl_3$).

(*S*)-3-Hydroxy-dihydro-furan-2-one (1.13):

To a stirred solution of **1.08** (280 mg, 1.40 mmol) in THF (1.5 mL) at 0 ^oC was added H_2SO_4 (3M, 0.5 mL) dropwise over a period of 3 minutes. The resulting solution was warmed to ambient temperature at which it was stirred for 36 h. The mixture was then diluted with ether and neutralized with excess solid $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (3/2 ethyl acetate/petroleum ether followed by ethyl acetate) to furnish 98 mg (70%) of **1.13** as a clear colorless gum.

IR ($CHCl_3$):

3441, 1776 cm^{-1}.

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

δ 2.16-2.43 (m, 1H, C*H*$_2$CH$_2$O), 2.52-2.72 (m, 1H, C*H*$_2$CH$_2$O), 3.58 (bs, 1H, O*H*), 4.25 (ddd, 1H, *J* = 6, 9, 10 Hz, C*H*OH), 4.37-4.62 (m, 2H, C*H*$_2$O).

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

δ 30.9 (*C*H$_2$CH$_2$O), 65.1 (*C*H$_2$O), 67.4 (*C*HOH), 177.7 (O*C*=O).

Optical rotation:

Observed optical rotation $[\alpha]_D^{25}$ = –66.0 (*c* 1.0, $CHCl_3$).

Reported optical rotation $[\alpha]_D^{25}$ = –65.2 (*c* 1.1, $CHCl_3$).[5]

(*S*)-3-Hydroxy-4,4-dimethyl-dihydro-furan-2-one (1.14):

This was prepared from **1.11** (72 mg, 0.31 mmol) in THF (1.5 mL) as described for **1.08** at ambient temperature for 15 h. Purification by flash chromatography on silica gel (3/7 ethyl acetate/petroleum ether) furnished 33 mg (82%) of **1.14** as a clear, colorless gum.

IR ($CHCl_3$):

3431, 1770 cm^{-1}.

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

δ 1.42 (s, 3H, C*H*$_3$), 1.52 (s, 3H, C*H*$_3$), 1.94-2.18 (dd, 1H, *J* = 9.7, 12.7 Hz, C*H*$_2$CH), 2.45-2.63 (dd, 1H, *J* = 8.3, 12.7 Hz, C*H*$_2$CH), 3.69 (bs, 1H, O*H*), 4.58-4.78 (dd, 1H, *J* = 8.3, 9.7 Hz, C*H*OH).

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

δ 27.7 (*C*H$_3$), 29.1 (*C*H$_3$), 42.9 (*C*H$_2$), 68.8 (*C*HOH), 82.3 (*C*(CH$_3$)$_2$), 177.1 (*C*=O).

HRMS for $C_6H_{10}O_3$:

Calculated: 130.0630; Found: 130.0635.

Optical rotation:

Observed optical rotation $[\alpha]_D^{25}$ = –22.2 (*c* 0.7, CH_3OH).

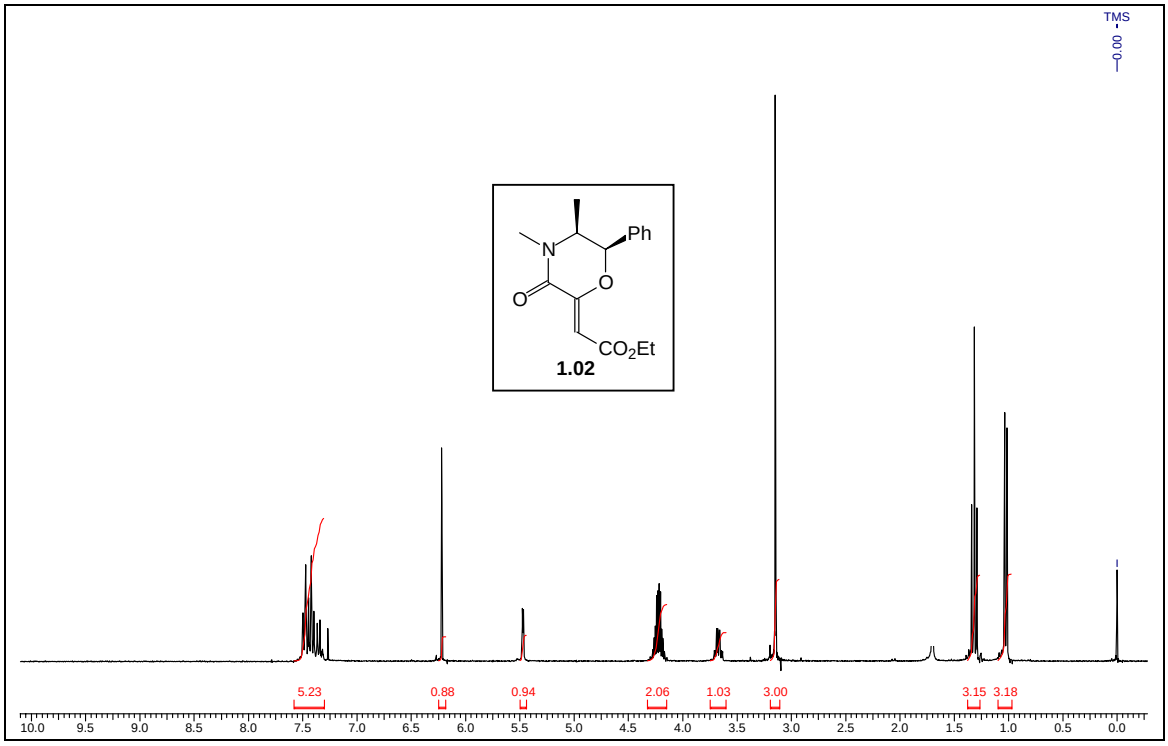
Reported optical rotation (for *R* isomer) $[\alpha]_D^{25}$ = +23.9 (*c* 0.6, MeOH).[11]

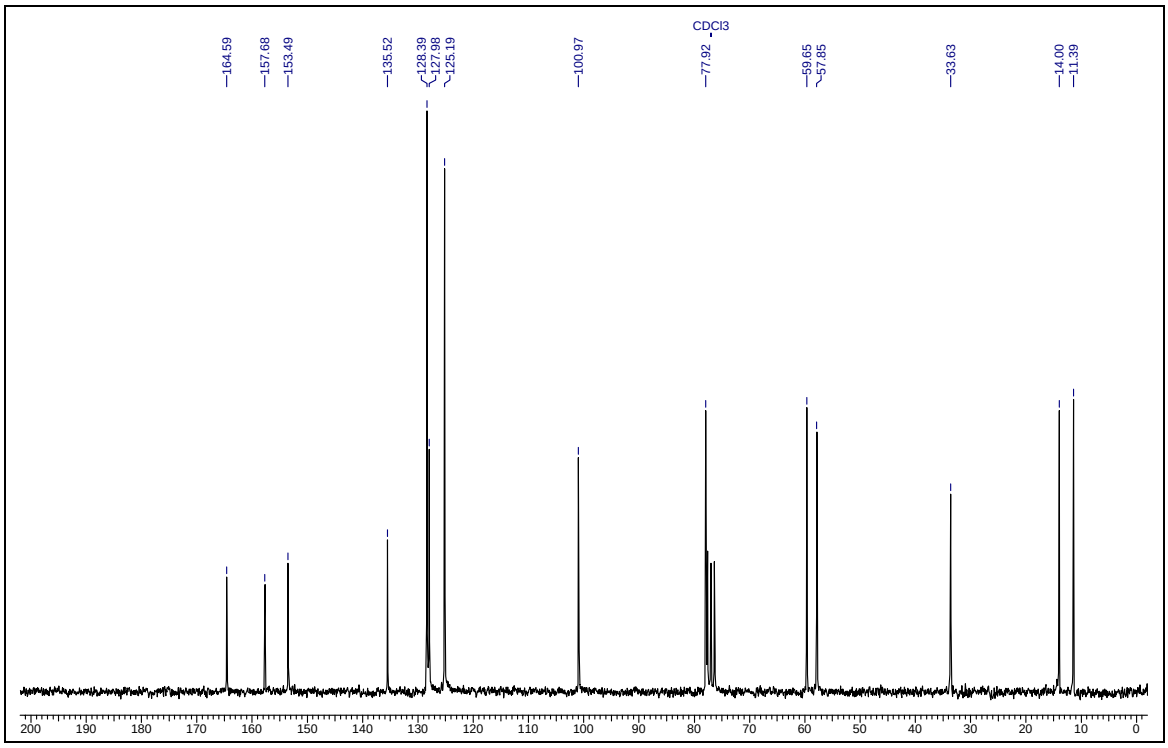
1.7: References

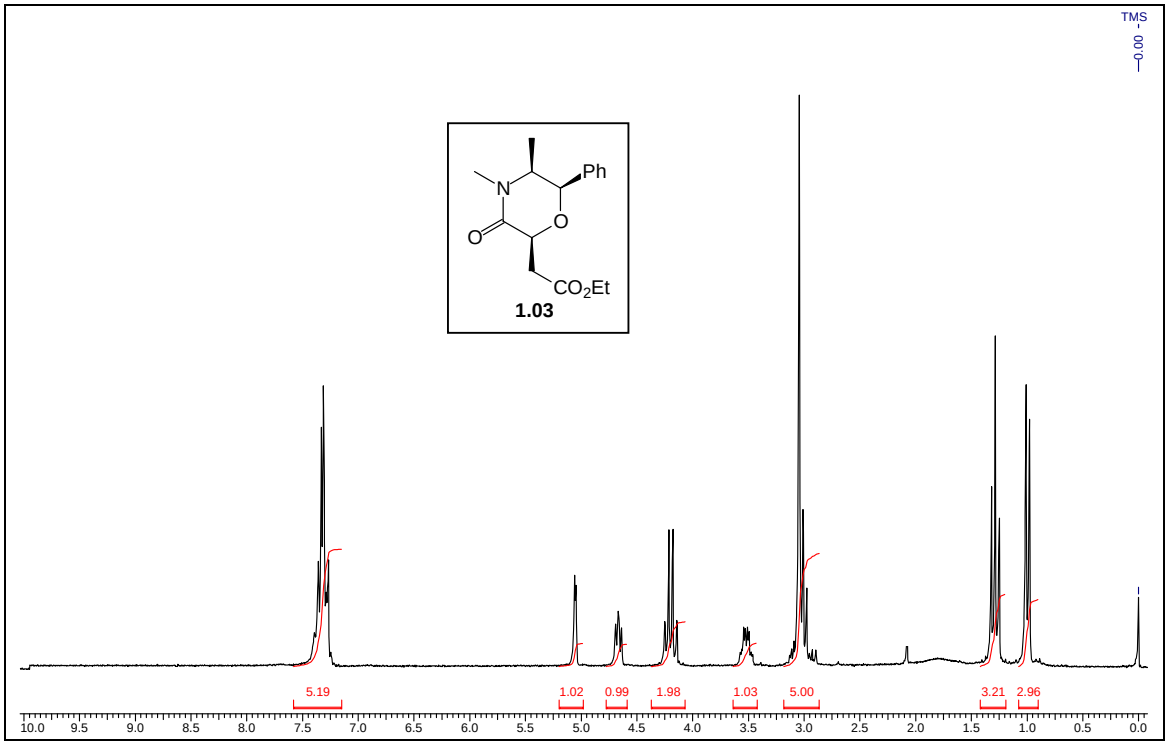
1. a) Peterson, M.; Kalbermatten, G. PCT Int. Appl. WO 2001018231 A2 **2001**. b) Ueki, T.; Ichinari, D.; Yoshihara, K.; Morimoto, Y.; Kinoshita, T. *Tetrahedron Lett.* **1998**, *39*, 667. c) Eliel, E. L.; Bai, X.; Ohwa, M. *J. Chin. Chem. Soc.* **2000**, *47*, 63. d) Blandin, V.; Carpentier, J.-F.; Mortreaux, A. *Eur. J. Org. Chem.* **1999**, 1787.
2. (a) Hooper, A. T.; Witiak, D. T.; Ziemniak, J. *J. Med. Chem*. **1998**, *41*, 420. (b) Mendik, M. T.; Cottard, M.; Rein, T.; Helquist, P. *Tetrahedron Lett*. **1997**, *38*, 6375. (c) Abdallah, M. A.; Shah, J. N. *J. Chem. Soc., Perkin Trans. 1*. **1975**, 888. (d) Rao, A. V. R.; Rao, S. M.; Sharma, G. V. M. *Tetrahedron Lett*. **1994**, *35*, 5735 and references cited therein. (e) Blandin, V.; Carpentier, J.-F.; Mortreaux, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2765 and references therein. (f) Ohfune, Y.; Tomita, M.; Nomoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2409.
3. a) Sefkow, M. *J. Org. Chem.* **2001**, *66*, 2343. b) Ichinari, D.; Ueki, T.; Yoshihara, K.; Kinoshita, T. *Chem. Commun.* **1997**, 1743.
4. Buser, H. P.; Pugin, B.; Spindler, F.; Sutter, M. *Tetrahedron* **1991**, *47*, 5709.
5. Shiuey, S-J.; Partridge, J. J.; Uskokovic, M. R. *J. Org. Chem.* **1988**, *53*, 1040.
6. White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129.
7. (a) Mulzer, J.; Mantoulidis, A.; Oehler, E. *J. Org. Chem.* **2000**, *65*, 7456. (b) Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2865.
8. Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.
9. Seo, S.-Y.; Jung, J.-K.; Paek, S.-M.; Lee, Y.-S.; Kim, S.-H.; Lee, K.-O.; Suh, Y.-G. *Org. Lett*. **2004**, *6*, 429.
10. a) Puthuraya, K.; Oomura, Y.; Shimizu, N. *Brain Research* **1985**, *332*, 165 and references cited therein. b) Nakano, T.; Ino, Y.; Nagai, Y. *Chem. Lett*. **1989**, 567. c) Xie, Z. –F.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1993**, *4*, 973. d) Murakami, M.; Huyashi, M. *J. Org. Chem*. **1994**, *59*, 7910. e) Niihata, S.; Ebata, T.; Kawakami, H.; Matsushita, H. *Bull. Chem. Soc. Jap.* **1995**, *68*, 1509.
11. Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.
12. Ikemoto, T.; Sakashita, K.; Kageyama, Y.; Terada, F.; Nakaoka, Y.; Ichimura, K.; Mori, K. *Chem. Lett.* **1992**, 567.
13. Rudchenko, V. F.; Shtamburg, V. G.; Pleshkova, A. P.; Kostyanovskii, R. G. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1981**, *30*, 825. For a preparation of

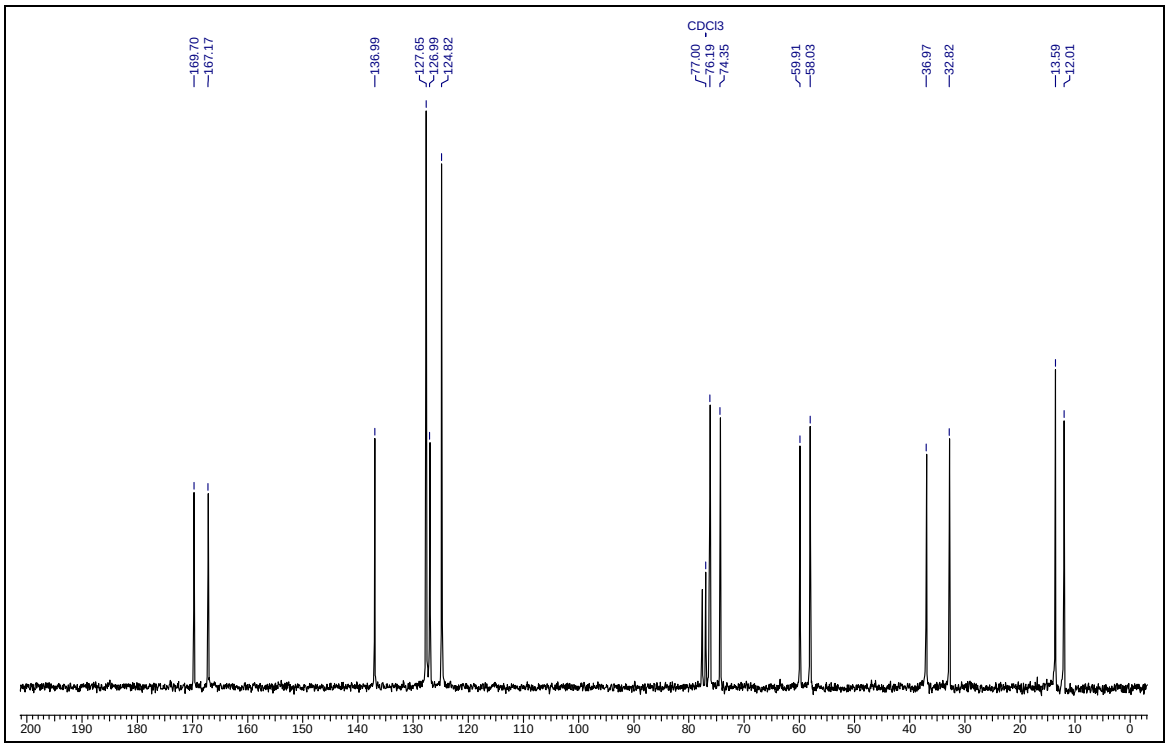
racemic **1.01** see: Drefahl, G.; Hartmann, M.; Skurk, A. *Chem. Ber*. **1963**, *96*, 1011. Synthetic applications of **1.01** were not described.

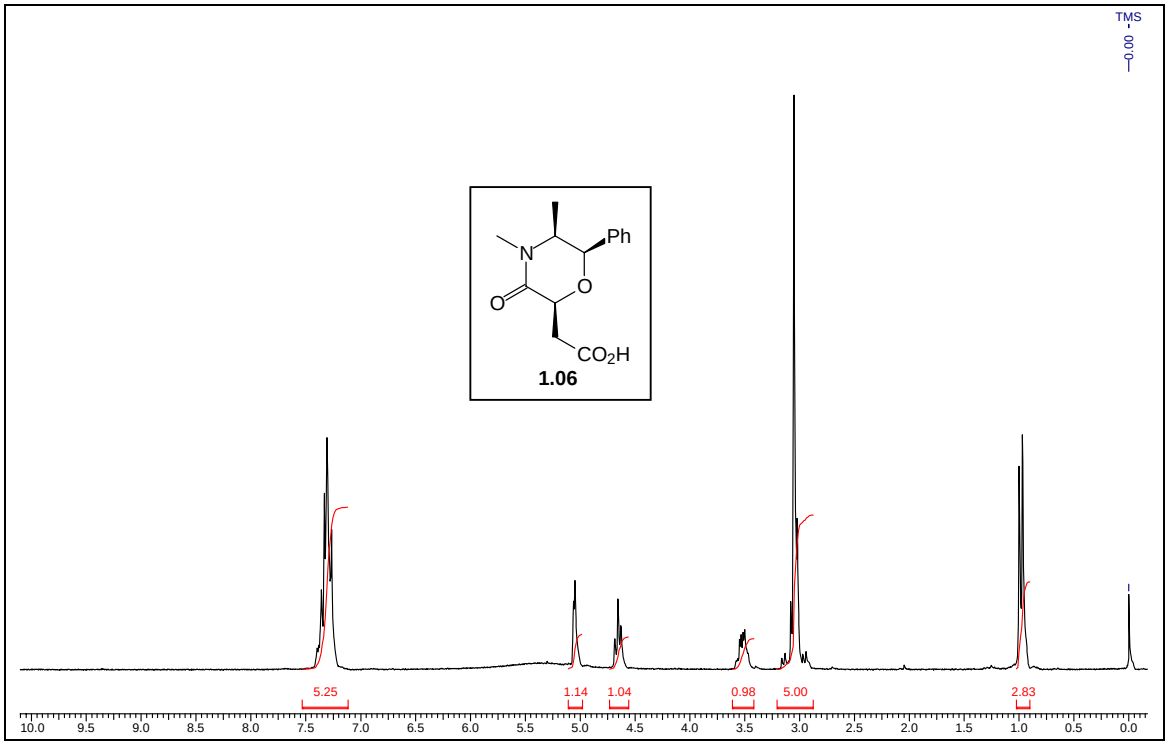
14. The stereochemical assignment is based on the reported trend in chemical shift for the olefinic methine protons in (*E*) and (*Z*) benzylidenecamphor derivatives, see: Kossanyi, J; Furth, B; Morizur J. P. *Tetrahedron* **1970**, *26*, 395.
15. The stereochemistry at the hemiacetal centre has been confirmed in an earlier study by X-ray crystallography, see: Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.
16. For the application of other aminoalcohol based morpholinones in the asymmetric synthesis of amino acids, see: a) Cox, G. G.; Harwood, L. M. *Tetrahedron: Asymmetry* **1994**, *9*, 1669. b) Sinclair, P. J.; Zhai, D; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103.
17. Kano, S.; Tanaka, Y.; Sugino, E.; Hibino, S. *Synthesis* **1980**, *9*, 695.
18. Evans, D. A.; Takacs, J. M. *Tetrahedron Lett*. **1980**, *21*, 4233
19. The enantiomeric excess of the lactones was determined by GC analysis with a HP Chiral (20% permethylated β-cyclodextrin) column (30 m x 0.32 mm x 0.25 μm).

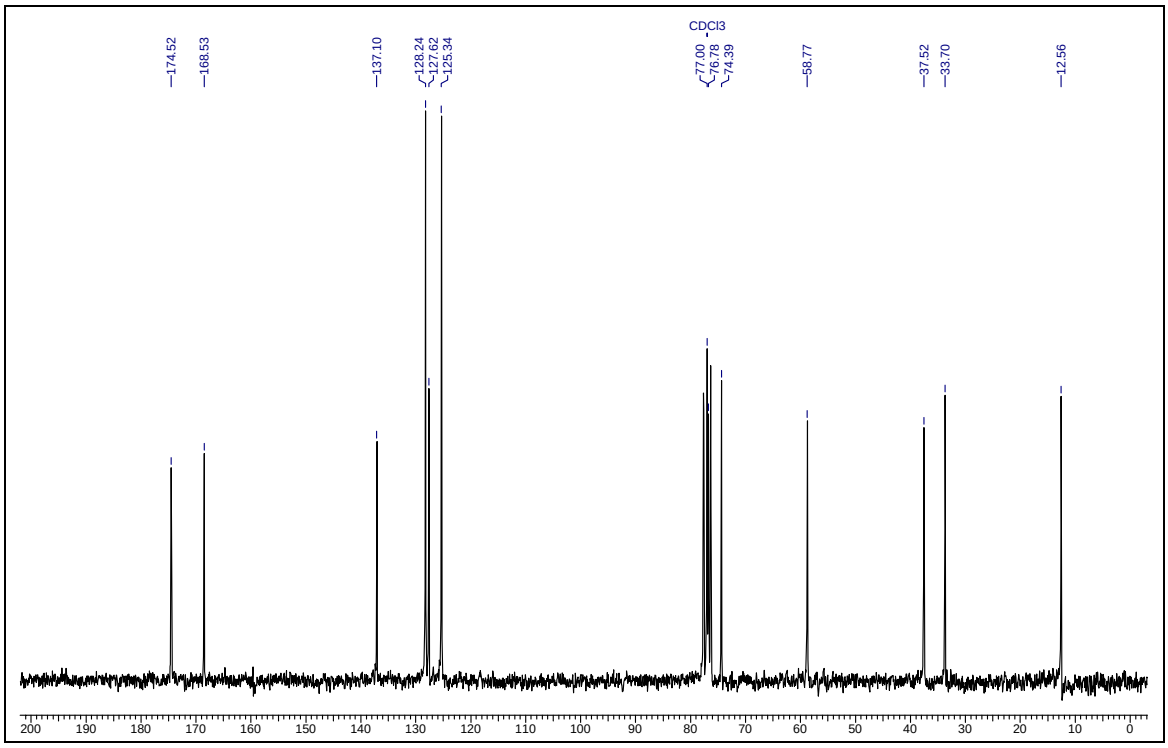

TMS
0.00
Ph
N
O
O
O
CO2Et
1.02
5.23
0.88
0.94
2.06
1.03
3.00
3.15
3.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

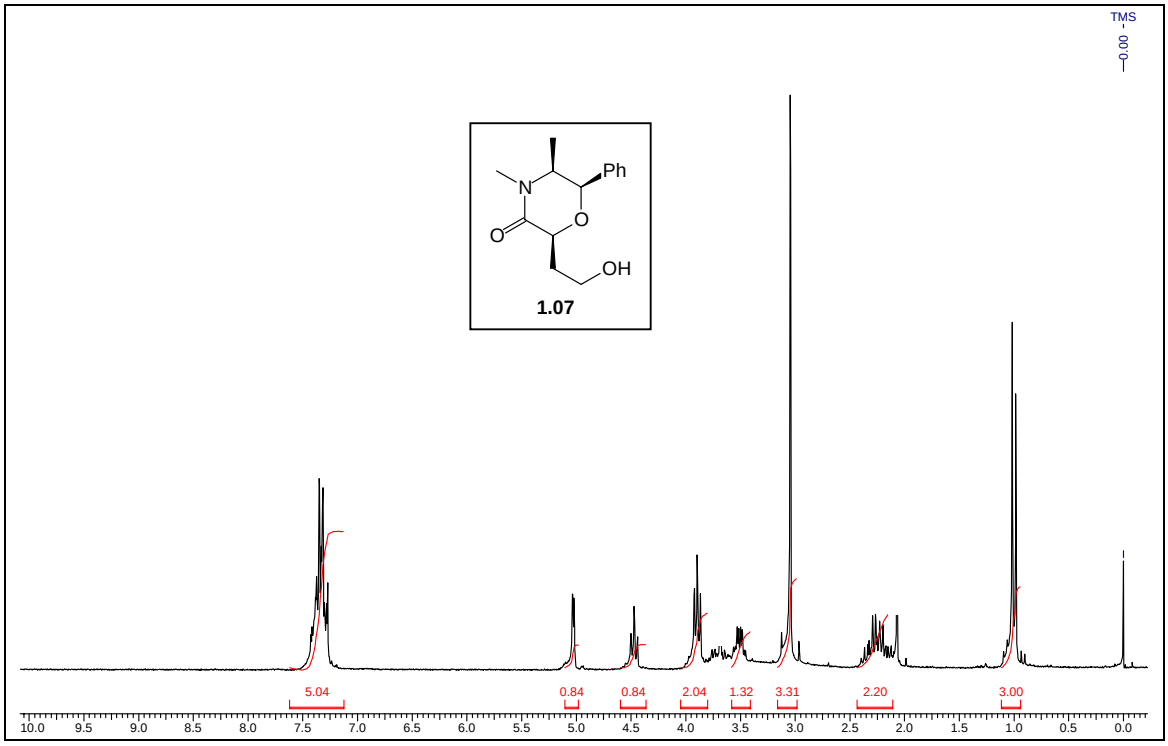

CDCl3
164.59
157.68
153.49
135.52
128.39
127.98
125.19
100.97
77.92
59.65
57.85
33.63
14.00
11.39
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

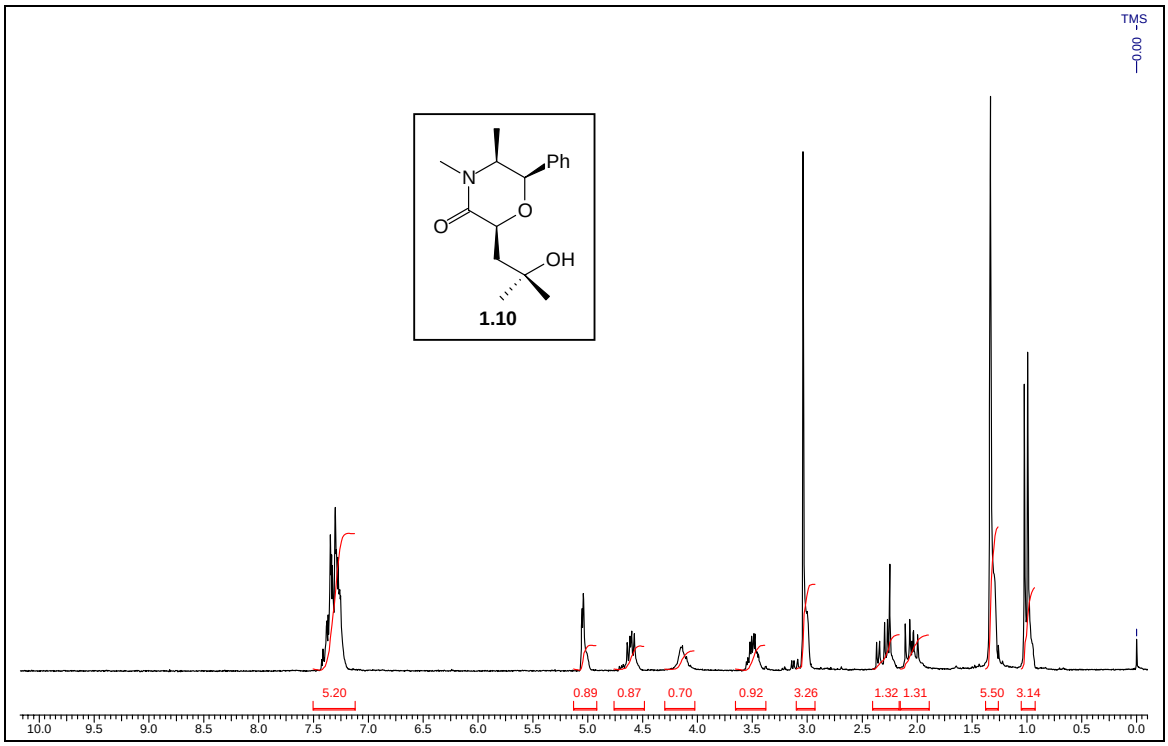

TMS
0.00
Ph
N
O
O
CO2Et
1.03
5.19
1.02
0.99
1.98
1.03
5.00
3.21
2.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

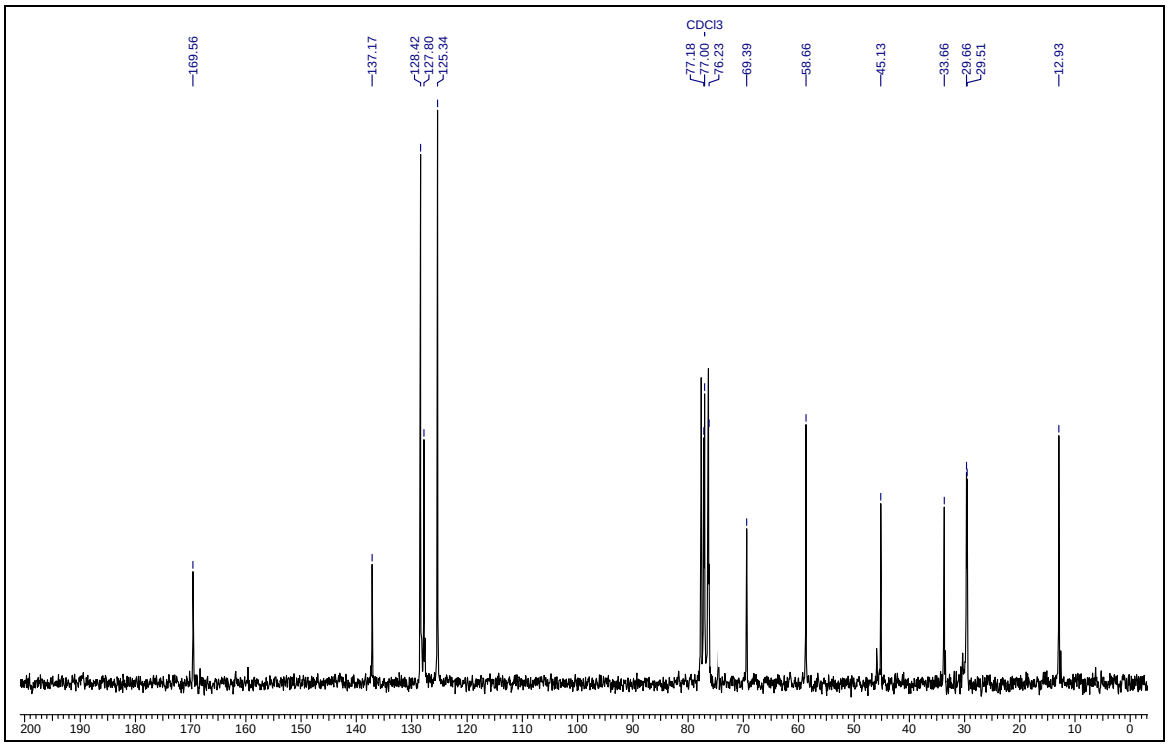

169.70
167.17
136.99
127.65
126.99
124.82
CDCl3
77.00
76.19
74.35
59.91
58.03
36.97
32.82
13.59
12.01
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

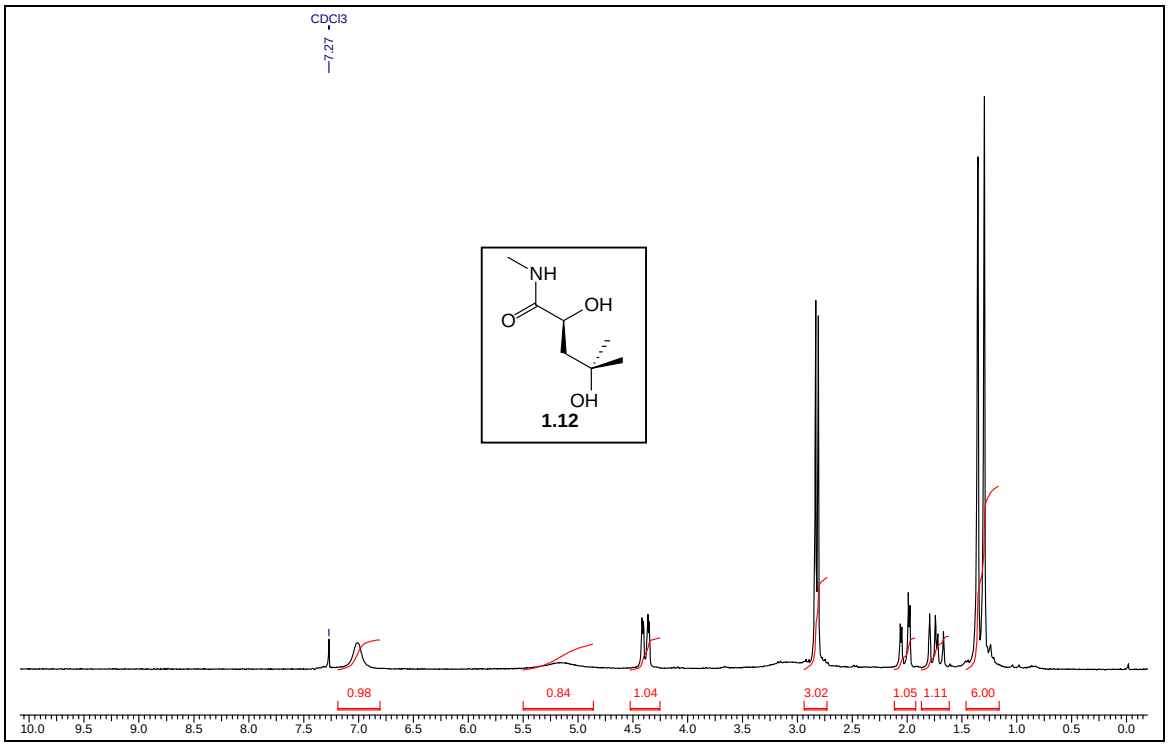

TMS
0.00
Ph
N
O
O
CO2H
1.06
5.25
1.14
1.04
0.98
5.00
2.83
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

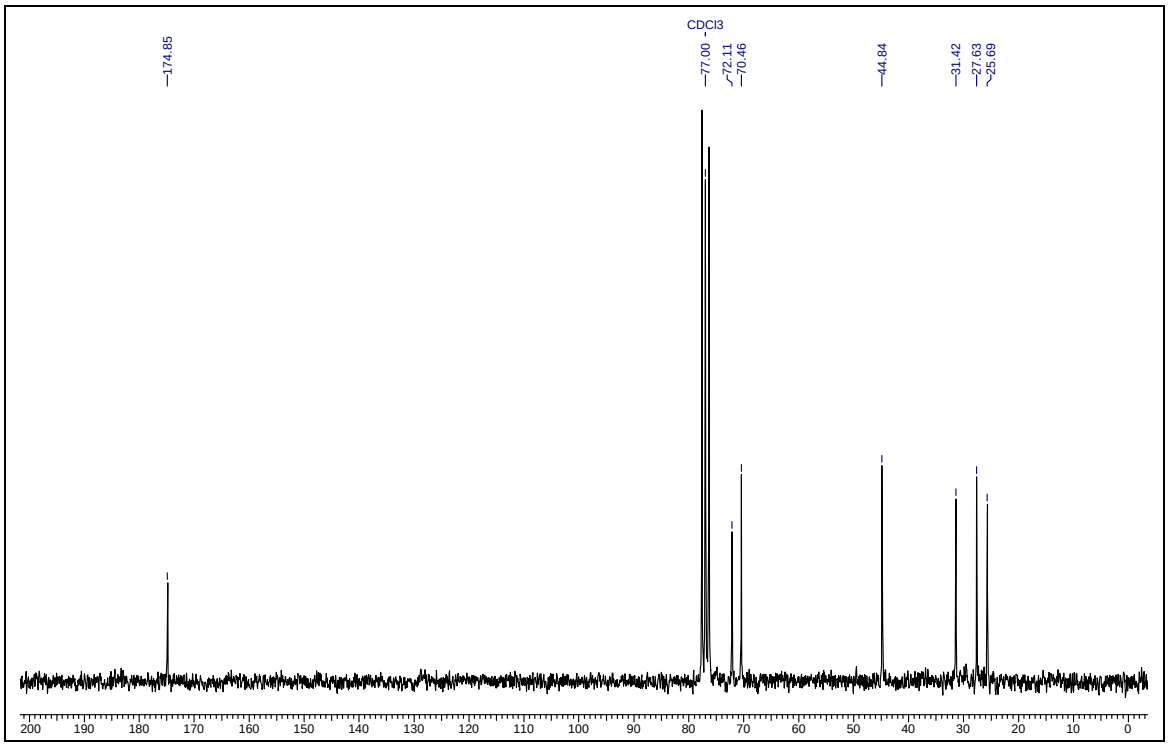

CDCl3
174.52
168.53
137.10
128.24
127.62
125.34
77.00
76.78
74.39
58.77
37.52
33.70
12.56
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

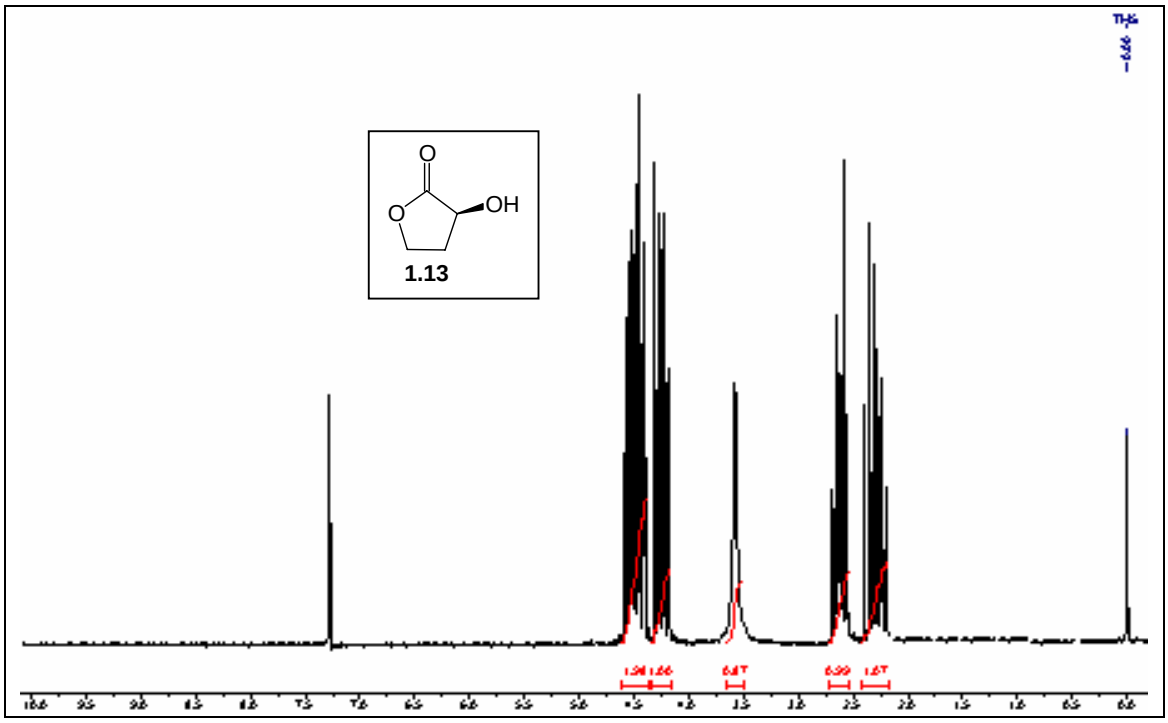

TMS
0.00
Ph
N
O
O
OH
1.07
5.04
0.84
0.84
2.04
1.32
3.31
2.20
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

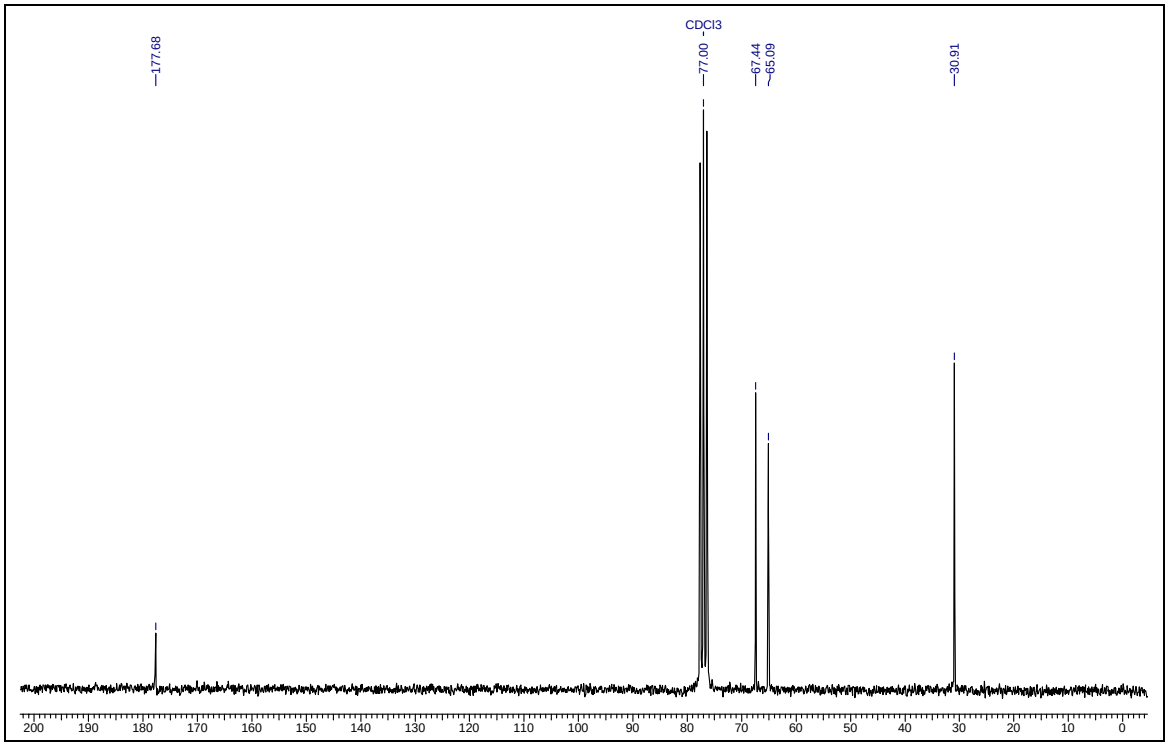

TMS
0.00
Ph
N
O
O
OH
1.10
5.20
0.89
0.87
0.70
0.92
3.26
1.32
1.31
5.50
3.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

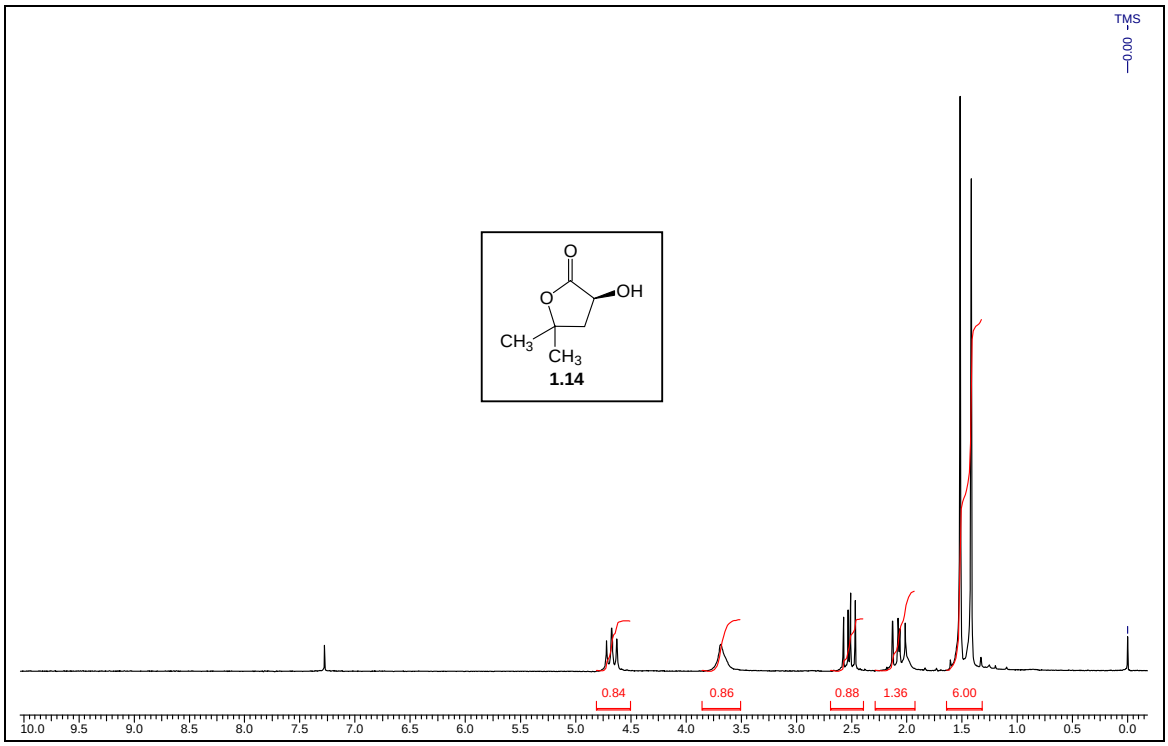

CDCl3
169.56
137.17
128.42
127.80
125.34
77.18
77.00
76.23
69.39
58.66
45.13
33.66
29.66
29.51
12.93
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

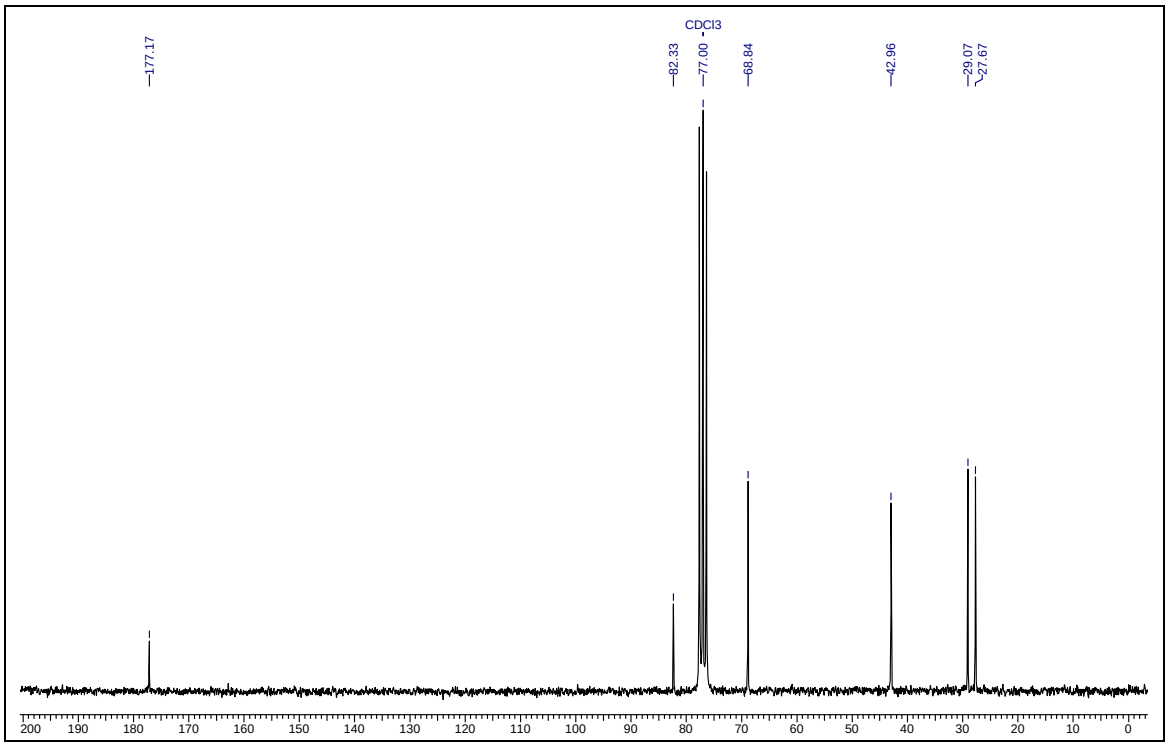

CDCl3
7.27
NH
O
OH
OH
1.12
0.98
0.84
1.04
3.02
1.05
1.11
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

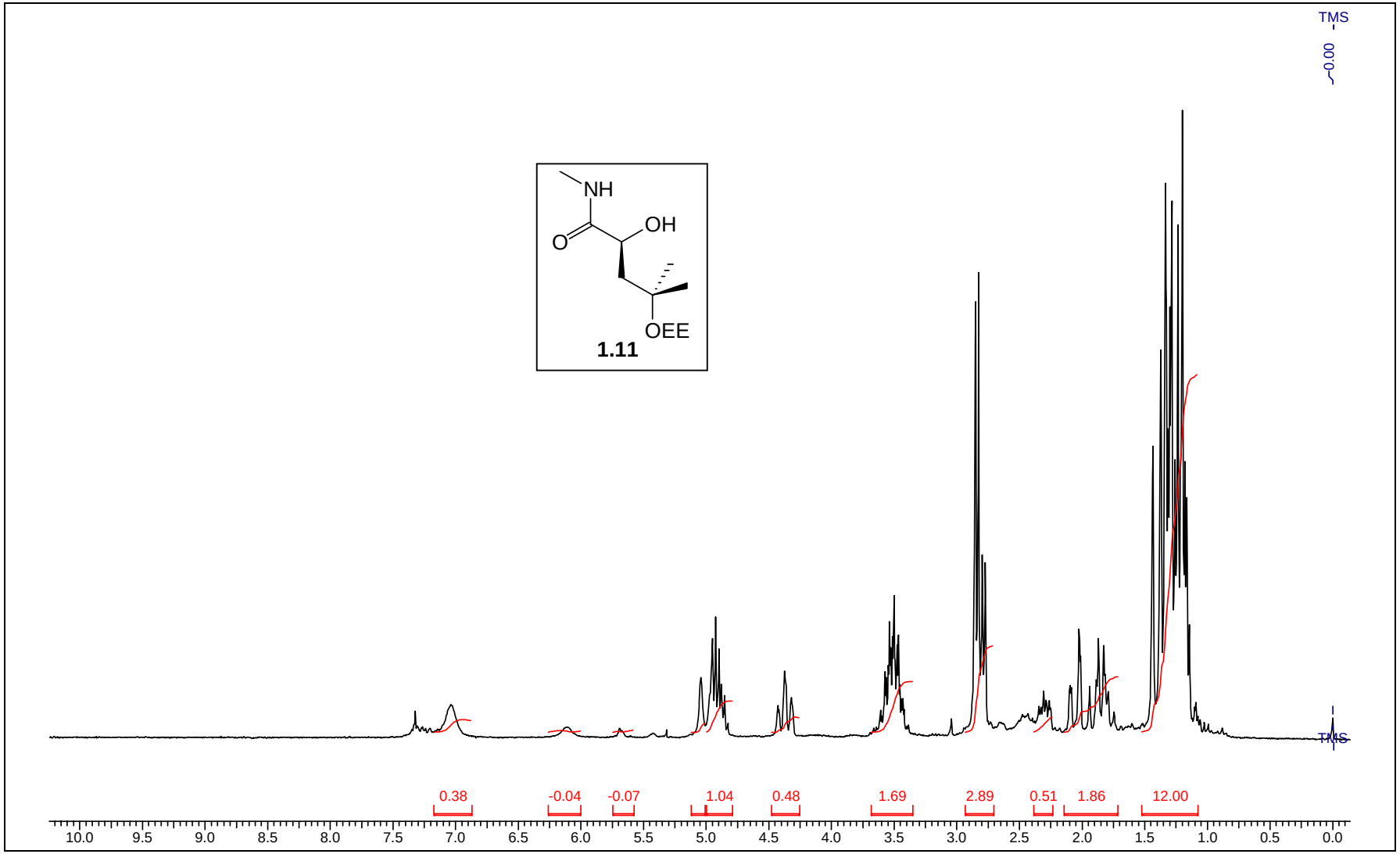

CDCl3
174.85
77.00
72.11
70.46
44.84
31.42
27.63
25.69
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

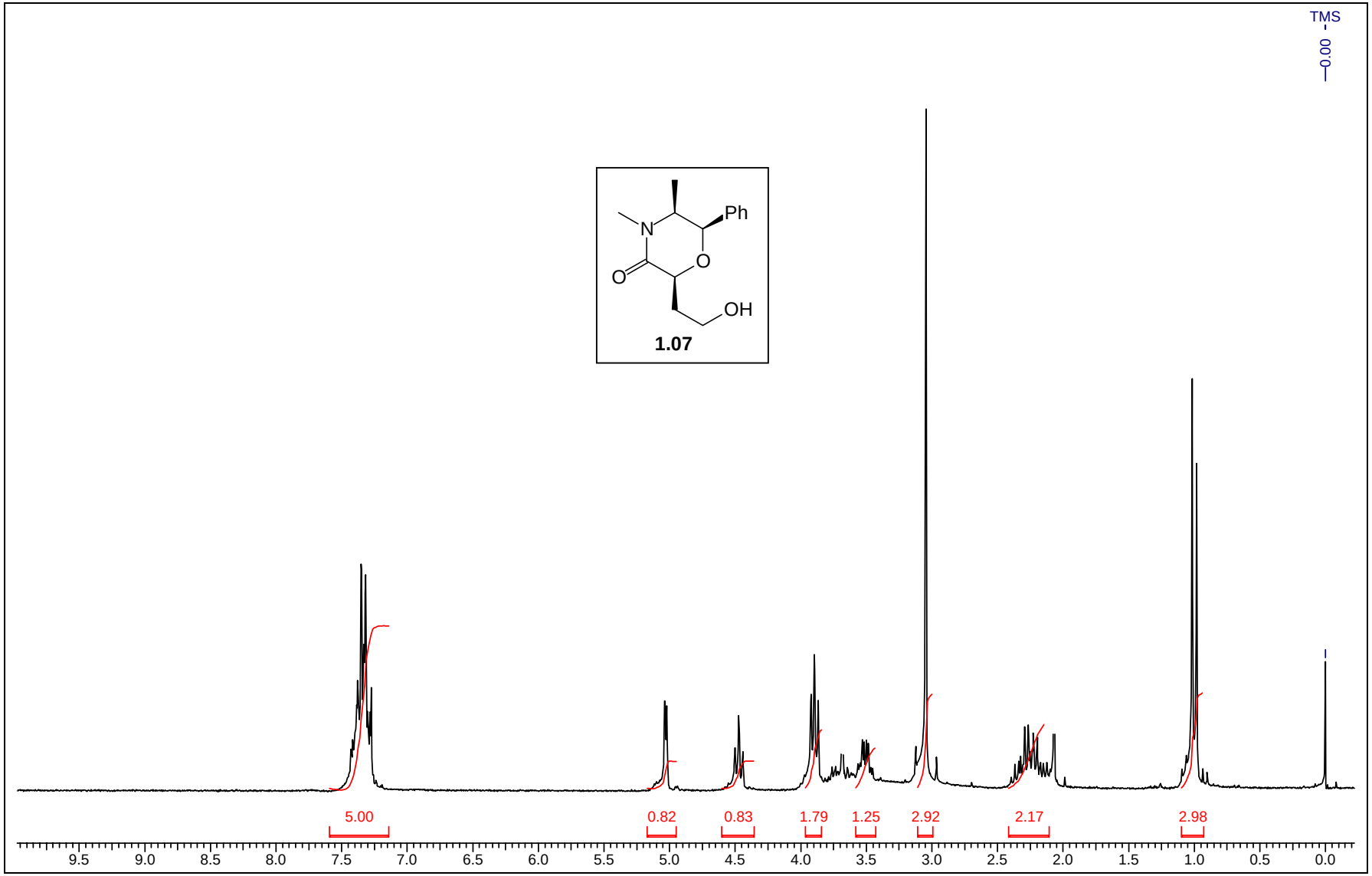

O
O
OH
1.13

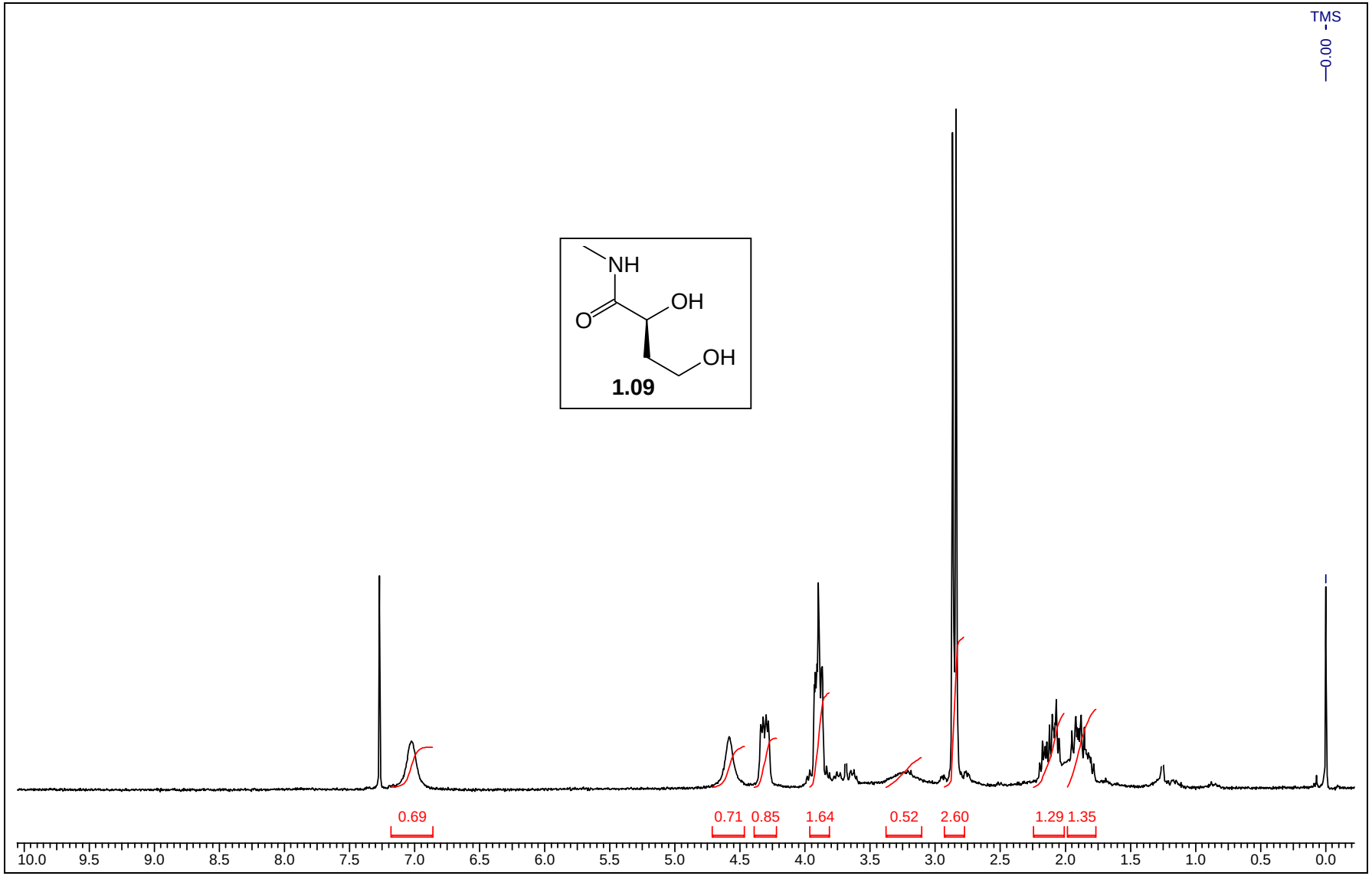

CDCl3
177.68
77.00
67.44
65.09
30.91
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

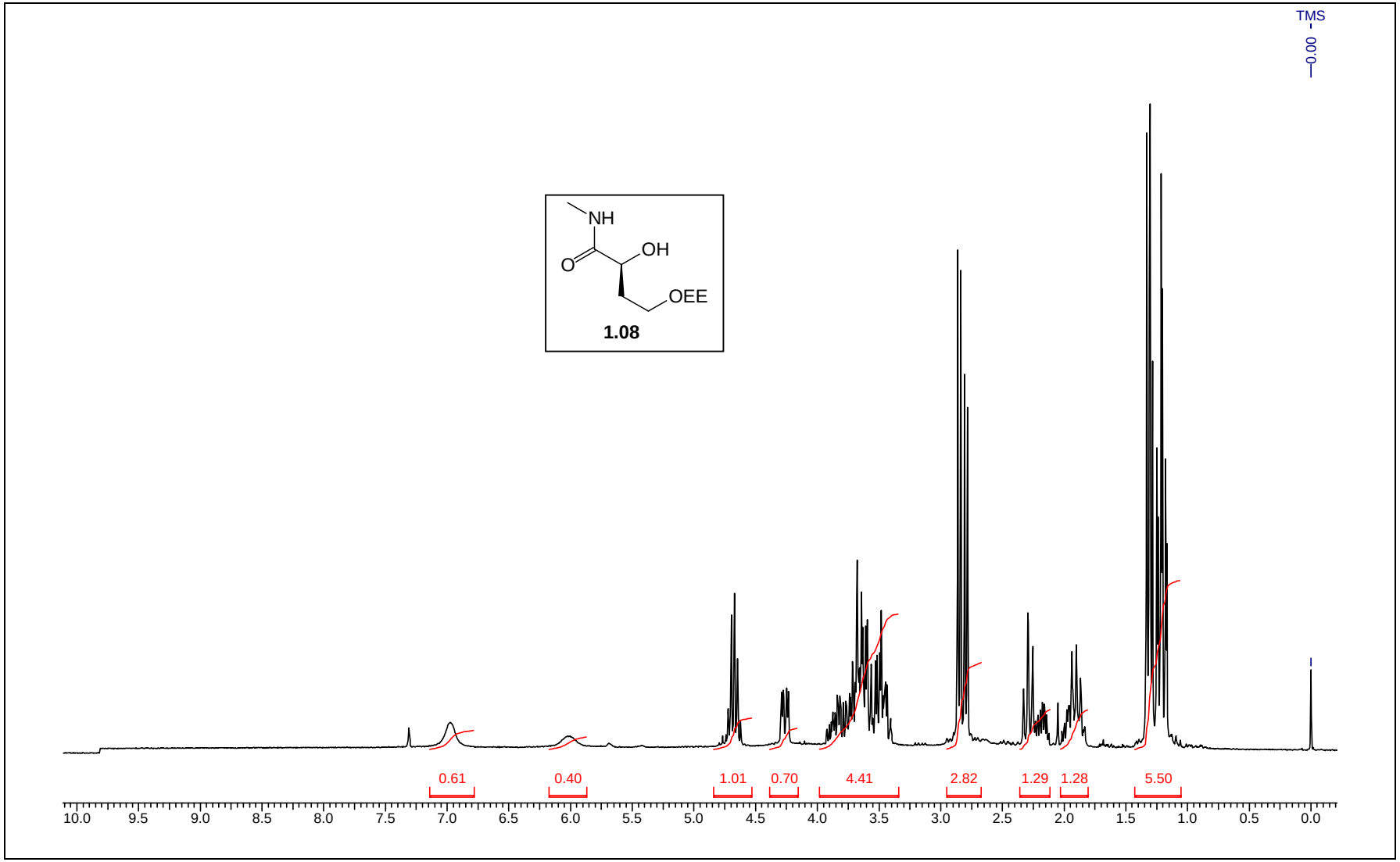

TMS
0.00
O
O
OH
CH3
CH3
1.14
0.84
0.86
0.88
1.36
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


CDCl3
177.17
82.33
77.00
68.84
42.96
29.07
27.67
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


TMS
0.00
NH
O
OH
OEE
1.11
TMS
0.38
-0.04
-0.07
1.04
0.48
1.69
2.89
0.51
1.86
12.00
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


TMS
0.00
Ph
N
O
O
OH
1.07
5.00
0.82
0.83
1.79
1.25
2.92
2.17
2.98
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

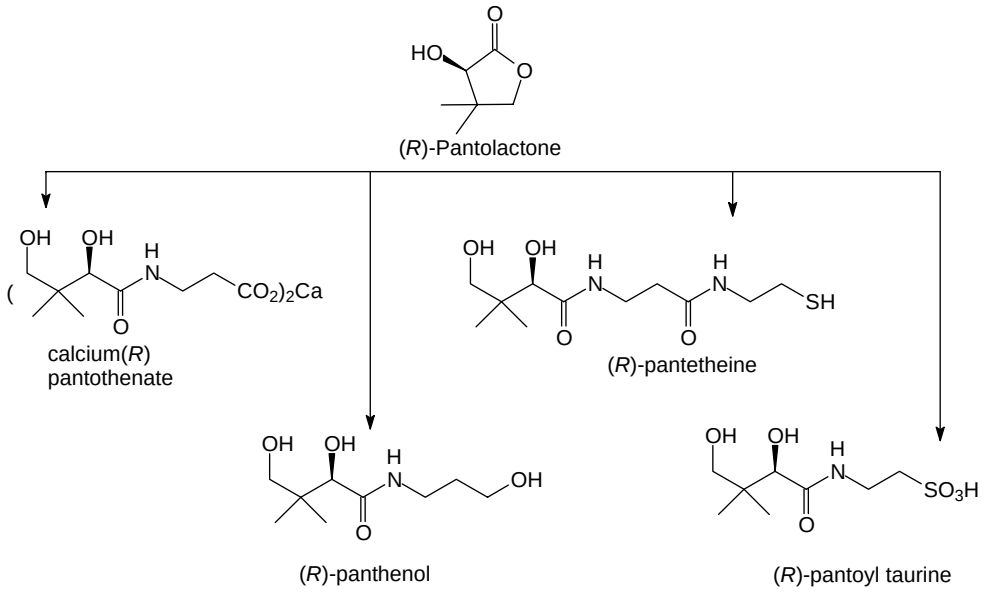

TMS
0.00
NH
O
OH
OH
1.09
0.69
0.71
0.85
1.64
0.52
2.60
1.29
1.35
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


TMS
0.00
NH
O
OH
OEE
1.08
0.61
0.40
1.01
0.70
4.41
2.82
1.29
1.28
5.50
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

2.1: Introduction

The asymmetric synthesis of pantolactone and its analogues continues to be an area of active interest to organic chemists as a consequence of their biological activity, utility as a building block in the synthesis of natural products and their analogues[1] and as a secondary alcohol derived chiral auxiliary.[2] The taurine derivative of pantothenic acid (pantoyl taurine)[3] has been shown to inhibit the growth of streptococci, pneumococci, plasmodium relictum[4] and certain strains of diptheria bacilli.[5] In addition, pantolactone is an important starting compound for pantothenic acid[6] (a member of B-complex vitamins), calcium pantothenate[7] (enzyme co-factor vitamin), *R*-Panthenol[8] (bactericide) and *R*-Pantetheine[9] (growth factor) (Figure 1).

Figure 1. Pantolactone derivatives



β,β-dialkyl-α-hydroxy-γ-butyrolactones (pantolactone analogues) have recently been employed as components of interleukin inhibitors.[10] This particular class of butyrolactones and the parent hydroxy acids are also of interest due to their structural similarity to pantolactone[11] and the potential for application as pantothenic acid analogues in biologically relevant molecules.[12]

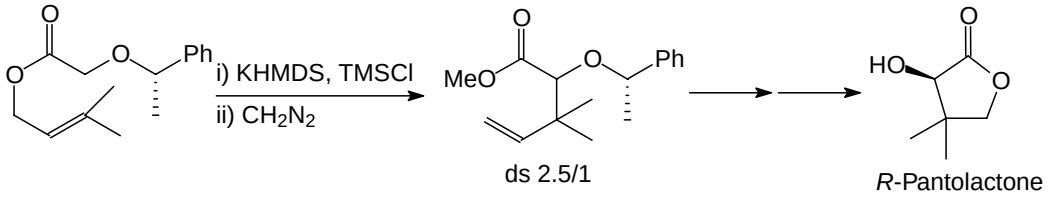
2.2: Background for present work

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-oxo-butyrolactone (ketopantolactone) and resolution of racemic pantolactone. These and several other approaches for the synthesis of pantolactone and its analogues are discussed in this section.

Asymmetric functionalization of linear or cyclic precursors

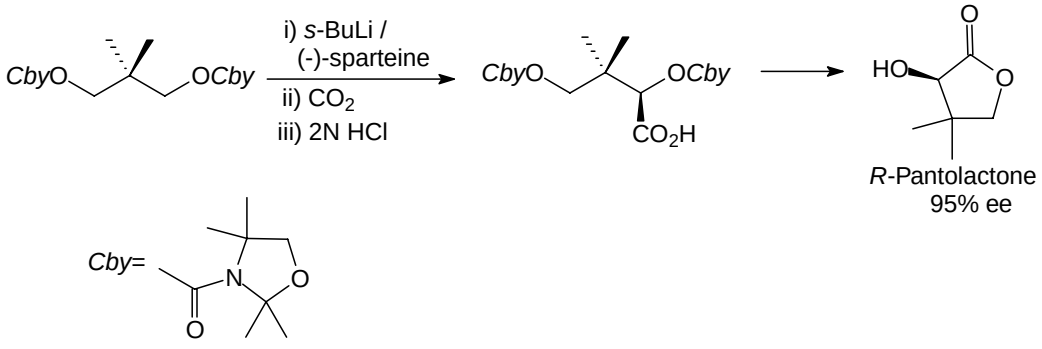
Kallmerten[13] has developed a synthesis of *R*-pantolactone that employs an asymmetric Claisen rearrangement of a chiral glycolate ester as the key step (Scheme 1). The stereochemical course of the reaction is controlled by the chiral substituent appended to the hydroxyl group of the glycolic acid.

Scheme 1



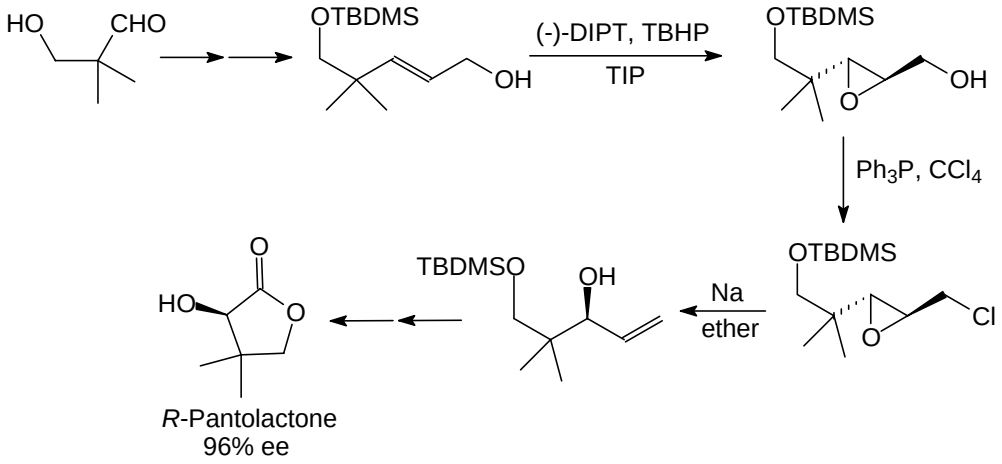
An efficient synthesis of *R*-pantolactone (ee> 95%) has been achieved by asymmetric carboxylation of the carbanion of a 1,3-propanediol dicarbamate. An asymmetric deprotonation employing a combination of *sec*-butyllithium and (-)-sparteine is the key step (Scheme 2).[14]

Scheme 2



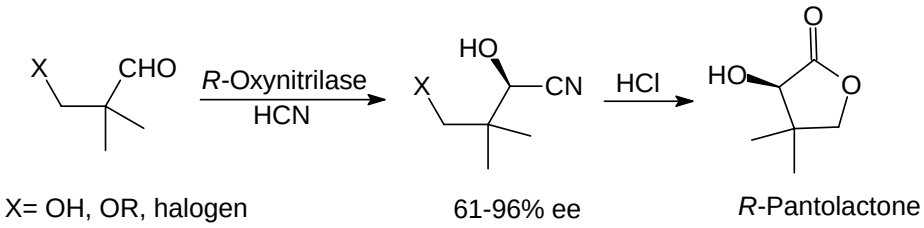
Rao *et al.*[15] have reported a synthesis of *R*-pantolactone that employs the Sharpless asymmetric epoxidation reaction as the key step in the construction of the lactone precursor. The synthesis begins with 3-hydroxy-2,2-dimethyl propanal which is functionalized as shown in the Scheme 3.

Scheme 3



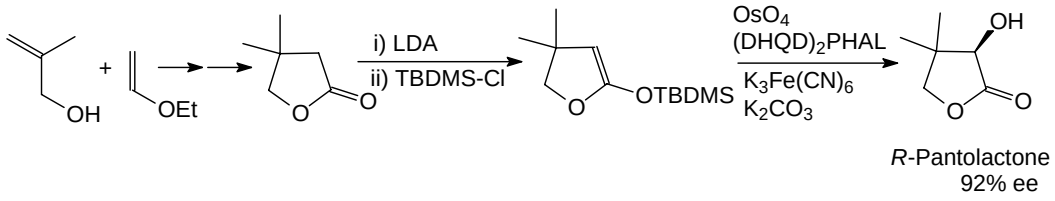
Effenberger[16] has examined the enzyme catalysed addition of hydrocyanic acid to substituted pivalaldehydes. The use of *R*-oxynitrilase in the presence of HCN affords the corresponding cyanohydrins in 61-96% ee. These are converted to *R*-pantolactone by acid catalysed hydrolysis of the nitrile that proceeds with concomitant lactonization (Scheme 4).

Scheme 4



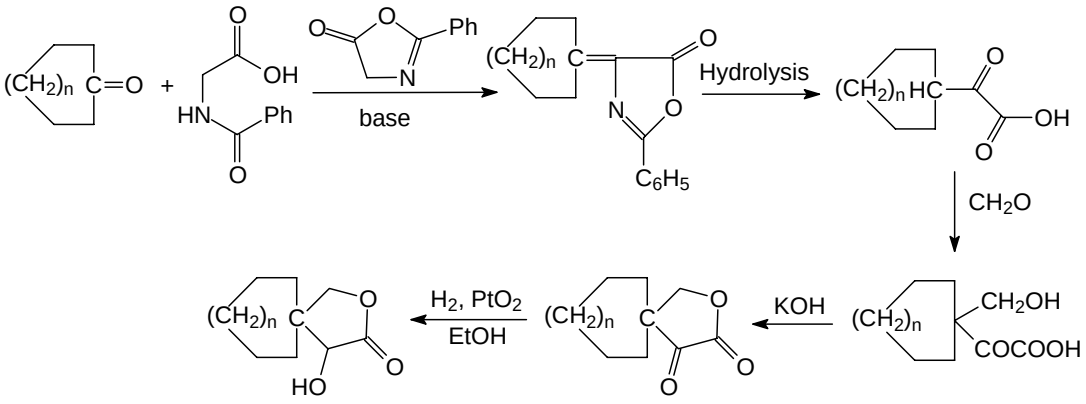
A recent synthesis of *R*-pantolactone[17] utilizes the Sharpless asymmetric dihydroxylation reaction as the key step. The silyl enol ether of 3,3-dimethyl-γ-butyrolactone is subjected to the asymmetric dihydroxylation reaction to generate *R*-pantolactone with 92% ee (Scheme 5).

Scheme 5



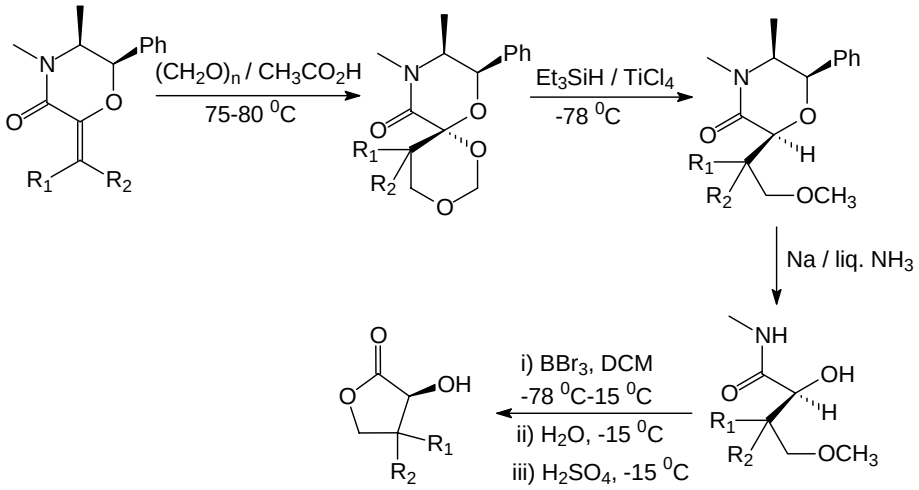
Fissekis[12a] and co-workers have demonstrated a synthesis of a racemic β-cycloalkyl α-hydroxy-γ-butyrolactone starting with the condensation of cycloalkanone and the azlactone derived from hippuric acid. The resulting cycloalkylglyoxalic acid was condensed with formaldehyde and the product was converted to the α-keto lactone. Hydrogenation furnished the required cycloalkyl analogue of pantolactone (Scheme 6). This protocol has also been employed for the synthesis of the cyclopentyl and cyclohexyl derivatives, which were converted to the pantothenic acid analogues which were tested for their biological activity.

Scheme 6



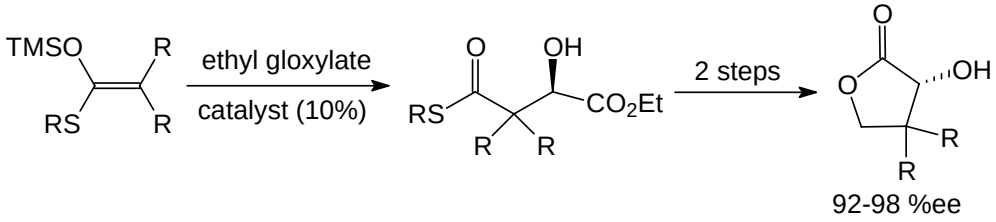
Pansare *et. al.*[18] have recently reported a method for the enantioselective synthesis of pantolactone derivatives using the Prins reaction of chiral alkylidine morpholinones which proceed with good diastereoselectivity to generate a spiro *bis*-acetal (Scheme 7). Lewis acid mediated reductive cleavage of the spiroacetal gave morpholinones in 90-96% yield. Subsequent removal of the ephedrine portion by Birch reduction furnished β,β-dialkyl-α-hydroxy-γ-methoxy butyramides (50-62% yield) which on demethylation followed by cyclization gave (*S*)-(+)-pantolactone and its analogues (70-86%) with high enantiomeric excesses (96-98%).

Scheme 7



Recently Evans[19] has also reported a method using an enantioselective scandium-catalysed aldol reaction of thiosilylketene acetal as the key step, which affords pantolactone and its derivatives in high enantiomeric excess. Thus the enantioselective aldol reaction of thiosilylketene acetal nucleophile with ethyl glyoxylate gave the thio ester which on reduction with Raney nickel afforded pantolactones in good yields. Using this method several pantolactone analogues (including the spiropantolactones) and γ-alkyl pantolactones were synthesized (Scheme 8).

Scheme 8



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

The asymmetric reduction of ketopantolactone employing chemical or microbial catalysis has been extensively investigated[20] as a general route to *R* and *S*-pantolactones (Figure 2).

Figure 2

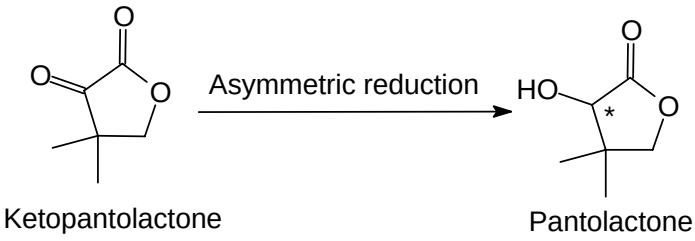
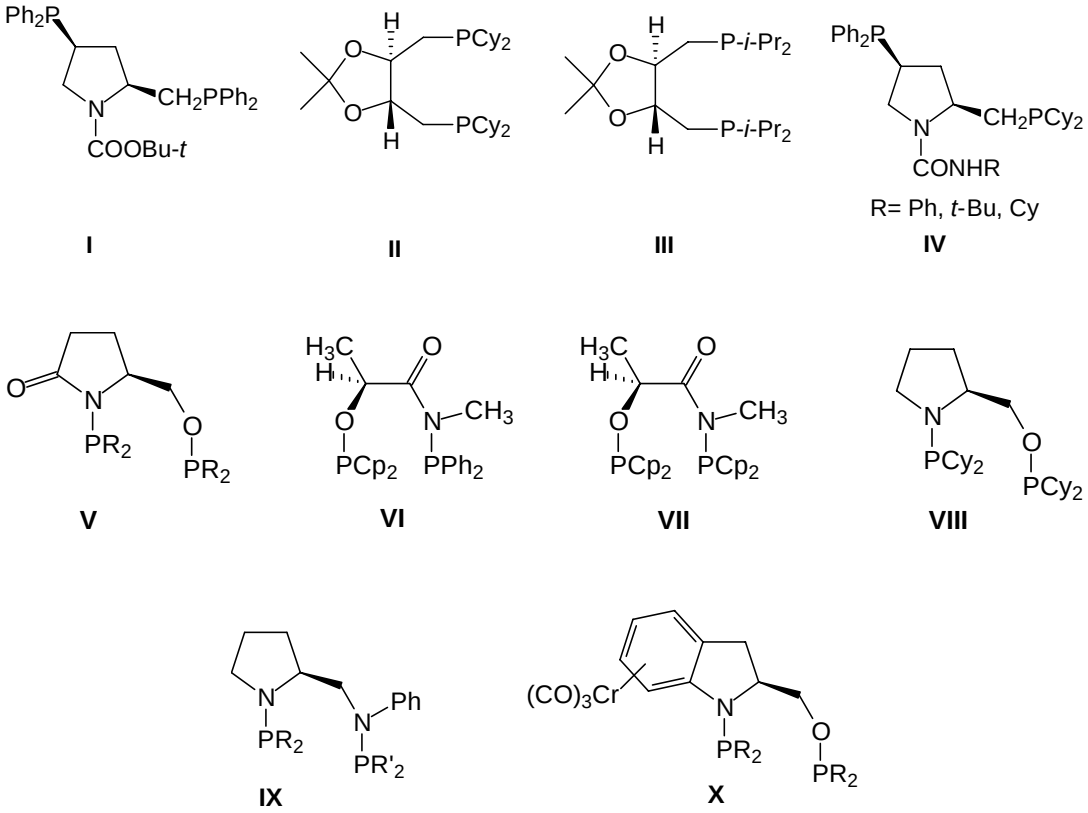


Figure 3. Chiral ligands



The catalytic asymmetric reduction of ketopantolactone with rhodium complexes containing chiral ligands provides pantolactone with high enantiomeric excess and excellent chemical yields (Figure 3). Ojima[21] has reported the reduction of ketopantolactone with BPPM-Rh (I) complex **I** (86% ee of *R*-pantolactone), Achiwa[22] has used 4*R*,5*R*-DIOCP-Rh (I) complex **II** (75% ee of *R*-pantolactone), Tani[23] has reported reduction with (-)-*i*-PrDIOP-Rh (I) complex **III** (54% ee of *R*-pantolactone) and (-)-*t*-Bu-CYCAPP-Rh (I) complex **IV** (66% ee of *S*-pantolactone), while Agbossou[24] has reported AMPP-Rh complex **V-VIII** (98% ee of *R*-pantolactone) and BAMP-Rh (I)

complex **IX** (87% ee of *S*-pantolactone). The reduction of ketopantolactone has also been achieved with $Cr(CO)_3$-complexed AMPP ligands **X** (99% ee of *S*-pantolactone).[25]

Microbial reduction of ketopantolactone has also been examined. Nakamura ***et. al.***[26] have reduced ketopantolactone using Baker's yeast to obtain *R*-pantolactone with 73% ee. Addition of β-dextrin increased the enantiomeric excess to 93%. Reduction of ketopantolactone with the ascomycete, *Byssochlamys fulva* provides *R*-pantolactone with 99% ee.[27]

Resolution of racemic pantolactone

Since racemic pantolactone is readily accessible in a one-pot reaction from hydroxypivalaldehyde, sodium cyanide, hydrochloric acid and calcium chloride,[28] 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[1a] and 1*R*-3-*endo*-aminoborneol.[29] An alternative approach involves resolution of the parent α,γ-dihydroxy-β,β-dimethylbutyric acid with chiral amines such as quinine[30] and (+)-3-aminomethylpinane.[31] The lactone is also resolved by complexation with brucine or by acylation with diacetyl-*d*-tartaric anhydride followed by separation of diastereomers.[32] Racemic pantolactone has also been resolved by hydrolysis with NaOH followed by partial neutralization with 1*S*-(+)-10-camphorsulfonic acid.[33] Enzymatic resolution[34] of racemic pantolactone has also been examined. Lipase catalysed enantioselective esterification of the racemate with vinyl acetate provides *R*-pantolactone in 88% ee.[35] Lipase catalysed transesterification of racemic pantolactone acetate in *t*-butanol gives *R*-pantolactone with 70% ee.[36]

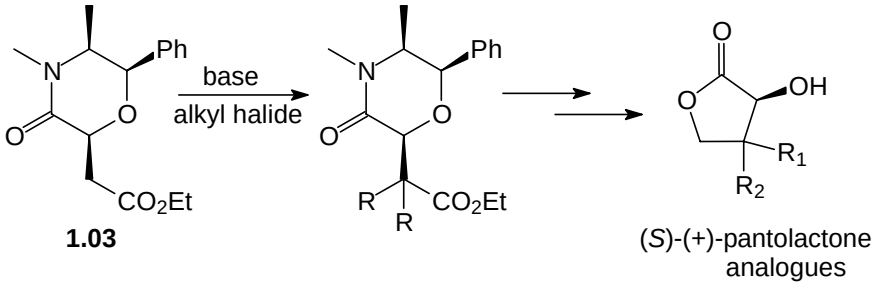
2.3: Present work

The objective of this investigation was to develop a general route for the enantioselective synthesis of (*S*)-(+)-pantolactone and its analogues. Selective dialkylation of an ephedrine-derived chiral template without epimerization was the key step in the synthesis which upon further functional group transformations, followed by removal of the ephedrine portion provided the hydroxy butyramides which on cyclization furnished (*S*)-(+)-pantolactone and its analogues in high enantiomeric excesses.

2.4: Results and discussion

Hydrogenated ester **1.03** which is the key intermediate in the synthesis of α-hydroxy-γ-butyrolactones (see Chapter 1) was chosen as the starting material for this study. We next investigated the introduction of the *gem*-dialkyl moiety, by selective dialkylation on the alpha carbon to the ester carbonyl as further functional group transformations would then give us pantolactone analogues (Figure 4).

Figure 4

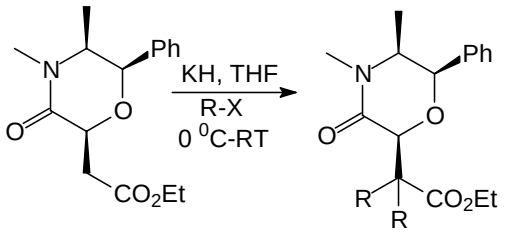


1.03

(*S*)-(+)-pantolactone analogues

Different bases were tried for selective dialkylation of ethyl ester **1.03**. The reaction didn't work with NaH either at room temperature or at reflux temperature and only starting material was recovered after the reaction. With strong base such as *n*-butyl lithium and LDA, the reaction gave a complex mixture of products, which could not be isolated or characterized. However, we could first succeed in getting the dimethylated compound **2.01a** in 65% yield by using potassium *tert*-butoxide (3.5 equiv.) in THF solvent and MeI. It should be noted that the reaction is very much dependant on the purity of potassium tertiary butoxide and the presence of potassium hydroxide as an impurity results in hydrolysis of the ester which poses a major problem. Further studies revealed that the base of choice for dialkylation was potassium hydride, which gave excellent yields (92-96%) of the dialkylated products **2.01a-c** in THF solvent (Scheme 9).

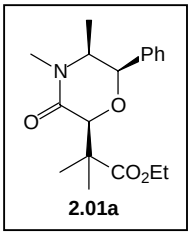
Scheme 9



1.03
R-X = MeI, EtI,
Allyl bromide/NaI

2.01a, R=Me (96%)
2.01b, R=Et (93%)
2.01c, R=allyl (92%)

No epimerization of the product was observed (^{1}H NMR) under the reaction conditions. Alkyl halides used were methyl iodide, ethyl iodide and allyl bromide/NaI. The structures of the dialkylated products **2.01a-c** were established by IR, ^{1}H NMR and ^{13}C NMR spectral data.



2.01a

2.01a was chosen for spectral discussion. IR spectrum of **2.01a** showed sharp peaks at 1728 cm^{-1} and 1649 cm^{-1} which corresponds to the ester carbonyl and amide carbonyl groups respectively.

The ^{1}H NMR spectrum of **2.01a** showed a doublet at 0.96 ppm (J = 6.8 Hz) which is attributed to the methyl group attached to the methine carbon. The methyl group of the ethyl ester appeared as a triplet at 1.28 ppm (J = 7.1 Hz). The two methyl groups in the *gem*-dimethyl part appeared as separate singlets at 1.32 ppm and 1.41 ppm. The sharp singlet at 3.01 ppm was attributed to the methyl group attached to nitrogen. The characteristic doublet of quartet in the range 3.49-3.55 ppm (J = 2.8, 6.8 Hz) is attributed to the proton on the methine carbon attached to nitrogen. Multiplet in the range 4.15-4.28 ppm corresponds to the methylene protons of the ester group. The sharp singlet at 4.68 ppm is attributed to the proton on the methine carbon attached to the amide carbonyl. The characteristic doublet for the benzylic proton appeared at 5.04 ppm (J = 2.8 Hz). The five aromatic protons appeared as a multiplet in the range 7.22-7.42 ppm.

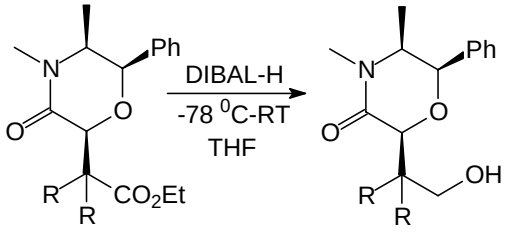
The ^{13}C NMR spectrum of **2.01a** showed two peaks at 175.4 and 167.4 ppm corresponding to the ester carbonyl and amide carbonyl respectively. The peak at 137.6 ppm corresponds to the aromatic *ipso* carbon. Other aromatic carbons appeared at 128.2, 127.4 and 125.1 ppm. The methine carbon attached to the amide carbonyl appeared at 81.8 ppm. The peak at 76.3 ppm is attributed to benzylic carbon. The peak at 60.4 ppm corresponds to the methylene carbon attached to oxygen. The methine carbon attached to

the nitrogen appeared at 58.3 ppm. The quaternary carbon attached to the ester carbonyl appeared at 45.9 ppm. The methyl carbon attached to the nitrogen appeared at 33.1 ppm. The methyl group in the ester part appeared at 23.2 ppm. The methyl group attached to the methine carbon appeared at 13.0 ppm. The two methyl carbons in the *gem*-dimethyl group appeared separately at 13.9 and 19.1 ppm. This compound gave satisfactory elemental analysis.

In a similar way **2.01b** and **2.01c** were characterized by spectral data. It is noteworthy in this regard that the procedure had to be slightly modified to get the diallyl ester **2.01c**, since the reaction didn't work when the ester-enolate was quenched with allyl bromide. Adding catalytic amount of DMF to the reaction mixture gave the product but in very low yield (30%). We presume that this could be because of low reactivity of allyl bromide. Hence allyl bromide was converted to allyl iodide by refluxing in THF and NaI for two hours and the supernatent solution was added to the ester-enolate solution in THF at 0 ^{o}C. This gave the diallylated ester **2.01c** in very good yield (92%).

Next, we investigated the selective reduction of ester **2.01** to alcohol **2.02**. In Chapter 1 we had experienced difficulty in this step and hence had to hydrolyze the ester to acid, which on reduction with a combination of $TiCl_4/NaBH_4$ reagent gave the desired alcohol. Further, we could improvise this method and get the alcohols **2.02a-c** in very good yields (76-80%) by using DIBAL-H as the reducing agent in THF solvent at –78 ^{o}C and gradually warming it to room temperature (Scheme 10).

Scheme 10



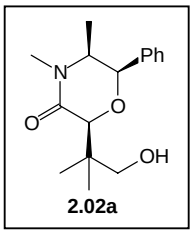
2.01a-c

2.02a, R=Me (80%)
2.02b, R=Et (77%)
2.02c, R=allyl (76%)

The structures of **2.02a-c** were established by IR, ^{1}H NMR and ^{13}C NMR spectral data. **2.02a** was chosen for spectral discussion.

IR spectrum of **2.02a** showed a broad band at 3354 cm^{-1} for the hydroxy group and a sharp peak at 1632 cm^{-1} for the amide carbonyl.

The ^{1}H NMR spectrum of **2.02a** showed a doublet at 1.01 ppm (J = 6.6 Hz) which is attributed to the methyl group attached to the methine carbon. The two methyl groups in the *gem*-dimethyl part appeared as separate singlets at 1.10 ppm and 1.19 ppm. The sharp singlet at 3.07 ppm is for the methyl group attached to nitrogen. The characteristic doublet of quartet in the range 3.49-3.55 ppm (J = 2.9, 6.6 Hz) is attributed to the proton on the methine carbon attached to nitrogen. The methylene protons attached to oxygen appeared as two separate doublets at 3.57 ppm (J = 11.5 Hz) and 3.67 ppm (J = 11.5 Hz). The broad singlet at 3.81 ppm is for the hydroxy proton. The sharp singlet at 4.21 ppm is attributed to the proton on the methine carbon attached to amide carbonyl. The characteristic doublet for the benzylic proton appeared at 4.97 ppm (J = 2.9 Hz). The five aromatic protons appeared as a multiplet in the range 7.30-7.42 ppm.

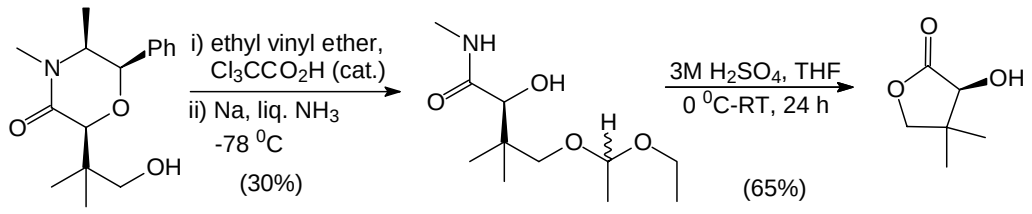


2.02a

The ^{13}C NMR spectrum of **2.02a** showed a peak at 169.5 ppm corresponding to the amide carbonyl. The peak at 137.5 ppm corresponds to the aromatic quaternary carbon. Other aromatic carbons appeared at 128.2, 127.5 and 125.2 ppm. The methine carbon attached to the amide carbonyl appeared at 83.5 ppm. The peak at 76.2 ppm is attributed to benzylic carbon. The peak at 77.1 ppm corresponds to the methylene carbon attached to oxygen. The methine carbon attached to the nitrogen appeared at 58.6 ppm. The quaternary carbon attached to the ester carbonyl appeared at 40.5 ppm. The methyl carbon attached to the nitrogen appeared at 33.7 ppm. The two methyl groups in the *gem*-dimethyl group appeared at 19.6 and 23.4 ppm. The methyl group attached to the methine carbon appeared at 12.9 ppm. This compound gave satisfactory elemental analysis. In a similar way **2.02b** and **2.02c** were characterized by spectral data.

Protection of the free hydroxy group in **2.02a** gave the ethoxyethyl derivative which was unstable and hence used as such for the Birch reduction. Several attempts to purify it by rapid flash column proved to be a failure and starting compound was isolated. Hence the crude protected **2.02a** was subjected to Birch reduction with Na/liq. NH_3 at –78 ^{o}C temperature. Quenching the reaction mixture with methanol after three minutes, followed by work-up gave **2.03a** as a mixture of diastereomers (Scheme 11). The cleaved compound **2.03a** (mixture of diastereomers) was also found to be unstable and obtained in very low yield (30%). It was characterized by IR and ^{1}H NMR and used for lactonization immediately.

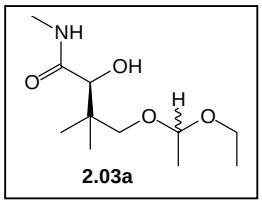
Scheme 11



2.02a **2.03a** **2.09a**

IR spectrum of **2.03a** showed a broad band at 3350 cm^{-1} for the hydroxyl group and a sharp peak at 1655 cm^{-1} for the amide carbonyl.

The ^1H NMR spectrum of **2.03a** (major diastereomer) showed two singlets at 0.94 and 1.03 ppm which corresponds to the two methyl groups. The methyl group in the ethoxy part appeared at 1.22 ppm as a triplet (J = 7.0 Hz). The methyl group attached to the methine carbon appeared at 1.32 ppm as a doublet (J = 5.1 Hz). The methyl group on the nitrogen appeared at 2.84 ppm as a doublet (J = 4.8 Hz). The two protons on the methylene carbon attached to oxygen appeared as a multiplet in the range 3.43-3.58 ppm and the other two protons on the methylene carbon attached to oxygen in the ethyl part appeared as a multiplet in the range 3.60-3.68 ppm. The singlet at 3.90 ppm is attributed to the proton attached to the methine carbon. The proton on the methine carbon attached on both sides by oxygen appeared as a multiplet in the range 4.67-4.75 ppm. The proton of the hydroxy group appeared as a broad singlet at 6.54 ppm. The proton on the amide nitrogen appeared as a broad singlet at 6.97 ppm.



2.03a

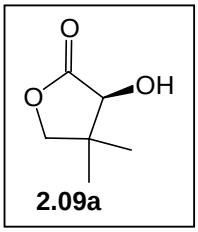
The ^1H NMR spectrum of **2.03a** (minor diastereomer) showed two singlets at 1.03 and 1.05 ppm which corresponds to the two methyl groups. The methyl group in the ethoxy part appeared at 1.25 ppm as a triplet (J = 7.0 Hz). The methyl group attached to the methine carbon appeared 1.39 ppm as a doublet (J = 4.8 Hz). The methyl group on the nitrogen appeared at 2.87 ppm as a doublet (J = 4.7 Hz). The two protons on the methylene carbon attached to oxygen appeared as a multiplet in the same range (3.43-3.58 ppm) as for the major diastereomer. The other two protons on the methylene carbon attached to oxygen in the ethyl part appeared as a multiplet in the range 3.70-3.76 ppm. The singlet at 4.08 ppm is attributed to the proton attached to the methine carbon. The proton on the methine carbon attached on both sides by oxygen appeared as a multiplet

in the range 4.62-4.67 ppm. The proton of the hydroxy group appeared as a broad singlet at 6.41 ppm. The proton on the amide nitrogen appeared as a broad singlet at 6.80 ppm.

The deprotection of **2.03a** under mild acidic conditions proceeded with concomitant lactonization to furnish *S*-(+)-pantolactone (**2.09a**) in 65% yield (Scheme 11) which was characterized by its spectral data.

IR spectrum of **2.09a** showed a broad band at 3346 cm^{-1} for the hydroxy group and a sharp band at 1782 cm^{-1} which is for the lactone carbonyl. Further the ^{1}H NMR and ^{13}C NMR confirmed its structure.

The ^{1}H NMR spectrum of **2.09a** showed two separate singlets at 1.11 and 1.26 ppm which corresponds to the *gem*-dimethyl group. The broad singlet at 2.34 ppm is for the hydroxy group. The methylene protons attached to oxygen appeared as two doublets at 3.97 ppm (J = 9.1 Hz) and 4.05 ppm (J = 9.1 Hz). The sharp singlet at 4.14 ppm is attributed to the proton on the methine carbon attached to the lactone carbonyl.



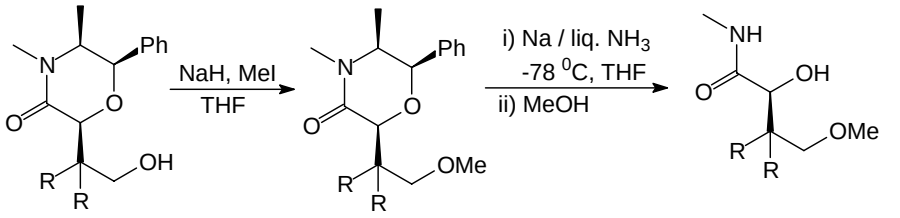
2.09a

The ^{13}C NMR spectrum of **2.09a** showed a peak at 177.3 ppm for the lactone carbonyl. The peak at 76.3 ppm is assigned to the methylene carbon. The methine carbon attached to the lactone carbonyl appeared at 75.8 ppm. The quaternary carbon carrying the *gem*-dimethyl group appeared at 40.9 ppm. The two methyl groups appeared separately at 22.9 and 18.8 ppm respectively. This compound gave satisfactory elemental analysis.

The optical rotation $\{[\alpha]_D^{25} = +51.8$ (c 2.0, $H_2O)\}$ matched with that of the reported value $\{[\alpha]_D^{25} = +50.1$ (c 2.0, $H_2O)\}$[30] and $\{[\alpha]_D^{25} = +51.6$ (c 2.0, $H_2O)\}$.[18a] Enantiomeric excess of **2.09a** was 91% by GC analysis on a chiral column.

Since the ethoxyethyl derivative of **2.02a** was unstable and also due to the low yield in the cleavage reaction it was decided to change the protecting group. Hence the alcohols **2.02a-c** were protected as methoxy derivatives **2.04a-c** which were stable compounds (Scheme 12). Moreover, **2.04a** was reported in literature and hence comparing the rotation of the compound with the reported value gave an indication about the diastereomeric excess of the compound (>90%) which was indeed later confirmed by chiral GC analysis of the final lactones. The structures of **2.04a-c** were established by IR, ^{1}H NMR and ^{13}C NMR data. **2.04a** was chosen for spectral discussion.

Scheme 12

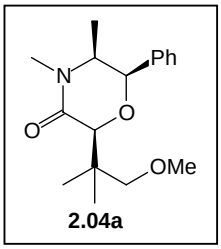


2.02a-c

2.04a, R= Me (97%)
2.04b, R= Et (96%)
2.04c, R= allyl (93%)

2.05a, R= Me (63%)
2.05b, R= Et (65%)
2.05c, R= allyl (56%)

IR spectrum of **2.04a** showed a sharp peak at 1649 cm^{-1} which is attributed to the amide carbonyl.



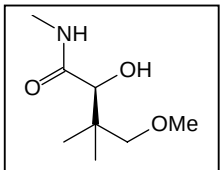
2.04a

The ^{1}H NMR spectrum of **2.04a** showed a doublet at 0.86 ppm (J = 6.4 Hz) which is attributed to the methyl group attached to the methine carbon in the chiral auxiliary part. The singlet at 1.06 ppm is attributed to the two methyl groups in the *gem*-dimethyl part. The methyl group attached to the nitrogen appeared as a singlet at 2.91 ppm. The methyl group attached to oxygen appeared as a singlet at 3.25 ppm. The methylene protons attached to the oxygen appeared as two separate doublets at 3.34 and 3.46 ppm (J = 8.7 Hz). The methine proton from the ephedrine part appeared as a doublet of quartet in the range 3.36-3.42 ppm (J = 2.8, 6.4 Hz). The proton on the methine carbon attached to the amide carbonyl appeared as a singlet at 4.13 ppm. The characteristic benzylic proton appeared as a doublet at 4.83 ppm (J = 2.8 Hz). The aromatic protons appeared as a multiplet in the range 7.15-7.30 ppm.

The ^{13}C NMR spectrum of **2.04a** showed a peak at 168.3 corresponding to the amide carbonyl. The peak at 138.0 ppm corresponds to the aromatic quaternary carbon. Other aromatic carbons appeared at 127.9, 127.1 and 125.1 ppm. The methine carbon attached to the amide carbonyl appeared at 81.3 ppm. The peak at 79.4 ppm corresponds to the methylene carbon attached to oxygen. The peak at 76.0 ppm is attributed to benzylic carbon. The methyl group attached to oxygen appeared at 58.7 ppm. The methine carbon attached to the nitrogen appeared at 58.4 ppm. The quaternary carbon bearing the *gem*-dimethyl group appeared at 39.8 ppm. The methyl carbon attached to the nitrogen appeared at 33.0 ppm. The two methyl carbons in the *gem*-dimethyl part appeared together at 21.7 ppm. The methyl group attached to the methine carbon appeared at 12.7 ppm. This compound gave satisfactory elemental analysis. In a similar way **2.04b** and **2.04c** were characterized by spectral data.

Cleavage of the chiral auxiliary from **2.04a-c** by Birch reduction with Na/liq. NH_3 (Scheme 12) gave the hydroxy butyramides **2.05a-c** in good yields (56-65%) and these cleaved compounds were found to be stable unlike the ethoxyethyl derivatives. The structures of **2.05a-c** were established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

IR spectrum of **2.05a** showed a broad band at 3431 cm^{-1} for the hydroxy group and a sharp peak at 1666 cm^{-1} for the amide carbonyl.



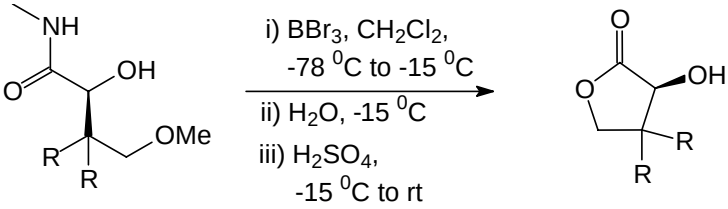
2.05a

The ^{1}H NMR spectrum of **2.05a** showed a singlet at 1.00 ppm which corresponds to the two methyl groups in the *gem*-dimethyl part. The methyl group attached to nitrogen appeared as a doublet at 2.85 ppm (J = 5.1 Hz). The protons on the methylene carbon attached to oxygen appeared as two separate doublets at 3.25 ppm (J = 9.2 Hz) and 3.35 ppm (J = 9.2 Hz). The methyl group attached to oxygen appeared as a singlet at 3.35 ppm. The methine proton appeared as a doublet at 4.00 ppm (J = 3.6 Hz). The doublet at 4.45 ppm (J = 3.6 Hz) is attributed to the hydroxy group. The broad singlet at 6.80 ppm is assigned to the amide proton.

The ^{13}C NMR spectrum of **2.05a** showed a peak at 172.9 corresponding to the amide carbonyl. The methine carbon attached to the amide carbonyl appeared at 81.7 ppm. The methylene carbon attached to oxygen appeared at 77.9 ppm. The methyl group attached to oxygen appeared at 59.1 ppm. The quaternary carbon appeared at 38.4 ppm. The methyl group attached to nitrogen appeared at 25.3 ppm. The two methyl groups appeared in the *gem*-dimethyl part appeared separately at 20.2 and 21.6 ppm. This compound gave satisfactory elemental analysis. In a similar way **2.05b** and **2.05c** were characterized by spectral data.

Conversion of the hydroxy butyramides **2.05a,b,d** to the target lactones **2.09a-c** was achieved in a one-pot reaction sequence. The primary hydroxyl group in hydroxy butyramides was liberated by demethylation with BBr_3 in DCM at –78 ^oC. Subsequent acid catalysed lactonisation at –15 ^oC which involves a very facile intramolecular acyl transfer from nitrogen to oxygen furnished (*S*)-(+)-pantolactone and its analogues in 70-97% yields with high enantiomeric excesses (Scheme 13).

Scheme 13



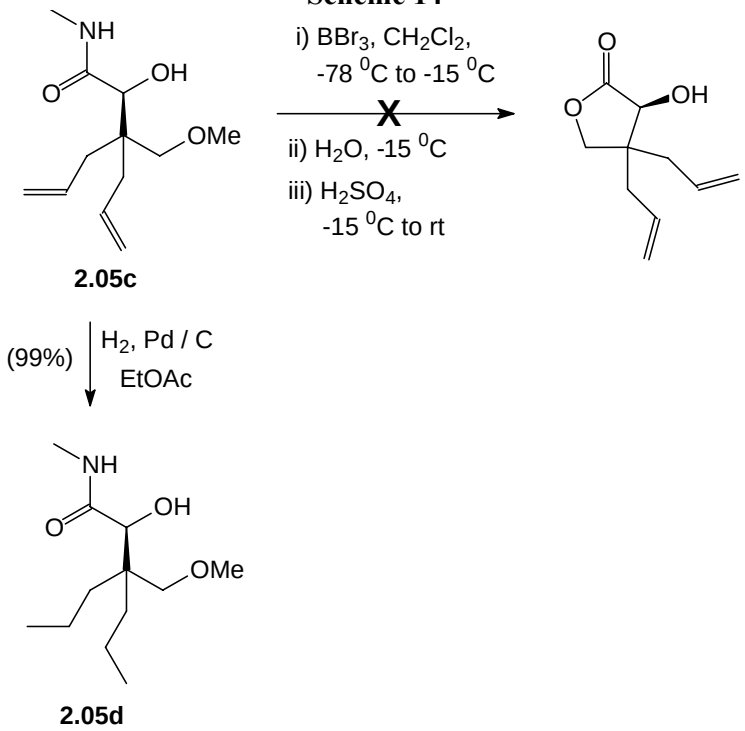
2.05a, R= Me
2.05b, R= Et
2.05d, R= *n*-propyl

2.09a, (*S*)-(+)-pantolactone, R= Me, 70%
2.09b, R= Et, 97%
2.09c, R= *n*-propyl, 88%

The spectral data for pantolactone **2.09a** obtained by using methoxy as a protecting group in the synthesis matched with the pantolactone **2.09a** obtained earlier by employing the ethoxyethyl protecting group. The structures of other pantolactone analogues **2.09b,c** were established by spectral data.

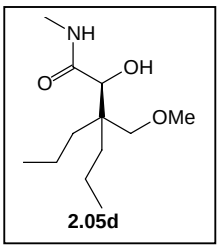
It is noteworthy in this regard that demethylation of the diallyl hydroxybutyramide **2.05c** by boron tribromide posed a problem and a mixture of products were obtained which could not be characterized (Scheme 14).

Scheme 14



The product (diallyl lactone) could not be obtained in this case. Hence **2.05c** was hydrogenated with Pd/C catalyst to give a di-*n*-propyl hydroxy butyramide **2.05d** in excellent yield.

The structure of **2.05d** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **2.05d** showed a broad band at 3381 cm^{-1} for the hydroxy group and a sharp peak at 1659 cm^{-1} for the amide carbonyl.



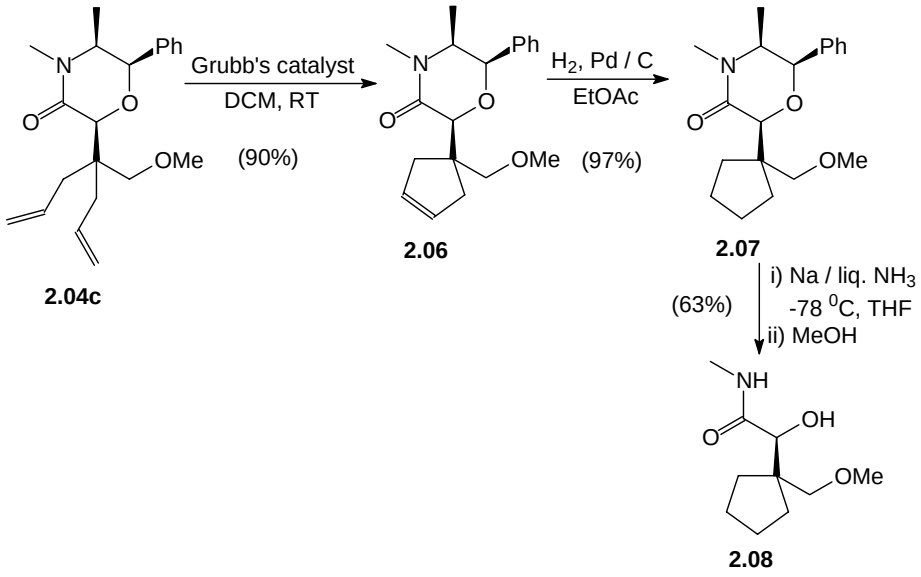
2.05d

The ^{1}H NMR data of **2.05d** showed a multiplet in the range 0.78-0.95 ppm which is attributed to the two methyl groups in the dipropyl part. The eight methylene protons appeared as a multiplet in the range 1.05-1.73 ppm. The methyl group attached to nitrogen appeared as a doublet at 2.81 ppm (J = 5.0 Hz). The methyl group attached to oxygen appeared as a singlet at 3.31 ppm. The methylene group attached to oxygen appeared as a multiplet in the range 3.32-3.43 ppm. The broad singlet at 3.92 ppm corresponds to the hydroxy group. The methine proton appeared as a singlet at 4.11 ppm. The broad singlet at 6.90 ppm is attributed to the amide proton.

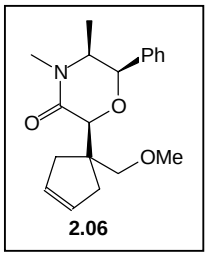
The ^{13}C NMR of **2.05d** showed a peak at 173.3 ppm corresponding to the amide carbonyl. The peak at 78.4 ppm corresponds to the methylene carbon attached to oxygen. The methine carbon attached to the amide carbonyl appeared at 76.8 ppm. The methyl group attached to oxygen appeared at 59.0 ppm. The quaternary carbon appeared at 43.1 ppm. The methyl carbon attached to the nitrogen appeared at 25.4 ppm. The four methylene carbons appeared separately at 34.3, 33.6, 16.3 and 16.2 ppm. The two methyl groups appeared together at 14.7 ppm. This compound gave satisfactory elemental analysis.

The diallyl compound **2.04c** offers an added advantage, as manipulation of the double bonds is possible. One such conversion of **2.04c** to a 5-membered cyclic alkene **2.06** was achieved by ring closing metathesis (RCM) using Grubb's catalyst (Scheme 15).

Scheme 15



The structure of **2.06** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **2.06** showed a sharp peak at 1649 cm^{-1} which is attributed to the amide carbonyl and the olefin.



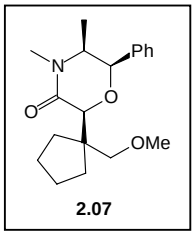
The ^{1}H NMR of **2.06** showed a doublet at 0.93 ppm (J = 6.6 Hz) which is for the methyl group attached to the methine carbon. The four allylic protons appeared as multiplets for two protons each in the range 2.18-2.53 ppm and 2.68-2.94 ppm. The methyl group attached to nitrogen appeared as a singlet at 2.98 ppm. The methyl group attached to oxygen appeared as a singlet at 3.29 ppm. The methylene protons attached to oxygen appeared separately as two doublets at 3.41 ppm (J = 8.6 Hz) and 3.64 ppm (J = 8.6 Hz). The characteristic doublet of quartet for the methine proton from the ephedrine part appeared in the range 3.42-3.56 ppm (J = 2.7, 6.6 Hz). The proton on the methine carbon attached to the amide carbonyl appeared as a singlet at 4.37 ppm. The characteristic benzylic proton of the chiral auxiliary appeared as a doublet at 4.94 ppm (J = 2.7 Hz). The two olefinic protons appeared as a multiplet in the range 5.55-5.70 ppm. The aromatic protons appeared as a multiplet in the range 7.12-7.50 ppm.

The ^{13}C NMR spectrum of **2.06** showed a peak at 168.9 ppm corresponding to the amide carbonyl. The peak at 138.0 ppm corresponds to the aromatic quaternary carbon. Other aromatic carbons and the two olefinic carbons appeared at 129.3, 128.4, 128.2, 127.4 and 125.2 ppm. The methine carbon attached to the amide carbonyl appeared at

80.4 ppm. The peak at 76.8 ppm corresponds to the methylene carbon attached to oxygen. The peak at 76.2 ppm is attributed to the benzylic carbon. The methyl group attached to oxygen appeared at 58.9 ppm. The methine carbon attached to the nitrogen appeared at 58.6 ppm. The quaternary carbon appeared at 49.7 ppm. The two allylic carbons appeared separately at 40.1 and 39.5 ppm. The methyl carbon attached to the nitrogen appeared at 33.4 ppm. The methyl group attached to the methine carbon appeared at 12.8 ppm. The HRMS data for this compound matched with the calculated value.

The RCM product was hydrogenated by Pd/C catalyst to give a cyclopentyl compound **2.07** (Scheme 15). The structure of **2.07** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

IR spectrum of **2.07** showed a sharp peak at 1643 cm^{-1} which is attributed to the amide carbonyl.



2.07

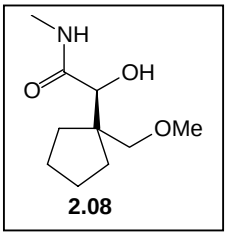
The ^{1}H NMR of **2.07** showed a doublet at 0.96 ppm (J = 6.7 Hz) which is for the methyl group attached to the methine carbon. The eight protons on the cyclopentyl group appeared as a multiplet in the range 1.40-2.25 ppm. The methyl group attached to nitrogen appeared as a singlet at 3.00 ppm. The methyl group attached to oxygen appeared as a singlet at 3.32 ppm. The methylene protons attached to oxygen appeared separately as two doublets at 3.33 ppm (J = 8.6 Hz) and 3.73 ppm (J = 8.6 Hz). The characteristic doublet of quartet for the methine proton from the ephedrine part appeared in the range 3.42-3.58 ppm (J = 3.1, 6.7 Hz). The proton on the methine carbon attached to the amide carbonyl appeared as a singlet at 4.30 ppm. The characteristic benzylic proton of the chiral auxiliary appeared as a doublet at 4.94 ppm (J = 3.1 Hz). The aromatic protons appeared as a multiplet in the range 7.17-7.48 ppm.

The ^{13}C NMR spectrum of **2.07** showed a peak at 169.3 corresponding to the amide carbonyl. The peak at 138.2 ppm corresponds to the aromatic quaternary carbon. Other aromatic carbons appeared at 128.2, 127.4 and 125.3 ppm. The methine carbon attached to the amide carbonyl appeared at 81.0 ppm. The peak at 77.3 ppm corresponded to the methylene carbon attached to oxygen. The peak at 76.3 ppm is attributed to benzylic carbon. The methyl group attached to oxygen appeared at 58.9 ppm. The methine carbon attached to the nitrogen appeared at 58.7 ppm. The quaternary carbon appeared at 50.9 ppm. The methyl carbon attached to the nitrogen appeared at 33.5 ppm. The four methylene carbons appeared as three peaks at 33.1, 26.2 and 25.5

ppm. The methyl group attached to the methine carbon appeared at 12.9 ppm. This compound gave satisfactory elemental analysis.

The cleavage of the ephedrine portion in the cyclopentyl compound **2.07** gave the cyclopentyl hydroxy butyramide **2.08** in good yield (Scheme 15). The structure of **2.08** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

IR spectrum of **2.08** showed a broad band at 3371 cm^{-1} corresponding to the hydroxy group and a sharp peak at 1659 cm^{-1} which is attributed to the amide carbonyl.



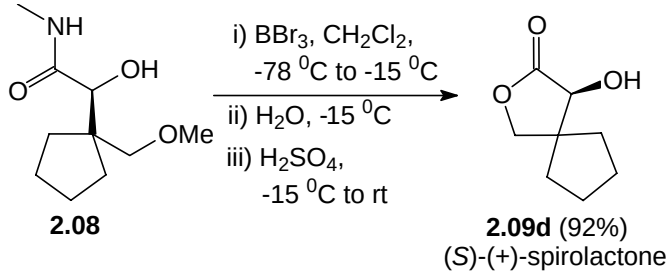
2.08

The ^{1}H NMR of **2.08** showed a multiplet for eight protons of the cyclopentyl group in the range 1.30-2.10 ppm. The methyl group attached to nitrogen appeared as a doublet at 2.83 ppm (J = 5.0 Hz). The protons on the methylene carbon attached to oxygen appeared as a multiplet in the range 3.12-3.41 ppm. The methyl group attached to oxygen appeared as a singlet at 3.33 ppm. The broad singlet at 3.59 ppm is attributed to the hydroxy group. The methine proton appeared as a singlet at 3.98 ppm. The broad singlet at 6.89 ppm is attributed to the amide proton.

The ^{13}C NMR spectrum of **2.08** showed a peak at 173.6 ppm corresponding to the amide carbonyl. The peak at 79.5 ppm corresponds to the methylene carbon attached to oxygen. The methine carbon attached to the amide carbonyl appeared at 79.1 ppm. The methyl group attached to oxygen appeared at 59.3 ppm. The quaternary carbon appeared at 49.8 ppm. The methyl carbon attached to the nitrogen appeared at 25.7 ppm. The four methylene carbons appeared at 32.3, 32.0, 25.2 and 24.8 ppm. This compound gave satisfactory elemental analysis.

Conversion of the hydroxy butyramide **2.08** to the target spirolactone **2.09d** was achieved in a one-pot reaction sequence as was done for the other pantolactone analogues **2.09a-c**. The primary hydroxyl group in hydroxy butyramides was liberated by demethylation with BBr_3 in dichloromethane at –78 ^{o}C. Subsequent acid catalysed lactonisation at –15 ^{o}C which involves a very facile intramolecular acyl transfer from nitrogen to oxygen furnished (*S*)-(+)-spirolactone **2.09d** in 92% yield with high enantiomeric excess (Scheme 16).

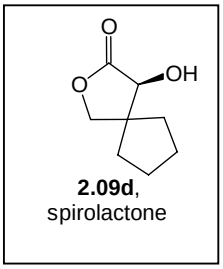
Scheme 16



2.08

2.09d (92%)
(*S*)-(+)-spirolactone

The structure of **2.09d** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **2.09d** showed a broad band at 3402 cm^{-1} corresponding to the hydroxy group and a characteristic sharp peak at 1780 cm^{-1} which is attributed to the five membered lactone carbonyl.



2.09d,
spirolactone

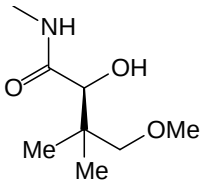
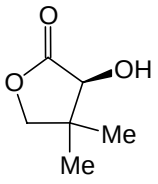
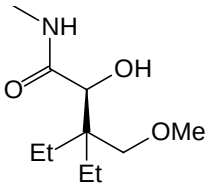
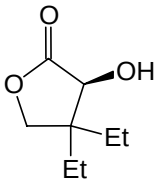
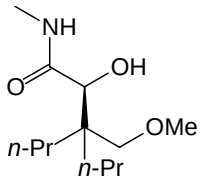
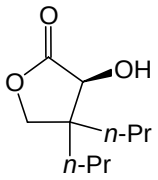
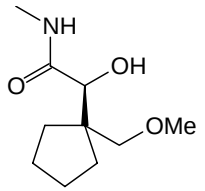
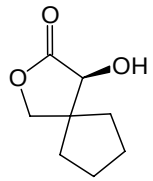
The ^{1}H NMR of **2.09d** showed a multiplet for eight protons which is attributed to the methylene protons of the cyclopentyl group. The broad singlet at 2.43 ppm is attributed to the hydroxy proton. The protons on the methylene group attached to oxygen appeared separately as doublets integrating for one proton each at 4.01 ppm and 4.12 ppm (J = 9.0 Hz). The methine proton attached to amide carbonyl appeared as a singlet at 4.28 ppm.

The ^{13}C NMR of **2.09d** showed a peak at 177.3 ppm which is attributed to the lactone carbonyl. The methylene carbon attached to oxygen appeared at 75.9 ppm. The methine carbon appeared at 73.8 ppm. The quaternary carbon appeared at 51.7 ppm. The four methylene carbons of the cyclopentyl ring appeared separately at 33.8, 29.2, 25.1 and 24.9 ppm. This compound gave satisfactory elemental analysis.

The optical rotation for **2.09d** {$[\alpha]_D^{25}$ = +18.6 (*c* 0.70, $CHCl_3$)} matched with the reported value {For (*R*)-isomer $[\alpha]_D^{25}$ = –19.3 (*c* 1.5, $CHCl_3$)}.[19] Enantiomeric excess of **2.09d** was 94% by GC analysis on a chiral column.

The overall conversion of morpholine-dione **1.01** to the target lactones **2.09a-d** constitutes a general route to these biologically important intermediates. The results are summarized in Table 1.

Table 1. Synthesis of (*S*)-(+)-pantolactone analogues (**2.09a-d**).

Entry No.	Substrate	Product	Yield[a] %	$[\alpha]_D^{25}$	ee[b] %
1	 **2.05a**	 **2.09a**	70	+51.8 (H_2O)	91
2	 **2.05b**	 **2.09b**	97	+14.9 (MeOH)	91
3	 **2.05d**	 **2.09c**	88	+8.4 ($CHCl_3$)	92
4	 **2.08**	 **2.09d**	92	+18.6 ($CHCl_3$)	94

[a]Isolated yields. [b]Enantiomeric excess of the lactones **2.09a-d** was determined by GC analysis on a CP-Chiracel-Dex CB column.

The absolute configuration of the lactones **2.09a-d** are based on that of the precursor **1.03** since epimerization of the newly generated stereocenter in **1.03** during its conversion to the target lactones **2.09a-d** is unlikely. Thus the lactones **2.09a-d** are assigned the '*S*' configuration. The enantiomeric excess of the lactones **2.09a-d** was determined using chiral GC and found to be 91-94%.

The simplicity of the above synthetic sequence makes it viable for the synthesis of pantolactone and its analogues on a preparative scale. In this regard it is noteworthy that several grams of the key intermediate **2.04a-c** and **2.07** can be prepared readily.

2.5: Conclusion

A general route for the enantioselective synthesis of (*S*)-(+)-pantolactone and its analogues has been developed from an ephedrine-derived morpholinone. Selective dialkylation on an ephedrine derived chiral template **1.03** without epimerization of the product was the key step for introduction of the *gem*-dialkyl moiety in pantolactone and its analogues. The above method should provide access to a variety of enantiomerically enriched β,β-dialkyl-α-hydroxy-γ-butyrolactones in either enantiomeric form, since both the enantiomers of ephedrine are commercially available.

2.6: Experimental

General procedure for selective dialkylation

To a stirred suspension of KH (3.5 equiv.) in anhydrous THF at 0 ^{o}C was added ester **1.03** (1 equiv.) solution in anhydrous THF dropwise over a period of 45 min. After stirring for 1 h at 0 ^{o}C, alkyl halide (4.5 equiv.) was added dropwise and the reaction mixture was allowed to warm up to RT at which it was stirred for 10-12 h. Saturated NH_4Cl solution was added and the solvent was removed under reduced pressure. Precipitated solids were dissolved in minimum water and extracted with ethyl acetate. Combined extracts were washed with brine solution, dried (Na_2SO_4) and concentrated to furnish crude product which was purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether as the eluant.

(2*S*,5S,6*R*)-2-(4,5-Dimethyl-3-oxo-6-phenyl-morpholin-2-yl)-2-methyl-propionic acid ethyl ester (2.01a):

Reaction of a stirred suspension of KH (712 mg, 17.7 mmol) and **1.03** (1.475 g, 5.07 mmol) in THF (30 mL) with methyl iodide (1.42 mL, 22.8 mmol) gave after purification by flash chromatography (1/1 EA/PE) 1.55 g (96%) of **2.01a** as a clear colorless gum.

IR ($CHCl_3$):

1649, 1728 cm^{-1}.

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

δ 0.96 (d, 3H, J = 6.8 Hz, C*H*$_3$CH), 1.28 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$), 1.32 (s, 3H, C*H*$_3$C), 1.41 (s, 3H, C*H*$_3$C), 3.01 (s, 3H, NC*H*$_3$), 3.49-3.55 (dq, 1H, J = 2.8, 6.8 Hz, C*H*CH$_3$), 4.15-4.28 (m, 2H, OC*H*$_2$), 4.68 (s, 1H, C*H*CO), 5.04 (d, 1H, J = 2.8 Hz, PhC*H*), 7.22-7.42 (m, 5H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$):

δ 13.0 (*C*H$_3$CH), 13.9 (C(*C*H$_3$)$_2$), 19.1 (C(*C*H$_3$)$_2$), 23.2 (*C*H$_3$CH$_2$), 33.1 (N*C*H$_3$), 45.9 (*C*(CH$_3$)$_2$), 58.3 (N*C*H), 60.4 (O*C*H$_2$), 76.3 (Ph*C*H), 81.8 (*C*HO), 125.1 (Ar*C*), 127.4 (Ar*C*), 128.2 (Ar*C*), 137.6 (Ar*C* *ipso*), 167.4 (N*C*O), 175.4 (*C*OO).

MS (*m/z*):

319 (M^{+}).

Analysis for $C_{18}H_{25}NO_4$:

Calculated: C, 67.69; H, 7.89; N, 4.39; Obtained: C, 67.80; H, 8.17; N, 4.22.

Optical rotation:

$[\alpha]_D^{25} = -131.5$ (*c* 1.17, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(4,5-Dimethyl-3-oxo-6-phenyl-morpholin-2-yl)-2-ethyl-butyric acid ethyl ester (2.01b):

Reaction of a stirred suspension of KH (748 mg, 18.6 mmol) and **1.03** (1.550 g, 5.33 mmol) in THF (30 mL) with ethyl iodide (1.92 mL, 24 mmol) gave after purification by flash chromatography (1/1 EA/PE) 1.72 g (93%) of **2.01b** as a clear colorless gum.

IR ($CHCl_3$):

1728, 1657 cm^{-1}.

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

δ 0.90 (t, 3H, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 0.96 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH), 1.03 (t, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.28 (t, 3H, *J* = 7.3 Hz, C*H*$_3$CH$_2$O), 1.77-2.12 (m, 4H, C*H*$_2$CH$_3$), 3.0 (s, 3H, NC*H*$_3$), 3.45-3.60 (dq, 1H, *J* = 3.0, 6.6 Hz, C*H*CH$_3$), 4.05-4.30 (m, 2H, C*H*$_2$O), 4.69 (s, 1H, C*H*CO), 5.0 (d, 1H, *J* = 3.0 Hz, PhC*H*), 7.15-7.45 (m, 5H, ArC*H*).

^{13}C NMR (125 MHz, $CDCl_3$):

δ 8.3 (*C*H$_3$CH$_2$), 8.8 (*C*H$_3$CH$_2$), 12.6 (*C*H$_3$CH), 13.7 (*C*H$_3$CH$_2$O), 22.8 (*C*H$_2$CH$_3$), 26.1 (*C*H$_2$CH$_3$), 32.8 (N*C*H$_3$), 52.0 (C*quat*), 58.0 (N*C*H), 59.7 (O*C*H$_2$), 76.8 (Ph*C*H), 81.7 (*C*HO), 124.8 (Ar*C*), 127.1 (Ar*C*), 127.9 (Ar*C*), 137.4 (Ar*Cipso*), 167.3 (N*C*O), 173.7 (*C*OO).

MS (*m/z*):

347 (M^+).

Analysis for $C_{20}H_{29}NO_4$:

Calculated: C, 69.14; H, 8.41; N, 4.03; Obtained: C, 69.30; H, 8.39; N, 4.29.

Optical rotation:

$[\alpha]_D^{25} = -139.6$ (*c* 0.5, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-Allyl-2-(4,5-dimethyl-3-oxo-6-phenyl-morpholin-2-yl)-pent-4-enoic acid ethyl ester (2.01c):

Reaction of a stirred suspension of KH (428 mg, 3.5 mmol) and **1.03** (886 mg, 3.04 mmol) in THF (20 mL) with allyl iodide solution in THF [generated in situ from allyl bromide (1.84 mL, 21.3 mmol) and NaI (3.597 g, 24 mmol) in THF (20 mL) at reflux temperature for 2 h] gave after purification by flash chromatography (1/3 EA/PE) 1.039 g (92%) of **2.01c** as a clear colorless gum.

IR ($CHCl_3$):

1655, 1730 cm^{-1}.

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

δ 0.94 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 1.26 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$), 2.57-2.71 (m, 4H, *allylic* C*H*$_2$), 2.96 (s, 3H, NC*H*$_3$), 3.43-3.60 (dq, 1H, *J* = 2.9, 6.3 Hz, C*H*CH$_3$), 4.05-4.34 (m, 2H, C*H*$_2$O), 4.67 (s, 1H, C*H*CO), 4.94-5.16 (m, 5H, PhC*H* and *olefinic* C*H*$_2$), 5.66-6.20 (m, 2H, *olefinic* C*H*), 7.16-7.48 (m, 5H, ArC*H*).

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

δ 13.1 (*C*H$_3$CH), 14.1 (*C*H$_3$CH$_2$O), 33.2 (NCH$_3$), 35.8 (*allylic C*H$_2$), 38.7 (*allylic C*H$_2$), 52.3 (C*quat*), 58.5 (NCH), 60.5 (OCH$_2$), 77.2 (PhCH), 81.1 (*C*HO), 117.2 (*C*H$_2$=CH), 118.1 (*C*H$_2$=CH), 125.1 (Ar*C*), 127.5 (Ar*C*), 128.3 (Ar*C*), 133.5 (CH$_2$=*C*H), 135.0 (CH$_2$=*C*H), 137.5 (Ar*Cipso*), 167.4 (N*C*O), 173.1 (*C*OO).

HRMS:

Calculated: 371.2097; Found: 371.2095.

Optical rotation:

$[\alpha]_D^{25} = -110.6$ (*c* 0.5, $CHCl_3$).

General procedure for reduction of esters

To a stirred solution of ester (**2.01a-c**, 1 equiv.) in anhydrous THF at -78 ^oC was added DIBAL-H (3 equiv., 1M solution in toluene) dropwise and the resulting mixture was allowed to warm up to RT at which it was stirred for 10-12 h. 2N HCl (1 mL) was then added to the reaction mixture at 0 ^oC and stirred for 5 min. Solvent was removed under reduced pressure. Residue was dissolved in minimum water and extracted with ethyl acetate. Combined extracts were washed with brine solution, dried (Na_2SO_4) and

concentrated to furnish the crude product which was purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether as the eluant.

(2*S*,5*S*,6*R*)-2-(2-Hydroxy-1,1-dimethyl-ethyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.02a):

Reaction of ester **2.01a** (1.445 g, 4.53 mmol) with DIBAL-H (13.6 mL, 13.6 mmol) in THF (25 mL) gave after purification by flash chromatography (2/3 EA/PE) 1.0 g (80%) of **2.02a** as a clear colorless gum.

IR ($CHCl_3$):

1632, 3354 cm^{-1}.

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

δ 1.01 (d, 3H, J = 6.6 Hz, CH_3CH), 1.10 (s, 3H, CH_3C), 1.19 (s, 3H, CH_3C), 3.07 (s, 3H, NCH_3), 3.49-3.55 (dq, 1H, J = 2.9, 6.6 Hz, CHCH$_3$), 3.57 (d, 1H, J = 11.5 Hz, CH_2O), 3.67 (d, 1H, J = 11.5 Hz, CH_2O), 3.81 (bs, 1H, OH), 4.21 (s, 1H, CHCO), 4.97 (d, 1H, J = 2.9 Hz, PhCH), 7.30-7.42 (m, 5H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$):

δ 12.9 (CH$_3$CH), 19.6 (C(CH$_3$)$_2$), 23.4 (C(CH$_3$)$_2$), 33.7 (NCH$_3$), 40.5 (C(CH$_3$)$_2$), 58.6 (NCH), 71.1(OCH$_2$), 76.2 (PhCH), 83.5 (CHO), 125.2 (ArC), 127.5 (ArC), 128.2 (ArC), 137.5 (Ar*Cipso*), 169.5 (NCO).

MS (*m/z*):

277 (M^+).

Analysis for $C_{16}H_{23}NO_3$:

Calculated: C, 69.29; H, 8.36; N, 5.05; Obtained C, 69.55; H, 8.53; N, 5.22.

Optical rotation:

$[\alpha]_D^{25} = -164.0$ (*c* 0.7, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(1-Ethyl-1-hydroxymethyl-propyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.02b):

Reaction of ester **2.01b** (1.370 g, 3.95 mmol) with DIBAL-H (13.8 mL, 13.8 mmol) in THF (25 mL) gave after purification by flash chromatography (3/7 EA/PE) 1.055 g (77%) of **2.02b** as a clear colorless gum.

IR ($CHCl_3$):

1625, 3385 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 0.80 (t, 3H, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 0.84 (t, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 0.89 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH), 1.42-1.54 (m, 3H, C*H*$_2$CH$_3$), 1.71-1.83 (m, 1H, C*H*$_2$CH$_3$), 2.96 (s, 3H, NC*H*$_3$), 3.38-3.48 (dq, 1H, *J* = 2.3, 6.4 Hz, C*H*CH$_3$), 3.56 (d, 1H, *J* = 12.4 Hz, C*H*$_2$O), 3.72 (d, 1H, *J* = 12.4 Hz, C*H*$_2$O), 4.29 (s, 1H, C*H*CO), 4.84 (d, 1H, *J* = 2.3 Hz, PhC*H*), 7.15-7.35 (m, 5H, ArC*H*).

^{13}C NMR (125 MHz, $CDCl_3$):

δ 7.7 (*C*H$_3$CH$_2$), 7.7 (*C*H$_3$CH$_2$), 12.8 (*C*H$_3$CH), 24.2 (CH$_3$*C*H$_2$), 27.0 (CH$_3$*C*H$_2$), 33.8 (N*C*H$_3$), 44.9 (C*quat*), 58.6 (N*C*H), 66.7 (*C*H$_2$O), 76.6 (Ph*C*H), 82.2 (*C*HO), 125.1 (Ar*C*), 127.5 (Ar*C*), 128.2 (Ar*C*), 137.6 (Ar*Cipso*), 170.4 (N*C*O).

MS (*m/z*):

305 (M^+).

Analysis for $C_{18}H_{27}NO_3$:

Calculated: C, 70.79; H, 8.91; N, 4.59; Obtained: C, 70.95; H, 9.10; N, 4.84.

Optical rotation:

$[\alpha]_D^{25} = -178.5$ (*c* 0.9, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(1-Allyl-1-hydroxymethyl-but-3-enyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.02c):

Reaction of ester **2.01c** (0.840 g, 2.26 mmol) with DIBAL-H (6.8 mL, 6.8 mmol) in THF (15 mL) gave after purification by flash chromatography (2/3 EA/PE) 585 mg (76%) of **2.02c** as a clear colorless gum.

IR ($CHCl_3$):

1626, 3384 cm^{-1}.

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

δ 0.98 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 2.10-2.50 (m, 3H, *allylic* C*H*$_2$), 2.54-2.77 (m, 1H, *allylic* C*H*$_2$), 3.03 (s, 3H, NC*H*$_3$), 3.45-3.59 (dq, 1H, *J* = 3.2, 6.3 Hz, C*H*CH$_3$), 3.64 (d, 1H, *J* = 12.2 Hz, C*H*$_2$O), 3.78 (d, 1H, *J* = 12.2 Hz, C*H*$_2$O), 4.32 (s, 1H, C*H*CO), 4.92 (d, 1H, *J* = 3.2 Hz, PhC*H*), 4.94-5.21 (m, 4H, *olefinic* C*H*$_2$), 5.70-6.08 (m, 2H, *olefinic* C*H*), 7.22-7.46 (m, 5H, ArC*H*).

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

δ 12.9 (*C*H$_3$CH), 33.8 (N*C*H$_3$), 36.2 (*allylic C*H$_2$), 39.3 (*allylic C*H$_2$), 45.5 (C*quat*), 58.5 (N*C*H), 66.9 (*C*H$_2$O), 76.5 (Ph*C*H), 82.0 (*C*HO), 117.9 (2x

CH_2=CH), 125.0 (Ar*C*), 127.5 (Ar*C*), 128.3 (Ar*C*), 133.8 (CH_2=*C*H), 134.2 (CH_2=*C*H), 137.3 (Ar*Cipso*), 169.9 (N*C*O).

MS (*m/z*):

329 (M^+).

Analysis for $C_{20}H_{27}NO_3$:

Calculated: C, 72.92; H, 8.26; N, 4.25; Obtained: C, 73.15; H, 8.43; N, 4.51.

Optical rotation:

$[\alpha]_D^{25} = -143.1$ (*c* 5.3, $CHCl_3$).

(2*S*)-2-Hydroxy-4-ethoxyethyl-butanoic acid *N*-methyl amide (2.03a):

To the solution of **2.02a** (250 mg, 1.07 mmol) in chloroform (3 mL) was added ethyl vinyl ether (0.82 mL, 8.56 mmol) and trichloroacetic acid (a few crystals). The resulting mixture was stirred at ambient temperature for 12 h. Saturated aqueous $NaHCO_3$ was added and the organic layer was separated. The bicarbonate layer was extracted with chloroform (3 x 5 mL) and all the $CHCl_3$ layers were combined, dried (Na_2SO_4) and concentrated to give the ethoxyethyl derivative of **2.02a** which was found to be unstable and hence used further without purification.

The above derivative was dissolved in anhydrous THF (2 mL) and added to a mixture of anhydrous liquid ammonia (7 mL, distilled over sodium) and sodium (207 mg, 9 mmol) at –78 ^oC. The mixture was stirred at –78 ^oC for 3 minutes and methanol (6 mL) was added. The mixture was warmed to ambient temperature to remove ammonia and the methanol was removed under reduced pressure. The residue was taken up in water and the mixture was saturated with sodium chloride. The aqueous phase was extracted with ethyl acetate and the combined extracts were concentrated. The residue was purified by rapid filtration through a short silica gel column (ethyl acetate) to furnish 63 mg (30%) of **2.03a** as a gum, which was immediately used further.

IR ($CHCl_3$):

3350, 1655 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$):

Major diastereomer:

δ 0.94 (s, 3H, C*H*$_3$), 1.03 (s, 3H, C*H*$_3$), 1.22 (t, 3H, *J* = 7 Hz, C*H*$_3$CH$_2$), 1.32 (d, 3H, *J* = 5.1 Hz, C*H*$_3$CH), 2.84 (d, 3H, *J* = 4.8 Hz, NC*H*$_3$), 3.43-3.58 (m, 2H,

OCH_2), 3.60-3.68 (m, 2H, OCH_2), 3.90 (s, 1H, CHOH), 4.67-4.75 (m, 1H, OCHO), 6.54 (bs, 1H, OH), 6.97 (bs, 1H, NH).

Minor diastereomer:

δ 1.03 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.25 (t, 3H, J = 7 Hz, CH_3CH$_2$), 1.39 (d, 3H, J = 4.8 Hz, CH_3CH), 2.87 (d, 3H, J = 4.7 Hz, NCH_3), 3.43-3.58 (m, 2H, OCH_2), 3.70-3.76 (m, 2H, OCH_2), 4.08 (s, 1H, CHOH), 4.62-4.67 (m, 1H, OCHO), 6.41 (bs, 1H, OH), 6.80 (bs, 1H, NH).

General procedure for protection of OH group

To a stirred suspension of NaH (1.5 equiv.) in anhydrous THF at 0 ^oC was added (**2.02a-c**, 1 equiv.) solution in anhydrous THF dropwise over a period of 5 minutes. The reaction mixture was stirred at 0-10 ^oC for 1 h and then methyl iodide (2.0 equiv.) was added dropwise. The reaction mixture was then allowed to warm-up to RT at which it was stirred for 8-10 h. Saturated solution of ammonium chloride was then added to the reaction mixture and solvent was removed under reduced pressure. It was then extracted with ethyl acetate three times. The combined extracts were washed with brine solution, dried (Na_2SO_4) and concentrated to give the crude product which was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether as the eluant.

(2*S*,5*S*,6*R*)-2-(2-Methoxy-1,1-dimethyl-ethyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.04a):

Reaction of stirred suspension of NaH (65 mg, 2.7 mmol) and **2.02a** (500 mg, 1.8 mmol) in THF with MeI (0.22 mL, 3.6 mmol) gave after purification by flash column chromatography (1/5 EA/PE) 509 mg (97%) of **2.04a** as a clear colorless gum.

IR ($CHCl_3$):

1649 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 0.86 (d, 3H, J = 6.4 Hz, CH_3CH), 1.06 (s, 6H, (CH_3C)$_2$), 2.91 (s, 3H, NCH_3), 3.25 (s, 3H, OCH_3), 3.34 (d, 1H, J = 8.7 Hz, OCH_2), 3.36-3.42 (dq, 1H, J = 2.8, 6.4 Hz, CHCH$_3$), 3.46 (d, 1H, J = 8.7 Hz, CH_2O), 4.13 (s, 1H, CHCO), 4.83 (d, 1H, J = 2.8 Hz, PhCH), 7.15-7.30 (m, 5H, ArH).

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

δ 12.7 (CH_3CH), 21.7 (2x$C(CH_3)_2$), 33.0 (NCH_3), 39.8 (*Cquat*), 58.4 (N*C*H), 58.7 (OCH_3), 76.0 (Ph*C*H), 79.4 (CH_2O), 81.3 (*C*HO), 125.1 (Ar*C*), 127.1 (Ar*C*), 127.9 (Ar*C*), 138.0 (Ar*Cipso*), 168.3 (N*C*O).

MS (*m/z*):

291 (M^+).

Analysis for $C_{17}H_{25}NO_3$:

Calculated: C, 70.07; H, 8.65; N, 4.81; Obtained: C, 70.30; H, 8.85; N, 5.05.

Optical rotation:

$[\alpha]_D^{25} = -191.7$ (*c* 3.6, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(1-Ethyl-1-methoxymethyl-propyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.04b):

Reaction of stirred suspension of NaH (49 mg, 2.04 mmol) and **2.02b** (415 mg, 1.36 mmol) in THF with MeI (0.17 mL, 2.72 mmol) gave after purification by flash column chromatography (1/4 EA/PE) 417 mg (96%) of **2.04b** as a clear colorless gum.

IR ($CHCl_3$):

1649 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 0.76-0.84 (m, 6H, CH_3CH_2), 0.86 (d, 3H, *J* = 6.4 Hz, CH_3CH), 1.46-1.75 (m, 4H, CH_2CH_3), 2.90 (s, 3H, NCH_3), 3.21 (s, 3H, OCH_3), 3.36-3.44 (m, 1H, $CHCH_3$), 3.40 (d, 1H, *J* = 9.2 Hz, CH_2O), 3.51 (d, 1H, *J* = 9.2 Hz, CH_2O), 4.14 (s, 1H, C*H*CO), 4.81 (d, 1H, *J* = 2.3 Hz, PhC*H*), 7.15-7.30 (m, 5H, ArC*H*).

^{13}C NMR (125 MHz, $CDCl_3$):

δ 8.0 (CH_3CH_2), 8.2 (CH_3CH_2), 12.9 (CH_3CH), 24.6 (CH_3CH_2), 24.8 (CH_3CH_2), 33.6 (NCH_3), 45.2 (*Cquat*), 58.7 (N*C*H), 58.8 (OCH_3), 75.3 (OCH_2), 76.6 (Ph*C*H), 79.8 (*C*HO), 125.3 (Ar*C*), 127.3 (Ar*C*), 128.2 (Ar*C*), 138.3 (Ar*Cipso*), 169.4 (N*C*O).

MS (*m/z*):

319 (M^+).

Analysis for $C_{19}H_{29}NO_3$:

Calculated: C, 71.44; H, 9.15; N, 4.38; Obtained: C, 71.73; H, 9.43; N, 4.52.

Optical rotation:

$[\alpha]_D^{25} = -168.6$ (*c* 0.9, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(1-Allyl-1-methoxymethyl-but-3-enyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.04c):

Reaction of stirred suspension of NaH (60 mg, 2.49 mmol) and **2.02c** (545 mg, 1.66 mmol) in THF with methyl iodide (0.21 mL, 3.32 mmol) gave after purification by flash column chromatography (1/4 EA/PE) 528 mg (93%) of **2.04c** as a clear colorless gum.

IR ($CHCl_3$):

1649 cm^{-1}.

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

δ 0.96 (d, 3H, *J* = 6.7 Hz, C*H*$_3$CH), 2.28-2.65 (m, 4H, *allylic* C*H*$_2$), 2.97 (s, 3H, NC*H*$_3$), 3.30 (s, 3H, OC*H*$_3$), 3.41-3.50 (m, 1H, C*H*CH$_3$), 3.53 (d, 1H, *J* = 9.0 Hz, C*H*$_2$O), 3.60 (d, 1H, *J* = 9.0 Hz, C*H*$_2$O), 4.19 (s, 1H, C*H*CO), 4.89 (d, 1H, *J* = 3.1 Hz, PhC*H*), 4.97-5.15 (m, 4H, *olefinic* C*H*$_2$), 5.77-6.04 (m, 2H, *olefinic* C*H*), 7.20-7.45 (m, 5H, ArC*H*).

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

12.8 (*C*H$_3$CH), 33.8 (NCH$_3$), 36.8 (*allylic C*H$_2$), 36.9 (*allylic C*H$_2$), 45.5 (*Cquat*), 58.5 (OCH$_3$), 58.6 (NCH), 74.7 (OCH$_2$), 76.4 (PhCH), 79.2 (*C*HO), 117.2 (*C*H$_2$=CH), 117.4 (*C*H$_2$=CH), 125.0 (Ar*C*), 127.3 (Ar*C*), 128.1 (Ar*C*), 134.6 (*C*H=CH$_2$), 134.7 (*C*H=CH$_2$), 137.9 (Ar*Cipso*), 168.8 (N*C*O).

MS (*m/z*):

343 (M^+).

Analysis for $C_{21}H_{29}NO_3$:

Calculated: C, 73.44; H, 8.51; N, 4.08; Obtained: C, 73.71; H, 8.48; N, 4.14.

Optical rotation:

$[\alpha]_D^{25} = -148.9$ (*c* 1.05, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(1-Methoxymethyl-cyclopent-3-enyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.06):

To a stirred solution of **2.04c** (170 mg, 0.5 mmol) in dichloromethane (5 mL) was added Grubb's catalyst (12 mg) and stirred at ambient temperature for 12 h. Solvent was

removed under reduced pressure and residue after purification by flash column chromatography (3/7 EA/PE) gave 140 mg (90%) of **2.06** as a gum.

IR ($CHCl_3$):

1649 cm^{-1}.

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

δ 0.93 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH), 2.18-2.53 (m, 2H, *allylic* C*H*$_2$), 2.68-2.94 (m, 2H, *allylic* C*H*$_2$), 2.98 (s, 3H, NC*H*$_3$), 3.29 (s, 3H, OC*H*$_3$), 3.41 (d, 1H, *J* = 8.6 Hz, C*H*$_2$O), 3.42-3.56 (dq, 1H, *J* = 2.7, 6.6 Hz, C*H*CH$_3$), 3.64 (d, 1H, *J* = 8.6 Hz, C*H*$_2$O), 4.37 (s, 1H, C*H*CO), 4.94 (d, 1H, *J* = 2.7 Hz, PhC*H*), 5.55-5.70 (m, 2H, *olefinic* C*H*), 7.12-7.50 (m, 5H, ArC*H*).

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

δ 12.8 (*C*H$_3$CH), 33.4 (N*C*H$_3$), 39.5 (*allylic C*H$_2$), 40.1 (*allylic C*H$_2$), 49.7 (*Cquat*), 58.6 (N*C*H), 58.9 (O*C*H$_3$), 76.2 (Ph*C*H), 76.8 (O*C*H$_2$), 80.4 (*C*HO), 125.2, 127.4, 128.2, 128.4, 129.3 (Ar*C*, *olefinic C*H, total 5 peaks), 138.0 (Ar*Cipso*), 168.9 (N*C*O).

HRMS:

Calculated: 315.1834; Found: 315.1833.

Optical rotation:

$[\alpha]_D^{25} = -160.3$ (*c* 2.5, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-(1-Methoxymethyl-cyclopentyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (2.07):

To a solution of **2.06** (315 mg, 1 mmol) in ethyl acetate (8 mL) was added 10% Pd/C (60 mg) and the mixture was stirred under an atmosphere of hydrogen (1 atm) for 12 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give 308 mg (97%) of **2.07** as a clear colorless gum.

IR ($CHCl_3$):

1643 cm^{-1}.

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

δ 0.96 (d, 3H, *J* = 6.7 Hz, C*H*$_3$CH), 1.40-2.25 (m, 8H, cyclopentyl C*H*$_2$), 3.00 (s, 3H, NC*H*$_3$), 3.32 (s, 3H, OC*H*$_3$), 3.33 (d, 1H, *J* = 8.6 Hz, C*H*$_2$O), 3.42-3.58 (dq, 1H, *J* = 3.1, 6.7 Hz, C*H*CH$_3$), 3.73 (d, 1H, *J* = 8.6 Hz, C*H*$_2$O), 4.30 (s, 1H, C*H*CO), 4.94 (d, 1H, *J* = 3.1 Hz, PhC*H*), 7.17-7.48 (m, 5H, ArC*H*).

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

δ 12.9 (*C*H_3CH), 25.5 (*C*H_2), 26.2 (*C*H_2), 33.1 (*C*H_2), 33.5 (N*C*H_3), 50.9 (*Cquat*), 58.7 (N*C*H), 58.9 (O*C*H_3), 76.3 (Ph*C*H), 77.3 (O*C*H_2), 81.0 (*C*HO), 125.3 (Ar*C*), 127.4 (Ar*C*), 128.2 (Ar*C*), 138.2 (Ar*Cipso*), 169.3 (N*C*O).

MS (*m/z*):

317 (M^+).

Analysis for $C_{19}H_{27}NO_3$:

Calculated: C, 71.89; H, 8.57; N, 4.41; Obtained: C, 72.04; H, 8.66; N, 4.42.

Optical rotation:

$[\alpha]_D^{25} = -144.6$ (*c* 2.6, $CHCl_3$).

General procedure for dissolving metal reduction of morpholinones 2.04a-c, 2.07:

To anhydrous liquid ammonia (distilled over sodium), was added sodium metal (10 equiv.) at –78 ^oC and the mixture was stirred for 15 minutes. To the resulting blue solution was added a solution of morpholinone (**2.04a-c**, **2.07**) dissolved in anhydrous THF. The mixture was stirred at -78 ^oC (3 minutes), methanol was added and the mixture was stirred at room temperature till ammonia was completely removed. Methanol was removed under reduced pressure and the residue was partitioned with ethyl acetate and water. The ethyl acetate layer was separated and the aqueous layer was extracted 3 times with ethyl acetate. The combined extracts were washed with brine solution, dried (Na_2SO_4) and concentrated to obtain crude product **2.05a-c** and **2.08**, which was purified by flash column chromatography.

(2*S*)-2-Hydroxy-4-methoxy-3,3,*N*-trimethylbutyramide (2.05a):

Prepared from **2.04a** (250 mg, 1.43 mmol) in THF (1.5 mL) and Na (329 mg, 14.3 mmol) in ammonia (10 mL). Purification by flash column chromatography (2/3 EA/PE) furnished 95 mg (63%) of **2.05a** as a gum.

IR ($CHCl_3$):

1666, 3431 cm^{-1}.

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

δ 1.0 (s, 6H, C(CH_3)$_2$), 2.85 (d, 3H, *J* = 5.1 Hz, NCH_3), 3.25 (d, 1H, *J* = 9.2 Hz, CH_2), 3.35 (d, 1H, *J* = 9.2 Hz, CH_2), 3.35 (s, 3H, OCH_3), 4.00 (d, 1H, *J* = 3.6 Hz, C*H*), 4.45 (d, 1H, *J* = 3.6 Hz, O*H*), 6.80 (bs, 1H, N*H*).

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

δ 20.2 ($C(CH_3)_2$)), 21.6 ($C(CH_3)_2$)), 25.3 (NCH_3), 38.4 (*Cquat*), 59.1 (OCH_3), 77.9 (OCH_2), 81.7 (*C*HO), 172.9 (N*C*O).

MS (*m/z*):

175 (M^+).

Analysis for $C_8H_{17}NO_3$:

Calculated: C, 54.84; H, 9.78; N, 7.99; Obtained: C, 54.99; H, 9.97; N, 8.23.

(2*S*)-3-Ethyl-2-hydroxy-3-methoxymethyl-pentanoic acid methylamide (2.05b):

Prepared from **2.04b** (300 mg, 0.94 mmol) in THF (1.5 mL) and Na (216 mg, 9.4 mmol) in ammonia (10 mL). Purification by flash column chromatography (2/3 EA/PE) furnished 124 mg (65%) of **2.05b** as a gum.

IR ($CHCl_3$):

1657, 3383 cm^{-1}.

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

δ 0.70-1.0 (m, 6H, CH_3CH_2), 1.20-1.75 (m, 4H, CH_2CH_3), 2.81 (d, 3H, J = 4.7 Hz, NCH_3), 3.32 (s, 3H, OCH_3), 3.34-3.40 (m, 2H, CH_2OCH_3), 3.57 (bs, 1H, OH), 4.12 (s, 1H, C*H*OH), 6.94 (bs, 1H, N*H*CO).

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

δ 7.6 (CH_3CH_2), 7.7 (CH_3CH_2), 23.4 (CH_3CH_2), 23.9 (CH_3CH_2), 25.6 (NCH_3), 43.3 (*Cquat*), 59.2 (OCH_3), 76.6 (*C*HO), 78.1 (OCH_2), 173.4 (N*C*O).

HRMS:

Calculated: 203.1521; Found: 203.1524.

Optical rotation:

$[\alpha]_D^{25} = -51.6$ (*c* 0.8, $CHCl_3$).

(2*S*)-3-Allyl-2-hydroxy-3-methoxymethyl-hex-5-enoicacid methylamide (2.05c):

Prepared from **2.04c** (430 mg, 1.25 mmol) in THF (2 mL) and Na (288 mg, 12.5 mmol) in ammonia (12 mL). Purification by flash column chromatography (1/1 EA/PE) furnished 159 mg (56%) of **2.05c** as a gum.

IR ($CHCl_3$):

1659, 3421 cm^{-1}.

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

δ 2.02-2.29 (m, 2H, *allylic* CH_2), 2.30-2.50 (m, 2H, *allylic* CH_2), 2.82 (d, 3H, *J* = 5.1 Hz, NCH_3), 3.32 (s, 3H, OCH_3), 3.35-3.43 (m, 2H, CH_2OCH_3), 4.14 (s, 1H, C*H*OH), 5.0-5.17 (m, 4H, *olefinic* CH_2), 5.68-6.20 (m, 2H, *olefinic* C*H*), 6.90 (bs, 1H, N*H*CO).

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

δ 25.7 (*C*H_3NH), 35.8 (*allylic C*H_2), 36.6 (*allylic C*H_2), 43.7 (*Cquat*), 59.2 (O*C*H_3), 76.3 (*C*HO), 77.9 (O*C*H_2), 118.4 (*C*H_2=CH), 133.8 (*C*H=CH_2), 172.9 (N*C*O).

MS (m/z):

227 (M^+).

Analysis for $C_{12}H_{21}NO_3$:

Calculated: C, 63.41; H, 9.31; N, 6.16; Obtained: C, 63.70; H, 9.43; N, 6.42.

Optical rotation:

$[\alpha]_D^{25} = -47.5$ (*c* 0.8, $CHCl_3$).

(2*S*)-2-Hydroxy-2-(1-methoxymethyl-cyclopentyl)-*N*-methyl-acetamide (2.08):

Prepared from **2.07** (100 mg, 0.31 mmol) in THF (0.5 mL) and Na (71 mg, 3.1 mmol) in ammonia (6 mL). Purification by flash column chromatography (1/1 EA/PE) furnished 40 mg (63%) of **2.08** as a solid.

IR ($CHCl_3$):

1659, 3371 cm^{-1}.

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

δ 1.30-2.10 (m, 8H, cyclopentyl CH_2), 2.83 (d, 3H, *J* = 5.0 Hz, NCH_3), 3.12-3.41 (m, 2H, CH_2O), 3.33 (s, 3H, OCH_3), 3.59 (bs, 1H, O*H*), 3.98 (s, 1H, C*H*CO), 6.89 (bs, 1H, N*H*CO).

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

δ 24.8 (*C*H_2), 25.2 (*C*H_2), 25.7 (N*C*H_3), 32.0 (*C*H_2), 32.3 (*C*H_2), 49.8 (*Cquat*), 59.3 (O*C*H_3), 79.1 (*C*HO), 79.5 (*C*H_2O), 173.6 (N*C*O).

MS (*m/z*):

201 (M^+).

Analysis for $C_{10}H_{19}NO_3$:

Calculated: C, 59.68; H, 9.51; N, 6.96; Obtained: C, 59.82; H, 9.75; N, 7.15.

Optical rotation:

$[\alpha]_D^{25} = -47.7$ (*c* 1.3, $CHCl_3$).

(2*S*)-2-Hydroxy-3-methoxymethyl-3-propyl-hexanoic acid methylamide (2.05d):

To a solution of **2.05c** (80 mg, 0.35 mmol) in ethyl acetate (8 mL) was added 10% Pd/C (20 mg) and the mixture was stirred under an atmosphere of hydrogen (1 atm.) for 12 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give 80 mg (99%) of **2.05d** as a clear colorless gum.

IR ($CHCl_3$):

1659, 3381 cm^{-1}.

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

δ 0.78-0.95 (m, 6H, C*H*$_3$CH$_2$), 1.05-1.73 (m, 8H, C*H*$_2$CH$_3$), 2.81 (d, 3H, *J* = 5.0 Hz, NC*H*$_3$), 3.31 (s, 3H, OC*H*$_3$), 3.32-3.43 (m, 2H, C*H*$_2$OCH$_3$), 3.92 (bs, 1H, O*H*), 4.11 (s, 1H, C*H*OH), 6.90 (bs, 1H, N*H*CO).

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

δ 14.7 (2x*C*H$_3$), 16.2 (*C*H$_2$), 16.3 (*C*H$_2$), 25.4 (N*C*H$_3$), 33.6 (*C*H$_2$), 34.3 (*C*H$_2$), 43.1 (*Cquat*), 59.0 (O*C*H$_3$), 76.8 (*C*HO), 78.4 (*C*H$_2$O), 173.3 (N*C*O).

MS (*m/z*):

231 (M^+).

Analysis for $C_{12}H_{25}NO_3$:

Calculated: C, 62.30; H, 10.89; N, 6.05; Obtained: C, 62.55; H, 11.10; N, 6.33.

Optical rotation:

$[\alpha]_D^{25} = -39.4$ (*c* 1.4, $CHCl_3$).

General procedure for lactonization

To a stirred solution of **2.05a,b,d** and **2.08** in anhydrous dichloromethane was added at –78 ^oC boron tribromide (1M solution in DCM) and the resulting reaction mixture was gradually warmed to –15 ^oC with continuous stirring. Reaction was kept at –15 ^oC for 2 h and water was then added over a period of five minutes. Further reaction mixture was stirred for 15 minutes and 6M H_2SO_4 was added. The mixture was then stirred overnight (approximately 12 h) during which time it warmed to ambient temperature. The mixture was then cooled in an ice bath and neutralized by addition of

small portions of solid sodium bicarbonate. The resulting semi-solid residue was then extracted with hot dichloromethane. The combined dichloromethane extracts were dried (Na_2SO_4) and concentrated to obtain the crude lactone (which was purified by flash column chromatography.

(3*S*)-3-Hydroxy-4,4-dimethyl-dihydro-furan-2-one (2.09a):

Demethylation of **2.05a** (120 mg 0.92 mmol) in anhydrous dichloromethane (7 mL) with 1M boron tribromide solution in DCM (9.2 mL, 9.2 mmol) followed by addition of water (3.5 mL) and 6M H_2SO_4 (3.5 mL), gave after purification by flash column chromatography (2/3 EA/PE) 62 mg (70 %) of **2.09a** as a white solid.

mp: 90-91 ^oC

IR ($CHCl_3$):

1782, 3446 cm^{-1}.

^{1}H NMR (500 $CDCl_3$):

δ 1.11 (s, 3H, C*H*$_3$C), 1.26 (s, 3H, C*H*$_3$C), 2.34 (bs, 1H, OH), 3.97 (d, 1H, *J* = 9.1 Hz, OC*H*$_2$), 4.05 (d, 1H, *J* = 9.1 Hz, C*H*$_2$O), 4.14 (s, 1H, C*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$):

δ 18.8 (C(*C*H$_3$)$_2$)), 22.9 (C(*C*H$_3$)$_2$)), 40.9 (*C*(CH$_3$)$_2$)), 75.8 (*C*HO), 76.3 (*C*H$_2$O), 177.3 (O*C*O).

MS (*m/z*):

130 (M^+).

Analysis for $C_6H_{10}O_3$:

Calculated: C, 55.37; H, 7.74; Obtained: C, 55.65; H, 7.96.

Optical rotation:

$[\alpha]_D^{25}$ = +51.8 (*c* 2, H_2O).

Reported value $[\alpha]_D^{25}$ = +50.1 (*c* 2.0, H_2O).[30]

Reported value $[\alpha]_D^{25}$ = +51.6 (*c* 2.0, H_2O).[18a]

Enantiomeric excess of **2.09a** was 91% by GC analysis on a chiral column.

(3*S*)-4,4-Diethyl-3-hydroxy-dihydro-furan-2-one (2.09b):

Demethylation of **2.05b** (80 mg 0.39 mmol) in anhydrous dichloromethane (6 mL) with 1M boron tribromide solution in DCM (3.9 mL, 3.9 mmol) followed by

addition of water (3 mL) and 6M H_2SO_4 (3 mL), gave after purification by flash column chromatography (1/4 EA/PE) 60 mg (97%) of **2.09b** as a gum.

IR ($CHCl_3$):

1776, 3445 cm^{-1}.

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

δ 0.80-1.02 (m, 6H, C*H*$_3$CH$_2$), 1.32-1.74 (m, 4H, C*H*$_2$CH$_3$), 2.95 (bs, 1H, O*H*), 3.87 (d, 1H, *J* = 9.4 Hz, OC*H*$_2$), 4.15 (d, 1H, *J* = 9.4 Hz, OC*H*$_2$), 4.23 (s, 1H, C*H*OH).

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

δ 8.1 (*C*H$_3$CH$_2$), 8.4 (*C*H$_3$CH$_2$), 21.5 (*C*H$_2$CH$_3$), 28.1 (*C*H$_2$CH$_3$), 46.5 (*Cquat*), 73.1 (*C*H$_2$O), 74.7 (*C*HO), 178.6 (O*C*O).

MS (*m/z*):

158 (M^+).

Analysis for $C_8H_{14}O_3$:

Calculated: C, 60.74; H, 8.92; Obtained: C, 60.97; H, 9.05.

Optical rotation:

$[\alpha]_D^{25}$ = +14.9 (*c* 1.95, MeOH).

Reported value for (*R*)-isomer $[\alpha]_D^{25}$ = –13.0 (*c* 18.0, MeOH).[20f]

Reported value for (*R*)-isomer $[\alpha]_D^{25}$ = –12.0 (*c* 0.33, MeOH).[19]

Enantiomeric excess of **2.09b** was 91% by GC analysis on a chiral column.

(3*S*)-3-Hydroxy-4,4-dipropyl-dihydro-furan-2-one (2.09c):

Demethylation of **2.05d** (100 mg 0.43 mmol) in anhydrous dichloromethane (6 mL) with 1M boron tribromide solution in DCM (4.3 mL, 4.3 mmol) followed by addition of water (3.5 mL) and 6M H_2SO_4 (3.5 mL), gave after purification by flash column chromatography (1/4 EA/PE) 71 mg (88%) of **2.09c** as a clear colorless gum which solidifies below 5 ^oC.

IR ($CHCl_3$):

1774, 3448 cm^{-1}.

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

δ 0.76-1.09 (m, 6H, C*H*$_3$CH$_2$), 1.11-1.65 (m, 8H, C*H*$_2$C*H*$_2$), 3.29 (bs, 1H, O*H*), 3.86 (d, 1H, *J* = 9.3 Hz, OC*H*$_2$), 4.13 (d, 1H, *J* = 9.3 Hz, OC*H*$_2$), 4.21 (s, 1H, C*H*OH).

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

δ 14.6 (*C*H_3), 14.7 (*C*H_3), 17.0 (*C*H_2), 17.3 (*C*H_2), 31.9 (*C*H_2), 38.4 (*C*H_2), 46.2 (*Cquat*), 73.8 (*C*H_2O), 74.8 (*C*HO), 178.6 (O*C*O).

MS (*m/z*):

186 (M^+).

Analysis for $C_{10}H_{18}O_3$:

Calculated: C, 64.49; H, 9.74; Obtained: C, 64.71; H, 9.97.

Optical rotation:

$[\alpha]_D^{25}$ = +8.4 (*c* 3.8, $CHCl_3$).

Enantiomeric excess of **2.09c** was 92% by GC analysis on a chiral column.

(3*S*)-4-Hydroxy-2-oxa-spiro[4.4] nonan-3-one (Spiro-pantolactone, 2.09d):

Demethylation of **2.08** (90 mg, 0.45 mmol) in anhydrous dichloromethane (6 mL) with 1M boron tribromide solution in DCM (4.5 mL, 4.5 mmol) followed by addition of water (3.5 mL) and 6M H_2SO_4 (3.5 mL), gave after purification by flash column chromatography (2/3 EA/PE) 64 mg (92%) of **2.09d** as a solid.

mp: 80-81 ^oC

IR ($CHCl_3$):

1780, 3402 cm^{-1}.

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

δ 1.30-2.12 (m, 8H, cyclopentyl C*H*$_2$), 2.43 (bs, 1H, O*H*), 4.01 (d, 1H, *J* = 9.0 Hz, C*H*$_2$O), 4.12 (d, 1H, *J* = 9.0 Hz, C*H*$_2$O), 4.28 (s, 1H, C*H*CO).

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

δ 24.9 (*C*H_2), 25.1 (*C*H_2), 29.2 (*C*H_2), 33.8 (*C*H_2), 51.7 (*Cquat*), 73.8 (*C*HO), 75.9 (*C*H_2O), 177.3 (O*C*O).

MS (*m/z*):

156 (M^+).

Analysis for $C_8H_{12}O_3$:

Calculated: C, 61.52; H, 7.74; Obtained: C, 61.70; H, 7.85.

Optical rotation:

$[\alpha]_D^{25}$ = +18.6 (*c* 0.70, $CHCl_3$).

Reported optical rotation for (*R*)-isomer $[\alpha]_D^{25}$ = –19.3 (*c* 1.5, $CHCl_3$).[19]

Enantiomeric excess of **2.09d** was 94% by GC analysis on a chiral column.

2.7: References

1. (a) Kagan, F.; Heinzelman, R. V.; Weisblat, D. I.; Greiner, W. *J. Am. Chem. Soc.* **1957**, *79*, 3545. (b) Neidlein, R.; Greulich, P. *Helv. Chim. Acta* **1992**, *75*, 2545. (c) Fischer, G. C.; Turakhia, R. H.; Morrow, C. J. *J. Org. Chem.* **1985**, *50*, 2011. (d) Dolle, R. E.; Nicolou, K. C. *J. Am. Chem. Soc*. **1985**, *107*, 1691. (e) Lavallee, P.; Ruel, R.; Greiner, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679. (f) Sone, H.; Suenaga, K.; Bessho, Y.; Kondo, T.; Kigoshi, H.; Yamada, K. *Chem. Lett*. **1998**, *85*. (g) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Chem. Soc. Perkin Trans. 1*. **1991**, 490. (h) Kabeya, M.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1997**, *53*, 9769. (i) Okabe, M.; Sun, R.-C.; Zenchoff, G. B. *J. Org. Chem.* **1991**, *56*, 4392. (j) Wieland, T.; Buck, W.; Fischer, R. *Biochemische Zeitschrift* **1960**, *333*, 296. (k) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774. l) Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48.
2. (a) O'Meara, J. A.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. J.; *J. Org. Chem.* **1998**, *63*, 3117. (b) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641 and references therein. (c) Hansen, M. M.; Bertsch, C. F.; Harkness, A. R.; Huff, B. E.; Hutchison, D. R.; Khau, V. V.; LeTourneau, M. E.; Martinelli, M. J.; Misner, J. W.; Peterson, B. C.; Rieck, J. A.; Sullivan, K. A.; Wright, I. G. *J. Org. Chem.* **1998**, *63*, 775. (d) Trost, B. M.; Flygare, J. A. *Tetrahedron Lett.* **1994**, *35*, 4059. (e) Cassidy, M. A.; Crockett, N.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc. Perkin Trans. 1*. **1996**, *17*, 2079. (f) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700. (g) Helmchen, G.; Abdel, H. A. F.; Hartmann, H.; Karge, R.; Krotz, A.; Sartor, K.; Urmann, M. *Pure and Applied Chemistry* **1989**, *61*, 409.
3. Kuhn, R.; Wieland, T.; Moller, E. F. *Ber.* **1941**, *74*, 1605.
4. Winterbottom, R.; Clapp, J. W.; Miller, W. H.; English, J. P.; Roblin, R. O., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1393.
5. Roblin, R. O., Jr. *Chem. Rev.* **1946**, *38*, 255.
6. (a) Lehninger, A. L. Principles of Biochemistry; Worth Publishers Inc.: New York, 1987; pp. 256-257. (b) Brown, G. M.; Williamson, M. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1982**, *53*, 345.
7. Lipmann, F. *Science* **1954**, *120*, 855.

8. Shimizu, S.; Tani, Y.; Ogata, K. *Agric. Biol. Chem.* **1974**, *38*, 1989.
9. King, T. E.; Stewart, C. J.; Cheldelin, V. H. *J. Am. Chem. Soc.* **1953**, *75*, 1290.
10. Lacrampe, J. F.; Armand, F.; Eddy, E. J.; Deroose, D. F.; Fortin, J. M. C.; Coesemans, E.. PCT Int. Appl. WO 0110866 A1 20010215, 2001.
11. For studies on the resolution and enantioselective synthesis of pantolactone, see (a) Kesseler, M.; Hauer, B.; Friedrich, T.; Mattes, R. PCT Int. Appl. WO 2001032890 A1, **2001** (b) Haughton, L.; Williams, J. M.; Zimmerman, J. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1697. (c) Paetow, M.; Ahrens, D.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5323 and references therein.
12. (a) Fissekis, J. D.; Skinner, C. G.; Shive, W. *J. Am. Chem. Soc.* **1960**, *82*, 1654. (b) Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schriner, M. Ger. Offen. DE 19735574 A1 19990211 **1999** (CAN 130: 1681 62).
13. Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1986**, *51*, 1152.
14. Paetow, M.; Ahrens, H.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5323.
15. Rao, A. V. R.; Rao, S. M.; Sharma, G. V. M. *Tetrahedron Lett.* **1994**, *35*, 5735.
16. Effenberger, F.; Eichhorn, J.; Roos, J. *Tetrahedron: Asymmetry* **1995**, *6*, 271.
17. Upadhya, T. T.; Gurunath, S.; Sudalai, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2899.
18. (a) Pansare, S. V.; Jain, R. P. *Org. Lett.* **2000**, *2*, 175. (b) Pansare, S. V.; Bhattacharyya, A. *Tetrahedron* **2003**, *59*, 3275.
19. Evans, D. A.; Wu, J.; Masse, C. E.; MacMillan, D. W. C. *Org. Lett.* **2002**, *4*, 3379.
20. (a) Kagan, H. B.; Tahar, M.; Fiaud, J.-C. *Tetrahedron Lett.* **1991**, *32*, 5959. (b) Genet, J.-P.; Pinel, C.; Mallart, S.; Juge, S.; Cailhol, H.; Laffittee, J. A. *Tetrahedron Lett.* **1992**, *33*, 5343. (c) Takahashi, H.; Hattori, M.; Chiba, M.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4477. (d) Roucoux, A.; Agbossou, F.; Mortreux, A; Petit, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2279. (e) Chiba, M.; Takahashi, H.; Takahashi, H.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1987**, *28*, 3675. (f) Hata, H.; Shimizu, S.; Hattori, S.; Yamada, H. *J. Org. Chem.* **1990**, *55*, 4377. (g) Pasquier, C.; Eilers, J.; Reiners, I.; Martens, J.; Mortreux, A.; Agbossou, F. *Synlett* **1998**, 1162.
21. Ojima, I.; Kogure, T.; Terasaki, T.; Achiwa, K. *J. Org. Chem.* **1978**, *43*, 3444.
22. Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 1149.

23. Tani, K.; Suwa, K.; Tanigawa, E.; Ise, T.; Yamagata, T.; Tatsuno, Y.; Otsuka, S. *J. Organomet. Chem.* **1989**, *370*, 203.

24. (a) Roucoux, A.; Devocelle, M.; Carpentier, J. F.; Agbossou, F.; Mortreux, A. *Synlett* **1995**, 358. (b) Roucoux, A.; Suisse, I.; Devocelle, M.; Carpentier, J. F.; Agbossou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1996**, *7*, 379.

25. Pasquier, C.; Naili, S.; Pelinski, L.; Brocard, J.; Mortreux, A.; Agbossou, F. *Tetrahedron: Asymmetry* **1998**, *9*, 193.

26. Nakamura, K.; Kondo, S.; Kawai, Y.; Ohno, A. *Tetrahedron: Asymmetry* **1993**, *4*, 1253.

27. Lanzilotta, R. P.; Bradley, D. G.; McDonald, K. M. *Appl. Microb.* **1974**, *27*, 130.

28. Ford, J. H. *J. Am. Chem. Soc.* **1944**, *66*, 20.

29. Fizet, C. *Helv. Chim. Acta* **1986**, *69*, 404.

30. Stiller, E. T.; Harris, S. A.; Finkelstein, J.; Keresztesy, J. C.; Folkers, K. *J. Am. Chem. Soc.* **1940**, *62*, 1785.

31. Paust, J.; Pfohl, S.; Reif, W.; Schimdt, W. *Liebigs Ann. Chem*. **1978**, 1024.

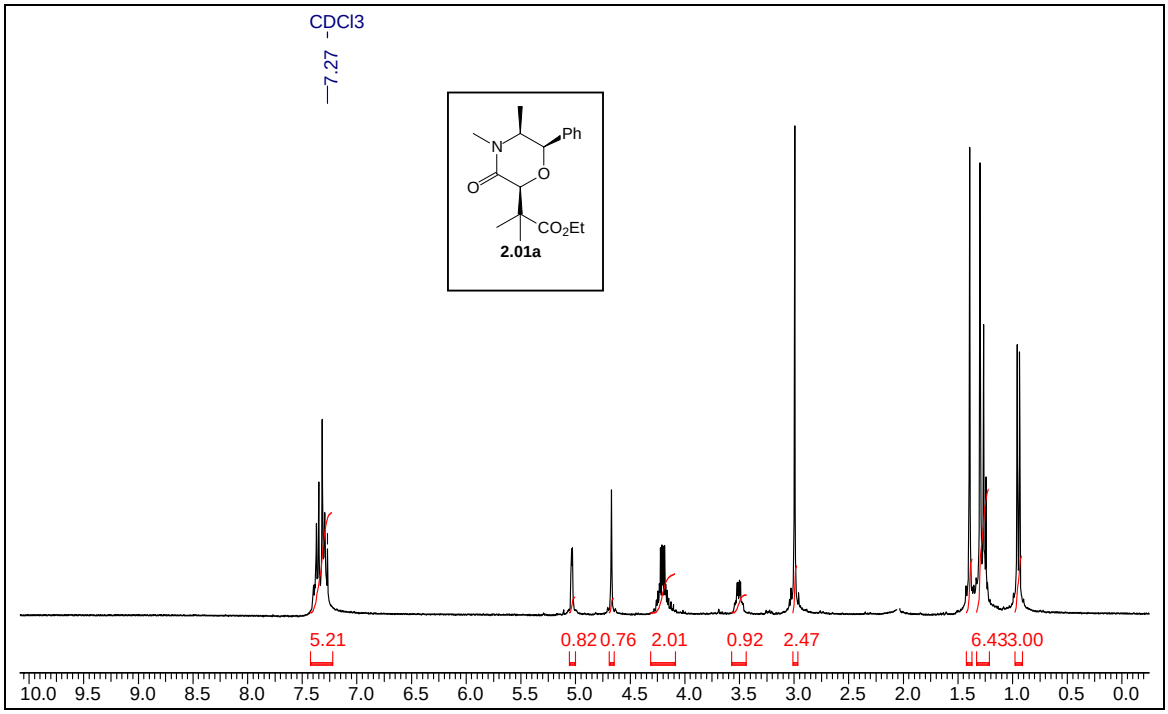
32. Beutel, R.; Tishler, M. *J. Am. Chem. Soc.* **1946**, *68*, 1463.

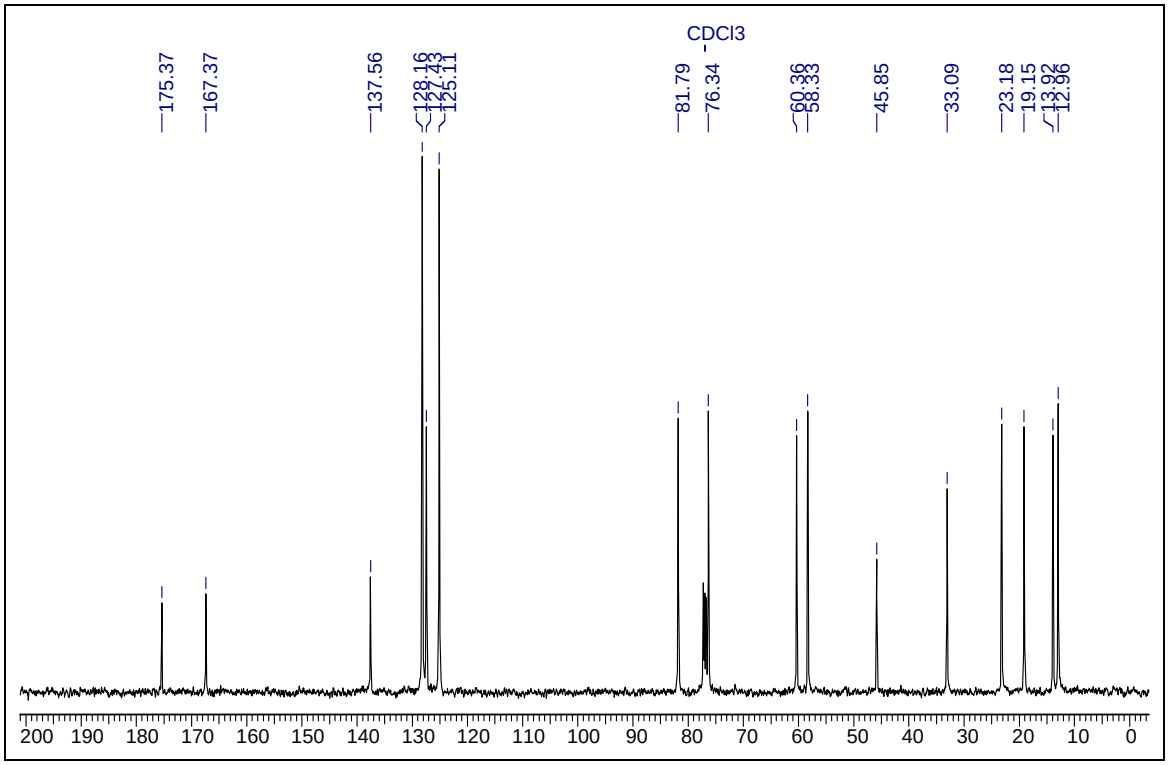
33. Fuji, K.; Node, M.; Murata, M.; Terada, S.; Hashimoto, M. *Tetrahedron Lett.* **1986**, *27*, 5381.

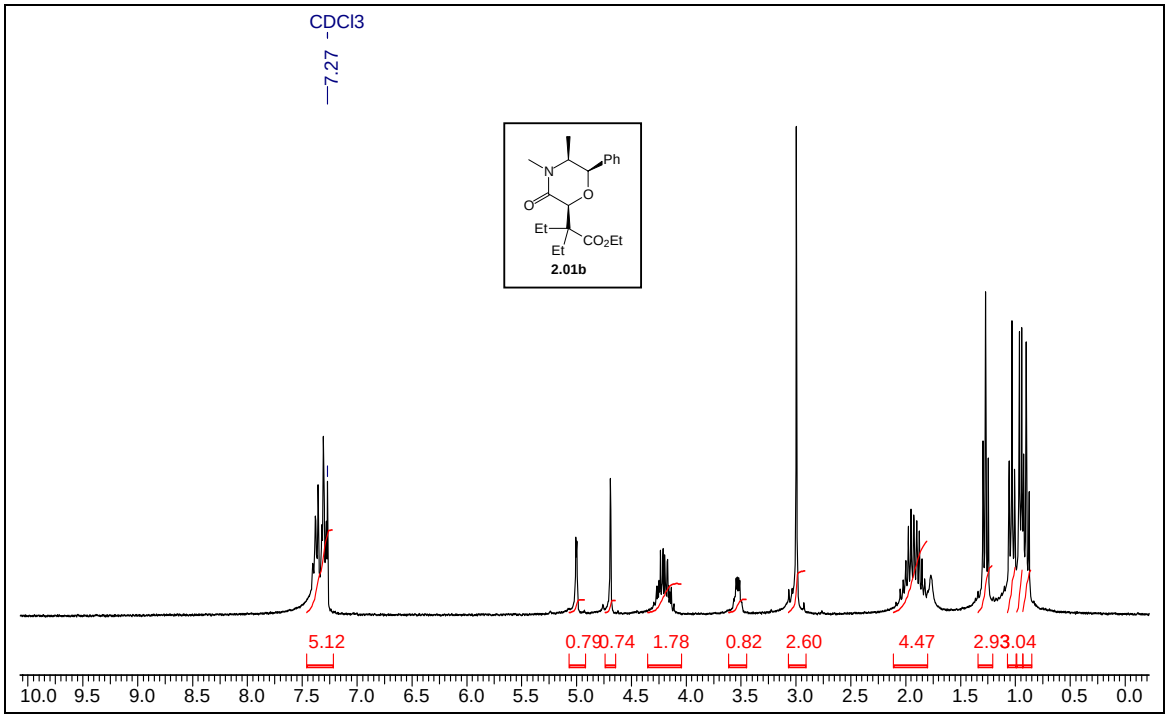
34. Baumann, M.; Hauer, B. H.; Bornscheuer, U. T. *Tetrahedron: Asymmetry* **2000**, *11*, 4781.

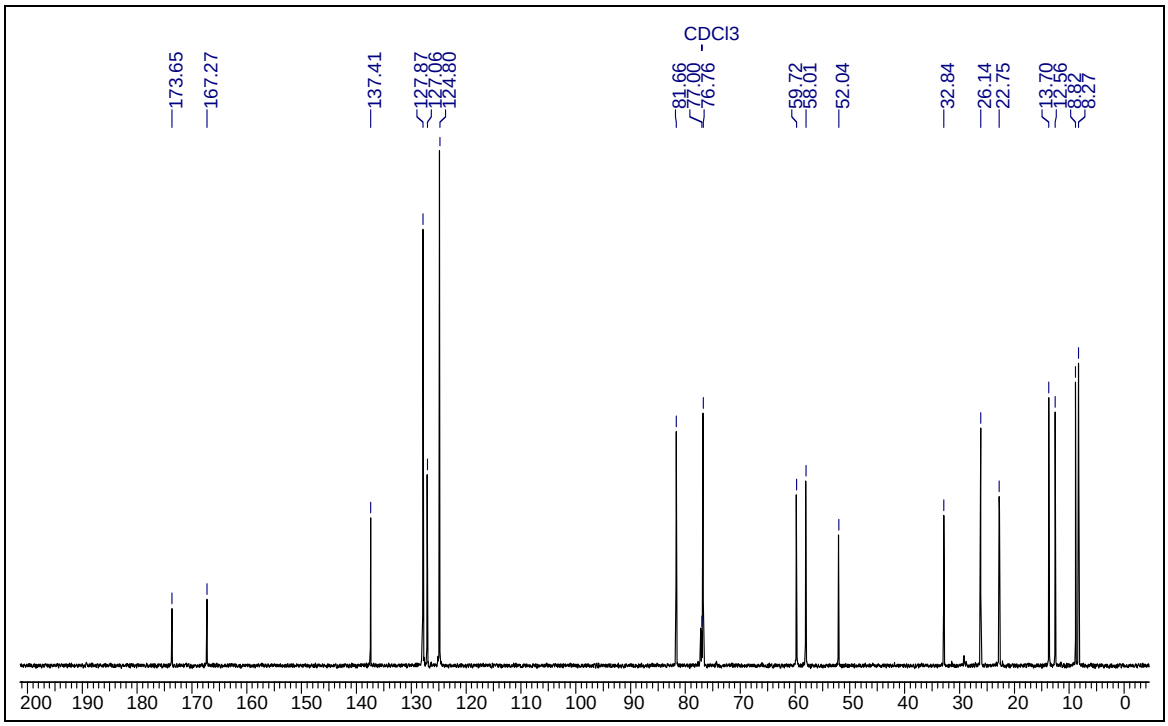
35. Fuelling, G.; Schudok, M. Ger. Offen. DE 4, 005, 150, 1990.

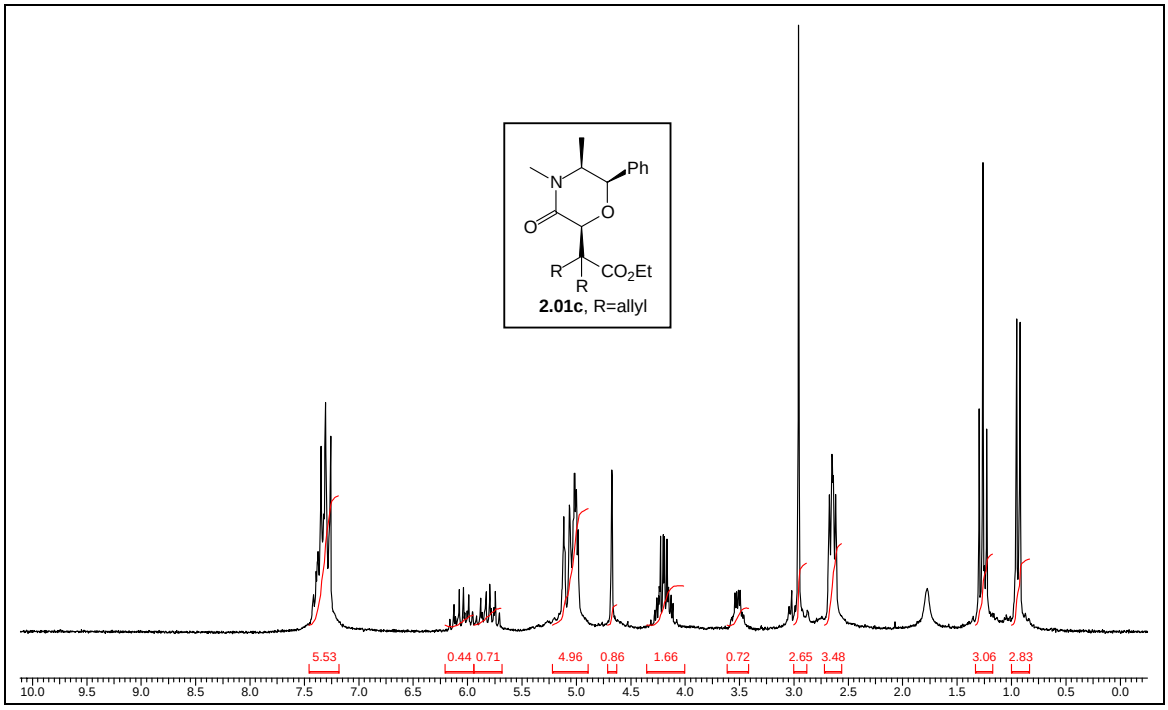
36. Bevinakatti, H. S.; Banerji, A. A.; Newadkar, R. V. *J. Org. Chem.* **1989**, *54*, 2453.

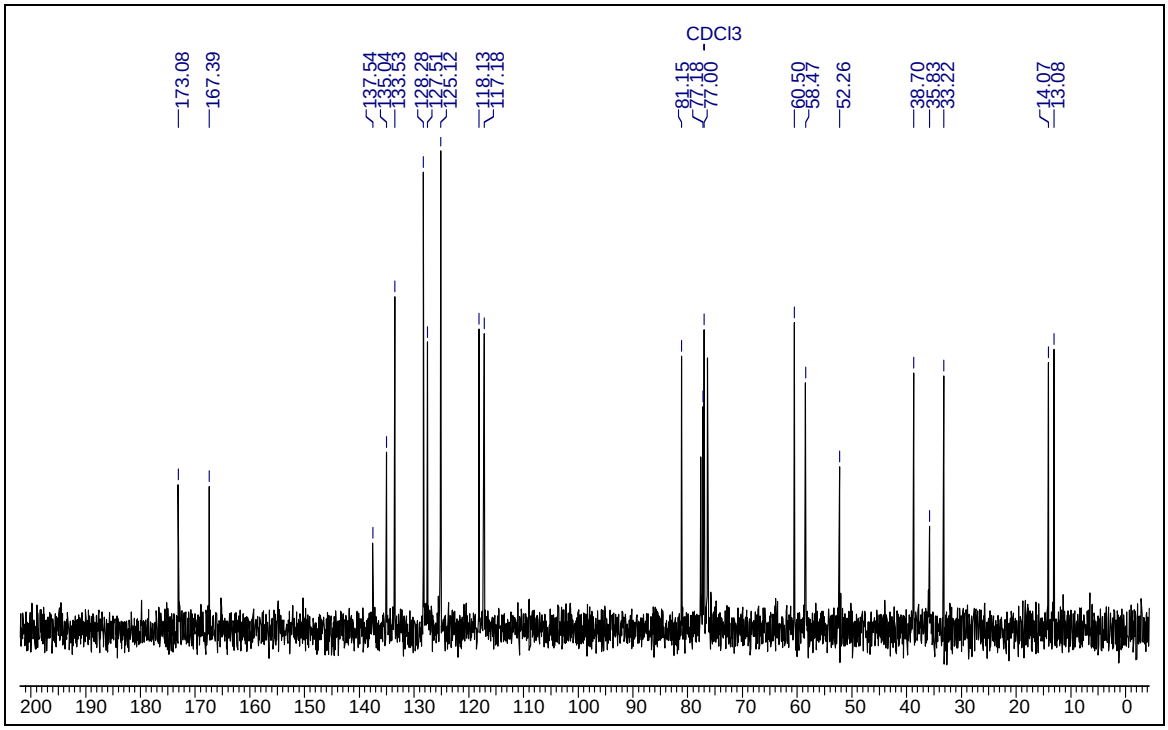

CDCl3
7.27
Ph
N
O
O
CO2Et
2.01a
5.21
0.82
0.76
2.01
0.92
2.47
6.43
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

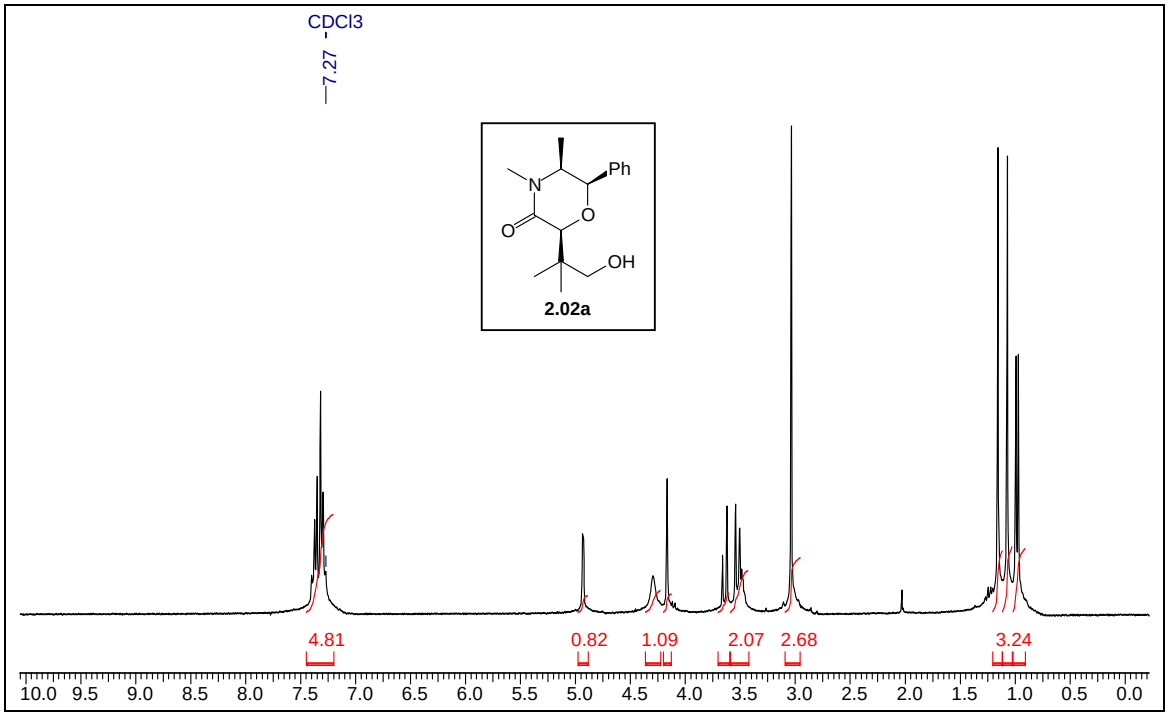

CDCl3
175.37
167.37
137.56
128.16
127.43
125.11
81.79
76.34
60.36
58.33
45.85
33.09
23.18
19.15
13.92
12.96
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

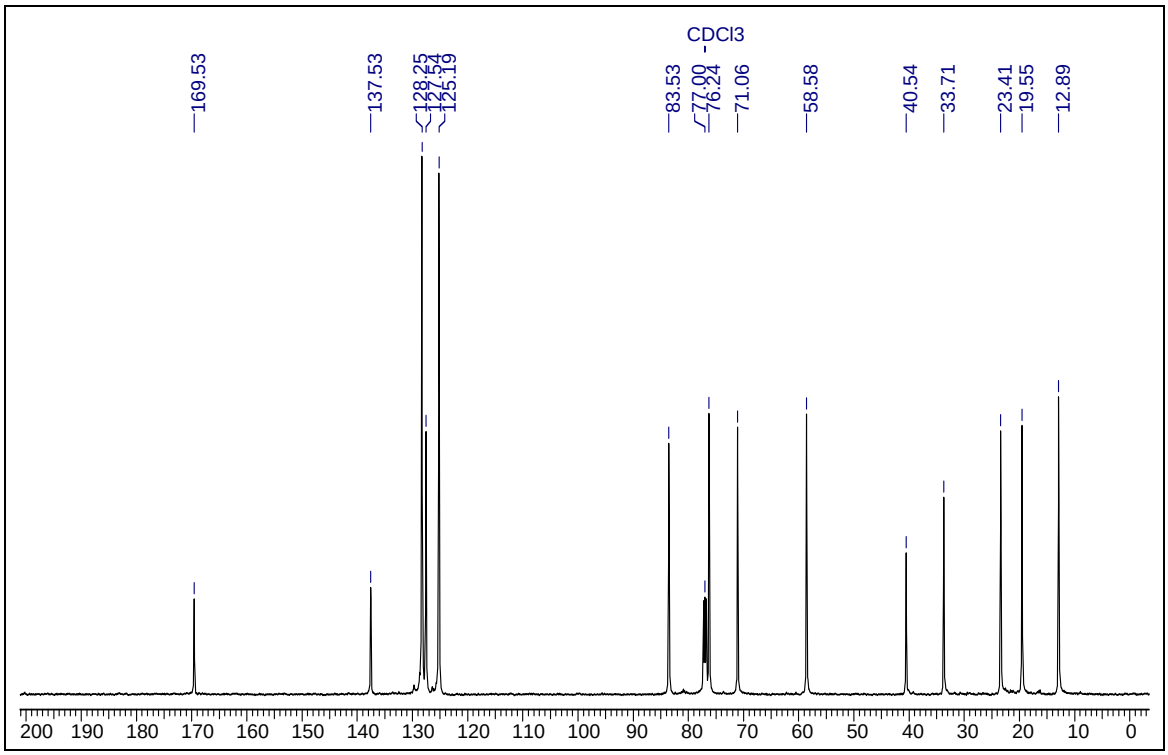

CDCl3
7.27
Ph
N
O
O
Et
Et
CO2Et
2.01b
5.12
0.79
0.74
1.78
0.82
2.60
4.47
2.93
3.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

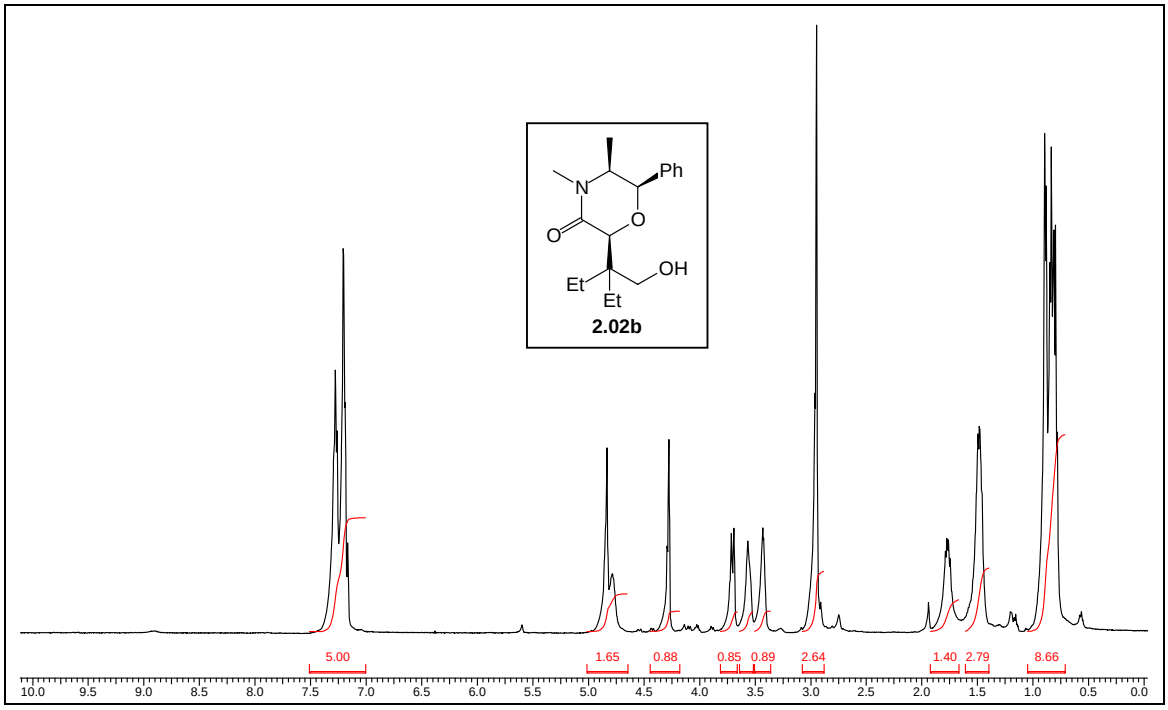

CDCl3
173.65
167.27
137.41
127.87
127.06
124.80
81.66
77.00
76.76
59.72
58.01
52.04
32.84
26.14
22.75
13.70
12.56
8.84
8.27
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

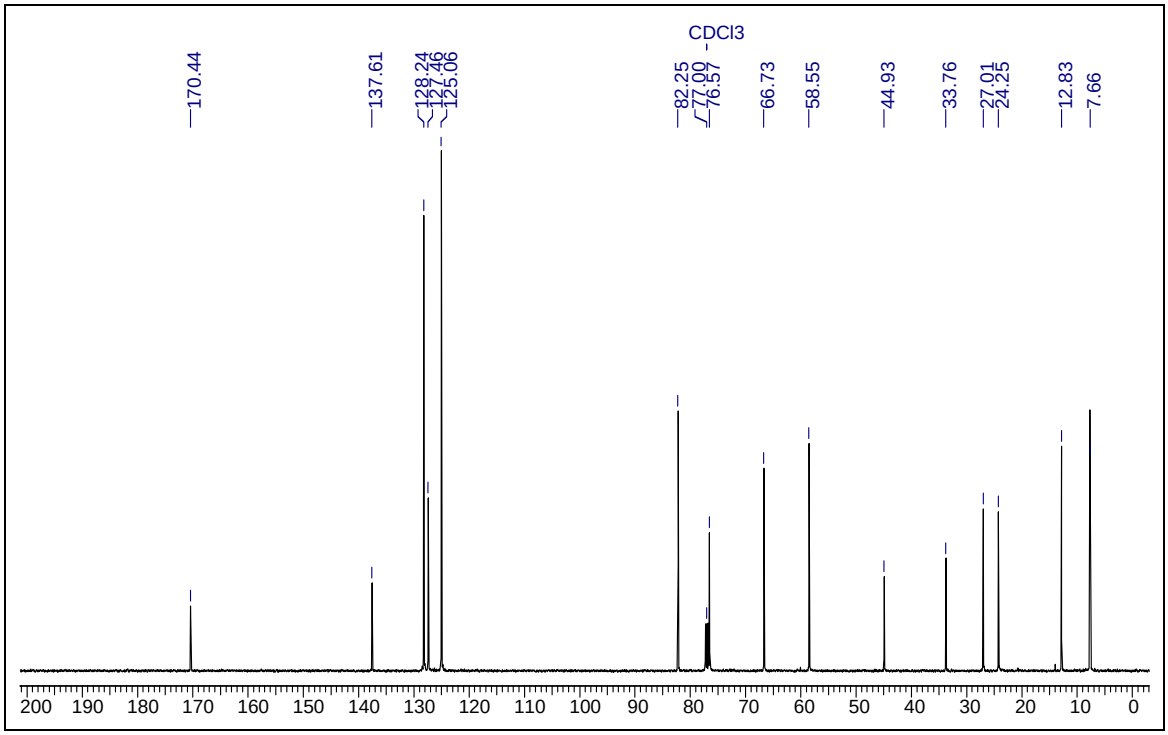

Ph
N
O
O
R
R
CO2Et
2.01c, R=allyl
5.53
0.44
0.71
4.96
0.86
1.66
0.72
2.65
3.48
3.06
2.83
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

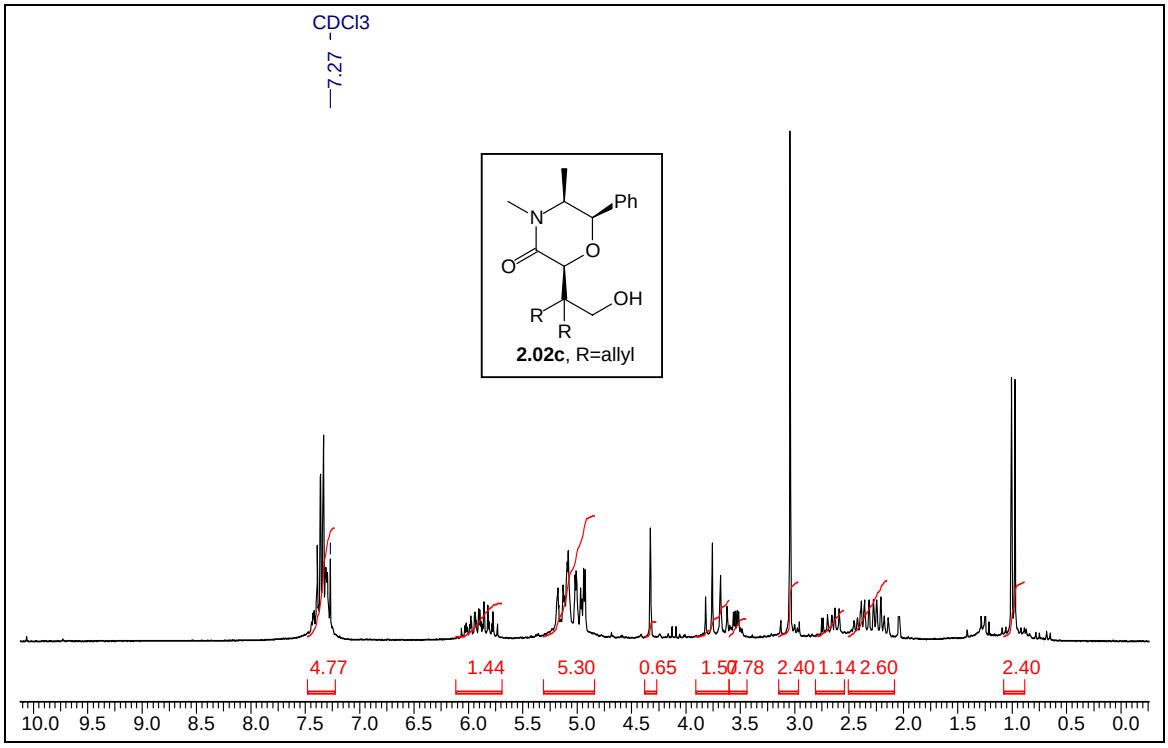

CDCl3
173.08
167.39
137.54
133.04
133.53
128.28
127.51
125.12
118.13
117.18
81.15
77.18
77.00
60.50
58.47
52.26
38.70
35.83
33.22
14.07
13.08
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

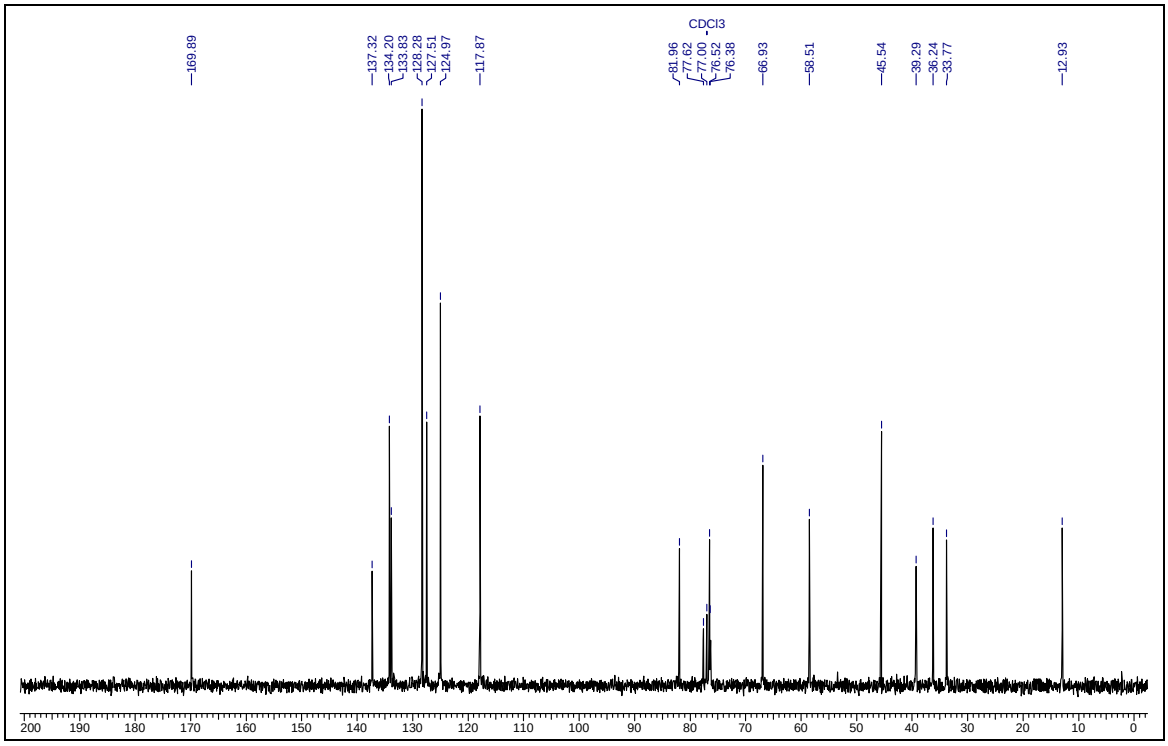

CDCl3
7.27
Ph
N
O
O
OH
2.02a
4.81
0.82
1.09
2.07
2.68
3.24
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

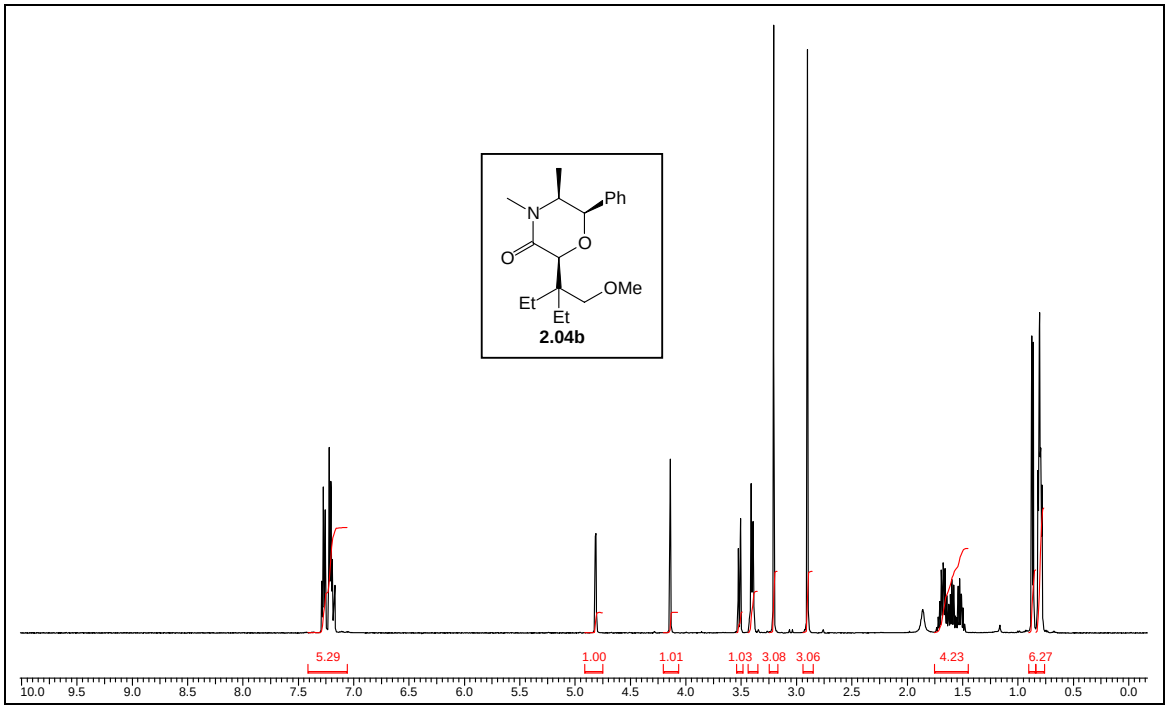

CDCl3
169.53
137.53
128.25
127.54
125.19
83.53
77.00
76.24
71.06
58.58
40.54
33.71
23.41
19.55
12.89
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

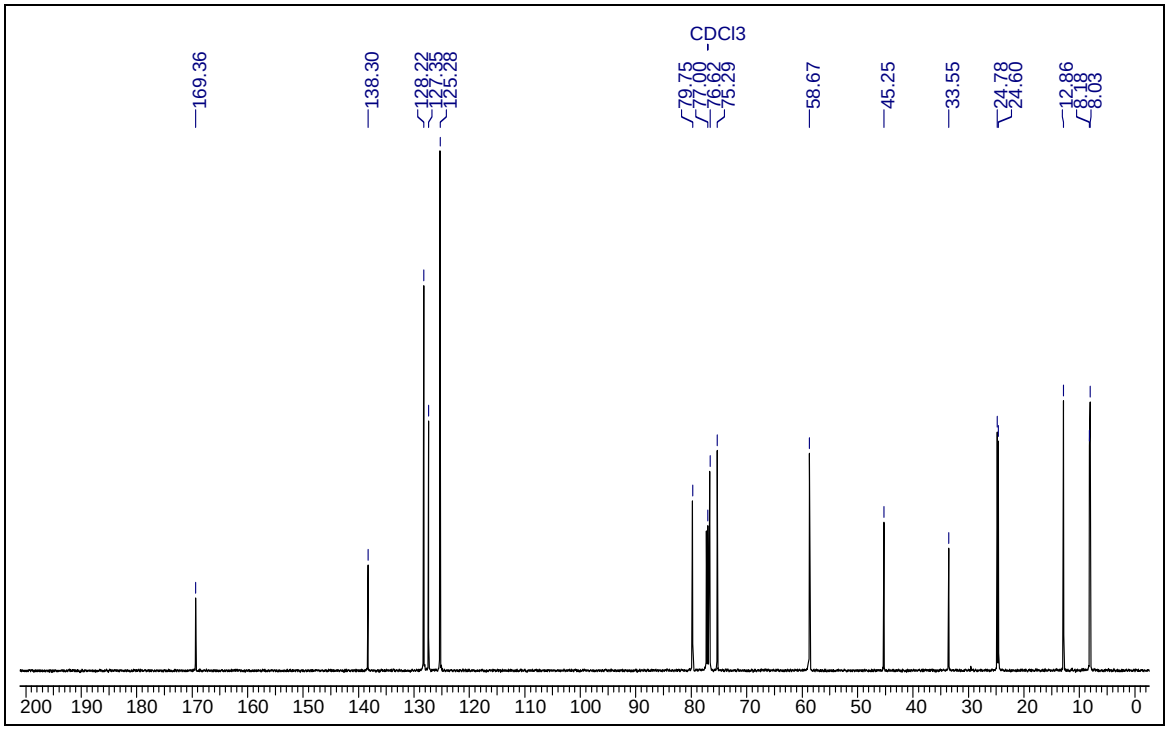

Ph
N
O
O
OH
Et
Et
2.02b
5.00
1.65
0.88
0.85
0.89
2.64
1.40
2.79
8.66
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

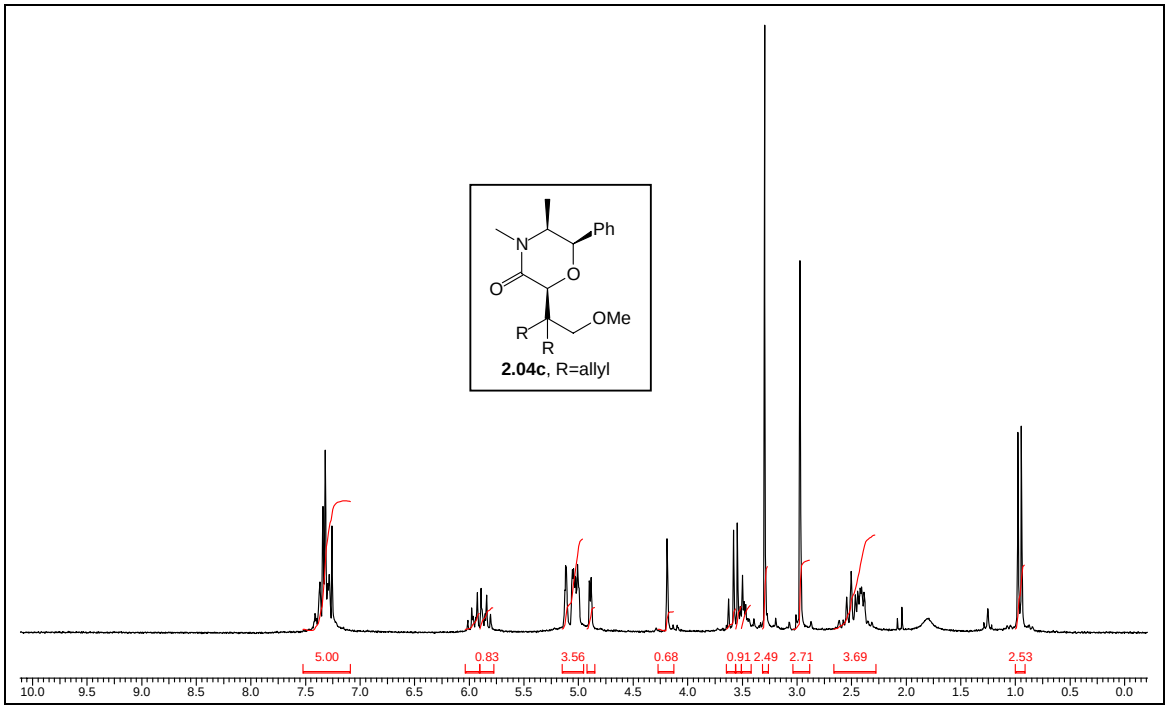

CDCl3
170.44
137.61
128.24
127.46
125.06
82.25
77.00
76.57
66.73
58.55
44.93
33.76
27.01
24.25
12.83
7.66
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

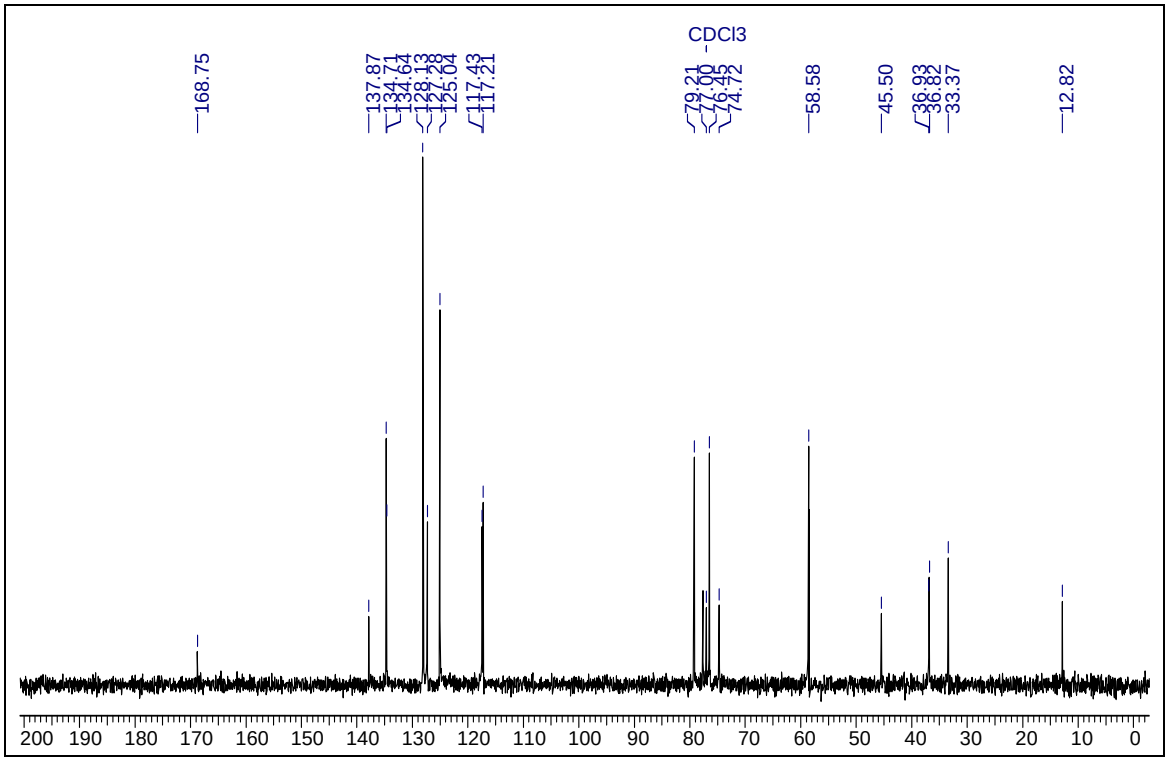

CDCl3
7.27
Ph
N
O
O
OH
R
R
2.02c, R=allyl
4.77
1.44
5.30
0.65
1.50
0.78
2.40
1.14
2.60
2.40
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

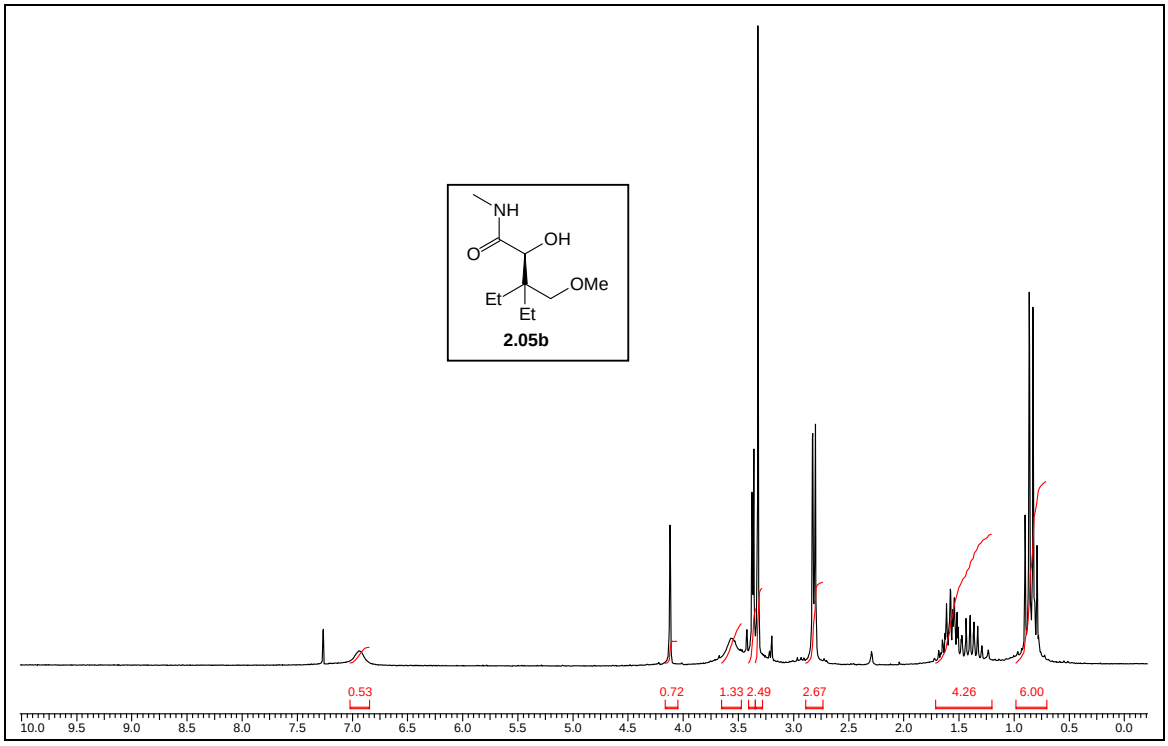

169.89
137.32
134.20
133.83
128.28
127.51
124.97
117.87
CDCl3
81.96
77.62
77.00
76.52
76.38
66.93
58.51
45.54
39.29
36.24
33.77
12.93
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

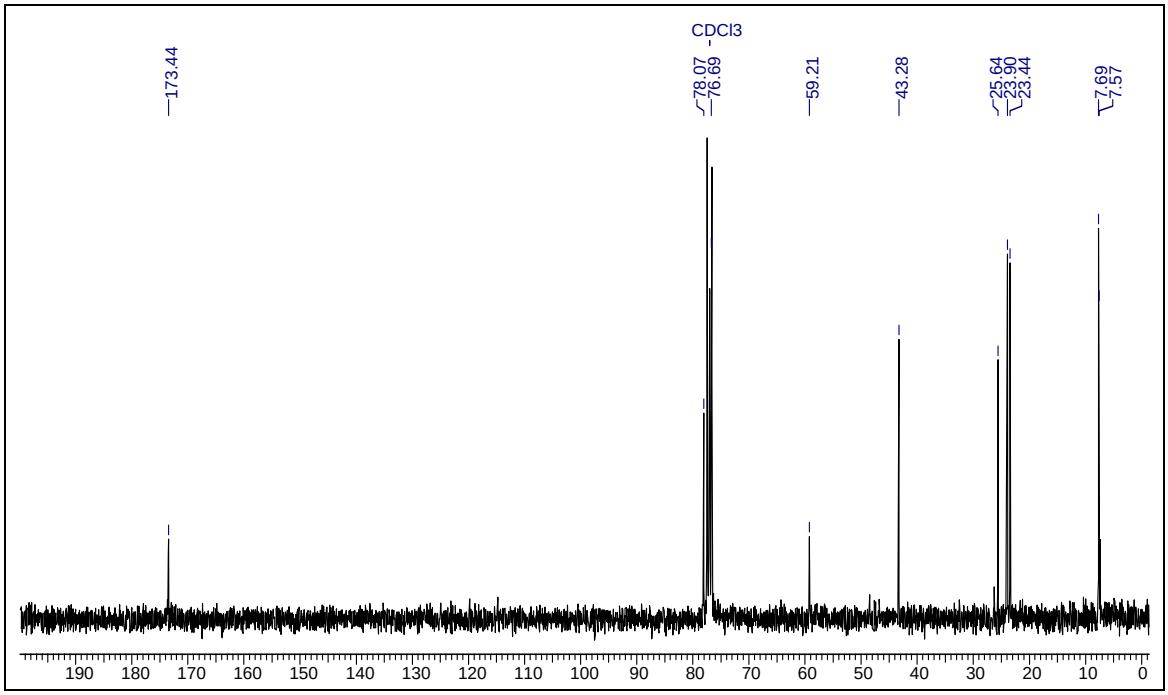

Ph
N
O
O
OMe
Et
Et
2.04b
5.29
1.00
1.01
1.03
3.08
3.06
4.23
6.27

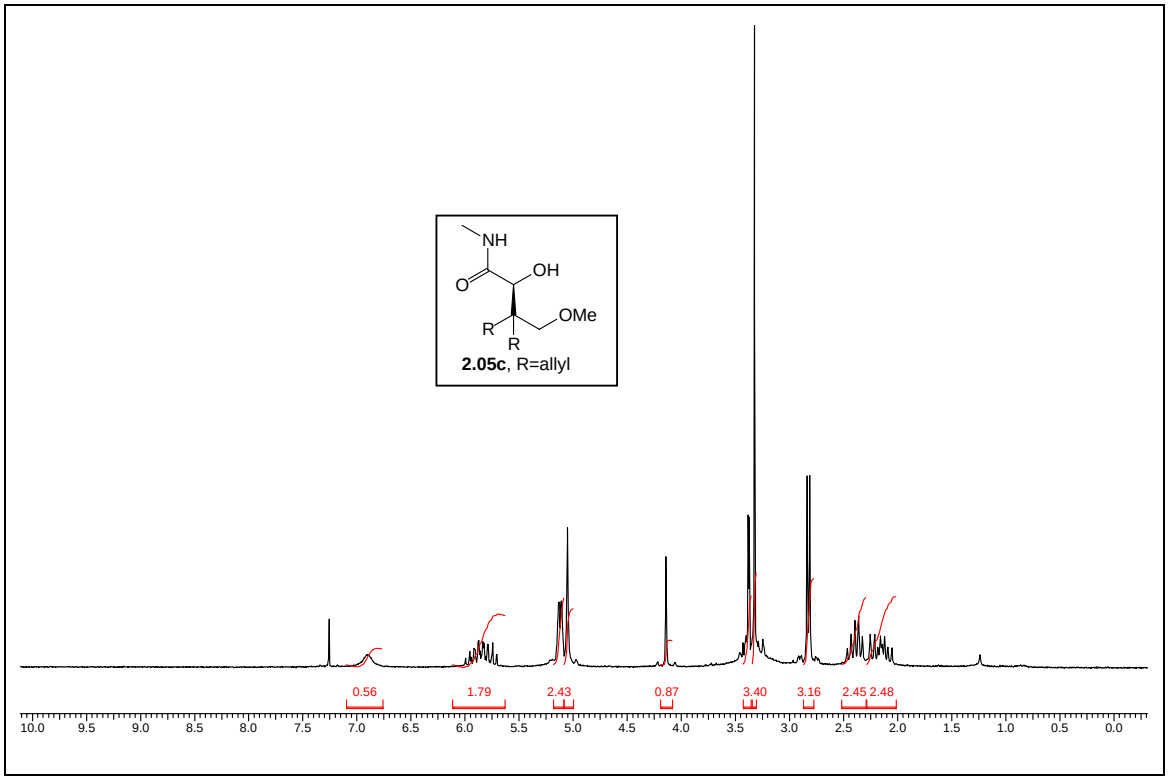

CDCl3
169.36
138.30
128.22
127.35
125.28
79.75
77.00
76.62
75.29
58.67
45.25
33.55
24.78
24.60
12.86
8.18
8.03

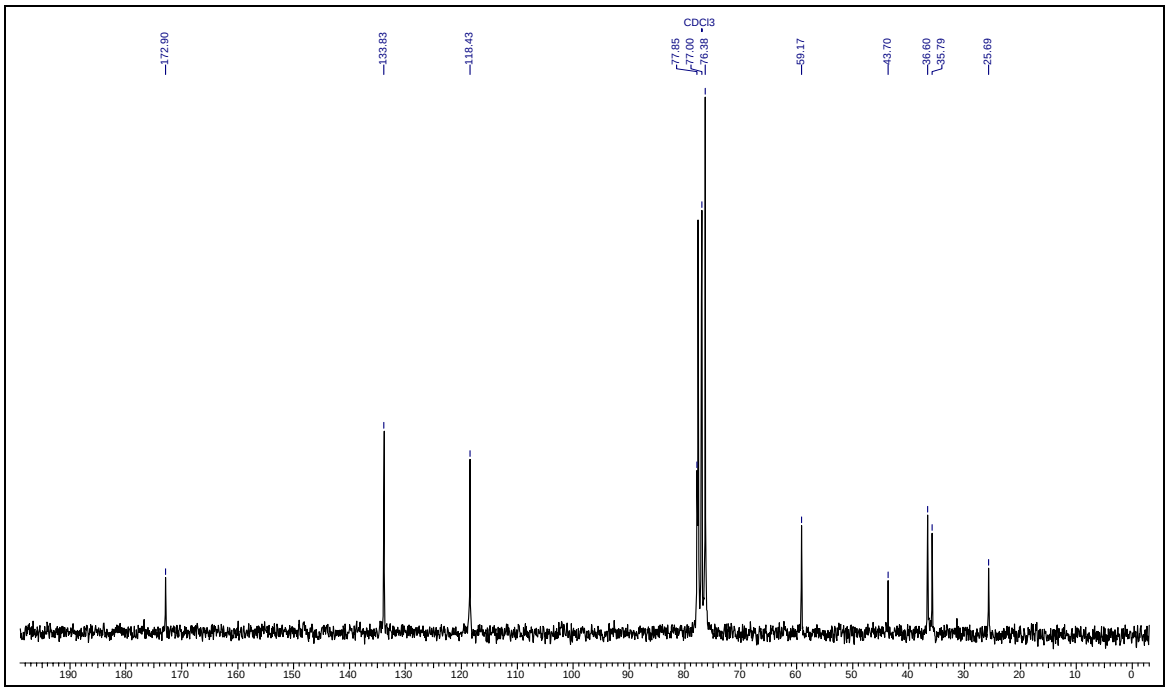

Ph
N
O
O
OMe
R
R
2.04c, R=allyl
5.00
0.83
3.56
0.68
0.91
2.49
2.71
3.69
2.53
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

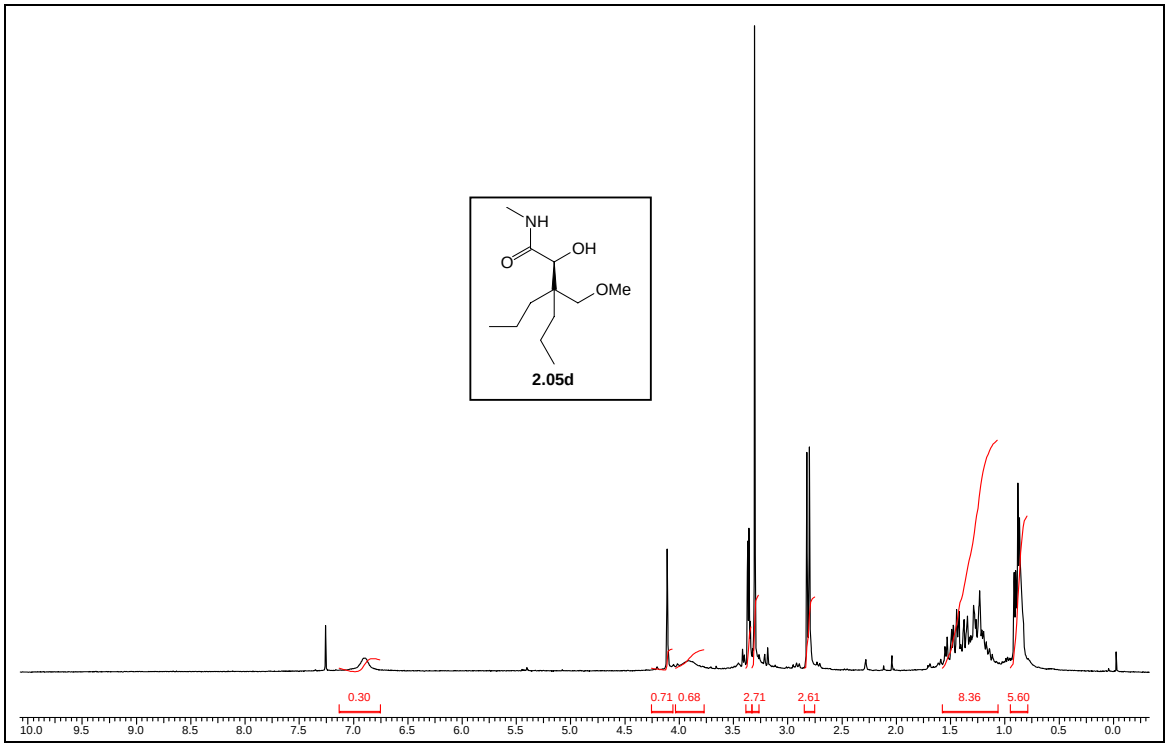

CDCl3
168.75
137.87
134.71
134.64
128.13
127.28
125.04
117.43
117.21
79.21
77.00
76.79
74.72
58.58
45.50
36.93
36.82
33.37
12.82
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

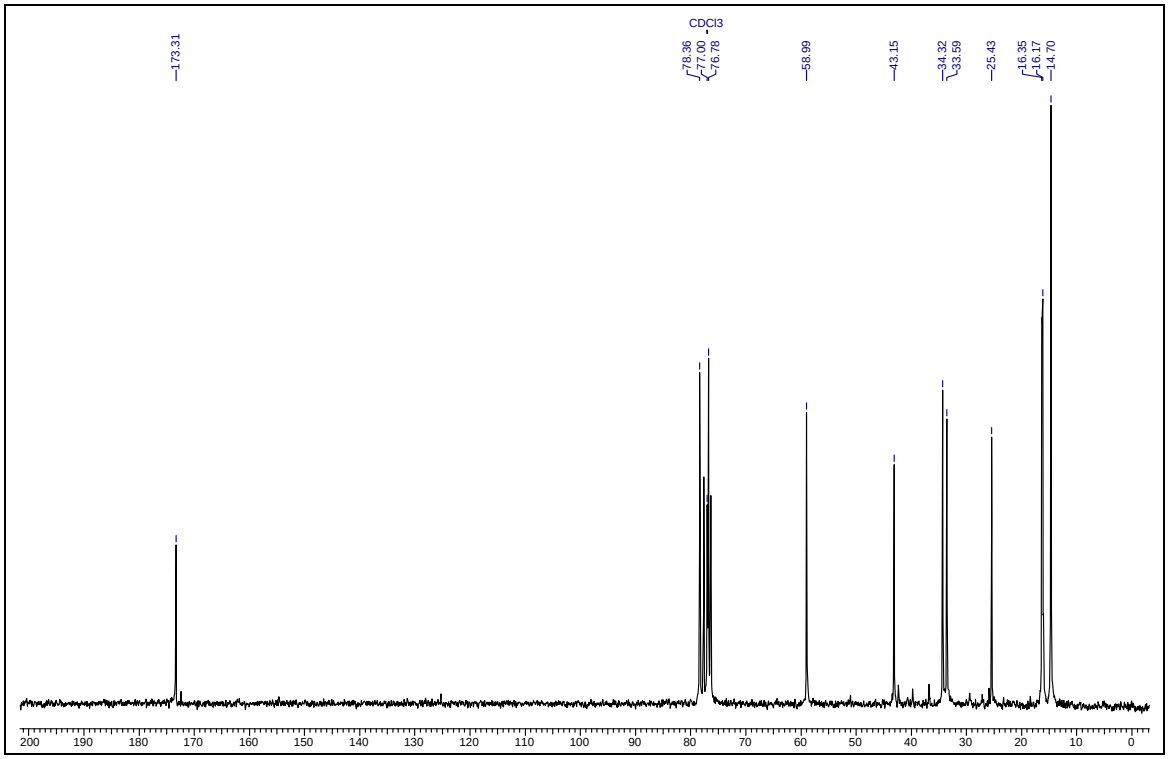

NH
O
OH
OMe
Et
Et
2.05b
0.53
0.72
1.33
2.49
2.67
4.26
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

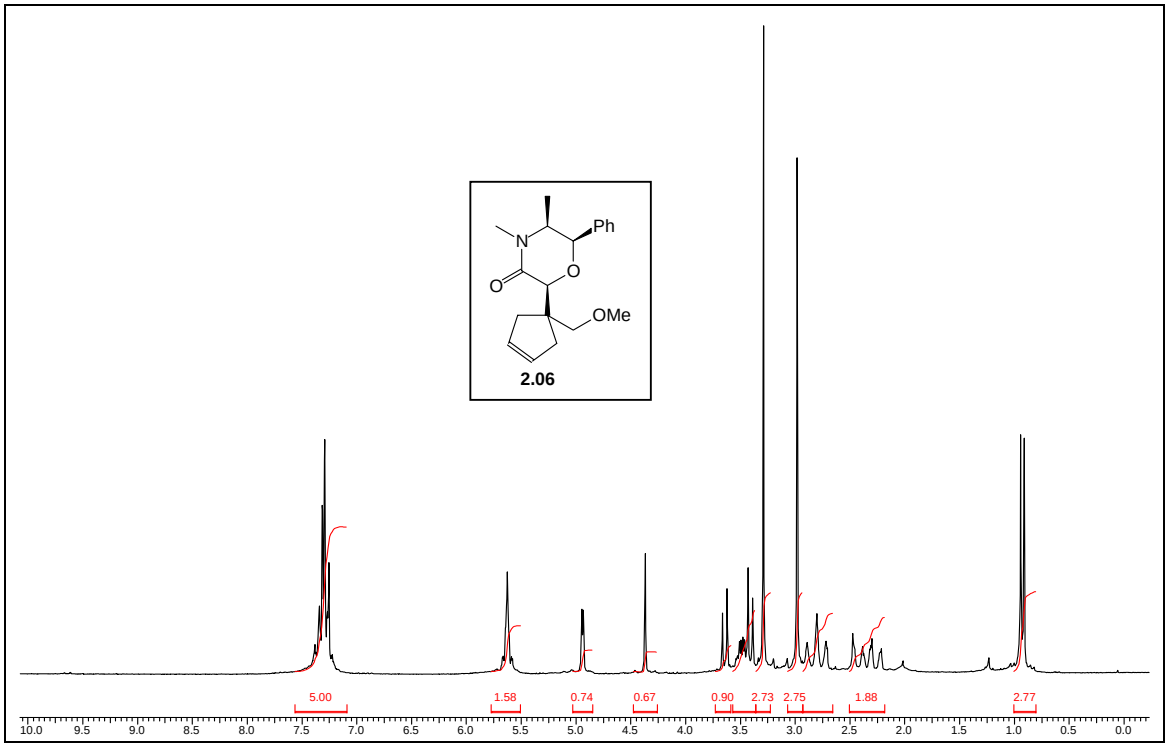

CDCl3
173.44
78.07
76.69
59.21
43.28
25.64
23.90
23.44
7.69
7.57
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

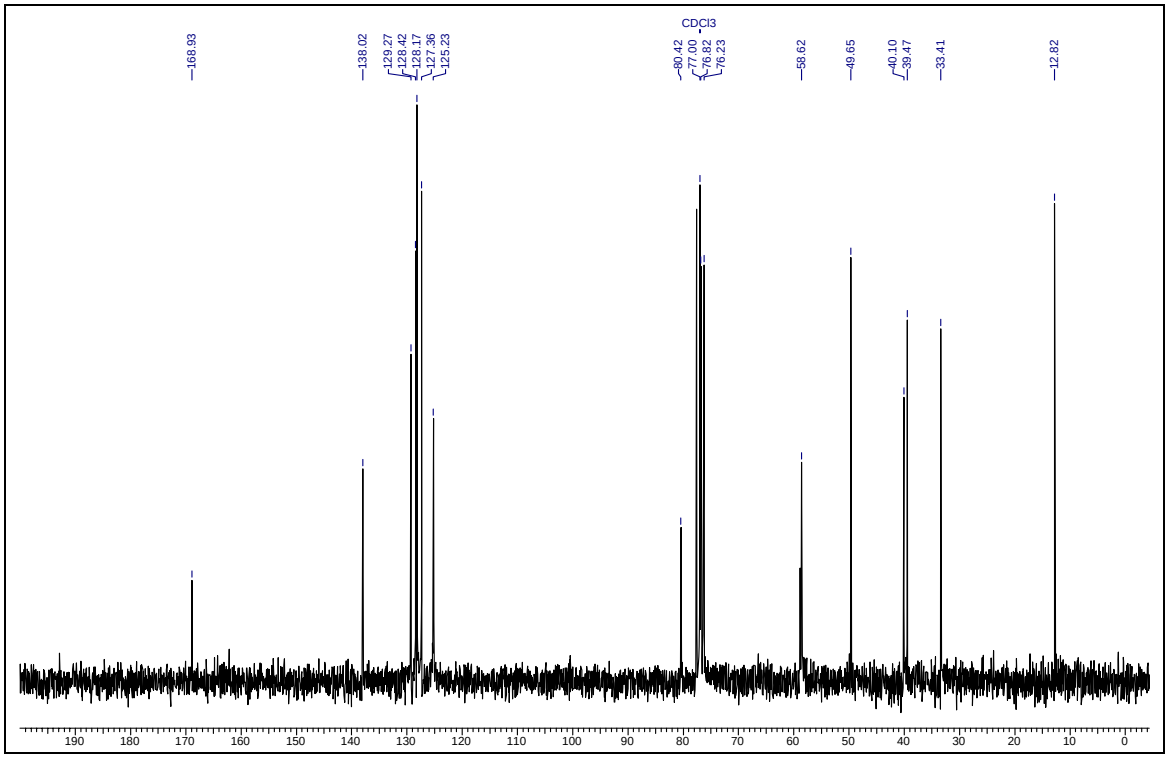

NH
O
OH
OMe
R
R
2.05c, R=allyl
0.56
1.79
2.43
0.87
3.40
3.16
2.45
2.48
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

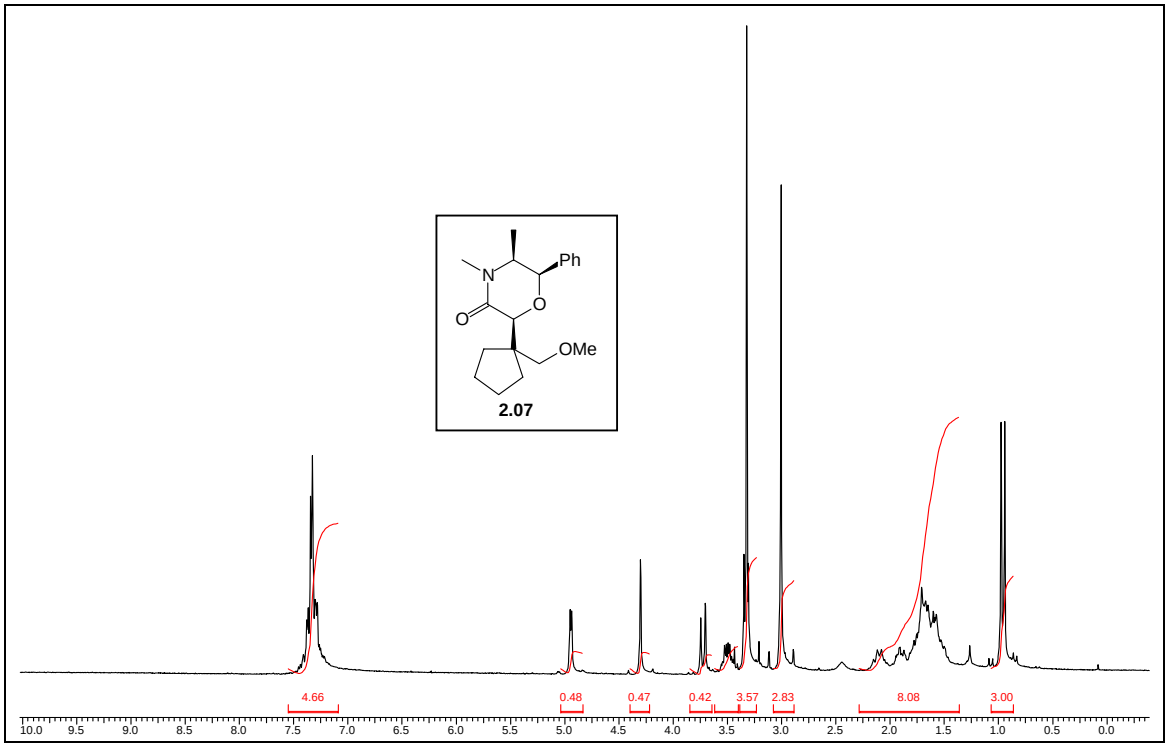

172.90
133.83
118.43
CDCl3
77.85
77.00
76.38
59.17
43.70
36.60
35.79
25.69
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

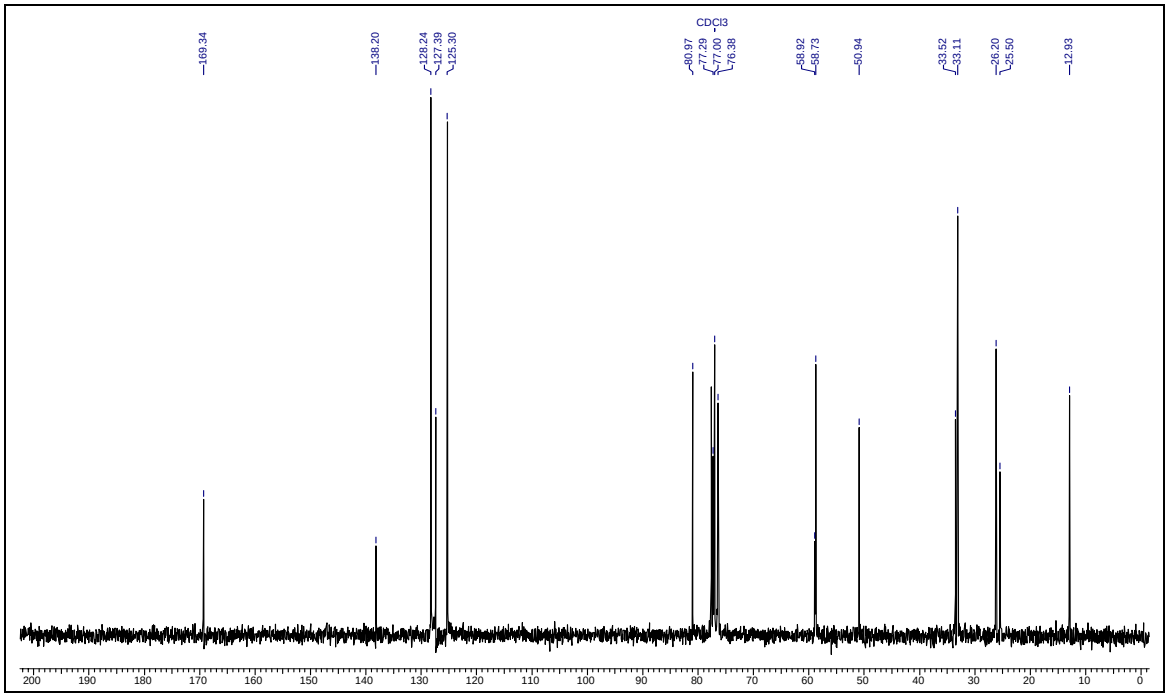

NH
O
OH
OMe
2.05d
0.30
0.71
0.68
2.71
2.61
8.36
5.60
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

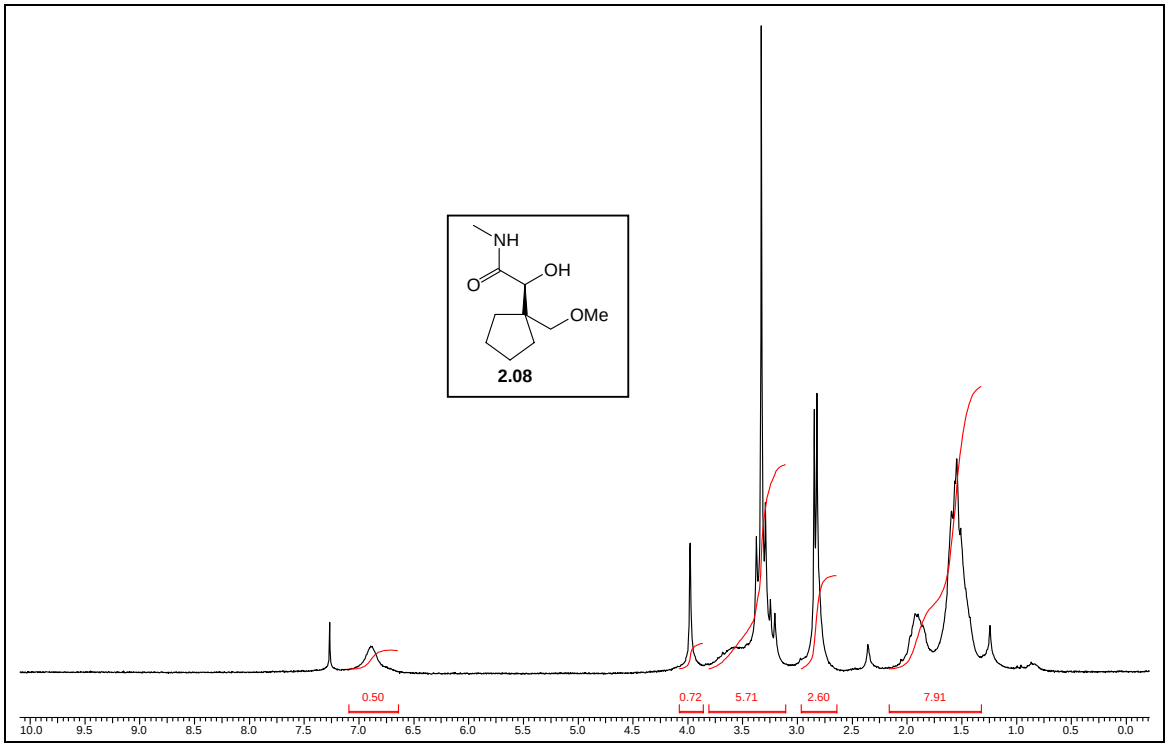

173.31
CDCl3
78.36
77.00
76.78
58.99
43.15
34.32
33.59
25.43
16.35
16.17
14.70
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

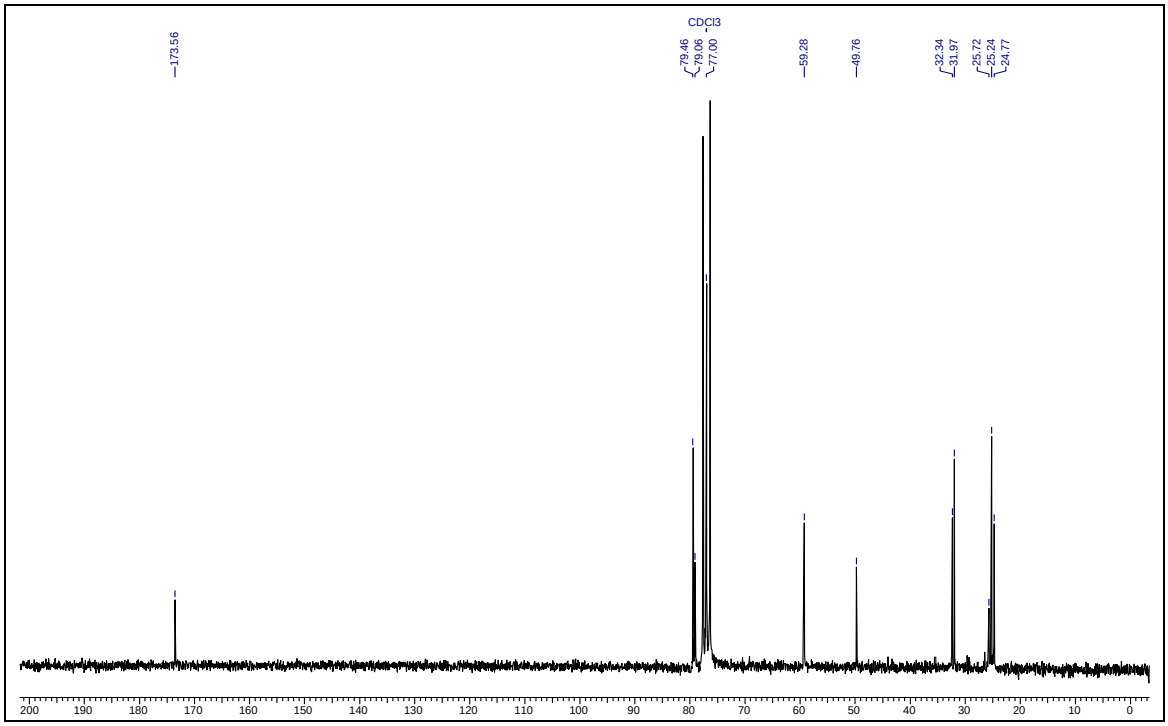

Ph
N
O
O
OMe
2.06
5.00
1.58
0.74
0.67
0.90
2.73
2.75
1.88
2.77
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

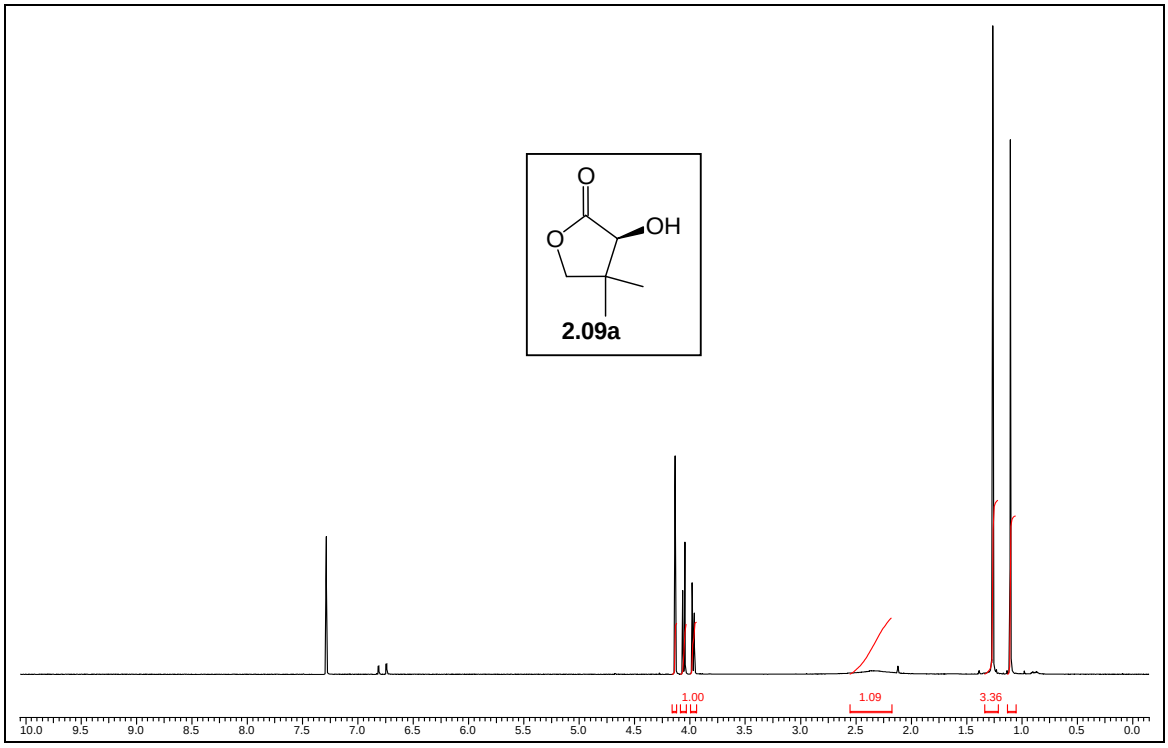

CDCl3
168.93
138.02
129.27
128.42
128.17
127.36
125.23
80.42
77.00
76.82
76.23
58.62
49.65
40.10
39.47
33.41
12.82
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

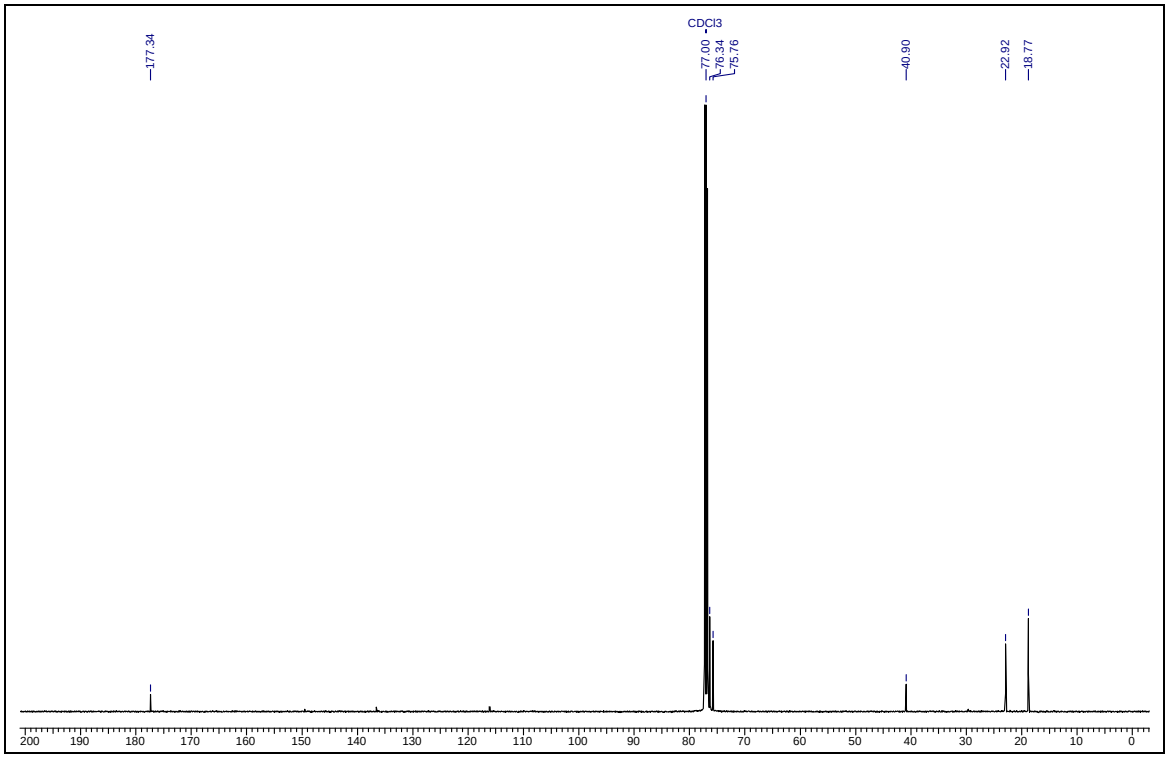

Ph
N
O
O
OMe
2.07
4.66
0.48
0.47
0.42
3.57
2.83
8.08
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

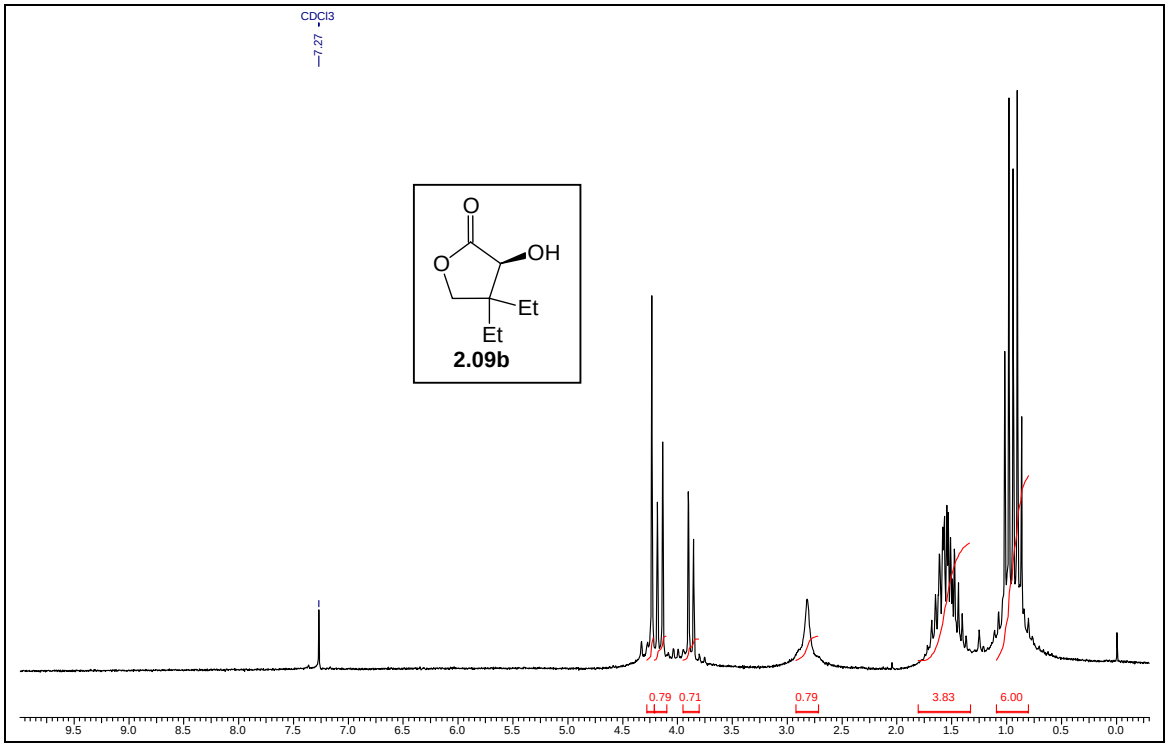

169.34
138.20
128.24
127.39
125.30
CDCl3
80.97
77.29
77.00
76.38
58.92
58.73
50.94
33.52
33.11
26.20
25.50
12.93
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

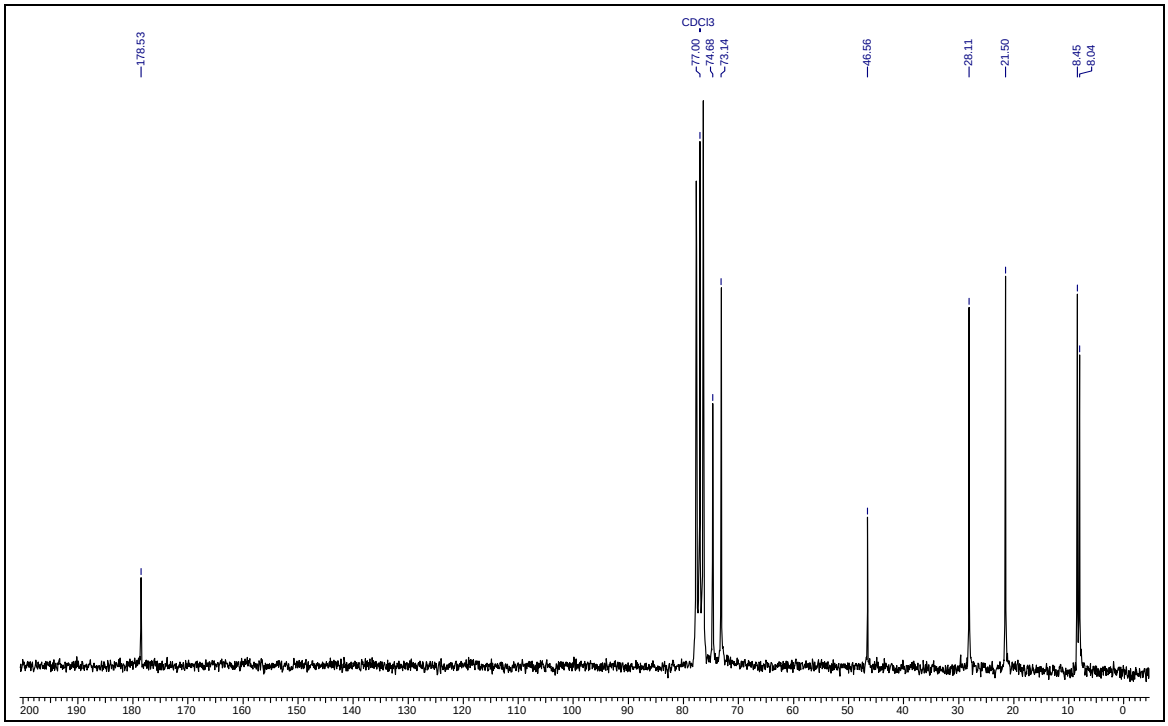

NH
O
OH
OMe
2.08
0.50
0.72
5.71
2.60
7.91
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

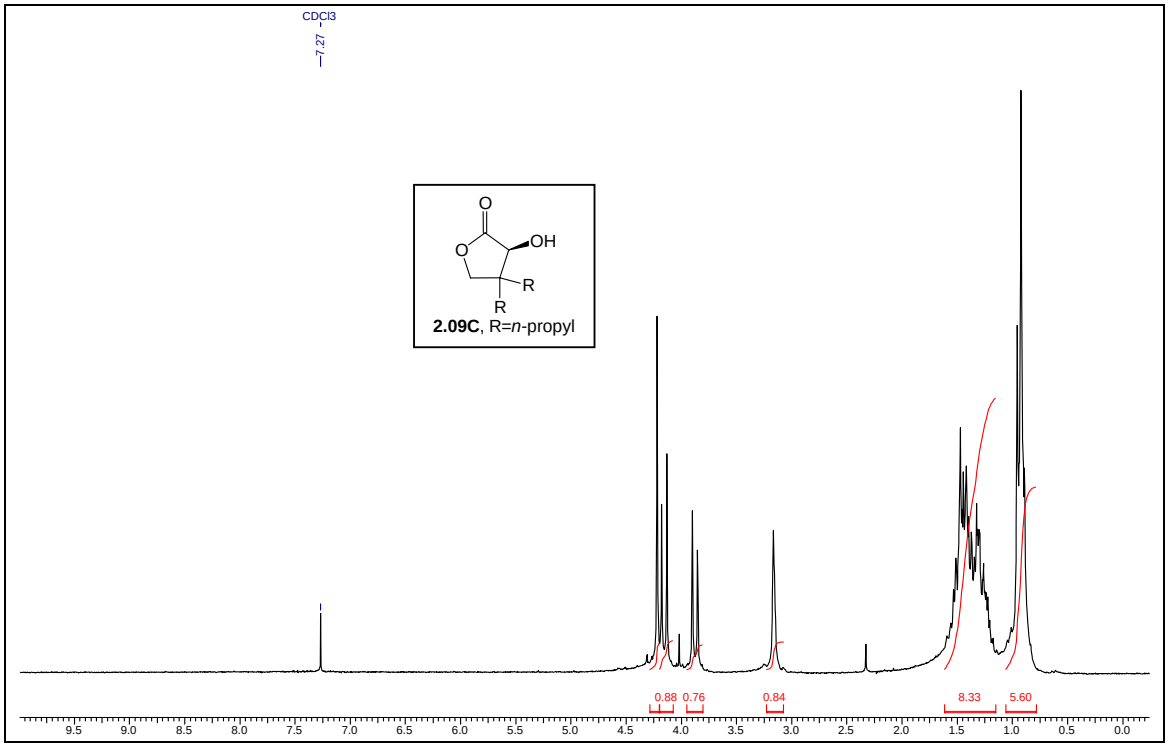

173.56
CDCl3
79.46
79.06
77.00
59.28
49.76
32.34
31.97
25.72
25.24
24.77
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

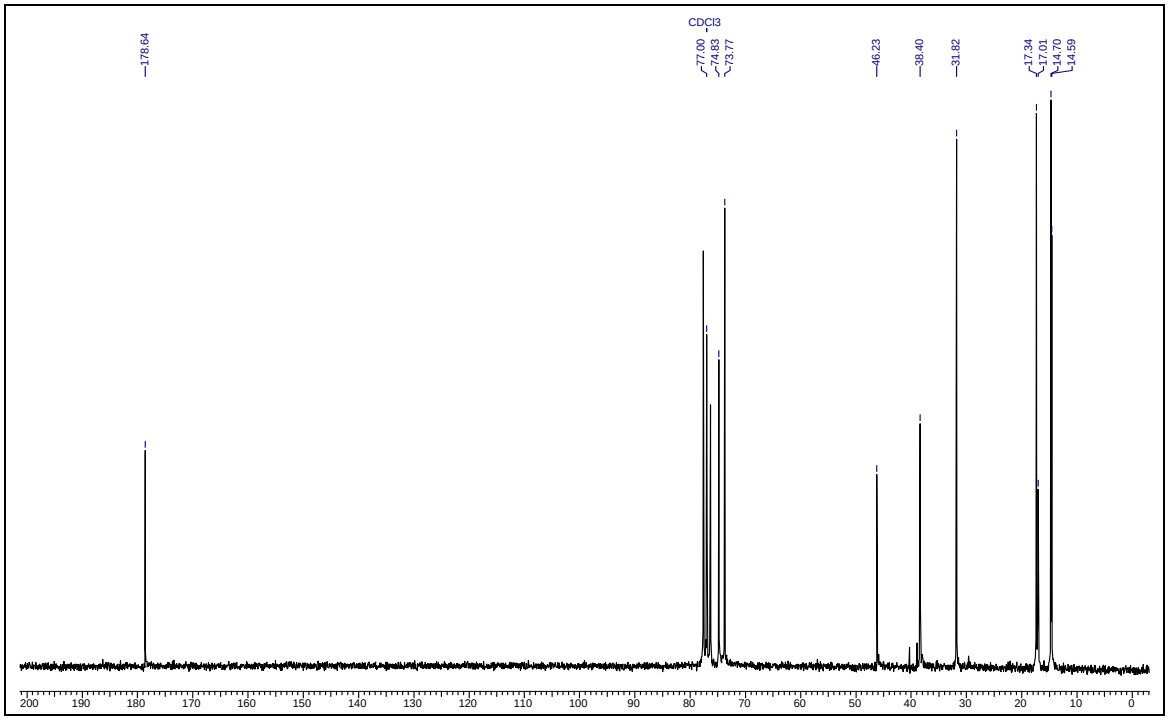

O
O
OH
2.09a
1.00
1.09
3.36
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

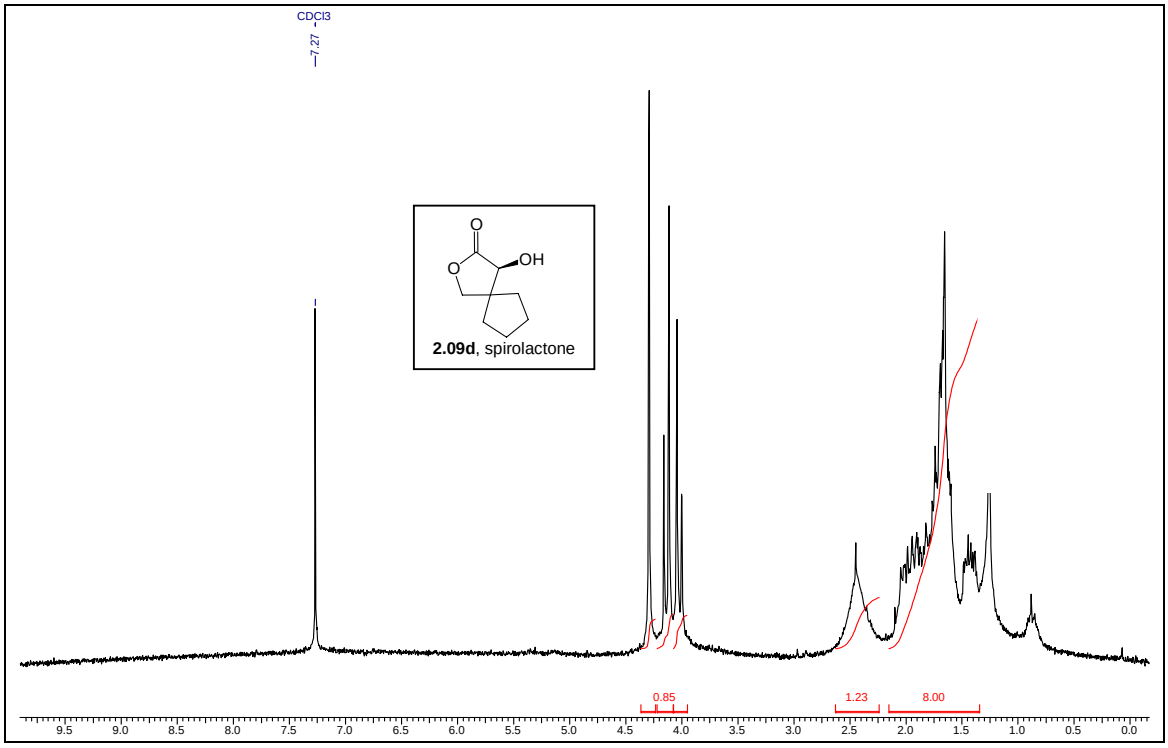

177.34
CDCl3
77.00
76.34
75.76
40.90
22.92
18.77
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

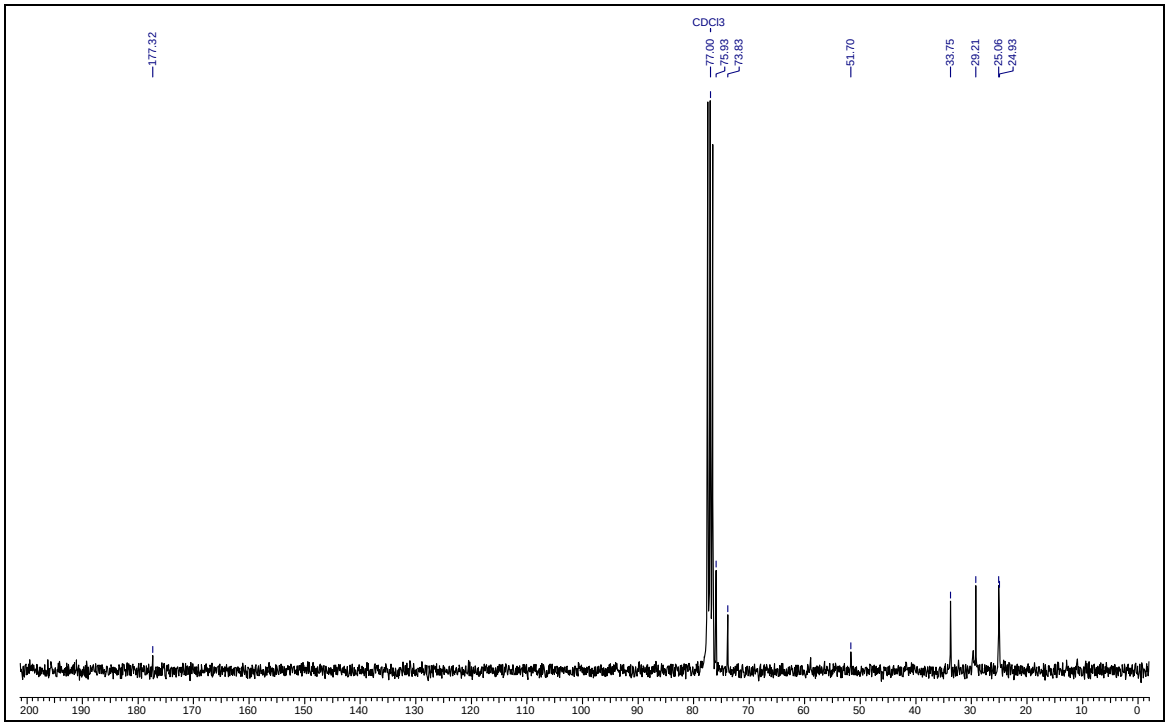

CDCl3
7.27
O
O
OH
Et
Et
2.09b
0.79
0.71
0.79
3.83
6.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

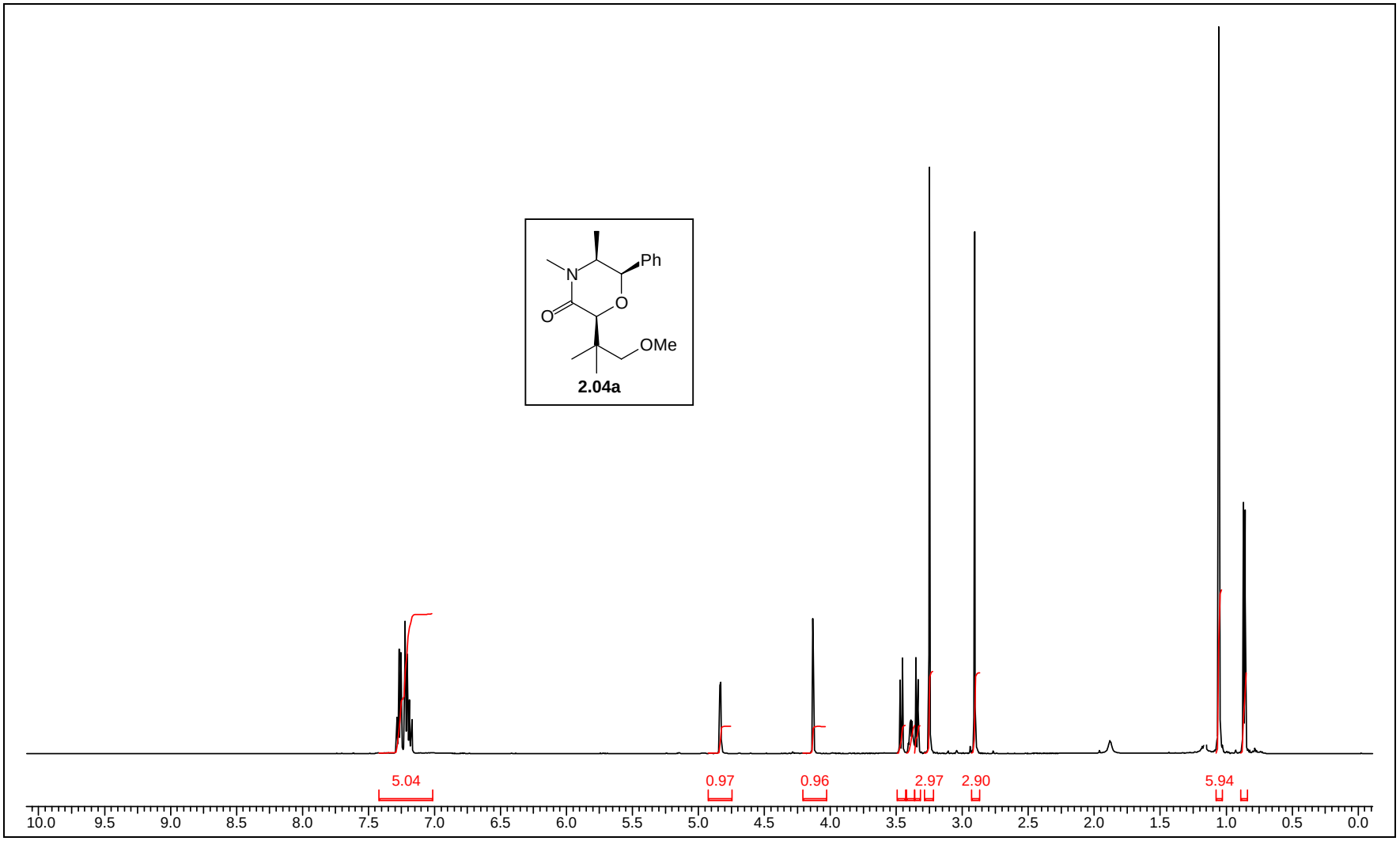

CDCl3
178.53
77.00
74.68
73.14
46.56
28.11
21.50
8.45
8.04
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


CDCl3
7.27
O
O
OH
R
R
2.09C, R=n-propyl
0.88
0.76
0.84
8.33
5.60
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


178.64
CDCl3
77.00
74.83
73.77
46.23
38.40
31.82
17.34
17.01
14.70
14.59
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

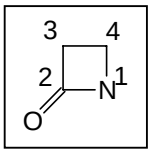

CDCl3
7.27
O
O
OH
2.09d, spirolactone
0.85
1.23
8.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


177.32
CDCl3
77.00
75.93
73.83
51.70
33.75
29.21
25.06
24.93
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Ph
N
O
O
OMe
2.04a
5.04
0.97
0.96
2.97
2.90
5.94
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

3.1: Introduction

Azetidin-2-one (β-lactam), a four membered cyclic amide (Figure 1), is a part structure of many biologically important antibiotics. The unique structural feature and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of synthetic chemists, as they provide variety of synthetic challenges. Although the first synthesis of β-lactam ring was reported way back in 1907[1] by Staudinger, β-lactams as a class acquired immense importance only after the discovery of penicillin by Fleming in 1928[2]. It was actually Prof. R. B. Woodward who first proposed the structure of penicillin based on a β-lactam ring, which was indeed later confirmed by X-ray crystallography[3] which unambiguously confirmed the presence of 4-membered amide ring (β-lactam). The azetidin-2-one ring was identified as the key structural unit responsible for the antibiotic activity.



Azetidin-2-one

(β-lactam ring)

Figure 1

Until 1970, penicillin and cephalosporins[4] were the only examples of naturally occurring β-lactam antibiotics. The discovery of 7-α-methoxycephalosporins[5] from "*Streptomyces*" in 1971 stimulated the search for novel antibiotics. The β-lactam antibiotics can be classified into several groups based on their structures (Figure 2).

- Penicillin
- Cephalosporin (penams)
- Cephamycin (Cephems)
- Oxacephems
- Penems
- Oxapenams like clavulanic acid
- Carbapenems like thienamycin
- Nocardicins
- Monobactams

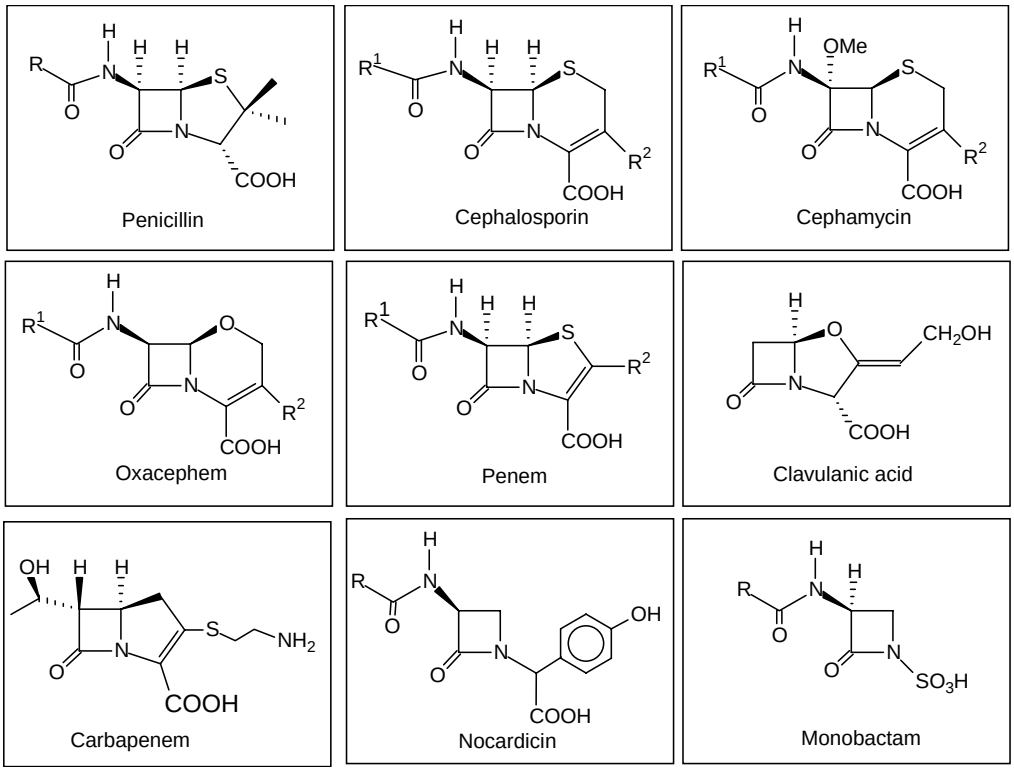


Figure 2. Classification of β-Lactam antibiotics based on structure

Carbacephems,[6] which are carbon analogues of cephalosporins are also being used as antibiotics. It has superior stability over cephalosporin. Loracarbef (lorabid) is the first carbacephem approved for clinical use (Figure 3).

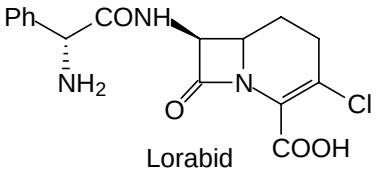
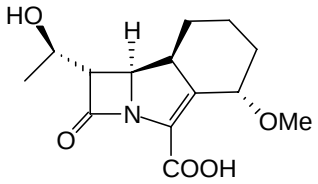


Figure 3

Tricyclic β-lactam antibiotics called trinems[7] (Figure 4) are also new class of tricyclic carbapenems. GV 104326, a highly potent, broad-spectrum antibacterial agent, effective against gram-positive, gram-negative and anaerobic pathogenic bacteria, is an example of tribactam antibiotic.



GV 104326 (tribactam)

Figure 4

In 1995, a new class of compounds was reported in which the antibiotic property of β-lactams and the antiviral property of nucleosides were incorporated together to afford dual properties of the drug.[8] Kehagia *et al.*[9] reported a new class of β-lactams in which a steroidal and β-lactam units were coupled together *via* Ugi reaction in a one step process (Figure 5).

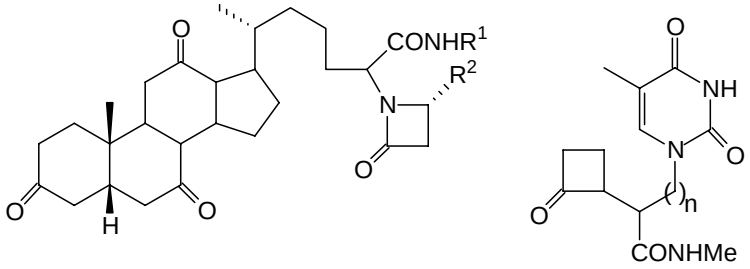


Figure 5

Apart from their antibacterial activities, β-lactams also shows biological activities that include cholesterol absorption inhibition[10] and human leukocyte elastase[11] (HLE).

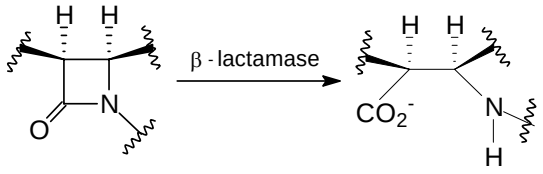
Mode of action:

The biological activity of β-lactam antibiotics is mainly due to the presence of the azetidin-2-one ring (β-lactam ring). The SAR[12] studies have shown that the main requirement for the antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in active form to the targets, which are the inner membrane enzymes that are responsible for the biosynthesis of the cell wall, thereby inactivating one or more enzymes involved in the cell wall synthesis. Penicillin binds to the so-called 'penicillin-binding proteins' (PCBs), which are specific molecules on the inner membrane of the cell wall. The binding of penicillin to the PCBs causes termination of the peptide chain linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.[13]

β-lactamases and β-lactamase inhibitors:

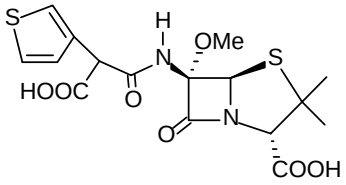
The β-lactamases[14] are group of bacterial enzymes that catalyze the hydrolysis of β-lactam antibiotics (Scheme 1). Since the hydrolyzed β-lactam has no antibiotic activity, the β-lactamases represents a source of bacterial resistance against β-lactam antibiotic.

Scheme 1

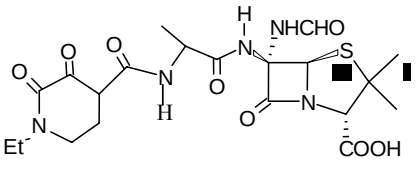


This phenomenon of bacterial resistance led to a serious research in this field and paved the way for development of novel β-lactams called β-lactamase inhibitors.[15] They are essentially structural variants of the classical β-lactams with modified skeleton. They may not have antibiotic activity of their own, but they are used in combination with the β-lactam antibiotic. Specifically they associate themselves with the β-lactamases, thereby protecting the antibiotic against the hydrolytic action of β-lactamase. Thus the antibiotic activity of the β-lactam is safeguarded and it can penetrate through the bacterial cell wall.

Temocillin and Formidacillin[15a] are some of the examples of β-lactamase inhibitors, which are the result of extensive SAR studies of penicillin (Figure 6).



Temocillin



Formidacillin

Figure 6

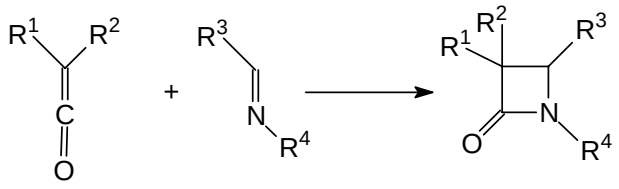
General methods for constructing azetidin-2-one (β-lactam) ring:

Over the past few decades, several methodologies[16] have been developed for the construction of the β-lactam ring. Few important methods will be discussed here.

Staudinger Reaction:

Staudinger achieved the first chemical synthesis of β-lactam ring in 1907 by [2+2] cycloaddition of ketenes with imines. This reaction is referred to as Staudinger reaction or ketene-imine cycloaddition reaction[17] (Scheme 2). Later it was modified, wherein acid chlorides or activated carboxylic acids were used in presence of a base as ketene precursor.

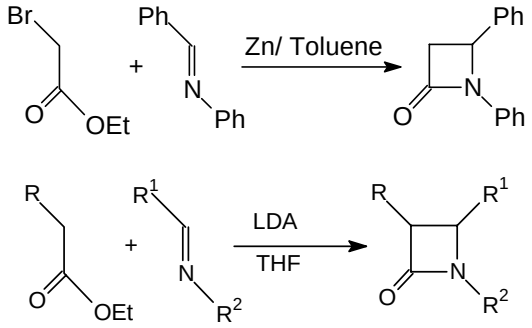
Scheme 2



Enolate-Imine condensation:

Gilman and Speeter first reported this reaction.[18] They constructed the β-lactam ring by condensation of Zn enolate (Reformatsky reagent) with imines. Later on, other metal enolates have also been used in the enolate imine condensation reaction to achieve good selectivities and yields in β-lactam formation[19] (Scheme 3).

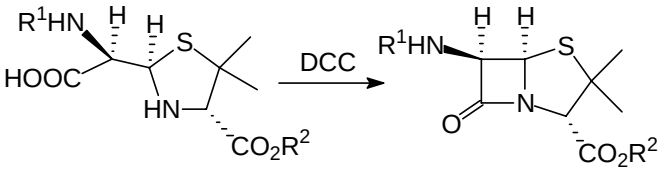
Scheme 3



Formation of N-C2 bond:

This approach was first reported by Staudinger, Klever and Kober in 1910.[20] Sheehan and Henery-Logan have used this method for their landmark synthesis of penicillin[21] by cyclization of β-amino acid using dicyclohexylcarbodiimide (DCC) as condensing reagent (Scheme 4).

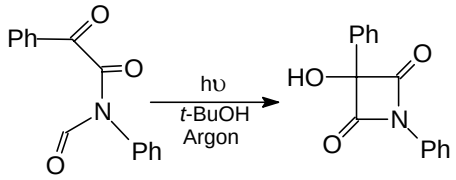
Scheme 4



Formation of C2-C3 bond:

Compared to the amide (N-C2) bond formation, azetidinone formation at the C2-C3 position is complicated by the difficulty in forming a C-C bond versus an amide bond. Hence this method is least used. A photochemical approach leading to formation of 4-keto-β-lactams has been developed[22] (Scheme 5).

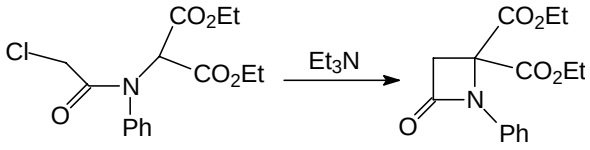
Scheme 5



Formation of C3-C4 bond:

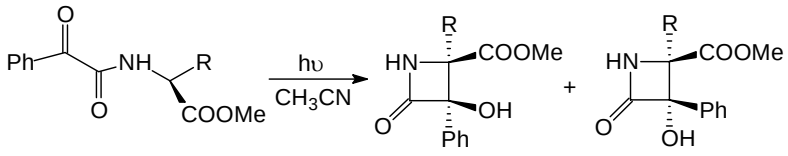
This involves formation of a nucleophilic center at C3 and an electrophilic center at C4 or *vice versa*. The first example of such an intramolecular nucleophilic displacement reaction was reported by Sheehan and Bose[23] wherein haloacylamino malonate was cyclized in an intramolecular fashion in the presence of a base (Scheme 6).

Scheme 6



Recently, a photocyclization of phenylglyoxyamides of α-amino acid methyl esters to 3-hydroxy β-lactams has been reported,[24] which involves the formation of C3-C4 bond (Scheme 7).

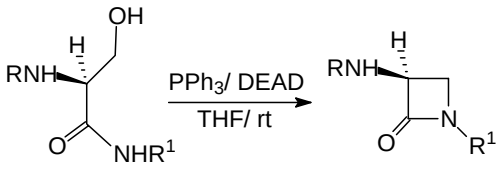
Scheme 7



Formation of C4 -N bond:

This is the route selected by nature for the biosynthesis of azetidinone containing antibiotics.[25] The essential strategy involved in the synthesis of β-lactams through C4–N bond is the intramolecular displacement of a leaving group attached to C4 with an appropriately activated nitrogen. Miller and coworkers[26] have made significant contribution to this methodology. The key feature of the Miller's hydroxamate approach is the intramolecular cyclization of chiral β-hydroxy amides under Mitsunobu reaction conditions[27] (Scheme 8).

Scheme 8

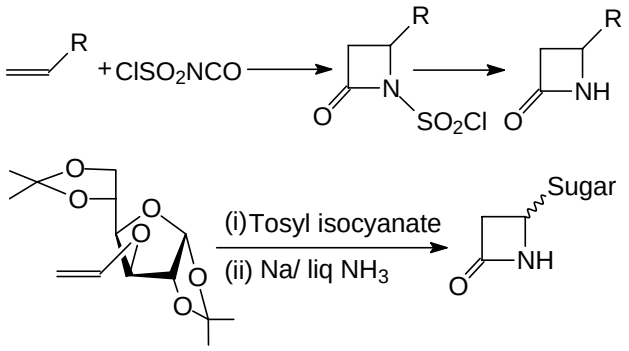


R= acyl or carbamate,
R^1= Ar

Isocyanate addition to alkenes:

Graf[28] reported the cycloaddition of N-chlorosulfonyl isocyanate (CSI) with alkenes to get 1-chlorosulfonyl azetidin-2-ones. Subsequent removal of the chlorosulfonyl group gave the NH β-lactam. The cycloaddition is promoted by activated alkenes like vinyl acetates. Chmielewski and coworkers have used the cycloaddition reaction between tosyl isocyanate and sugar derived vinyl acetates to obtain good diastereoselectivities in β-lactam formation[29] (Scheme 9).

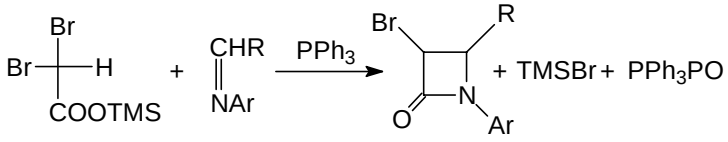
Scheme 9



Manhas's α-Bromo-β-Lactam approach:

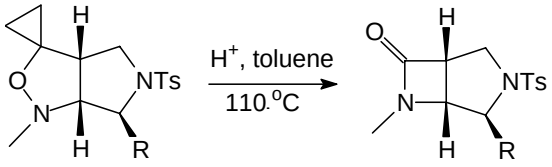
Manhas *et al.*[30] have developed this approach, which involves condensation of halo ester with imines in presence of triphenyl phosphine (Scheme 10).

Scheme 10



Recently, Cordero *et al.*[31] have reported that spirocyclopropane isoxazolidines undergo ring contraction to yield β-lactams on heating in the presence of protic acid (Scheme 11).

Scheme 11



R = Me, *iso*-propyl

Asymmetric Synthesis of β-lactams:

Asymmetric synthesis of β-lactams is an important area of research, as biological activity of β-lactam antibiotics is closely related to the stereochemistry. Among the various methods available for the asymmetric synthesis of β-lactams, the asymmetric Staudinger reaction[17,32] (ketene-imine cyclization) is the most widely used. This is mainly because of the simplicity in reaction procedures and versatility. Asymmetry can

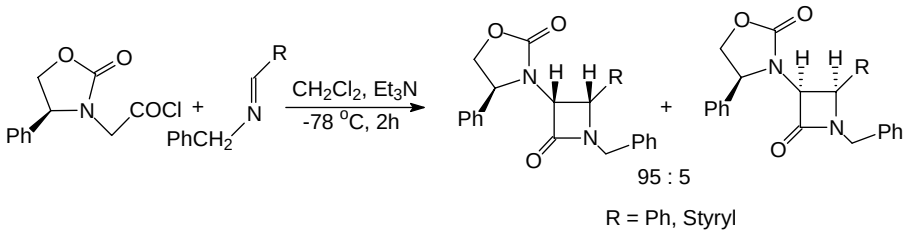
be induced in a ketene-imine cycloaddition reaction by using a chiral ketene or chiral imine or both (referred as double stereodifferentiation).

Asymmetric Staudinger reaction using chiral ketene precursors*:*

Various levels of diastereoselectivities in β-lactam formation using chiral auxiliary in the ketene component have been reported in literature. Following is a brief review of asymmetric Staudinger reaction using chiral ketenes.

Evans and Sjogren[33] developed a (*S*)-phenylglycine derived oxazolidinone as a chiral auxiliary attached to ketene component in the asymmetric Staudinger reaction and obtained very high diastereoselectivity (> 95%) in the *cis* β-lactam formation. No trace of the *trans* isomer was detected (Scheme 12).

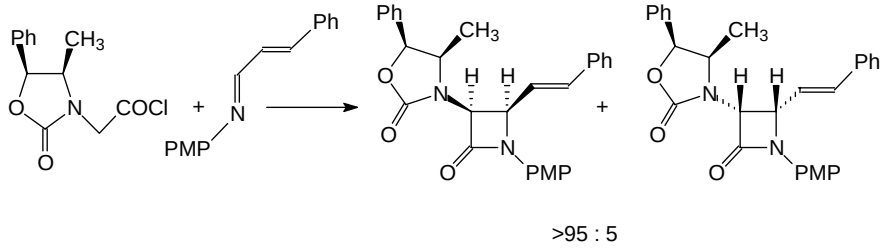
Scheme 12



Boger and Myers[34] used the enantiomeric oxazolidone to synthesize the other diastereomer of the β-lactam with very good diastereoselectivity.

Cooper *et al.*[35] have used a norephedrine derived oxazolidinone as the chiral auxiliary in the ketene component and achieved very high diastereoselectivity (>95%) in the *cis* β-lactam formation *via* asymmetric Staudinger reaction (Scheme 13).

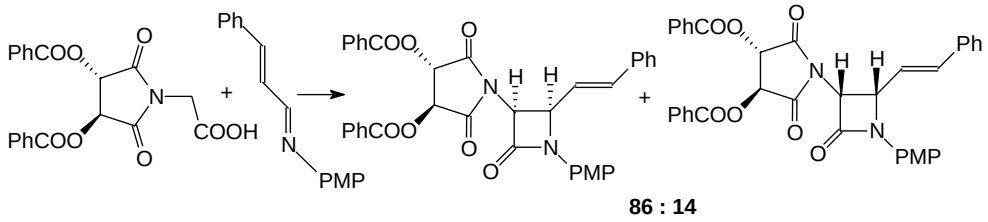
Scheme 13



Cooper *et al*.[35] have also reported the use of a tartarimidoacetic acid derived from *S*, *S*-tartaric acid as a chiral ketene precursor in the asymmetric Staudinger reaction.

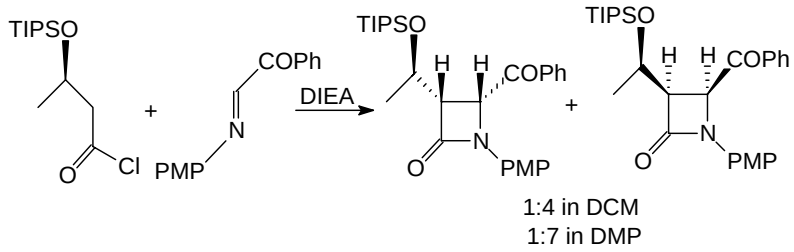
However, there was only moderate diastereoselectivity in the β-lactam formation (de upto 72%) as the chiral center is farther away from the amide nitrogen (Scheme 14).

Scheme 14



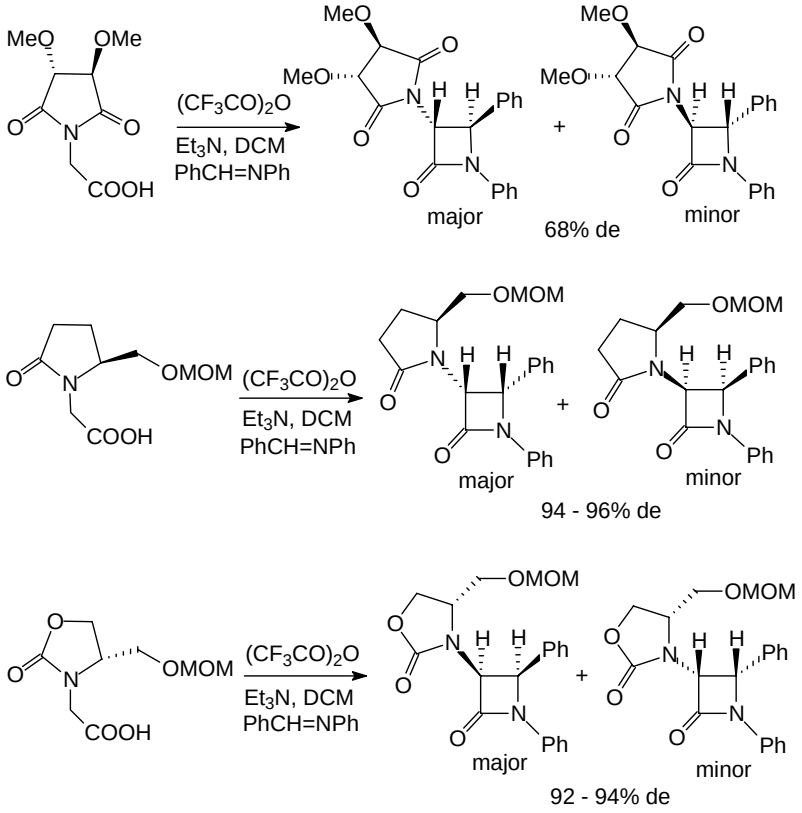
An acid chloride derived from *O*-protected 3-hydroxybutyric acid was used in the asymmetric Staudinger reaction, to yield diastereomeric mixture of β-lactams. The ratio depends on the solvent used. Increase in the diastereoselectivity was observed with the increase in bulkiness of the *O*-protecting group[36] (Scheme 15).

Scheme 15



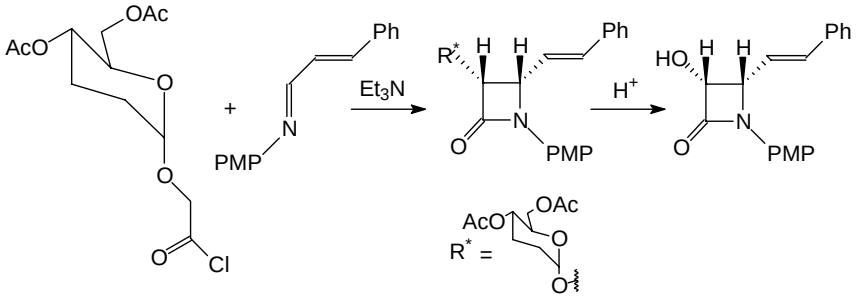
Ikota *et al.*[37] have used mixed anhydride of acetic acid derived form (L)–(+)–tartaric acid, (*S*)–glutamic acid, and (*S*)–serine as the chiral ketene precursor in the asymmetric Staudinger reaction with imines derived from benzylideneaniline and obtained very good diastereoselectivity in β-lactam formation (Scheme 16). The removal of the chiral auxiliary gave the 3-amino β-lactam derivatives.

Scheme 16



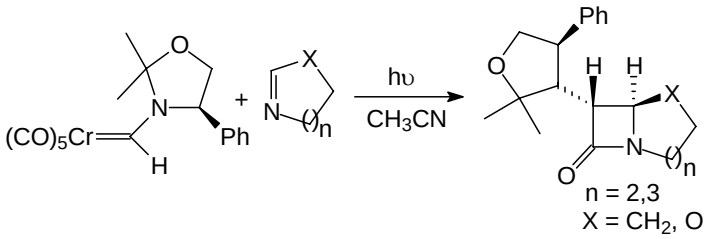
Borer and Balogh[38] have used a chiral ketene derived from carbohydrate (tri-*O*-acetyl-D-glucal) in the asymmetric Staudinger reaction to get *cis* β-lactams with good diastereoselectivity. Removal of the chiral auxiliary by hydrolysis using 4:1:1 THF/H_2O/HOAc gave the *cis* β-lactams with 70% enantiomeric excess (Scheme 17). An excellent review by Chemielewski, on the use of carbohydrates in β-lactam synthesis has appeared in 1994.[39]

Scheme 17



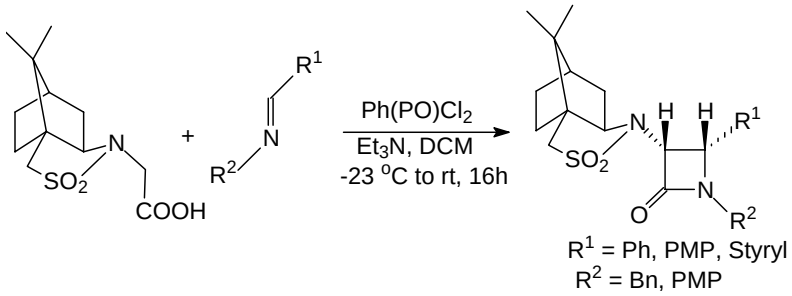
Hegedus *et al.*[40] have prepared *trans* β-lactams in excellent yields (75-95%) and diastereoselectivity (>95%) by the photolysis of optically active chromium carbene complexes with cyclic imines (Scheme 18).

Scheme 18



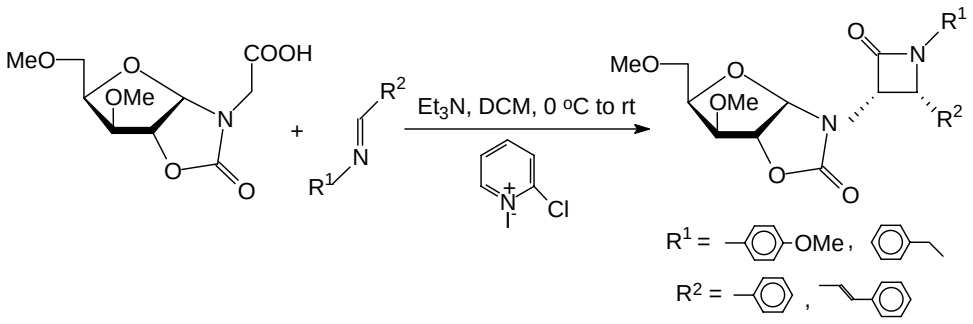
Chiral acid derived from Oppolzer's sultam has been used as chiral ketene precursor in the asymmetric Staudinger reaction to get diastereospecifically a single *cis* β-lactam[41] in good yields (Scheme 19).

Scheme 19



Recently Koll *et al.*[42] have achieved excellent diastereoselectivity (>99%) in β-lactam formation using a chiral oxazolidinone auxiliary based on D-Xylose as a ketene precursor in the asymmetric Staudinger reaction (Scheme 20).

Scheme 20



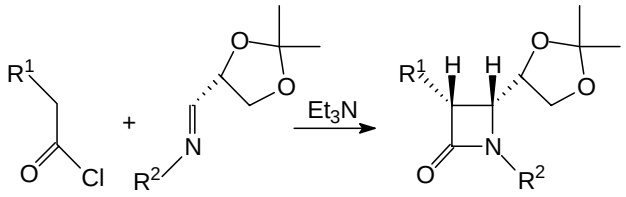
Asymmetric Staudinger reaction using chiral imines:

Asymmetric induction *via* chiral imines can be achieved by using either chiral aldehydes or chiral amines. The use of chiral aldehydes and chiral amines will be briefly discussed below.

Chiral Aldehydes:

Imines derived from D and L glyceraldehyde acetonide[43] gave complete *cis* diastereoselectivity in β-lactam formation *via* asymmetric Staudinger reaction (Scheme 21). Bose and co-workers, in series of papers,[44] have reported similar observation.

Scheme 21



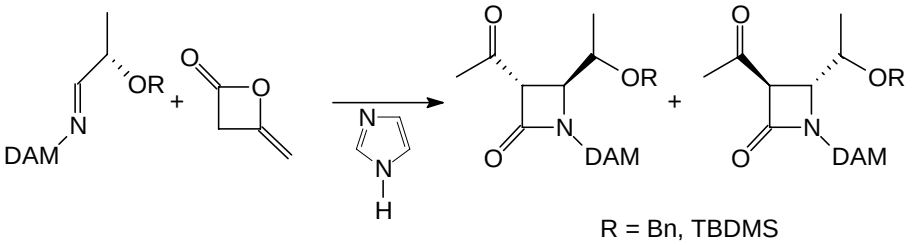
R^1 = PhO, CH_3O, AcO, N_3, Phth
R^2 = PMP, CH_2COOCH_3, Bn

Ikota has reported the use of an imine derived from 2, 3-O-isopropylidene–L–threitol in the asymmetric Staudinger reaction and achieved very good diastereoselectivity[45] (Scheme 22).

Scheme 22

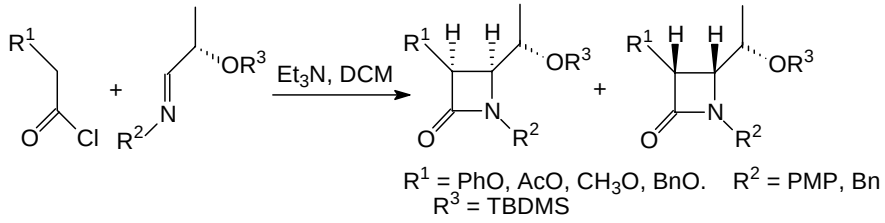
Terashima *et al.*[46] have used the diketenes along with the imine derived from commercially available (*S*)–ethyl lactate as the chiral aldehyde component in the asymmetric Staudinger reaction. The diastereoselectivities were solvent dependent, with acetonitrile giving the best results (90% de) (Scheme 23).

Scheme 23



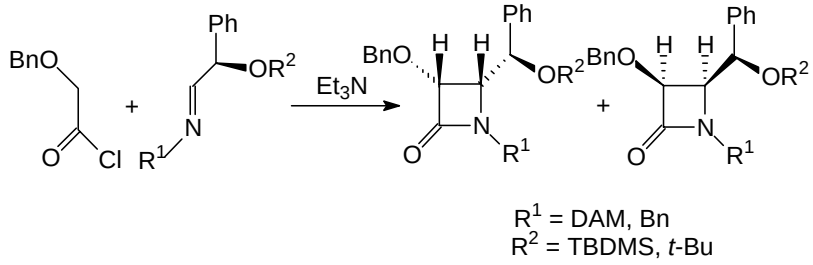
Palomo *et al.*[47]and Brown[48] have also used the chiral aldehyde derived from (*S*)–ethyl lactate in the ketene-imine cycloaddition reaction and achieved excellent diastereoselectivity by careful optimization of the protecting groups (Scheme 24).

Scheme 24



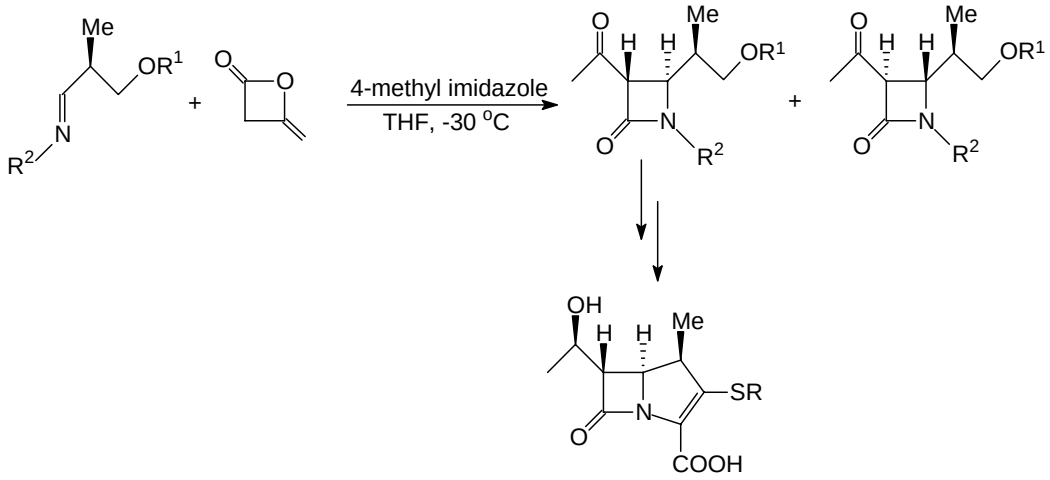
Terashima and co-workers[49] have reported the ketene-imine cycloaddition reaction with imines derived from optically active mandelate. The diastereoselectivity was dictated by the bulkiness of the protecting group (Scheme 25).

Scheme 25



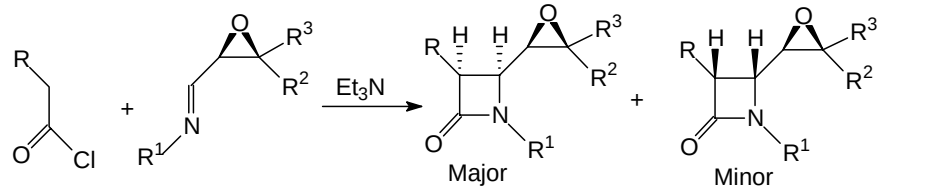
Imines derived from (*S*)–methyl–3–hydroxy–2–methylpropionate were used in the asymmetric Staudinger reaction to synthesize important precursor of 1–β–methyl carbapenem[50] (Scheme 26). A careful optimization of the reaction condition and protecting groups gave 15:1 ratio in favor of the desired diastereomer.

Scheme 26



Imines derived from chiral α, β–epoxyaldehydes[51] have also been employed in Staudinger reaction to achieve very high diastereoselectivity. The epoxy aldehydes were synthesized from (*S*)–malic acid[52], (+)–tartaric acid[53] or sodium erythorbate[51] (Scheme 27).

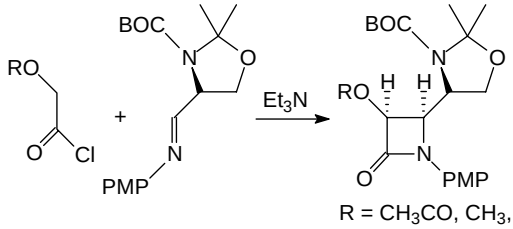
Scheme 27



R = PhthN, R^1 = PMP, Bn, R^2 = CH_3, H, R^3 = CH_3, Ph

Palomo *et al.*[54] have used the imines derived from N, O– diprotected L– serinal in the asymmetric Staudinger reaction and diastereospecifically obtained a single *cis* β-lactam (Scheme 28).

Scheme 28

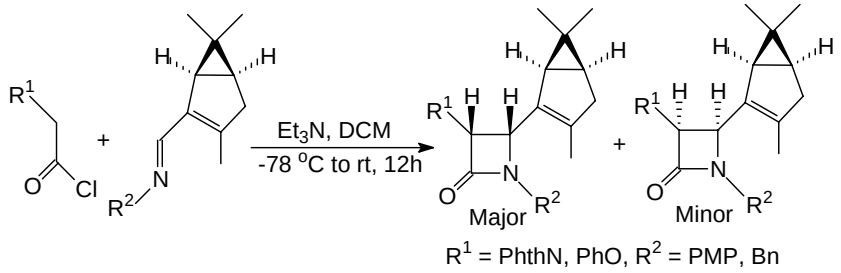


R = CH_3CO, CH_3, Bn

In our group[55] we have utilized the imine prepared from chiral aldehyde derived from (+)–3–carene in the ketene-imine cycloaddition reaction. Good diastereoselectivity

in the β-lactam formation was achieved, in spite of the chiral directing group being far away from the aldehyde carbon (Scheme 29).

Scheme 29

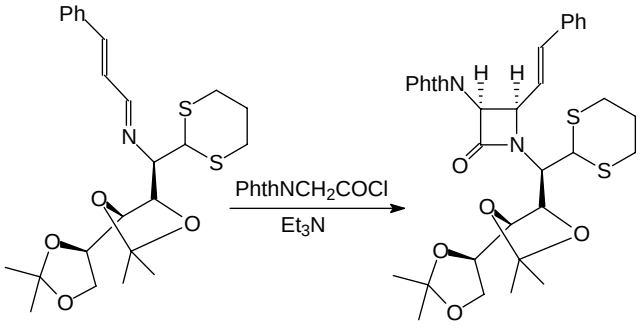


Chiral Amines:

Asymmetric Staudinger reaction using imines derived from achiral aldehydes and chiral amines often result in poor diastereoselectivity in β-lactam formation. This is because the stereo directing group in the chiral amine is far away from the newly formed chiral center. However there are few reports on efficient use of chiral amines in the asymmetric Staudinger reaction, which will be discussed here.

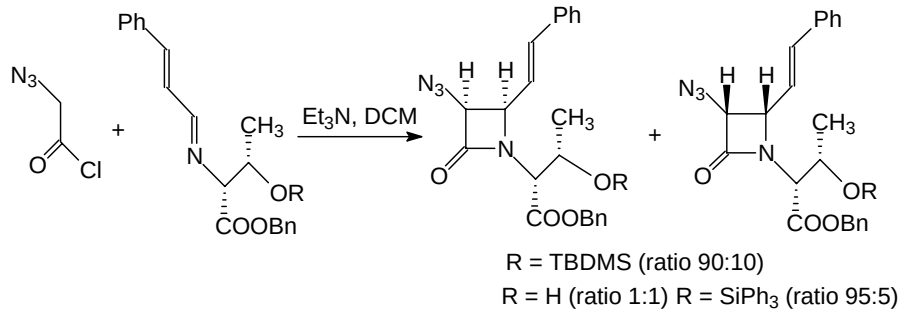
Asymmetric Staudinger reaction using imines derived from D–glucosamine[56] and cinnamaldehyde have resulted in diastereospecific formation of single *cis* β-lactam (Scheme 30).

Scheme 30



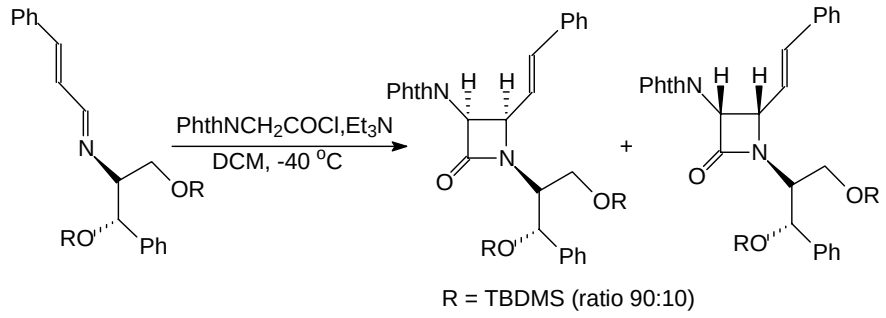
D–threonine has also been used as chiral auxiliary in the Staudinger reaction. In this case the diastereoselectivity was dependent on the bulkiness of the substituents[57] (Scheme 31).

Scheme 31



Gunda[58] has used a chiral imine derived from (1*S*, 2*S*)–2–amino–1–phenyl–1,3-propanediol in the ketene-imine cycloaddition reaction and here too, the diastereoselectivity was dictated by the hydroxy protecting group (Scheme 32).

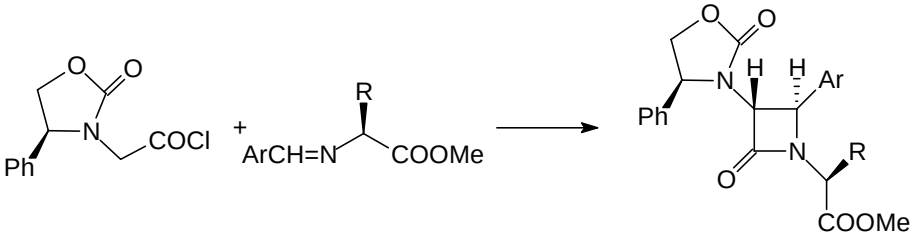
Scheme 32



Double Stereodifferentiation:

The concept of double asymmetric induction has been applied to Staudinger reaction with variable success. High levels of asymmetric induction has been achieved in Staudinger reaction between the Evans-Sjogrens ketene and imines derived from (*R*) and (*S*)-α-amino acid esters[59] (Scheme 33).

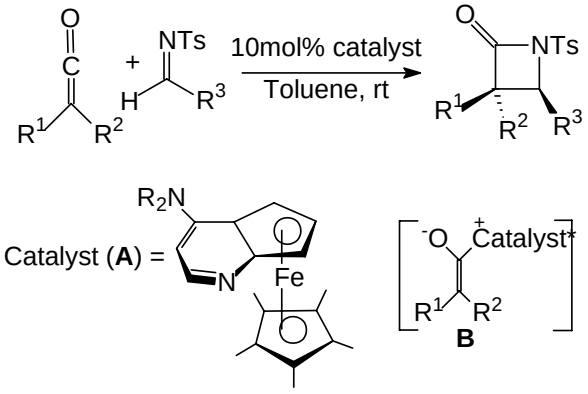
Scheme 33



Catalytic Asymmetric Staudinger reaction:

Recently Hodous and Fu[60] have reported a highly enantioselective synthesis of β-lactams catalyzed by a planar chiral nucleophile (**A**). This chiral catalyst (**A**) was found to be very effective in promoting the [2+2] cycloaddition reaction of symmetrical and unsymmetrical ketenes with variety of imines (Scheme 34). The reaction was proposed to proceed through the intermediate (**B**), similar to what Lectka[61] has observed.

Scheme 34



Mechanism of Staudinger reaction:

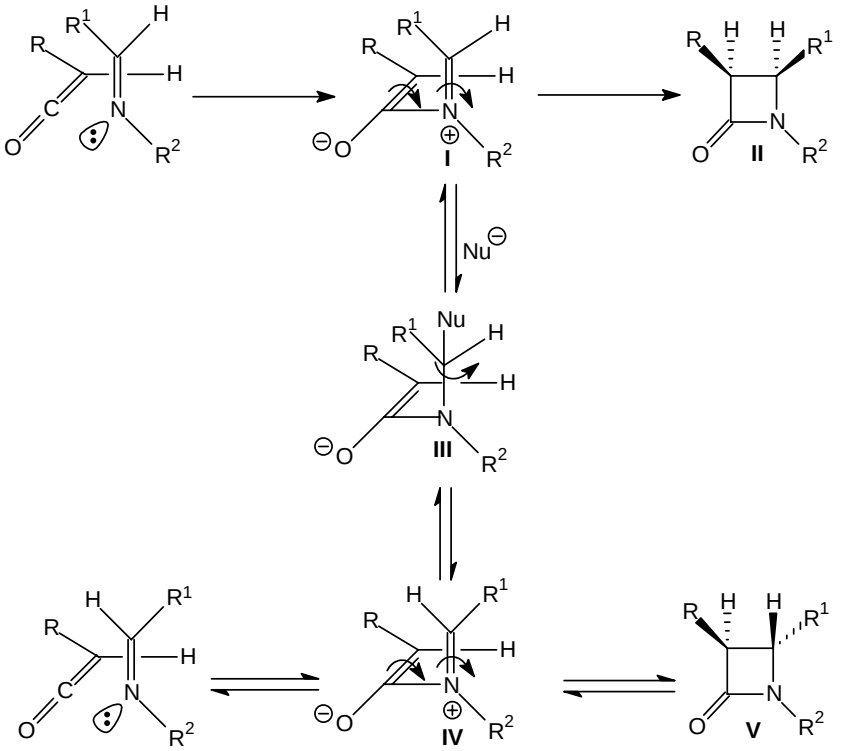
Although the ketene-imine cycloaddition reaction (Staudinger reaction) has been known for several decades, the mechanism and stereo chemical outcome of this reaction is still obscure. Efforts in this aspect have resulted in several papers by various groups.[62] Based on these results; a two-step zwitterionic mechanism has been preferred over a concerted [2+2] cycloaddition reaction. Lynch *et al.*[36a] have established the formation of intermediate ketene. They found that the treatment of (*R*)-3-hydroxybutyric acid chloride with diisopropylamine in a FT-IR cell displayed a strong band at 2120 cm^{-1}, which they assigned to a ketene. The involvement of zwitterionic intermediate has also been proven by various spectroscopic methods and trapping experiments.[63] The possibility of acylation of imine with acid chloride under the reaction condition has been ruled out as the acid chloride when it reacts with imine in the absence of base leads to the formation of amide instead of β-lactam

It has been postulated that the LUMO of the ketene carbonyl is attacked by the HOMO of the imine in an orthogonal approach, in a plane perpendicular to the substituents of the ketene, resulting in the formation of the zwitterionic intermediate **I** (Scheme 1.35).[64] This hypothesis was supported by semi-empirical molecular orbital

calculations (MNDO) of a transition intermediate between ketene and N-methyl-2-methylimine.[35] It is further believed that the attack of the imine occurs from the less hindered side of the ketene, resulting in the zwitterionic intermediate **I**. Rotation of the imine into the plane of the ketene followed by a conrotatory ring closure produces the thermodynamically less stable *cis* β-lactam **II** in which the two hydrogens (or small substituents) are *cis* to each other. The well-known preference for the formation of *trans* β-lactams with cyclic imines can be explained similarly. An orthogonal approach between the ketene and imine will produce the zwitterionic intermediate **IV**, which on conrotatory ring closure will give *trans* β-lactam (Scheme 35).

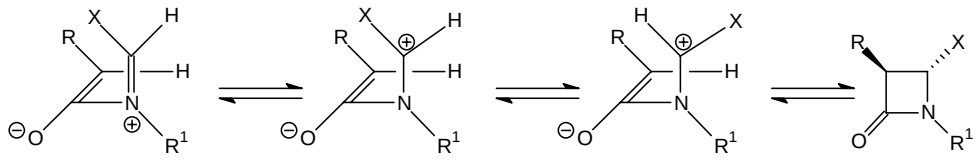
This mechanism also successfully explains the formation of *cis*-*trans* mixture in the Staudinger reaction. A nucleophile can add to the zwitterionic intermediate **I** or **IV** to form intermediate **III**. The loss of nucleophile from intermediate **III** after C-N bond rotation can result in formation of **IV** and subsequent trans β-lactam **V**. The intermediate **III** can also revert back to **I** and form *cis* β-lactam **II**. Thus the ratio of *cis* and *trans* isomers depends upon the formation and stability of intermediate **I** and **IV** (Scheme 35). It was also observed that the initially formed *cis* product could undergo base catalyzed isomerisation to produce more stable *trans* product.[65]

Scheme 35

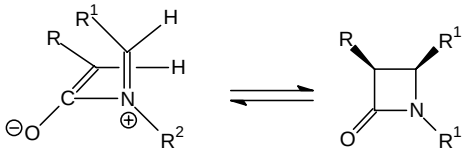


The formation of *trans* isomer by using imidates, thioimidates and sometimes C-aryl imines and potentially C-alkyl imines can be explained by the ability of these groups to stabilize the positive charge of the zwitterionic intermediate by the inductive or mesomeric effect. This allows the isomerisation of *trans* iminium ion to the sterically less crowded *cis* iminium ion, which on ring closure will generate, *trans* β-lactam (Scheme 36). On the contrary, imine possessing electron withdrawing substituents on the imine carbon, like α-carbonyl group or halomethyl group, prevents the C-N bond rotation of the zwitterionic intermediate and produces *cis* isomer. A detailed account of semi-empirical calculation reported by Cossio *et al.*[62c] also supports the Ketene-Imine cycloaddition mechanism.

Scheme 36



X = OR, SR, aryl, alkyl



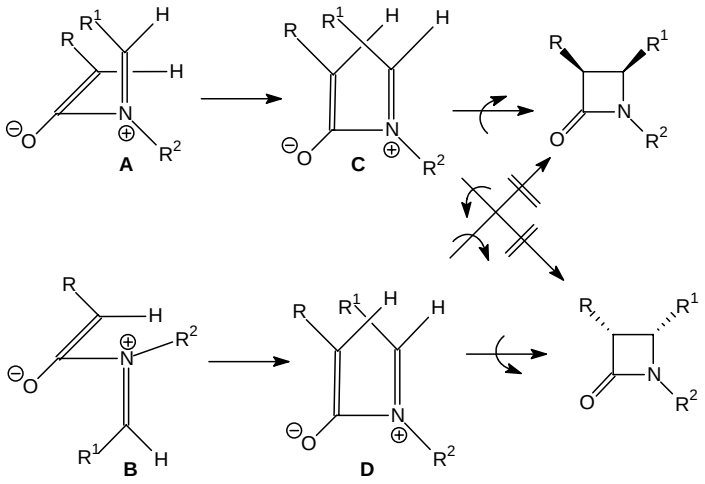
R^1 = COPh, $COOCH_3$, CH_2Cl, CH_2F

Asymmetric Induction:

Asymmetry can be induced in ketene-imine cycloaddition by controlling the orientation of the imine with respect to the plane of the ketene. The ketene can be approached by the imine either from the top face or from bottom face to produce two possible zwitterionic intermediates **A** and **B** respectively (Scheme 37). Before conrotatory ring closure can take place, the intermediates **A** and **B** have to undergo 90^o rotation around the C-N bond to produce two more intermediates **C** and **D** respectively. The conrotatory ring closure of these intermediates **C** and **D** will produce enantiomeric *cis* β-lactams. These intermediates **C** and **D** can also be formed from **A** and **B** by rotating through 270^o around the C-N bond. According to the principle of least motion, the transformation of **A** to **C** and **B** to **D** is favored, as this requires only 90^o rotation.

It has been pointed out by Hegedus *et al.*[62a] that the conrotatory ring closure of the intermediate **C** can occur only in clockwise direction as the counterclockwise ring closure would necessitate that the hydrogen of the ketene and R^1 of the imine to pass through each other. This is of importance for chiral induction, because a counterclockwise rotation would generate the enantiomeric β-lactam. The opposite is true for intermediate **D**, which can undergo only counterclockwise conrotatory ring closure.

Scheme 37



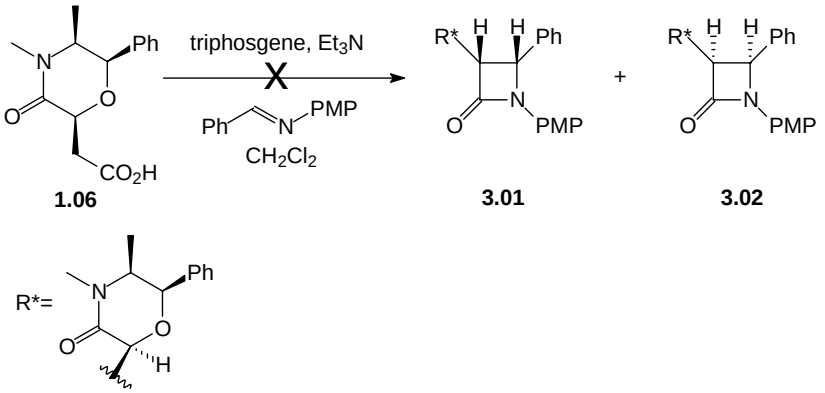
3.2: Present work

Our objective in undertaking this study was to probe the effect of steric disposition on the stereoselectivity in β-lactam ring construction *via* Staudinger reaction using chiral acids derived from 1*R*, 2*S* ephedrine as a chiral pool.

3.3: Results and discussion

The chiral acid **1.06** derived from ephedrine (see Chapter 1) was used in the Staudinger reaction in presence of triphosgene as an acid activator and imine (derived from benzaldehyde and aniline) in dichloromethane solvent at reflux temperature. This reaction did not work and β-lactam was not formed in the reaction either at room temperature or at reflux temperature (Scheme 38).

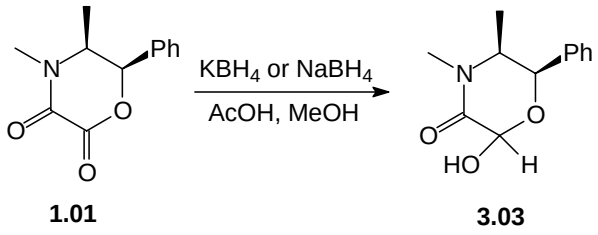
Scheme 38



We thought that the failure of the reaction could be due to the absence of a hetero-atom at the beta position which could stabilize the ketene which is an intermediate in the Staudinger reaction.

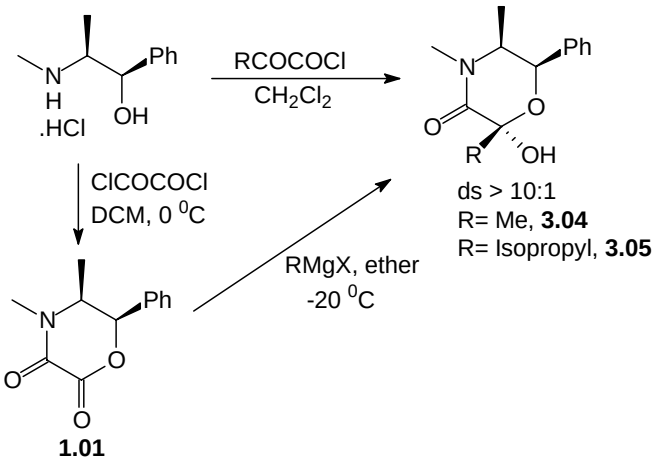
We next investigated the selective reduction of lactone carbonyl. Reduction was done by $NaBH_4$ or KBH_4 in methanol solvent in presence of acetic acid which gave the hemiketal **3.03** (75%) as a mixture of diastereomers (Scheme 39).

Scheme 39



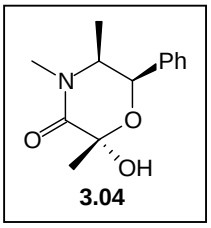
The diastereoselectivity for this reaction was 68% (84:16 diastereomer ratio). Next, we investigated the addition of Grignard reagents on the lactone carbonyl. In this case, the hemiketals were obtained in good yields (90-92%) and also the diastereoselectivity was found to be very high (>10/1, Scheme 40). The stereochemistry at the hemiketal carbon was assigned as '*S*' by comparison of the spectral data (IR, ^{1}H NMR and ^{13}C NMR) with the hemiketal obtained earlier.[66]

Scheme 40



Comparison of the optical rotation with the reported value also confirmed the stereochemistry at the hemiketal center which is '*S*'.

The IR spectrum of **3.04** showed a broad band at 3340 cm^{-1} which is attributed to the hydroxy group and a sharp peak at 1635 cm^{-1} that corresponds to the amide carbonyl. Further the ^1H NMR and ^{13}C NMR data confirmed its structure.



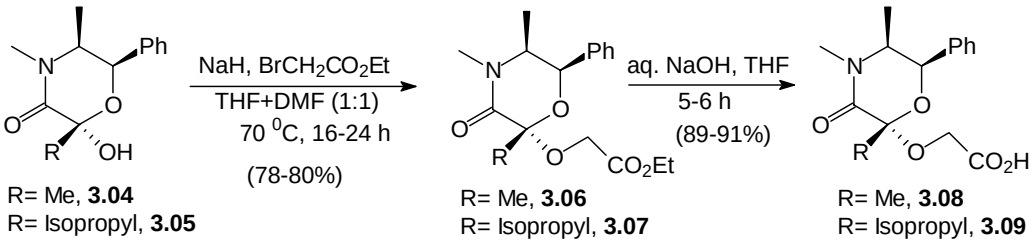
3.04

The ^1H NMR spectrum of **3.04** showed a doublet at 0.93 ppm (J = 6.5 Hz) which corresponds to the methyl group in the ephedrine part. The methyl group attached to the hemiketal center appeared as a singlet at 1.71 ppm. The methyl group attached to the nitrogen appeared as a singlet at 2.99 ppm. The characteristic doublet of quartet for the methine proton appeared at 3.43 ppm (J = 2.9, 6.5 Hz). The broad singlet at 4.58 ppm is for the hydroxy proton. The benzylic proton appeared at 5.47 ppm (J = 2.9 Hz). The aromatic protons appeared in the range 7.23-7.36 ppm. The visible peak for the minor diastereomer appeared at 5.16 ppm (J = 2.9 Hz) which is for the benzylic proton.

The ^{13}C NMR spectrum of **3.04** showed a peak at 168.7 ppm which is attributed to the carbonyl carbon of the amide. The aromatic *ipso* carbon appeared at 137.4 ppm. The peaks for the aromatic carbons appeared at 125.6, 127.4 and 128.1 ppm. The quaternary carbon attached to amide carbonyl appeared at 95.9 ppm. The benzylic carbon appeared at 71.2 ppm. The peak at 59.2 ppm was attributed to the methine carbon attached to nitrogen. The methyl group attached to the nitrogen appeared at 33.5 ppm. The methyl group attached to the hemiketal carbon appeared at 26.3 ppm. The methyl group from the ephedrine part appeared at 11.9 ppm.

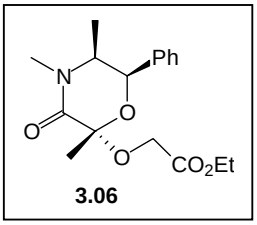
O-alkylation of the hemiketal OH with ethylbromoacetate in presence of NaH as a base in a mixture of THF and DMF (1:1) as a solvent gave the *O*-alkylated ester **3.06** and **3.07** (Scheme 41) in very good yields (78-80%).

Scheme 41



The structure of **3.06** was established by IR, ^{1}H NMR and ^{13}C NMR data. IR spectrum of **3.06** showed a sharp band at 1753 cm^{-1} which corresponds to the ester carbonyl and a peak at 1659 cm^{-1} for the amide carbonyl.

The ^{1}H NMR spectrum of **3.06** showed a doublet at 0.96 ppm (J = 6.3 Hz) which was attributed to the methyl group attached to the methine carbon. The triplet at 1.11 ppm (J = 7.3 Hz) corresponds to the methyl group in the ethyl ester part. The singlet at 1.67 ppm corresponds to the methyl group attached to the quaternary carbon. The methyl group attached to the nitrogen appeared at 3.04 ppm. The characteristic doublet of quartet for the methine proton in the chiral auxiliary part appeared in the range 3.43-3.53 ppm (J = 2.9, 6.3 Hz). The methylene protons in the ethyl group appeared as a quartet in the range 3.90-4.04 ppm (J = 7.3 Hz). The protons on the methylene carbon attached to ester carbonyl appeared as a singlet at 4.18 ppm. The benzylic proton appeared as a doublet at 5.62 ppm (J = 2.9 Hz). The aromatic protons appeared in the range 7.20-7.47 ppm.



3.06

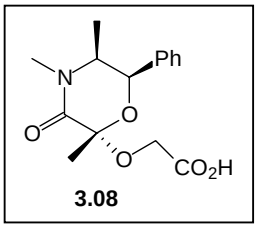
The ^{13}C NMR spectrum of **3.06** showed two peaks at 165.8 and 169.8 ppm which correspond to the amide carbonyl and the ester carbonyl respectively. The aromatic *ipso* carbon appeared at 137.0 ppm. The aromatic carbons appeared at 125.5, 127.5 and 128.2 ppm. The quaternary carbon attached to the amide carbonyl appeared at 99.3 ppm. The benzylic carbon appeared at 71.2 ppm. The methylene carbon attached to amide carbonyl appeared at 60.7 ppm. The peak at 59.8 ppm corresponds to the methylene carbon attached to oxygen. The methine carbon attached to nitrogen appeared at 59.0 ppm. The methyl group attached to the nitrogen appeared at 33.6 ppm. The methyl group attached

to the quaternary carbon appeared at 21.4 ppm. The peak at 13.9 ppm corresponds to the methyl carbon from the ethyl ester part. The peak at 12.2 ppm was attributed to the methyl carbon in the ephedrine part.

Hydrolysis of the esters **3.06** and **3.07** with aqueous NaOH (Scheme 41) gave the chiral acids **3.08** and **3.09** respectively in excellent yields (89-91%) which were characterized by spectral data. The structure of **3.08** was established by IR, ^{1}H NMR and ^{13}C NMR data.

IR spectrum of **3.08** showed a broad band at 3418 cm^{-1} which was attributed to the hydroxy group of the carboxylic acid. The sharp peaks at 1738 and 1651 cm^{-1} corresponds to the acid carbonyl and amide carbonyl groups respectively.

The ^{1}H NMR spectrum of **3.08** showed a doublet at 0.98 ppm (J = 6.4 Hz) which was attributed to the methyl group attached to the methine carbon. The singlet at 1.68 ppm corresponds to the methyl group attached to the quarternary carbon. The methyl group attached to the nitrogen appeared at 3.05 ppm. The characteristic doublet of quartet for the methine proton in the chiral auxiliary part appeared in the range 3.44-3.60 ppm (J = 2.9, 6.4 Hz). The methylene protons attached to the oxygen appeared as two doublets separately at 4.12 ppm and 4.20 ppm (J = 16.6 Hz). The benzylic proton appeared as a doublet at 5.46 ppm (J = 2.9 Hz). The aromatic protons appeared in the range 7.10-7.50 ppm. The broad singlet at 8.75 ppm was attributed to the proton of the carboxylic acid.



3.08

The ^{13}C NMR spectrum of **3.08** showed two peaks at 166.1 and 172.1 ppm which correspond to the amide carbonyl and the acid carbonyl respectively. The aromatic *ipso* carbon appeared at 136.3 ppm. The aromatic carbons appeared at 125.0, 127.2 and 127.9 ppm. The quaternary carbon attached to the amide carbonyl appeared at 98.7 ppm. The benzylic carbon appeared at 70.7 ppm. The methylene carbon attached to amide carbonyl appeared at 58.8 ppm. The methine carbon attached to nitrogen appeared at 58.6 ppm. The methyl group attached to nitrogen appeared at 33.4 ppm. The methyl group attached to the quaternary carbon appeared at 20.9 ppm. The peak at 11.7 ppm was attributed to the methyl carbon in the ephedrine part.

The chiral acids **3.08** and **3.09** derived from ephedrine were then subjected to Staudinger reaction with different imines in presence of triphosgene as an acid activator. Triphosgene converts acid to acid chloride *in situ* in presence of triethyl amine which

then reacts with imines to give β-lactams (Scheme 42). This reaction was found to be stereoselective and gave only *cis* β-lactams in good yields but moderate diastereoselectivity (1:1 to 1.5:1 by ^{1}H NMR of crude β-lactams). The assignment of *cis* stereochemistry for the β-lactam protons is based on the observed vicinal coupling constant (~4-5 Hz) of β-lactam ring protons. This reaction did not give *trans* β-lactams which has a low vicinal coupling constant (~1-1.5 Hz) for H3 and H4 protons of the β-lactam ring.

Scheme 42

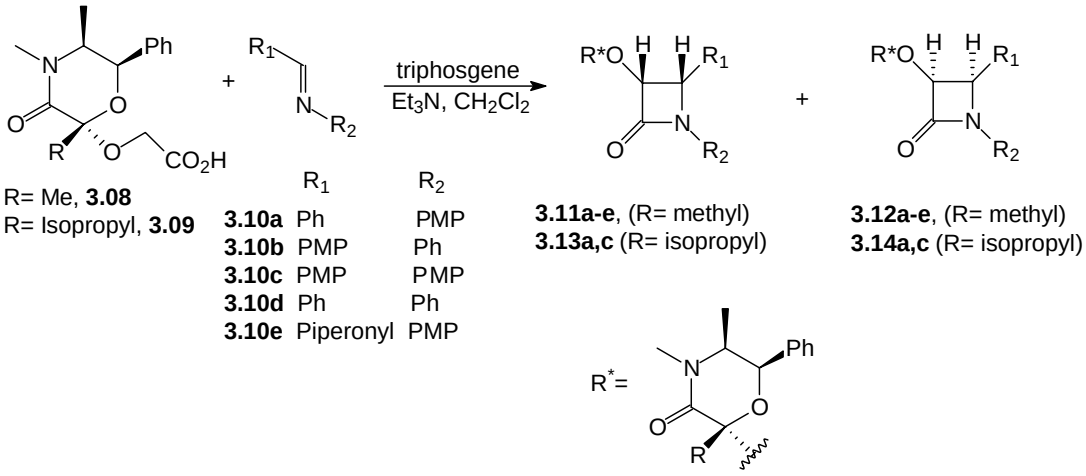


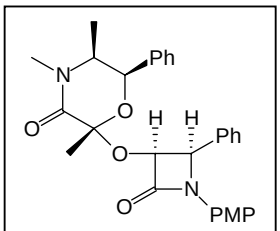
Table 1. Synthesis of β-lactams **3.11-3.14** by Staudinger reaction.

S. No.	R	R^1	R^2	Product (β-lactams) % yield[a]	Total yield[b] (%)	ds[c]
1	Me	Ph	PMP	**3.11a** (35%) & **3.12a** (35%)	70	50:50
2	Me	PMP	Ph	**3.11b** (36%) & **3.12b** (24%)	60	61:39
3	Me	PMP	PMP	**3.11c** (42%) & **3.12c** (23%)	65	65:35
4	Me	Ph	Ph	**3.11d** (36%) & **3.12d** (29%)	65	55:45
5	Me	piperonyl	PMP	**3.11e** & **3.12e** (30%)	55	62:38
6	*iso*-propyl	Ph	PMP	**3.13a** (30%) & **3.14a** (26%)	56	60:40
7	*iso*-propyl	PMP	PMP	**3.13c** (25%) & **3.14c**	50	65:35

[a] Isolated yield of the pure diastereomers after flash column chromatography
[b] Total yield of the pure diastereomers separated by flash column chromatography
[c] Ratio of diastereomers from ^{1}H NMR and also by HPLC of crude reaction mixture of β-lactams.

In most of the cases both the diastereomers of the β-lactams **3.11a-d**, **3.12a-e**, **3.13a** and **3.14a** could be separated by careful flash column chromatography while in some cases only one of the diastereomers **3.12e** and **3.13c** could be separated whereas the other diastereomer **3.11e** and **3.14c** came as a mixture with the amide (a side product obtained by reaction of amine and acid), which was difficult to separate by column chromatography or crystallization.

The structures of β-lactams **3.11**, **3.12**, **3.14** and **3.15** were established by IR, ^{1}H NMR and ^{13}C NMR spectral data.



3.12a

IR spectrum of **3.12a** showed a sharp peak at 1751 cm^{-1} which is characteristic of the β-lactam carbonyl group. The peak at 1649 cm^{-1} corresponds to the amide carbonyl.

The ^{1}H NMR spectrum of **3.12a** showed a doublet at 0.79 ppm (J = 6.4 Hz) which was attributed to the methyl group attached to the methine carbon. The singlet at 1.50 ppm for three protons corresponds to the methyl group attached to the quarternary carbon. The methyl group attached to the nitrogen appeared as a singlet at 2.87 ppm. The characteristic doublet of quartet for the methine proton in the chiral auxiliary part appeared in the range 2.89-3.05 ppm (J = 2.9, 6.4 Hz). The methyl group attached to oxygen appeared as a singlet at 3.71 ppm. The benzylic proton appeared as a doublet at 4.57 ppm (J = 2.9 Hz). The C3 and C4 protons of the β-lactam ring appeared as two characteristic doublets at 5.57 and 5.16 ppm (J = 4.9 Hz). The coupling constant of 4.9 Hz is typical of a *cis* β-lactam. The ortho protons of the *p*-methoxyphenyl group appeared as a doublet at 6.75 ppm (J = 8.3 Hz). All other aromatic protons (twelve) appeared as a multiplet in the range 7.09-7.50 ppm.

The ^{13}C NMR spectrum of **3.12a** showed two peaks at 163.7 and 165.3 ppm which correspond to the amide carbonyl and the β-lactam carbonyl groups. The aromatic *ipso* carbon attached to oxygen appeared at 157.0 ppm. The aromatic *ipso* carbon attached to nitrogen appeared at 136.8 ppm. The two aromatic *ipso* carbons attached to carbon appeared at 130.6 and 134.3 ppm. The aromatic carbons appeared at 114.1, 118.6, 125.4, 127.4, 128.0 and 128.6 ppm. The quaternary carbon attached to the amide carbonyl appeared at 98.5 ppm. The C3 carbon of the β-lactam ring appeared at 77.7 ppm. The benzylic carbon appeared at 70.6 ppm. The C4 carbon of the β-lactam ring appeared at 63.0 ppm. The methine carbon attached to nitrogen appeared at 58.8 ppm. The methyl group attached to oxygen appeared at 55.2 ppm. The methyl group attached

to the nitrogen appeared at 33.1 ppm. The methyl group attached to the quaternary carbon appeared at 22.2 ppm. The peak at 12.0 ppm is attributed to the methyl carbon in the ephedrine part. This compound gave satisfactory elemental analysis data.

The stereochemistry of the β-lactam ring was confirmed by single crystal X-ray analysis of **3.12b**.

X-Ray structure determination of 3.12b:

The stereochemistry of the newly formed centers (C-3 and C-4) in **3.12b** was ascertained from the single crystal X-ray analysis. X-ray quality crystals of **3.12b** were obtained by careful crystallization from methanol. The data were collected on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 23.27°. Based on the X-ray structure, the stereochemistry was assigned as 3*S*, 4*R* for the diastereomer **3.12b**.

Table 2. Crystal data and structure refinement for **3.12b**

Empirical formula	$C_{29}H_{30}N_2O_5$
Formula weight	486.55
Temperature	293(2) K
Wavelength	0.71073 A^o
Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 5.765 (2) A^o b = 15.103 (5) A^o c = 29.301 (9) A^o
Volume	2551.2 (14) A^{o3}
Z, Calculated density	4, 1.267 mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	1032
Crystal size	0.57 x 0.11 x 0.03 mm

Theta range for data collection	1.52 to 23.27 deg.
Limiting indices	-6<=h<=6, -16<=k<=16, -29<=l<=32
Reflections collected / unique	18110 / 3673 [R (int) = 0.0531]
Completeness to theta = 23.27	99.9 %
Max. and min. transmission	0.9978 and 0.9522
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3673 / 0 / 329
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma (I)]	R1 = 0.0373, wR2 = 0.0748
R indices (all data)	R1 = 0.0572, wR2 = 0.0815
Absolute structure parameter	0.4 (12)
Largest diff. peak and hole	0.115 and -0.110 e. A^{o-3}

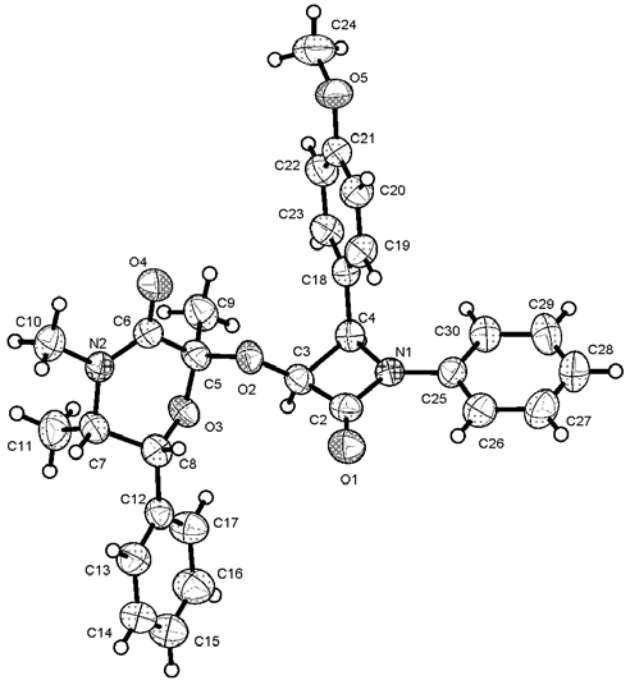


Figure 7. ORTEP diagram of **3.12b**

3.4: Conclusion

Application of ephedrine as a chiral auxiliary in the diastereoselective synthesis of β-lactams by Staudinger reaction has been studied. Chiral acids derived from ephedrine when subjected to Staudinger reaction gave a mixture of diastereomers with *cis* stereochemistry with moderate diastereoselectivity (1:1 to 1.5:1) by ^{1}H NMR of crude β-lactam. In most of the cases both the diastereomers of β-lactams could be effectively separated by flash column chromatography and the stereochemistry at the β-lactam ring was assigned on the basis of single crystal X-ray data.

3.5: Experimental

2-Hydroxy-4,5-dimethyl-6-phenyl-morpholin-3-one (3.03):

To a solution of dione **1.01** (499 mg, 2.28 mmol) in methanol (30 mL) was added acetic acid (0.9 mL, 0.06 mmol) and the resulting solution was cooled to 0 °C. KBH_4 (3.319 g, 61.5 mmol) was then added portionwise at 0 °C. Further the reaction mixture was stirred at RT for 2 h and ice was added. Solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 15 mL). Organic layer was washed with brine solution, dried (Na_2SO_4) and concentrated to give the crude compound which on purification by flash column chromatography gave **3.03** (378 mg, 75%) as a white solid with the diastereomeric ratio 84:16 (^{1}H NMR).

IR ($CHCl_3$):

1649, 3383 cm^{-1}.

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

δ 0.96 (d, 3H, *J* = 6.8 Hz, CHC*H*$_3$), 3.04 (s, 3H, NC*H*$_3$), 3.40-3.57 (dq, 1H, *J* = 3.0, 6.8 Hz, C*H*CH$_3$), 5.37 (bs, 1H, O*H*), 5.48 (s, 1H, *H*CO), 5.57 (d, 1H, *J* = 3.0 Hz, PHC*H*), 7.23-7.36 (m, 5H, Ar*H*).

Visible peaks for minor diastereomer:

δ 1.04 (d, 3H, *J* = 6.4 Hz, CHC*H*$_3$), 2.69 (s, 3H, NC*H*$_3$), 5.15 (d, *J* = 2.9 Hz, PhC*H*), 6.04 (bs, 1H, O*H*).

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

δ 12.2 (*C*H$_3$CH), 33.2 (N*C*H$_3$), 59.0 (N*C*H), 71.3 (Ph*C*H), 90.6 (O*C*O), 125.7 (Ar*C*), 127.6 (Ar*C*), 128.2 (Ar*C*), 137.4 (Ar*Cipso*), 166.8 (*C*=O).

MS (*m/z*):

221 (M^+).

Analysis for $C_{12}H_{15}NO_3$:

Calculated: C, 65.14; H, 6.83; N, 6.33; Obtained: C, 65.41; H, 6.72, N, 6.60.

General procedure for the preparation of hemiketals 3.04 and 3.05:

To a suspension of dione **1.01** (1 equiv.) in anhydrous ether at –20 °C was added the Grignard reagent (5 equiv.) and the mixture was stirred at –20 °C for 1 h. Saturated aqueous NH_4Cl was added and the reaction mixture was warmed up to ambient temperature. The precipitated solids were dissolved in water and the solution was

extracted in ethyl acetate. The combined organic layer was dried (Na_2SO_4) and concentrated to give hemiketals **3.04** and **3.05**, which were purified by column chromatography.

(2*S*,5*S*,6*R*)-2-Hydroxy-2,4,5-trimethyl-6-phenyl-morpholin-3-one (3.04):

The reaction of **1.01** (219 mg, 1 mmol) with MeMgI (5 mL, 1M solution in ether, 5 mmol) in anhydrous ether (3 mL) gave crude methyl hemiketal (de=85%, ^{1}H NMR). The crude compound upon purification by flash column chromatography (3/2 EA/PE) gave 219 mg (90%) of **3.04** (de>95%).

mp: 79-80 ^oC

IR ($CHCl_3$):

1635, 3340 cm^{-1}.

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

δ 0.93 (d, 3H, *J* = 6.5 Hz, CHC*H*$_3$), 1.71 (s, 3H, C*H*$_3$CO), 2.99 (s, 3H, NC*H*$_3$), 3.43 (dq, 1H, *J* = 2.9, 6.5 Hz, C*H*CH$_3$), 4.58 (bs, 1H, O*H*), 5.47 (d, 1H, *J* = 2.9 Hz, PhC*H*), 7.23-7.36 (m, 5H, Ar*H*).

Visible peak for minor diastereomer:

δ 5.16 (d, *J* = 2.9 Hz, PhC*H*).

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

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

MS (*m/z*):

235 (M^+).

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

Calculated: C, 66.36; H, 7.28; N, 5.05; Obtained: C, 66.38; H, 7.43, N, 5.97.

Optical rotation:

$[\alpha]_D^{25}$ = –107.4 (*c* 1.1, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-Hydroxy-2-isopropyl-4,5-dimethyl-6-phenyl-morpholin-3-one (3.05):

The reaction of **1.01** (219 mg, 1 mmol) with isopropyl magnesium bromide (5 mL, 1M solution in ether, 5 mmol) in anhydrous ether (3 mL) gave crude isopropyl hemiketal as a single diastereomer (by ^{1}H NMR), which was passed through a short silica gel column to furnish 242 mg (92%) of **3.05** as a solid.

mp: 100-102 ^{o}C

IR ($CHCl_3$):

1651, 3400 cm^{-1}.

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

δ 0.96 (d, 3H, *J* = 6.7 Hz, CHC*H*$_3$), 0.99 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)$_2$), 1.14 (d, 6H, *J* = 6.9 Hz, CH(CH$_3$)$_2$), 2.35-2.55 (m, 1H, C*H*(CH$_3$)$_2$), 3.03 (s, 3H, NC*H*$_3$), 3.48 (dq, 1H, *J* = 3.0, 6.7 Hz, CH$_3$C*H*), 3.70 (bs, 1H, O*H*), 5.5 (d, 1H, *J* = 3.0 Hz, PhC*H*), 7.20-7.45 (m, 5H, Ar*H*).

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

δ 12.2 (*C*H$_3$), 14.2 (*C*H$_3$), 17.7 (*C*H$_3$), 33.2 (N*C*H$_3$), 35.3 (*C*H(CH$_3$)$_2$), 58.7 (CH$_3$*C*H), 70.2 (Ph*C*H), 98.7 (*C*OH), 125.3 (Ar*C*), 127.1 (Ar*C*), 127.9 (Ar*C*), 137.6 (Ar*Cipso*), 168.9 (N*C*O).

MS (*m/z*):

263 (M^+).

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

Calculated: C, 68.42; H, 8.04; N, 5.32; Obtained: C, 68.42; H, 7.74; N, 5.28.

Optical rotation:

$[\alpha]_D^{25} = -146.5$ (*c* 2.0, $CHCl_3$).

Typical procedure for preparation of Ethyl (2*S*,5*S*,6*R*)-[(2,4,6-trimethyl-3-*oxo*-6-phenylmorpholin-2yl)oxy]acetate (3.06):

To a suspension of sodium hydride (108 mg, 4.5 mmol) in DMF (2 mL) and THF (2 mL) at 0 °C was added methyl hemiketal solution **3.04** (705 mg, 3 mmol) dropwise in DMF (2 mL) and THF (2 mL) and the resulting solution was stirred at 0 °C for 10 min. Ethyl bromoacetate (0.33 mL, 3 mmol) was then added dropwise and the resulting solution was heated at 70 °C for 16 h. Ice was added to the reaction mixture. Ethyl acetate (15 mL) and water (15 mL) were added and organic layer was separated. Organic layer was washed with water (3 x 15 mL), brine (3 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue upon purification by column chromatography (1:1) EA/PE furnished 750 mg (78%) of **3.06** as a white solid.

mp: 87-89 °C.

IR ($CHCl_3$):

1659, 1753 cm^{-1}.

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

δ 0.96 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 1.11 (t, 3H, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 1.67 (s, 3H, C*H*$_3$CO), 3.04 (s, 3H, NC*H*$_3$), 3.43-3.53 (dq, 1H, *J* = 2.9, 6.3 Hz, NC*H*), 3.90-4.04 (q, 2H, *J* = 7.3 Hz, C*H*$_2$O), 4.18 (s, 2H, C*H*$_2$CO), 5.62 (d, 1H, *J* = 2.9 Hz, PhC*H*), 7.20-7.47 (m, 5H, Ar*H*).

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

δ 12.2 (*C*H$_3$CH), 13.9 (*C*H$_3$CH$_2$), 21.4 (*C*H$_3$CO), 33.6 (N*C*H$_3$), 59.0 (N*C*H), 59.8 (*C*H$_2$O), 60.7 (*C*H$_2$CO), 71.2 (Ph*C*H), 99.3 (O*C*O), 125.5 (Ar*C*), 127.5 (Ar*C*), 128.2 (Ar*C*), 137.0 (Ar*Cipso*), 165.8 (amide *C*O), 169.8 (ester *C*O).

MS (*m/z*):

321 (M^+).

Analysis for $C_{17}H_{23}NO_5$:

Calculated: C, 63.53; H, 7.21; N, 4.36; Obtained: C, 63.80; H, 7.50; N, 4.69.

Optical rotation:

$[\alpha]_D^{25} = -80.7$ (*c* 1.1, $CHCl_3$).

(2*S*,5*S*,6*R*)-(2-Isopropyl-4,5-dimethyl-3-oxo-6-phenyl-morpholin-2-yloxy)-acetic acid ethyl ester (3.07):

Following the typical procedure, reaction of NaH (108 mg, 4.5 mmol) suspension in DMF (2 mL) and THF (2 mL) with isopropyl hemiketal **3.05** (789 mg, 3 mmol) solution in DMF (2 mL) and THF (2 mL) followed by the dropwise addition of ethylbromoacetate (0.33 mL, 3 mmol) and heating the resulting reaction mixture for 24 h gave after work-up 838 mg (80%) of **3.07** as a gum.

IR ($CHCl_3$):

1659, 1755, 3501 cm^{-1}.

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

δ 0.95 (d, 3H, *J* = 6.9 Hz, C*H*$_3$CH), 1.03-1.13 (two merged doublets, 6H, (C*H*$_3$)$_2$CH), 1.20 (t, 3H, *J* = 7.3 Hz, C*H*$_3$CH$_2$O), 2.38-2.59 (m, 1H, (CH$_3$)$_2$C*H*), 2.99 (s, 3H, NC*H*$_3$), 3.45-3.60 (dq, 1H, *J* = 3.4, 6.9 Hz, NC*H*), 3.98-4.15 (m, 2H, C*H*$_2$O), 4.19 (d, 1H, *J* = 16.1 Hz, C*H*$_2$CO), 4.43 (d, 1H, *J* = 16.1 Hz, C*H*$_2$CO), 5.77 (d, 1H, *J* = 3.4 Hz, PhC*H*), 7.10-7.50 (m, 5H, Ar*H*).

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

δ 12.3 (*C*H_3CH), 13.7 (*C*H_3), 15.2 (*C*H_3), 17.2 (*C*H_3), 31.6 (*C*H(CH_3)$_2$, 33.0 (NCH_3), 58.5 (N*C*H), 60.3 (*C*H_2O), 60.9 (*C*H_2CO), 70.5 (Ph*C*H), 101.6 (*Cquat*), 125.3 (Ar*C*), 127.2 (Ar*C*), 128.0 (Ar*C*), 137.2 (Ar*Cipso*), 165.1 (amide *C*O), 170.1 (ester *C*O).

MS (*m/z*):

349 (M^+).

Analysis for $C_{19}H_{27}NO_5$:

Calculated: C, 65.31; H, 7.79; N, 4.01; Obtained: C, 65.60; H, 7.98; N, 4.30.

Optical rotation:

$[\alpha]_D^{25} = -130.0$ (*c* 1.2, $CHCl_3$).

Typical procedure for (2*S*,5*S*,6*R*)-[(2,4,6-trimethyl-3-*oxo*-6-phenylmorpholin-2yl)oxy]acetic acid (3.08):

To the solution of **3.06** (963 mg, 3 mmol) in THF (9 mL) was added aqueous NaOH (1M, 9 mL) and stirred at ambient temperature for 5-6 h. THF was removed under reduced pressure. Aqueous layer was acidified with conc. HCl dropwise and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine solution (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish 800 mg (91%) of **3.08** as a white solid.

mp: 98-100 °C.

IR ($CHCl_3$):

1651, 1738, 3418 cm^{-1}.

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

δ 0.98 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH), 1.68 (s, 3H, C*H*$_3$CO), 3.05 (s, 3H, NC*H*$_3$), 3.44-3.60 (dq, 1H, *J* = 2.9, 6.4 Hz, NC*H*), 4.12 (d, 1H, *J* = 16.6 Hz, C*H*$_2$CO), 4.30 (d, 1H, *J* = 16.6 Hz, C*H*$_2$CO), 5.46 (d, 1H, *J* = 2.9 Hz, PhC*H*), 7.10-7.50 (m, 5H, Ar*H*), 8.75 (bs, 1H, COO*H*).

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

δ 11.7 (*C*H_3CH), 20.9 (*C*H_3CO), 33.4 (NC*H*$_3$), 58.6 (N*C*H), 58.8 (*C*H_2CO), 70.7 (PhCH), 98.7 (O*C*O), 125.0 (Ar*C*), 127.2 (Ar*C*), 127.9 (Ar*C*), 136.3 (Ar*Cipso*), 166.1 (amide *C*O), 172.1 (*C*OOH).

MS (*m/z*):

293 (M^+).

Analysis for $C_{15}H_{19}NO_5$:

Calculated: C, 61.42; H, 6.53; N, 4.78; Obtained: C, 61.70; H, 6.72; N, 4.99.

Optical rotation:

$[\alpha]_D^{25} = -64.9$ (*c* 0.9, $CHCl_3$).

Preparation of (2*S*,5*S*,6*R*)-(2-Isopropyl-4,5-dimethyl-3-oxo-6-phenyl-morpholin-2-yloxy)-acetic acid (3.09):

Reaction of **3.07** (1.047 g, 3 mmol) in THF (9 mL) with aqueous NaOH (1M, 9 mL) gave after work-up 857 mg (89%) of **3.09** as a gummy solid.

IR ($CHCl_3$):

1645, 1738, 3016 cm^{-1}.

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

δ 0.94 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 1.02-1.14 (two merged triplets, 6H, (C*H*$_3$)$_2$CH), 2.30-2.60 (m, 1H, (CH$_3$)$_2$C*H*), 3.00 (s, 3H, NC*H*$_3$), 3.42-3.62 (dq, 1H, *J* = 2.9, 6.3 Hz, NC*H*), 4.19 (d, 1H, *J* = 16.6 Hz, C*H*$_2$CO), 4.43 (d, 1H, *J* = 16.6 Hz, C*H*$_2$CO), 5.65 (d, 1H, *J* = 2.9 Hz, PhC*H*), 7.15-7.50 (m, 5H, Ar*H*), 7.72 (bs, 1H, COO*H*).

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

δ 12.2 (*C*H$_3$CH), 15.2 ((*C*H$_3$)$_2$CH), 17.1 ((*C*H$_3$)$_2$CH), 31.6 ((CH$_3$)$_2$*C*H), 33.3 (N*C*H$_3$), 58.5 (N*C*H), 60.4 (*C*H$_2$CO), 70.5 (Ph*C*H), 101.6 (*Cquat*), 125.1 (Ar*C*), 127.2 (Ar*C*), 128.0 (Ar*C*), 136.8 (Ar*Cipso*), 165.6 (amide *C*O), 173.4 (*C*OOH).

MS (*m/z*):

321 (M^+).

Analysis for $C_{17}H_{23}NO_5$:

Calculated: C, 63.53; H, 7.21; N, 4.36; Obtained: C, 63.75; H, 7.50; N, 4.62.

Optical rotation:

$[\alpha]_D^{25} = -143.3$ (*c* 0.6, $CHCl_3$).

General procedure for preparation of β-lactams 3.11, 3.12, 3.13 and 3.14:

To the solution of carboxylic acid **3.08**, **3.09** (1 equiv.) in dichloromethane was added triethylamine (6 equiv.) and imine (0.9 equiv.) at –5 °C. To this was added

triphosgene (0.7 equiv.) solution in dichloromethane dropwise over a period of 15 minutes. The reaction mixture was then allowed to warm-up to ambient temperature at which it was stirred for 12 h. The reaction mixture was then diluted with dichloromethane and washed successively with water, saturated $NaHCO_3$, brine solution, dried (Na_2SO_4) and concentrated under reduced pressure to afford β-lactams (mixture of diastereomers) which on purification by flash column chromatography gave pure diastereomers.

Typical procedure for 3.11a & 3.12a:

To a stirred solution of **3.08** (1.172 g, 4 mmol) in dichloromethane (15 mL) was added triethylamine (3.34 mL, 24 mmol) and **3.10a** (0.760 g, 3.6 mmol) at 0 °C. To the resulting solution was added triphosgene (0.831 g, 2.8 mmol) solution in dichloromethane (10 mL) dropwise over a period of 15 min. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 mL) and washed successively with water (2x15 mL), saturated $NaHCO_3$ solution (2 x 15 mL), brine (2 x 15 mL). Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue on purification by flash column chromatography (2:3, EA/PE) gave more polar compound **3.11a** (610 mg, 35%) and less polar compound **3.12a** (610 mg, 35%).

(3*R*,4*S*,2′*S*,5′*S*,6′*R*)-1-(4-methoxyphenyl)-4-phenyl-3-[(2′,4′,5′-trimethyl-3′-oxo-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.11a):

Isolated as a white solid; yield 35%.

mp: 113-115 °C.

IR ($CHCl_3$):

1649, 1751 cm^{-1}.

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

δ 0.84 (d, 3H, *J* = 6.8 Hz, C*H*$_3$CH), 1.70 (s, 3H, C*H*$_3$CO), 2.89 (s, 3H, NC*H*$_3$), 3.15-3.30 (dq, 1H, *J* = 2.9, 6.8 Hz, NC*H*), 3.71 (s, 3H, OC*H*$_3$), 4.63 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.00 (d, 1H, *J* = 5.4 Hz, β-lactam C4*H*), 5.36 (d, 1H, *J* = 5.4 Hz, β-lactam C3*H*), 6.73 (d, 2H, *J* = 8.8 Hz, PMP *ortho H*), 7.10-7.50 (m, 12H, Ar*H*).

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

δ 12.2 (*C*H_3CH), 23.4 (*C*H_3CO), 33.5 (NCH_3), 55.4 (OCH_3), 58.9 (N*C*H), 62.3 (β-lactam *C*4), 71.0 (Ph*C*H), 76.0 (β-lactam *C*3), 99.9 (O*C*O), 114.3 (Ar*C*), 118.7 (Ar*C*), 125.6 (Ar*C*), 127.8 (Ar*C*), 128.4 (Ar*C*), 130.9 (Ar*Cipso*), 133.8 (Ar*Cipso*), 137.1 (Ar*Cipso*), 156.3 (Ar*Cipso*), 164.3 (β-lactam *C*O), 165.2 (amide *C*O).

MS (*m/z*):

486 (M^+).

Analysis for $C_{29}H_{30}N_2O_5$:

Calculated: C, 71.59; H, 6.21; N, 5.76; Obtained: C, 71.80; H, 6.00; N, 5.98.

Optical rotation:

$[\alpha]_D^{25} = -51.0$ (*c* 0.9, $CHCl_3$).

(3*S*,4*R*,2′*S*,5′*S*,6′*R*)-1-(4-methoxyphenyl)-4-phenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.12a):

Isolated as a white solid; yield 35%.

mp: 108-110 °C.

IR ($CHCl_3$):

1649, 1751 cm^{-1}.

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

δ 0.79 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH), 1.50 (s, 3H, C*H*$_3$CO), 2.87 (s, 3H, NC*H*$_3$), 2.89-3.05 (dq, 1H, *J* = 2.9, 6.4 Hz, NC*H*), 3.71 (s, 3H, OC*H*$_3$), 4.57 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.16 (d, 1H, *J* = 4.9 Hz, β-lactam C4*H*), 5.57 (d, 1H, *J* = 4.9 Hz, β-lactam C3*H*), 6.75 (d, 2H, *J* = 8.3 Hz, PMP *ortho H*), 7.09-7.50 (m, 12H, Ar*H*).

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

δ 12.0 (*C*H_3CH), 22.2 (*C*H_3CO), 33.1 (NCH_3), 55.2 (OCH_3), 58.8 (N*C*H), 63.0 (β-lactam *C*4), 70.6 (Ph*C*H), 77.7 (β-lactam *C*3), 98.5 (O*C*O), 114.1 (Ar*C*), 118.6 (Ar*C*), 125.4 (Ar*C*), 127.4 (Ar*C*), 128.0 (Ar*C*), 128.6 (Ar*C*), 130.6 (Ar*Cipso*), 134.3 (Ar*Cipso*), 136.8 (Ar*Cipso*), 157.0 (Ar*Cipso*), 163.7 (β-lactam *C*O), 165.3 (amide *C*O).

MS (*m/z*):

486 (M^+).

Analysis for $C_{29}H_{30}N_2O_5$:

Calculated: C, 71.59; H, 6.21; N, 5.76; Obtained: C, 71.83; H, 6.45; N, 5.99.

Optical rotation:

$[\alpha]_D^{25} = -189.4$ (*c* 1.4, $CHCl_3$).

Other β-lactams **3.11b-d** & **3.12b-e**, **3.13a**, **3.14a** and **3.13c** were also prepared using the similar procedure and in most cases both the diastereomers could be separated by flash column chromatography.

Procedure for preparation of 3.11b & 3.12b:

Following the general procedure, addition of triphosgene (212 mg, 0.71 mmol) solution in DCM (6 mL) to a solution of acid **3.08** (300 mg, 1.02 mmol) and imine (194 mg, 0.92 mmol) in DCM (6 mL) in presence of triethyl amine (0.85 mL, 6.12 mmol) gave a diastereomeric mixture of β-lactams which on purification by flash column chromatography gave **3.11b** (161 mg, 36%) and **3.12b** (107 mg, 24%). Both the diastereomers could be separated by flash column chromatography and its structure was established by spectral data (IR, ^{1}H NMR, ^{13}C NMR).

(3*R*,4*S*,2′*S*,5′*S*,6′*R*)-4-(4-methoxyphenyl)-1-phenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.11b):

Isolated as a gum; yield 36%.

IR ($CHCl_3$):

1649, 1755 cm^{-1}.

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

δ 0.85 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH), 1.73 (s, 3H, C*H*$_3$CO), 2.91 (s, 3H, NC*H*$_3$), 3.16-3.33 (dq, 1H, *J* = 2.9, 6.4 Hz, NC*H*), 3.80 (s, 3H, OC*H*$_3$), 4.63 (d, 1H, *J* = 2.9 Hz, PhC*H*), 4.99 (d, 1H, *J* = 5.4 Hz, β-lactam C4*H*), 5.34 (d, 1H, *J* = 5.4 Hz, β-lactam C3*H*), 6.79 (d, 2H, *J* = 8.8 Hz, PMP *ortho H*), 6.90-7.50 (m, 12H, Ar*H*).

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

δ 12.1 (*C*H$_3$CH), 23.4 (*C*H$_3$CO), 33.5 (NCH$_3$), 55.2 (OCH$_3$), 58.9 (N*C*H), 61.9 (β-lactam *C*4), 71.0 (Ph*C*H), 75.8 (β-lactam *C*3), 100.0 (O*C*O), 113.9 (Ar*C*), 117.5 (Ar*C*), 124.0 (Ar*C*), 125.5 (Ar*C*), 125.6 (Ar*C*), 127.7 (Ar*C*), 128.4 (Ar*C*),

128.9 (Ar*C*), 129.7 (Ar*C*), 137.1 (Ar*Cipso*), 137.4 (Ar*Cipso*), 159.8 (Ar*Cipso*), 165.1 (*C*O), 165.3 (*C*O).

MS (*m/z*):

486 (M^+).

Analysis for $C_{29}H_{30}N_2O_5$:

Calculated: C, 71.59; H, 6.21; N, 5.76; Obtained: C, 71.85; H, 6.40; N, 5.96.

Optical rotation:

$[\alpha]_D^{25} = -64.4$ (*c* 0.9, $CHCl_3$).

(3*S*,4*R*,2′*S*,5′*S*,6′*R*)-4-(4-methoxyphenyl)-1-phenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.12b):

Isolated as a white solid; yield 24%.

mp: 204-205 °C.

IR ($CHCl_3$):

1649, 1755 cm^{-1}.

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

δ 0.81 (d, 3H, *J* = 6.8 Hz, C*H*$_3$CH), 1.50 (s, 3H, C*H*$_3$CO), 2.91 (s, 3H, NC*H*$_3$), 2.96-3.09 (dq, 1H, *J* = 2.9, 6.8 Hz, NC*H*), 3.84 (s, 3H, OC*H*$_3$), 4.57 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.17 (d, 1H, *J* = 4.9 Hz, β-lactam C4*H*), 5.57 (d, 1H, *J* = 4.9 Hz, β-lactam C3*H*), 6.92 (d, 2H, *J* = 8.3 Hz, PMP *ortho H*), 7.00-7.47 (m, 12H, Ar*H*).

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

δ 12.2 (*C*H$_3$CH), 22.5 (*C*H$_3$CO), 33.4 (NCH$_3$), 55.2 (OCH$_3$), 59.0 (NCH), 62.6 (β-lactam *C*4), 70.8 (PhCH), 77.6 (β-lactam *C*3), 98.7 (OCO), 113.6 (Ar*C*), 117.5 (Ar*C*), 124.1 (Ar*C*), 125.4 (Ar*C*), 126.0 (Ar*Cipso*), 127.5 (Ar*C*), 128.2 (Ar*C*), 129.0 (Ar*C*), 129.9 (Ar*C*), 136.9 (Ar*Cipso*), 137.1 (Ar*Cipso*), 159.7 (Ar*Cipso*), 164.6 (*C*O), 165.5 (*C*O).

MS (*m/z*):

486 (M^+).

Analysis for $C_{29}H_{30}N_2O_5$:

Calculated: C, 71.59; H, 6.21; N, 5.76; Obtained: C, 71.80; H, 6.48; N, 5.98.

Optical rotation:

$[\alpha]_D^{25} = -181.5$ (*c* 0.6, $CHCl_3$).

Procedure for preparation of 3.11c & 3.12c:

Following the general procedure, addition of triphosgene (227 mg, 0.76 mmol) solution in DCM (6 mL) to a solution of acid **3.08** (320 mg, 1.09 mmol) and imine (236 mg, 0.98 mmol) in DCM (6 mL) in presence of triethyl amine (0.91 mL, 6.54 mmol) gave a diastereomeric mixture of β-lactams which on purification by flash column chromatography gave **3.11c** (212 mg, 42%) and **3.12c** (116 mg, 23%). Both the diastereomers could be separated by flash column chromatography and their structures were established by spectral data (IR, ^{1}H NMR, ^{13}C NMR).

(3*R*,4*S*,2′*S*,5′*S*,6′*R*)-1,4-Di-(4-methoxyphenyl)-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.11c):

Isolated as a gum; yield 42%.

IR ($CHCl_3$):

1649, 1747 cm^{-1}.

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

δ 0.84 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH), 1.72 (s, 3H, C*H*$_3$CO), 2.91 (s, 3H, NC*H*$_3$), 3.16-3.32 (dq, 1H, *J* = 2.9, 6.4 Hz, NC*H*), 3.70 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 4.63 (d, 1H, *J* = 2.9 Hz, PhC*H*), 4.95 (d, 1H, *J* = 5.3 Hz, β-lactam C4*H*), 5.33 (d, 1H, *J* = 5.3 Hz, β-lactam C3*H*), 6.72 (d, 2H, *J* = 8.8 Hz, PMP *ortho H*), 6.80 (d, 2H, *J* = 8.8 Hz, PMP *ortho H*), 7.02-7.60 (m, 9H, Ar*H*).

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

δ 12.2 (*C*H$_3$CH), 23.4 (*C*H$_3$CO), 33.5 (N*C*H$_3$), 55.3 (O*C*H$_3$), 55.4 (O*C*H$_3$), 59.0 (N*C*H), 62.0 (β-lactam *C*4), 71.0 (Ph*C*H), 75.9 (β-lactam *C*3), 100.0 (O*C*O), 113.9 (Ar*C*), 114.4 (Ar*C*), 118.8 (Ar*C*), 125.6 (Ar*C*), 125.8 (Ar*Cipso*), 127.7 (Ar*C*), 128.4 (Ar*C*), 129.8 (Ar*C*), 131.0 (Ar*Cipso*), 137.2 (Ar*Cipso*), 156.3 (Ar*Cipso*), 159.9 (Ar*Cipso*), 164.5 (*C*O), 165.3 (*C*O).

MS (*m/z*):

516 (M^{+}).

Analysis for $C_{30}H_{32}N_2O_6$:

Calculated: C, 69.75; H, 6.24; N, 5.42; Obtained: C, 69.98; H, 6.49; N, 5.71.

Optical rotation:

$[\alpha]_D^{25} = -78.5$ (*c* 1.3, $CHCl_3$).

(3*S*,4*R*,2′*S*,5′*S*,6′*R*)-1,4-Di-(4-methoxyphenyl)-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.12c):

Isolated as a white solid; yield 23%.

mp: 207-208 °C.

IR ($CHCl_3$):

1649, 1747 cm^{-1}.

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

δ 0.80 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH), 1.49 (s, 3H, C*H*$_3$CO), 2.90 (s, 3H, NC*H*$_3$), 2.96-3.11 (dq, 1H, *J* = 2.9, 6.4 Hz, NC*H*), 3.72 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 4.57 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.12 (d, 1H, *J* = 4.9 Hz, β-lactam C4*H*), 5.55 (d, 1H, *J* = 4.9 Hz, β-lactam C3*H*), 6.75 (d, 2H, *J* = 8.8 Hz, PMP *ortho H*), 6.92 (d, 2H, *J* = 8.8 Hz, PMP *ortho H*), 7.06-7.45 (m, 9H, Ar*H*).

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

δ 12.1 (*C*H$_3$CH), 22.5 (*C*H$_3$CO), 33.4 (NCH$_3$), 55.2 (OCH$_3$), 55.3 (OCH$_3$), 59.0 (NCH), 62.6 (β-lactam *C*4), 70.7 (PhCH), 77.6 (β-lactam *C*3), 98.6 (O*C*O), 113.6 (Ar*C*), 114.2 (Ar*C*), 118.7 (Ar*C*), 125.4 (Ar*C*), 126.1 (Ar*C*), 127.5 (Ar*C*), 128.2 (Ar*C*), 129.9 (Ar*Cipso*), 130.7 (Ar*Cipso*), 137.0 (Ar*Cipso*), 156.1 (Ar*Cipso*), 159.6 (Ar*Cipso*), 163.9 (*C*O), 165.5 (*C*O).

MS (*m/z*):

516 (M^+).

Analysis for $C_{30}H_{32}N_2O_6$:

Calculated: C, 69.75; H, 6.24; N, 5.42; Obtained: C, 69.96; H, 6.48; N, 5.70.

Optical rotation:

$[\alpha]_D^{25}$ = –170.9 (*c* 2.0, $CHCl_3$).

Procedure for preparation of 3.11d & 3.12d:

Following the general procedure, addition of triphosgene (283 mg, 0.96 mmol) solution in DCM (6 mL) to a solution of acid **3.08** (400 mg, 1.37 mmol) and imine (223 mg, 1.23 mmol) in DCM (6 mL) in presence of triethyl amine (1.14 mL, 8.22 mmol) gave a diastereomeric mixture of β-lactams which on purification by flash column chromatography gave **3.11d** (202 mg, 36%) and **3.12d** (163 mg, 29%). Both the diastereomers could be separated by flash column chromatography and their structure was established by spectral data (IR, ^{1}H NMR, ^{13}C NMR).

(3*R*,4*S*,2′*S*,5′*S*,6′*R*)-1,4-Diphenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.11d):

Isolated as a gum; yield 36%.

IR ($CHCl_3$):

1649, 1753 cm^{-1}.

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

δ 0.84 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 1.72 (s, 3H, C*H*$_3$CO), 2.88 (s, 3H, NC*H*$_3$), 3.15-3.30 (dq, 1H, *J* = 2.4, 6.3 Hz, NC*H*), 4.60 (d, 1H, *J* = 2.4 Hz, PhC*H*), 5.03 (d, 1H, *J* = 5.4 Hz, β-lactam C4*H*), 5.37 (d, 1H, *J* = 5.4 Hz, β-lactam C3*H*), 6.94-7.50 (m, 15H, Ar*H*).

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

δ 12.4 (*C*H$_3$CH), 23.6 (*C*H$_3$CO), 33.7 (N*C*H$_3$), 59.2 (N*C*H), 62.5 (β-lactam *C*4), 71.4 (Ph*C*H), 76.2 (β-lactam *C*3), 100.2 (O*C*O), 117.8 (Ar*C*), 124.4 (Ar*C*), 125.9 (Ar*C*), 127.8 (Ar*C*), 128.5 (Ar*C*), 129.1 (Ar*C*), 129.3 (Ar*C*), 134.0 (Ar*Cipso*), 136.9 (Ar*Cipso*), 137.0 (Ar*Cipso*), 165.1 (*C*O), 165.5 (*C*O).

MS (*m/z*):

456 (M^+).

Analysis for $C_{28}H_{28}N_2O_4$:

Calculated: C, 73.66; H, 6.18; N, 6.13; Obtained: C, 73.88; H, 6.44; N, 6.36.

Optical rotation:

$[\alpha]_D^{25} = -61.0$ (*c* 1.0, $CHCl_3$).

(3*S*,4*R*,2′*S*,5′*S*,6′*R*)-1,4-Diphenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one (3.12d):

Isolated as a white solid; yield 29%.

mp: 99-100 °C.

IR ($CHCl_3$):

1649, 1753 cm^{-1}.

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

δ 0.79 (d, 3H, *J* = 6.8 Hz, C*H*$_3$CH), 1.51 (s, 3H, C*H*$_3$CO), 2.88 (s, 3H, NC*H*$_3$), 2.90-3.03 (dq, 1H, *J* = 3.4, 6.8 Hz, NC*H*), 4.55 (d, 1H, *J* = 3.4 Hz, PhC*H*), 5.21 (d, 1H, *J* = 4.9 Hz, β-lactam C4*H*), 5.60 (d, 1H, *J* = 4.9 Hz, β-lactam C3*H*), 6.95-7.55 (m, 15H, Ar*H*).

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

δ 12.2 (*C*H_3CH), 22.4 (*C*H_3CO), 33.3 (N*C*H_3), 59.1 (N*C*H), 63.1 (β-lactam *C*4), 70.9 (Ph*C*H), 77.9 (β-lactam *C*3), 98.8 (O*C*O), 117.5 (Ar*C*), 124.2 (Ar*C*), 125.6 (Ar*C*), 127.6 (Ar*C*), 128.2 (Ar*C*), 128.8 (Ar*C*), 129.0 (Ar*C*), 134.5 (Ar*Cipso*), 137.1 (Ar*Cipso*), 137.3 (Ar*Cipso*), 164.5 (*C*O), 165.6 (*C*O).

MS (*m/z*):

456 (M^+).

Analysis for $C_{28}H_{28}N_2O_4$:

Calculated: C, 73.66; H, 6.18; N, 6.13; Obtained: C, 73.90; H, 6.42; N, 6.35.

Optical rotation:

$[\alpha]_D^{25} = -194.6$ (*c* 1.5, $CHCl_3$).

Procedure for preparation of β-lactams 3.11e and 3.12e:

Following the general procedure, addition of triphosgene (272 mg, 0.92 mmol) solution in DCM (6 mL) to a solution of acid **3.08** (384 mg, 1.31 mmol) and imine (300 mg, 1.18 mmol) in DCM (6 mL) in presence of triethyl amine (1.1 ml, 7.86 mmol) gave a diastereomeric mixture of β-lactams which on purification by flash column chromatography gave **3.11e** and **3.12e**. One of the diastereomers (**3.11e**) came at the same RF as that of the by-product amide and hence could not be purified whereas the other diastereomer **3.12e** (187 mg, 30%) could be separated and its structure was established by spectral data (IR, ^{1}H NMR, ^{13}C NMR).

(3*S*,4*R*,2′*S*,5′*S*,6′*R*)-2-[2-Benzo[1,3]dioxol-5-yl-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yloxy]-2,4,5-trimethyl-6-phenyl-morpholin-3-one (3.12e):

IR ($CHCl_3$):

1649, 1747 cm^{-1}.

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

δ 0.85 (d, 3H, *J* = 6.9 Hz, C*H*$_3$CH), 1.51 (s, 3H, C*H*$_3$CO), 2.92 (s, 3H, NC*H*$_3$), 3.07-3.20 (dq, 1H, *J* = 2.9, 6.9 Hz, NC*H*), 3.73 (s, 3H, OC*H*$_3$), 4.78 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.08 (d, 1H, *J* = 4.7 Hz, β-lactam C4*H*), 5.52 (d, 1H, *J* = 4.7 Hz, β-lactam C3*H*), 5.99 (s, 2H, OC*H*$_2$O), 6.72-6.90 (m, 4H, Ar*H*), 7.10-7.45 (m, 8H, Ar*H*).

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

δ 12.2 (*C*H_3CH), 22.4 (*C*H_3CO), 33.3 (NCH_3), 55.3 (OCH_3), 59.0 (N*C*H), 62.9 (β-lactam *C*4), 70.9 (Ph*C*H), 77.2 (β-lactam *C*3), 98.7 (O*C*O), 101.2 (O*C*H_2O), 108.0 (Ar*C*), 108.9 (Ar*C*), 114.2 (Ar*C*), 118.7 (Ar*C*), 122.2 (Ar*C*), 125.5 (Ar*C*), 127.6 (Ar*C*), 128.1 (Ar*Cipso*), 128.2 (Ar*C*), 130.6 (Ar*Cipso*), 136.9 (Ar*Cipso*), 147.7 (Ar*Cipso*), 156.2 (Ar*Cipso*), 163.8 (*C*O), 165.4 (*C*O).

MS (*m/z*):

530 (M^+).

Analysis for $C_{30}H_{30}N_2O_7$:

Calculated: C, 67.91; H, 5.70; N, 5.28; Obtained: C, 67.99; H, 5.93; N, 5.57.

Optical rotation:

$[\alpha]_D^{25} = -140.0$ (*c* 0.9, $CHCl_3$).

Procedure for preparation of β-lactams 3.13a and 3.14a:

Following the general procedure, addition of triphosgene (382 mg, 1.29 mmol) solution in DCM (6 mL) to a solution of acid **3.09** (591 mg, 1.84 mmol) and imine (350 mg, 1.66 mmol) in DCM (6 mL) in presence of triethyl amine (1.54 ml, 11.0 mmol) gave a diastereomeric mixture of β-lactams which on purification by flash column chromatography gave **3.13a** (256 mg, 30%) and **3.14a** (222 mg, 26%). Both the diastereomers were separated by flash column chromatography and their structure was established by spectral data (IR, ^{1}H NMR, ^{13}C NMR).

(3*R*,4*S*,2′*S*,5′*S*,6′*R*)-2-Isopropyl-2-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yloxy]-4,5-dimethyl-6-phenyl-morpholin-3-one (3.13a):

IR ($CHCl_3$):

1645, 1747 cm^{-1}.

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

δ 0.70 (d, 3H, *J* = 6.8 Hz, CH(CH_3)$_2$), 0.87 (d, 3H, *J* = 6.3 Hz, CH_3CH), 0.98 (d, 3H, *J* = 6.8 Hz, CH(CH_3)$_2$), 1.95-2.20 (m, 1H, C*H*(CH$_3$)$_2$, 2.98 (s, 3H, NCH_3), 3.27-3.48 (m, 1H, NC*H*), 3.69 (s, 3H, OCH_3), 5.06 (d, 1H, *J* = 4.6 Hz, β-lactam C4*H*), 5.18 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.43 (d, 1H, *J* = 4.6 Hz, β-lactam C3*H*), 6.72 (d, 2H, *J* = 8.8 Hz, PMP ortho protons), 7.10-7.50 (m, 12H, Ar*H*).

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

δ 12.6 (*C*H_3CH), 14.9 ((*C*H_3)$_2$CH), 17.9 ((*C*H_3)$_2$CH), 33.4 (N*C*H_3), 34.9 ((CH$_3$)$_2$*C*H), 55.3 (O*C*H_3), 58.7 (N*C*H), 63.0 (β-lactam *C*4), 70.3 (Ph*C*H), 78.8 (β-lactam *C*3), 104.0 (O*C*O), 114.2 (Ar*C*), 118.7 (Ar*C*), 125.5 (Ar*C*), 127.5 (Ar*C*), 128.3 (Ar*C*), 130.7 (Ar*Cipso*), 133.8 (Ar*Cipso*), 137.3 (Ar*Cipso*), 156.1 (Ar*Cipso*), 164.7 (*C*O), 164.9 (*C*O).

MS (*m/z*):

514 (M^+).

Analysis for $C_{31}H_{34}N_2O_5$:

Calculated: C, 72.35; H, 6.66; N, 5.44; Obtained: C, 72.64; H, 6.93; N, 5.63.

Optical rotation:

$[\alpha]_D^{25} = -29.1$ (*c* 1.1, $CHCl_3$).

(3*S*,4*R*,2′*S*,5′*S*,6′*R*)-2-Isopropyl-2-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yloxy]-4,5-dimethyl-6-phenyl-morpholin-3-one (3.14a):

IR ($CHCl_3$):

1645, 1747 cm^{-1}.

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

δ 0.71 (d, 3H, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$), 0.89 (d, 3H, *J* = 6.9 Hz, C*H*$_3$CH), 1.18 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)$_2$), 2.50-2.71 (m, 1H, C*H*(CH$_3$)$_2$, 2.66-2.81 (m, 1H, NC*H*), 2.87 (s, 3H, NC*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 3.96 (d, 1H, *J* = 3.0 Hz, PhC*H*), 5.20 (d, 1H, *J* = 4.9 Hz, β-lactam C4*H*), 5.70 (d, 1H, *J* = 4.9 Hz, β-lactam C3*H*), 6.76 (d, 2H, *J* = 9.3 Hz, PMP ortho protons), 7.03 (d, 2H, *J* = 7.8 Hz, PMP ortho protons), 7.10-7.50 (m, 10H, Ar*H*).

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

δ 12.3 (*C*H_3CH), 13.7 ((*C*H_3)$_2$CH), 17.3 ((*C*H_3)$_2$CH), 30.8 ((CH$_3$)$_2$*C*H), 33.1 (N*C*H_3), 55.4 (O*C*H_3), 58.7 (N*C*H), 63.0 (β-lactam *C*4), 70.1 (Ph*C*H), 78.4 (β-lactam *C*3), 101.3 (O*C*O), 114.3 (Ar*C*), 118.7 (Ar*C*), 125.4 (Ar*C*), 127.4 (Ar*C*), 128.1 (Ar*C*), 128.8 (Ar*C*), 129.0 (Ar*C*), 130.8 (Ar*Cipso*), 135.0 (Ar*Cipso*), 137.3 (Ar*Cipso*), 156.1 (Ar*Cipso*), 163.9 (*C*O), 165.9 (*C*O).

MS (*m/z*):

514 (M^+).

Analysis for $C_{31}H_{34}N_2O_5$:

Calculated: C, 72.35; H, 6.66; N, 5.44; Obtained: C, 72.61; H, 6.95; N, 5.71.

Optical rotation:

$[\alpha]_D^{25} = -186.3$ (*c* 2.2, $CHCl_3$).

Procedure for preparation of β-lactams 3.13c and 3.14c:

Following the general procedure, addition of triphosgene (143 mg, 0.48 mmol) solution in DCM (6 mL) to a solution of acid **3.09** (221 mg, 0.69 mmol) and imine (150 mg, 0.62 mmol) in DCM (6 mL) in presence of triethyl amine (0.58 mL, 4.14 mmol) gave a diastereomeric mixture of β-lactams which on purification by flash column chromatography gave **3.13c** and **3.14c**. One of the diastereomers (**3.14c**) came at the same RF as that of the by-product amide and hence could not be purified whereas the other diastereomer **3.13c** (84 mg, 25%) could be separated and its structure was established by spectral data (IR, ^{1}H NMR, ^{13}C NMR).

2-[1,2-Bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yloxy]-2-isopropyl-4,5-dimethyl-6-phenyl-morpholin-3-one (3.13c):

IR ($CHCl_3$):

1649, 1745 cm^{-1}.

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

δ 0.77 (d, 3H, *J* = 6.4 Hz, CH(C*H*$_3$)$_2$), 0.88 (d, 3H, *J* = 6.3 Hz, C*H*$_3$CH), 1.01 (d, 3H, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$), 2.00-2.30 (m, 1H, C*H*(CH$_3$)$_2$, 2.98 (s, 3H, NC*H*$_3$), 3.30-3.55 (m, 1H, NC*H*), 3.71 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 5.02 (d, 1H, *J* = 4.9 Hz, β-lactam C4*H*), 5.14 (d, 1H, *J* = 2.5 Hz, PhC*H*), 5.42 (d, 1H, *J* = 4.9 Hz, β-lactam C3*H*), 6.74 (d, 2H, *J* = 9.3 Hz, PMP ortho protons), 6.85 (d, 2H, *J* = 8.8 Hz, PMP ortho protons), 7.15-7.60 (m, 9H, Ar*H*).

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

δ 12.6 (*C*H$_3$CH), 14.9 ((*C*H$_3$)$_2$CH), 17.9 ((*C*H$_3$)$_2$CH), 33.4 (N*C*H$_3$), 34.9 ((CH$_3$)$_2$*C*H), 55.3 (O*C*H$_3$), 58.7 (N*C*H), 63.0 (β-lactam *C*4), 70.3 (Ph*C*H), 78.8 (β-lactam *C*3), 104.0 (O*C*O), 114.2 (Ar*C*), 118.7 (Ar*C*), 125.5 (Ar*C*), 127.5 (Ar*C*), 128.3 (Ar*C*), 130.7 (Ar*Cipso*), 133.8 (Ar*Cipso*), 137.3 (Ar*Cipso*), 156.1 (Ar*Cipso*), 164.7 (*C*O), 164.9 (*C*O).

MS (*m/z*):

544 (M^+).

Analysis for $C_{32}H_{36}N_2O_6$:

Calculated: C, 70.57; H, 6.66; N, 5.14; Obtained: C, 70.83; H, 6.92; N, 5.35.

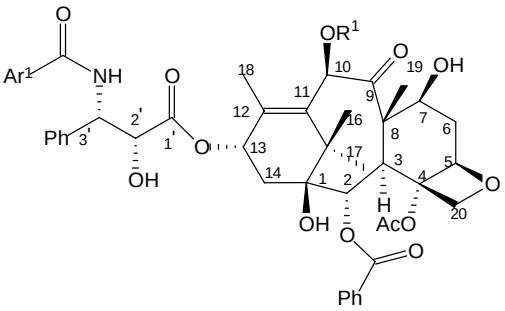
Optical rotation:

$[\alpha]_D^{25} = -22.8$ (*c* 0.7, $CHCl_3$).

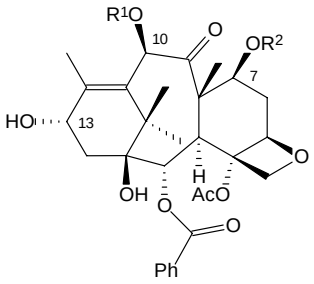
3.6: Introduction

In addition to its use in the synthesis of variety of β-lactam antibiotics, the β-lactam skeleton has been recognized as a useful building block by exploiting its strain energy associated with four membered ring. The importance of the β-lactam unit as a synthon has been recognized in the synthesis of a variety of biologically important β-lactam and non-β-lactam derivatives.[67] Efforts have been made in exploring such new aspects of β-lactam chemistry using enantiomerically pure β-lactams as versatile intermediates for the synthesis of aromatic β-amino acids and their derivatives,[68] oligopeptides,[69] labelled peptides, and azetidines which are further converted to polyamines, polyamino alcohols, amino sugars and polyamino ethers. In fact the development of methodologies based on β-lactams nucleus has reached to such a level of importance as to merit its own name 'the β-lactam synthon methods'.[70] The selective bond cleavage of the strained ring coupled with further interesting transformation render this fascinating molecule as a powerful building block.[71] This provides an access to diverse structural type of reactions of synthetic target molecules lacking β-lactam ring structure.

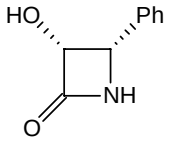
One such important synthon is 3-hydroxy-4-aryl-β-lactam (3-hydroxyazetidin-2-one). It has been shown that a suitably substituted 3-hydroxy-β-lactam can serve as a synthetic equivalent for the phenylisoserine side chain of taxol (Figure 8). In recent years, taxol, a unique complex diterpene, isolated from the bark of *Taxus brevifolia*[72] (pacific yew) is considered to be the most exciting drug in the anticancer chemotherapy, in particular, for the treatment of lung, breast and ovarian cancer.[73] Unfortunately, this wonder drug is a plant derived product that too available in very small quantities. Large-scale sacrifice of yew tree in order to produce this drug is not an acceptable solution to the problem of making the drug available in sufficient quantities.[74] This has led to the search for semi-synthetic routes to taxol using other plant-derived products isolated in useful quantities. For instance 10-deacetylbaccatin III is available in the needles and leaves of *Taxus baccata*[75] (regenerable sources) in sufficient quantities and can be linked with (2*R*, 3*S*)-*N*-benzoyl-3-phenylisoserine[76] to produce taxol.



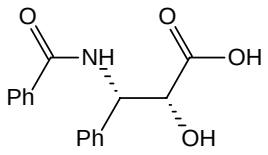
Taxol (Paclitaxel) Ar^1= Ph, R^1= Ac
Taxotere (Docetaxel) Ar^1= *t*-butoxy, R^1= H



Baccatin III R^1= Ac, R^2 = H
10-deacetyl baccatin III $R^1 = R^2 = H$
7-triethylsilyl baccatin III
R^1 = Ac, R^2 = $SiEt_3$



(3*R*, 4*S*)-3-hydroxy-4-phenyl-β-lactam



Taxol side chain [*N*-benzoyl-(2*R*, 3*S*)-phenylisoserine]

Figure 8

A study of natural and semi-synthetic congeners of taxol has revealed that both an intact taxane ring and an ester linkage for C-13 side chain are required for cytotoxicity.[77] It was also proved by a study of the structure-activity relationship (SAR) of analogues that the presence of hydroxyl group at C-2′ atom of the phenylisoserine unit is crucial as it participates in the intermolecular hydrogen bonding at the receptor site.[78] It has been shown that a suitably protected 3-hydroxy-β-lactam can serve as a synthetic equivalent for the phenylisoserine.[75, 79] A direct coupling of 7-(triethylsilyl)baccatin III with a protected 3-hydroxy-β-lactam has also been used for the synthesis of taxol.[80]

Apart from the application of 3-hydroxy-β-lactams in the synthesis of taxoids, they are also a source of enantiomerically pure α-hydroxy-β-amino acids, which are present in many biologically important compounds. Enantiomerically pure α-hydroxy-β-amino acids constitute an important class of compounds due to their utility as substrates

for the synthesis of a wide variety of peptide isosteres[81] and as being constituents of several natural products that exhibit potent biological activity such as bestatin[82] (an inhibitor of amino peptidases), KRI 1314[83] (a renin inhibitor), microginin[84] (an ACE inhibitor) and dideoxykanamycin A[85] (an antibacterial agent).

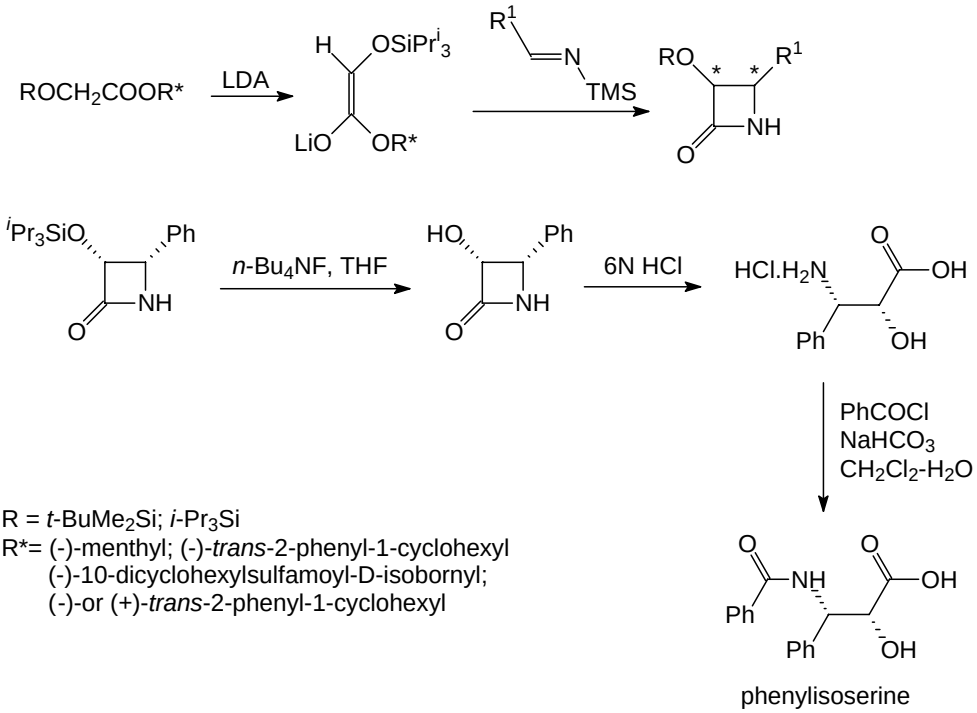
3.7: Background for present work

There are various strategies employed for the synthesis of phenylisoserine and 3-hydroxy-β-lactam. The most commonly used methods are 1) enolate–imine cycloaddition and 2) ketene-imine cycloaddition.

1. Chiral ester enolate imine cyclocondensation strategy for the stereoselective synthesis of 3-hydroxyazetidin-2-ones:

The ester enolate-imine cyclocondensation method[72a] provides the first efficient and practical route to 3-hydroxy-β-lactams with extremely high enantiomeric purity (>96%).

Scheme 43



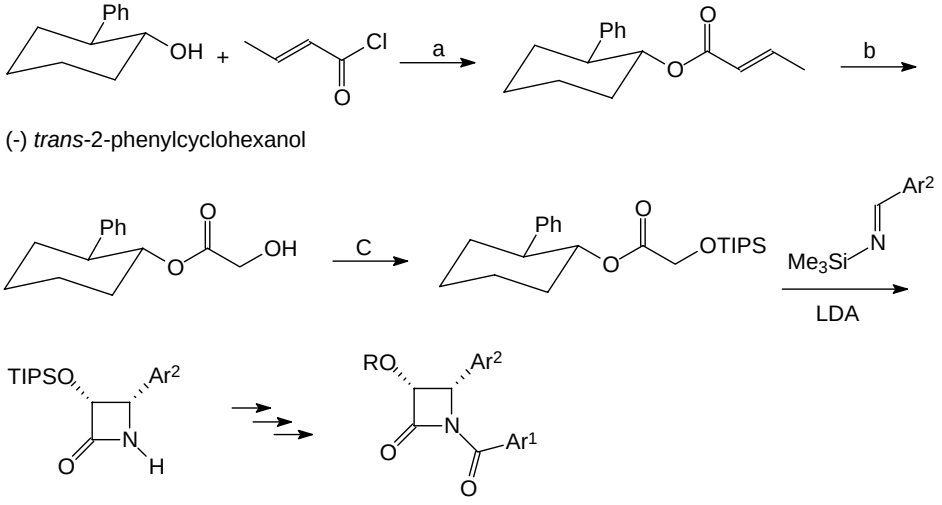
The most efficient and crucial chiral auxiliary, (-)-trans-2-phenylcyclohexanol, can be readily obtained in 100 g quantities using the lipase-catalyzed kinetic resolution of its racemic chloroacetate, as developed by Whitesell *et al.*,[86] and is fully recyclable after the reaction. This synthetic method (Scheme 43) provides efficient and practical routes to a variety of modified taxol C-13 side chains, which are required to test the antitumor activity and to improve the solubility of taxol derivatives.

Other chiral auxiliaries such as menthol, borneol etc. are also used for ester enolate-imine cycloaddition reaction with moderate to low diastereoselectivity[86] (Scheme 43).

Different research groups, follow the same strategy by varying the substituents on enolates and imines, to get analogues of 3-hydroxy-4-aryl-β-lactams, which are further coupled with Baccatin III, to get the taxol analogs that are tested for their biological activity.

The synthesis of novel phenylisoserine side chain was achieved through the asymmetric synthesis of 3-hydroxy-4-aryl-azetidin-2-one derivatives *via* the ester enolate-imine cyclocondensation reaction by Georg, *et al.*[78d]. Cyclohexanol was used as the chiral pool to get good diastereoselectivity in the cyclocondensation. The 2-azetidinones were acylated with *p*-chlorobenzoyl chloride and benzoyl chloride, to get the *N*-acyl-β-lactams (Scheme 44).

Scheme 44

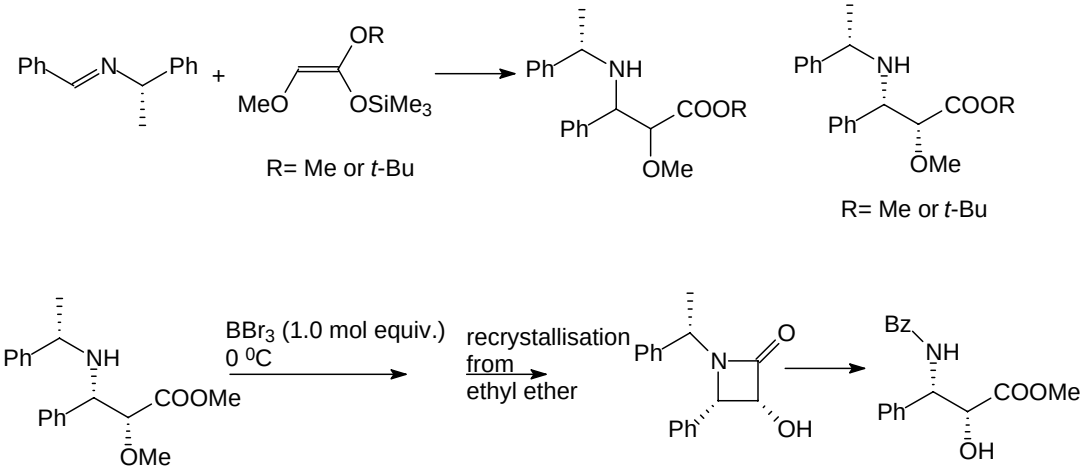


a) AgCN, Toluene, 7 h reflux; b) O_3, $NaBH_4$; c) *i*-Pr_3SiCl, imidazole, DMF.

Ojima, *et al.*[87] used the same chiral pool for the synthesis of fluorine containing 3-hydroxy azetidin-2-one. In a similar manner, synthesis of (3*R*, 4*S*)-1-*t*-Boc-3-TIPSO-4-(3,3,3-trifluoropropyl)-β-lactam was achieved using Oppolzer chiral auxiliary, [(-)-10-dicyclohexylsulfamoyl-D-isoborneol,[87] instead of 2-phenylcyclohexanol and trifluoropropylaldimine as an imine with 93% ee.

Ha *et al.*[88] have developed a practical large scale synthesis of *N*-benzoyl-(2*R*, 3*S*)-phenylisoserine methyl ester of the taxol side chain from the coupling of chiral imine of *N*-[(*S*)-methylbenzyl]benzaldimine with (*Z*)-α-methoxytrimethylsilyl ketene acetal followed by the sequential reactions of lactamization, demethylation, methanolysis and *N*-benzoylation (Scheme 45).

Scheme 45



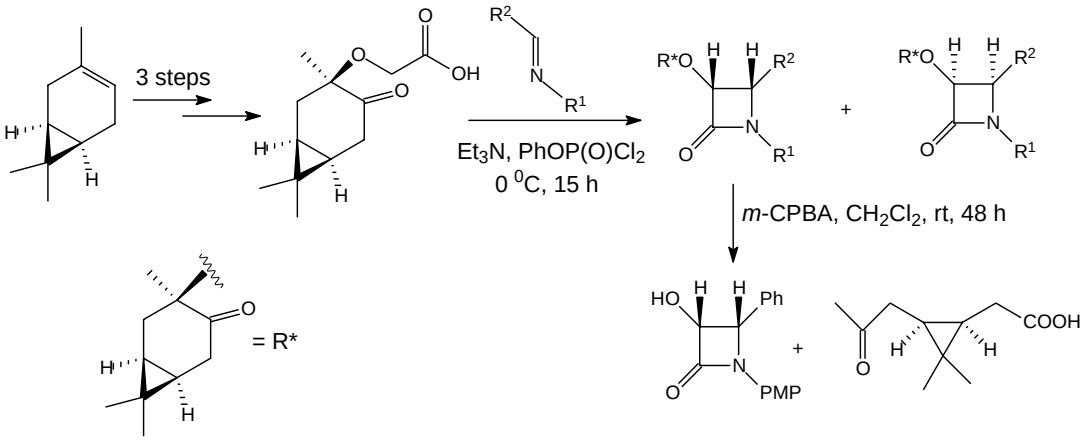
The reaction of chiral imine with enolate gave a major product among all four possible stereoisomers in 59% isolated yield (Scheme 45) after flash column chromatography (syn: anti = 78:22, diastereofacial ratio = 92:8). Demethylation with 1 mol of BBr_3 at 0 ^{0}C followed by crystallization from ether afforded the azetidin-2-one which on methanolysis and *N*-benzoylation gave *N*-benzoyl-(2*R*, 3*S*)-phenylisoserine methyl ester. This reaction sequence starting from chiral imine and ketene acetal was applied for multi-gram scale preparation taxol side chain with about 25-30% overall yield.

2. Chiral ketene-imine cyclocondensation strategy for the stereoselective synthesis of 3-hydroxyazetidin-2-ones:

Another most commonly used method for asymmetric synthesis of 3-hydroxy-azetidin-2-one is ketene-imine cycloaddition (Staundinger reaction) reaction. In this reaction either chiral ketene or chiral imine are used for asymmetric induction in the cycloaddition reaction. In our group, we have used abundantly available monoterpene, (+)-3-carene, as chiral source for asymmetric induction in the cycloaddition reaction.[89, 90]

A chiral acid was derived from (+)-3-carene in three steps and this acid was used for the cycloaddition reaction[89] with various achiral imines which gave *cis*-β-lactams in very high yield with moderate diastereoselectivity (Scheme 46).

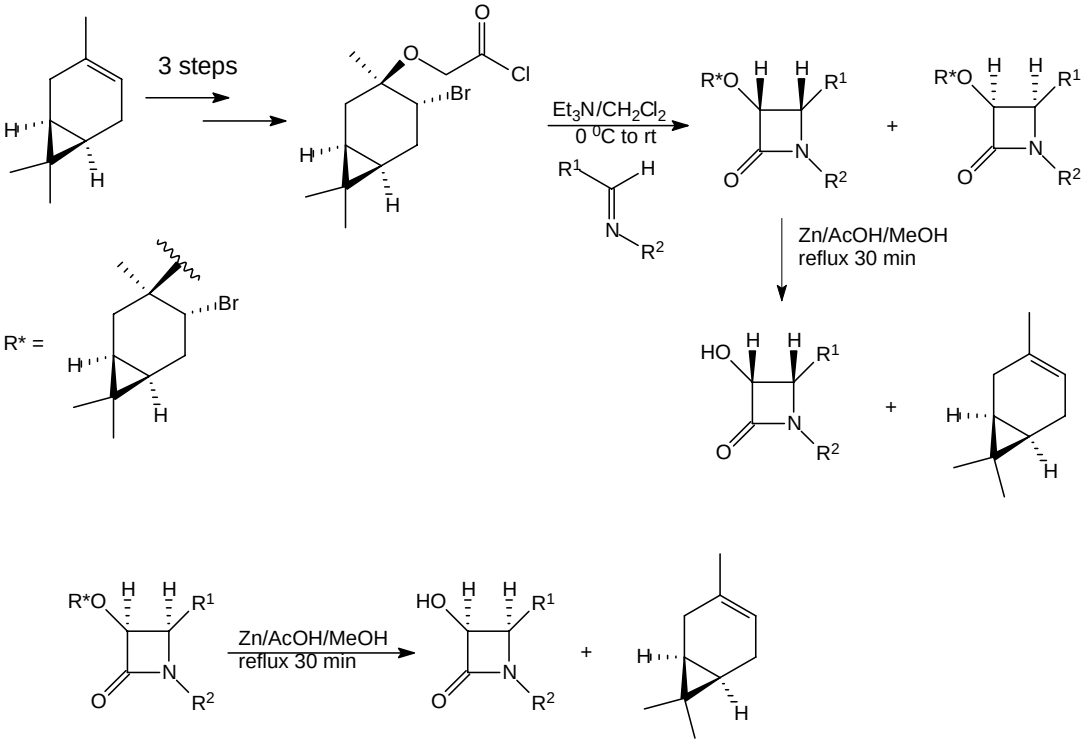
Scheme 46



The major isomer was obtained in enantiopure form by crystallization, which on Baeyer-Villeger oxidation gave (3*R*, 4*S*)-3-hydroxy-4-phenyl-β-lactam in good yield along with the keto acid (Scheme 46).

The only disadvantage of this method is that the chiral auxiliary is lost during the oxidative removal of 3-hydroxy-β-lactam. This problem was addressed[90] by modifying the chiral acid derived from (+)-3-carene. The bromoacid chloride was prepared from (+)-3-carene in three steps which on cycloaddition reaction with various achiral imines gave *cis*-β–lactams in good yields with moderate diastereoselectivities (Scheme 47).

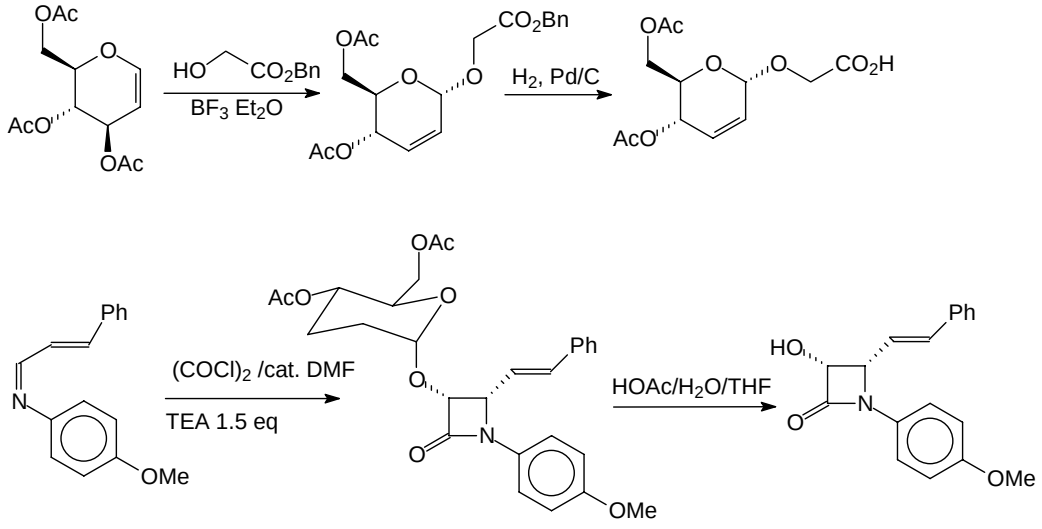
Scheme 47



Zinc induced removal of chiral auxiliary from the pure diastereomer gave enantiopure 3-hydroxy-β–lactams. Both the enantiomers could be obtained in pure form by this method.

Borer *et al.*[38] utilized a chiral carbohydrate based-ketene for the cycloaddition reaction with imine to get diastereomeric mixture of β-lactams.

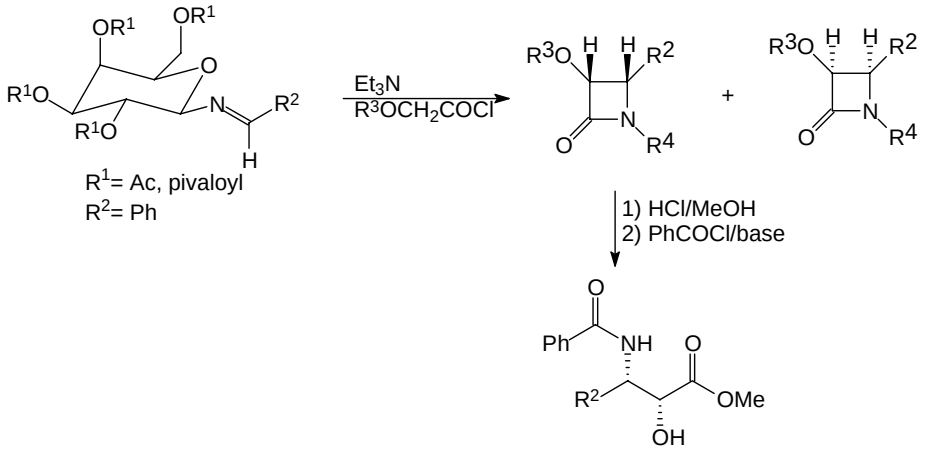
Scheme 48



The sugar part was removed by acid hydrolysis to get *cis*-3-hydroxy-β-lactam in moderate yield with 70% ee (Scheme 48).

Georg *et al.*[91] have used chiral imine derived from galactose and various acid chlorides to get mixture of *cis*-β-lactams in about 60:40 ratios (Scheme 49).

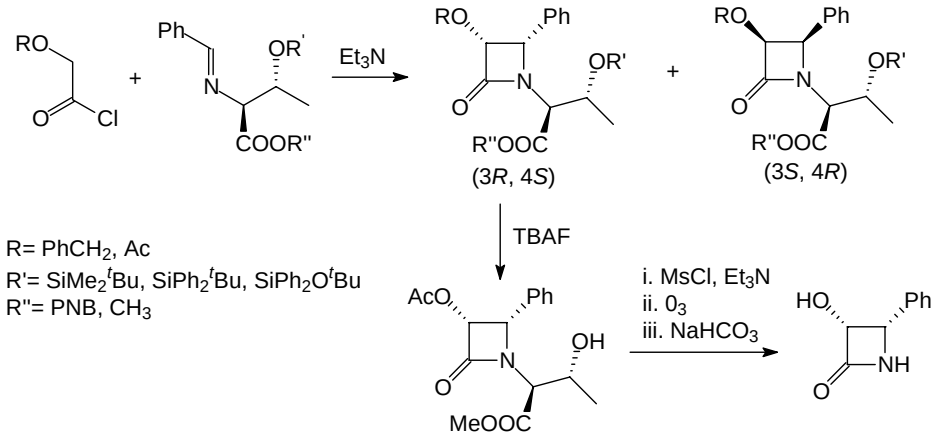
Scheme 49



The resulting β-lactams were hydrolyzed and subsequently benzoylated to give phenylisoserine, side chain of taxol.

A highly diastereoselective synthesis of (3*R*, 4*S*)-3-hydroxy-4-phenyl-2-azetidinone using L-threonine as a chiral template was achieved by Farina *et al.*[92] as shown in Scheme 50.

Scheme 50

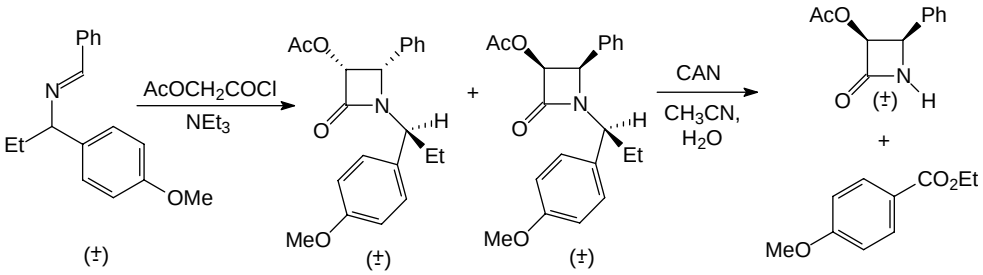


A practical diastereoselective synthesis of phenylisoserine methyl esters was described by Bourzat *et al.*[93] α-Methyl benzyl amine was used as chiral template for the Staudinger reaction and the optically pure diastereomers were easily separated by

crystallization. Azetidinone ring was opened up with methanolic hydrochloric acid and the chiral auxiliary was regioselectively cleaved by hydrogenation over Pd/C.

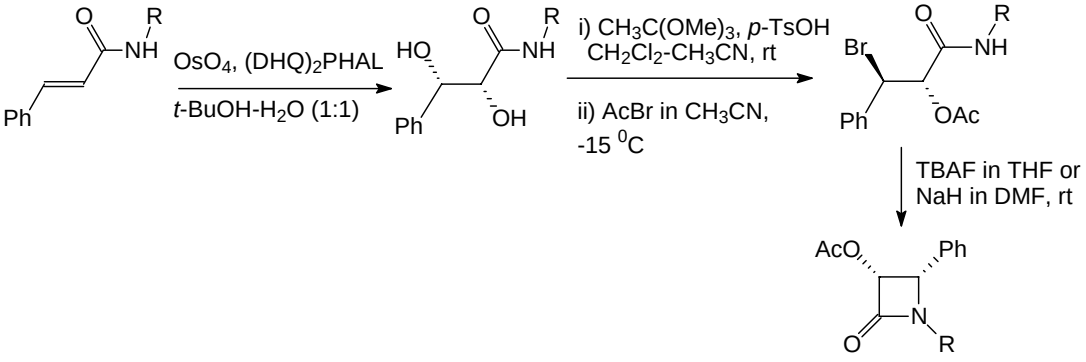
Brown[94] has recently reported asymmetric synthesis of 3-acetoxy-β-lactam, which involve the use of 1-(*p*-methoxyphenyl)propylamine as a chiral amine (Scheme 51).

Scheme 51



Intramolecular cyclization of β-bromocaboxamides, which could be prepared starting from *trans* cinnamide derivatives *via* catalytic asymmetric dihydroxylation (AD), followed by bromoacetylation, was used by Song *et al.*[95] (Scheme 52).

Scheme 52

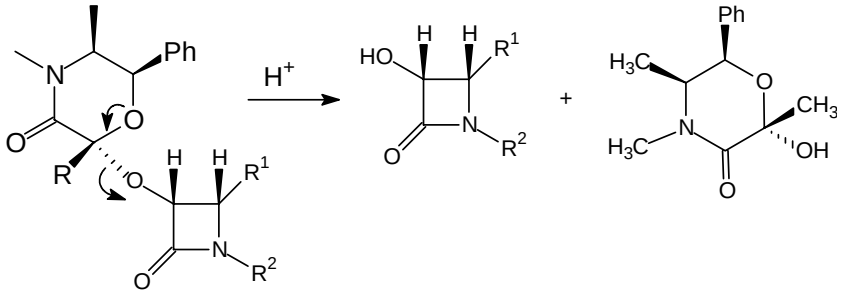


Apart from the methods of preparation of suitably substituted enantiopure 3-hydroxy-β-lactams by diastereoselective cycloaddition reaction, borohydride reduction of 3-ketoazetidinones[79,96] and the resolution of racemic 3-hydroxy-β-lactams[74,97] have also been reported.

3.8: Present work

The Chapter 3 (Section A) dealt with the use of ephedrine derived chiral acid effectively as a chiral ketene precursor in the asymmetric synthesis of novel β-lactam derivatives. It was necessary to recover the chiral auxiliary from the β-lactam derivatives. We envisioned that the removal of the hemiketal should be possible under acidic condition (Figure 9). This section describes our attempts towards the development of a methodology to get enantiomerically pure 3-hydroxy-β-lactams, one of which is an advanced intermediate for taxol side chain.

Figure 9

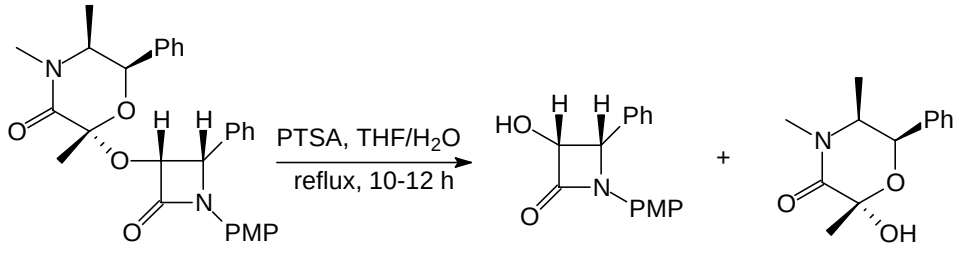


3.9: Results and discussion

Our initial attempts to cleave the chiral auxiliary using the reported procedure[38] in which the carbohydrate moiety was cleaved using a mixture of THF, water and acetic acid (4:1:1) at room temperature (Scheme 48) failed in our substrate at room temperature and even at reflux temperature.

The chiral auxiliary could be effectively cleaved by refluxing the pure diastereomer **3.11a** in a mixture of THF and water (4:1) using PTSA (excess) for 10-12 h (Scheme 53).

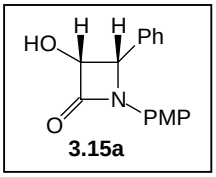
Scheme 53



3.11a **3.15a** **3.04**

The cleavage of chiral auxiliary from **3.11a** gave enantiomerically pure 3-hydroxy-β-lactam **3.15a** in excellent yield along with the recovery of chiral auxiliary **3.04** in optically pure form. The structures of **3.11a** and **3.04** were confirmed by spectral data (IR, ^{1}H NMR).

IR spectrum of **3.15a** showed a broad band at 3315 cm^{-1} which is for the hydroxy group and the sharp peak at 1713 cm^{-1} is attributed to the β-lactam carbonyl.

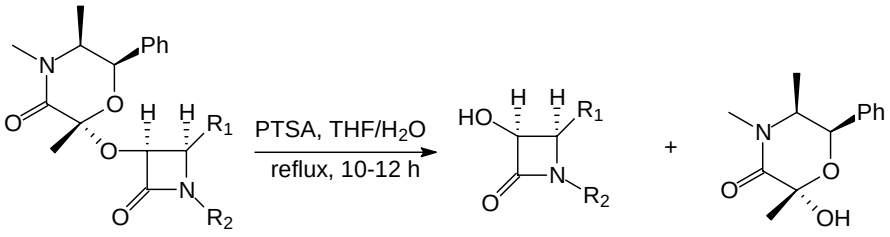


3.15a

The ^{1}H NMR spectrum of **3.15a** showed a doublet at 2.87 ppm (J = 6.9 Hz) which is for the hydroxy proton. The sharp singlet at 3.76 ppm corresponds to the methoxy group. The C3 β-lactam proton appeared as a doublet at 5.20 ppm (J = 5.4 Hz) and the C4 β-lactam as a doublet at 5.27 ppm (J = 5.4 Hz). The ortho protons of the *p*-methoxy phenyl group appeared as a doublet (J = 8.8 Hz) and the remaining aromatic protons appeared as a multiplet in the range 7.23-7.55 ppm. This compound showed the molecular ion peak at 269 (M^+) and gave satisfactory elemental analysis. The optical rotation for **3.15a** {$[\alpha]_D^{25}$ = +180.0 (*c* 0.40, $CHCl_3$)} matched with that reported in the literature[90] {$[\alpha]_D^{25}$ = +176.0 (*c* 1.00, $CHCl_3$)} and the sign of the optical rotation confirmed the stereochemistry of the β-lactam ring which is 3*R*, 4*S*.

In a similar way, the cleavage of chiral auxiliary from **3.12a-d** gave enantiomerically pure 3-hydroxy-β-lactams **3.16a-d** in excellent yield along with the recovery of chiral auxiliary **3.04** in optically pure form (Scheme 54).

Scheme 54



3.12a-d

3.16a R_1=Ph, R_2=PMP
3.16b R_1=PMP, R_2=Ph
3.16c R_1=R_2=PMP
3.16d R_1=R_2=Ph

3.04

The chiral auxiliary was separated from the β-lactam simply by column chromatography in pure form, which was recycled. There was no loss in optical activity of the recovered auxiliary as it showed the same optical rotation as that of the starting

hemiketal **3.04**. This can be explained by having an oxocarbenium-ion type of transition state (Figure 10). Considering pseudoequatorial orientation of the phenyl group in the oxocarbenium ion transition state, attack of the water molecule from the axial side (less hindered) would give the hemiketal product **3.04** with the observed stereochemistry which is '*S*'.

Figure 10. Oxocarbenium-ion transition state

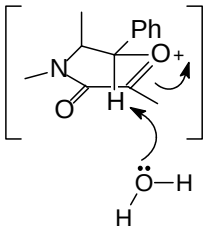


Table 3. Synthesis of 3-hydroxy-*cis*-β-lactams **3.15a** and **3.16a-d** from optically pure diastereomers **3.11a** and **3.12a-d**

S. No.	**R^1**	**R^2**	**Product**	**Yield (%)[a]**	**M.P (^oC)**	**$[\alpha]_D^{25}$ ($CHCl_3$)**	**Configuration**
1	Ph	PMP	**3.15a**	90	196-197	+180.0 (*c* 0.40) lit.[90] +176.0 (*c* 1.00)	3*R*, 4*S*
2	Ph	PMP	**3.16a**	90	201-202	–178.0 (*c* 0.90) lit.[90] –179 (*c* 1.00)	3*S,* 4*R*
3	PMP	Ph	**3.16b**	85	212-213	–173.7 (*c* 1.00)	3*S*, 4*R*
4	PMP	PMP	**3.16c**	88	132-133	–179.1 (*c* 2.20) lit.[90] –181.9 (*c* 0.93)	***3*S, *4*R**
5	Ph	Ph	**3.16d**	84	216-217	–188.4 (*c* 0.90) lit.[90] –188.7 (*c* 0.39)	3*S*, 4*R*

[a]Isolated yield of pure enantiomers

Thus, both the diastereomers **3.11a** and **3.12a** were cleaved in separate reactions and the products obtained were characterized. On comparison of optical rotations of the

products obtained in both the reactions with the reported value,[90] the absolute configuration for **3.15a** was assigned as (3*R*, 4*S*) and (3*S*, 4*R*) for **3.16a**.

3.10: Conclusion

A general method has been developed for the synthesis of 3-hydroxy-4-aryl *cis*-β-lactams in enantiomerically pure form. This method gives an access to both the enantiomers of 3-hydroxy-β-lactams one of which **3.15a**, is an advanced intermediate for the synthesis of taxol side chain. The advantage of this method is that the chiral auxiliary is recovered without the loss of optical activity which is recycled.

3.11: Experimental

Typical procedure for the preparation of (3*S*,4*R*)-1-(4-methoxyphenyl)-4-phenyl-3-hydroxyazetidin-2-one (3.16a):

To a stirred solution of **3.12a** (0.243 g, 0.5 mmol) in a mixture of THF (5 mL) and water (1 mL) was added PTSA (0.951 g, 5 mmol) and refluxed for 10 h. THF was then removed under reduced pressure and reaction mixture was then diluted with water (5 mL). Solid $NaHCO_3$ was added to the reaction mixture till basic pH and extracted with dichloromethane (3 x 10 mL). Combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue on purification by column chromatography EA/PE (1:1) gave **3.16a** (0.121 g, 90 %) as a white solid and chiral auxiliary **3.04** (0.103 g, 88 %).

mp: 201-202 °C.

IR ($CHCl_3$):

1713, 3315 cm^{-1}.

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

δ 2.87 (d, 1H, *J* = 6.9 Hz, O*H*), 3.76 (s, 3H, OCH_3), 5.20 (d, 1H, *J* = 5.4 Hz, C*H*O), 5.27 (d, 1H, *J* = 5.4 Hz, C*H*N), 6.80 (d, 2H, *J* = 8.8 Hz, ArC*H*), 7.23-7.55 (m, 7H, ArC*H*).

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

δ 55.5 (O*C*H_3), 62.3 (*C*HN), 77.26 (*C*HO), 114.5 (Ar*C*), 118.9 (Ar*C*), 127.5 (Ar*C*), 129.0 (Ar*C*), 129.1 (Ar*C*), 130.6 (Ar*Cipso*), 133.2 (Ar*Cipso*), 156.5 (Ar*Cipso*), 165.4 (β-lactam carbonyl).

MS (m/z):

269 (M^+).

Analysis for $C_{16}H_{15}NO_3$:

Calculated: C, 71.36; H, 5.61; N, 5.20; Obtained: C, 71.60; H, 5.81; N, 5.35.

Optical rotation:

Observed: $[\alpha]_D^{25} = -178.0$ (*c* 0.9, $CHCl_3$).

Reported: $[\alpha]_D^{25} = -179.0$ (*c* 1.0, $CHCl_3$).[90]

Optical rotation for recovered chiral auxiliary **3.04**

$[\alpha]_D^{25} = -107.6$ (*c* 1.4, $CHCl_3$); [(Lit.[98] $[\alpha]_D^{25} = -107.4$ (*c* 1.1, $CHCl_3$)]

Other 3-hydroxy β-lactams **3.15a** & **3.16b-d** were prepared from **3.11a** & **3.12b-d** respectively using the similar procedure.

(3*R*,4*S*)-1-(4-Methoxyphenyl)-4-phenyl-3-hydroxyazetidin-2-one (3.15a):

Following the typical procedure, reaction of **3.11a** (300 mg, 0.66 mmol) with PTSA (1.255 g, 6.6 mmol) in a mixture of THF (5 mL) and water (1 mL) at reflux temperature gave **3.15a** (149 mg, 90%) as a white solid and chiral auxiliary **3.04** (126 mg, 87%) after purification by flash column chromatography.

mp: 196-197 °C.

IR ($CHCl_3$):

1713, 3315 cm^{-1}.

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

δ 2.87 (d, 1H, *J* = 6.9 Hz, O*H*), 3.76 (s, 3H, OCH_3), 5.20 (d, 1H, *J* = 5.4 Hz, C*H*O), 5.27 (d, 1H, *J* = 5.4 Hz, C*H*N), 6.80 (d, 2H, *J* = 8.8 Hz, ArC*H*), 7.23-7.55 (m, 7H, ArC*H*).

MS (m/z):

269 (M^+).

Analysis for $C_{16}H_{15}NO_3$:

Calculated: C, 71.36; H, 5.61; N, 5.20; Obtained: C, 71.60; H, 5.90; N, 5.45.

Optical rotation:

Observed: $[\alpha]_D^{25}$ = +180.0 (*c* 0.4, $CHCl_3$).

Reported: $[\alpha]_D^{25}$ = +176.0 (*c* 1.0, $CHCl_3$).[90]

(3*S*,4*R*)-4-(4-Methoxyphenyl)-1-phenyl-3-hydroxyazetidin-2-one (3.16b):

Following the typical procedure, reaction of **3.12b** (250 mg, 0.51 mmol) with PTSA (970 mg, 5.1 mmol) in a mixture of THF (5 mL) and water (1 mL) at reflux temperature gave **3.16b** (118 mg, 85%) as a white solid and chiral auxiliary **3.04** (102 mg, 84%) after purification by flash column chromatography.

mp: 212-213 °C.

IR ($CHCl_3$):

1713, 3315 cm^{-1}.

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

δ 2.65 (bs, 1H, O*H*), 3.82 (s, 3H, OCH_3), 5.18 (d, 1H, *J* = 5.4 Hz, C*H*N), 5.29 (d, 1H, *J* = 5.4 Hz, C*H*O), 6.95 (d, 2H, *J* = 8.3 Hz, ArC*H*), 7.01-7.45 (m, 7H, ArC*H*).

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

δ 55.3 (O*C*H$_3$), 61.8 (*C*HN), 77.1 (*C*HO), 114.6 (Ar*C*), 117.6 (Ar*C*), 124.4 (Ar*C*), 124.6 (Ar*C*), 128.7 (Ar*C*), 129.1 (ArC), 137.0 (Ar*Cipso*), 160.1 (Ar*Cipso*), 166.2 (β-lactam carbonyl).

Analysis for $C_{16}H_{15}NO_3$:

Calculated: C, 71.36; H, 5.61; N, 5.20; Obtained: C, 71.63; H, 5.89; N, 5.48.

Optical rotation:

$[\alpha]_D^{25} = -173.7$ (*c* 1, $CHCl_3$).

(3*S*,4*R*)-1,4-Di-(4-methoxyphenyl)-3-hydroxyazetidin-2-one (3.16c):

Following the typical procedure, reaction of **3.12c** (200 mg, 0.39 mmol) with PTSA (742 mg, 3.9 mmol) in a mixture of THF (5 mL) and water (1 mL) at reflux temperature gave **3.16c** (102 mg, 88%) as a white solid and chiral auxiliary **3.04** (77 mg, 85%) after purification by flash column chromatography.

mp: 132-133 °C.

IR ($CHCl_3$):

1728, 3310 cm^{-1}.

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

δ 3.04 (bs, 1H, O*H*), 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.15 (d, 1H, *J* = 5.3 Hz, C*H*N), 5.21 (d, 1H, *J* = 5.3 Hz, C*H*O), 6.79 (d, 2H, *J* = 8.8 Hz, ArC*H*), 6.92 (d, 2H, *J* = 8.7 Hz, ArC*H*), 7.10-7.40 (m, 4H, ArC*H*).

Analysis for $C_{17}H_{17}NO_4$:

Calculated: C, 68.21; H, 5.72; N, 4.68; Obtained: C, 68.50; H, 5.82; N, 4.87.

Optical rotation:

Observed: $[\alpha]_D^{25} = -179.1$ (*c* 2.2, $CHCl_3$).

Reported: $[\alpha]_D^{25} = -181.9$ (*c* 0.93, $CHCl_3$).[90]

(3*S*,4*R*)-1,4-Diphenyl-3-hydroxyazetidin-2-one (3.16d):

Following the typical procedure, reaction of **3.12d** (150 mg, 0.33 mmol) with PTSA (628 mg, 3.3 mmol) in a mixture of THF (5 mL) and water (1 mL) at reflux

temperature gave **3.16d** (66 mg, 84%) as a white solid and chiral auxiliary **3.04** (63 mg, 82%) after purification by flash column chromatography.

mp: 216-217 °C.

IR ($CHCl_3$):

1713, 3325 cm^{-1}.

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

δ 2.65 (bs, 1H, O*H*), 5.21 (d, 1H, *J* = 5.4 Hz, C*H*N), 5.33 (d, 1H, *J* = 5.4 Hz, C*H*O), 6.90-7.55 (m, 10H, ArCH).

Analysis for $C_{15}H_{13}NO_2$:

Calculated: C, 75.30; H, 5.48; N, 5.85; Obtained: C, 75.50; H, 5.69; N, 5.97.

Optical rotation:

Observed: $[\alpha]_D^{25} = -188.4$ (*c* 0.9, $CHCl_3$).

Observed: $[\alpha]_D^{25} = -188.7$ (*c* 0.39, $CHCl_3$).[90]

3.12: References

1. a) Staudinger, H. *Liebigs. Ann. Chem*. **1907**, *356*, 51 (b) Staudinger, H.; Jelagin, S. *Ber. Disch. Chem*. Ges. **1911**, *44*, 365. (c) Staudinger, H. *Ber. Disch. Chem. Ges*. **1917**, *50*, 1035.
2. Fleming, A. J. *Exp. Patho.* **1929**, *10*, 226.
3. Crowfoot, D.; Bunn, C. W.; Roger-Low, B. W.; Turner-Jones, A. In *The Chemistry of Penicillin*; Clarke, H. T.; Johnson, J. R.; Robinson, R., Eds.; Princeton University Press, NJ, 1949, 367.
4. *Cephalosporins and Penicillins: Chemistry and Biology*; Flynn, E. H. Ed.; Academic Press, New York, 1972.
5. Gordon, E. M.; Syker, R. B. In *Chemistry and Biology of β-Lactam Antibiotics;* Morin, R. B., Gorman, M., Eds.; Academic Press, New York, 1982; *Vol. 1*, p. 199.
6. For detailed discussion see: Cooper, R. D. J. In *The Chemistry of β-Lactams*; Page M. I., Ed.; Blackie Academic & Professional: London, 1992; p 272.
7. (a) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D. A.; Gaviraghi, G.; Carlesso, R.; Bismara, C. (Glaxo S. P. A.) Eur. Pat. Appl. **1991**, 0416953 A2, Bulletin 91/11. (b) Chem. Abst. *116*, 235337t (**1972**).
8. Domling, A.; Starnecker, M.; Ugi, I. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2238.
9. Kehagia, K.; Domling, A.; Ugi, I. *Tetrahedron* **1995**, *51*, 9519.
10. (a) Burnett, D. A.; Caplen, M. A.; Davis, H. R., Jr.; Burrier, R. E.; Clader, J. W. *J. Med. Chem*. **1994**, *37*, 1733. (b) Dugar, S.; Yumibe, N.; Clader, J. W.; Vizziano, M.; Huie, K.; van Heek, M.; Compton, D. S.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1271. (c) Wu, G. C. *Organic Process Research & Development* **2000**, *4*, 298.
11. Doherty, J. B.; Ashe, B. M.; Agrenbright, L. W.; Barker, P. L.; Bonney, R. J.; Chandler, G. O.; Dahlgren, M. E.; Dorn, C. P., Jr.; Finke, P. E.; Firestone, R. A.; Fletcher, D.; Hagemann, W. K.; Munford, R.; O'Grady, L.; Maycock, A. L.; Pisano, J. M.; Shah, S. K.; Thomson, K. R.; Zimmerman, M. *Nature* **1986**, *322*, 192.
12. For references on SAR studies on β-lactam antibiotics see: (a) Boyd, D. B.; Eigenbrot, C. H.; Indelicato, J. M.; Miller, M.; Painin, C. E.; Woulfe, S. R. *J. Med. Chem.* **1987**, *30*, 528. (b) Durkin, K. A.; Sherrod, M. J.; Liotta, D. *J. Org. Chem.*

1989, *54*, 5839. (c) Cimarusti, C. M. *J. Med. Chem.* **1984**, *27*, 427. (d) Cohen, C. N. *J. Med. Chem.* **1983**, *26*, 259. (e) Boyd, D. B. In *Chemistry and Biology of β-Lactam Antibiotics;* Morin, R. B., Gorman, M., Ed.; Academic: New York, 1982; Vol. 1, p. 437. (f) Blainpain, P. C.; Nagy, J. B.; Laurent, G. H.; Durant, F. V. *J. Med. Chem.* **1980**, *146*, 837.

13. For the biochemical modes of action of *β*-lactam antibiotics see: (a) Waxman, D. J.; Strominger, J. L. In *Chemistry and Biology of β-Lactam Antibiotics.* Morin, R. B., Gorman, M., Ed.; Academic Press, New York, 1982, Vol. 3. (b) Tipper, D. J. In *Antibiotic Inhibitors of Bacterial Cell Wall Biosynthesis. International Encyclopedia of Pharmacology and Therapeutics*; Tipper, D. J., Ed.; Pergamon, oxford, Section 127, p 133. (c) Tomasz, A. *Rev. Infect. Dis.* **1979**, *1*, 434. (d) Tipper, D. J. *Pharmacol. Ther.* **1985**, *27*, 1.

14. For the references on β-lactamases, see: (a) Mossakowska, D.; Ali, N. A.; Dale, J. N. *Eur. J. Biochem.* **1989**, *180*, 309. (b) Kelly, J. A.; Dideberg, O.; Charlier, P.; Wery, J. P.; Libert, M.; Moews, P. C.; Knox, J. R.; Duez, C.; Fraipont, C. L.; Joris, B.; Dusart, J.; Frere, J-M.; Ghuysen, J-M. *Science* **1986**, *231*, 1429. (c) Samraoui, B.; Sutton, B. J.; Todd, R. J.; Artymiuk, P. J; Waley, S. G.; Phillips, D. C. *Nature* **1986**, *320*, 378. (d) Joris, B.; Ghuysen, J-M.; Dive, G.; Renard, A.; Dideberg, O.; Charlier, P.; Frere, J-M.; Kelly, J. A.; Boyington, J. C.; Moews, P. C.; Knox, J. R. *Biochem. J.* **1988**, *250*, 313. (e) Pratt, R. R.; Govardhan, C. P. *Proc. Natt. Acad. Sci.* USA **1984**, *84*, 1302. (f) Tipper, D. J.; Schrominger, J. L. *Proc. Natt. Acad. Sci.* USA **1965**, *54*, 1133.

15. (a) Lambert, H. P.; O'Grady, F. W. In *Antibiotics and Chemotherapy;* Lambert, H. P.; O'Grady, F. W.; Eds.; Churchill: Livingstone, 1992, p 191. (b) Abraham, E. P.; Chain, E. *Nature* **1940**, *146*, 837. (c) Kirby, W. M. M. *Science* **1944**, *99*, 452.

16. Ternansky, R. J.; Mortin, J. M. Jr. In *The Organic Chemistry of β-lactams*. George, G, I.; Ed, VCH, New York, 1993, 257.

17. George, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-lac*tams. George, G. I.; Ed. VCH, New York, 1993, 295.

18. Gilman, H.; Speeter, M. *J. Am. Chem. Soc*. **1943**, *65*, 2255.

19. (a) Hart, D. J.; Ha, D. C.; *Chem. Rev*. **1989**, *89*, 1447. (b) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (c) Andreoli, P.; Gainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunda, G. *J. Org. Chem*. **1991**, *56*, 5984. (d) Annunziata, R.;

Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem*. **1993**, *58*, 4746. (e) Fujisawa, T.; Ukai, Y.; Noro, T.; Date, K.; Shimizu, M. *Tetrahedron Lett*. **1991**, *32*, 7563.

20. Staudinger, H.; Klever, H. W.; Koper, P. *Liebigs. Ann. Chem*. **1910**, *374*, 1.
21. (a) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc*. **1957**, *79*, 1262. (b) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc*. **1959**, *81*, 3089.
22. (a) Maruyama, K.; Ishitoku, T.; Kubo, Y. *Chem. Lett*. **1980**, 265. (b) Aoyama, H.; Sakamoto, M.; Omote, Y. *Chem. Lett*. **1982**, 1211. (c) Aoyama, H.; Sakamoto, M.; Omote, Y. *J. Chem. Soc., Chem. Commun*. **1982**, 119.
23. (a) Sheehan, J. C.; Bose, A. K. *J. Am. Chem. Soc.* **1950**, *72*, 5158. (b) Sheehan, J. C.; Bose, A. K. *J. Am. Chem. Soc.* **1951**, *73*, 1761.
24. Griesbeck, A. G.; Heckroth. *Synlett* **2002**, *1*, 131.
25. Queener, S. W.; Neuss, N. In *Chemistry and Biology of β-Lactam Antibiotics*, Vol 3, Morin, R. B.; Gorman, M.; Eds. Academic Press, New York, 1982, p 1.
26. Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
27. (a) Mitsunobu, O. *Synthesis* **1981**, 1 (b) Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, 1279.
28. Graf, R. *Liebigs Ann*. **1963**, *666*, 111.
29. Kaluza, Z.; Fudong, W.; Belzecki, C.; Chmielewski, M. *Tetrahedron Lett*. **1989**, *30*, 5171.
30. Manhas, M. S.; Khajavi, M. S.; Bari, S. S.; Bose, A. K. *Tetrahedron Lett.* **1983**, *24*, 2323.
31. Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaun, J.; Brandi. A. *J. Am. Chem. Soc*. **2000**, *122*, 8075.
32. (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem*. **1999**, 3223. (b) Van Der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503.
33. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett*. **1985**, *26*, 3783.
34. Boger, D. L; Myers, J. B. *J. Org. Chem*. **1991**, *56*, 5385.
35. Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem*. **1987**, *59*, 485.
36. a) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem*. **1989**, *54*, 3792. (b) Tschaen, D. M.; Fuentes, L. M.; Lynch, J. E.; Laswell, W. L.; Volante, R. P.; Shinkay, I. *Tetrahedron Lett*. **1988**, *29*, 2779.

37. Ikota, N.; Hanaki, A. *Heterocycles* **1984**, *22*, 2227.
38. Borer, B.C.; Balogh, D. W. *Tetrahedron Lett*. **1991**, *32*, 1039.
39. Kaluza, Z.; Abramski, W.; Chmielewski, M. *Indian Journal of Chemistry* **1994**, *33*(*b*), 913.
40. (a) Hegedus, L. S.; de Weck, G.; D'Andrea, S. *J. Am. Chem. Soc*. **1988**, *110*, 2122. (b) Hegedus, L. S. *Pure Appl*. *Chem*. **1990**, *62*, 691.
41. Srirajan, V.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5579.
42. Saul, R.; Kopf, J.; Koll, P. *Tetrahedron: Asymmetry* **2000**, *11*, 423.
43. Hubschwerlen, C.; Schmid, G. *Helv. Chim. Acta*. **1983**, *66*, 2206.
44. (a) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R.; Hegde, V. R.; Krishnan, L. *Tetrahedron Lett*. **1985**, *26*, 33. (b) Bose, A. K.; Hegde, V. R.; Wagle, D. R.; Bari, S. S.; Manhas, M. S. *J. Chem*. *Soc*., *Chem*. *Commun*. **1986**, 161. (c) Wagle, D. R.; Garai, C.; Monteleone, M. G.; Bose, A. K. *Tetrahedron Lett*. **1988**, *29*, 1649. (d) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem*. **1988**, *53*, 4227.
45. Ikota, N. *Chem*. *Pharm*. *Bull*. **1990**, *38*, 1601.
46. (a) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767. (b) Ito, Y.; Kawabata, T.; Terashima, S. *Tetrahedron Lett*. **1986**, *27*, 5751.
47. Palomo, C.; Cossio, F. P.; Ontoria, J. M.; Odriozola, J. M. *Tetrahedron Lett*. **1991**, *32*, 3105.
48. Brown, A. D.; Colvin, E. W. *Tetrahedron Lett*. **1991**, *32*, 5187.
49. Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Terashima, S. *Tetrahedron Lett*. **1990**, *31*, 3031.
50. Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron Lett*. **1988**, *44*, 2149.
51. Evans, D. A.; Williams, J. M. *Tetrahedron Lett*. **1988**, *29*, 5065.
52. Seebach, D.; Wasmuth, D. *Helv*. *Chim*. *Acta*. **1980**, *197*, 5
53. Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87.
54. Palomo, C.; Cossio, F. P.; Cuevas, C. *Tetrahedron Lett*. **1991**, *32*, 3109
55. (a) Jayaraman, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Synlett* **1992**, 749. (b)

Bhawal, B. M.; Joshi, S. N.; Krishnaswamy, D.; Deshmukh, A. R. A. S. *J. Indian Inst. Sci.* **2001**, *81*, 265.

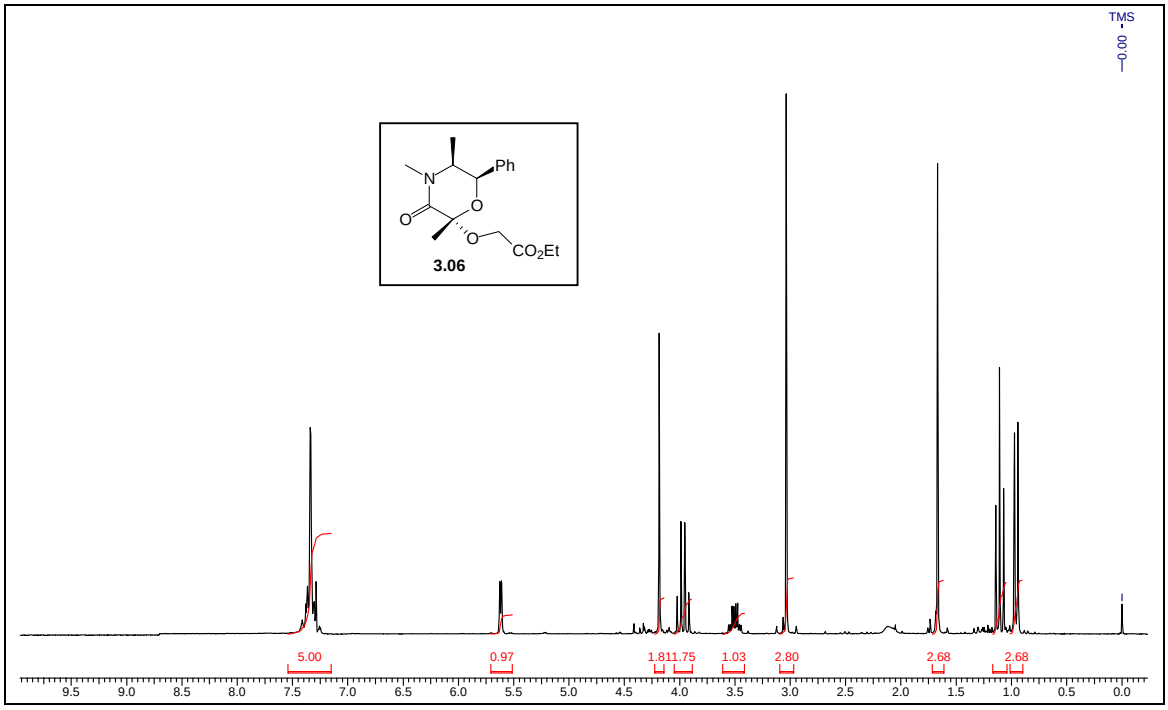
56. (a) Barton, D. H. R.; Getau-Olesker, A.; Anaya-Mateos, J.; Cleophax, J.; Gero, S. D.; Chiaroni, A.; Riche, C. *J. Chem. Soc., Perkin Trans. I* **1990**, 3211. (b) Hernando, J. I. M.; Laso, N. M.; Anaya, J.; Gero, S. D.; Grande, M. *Synlett* **1997**, 281. (c) Anaya, J.; Gero, S. D.; Grande, M.; Hernando, J. I. M.; Laso, N. M. *Bioorg. Med. Chem.* **1999**, *7*, 837.
57. Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R. *Tetrahedron* **1992**, *48*, 4831.
58. Gunda, T. E.; Vieth, S.; Kover, K. E.; Sztarickskai, F. *Tetrahedron Lett.* **1990**, *31*, 6707.
59. Ojima, I.; Hauh-Jyun, C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307.
60. Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578.
61. (a) Wack, H.; Drury, W. J., III; Taggi, A. E.; Ferraris, D.; Lectka, T. *Org. Lett.* **1999**, *1*, 1985. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka. *J. Am. Chem. Soc.* **2000**, *122*, 7831.
62. (a) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (b) Sardo, J. A.; Gonzalzez, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249. (c) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (d) Lopez, R.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem.* **1993**, *58*, 7036. (e) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. (f) Arrieta, A.; Ugalde, J. M.; Cossio, F. P.; Lecea, B. *Tetrahedron Lett.* **1994**, *35*, 4465. (g) Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **2000**, *65*, 8458.
63. (a) Moore, H. W.; Hernandez, L.; Chambers, R. *J. Am. Chem. Soc.* **1978**, *100*, 2245. (b) Decazes, J. M.; Luche, J. L.; Kagan, H. B.; Parthasarathy, R.; Ohrt, J. T. *Tetrahedron Lett.* **1972**, 3633. (c) Bellus, D. *Helv. Chim. Acta*. **1975**, *58*, 2509. (d) Moore, H. W. *Acc. Chem. Res.* **1979**, *12*, 125.
64. Seikali, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587.
65. George, G. I.; Mashava, P. M.; Guan, X. *Tetrahedron Lett.* **1991**, *32*, 581.
66. Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.
67. (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 699; (b) Ojima, I. In *The Chemistry of β-Lactams*; Georg, G. I.; Ed.; VCH: New York, 1993; p. 197;

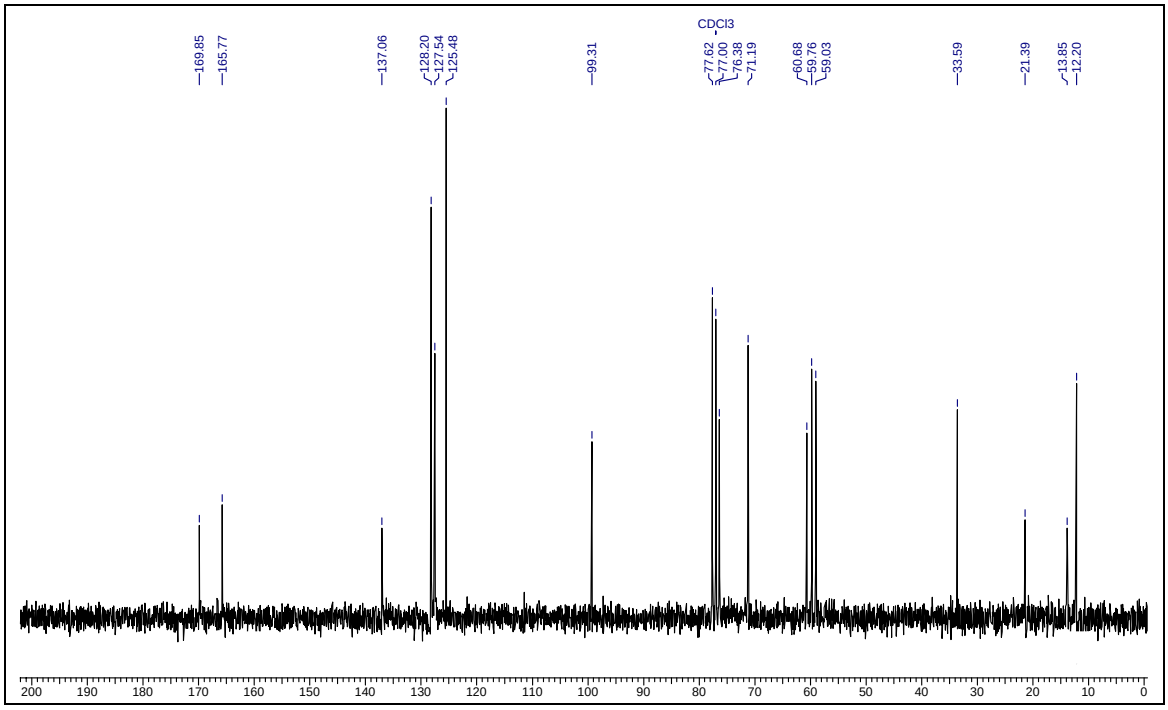
(c) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383.

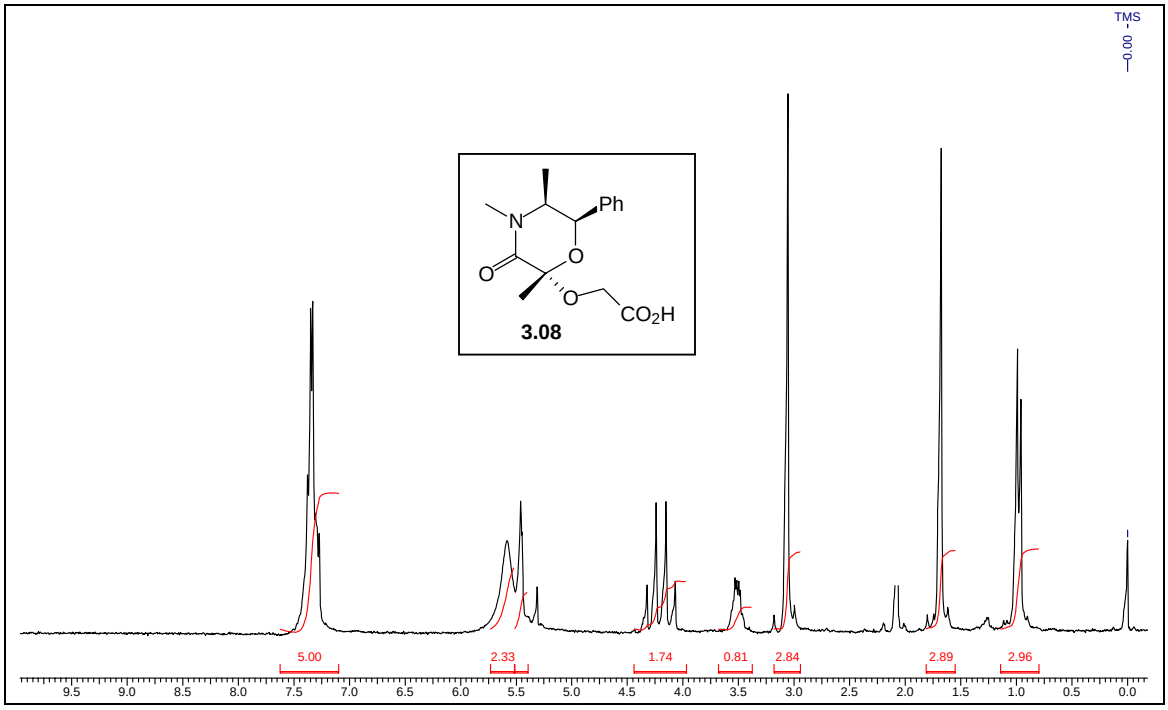
68. Palomo, C.; Aizpurua, J.; Ganboa, I. In "*Enantioselective Synthesis of Beta-Amino Acids*" ed. Juaristi, E., Wiley-VCH, New York, 1997, pp. 279-357 and references cited therein.
69. For review on this subject see: Ojima, I.; Delalopge, F. *Chem. Soc. Rev*. **1997**, *26*, 377.
70. Ojima, I. In "*The Chemistry of β-Lactams*" Georg, G. I.; Ed. VCH: New York, 1993, p. 197.
71. a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev*. **2001**, *30*, 226. b) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381.
72. a) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681. b) Ojima, I.; Habus, I.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.
73. a) Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *J. Natl. Cancer. Inst.* **1991**, *83*, 1797. b) Rowinsky, E. K.; Casenave, L. A.; Donehower, R. C.; *J. Natl. Cancer. Inst.* **1990**, *82*, 1247. c) Blume, E. *J. Natl. Cancer. Inst.* **1989**, *81*, 1122.
74. Brieva, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 1068.
75. Denis, J.-N.; Greene, A. E.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
76. For review see: a) Kingston, D. G. I. *Pharm. Ther.* **1991**, *52*, 1. b) Senilh, V.; Gueritte, F.; Guenard, D.; Colin, M.; Potier, P. C. *Acad. Sci. Paris.* **1994**. t. 299, Serie II, no. 15, 1039. c) Gueritte-Voegelein, F.; Senilh, V.; David, B.; Guenard, D.; Potier, P. *Tetrahedron* **1986**, *42*, 4451. d) Wender, P. A.; Macciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.
77. Parness, J.; Kingston, D. G. I.; Powell, R. G.; Harracksingh, S B. *Biochem. Biophys. Res. Commun.* **1982**, *105*, 1082.
78. a) Gueritte-Voegelein, F.; Guenard, D.; Mangatal, L.; Potier, P.; Guilhem, J.; Cesario, M.; Pascard, C. *Acta. Cryst.* **1990**, *C46*, 781. b) Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1991**, *34*, 1176. c) Kant, J.; Huang, S.; Wong, H.; Fairchild, C.; Vyas, D.; Farina, V. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2471. d) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R.; Burke, C. T. *J. Med. Chem.* **1992**, *35*, 4230.

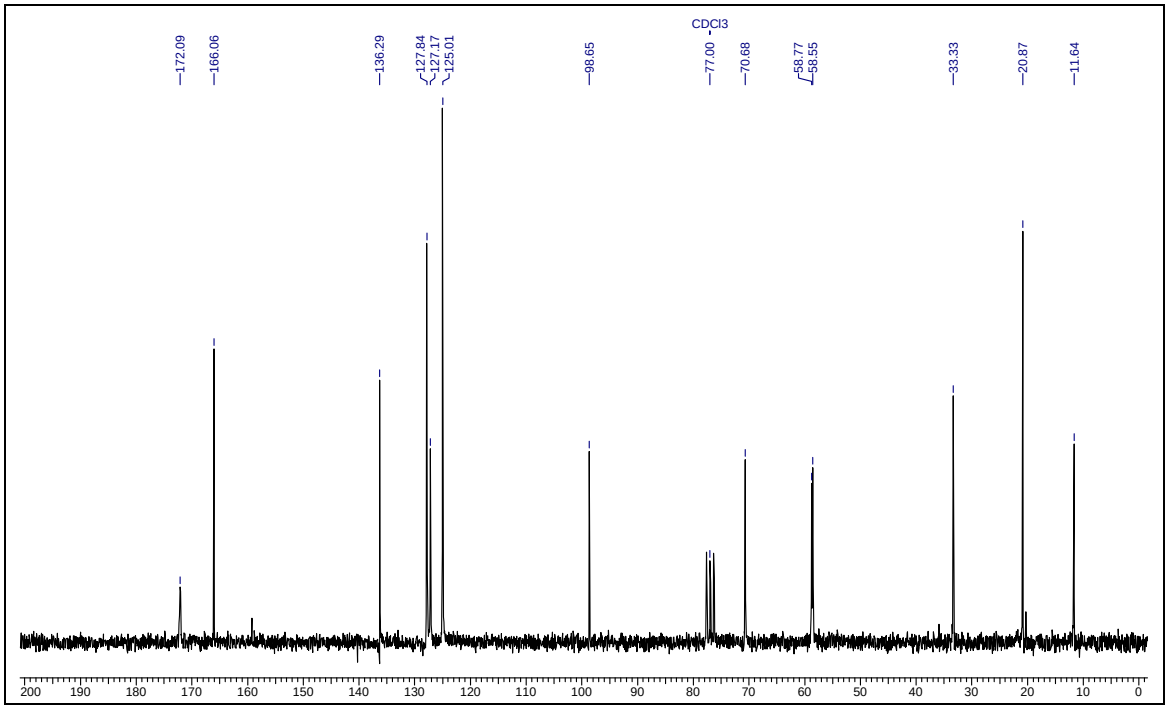
79. Holton, R. A.; Liu, J. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2475.
80. Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2467.
81. For recent reviews, see: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3.
82. (a) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 600. (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem*. **1989**, *54*, 4235 and references therein.
83. Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Kiso, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1678.
84. Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501.
85. Umemura, E.; Tsuchiya, T.; Umezawa, S.; *J. Antibiot.* **1988**, *41*, 530.
86. Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1.
87. Ojima, I.; Kuduk, S. D.; Slater, J. C.; Gimi, R. H.; Sun, C. M. *Tetrahedron* **1996,** *52*, 209.
88. Ha, H-J.; Park, G-S.; Ahn, Y-G.; Lee, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1619. For synthesis of taxol side chain by other methods see references cited therein.
89. Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5585.
90. Joshi, S. N.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron: Asymmetry* **2000**, *11*, 1477.
91. Georg, G. I.; Akgun, E.; Mashava, P. M.; Milstead, M.; Ping, H.; Wu, Z-J.; Velde, D. V. *Tetrahedron Lett.* **1992**, *33*, 2111.
92. Farina, V.; Hauck, S. I.; Walker, D. G. *Synlett* **1992***, 9*, 761.
93. Bourzat, J. D.; Commercon, A. *Tetrahedron Lett.* **1993**, *34*, 6049.
94. Brown, S.; Jordan, A. M.; Lawrence, N. J.; Pitchard, R. G. *Tetrahedron Lett.* **1998**, *39*, 3559.
95. Song, C. E.; Lee, S. W.; Roh, E. J.; Lee, S-g.; Lee, W. K. *Tetrahedron: Asymmetry* **1998**, *9*, 983. For phenylisoserine side chain preparation by other methods see references cited therein.
96. Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A. I.; Lopez, M. C.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429.
97. (a) Basak, A.; Mahato, T.; Bhattacharya, G.; Mukherjee, B. *Tetrahedron Lett.* **1997**, *38*, 643. (b) Patel, R. N.; Howell, J.; Chidambaram, R.; Benoit, S.; Kant, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3673.

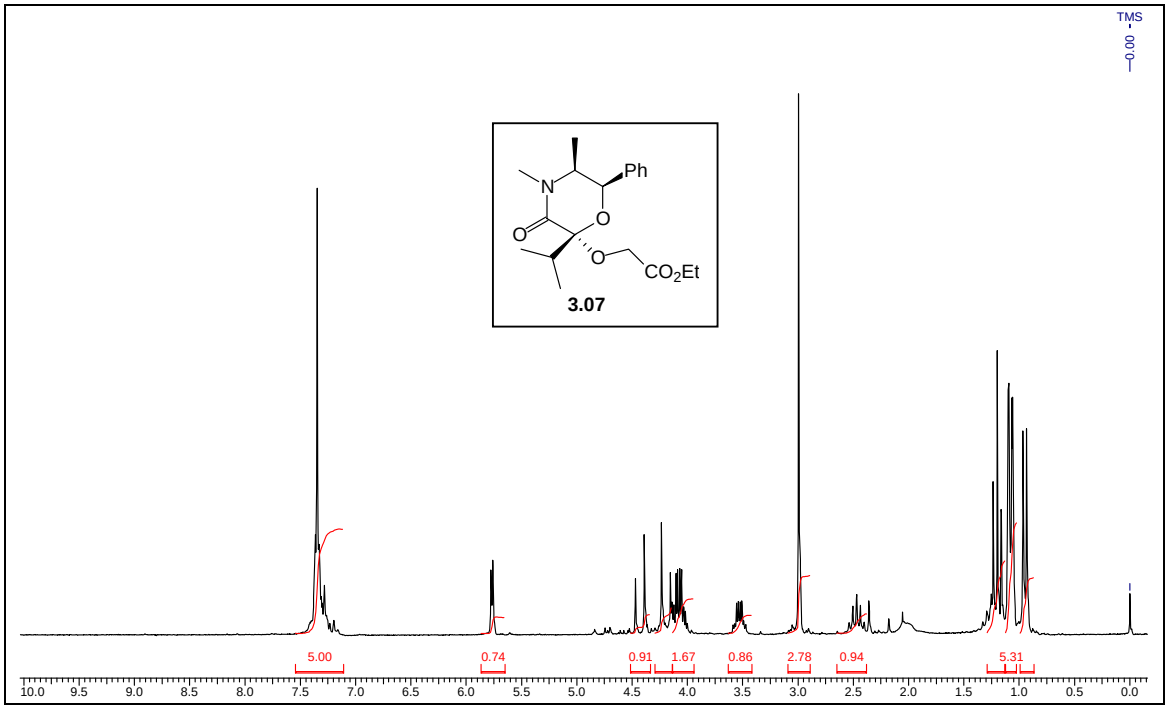
98. Pansare, S. V.; Shinkre, B. A.; Bhattacharyya, A. *Tetrahedron* **2002**, *58*, 8985.

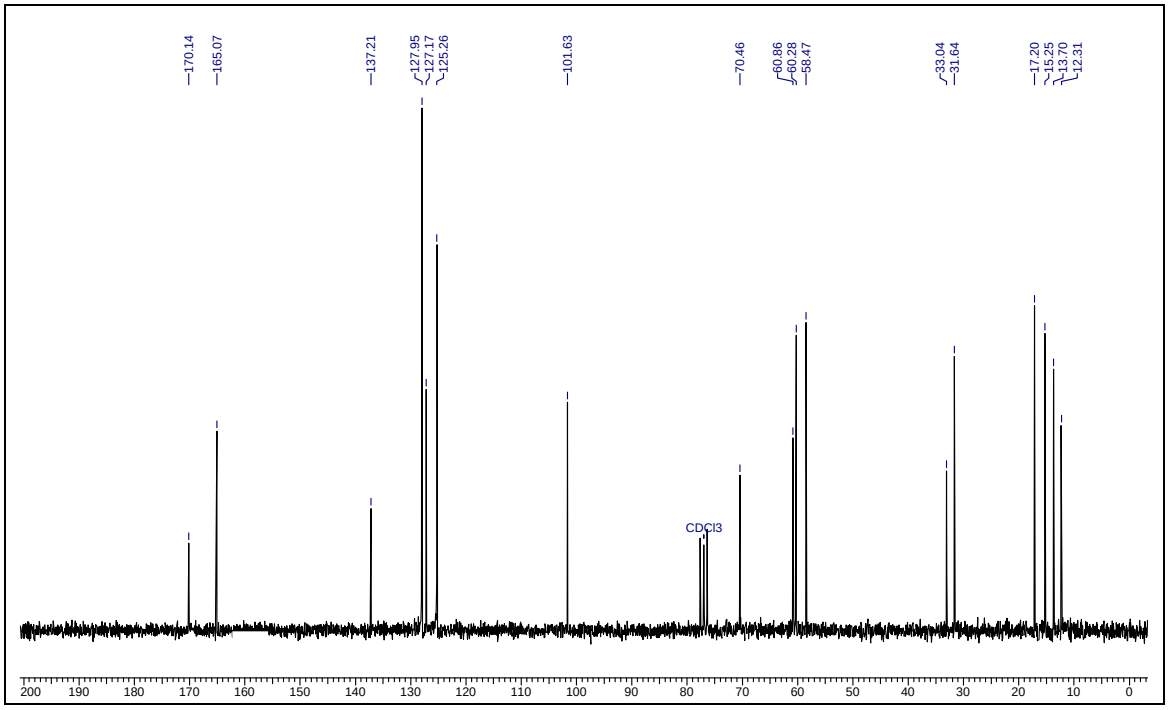

TMS
0.00
Ph
N
O
O
O
CO2Et
3.06
5.00
0.97
1.81
1.75
1.03
2.80
2.68
2.68
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

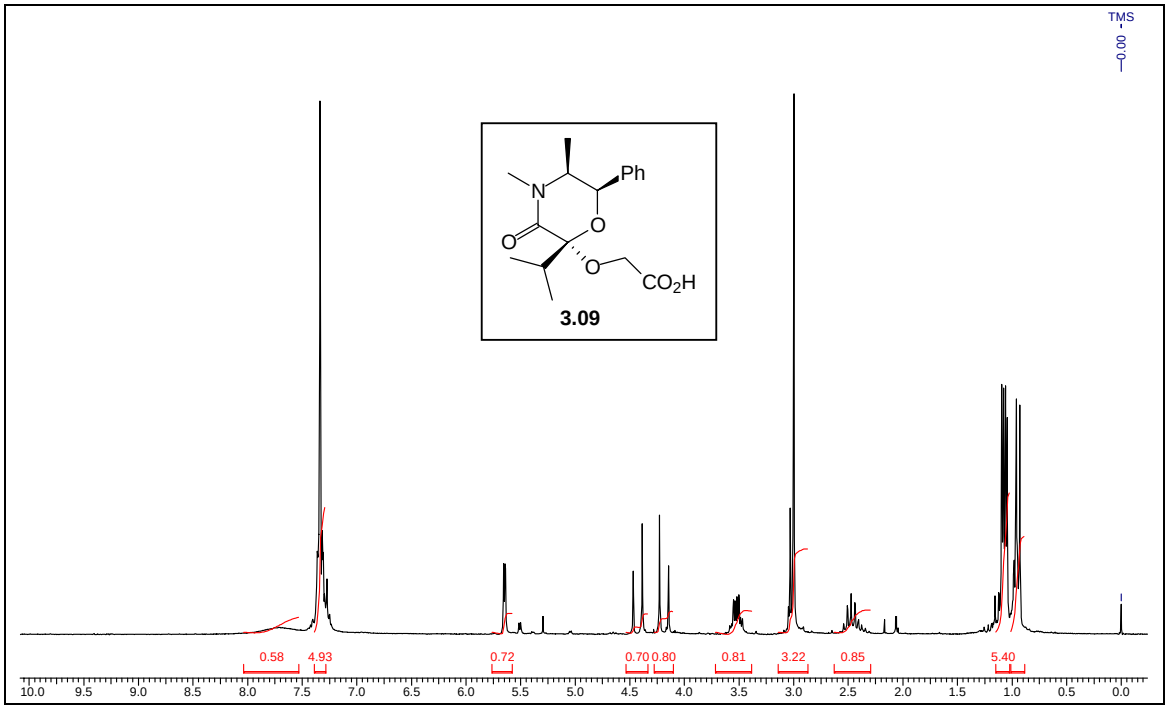

CDCl3
169.85
165.77
137.06
128.20
127.54
125.48
99.31
77.62
77.00
76.38
71.19
60.68
59.76
59.03
33.59
21.39
13.85
12.20
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

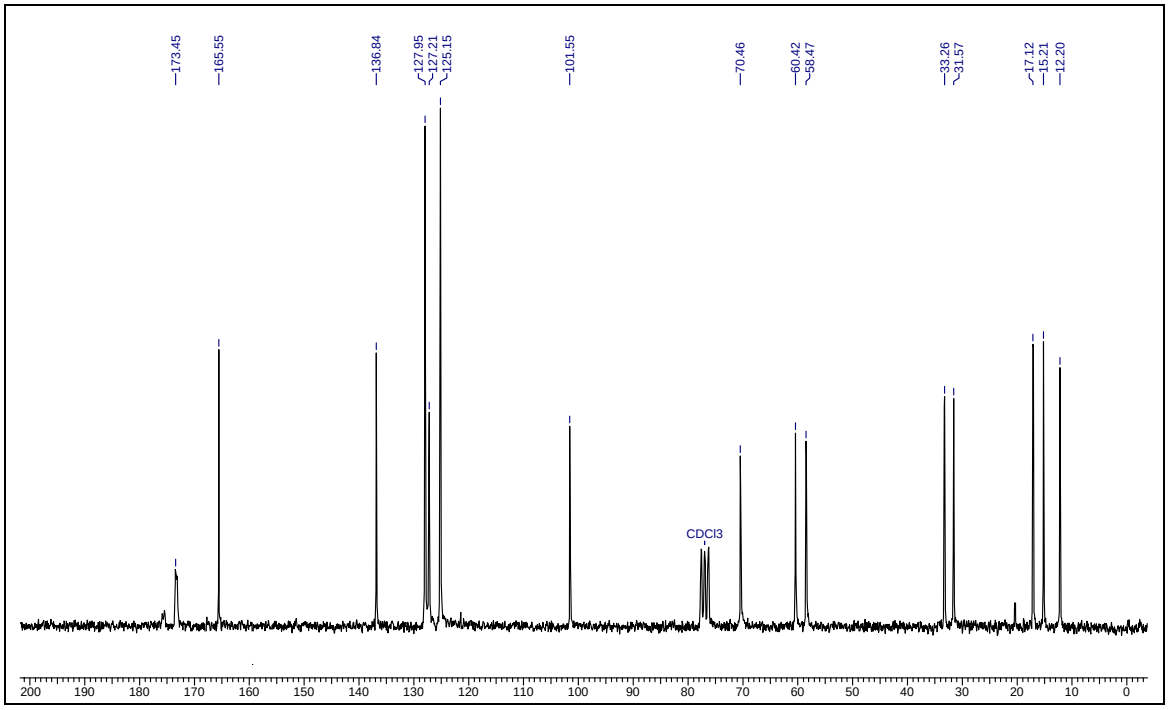

TMS
0.00
Ph
N
O
O
O
O
CO2H
3.08
5.00
2.33
1.74
0.81
2.84
2.89
2.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

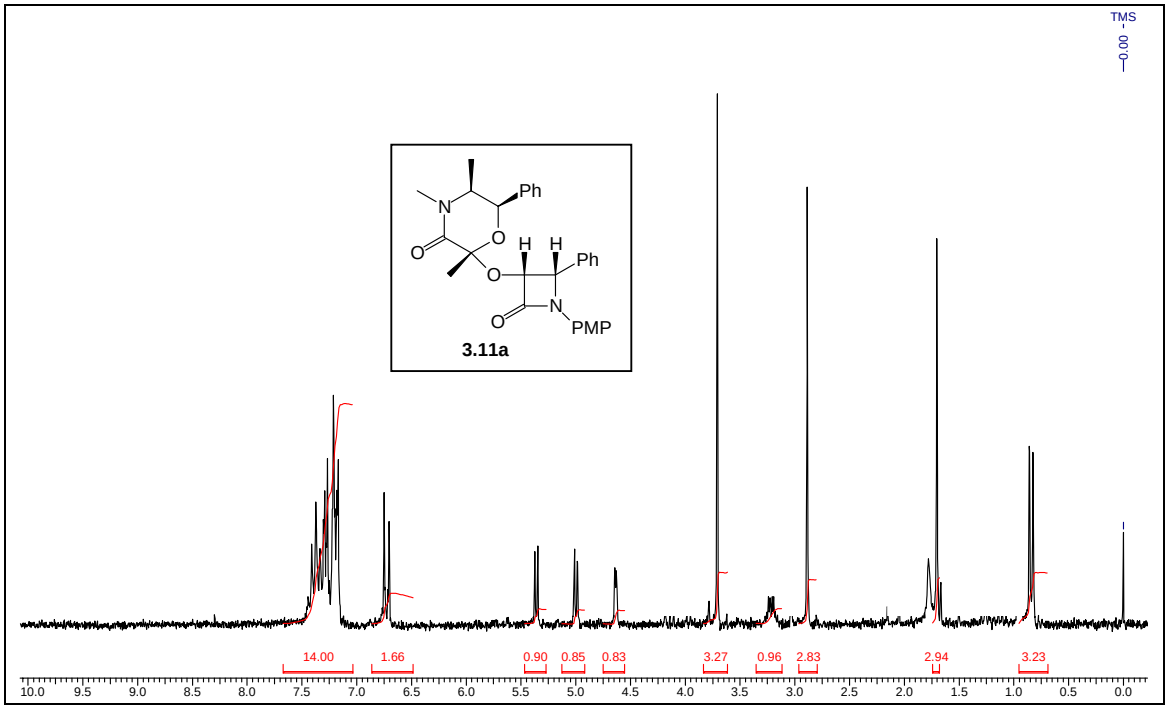

CDCl3
172.09
166.06
136.29
127.84
127.17
125.01
98.65
77.00
70.68
58.77
58.55
33.33
20.87
11.64
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

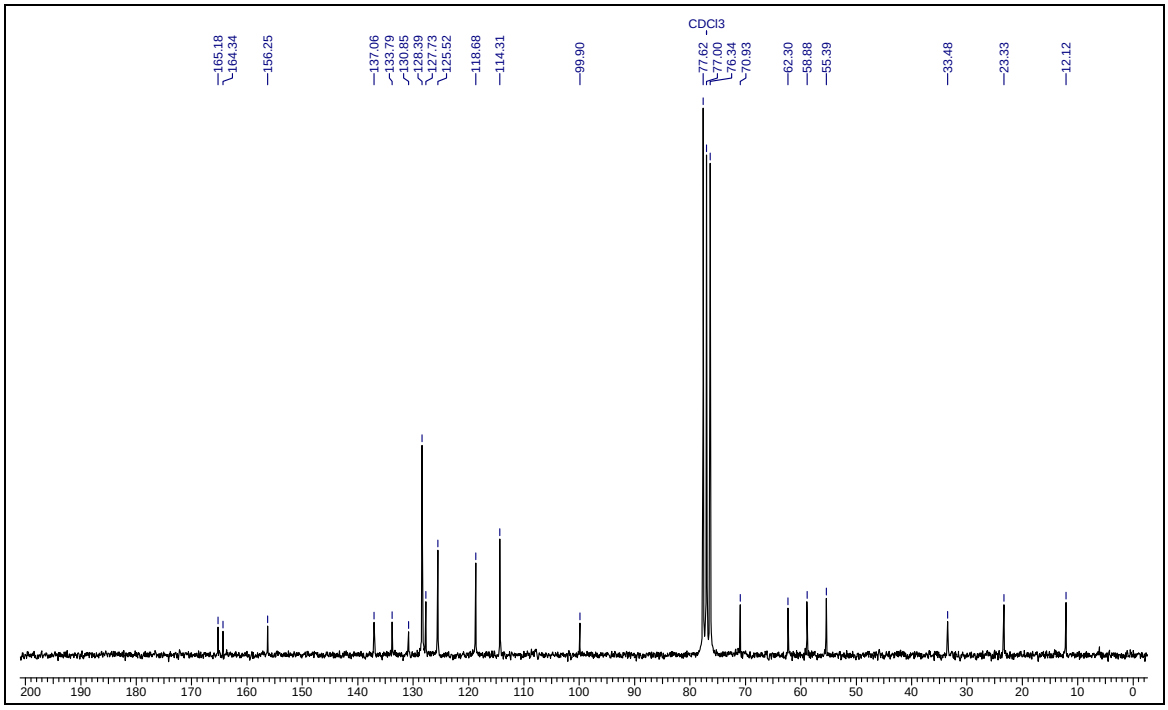

TMS
0.00
Ph
N
O
O
O
O
CO_2Et
3.07
5.00
0.74
0.91
1.67
0.86
2.78
0.94
5.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

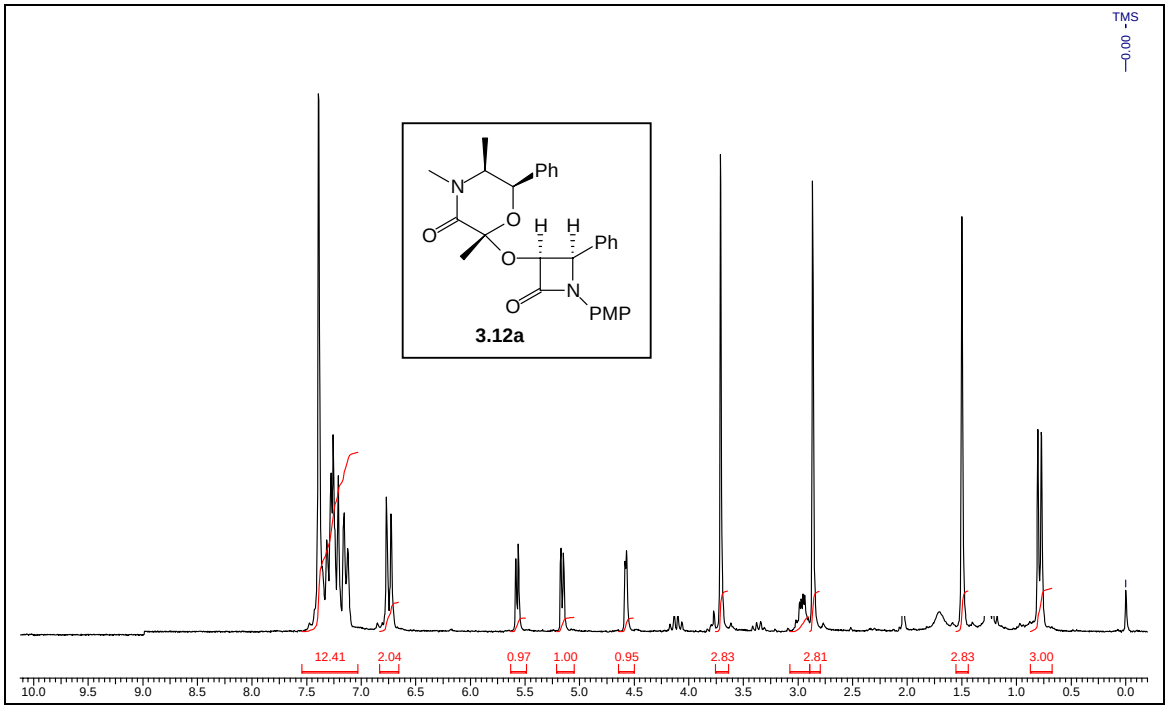

170.14
165.07
137.21
127.95
127.17
125.26
101.63
70.46
60.86
60.28
58.47
33.04
31.64
17.20
15.25
13.70
12.31
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

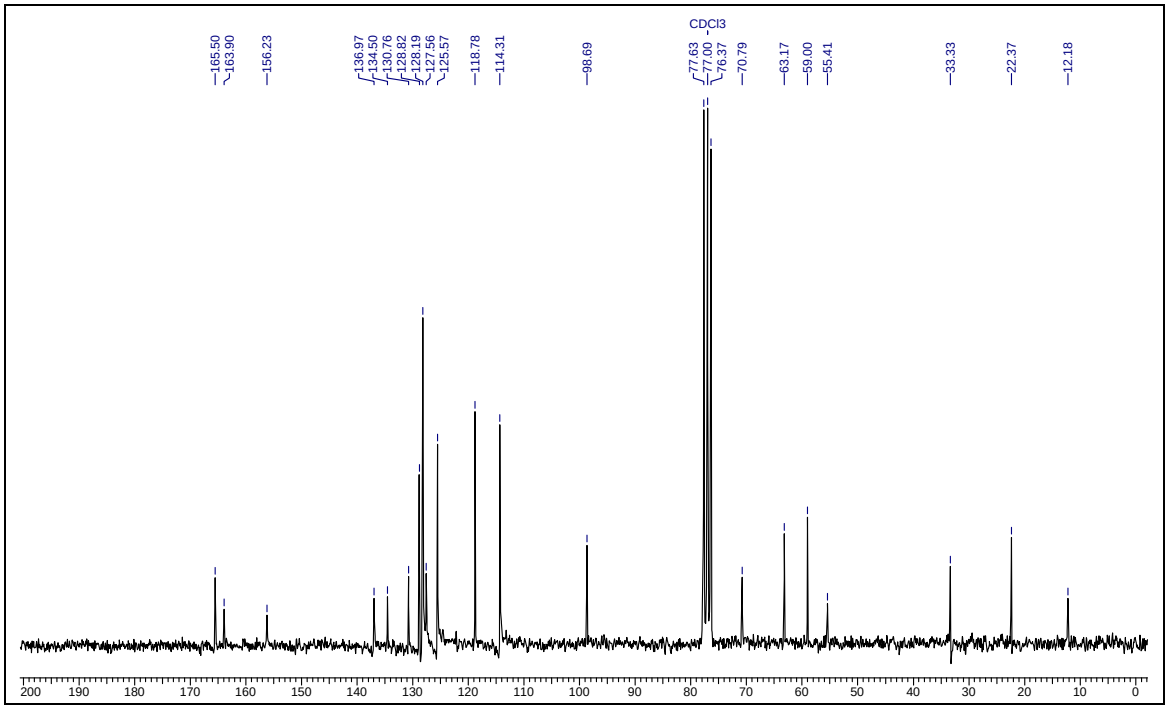

TMS
0.00
Ph
N
O
O
O
O
CO2H
3.09
0.58
4.93
0.72
0.70
0.80
0.81
3.22
0.85
5.40
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

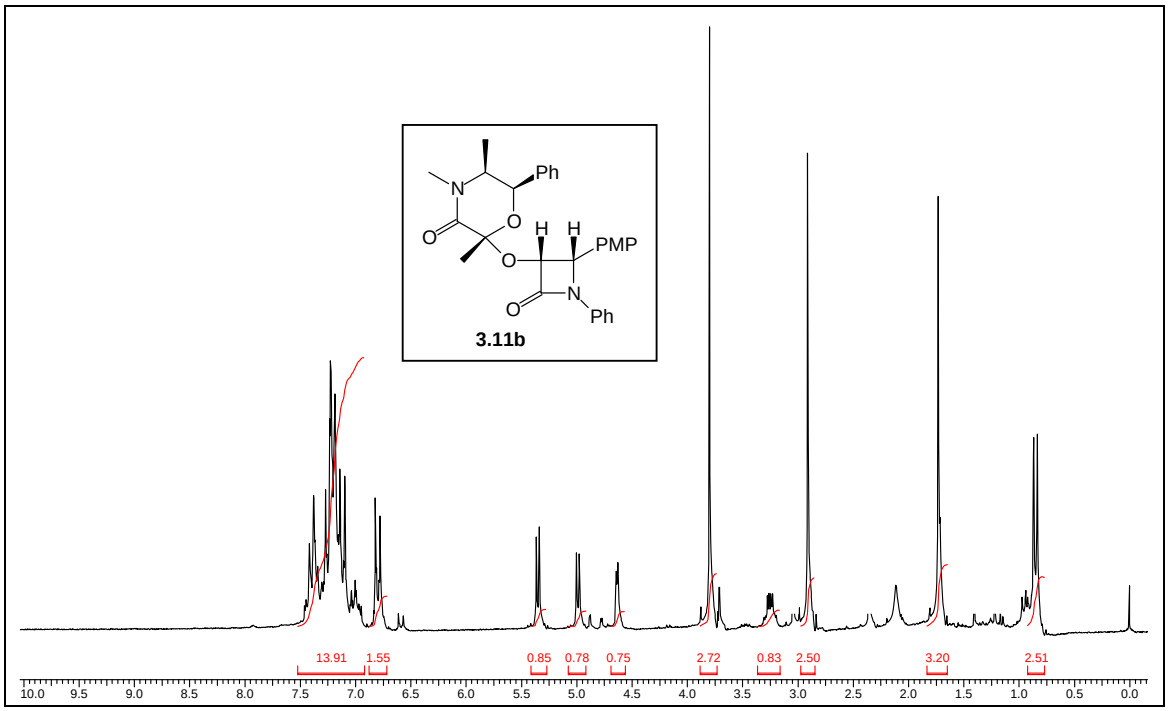

173.45
165.55
136.84
127.95
127.21
125.15
101.55
70.46
60.42
58.47
33.26
31.57
17.12
15.21
12.20
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

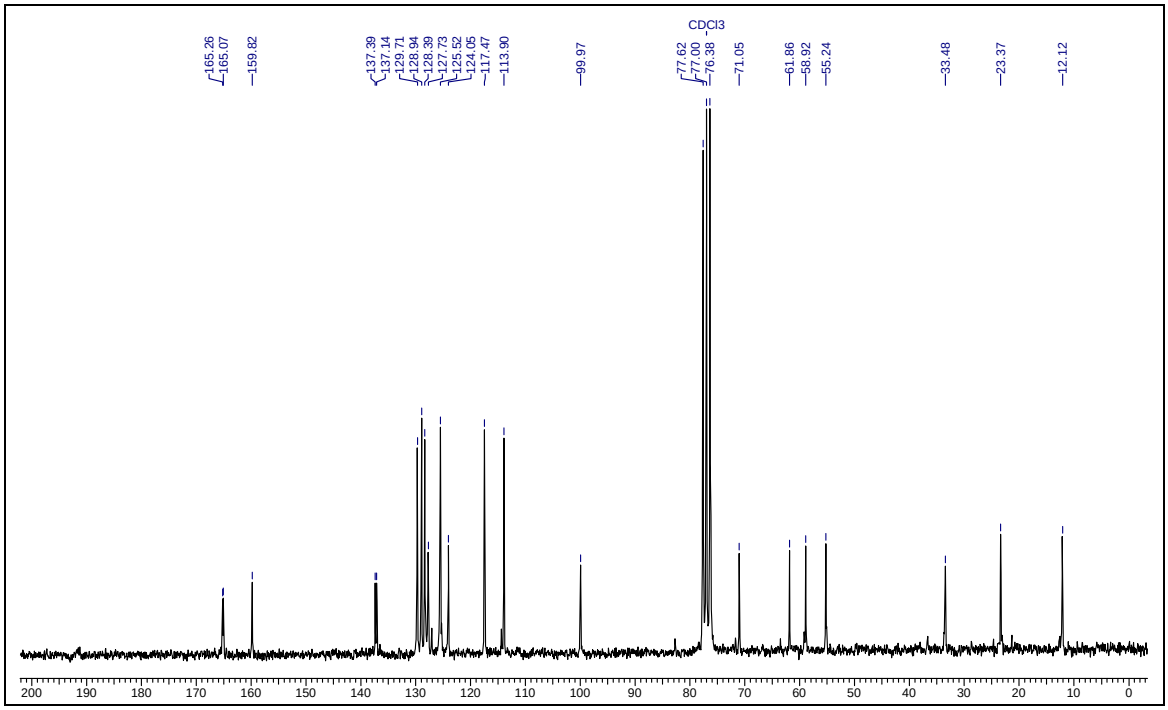

TMS
0.00
Ph
N
O
O
H
H
Ph
O
O
N
PMP
3.11a
14.00
1.66
0.90
0.85
0.83
3.27
0.96
2.83
2.94
3.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

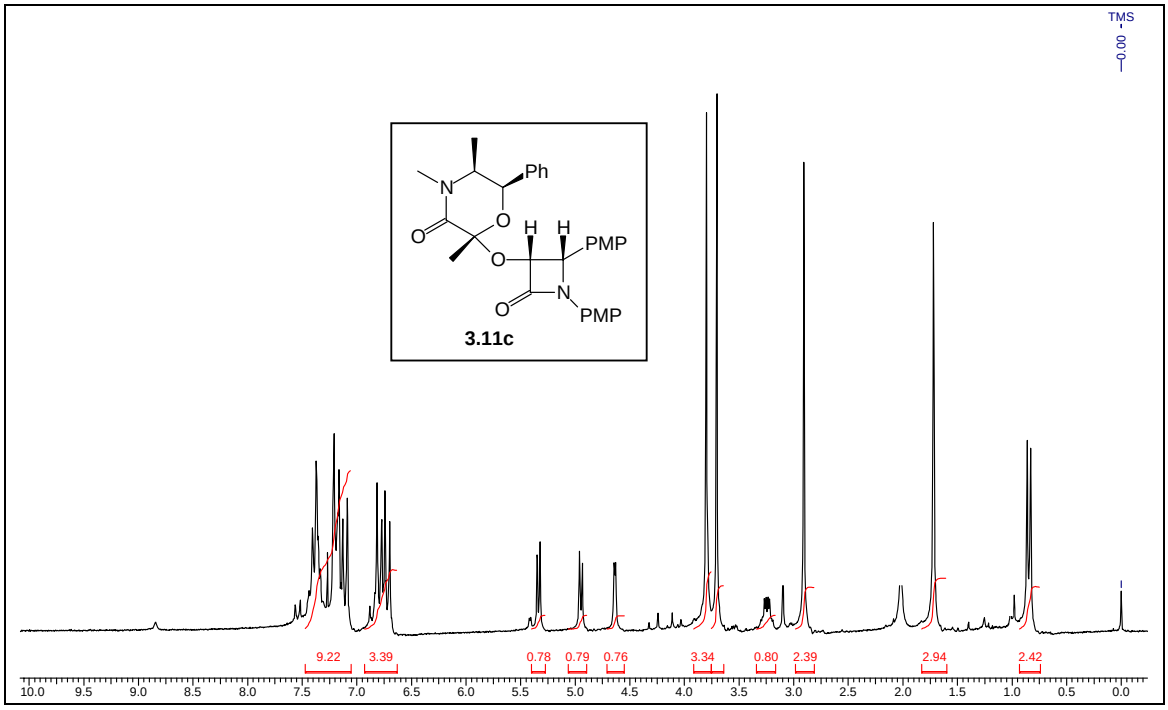

CDCl3
165.18
164.34
156.25
137.06
133.79
130.85
128.39
127.73
125.52
118.68
114.31
99.90
77.62
77.00
76.34
70.93
62.30
58.88
55.39
33.48
23.33
12.12
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

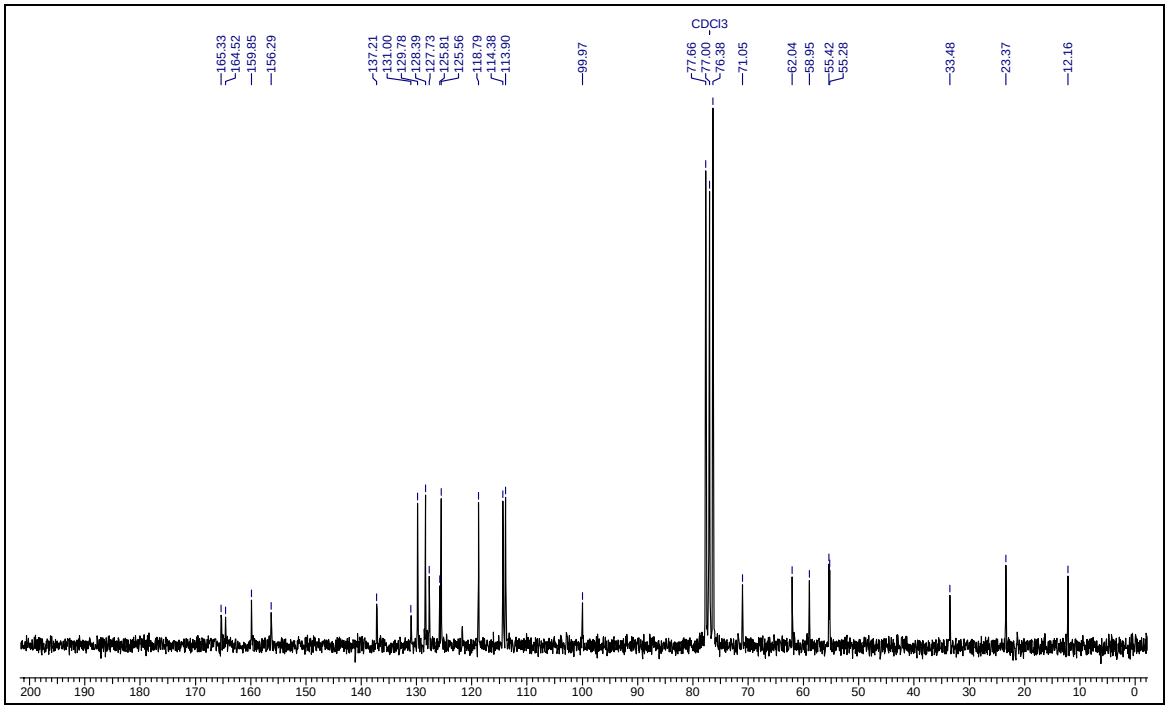

TMS
0.00
Ph
N
O
O
H
H
Ph
O
O
N
PMP
3.12a
12.41
2.04
0.97
1.00
0.95
2.83
2.81
2.83
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

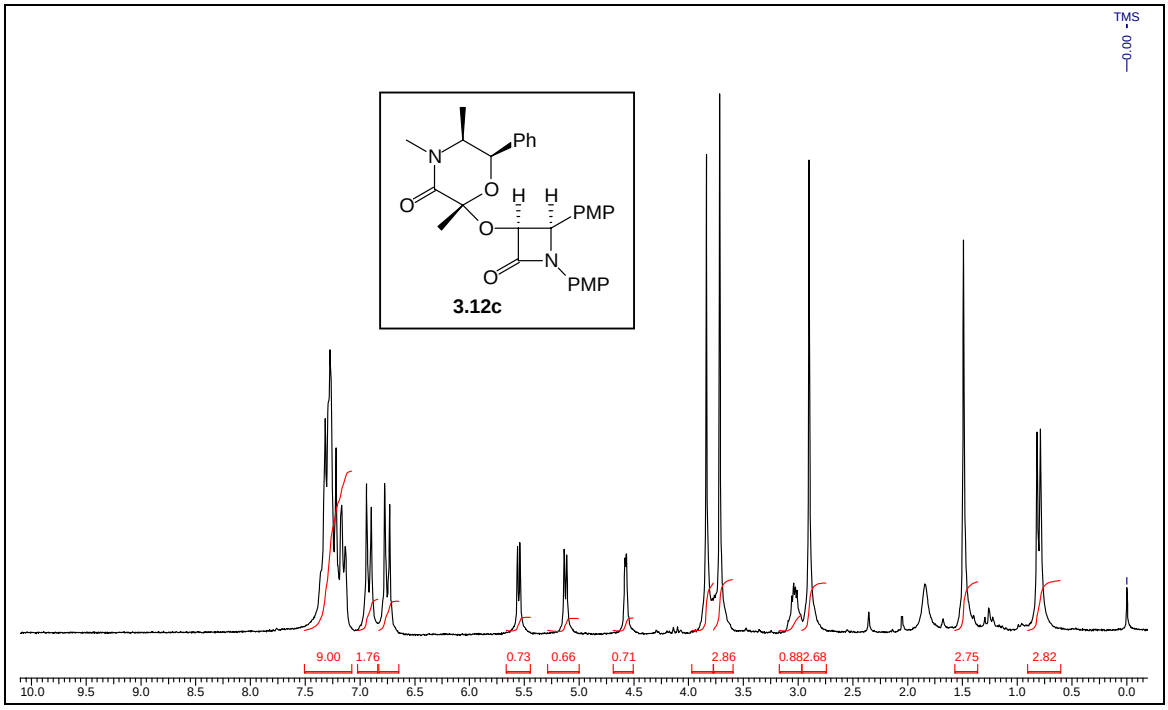

CDCl3
165.50
163.90
156.23
136.97
134.50
130.76
128.82
128.19
127.56
125.57
118.78
114.31
98.69
77.63
77.00
76.37
70.79
63.17
59.00
55.41
33.33
22.37
12.18
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

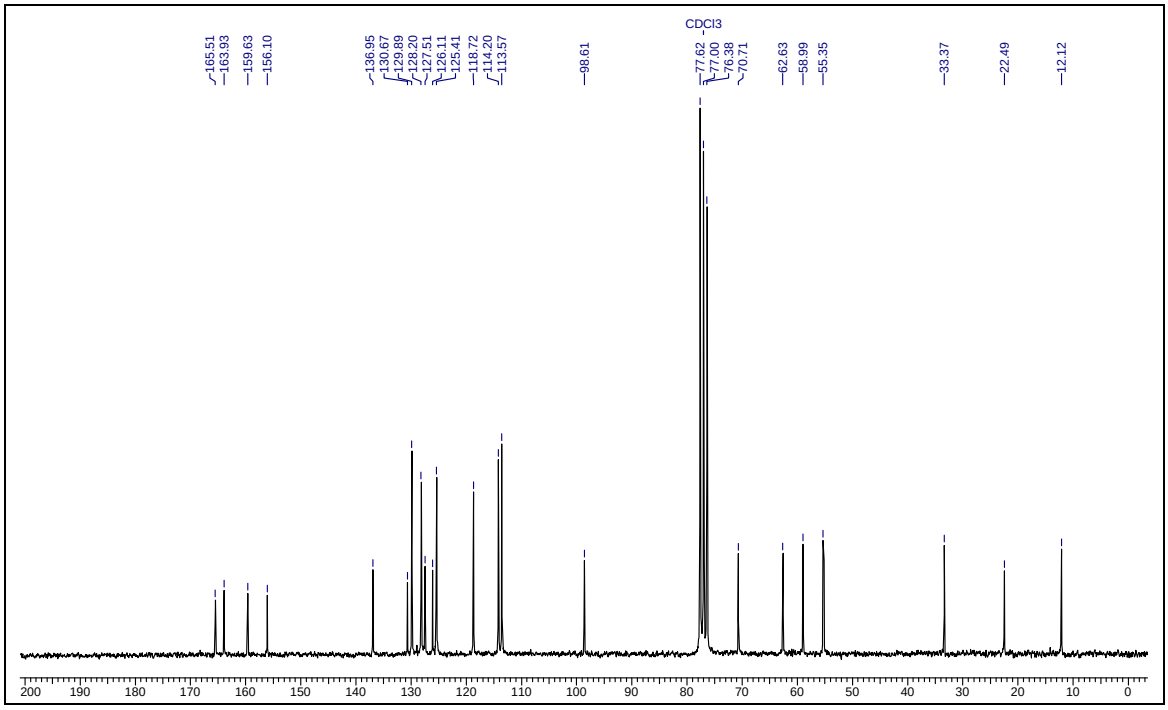

Ph
N
O
O
H
H
PMP
O
O
N
Ph
3.11b
13.91
1.55
0.85
0.78
0.75
2.72
0.83
2.50
3.20
2.51
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

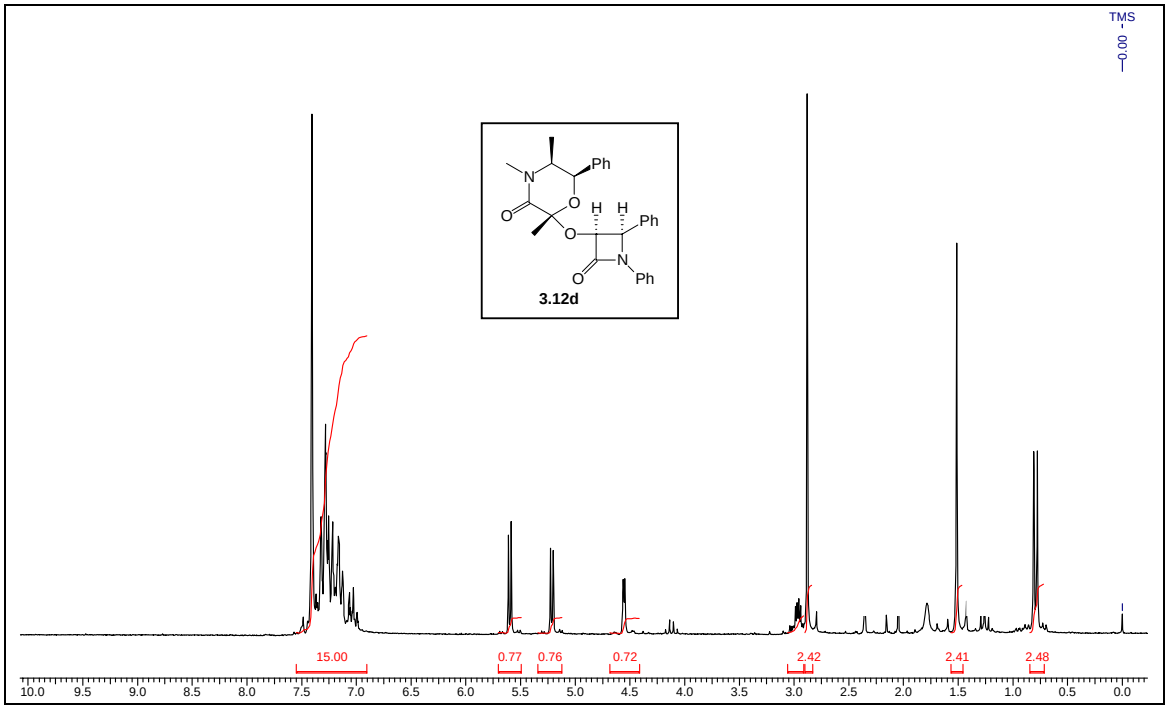

CDCl3
165.26
165.07
159.82
137.39
137.14
129.71
128.94
128.39
127.73
125.52
124.05
117.47
113.90
99.97
77.62
77.00
76.38
71.05
61.86
58.92
55.24
33.48
23.37
12.12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

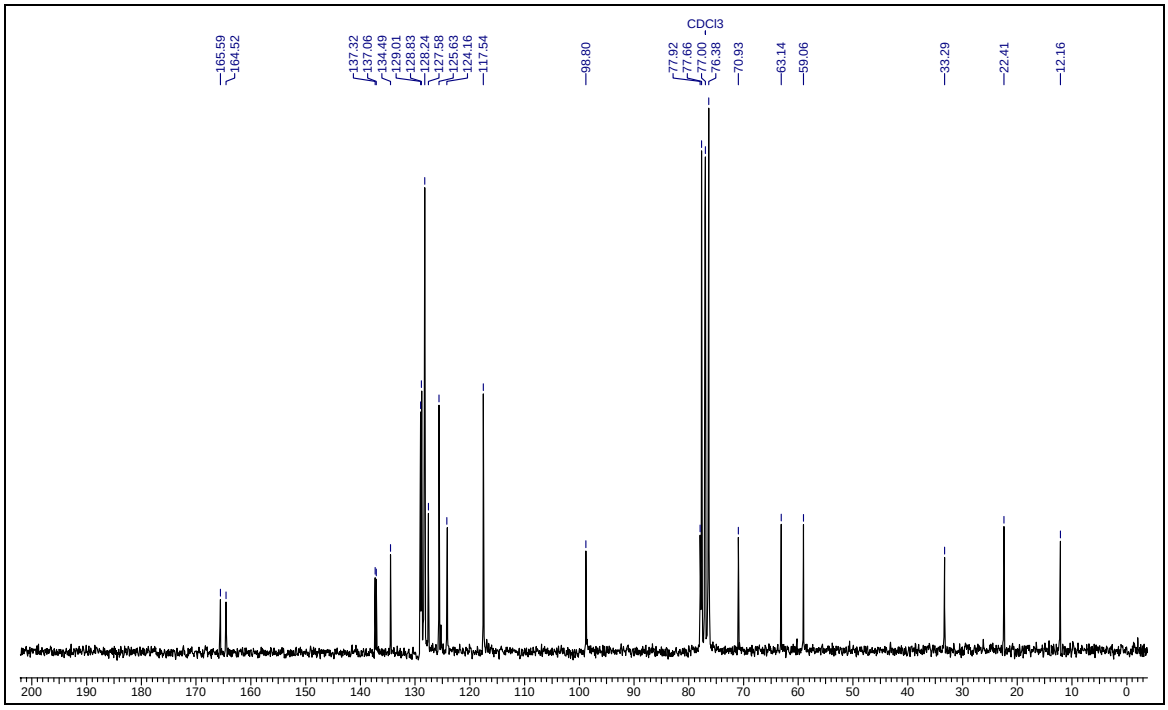

TMS
0.00
Ph
N
O
O
H
H
PMP
O
O
N
O
PMP
3.11c
9.22
3.39
0.78
0.79
0.76
3.34
0.80
2.39
2.94
2.42
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

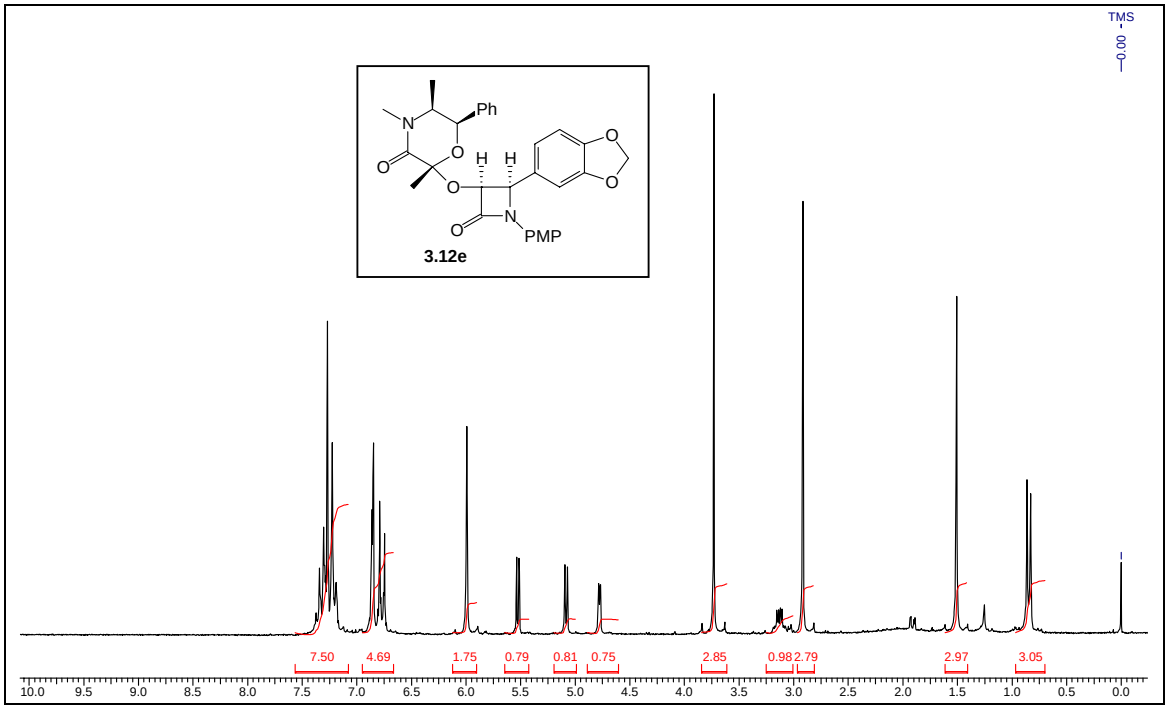

CDCl3
165.33
164.52
159.85
156.29
137.21
131.00
129.78
128.39
127.73
125.81
125.56
118.79
114.38
113.90
99.97
77.66
77.00
76.38
71.05
62.04
58.95
55.42
55.28
33.48
23.37
12.16
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

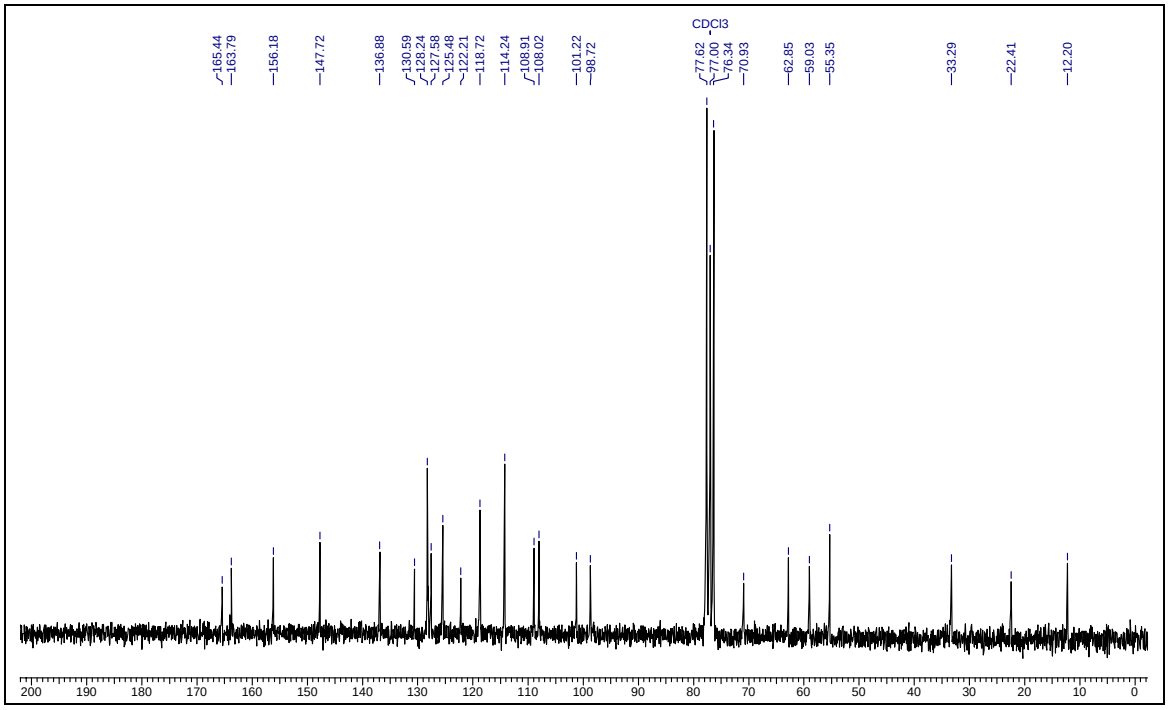

TMS
0.00
Ph
N
O
O
H
H
PMP
O
N
O
PMP
3.12c
9.00
1.76
0.73
0.66
0.71
2.86
0.88
2.68
2.75
2.82
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

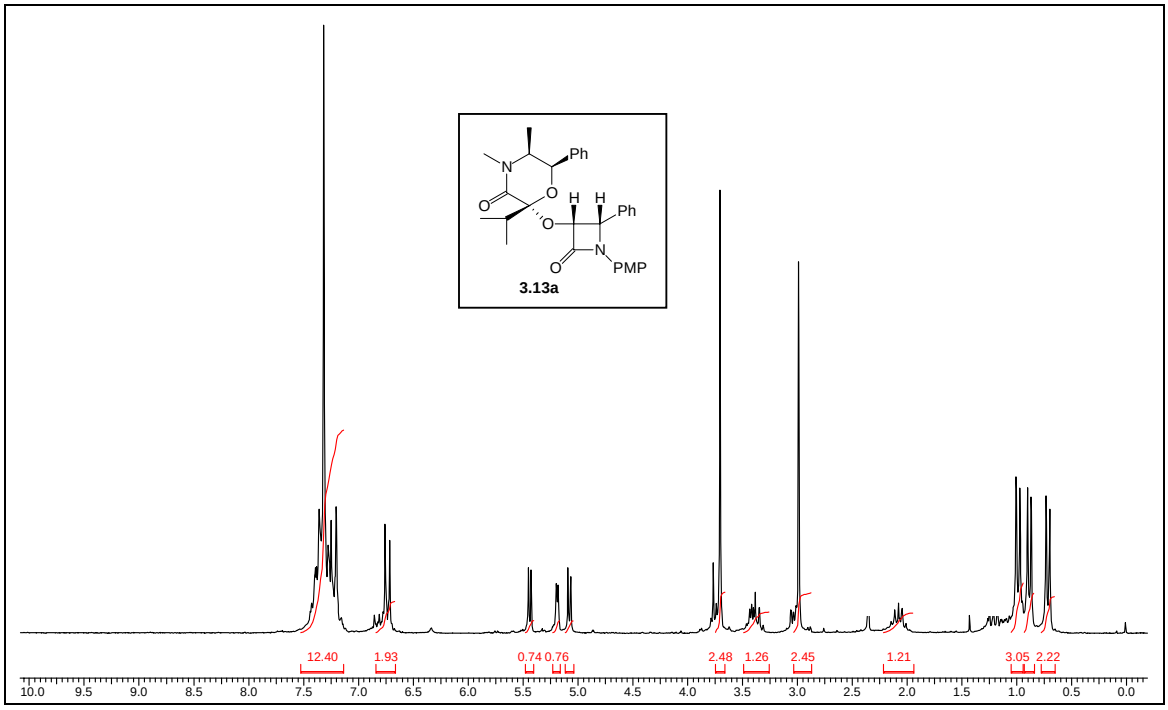

CDCl3
165.51
163.93
159.63
156.10
136.95
130.67
129.89
128.20
127.51
126.11
125.41
118.72
114.20
113.57
98.61
77.62
77.00
76.38
70.71
62.63
58.99
55.35
33.37
22.49
12.12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

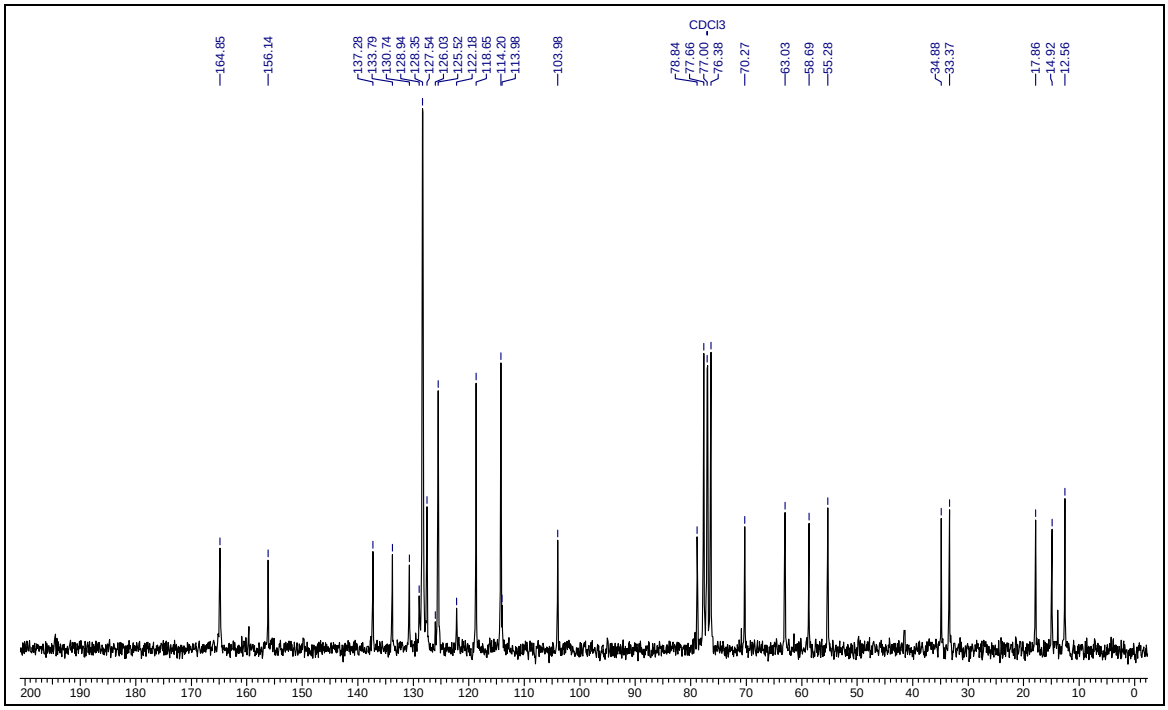

TMS
0.00
Ph
N
O
O
H
H
Ph
O
N
O
Ph
3.12d
15.00
0.77
0.76
0.72
2.42
2.41
2.48
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

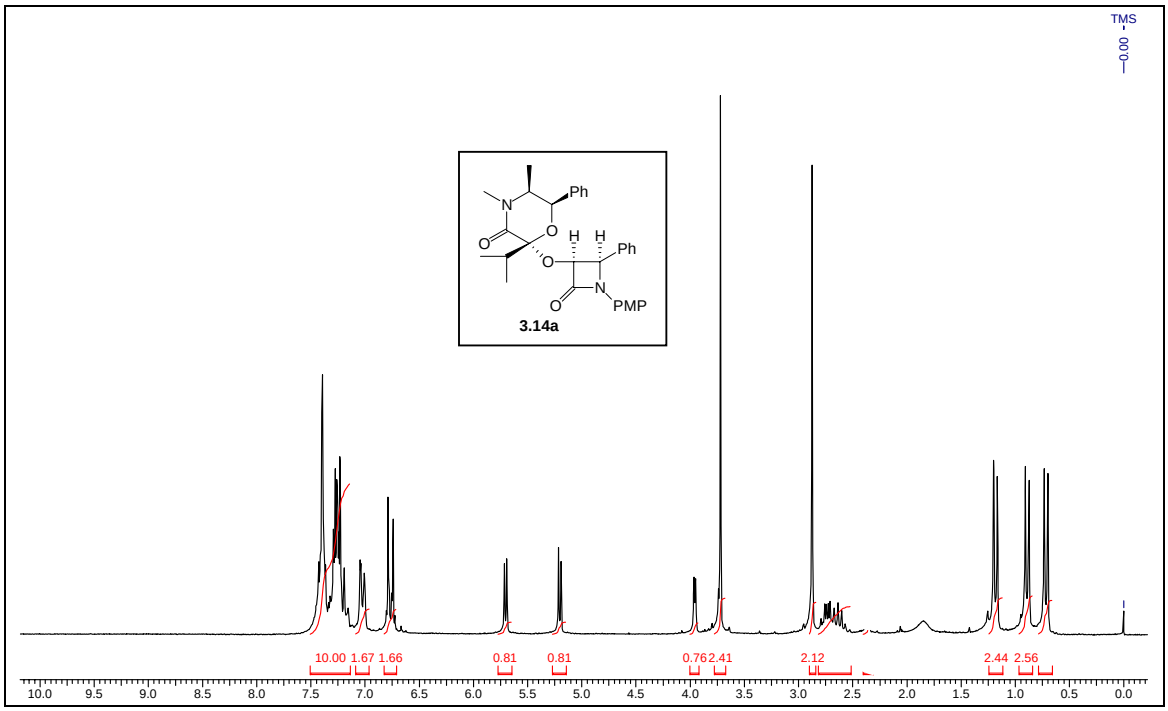

CDCl3
165.59
164.52
137.32
137.06
134.49
129.01
128.83
128.24
127.58
125.63
124.16
117.54
98.80
77.92
77.66
77.00
76.38
70.93
63.14
59.06
33.29
22.41
12.16
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

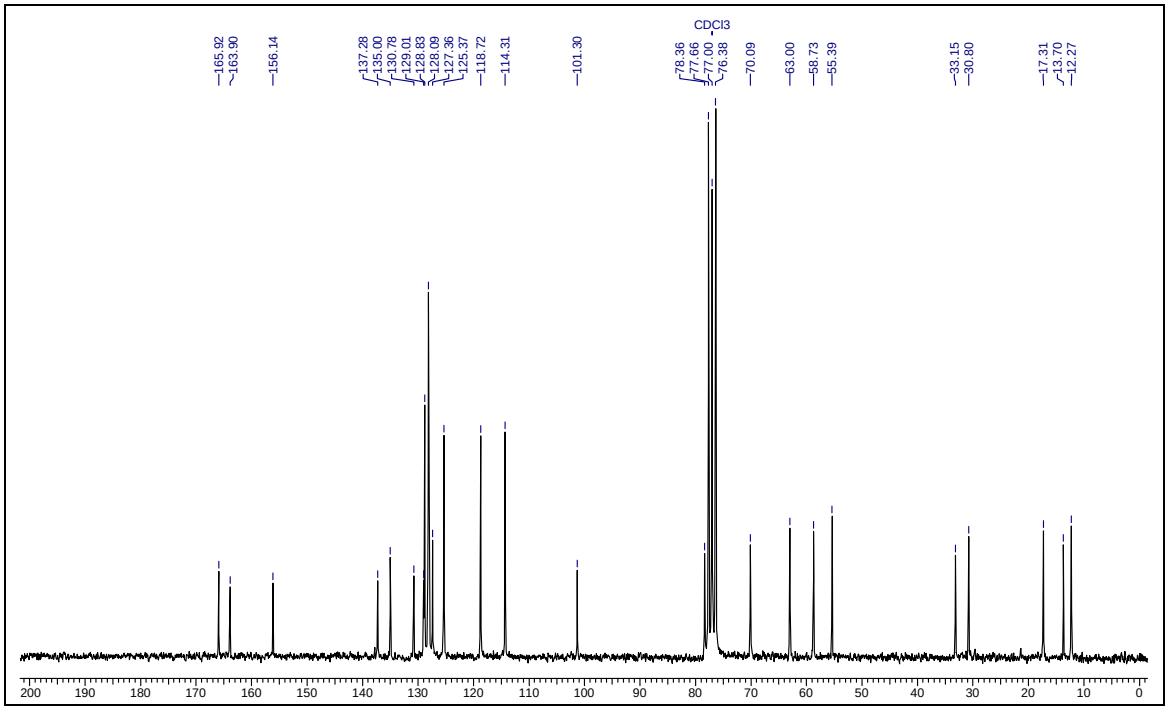

TMS
0.00
Ph
N
O
O
H
H
O
O
O
N
O
PMP
3.12e
7.50
4.69
1.75
0.79
0.81
0.75
2.85
0.98
2.79
2.97
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

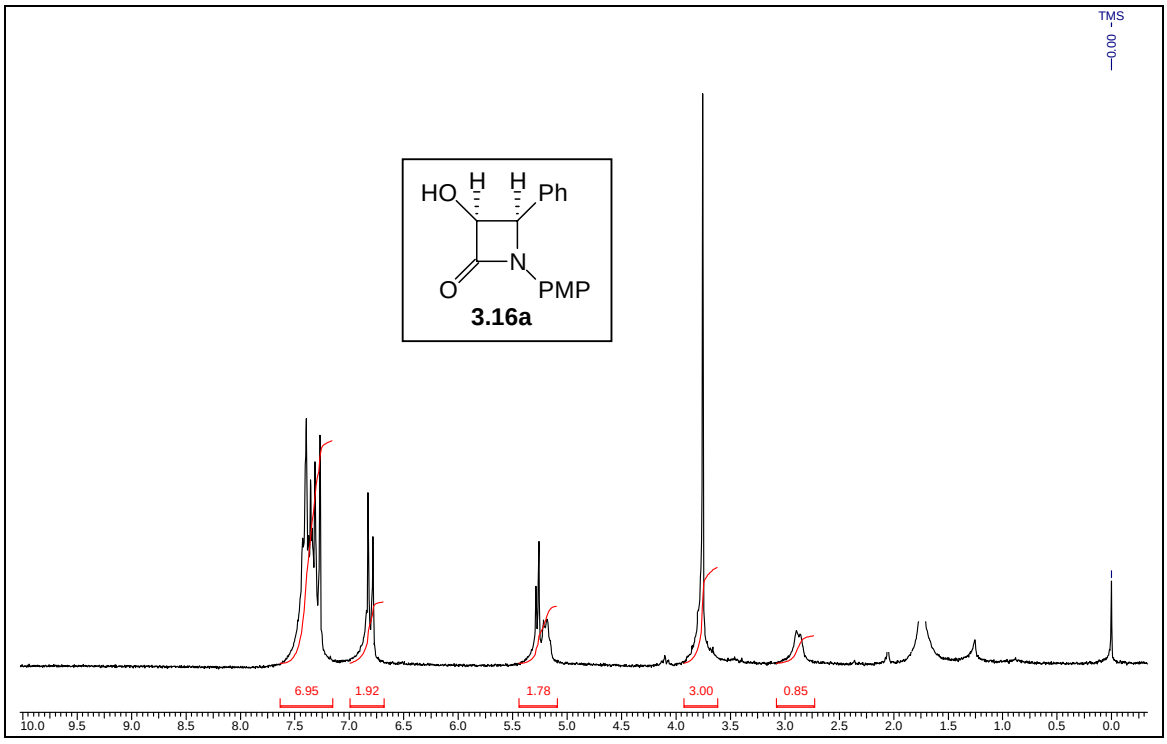

CDCl3
165.44
163.79
156.18
147.72
136.88
130.59
128.24
127.58
125.48
122.21
118.72
114.24
108.91
108.02
101.22
98.72
77.62
77.00
76.34
70.93
62.85
59.03
55.35
33.29
22.41
12.20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

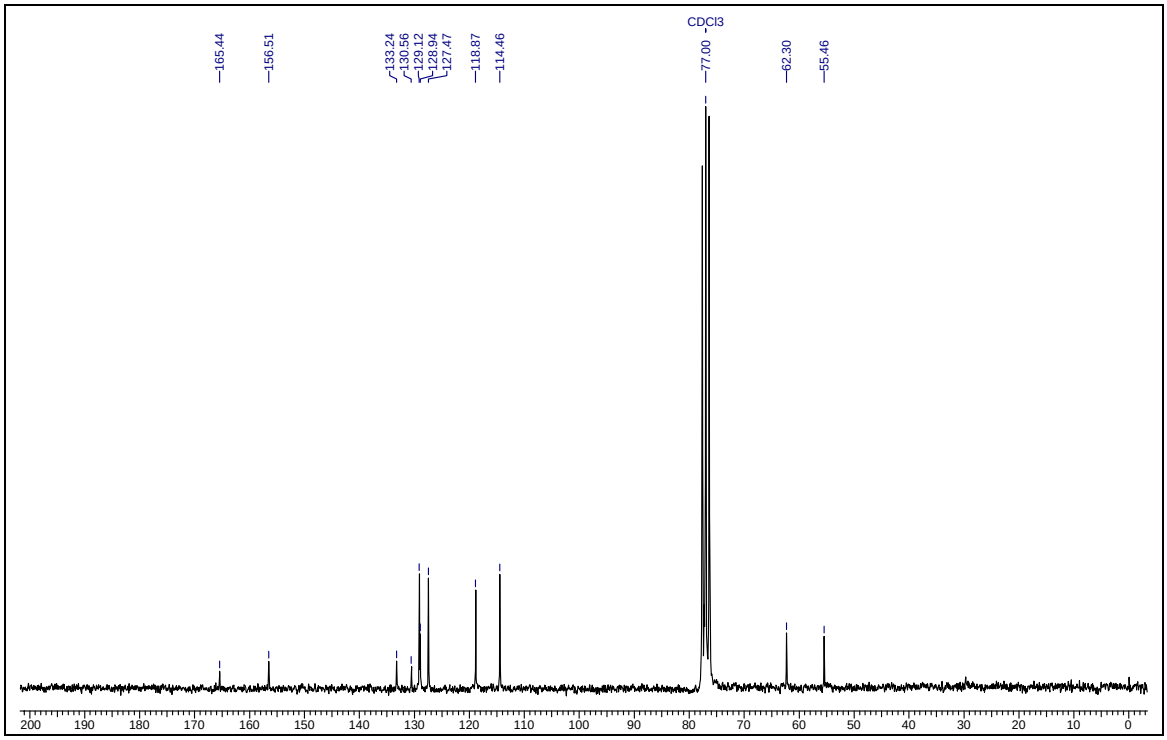

Ph
N
O
O
H
H
Ph
O
N
O
PMP
3.13a
12.40
1.93
0.74
0.76
2.48
1.26
2.45
1.21
3.05
2.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

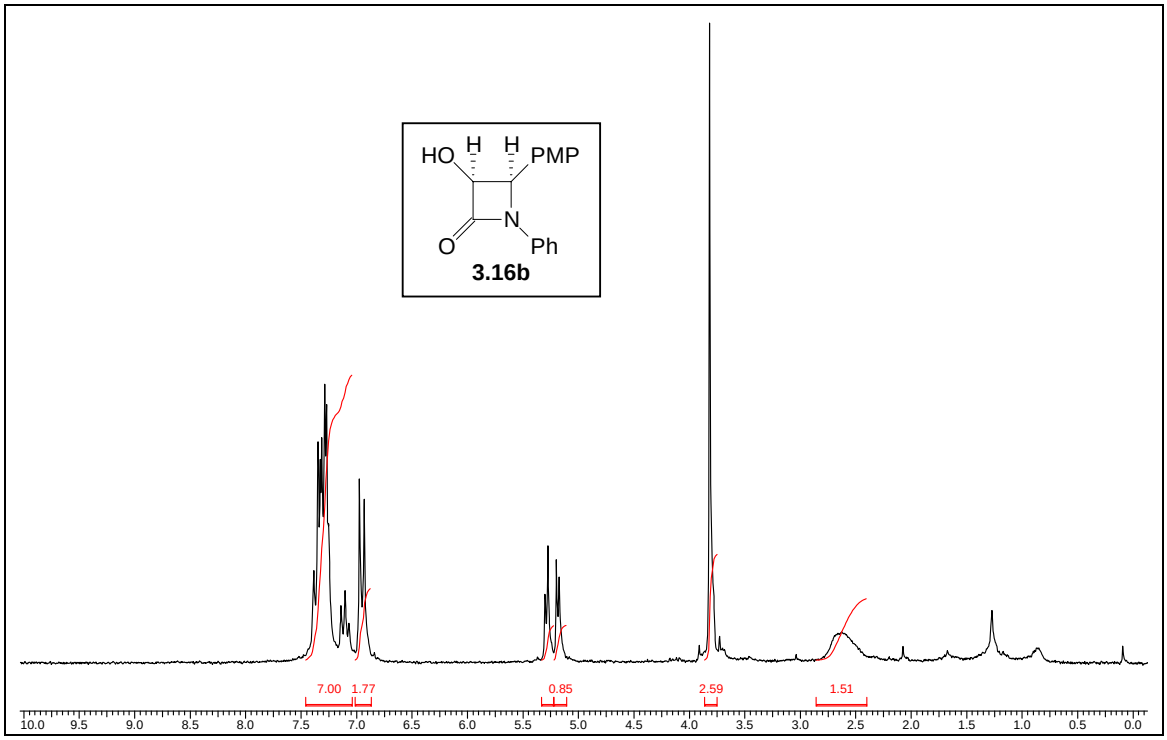

CDCl3
164.85
156.14
137.28
133.79
130.74
128.94
128.35
127.54
126.03
125.52
122.18
118.65
114.20
113.98
103.98
78.84
77.66
77.00
76.38
70.27
63.03
58.69
55.28
34.88
33.37
17.86
14.92
12.56
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

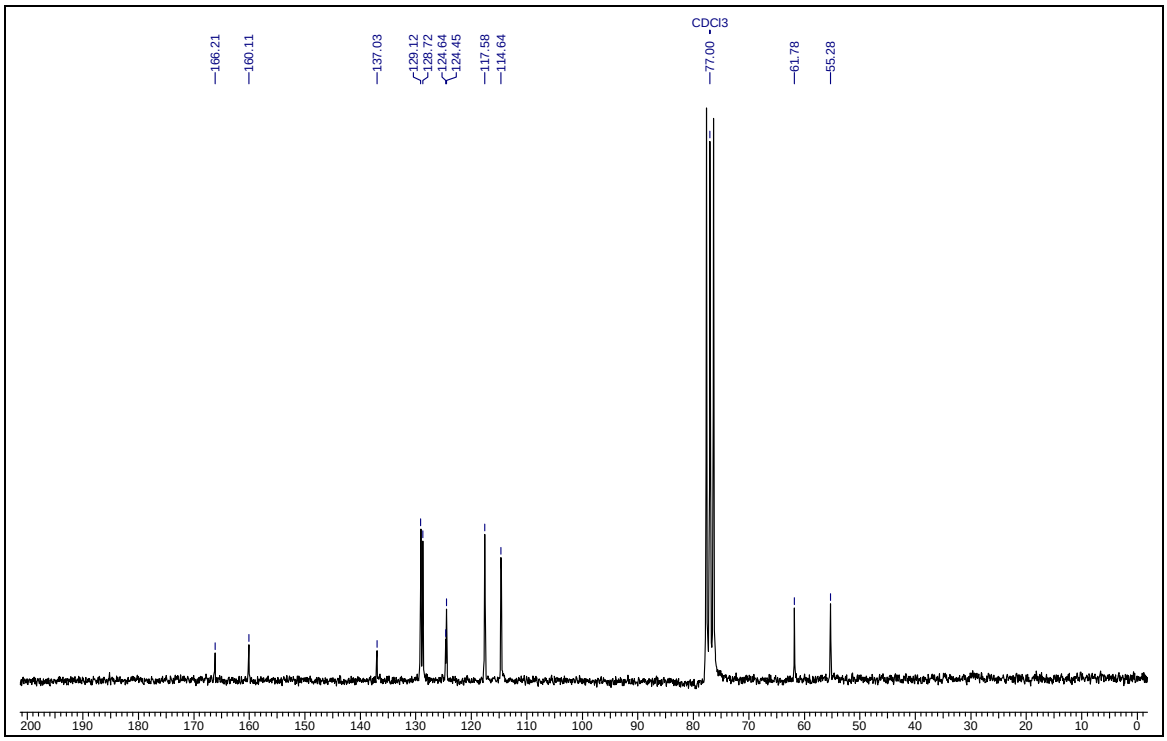

TMS
0.00
Ph
N
O
O
H
H
Ph
O
O
N
PMP
3.14a
10.00 1.67 1.66 0.81 0.81 0.76 2.41 2.12 2.44 2.56
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

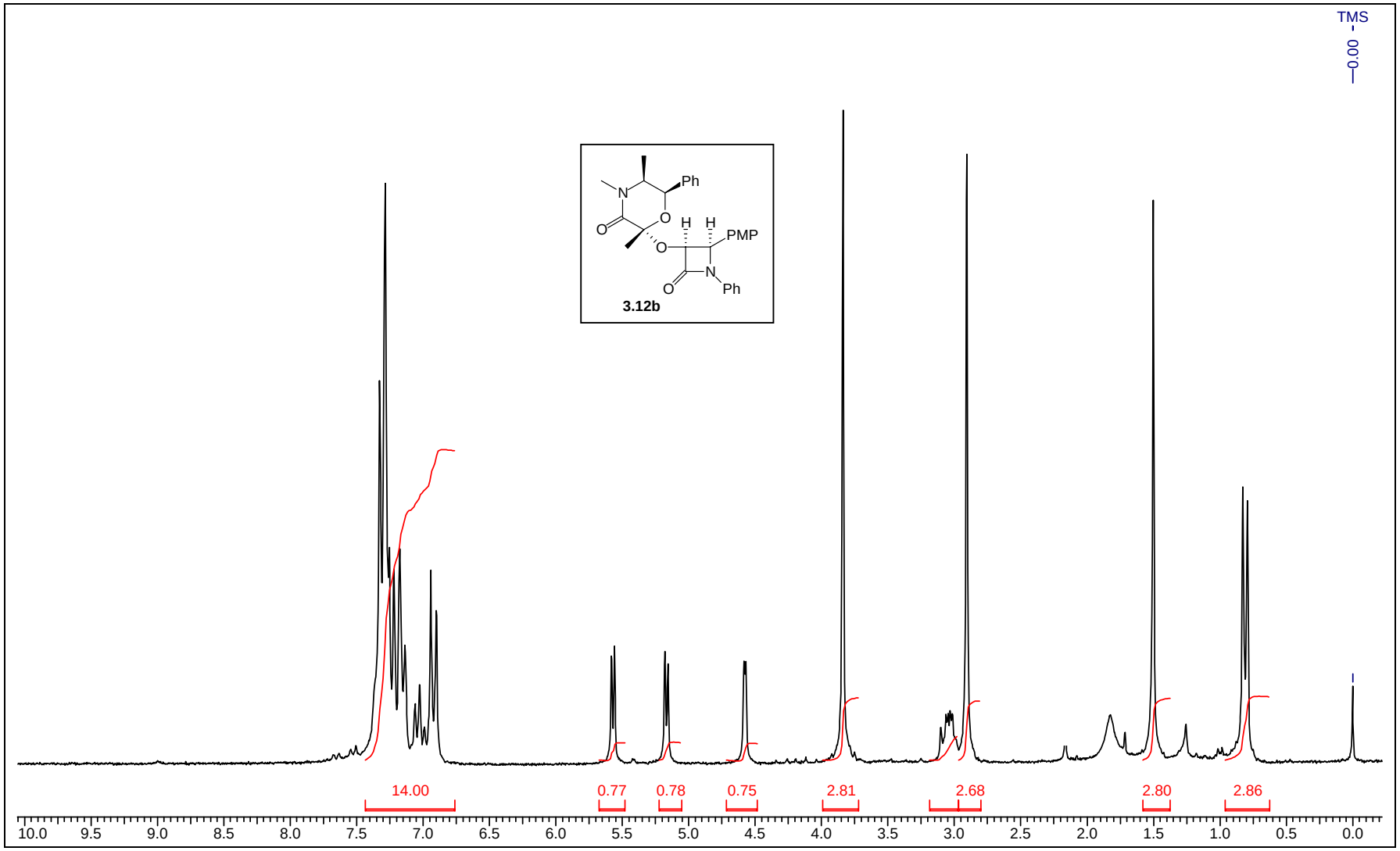

CDCl3
165.92
163.90
156.14
137.28
135.00
130.78
129.01
128.83
128.09
127.36
125.37
118.72
114.31
101.30
78.36
77.66
77.00
76.38
70.09
63.00
58.73
55.39
33.15
30.80
17.31
13.70
12.27
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

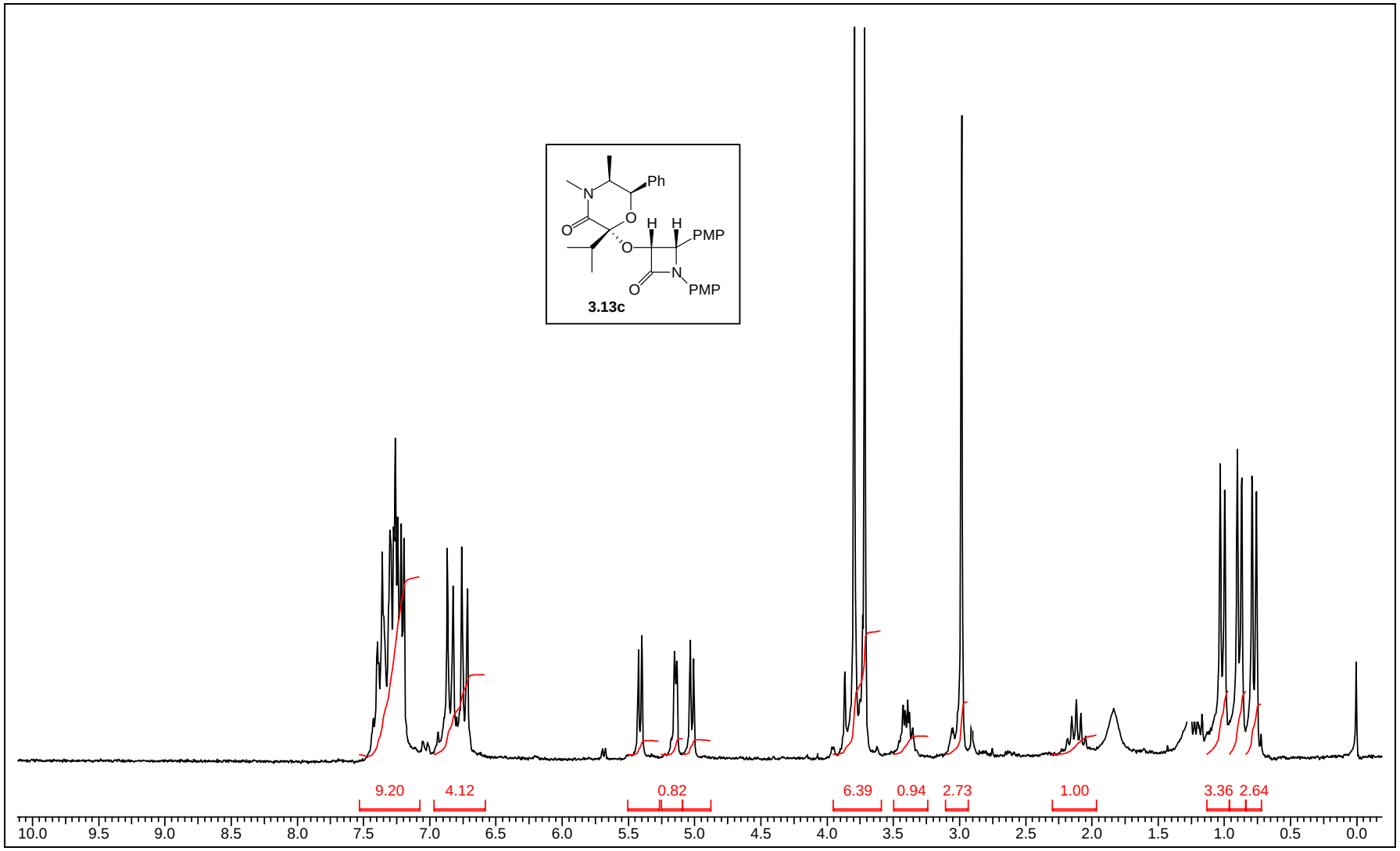

TMS
0.00
HO
H
H
Ph
N
O
PMP
3.16a
6.95
1.92
1.78
3.00
0.85
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

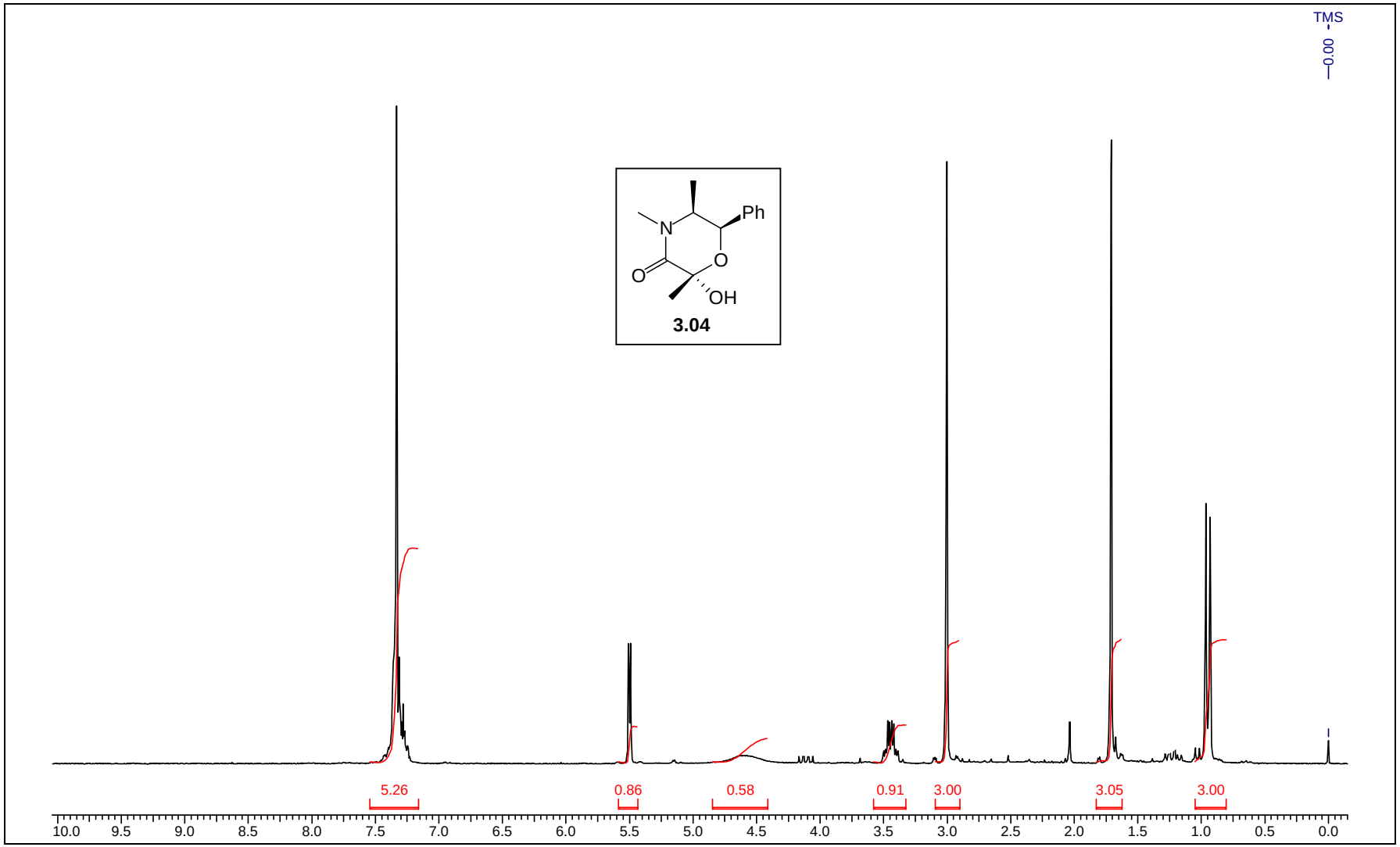

CDCl3
165.44
156.51
133.24
130.56
129.12
128.94
127.47
118.87
114.46
77.00
62.30
55.46
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

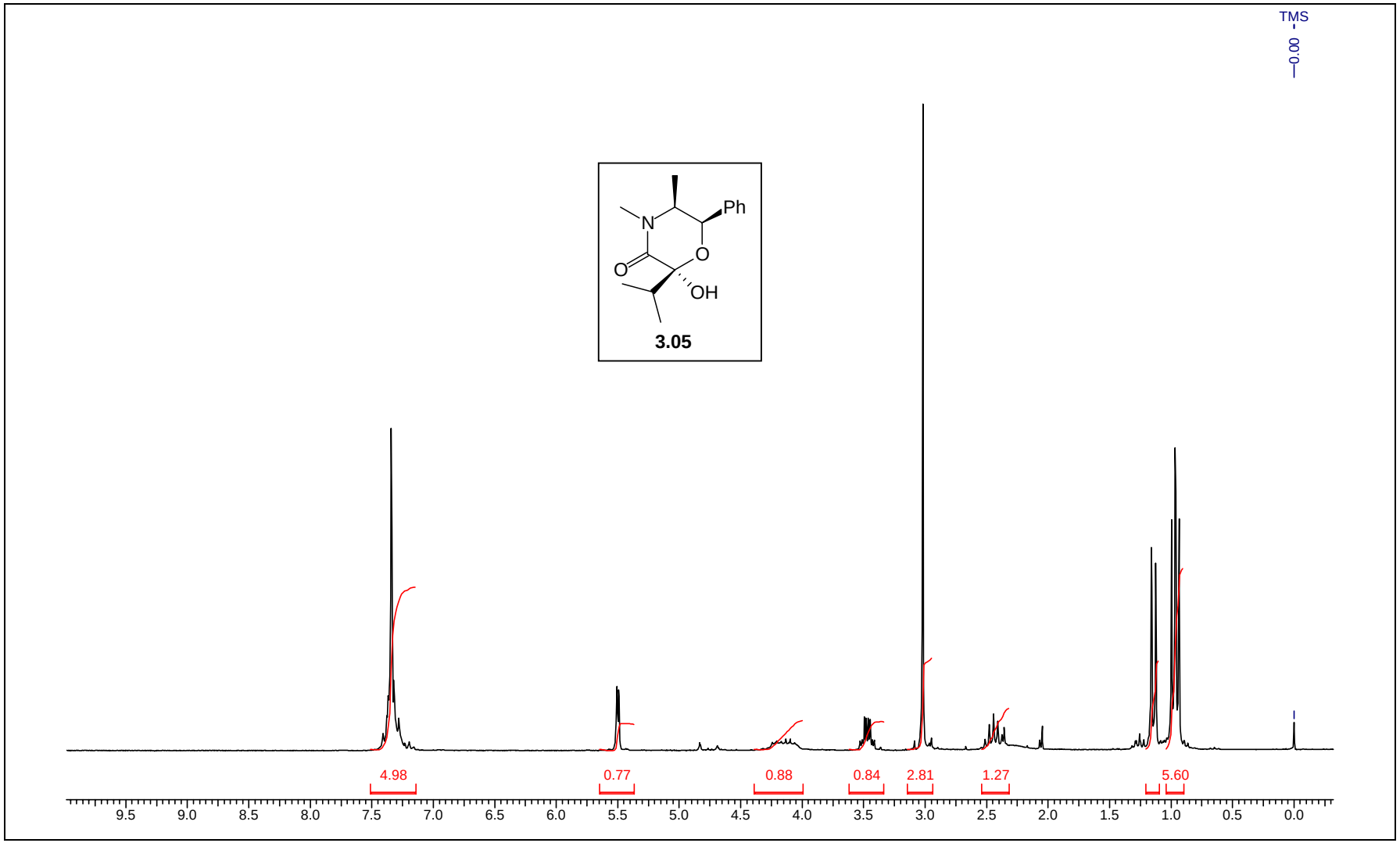

HO
H
H
PMP
N
O
Ph
3.16b
7.00
1.77
0.85
2.59
1.51
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

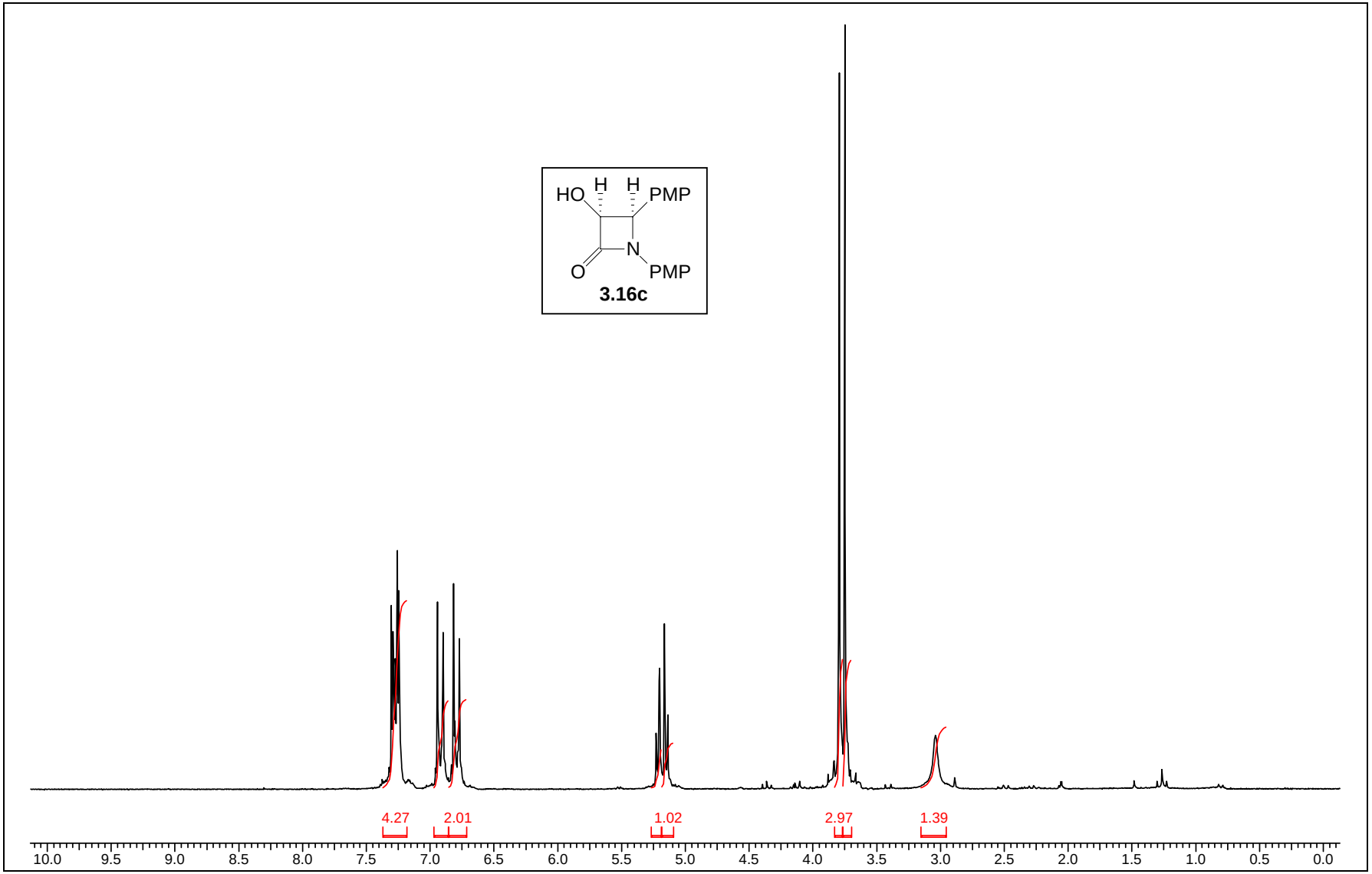

166.21
160.11
137.03
129.12
128.72
124.64
124.45
117.58
114.64
CDCl3
77.00
61.78
55.28
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

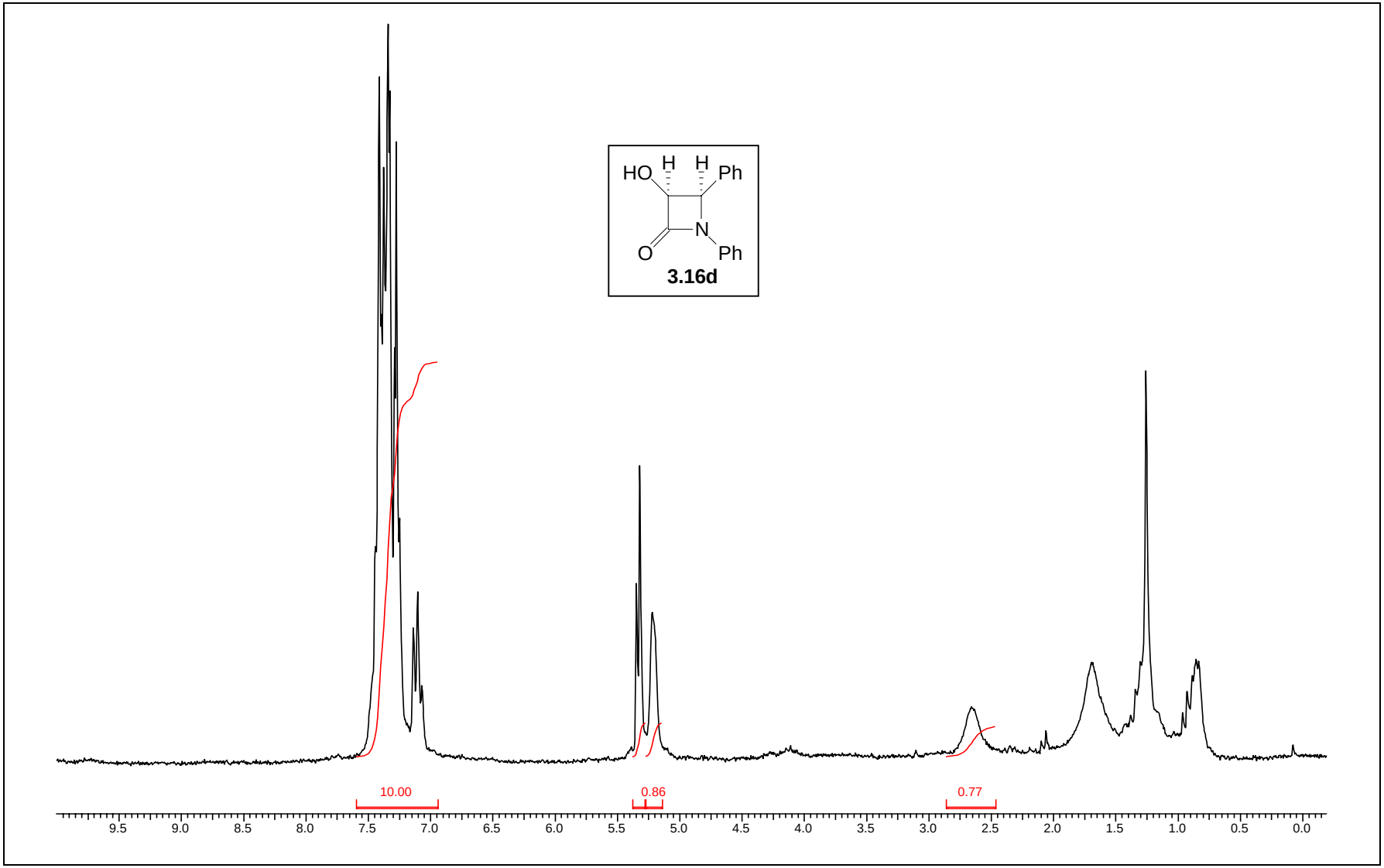

TMS
0.00
Ph
N
O
O
H
H
PMP
O
N
O
Ph
3.12b
14.00
0.77
0.78
0.75
2.81
2.68
2.80
2.86
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

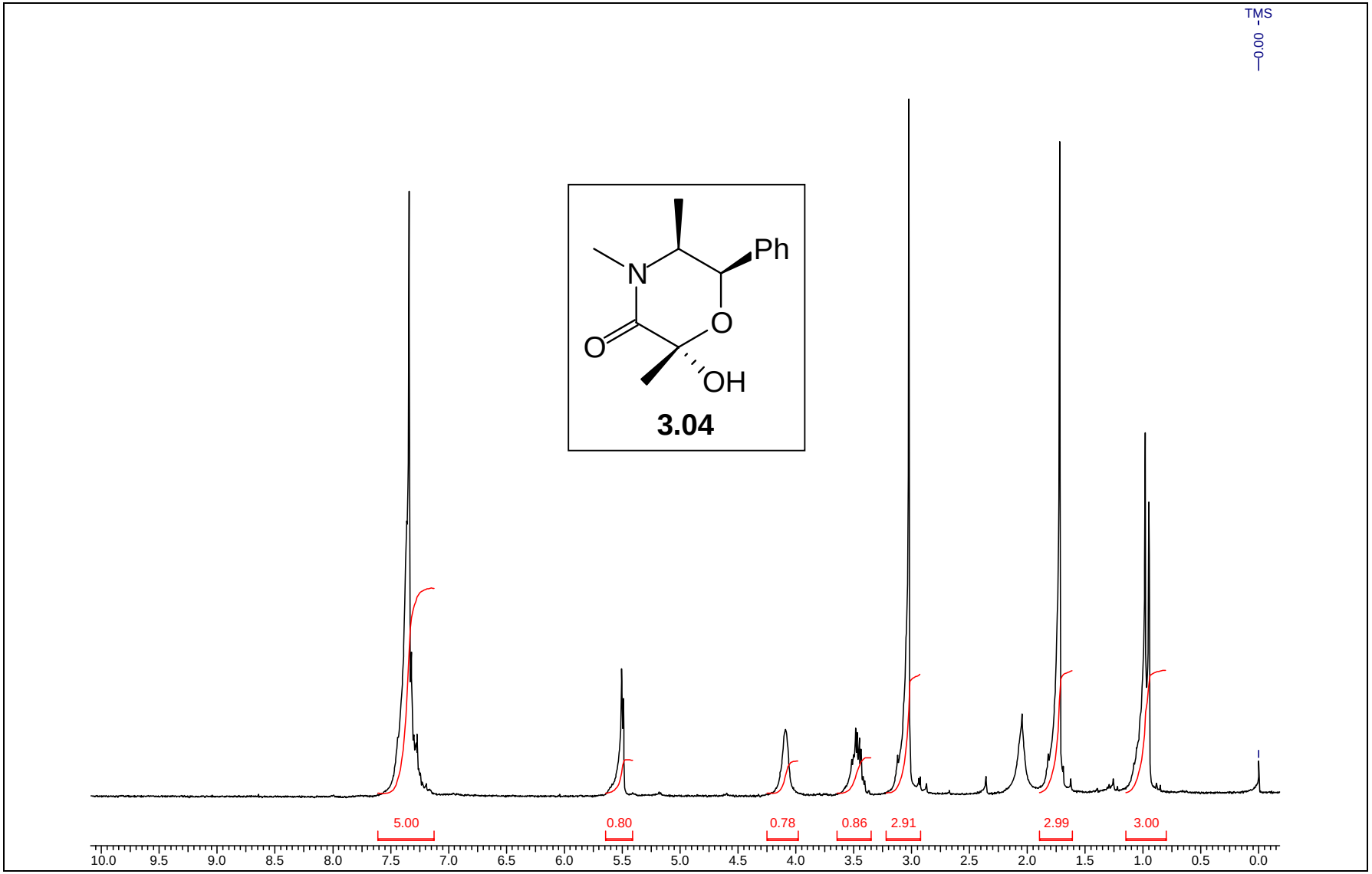

Ph
N
O
O
H
H
PMP
O
N
O
PMP
3.13c
9.20
4.12
0.82
6.39
0.94
2.73
1.00
3.36
2.64
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


TMS
0.00
Ph
N
O
O
OH
3.04
5.26
0.86
0.58
0.91
3.00
3.05
3.00
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


TMS
0.00
Ph
N
O
O
OH
3.05
4.98
0.77
0.88
0.84
2.81
1.27
5.60
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


HO
H
H
PMP
N
O
PMP
3.16c
4.27
2.01
1.02
2.97
1.39
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


HO
H
H
Ph
N
O
Ph
3.16d
10.00
0.86
0.77
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


TMS
Ph
N
O
O
OH
3.04
5.00
0.80
0.78
0.86
2.91
2.99
3.00
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

4.1: Introduction

Enantiomerically pure α-hydroxy acids constitute 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 stationery 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. The methods reported in literature to synthesize racemic α-allyl-α-hydroxy acids are also included.

4.2: Background for present work

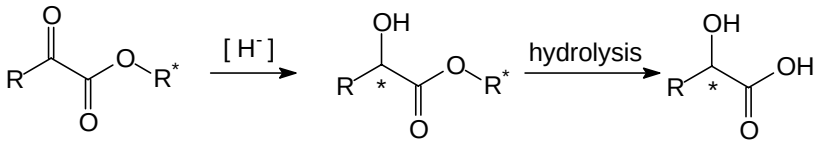
There are many general methods available in literature for stereoselective synthesis of α-hydroxy acids, racemic α-hydroxy acids and enzymatic resolution of α-hydroxy acids. This section describes the reported methods (both stereoselective synthesis and racemic synthesis) for synthesis of α-hydroxy acids.

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

Stereoselective reduction of chiral α-keto esters

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

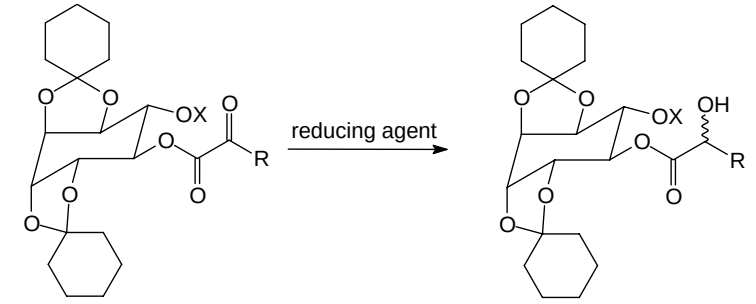
Figure 1. Reduction of chiral α-keto esters



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[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 the lactic acid). Four years later McKenzie[7] repeated the same reactions, and also successfully applied 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. Inspite of these extensive studies, the stereoselectivities of reduction of chiral α-keto esters remained only poor to moderate [(Figure 1, R* = (-)-menthyl (maximum 41% ee),[9] 1,2:5,6 di-*O*-cyclohexylidine D-glucofuranose (maximum 45% ee),[10] (+)-bornyl (3% ee),[11] (+)-phenyldihydrothebainyl (maximum 69% ee),[12] α-amyrinyl (6% ee),[11] cholesteryl (maximum 4% ee),[9b,c] (-)-1-phenylethanol (maximum 7% ee)].[13]

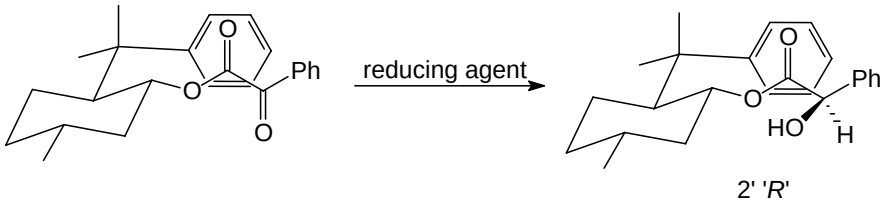
Interest in the asymmetric reductions of chiral α-keto esters has reemerged only recently and a significant improvement in diastereoselectivity has been achieved, although only in a few cases. Synthesis of α-hydroxy esters (22-70% de) by the diastereoselective reduction of α-keto esters derived from cholic acid[14] has been reported. 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% de) 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% ee) (Scheme 1).

Scheme 1



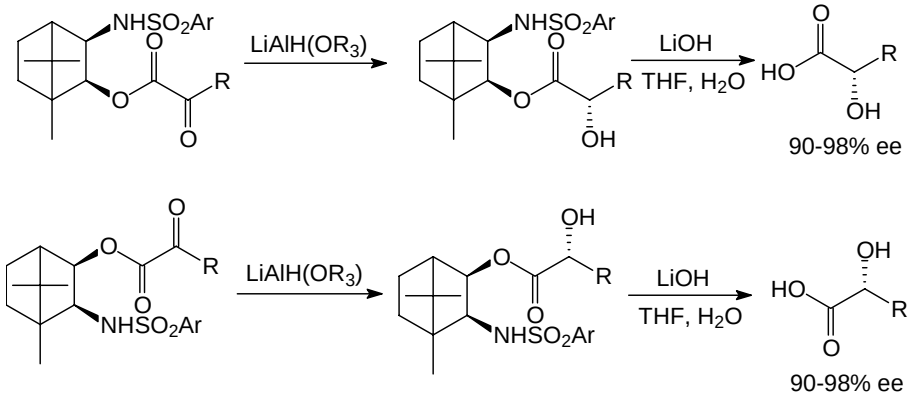
In another approach,[16] 8-phenyl menthol was used as the chiral auxiliary. Diastereoselectivities of maximum 94% could be obtained in the reduction of phenylglyoxylate esters (Scheme 2).

Scheme 2



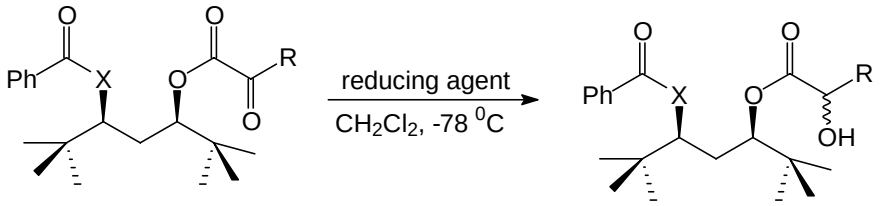
Very high diastereoselectivities (90-98% de) have been reported by Xiang[17] *et. al.* in the reduction of chiral α-keto esters derived from α-(arylsulfonamido) borneols with modified lithium aluminium hydride reagents (Scheme 3).

Scheme 3



Yamamoto and coworkers reported[18] new acyclic amino alcohol and diol auxiliaries. 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% de, Scheme 4) is highly dependant on the reducing agent. DIBAL-H gave the best results.

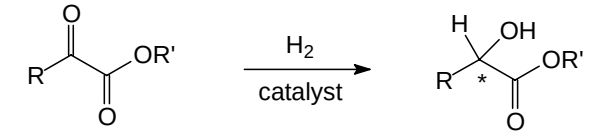
Scheme 4



Asymmetric hydrogenation of α-keto esters

The stereoselective hydrogenation of α-keto esters has also been extensively investigated. Most of the chiral substrates in the reaction studies employing hydride as 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

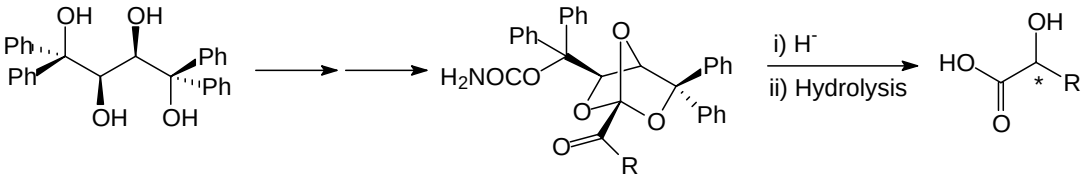
Extensive studies on catalytic hydrogenation of α-keto esters derived from (-)-menthol, (+)-borneol, and various sugars employing PtO_2, Raney Ni, Pd/C, $Pd/CaCO_3$, $Pd/BaSO_4$ etc. as catalysts have been reported in the literature.[9c,13,19] Relatively high enantioselectivity was reported by Harada[20] *et. al.* in the hydrogenation of chiral amides of optically active benzylic amines with palladium. Noyori *et. al.* have reported[21] Binap-Ru catalysed hydrogenation of methyl pyruvate which generates '*R*' lactic acid with 83% ee. Blaser *et. al.* have studied[22] the enantioselective hydrogenation of ethyl pyruvate to

ethyl lactate (maximum 90% ee) catalysed by Cinchona-modified Pt/Al_2O_3. A general method[23] for synthesizing heterogenous 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 reductions were found to be low (37% ee). Baiker *et. al.* have reported[24] 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 maximum enantioselectivities of 75%. Agbossou and coworkers have synthesized new chiral ruthenium complexes from chiral bidentate amino(amido)phosphinephosphinite biphosphines and demonstrated that these complexes act as efficient catalysts for the homogenous asymmetric hydrogenation of α-keto esters with maximum enantiomeric excess of 79%.[25]

Stereoselective reduction of chiral orthoesters

The use of chiral orthoesters[26] of α-keto acids for the synthesis of α-hydroxy acids has been reported by Dube. Reduction of these chiral orthoesters proceeds with very high selectivity (>99% de). Hydrolysis affords enantiomerically enriched α-hydroxy acids with '*R*' configuration (Scheme 5).

Scheme 5

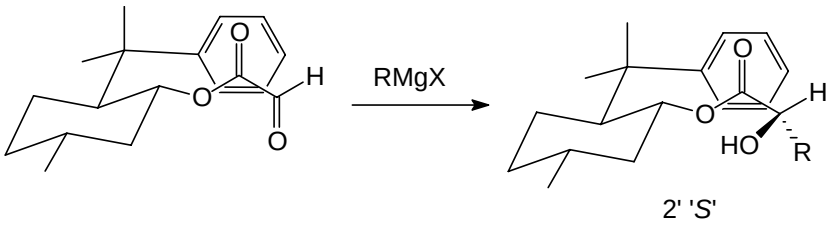


Stereoselective alkylation of chiral glyoxylate esters

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[27] in high chemical yield and excellent levels of asymmetric induction (98-99% ee, Scheme 6). The stereoselectivity is due to effective shielding of one face of the aldehyde carbonyl by the phenyl group. It has also been shown that the diastereomer with '*R*' configuration for the newly generated

stereocenter (de>90%) can be obtained by the hydride reduction of the α-ketoesters of 8-phenylmenthol.[28]

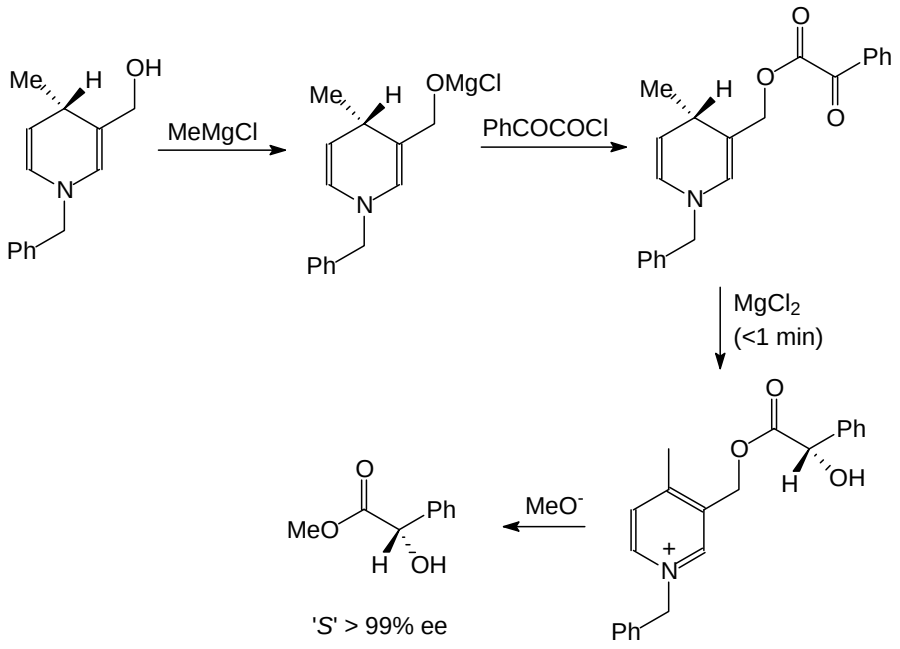
Scheme 6



Intramolecular reduction of α-keto esters

The only example[29] of an intramolecular reduction of an α-keto acid derivative has been reported by Meyers. The method employs a chiral NADH analogue which forms the chiral ester portion in the α-keto ester. 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 (Scheme 7).

Scheme 7



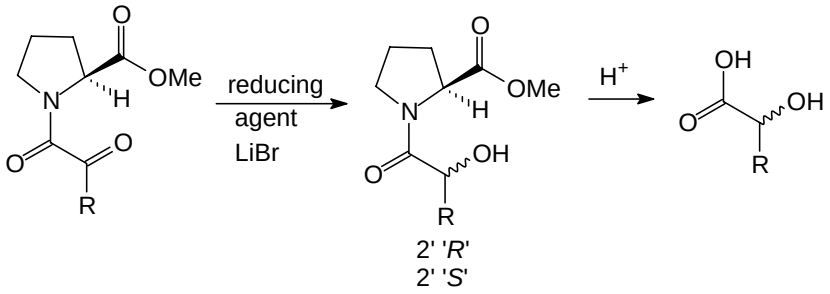
In some of the above studies, the difficulty in obtaining good stereoselectivities in ester based systems may be due to the inherent conformational flexibility of the ester linkage. Most of the recent studies have focussed on chiral amides of α-keto acids and these approaches have been discussed below.

Stereoselective reduction of chiral α-keto amides

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

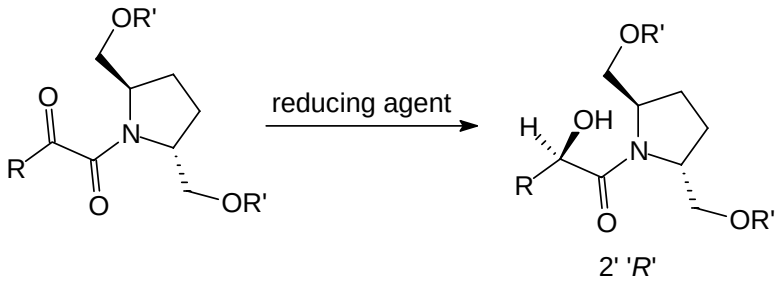
Asymmetric synthesis of both the enantiomers of α-hydroxy acids by the diastereoselective reduction of a chiral α-keto amide derived from '*S*' methyl prolinate has been reported by Soai.[30] Reduction with lithium borohydride afforded '*S*' α-hydroxy acids (80% ee), whereas DIBAL-H afforded '*R*' α-hydroxy acids (66% ee) (Scheme 8).

Scheme 8



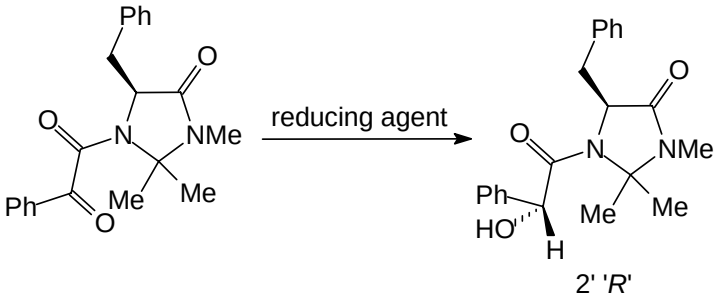
In related work, Kawanami[31] *et. al.* have showed that α-keto amides derived from a C_2 symmetric pyrrolidine are more beneficial , and the diastereoselectivity of reduction may be improved to 98% (Scheme 9).

Scheme 9



Reduction of a chiral α-keto amide derived from 5*S*-5-benzyl-2,2,3-trimethyl imidazolidin-4-one, reported by Solodin[32] proceeds with 90-100% diastereoselectivity and the newly formed stereocenter was found to have '*R*' configuration (Scheme 10).

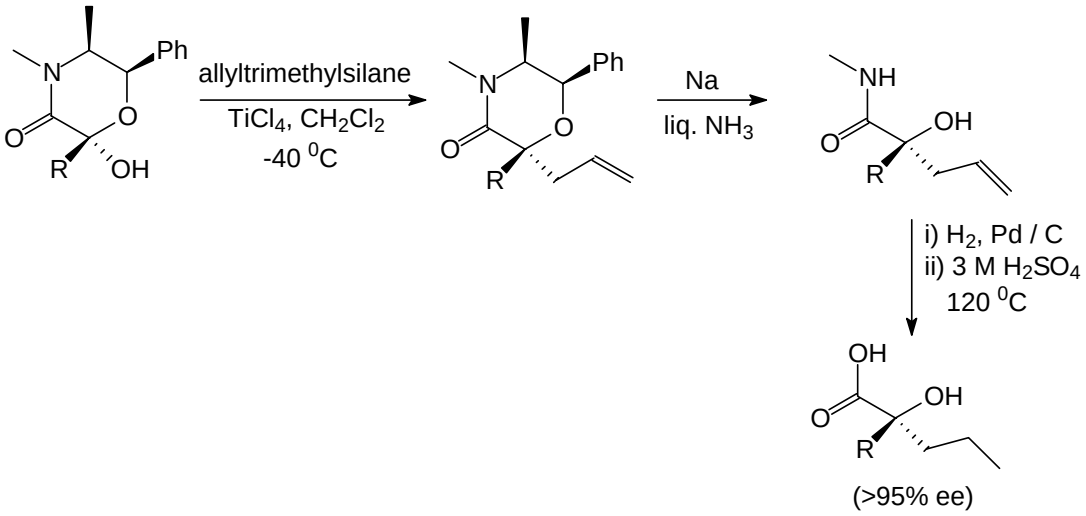
Scheme 10



Stereoselective allylation of α-keto carboxylic acid derivatives

Pansare *et. al.* have synthesized[33] α-allyl and α-alkyl-α-hydroxy acids by stereoselective allylation of 1*R*, 2*S* ephedrine derived hemiacetals (Scheme 11).

Scheme 11

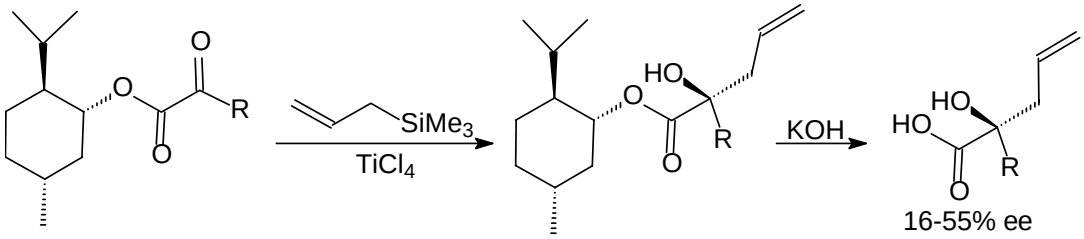


Stereoselective allylation of α-ketoacid menthyl esters

In the first report[34] of an asymmetric allylation of α-ketoesters, Ojima reported the reaction of (-)-menthyl pyruvate and menthyl phenyl glyoxalate with allyltrimethylsilane in the presence of titanium tetrachloride. The diastereoselectivity of

the process is not very high (16-55% ee of the acid after hydrolysis). The α-hydroxy acids were liberated by basic hydrolysis of the ester (Scheme 12).

Scheme 12



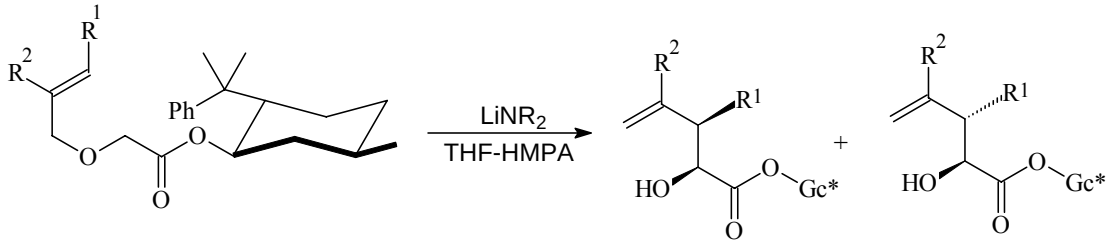
Stereoselective synthesis of α-hydroxy acids from substrates other than α-keto acid derivatives

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

Stereoselective (2,3)-Wittig rearrangement approach to α-allyl-α-hydroxy acids

A highly efficient method for the enantioselective synthesis of α-allyl-α-hydroxy acids has been reported[35a,35b] by Nakai. In this study, the asymmetric (2,3)-Wittig rearrangement of (*E*-2-alkenyloxy) acetates derived from (-)–8-phenylmenthol proceeds with high erythro selectivity (>90%). The level of asymmetric induction in this rearrangement is dictated by the alkyl substituent on the allylic moiety (Scheme 13). This rearrangement provides important α-allyl-α-H-α-hydroxy acids which are intermediates for the synthesis of natural products such as (-)-verrucarinolactone.[35c]

Scheme 13



a) R^1= CH_3, R^2 = H
b) R^1= *n*Bu, R^2= H
c) $(CH_3)CCHCH_2OCH_2COOGc^*$
d) R^1= H , R^2= H
e) R^1= H, R^2= CH_3

2*S*, 3*R* Erythro
+
2*R*, 3*S* Erythro

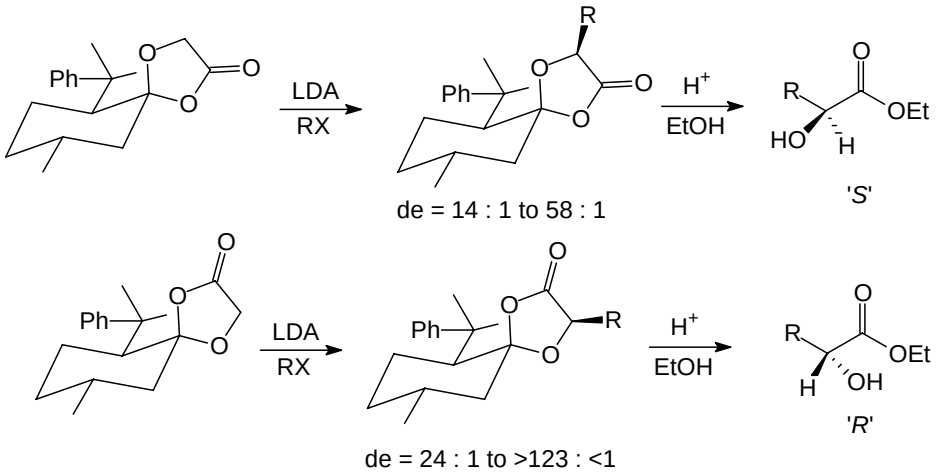
2*S*, 3*S* Threo
+
2*R*, 3*R* Threo

Gc* = 8- phenylmenthyl

Stereoselective alkylation of chiral dioxolanes

Highly diastereoselective alkylation of chiral glycolate enolates derived from menthone and 8-phenylmenthone has been reported[36] by Pearson (Scheme 14). Acid hydrolysis of the alkylated dioxolanes provides the requisite α-hydroxy acids.

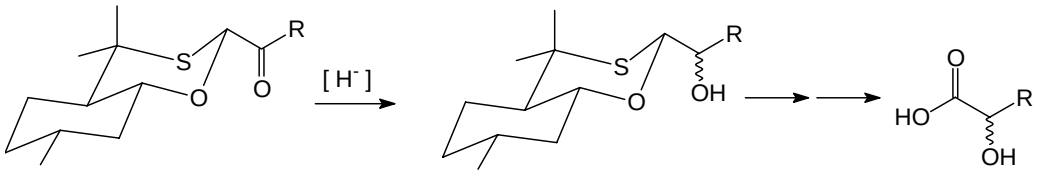
Scheme 14



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

Reduction of chiral 2-acyl-1,3-oxathianes[37] (derived from (+)-pulegone) with moderate diastereoselectivity (60-80% de), has been reported by Eliel and the resulting alcohols can be converted to the free α-hydroxy acids without racemization (Scheme 15).

Scheme 15

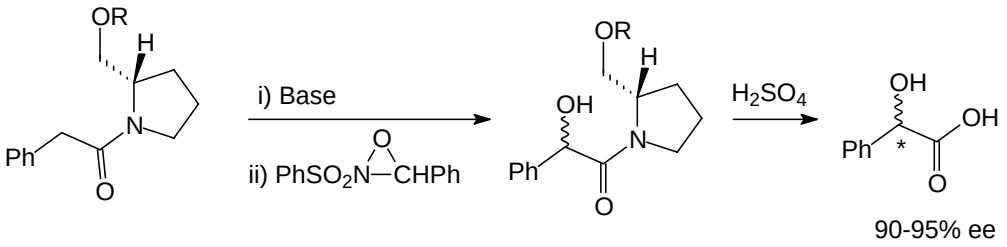


Oxidation of chiral amide enolates

The direct oxidation of chiral enolates also provides an efficient approach to α-hydroxy acids. 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.[38] The method generates mandelic acid with >90-95% ee. The stereoselectivity is highly dependant on the counterion used and by changing the metal

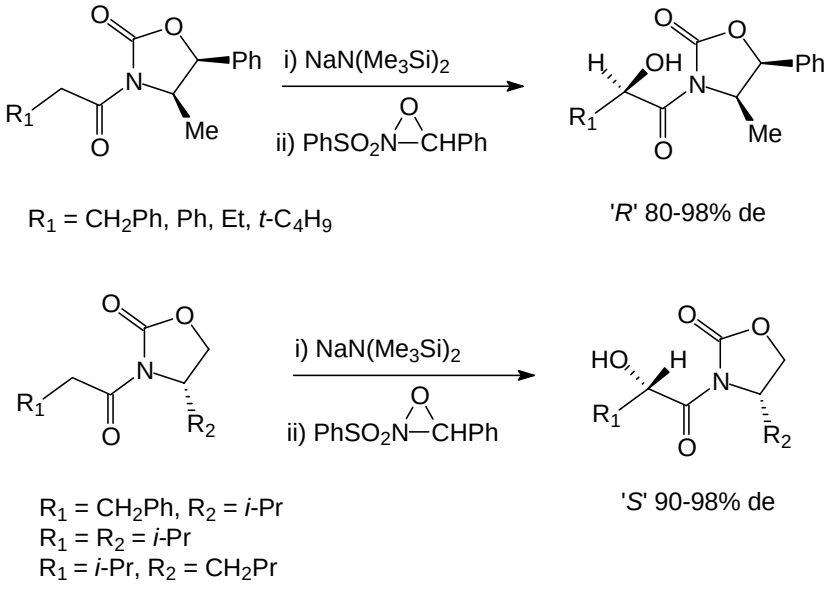
ion both the enantiomers of mandelic acid can be obtained. Lithioenolates afford '*S*' mandelic acid, whereas sodioenolates afford '*R*' mandelic acid (Scheme 16).

Scheme 16



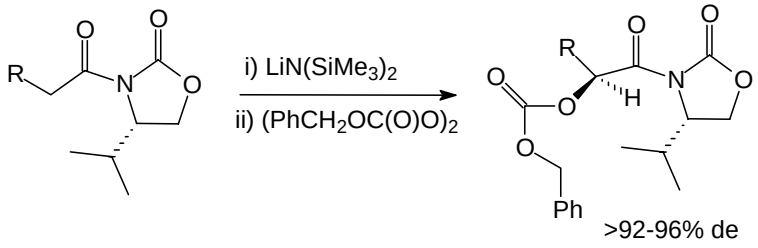
Good stereoselectivity has been achieved in the synthesis of α-hydroxy acid precursors by Evans[39] from oxazolidone derived chiral amide enolates. '*Z*' sodium enolates could be oxidized with a slight excess of oxaziridine to furnish the α-hydroxy amides with maximum 98% diastereoselectivity (Scheme 17).

Scheme 17



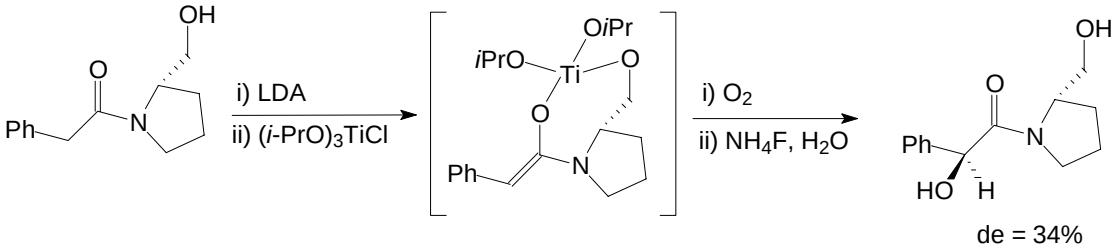
Oxidation of oxazolidone based enolates using dibenzylperoxydicarbonate as the oxidizing agent has been reported by Vederas[40] (Scheme 18). The advantage of this method is the direct preparation of '*O*'-protected α-hydroxy carbonyl compounds with more than 98% diastereoselectivity. The procedure is also applicable to the oxidation of other carbon nucleophiles.

Scheme 18



Adam *et. al.*[41] have reported a synthesis of α-hydroxy amides and esters by direct oxidation of their titanium enolates (Scheme 19). However, the diastereoselectivity of this procedure is low (34% de of the hydroxy amide).

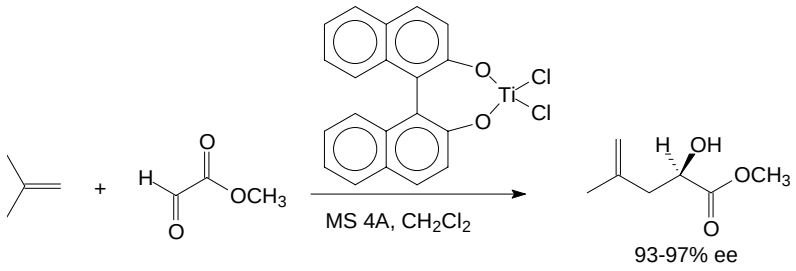
Scheme 19



Synthesis 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.[42] The method provides a useful route to functionalized '*R*' α-hydroxy esters (Scheme 20).

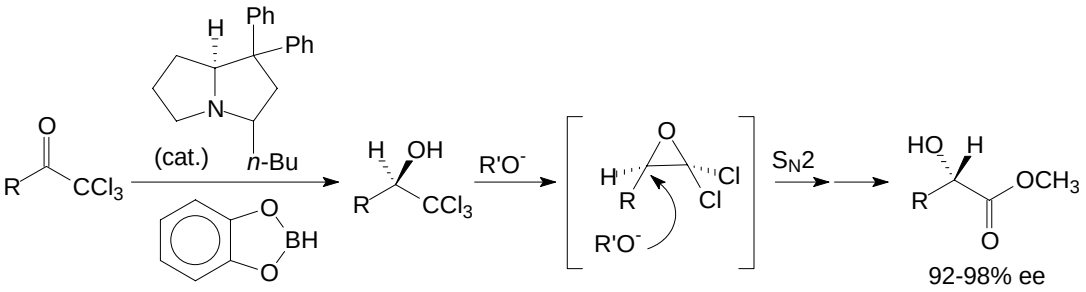
Scheme 20



Corey has reported[43] a highly enantioselective reduction of trichloromethyl ketones by catecholborane in the presence of an oxazaborolidine catalyst. The product

trichloromethyl carbinols, obtained in 92-98% ee, can be readily converted to α-hydroxy acids with inversion of configuration (Scheme 21).

Scheme 21



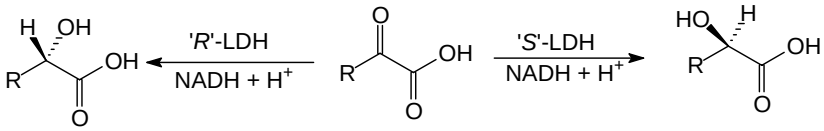
Other stereoselective synthesis of α-hydroxy acids

Other stereoselective synthesis of α-hydroxy acids and derivatives include asymmetric reduction of propargyl ketones (74-100% ee) followed by oxidation of the acetylene to acids,[44] regioselective ring opening of chiral 2,3-epoxy alcohols (readily prepared by Sharpless epoxidation) followed by ruthenium dioxide oxidation,[45] reaction of aromatic aldehydes with *trans*-1,3-dithiane-1,3-dioxide followed by Pummerer rearrangement to a thiolester which is easily converted to α-hydroxy acid derivatives (>95-98% ee),[46] diastereoselective O-H insertion of rhodium carbenoids derived from chiral phenyldiazoacetates[47] and nucleophilic substitution in chiral α-bromo amides.[48]

Enzymatic synthesis of α-hydroxy acids

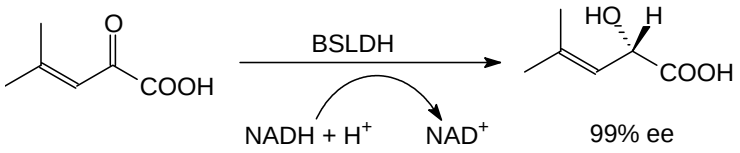
The use of enzymes has been particularly useful for the synthesis of enantioenriched α-hydroxy acids. The application of the enzyme lactase dehydrogenase (LDH) as a catalyst for the stereospecific reduction of α-keto acids has been established as a useful method for the preparation of both the enantiomers of the α-hydroxy acids[49] (Scheme 22).

Scheme 22



Casy *et. al.* have synthesized β,γ-unsaturated α-hydroxy acids in very high enantiomeric excesses (97-99%) by the enantioselective hydrogenation of the corresponding α-keto acids using *Bacillus stearothermophilus* lactase dehydrogenase (BSLDH)[50] (Scheme 23).

Scheme 23

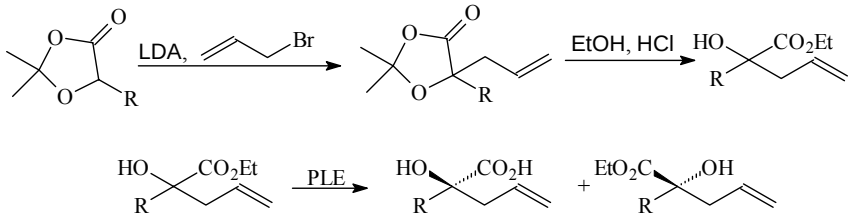


Lipase catalysed enantioselective esterification (maximum 100% ee) of α-hydroxy acids in anhydrous organic solvents with primary alcohols has been reported[51] by Dordic. Enantioselective oxidation of 1,2-diols to α-hydroxy aldehydes using alcohol dehydrogenase enzyme (ADH), followed by the oxidation to the α-hydroxy acids using the enzyme aldehyde dehydrogenase (AldDH) as catalysts has also been reported.[52] Reduction of α-keto esters by baker's yeast provides the '*S*' α-hydroxy acid (94% ee).[53] Enantioselective α-hydroxylation of carboxylic acids with molecular oxygen catalysed by the α-oxidation enzyme system of young pea leaves (*pisum sativum*) provides enantiomerically pure '*R*' α-hydroxy acids (>99% ee).[54]

The microbial transformation[55] of α-keto esters to the corresponding α-hydroxy acids reported by Qiang gives maximum 100% enantioselectivity using the fungus Geotrichum *sp.* G38 and thus provides a useful method for the synthesis of optically pure α-hydroxy acids.

α-allyl-α-hydroxy acids were also prepared by allylation[56] of the acetonides of lactic and mandelic acids. Pig liver esterase (PLE) catalyzed hydrolysis of these esters provided enantiomerically enriched acids (22-94% ee, Scheme 24). However, the scope of this reaction remains to be established since only a few substrates have been examined. Also a phenyl group in the allyl portion is not tolerated by the enzyme and the substrate remains unhydrolyzed.

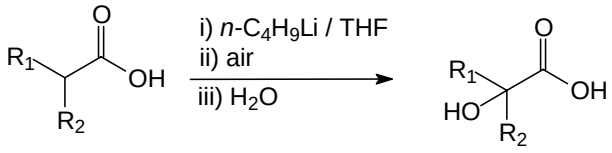
Scheme 24



General synthesis of racemic α-hydroxy acids

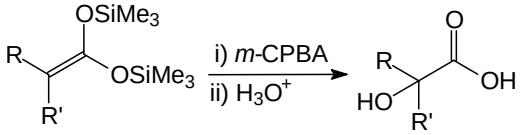
Several methods are available for the preparation of α-hydroxy acids in racemic form. For example, Pummerer reaction of β-keto sulfoxides with acetic anhydride in the presence of sodium acetate gives in one step high yields of α-acetoxy acid thioesters which are transformed into various types of α-hydroxy acid derivatives.[57] Aeration of lithiated carboxylic acids in tetrahydrofuran solution is a very simple and effective route to the α-hydroxy acids (Scheme 25).[58]

Scheme 25



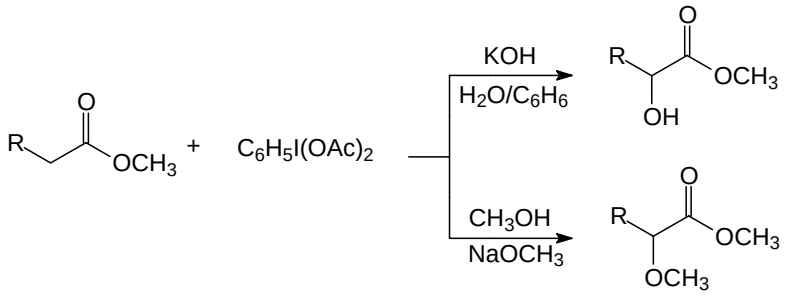
Similarly, oxidation of ketene bis(trimethylsilyl) acetals with *m*-chloroperbenzoic acid followed by mild acid hydrolysis is an extremely general, high yield method for the preparation of α-hydroxy acids[59] (Scheme 26).

Scheme 26



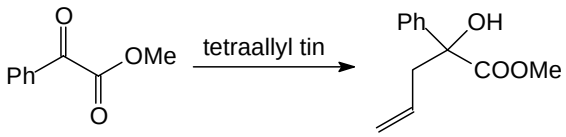
Aryl and alkyl carboxylate esters are converted into the corresponding α-hydroxy acids or α-alkoxy esters upon treatment with hypervalent iodine compounds such as $C_6H_5I(OAc)_2$ and base in appropriate solvent[60] (Scheme 27).

Scheme 27



Kobayashi *et. al.*[61] have reported synthesis of methyl ester of racemic α-allyl-α-hydroxy acids by allylation of α-keto esters by using tetraallyl tin as the allylating reagent (Scheme 28). Polymer (Nafion) supported scandium catalyst was used for the reaction.

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.

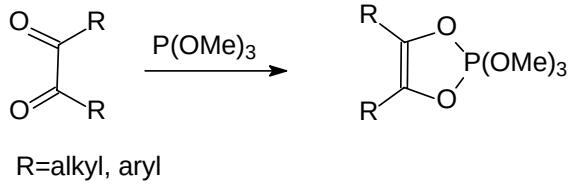
4.3: Present work

The synthesis of α-allyl-α-hydroxy acids and their derivatives has received less attention although these molecules are attractive synthetic intermediates. Their utility has been demonstrated by further elaboration of the carbon-carbon double bond into several attractive synthetic intermediates.[62-64]

Our objective was to develop a short synthesis of racemic α-allyl-α-hydroxy acids by trimethyl phosphite induced Claisen rearrangement of allyl phenyl glyoxylate (**4.2a**).

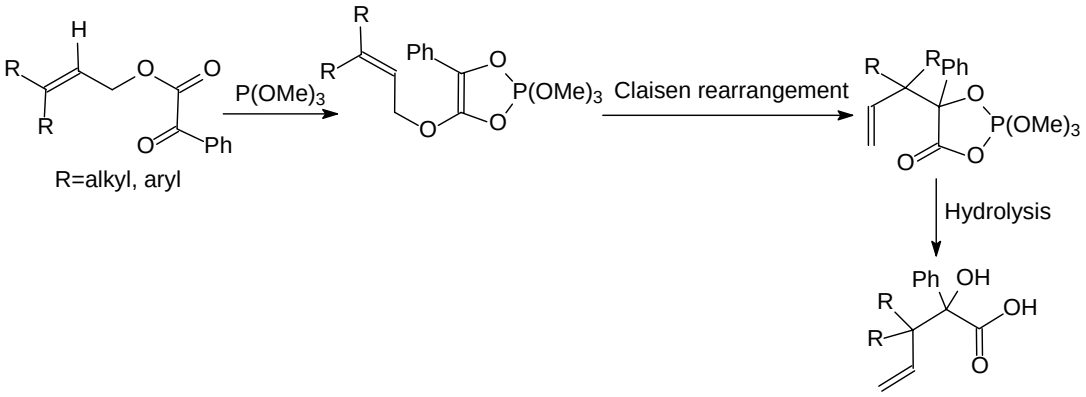
Formation of a 5-membered phosphite complex with 1,2-dicarbonyl compound has been reported in literature (Figure 3).[65] A detailed study of such complexes has been done earlier by Ramirez and coworkers.[66]

Figure 3



We anticipated that in case of complexed allyl esters of α-keto acids, we should be able to induce Claisen rearrangement and the intermediate phosphite complex after hydrolysis should give us α-allyl-α-hydroxy acids (Figure 4).

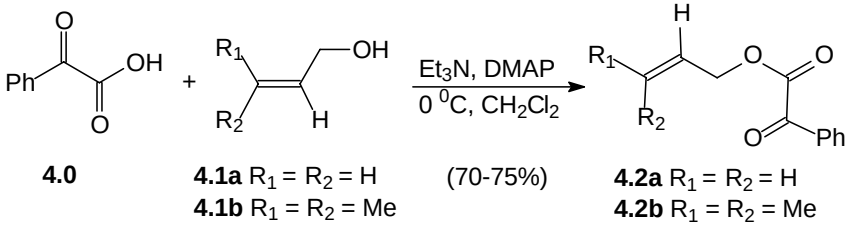
Figure 4



4.4: Results and discussion

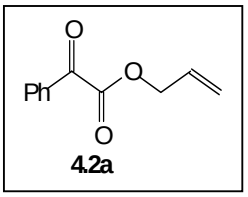
Allyl phenyl glyoxylate (**4.2a**) was chosen as the starting material for the study which was prepared easily by esterification of phenyl glyoxylic acid with allyl alcohol in 70-75% yield (Scheme 29).

Scheme 29



Spectral data for **4.2a** matched with the compound reported in literature.[67] The ^{1}H NMR and ^{13}C NMR data for **4.2a** are discussed below.

The ^{1}H NMR spectrum of **4.2a** showed a multiplet in the range 4.80-4.97 ppm which was attributed to the allylic protons attached to oxygen. The olefinic methylene protons appeared as a multiplet in the range 5.30-5.55 ppm. The olefinic methine proton appeared as a multiplet in the range 5.90-6.15 ppm. The two aromatic protons appeared as a multiplet in the range 7.47-7.57 ppm. One of the aromatic proton appeared as a multiplet in the range 7.62-7.72 ppm. The remaining two aromatic protons appeared as a multiplet in the range 7.95-8.10 ppm.



4.2a

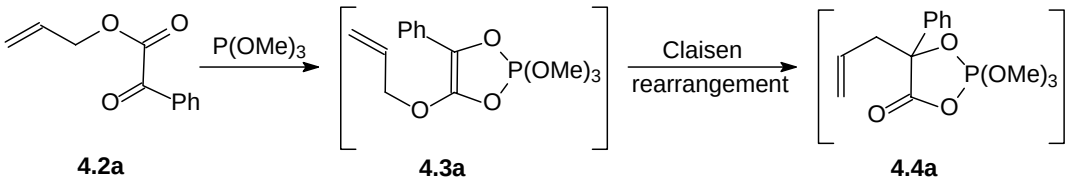
The ^{13}C NMR spectrum of **4.2a** showed a peak at 186.0 ppm for the ketone carbonyl and a peak at 163.4 ppm for the ester carbonyl. The aromatic *ipso* carbon and the olefinic methine carbon appeared at 132.9 and 134.9 ppm. The peaks at 128.9, 130.0 and 130.7 ppm are attributed to the aromatic carbons. The olefinic methylene carbon appeared at 120.0 ppm. The peak at 66.6 ppm is attributed to the allylic carbon attached to oxygen. This compound gave satisfactory elemental analysis.

The rearrangement study was done on allyl phenyl glyoxylate (**4.2a**). Reaction was done by mixing equimolar proportions of **4.2a** and trimethyl phosphite in absence of solvent at room temperature. The reaction was monitored by TLC and ^{1}H NMR. TLC indicated no reaction and hence the reaction mixture was further heated (60 ^{o}C and 110 ^{o}C) but still there was no reaction. Heating for more time in absence of solvent caused decomposition of the starting material.

Since the reaction did not work in absence of solvent, non-polar solvents such as benzene and toluene were tried at room temperature or at reflux temperature but the reaction failed. ^{1}H NMR of the small aliquots taken from the reaction mixture showed no rearrangement, which was evident from the peak position of the *O*-allyl group.

The rearrangement was first observed in ethereal solvent such as THF at room temperature. The reaction worked even better in dioxane and acetonitrile solvents. TLC indicated disappearance of the starting ester **4.2a**. It is noteworthy in this regard that the rearranged complex **4.4a** was found to be unstable to column chromatography and also purification of the rearranged complex by distillation did not work. Rearrangement was also monitored by ^{1}H NMR by taking small aliquots from the reaction mixture and noting the shift in the peak position of the allyl group. In this case there was a marked difference in the chemical shifts of the *O*-allyl group in the starting material **4.2a** and the *C*-allyl group in the rearranged phosphite complex (Scheme 30). The ^{1}H NMR spectrum of the crude rearranged complex also showed peaks arising from other side products.

Scheme 30



4.2a **4.3a** **4.4a**

In the first step, trimethyl phosphite adds to the dicarbonyl compound **4.2a** resulting in the formation of an intermediate 5-membered phosphite complex **4.3a**. This then rearranges to **4.4a** by a (3,3) sigmatropic rearrangement. It is noteworthy in this regard that related cyclopentaoxyphosphoranes (phosphite complexes with 1,2-dicarbonyl compounds) have been studied in details by Ramirez and co-workers[66] and in some cases these complexes were found to be stable, which were characterized. But the phosphite complexes **4.3a** and **4.4a** in our study were found to be highly unstable.

In the rearrangement reaction, in order to minimize the self-condensation of two moles of ester with one mole of trimethyl phosphite, inverse dropwise addition of dilute ester solution to a diluted solution of trimethyl phosphite was done, which ensured that the allyl ester was not there in excess in the reaction mixture.

The rearrangement study was done in different solvents at different temperatures and is summarized in Table 1.

Table 1. Rearrangement under different reaction conditions.

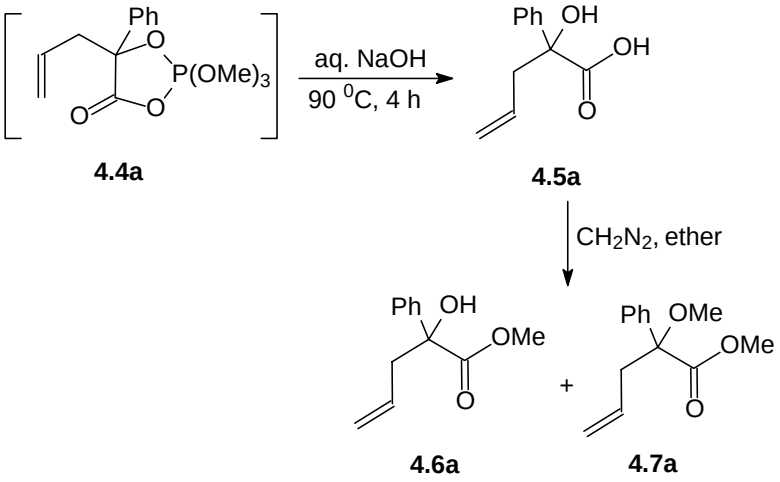
Compound	Molar ratio 4.2a : $P(OMe)_3$	T (deg)	Time h	Solvent	Results
4.2a	1:1	RT	72	Neat	No rearrangement
4.2a	1:1	60	30	Neat	No rearrangement
4.2a	1:1	110	24	Neat	No rearrangement
4.2a	1:1	RT	24	CH_2Cl_2	No rearrangement
4.2a	1:1	RT	48	Benzene	No rearrangement
4.2a	1:1	0	48	THF	No rearrangement
4.2a	1:1	RT	48	THF	Rearrangement
4.2a	1:7	RT	48	THF	Rearrangement
4.2a	1:7	RT	48	Dioxane	Rearrangement
4.2a	1:1	Reflux	2	Dioxane	Rearrangement
4.2a	1:1	Reflux	4	Dioxane	Rearrangement
4.2a	1:1	Reflux	24	Dioxane	Rearrangement
4.2a	1:1	Reflux	24	Acetonitrile	Rearrangement

RT = room temperature

From Table 1 it is clear that the choice of solvent is an important factor for rearrangement to proceed to a considerable extent and that the rearrangement is inhibited in the absence of solvent.

After a considerable rearrangement (as seen in ^{1}H NMR) in dioxane and acetonitrile solvents, the crude rearranged allyl complex **4.2a** was subjected to hydrolysis with aqueous NaOH. The crude acid **4.5a** could not be obtained in pure form as it was accompanied by other side products, hence **4.5a** was converted to its methyl ester by diazomethane (generated *in situ* from *N*-nitrosomethyl urea and NaOH in ether at 0 ^{o}C) in ether (Scheme 31) and purified by column chromatography.

Scheme 31

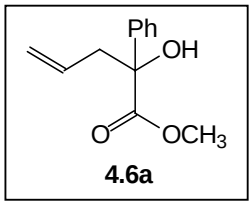


4.4a **4.5a** **4.6a** **4.7a**

The structure of rearranged allyl ester **4.6a** was established by its spectral data (IR, ^{1}H NMR and ^{13}C NMR) which matched with the reported[61,68] data.

IR spectrum of **4.6a** showed a broad band at 3508 cm[1] for the hydroxy group. The sharp peaks at 1730 and 1641 cm^{-1} are attributed to the ester carbonyl and the double bond respectively.

The ^{1}H NMR spectrum of **4.6a** showed a multiplet in the range 2.67-2.85 ppm and 2.88-3.07 ppm which was attributed to the allylic protons. The proton of the hydroxy group appeared as a singlet at 3.73 ppm. The protons on the methyl group attached to oxygen appeared as a singlet at 3.77 ppm. The two olefinic methylene protons appeared as a multiplet in the range 5.08-5.24 ppm.



4.6a

The olefinic methine proton appeared as a multiplet in the range 5.66-5.92 ppm. Three aromatic protons appeared as a multiplet in the range 7.20-7.45 ppm. The remaining two aromatic protons appeared as a multiplet in the range 7.54-7.65 ppm.

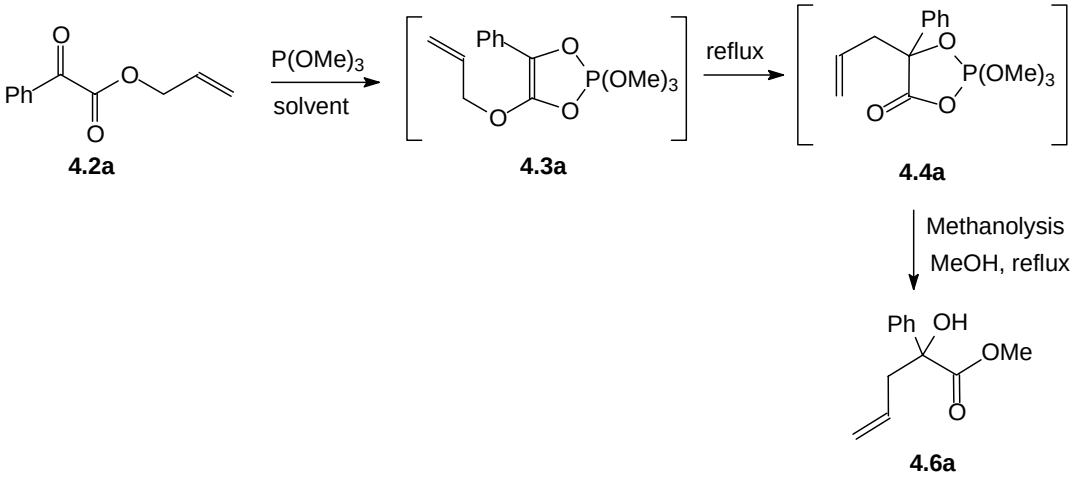
The ^{13}C NMR spectrum of **4.6a** showed a peak at 174.9 ppm which is attributed to the ester carbonyl. The aromatic *ipso* carbon appeared at 141.1 ppm. The olefinic methine carbon appeared at 132.3 ppm. The three aromatic carbons appeared at 125.4, 127.7 and 128.2 ppm. The olefinic methylene carbon appeared at 119.2 ppm. The quaternary carbon attached to oxygen appeared at 78.1 ppm. The methyl group attached to oxygen appeared at 53.1 ppm. The peak at 44.0 ppm corresponds to the allylic carbon. This compound gave satisfactory elemental analysis.

It is noteworthy that in the esterification with diazomethane the benzylic hydroxyl group is also methylated and is obtained as a side product **4.7a** (10%) in the reaction. The yield of the reaction from **4.2a** to **4.6a** (over 3 steps) was 20%.

In order to avoid the competing *O*-methylation during esterification of acid we chose to examine methanolysis of the rearranged complex **4.4a** as an alternative to get the methyl ester **4.6a** directly from the rearranged allyl complex **4.4a**. Methanolysis reaction was done by directly refluxing **4.4a** with methanol without subjecting it to basic hydrolysis.

Thus, equimolar proportion of allyl ester **4.2a** and trimethyl phosphite was refluxed at various temperatures in different solvents. After considerable rearrangement was seen (^{1}H NMR), the solvent was removed under reduced pressure and to the residue was added dry methanol and the reaction mixture was further refluxed for methanolysis (Scheme 32).

Scheme 32



The isolation of the product after the reaction was done by removing methanol under reduced pressure and extracting the crude compound with ethyl acetate. Further purification of the compound was done by flash column chromatography. Methanolysis done in various solvents for different reaction times is summarized in Table 2.

Table 2. Methanolysis under various reaction conditions

No	Conditions for allyl complex rearrangement			Conditions for methanolysis reaction	Yield %
	Temp	Time	Solvent		
1	RT	12 days	CH_3CN	MeOH, 8 h reflux	14%
2	Reflux	24 h	CH_3CN	MeOH, 10 h reflux	24%
3	Reflux	2 h	CH_3CN	MeOH, 20 h reflux	30%
4	Reflux	5 h	CH_3CN	PTSA, MeOH,3 h reflux	19%
5	Reflux	5 h	CH_3CN	H_2SO_4, MeOH, 8 h reflux	16%
6	Reflux	5 h	Benzene	MeOH, 6 h reflux	No product
7	Reflux	5 h	Toluene	MeOH, 6 h reflux	No product
8	80 ^oC	5 h	DMF	MeOH, 6 h reflux	No product
9	Reflux	5 h	THF	MeOH, 10 h reflux	13%
10	Reflux	5 h	Dioxane	MeOH, 6 h reflux	15%
11	Reflux	5 h	Methanol	-	No product

RT = room temperature

Table 2 (entry 3) shows that acetonitrile is the best solvent for the rearrangement and subsequent methanolysis. There was no rearrangement in non-polar solvents such as benzene and toluene.

4.5: Conclusion

Trimethyl phosphite induced Claisen rearrangement of allyl phenyl glyoxylate was studied in various solvents and at different temperatures. Rearranged complex was converted to racemic α-allyl-α-hydroxy acid, which was purified as its methyl ester however the maximum yield obtained in the process was 30%.

4.6: Experimental

Oxo-phenyl-acetic acid allyl ester (4.2a):

The solution of phenyl glyoxylic acid (**4.0**) (1.0 g, 6.67 mmol) in oxalyl chloride (4.07 mL, 46.7 mmol) was refluxed for 2 h. Excess oxalyl chloride was removed under vacuum. The crude acid chloride was dissolved in anhydrous DCM (15 mL). This solution was then added dropwise to a reaction mixture containing allyl alcohol (**4.1a**) (0.39 mL, 6.67 mmol), DMAP (41 mg, 0.33 mmol), triethyl amine (1.86 mL, 13.3 mmol) and DCM (15 mL) at 0 ^{o}C. The resulting reaction mixture was stirred for 12 h at ambient temperature. Water was added and the resulting solution was diluted with DCM. Aqueous layer was extracted with DCM (2 x 15 mL). Combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude compound which on purification by flash column chromatography with EA/PE (1/20) furnished 950 mg (75%) of **4.2a** as a clear colorless oil.

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

δ 4.80-4.97 (m, 2H, *allylic* C*H*$_2$), 5.30-5.55 (m, 2H, *olefinic* C*H*$_2$), 5.90-6.15 (m, 1H, *olefinic* C*H*), 7.47-7.57 (m, 2H, Ar*H*), 7.62-7.72 (m, 1H, Ar*H*), 7.95-8.10 (m, 2H, Ar*H*).

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

δ 66.6 (*allylic C*H$_2$), 120.0 (*olefinic C*H$_2$), 128.9 (Ar*C*), 130.0 (Ar*C*), 130.7 (Ar*C*), 132.9 and 134.9 (Ar*Cipso*, *olefinic C*H), 163.4 (*C*OO), 186.0(Ph*C*O).

MS (EI, 70 ev):

m/z 190 (M^+).

Analysis for $C_{11}H_{10}O_3$:

Calculated: C, 69.46; H, 5.30; Obtained: C, 69.75; H, 5.55.

Oxo-phenyl-acetic acid 3-methyl-but-2-enyl ester (4.2b):

The solution of phenyl glyoxylic acid (**4.0**) (1.0 g, 6.67 mmol) in oxalyl chloride (4.07 mL, 46.7 mmol) was refluxed for 2 h. Excess oxalyl chloride was removed under vacuum. The crude acid chloride was dissolved in anhydrous DCM (15 mL). This solution was then added dropwise to a reaction mixture containing **4.1b** (0.68 mL, 6.67 mmol), DMAP (41 mg, 0.33 mmol), triethyl amine (1.86 mL, 13.3 mmol) and DCM (15 mL) at 0 ^{o}C. The resulting mixture was stirred for 12 h at ambient temperature. Water

was added and the resulting solution was diluted with DCM. Aqueous layer was extracted with DCM (2 x 15 mL). Combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude compound which on purification by flash column chromatography with EA/PE (1/20) furnished 1.017 g (70%) of **4.2b** as a clear colorless oil.

IR ($CHCl_3$):

1736, 1690, 1597 cm^{-1}.

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

δ 1.78 (s, 3H, C*H*$_3$), 1.80 (s, 3H, C*H*$_3$), 4.80-5.0 (m, 2H, *allylic* C*H*$_2$), 5.35-5.55 (m, 1H, *olefinic* C*H*), 7.45-7.58 (m, 2H, Ar*H*), 7.60-7.70 (m, 1H, Ar*H*), 7.95-8.07 (m, 2H, Ar*H*).

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

δ 18.1 (*C*H$_3$), 25.7 (*C*H$_3$), 62.9 (*allylic C*H$_2$), 117.2 (*olefinic C*H$_2$), 128.8 (Ar*C*), 129.9 (Ar*C*), 132.4 (Ar*C*), 134.8 and 141.1 (Ar*Cipso*, *olefinic C*H), 163.8 (*C*OO), 186.3 (Ph*C*O).

MS (EI, 70 ev):

m/z 218 (M^+).

Analysis for $C_{13}H_{14}O_3$:

Calculated: C, 71.54; H, 6.47; Obtained: C, 71.78; H, 6.69.

2-Hydroxy-2-phenyl-pent-4-enoic acid methyl ester (4.6a):

Solution of **4.2a** (500 mg, 2.63 mmol) in dry acetonitrile (8 mL) was added diluted solution of trimethyl phosphite (0.47 mL, 3.94 mmol) in acetonitrile (8 mL) dropwise over a period of 1 h. The reaction mixture was further refluxed for 24 h. Solvent was removed under reduced pressure and to the residue was added 2N NaOH solution (5 mL) and further heated at 90 ^oC for 4 h. The aqueous layer was washed with DCM (2 x 10 mL) and then acidified with conc. HCl dropwise at 0 ^oC. After acidification, the aqueous layer was extracted with ethyl acetate (3 x 15 mL). Combined organic layer was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure to furnish 500 mg of crude acid **4.5a**, which was purified by converting it to its methyl ester.

In a separate conical flask ether (15 mL) was taken and 10% NaOH (15 mL) was added at 0 ^{o}C. To this was added *N*-nitrosomethylurea (1.159 g, 13.0 mmol) and shaken vigorously. The supernatent organic layer was decanted in a conical flask containing KOH pellets at 0 ^{o}C. This solution was then added to the crude acid (500 mg, 2.6 mmol) in ether (10 mL) at 0 ^{o}C and stirred for 30 min. Solvent was removed under reduced pressure to furnish the crude compound which on purification by flash column chromatography EA/PE (3:97) gave 108 mg (20%) of **4.6a** and 58mg (10%) of **4.7a** as a side product.

IR ($CHCl_3$):

3508, 1730, 1641 cm^{-1}.

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

δ 2.67-2.85 (m, 1H, *allylic* C*H*$_2$), 2.88-3.07 (m, 1H, *allylic* C*H*$_2$), 3.73 (s, 1H, O*H*), 3.77 (s, 3H, OC*H*$_3$), 5.08-5.24 (m, 2H, *olefinic* C*H*$_2$), 5.66-5.92 (m, 1H, *olefinic* C*H*), 7.20-7.45 (m, 3H, Ar*H*), 7.54-7.65 (m, 2H, Ar*H*).

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

δ 44.0 (*allylic C*H$_2$), 53.1 (OCH$_3$), 78.1 (*Cquat*), 119.2 (*olefinic C*H$_2$), 125.4 (Ar*C*), 127.7 (Ar*C*), 128.2 (Ar*C*), 132.3 (*olefinic C*H), 141.1 (Ar*Cipso*), 174.9 (*C*=O).

MS (EI, 70 ev):

m/z 206 (M^+).

Analysis for $C_{12}H_{14}O_3$:

Calculated: C, 69.89; H, 6.84; Obtained: C, 70.10; H, 6.98.

2-Methoxy-2-phenyl-pent-4-enoic acid methyl ester (4.7a):

IR ($CHCl_3$):

1732, 1643 cm^{-1}.

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

δ 2.86-3.19 (m, 2H, *allylic* C*H*$_2$), 3.26 (s, 3H, OC*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 5.02-5.20 (m, 2H, *olefinic* C*H*$_2$), 5.54-5.80 (m, 1H, *olefinic* C*H*), 7.24-7.54 (m, 5H, Ar*H*).

MS (EI, 70 ev):

m/z 220 (M^+).

Analysis for $C_{13}H_{16}O_3$:

Calculated: C, 70.89; H, 7.32; Obtained: C, 70.93; H, 7.55.

Alternate procedure for preparation of 4.6a by methanolysis of crude rearranged complex 4.4a.

Solution of **4.2a** (400 mg, 2.10 mmol) in dry acetonitrile (10 mL) was added to a diluted solution of trimethyl phosphite (0.25 mL, 2.1 mmol) in acetonitrile (10 mL) at 0 ^{o}C dropwise over a period of 1 h and the reaction mixture was then refluxed for 2 h. Acetonitrile was removed under reduced pressure and dry methanol (10 mL) was added and the reaction mixture was further refluxed for 24 h. Solvent was removed and the residue was taken up in ethyl acetate (15 mL). Organic layer was washed with water (2 x 10 mL), brine solution, dried (Na_2SO_4) and concentrated to furnish the crude rearranged allyl ester **4.6a** directly, which on purification by flash column chromatography gave 130 mg (30%) of **4.6a** as a clear colorless oil.

4.7: References

1. a) Hanessian, S. Total Synthesis of Natural Products: The Chiron Approach; Pergamon Press: New York, 1983, Chapter 2. b) Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175-1181.
2. Patino, N.; Frerot, E.; Galleotti, G.; Poncet, J.; Coste, J.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1992**, *48*, 4115.
3. Gennaro, M. C.; Abrizo, C.; Marengo, E. *Chromatographia* **1990**, *30*, 311.
4. Kirschner, E. M. *Chem. and Engg. News* **1996**, July 1, 13.
5. Kipping, F. S. *Proc. Chem. Soc.* **1900**, *16*, 226.
6. a) Cohen, J. B.; Whiteley, C. E. *Proc. Chem. Soc.* **1900**, *16*, 212. b) Cohen, J. B.; Whiteley, C. E. *J. Chem. Soc.* **1901**, *80*, 1305.
7. McKenzie, A. *J. Chem. Soc.* **1904**, *85*, 1249.
8. Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308.
9. a) Mitsui, S.; Kanai, A. *Nippon Kogaku Zasshi* **1966**, *87*, 179. b) Bakshi, S. P.; Turner, E. E. *J. Chem. Soc.* **1961**, 168. c) Kamaishi, T.; Mitsui, S. *Nippon Kogaku Zasshi* **1965** *86*, 623. d) Mitsui, S.; Imai, Y. *Nippon Kogaku Zasshi* **1967** *88*, 86. e) McMenzie, A. *J. Chem. Soc.* **1904**, *85*, 1249.
10. Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2168.
11. Prelog, V.; Wilhelm, M.; Bright, D. B. *Helv. Chim. Acta* **1954**, *37*, 221.
12. Berson, J. A.; Greenbaum, M. A. *J. Am. Chem. Soc.* **1959**, *81*, 6456.
13. Mitsui, S.; Kanai, A. *Nippon Kogaku Zasshi* **1965**, *86*, 627.
14. Maitra, U.; Mathivanan, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1171.
15. Akiyama, T.; Nishimoto, S.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1335.
16. Solladie-Cavallo, A.; Bencheqroun, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1165.
17. Xiang, Y. B.; Snow, K.; Belly, M. *J. Org. Chem.* **1993**, *58*, 993.
18. Yamamoto, Y.; Kin, H.; Suzuki, I.; Asao, N. *Tetrahedron Lett.* **1996**, *37*, 1863.
19. a) Mitsui, S.; Kamaishi, T.; Imaizumi, T.; Takamura, I. *Nippon Kagaku Zasshi* **1962**, *83*, 1115. b) Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 259.
20. Harada, K.; Munegumi, T.; Nomoto, S. *Tetrahedron Lett.* **1981**, *22*, 111.
21. Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.
22. Garland, M.; Blaser, H. U. *J. Am. Chem. Soc.* **1990**, *112*, 7048.

23. Bhaduri, S.; Darshane, V. S.; Sharma, K.; Mukesh, D. *J. Chem. Soc., Chem. Commun.* **1992**, 1738.
24. Wang, G.; Heinz, T.; Pfaltz, A.; Minder, B.; Mallat, T.; Baiker, A. *J. Chem. Soc., Chem. Commun.* **1994**, 2047.
25. Hapiot, F.; Agbossou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1995**, *6*, 11.
26. Dube, D.; Deschenes, D.; Tweddell, J.; Gagnon, H.; Carlini, R. *Tetrahedron Lett.* **1995**, *36*, 1827.
27. Whitesell, J. K.; Bhattacharyya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988.
28. Whitesell, J. K.; Deyo, D.; Bhattacharyya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.
29. Meyers, A. I.; Brown, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 3155.
30. Soia, K.; Isoda, T.; Hasegawa, H.; Ishizaki, M. *Chem. Lett.* **1986**, 1897.
31. Kawanami, Y.; Fujita, I.; Taniguchi, Y. *Chem. Lett.* **1987**, 2021.
32. Solodin, I.; Goldberg, Y.; Zelcans, G.; Lukevics, E. *J. Chem. Soc., Chem. Commun.* **1990**, 1321.
33. Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120. Also see: a) Pansare, S. V.; Ravi, R. G. *Tetrahedron Lett.* **1995**, *36*, 5959. b) Pansare, S. V.; Ravi, R. G. *Tetrahedron* **1998**, *54*, 14549. c) Pansare, S. V.; Shinkre, B. A.; Bhattacharyya, A. *Tetrahedron* **2002**, *58*, 8985.
34. Ojima, I.; Miyazawa, Y.; Kumagai, M. *J. Chem. Soc., Chem. Commun.* **1976**, 927.
35. a) Mikami, K.; Takahashi, O.; Tabei, T.; Nakai, T. *Tetrahedron Lett.* **1986**, *27*, 4511. b) Takahashi, O.; Mikami, K.; Nakai, T. *Chem. Lett.* **1987**, 69. c) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239.
36. Pearson, W. H.; Cheng, M. C. *J. Org. Chem.* **1986**, *51*, 3746.
37. Ko, K. W.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1343.
38. Davis, F. A.; Viswakarma, L. C. *Tetrahedron Lett.* **1985**, *26*, 3539.
39. Evans, D. A.; Morresey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
40. Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700.
41. Adam, W.; Metz, M.; Prechtl, F.; Renz, M. *Synthesis* **1994**, 563.
42. Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

43. Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431.
44. Midland, M. M.; Lee, P. E. *J. Org. Chem.* **1981**, *46*, 3933.
45. Martin, V. S.; Nunez, M. T.; Tonn, C. E. *Tetrahedron Lett.* **1988**, *29*, 2701.
46. Aggarwal,V. K.; Thomas, A.; Franklin, R. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1653.
47. Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. *J. Org. Chem.* **1995**, *60*, 4449.
48. Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 93.
49. a) Kim, M. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 2959. b) Bur, D.; Luyten, M. A.; Wynn, H.; Provencher, L. R.; Jones, J. B.; Gold, M.; Friesen, J. D.; Clarke, A. R.; Holbrook, J. J. *Can. J. Chem.* **1989**, *67*, 1065. c) Simon, E. S.; Plante, R.; Whitesides, G. M. *Appl. Biochem. Biotechnol.* **1989**, *22*, 169. d) Kim, M. J.; Kim, J. Y. *J. Chem. Soc., Chem. Commun.* **1991**, 326.
50. a) Casy, G.; Lee, T. V.; Lovell, H.; Nichols, B. J.; Sessions, R. B.; Holbrook, J. J. *J. Chem. Soc., Chem. Commun.* **1992**, 924. b) Casy, G.; Lee, T. V.; Lovell, H. *Tetrahedron Lett.* **1992**, *33*, 817.
51. Parida, S.; Dordic, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 2253.
52. Wong, C. H.; Matos, J. R. *J. Org. Chem.* **1985**, *19*, 92.
53. Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *J. Org. Chem.* **1988**, *53*, 2589.
54. Adam, W.; Lazarus, M.; Saha-Moller, C. R.; Schreier, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2287.
55. Jian-xin, G.; Zu-yi, L.; Guo-Qiang, L. *Tetrahedron* **1993**, *49*, 5805.
56. Moorlag, H.; Kellogg, R. *J. Org. Chem.* **1990**, *55*, 5878.
57. Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1975**, *97*, 596.
58. Moersch, G. W.; Zwiesler, M. L. *Synthesis* **1971**, 647.
59. Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 3783.
60. Moriarty, R. M.; Hu, H. *Tetrahedron Lett.* **1981**, *22*, 2747.
61. a) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256. b) Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958.
62. Kitagawa, O.; Sato, T.; Taguchi, T. *Chem. Lett.* **1991**, 177.
63. Ohfune, Y.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079 and references therein.

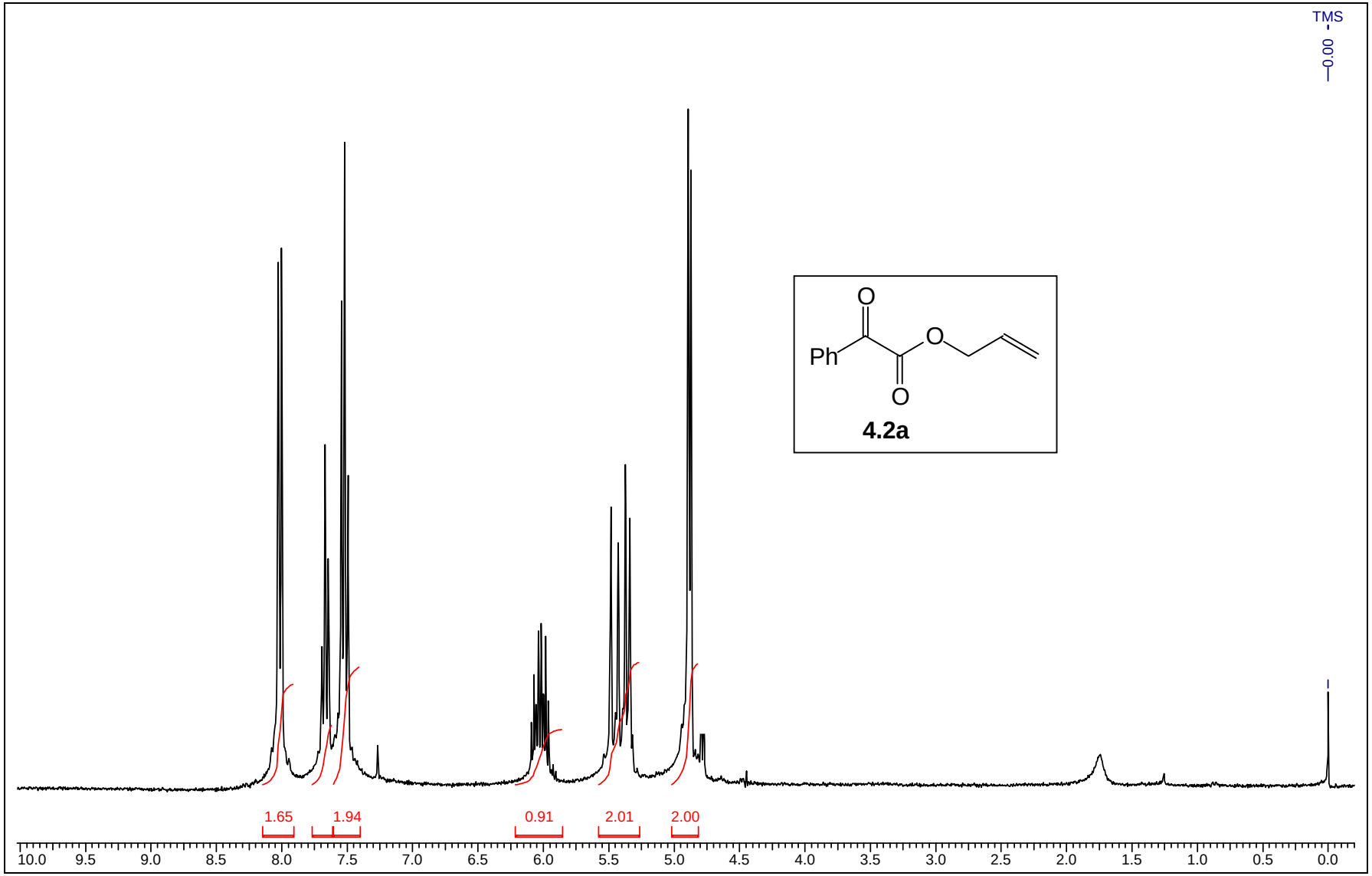
64. Chung, S-K.; Jeong, T.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 5.

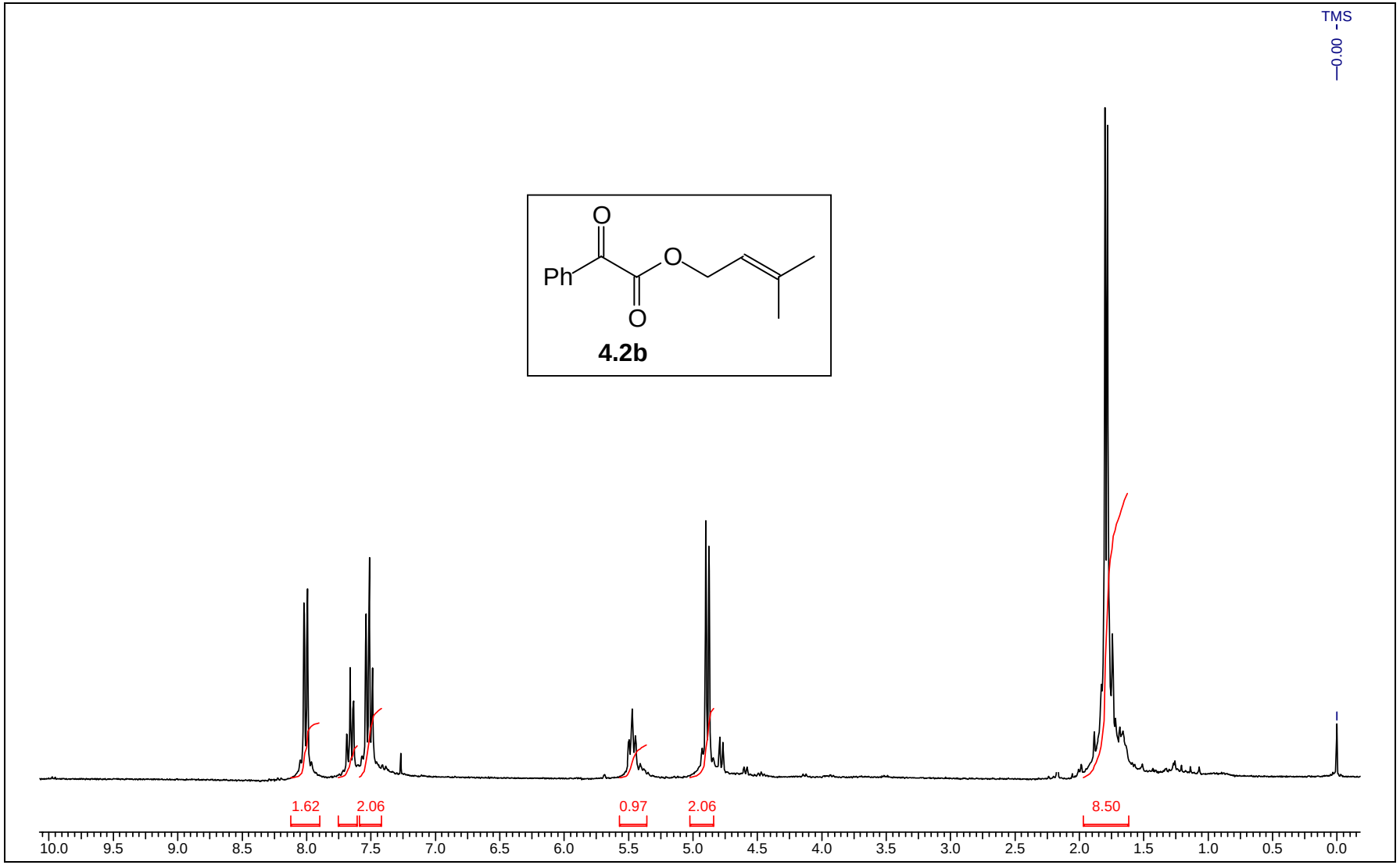
65. a) Burger, K.; Fehn, J.; Moll, E. *Chem. Ber.* **1971**, *104*, 1826. b) Burger, K.; Fehn, J. *Angew. Chem.* **1971**, *83*, 761. c) Burger, K.; Fehn, J. *Angew. Chem.* **1972**, *84*, 35. d) Burger, K.; Fehn, J. *Angew. Chem. Int. Ed.* **1972**, *11*, 29. e) Clark, V. M.; Kirby, A. J. *J. Am. Chem. Soc.* **1963**, *85*, 3705.

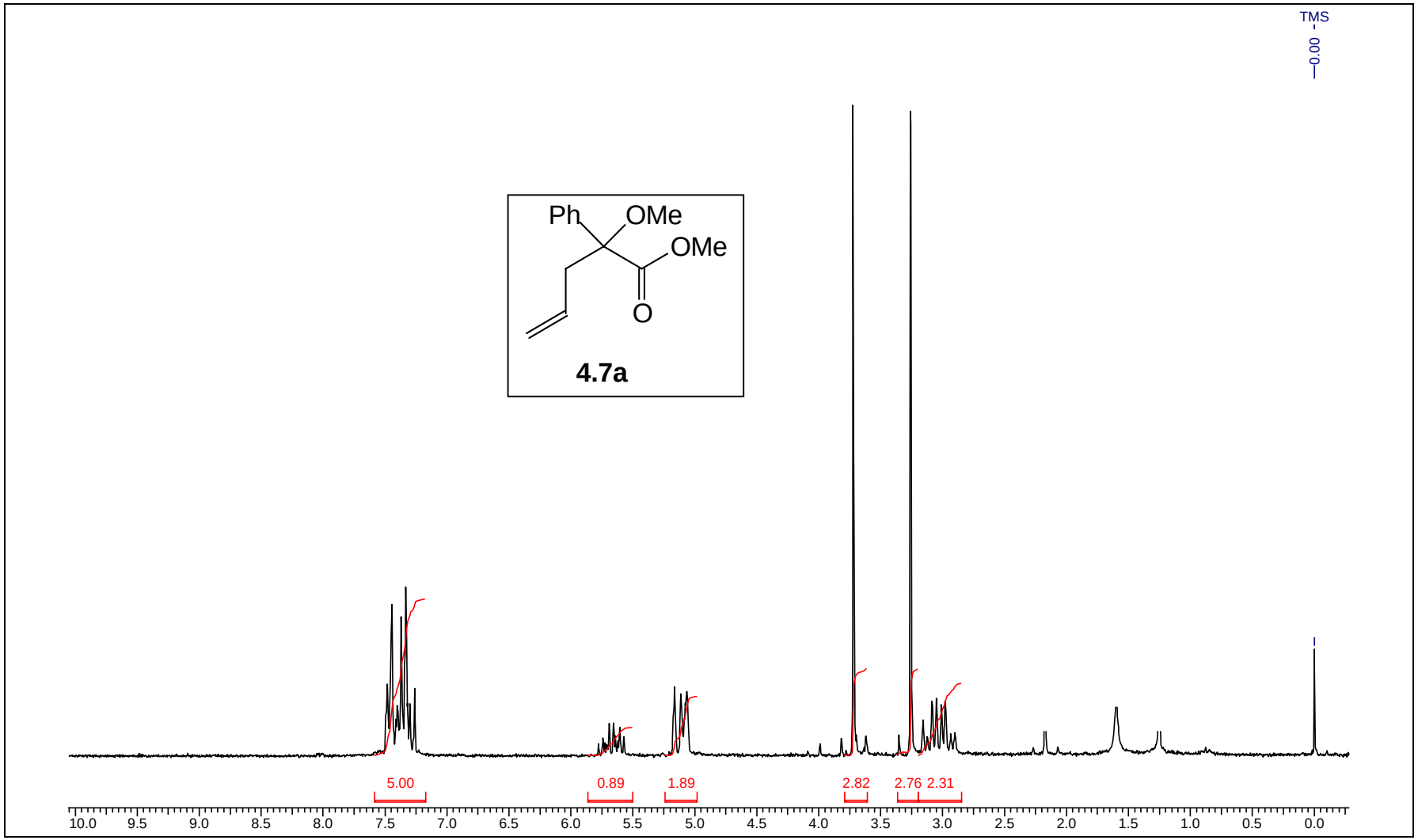
66. a) Ramirez, F.; Desai, N. B.; Ramanathan, N. *Tetrahedron Lett.* **1963**, *5*, 323. b) Ramirez, F.; Ramanathan, N. *J. Org. Chem.* **1961**, *26*, 3041. c) Ramirez, F.; Desai, N. B. *J. Am. Chem. Soc.* **1960**, *82*, 2652. d) Ramirez, F.; Ramanathan, N.; Desai, N. B. *J. Am. Chem. Soc.* **1962**, *84*, 1317. e) Ramirez, F.; Glaser, S. L.; Stern, P. *Tetrahedron* **1973**, *29*, 3741. f) Ramirez, F. *Synthesis* **1974**, 90 and references cited therein. g) Ramirez, F.; Dershowitz, S. *J. Am. Chem. Soc.* **1959**, *81*, 587. h) Ramirez, F.; Mitra, R. B.; Desai, N. B. *J. Am. Chem. Soc.* **1960**, *82*, 5763. i) Ramirez, F.; Bhatia, S. B.; Smith, C. P. *J. Am. Chem. Soc.* **1967**, *89*, 3026. j) Ramirez, F. *Bull. Soc. Chim. France* **1966**, 2443. k) Ramirez, F. *Pure and Applied Chemistry* **1964**, *9*, 337. l) Smith, G. D.; Caughlan, C. N.; Ramirez, F.; Glaser, S. L.; Stern, P. *J. Am. Chem. Soc.* **1974**, *96*, 2698. m) Ramirez, F. *Acc. Chem. Res.* **1968**, *1*, 168.

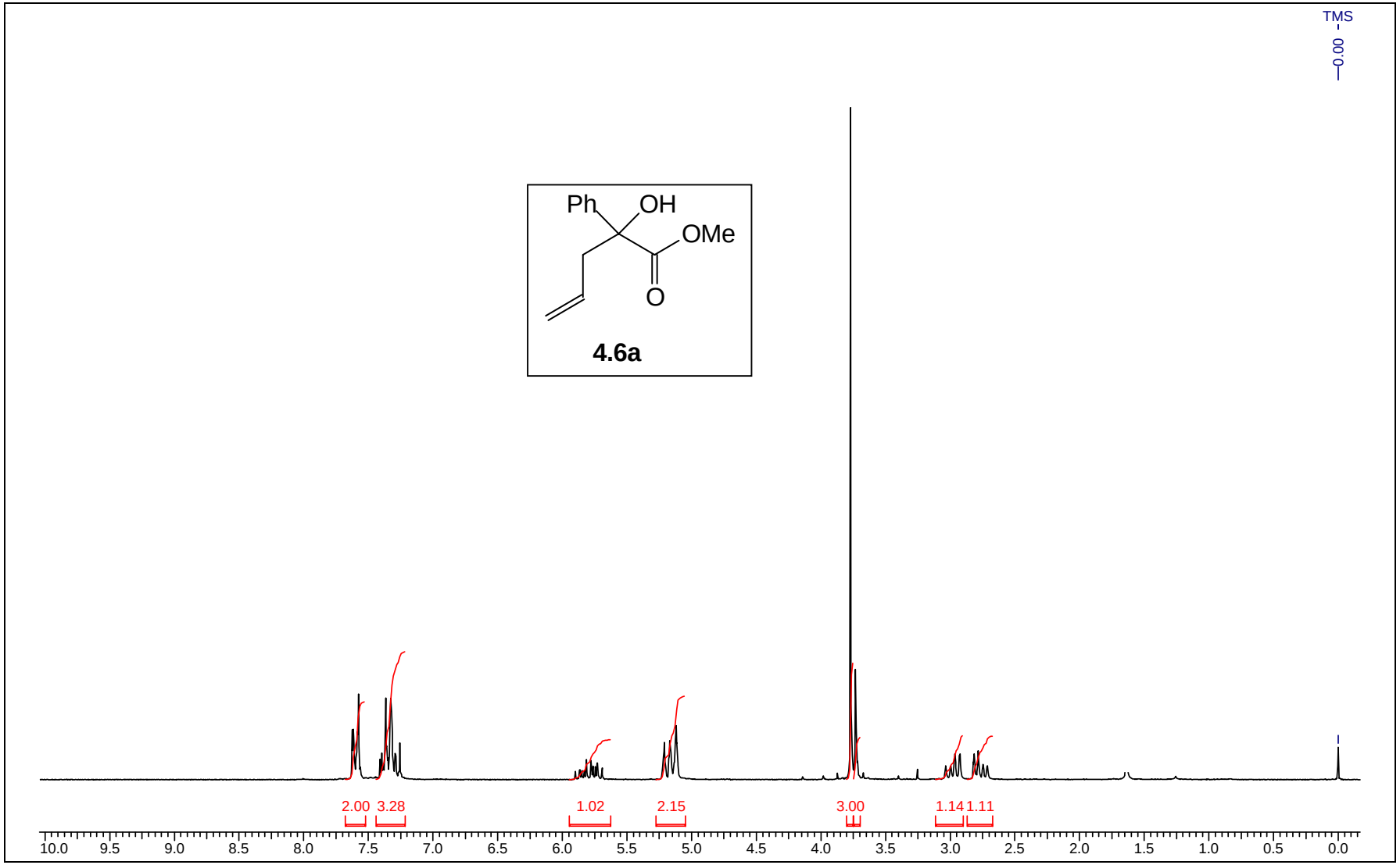
67. Hu, S.; Neckers, D. C. *J. Org. Chem.* **1997**, *62*, 6820.

68. Kim, Y. H.; Kim, S. H. *Tetrahedron Lett.* **1995**, *36*, 6895.


TMS
0.00
O
Ph
O
O
4.2a
1.65
1.94
0.91
2.01
2.00
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


TMS
O
Ph
O
O
4.2b
1.62
2.06
0.97
2.06
8.50
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


TMS
0.00
Ph
OMe
OMe
O
4.7a
5.00
0.89
1.89
2.82
2.76
2.31
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


TMS
Ph
OH
OMe
O
4.6a
2.00
3.28
1.02
2.15
3.00
1.14
1.11
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