STEREOSELECTIVE SYNTHESIS AND APPLICATIONS OF AZETIDIN-2-ONES

BY

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DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

RESEARCH GUIDE

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A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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PUNE - 411 008

Dedicated to
my parents

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Stereoselective synthesis and applications of azetidin-2-ones"** submitted by Mr. Nilesh M. Shirode 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: .11.2007

National Chemical Laboratory
Pune 411 008

Dr. A. R. A. S. Deshmukh
Research Guide

DECLARATION

I hereby declare that the work incorporated in the thesis entitled "**Stereoselective synthesis and applications of azetidin-2-ones**" 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: .11.2007

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Nilesh M. Shirode
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Finally I thank the Almighty for giving me the strength and the determination to keep going with my chin up whenever I was faced with hardships in my life.

Nilesh M. Shirode

CONTENTS

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 as Nujol mull or in Chloroform or neat, on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FT-IR and ATI Mattason, UK, Model-RS-1 FT-IR, 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, AV-200, Bruker MSL-300, Bruker AV-400 and DRX-500. Chemical shifts were recorded in parts per million (δ). Abbreviations, viz., s = singlet, d = doublet, t = triplet, dd = doublet of doublet, bs = broad singlet, m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker AC-200, AV-200, Bruker MSL-300, Bruker AV-400 and Bruker DRX-500 instrument operating at 50 MHz, 75 MHz 100 MHz and 125 MHz.
5. Elemental analysis (C, H, N) was obtained on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL.
6. Optical rotation was measured on a JASCO-181 digital Polarimeter, JASCO P-1020 Polarimeter and ADP-220 Polarimeter using sodium D line (5893 Å). Concentration is expressed in g/100 mL).
7. EI Mass spectra were recorded on a Finnigan Mat-1020 spectrometer with a direct inlet system and electron spray ionization method (EI).
8. The progress of the reaction was monitored by analytical thin layer chromatography plates pre-coated with silica gel 60 F_{254} (Merck). Column purification of compounds was carried out with silica gel obtained from Merck (230-400 mesh and 60-120 mesh).
9. ^{1}H NMR and ^{13}C NMR spectra of the compounds are attached at the end of the corresponding parts. For all the samples containing methylene and quaternary carbons DEPT spectrum was scanned after scanning ^{13}C NMR spectrum and then the assignment of the peaks in ^{13}C NMR was done.
10. Known compounds were characterized by IR and proton NMR spectroscopy.
11. Petroleum ether refers to the fraction boiling between 60-80 °C.

12. Solvents for chromatography were distilled at their respective constant boiling points.
13. All reactions requiring anhydrous conditions were performed under a positive pressure of Argon using oven-dried glassware (120 °C), which was cooled under nitrogen.
14. Dichloromethane was dried over anhydrous P_2O_5 and stored over 4Å molecular sieves. Ether, THF and dioxane were distilled over sodium benzophenone ketyl.
15. All other solvents were dried following the procedure given in the book "Purification of Laboratory Chemicals" by Armarego and Perin (third edition).
16. Compounds have been named based on nomenclature provided by Chem Draw software.

Abbreviations

Ac	Acetyl
AIBN	2,2'-Azabisisobutyronitrile ($Me_2C(CN)N=N(CN)CMe_2$
BF_3	Boron trifluoride
Bn	Benzyl
Boc	t-butoxy carbonyl
Bu_3SnH	tributyltin hydride
COSY	2D-Correlation spectroscopy
d	Day(s)
DIC	Diisopropylcarbodiimide
DCC	Dicyclohexylcarbodiimide
de	Diastereomeric excess
DIAD	Disiopropyl azodicarboxylate
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DME	1,2 Dimethoxy ethane
ee	Enantiomeric excess
Equiv.	Equivalent(s)
g	Gram(s)
h	Hour (s)
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
Hz	Hertz
IR	Infrared
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
Me_3SiN_3	Trimethylsilyl azide
Me_3SiCl	Trimethylsilyl chloride
Me_3SiI	Trimethylsilyl iodide
MCPBA	*m*-Chloroperoxybenzoic acid
Mg	Milli gram(s)

mL	Milli litre(s)
mmol	Milli mole(s)
m.p.	Melting point
MS	Mass spectrum
MWI	Microwave irridiation
NBS	N-bromo succinimide
NOESY	2D-Nuclear Overhauser Enhancement spectroscopy
Ph	Phenyl
PMP	*p*-Methoxy phenyl
Phth	Phthalimido
PPh_3	Triphenylphosphine
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
r.t.	Room temperature
TBAI	Tetrabutylammonium iodide
TBAF	Tetrabutylammonium fluoride
TBS	Tertiarybutyldimethylsilyl
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride

Abstract of the thesis

Compound numbers in the abstract are different from those in the thesis

Name of student: **Nilesh M. Shirode**

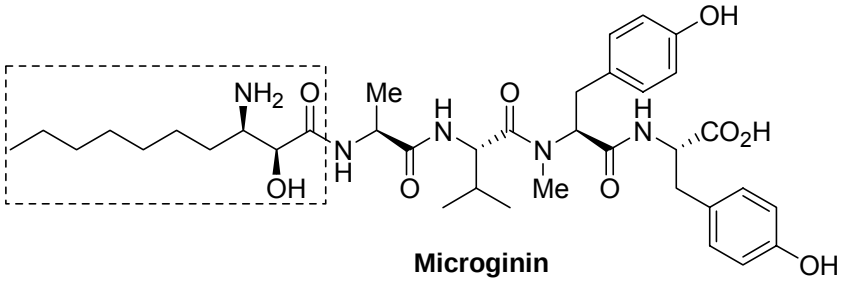
Name of Research Supervisor: **Dr. A. R. A. S. Deshmukh**

Abstract of thesis entitled: "**Stereoselective synthesis and applications of azetidin-2-ones**"

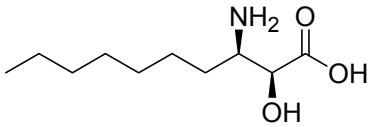
CHAPTER I

Synthesis of (2*R*,3*S*) and (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA) *via* 3-benzyloxy-4-formylazetidin-2-ones

(2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (AHDA) (**18b**) is an unusual novel amino acid, which is the N-terminal component of the recently isolated angiotensin-converting enzyme inhibitor microginin (Figure 1). Microginin is a small linear peptide isolated from the bluegreen alga *Microcystis aeruginosa*.



Microginin

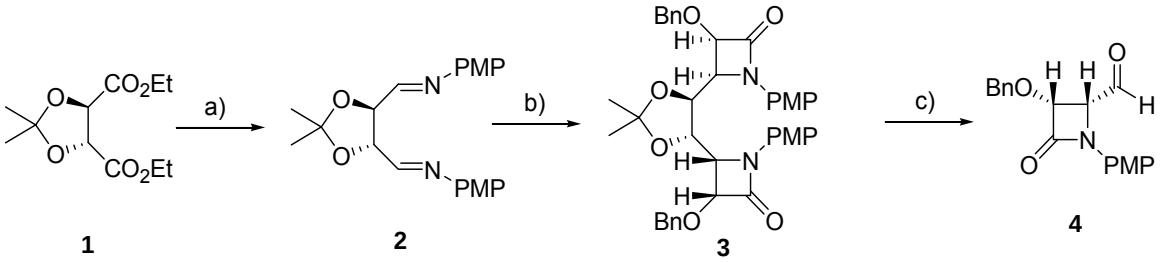


(2*S*, 3*R*)-3-Amino-2-hydroxydecanoic acid (AHDA) (**18b**)

Figure 1

Enantiomerically pure (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**4**) was prepared from L-diethyl tartrate. Bisimine **2** on Staudinger cycloaddition gave bis β-lactam **3**. A C_2-Symmetry of natural tartaric acid has been exploited to achieve the synthesis of 2 mol of *cis*-4-formylazetidin-2-one (**4**) from 1 mol of diethyl tartrate acetonide (**1**).

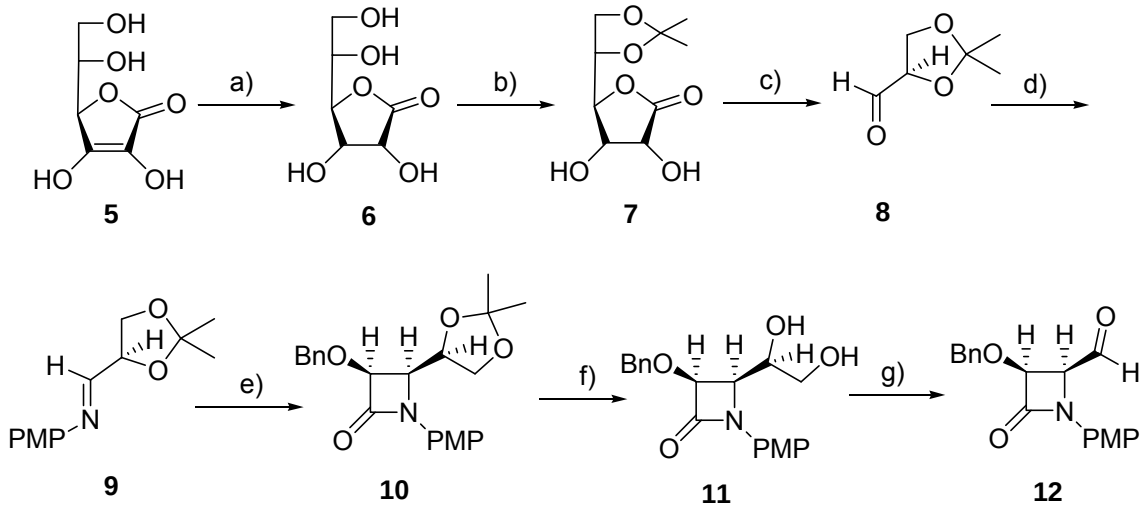
Scheme 1



Reagents and conditions: a) DIABAL-H, PMP-NH_2, toluene, -78 °C to r. t., 15 h; b) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, -23 °C to r. t., 14 h; c) i) 2.5 M $HClO_4$, THF, r. t., 4-8 h; ii) $NaIO_4$, acetone/H_2O, r. t., 4-12 h.

The other enantiomer (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**12**) was synthesized from L-glyceraldehyde acetonide (**8**), which was obtained from L-ascorbic acid (**5**) in three steps.

Scheme 2

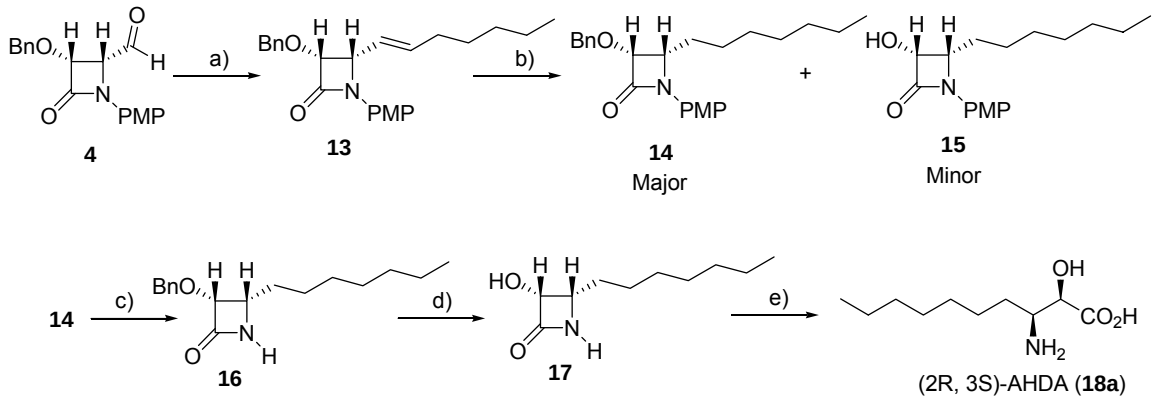


Reagents and conditions: a) H_2, Pd/C (10%), 50Psi, 50 °C, H_2O, 95%; b) 2-Methoxypropene, DMF, PTSA, 24 h, r. t., 70%; c) $NaIO_4$, H_2O, 0 °C to r. t., 2 h; d) PMP-NH_2, CH_2Cl_2, 2 h, r. t.; e) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to r. t., 12 h, 50%; f) PTSA, THF/H_2O, reflux, 18 h, 98%; g) $NaIO_4$, Acetone/H_2O, 85%.

The aldehyde **4**, on Wittig olefination reaction, gave olefin **13.** The olefin **13** on catalytic hydrogenation gave 4-heptanyl-β-lactam **14**, alongwith small amount of debenzylated compound **15**. The PMP group from 4-heptanyl-β-lactam **14** was deprotected using CAN to get (3*R*,4*S*)-3-benzyloxy-4-heptanyl-azetidin-2-one (**16**). The benzyl group was removed by transfer hydrogenation to afford 3-hydroxy-β-lactam **17.** Hydrolysis of **17**

using 3M HCl and purification by ion-exchange chromatography gives pure (2*R*, 3*S*)-AHDA (**18a).**

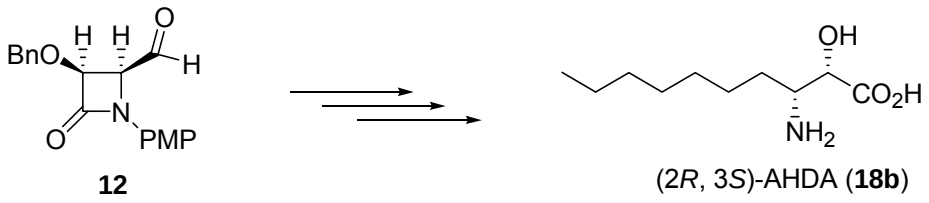
Scheme 3



Reagents and conditions: a) $CH_3(CH_2)_5PPh_3^+Br^-$, n-BuLi, 0 °C, 6 h, dry THF, 75%; b) H_2, Pd/C (10%), 50 Psi, 6 h, EtOAc, 90%; c) CAN, CH_3CN/H_2O, 0 °C, 25 min, 85%; d) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 6 h, 95%; e) 3M HCl, 60 °C, 6 h, Ion exchange resin, Dowex 50W x 2-400, 5% NH_4OH, 70%.

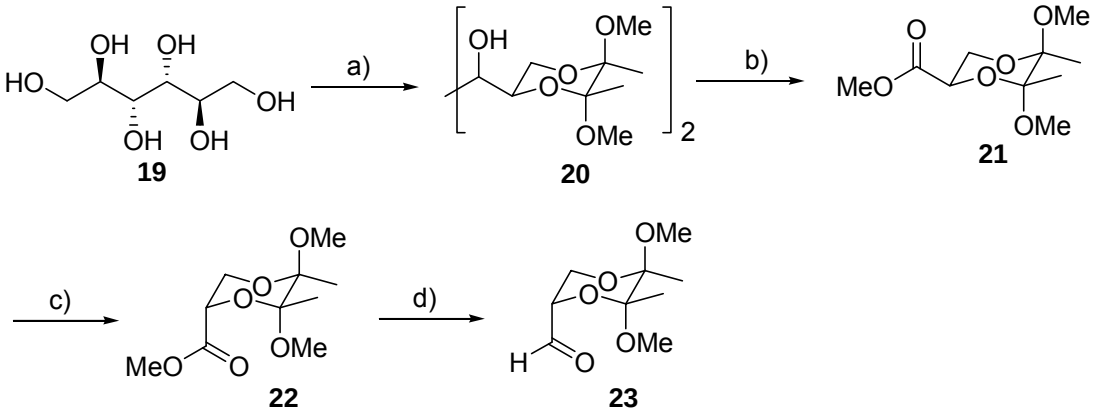
The other enantiomer, (2*S*,3*R*)-AHDA **18b** was also synthesized (Scheme 4) from (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**12**) by following a similar synthetic protocol as shown in Scheme 3.

Scheme 4



Another method for synthesis of diacetyl protected L-glyceraldehyde (**23**) was also available as shown in Scheme 5. Commercially available D-mannitol (**19**) on diacetyl protection gave diacetyl protected diol **20.** Oxidative cleavage with $NaIO_4$ followed by Br_2 oxidation gave ester **21**. Treatment of ester **21** with LDA at -78 °C gave inverted ester **22**. LAH reduction of ester **22** followed by swern oxidation furnished diacetyl protected axial aldehyde **23**.

Scheme 5

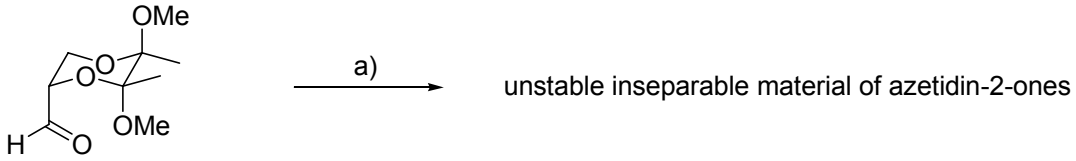


19 **20** **21** **22** **23**

Reagents and conditions: a) Butane-2-3-dione, $HC(OMe)_3$, MeOH, $BF_3.Et_2O$; b) $NaIO_4$, $MeOH/H_2O$, $NaHCO_3$, Br_2; c) LDA, THF, *t*-BuOH; d) $LiAlH_4$, THF, $(COCl)_2$, DMSO.

Aldehyde **23** was converted to its Schiff base with *p*-anisidine, which under the conditions of β-lactam formation gave unstable, inseparable mixture of β-lactams. Efforts to get pure product under different conditions were unsuccessful. (Scheme 6)

Scheme 6

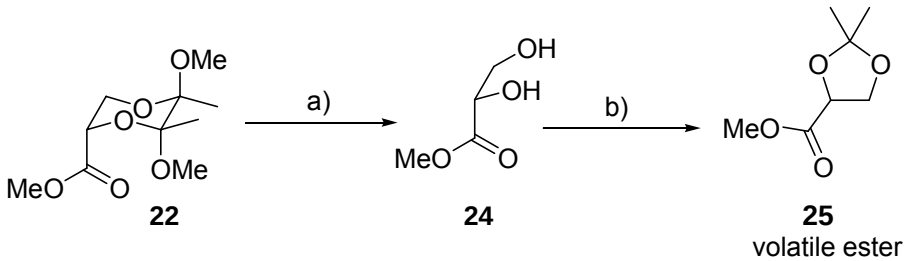


23

Reagents and conditions: a) PMP-NH_2, CH_2Cl_2, 6 h; $BnOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C

Therefore, we decided to replace diacetyl protection by acetonide protection as depicted in (Scheme 7). However, diol **24** obtained on acetonide protection resulted into a volatile ester **25**, in very low yield.

Scheme 7



22 **24** **25**
volatile ester

Reagents and conditions: a) TFA:H_2O (9:1) 10 min; b) 2,2 dimethoxy propane, clay, reflux 6 h.

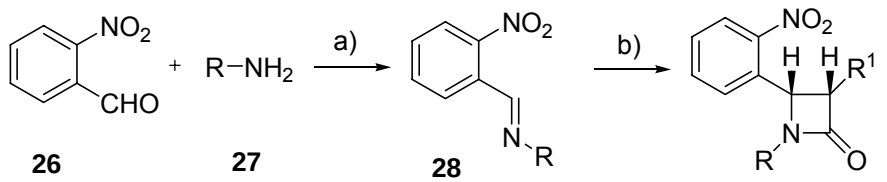
CHAPTER II

Microwave assisted rapid synthesis of 4-amino-3,4-dihydroquinolin-2-ones from azetidin-2-ones

Apart from the substructure of widely used antibiotics such as penicillin, cephalosproins, monobactams etc., the azetidin-2-one (β-lactam) skeleton has been recognized as a useful building block in stereoselective synthesis of biologically important compounds. To develop a methodology for synthesis of various substituted 4-amino-3, 4-dihydroquinolin-2-ones is an important task for biological evaluation.

This chapter deals with a rapid synthesis of 4-amino-3, 4-dihydroquinolin-2-ones from azetidin-2-ones. It involves stereoselective formation of *cis* azetidin-2-ones (**30a-l**) by Staudinger cycloaddition reaction of ketenes, generated *in situ* from substituted acetyl chlorides (**29**) and imine (**28**) (Scheme 8).

Scheme 8



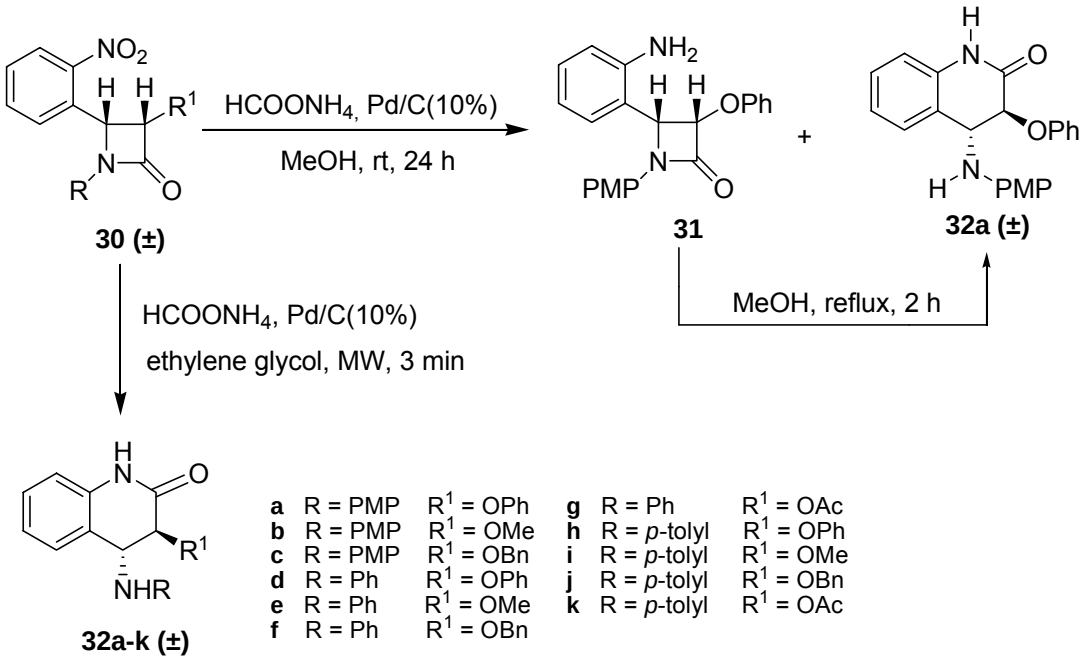
26 **27** **28** **30 a-l(±)**

a	R = PMP	R^1 = OPh	**g**	R = Ph	R^1 = OBn
b	R = PMP	R^1 = OMe	**h**	R = Ph	R^1 = OAc
c	R = PMP	R^1 = OBn	**i**	R = *p*-tolyl	R^1 = OPh
d	R = PMP	R^1 = OAc	**j**	R = *p*-tolyl	R^1 = OMe
e	R = Ph	R^1 = OPh	**k**	R = *p*-tolyl	R^1 = OBn
f	R = Ph	R^1 = OMe	**l**	R = *p*-tolyl	R^1 = OAc

Reagents and conditions: a) CH_2Cl_2, anhyd. $MgSO_4$, r. t., 15 h; b) R^1CH_2COCl [**29**], Et_3N, 0 °C to r. t., 18 h.

Azetidin-2-one **30a** by transfer hydrogenation gave amino-β-lactam **31** along with trace amounts of cyclized 4-amino-3, 4-dihydroquinolin-2-one (**32a**). The amino β-lactam **31** by refluxing in methanol gave dihydroquinolin-2-one **32a.** A direct transfer hydrogenation of **30a** in refluxing methanol gave mixtures of amino-β-lactam (**31**) and 4-amino-3,4-dihydroquinolin-2-one (**32a**) along with several other unidentified products.

Scheme 9



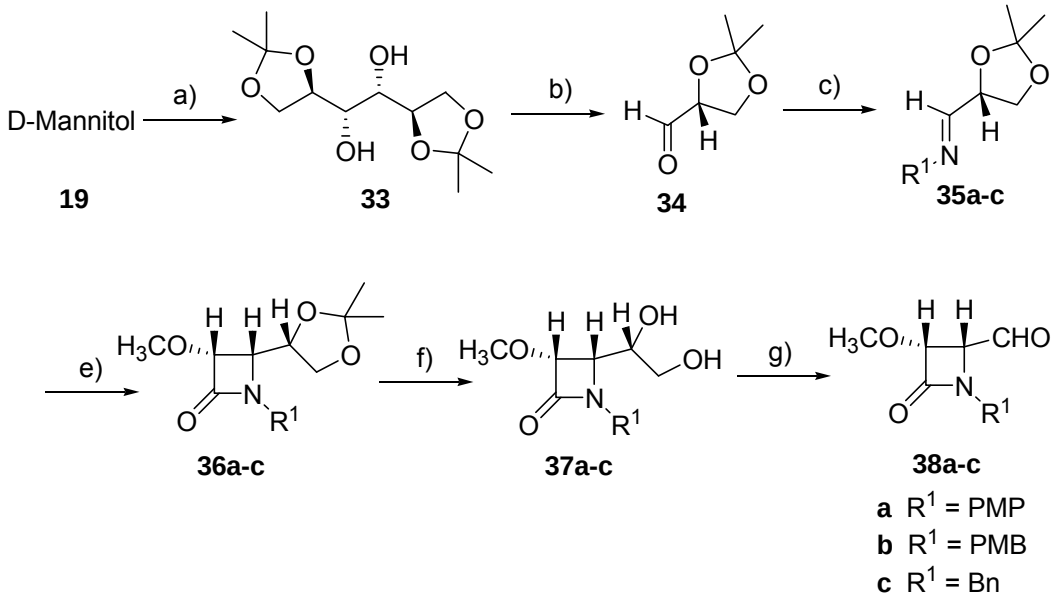
Transfer hydrogenation of **30a-l** using ammonium formate and catalytic amount of Pd/C (10%) in domestic microwave oven gave 4-amino-3,4-dihydroquinolin-2-one **32**(**a-k**) in 80-95% yields. They are screened for antifungal activity against *benjaminiella poittrasii* and *candida alibicans*. Some of these 4-amino 3,4-dihyroquinolin-2-ones have shown good antifungal activity.

CHAPTER III

Synthesis of 4-amino piperidines from 4-formyl azetidin-2-ones: Studies towards the synthesis of (3*S*,4*R*)-Cisapride.

Substituted piperidines are part structures of several natural products and also key pharmacophores in large number of biologically active compounds. As a part of our research program on transformation of β-lactams we were interested in synthesis of piperidine derivatives using β-lactams as starting building block. With this idea in mind we synthesized optically pure 4-formyl β-lactams **38a-c** from commercially available D-Mannitol (**26**) by reaction sequence shown in Scheme 10. Azetidin-2-ones **36a-c** were synthesized by Staudinger reaction between Schiff's bases **35a-c** and ketene obtained from methoxy acetyl chloride.

Scheme 10

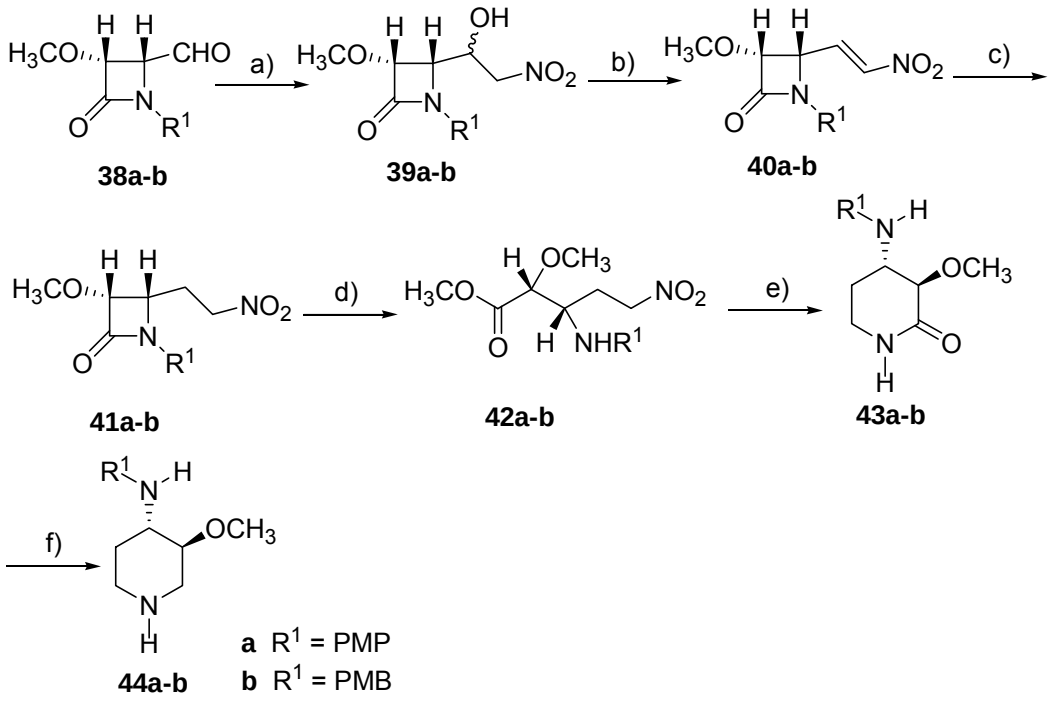


Reagents and conditions: a) $ZnCl_2$, anhyd. acetone, 24 h, 50%; b) $NaIO_4$, H_2O, 30 min, 0 °C; c) R^1-NH_2, H_2O-EDC, r. t., 2 h; d) Et_3N, CH_2Cl_2, $MeOCH_2COCl$, 0 °C-r. t., 12 h, 50%; e) PTSA, THF-H_2O, reflux 15 h, 90%; f) $NaIO_4$, SiO_2, CH_2Cl_2, 30 min, 95%.

The β-lactams **38a-b** on treatment with nitromethane in presence of Et_3N underwent nitro aldol reaction to give nitro alcohols **39a-b**, which on acetylation followed by elimination using $NaHCO_3$ gave nitro olefins **40a-b**. It was reduced by tributyltinhydride to nitroalkanes **41a-b**, which on treatment with methanolic HCl gave β-amino esters **42a-b**. Reduction of the nitro group was achieved by transfer hydrogenation using Pd/C to afford

the (3*S*,4*S*)-4-amino piperidin-2-one **43a-b**. Reduction of cyclic amide with BH_3:DMS complex gave 4-amino piperidine **44a-b**.

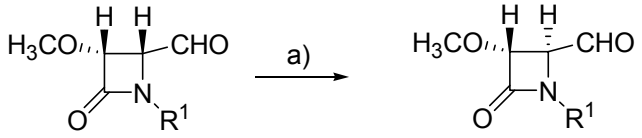
Scheme 11



Reagents and conditions: a) CH_3NO_2, Et_3N, 5 h, 95%; b) i) Ac_2O, Conc. H_2SO_4, 0 °C, 1 h, ii) $NaHCO_3$, benzene, reflux, 4 h, 80%; c) Bu_3SnH, CH_2Cl_2:MeOH (10:1), r. t., 3 h, 50-60%; d) methanolic HCl (20%), r. t., 12 h, 80%; e) 10% Pd/C, $HCOONH_4$, MeOH, r. t., 5 h, 60-70%; f) BH_3:DMS, toluene, reflux 4 h, 50%.

Since some of the fentanyl derivatives and drug molecule like cisapride possess *cis* stereochemistry at C-3 and C-4 positions in piperidine ring. To get *cis* stereochemistry it is essential to start with *trans* 4-formyl azetidin-2-ones (**45a-c**). It was achieved by chemoselective epimerization of 4-formylazetidin-2-one (**38a-c**) using 40% dimethylamine for **38a** and using sodium carbonate for **38b-c** (Scheme 12).

Scheme 12



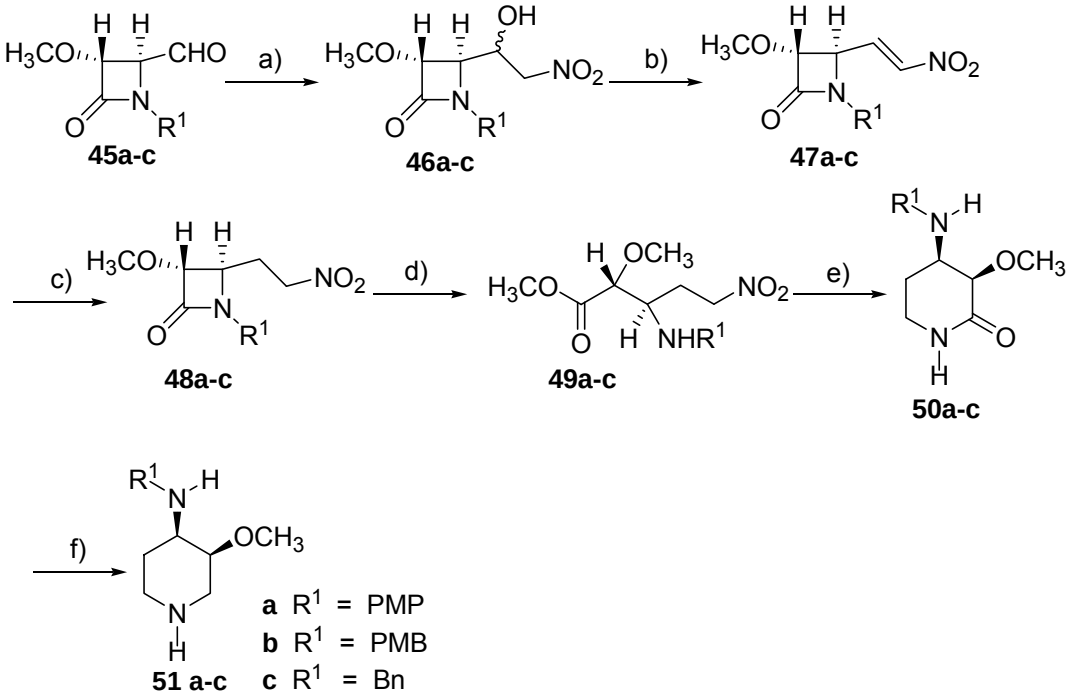
38a-c **45a-c**

a R^1= PMP
b R^1= PMB
c R^1 = Bn

Reagents and condtions: a) dimethylamine 40%, benzene, r. t., 24 h, for **38a**/ Na_2CO_3, CH_3CN-H_2O,(1:1) r. t., 48 h, 70% for **38b-c**,

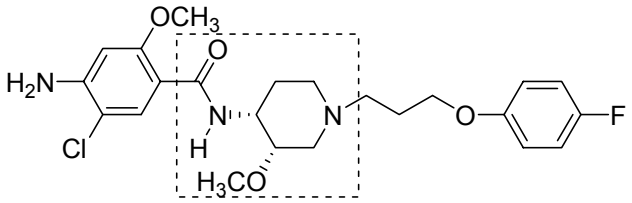
(3*R*,4*S*)-*trans* 4-Formyl azetidin-2-ones (**45a-c**) were converted into (3*S*,4*R*)-*cis* 4-amino piperidines (**51a-c**) by following a similar reaction sequence as in Scheme 11.

Scheme 13



Reagents and conditions: a) CH_3NO_2, Et_3N, 5 h, 95%; b) i) Ac_2O, Conc. H_2SO_4, 0 °C, 1 h, ii) $NaHCO_3$, benzene, reflux, 4 h, 70%; c) Bu_3SnH, CH_2Cl_2:MeOH (10:1), r. t., 3 h, 50-60%; d) methanolic HCl (20%), r. t., 12 h, 80%; e) 10% Pd/C, $HCOONH_4$, MeOH, r. t., 5 h, 60-70%; f) BH_3;DMS, toluene, reflux 4 h, 50%.

After achieving the synthesis of piperidine we have planned the synthesis of important drug Cisapride which is particularly useful in treatment of gastro-esophageal reflux disease since it has a 4-aminopiperidine as a core structure (Figure 2), which can be obtained by reduction of 4-amino piperidin-2-one as shown in Scheme (11 and 13).

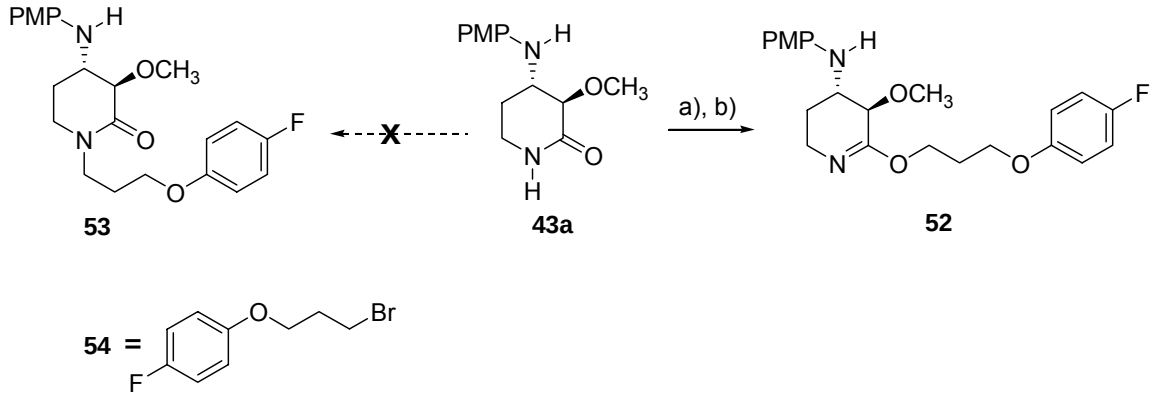


(3*S*,4*R*)-Cisapride

Figure 2

4-Amino piperidin-2-one (**43a**) on treatment with Boc_2O using Et_3N as a base followed by alkylation using NaH gave *O*-alkylated product **52** instead of desired N-alkylated product **53** (Scheme 14).

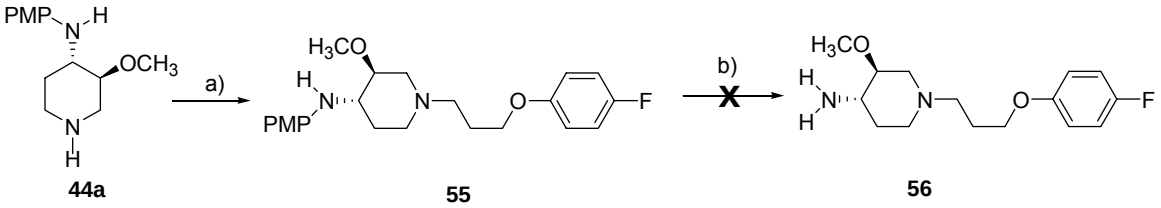
Scheme 14



Reagents and conditions: a) Boc_2O, Et_3N, CH_2Cl_2, 30 min; b) NaH, THF, **50**, reflux, 12 h/ NaH, DMF, **54**, r. t., 12 h.

However, direct *N*-alkylation of cyclic nitrogen of 4-amino piperidine **44a** was achieved by using Et_3N as a base in anhyd. DMF as solvent to get *N*-alkylated product **55**. The deprotection of PMP group was found to be difficult in case of **55** (Scheme 15).

Scheme 15

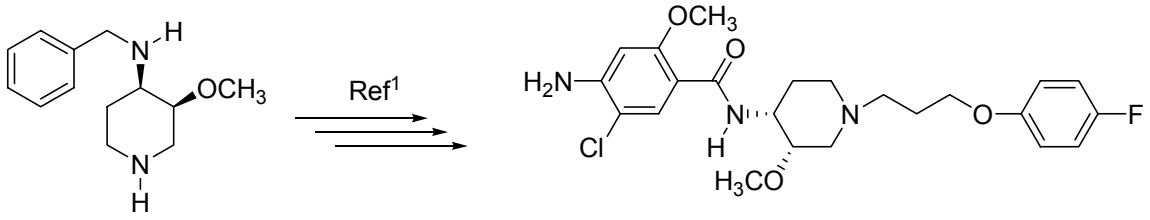


Reagents and conditions: a) DMF, Et_3N, **54**, r.t. 18 h b) CAN, CH_3CN-H_2O, 30 min.

There is a report on synthesis of racemic Cisapride in which benzyl protected aminopiperidine is converted to target molecule Cisapride[1] in three steps therefore we also

synthesized benzyl protected amino piperidine (**51c**) which can be further converted to target molecule (3*S*,4*R*)-Cisapride (Scheme 16).

Scheme 16



51c **(3*S*,4*R*)-Cisapride**

CHAPTER IV

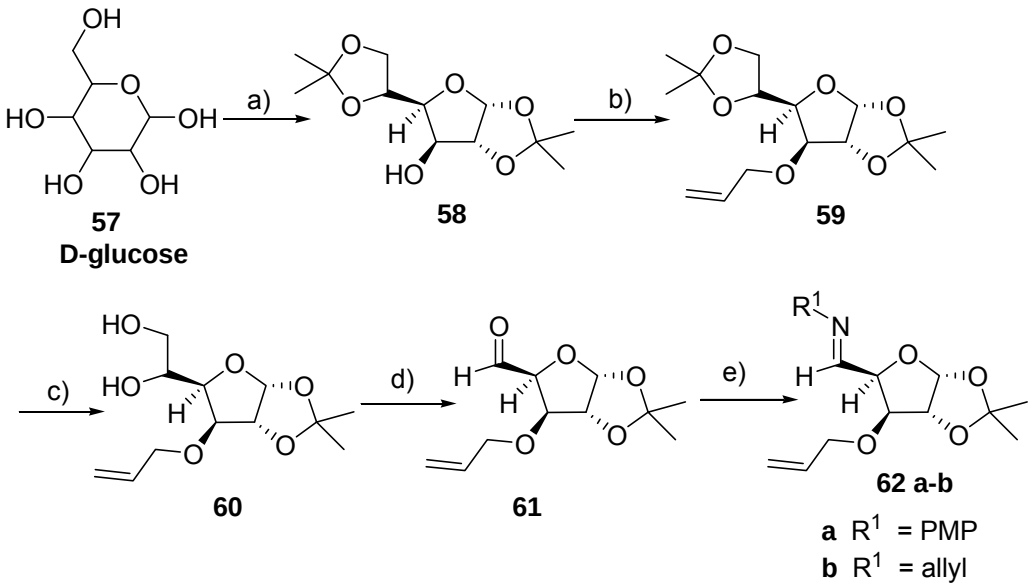
Stereoselective synthesis of new β-lactam derivatives from D-glucose derived chiral pools

Carbohydrates have been extensively exploited as chiral source in asymmetric organic synthesis. This is mainly because they have well defined multiple stereocentres and also they are available in large quantities in optically pure form. Application of carbohydrate derived chiral auxillaries for asymmetric synthesis β-lactams is a recently developed area. We have been working in this area for the last couple of years and it has been found that D-glucose derived chiral aldehyde, a chiral imine precursor showed high levels of stereoselectivity in formation of azetidin-2-ones in [2+2] cycloaddition reaction with ketenes. The carbohydrate derived chiral pool have been used in the synthesis of antibiotic such as thienamycin and its analogues. The fused bicyclic and polycyclic structural frameworks with β-lactam unit represent important substructures in many antibiotics. Therefore, asymmetric synthesis of fused bicyclic/polycyclic β-lactams using D-glucose was the major objective of this research. With this goal in mind we decided to synthesize new β-lactam derivatives from D-glucose and further use them as synthons for the synthesis of polycyclic β-lactams.

Synthesis of mono-*O*-alkylated–3-substituted azetidin-2-ones:

Commercially available D-glucose (**57**) was converted into chiral aldehyde **61** by known reaction sequence (Scheme 17). Imines **62a-b** were obtained using amines (*p*-anisidine, allyl amine).

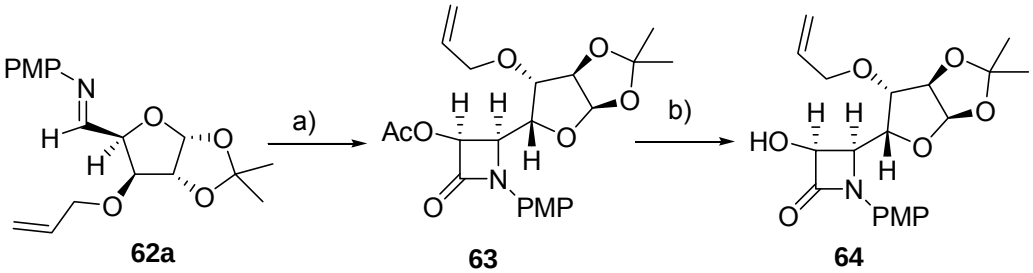
Scheme 17



Reagents and conditions: a) $CuSO_4$, acetone, H_2SO_4, 48 h, 50%; b) aq. NaOH, Allyl bromide, TBAB, CH_2Cl_2, 24 h, 90%; c) 75% AcOH in H_2O, 75 °C, 3 h, 84%; d) $NaIO_4$, acetone/H_2O 0 °C, 1.5 h, 80%; e) R^1-NH_2, CH_2Cl_2, anhyd. $MgSO_4$, 6 h.

Imine **62a** on Staudinger reaction with acetoxy acetyl chloride in the presence of Et_3N gave stereoselectively 3-acetoxy azetidin-2-one **63**. Hydrolysis of the acetoxy functional group gave 3-hydroxy azetidin-2-one **64**.

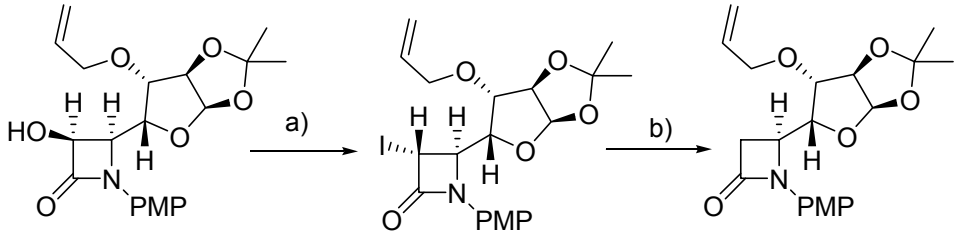
Scheme 18



Reagents and conditions: a) $AcOCH_2COCl$, Et_3N, 0 °C-r. t., 12 h, 80%; b) aq. $NaHCO_3$, MeOH, r. t.

3-Hydroxy azetidin-2-one **64** gave 3-iodo azetidin-2-one **65** using triphenyl phosphine, iodine, and imidazole. Attempts at radical cyclization of the 3-iodo azetidin-2-one **65** resulted in the formation of reduced product **66** instead of the desired cyclized product.

Scheme 19



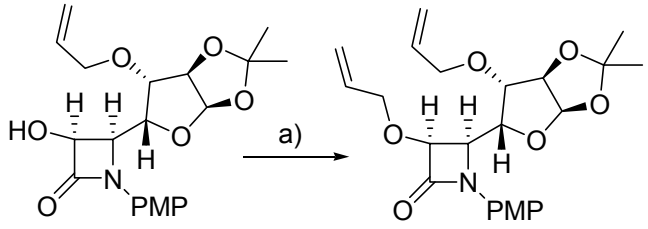
64 **65** **66**

Reagents and conditions: a) PPh_3, I_2, Imidazole, toluene, reflux, 18 h, 75%; b) Bu_3SnH, AIBN, toluene, reflux, 6 h, 70%.

Synthesis of *O-O*', *O-C* and *O-N* dialkylated–3-substituted azetidin-2-ones for polycyclic β-lactam:

3-Hydroxy azetidin-2-one **64** on reaction with allyl bromide using NaH as a base and TBAI as PC gave 3-O-allyl azetidin-2-one **67**.

Scheme 20

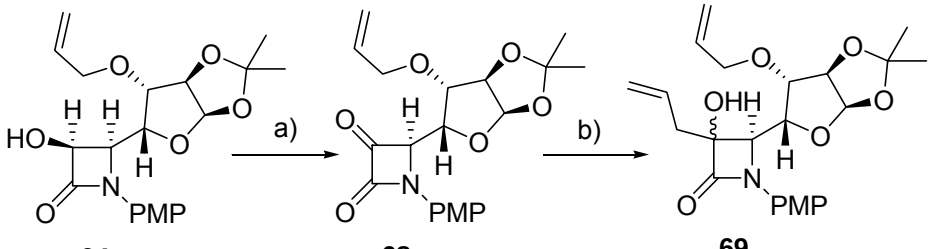


64 **67**

Reagents and conditions: a) NaH, allyl bromide, TBAI, THF.

3-Hydroxy azetidin-2-one **64** on oxidation with iodoxo benzoic acid (IBX) gives 3-keto azetidin-2-one **68.** Ketone **68** on Grignard reaction with allyl magnesium bromide gives 3-allyl 3-hydroxy azetidin-2-one **69** in 3:1 diasteromeric ratio.

Scheme 21

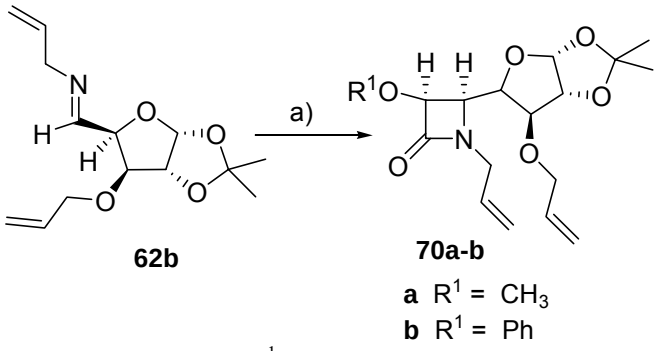


64 **68** **69**

Reagents and conditions: a) IBX, EtOAc, reflux 6 h; b)allyl magnesium bromide, THF, 0 °C, 30 min., 70%.

Imine **62b** on Staudinger reaction give stereoselectively azetidin-2-ones **70a-b**.

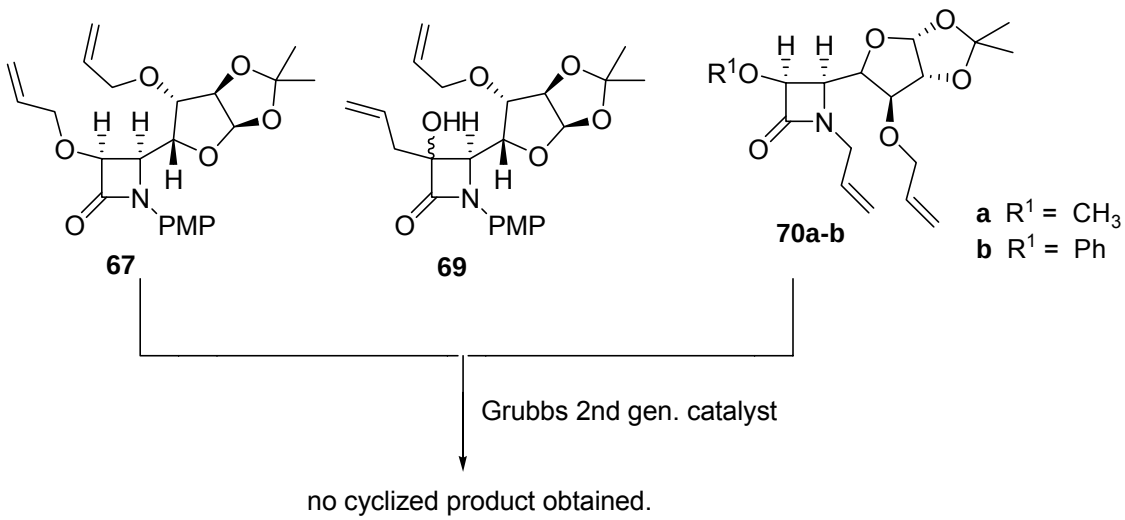
Scheme 22



Reagents and conditions: a) Et_3N, R^1OCH_2COCl, CH_2Cl_2, 0 °C-r. t., 12-14 h, 75%.

Cyclization of substrates **67**, **69**, **70a-b** using Grubbs 2nd generation catalyst resulted in a recovery of starting material and resulted in a complex reaction mixture under reflux conditions in toluene or CH_2Cl_2.

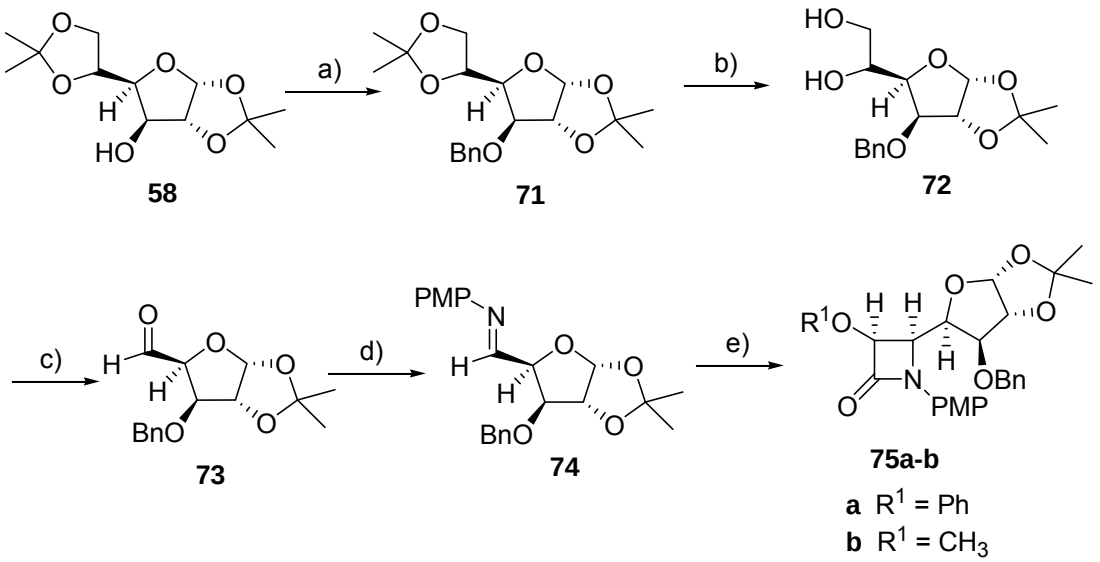
Scheme 23



Synthesis of 3-substituted azetidin-2-ones for new class of polycyclic carbapenem derivatives:

Chiral aldehyde **73** was obtained by known reaction sequence as shown in Scheme 21. The chiral imine **74** derived from aldehyde **73** and *p*-anisidine was subjected to Staudinger reaction with acid chlorides (phenoxy, methoxy) in the presence of excess Et_3N to give *N*-PMP protected azetidin-2-ones **75a-b** in good yield.

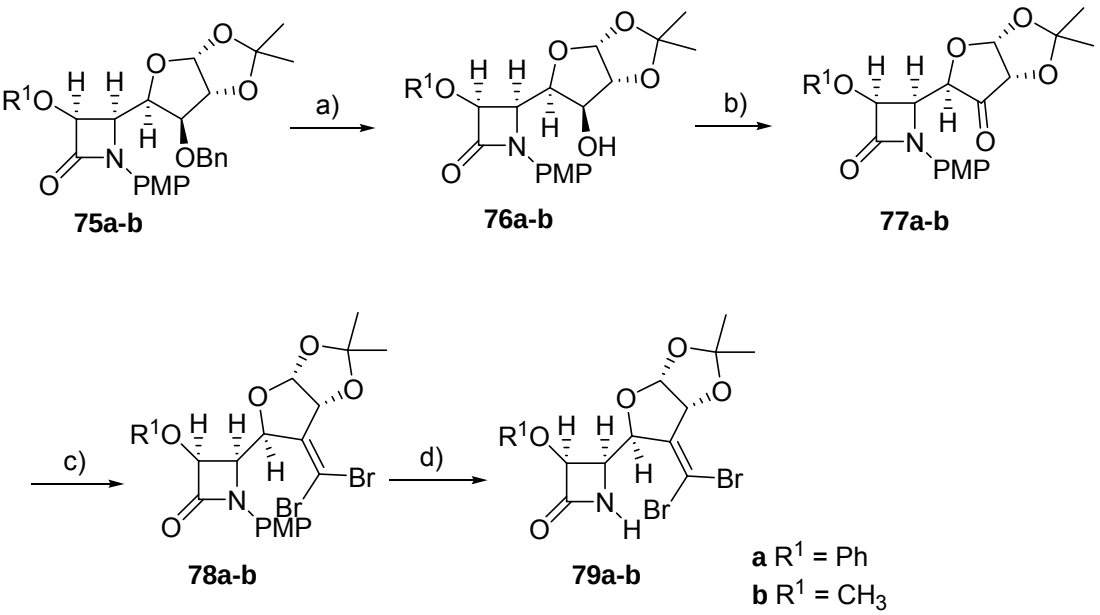
Scheme 24



Reagents and conditions: a) NaH, BnBr, THF, TBAI, 2.5 h, 90%; b) 75% AcOH in H_2O, 75 °C, 3 h, 84%; c) $NaIO_4$, acetone/H_2O 0 °C, 1.5 h, 80%; d) PMP-NH_2, CH_2Cl_2, anhyd. $MgSO_4$, 6 h; e) R^1OCH_2COCl, Et_3N, 0 °C-r. t., 12 h, 80%.

Azetidin-2-ones **75a-b** on catalytic hyrogenation followed by iodoxobenzoic acid (IBX) oxidation gave ketones **77a-b**, which on reaction with triphenylphospine/carbon tetrabromide gives vinylic dibromo azetidin-2-ones **78a-b**. Removal of PMP from azetidin-2-ones **78a-b** using CAN gave N-H β-lactams **79a-b**.

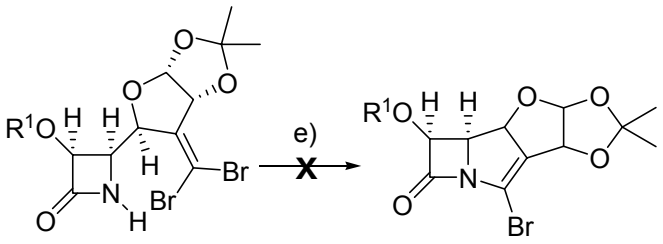
Scheme 25



Reagents and conditions: a) H_2, EtOAc, 50 psi, 24 h, 90%; b) IBX, CH_3CN, Acetonitrile, reflux 6 h; c) PPh_3, CBr_4, toluene, 80 °C, 12 h, 70%; d) CAN, CH_3CN-H_2O, 60%.

Vinylic dibromo azetidin-2-ones **79a-b** were found to be unfruitful to get cyclized product (new class of carbapenem **80a-b**) using Buchwald-Hartwig C-N bond forming reaction (Scheme 26).

Scheme 26



79a-b **80a-b**

a R^1 = Ph
b R^1 = CH_3

Reagents and conditions: a) $Pd(OAc)_2$, ligand, base toluene, 100 °C

References:

1) *Drug. Dev. Res.* **1986**, 8, 225.

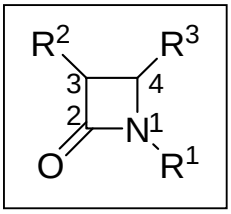
Chapter I

Synthesis of (2*R*,3*S*) and (2*S*,3*R*)-3-amino-2-hydroxy decanoic acid (AHDA) *via* 3-benzyloxy-4-Formyl azetidin-2-ones

Part of this work has been published in *Tetrahedron*, **2005**, *61*, 2441-2451

1.1 Introduction:

Azetidin-2-one (β-lactam), a four membered cyclic amide, 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 much for their pharmaceutical value as for the variety they provide in terms of synthetic challenges. Although the first synthesis of β-lactam ring was reported way back in 1907[1] by Staudinger, β-lactam as a class acquired immense importance only after the discovery of penicillin by Prof. 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 proved 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

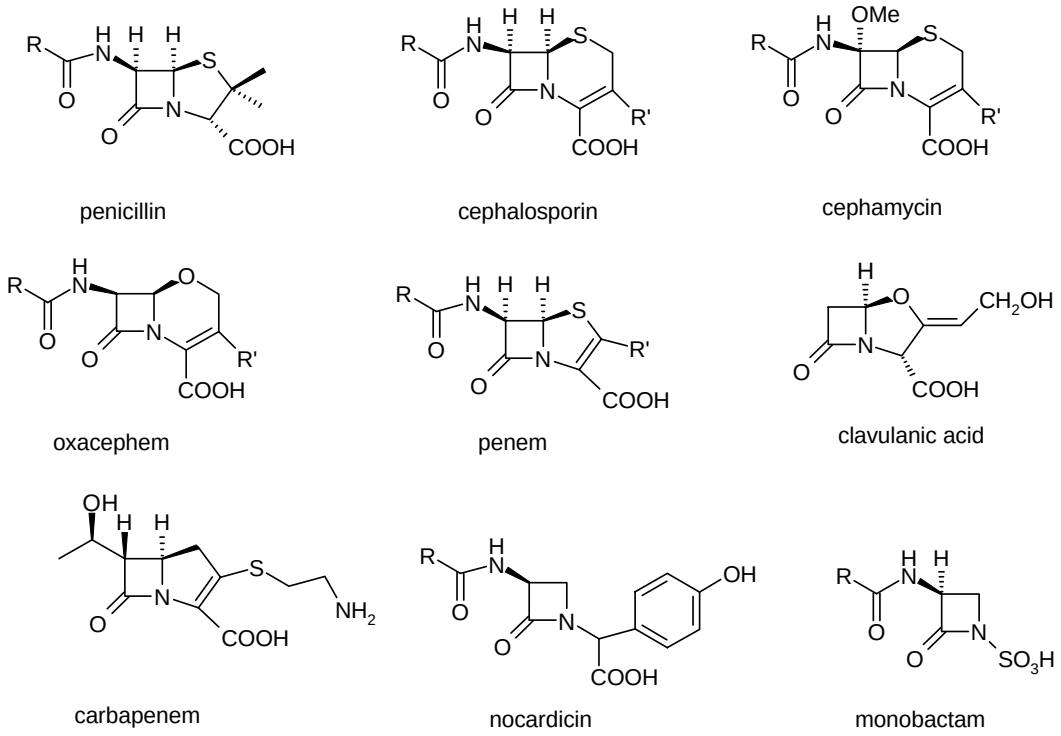


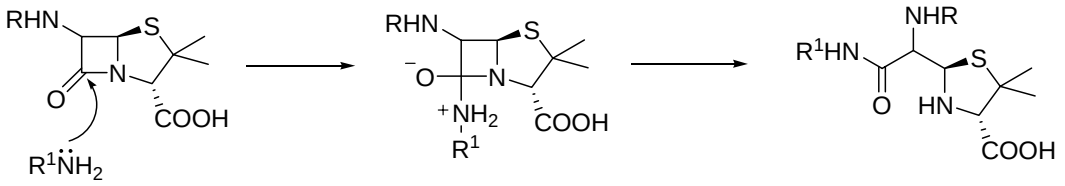
Figure 2. Classification of β-lactam antibiotics based on core structure

Mode of action of penicillin:

The biological activity of these antibiotics is mainly due to the presence of β-lactam ring. The SAR (structure activity relationship) studies[6] have shown that the essential requirement for an antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in an active form to the target site. 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.[7] The schematic representation of this phenomenon in the case of penicillin and cephalosporin is shown below.

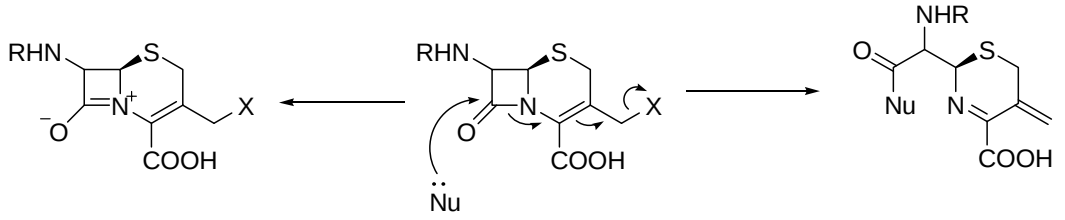
Biological activity of penicillin:[8]

Scheme 1.01



Biological activity of cephalosporin:[9]

Scheme 1.02

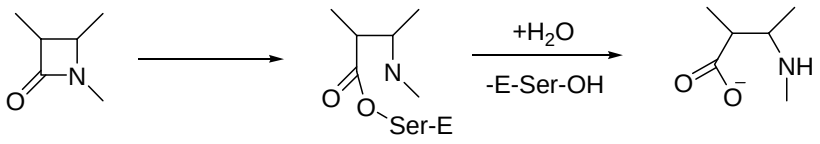


β-Lactamases and β-lactamase inhibitors:

β-Lactamases[10] are bacterial enzymes mainly responsible for resistance against β-lactam antibiotics. They present a serious and growing threat to the efficacy of antibacterial chemotherapy and thus pose a major challenge to human health. These defensive enzymes, prevalent in nearly every pathogenic bacterial strain, hydrolyze the β-lactam ring and release the cleaved inactive antibiotics as amino acids.

There are four different classes of β-lactamase enzymes and they have been divided into two categories according to their catalytic active site. Class A, class C and class D enzymes, named as serine enzyme lactamases, possess serine in their active site and act by covalent acyl enzyme mechanism as shown below.[10] Class B enzymes on the other hand, called as Zinc enzyme lactamases, possess Zn metal ion in their active site and act via a non ionic intermediate mechanism.

Scheme 1.03



The problem of bacterial resistance to commercial antibiotics has opened a gateway to develop novel β-lactam antibiotics as β-lactamase inhibitors.[11-12] These β-

lactamase inhibitors are compounds which are structural variants of natural antibiotics with a modified β-lactam skeleton. These compounds may not themselves possess antibiotic activity and hence would have to be used in combination with biologically active antibiotics. More specifically, they associate themselves with the lactamases, preventing prior interaction of β-lactamase with the β-lactam antibiotics and thereby safeguarding the antibiotic activity of the β-lactams.

Clavulanic acid in combination with amoxicillin or ticarcillin, sulbactam in combination with ampicillin and tazobactam in combination with piperacillin are a few examples of clinically used β-lactamase inhibitors.

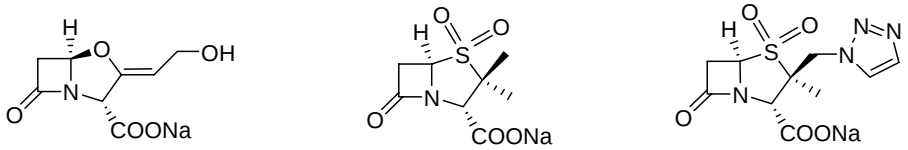


Figure 3

Temocillin, Formidacillin[12] and tricyclic tribactams[13] are other examples of effective β-lactamase inhibitors.

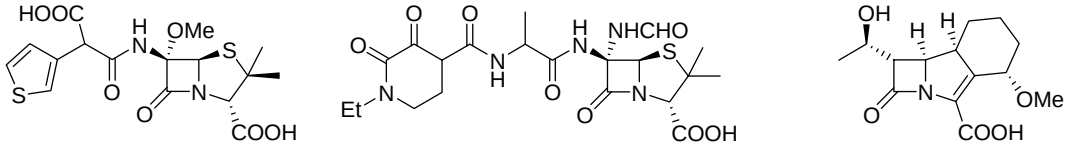


Figure 4

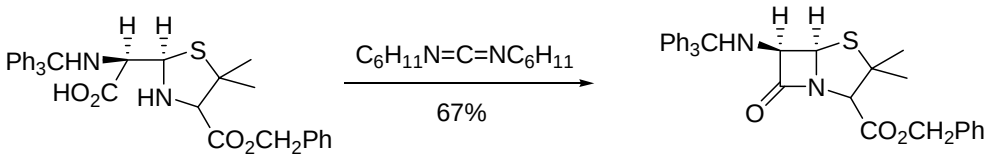
Methods for constructing β-lactam ring:

There are several approaches available to construct these β-lactams and a few important methods will be discussed here.

Formation of the amide N1-C2 bond:

The simplest approach to the synthesis of azetidinone structures is via dehydration of β-amino acids. This method has been used in the landmark synthesis of penicillin by Sheehan et al. using dicyclohexylcarbodiimide as a condensing agent[14] (Scheme 1.04).

Scheme 1.04

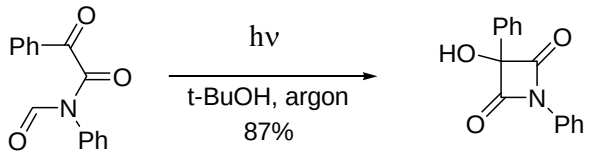


Triphenylphosphine-pyridine disulfide, methanesulfonyl chloride in combination with base and Grignard reagent (RMgX) can also be used instead of DCC to form the amide bond from β-amino acids.

Formation of C2-C3 bond:

The formation of carbon-carbon bond at C2-C3 position is inherently more difficult compared to the N1-C2 amide bond formation. Maruyama et al. have achieved it via a photochemical approach to synthesize 4-keto-β-lactam[15] (Scheme 1.05).

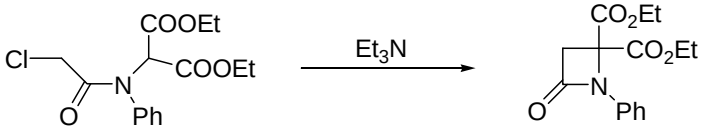
Scheme 1.05



Formation of C3-C4 bond:

The simplest method for the formation of C3-C4 bond is to generate the nucleophilic center at C3 and an electrophilic center at C4, or vice versa. Sheehan and Bose have first reported azetidinone formation via an intramolecular nucleophilic displacement reaction using malonate anions and halides as the nucleophilic and electrophilic components respectively[16] (Scheme 1.06).

Scheme 1.06

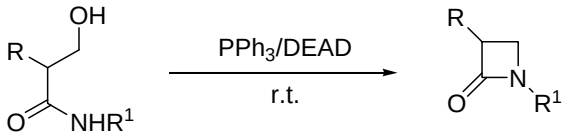


Formation of C4-N1 bond:

This methodology involves an S_N2 displacement of a good leaving group attached at β-carbon amide by an intramolecular amide nitrogen under basic conditions.

Miller has reported the synthesis of β-lactams by the cyclization of β-hydroxy amides under Mitsunobu reaction conditions[17] (Scheme 1.07).

Scheme 1.07

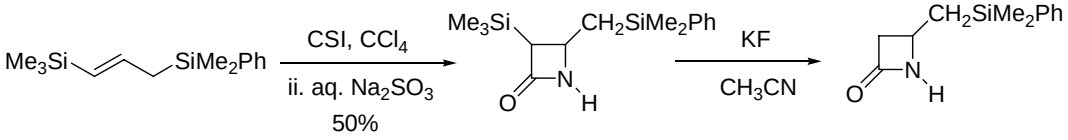


Multiple bond forming reactions:

Olefin-isocyanate cycloaddition reaction:

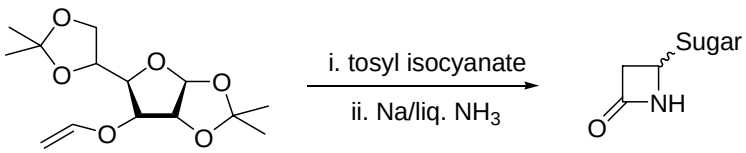
The addition of chlorosulfonyl isocyanate to olefins is a well-known method for the construction of β-lactams.[18] Colvin et al.[19] have reported the addition of chlorosulfonyl isocyante to various allyl and allenyl silanes to give functionalized β-lactams, which were then converted into synthetically important 3-unsubstituted *NH*-β-lactams by removal of the chlorosulfonyl group followed by silyl deprotection (Scheme 1.08).

Scheme 1.08



Chmielewski and co-workers have used this cycloaddition reaction between tosyl isocyanate and sugar derived vinyl ethers to obtain good diastereoselectivities in β-lactam formation[20] (Scheme 1.09)

Scheme 1.09

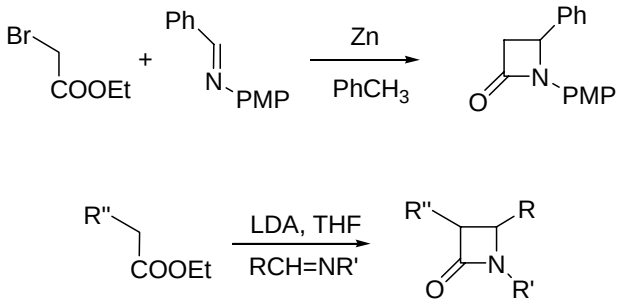


Enolate-imine condensation:

The first example of this type of reaction has been reported by Gilman and Speeter by the condensation of zinc enolate (Reformatsky reagent) with imines to give

β-lactams. Other metal enolates have also been used in enolate-imine cycloaddition to achieve disatereoselective synthesis of β-lactams[21] (Scheme 1.10).

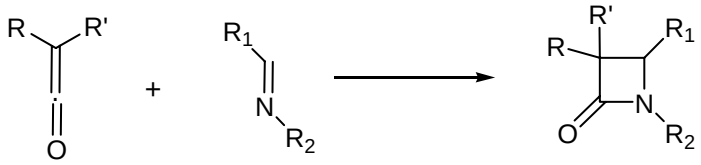
Scheme 1.10



Staudinger reaction:

The first synthesis of a β-lactam was achieved by Staudinger[1] in 1907 by the [2+2] cycloaddition of ketene and imine. This reaction is called as Staudinger or ketene-imine cycloaddition reaction (Scheme 1.11). In the modified Staudinger reaction, acid chlorides or activated carboxylic acids in the presence of a base were used as a ketene precursor. It is an excellent and well adopted method in the literature for the construction of β-lactam rings.

Scheme 1.11

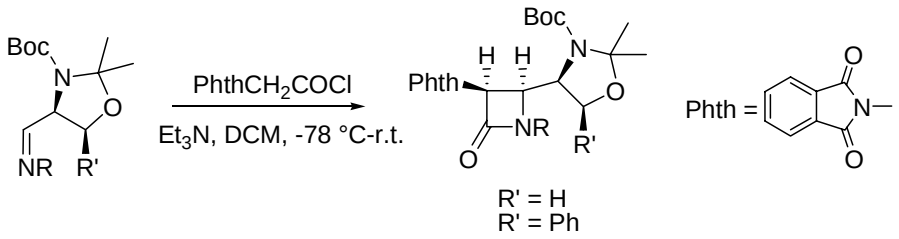


Asymmetric synthesis of β-lactams using Staudinger reaction:

Better understanding of the mechanistic aspects of the β-lactams' biological activity and their inhibition and the chemical exploitation of β-lactams as synthetic intermediates in organic chemistry have led to profound development in this field. In this regard, the accessibility of enantiopure β-lactams is an important requirement considering their pharmaceutical importance. The asymmetric Staudinger reaction is the most attractive and widely used method for this purpose because of its simplicity and predictability of stereo chemical outcome of the reaction. Asymmetry can be induced by using either chiral ketenes derived from acid precursors or chiral imines (derived from either chiral aldehydes or amines).

Chiral imines, derived from chiral aldehydes and achiral amines are the most effective for introducing asymmetry in the asymmetric Staudinger reaction. Generally, these imines give a very high level of diastereoselectivity in the cycloaddition reaction. Among the useful chiral imines, the *N*, *O*-protected aldimines are the most efficient ones[22] (Scheme 1.12).

Scheme 1.12



The most common approaches in the Staudinger reaction involve the use of α-oxyaldehyde derived imines, sugar derived imines and α, β-epoxyimines.[23]

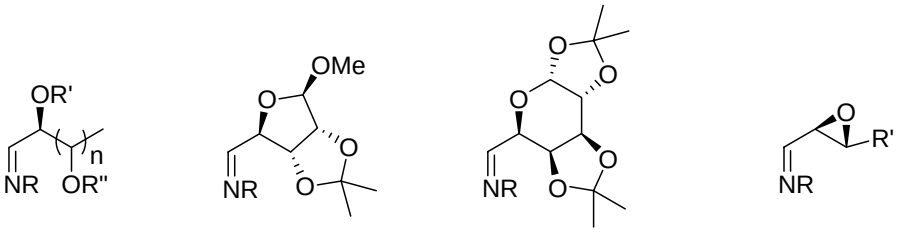
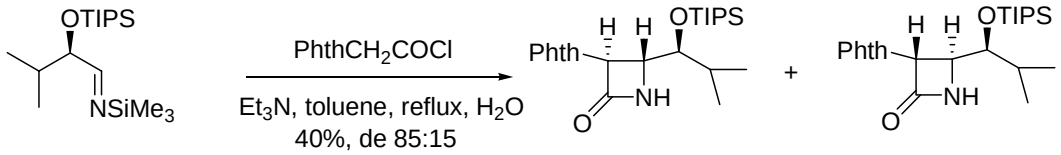


Figure 5

Formation of *cis* isomer is generally favoured in all these cases with the observed ratios being as high as 90:10 in favour of the *cis* diastereomer.

Recently, Panunzio and co-workers have reported a case of *trans*-selectivity preference in cycloaddition reaction. The method involves the reaction of phthalimidoacetyl chloride with *N*-trimethylsilyl imines and triethylamine in refluxing toluene[24] (Scheme 1.13).

Scheme 1.13

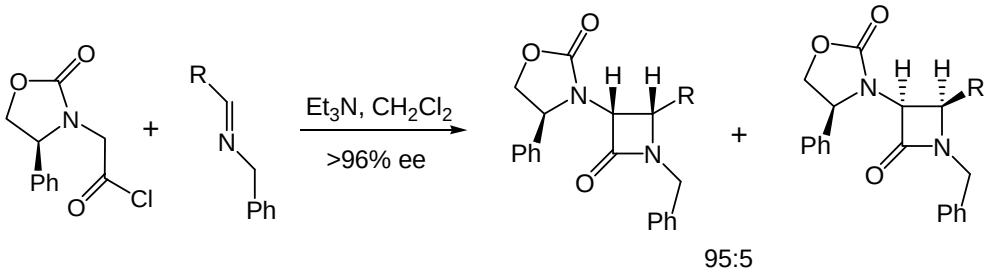


Chiral Ketenes:

Over the past several years the Staudinger reaction has been extensively developed by using a combination of either chiral ketenes and chiral imines or achiral ketenes and chiral imines, generally providing good yields with excellent diastereo-selectivity.

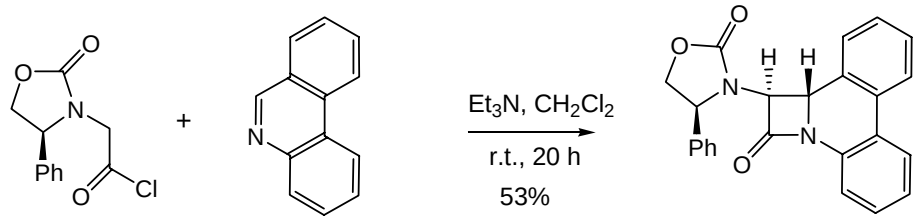
The cycloaddition of Evans-Sjogren ketenes, generated from chiral oxazolidinyl acid chlorides and triethylamine, with achiral imines afforded optically active β-lactams with high levels of asymmetric induction, typically greater than 96% ee[25] (Scheme 1.14).

Scheme 1.14



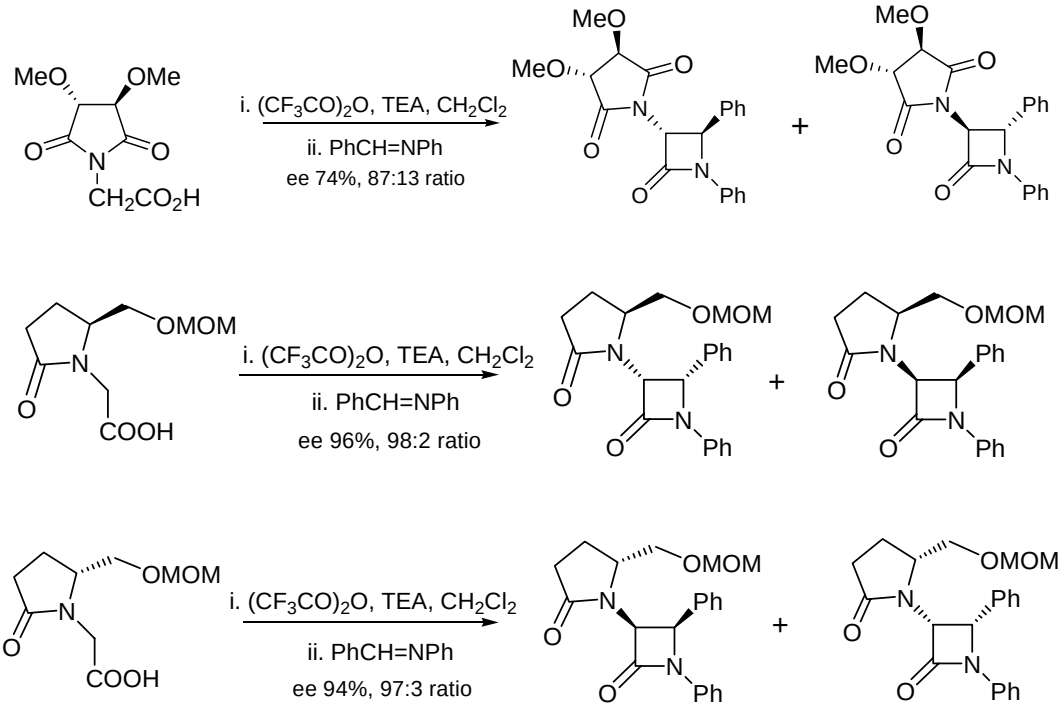
Recently, phenanthridine has been reported to give exclusively *trans* β-lactam with Evans-Sjogren chiral ketene[26] (Scheme 1.15).

Scheme 1.15



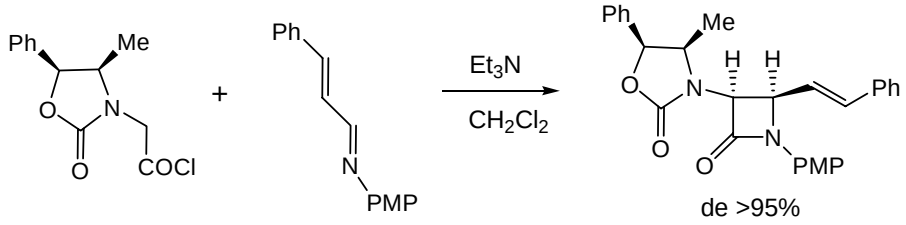
Ikota, in a series of papers, has reported a highly stereoselective β-lactam formation by asymmetric cyclo-condensation employing chiral heterocycles derived from L-(+)-tartaric acid, (*S*)-glutamic acid and (*S*)-serine as ketene precursors. Ikota used these acids in the presence of trifluoroacetic anhydride and a base to achieve high levels of diastereoselectivity[27a-b] (Scheme 1.16).

Scheme 1.16



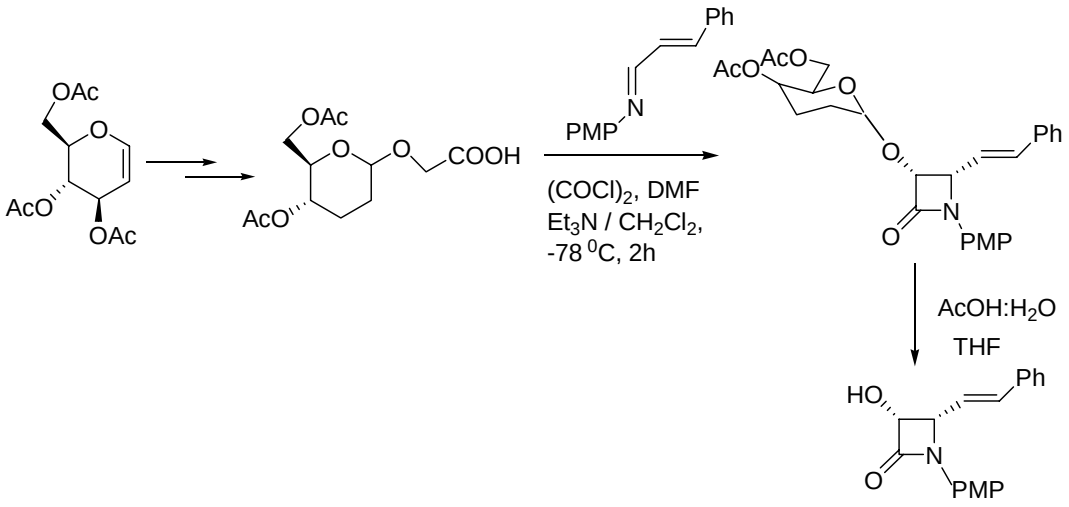
Cooper et al. used a norephedrine derived oxazolidinone derivative as the chiral ketene and achieved >95% diastereoselectivity in the β-lactam formation[28] (Scheme 1.17).

Scheme 1.17



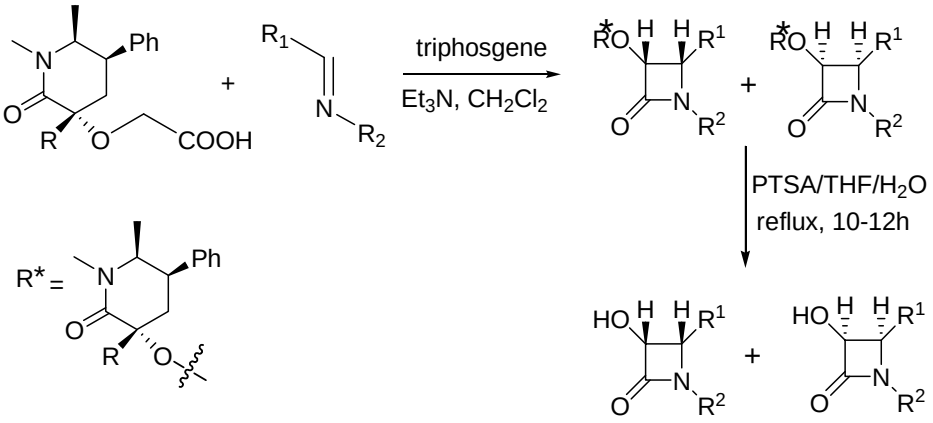
Borer et al. have employed tri-*O*-acetyl-D-glucal derived chiral acid as ketene precursor for diastereoselective synthesis of β-lactams and obtained a diastereoselectivity of 70:30 in this reaction. The sugar moiety was deprotected upon treatment with acetic acid/water to generate 3-hydroxy-β-lactam, which may be used in the synthesis of taxol side chain.[27c]

Scheme 1.18



Shinkre et al. have reported the ephedrine derived chiral acid for the asymmetric Staudinger reaction with various imines in the presence of triphosgene as an acid activator to afford a diastereomeric mixture of *cis* β-lactams in good yields. The chiral auxiliary, ephedrine, was removed under acidic hydrolysis and furnished both the enantiomers of 3-hydroxy-4-aryl β-lactams. One of these hydroxy β-lactams (β isomer) is an advanced intermediate for the synthesis of taxol side chain[27d] (Scheme 1.19).

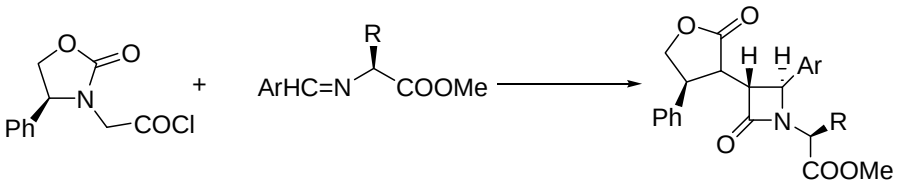
Scheme 1.19



Double Stereodifferentiation:

The concept of double asymmetric induction has been applied to Staudinger reaction with variable success. High levels of asymmetric induction have been achieved in Staudinger reaction between the Evans-Sjogrens ketene and imines derived from (*R*) and (*S*)-α-amino acid esters[29] (Scheme 1.20).

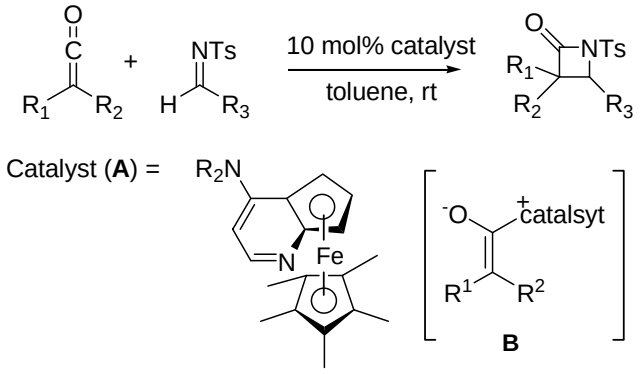
Scheme 1.20



Catalytic Asymmetric Staudinger reaction:

Recently Hodous and Fu[30] have reported a highly enantioselective synthesis of β-lactams catalyzed by a chiral catalyst (**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 1.21). The reaction was proposed to proceed through the intermediate (**B**), similar to what Lectka[31] has observed.

Scheme 1.21



Mechanism of Staudinger reaction:

Although the ketene-imine cycloaddition (Staudinger reaction) has been known for over nine decades, the mechanism and the stereochemical course of this reaction are still obscure. Recent efforts in this aspect have resulted in a series of papers by various groups.[32] Based on these results, a two-step zwitterionic mechanism has been preferred to a concerted [2+2] cycloaddition.

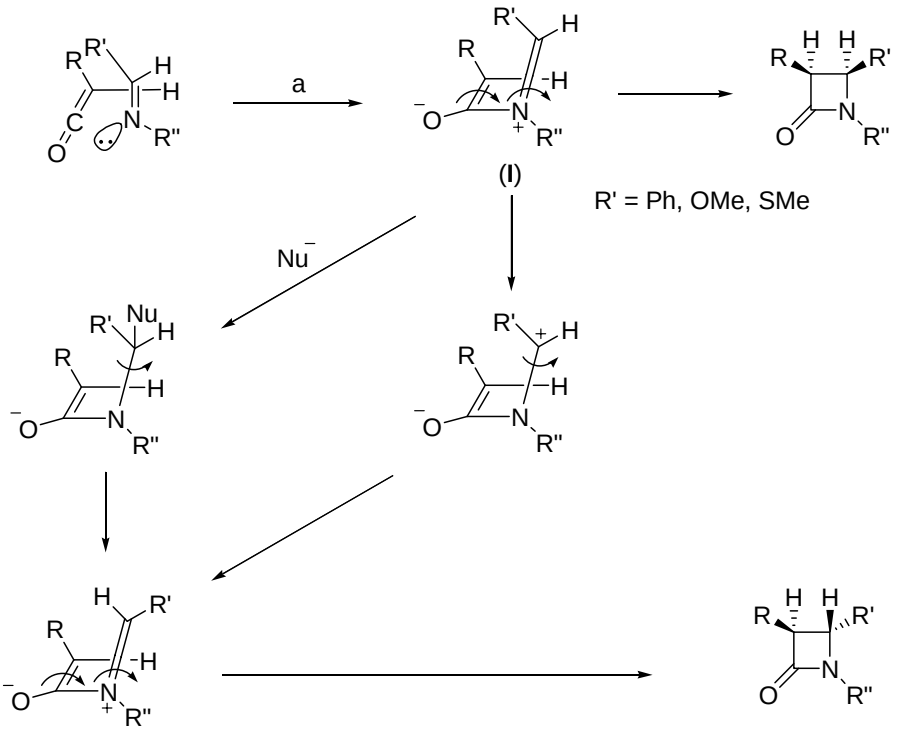
The involvement of a zwitterionic intermediate has been proved by various spectroscopic methods and zwitterion trapping experiments.[33] That the zwitterion intermediate was indeed formed from a ketene precursor was proved by results from Lynch's group[34] wherein, treatment of the acid chloride with diisopropylamine in an FT-IR cell displayed a strong band at 2120, which was assigned to the ketene.

It has been postulated that the LUMO of the ketene carbonyl is attacked by the HOMO of the imine in an orthogonal approach, that is, in a plane perpendicular to the

substituents of the ketene, resulting in the formation of the zwitterionic intermediate (I).[35] This hypothesis was supported by semi empirical molecular orbital calculations (MNDO) of a transition intermediate in the reaction between methyl ketene and *N*-methyl-2-methylimine.[28]

It is further believed that the attack of the imine occurs from the less hindered side of the ketene while forming the zwitterionic intermediate (I). Rotation of the imine into the plane of the ketene followed by a *con*-rotatory ring closure produces the thermodynamically less stable β-lactam in which the smaller group on the imine (hydrogen) and the smaller substituent on the ketene are *cis* to each other. The *con*-rotatory ring closure can occur only in a clockwise direction since ring closure in other direction (anticlockwise) would necessitate the imine and ketene substituent to pass through each other. These stereochemical explanations are in good agreement with the results obtained from many acyclic imines and ketenes.

Scheme 1.22

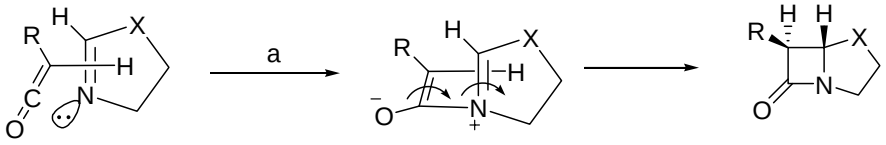


When the substituent R′ on the sp^2 carbon can stabilize a positive charge (e.g. Ph, OMe, or SMe), the zwitterionic intermediate may undergo isomerization from the more stable imine geometry to the *syn* imine geometry, before cyclization, producing the thermodynamically more stable *trans* β-lactam. This is the case with imidates,

thioimidates and in some cases with benzaldimines. If the amino substituent R" is large, this isomerization can be suppressed.

Isomerization of the zwitterionic intermediate can also occur by addition of nucleophiles to the zwitterion followed by rotation and elimination. The relative rate of each of these processes determines the stereochemical outcome of the reaction. In the case of cyclic imines one should always get a *trans* β-lactam since the imine substituents are held in *syn* geometry and the same has been observed in most cases (Scheme 1.23).

Scheme 1.23



Asymmetric Induction:

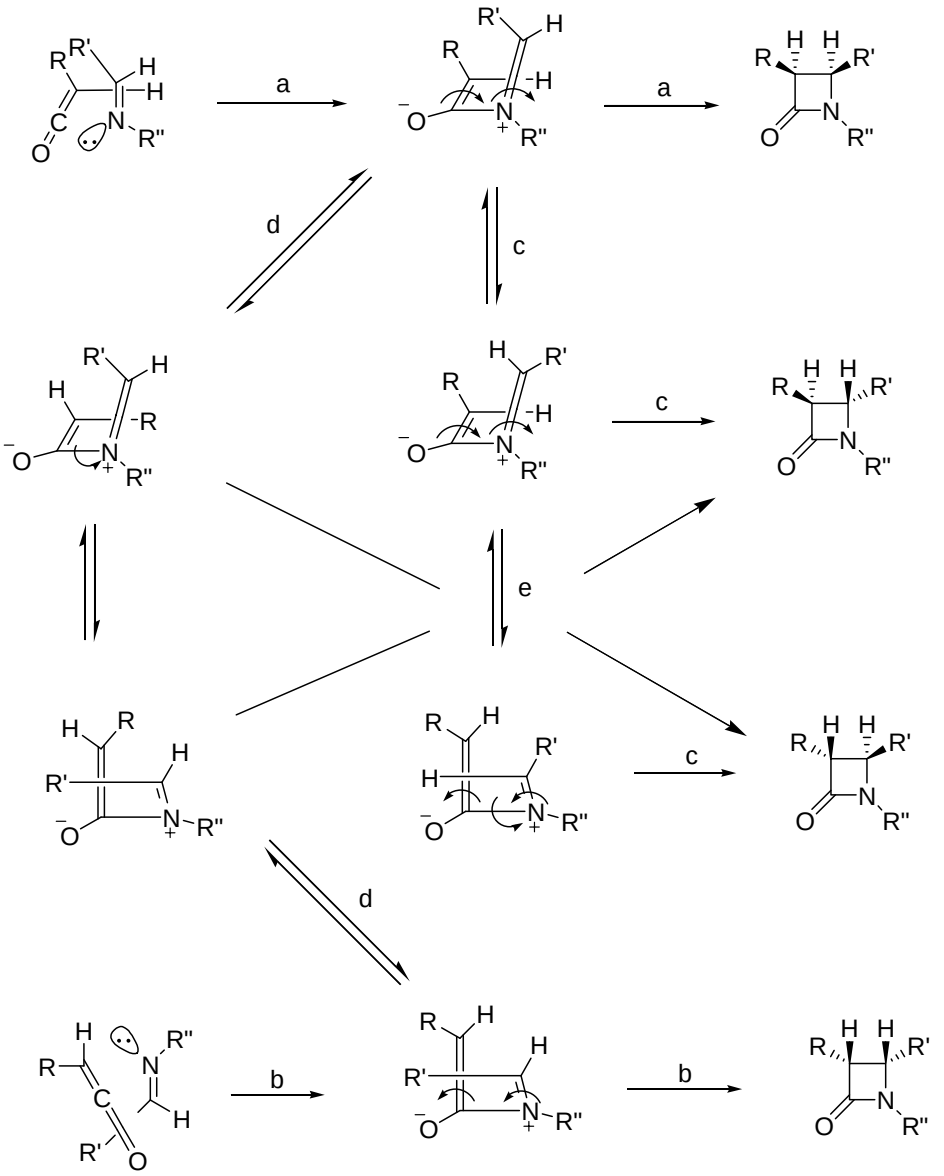
Asymmetry can be induced in ketene-imine cycloaddition by controlling the orientation of the imine with respect to the plane of the ketene; attack of the imine over the top face of the ketene followed by *con*-rotatory ring closure will produce one enantiomer, while the attack of the imine from the bottom face followed by *con*-rotatory ring closure will produce the other enantiomer. Since two new chiral centers are formed during β-lactam ring formation, four isomers are possible, i.e. a pair each of *cis* and *trans* isomers. Depending upon the reaction conditions and the different paths followed, the formation of a single or all four isomers are possible. The chart below explains the formation of all four isomers depending on the stereochemical course of the reaction.

The attack of the imine from the less hindered side of the ketene can occur with two different perpendicular orientations; as in *path a* or as in *path b*. For reactions exhibiting high diastereoselectivity in *cis* manifold, differentiation between these two must be high and cyclization of the zwitterions must be faster than any of the possible isomerizations. If reaction conditions or structural features in the ketene or imine slow down the cyclization step or accelerate the isomerization or both, stereoselectivity may be drastically altered, even if the initial selectivity between *path a* and *b* is high.

The formation of the thermodynamically more stable *trans* β-lactam from a *trans* imine can only result from isomerization of either the iminium portion (*path c*) or the enolate portion *(path d)* of the zwitterions prior to cyclization. Isomerization should be

promoted by substituents that stabilize positive charge on the iminium carbon and / or by substituents that stabilize the enolate, slowing cyclization relative to isomerization. If the cyclization of the initially formed zwitterions is very slow, all four diastereomeric β-lactams are then accessible from any single zwitterion by isomerization followed by rotation about the C-N single bond (*path e*).

Scheme 1.24



Applications of Azetidin-2-ones:

Besides the significance as bioactive agents, the importance of β-lactams as synthetic intermediates has been widely recognized in organic synthesis because ring cleavage of any of the four single bonds of the β-lactam system is enhanced by ring strain. Selective bond cleavage of the 2-azetidinone ring coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks.[36] Access to diverse structural types of natural or synthetic compounds lacking the β-lactam ring have been reported by cleavage of the azetidin-2-one ring through any of the four possibilities.

Selective bond cleavage of the azetidin-2-one nucleus can occur through

1. N1-C2 Bond Breakage
2. C2-C3 Bond Breakage
3. C3-C4 Bond Breakage
4. C4-N1 Bond Breakage

Following figure 6 shows the applications of azetidin-2-ones through various bond cleavage.

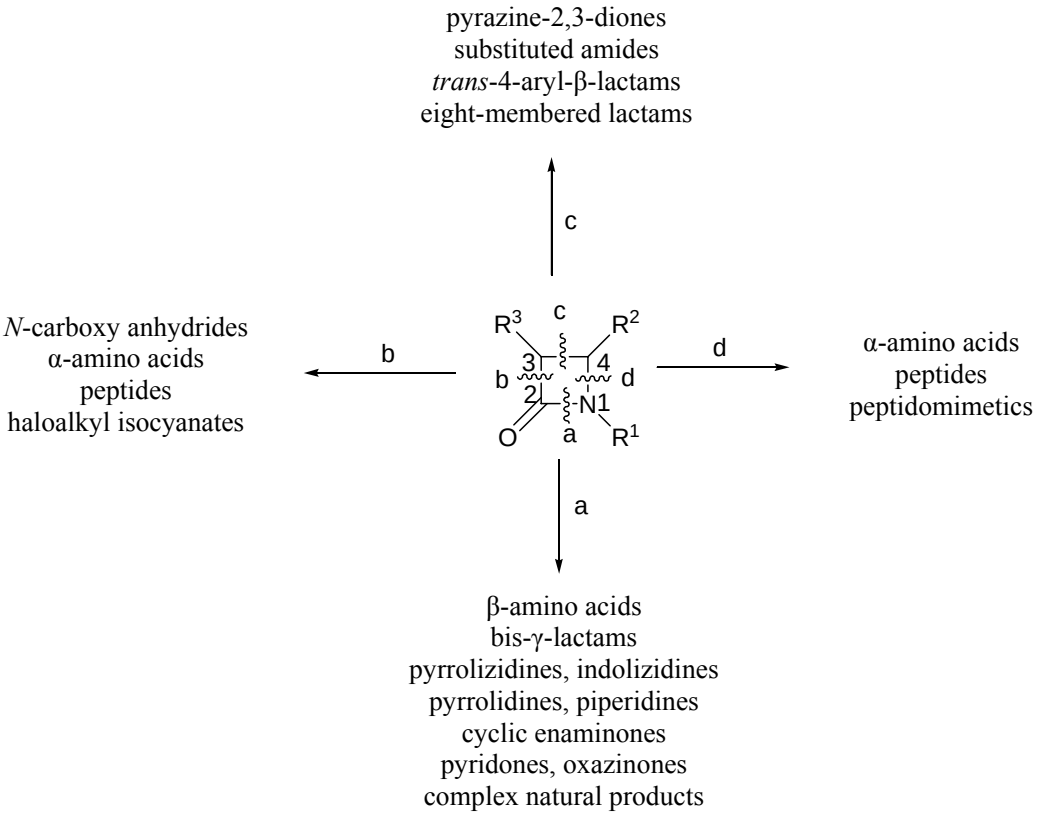


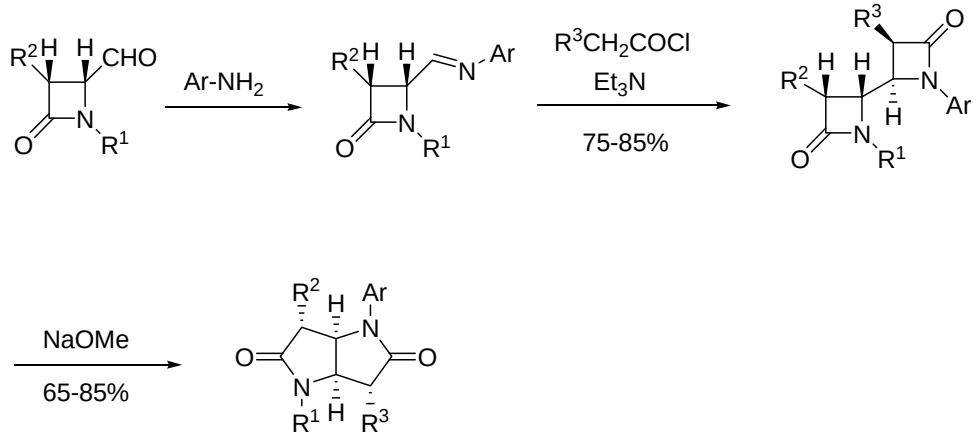
Figure 6

N1-C2 Bond Breakage:

From the pioneer report of Bose et al.[37] cleavage of the amide bond has been the subject of many investigations. Azetidin-2-one ring cleavage takes place usually at the N1-C2 bond by nucleophilic reagents including water. Since, β-lactams may be considered as cyclized forms of β-amino acids in which the amino and the carboxyl groups are simultaneously protected, the more obvious application is the synthesis of β-amino acids.[38]

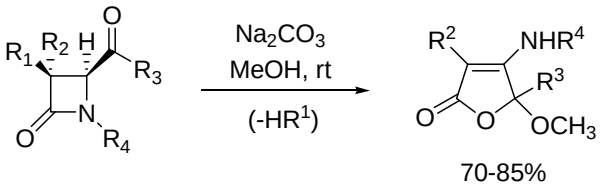
4-Formyl β-lactam on sequential imine formation and ketene cycloaddition gives differently substituted *cis, cis*-C4, C4'-bis-β-lactams as a single diastereomer. Bis-β-lactams smoothly rearranged to fused *trans, trans*-bis-γ-lactams by treatment with NaOMe/MeOH in a totally stereoselective process[39] (Scheme 1.25). These type of bis-γ-lactams have interesting biological activities.

Scheme 1.25



4-Formyl β-lactams having at least one good leaving group on C3 gives enamine lactone[40] in 70-85% yield using Na_2CO_3 in MeOH (Scheme 1.26).

Scheme 1.26

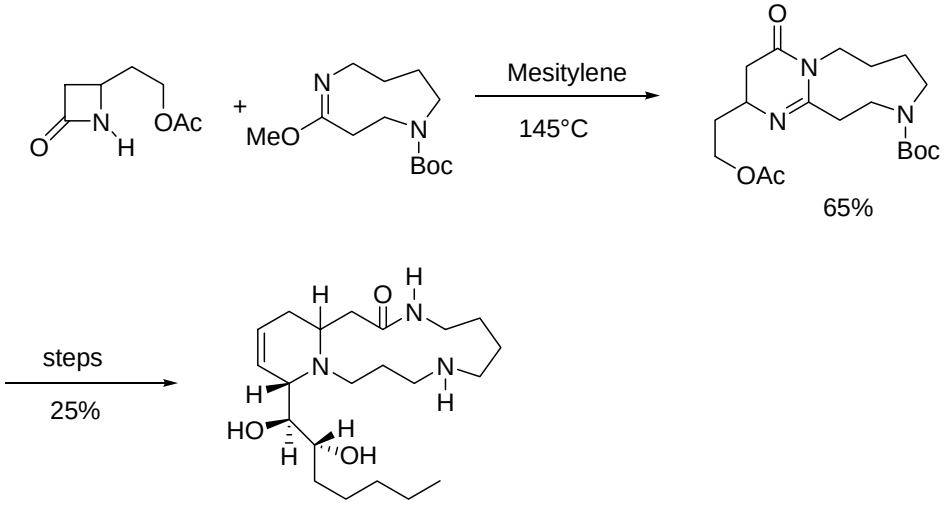


R_1 = Br, Cl, BnO, PhO.

Thomas and co-workers,[41] reported advanced macrocyclic precursor of the antitumor antibiotic lankacidin C. Ring opening of the azetidin-2-one was carried out by

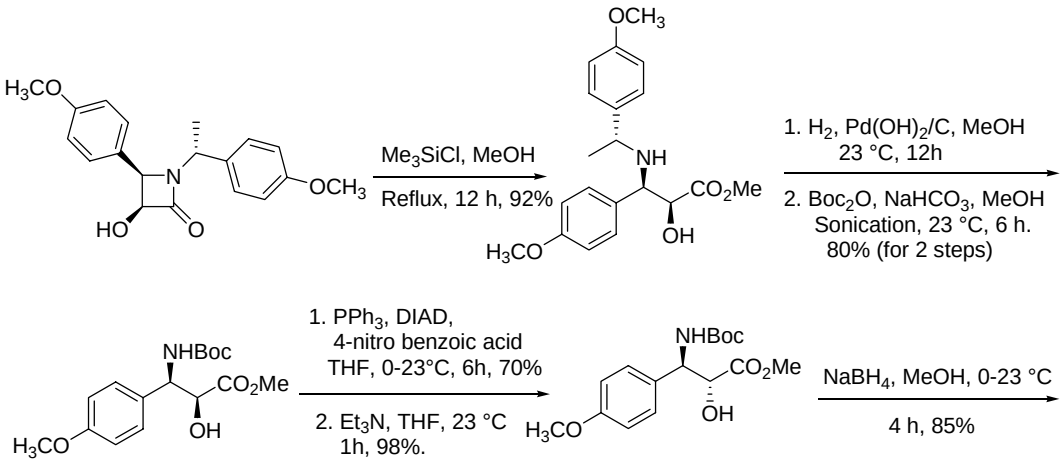
using potassium cyanide in methanolic *N*,*N*-dimethylformamide to give the protected amino ester (Scheme 1.27).

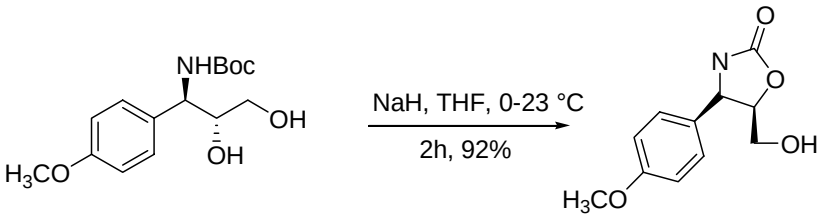
Scheme 1.27



Recently Turos et al. [42] have reported the synthesis of (-)-Cytoxazone and its stereoisomers through N1-C2 bond breakage. Methanolysis of 3-hydroxy β-lactam with Me_3SiCl in refluxing MeOH gave *syn*-amino alcohol, which on hydrogenation with Pearlman's catalyst chemoselectively cleave the *R*-methyl-(4-methoxybenzyl) moiety. The resultant amine was protected with Boc_2O. The free hydroxyl group of Boc protected ester inverted under Mitsunobu conditions to afford the *anti*-amino alcohol. Borohydride reduction and base promoted cyclization of the diol gave the (-)-cytoxazone (Scheme 1.28).

Scheme 1.28





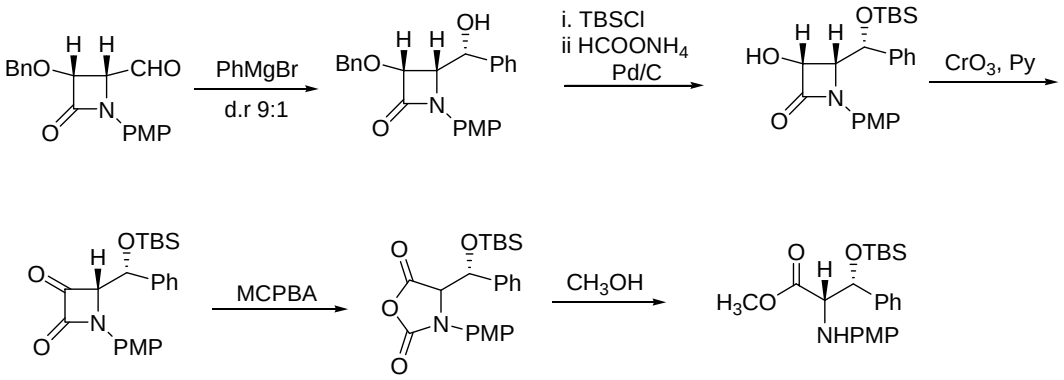
(-)-cytoxazone

C2-C3 Bond Breakage

The first report of this type of cleavage was described to occur in *N*-haloazetidin-2-ones to form haloalkylisocyanates.[43] However, despite some scarce reports,[44] little was known about the application of the C2-C3 bond breakage until Palomo and colleagues elegantly entered into this field, utilizing an azetidine-2,3-dione approach in the synthesis of α-amino acids.[45]

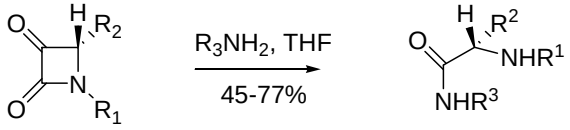
Baeyer-Villiger oxidation of azetidin-2,3-diones gave *N*-carboxy anhydrides (NCA), which after coupling with amines or alcohols produced α-amino acid derivatives in 70-80% yield (Scheme 1.29).

Scheme 1.29



A different strategy to acess α-amino acid derivatives from azetidine-2,3-diones involving a C2-C3 bond cleavage was achieved by Alcaide B. et al.[46] The coupling of azetidin-2,3-diones with a variety of primary amines forms in a one-step α-amino acids derivatives in 45-77% yield (Scheme 1.30).

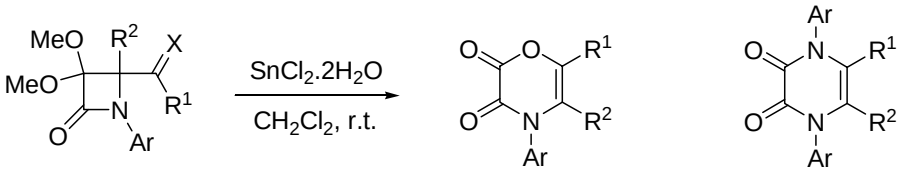
Scheme 1.30



C3-C4 Bond Breakage

3,3-Diphenyl-4-amino β-lactams were reported to undergo C3-C4 bond cleavage through carbanion intermediates in the presence of moisture to give substituted amides.[47] The first example is the tandem C3–C4 bond breakage-carbocationic rearrangement of 4-acyl- or 4-imino-3,3-dimethoxy-2-azetidinones **a** and **b** promoted by tin (II) chloride to give dihydro-1,4-oxazines or pyrazine-2,3-diones derivatives **c** and **d**.[48] The above rearrangements also take place in the presence of protic acids (H_2SO_4 or HCl). However, yields were erratic and mixtures of the different products were usually obtained.

Scheme 1.31

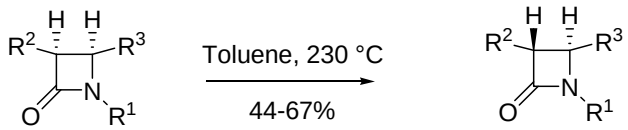


a X = O
b X = NAr

c **d**

cis-4-Aryl-β-lactam ring can be converted to *trans* β-lactam involving a homolytic cleavage of the C3-C4 bond[49] (Scheme 1.32).

Scheme 1.32

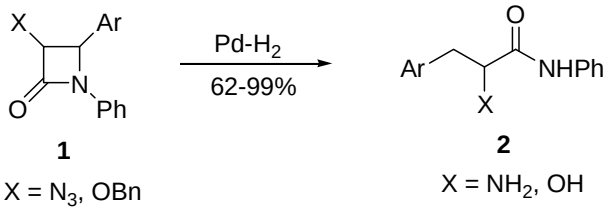


It is believed that a thermally C3-C4 bond cleavage occurs, followed by cyclization, to get thermochemically more stable *trans* isomer.

C4-N1 Bond Breakage

Ojima and co-workers observed a facile C4-N1 bond cleavage in azetidin-2-ones by palladium-catalyzed hydrogenolysis when an aryl substituents is attached to the C4 position.[50] The ring strain of the β-lactam greatly accelerates the cleavage of the C4-N1 bond rather than the more usual N1-C2 bond breakage, to give 2-amino or 2-hydroxy amides (Scheme 1.33).

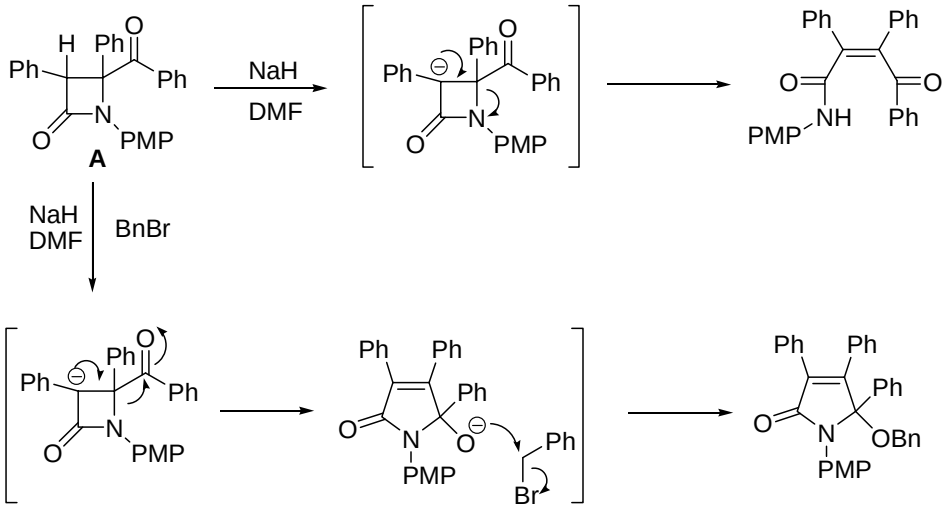
Scheme 1.33



This finding led Ojima's group to develop the β-lactam synthon method for the synthesis of α-amino acids, α-hydroxy acids, dipeptides, dipeptide isosteres, oligopeptides, peptidomimetics, taxoids, polyamines and polyaminoalcohols.[51]

β-Lactams of type **A** on treatment with sodium hydride or sodium hydride/alkyl halide afforded α,β-unsaturated amides or α,β-unsaturated γ-lactams respectively[52] (Scheme 1.34). It can be explained *via* a C4-N1 bond breakage in the intermediate carbanion.

Scheme 1.34



Cleavage of Two Bonds of the Azetidin-2-one Ring:

The sequential or simultaneous fragmentation of two bonds of the azetidin-2-one ring has been seldom reported. Cleavage of monocyclic β-lactams under electron-impact mass spectrometry occurs by two different fragmentation patterns, leading to ketene and /or imine ions (A in Figure 7) or to olefin and/or isocyanate ions (B in Figure 7). Also, it is known that photolysis[53] promotes cleavage of the azetidin-2-one ring through an A-type fragmentation while pyrolysis[54] promotes the B-type fragmentation.

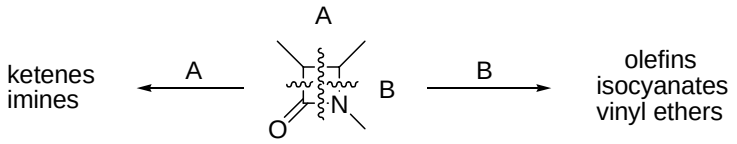
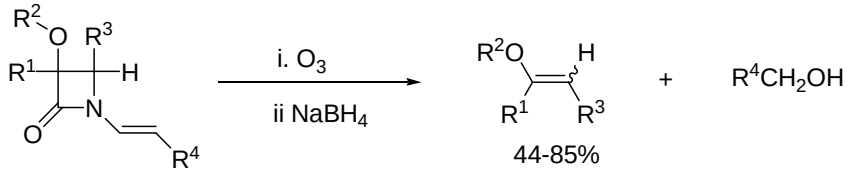


Figure 7

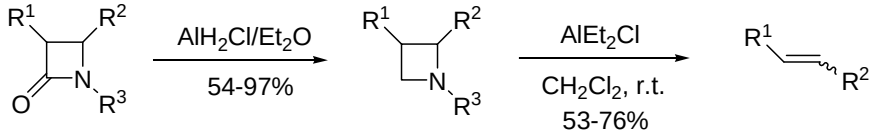
Alcaide et al.[55] in 1990 reported a unusual fragmentation process of *N*-arylidene – or *N*-alkylidene amino-β-lactams. Reaction of *N*-(arylidene (or alkylidene)amino) azetidin-2-ones on ozonolysis followed by reductive work up with sodium borohydride reductive work-up afforded vinyl ethers (Scheme 1.35).

Scheme 1.35



Azetidin-2-ones with a 4-methoxyphenyl, a 2-furyl or a styryl moiety at C4 position, and a benzyl or allyl group is the substituents at the nitrogen, are converted into alkenes *via* sequential treatment with monochloroalane (to give the corresponding azetidin) and diethylaluminium chloride through a fragmentation process (Scheme 1.36).[56]

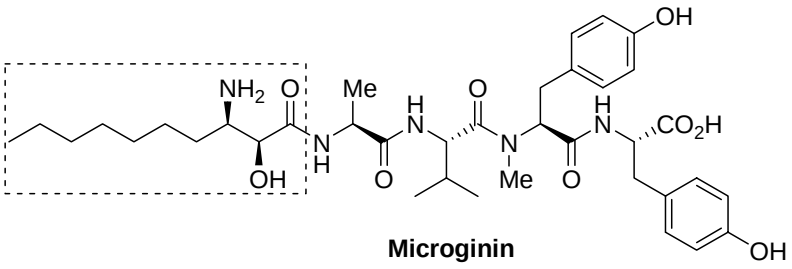
Scheme 1.36



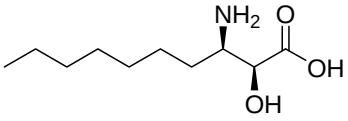
1.2 Background for the present work:

Apart from the antibacterial agents,[57-59] azetidin-2-ones are increasingly used as synthons for the synthesis of variety of pharmaceutically useful products.[60] This is mainly because of the strain energy associated with the four membered azetidinone ring, that is responsible for selective bond cleavage, giving a variety of transformation products. Moreover, there are many methods available to prepare them in reasonable quantities required for synthetic purpose. One such synthon, 4-formylazetidin-2-one, has wide applications as a building block[61, 62] for the synthesis of monobactams, isocephams, carbapenems and several other non-β-lactam compounds like α-hydroxy aspartate and hydroxybutanoic acids.

The objective of the present work is to synthesize (2*S*,3*R*)-3-amino-2-hydroxy decanoic acid using substituted 4-formyl azetidin-2-one as a building block. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (**1.01b**) is an unusual novel amino acid, which is the *N*-terminal component of the recently isolated angiotensin-converting enzyme inhibitor microginin (**2**).[64]



Microginin



(2*S*, 3*R*)-3-Amino-2-hydroxydecanoic acid (AHDA) (**1.01b**)

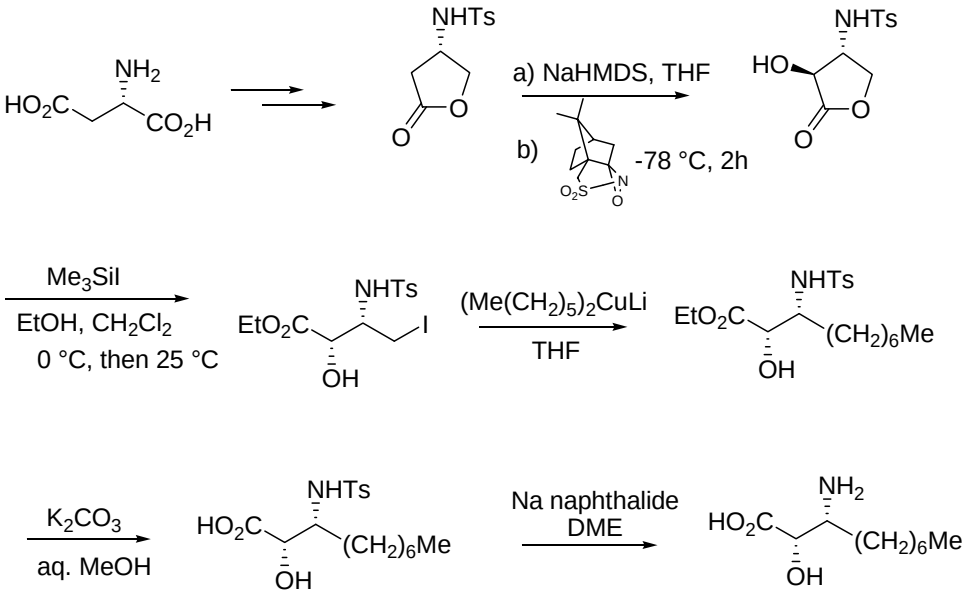
Figure 8

Microginin is a small linear peptide isolated from the blue-green alga *Microcystis aeruginosa* and its structure was established on the basis of degradation studies, spectral data and total synthesis.[63,64] It was shown that a linear α-hydroxy-β-aminodecanoic acid is at the *N*-terminal of the peptide chain. Subsequently it was also found that AHDA is common to other linear peptides isolated from the same species.[63b,c]

There are to date eight syntheses reported for (2*S*,3*R*)-AHDA. These synthesis involves three key strategies.[65] The first strategy involves use of a "chiral pool" starting material.[65a,64b,65g] The second strategy employed chiral *vic*-amino alcohols or their 2-oxazolidinone derivatives, which were prepared *via* the asymmetric functionalization of appropriately constituted alkenes.[64a,b,65c-d] The third strategy involved the Lewis acid-mediated nucleophilic addition of ketene acetals to chiral imines.[65e]

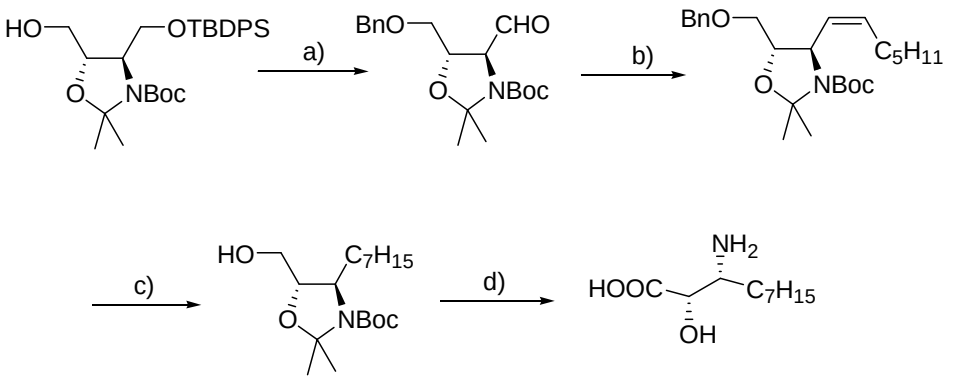
Jefford et al.[65a] have used L-aspartic acid for the syntheis of (3*S*)-3-(*N*-tosylamino) butano-4-lactone. In this synthesis α-hydroxylation is achieved by using (+)-camphor sulfonyl oxaziridine. Futher transformation by a multistep sequence gave (2*S*,3*R*)-AHDA (Scheme 1.37). By using similar synthetic sequence (2*R*,3*S*)-AHDA obtained using D-aspartic acid

Scheme 1.37



D-Isoascorbic acid derived chiral synthon syn-2*R*-amino-1,3,4-triol derivative is used by Merrer et al.[64b] The side chain was introduced by Wittig reaction to get (2*S*,3*R*)-AHDA (Scheme 1.38).

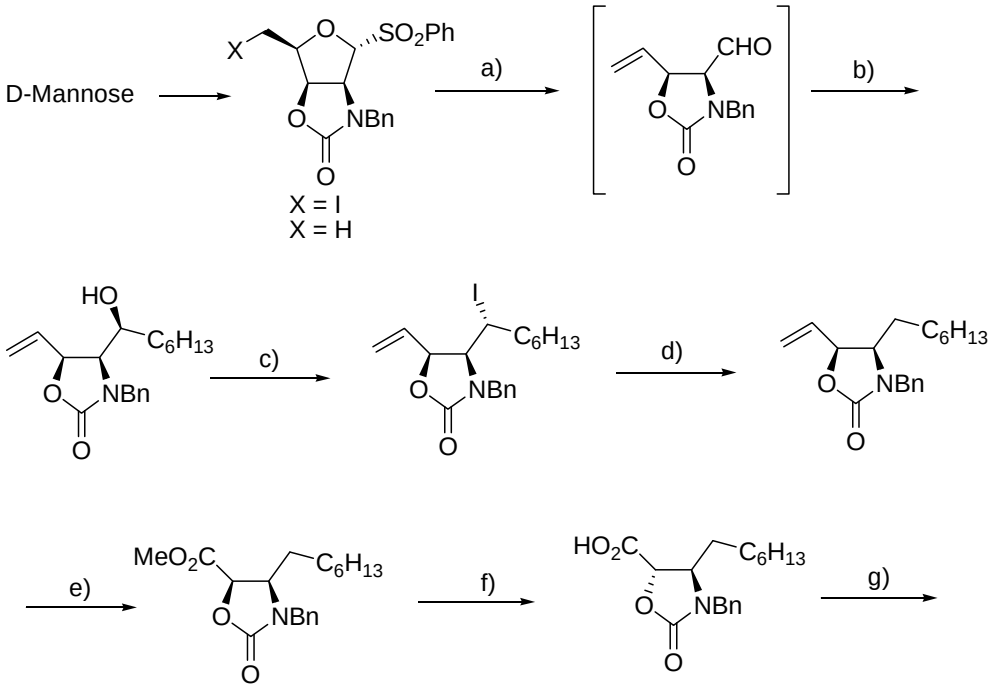
Scheme 1.38

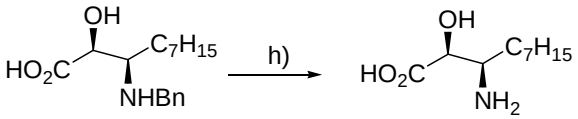


Reagents and conditions: a) i-$PhCH_2Cl$, Ag_2O, DMF, 24 h, 20 °C, 87%, ii-TBAF, THF, 20 °C, 89%, iii-$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. b) $C_6H_{13}PPh_3Br$, nBuLi, THF, -78 °C, 64%, c) H_2, Pd/C (10%), EtOH, 94%. d) i-$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii-$NaClO_2$, NH_2SO_3H, dioxane, H_2O, 0 °C, iii-TFA, H_2O, 20 °C, then Dowex.

Recently a multistep synthesis is reported by Andrew et al.[65g] where they used D-mannose derived bifunctionalized oxazolidinone as a chiral starting material. Zn-Hg Couple-mediated reductive elimination of the iodo phenyl sulfone provided aldehyde which is converted to *syn* alcohol by treatment with organocerium reagent and further synthetic transformations gave (2*S*,3*R*)-AHDA (Scheme 1.39).

Scheme 1.39

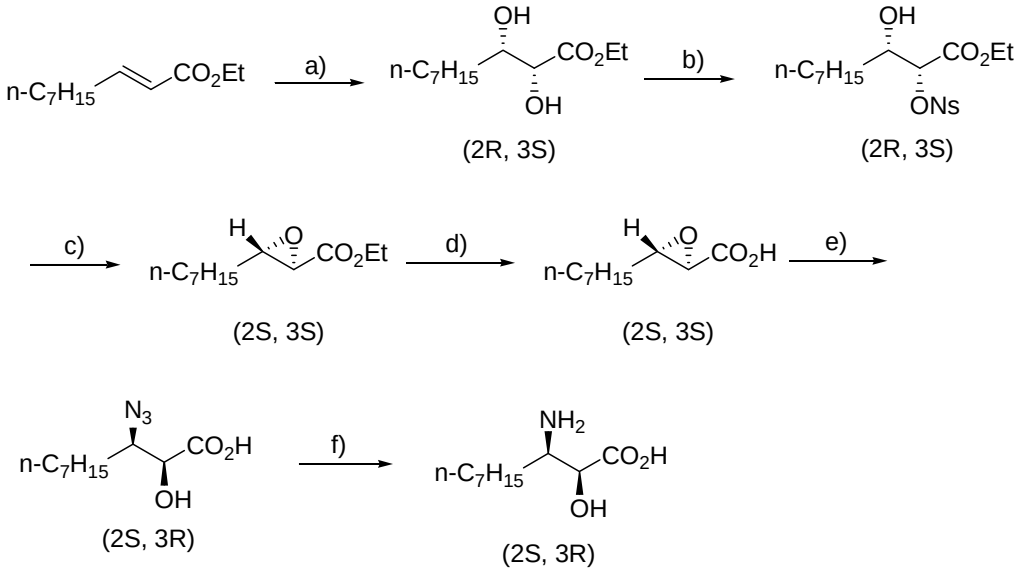




Reagents and conditions: a) Zn/Hg, glacial AcOH. b) $C_6H_{13}CeCl_2$, -78 °C, 78%. c) Ph_3P, I_2, imidazole, toluene, 120 °C, 64%. d) Bu_3SnH, cat. AIBN, toluene, 110 °C, 85%. e) O_3, 2.5 M aq. NaOH, MeOH, -78 °C, 69%. f) NaOMe (4 mol equiv), MeOH; then 1M aq HCl, 99%. g) 2 M aq. KOH, 95% EtOH, reflux, quant. h) 20% $Pd(OH)_2$, H_2, MeOH, 94%.

Shioiri et al.[64a] reported the synthesis of (2*S*,3*R*)-AHDA by using asymmetric dihydroxylation strategy (Scheme 1.40).

Scheme 1.40

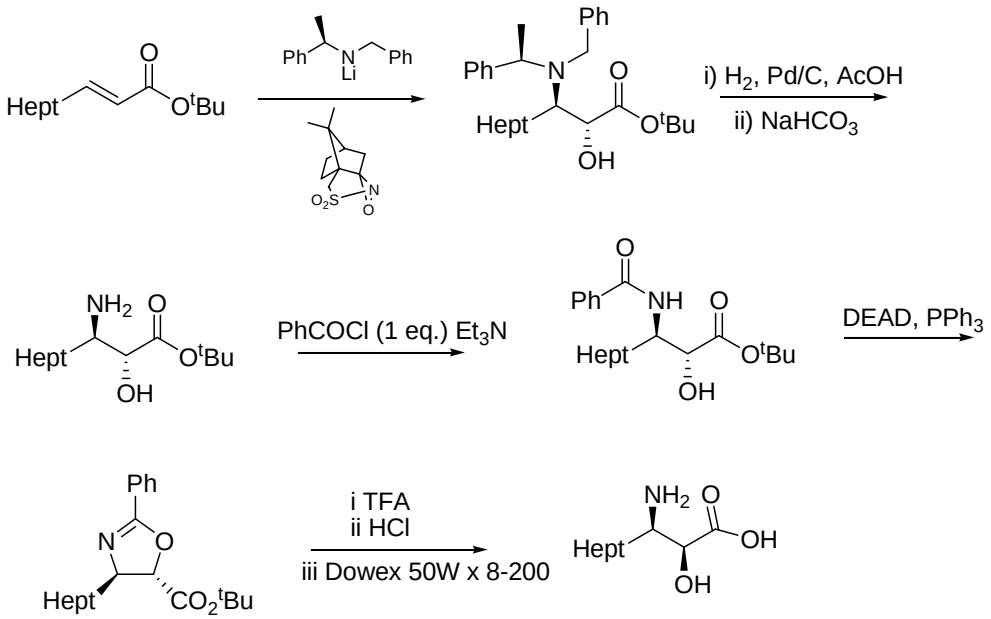


Reagents and Conditions: a) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH-H_2O, b) i) 25%HBr-AcOH, ii) $Ti(OiPr)_4$, EtOH, c) K_2CO_3, EtOH, d) 1N NaOH, e) LiN_3, $Ti(OiPr)_4$, f) 5% Pd-C, $HCOONH_4$, MeOH.

Ethyl (*E*)-2-decenoate on asymmetric dihydroxylation using AD-mix-α gave diol ester, which was further converted to its epoxide. The regioselective opening of epoxide with lithium azide followed by reduction gave (2*S*,3*R*)-3-amino-2-hydroxy decanoic acid. Similar synthetic protocol has been used for the synthesis of (2*R*,3*S*)-3-amino-2-hydroxy decanoic acid using AD-mix-β.

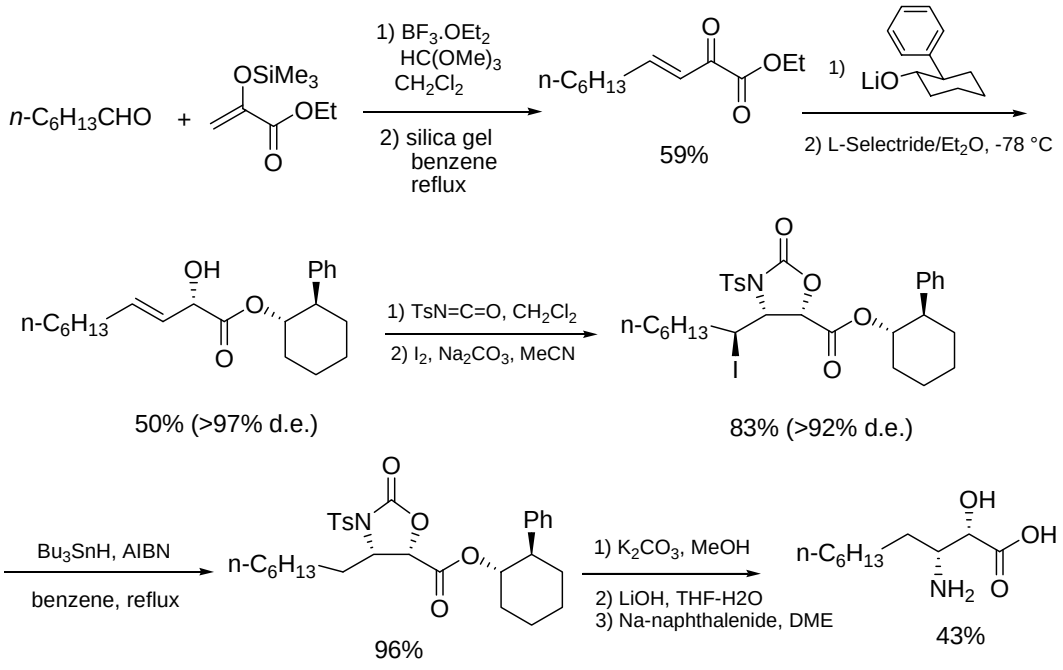
In an another approach Davies et al.[64b] have employed conjugate addition of lithium (*R*)-(α-methyl benzyl) benzylamide to α, β-unsaturated ester followed by *in situ* hydroxylation with (+)-(camphorsulfonyl) oxaziridine for the hydrolysis of β-amino ester. Further transformation of this ester to the desired product is achieved *via* inversion of configuration using Mitsunobu reaction (Scheme 1.41).

Scheme 1.41



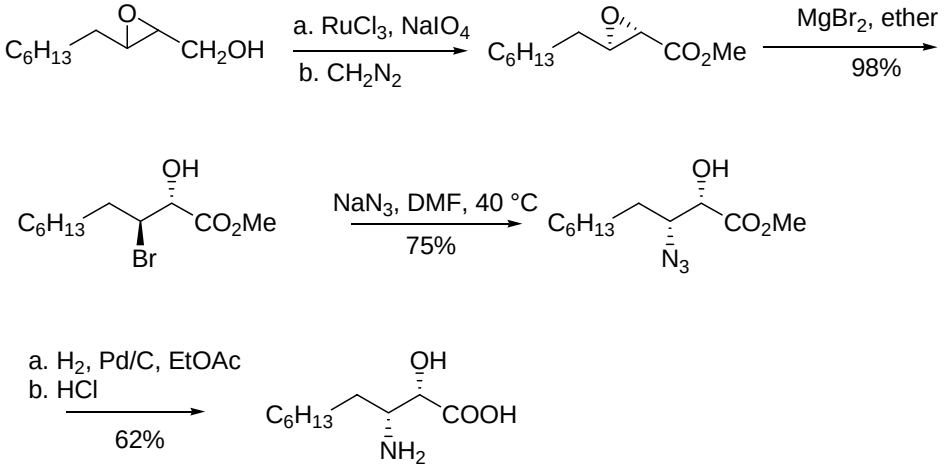
Sugimura et al.[65c] have used α,β-unsaturated ester for the synthesis of (2*S*,3R)-AHDA. Chrial auxilary (+)-*trans*-2-phenylcyclohexyl introduced *via trans* esterification followed by stereoselective reduction of the keto group using L-selectride gave hydroxy esters. Amino function is introduced using *N*-tosyl isocyanate and iodine. Removal of iodo group and chiral auxiliary provided (2*S*,3*R*)-AHDA (Scheme 1.42).

Scheme 1.42



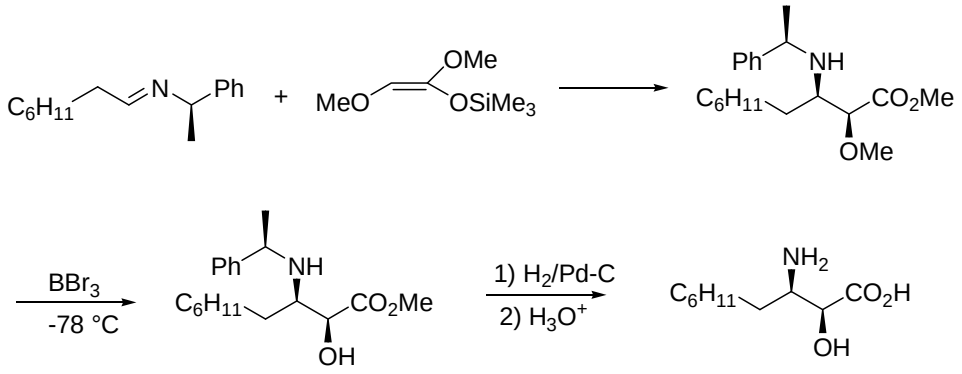
Righi et al.[65d] have reported the synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid by using chrial epoxy alcohol as a starting material. The alcohol is oxidized to ester and further synthetic transformations using regioselective epoxide opening provided desired AHDA (Scheme 1.43).

Scheme 1.43



Lee et al.[65f] have reported another approach wherein trimethylsilyl ketene acetals is added to appropriately substituted chiral imine derived from α-methyl benzyl amine. Further removal of α-methyl benzyl and *O*-methyl group provided the desired product (Scheme 1.44).

Scheme 1.44



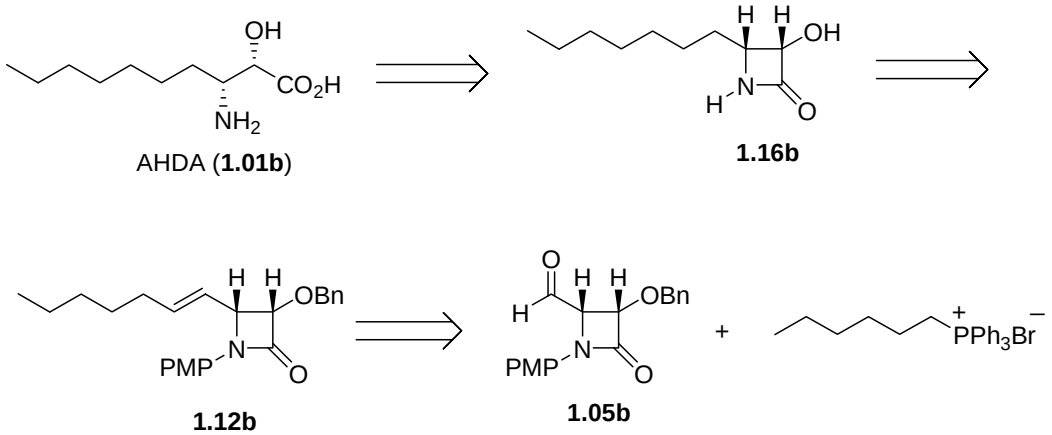
1.3 Present Work:

In continuation of our efforts towards the synthesis of substituted β-lactams *via* the Staudinger reaction[66] and their utility as synthons[67, 68, 69] for the synthesis of various biologically important compounds, we were interested in the synthesis of 3-amino-2-hydroxydecanoic acid (AHDA) from the 4-formyl-β-lactam synthon.

As discussed in the background for the present work there are various approaches for the synthesis of AHDA. However, no approach was there which utilizes β-lactam as a building block. Since β-amino acids are easily accessible by hydrolysis of the azetidin-2-ones,[70,71] we planned our synthesis from substituted 4-formylazetidin-2-one. Our synthesis is based on the application of well-defined stereochemistry at both the stereocentres of *cis* 3-benzyloxy-4-formylazetidin-2-one ring, which is required for the synthesis of natural AHDA.

The retrosynthetic strategy for the synthesis of (2*S*,3*R*)-3-amino 2-hydroxy decanoic acid is shown in (Scheme 1.45). We envisioned that it can be synthesized from 3-hydroxy β-lactam **1.16b**, which in turn can be obtained from 3-benzyloxy substituted β-lactam **1.12b**. 3-Benzyloxy substituted β-lactam **1.12b** can be obtained from (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b**) by Wittig reaction with Wittig salt derived from hexyl bromide.

Scheme 1.45

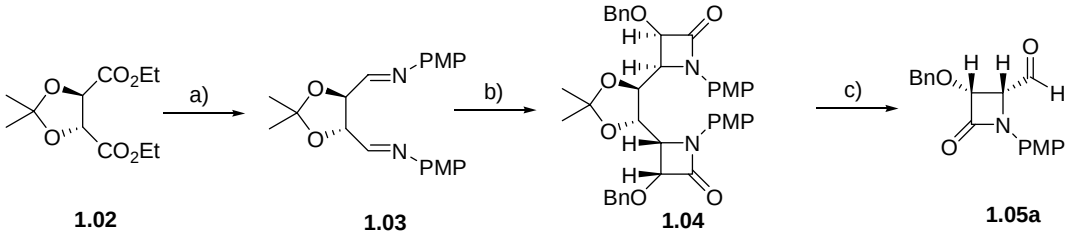


1.4 Results and Discussion:

As enantiomerically pure (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**1.05a**) can be prepared easily from L-(+)-diethyl tartrate using a synthetic method developed in our group,[67a] we planned the synthesis of (2*R*,3*S*)-3-amino-2-hydroxy decanoic acid and study the efficiency of the synthetic protocol. L-(+)-Diethyl tartrate acetonide **1.02** on

reduction with DIBAL-H gave bisaldehyde, which *in situ* converted to bisimine **1.03** by using *p*-anisidine. Bisimine **1.03** on [2+2] cycloaddition reaction with ketene obtained from benzyloxy acetyl chloride gave bis β-lactams **1.04** in good yield**.** Bis β-lactam **1.04** on acetonide cleavage using 2.5 M perchloric acid afforded diol, which was purified by column chromatography to get pure diol in 97% yield. The diol on oxidative cleavage using sodium metaperiodate gave enantiopure 4-formyl β-lactam **1.05** in 99% yield. The C_2-Symmetry of natural tartaric acid has been exploited to achieve the synthesis of 2 moles of *cis*-4-formylazetidin-2-ones **1.05a** in 49% overall yield from 1 mole of L-(+)-diethyl tartrate acetonide (Scheme 1.46).

Scheme 1.46

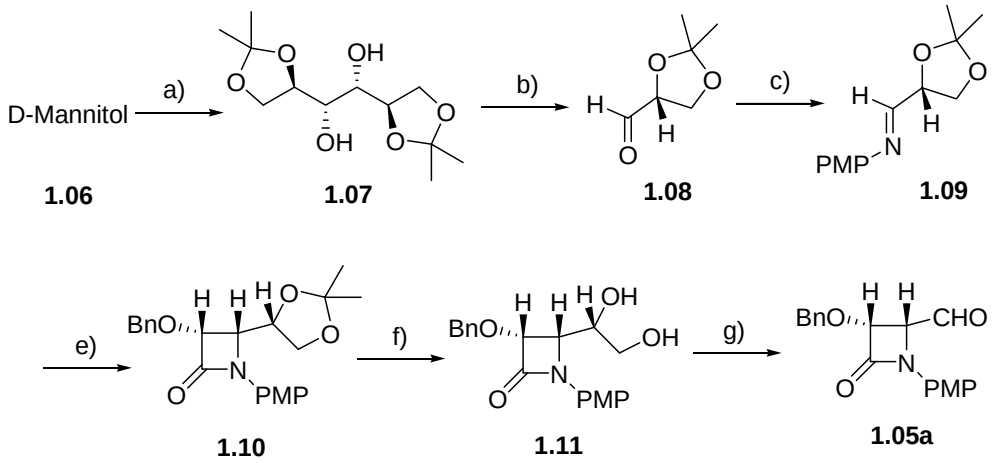


1.02 **1.03** **1.04** **1.05a**

Reagents and conditions: a) DIBAL-H, PMP-NH_2, toluene, -78 °C to r. t., 15 h; b) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, -23 °C to r. t., 14 h; c) i) 2.5 M $HClO_4$, THF, r. t., 4-8 h; ii) $NaIO_4$, acetone/H_2O, r. t., 4-12 h.

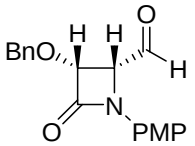
Alternatively enantiopure **1.05a** was prepared from D-mannitol diacetonide (**1.07**) in four steps[72, 67a] (Scheme 1.47). Schiff base **1.09,** obtained from D-glyceraldehyde acetonide, on [2+2] cycloaddition reaction with ketene derived from benzyloxy acetyl chloride provided acetonide protected azetidin-2-one **1.10** in good yield. The acetonide group of the azetidin-2-one **1.10** was cleaved by using PTSA to get diol **1.11** which on oxidative cleavage using sodium metaperiodate gave enantiopure **1.05a** in 50% overall yield.

Scheme 1.47



Reagents and conditions: a) $ZnCl_2$, anhyd. acetone, 24 h, 50%; b) $NaIO_4$, H_2O, 30 min, 0 °C; c) PMP-NH_2, H_2O-EDC, r. t., 2 h; d) Et_3N, CH_2Cl_2, $BnOCH_2COCl$, 0 °C-r. t., 12 h, 50%; e) PTSA, THF-H_2O, reflux 15 h, 90%; f) $NaIO_4$, Acetone/H_2O, CH_2Cl_2, 30 min, 95%.

The structure of **1.05a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.05a** showed a sharp peak at 1753 cm^{-1} for the azetidin-2-one amide carbonyl.

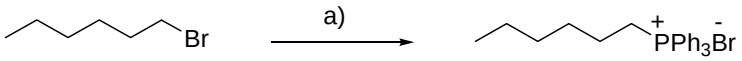


1.05a

The ^{1}H NMR spectrum showed a singlet at 3.79 ppm for –OMe protons of PMP group. The H-4 β-lactam proton appeared as doublet of doublet at 4.51 ppm (J = 5.3 Hz and 3.7 Hz). The H-3 β-lactam proton appeared as a doublet at 5.03 ppm (J = 5.3 Hz). Benzylic methylene protons appeared as two doublets at 4.71 ppm and 4.84 ppm (J = 11.3 Hz). The aromatic protons of the PMP group appeared as doublets at 6.88 ppm and 7.26 ppm (J = 9.1 Hz). The remaining aromatic protons appeared as multiplets between 7.30 to 7.50 ppm. The aldehyde proton appeared as doublet at 9.72 ppm (J = 3.7 Hz).

Wittig reagent is prepared by refluxing *n*-1-bromohexane with one equivalent of triphenylphosphine in toluene for 24 h (Scheme 1.48).

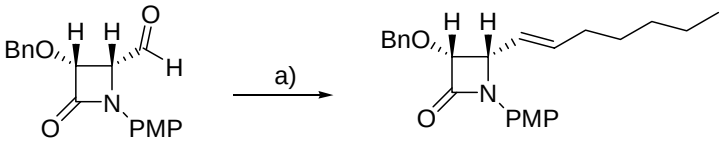
Scheme 1.48



Reagents and conditions: a) PPh_3, toluene reflux, 24 h.

(3*R*,4*R*)-3-Benzyloxy-4-formylazetidin-2-one (**1.05a**) on Wittig reaction with the Wittig reagent derived from *n*-1-bromohexane, using *n*-BuLi at 0 °C gave inseparable mixture of *E*/*Z*-olefin **1.12a** in 75% yield (Scheme 1.49).

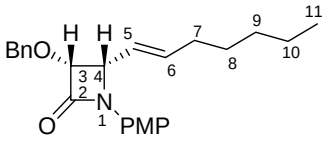
Scheme 1.49



1.05a **1.12a**

Reagents and conditions: a) $CH_3(CH_2)_5PPh_3^+Br^-$, n-BuLi, 0 °C, 6 h, dry THF, 75%.

The structure of **1.12a** was established by IR, ^{1}H NMR spectral data. IR spectrum of **1.12a** showed a strong band at 1747 cm^{-1} for the amide carbonyl of azetidin-2-one.



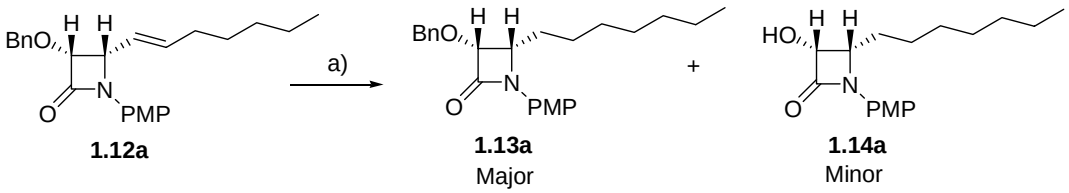
1.12a

The ^{1}H NMR spectrum of **1.12a** showed a multiplet at 0.94 ppm for H-11 methyl protons. A multiplet at 1.21-1.51 ppm integrating for six protons was assigned for H-8, H-9 and H-10 methylene protons. Allylic methylene H-7 protons appeared as multiplet from 2.08-2.40 ppm integrating for two protons. A singlet at 3.79 ppm corresponds to –OMe of PMP group. β-lactam H-3, H-4 protons and benzylic methylene appears as multiplet from 4.54 to 4.95 ppm integrating for four protons. The H-6 vinylic proton appeared as a multiplet at 5.56 to 5.68 ppm. A multiplet at 5.83-6.06 ppm assigned for H-5 vinylic proton. One of the doublet of PMP group appeared at 6.85 ppm (J = 9.1 Hz), remaining seven aromatic protons showed a multiplet from 7.28-7.43 ppm.

The ^{13}C NMR spectra of **1.12a** showed a peak at 163.5 ppm for the amide carbonyl carbon of azetidin-2-one. The quaternary aromatic carbons appeared at 156.4, 138.8, 137.5, 137.0, 131.1 ppm. The remaining aromatic proton seen at 128.4, 128.0, 124.3, 124.0 ppm. The vinylic C-5 and C-6 carbons appeared at 118.7, 118.6, 114.4 ppm. The C-3 carbon of azetidin-2-one assigned at 82.4, 82.2 ppm. Benzylic methylene carbon appeared at 72.7, 72.6 ppm. The C-4 carbon of azetidin-2-one appeared at 60.9 ppm. Methoxy carbon appear at 55.5, 55.4 ppm. Allylic C-7 carbon appeared at 32.4 ppm. Remaining C-8 to C-10 methylene carbons seen at 31.6, 31.2, 29.1, 28.5, 27.9, 22.5 ppm respectively. Methyl carbon appeared at 14.0 ppm. The mass spectrum of **1.25a** gave M+1 peak at m/z 380, also supporting the structure of the compound.

The olefin **1.12a** on catalytic hydrogenation with Pd/C (10%) gave 4-heptanyl-β-lactam **1.13a**, in very good yield (90%). A small amount of debenzylated compound **1.14a** (6%) was also obtained along with **1.13a**, which were separated by flash column chromatography (Scheme 1.50).

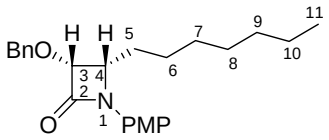
Scheme 1.50



1.12a | **1.13a** Major | **1.14a** Minor

Reagents and conditions: a) H_2, Pd/C (10%), 50 Psi, 6 h, EtOAc.

The structure of **1.13a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.13a** showed a strong band at 1742 cm^{-1} for the amide carbonyl of azetidin-2-one.



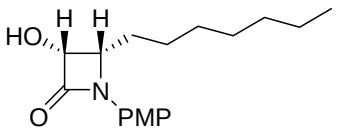
1.13a

The ^{1}H NMR spectrum of **1.13a** showed a triplet at 0.89 ppm (J = 6.5 Hz) for H-11 methyl protons. A multiplet in the range 1.20-1.50 ppm integrating for 10 protons corresponds to H-6 to H-10 methylene protons. A multiplet in the range 1.83-1.94 ppm was assigned for H-5 methylene protons. A sharp singlet at 3.80 ppm corresponds to methyl protons of –OMe group. A multiplet from 4.11-4.19 ppm corresponds to H-4 proton of β-lactam. A H-3 proton of β-lactam and one of the proton of benzylic methylene appears as multiplet from 4.74 to 4.80 ppm integrating for two protons. A doublet at 4.98 ppm (J = 11.9 Hz) assigned for one of the benzylic methylene proton. One of the doublet of PMP group appeared at 6.89 ppm (J = 9.1 Hz) integrating for two protons. Remaining seven aromatic protons showed a multiplet from 7.28-7.43 ppm.

The ^{13}C NMR spectrum of **1.13a** showed a peak at 164.4 ppm for the amide carbonyl of azetidin-2-one. The aromatic quaternary carbons appeared at 156.4, 137.1, 130.5 ppm. The remaining aromatic carbons appeared at 128.0, 127.4, 127.3, 118.3, 114.1 ppm. The C-3 carbon of azetidin-2-one appeared at 80.7. Benzylic methylene carbon appeared at 72.7 ppm. The C-4 carbon of azetidin-2-one appeared at 57.5 ppm respectively. Methoxy carbon of PMP group appeared at 54.9 ppm. C-5 to C-10 methylene carbon seen at 31.3, 29.3, 28.7, 27.0, 25.3, 22.2 ppm respectively. The C-11 methyl carbon seen at 13.7 ppm.

The mass spectrum of **1.13a** gave M+1 peak at m/z 382, also supporting the structure of the compound. Specific rotation for **1.13a** were found to be $[\alpha]_D^{30} = +112.4$ (c 1.05, $CHCl_3$).

The structure of **1.14a** was established by IR, ^1H NMR and ^{13}C NMR spectral data. IR spectrum of **1.14a** showed a broad band at 3365 cm^{-1} hydroxy group and sharp band at 1724 cm^{-1} for the carbonyl of azetidin-2-one.



1.14a

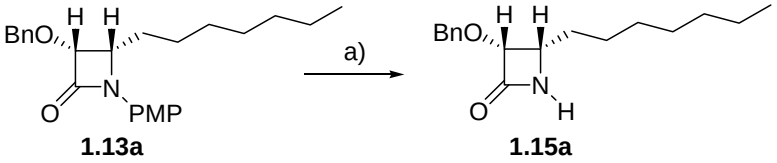
The ^1H NMR spectrum of **1.14a** showed a triplet at 0.89 ppm (J = 6.8 Hz) for H-11 methyl protons. A multiplet in the range 1.28-1.50 ppm integrating for 10 protons corresponds to H-6 to H-10 methylene protons. A multiplet at 1.80-2.00 ppm integrating for 2 protons assigned for H-5 methylene protons. A broad singlet at 2.88 ppm corresponds to –OH group proton. A singlet at 3.81 ppm corresponds to methyl protons of –OMe group. A multiplet from 4.14-4.20 ppm corresponds to H-4 proton of azetidin-2-one. H-3 proton of azetidine-2-one appeared as doublet at 5.05 ppm (J = 5.2 Hz). The doublets of PMP group appear at 6.85 ppm (J = 9.0 Hz), 7.32 ppm (J = 9.0) respectively.

The ^{13}C NMR spectrum of **1.14a** showed a peak at 167.2 ppm for the carbonyl carbon of azetidin-2-one. The quaternary aromatic carbons appeared at 156.5, 130.5 ppm and remaining aromatic carbons appeared at 119.0, 114.4 ppm. C-3 and C-4 carbon of azetidin-2-one assigned at 75.1 and 59.1 ppm respectively. The methoxy carbon seen at 55.4 ppm. The C-5 to C-10 methylene carbons seen at 31.7, 29.6, 29.1, 27.1, 25.7 and 22.5 ppm respectively. The C-11 methyl carbon appeared at 13.9 ppm.

The mass spectrum of **1.14a** gave M+1 peak at m/z 292, also supporting the structure of the compound. Specific rotation for **1.14a** were found to be $[\alpha]_D^{30} = +107.5$ (c 0.4, $CHCl_3$).

The oxidative removal of the *p*-methoxyphenyl (PMP) group from **1.13a** was achieved by cerric ammonium nitrate (CAN) [75] to get (3*R*,4*S*)-3-benzyloxy-4-heptanyl-azetidin-2-one (**1.15a**) in 85% yield (Scheme 1.51).

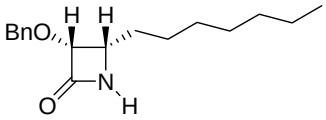
Scheme 1.51



1.13a **1.15a**

Reagents and conditions: a) CAN, CH_3CN/H_2O, 0 °C, 25 min, 85%.

The structure of **1.15a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.15a** showed a strong band at 1757 cm^{-1} for the amide carbonyl of azetidin-2-one.



1.15a

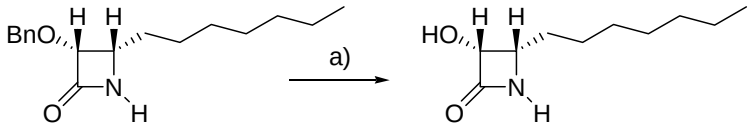
The ^{1}H NMR spectrum of **1.15a** showed a triplet at 0.89 ppm (J = 6.4 Hz) integrating for three protons for H-11 methyl protons. A multiplet in the range 1.05-1.45 integrating for 10 protons corresponds to H-6 to H-10 methylene protons. A multiplet in the range 1.50-1.75 ppm for two protons was assigned H-5 methylene protons. The H-4 proton of β-lactam shows a multiplet from 3.67-3.77 ppm. The H-3 proton of β-lactam and one of the benzylic methylene proton appears as multiplet from 4.66- 4.72 ppm. A doublet at 4.87 ppm (J = 11.9 Hz) assigned for one of the benzylic methylene proton. A broad singlet at 6.21 ppm corresponds to amide –N-H of azetidin-2-one ring. The aromatic protons appeared as a multiplet from 7.25-7.45 ppm.

The ^{13}C NMR spectrum of **1.15a** showed a peak at 169.4 ppm for the amide carbonyl carbon of azetidin-2-one. The quaternary aromatic carbons appeared at 137.1 ppm. The remaining aromatic carbons appeared at 128.1, 127.6, 127.4 ppm. The C-3 carbon of azetidin-2-one appeared at 82.2 ppm. Benzylic methylene carbon appeared at 72.5 ppm. The C-4 carbon of azetidin-2-one appeared at 55.0 ppm. The C-5 to C-10 methylene carbons appeared at 31.5, 29.7, 29.2, 28.9, 25.7 and 22.3 ppm respectively. The C-11 methyl carbon appeared at 13.8 ppm.

The mass spectrum of **1.15a** gave M+1 peak at m/z 276, also supporting the structure of the compound. Specific rotation for **1.15a** were found to be $[\alpha]_D^{30}$ = +40.6 (c 0.30, $CHCl_3$).

The benzyl group was removed by transfer hydrogenation[76] using Pd/C (10%) to afford 3-hydroxy-β-lactam **1.16a** in quantitative yield (Scheme 1.52).

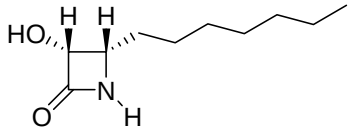
Scheme 1.52



1.15a **1.16a**

Reagents and conditions: a) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 6 h, 95%.

The structure of **1.16a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.16a** showed a strong band at 1751 cm^{-1} for the amide carbonyl of azetidin-2-one.



1.16a

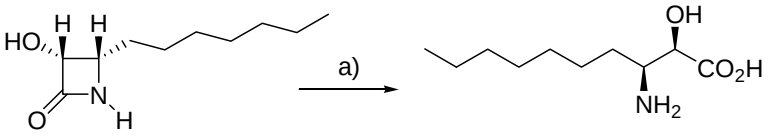
The ^{1}H NMR spectrum of **1.16a** showed a triplet at 0.88 ppm (J = 6.3 Hz) for three protons of H-11 methyl group. A multiplet in the range 1.15-1.65 ppm integrating for 12 protons corresponds to H-5 to H-10 methylene protons. A multiplet from 3.65-3.85 ppm corresponds to H-4 proton of azetidin-2-one. The H-3 proton of azetidine-2-one appeared as multiplet from 4.55-4.85 ppm. Two broad singlets at 4.91 ppm and 6.80 ppm corresponds to 3-hydroxy and amide –N-H proton of azetidin-2-one ring respectively.

The ^{13}C NMR spectrum of **1.16a** showed a peak at 172.0 ppm for the amide carbonyl carbon of azetidin-2-one. The C-3 and C-4 carbon of azetidin-2-one appeared at 76.5, 56.7 ppm respectively. The C-5 to C-10 methylene carbons appeared at 31.7, 29.7, 29.5, 29.2, 25.9 and 22.6 ppm respectively. The C-11 methyl carbon appeared at 14.1 ppm.

The mass spectrum of **1.16a** gave M+1 peak at m/z 186, also supporting the structure of the compound. Specific rotation for **1.16a** were found to be $[\alpha]_D^{30}$ = +40.0 (c 0.25, $CHCl_3$).

Hydrolysis of **1.16a** was achieved by heating with 3M HCl at 60 ˚C for 6 h to get (2*R*,3*S*)-3-amino 2-hydroxy decanoic acid hydrochloride. This hydrochloride obtained was purified by ion-exchange chromatography (Dowex 50W x 2-400) using 5% NH_4OH as the eluent to afford pure (2*R*,3*S*)-AHDA (**1.01a**) in 70% yield (Scheme1.53).

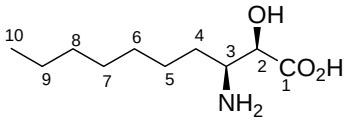
Scheme 1.53



1.16a (2*R*, 3*S*)-AHDA (**1.01a**)

Reagents and conditions: a) 3M HCl, 60 °C, 6 h, Ion exchange resin, Dowex 50W x 2-400, 5% NH_4OH, 70%.

The structure of **1.01a** was established by ^1H NMR, ^{13}C NMR spectral data.



(2*R*, 3*S*)-AHDA (**1.01a**)

The ^1H NMR spectrum of **1.01a** showed a triplet at 0.84 ppm (J = 6.7 Hz) for H-10 methyl protons. A multiplet in the range 1.19-1.45 ppm integrating for 10 protons corresponds to H-5 to H-9 methylene protons. A multiplet from 1.50-1.83 ppm for 2 protons corresponds to H-4 methylene protons. A multiplet from 3.38-3.50 ppm corresponds to H-3 proton. A doublet at 4.08 ppm assigned for H-2 proton of (2*R*,3*S*)-3-amino 2-hydroxy decanoic acid.

The ^{13}C NMR of **1.01a** showed a peak at 172.9 ppm for the acid carbonyl carbon. A C-2 and C-3 carbon of AHDA appeared at 69.3 ppm and 52.7 ppm respectively. The C-4 to C-9 methylene carbons appeared at 31.2, 29.1, 28.7, 28.4, 24.7 and 22.1 ppm respectively. The methyl carbon appeared at 14.0 ppm.

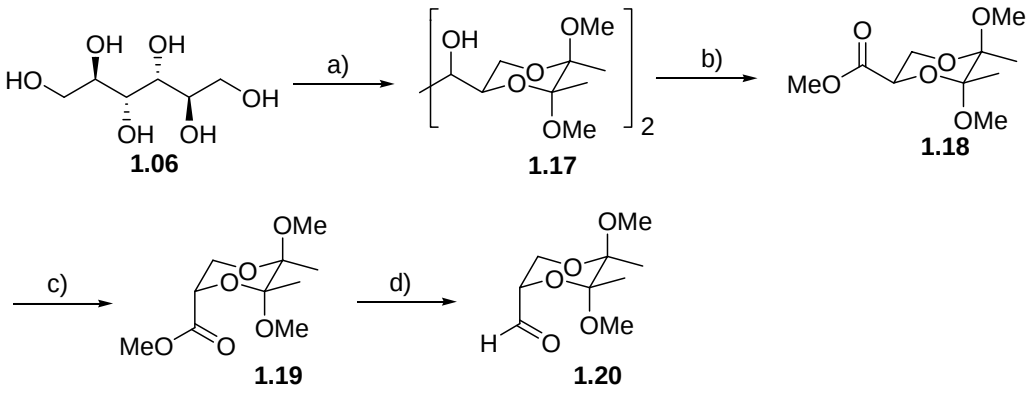
The mass spectrum of **1.01a** gave M+1 peak at m/z 204, also supporting the structure of the compound. Specific rotation for **1.01a** were found to be $[\alpha]_D^{30}$ = -6.2 (c 0.40, 1M HCl).

After establisihing the synthesis of (2*R*,3*S*)-3-amino 2-hydroxy decanoic acid which is an antipode of the desired (2*S*,3*R*)-3-amino 2-hydroxy decanoic acid (AHDA), we started synthesis of (2*S*,3*R*)-3-amino 2-hydroxy decanoic acid (AHDA), *N*-terminal component of Microginin. To get (2*S*,3*R*)-AHDA it is essential to start the synthesis from (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b**) which can be obtained from L-glyceraldehyde acetonide or its equivalent like diacetyl protected L-glyceraldehyde. Since diacetyl protected L-glyceraldehyde can be easily prepared from D-mannitol (**1.06**)[73] (Scheme 1.53).

D-mannitol (**1.06**) was treated with butane-2, 3-dione in the presence of anhydrous trimethyl orthoformate in MeOH, with a catalytic amount of $BF_3.Et_2O$ to

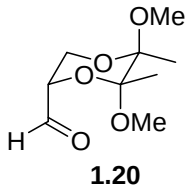
give the diol **1.17**. The crude diol **1.17** obtained on oxidative cleavage with sodium metaperiodate in MeOH-water, followed by bromine oxidation of the methyl hemiacetal gave the ester **1.18** which is purifed by distillation under *vacuo*. Treatment of ester **1.18** with lithium diisopropylamide (LDA) at -78 °C followed by quenching with *t*-BuOH at low temperature afforded the inverted ester **1.19**. Reduction of ester **1.19** with $LiAlH_4$ followed by oxidation with oxalyl chloride and DMSO gave the axial aldehyde **1.20** as a white solid (Scheme 1.54).

Scheme 1.54



Reagents and conditions: a) Butane-2-3-dione, $HC(OMe)_3$, MeOH, $BF_3.Et_2O$; b) $NaIO_4$, $MeOH/H_2O$, $NaHCO_3$, Br_2; c) LDA, THF, *t*-BuOH; d) $LiAlH_4$, THF, $(COCl)_2$, DMSO.

The structure of **1.20a** was established by IR, ^1H NMR spectral data. IR spectrum of **1.20a** showed a peak at 2928 cm^{-1} for C-H stretching and a sharp peak at 1729 cm^{-1} for aldehyde carbonyl.

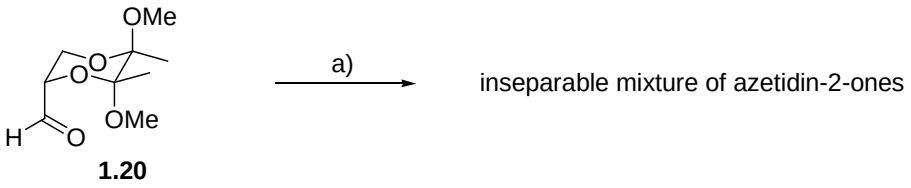


1.20

The ^1H NMR spectrum showed two singlets at 1.25 ppm and 1.39 ppm for methyl group protons. Two singlets at 3.30 ppm and 3.39 ppm for two –OMe group protons. A doublet at 3.79 ppm corresponds to methine hydrogen. A multiplet from 3.86-3.94 ppm corresponds to one of the methylene proton. A doublet at 4.09 ppm corresponds to other methylene proton. Aldehyde proton appeared as a singlet at 9.74 ppm.

The aldehyde **1.20** was further converted to its imine by using *p*-anisidine. This imine on [2+2] cycloaddition reaction with ketene derived from benzyloxy acetyl chloride resulted into inseparable mixture of azetidin-2-ones (IR = 1751 cm^{-1}) (Scheme 1.55).

Scheme 1.55

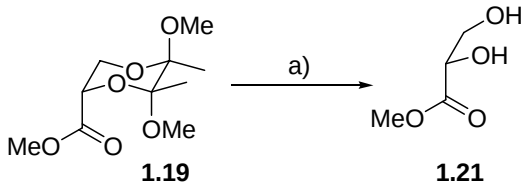


1.20

Reagents and conditions: a) PMP-NH_2, CH_2Cl_2, 6 h; $BnOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C

Therefore we decided to replace diacetyl protection of **1.19** with acetonide protection. Diacetyl protected ester **1.19** on treatment with trifluoroacetic acid and water (9:1) gave diol **1.21** in 80% yield. ^{1}H NMR and ^{13}C NMR spectrums of diol **1.21** shows two sets of signals which suggest that diol **1.21** is a mixture of two compounds and all our efforts to separate them were unsuccessful (Scheme 1.56).

Scheme 1.56



1.19 **1.21**
(Mixture)

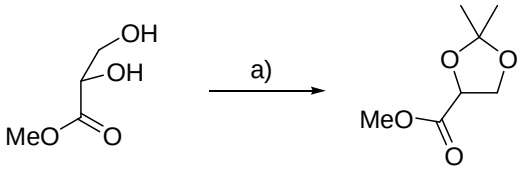
Reagents and conditions: a) TFA:H_2O (9:1) 10 min; b) 2,2 dimethoxy propane, clay, reflux 6 h.

IR spectrum of **1.21** showed a sharp peak at 1741 cm^{-1} due to ester carbonyl. The ^{1}H NMR spectrum showed a broad singlet at 3.57 ppm and 3.65 ppm for hydroxy group. Two singlets at 3.82 and 3.89 ppm appeared for –OMe protons of ester group. A multiplet between 3.86 to 3.92 ppm corresponds to one of the hydrogen of methylene group, another hydrogen appeared as multiplet from 4.27-4.33 ppm. Methine proton appeared as multiplet from 4.50 to 4.72 ppm.

The ^{13}C NMR spectrum showed peaks at 173.3, 171.5 ppm corresponding to ester carbonyl carbon. The –OMe carbon appeared at 71.6, 68.6 ppm. The methylene carbon appeared at 67.9, 63.9 ppm. The methine carbon appeared at 53.2, 52.7 ppm.

This mixture of diol **1.21** as such subjected to acetonide protection using 2,2-dimethoxy propane to get acetonide protected ester **1.17** which is found to be volatile compound resulting in low yield (Scheme 1.57).

Scheme 1.57

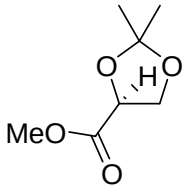


1.21 (Mixture) **1.22**

Reagents and conditions: a) 2,2 dimethoxy propane, clay, reflux 6 h.

The structure of ester **1.22** was established by using IR and ^{1}H NMR analysis. IR spectrum shows strong band at 1751 cm^{-1} for ester carbonyl.

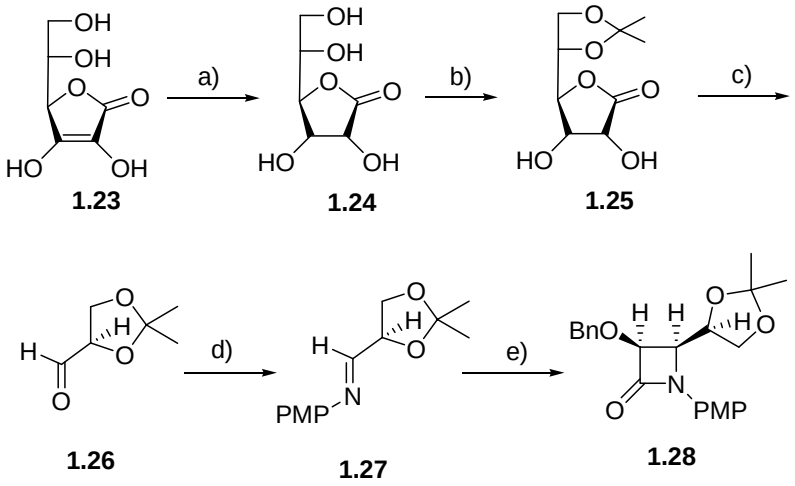
^{1}H NMR shows acetonide methyl singlets at 1.38 ppm and 1.48 ppm respectively. A sharp singlet at 3.76 ppm corresponds to methyl protons of –OMe group. A doublet of doublet at 4.08 ppm (J = 9.0 Hz, 5.0 Hz) corresponds to one of the proton of methylene while other methylene proton appears as doublet of doublet at 4.22 ppm (J = 9.0 Hz, 7.0 Hz). The methine proton appeared as doublet of doublet at 4.58 ppm (J = 7.0 Hz, 5.0 Hz).



1.22

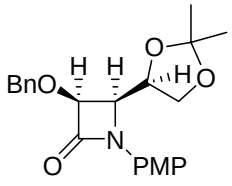
We could not get ester **1.22** in substantial quantity to proceed further. Therefore we have decided to synthesize (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b**) from L-glyceraldehyde acetonide which can be prepared from L-ascorbic acid **1.23** in three steps[74] (Scheme 1.58). L-Ascorbic acid on hydrogenation at 50 °C and at 50 psi gave L-Gulono-1,4-lactone (**1.24**). L-Gulono-1,4-lactone (**1.24**) on acetonide protection using 2-methoxy propene in DMF gave 5,6-O-isopropylidine-L-gulono-1,4-lactone (**1.25**). The lactone **1.25** on oxidative cleavage using sodium meta periodate gave crude aqueous solution of L-glyceraldehyde acetonide (**1.26)** which *in situ* converted into imine **1.27** which on [2+2] cycloaddition i.e. Staudinger reaction with ketene obtained from benzyloxy acetyl chloride gave (3*S*,4*R*)-3-Benzyloxy-4-(2,2-dimethyl-1,3-dioxaolan-4-yl)-1-(4-methoxyphenyl)azetidine-2-one (**1.28)** in 50 % yield (Scheme 1.58).

Scheme 1.58



Reagents and conditions: a) H_2, Pd/C (10%), 50Psi, 50 °C, H_2O, 95%; b) 2-Methoxypropene, DMF, PTSA, 24 h, r. t., 70%; c) $NaIO_4$, H_2O, 0 °C to r. t., 2 h; d) PMP-NH_2, CH_2Cl_2, 2 h, r. t.; e) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to r. t., 12 h, 50%.

The structure of **1.28** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **1.28** showed a sharp band at 1735 cm^{-1} for the amide carbonyl of azetidin-2-one.



1.28

The ^{1}H NMR spectrum of **1.28** showed singlets at 1.35 and 1.53 ppm corresponds to acetonide methyl group protons. A multiplet from 3.73 ppm to 3.79 ppm corresponds to H_a-6 methylene proton. The aromatic –OCH_3 protons seen as a singlet at 3.80 ppm. The H_b-6 methylene proton, H-4 proton of azetidin-2-one and H-5 methine proton shows multiplet from 4.15 ppm to 4.51 ppm integrating for three protons. A multiplet from 4.71 to 4.76 ppm integrating for two protons corresponds to H-3 proton of azetidin-2-one and one of the benzylic methylene proton. Other benzylic methylene proton appears as a doublet at 5.00 ppm (J = 11.8 Hz). The doublets of PMP group appear at 6.87 ppm and 7.67 ppm with coupling constant J = 9.2 Hz.

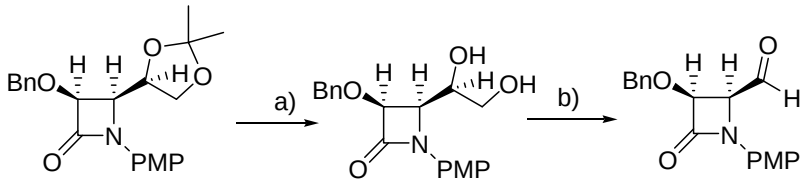
The ^{13}C NMR of **1.28** showed a peak at 164.8 ppm for the carbonyl of azetidin-2-one. The quaternary aromatic carbons appeared at 156.3, 136.6, 131.1 ppm and remaining aromatic carbons appeared at 128.4, 128.1, 127.8, 119.4, 113.8 ppm. The quaternary carbon of the acetonide group assigned at 109.6 ppm. The C-3 and C-4 carbon of azetidin-2-one assigned at 79.6 and 77.0 ppm respectively. The benzyloxy methylene carbon seen at 73.1 ppm. Other methylene carbon seen at 66.9 ppm. The

methoxy carbon seen at 55.3 ppm. The acetonide methyl carbon seen at 26.5, 24.8 ppm respectively.

The mass spectrum of **1.28** gave M+1 peak at m/z 384, also supporting the structure of the compound. Specific rotation for **1.28** were found to be $[\alpha]_D^{30}$ = -113.4 (c 0.70, $CHCl_3$).

Azetidin-2-one **1.28** on acetonide deprotection using catalytic PTSA in THF and water converted to diol **1.29** in quantitative yield. Diol **1.29** on oxidative cleavage using sodium metaperiodate gave (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b)** in 85% yield (Scheme 1.59).

Scheme 1.59



Reagents and conditions: a) PTSA, THF/H_2O, reflux, 18 h, 98%; b) $NaIO_4$, Acetone/H_2O, 85%.

Specific rotation of (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b**) was compared with the rotation of (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**1.05a**).[67a] Melting point and specific rotation of compound **1.05a** and **1.05b** were summarized in (Table 1).

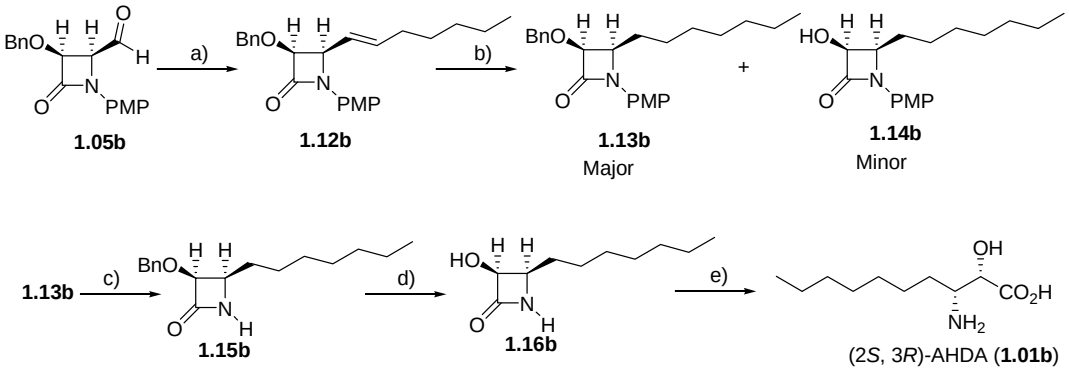
Table 1: Comparision data of specific rotation and M.P for **1.05 b** with **1.05 a**

(3*S*,4*S*)-4-formylazetidin-2-one 1.05b	**(3*R*,4*R*)-4-formylazetidin-2-one 1.05a**
a) $[\alpha]_D^{30}$ = -176.2 (c, 0.42, $CHCl_3$)	**a)** $[\alpha]_D^{25}$ = +176.3 (c, 1.0, CH_2Cl_2).[67a]
b) M. P. = 152-153 °C	**b)** M. P. = 154-155 °C.[67a]

Specific rotation of (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b**) was found to be exactly opposite to that of its antipode (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**1.05a**). Melting point of (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b**) was comparable with that of its antipode (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**1.05a**).

(2*S*,3*R*)-AHDA (**1.01b**) was synthesized from (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**1.05b**) by following a synthetic protocol as shown in (Scheme 1.60), which is similar to that explained for its antipode (2*R*,3*S*)-AHDA earlier.

Scheme 1.60



Reagents and conditions: a) $CH_3(CH_2)_5PPh_3^+Br^-$, n-BuLi, 0 °C, 6 h, dry THF, 75%; b) H_2, Pd/C (10%), 50 Psi, 6 h, EtOAc, 90%; c) CAN, CH_3CN/H_2O, 0 °C, 25 min, 85%; d) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 6 h, 95%; e) 3M HCl, 60 °C, 6 h, Ion exchange resin, Dowex 50W x 2-400, 5% NH_4OH, 70%.

Melting point and the specific rotations of (2*S*,3*R*)-3-amino-2-hydroxy decanoic acid (AHDA) obtained are compaired with natural (2*S*,3*R*)-AHDA previously synthesized[65g, 64b] is summarized in (Table 2).

Table 2: Comparision data of specific rotation and M.P for (2*S*,3*R*)-AHDA

1.01b	**Natural (2*S*,3*R*)-AHDA**
a) $[\alpha]_D^{30}$ = + 6.5 (c, 0.47, 1N HCl)	**a)** $[\alpha]_D^{22}$ = +7.3 (c, 0.34, 1N HCl).[65g] $[\alpha]_D^{25}$ = +5.4 (c, 0.59, 1N HCl).[64]
b) M. P. = 219-220 °C (dec)	**b)** M. P. = 218.4-219.7 °C (dec).[65g]

Specific rotation and M. P. of (2*S*,3*R*)-AHDA synthesized are comparable with the natural (2*S*,3*R*)-AHDA. Spectroscopic data and analytical data of (2*S*,3*R*)-AHDA is similar with that of its antipode (2*R*,3*S*)-AHDA.

1.5 Conclusion:

In conclusion, we have accomplished the synthesis of both the enantiomers of 4-formyl-3-benzyloxy azetidin-2-one and used them for the synthesis of (2*R*,3*S*)-3-amino 2-hydroxy decanoic acid (**1.01a**) and its antipode (2*S*,3*R*)-3-amino 2-hydroxy decanoic acid (**1.01b**) which is the *N*-terminal component of Microginin.

1.6 Experimental:

1.6.1: Preperation of (4*R*,5*R*)-(-)-diethyl-2,3-O-isopropylidene-L-tartarate (1.02):

A mixture of diethyl-L-tartarate (10.3 g, 0.05 mol), 2,2-dimethoxypropane (7.8 g, 0.075 mol) and *p*-toluene sulphonic acid monohydrate (50 mg) in benzene (100 mL) was heated under reflux under a soxhlet extractor containing freshly conditioned 4A sieves (20 g) for 4 h.[77] Then the reaction mixture was cooled and anhydrous K_2CO_3 (200 mg) was added and stirred at room temperature for 4 h, filtered and concentrated under reduced pressure. The residue was taken in CH_2Cl_2 and then washed with brine and dried over Na_2SO_4. Evaporation of the solvent provided the crude product which was then chromatographed (petroleum ether/EtOAc mixtures) and the product obtained after chromatographic separation was distilled under vacuo (120 oil bath temperature) to get pure **1.02** (10.4 g, 85%) product.

1.6.2: Procedure for the preparation of diimine (1.03):

To a solution of (4*R*,5*R*)-(-)-diethyl-2,3-O-isopropylidene-L-tartrate **1.02** (2.46 g, 10 mmol) in dry toluene (30 mL), a 1M solution of DIBAL-H (20 mL) in toluene was added dropwise using a syringe over a period of 30 min under argon and it was stirred at -78 °C for 3 h. After the completion of the reaction (TLC) *p*-anisidine (2.46 g, 20 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The argon baloon was then removed and the reaction mixture was stirred under air for 8 h, the precipitate formed was filtered off and the filtrate was concentrated to get diimine **1.03** (3.31 g, 90%) which was used as such without further purification.

1.6.3: Procedure for the preparation of β-lactam (1.04):

A solution of benzyloxy acid chloride (0.950 ml, 6 mmol) in anhydrous CH_2Cl_2 (40 mL) was added to a solution of diimine **1.03** (0.736 g, 2 mmol) and triethylamine (2.50 ml, 18 mmol) in CH_2Cl_2 (30 mL) at -23 °C under argon. The resulting mixture was allowed to warm up to room temperature and stirred for 14 h. The reaction mixture was then successively washed with water (30 mL), satd. $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4), and concentrated to give the crude product, which was then column chromatographed (silica gel, pet. ether/acetone mixtures) to give pure β-lactam **1.04** in 60% yield.

1.6.4: Procedure for the preparation of (3*S*,4*S*)-3-Benzyloxy-1-(4-methoxyphenyl)-4-oxo-azetidin-2-carbaldehyde (1.05a):

To a solution of protected β-lactam **1.04** (1.0 g, 1.5 mmol) in THF (15 mL), a 2.5 M aqueous solution of perchloric acid (9 mL) was added and the reaction mixture was stirred at room temperature for 4-8 h. After the completion of reaction, the reaction mixture was neutralized by slow addition of solid $NaHCO_3$, then diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated to get the diol which was then column chromatographed (silica gel, $CHCl_3$/EtOAc mixtures) to get pure diol (0.850 g, 91%). To a solution of diol (0.625 g, 1 mmol) in acetone (15 mL) and water (3 mL), $NaIO_4$ (0.640 g, 3 mmol) was added at room temperature and the reaction mixture was stirred for 4-12 h. As the reaction progressed a white solid precipitated. After the completion of reaction (TLC) the reaction mixture was filtered, the residue washed with acetone and the combined filtrates were concentrated on a rotary evaporator. The residue was treated with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was dried over Na_2SO_4 and the solvent evaporated to get the 4-formyl-β-lactam, which was then filtered through a column (60-120 mesh silica gel, acetone/pet. ether, 1:4) to get pure **1.05a** (0.6 g, 96%) as a white solid.

m.p. 157-158 °C

$[\alpha]_D^{30}$ = -176.2 (c 0.42, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1753 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 3H, Ar-OC*H*$_3$), 4.51 (dd, *J* = 5.3 Hz, 3.7 Hz, 1H, *H*-4), 4.71 (d, *J* = 11.3 Hz, 1H, -OC*H*$_a$H$_b$Ph), 4.84 (d, *J* = 11.3 Hz, 1H, -OCHa*H*$_b$Ph), 5.05 (d , *J* = 5.3 Hz, 1H, *H*-3), 6.88 (d, *J* = 9.1 Hz, 2H, Ar), 7.26 (d, *J* = 9.1 Hz, 2H, Ar), 7.30-7.50 (m, 5H, Ar), 9.72 (d, *J* = 3.7 Hz, 1H, -C*H*O).

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.5, 63.2, 73.5, 82.6, 114.6, 118.1, 128.3, 128.5, 128.6, 130.5, 135.8, 156.9, 162.9, 198.9

MS: (*m/z*) = 312 (M+1)

Anal. Calcd. for **$C_{18}H_{17}NO_4$:** C, 69.43; H, 5.51; N, 4.50%

Found C, 69.33; H, 5.58; N, 4.63%.

1.6.5: (3*R*,4*S*)-3-Benzyloxy-4-hept-1-enyl-1-(4-methoxyphenyl)-azetidin-2-one (1.12a):

To a solution of a *n*-hexyltriphenylphosphonium bromide (1.538 g, 3.6 mmol) in anhydrous THF at 0 °C was added *n*-butyl lithium (2.20 ml, 3.3 mmol, 1.5 M, colour change from yellow to orange red was observed). Reaction mixture was stirred at this temperature for 45 min. A solution of azetidin-2-one **1.05a** (0.934 g, 3 mmol) in anhydrous THF (20 ml) was added drop-wise at 0 °C to the reaction mixture and then allowed to warm up to room temperature. After 6 h, the reaction mixture was quenched with saturated solution of NH_4Cl (5 mL). The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL), washed with water (10 ml) and then with saturated brine solution (5 mL) to afford the crude **1.12a**, which was then purified by flash column on silica gel (EtOAc/pet. ether 1:9 as eluent), to get *E/Z* isomeric mixture of **1.05a** (0.853 g, 75%) as a viscous oil. The geometrical isomers were difficult to separate by flash column chromatography and used as such for further reaction.

IR ($CHCl_3$): υ_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 0.94 (m 3H), C*H*$_3$(CH$_2$)$_6$), 1.28-1.51 (m, 6 H, =CH-CH$_2$-(C*H*$_2$)$_3$-CH$_3$), 2.08-2.40 (m, 2 H, CH=CH-C*H*$_2$), 3.79 (s, 3 H, Ar-OC*H*$_3$), 4.54-4.95 (m, 4H, *H*-3, *H*-4, *OCH$_2$Ph*), 5.56-5.68 (m, 1H, CH=C*H*-CH$_2$-(CH$_2$)$_3$-CH$_3$), 5.83-6.06 (m, 1H, C*H*=CH-CH$_2$-(CH$_2$)$_3$-CH$_3$), 6.85 (d, *J* = 9.1 Hz, 2H, Ar), 7.28-7.43 (m, 7H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): 14.0, 22.5, 27.9, 28.5, 29.1, 31.2, 31.6, 32.4, 55.4, 55.5, 60.9, 72.6, 72.7, 82.2, 82.4, 114.4, 118.6, 118.7, 124.0, 124.3, 128.0, 128.4, 131.1, 137.0, 137.5, 138.8, 156.4, 163.5

MS: (*m/z*) = 380 (M+1)

Anal. Calcd. for **$C_{24}H_{29}NO_3$:** C, 75.95; H, 7.72; N, 3.69%

Found C, 75.65; H, 7.52; N, 3.80%.

1.6.6: (3*R*,4*S*)-3-Benzyloxy-4-heptyl-1-(4-methoxyphenyl)-azetidine-2-one (1.13a) and (3*R*,4*S*)-4-heptyl-3-hydroxy-1-(4-methoxyphenyl)-azetidine-2-one (1.14a):

Compound **1.12a** (0.760 g, 2 mmol) was dissolved in EtOAc (20 mL) and Pd/C (10%) (70 mg) was added. The mixture was hydrogenated at 50 psi of H_2 in a Parr hydrogenator for 6 h at room temperature. The catalyst was removed by filtration through Celite and washed with EtOAc. The solvent was distilled off under reduced pressure and the crude product was purified by flash column chromatography on silica

gel (EtOAc/pet. ether 15:85 as eluent) to afford compound **1.13a**; (0.688 g, 90%) as viscous oil and **1.14a** (0.035 g, 6%) as a white crystalline solid.

Compound **1.13a:**

$[\alpha]_D^{30}$ = +112.4 (c 1.05, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1742 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 0.89 (t, *J* = 6.5 Hz, 3H, -$(CH_2)_6CH_3$), 1.2-1.5 (m, 10H, $CH_2(CH_2)_5CH_3$), 1.83-1.94 (m, 2H, $CH_2(CH_2)_5CH_3$), 3.80 (m, 3H, Ar-OCH_3), 4.11-4.19 (m, 1H, *H*-4), 4.74-4.80 (m, 2H, *H*-3, -CH_aH_bPh), 4.98 (d, *J* = 11.9 Hz, 1H, -CHa*H*bPh), 6.89 (d, *J* = 9.1 Hz, 2H, Ar), 7.28-7.43 (m, 7H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): 13.7, 22.2, 25.3, 27.0, 28.7, 29.3, 31.3, 54.9, 57.5, 72.7, 80.7, 114.1, 118.3, 127.3, 127.4, 128.0, 130.5, 137.1, 156.0, 164.4

MS: (*m/z*) = 382 (M+1)

Anal. Calcd. for **$C_{24}H_{31}NO_3$:** C, 75.57; H, 8.21; N, 3.67%

Found C, 75.47; H, 8.35; N, 3.61%.

Compound **1.14a:**

The compound **1.14a** (0.035 g, 6%) was obtained as a white crystalline solid.

m.p. 105-107 °C

$[\alpha]_D^{30}$ = +107.5 (c 0.4, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1724, 3365 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 0.89 (t, *J* = 6.8 Hz, 3H, $(CH_2)_6CH_3$), 1.28-1.50 (m, 10H, $CH_2(CH_2)_5CH_3$), 1.80-2.00 (m, 2H, $CH_2(CH_2)_5CH_3$), 2.88 (bs, 1H, O*H*), 3.81 (s, 3H, Ar-OCH_3), 4.14-4.20 (m, 1H, *H*-4), 5.05 (d, *J* = 5.2 Hz, 1H, *H*-3), 6.85 (d, *J* = 9.0 Hz, 2H, Ar), 7.32 (d, *J* = 9.0 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): 13.9, 22.5, 25.7, 27.1, 29.1, 29.6, 31.7, 55.4, 59.1, 75.1, 114.4, 119.0, 130.5, 156.5, 167.2

MS: (*m/z*) = 292 (M+1)

Anal. Calcd. for **$C_{17}H_{25}NO_3$:** C, 70.06, H, 8.66; N, 4.81%

Found C, 70.20; H, 8.70; N, 4.93%.

1.6.7: (3*R*,4*S*)-3-Benzyloxy-4-heptylazetidin-2-one (1.15a):

A solution of **1.13a** (0.572 g, 1.5 mmol) in acetonitrile (15 mL) was cooled to 0 °C and treated with a solution of CAN (2.469 g, 4.51 mmol) in water (20 mL) over 3 min. The reaction mixture was stirred at –5 to 0 °C for 25 min and diluted with water

(110 mL). The mixture was extracted with EtOAc (3 x 25 ml). The organic extracts were washed with 5% $NaHCO_3$ (2 x 25 mL) and the aqueous extracts back washed with EtOAc (10 mL). The combined organic layer was washed with 10% sodium sulfite (until the aqueous layer remained colorless), 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, evaporated under reduced pressure to yield the crude product **1.15a**, which was then purified by flash column chromatography on silica gel (EtOAc/pet. ether 3:7 as eluent) to get pure **1.15a** (0.351 g, 85%) as a white solid.

m.p. 53-55 °C

$[\alpha]_D^{30}$ = +40.6 (c 0.30, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 0.89 (t, *J* = 6.4 Hz, 3 H, C*H*$_3$(CH$_2$)$_6$), 1.05-1.45 (m, 10 H, CH$_2$(C*H*$_2$)$_5$CH$_3$), 1.50-1.75 (m, 2 H, C*H*$_2$(CH$_2$)$_5$CH$_3$), 3.67-3.77 (m, 1 H, C4H), 4.66-4.72 (m, 2 H, C3H, C*H*$_a$H$_b$Ph,), 4.87 (d, *J* = 11.9 Hz, 1 H, CHa*H*$_b$Ph), 6.21 (bs, 1 H, N-H), 7.25-7.45 (m, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): 13.8, 22.3, 25.7, 28.9, 29.2, 29.4, 29.7, 31.5, 55.0, 72.5, 82.2, 127.4, 127.6, 128.1, 137.1, 169.4

MS: (*m/z*) = 276 (M+1)

Anal. Calcd. for **$C_{17}H_{25}NO_2$:** C, 74.13; H, 9.17; N, 5.08%

Found C, 74.13; H, 8.93; N, 4.95%.

1.6.8: (3*R*,4*S*)-4-Heptyl-3-hydroxyazetidin-2-one (1.16a):

To a solution of **1.15a** (0.275 g, 1 mmol) in methanol (10 mL), 10% Pd/C (30 mg) was added followed by ammonium formate (0.315 g, 5 mmol) and the reaction mixture was heated at reflux under argon for 6 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and filtered through Celite. The solvent was distilled off under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave crude product, which was then purified by flash column chromatography on silica gel (EtOAc/pet. ether 6:4 as eluent) to get pure **1.16a** (0.176 g, 95%) as a white solid.

m.p. 112-113 °C

$[\alpha]_D^{30}$ = +40.0 (c 0.25, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 0.88 (t, *J* = 6.3 Hz, 3H, $CH_3(CH_2)_6$), 1.15-1.65 (m, 12 H, $-(CH_2)_6CH_3$), 3.65-3.85 (m, 1 H, *H*-4), 4.55-4.85 (m, 1 H, *H*-3), 4.91 (bs, 1 H, OH), 6.80 (bs, 1 H, -N-*H*).

^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 22.6, 25.9, 29.2, 29.5, 29.7, 31.7, 56.7, 76.5, 172.0.

MS: (*m/z*) = 186 (M+1)

Anal. Calcd. for **$C_{10}H_{19}NO_2$:** C, 64.81; H, 10.36; N, 7.56%

Found C, 64.91; H, 10.40; N, 7.77%.

1.6.9: (2*R*,3*S*)-3-Amino-2-hydroxydecanoic acid (1.01a):

A solution of **1.16a** (93 mg, 0.5 mmol) in 3M HCl (5 mL) was heated at 60 °C for 6 h. After completion of the reaction (TLC), the solution was cooled to room temperature and extracted with CH_2Cl_2 (3 mL). The aqueous layer was evaporated to dryness under reduced pressure and the residue was further subjected to ion exchange chromatography (Dowex 50W x 2-400) using 5% NH_4OH as the eluent to afford **1.01a** (71 mg, 70%) as a white solid.

m.p. 220-223°C (dec), lit. m.p. 152-156 °C (dec)[64a]

$[\alpha]_D^{30}$ = -6.2 (c 0.40, 1M HCl)

^{1}H NMR (200 MHz, D_2O): 0.84 (t, *J* = 6.7 Hz, 3H, $CH_3(CH_2)_6$), 1.19-1.45 (m, 10H, $CH_2(CH_2)_5CH_3$), 1.50-1.83 (m, 2H, $CH_2(CH_2)_5CH_3$), 3.38-3.50 (m, 1H, *H*-3), 4.08 (d, *J* = 3.8 Hz, 1H, *H*-2).

^{13}C NMR (50 MHz, DMSO-d_6): 14.0, 22.1, 24.7, 28.4, 28.7, 29.1, 31.2, 52.7, 69.3, 172.9

MS: (*m/z*) = 204 (M+1)

Anal. Calcd. for **$C_{10}H_{21}NO_3$:** C, 59.07; H, 10.43; N, 6.89%

Found C, 59.28; H, 10.53; N, 7.10%.

1.6.10: (2*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylicAcid Methyl Ester (1.18):

$BF_3{\cdot}Et_2O$ (5 mL, 40.65 mmol) was added to a stirred solution of D-mannitol (**1.06**) (30.95 g, 169.9 mmol), anhydrous trimethyl orthoformate (75 mL, 0.68 mol) and butanedione (31.5 mL, 358.9 mmol) in MeOH (150 mL) at room temperature., under an atmosphere of argon. After 5 h, the reaction mixture was neutralized by the addition of Et_3N (5 mL, 35.87 mmol) and the solvent was removed in *vacuo*. The residue was dissolved in CH_2Cl_2 (600 mL) and washed with water (300 mL) and brine (150 mL).

The organic phase was dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude residue was used without further purification. Sodium metaperiodate (47.7 g, 209.25 mmol) was added slowly to a stirred solution of the crude diol **1.17** in MeOH (175 mL) and water (350 mL) at 0 ºC. After stirring overnight at r.t., $NaHCO_3$ (54.8 g, 0.65 mol) was added, followed by dropwise addition of Br_2 (13 mL, 253.7 mmol) until a permanent yellow colour remained. Excess Br_2 was quenched by $Na_2S_2O_3$. The slurry was filtered and the filtrate was extracted with CH_2Cl_2 (2 × 400 mL). The organic phases were washed with water (200 mL) and brine (200 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude product was purified by fractional distillation to afford **1.18** as a colourless oil (36.7 g, 157 mmol, 46%);

$[\alpha]_D^{30} = -158.2$ (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{25} = -158.8$ (*c* 1.22, $CHCl_3$)[73]

IR ($CHCl_3$): υ_{max} 2953, 1764, 1735 cm^{-1}

1.6.11: (2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylicAcid Methyl Ester (1.19):

n-BuLi (77 mL, 1.5 M in petroleum ether, 115 mmol) was added to a stirred solution of diisopropylamine (17 mL, 121.3 mmol) in THF, under Ar, at –20 °C to 0 °C. After 30 min, the solution was cooled to –78 °C and ester **1.18** (23.6 g, 100.8 mmol) diluted in THF (20 mL) was added within 10 min. After 30 min, *t*-BuOH (25 mL, 270.8 mmol) was added dropwise, then stirring was carried on for additional 30 min. The reaction mixture was quenched at –78 °C with sat. NH_4Cl and diluted with Et_2O (400 mL). The organic phase was washed with sat. NH_4Cl (2 × 400 mL) and brine (400 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue (solubilized in CH_2Cl_2 if necessary) was vacuum-filtered through a glass frit filter charged with silica gel (50 g). The filter cake was washed with hexane–Et_2O (1:1, 500 mL). The solvents were removed in vacuo and the pale yellow solid was purified by recrystallisation from hexane to afford **1.19** as a white solid (11.3 g, 48.1 mmol, 48%).

m.p. 77 ºC

$[\alpha]_D^{30} = -157.0$ (c 1.0, $CHCl_3$), lit. $[\alpha]_D^{25} = -157.6$ (c 1.02, $CHCl_3$)[73]

IR ($CHCl_3$): υ_{max} 2996, 2954, 1739 cm^{-1}

1.6.12: (2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4] dioxane-2-carbaldehyde(1.20):

Ester **1.19** (10 g, 43.0 mmol) solubilized in THF (15 mL) was added slowly to a stirred suspension of $LiAlH_4$ (1.17 g, 30.74 mmol) in THF (120 mL) at 0 °C under Ar. The mixture was stirred overnight at room temperature. Excess hydride was quenched by successive addition of water (1.2 mL), 15% aq. NaOH (1.2 mL) and water (3.5 mL). The resulting suspension was filtered through Celite, rinsed with Et_2O, and the solvents were removed in *vacuo*. The crude residue was used without further purification. DMSO (6.70 mL, 94.0 mmol) was added dropwise to a stirred solution of oxalyl chloride (4 mL, 45.83 mmol) in CH_2Cl_2 (120 mL) at –50 °C to –60 °C, under Ar. After 2 min, a solution of the crude alcohol in CH_2Cl_2 (10 mL) was added. After stirring for 15 min, Et_3N (16 mL, 115.0 mmol) was added. The mixture was stirred for 5 min and then allowed to warm to r.t. Water (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (70 mL). The organic layers were combined, washed with brine (50 mL), 1 N HCl solution (100 mL), water (50 mL), sat. $NaHCO_3$ (100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give a crude aldehyde **1.20** which was purified by recrystallisation from hexane to afford pure aldehyde **1.20** as a white solid (8.3 g, 40.84 mmol, 95%).

m.p. 77 ºC

$[\alpha]_D^{30} = -265.5$ (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{25} = -266.5$ (*c* 1.6, $CHCl_3$)[73]

IR ($CHCl_3$): υ_{max} 2928, 1729 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 1.25 (s, 3H, CC*H*$_3$), 1.39 (s, 3H, CC*H*$_3$), 3.30 (s, 3H, OC*H*$_3$)**,** 3.39 (s, 3H, OC*H*$_3$), 3.79 (d, *J* = 4.4 Hz, 1H, C*H*), 3.86-3.94 (m, 1H, -C*H*H), 4.09 (d, *J* = 11.6 Hz, 1H, C*H*H), 9.74 (s, 1H, -C*H*O).

1.6.13: 2-(*S*)-Methyl 2,3-dihydroxypropanoate (1.21):

To a (2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylicAcid methyl ester (**1.19**) (2.340 g, 10 mmol) a solution of trifluoroacetic acid and water (20:1, 15 mL) was added and stirred for 5 min. Trifluoroacetic acid and water were removed under *vacuo* to gave a inseparable mixture of diol (**1.21**) which passed through column (EtOAc/ pet. ether 2:3 as eluent) to get a pure mixture of diol **1.21** as a viscous liquid (0.96 g, 80%).

IR ($CHCl_3$): υ_{max} 3384, 1741 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 3.57, 3.65 (bs, 2H, 2 x -O*H*), 3.82, 3.85 (s, 3H, -OCH_3), 3.88-3.92 (m, 1H, -CH_aH$_b$OH), 4.27-4.33 (m, 1H, -CH$_a$$H_b$OH), 4.49-4.72 (m, 1H, -C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$):52.7, 53.2, 64.0, 68.0, 68.7, 71.6, 171.5, 173.3.

MS: (*m/z*) = 121 (M+1)

1.6.14: Methyl 2,2-dimethyl-1,3-dioxolan-4-carboxylate (1.22):

A mixture of diol **1.21** (0.360 g, 3 mmol), 2,2-dimethoxy propane (10 mL), Montmorillite clay (100 mg) refluxed for 5 h. Excess 2,2 dimethoxy propane removed under *vacuo* to furnish crude methyl 2,2-dimethyl-1,3-dioxolan-4-carboxylate(**1.22**) which is purified by flash column chromatography (EtOAc/pet. ether 15:85 as eluent) to gave pure **1.22** which is found to be volatile (0.058 g, 12%).

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.08 (dd, *J* = 9.0 Hz, 5.0 Hz, 1H, C*H*H), 4.22 (dd, *J* = 9.0 Hz, 7Hz, C*H*H), 4.58 (dd, *J* = 7.0 Hz, 5.0 Hz, 1H).

1.6.15: L-Gulono-1,4-lactone (1.24):

A solution of 2.31 g (0.013mol) of L-ascorbic acid (**1.23**) in 17 ml of H_2O was hydrogenated over Pd/C 10% (0.22 g) in a parr hydrogenator at 50 °C and 50 psi hydrogen pressure for 24 h. The catalyst was removed by filtration and the water removed in vacuo to afford 2.32 g (0.013 mol, 99%) of a white crystalline solid. On crystallization of a sample from MeOH-EtOAc, material which was identical with authentic L-gulono-1,4-lactone (**1.24**) was obtained.

m.p. 182-183 °C (lit[74a] m.p. 180-181 °C)

$[\alpha]_D^{30}$ = +55.0 (c 0.5, H_2O)

IR ($CHCl_3$): υ_{max} 1770 cm^{-1}

^{1}H NMR (200 MHz, DMSO-d_6): δ 3.41-3.60 (m, 2H), 3.67-3.80 (m, 1H), 4.14-4.26 (m, 2H), 4.40-4.48 (m, 1H), 4.68 (t, 1H, OH), 4.99 (d, 1H, OH), 5.35 (d, 1H, OH), 5.81(d, 1H, OH).

^{13}C NMR (50 MHz, DMSO-d_6):61.96, 69.48, 70.11, 70.75, 80.84, 176.25.

1.6.16: 5,6-O-isopropylidine-L-gulono-1,4-lactone (1.25):

A solution of L-gulono-1,4 lactone (**1.24**) (2.216 g, 12.40 mmol) in dimethylformamide (20 ml) is cooled to 10 °C and *p*-toluenesulfonic acid (18 mg, 0.1 mmol) is added portionwise with stirring to the resultant solution, isopropenyl methyl ether (1.166 g, 16.1 mmol) is added dropwise at 10 °C. The cooling bath is removed and the solution is further stirred at room temperature for 24 h. The solution is then treated with sodium carbonate decahydrate (2.20 g) and the suspension is vigorously stirred for 2 h. It is then filtered over speedex and the filtrate is evaporated (40 °C, 0.2 torr). To the residue obtained toluene (10 ml) added whereupon crystallization begins. The product is isolated by suction, washed with hexane/ethanol (9:1; 10 ml), and dried; yield of crystalline compound 1.91 g (70%).

m.p. 165-166 °C

$[\alpha]_D^{30}$ = +35.0 (c 0.5, CH_3OH).

1.6.17: (3*S*,4*R*)-3-Benzyloxy-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-ethoxyphenyl)azetidine-2-one (1.28):

To a stirred solution of 5,6-*O*-isopropylidene-L-gulono-1,4-lactone **1.25** (10.90 g, 50 mmol) in water (150 mL), $NaIO_4$ (21.37 g, 100 mmol) was added portion-wise at 0 °C, over 30 min, at pH 5.5 (adjusted by addition of 2M NaOH). The suspension was further stirred at room temperature for 2 h, and filtered through filter paper to get a crude aqueous solution of L-(S)-glyceraldehyde acetonide (**1.26**), which was then cooled to 10 °C under argon and vigorously stirred with a solution of *p*-anisidine (5.72 g, 46.5 mmol) in CH_2Cl_2 (150 mL) for 30 min. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers dried over anhydrous Na_2SO_4 under argon. The organic layers were collected and reduced in volume to 30 mL. To this solution dry triethylamine (6.22 g, 61.5 mmol) was added and the reaction mixture was then cooled to 0 °C. A solution of benzyloxyacetyl chloride (8.59 g, 46.5 mmol) in dry CH_2Cl_2 (100 mL) was added drop-wise to the above reaction mixture. The reaction mixture was further stirred for 12 h at room temperature and then washed with water (3 x 15 mL), 1N hydrochloric acid (10 mL), saturated $NaHCO_3$ (25 mL), water (25 mL) and brine solution (20 mL). The organic phase dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product **1.28** was purified by flash column chromatography (EtOAc/Petroleum ether 15:85 as eluent) to get a pure product **1.28** (8.90 g, 50%) as a white solid.

m.p. 117 °C

$[\alpha]_D^{30}$ = -113.4 (c 0.70, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1735 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 1.35 (s, 3H, C*H*$_3$), 1.53 (s, 3H, C*H*$_3$), 3.73-3.79 (m, 1H, OC*H*CH$_2$), 3.80(s, 3H, Ar-OC*H*$_3$), 4.15-4.51 (m, 3H, C4*H*, OC*H*$_2$CHO), 4.71-4.76 (m, 2H, C3*H*, OC*H*$_a$H$_b$Ph), 5.00 (d, *J* = 11.8 Hz, 1H, OCHa*H*$_b$Ph), 6.87 (d, *J* = 9.2 Hz, 2H, Ar), 7.30-7.45 (m, 5H, Ar), 7.67 (d, *J* = 9.2 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): 24.8, 26.5, 55.3, 61.6, 66.9, 73.1, 79.6, 109.6, 113.8, 119.4, 127.8, 128.1, 128.4, 131.1, 136.6, 156.3, 164.8

MS: (*m/z*) = 384 (M+1)

Anal. Calcd. for **$C_{22}H_{25}NO_5$:** C, 68.90; H, 6.58; N, 3.65%

Found C, 68.98; H, 6.73; N, 3.61%.

1.6.18: (3*S*,4*S*)-3-Benzyloxy-1-(4-methoxyphenyl)-4-oxo-azetidin-2-carbaldehyde (1.05b):

A mixture of azetidin-2-one **1.28** (3.83 g, 10 mmol) and PTSA (0.570 g, 3 mmol) in THF (40 mL) and water (15 mL) was refluxed for 24 h. After completion of reaction (TLC), the reaction mixture was neutralized with $NaHCO_3$ and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (25 mL) and the organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diol **1.29**, which was then dissolved in acetone (50 mL) and water (25 mL) and cooled to 0 °C. To the cooled diol solution, $NaIO_4$ (2.60 g, 12 mmol) was added in portions. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent was removed and the residue was dissolved in CH_2Cl_2 (30 mL), washed with water (2 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL), brine solution (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford **1.05b** (2.65 g, 85%) as a white solid.

m.p. 157-158 °C

$[\alpha]_D^{30}$ = -176.2 (c 0.42, $CHCl_3$)

IR, ^{1}H NMR, ^{13}C NMR spectral data same as for **1.05a**.

MS: (*m/z*) = 312 (M+1)

Anal. Calcd. for **$C_{18}H_{17}NO_4$:** C, 69.43; H, 5.51; N, 4.50%

Found C, 69.37; H, 5.68; N, 4.63%.

1.6.19: (3*R*,4*S*)-3-Benzyloxy-4-hept-1-enyl-1-(4-methoxyphenyl)azetidin-2-one(1.12b):

Following the similar procedure described for **1.12a** a solution of a *n*-hexyltriphenylphosphonium bromide (1.538 g, 3.6 mmol) in anhydrous THF at 0 °C was added *n*-butyl lithium (2.20 ml, 3.3 mmol, 1.5 M, colour change from yellow to orange red was observed). A solution of azetidin-2-one **1.05b** (0.934 g, 3 mmol) in anhydrous THF (20 ml) was added drop-wise at 0 °C to the reaction mixture and then allowed to warm up to room temperature to get an inseparable mixture of *E* and *Z* isomers **1.12b** (0.853 g, 75%) as a colourless viscous oil by flash column on silica gel (EtOAc/pet. ether 1:9 as eluent).

1.6.20: (3*S*,4*R*)-3-Benzyloxy-4-heptyl-1-(4-methoxyphenyl)azetidine-2-one (1.13b) and (3*S*,4*R*)-4-heptyl–3-hydroxy-1-(4-methoxyphenyl)azetidine-2-one (1.14b):

Following the similar procedure described for **1.13a** and **1.14a,** compound **1.13b** and **1.14b** were prepared by hydrogenation of **1.12b** (0.760 g, 2 mmol).

Compound **1.13b** was obtained as viscous oil (0.688 g, 90%).

$[\alpha]_D^{30}$ = -113.4 (c 0.80, $CHCl_3$)

IR, ^{1}H NMR, ^{13}C NMR spectral data same as for **1.13a**.

MS: (*m/z*) = 382 (M+1)

Anal. Calcd. for **$C_{24}H_{31}NO_3$:** C, 75.57; H, 8.21; N, 3.67%

Found C, 75.57; H, 8.35; N, 3.61%.

Compound **1.14b**:

Compound **1.14b** was obtained as white crystals; (0.035 g, 6%).

m.p. 106-107 °C

$[\alpha]_D^{30}$ = -110.3 (c 0.52, $CHCl_3$)

^{1}H NMR, ^{13}C NMR spectral data same as for **1.14a**.

MS: (*m/z*) = 292 (M+1)

Anal. Calcd. for **$C_{17}H_{25}NO_3$:** C, 70.06, H, 8.66; N, 4.81%

Found C, 70.33; H, 8.79; N, 4.95%.

1.6.21: (3*S*,4*R*)-3-Benzyloxy-4-heptylazetidin-2-one (1.15b):

Following the similar procedure described for **1.15a**, compound **1.15b** was prepared from **1.13b** (0.572 g, 1.5 mmol) using CAN (2.469 g, 4.51 mmol). It was obtained as a white solid; (0.351 g, 85%).

m.p. 55-56 °C

$[\alpha]_D^{30}$ = -38.6 (c 0.7, $CHCl_3$)

IR, ^{1}H NMR, ^{13}C NMR spectral data same as for **1.15a.**

MS: (*m/z*) = 276 (M+1)

Anal. Calcd. for **$C_{17}H_{25}NO_2$:** C, 74.13; H, 9.17; N, 5.08%

Found C, 74.18; H, 9.09; N, 4.96%.

1.6.22: (3*S*,4*R*)-4-Heptyl-3-hydroxyazetidin-2-one (1.16b):

Following the similar procedure described for **1.16a**, compound **1.16b** was prepared from **1.15b** (0.275 g, 1 mmol) by transfer hydrogenation using ammonium formate (0.315 g, 5 mmol). It was obtained as a white crystalline solid; (0.176 g, 95%).

m.p. 111-113 °C

$[\alpha]_D^{30}$ = -40.5 (c 0.25, $CHCl_3$)

IR, ^{1}H NMR, ^{13}C NMR spectral data same as for **1.16a**.

MS: (*m/z*) = 186 (M+1)

Anal. Calcd. for **$C_{10}H_{19}NO_2$:** C, 64.81; H, 10.36 ; N, 7.56%

Found C, 64.97; H, 10.33; N, 7.73%.

1.6.23: (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (1.01b):

Following the similar procedure described for **1.01a**, compound **1.01b** was prepared from **1.16b** (93 mg, 0.5 mmol) by hydrolysis using 3M HCl (5 mL). It was obtained as a white solid; (71 mg, 70%).

m.p. 219-220°C (dec), lit. m.p. 218.4-219.7 °C (dec)[65g]

$[\alpha]_D^{30}$ = +6.5 (c 0.47, 1N HCl), lit. $[\alpha]_D^{22}$ = +7.3 (c 0.34, 1N HCl),[65g] $[\alpha]_D^{25}$ = +5.4 (c 0.59, 1M HCl)[64b]

^{1}H NMR, ^{13}C NMR spectral data same as for **1.01a**.

MS: (*m/z*) = 204 (M+1)

Anal. Calcd. for **$C_{10}H_{21}NO_3$:** C, 59.07; H, 10.43; N, 6.89%

Found C, 59.33; H, 10.48; N, 6.95%.

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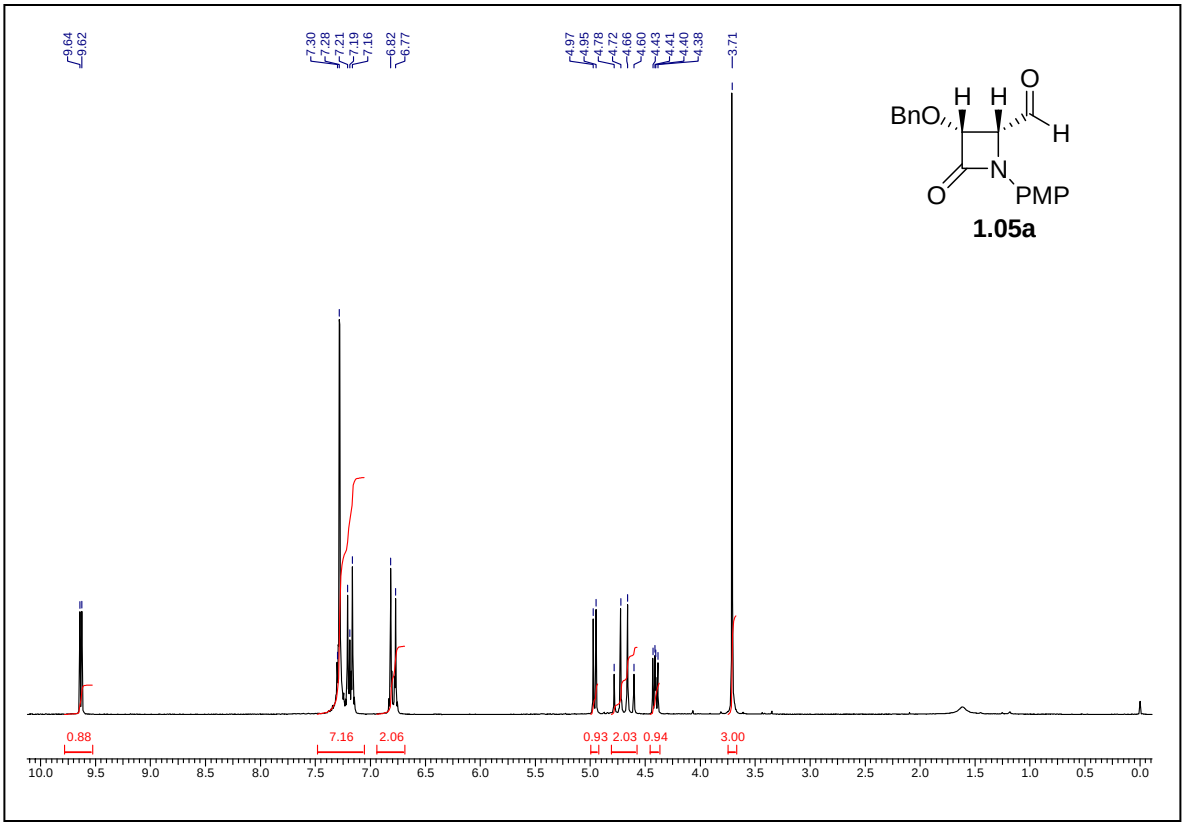
Chapter I

Spectra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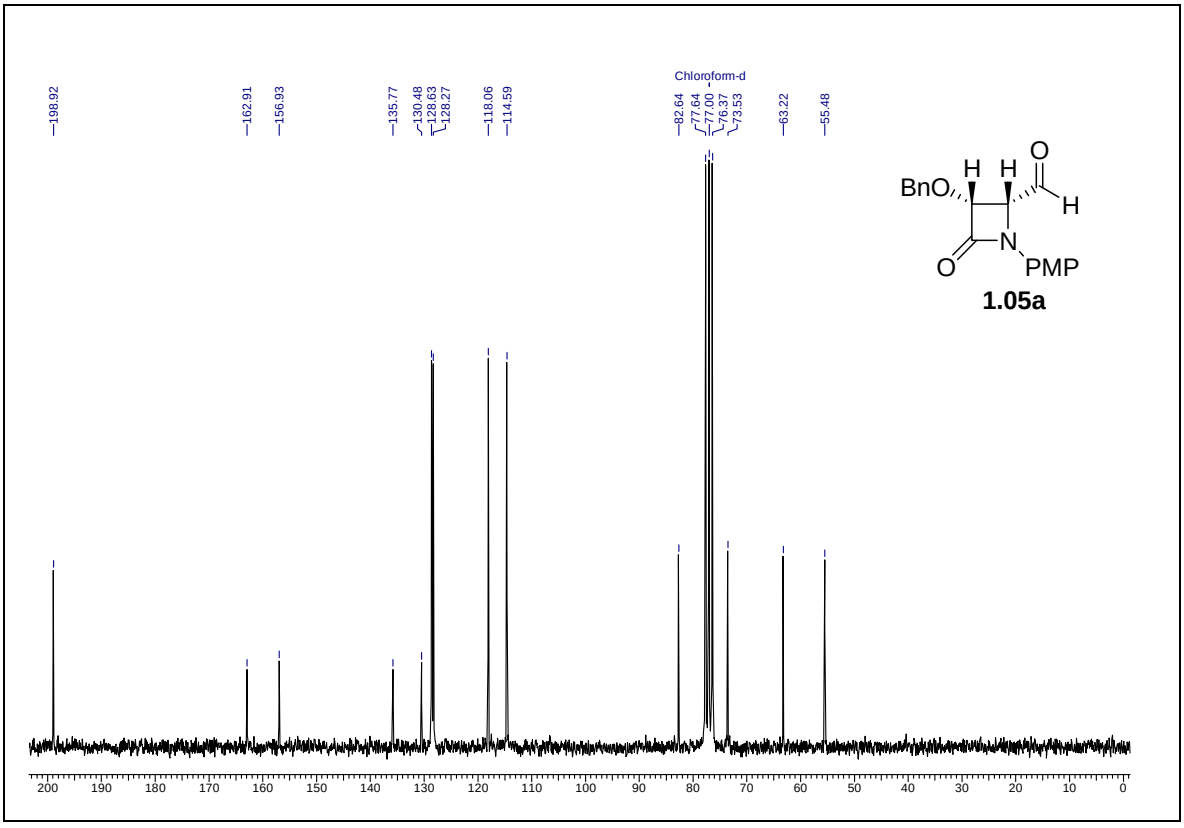
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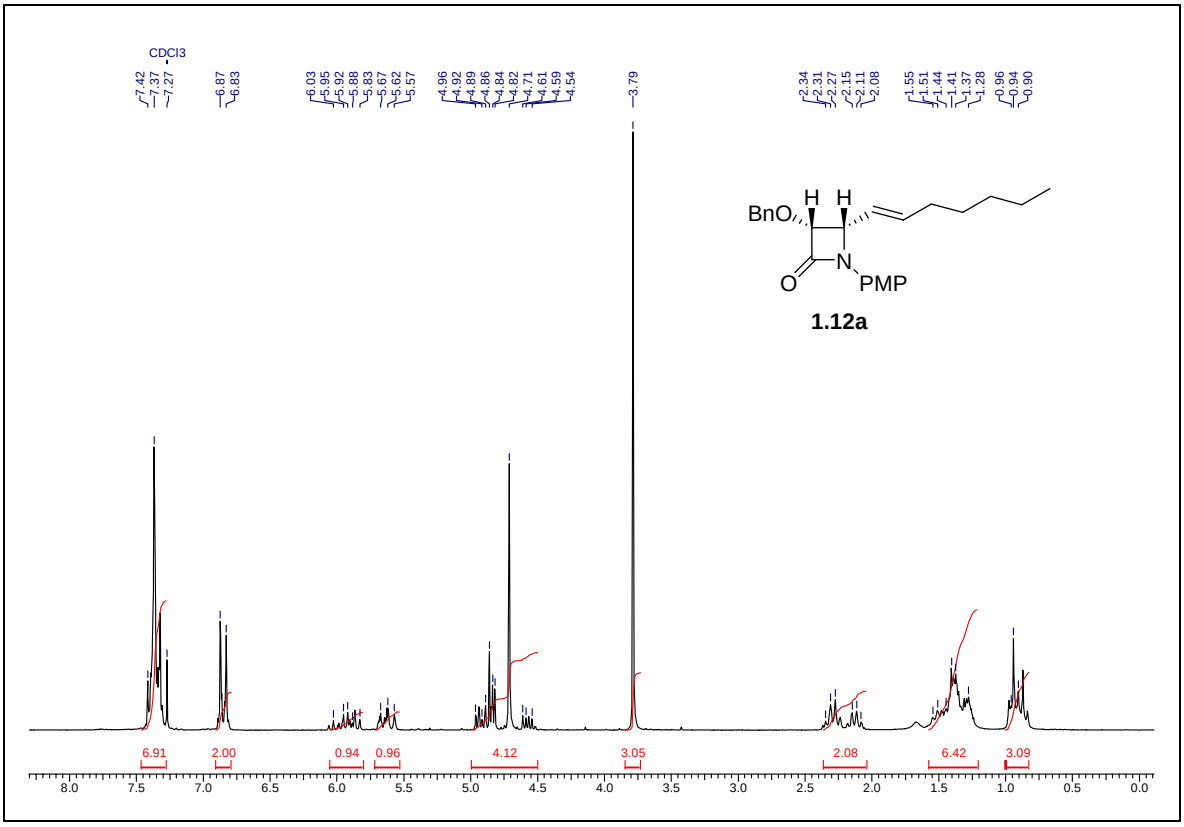
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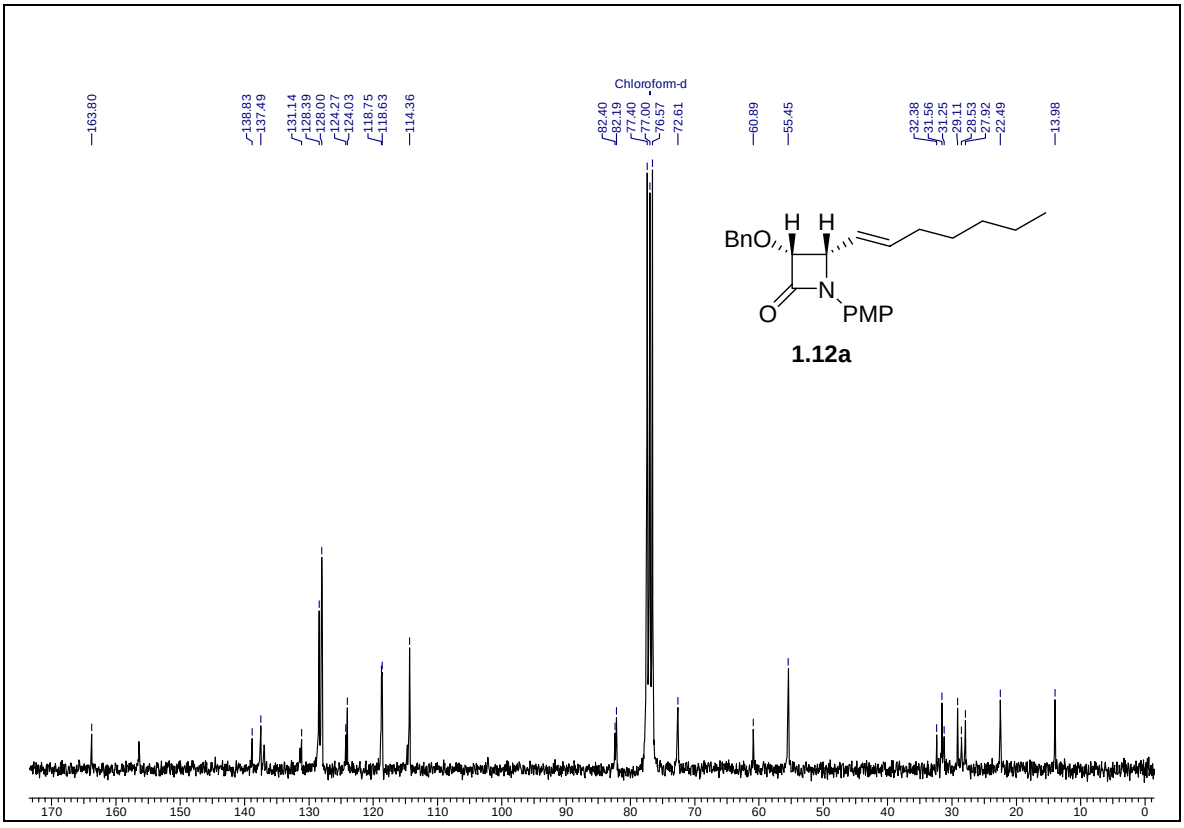
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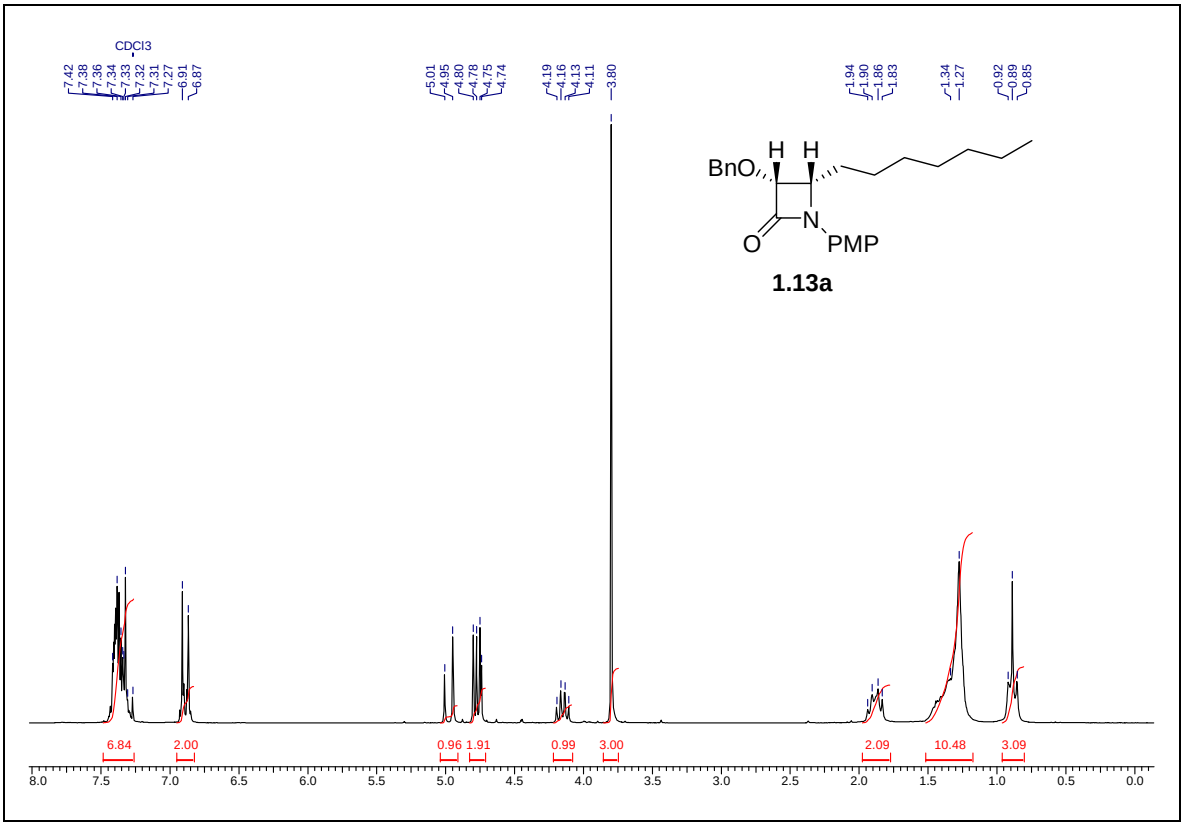
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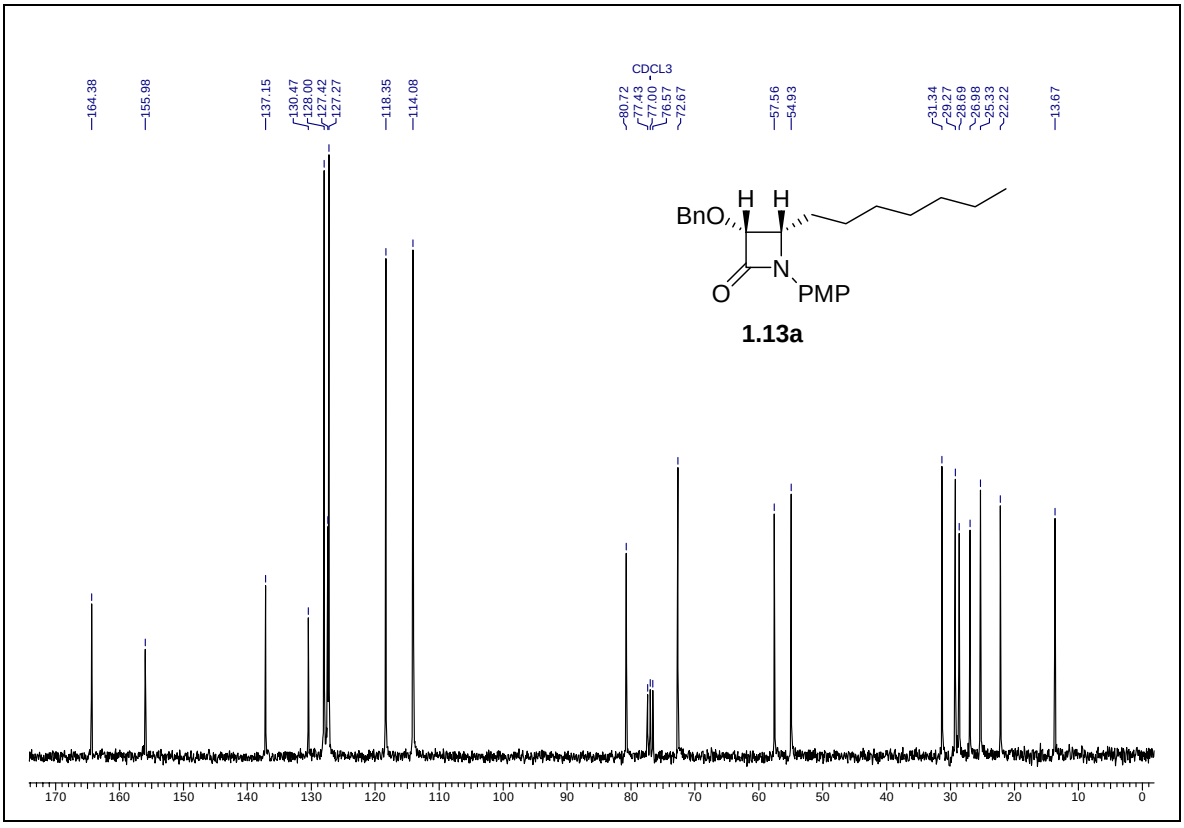
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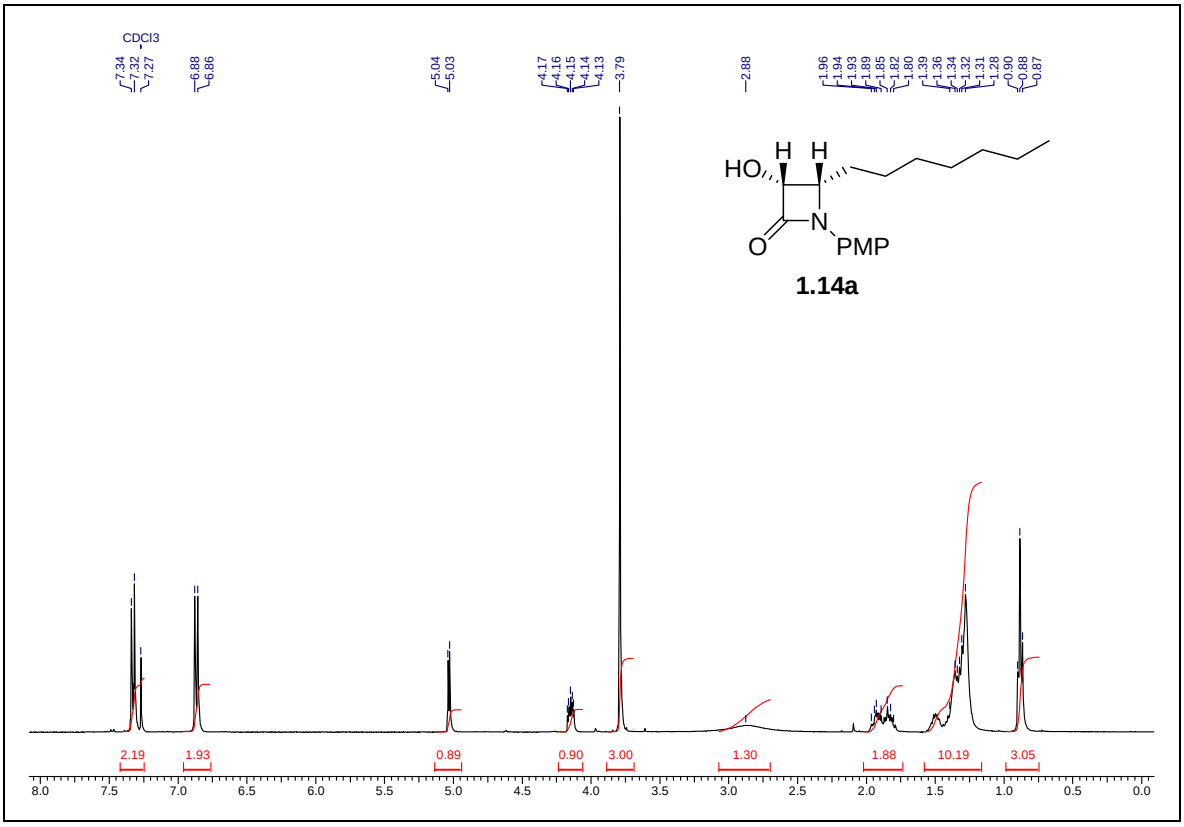
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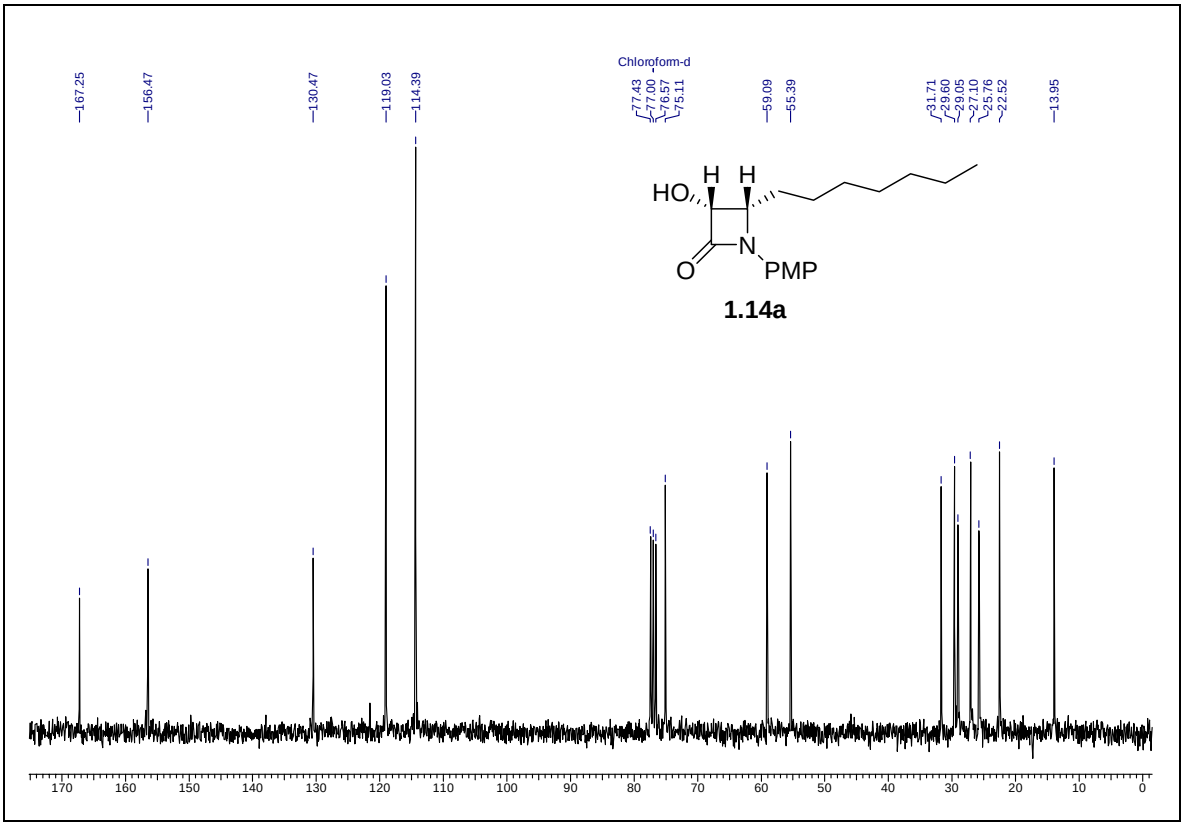
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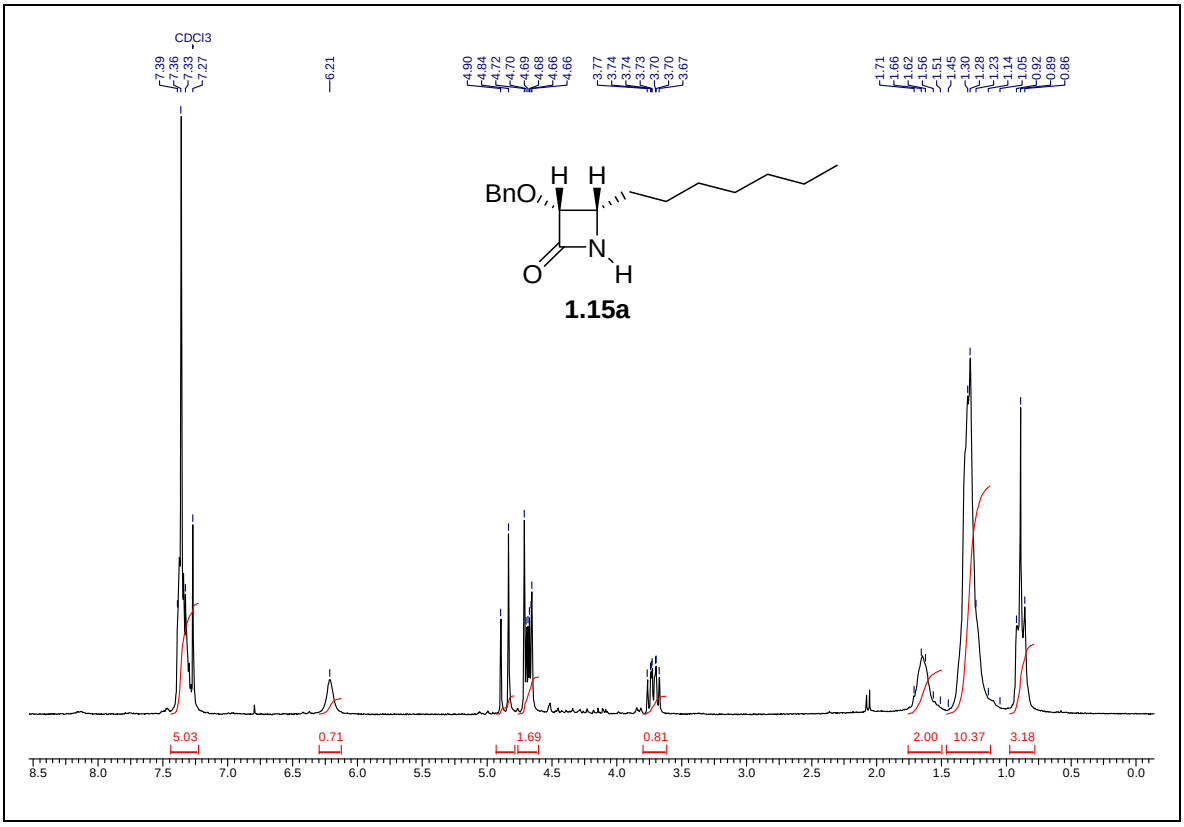
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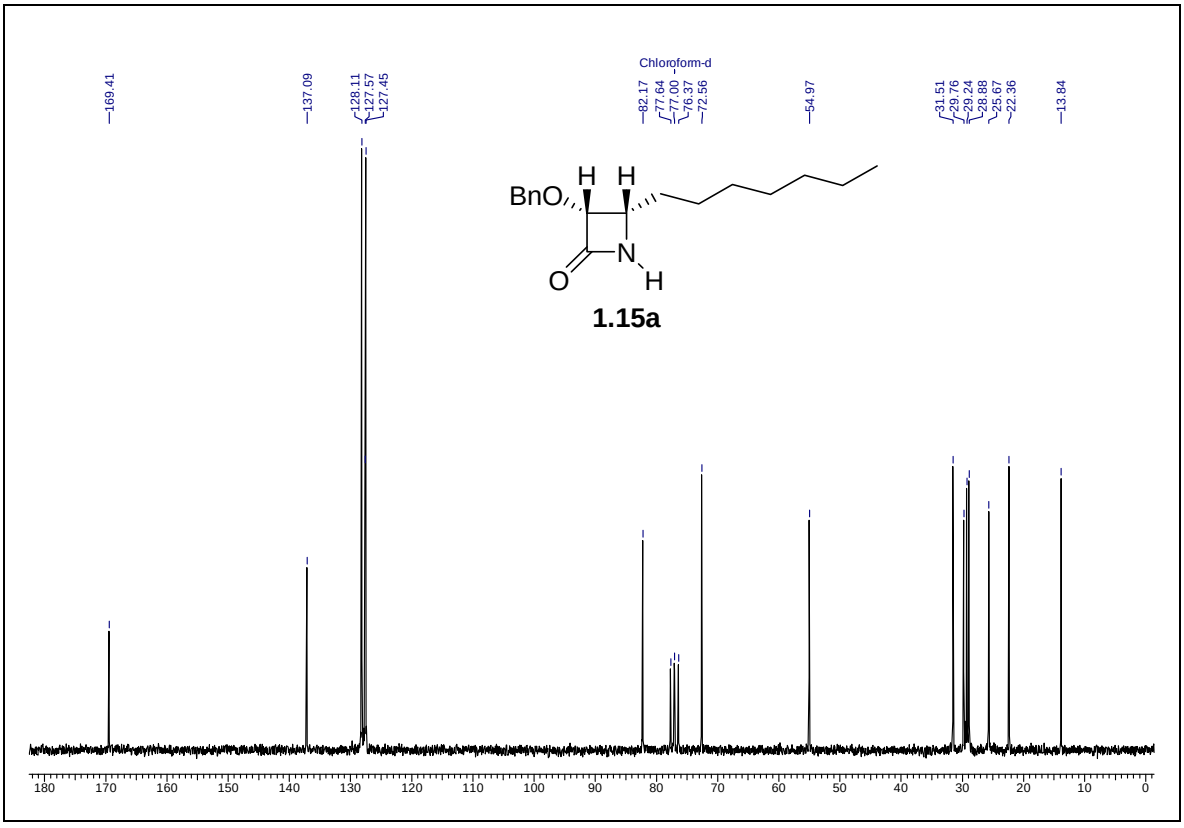
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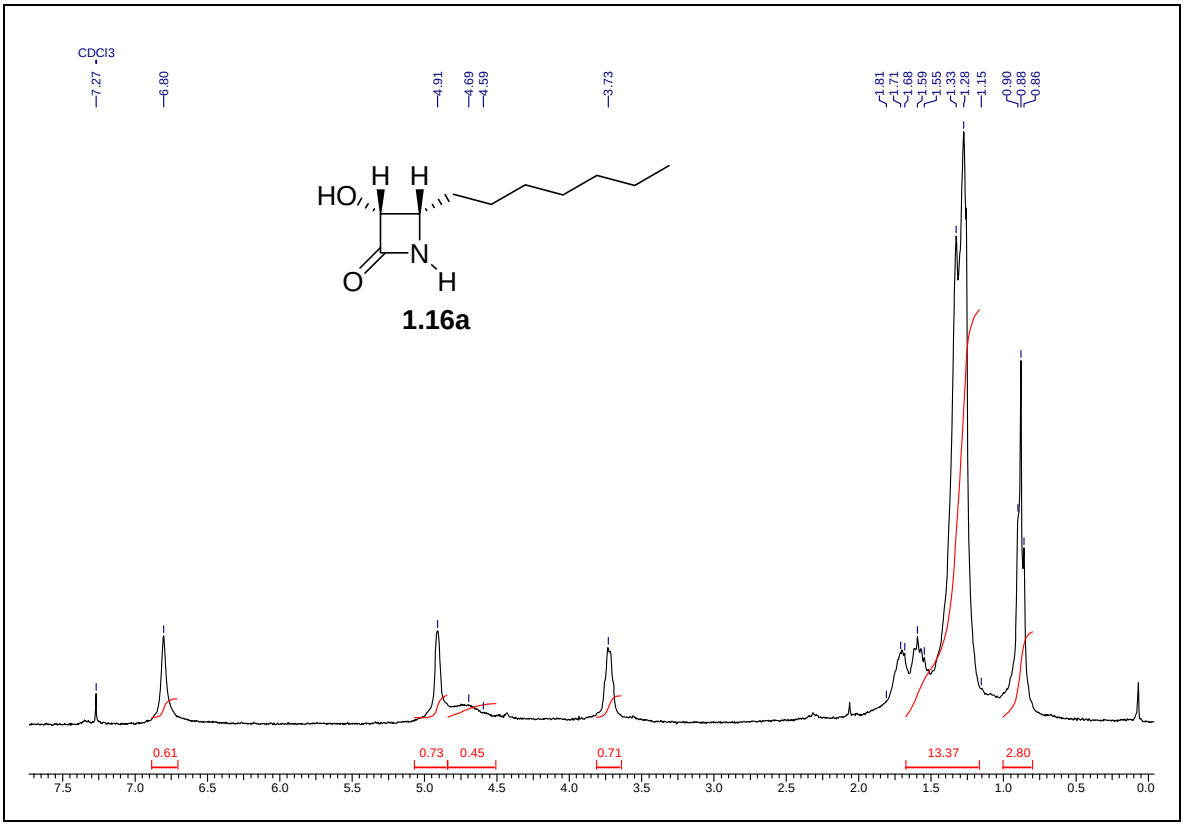
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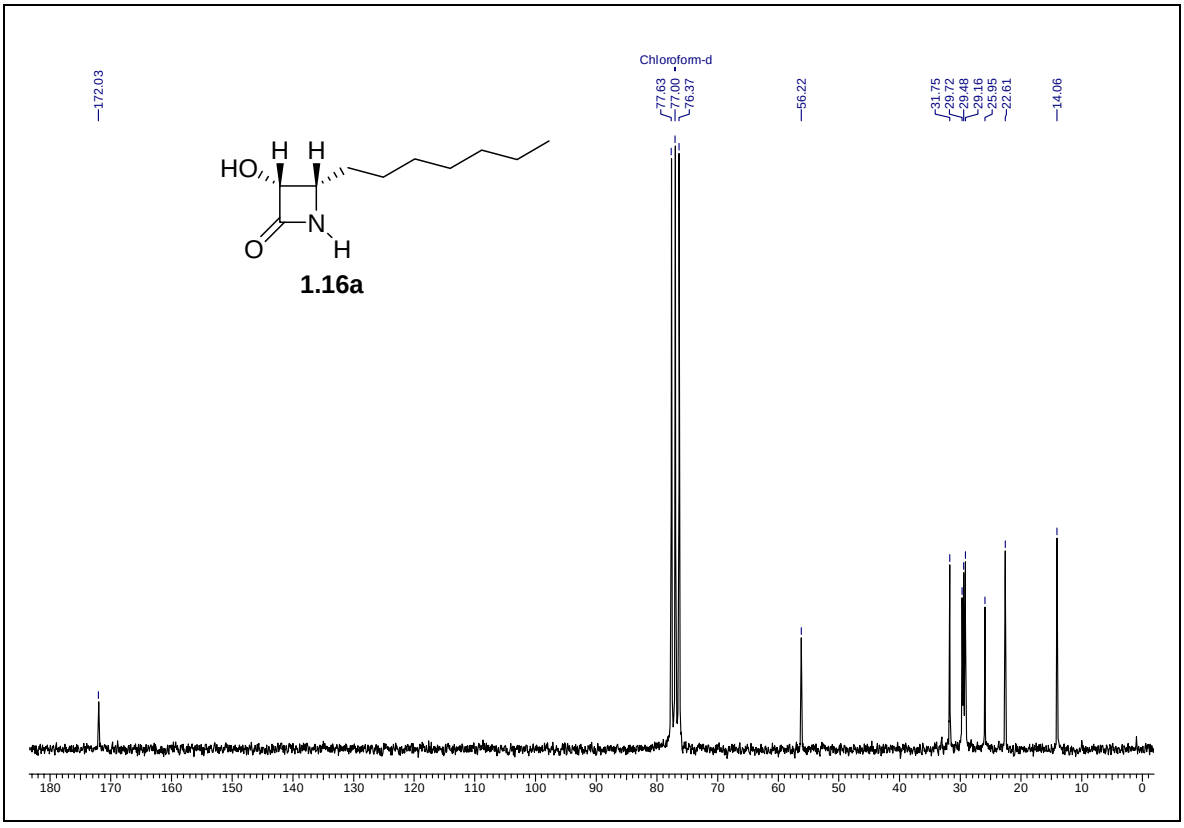
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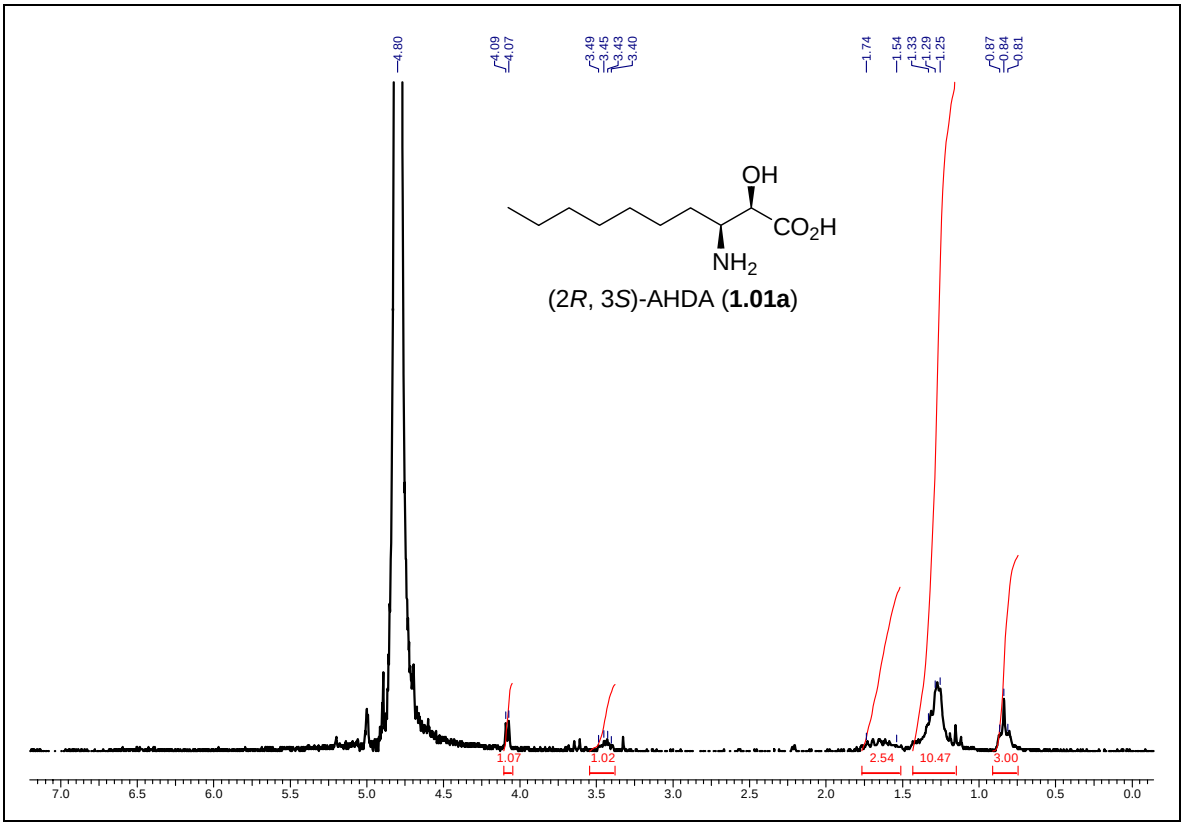

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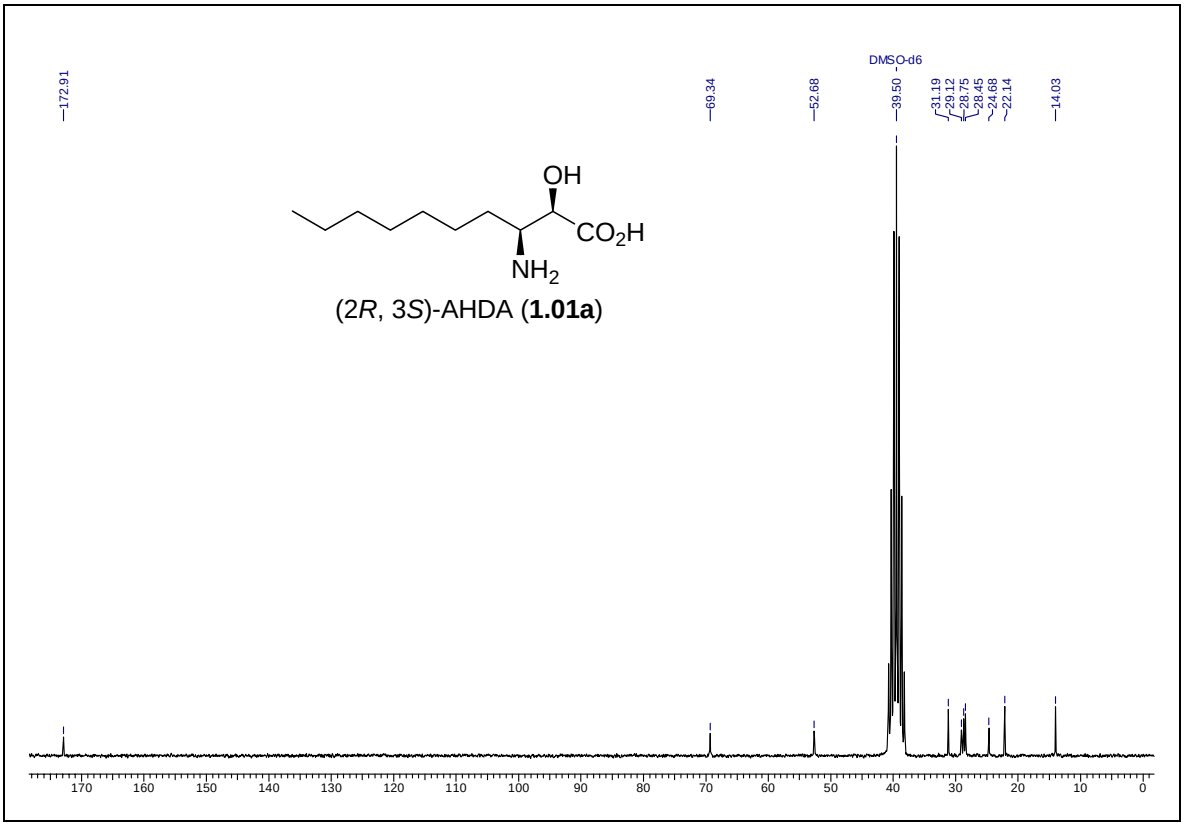

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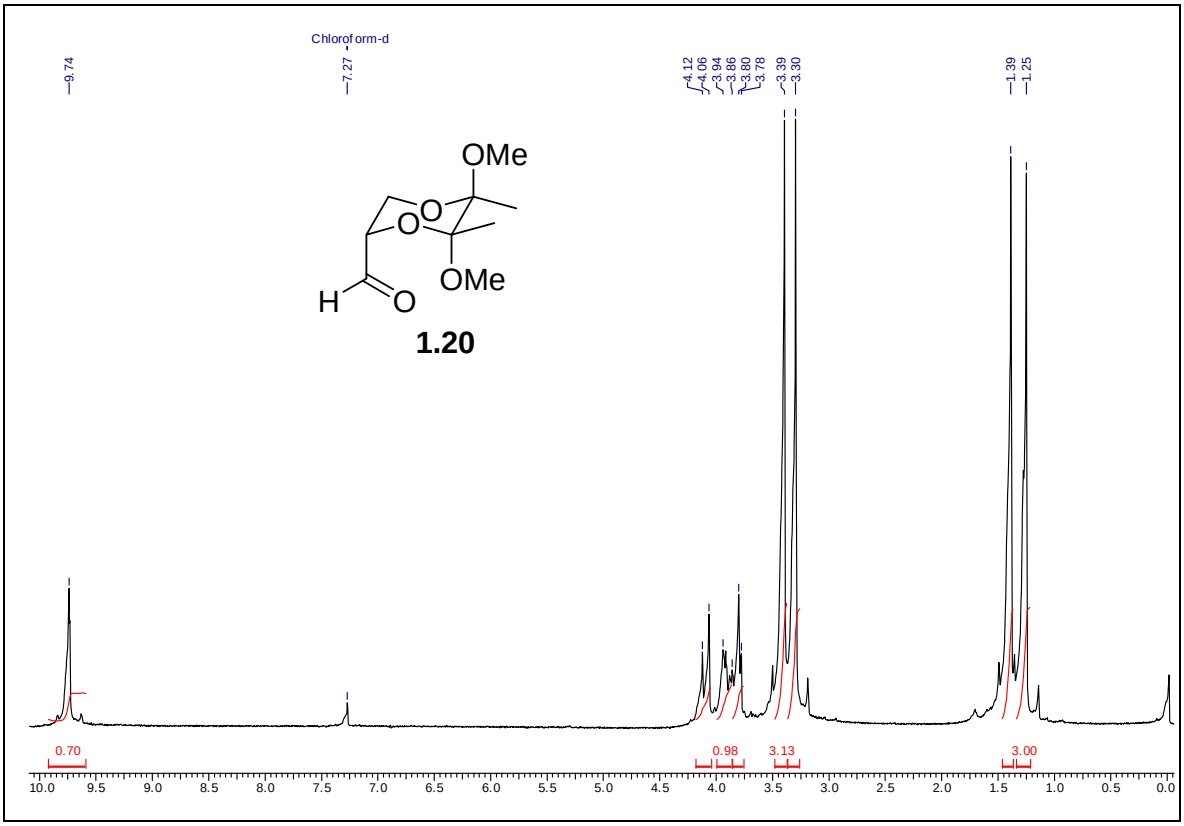
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3.80
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1.25
OMe
O
O
OMe
H
O
1.20
0.70
0.98
3.13
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
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3.5
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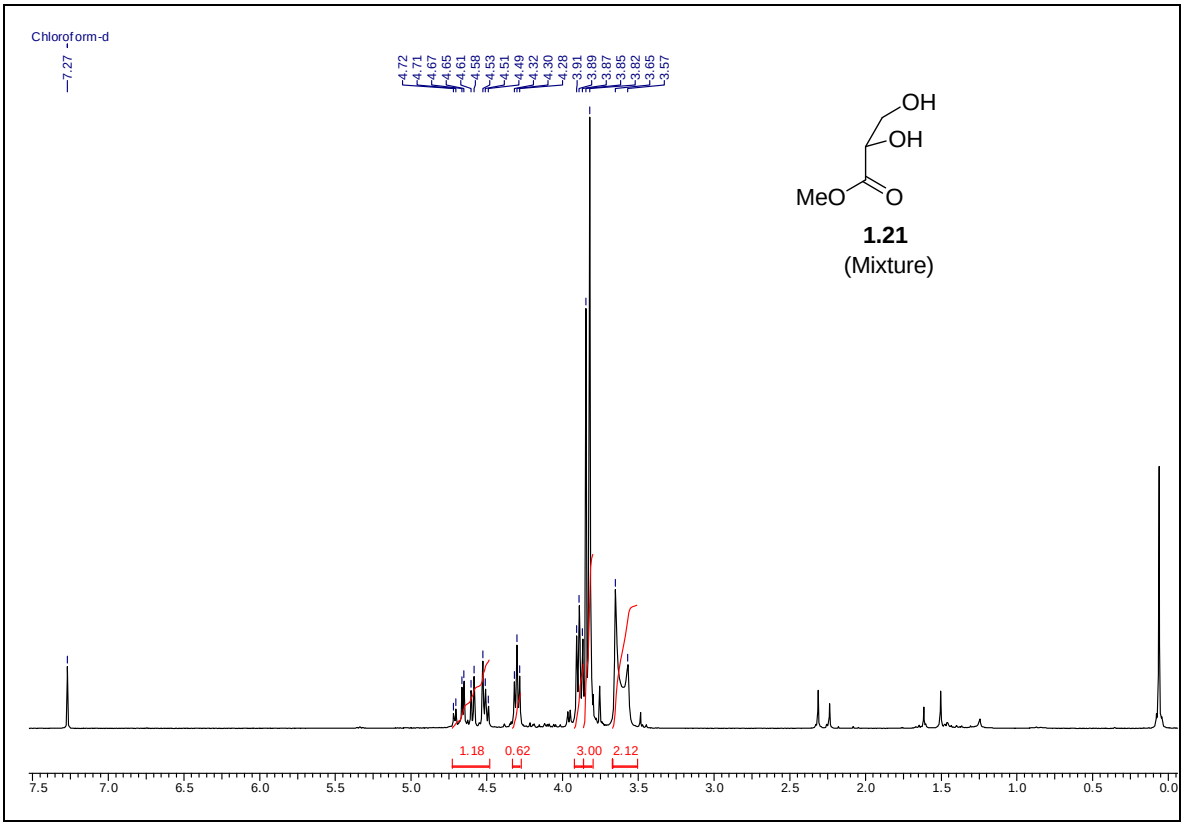
0.0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4.30
4.28
3.91
3.89
3.87
3.85
3.82
3.65
3.57
OH
OH
MeO
O
1.21
(Mixture)
1.18
0.62
3.00
2.12
7.5
7.0
6.5
6.0
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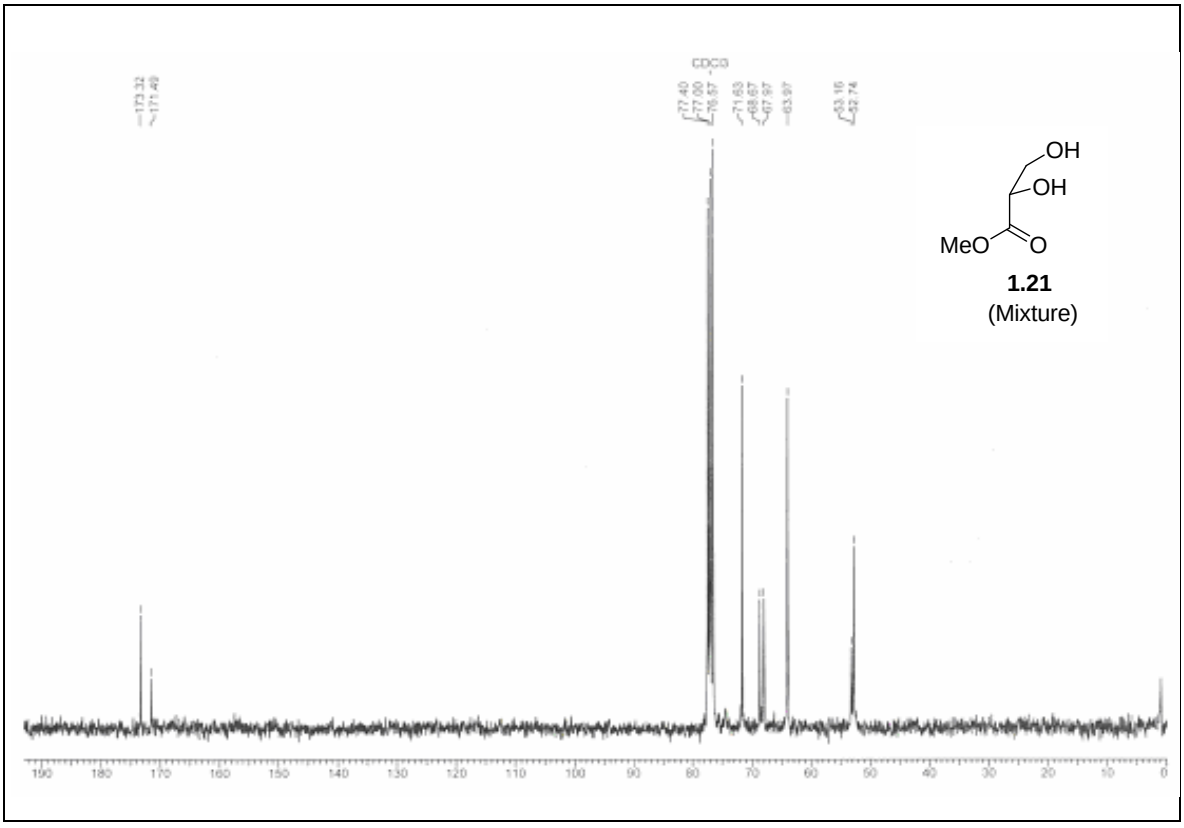
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68.67
67.97
63.97
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OH
MeO
O
1.21
(Mixture)
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150
140
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70
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10
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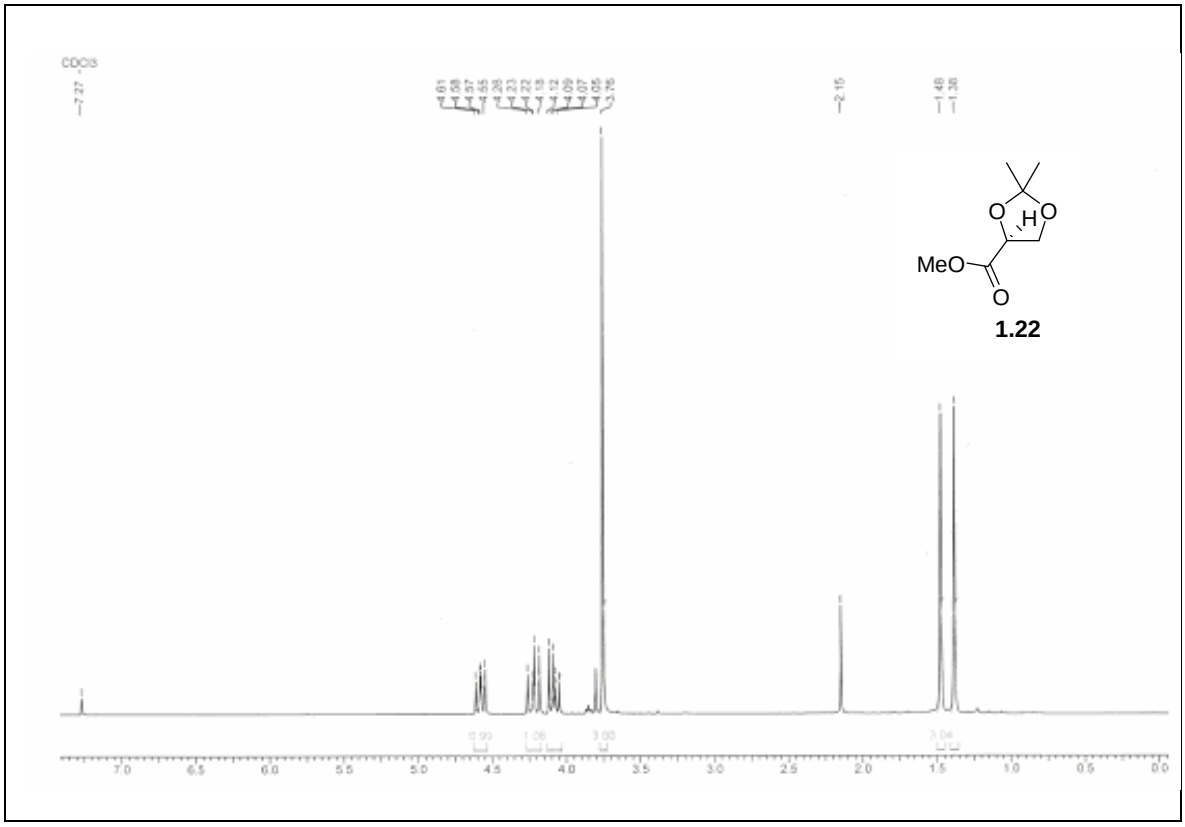
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4.07
4.05
3.75
2.15
1.49
1.38
O
H
O
MeO
O
1.22
0.99
1.06
3.00
3.04
7.0
6.5
6.0
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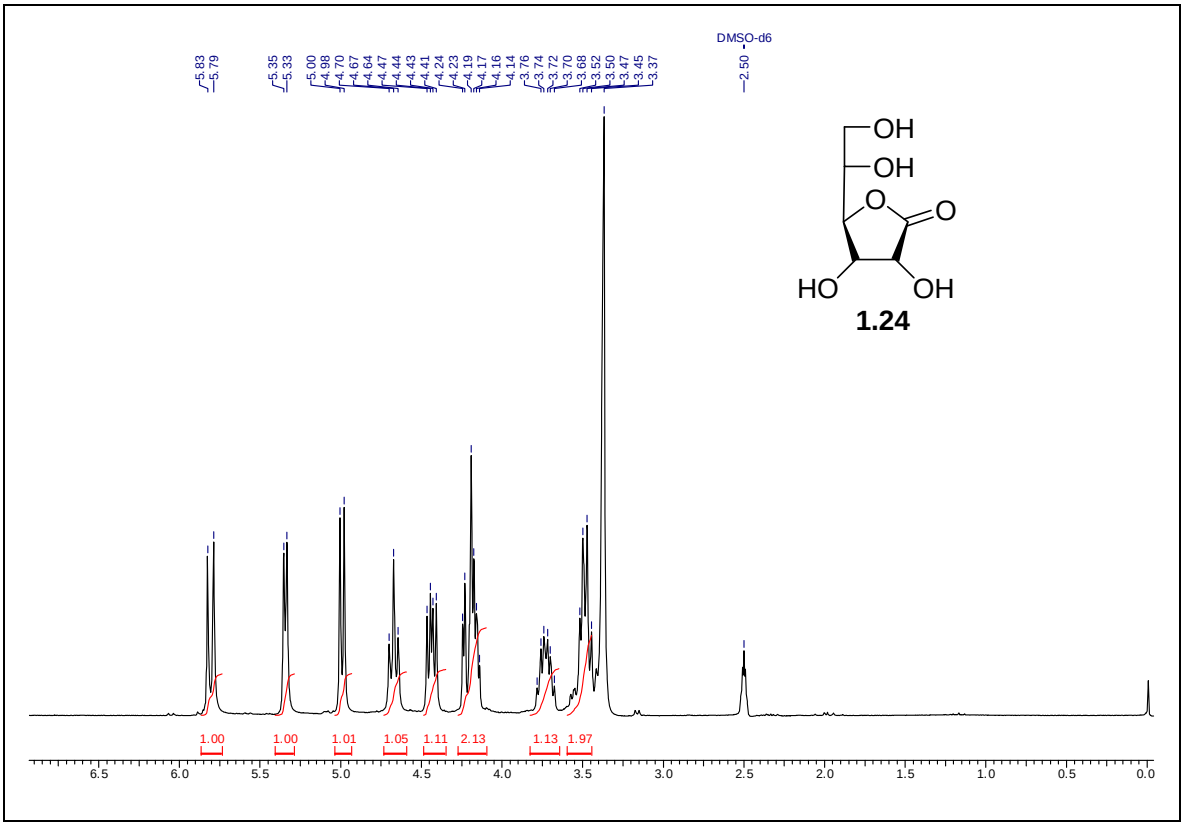
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4.41
4.24
4.23
4.19
4.17
4.16
4.14
3.76
3.74
3.72
3.70
3.68
3.52
3.50
3.47
3.45
3.37
2.50
OH
OH
O
O
HO
OH
1.24
1.00
1.00
1.01
1.05
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2.13
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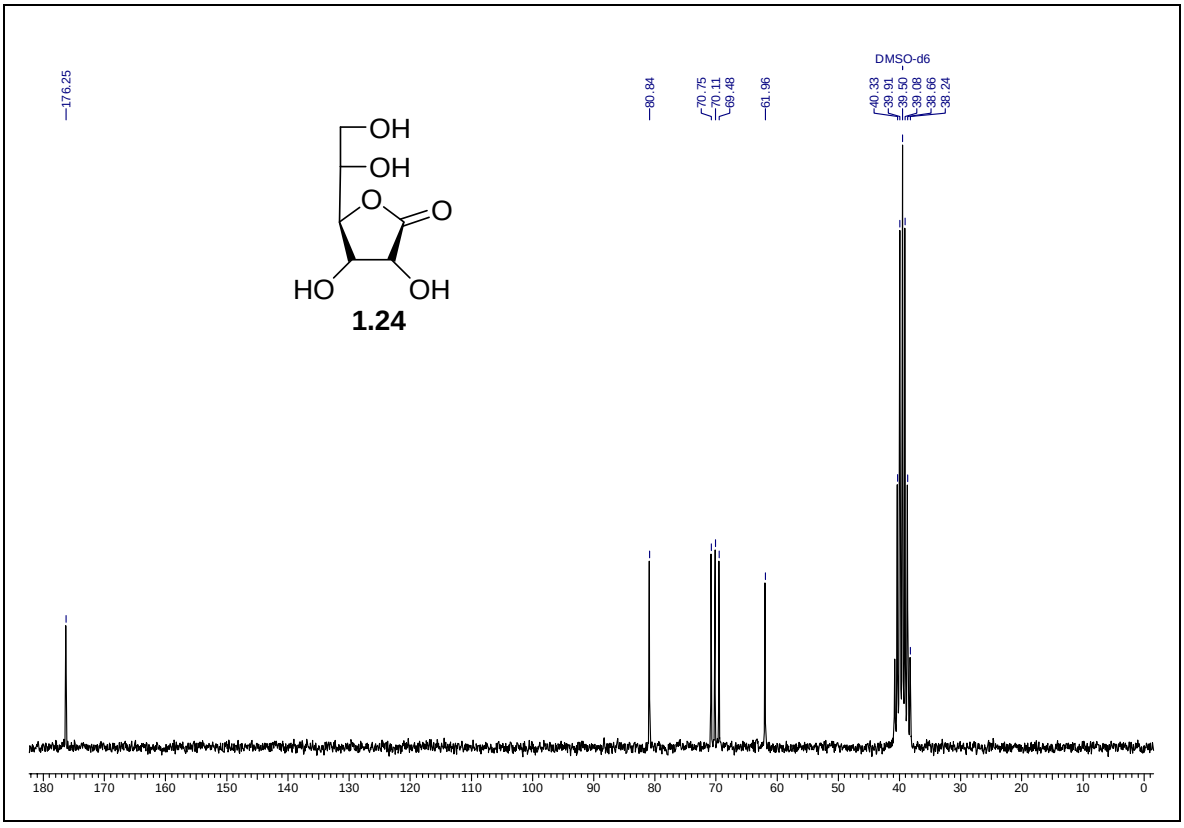
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69.48
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DMSO-d6
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39.50
39.08
38.66
38.24
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OH
O
O
HO
OH
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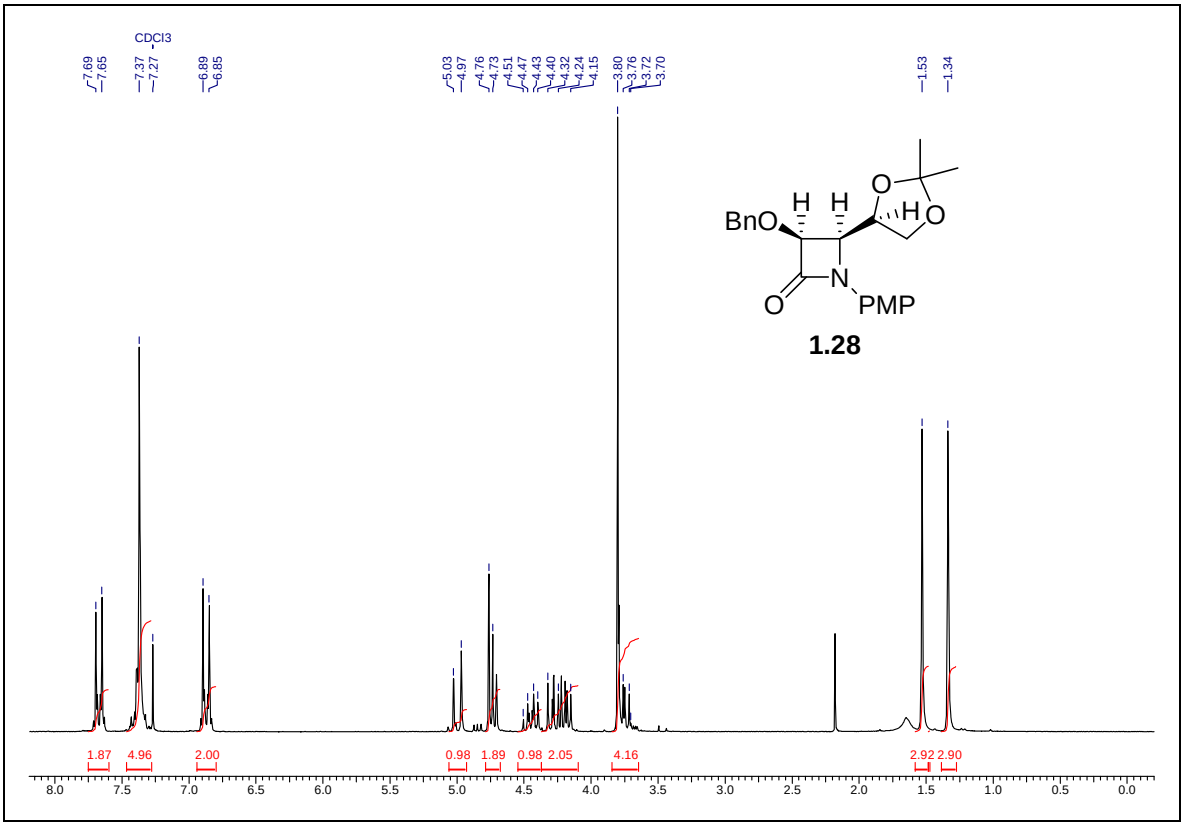
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4.43
4.40
4.32
4.24
4.15
3.80
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3.70
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1.34
BnO
H
H
O
H
O
N
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PMP
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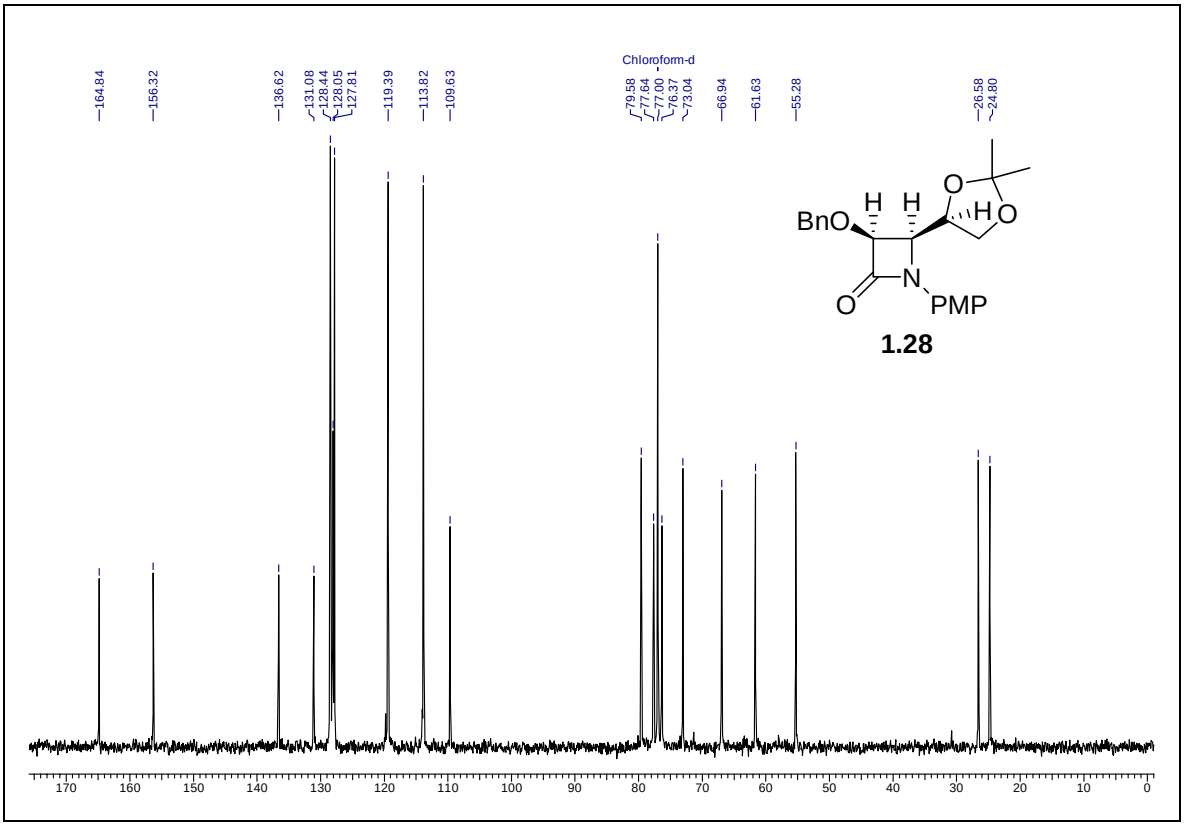
0.98
2.05
4.16
2.92
2.90


Chloroform-d
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136.62
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127.81
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113.82
109.63
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77.64
77.00
76.37
73.04
66.94
61.63
55.28
26.58
24.80
BnO
H
H
O
H
O
N
O
PMP
1.28

Chapter II

Microwave assisted rapid synthesis of 4-amino-3, 4-dihydroquinoline-2-ones from azetidin-2-ones

Part of this work has been published in *Arkivoc*, **2005** (i), 53-64

2.1 Introduction:

Synthesis using microwave has become an important area for developments. It gives organic chemists more time to expand their scientific creativity, test new theories and develop new processes. Instead of spending hours or even days synthesizing a single compound, now same can be synthesized in minutes. In view of its rapidly expanding applications, microwave synthesis can be effectively applied to many organic reactions, not only for rate enhancements but also to improve the yields.[6a]

In addition microwave synthesis creates completely new possibilities in performing chemical transformations. The microwave radiations can transfer energy directly to the reactive species, they can promote transformations that are currently not possible using conventional heating. This is creating a new realm in synthetic organic chemistry.[6a]

The microwave is a form of electromagnetic energy that falls at the lower frequency end of the electromagnetic spectrum, and is defined in the 300 to about 300,000 MHz frequency range. Within this range of electromagnetic energy, only molecular rotation is affected, not molecular structure.[2a] Out of four available frequencies for industrial, scientific, or medical applications, 2450 MHz is preferred because it has the right penetration depth to interact with the laboratory scale samples, and there are power sources available to generate microwaves at this frequency.

Microwave energy consists of an electric field and a magnetic field, though only the electric field transfers energy to heat a substance.[2a] Magnetic field interactions do not normally occur in chemical synthesis. Microwaves moves at the speed of light (300,000km/sec). The energy in microwave photons (0.037kcal/mole) is very low relative to the typical energy required to cleave molecular bonds (80-120kcal/mole); thus, microwaves will not affect the structure of an organic molecule. In the excitation of a molecules, the effect of microwave absorption is purely kinetic.

The ability of a substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the following equation:

$$\varepsilon''/\varepsilon' = \tan \delta$$

Where, tan δ is the dissipation factor of the sample or how efficiently microwave energy is converted into thermal energy. Dielectric loss (ε") is the amount of input microwave energy

that is lost to the sample by being dissipated as heat. Dielectric constant (ε') measures the ability of a solvent to store electric charges.

The high absorbing solvents are ones that have dielectric losses greater than 14.00. Medium absorbers would generally have dielectric loss values between 1.00 and 13.99 and low absorbing molecules have dielectric losses that are less than 1.00. High absorbers like small chain alcohols, DMSO, and nitrobenzene all have large dielectric losses, so they heat very quickly within the microwave chamber. Medium absorbing solvents include DMF, acetonitrile, butanols, ketones and water these also gets heated in microwave but requires more time to reach desired temperature. Additionally, chloroform, dichloromethane, ethyl acetate, ethers, and hydrocarbons, are very low microwave absorbing solvents.[6a] They can be heated to temperatures well above their boiling points, but they take much longer time. However, it is possible to use mixtures comprising of microwave active/microwave inactive solvents.[6f,g]

Reaction in microwave can be carried out either in a open erlenmeyer flasks at atmospheric pressure or in a closed vessel under inert conditions.[2b,6a] One can carry out a thermally driven reaction in a microwave oven with one of the component microwave active. If neither the reagents or solvents couple then it may be possible to use a microwave active additive or solid support generate heat[3]. Some of these inorganic additives can easily reach temperatures in excess of 1000 °C[4] very rapidly and decomposition of materials may be problematic, therefore some precautions regarding superheating and associated fire hazards or explosion should be taken into consideration.

If the solvents are to be used as the source of heat then they must couple effectively with microwave radiation. Solvents such as DMF, MeCN, and CH_2Cl_2 are all useful for carrying out organic reactions but obviously there are some limitations to each. The use of water is appealing. Microwave irradiation solvents can be heated above their boiling points and it may be argued this form of superheating which leads to observed rate enchancements for many reactions.[5,6f]

Neverthless the use of microwave irradiation in enhancing chemical transformation has gained considerable attention in recent years due to the advantages such as rapid reaction rate and pure product formation with higher yields.[6] Although the reason for the

rate enhancement is not clear, selective absorption of microwave energy by polar molecules or transition state may be responsible for the acceleration of the reaction.

Applications of Microwave in Organic Synthesis:

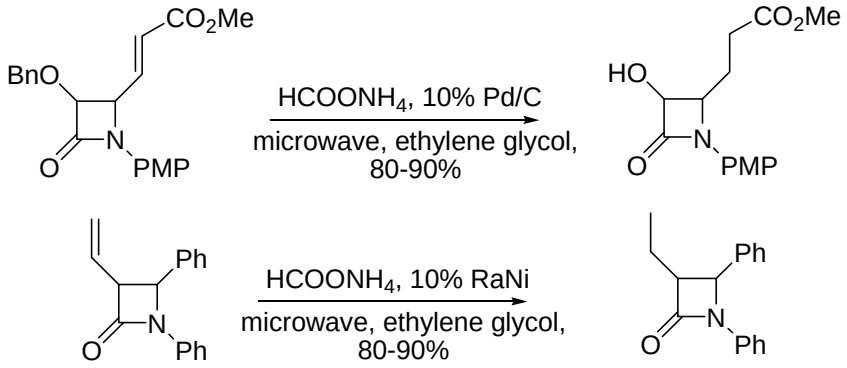
There are several applications of microwave assisted organic synthesis and the topic has been reviewed well. Only some of the relevant reactions have been selected for discussion in this chapter.

Bose et al. have effectively used microwaves in β-lactam chemistry. The monodebromination of 6,6-dibromo penicillanic acid has been achieved using tributyltinhdyride and AIBN in microwave[1]. The reaction is over in just 3 mins in good yield (Scheme 2.01).

Scheme 2.01

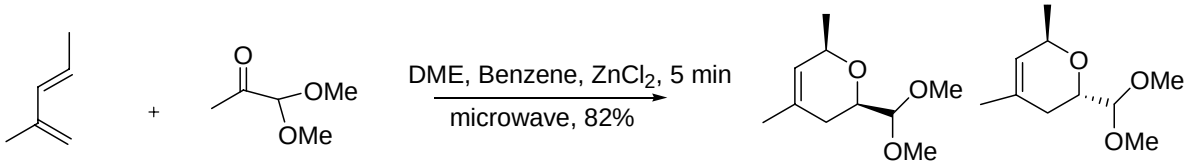
Bose and co-workers also reported the hydrogenation of substituted β-lactams using Pd/C or Raney nickel in microwave in excellent yields[7] (Scheme 2.02).

Scheme 2.02



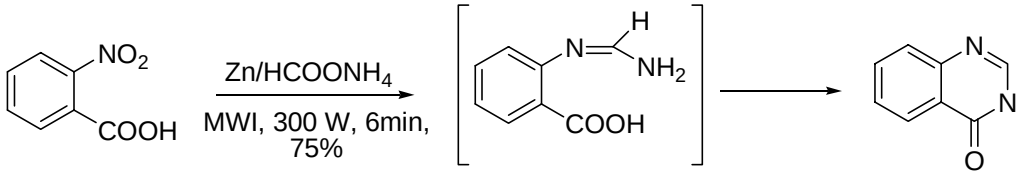
Soufiaoui et al.[8] demonstrated the benefits of microwave irradiation for the isolation of products from hetero-Diels-Alder reaction. Cycloaddition of diene with dienophile under microwave irradiation leads to diastereomeric mixture of products in good yield while under conventional heating no products are isolated (Scheme 2.03).

Scheme 2.03



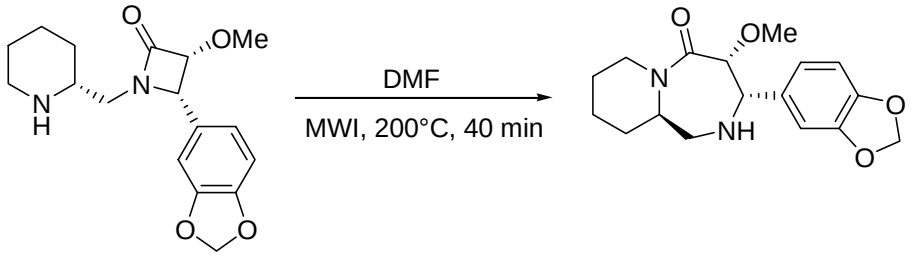
Recently, Kamal et al.[9] have employed microwave in the synthesis of pharmaceutically important 4(3*H*)-quinazolinones. *O*-Nitro benzoic acid on reduction with Zn/$HCOONH_4$ gives a formamide intermediate, which on further cylization give 4(3*H*)-quinazolinones (Scheme 2.04).

Scheme 2.04



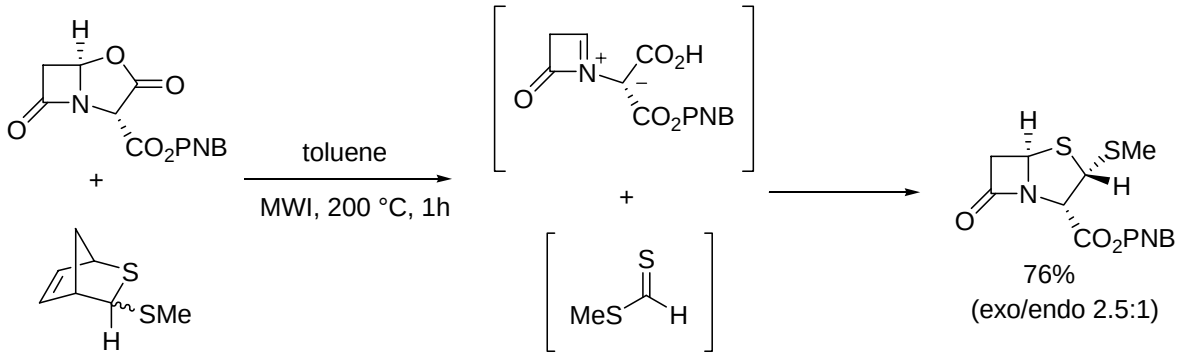
Vasudevan et al.[10] have used microwave irradiation for intramolecular transamidation of azetidin-2-one to generate a collection of bicyclic fused azepinones in about 50% yield (Scheme 2.05).

Scheme 2.05



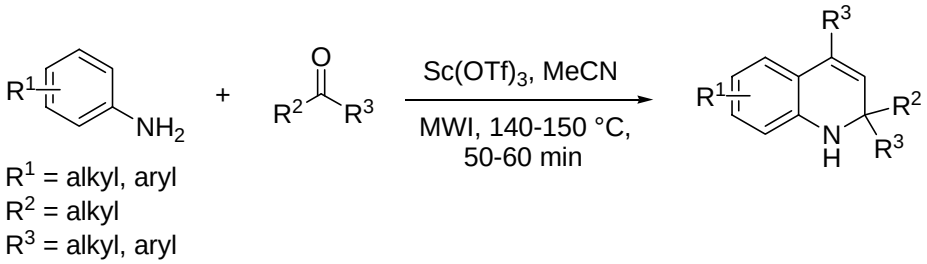
Gallagher and co-workers reported the synthesis of penem derivatives using microwave irradiation by azomethine ylide-thione cycloaddition reaction[11] (Scheme 2.06).

Scheme 2.06



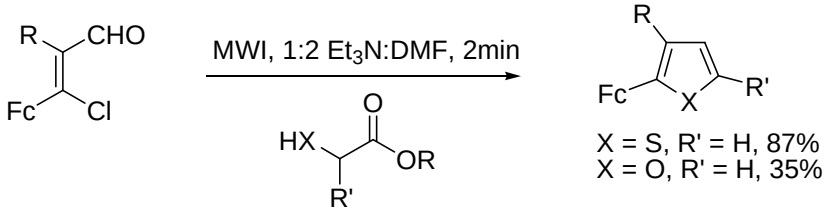
Theoclitou and Robinson have synthesized 2,2,4-trisubstituted 1,2-dihydroquinoline by the Lewis acid-catalyzed Skraup cyclization of substituted anilines with appropriate ketones using microwave irradiation [12] in good yield (Scheme 2.07).

Scheme 2.07



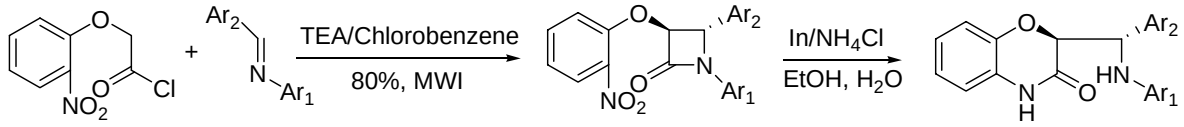
Pucivoa, Ertl and Toma have utilized microwave irradiation in the preparation of ferrocenyl (Fc) substituted heteroaromatic systems.[13] Treatment of ferrocenyl substituted acrylaldehyde with ester gave ferrocenyl substituted heterocycles in moderate to good yield (Scheme 2.08).

Scheme 2.08



Banik et al.[14] have reported the synthesis of oxazines through microwave assisted synthesis of azetidin-2-one in good yield (Scheme 2.09).

Scheme 2.09



Ar_1 = *p*-anisyl

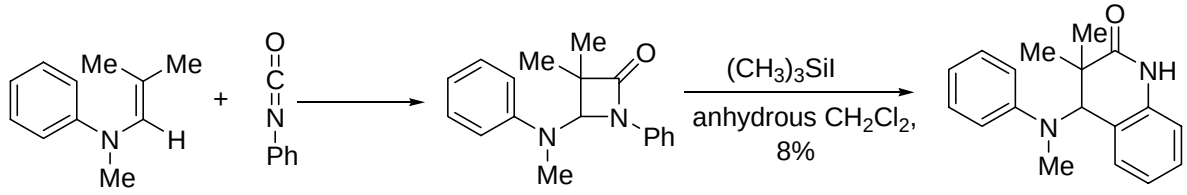
Ar_2 = phenyl

2.2 Background for the present work:

The amide bond of β-lactams is prone to cleavage by nucleophiles such as amino and hydroxyl group to form an open chain amide or ester functionality.[15,16] This high chemical reactivity of β-lactams has been applied to a synthesis of some of the heterocycles in order to demonstrate clearly the synthetic utility of monocyclic β-lactams.[17,18,19] Some of the synthetic applications have been discussed here.

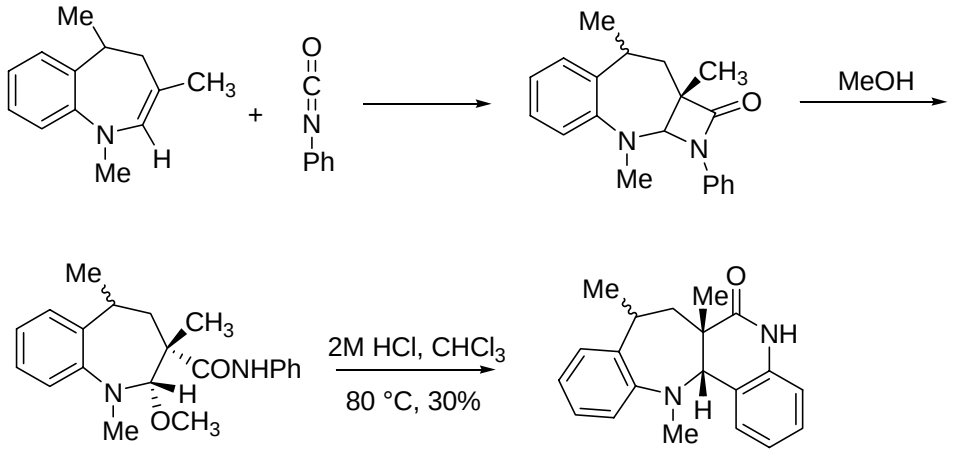
Uriac et al. and coworkers have reported a [2+2] cycloaddition reaction of phenyl isocyanate with ketene to give 3,3 dimethyl 4-amino substituted β-lactam. This β-lactam on C4-N1 bond cleavage using trimethyl silyl iodide gave 4-amino 3,3-dimethyl 4-hydro quinolin-2-one in poor yield[20a,b,c] (Scheme 2.10).

Scheme 2.10



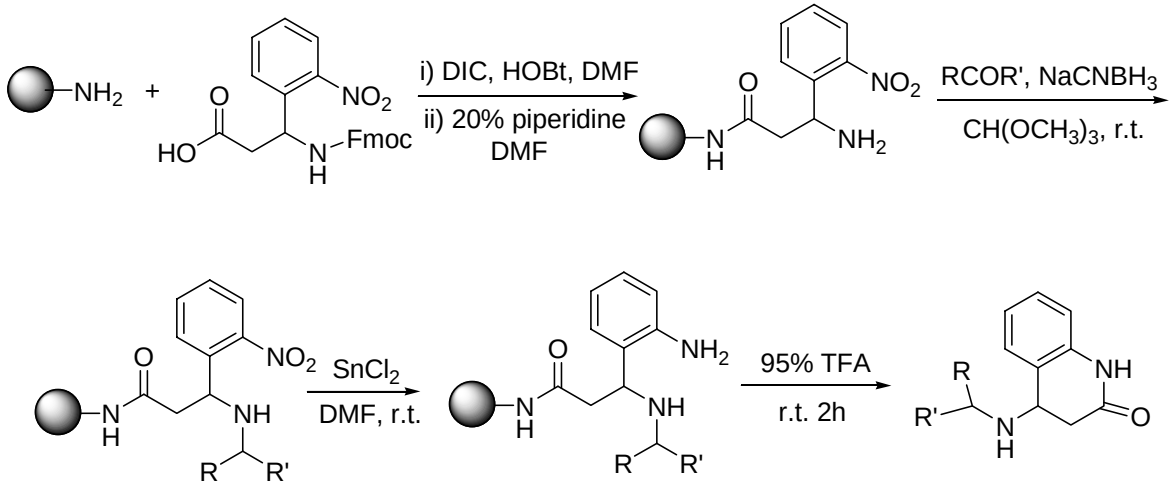
They have also reported the synthesis of polycyclic 4-amino quinolin-2-one by C4-N1 bond cleavage of azetidin-2-one using MeOH, which on further rearrangement in acidic medium gave polycyclic 4-amino quinolin-2-one in low yield[20b,c] (Scheme 2.11).

Scheme 2.11



Lam K. S. et al.[21] have reported the synthesis of 3-unsubstituted 4-amino quinolin-2-one from *N*-Fmoc-β-amino-2-nitrobenzenepropanoic acid on solid support using rink amide resin (Scheme 2.12).

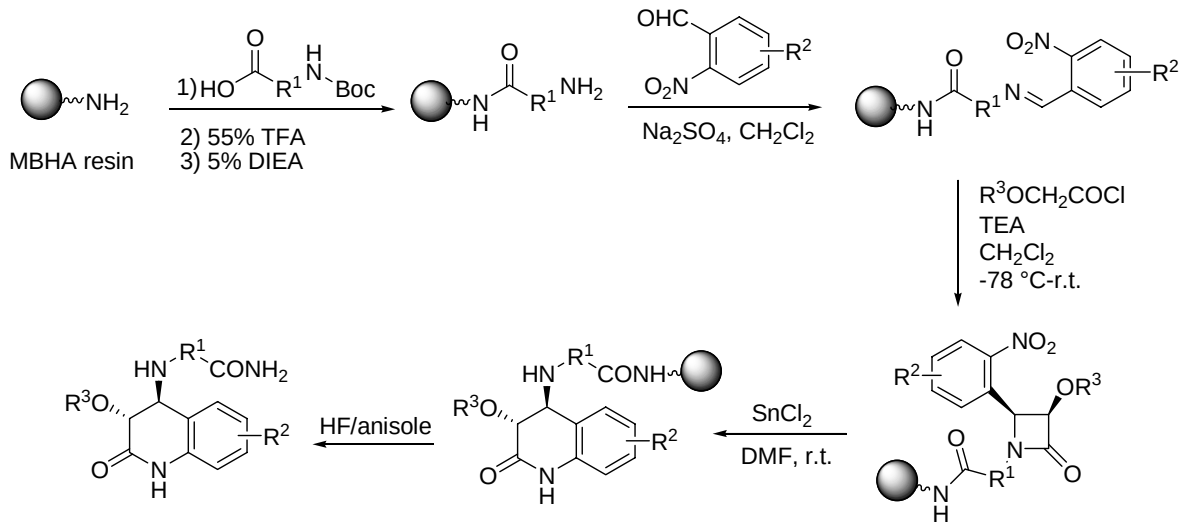
Scheme 2.12



The amino group of solid supported 3-amino-3-(2-nitrophenyl) propanamide was reductively alkylated with aldehyde or ketone. The nitro group of this alkylated compound was reduced with Sn(H) chloride to afford resin supported 1,3-diamine. Resin supported 1,3 diamine on treatment with trifluoroacetic acid gave 3-unsubstituted 4-amino quinolin-2-one.

Pei et al.[22] have reported a solid supported synthesis of 4-amino-3, 4-dihydroquinolin-2-ones (Scheme 2.13).

Scheme 2.13



Polystyrene *p*-Methylbenzhydrylamine resin (MBHA) supported amines using normal peptide coupling with *N*-Boc protected amino acid and subsequent removal of Boc-protecting group by treatment with 55% trifluoroacetic acid gave resin bound amines. These amines were condensed with *o*-nitrobenzaldehyde in CH_2Cl_2 gave imines. These imines on [2+2] cycloaddition reaction with ketenes obtained from various acid chloride in CH_2Cl_2 at -78 °C gave solid supported β-lactams. The nitro group of solid supported β-lactam was reduced to amine using tin(H) chloride (2.0 M) in DMF at room temperature. Under this reaction condition, the β-lactam ring underwent rearrangement to give the 3,4-dihydroquinolin-2-ones.

Although synthesis of 3, 4-dihydroquinolin-2-ones has been reported on solid support there are limitations associated in this synthesis. a) we can not apply this synthesis for large scale preparation. b) The solid support are expensive and not easily available for our work c) we have to modify these support by putting additive spacers which is an added cost for the synthesis.

Therefore, we were looking for better alternative to develop a simple method, which can be easily adopted for gram scale preparation.

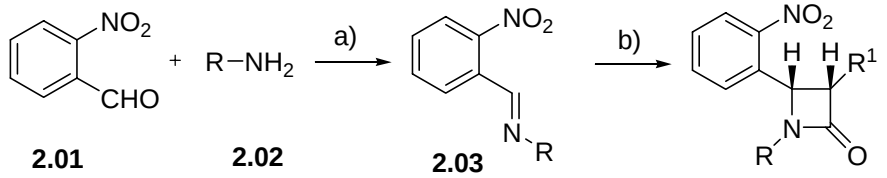
2.3 Present work:

The objective of this study is to develop a rapid and economically efficient method for synthesis of 4-amino-3,4-dihydroquinolin-2-one using azetidin-2-one.

2.4 Results and discussion:

O-Nitrobenzaldehyde (**2.01**) on condensation with various amines **2.02** (*p*-anisidine, aniline, *p*-toluidine) in presence of anhydrous magnesium sulphate gave imines **2.03a-c** in quantitative yield. These imines **2.03a-c** on [2+2] cycloaddition (Staudinger reaction) reaction with ketenes **2.04a-d**, generated *in situ* from various acid chlorides (phenoxy, methoxy, benzyloxy, acetoxy) in presence of tertiary amine and anhydrous CH_2Cl_2 as a solvent at 0 ^oC to room temperature for 14 h gave monocyclic 1,3-disubstituted-4-(2-nitrophenyl) azetidin-2-ones (**2.05a-l**) in 70-90% yields, which were purified by crystalisation from MeOH (Scheme 2.14)

Scheme 2.14



2.01 **2.02** **2.03** **2.05 a-l(±)**

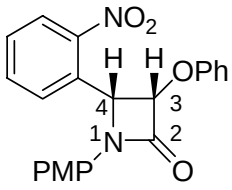
a	R = PMP	R^1 = OPh	**g**	R = Ph	R^1 = OBn
b	R = PMP	R^1 = OMe	**h**	R = Ph	R^1 = OAc
c	R = PMP	R^1 = OBn	**i**	R = *p*-tolyl	R^1 = OPh
d	R = PMP	R^1 = OAc	**j**	R = *p*-tolyl	R^1 = OMe
e	R = Ph	R^1 = OPh	**k**	R = *p*-tolyl	R^1 = OBn
f	R = Ph	R^1 = OMe	**l**	R = *p*-tolyl	R^1 = OAc

Reagents and conditions: a) CH_2Cl_2, anhyd. $MgSO_4$, r. t., 15 h; b) R^1CH_2COCl [**2.04**], Et_3N, 0 °C to r. t., 18 h.

The cycloaddition reaction was highly stereoselective and gave *cis* β-lactams (**2.05 a-l**) (*J* = 5-6 Hz for *cis* β-lactam ring protons) in good to moderate yields (Table 1).

The structure of **2.05a** was established by IR, ^1H NMR and ^{13}C NMR spectral data. IR spectrum of **2.05a** showed a strong band at 1757 cm^{-1} for the amide carbonyl of azetidin-2-one.

The ^1H NMR spectrum of **2.05a** showed a singlet at 3.81 ppm integrating for three protons corresponds to –OMe protons of PMP group. Doublets at 5.71 and 6.18 ppm corresponds to H-3 and H-4 *cis*-β-lactam ring protons (*J* = 5.3 Hz for *cis*-isomer). Remaining thirteen aromatic protons showed a multiplet from 6.88-8.28 ppm.



2.05a(±)

The ^{13}C NMR spectra of **2.05a** showed a peak at 163.5 ppm for the amide carbonyl carbon of azetidin-2-one. The quaternary aromatic carbons appeared at 157.1, 156.6, 148.0, 133.9, 130.3 ppm. The remaining aromatic carbons appeared at 130.1, 129.3, 129.1, 129.0, 125.3, 122.6, 118.5, 116.2, 114.5 ppm. C-3 and C-4 carbons of azetidin-2-one appeared at 82.1, 59.0 ppm respectively. Methoxy carbon of PMP group appeared at 55.3 ppm. The mass spectrum of **2.05a** gave M+1 peak at m/z 391, also supporting the structure of the compound.

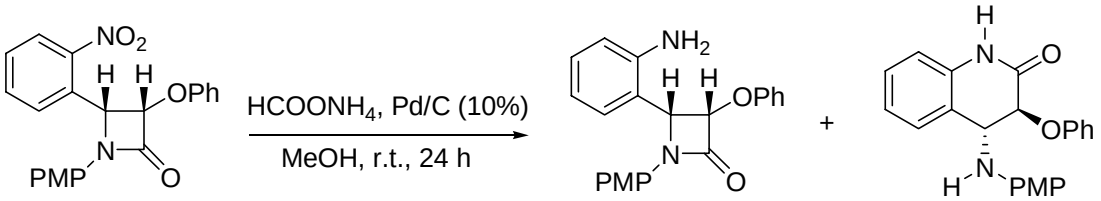
Table 1: Synthesis of 4-(2-nitrophenyl)-1,3-disubstituted azetidin-2-ones (**2.05a-l**)

Entry No.	**Compound**	**R**	**R^1**	**Yield[a] (%)**	**Mp (˚C)**
1	**2.05a**	4-Methoxyphenyl	Phenoxy	90	142
2	**2.05b**	4-Methoxyphenyl	Methoxy	65	158
3	**2.05c**	4-Methoxyphenyl	Benzyloxy	82	181
4	**2.05d**	4-Methoxyphenyl	Acetoxy	79	180
5	**2.05e**	Phenyl	Phenoxy	74	137
6	**2.05f**	Phenyl	Methoxy	68	135
7	**2.05g**	Phenyl	Benzyloxy	70	143
8	**2.05h**	Phenyl	Acetoxy	65	180
9	**2.05i**	*p*-tolyl	Phenoxy	82	153
10	**2.05j**	*p*-tolyl	Methoxy	63	157
11	**2.05k**	*p*-tolyl	Benzyloxy	79	165
12	**2.05l**	*p*-tolyl	Acetoxy	72	157

[a] Isolated yields.

Initially the reduction of **2.05a** was carried out by transfer hydrogenation using ammonium formate and Pd/C (10%) in dry methanol at room temperature for 24 h resulted into formation of amino-β-lactam **2.06** in good yield along with trace amount of cyclized 4-amino-3, 4-dihydroquinolin-2-one (**2.07a**) (Scheme 2.15). The cyclized product **2.07a** was difficult to separate from amino-β-lactam **2.06**. However, its formation was deduced from IR and ^{1}H NMR spectra of the crude reaction mixture. The IR spectrum of amino-β-lactam **2.06** showed a characteristic β-lactam carbonyl absorption at 1730 cm^{-1} and amino group absorptions at 3398, 3485 cm^{-1}, while the cyclized product **2.07** a showed δ-lactam carbonyl absorption at 1687 cm^{-1} and the NH absorption at 3373 cm^{-1}.

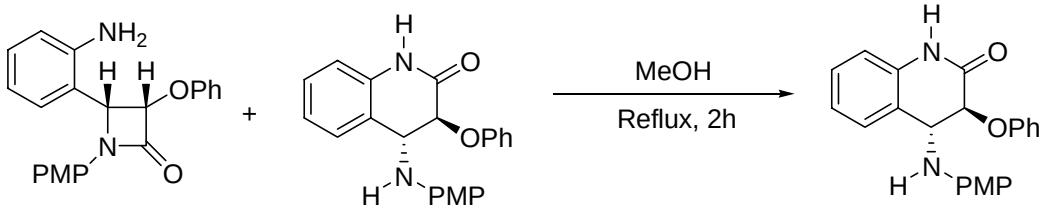
Scheme 2.15



2.05a (±) **2.06** **2.07a (±)**

The amino β-lactam underwent smooth cyclization by refluxing in methanol for 2 h to give dihydroquinolin-2-one **2.07a** in quantitative yield (Scheme 2.16). A direct transfer hydrogenation of **2.05a** was also tried in refluxing methanol for 2 h, which gave mixture of amino-β-lactam **2.06** and 4-amino-3, 4-dihydroqunolin-2-one **2.07a** along with several other unidentified products.

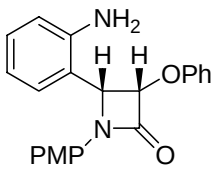
Scheme 2.16



2.06 **2.07a (±)** **2.07a (±)**

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 characteristic β-lactam carbonyl absorption at 1730 cm^{-1} and amino group absorption at 3398, 3485 cm^{-1}.

The ^{1}H NMR spectrum of **2.06** showed a singlet at 3.80 ppm corresponds to –OCH_3 protons of PMP group. Doublets at 5.47 and 5.65 ppm corresponds to H-3 and H-4 *cis*-β-lactam ring protons (J = 4.9 Hz for *cis*-isomer) respectively. Remaining thirteen aromatic protons showed a multiplet from 6.74-7.41 ppm.



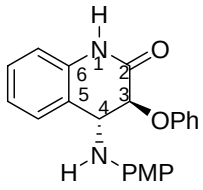
2.06 (±)

The ^{13}C NMR spectra of **2.06** showed a peak at 162.6 ppm for the amide carbonyl of azetidin-2-one. The quaternary aromatic carbons appeared at 157.2, 156.5, 145.3, 131.8, 129.9 ppm. The remaining aromatic carbons appeared at 129.4, 129.2, 128.1, 122.5, 118.8, 116.4, 115.6, 114.4, 114.1 ppm. C-3 and C-4 carbon of azetidin-2-one appeared at 81.3, 55.5 ppm respectively. Methoxy carbon of PMP group appeared at 55.4 ppm.

The amino β-lactam **2.06** underwent smooth cyclization by refluxing in methanol for 2 h to give dihydroquinolin-2-one **2.07a** in quantitative yield.

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 δ-lactam carbonyl absorption at 1687 cm^{-1} and the NH absorption at 3373 cm^{-1}.

The ^{1}H NMR spectrum of **2.07a** showed a singlet at 4.01 ppm integrating for three protons corresponds to –OCH_3 group of PMP. Doublets at δ 5.13 and 5.23 ppm correspond to H-3 and H-4 *trans*-δ-lactam ring protons (J = 8.6 Hz) respectively. Remaining thirteen aromatic protons showed a multiplet from 6.96-7.77 ppm. A singlet at 10.42 ppm corresponds to cyclic amide –N-H proton.



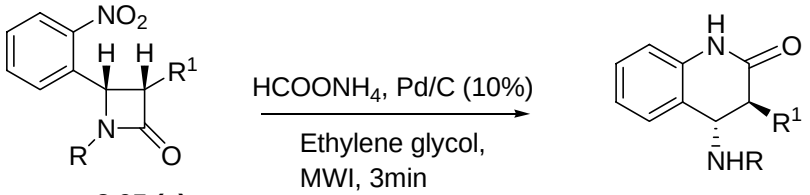
2.07a (±)

The ^{13}C NMR spectra of **2.07a** showed a peak at 167.1 ppm for the amide carbonyl. The quaternary aromatic carbons appeared at 158.1, 152.2, 135.5 ppm. The remaining aromatic carbons appeared at 128.8, 128.5, 127.5, 122.6, 121.3, 115.8, 115.5, 115.0, 114.2 ppm. C-3 and C-4 carbons of 4-amino 3, 4-dihydroquinolin-2-one appeared at 75.9, 56.0 ppm respectively. Methoxy carbon of PMP group appeared at 55.2 ppm. The mass spectrum of **2.07a** gave M+1 peak at m/z 361, also supporting the structure of the compound.

A direct transfer hydrogenation of **2.05a** in refluxing methanol for 2 h, gave mixtures of amino-β-lactam **2.06** and 4-amino 3,4-dihydroquinolin-2-one **2.07a** along with several other unidentified products. Therefore we have decided to employ microwave irradiation in transforming *o*-nitrobenzaldehyde derived azetidin-2-one **2.05a-l** to their corresponding 4-amino 3,4-dihydroquinolin-2-one derivatives. Microwave irradiation of **2.05a** using ammonium formate and catalytic amount of Pd/C (10%) in the presence of small quantity of ethylene glycol was carried out in an open glass vessel using a domestic microwave. The reaction was over in just three minutes at 60% power of the domestic microwave oven. The reaction mixture was diluted with water, CH_2Cl_2 and the catalyst was removed by filtration through a small bed of celite. The filtrate was extracted with CH_2Cl_2 and the removal of CH_2Cl_2 under reduced pressure gave almost pure product **2.07a** in very good yield, which was further purified by crystallization from ethyl acetate-petroleum ether mixture (6:4) (Scheme 2.17).

This product was formed by the reduction of nitro group followed by the nucleophilic β-lactam ring cleavage with the newly generated amino group. Several 4-amino-3, 4-dihydroquinolin-2-ones (**2.07a-k**) were prepared by transfer hydrogenation under microwave irradiation in very good yields shows the generality of this reaction. In case of acetoxy compounds **2.07g**, **k** (Table 2, entries 7 and 11) a small amount of corresponding uncyclized amino-β-lactam was also observed along with the required dihydroquinolin-2-one, which was removed by crystallization from ethyl acetate-petroleum ether mixture (6:4).

Scheme 2.17



2.05 (±) **2.07a-k (±)**

a	R = PMP	R^1 = OPh	**g**	R = Ph	R^1 = OAc
b	R = PMP	R^1 = OMe	**h**	R = *p*-tolyl	R^1 = OPh
c	R = PMP	R^1 = OBn	**i**	R = *p*-tolyl	R^1 = OMe
d	R = Ph	R^1 = OPh	**j**	R = *p*-tolyl	R^1 = OBn
e	R = Ph	R^1 = OMe	**k**	R = *p*-tolyl	R^1 = OAc
f	R = Ph	R^1 = OBn			

Yields, melting points and generality of microwave assisted synthesis of 4-amino-3, 4-dihydroquinolin-2-ones (**2.07a-k**) are summarized in (Table 2).

Table 2: Synthesis of 4-amino-3, 4-dihydroquinolin-2-ones (**2.07a-k**)

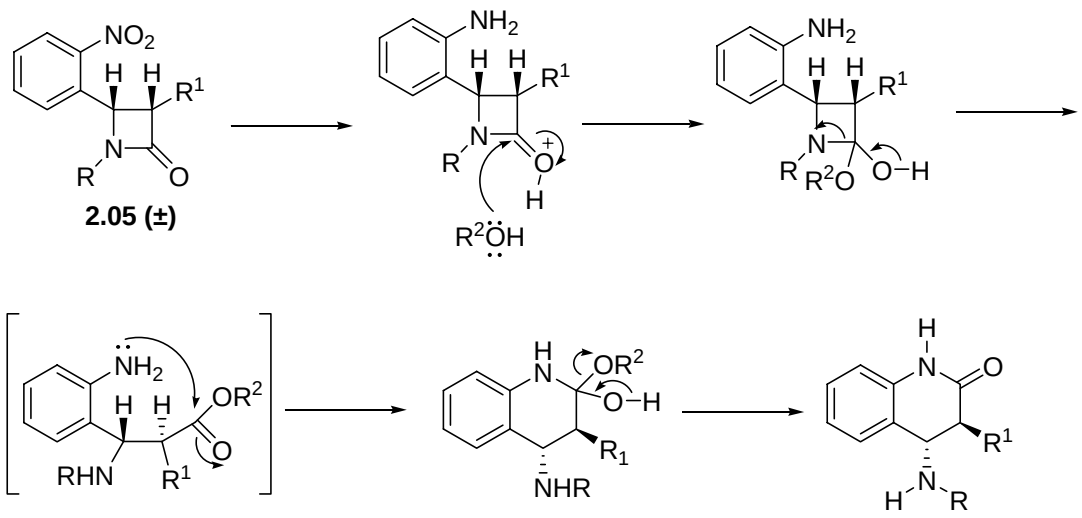
Entry No.	**Compound**	**R**	**R^1**	**Yield[a] (%)**	**Mp (˚C)**
1	**2.07a**	4-Methoxyphenyl	Phenoxy	89	229
2	**2.07b**	4-Methoxyphenyl	Methoxy	90	208
3	**2.07c**	4-Methoxyphenyl	Benzyloxy	86	201
4	**2.07d**	Phenyl	Phenoxy	87	225
5	**2.07e**	Phenyl	Methoxy	81	209
6	**2.07f**	Phenyl	Benzyloxy	82	218
7	**2.07g**	Phenyl	Acetoxy	74	221
8	**2.07h**	*p*-tolyl	Phenoxy	87	248
9	**2.07i**	*p*-tolyl	Methoxy	86	211
10	**2.07j**	*p*-tolyl	Benzyloxy	78	203
11	**2.07k**	*p*-tolyl	Acetoxy	77	238

[a] Isolated yields.

Plausible mechanism for the formation of 4-amino 3,4-dihydroquinolin-2-one:

We believe that formation of 4-amino 3,4-dihydroquinolin-2-one takes place through the formation of amino β-lactam. Due to ring strain associated with the four membered azetidin-2-one amino β-lactam opens with alcohol (methanol or ethylene glycol) to give corresponding ester which is rapidly cyclizes to give 4-amino 3,4-dihydroquinolin-2-one by intramolecular cyclization (Scheme 2.18).

Scheme 2.18



2.5 Antifungal activity testing of 4-amino 3,4-dihydroquinolin-2-one against *Benjaminiella poitrasii* and *Candida albicans* fungus:

Some of the 4-amino-3, 4-dihydroquinolin-2-ones **2.07** were screened for antifungal activity against a dimorphic fungus, *B. poitrasii* and *C. albicans*, Whole cell based plate assay method was employed for the primary screening of antifungal activity of 4-amino 3,4-dihydroquinolin-2-ones.

Whole cell based plate assay:

The whole cell based plate assay was carried out for the primary screening of antifungal compounds. The method involved the simple procedure in which a disk of Whatmann paper No. 1 impregnated with known amount of compound under test was placed on agar plate spreaded with fungal cell suspension. After the incubation at specified temperature and time, the inhibition of fungal growth was measured. The minimum concentration of test compound that gave the zone of inhibition was determined as minimum inhibitory concentration (MIC) for that fungal culture. The whole cell based plate assays provided a simple, easy and cost effective means for screening of antifungal compounds.

Test compounds (Table 3) were screened for the antifungal activity against dimorphic fungus, *B. poitrasii* (saprophyte) and *C. albicans* (human pathogen) using whole

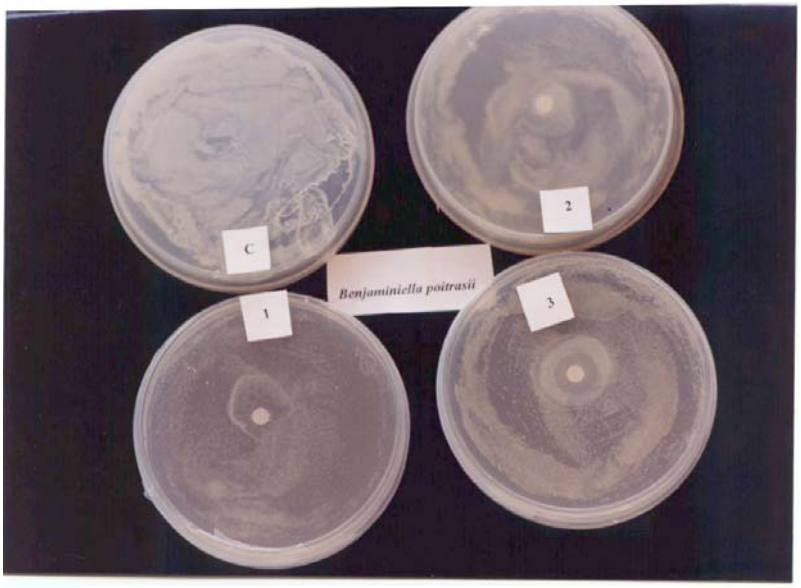
cell based plate assay. *B. poitrasii* and *C. albicans* were maintained on yeast extract peptone glucose (YPG) agar. For the whole cell based assay both the fungi were grown in YPG broth under shaking conditions (180 rpm) for 24 h at 28 ^{o}C. The liquid culture of *B. poitrasii* (100 µl) or *C. albicans* (100 µl) was spreaded on YPG plate. The test compounds and amphotericin B were dissolved in DMSO (50% v/v). Whatmann filter paper (No. 1) discs were placed on YPG plates spreaded with fungal cultures. The test compounds as listed in (Table 3) and standard antifungal drug amphotericin B (15 µg/ml) were added on discs. The plates were then incubated for 24 h at 28 ^{o}C and then the zone of inhibition if any, was measured. The experiment was carried out in triplicate under similar experimental conditions.

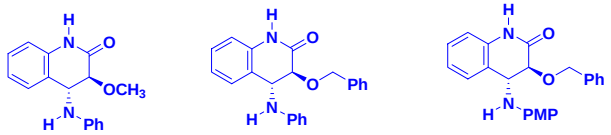
Effect of amphotericin B on the vegetative growth of *Benjaminiella poittrasii* and *Candida albicans*:

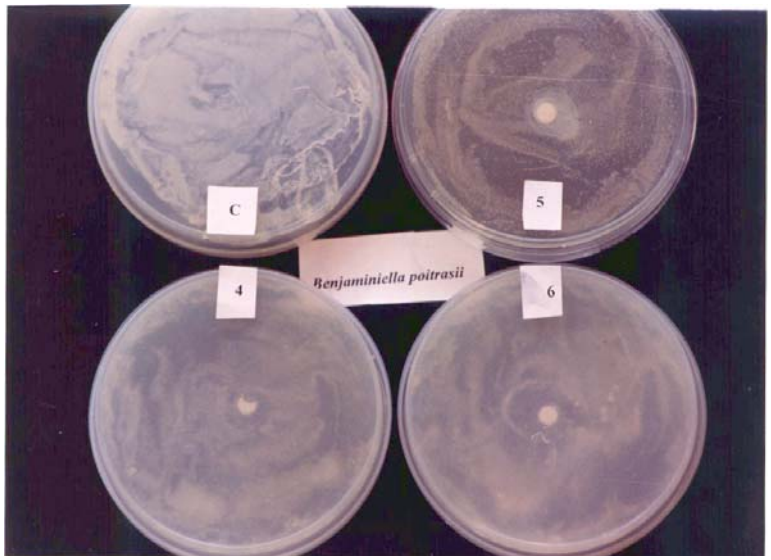
Concentration (15 µg/ml) – *B. poitrasii* - 4-5 mm

C. albicans - 6-7 mm

After analysing the results, we found that compound **1** (in table 3) has shown maximum inhibitory activity against vegetative growth of *B. poitrasii* with zone of inhibition 11-12 mm at concentration 45 µg/ml. Compound **1** also showed maximum inhibitory activity against vegetative growth of *C. albicans* with zone of inhibition 9-10 mm at concentration 100 µg/ml. Compound **3** showed inhibitory activity against vegetative growth of *B. poitrasii* with zone of inhibition 7-8 mm. These test compounds (Table 3) showed the zone of inhibition in the range 2-3 mm to 9-10 mm with *C. albicans*. This suggested 4-amino 3,4-dihydroquinolin-2-ones (Table 3) in which C-3 carbon is attached to methoxy or benzyloxy group have showed good antifungal activity in comparision to phenoxy and acetoxy group.


C
2
Benjaminiella poitrasii
1
3


H
N
O
OCH3
H
N
Ph
1
H
N
O
O
Ph
H
N
Ph
2
H
N
O
O
Ph
H
N
PMP
3


C
5
Benjaminiella poitrasii
4
6

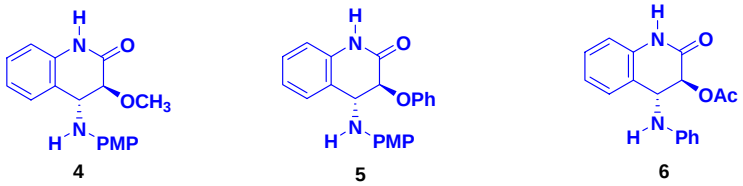
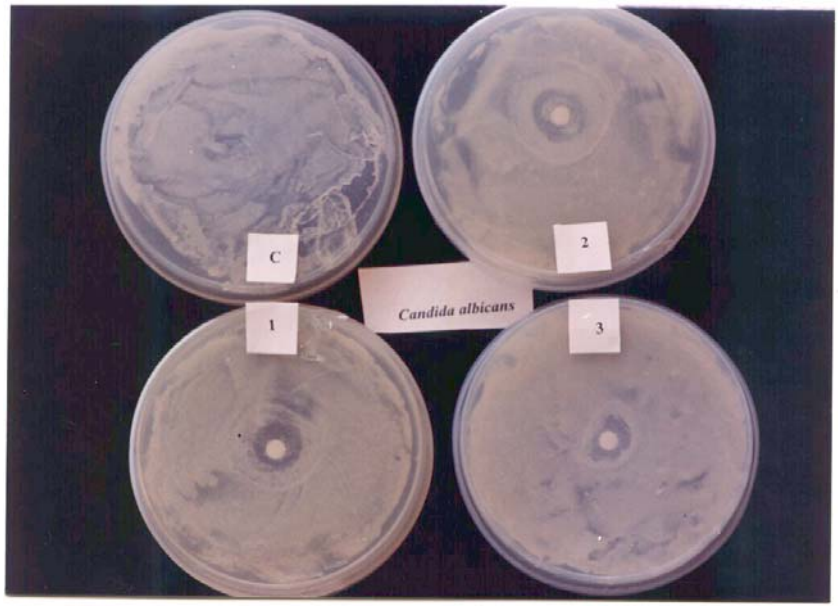
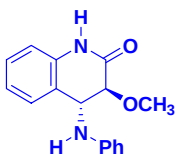
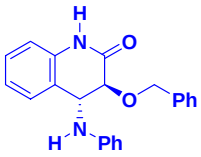

H
N
O
OCH3
H
N
PMP
4
H
N
O
OPh
H
N
PMP
5
H
N
O
OAc
H
N
Ph
6

Figure 1

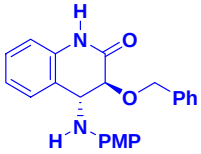




1



2



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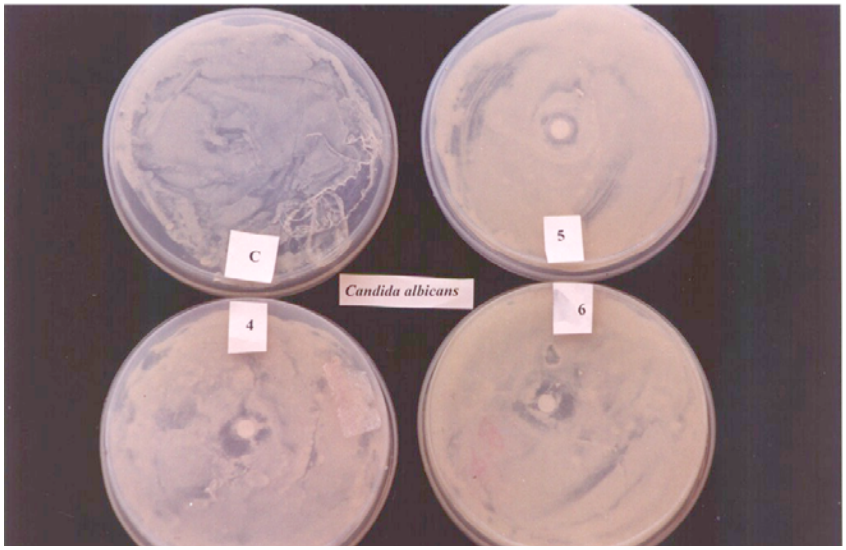
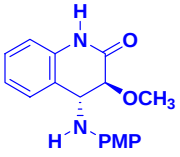
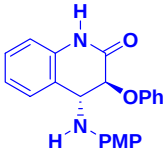




4



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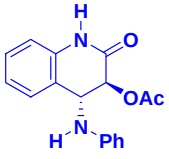
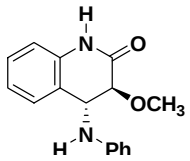
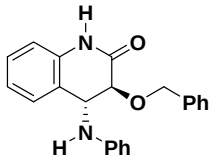
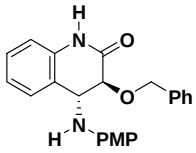
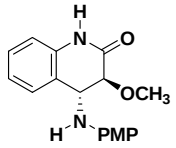
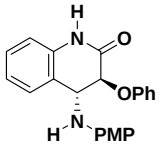
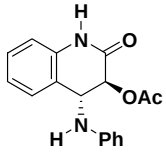


6

Figure 2

Table 3: Antifungal activity of 4-amino 3,4-dihydroquinolin-2-ones

Sr. No.	4-amino 3, 4-dihydroquinolin-2-one	*Benjaminiella Poitrasii*	*Candida Albicans*
	Concentration	**45 μg/ml**	**100 μg/ml**
1.		11-12 mm	9-10 mm
2.		-*	7-8 mm
3.		7-8 mm	5-6 mm
4.		3-4mm	5-6 mm
5.		-*	2-3 mm
6.		4-5 mm	3-4 mm

-* = Not detected

2.5 Conclusion:

In conclusion we have developed rapid and efficient method for the synthesis of 4-amino 3,4-dihydroquinolin-2-ones using microwave. Some of these dihydroquinolin-2-ones have showed good antifungal activity against fungi like *B. poittrasii* and *C. albicans*.

2.6 Experimental:

2.6.1: General procedure for the synthesis of Imines (2.03):

To a solution of amine **2.02a-c** (*p*-anisidine, aniline, *p*-toluidine) (1.0 equivalent) and anhydrous $MgSO_4$ (one equivalent) in CH_2Cl_2, a solution of *o*-nitro benzaldehyde **2.01** (1.1 equivalent) in CH_2Cl_2 was added at room temperature. The reaction mixture was stirred at room temperature for 6 to 7 h and filtered through a sintered glass crucible. The filtrate was concentrated and the resulting imine **2.03a-c** (quantitative yield) was used as such for the β-lactam formation.

2.6.2: General procedure for the synthesis of azetidine-2-ones (2.05a-l):

To a solution of imine **2.03a-c** (5 mmol), triethylamine (20 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of acid chloride (phenoxy, methoxy, benzyloxy, acetoxy acetyl chloride) **2.04** (7.5 mmol) in dry CH_2Cl_2 (10 mL) with stirring at 0 ºC in about 20 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 14 h. It was then washed with water (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL) and dried over anhyd. Na_2SO_4. The solvent was removed in *vacuo* to gave crude azetidine-2-one, which was recrystallized from methanol to get pure azetidine-2-one **2.05a-l**.

2.6.2a: 1-(4-Methoxyphenyl)-4-(2-nitrophenyl)-3-phenoxyazetidin-2-one (2.05a):

Yield, 1.76 g, 90%; yellow crystalline solid.

m.p. 142 ºC

IR ($CHCl_3$): υ_{max} 1757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 3H, Ar-OC*H*$_3$), 5.71 (d, *J* = 5.5 Hz, 1H, *H*-4), 6.16 (d, *J* = 5.5 Hz, 1H, *H*-3), 6.86-7.00 (m, 5H, Ar), 7.17-7.26 (m, 2H, Ar), 7.36 (d, *J* = 9.4 Hz, 2H, Ar), 7.49-7.64 (m, 3H, Ar), 8.21-8.26 (m, 1H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 163.1, 157.1, 156.6, 148.0, 133.9, 130.3, 130.1, 129.3, 129.1, 129.1, 125.3, 122.6, 118.5, 116.2, 114.5, 82.1, 59.0, 55.3

MS: (*m/z*) = 391 (M+1)

Anal. Calcd. for **$C_{22}H_{18}N_2O_5$:** C, 67.69; H, 4.61; N, 7.18%

Found C, 67.93; H, 4.48; N, 7.51%.

2.6.2b: 3-Methoxy-1-(4-methoxyphenyl)-4-(2-nitrophenyl) azetidin-2-one (2.05b):

Yield, 1.07 g, 65%; white solid.

m.p. 158 ºC

IR ($CHCl_3$): υ_{max} 1753 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 (s, 3H, -OC*H*$_3$), 3.77 (s, 3H, Ar-OC*H*$_3$), 5.00 (d, *J* = 5.0 Hz, 1H, *H*-4), 5.88 (d, *J* = 5.0 Hz, 1H, *H*-3), 6.84 (d, *J* = 9.2 Hz, 2H, Ar), 7.28 (d, *J* = 9.2 Hz, 2H, Ar), 7.45 (d, *J* = 7.8 Hz, 1H, Ar), 7.50-7.53 (m, 1H, Ar), 7.58-7.61 (m, 1H, Ar), 8.21-8.23 (m, 1H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 164.3, 156.7, 148.3, 133.8, 130.7, 130.5, 129.4, 128.9, 125.3, 118.5, 114.6, 85.6, 59.6, 59.5, 55.5

MS: (*m/z*) = 329 (M+1)

Anal. Calcd. for **$C_{17}H_{16}N_2O_5$:** C, 62.19; H, 4.87, N, 8.53%

Found C, 62.37; H, 4.64; N, 8.49%.

2.6.2c: 3-Benzyloxy-1-(4-methoxyphenyl)-4-(2-nitrophenyl) azetidin-2-one (2.05c):

Yield, 1.66 g, 82%; white solid.

m.p. 181 ºC

IR ($CHCl_3$): υ_{max} 1753 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.78 (s, 3H, Ar-OC*H*$_3$), 4.54 (d, *J* = 11.8 Hz, 1H, -OC*H*$_a$H$_b$Ph), 4.63 (d, *J* = 11.8 Hz, 1H, -OCH$_a$*H*$_b$Ph), 5.22 (d, *J* = 5.1 Hz, 1H, *H*-4), 5.91 (d, *J* = 5.1 Hz, 1H, *H*-3), 6.86 (d, *J* = 9.0 Hz, 2H, Ar), 7.03-7.08 (m, 2H, Ar), 7.23-7.33 (m, 5H, Ar), 7.49-7.64 (m, 3H, Ar), 8.20-8.25 (m, 1H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 164.2, 156.5, 148.2, 136.5, 133.8, 130.7, 130.4, 129.4, 128.9, 128.2, 127.8, 127.5, 125.3, 118.4, 114.5, 83.4, 73.2, 59.5, 55.4

MS: (*m/z*) = 405 (M+1)

Anal. Calcd. for **$C_{23}H_{20}N_2O_5$:** C, 68.30; H, 4.99; N, 6.93%

Found C, 68.14; H, 5.10; N, 6.71%.

2.6.2d: 3-Acetoxy-1-(4-methoxyphenyl)-4-(2-nitrophenyl) azetidin-2-one (2.05d):

Yield, 1.41 g, 79%; creamy white solid.

m.p. 180 ºC

IR ($CHCl_3$): υ_{max} 1759 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77 (s, 3H, -COC*H*$_3$), 3.78 (s, 3H, Ar-OC*H*$_3$), 6.05 (d, *J* = 5.5 Hz, 1H, *H*-4), 6.36 (d, *J* = 5.5 Hz, 1H, *H*-3), 6.87 (d, *J* = 9.0 Hz, 2H, Ar), 7.31 (d, *J* = 9.0 Hz, 2H, Ar), 7.48-7.65 (m, 3H, Ar), 8.18-8.23 (m, 1H, Ar),.

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 168.2, 161.6, 156.7, 148.1, 133.7, 129.9, 129.4, 129.2, 129.1, 125.3, 118.4, 114.5, 75.8, 58.2, 55.3, 19.8

MS: (*m/z*) = 357 (M+1)

Anal. Calcd. for **$C_{18}H_{16}N_2O_6$:** C, 60.66; H, 4.53; N, 7.86%

Found C, 60.91; H, 4.35; N, 7.86%.

2.6.2e: 4-(2-Nitrophenyl)-3-phenoxy-1-phenyl azetidin-2-one (2.05e):

Yield, 1.33 g, 74%; creamy white solid.

m.p. 137 ºC

IR ($CHCl_3$): υ_{max} 1759 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.73 (d, *J* = 5.4 Hz, 1H, *H*-4), 6.22 (d, *J* = 5.5 Hz, 1H, *H*-3), 6.91 (d, *J* = 7.8 Hz, 2H, Ar), 7.00 (d, *J* = 7.5 Hz, 1H, Ar), 7.21 (d, *J* = 8.3 Hz, 2H, Ar), 7.25-7.28 (m, 1H, Ar), 7.32-7.47 (m, 4H, Ar), 7.51-7.68 (m, 3H, Ar), 8.24-8.29 (m, 1H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 163.6, 157.1, 148.1, 136.9, 133.7, 129.9, 129.3, 129.1, 125.2, 124.8, 122.6, 117.2, 116.3, 82.1, 58.9

MS: (*m/z*) = 361 (M+1)

Anal. Calcd. for **$C_{21}H_{16}N_2O_4$:** C, 69.98; H, 4.48; N, 7.77%

Found C, 69.90; H, 4.58; N, 7.65%.

2.6.2f: 3-Methoxy-4-(2-nitrophenyl)-1-phenyl azetidin-2-one (2.05f):

Yield, 1.02 g, 68%; pale yellow solid.

m.p.135 ºC

IR ($CHCl_3$): υ_{max} 1757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.38 (s, 3H, -OC*H*$_3$), 5.03 (d, *J* = 5.5 Hz, 1H, *H*-4), 5.94 (d, *J* = 5.5 Hz, 1H, *H*-3), 7.13-7.27 (m, 1H, Ar), 7.30-7.34 (m, 4H, Ar), 7.48-7.61 (m, 3H, Ar), 8.22-8.27 (m, 1H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 164.8, 148.1, 136.9, 133.9, 130.4, 129.2, 128.8, 125.2, 124.6, 117.4, 117.1, 85.4, 59.3, 58.1

MS: (*m/z*) = 299 (M+1)

Anal. Calcd. for **$C_{16}H_{14}N_2O_4$:** C, 64.41; H, 4.74; N, 9.39%

Found C, 64.14; H, 4.72; N, 9.28%.

2.6.2g: 3-Benzyloxy-4-(2-nitrophenyl)-1-phenyl azetidin-2-one (2.05g):

Yield, 1.31 g, 70%; creamy white solid.

m.p. 143 ºC

IR ($CHCl_3$): υ_{max} 1755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.55 (d, *J* = 11.7 Hz, 1H, -OC*H*$_a$H$_b$Ph), 4.65 (d, *J* = 11.7 Hz, 1H, -OCH$_a$*H*$_b$Ph), 5.23 (d, *J* = 5.5 Hz, 1H, *H*-4), 5.96 (d, *J* = 5.5 Hz, 1H, *H*-3), 7.04 (d, *J* = 2.3 Hz, 1H, Ar), 7.08 (d, *J* = 3.5 Hz, 1H, Ar), 7.12-7.18 (m, 1H, Ar), 7.24 (d, *J* = 2.4 Hz, 2H, Ar), 7.28 (d, *J* = 1.2 Hz, 1H, Ar), 7.33 (d, *J* = 2.4 Hz, 2H, Ar), 7.35-7.38 (m, 2H, Ar), 7.48-7.66 (m, 3H, Ar), 8.21-8.26 (m, 1H, Ar),

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 164.7, 148.3, 136.9, 136.5, 133.7, 130.5, 129.2, 128.8, 128.2, 127.7, 127.4, 125.2, 124.6, 117.1, 83.3, 73.2, 59.4.

MS: (*m/z*) = 375 (M+1)

Anal. Calcd. for **$C_{22}H_{18}N_2O_4$:** C, 70.57; H, 4.86; N, 7.48%

Found C, 70.42; H, 4.93; N, 7.42%.

2.6.2h: 3-Acetoxy-4-(2-nitrophenyl)-1-phenyl azetidin-2-one (2.05h).

Yield, 1.06 g, 65%; creamy white solid.

m.p. 180 ºC

IR ($CHCl_3$): υ_{max} 1755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77 (s, 3H, -COC*H*$_3$), 6.09 (d, *J* = 5.5 Hz, 1H, *H*-4), 6.36 (d, *J* = 5.5 Hz, 1H, *H*-3), 7.10-7.19 (m, 1H, Ar), 7.26-7.38 (m, 3H, Ar), 7.47-7.68 (m, 4H, Ar), 8.18-8.23 (m, 1H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 167.9, 162.1, 148.0, 136.5, 133.6, 129.3, 129.2, 128.9, 125.2, 124.8, 117.0, 75.6, 58.1, 19.5.

MS: (*m/z*) = 327 (M+1)

Anal. Calcd. for **$C_{17}H_{14}N_2O_5$:** C, 62.57; H, 4.33; N, 8.59%

Found C, 62.50; H, 4.28; N, 8.42%.

2.6.2i: 4-(2-Nitrophenyl)-3-phenoxy-1-*p*-tolyl azetidin-2-one (2.05i):

Yield, 1.53 g, 82%; pale yellow solid.

m.p. 153 ºC

IR ($CHCl_3$): υ_{max} 1759 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, 3H, Ar-C*H*$_3$), 5.70 (d, *J* = 5.5 Hz, 1H, *H*-4), 6.17 (d, *J* = 5.5 Hz, 1H, *H*-3), 6.87-6.99 (m, 3H, Ar), 7.13-7.32 (m, 6H, Ar), 7.50-7.64 (m, 3H, Ar), 8.21-8.26 (m, 1H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 163.4, 157.2, 148.1, 134.6, 133.7, 130.1, 129.8, 129.3, 129.2, 129.0, 125.2, 122.6, 117.1, 116.3, 82.2, 58.9, 20.7

MS: (*m/z*) = 375 (M+1)

Anal. Calcd. for **$C_{22}H_{18}N_2O_4$:** C, 70.57; H, 4.85; N, 7.48%

Found C, 70.35; H, 4.96; N, 7.42%.

2.6.2j: 3-Methoxy-4-(2-nitrophenyl)-1-*p*-tolyl azetidin-2-one (2.05j).

Yield, 0.98 g, 63%; pale yellow solid.

m.p. 157 ºC

IR ($CHCl_3$): υ_{max} 1753 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, 3H, Ar-C*H*$_3$), 3.38 (s, 3H, -OC*H*$_3$), 5.02 (d, *J* = 5.0 Hz, 1H, *H*-4), 5.91 (d, *J* = 5.0 Hz, 1H, *H*-3), 7.10-7.26 (m, 4H, Ar), 7.43-7.64 (m, 3H, Ar), 8.22-8.27 (m, 1H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 164.5, 148.2, 134.5, 134.3, 133.6, 130.6, 129.7, 129.2, 128.7, 125.2, 117.0, 85.4, 59.3, 20.7.

MS: (*m/z*) = 313 (M+1)

Anal. Calcd. for **$C_{17}H_{16}N_2O_4$:** C, 65.37; H, 5.17; N, 8.97%

Found C, 65.44; H, 5.39; N, 9.03%.

2.6.2k: 3-Benzyloxy-4-(2-nitrophenyl)-1-*p*-tolyl azetidin-2-one (2.05k).

Yield, 1.53 g, 79%; creamy white solid.

m.p. 165 ºC

IR ($CHCl_3$): υ_{max} 1755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.31 (s, 3H, Ar-C*H*$_3$), 4.54 (d, *J* = 11.8 Hz, 1H, -OC*H*$_a$H$_b$Ph), 4.64 (d, *J* = 11.8 Hz, 1H, -OCH$_a$*H*$_b$Ph), 5.21 (d, *J* = 5.5 Hz, 1H, *H*-4), 5.92 (d, *J* = 5.5 Hz, 1H, *H*-3), 7.08-7.22 (m, 4H, Ar), 7.24-7.26 (m, 5H, Ar), 7.48-7.64 (m, 3H, Ar), 8.20-8.25 (m, 1H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 164.4, 148.2, 136.5, 134.5, 134.3, 133.7, 130.6, 129.7, 129.3, 128.7, 128.1, 127.7, 127.4, 125.2, 117.0, 83.4, 73.1, 59.3, 20.7.

MS: (*m/z*) = 389 (M+1)

Anal. Calcd. for **$C_{23}H_{20}N_2O_4$:** C, 71.11; H, 5.20; N, 7.21%

Found C, 70.80; H, 5.27; N, 6.96%.

2.6.2l: 3-Acetoxy-4-(2-nitrophenyl)-1-*p*-tolyl azetidin-2-one (2.05l):

Yield, 1.23 g, 72%; pale brown solid.

m.p. 157 ºC

IR ($CHCl_3$): υ_{max} 1759 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77 (s, 3H, -COC*H*$_3$), 2.31 (s, 3H, Ar-C*H*$_3$), 6.05 (d, *J* = 5.5 Hz, 1H, *H*-4), 6.35 (d, *J* = 5.5 Hz, 1H, *H*-3), 7.11-7.26 (m, 4H, Ar), 7.47-7.64 (m, 3H, Ar), 8.19-8.23 (m, 1H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 168.0, 161.9, 148.1, 134.6, 134.1, 133.6, 129.7, 129.3, 129.0, 125.2, 117.0, 75.7, 58.1, 20.7, 19.6

MS: (*m/z*) = 341 (M+1)

Anal. Calcd. for **$C_{18}H_{16}N_2O_5$:** C, 63.52; H, 4.75; N, 8.23%

Found C, 63.71; H, 4.65; N, 7.90%.

2.6.2: 4-(2-aminophenyl)-1-*p*-methoxyphenyl-3-phenoxy azetidin-2-one (2.06):

To a solution of **2.05a** (0.195 g, 0.5 mmol) in dry MeOH (3 mL) was added ammonium formate (0.157 g, 2.5 mmol) followed by Pd/C (10%, 30 mg). This reaction mixture was stirred at room temperature under argon for 24 h. It was then filtered through a short celite bed, washed with CH_2Cl_2 (15 mL). The filtrate was diluted with water (2 mL), the organic layer was separated and dried over anhyd. Na_2SO_4. Solvent was removed under

vacuum to get 4-(2-aminophenyl)-1-*p*-methoxyphenyl-3-phenoxy azetidin-2-one (**2.06**) as a major product along with a trace amount of desired 4-amino 3,4-dihydroquinolin-2-one (**2.07a**) which were difficult to separate by column chromatography.

Yield, 0.176 g, 98%; pale yellow solid.

m.p. 195-199 ºC

IR ($CHCl_3$): υ_{max} 3485, 3398, 1730 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80 (s, 3H, Ar-OC*H*$_3$), 5.47 (d, *J* = 4.9 Hz, 1H, *H*-4), 5.65 (d, *J* = 4.9 Hz, 1H, *H*-3), 6.74-7.41 (m, 13H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$) δ 162.6, 157.2, 156.5, 145.3, 131.8, 129.9, 129.4, 129.2, 128.1, 122.5, 118.8, 116.4, 115.6, 114.4, 114.1, 81.3, 55.5, 55.4

2.6.3: 4-(4-methoxy-phenylamino)-3-phenoxy-3, 4-dihydro-1*H*-quinolin-2-one (2.07a):

4-(2-aminophenyl)-1-*p*-methoxyphenyl-3-phenoxy azetidin-2-one (**2.06**) (0.176 g, 0.48 mmol) was dissolved in methanol (10 mL) and refluxed for 2 h. The solvent was removed under reduced pressure to get 4-(4-methoxy-phenylamino)-3-phenoxy-3, 4-dihydro-1*H*-quinolin-2-one (**2.07a**) as a white solid, which was recrystallized from EtOAc-petroleum ether mixture (6:4, 10 mL).

Yield, 0.162 g, 90%;

m.p. 229 ºC

IR ($CHCl_3$): υ_{max} 3373, 1686 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 4.01 (s, 3H, Ar-OC*H*$_3$), 5.13 (d, *J* = 8.6 Hz, 1H, *H*-4), 5.23(d, *J* = 8.6 Hz, 1H, *H*-3), 6.93 (d, *J* = 9.0 Hz, 2H, Ar), 7.25 (d, *J* = 9.0 Hz, 2H, Ar), 7.24 (m, 5H, Ar), 7.49 (m, 3H, Ar), 7.69 (m, 1H, Ar), 10.42 (s, 1H, -CON*H*).

^{13}C NMR (125.76 MHz, $CDCl_3$+DMSO-d_6): δ 167.1, 158.0, 152.2, 135.5, 128.7, 128.5, 127.5, 122.6, 121.3, 115.8, 115.5, 115.0, 114.2, 75.9, 56.0, 55.2.

MS: (*m/z*) = 361 (M+1).

Anal. Calcd. for **$C_{22}H_{20}N_2O_3$:** C, 73.30; H, 5.60; N, 7.77%

Found C, 73.00; H, 5.43; N, 7.65%.

2.6.4: Transfer hydrogenation of 1-(4-methoxyphenyl)-4-(2-nitrophenyl)-3-phenoxyazetidin-2-one (2.05a) in refluxing methanol.

To a solution of **2.05a** (0.195 g, 0.5 mmol) in dry methanol (3 mL) was added ammonium formate (0.157 g, 2.5 mmol) followed by Pd/C (10%, 30 mg). This reaction mixture was refluxed with stirring for 2 h till the starting material was consumed completely (TLC). The reaction mixture was cooled to room temperature, filtered through a short celite bed and the bed was washed with methylene chloride (15 mL). The filtrate was diluted with water (2 mL), the organic layer was separated and dried over anhyd. Na_2SO_4. Solvent was removed under reduced pressure to get white solid (0.172 g). It was found to be a 2:1 mixture of 4-(2-aminophenyl)-1-*p*-methoxyphenyl-3-phenoxy azetidin-2-one (**2.06**), 4-(4-methoxy-phenylamino)-3-phenoxy-3, 4-dihydro-1*H*-quinolin-2-one (**2.07a**) along with several other unidentified products. The compounds **2.06** and **2.07a** (total 0.13 g, 70%) was obtained as a mixture by column chromatography.

2.6.5: General procedure for microwave assisted synthesis of 3, 4-dihydro-1*H*-quinolin-2-one (2.07a-k):

To a solution of azetidin-2-one (**2.05**, 0.5 mmol), in ethylene glycol (3 mL) was added ammonium formate (2.5 mmol) followed by Pd/C (10%, 30 mg). The mixture was then subjected to microwave irradiation at low power setting (60%) for 3 min. in an open glass vessel. It was then allowed to come to room temperature, diluted with water (2 mL) and filtered through small pad of celite. The residue was washed with methylene chloride (2 x 10 mL), organic layer was separated, washed with brine (2 mL), dried over anhyd. Na_2SO_4 and the solvent was removed *in vacuo* to get crude quinolin-2-one **2.07**, which was recrystallized from EtOAc-petroleum ether mixture (6:4).

2.6.5a: 4-(4-Methoxy-phenylamino)-3-phenoxy-3, 4-dihydro-1*H*-quinolin-2-one (2.07a):

Yield, 0.160 g, 89%; physical and spectral data was same as obtained earlier.

2.6.5b: 3-Methoxy-4-(4-Methoxy-phenylamino)-3, 4-dihydro-1*H*-quinolin-2-one (2.07b):

Yield, 0.134 g, 90%; white solid.

m.p. 208 ºC

IR ($CHCl_3$): υ_{max} 3387, 1678 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 3.26 (s, 3H, -OC*H*$_3$), 3.47 (s, 3H, Ar-OC*H*$_3$), 3.74 (d, *J* = 7.8 Hz, 1H, *H*-4), 4.31(d, *J* = 7.8 Hz, 1H, *H*-3), 6.39 (d, *J* = 8.7 Hz, 2H, Ar), 6.48 (d, *J* = 9.2 Hz, 2H, Ar), 6.69-6.73 (m, 2H, Ar), 6.94-7.06 (m, 2H, Ar), 9.69 (s, 1H, -CON*H*).

^{13}C NMR (125.76 MHz, $CDCl_3$+DMSO-d_6): δ 168.1, 151.8, 140.3, 135.4, 128.2, 128.1, 123.5, 122.3, 115.2, 114.4, 114.1, 77.5, 58.1, 55.3, 55.0

MS: (*m/z*) = 299 (M+1)

Anal. Calcd. for **$C_{17}H_{18}N_2O_3$:** C, 68.43; H, 6.09, N, 9.39%

Found C, 68.72; H, 6.20; N, 9.11%.

2.6.5c: 3-Benzyloxy-4-(4-Methoxy-phenylamino)-3, 4-dihydro-1*H*-quinolin-2-one (2.07c):

Yield, 0.159 g, 85%; white solid.

m.p. 201 ºC

IR ($CHCl_3$): υ_{max} 3367, 1680 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 3.50 (s, 3H, Ar-OC*H*$_3$), 4.03 (m, 1H, *H*-4), 4.35 (d, *J* = 7.7 Hz, 1H, *H*-3), 4.41 (d, *J* = 11.5 Hz, 1H, -OCH$_a$*H*$_b$Ph), 4.97 (d, *J* = 11.5 Hz, 1H, -OC*H*$_a$H$_b$Ph), 6.22-6.27 (m, 2H, Ar), 6.48 (d, *J* = 8.8 Hz, 2H, Ar), 6.63-6.68 (m, 1H, Ar), 6.78-6.82 (m, 1H, Ar), 6.99-7.04 (m, 2H, Ar), 7.06-7.12 (m, 5H, Ar), 8.41 (bs, 1H, -CON*H*).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ 168.3, 151.5, 141.8, 138.1, 136.9, 128.9, 128.7, 128.4, 128.2, 127.8, 124.3, 122.6, 115.6, 114.9, 114.1, 76.0, 72.1, 55.6, 55.2

MS: (*m/z*) = 375 (M+1)

Anal. Calcd. for **$C_{23}H_{22}N_2O_3$:** C, 73.77; H, 5.93; N, 7.48%

Found C, 73.53; H, 5.84; N, 7.32%.

2.6.5d: 3-Phenoxy-4-phenylamino-3, 4-dihydro-1*H*-quinolin-2-one (2.07d):

Yield, 0.144 g, 87%; fluppy white solid.

m.p. 225 ºC

IR ($CHCl_3$): υ_{max} 3383, 1682 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 4.25 (d, *J* = 9.2 Hz, 1H, *H*-4) 4.29 (d, *J* = 9.1 Hz, 1H, *H*-3), 5.91-5.94 (m, 1H, Ar), 6.01 (d, *J* = 7.8 Hz, 2H, Ar), 6.22-6.24 (m, 3H, Ar), 6.30-6.32 (m, 2H, Ar), 6.39-6.42 (m, 2H, Ar), 6.49-6.56 (m, 3H, Ar), 6.69 (d, *J* = 7.3 Hz, 1H, Ar), 9.73 (s, 1H, -CON*H*).

^{13}C NMR (125.76 MHz, $CDCl_3$+DMSO-d_6): δ 166.0, 157.3, 146.3, 134.8, 127.6, 127.5, 127.1, 126.2, 122.8, 121.2, 119.9, 115.3, 114.8, 114.3, 111.4, 74.9, 53.0

MS: (*m/z*) = 331 (M+1)

Anal. Calcd. for **$C_{21}H_{18}N_2O_2$:** C, 76.33; H, 5.50, N, 8.48%

Found C, 76.51; H, 5.58; N, 8.19%.

2.6.5e: 3-Methoxy-4-phenylamino-3, 4-dihydro-1*H*-quinolin-2-one (2.07e):

Yield, 0.108 g, 81%; white crystalline solid.

m.p. 209 ºC

IR ($CHCl_3$): υ_{max} 3392, 1687 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.49 (s, 3H, -OCH_3) 4.06 (d, *J* = 7.3 Hz, 1H, *H*-4), 4.64 (d, *J* = 7.3 Hz, 1H, *H*-3), 6.62 (d, *J* = 7.8 Hz, 2H, Ar), 6.71-6.74 (m, 1H, Ar), 6.84 (d, *J* = 7.8 Hz, 1H, Ar), 6.94-6.97 (m, 1H, Ar), 7.11-7.19 (m, 3H, Ar), 7.26 (d, *J* = 7.4 Hz, 1H, Ar), 9.08 (s, 1H, -CON*H*).

MS: (*m/z*) = 269 (M+1)

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 169.2, 146.2, 135.2, 129.4, 129.2, 128.8, 123.8, 123.6, 118.9, 116.0, 114.0, 77.9, 58.9, 55.4

Anal. Calcd. for **$C_{16}H_{16}N_2O_2$:** C, 71.61; H, 6.02; N, 10.44%

Found C, 71.32; H, 6.00; N, 10.15%.

2.6.5f: 3-Benzyloxy-4-phenylamino-3, 4-dihydro-1*H*-quinolin-2-one (2.07f):

Yield, 0.141 g, 82%; white solid.

m.p. 218 ºC

IR ($CHCl_3$): υ_{max} 3389, 1680 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.28 (d, *J* = 7.4 Hz, 1H, *H*-4), 4.70 (m, 2H, -OC*H*$_a$H$_b$Ph, *H*-3), 4.97 (d, *J* = 11.7 Hz, 1H, -OCH$_a$*H*$_b$Ph), 6.53 (d, *J* = 7.8 Hz, 2H, Ar), 6.78 (m, 1H, Ar), 6.92 (d, *J* = 7.9 Hz, 1H, Ar), 7.12 (m, 3H, Ar), 7.34 (m, 7H, Ar), 8.79 (s, 1H, -CON*H*).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ 168.2, 147.8, 138.1, 136.9, 129.1, 128.9, 128.8, 128.4, 128.2, 127.9, 124.0, 122.7, 116.6, 115.7, 112.8, 75.8, 72.0, 54.3

MS: (*m/z*) = 345 (M+1)

Anal. Calcd. for **$C_{22}H_{20}N_2O_2$:** C, 76.71; H, 5.86; N, 8.13%

Found C, 76.51; H, 6.00; N, 7.90%.

2.6.5g: 3-Acetoxy-4-phenylamino-3,4-dihydro-1*H*-quinolin-2-one (2.07g):

Yield, 0.109 g, 74%; fluppy white solid.

m.p. 221 ºC

IR ($CHCl_3$): υ_{max} 3381, 1757, 1691 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.89 (s, 3H, -OCOC*H*$_3$), 4.93 (d, *J* = 11.0 Hz, 1H, *H*-4), 5.51 (d, *J* = 11.0 Hz, 1H, *H*-3), 6.68 (d, *J* = 7.9 Hz, 2H, Ar), 6.93 (m, 2H, Ar), 7.13 (m, 4H, Ar), 7.35 (d, *J* = 7.4 Hz, 1H, Ar), 10.24 (s, 1H, -CON*H*).

^{13}C NMR (125.76 MHz, $CDCl_3$+DMSO-d_6): δ 169.7, 165.8, 146.8, 135.2, 128.5, 128.3, 126.1, 123.5, 122.5, 117.1, 115.4, 112.7, 70.9, 53.4, 19.9

MS: (*m/z*) = 297 (M+1)

Anal. Calcd. for **$C_{17}H_{16}N_2O_3$:** C, 68.89; H, 5.45; N, 9.45%

Found C, 68.71; H, 5.20; N, 9.12%.

2.6.5h: 3-Phenoxy-4-*p*-tolylamino-3,4-dihydro-1-*H*-quinolone-2-one (2.07h):

Yield, 0.150 g, 87%; fluppy white solid.

m.p. 248 ºC

IR ($CHCl_3$): υ_{max} 3360, 1690 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 1.53 (s, 3H, Ar-C*H*$_3$), 4.23-4.27 (m, 2H, *H*-3, *H*-4), 5.94 (d, *J* = 8.3 Hz, 2H, Ar), 6.23-6.26 (m, 5H, Ar), 6.30-6.33 (m, 2H, Ar), 6.51-6.56 (m, 3H, Ar), 6.69 (d, *J* = 7.3 Hz, 1H, Ar), 9.73 (s, 1H, -CON*H*).

^{13}C NMR (125.76 MHz, $CDCl_3$+DMSO-d_6): δ 165.9, 157.3, 143.8, 134.9, 128.0, 127.6, 127.1, 126.3, 124.2, 122.8, 121.2, 120.0, 114.8, 114.3, 111.7, 74.9, 53.4, 18.8

MS: (*m/z*) = 345 (M+1)

Anal. Calcd. for **$C_{22}H_{20}N_2O_2$:** C, 76.71; H, 5.86; N, 8.14%

Found C, 76.53; H, 5.68; N, 7.92%.

2.6.5i: 3-Methoxy-4-*p*-tolylamino-3, 4-dihydro-1-*H*-quinolin-2-one (2.07i):

Yield, 0.121 g, 86%; white crystalline solid.

m.p. 211 ºC

IR ($CHCl_3$): υ_{max} 3373, 1689 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.27 (s, 3H, Ar-CH_3), 3.58 (s, 3H, -OCH_3), 4.14 (d, *J* = 7.4 Hz, 1H, *H*-4), 4.69 (d, *J* = 7.4 Hz, 1H, *H-3*), 6.63 (d, *J* = 6.7 Hz, 2H, Ar), 6.89-7.08 (m, 4H, Ar), 7.23-7.36 (m, 2H, Ar), 8.85 (s, 1H, -CON*H*).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ 167.7, 145.3, 136.6, 129.4, 128.5, 128.3, 124.8, 124.1, 122.2, 115.3, 112.7, 78.0, 57.9, 53.9, 20.0

MS: (*m/z*) = 283 (M+1).

Anal. Calcd. for **$C_{17}H_{18}N_2O_2$:** C, 72.31; H, 6.44; N, 9.92%

Found C, 72.10; H, 6.53; N, 9.83%.

2.6.5j: 3-Benzyloxy-4-*p*-tolylamino-3,4-dihydro-1-*H*-quinolin-2-one (2.07j).

Yield, 0.139 g, 78%; fluppy white solid.

m.p. 203 ºC

IR ($CHCl_3$): υ_{max} 3371, 1677 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.16 (s, 3H, Ar-CH_3), 4.24 (m, 1H, *H*-4), 4.54 (d, *J* = 7.4 Hz, 1H, *H*-3), 4.58 (d, *J* = 12.0 Hz, 1H, -OC$H_a$$H_b$Ph), 4.83 (d, *J* = 12.0 Hz, 1H, -OC$H_a$$H_b$Ph), 6.39 (m, 2H, Ar), 6.80-6.95 (m, 2H, Ar), 7.17-7.20 (m, 2H, Ar), 7.25 (m, 5H, Ar), 8.46 (bs, 1H, -CON*H*).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ 168.1, 145.3, 137.9, 136.7, 129.4, 128.7, 128.6, 128.2, 127.9, 127.6, 124.9, 124.1, 122.4, 115.5, 112.8, 75.8, 71.9, 54.4, 20.1

MS: (*m/z*) = 359 (M+1)

Anal. Calcd. for **$C_{23}H_{22}N_2O_2$:** C, 77.06; H, 6.20; N, 7.82%

Found C, 76.81; H, 6.10; N, 7.56%.

2.6.5k: 3-Acetoxy-4-*p*-tolylamino-3, 4-dihydro-1-*H*-quinolin-2-one (2.07k):

Yield, 0.119 g, 77%; fluppy white solid.

m.p. 238 ºC

IR ($CHCl_3$): υ_{max} 3379, 1755, 1693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 1.54 (s, 3H, -OCOC*H*$_3$), 1.79 (s, 3H, Ar-C*H*$_3$), 4.50 (d, *J* = 11.5 Hz, 1H, *H*-4), 5.09 (d, *J* = 11.5 Hz, 1H, *H*-3), 6.22 (d, *J* = 8.3 Hz, 2H, Ar), 6.51-6.58 (m, 4H, Ar), 6.77-6.80 (m, 1H, Ar), 6.97 (d, *J* = 7.3 Hz, 1H, Ar), 9.94 (s, 1H, -CON*H*).

^{13}C NMR (125.76 MHz, $CDCl_3$+DMSO-d_6): δ 169.2, 165.4, 144.3, 134.9, 128.6, 127.8, 125.6, 125.4, 123.4, 122.0, 114.9, 112.5, 70.5, 53.1, 19.6, 19.3.

MS: (*m/z*) = 311 (M+1).

Anal. Calcd. for **$C_{18}H_{18}N_2O_3$:** C, 69.65; H, 5.86; N, 9.03%

Found C, 69.53; H, 5.67; N, 9.00%.

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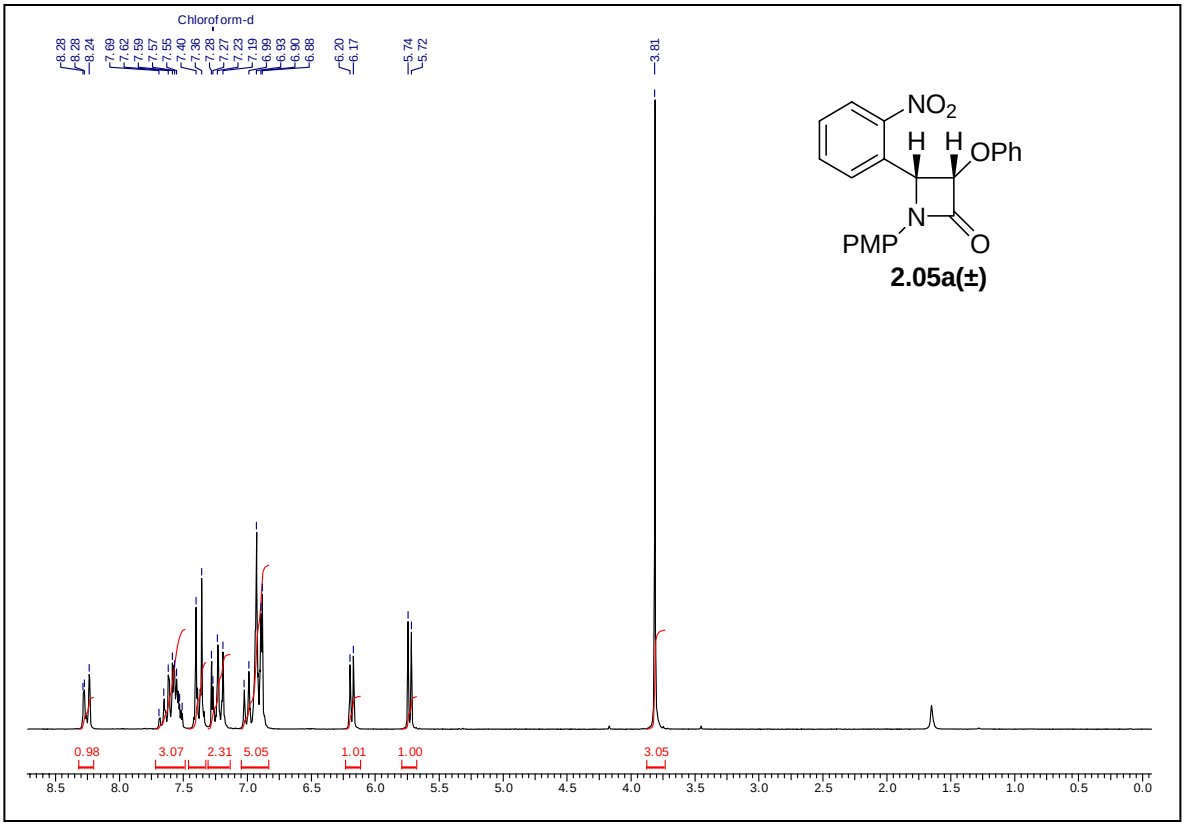
Chapter II

Spectra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7.23
7.19
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6.93
6.90
6.88
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6.17
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5.72
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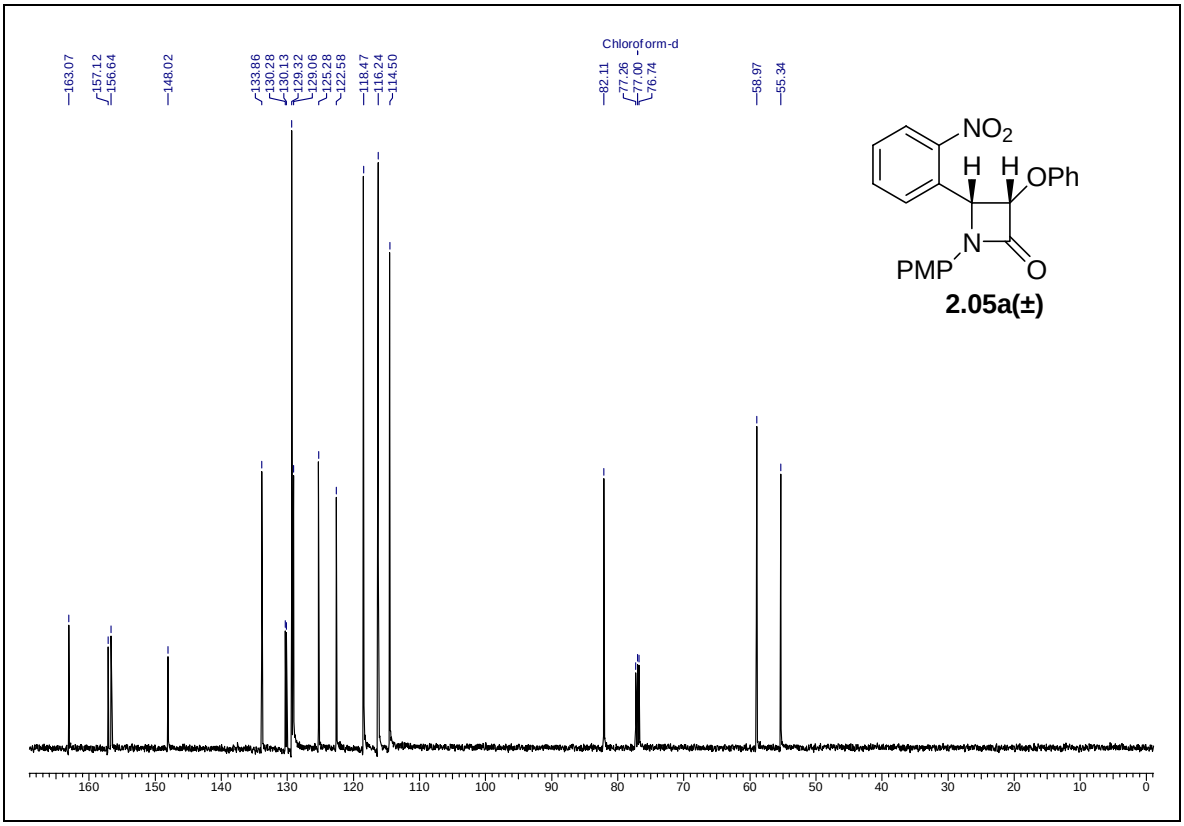
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114.50
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55.34
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O
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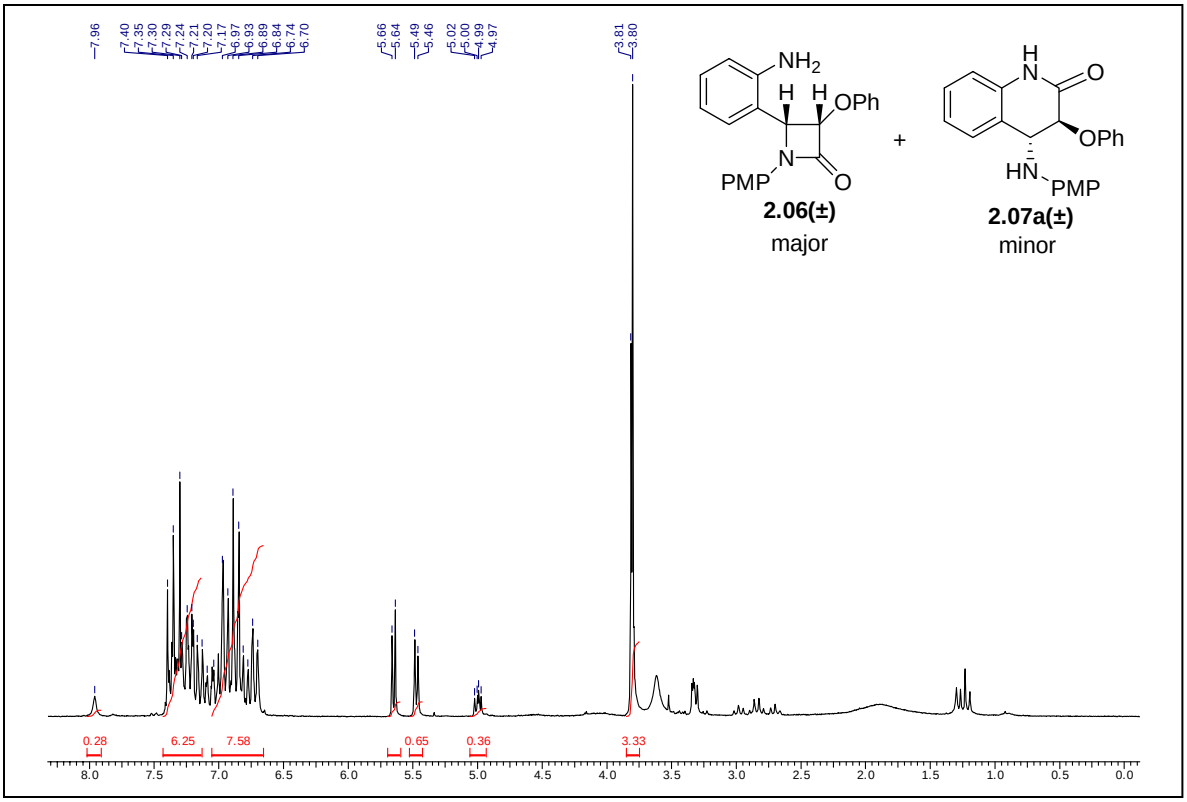
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6.70
5.66
5.64
5.49
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5.02
5.00
4.99
4.97
3.81
3.80
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N
PMP
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OPh
HN
PMP
2.07a(±)
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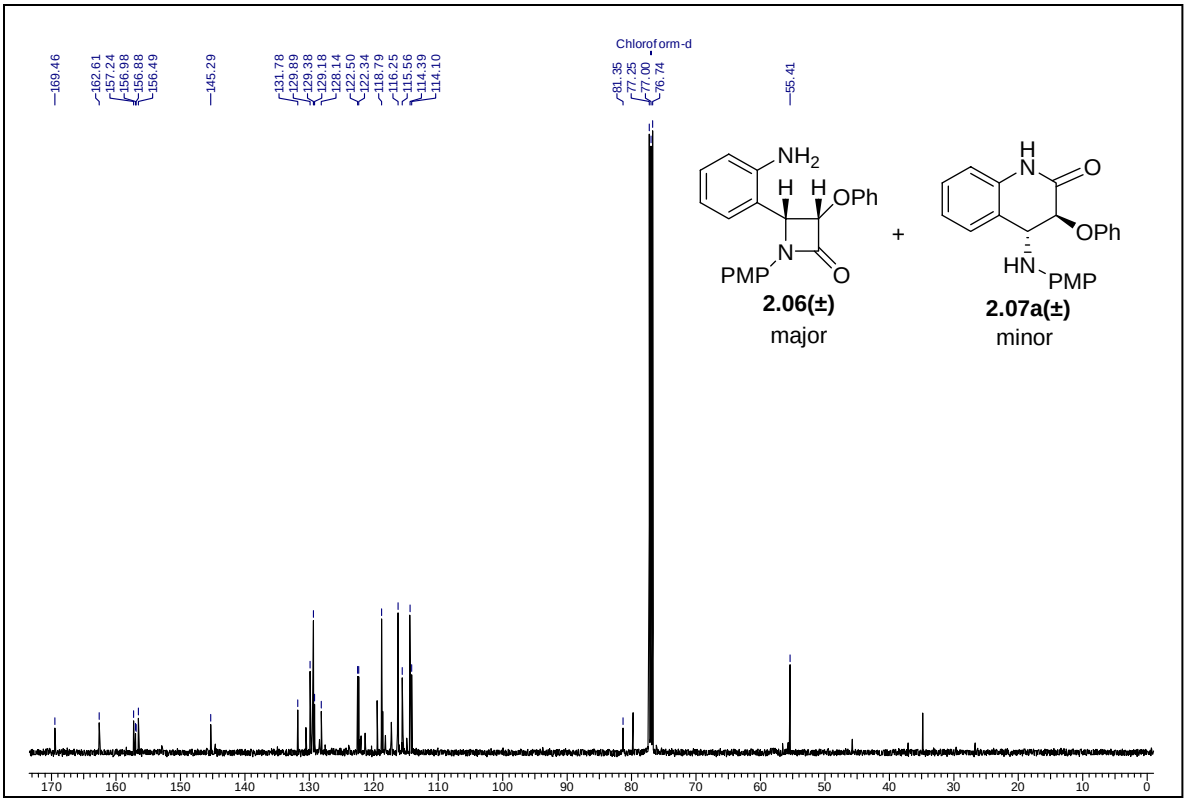
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118.79
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115.55
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114.10
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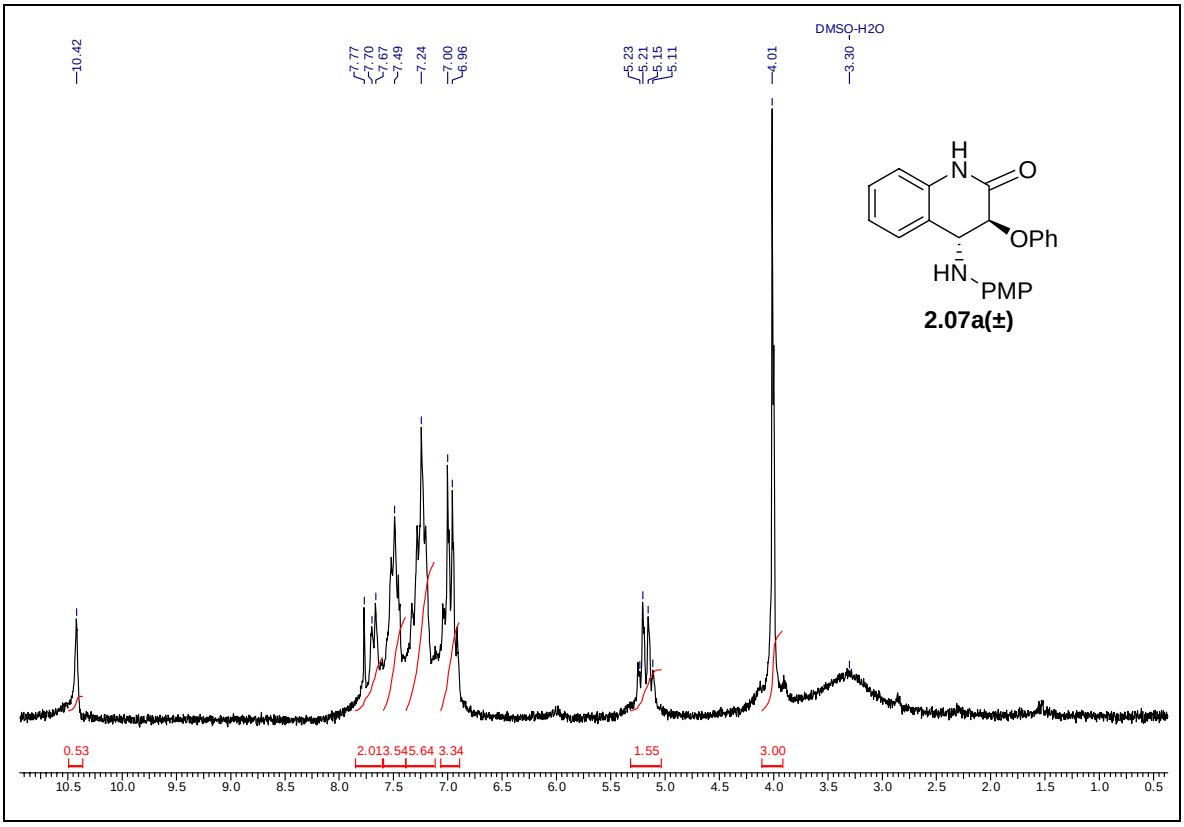
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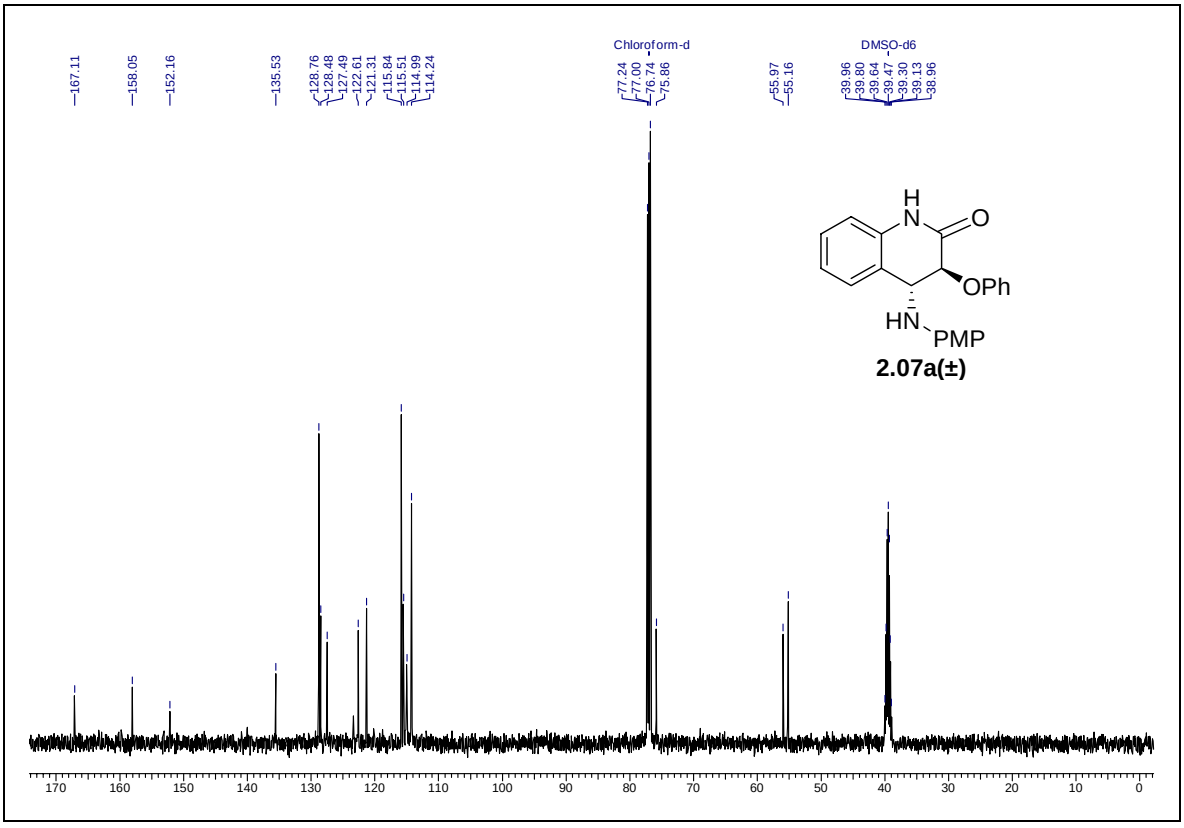
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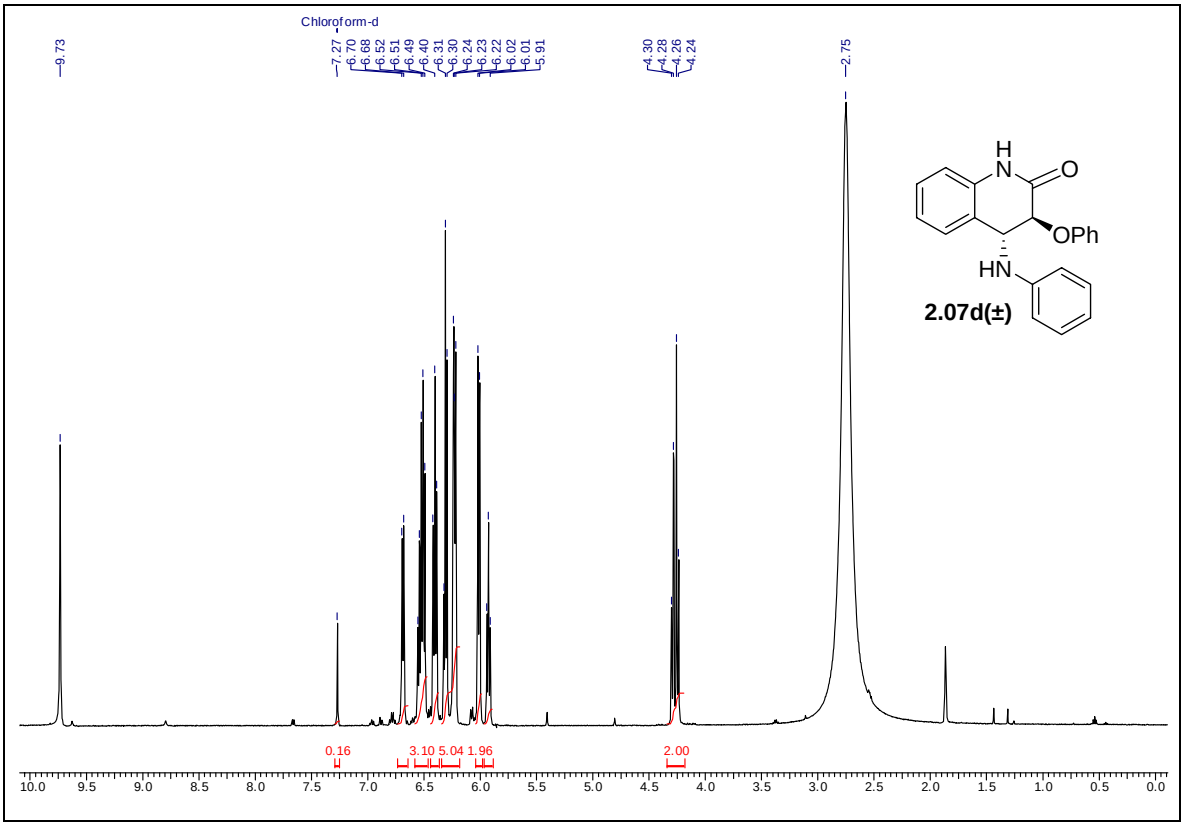
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6.01
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N
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HN
2.07d(±)
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7.0
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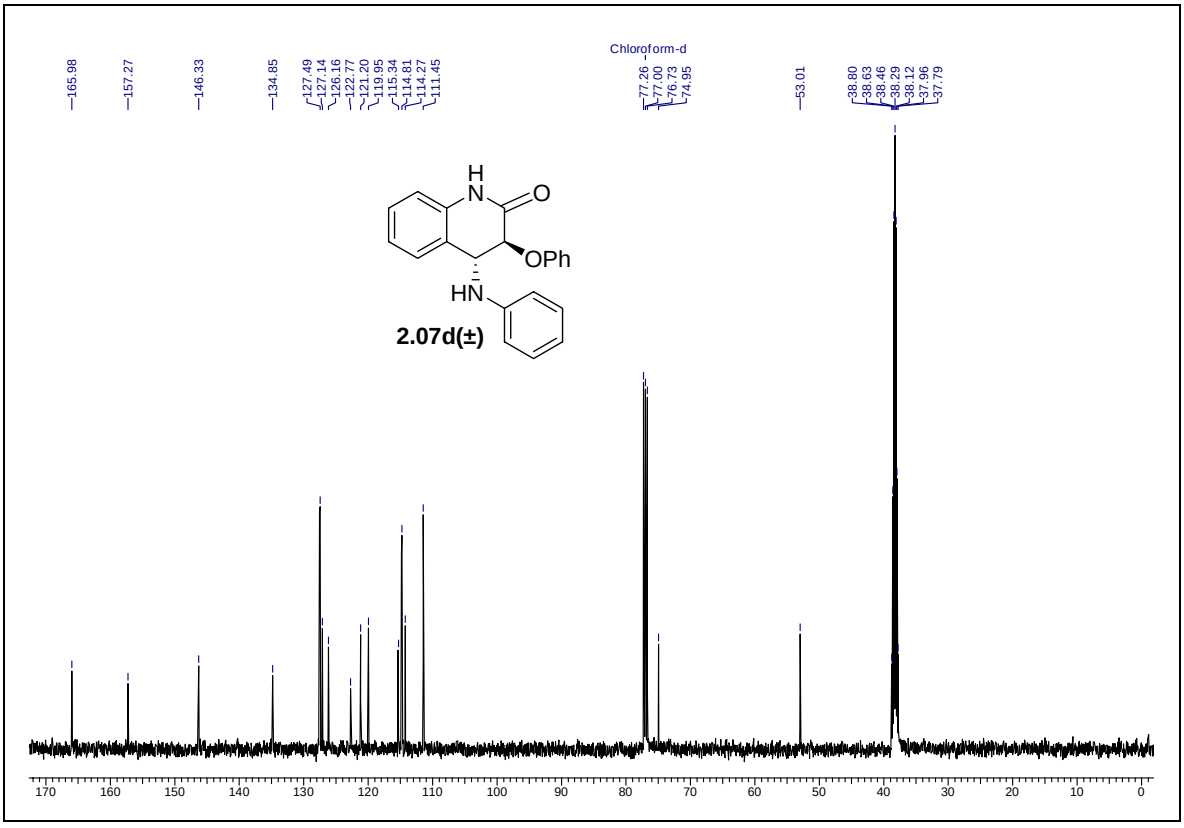
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111.45
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HN
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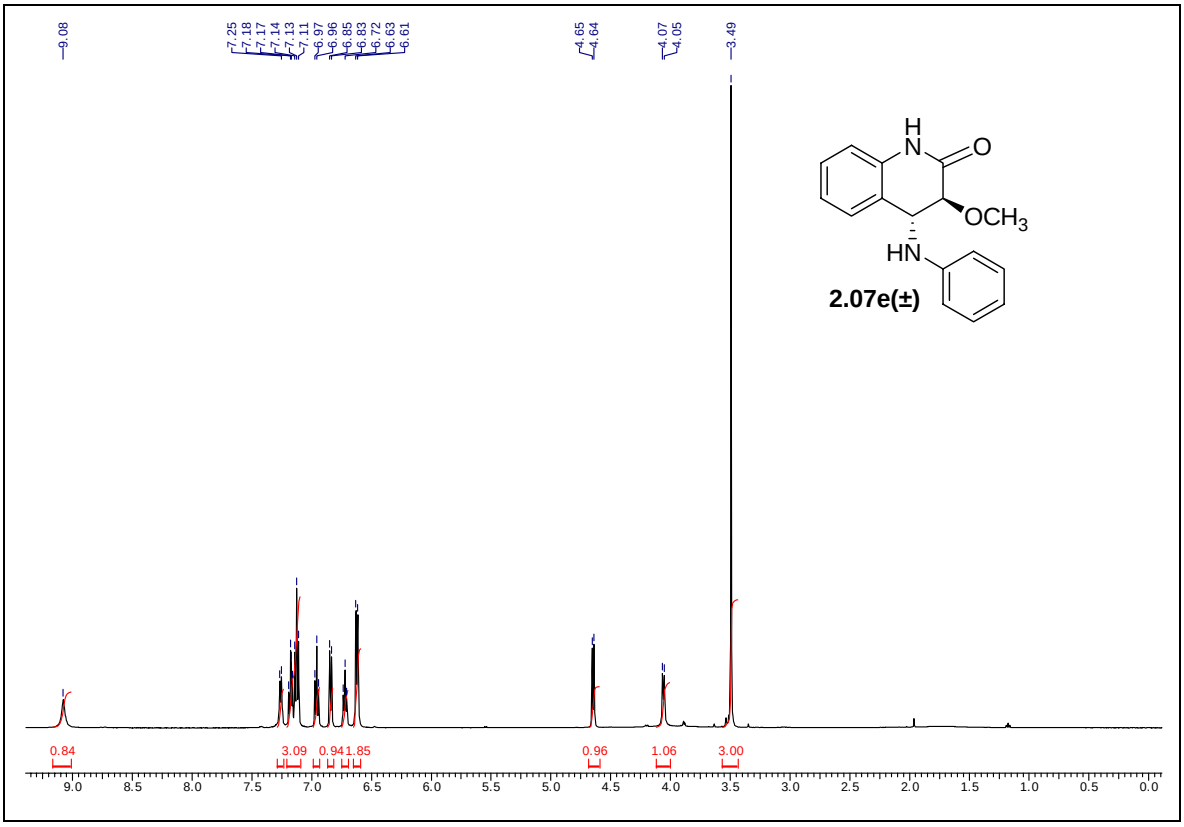
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6.61
4.65
4.64
4.07
4.05
3.49
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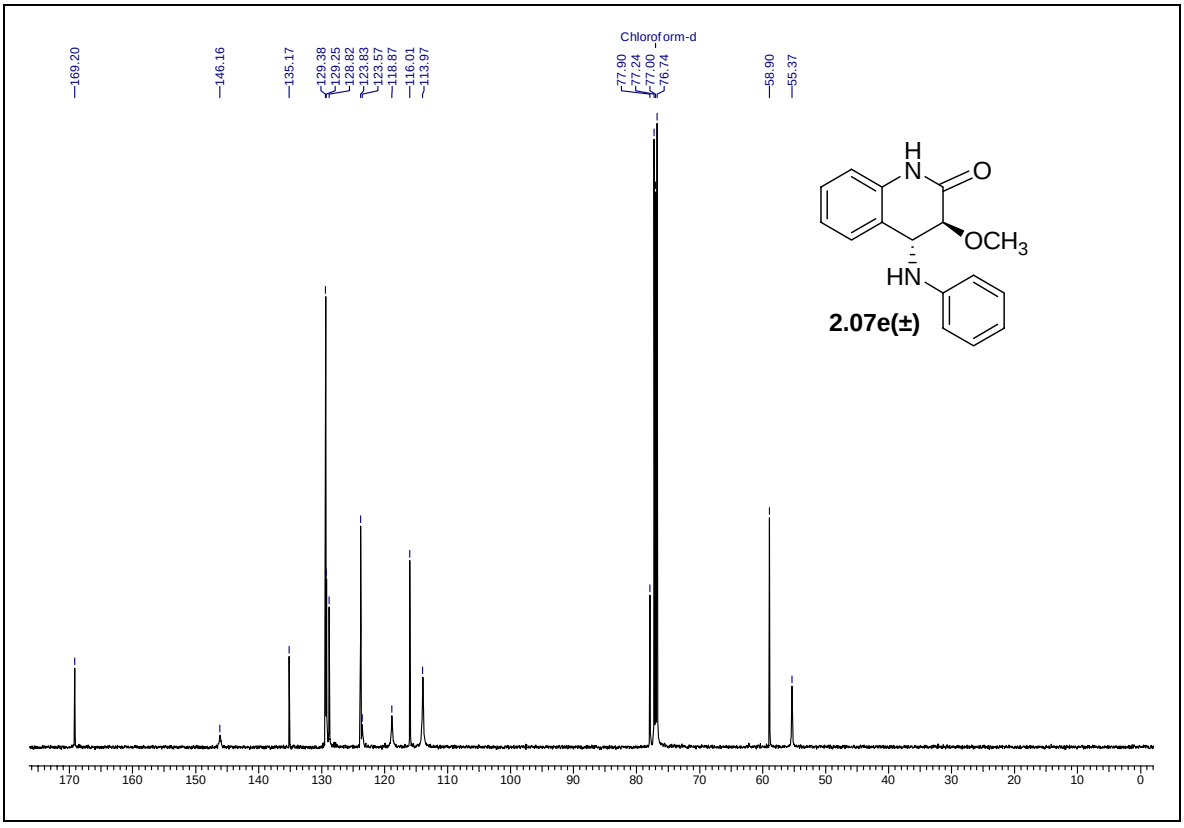
2.07e(±)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113.97
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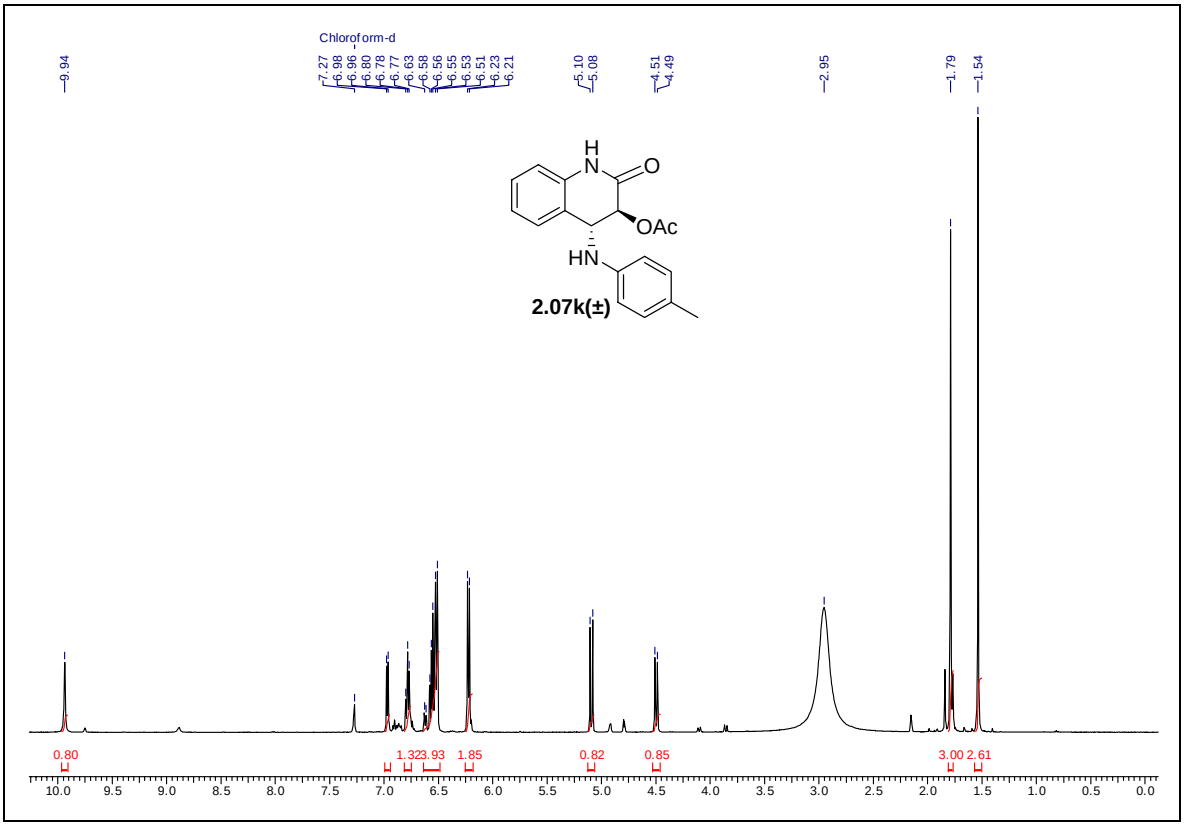
58.90
55.37
H
N
O
OCH3
HN
2.07e(±)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6.53
6.51
6.23
6.21
5.10
5.08
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O
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HN
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1.85
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0.85
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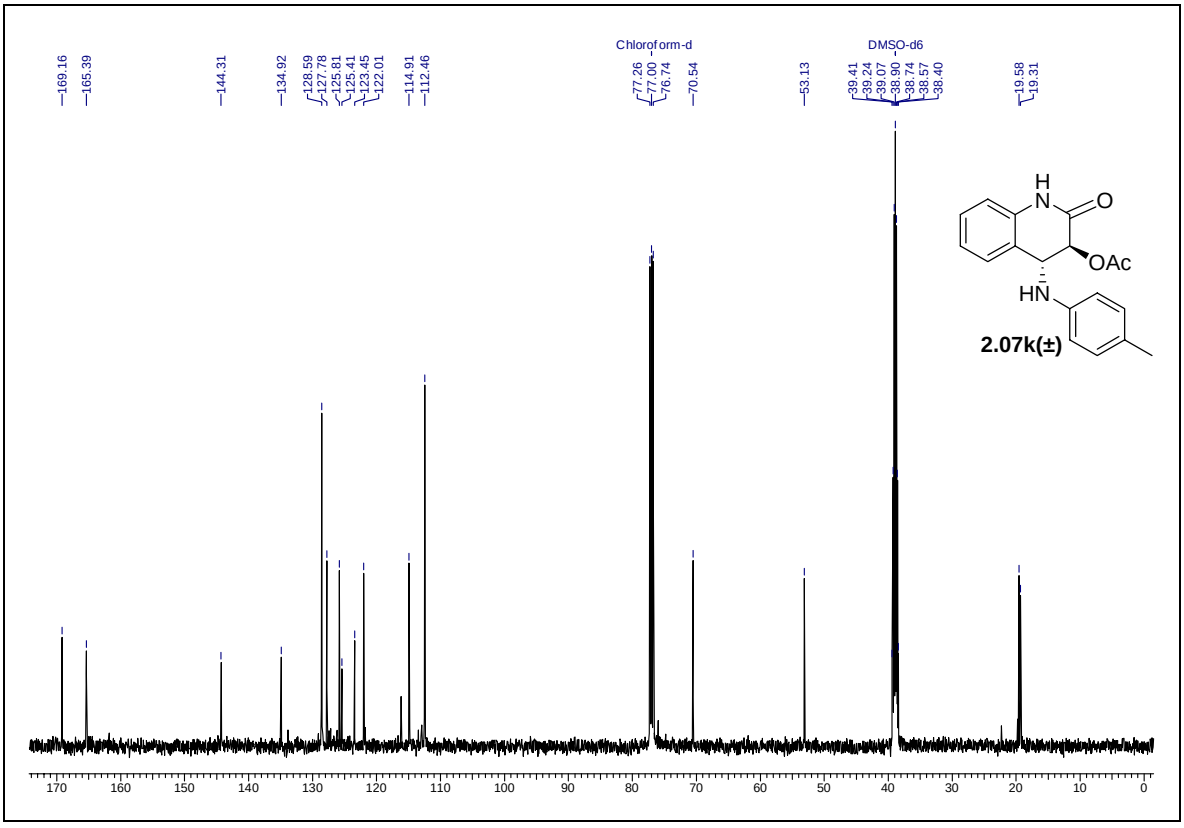
2.0
1.5
1.0
0.5
0.0

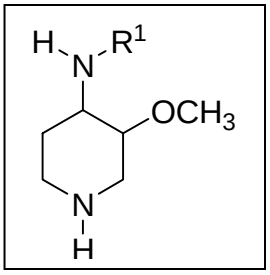

169.16
165.39
144.31
134.92
128.59
127.78
125.81
125.41
123.45
122.01
114.91
112.46
Chloroform-d
77.26
77.00
76.74
70.54
53.13
DMSO-d6
39.41
39.24
39.07
38.90
38.74
38.57
38.40
19.58
19.31
H
N
O
OAc
HN
2.07k(±)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Chapter III

Synthesis of 4-amino piperidines from 4-formyl azetidin-2-ones: Studies towards the synthesis of (3*S*,4*R*)-Cisapride

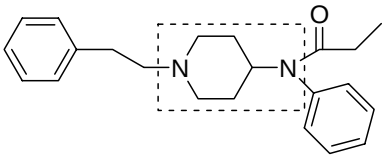
3.1 Introduction:

Piperidine units are found in many natural products and are key pharmacophores in several biologically active compounds. Their stereoselective synthesis remains a great challenge.[1,2] A survey of the structures of both naturally occurring and synthetic compounds with a wide spectrum of interesting pharmacological properties shows the frequent occurrence of the ethanolamine (N-C-C-O) moiety. This suggest that the introduction of an oxygen atom at the 3-position of the piperidine ring might well lead to compounds with new or more specific activities.[3] This chapter deals with the synthesis of chiral 4-amino 3-substituted piperidines and its further studies towards the drug molecule Cisapride.

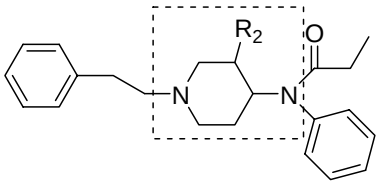


4-Amino piperidine

4-Amino 3-substituted piperidines forms a part structure of fentanyl and its derivatives,[4] useful as analgesics and a drug molecule like Cisapride[3,5] and its analogs such as ATI 7505,[6] novel *N*-aryl-*N*-[*N*-substituted 3-alkoxy-4-piperidinyl] amides useful as analgesics.[6]

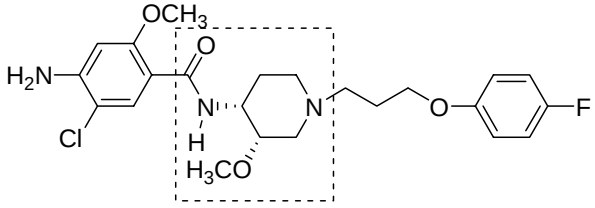


Fentanyl

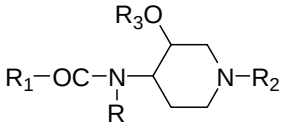


Fentanyl derivatives

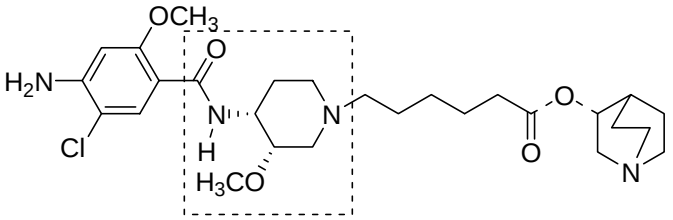
1: $R_1 = R_2 = H$ 2: R_1 = NCS, $R_2 = H$
3: $R_1 = H$, $R_2 = CH_3$ 4: R_1 = NCS, $R_2 = CH_3$



Cisapride



N-aryl-N-[N-substituted 3-alkoxy-4-piperidinyl]

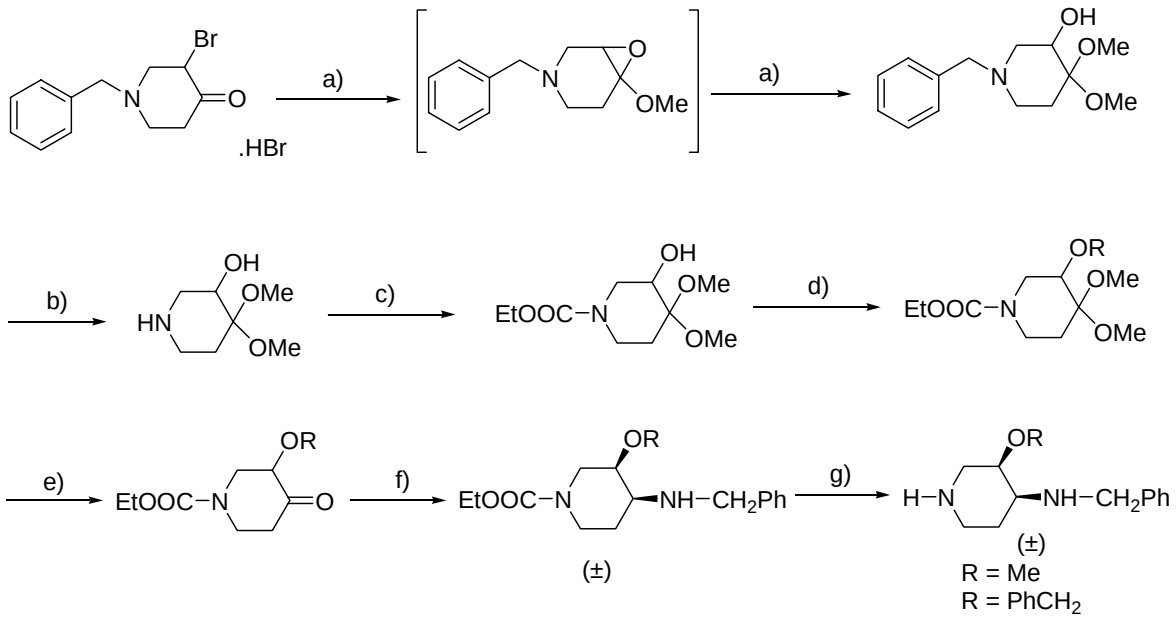


ATI 7505

3.2 Background for the present work:

Synthesis of 4-amino 3-substituted piperidines were reported by various groups.[3,4,5,8] Van Daele et al.[3] have reported the synthesis of *cis*-3-oxygenated-4-piperidinamines. N-phenylmethylpiperidine on bromination in acetic acid gave hydrobromide, which on treatment with sodium methoxide gave 3-hydroxy-4-piperidone in 55% total yield. 3-Hdyroxy-4-piperidone on further synthetic transformations converted to racemic 4-amino *cis*-3-oxygenated piperidinamines (Scheme 3.01).

Scheme 3.01

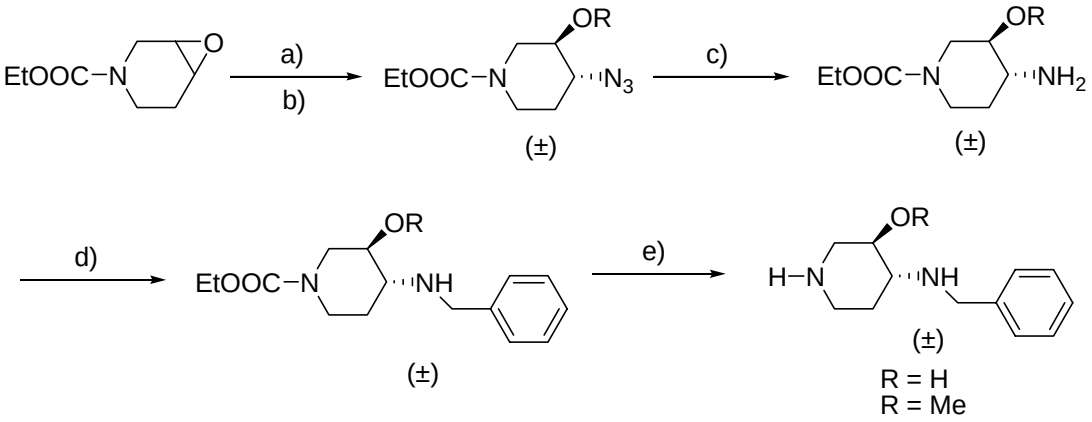


Reagents and conditions: a) MeOH-MeONa, 1.5 h, r.t.; b) H_2, 10% Pd/C, MeOH; (c) ClCOOEt, 1N NaOH, THF, 4 h, 0 °C; d) RX, 50% NaH, DMF, r.t.; e) 1% H_2SO_4, 3 h, reflux, (f) H_2, 10% Pd/C; thiophene, MeOH. h) 10eq KOH-*i*-PrOH, 3.5 h, reflux.

Van Daele et al.[3] have also reported the synthesis of *trans*-3-oxygenated-4-piperidinamines starting from readily accessible oxirane.[7] Regioselective opening of

oxirane with NaN_3 gave *trans*-3-hydroxy isomer which on further synthetic transformations gave *trans*-3-oxygenated 4-piperidinamines (Scheme 3.02).

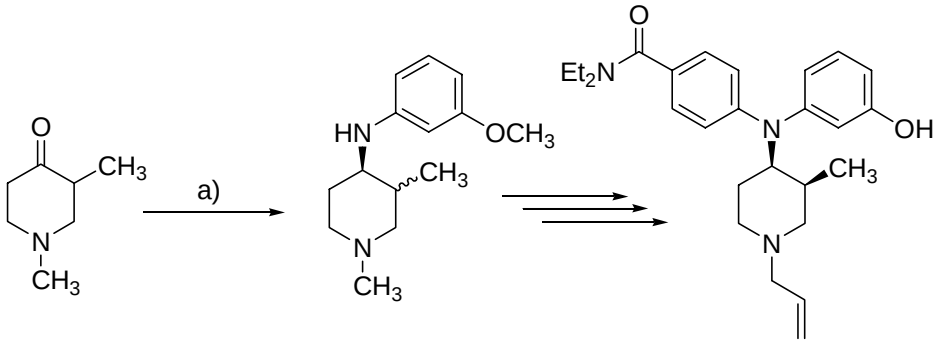
Scheme 3.02



Reagents and conditions: a) NaN_3, H_2O-EtOH, r.t.; b) 50% NaH, MeI, DMF, r.t.; c) H_2, 10% Pd/C, MeOH, exothermic, maximum 0.2 mol; (d) PhCHO, H_2, 10% Pd/C, MeOH, thiopene; (e) 10 eq. KOH-*i*-Pr-OH, reflux.

Thomas et al.[4d] have reported a method in which commercially available 1,3-dimethyl-4-piperidone on reductive amination with *m*-anisidine and titatnium (IV) isopropoxide gave diastereomeric mixture of piperidines which were separated and further converted to substituted piperidine (Scheme 3.03).

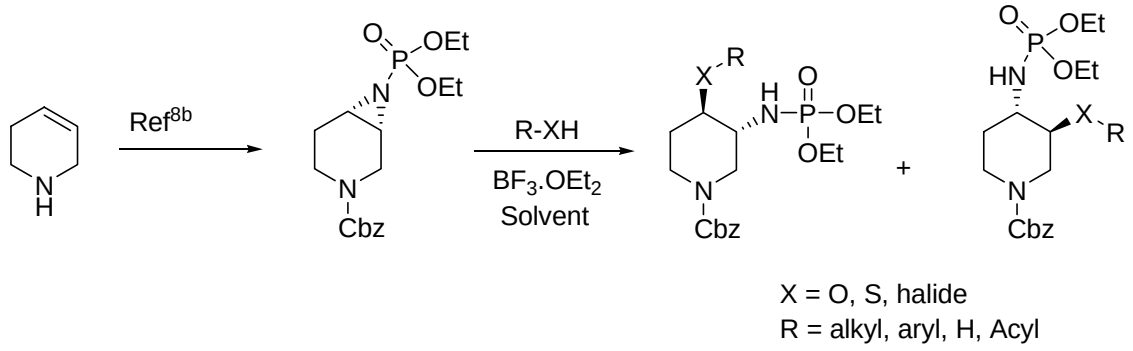
Scheme 3.03



Reagents and conditions: a) Ti(O*i*-Pr)$_4$, aniline derivative then $NaBH_4$, EtOH.

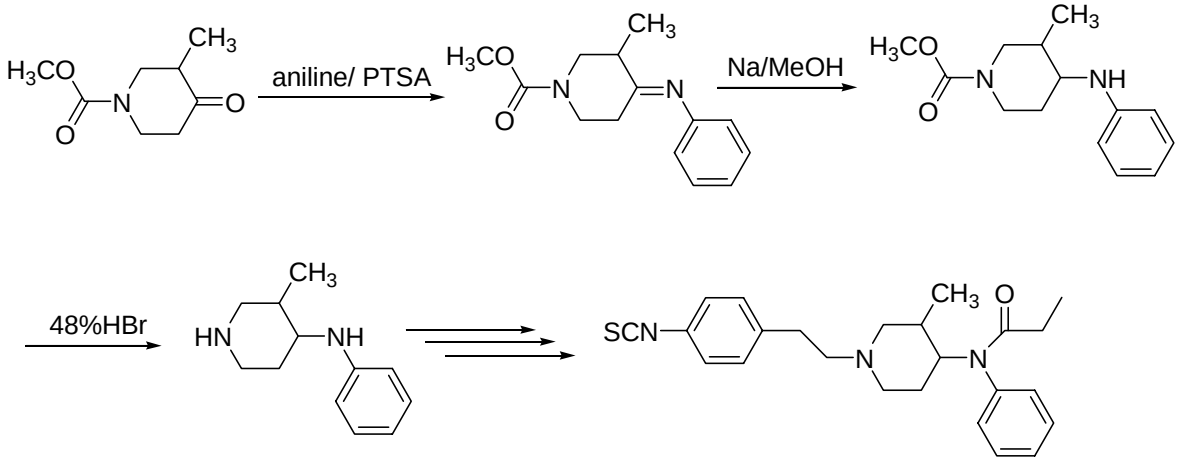
Hu et al.[8a] have reported that an activated aziridine undergo Lewis acid catalyzed nucleophilic addition to gave 3-amino substituted piperidine and 4-amino substituted piperidine in > 20:1 ratio regioselectively (Scheme 3.04).

Scheme 3.04



Rice et al.[4c] have reported the synthesis of 3-methyl 4-amino piperidine from piperidin-4-one which can be obtained from commercially available 3-carbomethoxy-4-oxopiperidin in three steps.[4a] 3-Methyl 4-amino piperidine on further synthetic transformation converted to fentanyl derivative (Scheme 3.05).

Scheme 3.05

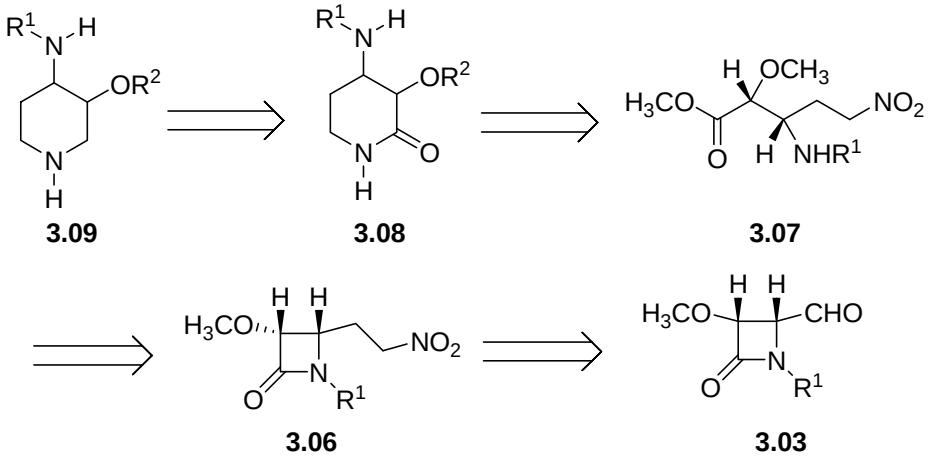


Although there are many methods available for synthesis of racemic (*cis* / *trans*)-4-amino 3-substituted piperidine, however there is no report for there synthesis using azetidin-2-one synthon. Also there is no report for chiral synthesis of 4-amino 3-substituted piperidine, using chiral starting material.

3.3 Present work:

We planned the chiral synthesis of 4-amino 3-substituted piperidine **3.09** using azetidin-2-one as a synthon. 4-Amino 3-substituted piperidine **3.09** can be obtained from their corresponding pyridone derivative **3.08**. The 4-amino 3-substituted pyridone **3.08** could be synthesized from nitro ester **3.07** by reduction of nitro group followed by intramolecular cyclization. Nitro ester **3.07** could be obtained from azetidin-2-one **3.06** which in turn could be obtained from 4-formyl azetidin-2-one **3.03**. The retrosynthetic strategy for the synthesis of 4-amino 3-substituted piperidine is depicted in the (Scheme 3.06).

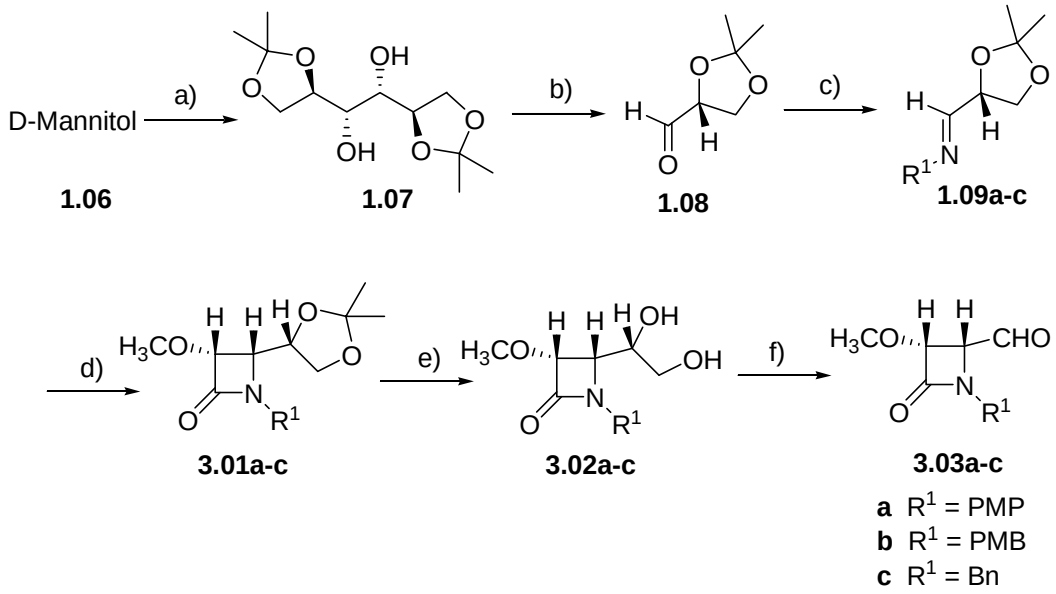
Scheme 3.06



3.4 Results and Discussion:

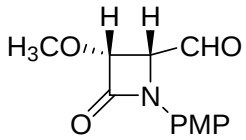
The enantiopure **3.01a-c** were obtained by the [2+2] cycloaddition reaction of Schiff base **1.09a-c** (derived from D-glyceraldehyde acetonide **1.08**) with ketene obtained from methoxy acetyl chloride following a reported procedure in 50% overall yield.[9] The acetonide group of the azetidin-2-ones **3.01a-c** was cleaved by using PTSA[10] to get the diols **3.02a-c** in quantitative yield, which on oxidative cleavage using $NaIO_4$ gave enantiopure 4-formylazetidin-2-ones **3.03a-c**[11] (Scheme 3.07).

Scheme 3.07



Reagents and conditions: a) $ZnCl_2$, anhyd. acetone, 24 h, 50%; b) $NaIO_4$, H_2O, 30 min, 0 °C; c) R^1-NH_2, H_2O-EDC, r. t., 2 h; d) Et_3N, CH_2Cl_2, $MeOCH_2COCl$, 0 °C-r. t., 12 h, 50%; e) PTSA, THF-H_2O, reflux 15 h, 90%; f) $NaIO_4$, SiO_2, CH_2Cl_2, 30 min, 95%.

The structure of **3.03a** was established by IR and ^{1}H NMR spectral data. IR spectrum of **3.03a** showed a sharp peak at 1761 cm^{-1} for the azetidin-2-one amide carbonyl.

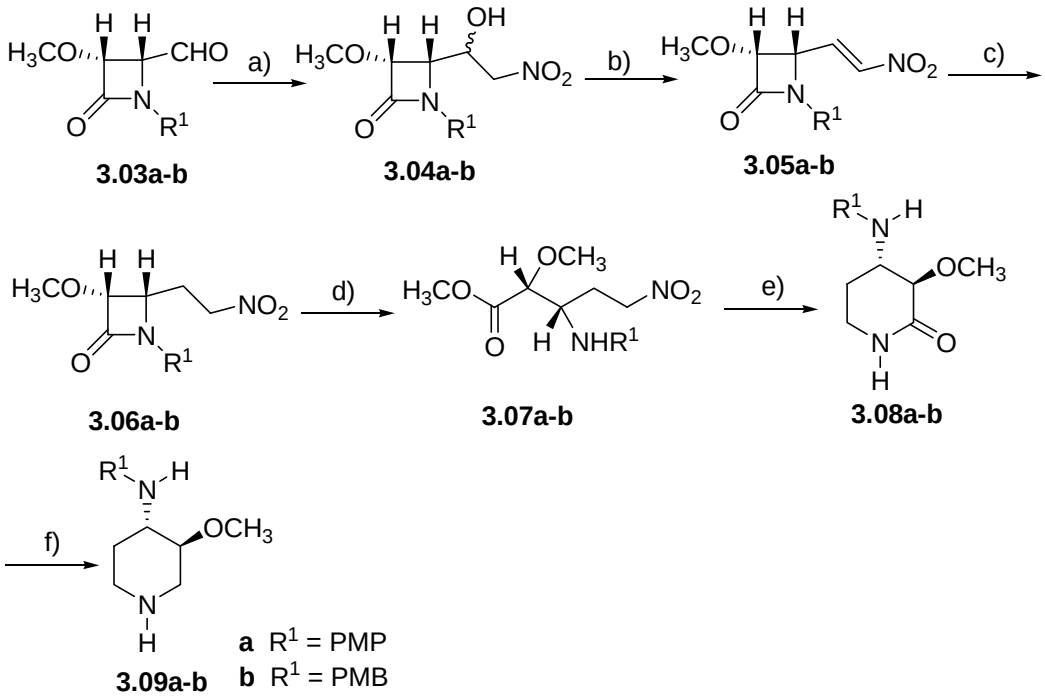


3.03a

The ^{1}H NMR spectrum showed a singlet at 3.57 ppm integrating for three protons corresponds to $–OCH_3$ group protons. A singlet at 3.79 ppm assigned for $–OCH_3$ protons of PMP group. The H-4 β-lactam proton seen as doublet of doublet at 4.53 ppm (J = 5.2 Hz and 3.9 Hz). The H-3 β-lactam proton appeared as a doublet at 4.88 ppm (J = 5.2 Hz). The aromatic protons of the PMP group appeared as doublets at 6.87 ppm and 7.28 ppm (J = 8.7 Hz). The aldehyde proton seen at doublet at 9.76 ppm (J = 3.9 Hz).

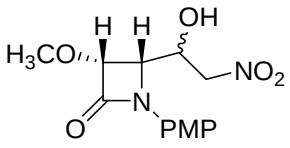
The 4-formylazetidin-2-one **3.03a** on treatment with nitromethane in the presence of catalytic amount of triethylamine at room temperature for 5 h gave diastereomeric mixture of nitro alcohol **3.04a** in 95% yield. (Scheme 3.08).

Scheme 3.08



Reagents and conditions: a) CH_3NO_2, Et_3N, 5 h, 95%; b) i) Ac_2O, Conc. H_2SO_4, 0 °C, 1 h, ii) $NaHCO_3$, benzene, reflux, 4 h, 80%; c) Bu_3SnH, CH_2Cl_2:MeOH (10:1), r. t., 3 h, 50-60%; d) methanolic HCl (20%), r. t., 12 h, 80%; e) 10% Pd/C, $HCOONH_4$, MeOH, r. t., 5 h, 60-70%; f) BH_3:DMS, toluene, reflux 4 h, 50%.

The structure of **3.04a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.04a** showed a sharp peak at 1751 cm^{-1} for the amide carbonyl of azetidin-2-one.

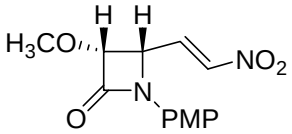

3.04a

The ^{1}H NMR spectrum showed a broad singlet at 3.04 ppm corresponds to –OH group proton. A singlet at 3.71 ppm integrating for three protons corresponds to $–OCH_3$ group protons. A singlet at 3.80 ppm assigned for $–OCH_3$ protons of PMP group. The H-4 β-lactam proton appeared as multiplet at 4.39-4.44 ppm. The methylene protons of C-4 side chain seen as multiplet at 4.50-4.62 ppm. The methine proton of C-4 side chain appeared as multiplet at 4.69-4.73 ppm. The H-3 β-lactam proton showed multiplet at 4.80-4.90 ppm. The aromatic protons of the PMP group resonated as multiplet at 6.85-6.92 ppm and 7.36-7.40 ppm.

The ^{13}C NMR spectrum showed a peak at 164.5, 164.0 ppm for azetidin-2-one carbonyl. The aromatic quaternary carbons appeared at 157.0, 129.9, 129.7 ppm. The remaining aromatic carbons seen at 119.9, 119.4, 114.6, 114.4 ppm. The methylene carbon of C-4 side chain appeared at 82.8, 82.4 ppm. The C-3 carbon of azetidin-2-one seen at 77.7, 77.5 ppm. The methine carbon of C-4 side chain appeared at 68.6, 67.1 ppm. The C-4 carbon of azetidin-2-one assigned at 59.7, 59.6 ppm. The $-OCH_3$ group carbon appeared at 58.7, 58.1 ppm. The $-OCH_3$ carbon of PMP group seen at 55.4 ppm.

The hydroxy group of **3.04a** was acetylated[12] by acetic anhydride in the presence of catalytic amount of conc. H_2SO_4 at 0 °C to get a of diastereomeric mixture of nitro acetate alongwith nitro alkene **3.05a**. This crude mixture of products was refluxed in benzene in the presence of sodium bicarbonate to afford nitroalkene **3.05a** which is further purified by column chromatography on silica gel to get pure nitroalkene **3.05a** in 80% yield. (Scheme 3.08).

The structure of **3.05a** was established by IR, ^1H NMR and ^{13}C NMR spectral data. IR spectrum of **3.05a** showed a sharp peak at 1757 cm^{-1} for the azetidin-2-one amide carbonyl.



3.05a

The ^1H NMR spectrum of **3.05a** showed a singlet at 3.57 ppm integrating for three protons corresponds to $-OCH_3$ group protons. A singlet at 3.80 ppm corresponds to $-OCH_3$ protons of PMP group. The H-4 and H-3 β-lactam proton appeared as multiplet at 4.83-4.92 ppm. One of the doublet of PMP group appeared at 6.88 ppm (J = 8.9 Hz). The remaining aromatic as well as olefinic protons assigned as multiplet at 7.12-7.32 ppm.

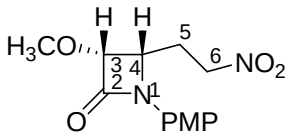
The ^{13}C NMR spectrum of **3.05a** showed a peak at 162.4 ppm corresponding to azetidin-2-one carbonyl carbon. The aromatic quaternary carbons appeared at 156.8 and 142.6. The olefinic carbons appeared at 135.5 and 129.7 ppm. The remaining aromatic carbons appeared at 118.3 and 114.5 ppm. The C-3 carbon of azetidin-2-one appeared at 85.3 ppm. The $-OCH_3$ carbon seen at 59.1 ppm. The $-OCH_3$ carbon of PMP group and C-4 carbon of azetidin-2-one assigned at 55.2 ppm.

The mass spectrum of **3.05a** gave M+1 peak at m/z 279, also supporting the structure of the compound. Specific rotation for **3.05a** were found to be $[\alpha]^{30}_{D}$ = +177.4 (*c* 0.62, $CHCl_3$).

The double bond of the nitro alkene **3.05a** was reduced using tributyltinhydride.[13] To a solution of nitroalkene **3.05a** in anhydrous CH_2Cl_2:MeOH (10:1), tributyltinhydride was added at room temperature and stirred for 3 h. After completion of reaction, the solvent was removed under *vacuo* to get crude product, which was purified by flash column chromatography to afford pure nitroalkane **3.06a** in 60% yield (Scheme 3.08).

The structure of **3.06a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.06a** showed a sharp peak at 1745 cm^{-1} for the azetidin-2-one amide carbonyl.

The ^{1}H NMR spectrum of **3.06a** showed two set of multiplet at 2.35-2.49 ppm and 2.66-2.79 ppm for H-5 methylene protons. A singlet at 3.68 ppm corresponds to –OCH_3 group protons. A singlet at 3.81 ppm assigned for –OCH_3 protons of PMP group. The H-4 β-lactam proton appeared as multiplet at 4.31-4.39 ppm. The H-6 methylene protons bearing the nitro group seen as multiplet at 4.51-4.58 ppm. The H-3 β-lactam proton resonated as doublet at 4.65 ppm (*J* = 5.1 Hz). The doublets of PMP group appeared at 6.91 ppm and 7.35 ppm (*J* = 8.8 Hz)



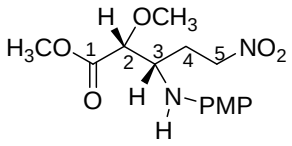
3.06a

The ^{13}C NMR spectrum of **3.06a** showed a peak at 163.9 ppm corresponding to azetidin-2-one carbonyl. The aromatic quaternary carbons appeared at 156.7 and 129.9 ppm. The remaining aromatic carbons resonated at 118.6 and 114.7 ppm. The C-3 carbon of azetidin-2-one appeared at 82.7 ppm. The C-6 methylene carbon seen at 71.6 ppm. The –OCH_3 carbon assigned at 59.2 ppm. The –OCH_3 carbon of PMP group appeared at 55.4 ppm. The C-4 carbon appeared at 53.9 ppm. The C-5 methylene carbon resonated at 25.0 ppm.

The mass spectrum of **3.06a** gave M+1 peak at m/z 281, also supporting the structure of the compound. Specific rotation for **3.06a** were found to be $[\alpha]^{30}_{D}$ = +158.8 (*c* 1.02, $CHCl_3$).

The β-lactam ring of the nitro alkane **3.06a** was cleaved by stirring with methanolic HCl (20%) at room temperature for 12 h to get the nitro ester **3.07a** in 80% yield (Scheme 3.08).

The structure of **3.07a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.07a** showed a sharp peak at 1749 cm^{-1} for the ester carbonyl.



3.07a

The ^{1}H NMR spectrum of **3.07a** showed multiplet at 2.24-2.38 ppm for H-4 methylene protons. A singlet at 3.47 ppm corresponds to –OCH_3 group protons. A singlet at 3.51 ppm assigned for –OCH_3 protons of ester group. A singlet at 3.73 ppm corresponds to –OCH_3 protons of PMP group. The H-2, H-3 methine proton and N-H group proton assigned as a multiplet at 3.78-4.02 ppm. The H-5 methylene protons bearing the nitro group appeared as multiplet at 4.51-4.61 ppm. The doublets of PMP group resonated at 6.60 ppm and 6.75 ppm (J = 9.0 Hz).

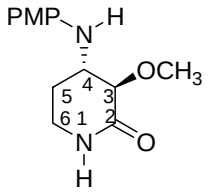
The ^{13}C NMR spectrum of **3.07a** showed a peak at 170.6 ppm for ester carbonyl carbon. The aromatic quaternary carbons appeared at 152.7 and 140.5 ppm. The remaining aromatic carbons appeared at 115.6 and 114.7 ppm. The C-2 carbon of ester appeared at 81.0 ppm. The C-5 methylene carbon resonated at 72.4 ppm. The –OCH_3 carbon of ester group appeared at 58.8 ppm. The –OCH_3 carbon assigned at 55.5 ppm. The –OCH_3 carbon of PMP group assigned at 54.5 ppm. The C-3 and C-4 carbon appeared at 51.7 ppm and 29.9 ppm respectively.

The mass spectrum of **3.07a** gave M+1 peak at m/z 313, also supporting the structure of the compound. Specific rotation for **3.07a** were found to be $[\alpha]^{30}_{D}$ = -27.7 (*c* 1.08, $CHCl_3$).

The nitro group of the ester **3.07a** on reduction by transfer hydrogenation[14] using ammonium formate and Pd/C (10%) in methanol as solvent, at room temperature gave crude N-substituted-4-aminopiperidin-2-one **3.08a** by *insitu* intramolecular cyclization. The crude product was further purified by flash column chromatography to gave pure **3.08a** in 70% yield (Scheme 3.08).

The structure of **3.08a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.08a** showed a sharp peak at 1649 cm^{-1} for the amide carbonyl.

The ^{1}H NMR spectrum of **3.08a** showed two set of multiplet at 1.89-2.09 ppm and 2.34-2.51 ppm for H-5 methylene protons. A singlet at 3.62 ppm corresponds to $–OCH_3$ group protons. The H-6 methylene and H-4 methine proton appeared as a multiplet at 3.64-3.74 ppm. A singlet at 3.76 ppm corresponds to $–OCH_3$ protons of PMP group. The H-3 methine proton appeared as a doublet at 3.87 ppm (J = 6.3 Hz). The doublets of PMP group resonated at 6.76 ppm and 6.82 ppm (J = 9.2 Hz).



3.08a

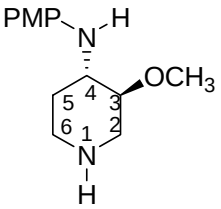
The ^{13}C NMR spectrum of **3.08a** showed a peak at 163.6 ppm for amide carbonyl carbon. The aromatic quaternary carbons appeared at 153.2 and 139.9 ppm. The remaining aromatic carbons assigned at 116.1 and 114.9 ppm. The C-3 carbon resonated at 79.8 ppm. The C-4 methine carbon appeared at 59.2 ppm. The $–OCH_3$ carbon assigned at 55.6 ppm. The $–OCH_3$ carbon of PMP group appeared at 52.3 ppm. The C-6 and C-5 methylene carbon resonated at 46.1 ppm and 24.1 ppm respectively.

The mass spectrum of **3.08a** gave M+1 peak at m/z 251, also supporting the structure of the compound. Specific rotation for **3.08a** were found to be $[\alpha]^{30}_{D}$ = +36.44 (*c* 1.18, $CHCl_3$).

Reduction of amide carbonyl of N-substituted-4-aminopiperidine-2-one **3.08a** was achieved by using BH_3:DMS[15] in refluxing toluene to gave N-substituted-4-aminopiperidine **3.09a** in 50% yield.

The structure of **3.09a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.09a** showed a peak at 3215, 3375 cm^{-1} for N-H stretchings.

The ^{1}H NMR spectrum of **3.09a** showed multiplet at 1.67-2.24 ppm for H-5 methylene proton. A multiplet at 2.36-2.63 ppm corresponds to H-6 methylene protons. A H-2 methylene protons and H-4 methine proton appeared as a multiplet at 2.86-3.32 ppm integrating for three protons. A singlet at 3.43 ppm corresponds to $–OCH_3$ group protons. A multiplet at 3.48-3.68 ppm assigned for H-3



3.09a

methine proton. A singlet at 3.74 ppm corresponds to $-OCH_3$ protons of PMP group. The doublets of PMP group appeared at 6.67 ppm and 6.78 ppm (J = 7.8 Hz).

The ^{13}C NMR spectrum of **3.09a** showed aromatic quaternary carbons at 152.5 152.1, 141.2, 140.5 ppm. The remaining aromatic carbons appeared at 116.3, 114.7, 114.5 ppm. The C-3 carbon assigned at 79.6, 77.3 ppm. The C-2 carbon appeared at 60.4 ppm. The $-OCH_3$ carbon appeared at 57.2, 56.8 ppm. The $-OCH_3$ carbon of PMP group appeared at 55.4 ppm. The C-6 carbon assigned at 56.1, 53.2 ppm. The C-4 carbon appeared at 50.4. The C-5 carbon assigned at 28.6, 25.8 ppm.

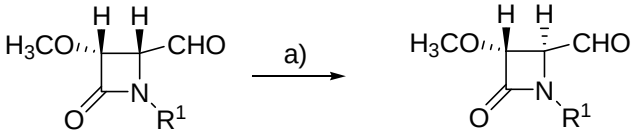
The mass spectrum of **3.09a** gave M+1 peak at m/z 237, also supporting the structure of the compound. Specific rotation for **3.09a** were found to be $[\alpha]^{30}_D$ = +12.9 (*c* 0.7, $CHCl_3$).

.By following a similar synthetic sequence (Scheme 3.08) *trans*-N-substituted-4-aminopiperidine **3.09b** was also synthesized.

Since drug molecule like Cisapride, fentanyl derivatives, and its analogue containing *cis* stereochemistry are more effective in potentiating the contractile response of the ileum to coaxial stimulation.[3] We were also interested in getting *cis* stereochemistry at C-3 and C-4 position of piperidine, to get *cis* stereochemistry at C-3 and C-4 position it is essential to start synthesis from *trans* 4-formyl azetidin-2-one.

cis-4-Formyl azetidin-2-one **3.03a** on treatment with 40% dimethylamine[16] in benzene gave crude *trans*-4-formyl azetidin-2-one **3.10a** in 50% yield. The crude product was purified by flash column chromatography to get pure **3.10a** (Scheme 3.09).

Scheme 3.09



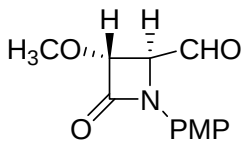
3.03a-c **3.10a-c**

a R^1= PMP
b R^1= PMB
c R^1 = Bn

Reagents and conditions: a) dimethylamine 40%, benzene, r. t., 24 h, for **3.03a/** Na_2CO_3, CH_3CN-H_2O,(1:1) r. t., 48 h, 70% for **3.03b-c**.

The structure of **3.10a** was established by IR, ^1H NMR and ^{13}C NMR spectral data. IR spectrum of **3.10a** showed a sharp peak at 1747 cm^{-1} for the amide carbonyl carbon.

The ^{1}H NMR spectrum of **3.10a** showed a singlet at 3.56 ppm integrating for three protons corresponds to –OCH_3 group protons. A singlet at 3.78 ppm assigned for –OCH_3 protons of PMP group. The H-4 β-lactam proton resonated as doublet of doublet at 4.47 ppm (J = 1.8 Hz and 3.2 Hz). The H-3 β-lactam proton seen as a doublet at 4.69 ppm (J = 1.8 Hz). The aromatic protons of the PMP group appeared as doublets at 6.86 ppm and 7.24 ppm (J = 9.0 Hz). The aldehyde proton seen as doublet at 9.81 ppm (J = 3.2 Hz).



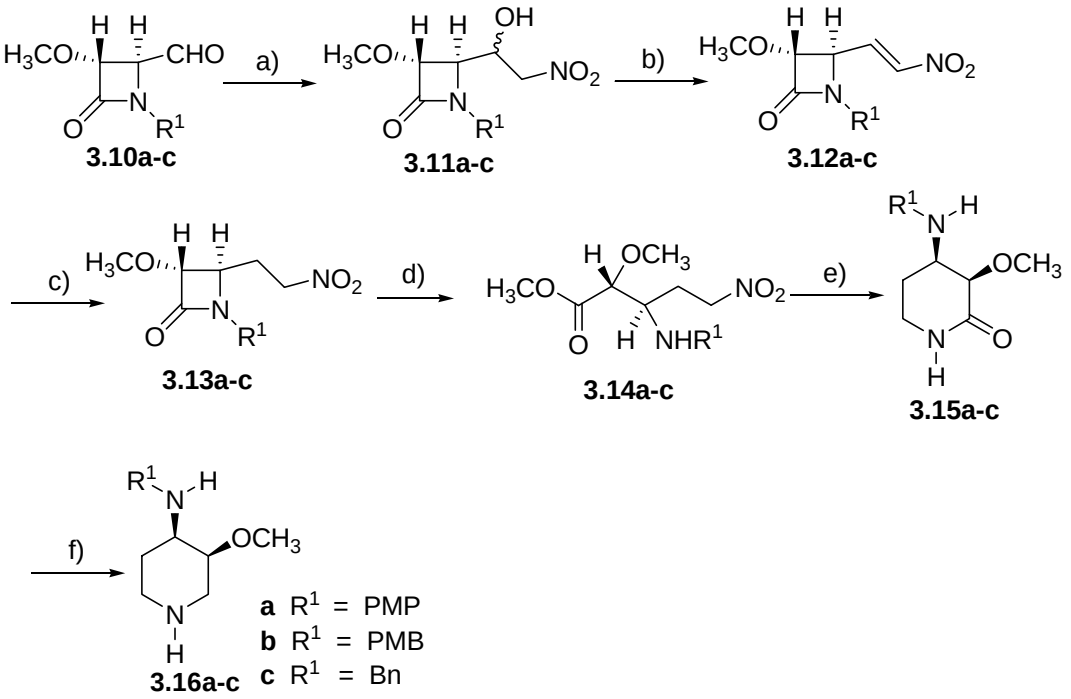
3.10a

The ^{13}C NMR spectrum of **3.10a** showed a peak at 197.1, 161.8 ppm for aldehyde and azetidin-2-one carbonyl carbon respectively. The aromatic quaternary carbons appeared at 156.9, 130.2 ppm. Remaining aromatic carbons assigned at 118.3, 114.6 ppm. The C-3 carbon appeared at 85.0 ppm. The C-4 carbon seen at 65.1 ppm. The –OCH_3 carbon assigned at 58.1 ppm. The –OCH_3 carbon of PMP group appeared at 55.4 ppm.

The mass spectrum of **3.10a** gave M+1 peak at m/z 236, also supporting the structure of the compound. Specific rotation for **3.10a** were found to be $[\alpha]^{30}_{D}$ = -51.2 (*c* 0.82, $CHCl_3$).

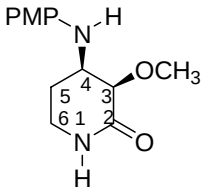
trans-4-Formyl azetidin-2-one **3.10a** was converted to *cis*-N-substituted-4-aminopiperidine **3.16a** (Scheme 3.10), by following a similar synthetic sequence as shown in (Scheme 3.08).

Scheme 3.10



Reagents and conditions: a) CH_3NO_2, Et_3N, 5 h, 95%; b) i) Ac_2O, Conc. H_2SO_4, 0 °C, 1 h, ii) $NaHCO_3$, benzene, reflux, 4 h, 70%; c) Bu_3SnH, CH_2Cl_2:MeOH (10:1), r. t., 3 h, 50-60%; d) methanolic HCl (20%), r. t., 12 h, 80%; e) 10% Pd/C, $HCOONH_4$, MeOH, r. t., 5 h, 60-70%; f) BH_3;DMS, toluene, reflux 4 h, 50%.

The structure of **3.15a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.15a** showed a sharp peak at 1649 cm^{-1} for the amide carbonyl.



3.15a

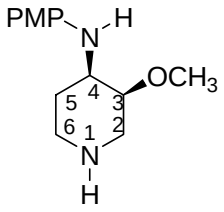
The ^{1}H NMR spectrum of **3.15a** showed multiplet at 2.00-2.28 ppm for H-5 methylene protons. A singlet at 3.56 ppm corresponds to –OCH_3 group protons. The H-6 methylene and H-4 methine proton appeared as a multiplet at 3.58-3.73 ppm. A singlet at 3.75 ppm corresponds to –OCH_3 protons of PMP group. The H-3 methine proton appeared as a doublet at 3.90 ppm (J = 3.5 Hz). The doublets of PMP group appeared at 6.65 ppm and 6.80 ppm (J = 9.0 Hz).

The ^{13}C NMR spectrum of **3.15a** showed a peak at 162.9 ppm corresponding to amide carbonyl. The aromatic quaternary carbons appeared at 153.1 and 139.5 ppm. The remaining aromatic carbons appeared at 116.2 and 114.9 ppm. The C-3 carbon seen at 77.3 ppm. The C-4 methine carbon assigned at 59.3 ppm. The –OCH_3 carbon appeared at 55.6

ppm. The $-OCH_3$ carbon of PMP group seen at 51.7 ppm. The C-6 and C-5 methylene carbon appeared at 47.2 ppm and 23.3 ppm respectively.

The mass spectrum of **3.15a** gave M+1 peak at m/z 251, also supporting the structure of the compound. Specific rotation for **3.15a** were found to be $[\alpha]^{30}_{D}$ = +38.2 (*c* 0.55, $CHCl_3$).

The structure of **3.16a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.16a** showed a peak at 3215, 3375 cm^{-1} for N-H stretchings.



3.16a

The ^{1}H NMR spectrum of **3.16a** showed multiplet at 1.69-1.98 ppm for H-5 methylene proton. A multiplet at 2.69-2.79 ppm corresponds to H-6 methylene protons. A multiplet at 3.25-3.38 ppm integrating for two protons assigned for H-2 methylene protons. A singlet at 3.40 ppm appeared for $-OCH_3$ group protons. A multiplet at 3.57-3.70 ppm corresponds to H-4 and H-3 methine protons. A singlet at 3.74 ppm assigned for $-OCH_3$ protons of PMP group. The doublets of PMP group resonated at 6.62 ppm and 6.78 ppm (*J* = 9.0 Hz). A broad singlet at 7.63 ppm corresponds to Ar-N-H proton.

The ^{13}C NMR spectrum of **3.16a** showed aromatic quaternary carbons at 152.9, 140.2 ppm. The remaining aromatic carbons appeared at 116.3, 114.9 ppm. The C-3 carbon resonated at 76.0 ppm. The $-OCH_3$ carbon assigned at 57.0 ppm. The C-2 carbon appeared at 56.9 ppm. The C-6 carbon resonated at 55.9 ppm. The $-OCH_3$ carbon of PMP group appeared at 55.6 ppm. The C-4 carbon assigned at 52.9. The C-5 carbon appeared at 25.6 ppm.

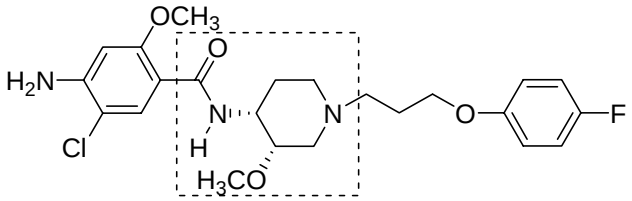
The mass spectrum of **3.16a** gave M+1 peak at m/z 237, also supporting the structure of the compound. Specific rotation for **3.16a** were found to be $[\alpha]^{30}_{D}$ = +12.5 (*c* 0.72, $CHCl_3$).

By following a similar synthetic sequence (Scheme 3.10) *cis*-*N*-substituted-4-aminopiperidines **3.16b-c** were also synthesized.

3.4 Studies towards the synthesis of (3*S*, 4*R*)-Cisapride:

3.4a Introduction:

Cisapride is a drug molecule particularly useful in the treatment of gastro-esophageal reflux disease and other disorders.[17,5a,18,19] It contains *cis*-4-amino-3-methoxy piperidine as a core structure (Fig. 2).



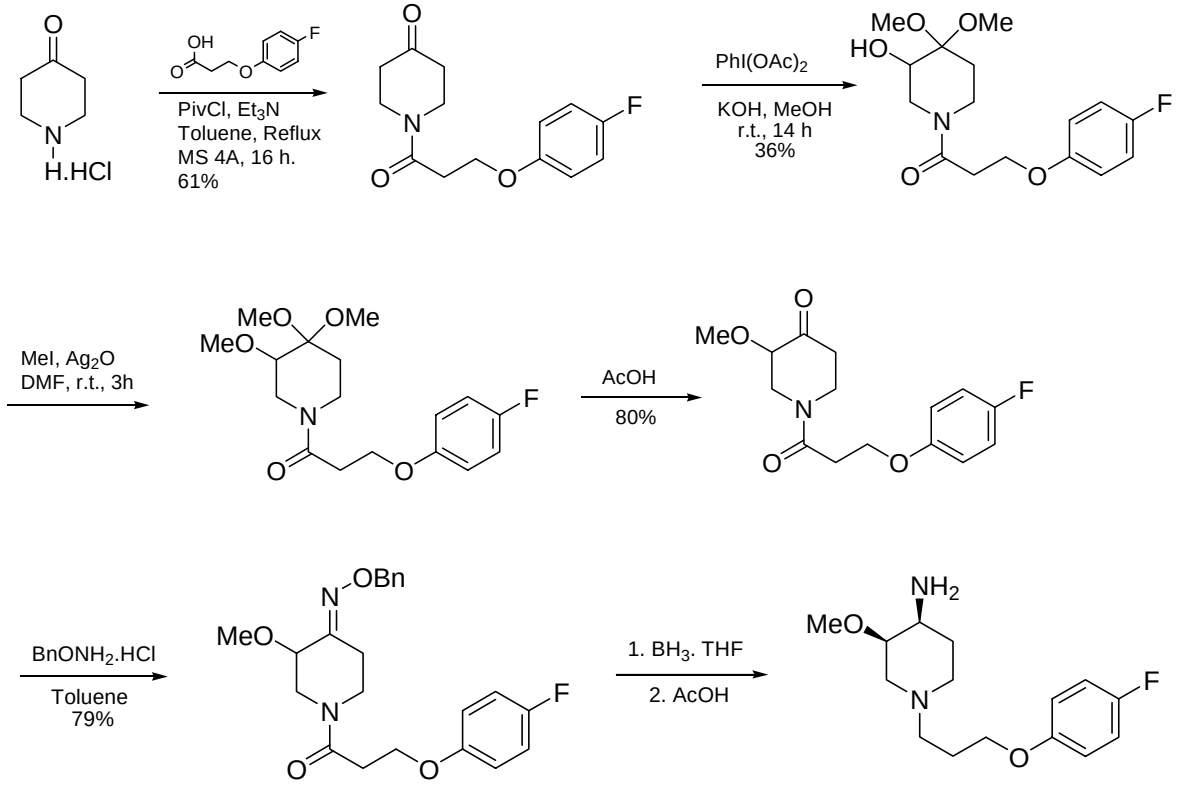
(3*S*, 4*R*)-Cisapride

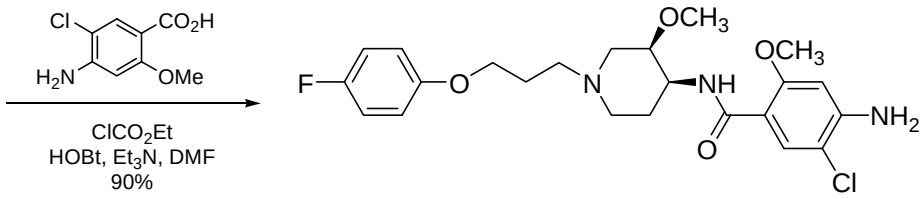
Figure 2

It has been previously synthesized from piperidin-4-one by various groups.[3,5] Apart from this its analogues were also synthesized by few other groups.[3, 18,19]

Cossy et al.[5e] have reported the synthesis of Cisapride from piperidin-4-one in seven steps with 4.5% overall yield (Scheme 3.11).

Scheme 3.11



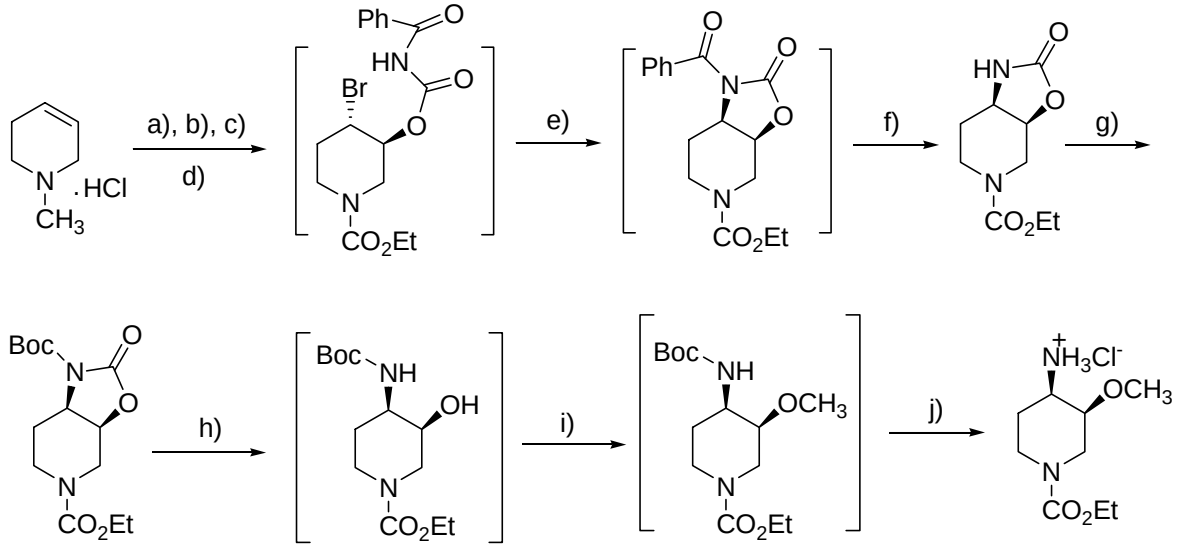


Cisapride (±)

Piperidine-4-one hydrochloride on treatment with carboxylic acid gave amide in 61% yield. Amide on treatment with phenyl iodo acetate followed by treatment with methyl iodide gave 3-methoxy substituted piperidine. 3-Methoxy substituted piperidine on deprotection with AcOH gave α-methoxy ketone which on treatment with *o*-benzylhydroxylamine hydrochloride in presence of pyridine gave oximino ether. The oxime was then reduced diastereoselectively using BH_3.THF to gave amine in 51% yield which on treatment with carboxylic acid gave Cisapride in 90% yield.

Lee et al.[5f] have reported the synthesis of key intermediate of Cisapride from *N*-methyl tetrahydropiperidine in 10 steps.

Scheme 3.12



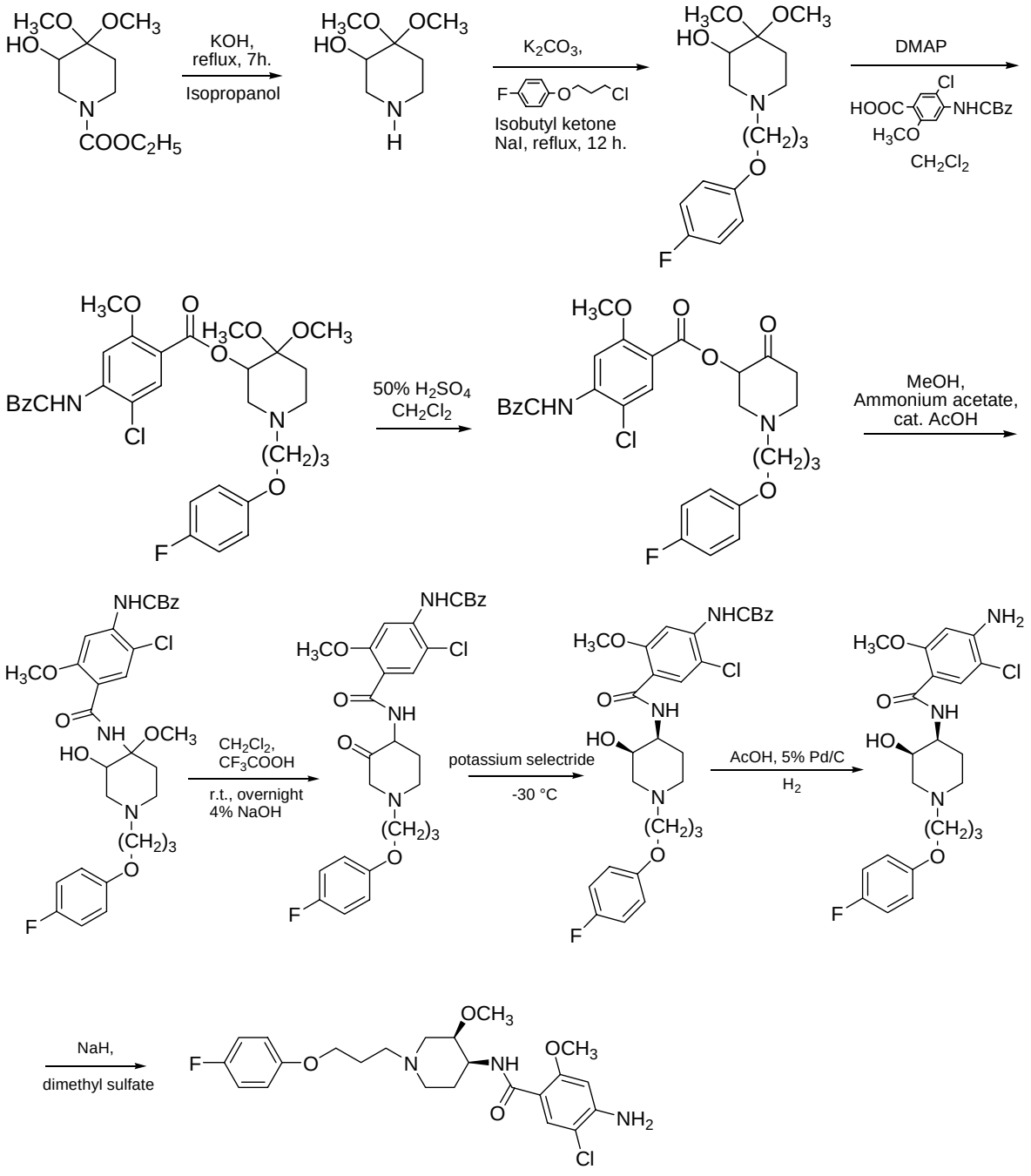
Reagents and conditions: a) (i) K_2CO_3/ toluene, r.t.; (ii) EtOCOCl, toluene, reflux. b) (i) NBS, DMSO, H_2O, r.t.; (ii) K_2CO_3, MeOH, r.t. c) 48% HBr/$CHCl_3$, -40 °C. d) Benzoyl isocyanate, THF, r.t. e) t-BuOK, THF, reflux. f) LiOH, THF, H_2O, r.t. g) Boc_2O, Et_3N, DMAP (cat.), CH_2Cl_2. h) Cs_2CO_3, MeOH, r.t.; i) dimethylsulfate, aq. 50% NaOH, r.t. j) 13% HCl, in EtOAc, r.t. k) i) ArCOOH, EtOCOCl, Et_3N, $CHCl_3$, 0 °C; ii) KOH, *i*-PrOH, reflux. iii) RX, Et_3N, DMF.

N-methyl tetrahydropiperidine on reaction with ethylchloroformate was converted to 1,2,3,6-tetrahydropiperidine-1-carboxylate which on epoxidation followed by epoxide opening with 48% HBr gave bromohydrin in quantitative yield. Bromohydrin obtained gave *cis*-fused bicyclic oxazolinopiperidin. It was achieved by one–pot synthesis as shown in Scheme 3.12. Oxazolinopiperidin was converted to N-Boc protected oxazolidinone. oxazolidin-2-one ring was cleaved using catalytic amount of cesium carbonate to gave N-Boc-amino alcohol in a regioselective manner. N-Boc-amino alcohol was converted to O-methylated piperidine by treatment with dimethylsulfate in aqueous NaOH. O-methylated piperidine on treatment with 13% HCl converted to key intermediate ethyl *cis*-4-amino-3-methoxy-1-piperidinecarboxylate which can be further converted to Cisapride in three steps.[3]

De Knaep et al.[5c] have reported the synthesis of Cisapride by reductively aminating 1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinone in the presence of benzylamine, yielding 1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine. This piperidineamine obtained was having a *cis*/*trans* ratio of about 93/7, which was enriched in the amount of *cis*-steroisomer by converting it into its acid addition salt. Subsequently, *cis*-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine was reacted with the mixed anhydride of 4-amino-5-chloro-2-methoxy-benzoic acid and ethyl chloroformate in a reaction-inert solvent yielding Cisapride.

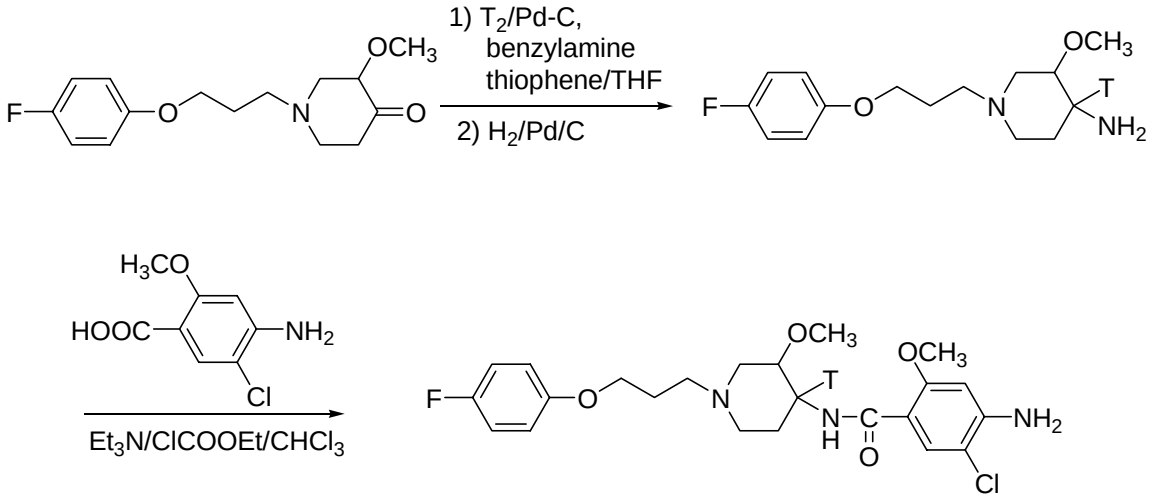
Lu Y. –F. et al[5d] have reported the synthesis of Cisapride in 9 steps with an overall yield of 3%. 3-oxo-4-arylamido-piperidine derivative on reduction in the presence of potassium selectride thereby introducing a hydroxy group on the 3 position of the piperidine moiety having a *cis*-orientation with respect to the substituents on the 4-position, followed by deprotecting the amino group and methylating the hydroxy group on the piperidine moiety (Scheme 3.13).

Scheme 3.13



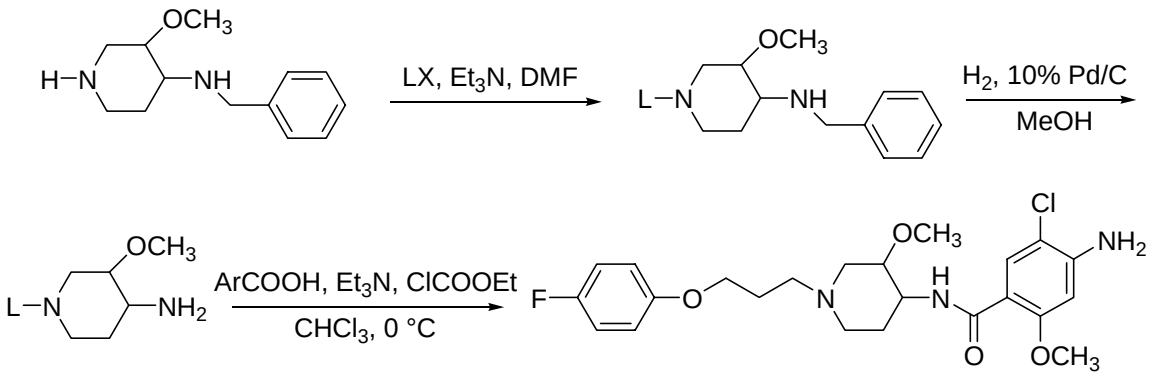
Janseen C. G. M. et al.[5b] have reported another an elegant process for preparing the tritated analogue of Cisapride, as depicted in (Scheme 3.14).

Scheme 3.14



Van daele et al.[3] have reported the synthesis of Cisapride from *trans* as well as *cis* 4-amino-3-methoxy piperidine. Synthesis of *cis* as well as *trans* piperidine by Van daele et al. was explained previously (Scheme 3.01, Scheme 3.02). 4-Amino-3-methoxy piperidine (*cis*/*trans*) on selective N-alkylation in DMF followed by debenzylation gave primary amine which on carboxylation using ethylchloroformate gave target molecule Cisapride (Scheme 3.15). They have also synthesized various analogs of Cisapride.[3]

Scheme 3.15

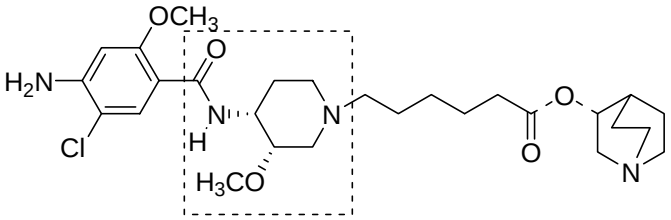


L = 4F-Ph-O-$(CH_2)_3$

Irwin et al.[18] have also synthesized various analogs of Cisapride for therapeutic use and 5-HT_4 receptor antagonist and were claimed for use in the treatment of central nervous system disorders, and various gastrointestinal disorders including, gastroparesis,

gastroesophageal reflux, emesis, dyspepsia, constipation, intestinal pseudo-obstruction or postoperative ileus.

Kolbot et al.[19] have reported the synthesis of Cisapride analogs, such as ATI 7505 (I). These compounds are the safe and effective for treatment of various gastrointestinal disorders including, gastroparesis, gastroesophageal reflux and related conditions and are also useful in treating a variety of conditions involving the central nervous system. ATI 7505 was tested for 5-HT_4 receptor binding activity, for gastric emptying activity as well as other pharmacological activities.

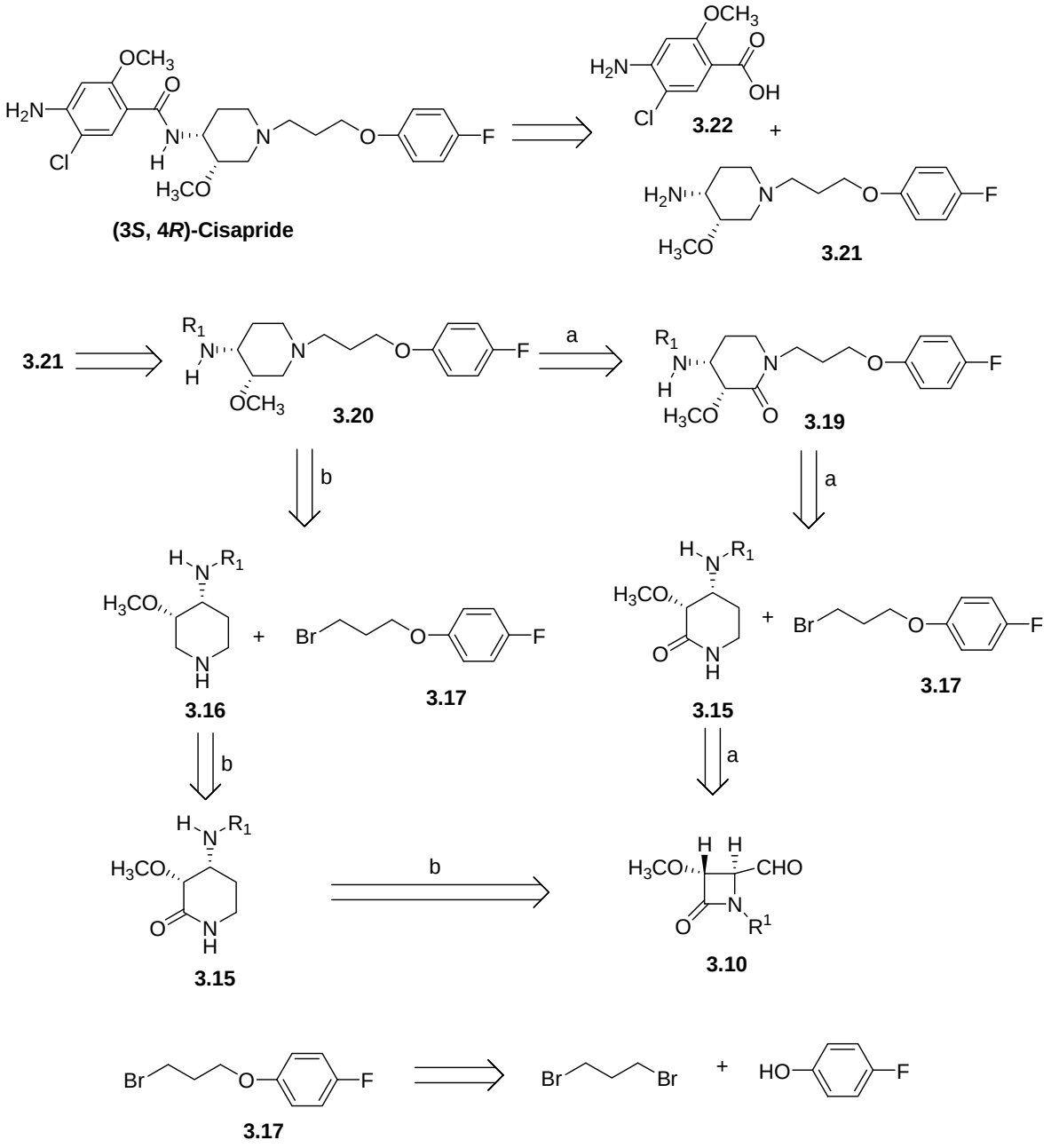


ATI 7505

3.4b Present Work:

After achieving the synthesis of *cis* as well as *trans*- 4-amino 3-substitued piperidine we planned the synthesis of (3*S*,4*R*)-Cisapride from 4-amino 3-substituted piperidin-2-one The retrosynthetic strategy for the synthesis of Cisapride is depicted below (Scheme 3.16).

Scheme 3.16



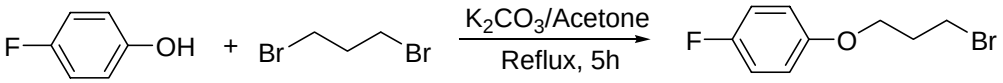
We envisioned that (3*S*,4*R*)-Cisapride could be synthesized from amino compound **3.21** by carboxylation with acid **3.22**. Amino compound **3.21** could be obtained from its N-

protected derivative **3.20**. N-protected compound could be obtained from 4-amino pyridone **3.15** (path a) or from 4-amino piperidine **3.16** (path b) by selective N-alkylation. Bromo compound **3.17** required for alkylation can be obtained from fluorophenol and 1,3 dibromo propane.

3.4c Results and Discussion:

Fluorophenol on alkylation with 1,3 dibromo propane in refluxing acetone using K_2CO_3 as base gave crude monobromo compound **3.17** which was purified by flash column chromatography to gave pure **3.17** (Scheme 3.17).

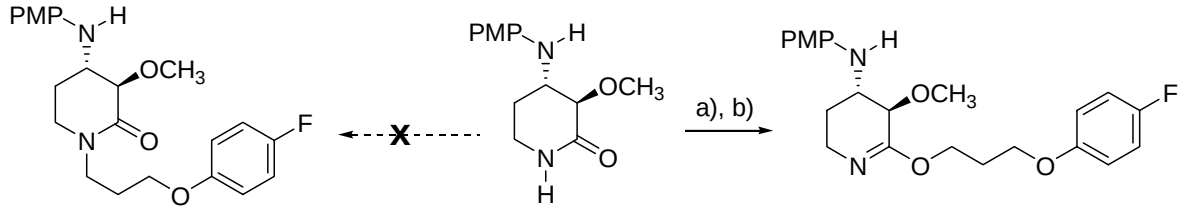
Scheme 3.17



3.17

4-Amino piperidin-2-one **3.08a** on Boc protection using Boc_2O and Et_3N as a base followed by alkylation using sodium hydride as a base in refluxing THF gave *O*-alkylated product **3.18** instead of desired *N*-alkylated product **3.19** (Scheme 3.18).

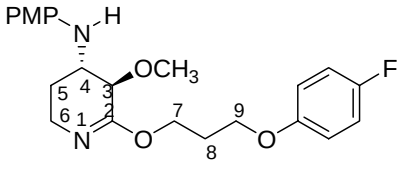
Scheme 3.18



3.19 **3.08a** **3.18**

Reagents and conditions: a) Boc_2O, Et_3N, CH_2Cl_2, 30 min; b) NaH, THF, **3.17**, reflux, 12 h/ NaH, DMF, **3.17**, r. t., 12h.

The structure of **3.18** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.18** showed a sharp peak at 1672 cm^{-1} for the oximino ether.



3.18

The ^{1}H NMR spectrum of **3.18** showed multiplet at 1.95-2.95 ppm integrating for three protons corresponds to H-8 methylene protons and one of the H-5 methylene proton. Remaining H-5 methylene proton showed multiplet at 2.35-2.45 ppm. A multiplet

at 3.49-3.60 ppm integrating for three protons corresponds H-6 methylene protons and H-4 methine proton. A singlet at 3.64 ppm assigned for $–OCH_3$ group protons. A singlet at 3.77 ppm corresponds to $–OCH_3$ protons of PMP group. A multiplet at 3.82-3.87 ppm assigned for H-3 methine proton. A triplet at 4.08 ppm (J = 6.2 Hz) corresponds to H-7 methylene protons. A triplet at 4.14 ppm (J = 6.2 Hz) assigned for H-9 methylene protons. Aroamtic protons appeared as a multiplet at 6.75-7.00 ppm integrating for eight protons.

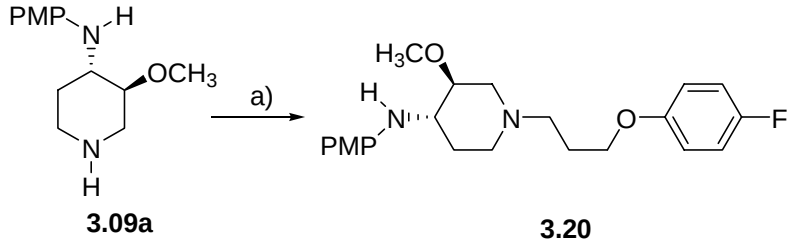
The ^{13}C NMR spectrum of **3.18** showed a peak at 165.9 ppm corresponding to oximino ether carbon. The quaternary aromatic carbons appeared at 158.3, 156.4, and 155.0 ppm. The remaining aromatic carbons appeared at 115.9, 115.7, 115.6 and 115.0 ppm. The C-3 carbon seen at 80.2 ppm. The C-9 carbon appeared at 70.4 ppm. The C-7 carbon appeared at 65.1 ppm. The $–OCH_3$ carbon seen at 59.7 ppm. The $–OCH_3$ carbon of PMP group assigned at 55.7 ppm. The C-4 carbon seen at 55.6 ppm. The C-6 carbon appeared at 45.9 ppm. The C-5 carbon seen at 28.3 ppm. The C-7 carbon assigned at 24.3 ppm.

The mass spectrum of **3.18** gave M+1 peak at m/z 403, also supporting the structure of the compound. Specific rotation for **3.18** were found to be $[\alpha]^{30}_D$ = +27.9 (*c* 0.43, $CHCl_3$).

To get selectively *N*-alkylated product **3.19** we tried alkylation of **3.08a** in anhydrous DMF using NaH as a base, but to our dismay we obtained exclusively *O*-alkylated product **3.18** in 90% yield (Scheme 3.18).

However, direct *N*-alkylation of cyclic nitrogen of 4-amino piperidine[3] (**3.09a**) was achieved by using Et_3N as a base in anhyd. DMF to get *N*-alkylated product **3.20** (Scheme 3.19).

Scheme 3.19

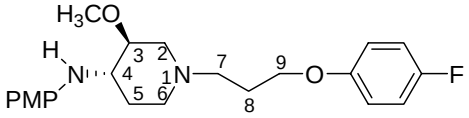


3.09a **3.20**

Reagents and conditions: a) DMF, Et_3N, **3.17**, r.t., 18 h.

The structure of **3.20** was established by IR, ^1H NMR and ^{13}C NMR spectral data. IR spectrum of **3.20** showed a peak at 3369 cm^{-1} for N-H stretching.

The ^{1}H NMR spectrum of **3.20** showed multiplet at 2.05-2.45 ppm integrating for four protons corresponds to H-5 methylene and H-8 methylene protons. A multiplet at 3.05-3.40 ppm integrating for two protons assigned for H-6 methylene protons. A singlet at 3.44 ppm assigned for –OCH_3 group protons. A multiplet at 3.46-3.70 ppm integrating for three protons corresponds to H-7 methylene protons and one proton from H-2 methylene. A singlet at 3.71 ppm assigned for -OC*H*$_3$ protons of PMP group. One of the H-2 methylene proton, H-4 and H-3 methine proton assigned as a multiplet at 3.72-3.92 ppm integrating for three protons. A triplet at 4.02 ppm (J = 6.2 Hz) corresponds to H-9 methylene protons. Aromatic protons appeared as a multiplet from 6.73-7.00 ppm.



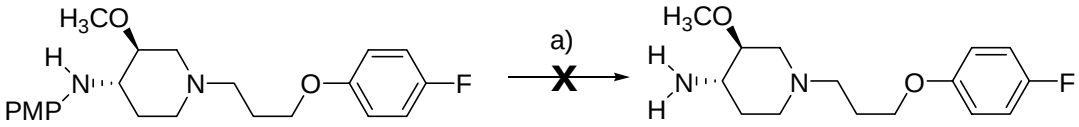
3.20

The ^{13}C NMR spectrum of **3.20** showed quaternary aromatic carbons at 152.5, 141.1 ppm. The remaining aromatic carbons appeared at 115.9, 115.6, 115.4, 114.8 ppm. The C-3 carbon assigned at 76.9 ppm. The C-9 carbon seen at 65.9 ppm. The C–2 carbon appeared at 65.6 ppm. The C-7 and C-6 carbon seen at 63.7 ppm and 62.2 ppm respectively. The –OCH_3 group carbon appeared at 58.3 ppm. The –OCH_3 carbon of PMP group assigned at 55.7 ppm. The C-4 carbon seen at 52.1. The C-8 and C-5 carbon assigned at 24.8 ppm and 22.9 ppm respectively.

The mass spectrum of **3.20** gave M+1 peak at m/z 389, also supporting the structure of the compound. Specific rotation for **3.18** were found to $[\alpha]^{30}_{D}$ = +11.1 (*c* 0.36, $CHCl_3$).

It is essential to deprotect PMP group from piperidine **3.20** to get 4-amino piperidine **3.21**, but our efforts to deprotect it using cerric ammonium nitrate (CAN)[20] were unfruitful (Scheme 3.20).

Scheme 3.20

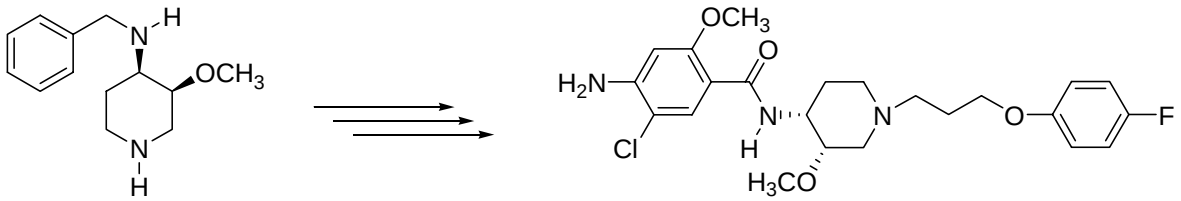


3.20 **3.21**

Reagents and conditions: a) CAN, CH_3CN-H_2O, 30 min.

However, we came across a report on the synthesis of racemic Cisapride in which benzyl protected aminopiperidine was converted to target molecule Cisapride[3] (Scheme 3.15) in three steps. Therefore we also thought of synthesizing benzyl protected amino piperidine **3.16c** and synthesized it as shown in Scheme 3.10 which can be further converted to target molecule (3*S*,4*R*)-Cisapride (Scheme 3.21).

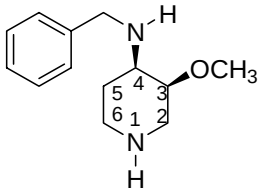
Scheme 3.21



3.16c **(3*S*, 4*R*)-Cisapride**

The structure of **3.16c** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **3.16c** showed a peak at 3211, 3319 cm^{-1} for N-H stretchings.

The ^{1}H NMR spectrum of **3.16c** showed multiplet at 1.65-1.96 ppm for H-5 methylene proton. A multiplet at 2.34-2.70 ppm corresponds to H-6 methylene protons. A multiplet at 2.81-3.19 ppm integrating for two protons corresponds to H-2 methylene protons. A broad singlet at 3.26 ppm integrating for two protons corresponds to N-H protons. A singlet at 3.38 ppm corresponds to –OCH_3 group protons. A multiplet at 3.42-3.60 ppm corresponds to H-4 and H-3 methine protons. A multiplet at 3.71-3.81 ppm corresponds to benzylic methylene protons. The aromatic protons appeared as multiplet at 7.20-7.33 ppm integrating for five protons.



3.16c

The ^{13}C NMR spectrum of **3.16c** showed aromatic quaternary carbon at 139.6 ppm. The remaining aromatic carbons appeared at 128.4, 128.1, 127.0 ppm. The C-3 carbon assigned at 75.9 ppm. The benzylic methylene carbon appeared at 57.4 ppm. The –OCH_3 carbon seen at 56.9 ppm. The C-2 carbon appeared at 56.5 ppm. The C-4 carbon assigned at 55.0 ppm. The C-6 carbon assigned at 50.3 ppm. The C-5 carbon appeared at 26.5 ppm.

The mass spectrum of **3.16c** gave M+1 peak at m/z 221, also supporting the structure of the compound. Specific rotation for **3.16c** were found to $[\alpha]^{30}_{D}$ = +11.2 (*c* 0.72, $CHCl_3$).

3.5 Conclusion:

In conclusion, we have successfully synthesized *cis* as well as *trans* 4-formyl azetidin-2-ones and used them for synthesis of (*cis* / *trans*)-4-amino-3-substituted piperidines, and further studied their application towards first chiral synthesis of (3*S*,4*R*)-Cisapride.

3.6 Experimental:

3.6.1: General procedure for the preparation of azetidin-2-ones 3.01a-c:

$NaIO_4$ (4.278 g, 20 mmol) was dissolved in H_2O (30 mL) and cooled to 0 °C. To the cooled solution, 1,2,5,6-Di-isopropylidine-D-mannitol **1.07** (5.24 g, 20 mmol) was added in portions with stirring. After completion of addition, the reaction mixture was stirred for 30 min at 0 °C and was filtered to provide an aqueous solution of D-glyceraldehyde acetonide **1.08**. To the cooled (0-5 °C) filtrate, was added a solution of amine (40 mmol) in 1,2 dichloroethane (40 mL). The reaction mixture was stirred at room temperature for 2 h after which the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with dichloroethane (2 x 20 mL). The combined organic layer containing the Schiff base **1.09a-c** was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. To a stirred solution of Schiff base **1.09a-c** and Et_3N (20 mL, 143.76 mmol) in CH_2Cl_2 (30 mL) at 0 °C a solution of acid chloride (48 mmol) in CH_2Cl_2 (30 mL) added dropwise over a period of 15 min. Allowed to stirr at room temperature for 12 h, diluted with CH_2Cl_2 (20 mL) washed with water (20 mL), $NaHCO_3$ (20 mL), and brine dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure to get crude **3.01a-c**, which was then purified by column chromatography on silica gel (EtOAc/pet. ether 3:7 as eluent) to get pure **3.01a-c**.

3.6.1a: Preperation of (3*R*,4*S*)-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-methoxy-1-(4-methoxyphenyl)-azetidin-2-one (3.01a):

Following the general procedure, imine **1.09a** prepared from D-glyceraldehyde acetonide **1.08** and *p*-anisidine (4.920 g, 40mmol) was treated with triethylamine (20 mL, 143.76 mmol) and methoxy acetyl chloride (4.38 mL, 48 mmol) in anhydrous CH_2Cl_2 to get azetidin-2-one **3.01a** as a white crystalline solid (6.14 g, 50%).

m.p. 88-89 ºC

$[\alpha]_D^{30} = +127.5$ (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1752 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H, -CH_3), 1.54 (s, 3H, -CH_3), 3.62 (s, 3H, -OCH_3), 3.69-3.74 (m, 1H, H_a-6), 3.80 (s, 3H, Ar-OCH_3), 4.14-4.44 (m, 3H, H_b-6, *H*-5, *H*-4), 4.56 (d, *J* = 5.6 Hz, 1H, *H*-3), 6.87 (d, *J* = 9.1 Hz, 2H, Ar), 7.66 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 24.8, 26.6, 55.3, 59.2, 61.7, 66.8, 76.8, 82.1, 109.6, 113.9, 119.5, 131.1, 156.4, 164.7

MS: (*m/z*) = 308 (M+1)

Anal. Calcd. for **$C_{16}H_{21}NO_5$:** C, 62.53; H, 6.89; N, 4.56%

Found C, 62.87; H, 6.93; N, 4.43%.

3.6.1b: Preperation of (3*R*,4*S*)-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-methoxy-1-(4-methoxybenzyl)-azetidin-2-one (3.01b):

Following the general procedure, imine **1.09a** prepared from D-glyceraldehyde acetonide **1.08** and *p*-methoxy benzyl amine (5.23 mL, 40 mmol) was treated with triethylamine (20 mL, 143.76 mmol) and methoxy acetyl chloride (4.38 mL, 48 mmol) in anhydrous CH_2Cl_2 to get azetidin-2-one **3.01b** as a white crystalline solid (7.06g, 55%).

m.p. 77-78 ºC

$[\alpha]_D^{30}$ = -8.04 (*c* 1, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H, -C*H*$_3$), 1.38 (s, 3H, -C*H*$_3$), 3.45-3.65 (m, 5H, -OC*H*$_3$, *H*-6), 3.79 (s, 3H, Ar-OC*H*$_3$), 4.05-4.20 (m, 2H, -NC*H*$_a$H$_b$, C4*H*), 4.24-4.31 (m, 1H, C5*H*), 4.36 (d, *J* = 5.1 Hz, C3*H*), 4.73 (d, *J* = 14.4 Hz, 1H, -NCH$_a$*H*$_b$), 6.84 (d, *J* = 9.1 Hz, 2H, Ar), 7.23 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 24.8, 26.4, 43.9, 54.8, 58.7, 58.9, 66.4, 76.7, 82.6, 109.1, 113.6, 127.6, 129.7, 158.8, 166.8

MS: (*m/z*) = 322 (M+1)

Anal. Calcd. for **$C_{17}H_{23}NO_5$:** C, 63.52; H, 7.23; N, 4.36%

Found C, 63.75; H, 7.51; N, 4.38%.

3.6.1c: Preperation of (3*R*,4*S*)-1-benzyl-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-methoxy azetidin-2-one (3.01c):

Following the general procedure, imine **1.09a** prepared from D-glyceraldehyde acetonide **1.08** and benzyl amine (mL, 40 mmol) was treated with triethylamine (20 mL, 143.76 mmol) and methoxy acetyl chloride (4.38 mL, 48 mmol) in anhydrous CH_2Cl_2 to get azetidin-2-one **3.01c** as a white crystalline solid (6.10 g, 52%).

m.p. 76-77 ºC

$[\alpha]_D^{30}$ = +4.0 (*c* 1, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H, -C*H*$_3$), 1.35 (s, 3H, -C*H*$_3$), 3.48-3.62 (m, 5H, -OC*H*$_3$, *H*-6), 4.05-4.13 (m, 1H, *H*-4), 4.19 (d, *J* = 14.5 Hz, 1H, -NC*H*$_a$H$_b$), 4.25-4.36 (m, 1H, *H*-5), 4.39 (d, *J* = 5.1 Hz, 1H, *H*-3), 4.80 (d, *J* = 14.5 Hz, 1H, -NCH$_a$*H*$_b$), 7.26-735 (m, 5H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 25.0, 26.6, 44.9, 59.1, 59.3, 66.6, 76.9, 82.9, 109.5, 127.6, 128.5, 128.7, 135.7, 167.3

MS: (*m/z*) = 292 (M+1)

Anal. Calcd. for **$C_{16}H_{21}NO_4$:** C, 65.96; H, 7.27; N, 4.81%

Found C, 65.83; H, 7.34; N, 4.87%.

3.6.2: General procedure for the preparation of 4-formyl azetidin-2-ones (3.03a-c):

A mixture of azetidin-2-one **3.01a-c** (20 mmol) and PTSA (1.103 g, 5.8 mmol) in THF (80 mL) and water (30 mL) was refluxed for 18 h. After completion of reaction (TLC) the reaction mixture was neutralized with $NaHCO_3$ and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with saturated brine solution (10 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the diol **3.02a-c** in quantitative yield**.** To a vigorously stirred suspension of chromatographic grade silica gel (40 g) in CH_2Cl_2 (250 mL) in a 500 mL flask was added a 0.65 M aqueous solution of $NaIO_4$ (40 mL) dropwise with stirring. Diol **3.02a** (5.62 g, 20 mmol) in CH_2Cl_2 (80 mL) was then added slowly. After completion of the reaction (TLC), the supernant solution was filtered through sintered funnel, washed with CH_2Cl_2 (2 x 50 mL) dried over Na_2SO_4 and concentrated to gave pure **3.03a-c**.

3.6.2a: (3*R*,4*R*)-3-Methoxy-1-(4-methoxy-phenyl)-4-oxo-azetidin-2-carbaldehyde (3.03a):

Following the general procedure, treatment of azetidin-2-one **3.01a** (6.0 g, 19.54 mmol) with PTSA (1.080 g, 5.66 mmol) followed by oxidation of the diol **3.02a** using 0.65 M $NaIO_4$ (40 mL) gave the 4-formyl azetidin-2-one **3.03a** as a white solid (4.41 g, 96%).

m.p. 120-121 °C

$[\alpha]_D^{30}$ = +242.8 (*c* 0.56, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1761 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.57 (s, 3H, -OC*H*$_3$), 3.79 (s, 3H, Ar-OC*H*$_3$), 4.53 (dd, *J* = 5.2Hz, 3.9 Hz, 1H, *H*-4), 4.88 (d, *J* = 5.2 Hz, 1H, *H*-3), 6.87 (d, *J* = 8.7 Hz, 2H, Ar), 7.28 (d, *J* = 8.7 Hz, 2H, Ar), 9.76 (d, *J* = 3.9 Hz, 1H, -C*H*O).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 55.5, 59.4, 63.2, 85.1, 114.6, 118.1, 130.5, 157.0, 162.8, 199.0

MS: (*m/z*) = 236 (M+1)

Anal. Calcd. for **$C_{12}H_{13}NO_4$:** C, 61.27; H, 5.57; N, 5.95%

Found C, 61.34; H, 5.48; N, 6.07%.

3.6.2b: (3*R*,4*R*)-3-Methoxy-1-(4-methoxy-benzyl)-4-oxo-azetidin-2-carbaldehyde (3.03b):

Following the general procedure, treatment of azetidin-2-one **3.01b** (7.0g, 21.80 mmol) with PTSA (1.20 g, 6.32 mmol) followed by oxidation of the diol **3.02b** using 0.65 M $NaIO_4$ (43.50 mL) gave the 4-formyl azetidin-2-one **3.03b** as a white solid (5.16 g, 95%).

m.p. 95-96°C

$[\alpha]_D^{30}$ = +84.4 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1762 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.48 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, Ar-OC*H*$_3$), 4.00 (dd, *J* = 5.1 Hz, 3.2 Hz, 1H, *H*-4), 4.41 (d, *J* = 14.5 Hz, 1H, -NC*H*$_a$H$_b$), 4.50 (d, *J* = 14.5 Hz, 1H, -NCH$_a$*H*$_b$), 4.73 (d, *J* = 5.1 Hz, 1H, *H*-3), 6.86 (d, *J* = 8.7 Hz, 2H, Ar), 7.15 (d, *J* = 8.7 Hz, 2H), 9.39 (d, *J* = 3.2 Hz, 1H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 45.1, 55.2, 59.1, 63.2, 85.7, 114.3, 126.2, 129.9, 159.5, 165.6, 198.6

MS: (*m/z*) = 250 (M+1)

Anal. Calcd. for **$C_{13}H_{15}NO_4$:** C, 59.30; H, 5.75; N, 10.64%

Found C, 59.44; H, 5.94; N, 10.68%.

3.6.2c: (3*R*,4*R*)-1-Benzyl-3-methoxy-4-oxo-azetidin-2-carbaldehyde (3.03c):

Following the general procedure, treatment of azetidin-2-one **3.01c** (6.0 g, 20.62 mmol) with PTSA (1.140 g, 5.98 mmol) followed by oxidation of the diol **3.02c** using 0.65 M $NaIO_4$ (42 mL) gave the 4-formyl azetidin-2-one **3.03c** as a white solid (4.38 g, 97%).

m.p. 53-54 °C

$[\alpha]_D^{30}$ = +90.0 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1763 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.48 (s, 3H, -OC*H*$_3$), 4.03 (dd, *J* = 5.2 Hz, 3.1 Hz, 1H, *H*-4), 4.44 (d, *J* = 14.7 Hz, 1H, -N*H*$_a$H$_b$), 4.60 (d, *J* = 14.7 Hz, 1H, -NH$_a$*H*$_b$), 4.76 (d, *J* = 5.2 Hz, 1H, *H*-3), 7.20-7.35 (m, 5H, Ar), 9.41 (d, *J* = 3.1 Hz, 1H, -C*H*O).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 45.8, 59.2, 63.2, 85.8, 128.4, 128.7, 129.1, 134.2, 165.9, 198.5

MS: (*m/z*) = 220 (M+1)

Anal. Calcd. for **$C_{12}H_{13}NO_3$:** C, 65.74; H, 5.98; N, 6.39%

Found C, 65.53; H, 6.03; N, 6.67%.

3.6.3: General procedure for the preparation of nitro alcohols 3.04a-b:

To a solution of 4-formyl azetidin-2-one **3.03a-b** (15 mmol) in nitromethane (30 mL) was added Et_3N (0.31 mL, 2.25 mmol) at room temperature and the reaction mixture was stirred for 6 h. The excess nitromethane was removed under reduced pressure, residue obtained dissolved in CH_2Cl_2 (50 mL) washed with water (5 mL), organic layer was dried over Na_2SO_4, concentrated under *vacuo* to afford an inseparable diastereomeric mixture of nitroalcohols **3.04a-b**.

3.6.3a: (3*R*,4*S*)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-phenyl)-azetidin-2-one (3.04a):

Following the general procedure, treatment of 4-formyl azetidin-2-one **3.03a** (4.30 g, 18.30 mmol) with nitromethane (30 mL) in presence of Et_3N (0.38 mL, 2.74 mmol) gave inseparable diastereomeric mixture of nitroalcohols **3.04a** (5.302 g, 98%) as a pale yellow solid.

m.p. = 97-101 °C

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.04 (bs, 1H, -O*H*), 3.71 (s, 3H, -OCH_3), 3.80 (s, 3H, Ar-OCH_3), 4.39-4.44 (m, 1H, *H*-4), 4.50-4.62 (m, 2H, *H*-5, *H*-3), 4.69-4.73 (m, 1H, *H*a-6), 4.80-4.90 (m, 1H, H_b-6), 6.85-6.92 (m, 2H, Ar), 7.36-7.40 (m, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 55.4, 58.1, 58.7, 59.6, 59.7, 67.1, 68.6, 77.5, 77.7, 82.4, 82.8, 114.4, 114.6, 119.4, 119.9, 129.7, 129.9, 157.0, 164.0, 164.5

MS: (*m/z*) = 297 (M+1)

Anal. Calcd. for **$C_{13}H_{16}N_2O_6$:** C, 52.70; H, 5.44; N, 9.46%

Found C, 52.93; H, 5.33; N, 9.43%.

3.6.3b: (3*R*,4*S*)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-benzyl)-azetidin-2-one (3.04b):

Following the general procedure, treatment of 4-formyl azetidin-2-one **3.03b** (5.0 g, 20.08 mmol) with nitromethane (40 mL) in presence of Et_3N (0.420 mL, 3.01 mmol) gave inseparable diastereomeric mixture of nitroalcohols **3.04b** (5.843 g, 97%) as semisolid.

IR ($CHCl_3$): υ_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.55-3.75 (m, 4H, -OCH_3, *H*-4), 3.80 (s, 3H, Ar-OCH_3), 4.10-4.70 (m, 6H, *H*-3, *H*-5, *H*-6, -NCH_2), 6.80-6.95 (m, 2H, Ar), 7.15-7.25 (m, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 44.4, 44.9, 55.2, 57.4, 59.3, 59.6, 67.5, 68.9, 77.5, 77.9, 82.6, 83.7, 114.3, 126.6, 127.1, 129.7, 159.3, 159.4, 166.8, 167.2

MS: (*m/z*) = 311 (M+1)

Anal. Calcd. for **$C_{14}H_{18}N_2O_6$:** C, 54.18; H, 5.86; N, 9.03%

Found C, 54.23; H, 5.77; N, 9.18%.

3.6.4: General procedure for the preparation of nitro alkenes 3.05a-b:

Diasteromeric mixture of nitro alcohols **3.04a-b** (14 mmol) was dissolved in acetic anhydride (30 mL) and cooled to 0 °C. Three to four drops of conc. H_2SO_4 was added to the reaction mixture and stirred for 1 h at 0 °C. After completion of the reaction (TLC), H_2O (2 mL) was added at 0 °C and stirred for 10 min. It was extracted with EtOAc (2 x 40 mL) and the organic layer was washed with sat. aq. $NaHCO_3$ (3 x 15 mL), brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a diastereomeric

mixture of nitroacetates along with nitroalkene **3.05a-b**, however to convert all nitroacetate into nitroalkene it was refluxed with benzene (50 mL) in the presence of $NaHCO_3$ (9.41 g, 112 mmol) for 6 h. After completion of reaction (TLC), solid was removed by filtration, and the solvent was removed from the filtrate under reduced pressure to afford the crude nitroalkene **7** which was further purified by column chromatography on silica gel (EtOAc/pet. ether 3:7 as eluent) to get pure **3.05a-b**.

3.6.4a: (3*R*,4*S*)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-vinyl)-azetidine-2-one (3.05a):

Following the general procedure, treatment of diasteromeric mixture of nitro alcohols **3.04a** (5.20 g, 17.57 mmol) with acetic anhydride (40 mL), followed by elimination gave the nitro alkene **3.05a** (3.904 g, 80%) as a yellow crystalline solid.

m.p. 119 °C

$[\alpha]^{30}_{D}$ = +177.4 (*c* 0.62, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.57 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, Ar-OC*H*$_3$), 4.83-4.92 (m, 2H, *H*-3, *H*-4), 6.88 (d, *J* = 8.9 Hz, 2H, Ar), 7.12-7.32 (m, 4H, Ar, *H*-5, *H*-6).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 55.2, 59.1, 85.3, 114.5, 118.3, 129.7, 135.5, 142.6, 156.8, 162.4

MS: (*m/z*) = 279 (M+1)

Anal. Calcd. for **$C_{13}H_{14}N_2O_5$:** C, 56.11; H, 5.07; N, 10.07%

Found C, 56.43; H, 5.18; N, 10.33%.

3.6.4b: (3*R*,4*S*)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-vinyl)-azetidine-2-one (3.05b):

Following the general procedure, treatment of diasteromeric mixture of nitro alcohols **3.04b** (5.7 g, 18.39 mmol) with acetic anhydride (40 mL), followed by elimination gave the nitro alkene **3.05b** (4.080 g, 76%).

$[\alpha]^{30}_{D}$ = +128.0 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1763 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.47 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, Ar-OC*H*$_3$), 4.10-4.25 (m, 2H, -NCH$_a$*H*$_b$, *H*-4), 4.53 (d, *J* = 14.7 Hz, 1H, -NC*H*$_a$H$_b$), 4.67 (d, *J* = 4.5 Hz, 1H, *H*-3), 6.82-7.05 (m, 4H, Ar, *H*-5, *H*-6), 7.13 (d, *J* = 8.7 Hz, 2H, Ar).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 44.5, 54.8, 55.3, 59.1, 85.9, 114.5, 126.1, 130.0, 135.6, 142.2, 159.7, 165.5

MS: (*m/z*) = 293 (M+1)

Anal. Calcd. for **$C_{14}H_{16}N_2O_5$:** C, 57.52; H, 5.53; N, 9.58%

Found C, 57.73; H, 5.43; N, 9.76%.

3.6.5: General procedure for the preparation of nitro alkanes 3.06a-b:

To a solution of nitroalkenes **3.05a-b** (10.26 mmol) in anhydrous CH_2Cl_2-MeOH (10:1; 30 mL), tributyltinhydride (3.30 mL, 11.29 mmol) was added at room temperature and stirred for 2 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (EtOAc/pet. ether as eluent) to gave pure nitro alkane **3.06a-b** as a viscous liquid.

3.6.5a: (3*R*,4*S*)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-ethyl)-azetidin-2-one (3.06a):

Following the general procedure, nitroalkene **3.05a** (3.81 g, 13.67 mmol) was treated with tributyltinhydride (4.40 mL, 15.07 mmol) to gave nitroalkane **3.06a** which was further purifed by flash column chromatography (EtOAc/pet. ether 25:75 as eluent) to get pure **3.06a** (2.686 g, 70%) as a yellow solid.

m. p. 140 °C

$[\alpha]^{30}_D$ = +158.8 (*c* 1.02, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1745 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35-2.49 (m, 1H, *H*$_a$-5), 2.66-2.79 (m, 1H, *H*$_b$-5), 3.68 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, Ar-OC*H*$_3$), 4.31-4.39 (m, 1H, *H*-4), 4.51-4.58 (m, 2H, *H*-6), 4.65 (d, *J* = 5.1 Hz, 1H, H-3), 6.91 (d, *J* = 8.8 Hz, 2H, Ar), 7.35 (d, *J* = 8.8 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 25.0, 53.9, 55.4, 59.2, 71.6, 82.7, 114.7, 118.6, 129.9, 156.7, 163.9

MS: (*m/z*) = 281 (M+1)

Anal. Calcd. for **$C_{13}H_{16}N_2O_5$:** C, 55.71; H, 5.75; N, 9.99%

Found C, 55.92; H, 5.85; N, 10.23%.

3.6.5b: (3*R*,4*S*)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-ethyl)-azetidin-2-one (3.06b):

Following the general procedure, nitroalkene **3.05b** (4.0 g, 13.70 mmol) was treated with tributyltinhydride (4.40 mL, 15.07 mmol) to gave nitroalkane **3.06b** which was further purifed by flash column chromatography (EtOAc/pet. ether 35:65 as eluent) to get pure **3.06b** (2.698 g, 67%) as a semisolid.

$[\alpha]^{30}_{D}$ = +81.2 (*c* 0.64, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1749 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15-2.30 (m, 2H, *H*-5), 3.58 (s, 3H, -OCH_3), 3.62-3.73 (m, 1H, *H*-4), 3.80 (s, 3H, Ar-OCH_3), 4.18 (d, *J* = 15.0 Hz, 1H, -NCH_aH$_b$), 4.28-4.37 (m, 2H, -NCH$_a$$H_b$, *H*-3), 4.38-4.50 (m, 2H, *H*-6), 6.87 (d, *J* = 8.8 Hz, 2H, Ar), 7.17 (d, *J* = 8.8 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 25.9, 44.0, 54.3, 55.2, 59.1, 71.7, 83.5, 114.3, 127.0, 129.5, 159.4, 167.0

MS: (*m/z*) = 295 (M+1)

Anal. Calcd. for **$C_{14}H_{18}N_2O_5$:** C, 57.12; H, 6.18; N, 9.52%

Found C, 57.47; H, 6.40; N, 9.57%.

3.6.6: General procedure for the preparation of nitro esters 3.07a-b:

A solution of nitro alkane **3.06a-b** (10 mmol) in methanolic HCl (20%; 25 mL) was stirred at room temperature for 12 h. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (30 mL), neutralized with solid $NaHCO_3$, filtered through celite bed. Filtrate obtained concentrated under *vacuo* to gave nitro ester **3.07a-b**.

3.6.6a: (2*R*,3*S*)-2-Methoxy-3-(4-methoxy-phenylamino)-5-nitro-pentanoic acid methyl ester (3.07a):

Following the general procedure, nitro alkane **3.06a** (2.60 g, 9.28 mmol) was stirred in methanolic HCl (20%; 25 mL) for 12 h to get the nitro ester **3.07a** as a viscous liquid (2.665 g, 92%).

$[\alpha]^{30}_{D}$ = -27.7 (*c* 1.08, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1749 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24-2.38 (m, 2H, *H*-4), 3.47 (s, 3H, -OCH_3), 3.51 (s, 3H, -COOCH_3), 3.73 (s, 3H, Ar-OCH_3), 3.78-4.02 (m, 3H, -N*H*, *H*-3, *H*-2), 4.51-4.61 (m, 2H, *H*-5), 6.60 (d, *J* = 9.0 Hz, 2H, Ar), 6.75 (d, *J* = 9.0 Hz, 2H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 29.9, 51.7, 54.5, 55.5, 58.8, 72.4, 81.0, 114.7, 115.6, 140.5, 152.7, 170.6

MS: (*m/z*) = 313 (M+1)

Anal. Calcd. for **$C_{14}H_{20}N_2O_6$:** C, 53.84; H, 6.45; N, 8.97%

Found C, 53.81; H, 6.63; N, 8.90%.

3.6.6b: (2*R*,3*S*)-2-Methoxy-3-(4-methoxy-benzylamino)-5-nitro-pentanoic acid methyl ester (3.07b):

Following the general procedure, nitro alkane **3.06b** (2.60 g, 8.84 mmol) was stirred in methanolic HCl (20%; 25 mL) for 12 h to get the nitro ester **3.07b** as yellow viscous liquid (2.739 g, 95%).

$[\alpha]^{30}_{D}$ = -2.8 (*c* 1, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05-2.35 (m, 2H, *H*-4), 3.05-3.20 (m, 1H, *H*-3), 3.44 (s, 3H, -OCH_3), 3.60-3.73 (m, 2H), 3.79 (s, 3H, -COOCH_3), 3.80 (s, 3H , Ar-OCH_3), 3.85 (d, *J* = 3.9 Hz, 1H, *H*-2), 4.51 (t, *J* = 6.8 Hz, 2H, *H*-5), 6.86 (d, *J* = 8.7 Hz, 2H, Ar), 7.22 (d, *J* = 8.7 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 29.2, 50.5, 52.1, 55.2, 55.9, 58.8, 72.6, 81.2, 113.8, 129.6, 158.9, 171.4

MS: (*m/z*) = 327 (M+1)

Anal. Calcd. for **$C_{15}H_{22}N_2O_6$:** C, 55.19; H, 6.81; N, 8.58%

Found C, 55.44; H, 6.83; N, 8.76%.

3.6.7: General procedure for the preparation of 4-aminopiperidin-2-ones 3.08a-b:

To a solution of nitro ester **3.07a-b** (10 mmol) in anhydrous MeOH (40 mL), 10% Pd/C (600 mg) was added, followed by ammonium formate (3.15 g, 50 mmol), and the reaction mixture was stirred at room temperature under argon for 5 h. After completion of reaction (TLC), the reaction mixture was filtered through a Celite bed and the bed was washed with MeOH. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (5 mL), brine (5 mL), organic layer was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave crude product which was purified by flash column chromatography on silica gel to get pure **3.08a-b**.

3.6.7a: (3*R*,4*S*)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine-2-one (3.08a):

Following the general procedure, nitro ester **3.07a** (2.6 g, 8.33 mmol) was treated with 10% Pd/C (500 mg) and ammonium formate (2.624 g, 41.65 mmol) at room temperature for 5 h to gave the crude 4-aminopiperidin-2-one, which was further purified by flash column chromatography (EtOAc/pet. ether 6:4 as eluent) to get pure **3.08a** (1.458 g, 70%).

m.p. 127-129 °C

$[\alpha]^{30}_{D}$ = +36.44 (*c* 1.18, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1649 cm^{-1}

^{1}H NMR (200 MHz, **$CDCl_3$):** δ 1.89-2.09 (m, 1H, H_a-5), 2.34-2.51 (m, 1H, H_b-5), 3.62 (s, 3H, -OCH_3), 3.64-3.74 (m, 3H, *H*-4, *H*-6), 3.76 (s, 3H, Ar-OCH_3), 3.87 (d, *J* = 6.3 Hz, 1H, *H*-3), 6.76 (d, *J* = 9.2 Hz, 2H, Ar), 6.82 (d, *J* = 9.2 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, **$CDCl_3$):** δ 24.1, 46.1, 52.3, 55.6, 59.2, 79.8, 114.9, 116.1, 139.9, 153.2, 163.6

MS: (*m/z*) = 251 (M+1)

Anal. Calcd. for **$C_{13}H_{18}N_2O_3$:** C, 62.38; H, 7.25; N, 11.19%

Found C, 62.32; H, 7.33; N, 11.47%.

3.6.7b: (3*R*,4*S*)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine-2-one (3.08b):

Following the general procedure, nitro ester **3.07b** (2.65 g, 8.13 mmol) was treated with 10% Pd/C (490 mg) and ammonium formate (2.561 g, 40.65 mmol) at room temperature for 5 h to gave the 4-aminopiperidin-2-one **3.08b**, which was further purified by flash column chromatography (acetone/pet. ether 6:4 as eluent) to get pure **3.08b** (1.330 g, 62%) as a gummy solid.

$[\alpha]^{30}_{D}$ = +70.0 (*c* 0.60, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1651 cm^{-1}

^{1}H NMR (200 MHz, **$CDCl_3$):** δ 1.75-1.95 (m, 1H, *H*-5), 2.20-2.40 (m, 1H, *H*-5), 3.00-3.10 (m, 1H, H-4), 3.47-3.71 (m, 5H, H-6, -OC*H*$_3$), 3.73-3.82 (m, 2H, -NC*H*$_a$H$_b$, H-3), 3.72-3.82 (m, 3H, -NCH$_a$*H*$_b$), 3.84 (s, 3H, Ar-OC*H*$_3$), 3.91 (d, *J* = 12.9 Hz, 1H, -NCH$_a$*H*$_b$), 4.40 (bs, 2H, -N*H*), 6.91 (d, *J* = 8.7 Hz, 2H, Ar), 7.28 (d, *J* = 8.7 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, **$CDCl_3$):** δ 24.1, 46.2, 50.4, 55.0, 55.3, 59.9, 80.1, 114.0, 129.5, 130.7, 159.0, 164.0

MS: (*m/z*) = 265 (M+1)

Anal. Calcd. for **$C_{14}H_{20}N_2O_3$:** C, 63.60; H, 7.64; N, 10.60%

Found C, 63.83; H, 7.69; N, 10.74%.

3.6.8: General procedure for the preparation of 4-amino piperidines 3.09a-b:

To a solution of 4-amino piperidin-2-one **3.08a-b** (10 mmol) in dry toluene (30 mL) BH_3:DMS (10.0mM, 1.10 mL 10% excess) was added dropwise under nitrogen at 0 °C, stirred at this temperature for 15 min and then refluxed for 3 h. The reaction was then quenched by adding 15 mL of 10% aq Na_2CO_3 at 20 °C. This reaction mixture was stirred for 3 h at 20 °C. The toluene layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude piperidine, was purified by flash column chromatography to get pure 4-amino piperidine **3.09a-b**.

3.6.8a: (3*S*,4*S*)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine (3.09a):

Following the general procedure, reduction of 4-amino piperidin-2-one **3.08a** (1.40 g, 5.60 mmol) using BH_3:DMS (10.0mM, 0.62 mL 10% excess) gave crude 4-amino

piperidine which was further purified by flash column chromatography (EtOAc/pet. ether 8:2 as eluent) to get pure **3.09a** (0.660 g, 50%).

$[\alpha]^{30}_{D}$ = +12.9 (*c* 0.7, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 3215, 3375 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67-2.24 (m, 2H, *H*-5), 2.36-2.63 (m, 2H, *H*-6), 2.86-3.32 (m, 3H, *H*-2, *H*-4), 3.43 (s, 3H, -OC*H*$_3$), 3.48-3.68 (m, 1H, *H*-3), 3.74 (s, 3H, Ar-OC*H*$_3$), 6.67 (d, *J* = 7.8 Hz, 2H, Ar), 6.78 (d, *J* = 7.8 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 25.8, 28.6, 50.4, 53.2, 55.4, 56.1, 56.8, 57.2, 60.4, 77.3, 79.6, 114.5, 114.7, 116.3, 140.5, 141.2, 152.1, 152.5

MS: (*m/z*) = 237.0 (M+1)

Anal. Calcd. for **$C_{13}H_{20}N_2O_2$:** C, 66.07; H, 8.53; N, 11.85%

Found C, 66.24; H, 8.47; N, 12.03%.

3.6.8b: (3*S*,4*S*)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine (3.09b):

Following the general procedure, reduction of 4-amino piperidin-2-one **3.08b** (1.20 g, 4.54 mmol) using BH_3:DMS (10.0mM, 0.50 mL, 10% excess) gave 4-amino piperidine which was further purified by column chromatography (EtOAc/pet. ether 9:1 as eluent) to gave pure **3.09b** (0.579 g, 51%) as a viscous liquid.

$[\alpha]^{30}_{D}$ = +33.3 (*c* 0.66, Acetone)

IR ($CHCl_3$): υ_{max} 3215, 3375 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70-2.15 (m, 2H, *H*-5), 2.20-2.70 (m, 3H, *H*-6, -N*H*), 3.00-3.37 (m, 3H, *H*-2, *H*-4), 3.39 (s, 3H, -OC*H*$_3$), 3.50-3.95 (m, 7H, *H*-3, -NC*H*$_2$, Ar-OC*H*$_3$, -N*H*), 6.86 (d, *J* = 8.5 Hz, 2H, Ar), 7.26 (d, *J* = 8.5 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 27.0, 50.4, 55.2, 56.7, 57.2, 58.6, 59.9, 72.1, 113.9, 129.5, 131.0, 158.8

MS: (*m/z*) = 251.0 (M+1)

Anal. Calcd. for **$C_{14}H_{22}N_2O_2$:** C, 67.17; H, 8.86; N, 11.19%

Found C, 67.34; H, 8.92; N, 11.27%.

3.6.9a:(3*R*,4*S*)-3-Methoxy-1-(4-methoxy-phenyl)-4-oxo-azetidin-2-carbaldehyde (3.10a):

To a stirred solution of *cis*-4-formyl azetidin-2-one **3.03a** (0.940 g, 4 mmol) in benzene (40 mL), dimethylamine (40% aq, 4.0 mL) was added and reaction mixture was stirred at room temperature for 24 h, after the completion of reaction (TLC), organic layer was separated concentrated under *vacuo* and further purified by flash column chromatography (EtOAc/pet. ether 25:75 as eluent) to *trans*-4-formyl azetidin-2-one **3.10a** as viscous liquid (0.470 g, 50%).

$[\alpha]^{30}_{D}$ = -51.2 (*c* 0.82, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.56 (s, 3H, -OC*H*$_3$), 3.78 (s, 3H, Ar-OC*H*$_3$), 4.47 (dd, *J* = 1.8 Hz, 3.2 Hz, 1H, *H*-4), 4.69 (d, *J* = 1.8 Hz, 1H, *H*-3), 6.86 (d, *J* = 9.0 Hz, 2H, Ar), 7.24 (d, *J* = 9.0 Hz, 2H, Ar), 9.81 (d, *J* = 3.2 Hz, 1H, -C*H*O).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 55.4, 58.1, 65.1, 85.0, 114.6, 118.3, 130.2, 156.9, 161.8, 197.1

MS: (*m/z*) = 236 (M+1)

Anal. Calcd. for **$C_{12}H_{13}NO_4$:** C, 61.27; H, 5.57; N 5.95%

Found C, 61.34; H, 5.66; N, 5.87%.

3.6.9b: (3*R*,4*S*)-3-Methoxy-1-(4-methoxy-benzyl)-4-oxo-azetidin-2-carbaldehyde (3.10b):

To a stirred solution of *cis*-4-formyl azetidin-2-one **3.03b** (5 g, 17.79 mmol) in acetonitrile and water (1:1, 602 mL), Na_2CO_3 (3.77 g, 35.58 mmol) was added and stirred at room temperature for 48 h. Acetonitrile was removed under reduced pressure and the aqueous layer was extracted with EtOAc (5 x 75 mL). Organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* to gave crude **3.10b**, which was then purified by flash column chromatography on silica gel (EtOAc/pet. ether 7:3 as eluent) to get pure *trans*-4-formyl azetidin-2-one **3.10b** as gummy solid (3.5 g, 70%).

$[\alpha]^{30}_{D}$ = +42.8 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.48 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, Ar-OC*H*$_3$), 3.94 (t, 1H, *H*-4), 4.24 (d, *J* = 14.6 Hz, 1H, -NC*H*$_a$H$_b$), 4.55 (d, *J* = 1.5 Hz, 1H, *H*-3), 4.68 (d, *J* = 14.6 Hz, 1H, -NCH$_a$*H*$_b$), 6.86 (d, *J* = 8.7 Hz, 2H, Ar), 7.15 (d, *J* = 8.7 Hz, 2H, Ar), 9.54 (d, *J* = 3.2 Hz, 1H, -C*H*O).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 45.2, 55.2, 57.8, 64.5, 85.4, 114.4, 126.2, 130.0, 159.5, 164.9, 196.9

MS: (*m/z*) = 250 (M+1)

Anal. Calcd. for **$C_{13}H_{15}NO_4$:** C, 59.30; H, 5.75; N, 10.64%

Found C, 59.44; H, 5.94; N, 10.68%.

3.6.9c: (3*R*,4*S*)-1-benzyl-3-Methoxy-4-oxo-azetidin-2-carbaldehyde (3.10c):

To a stirred solution of cis-4-formyl azetidin-2-one **3.03c** (5 g, 22.83 mmol) in acetonitrile and water (1:1, 684 mL), Na_2CO_3 (4.84 g, 45.66 mmol) was added and stirred at room temperature for 48 h. Acetonitrile was removed under reduced pressure and the aqueous layer was extracted with EtOAc (5 x 80 mL). Organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* to gave **3.10c**, which was then purified by flash column chromatography on silica gel (EtOAc/pet. ether 8:2 as eluent) to get pure *trans*-4-formyl azetidin-2-one **3.10c** as a viscous liquid (3.214 g, 64.28%).

$[\alpha]^{30}_D$ = +20.4 (*c* 0.44, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.50 (s, 3H, -OC*H*$_3$), 3.98-4.00 (m, 1H, *H*-4), 4.28 (d, *J* = 14.8 Hz, 1H, -NC*H*$_a$H$_b$), 4.57 (d, *J* = 1.9 Hz, 1H, *H*-3), 4.77 (d, *J* = 14.8 Hz, 1H, -NCH$_a$*H*$_b$), 7.24-7.38 (m, 5H, Ar), 9.58 (d, *J* = 1.9 Hz, 1H, -C*H*O).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 45.8, 57.8, 64.5, 85.5, 128.3, 128.6, 129.1, 134.2, 165.0, 196.7

MS: (*m/z*) = 220 (M+1)

Anal. Calcd. for **$C_{12}H_{13}NO_3$:** C, 65.74; H, 5.98; N, 6.39%

Found C, 66.25; H, 6.34; N, 6.77%.

3.6.10a: (3*R*,4*R*)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-phenyl)-azetidin-2-one (3.11a):

Following a general procedure as for **3.04a-b**, treatment of *trans*-4-formyl azetidin-2-one **3.10a** (1.50 g, 6.38 mmol) with nitromethane (20 mL) in presence of Et_3N (0.13 mL, 0.96 mmol) gave inseparable diastereomeric mixture of nitroalcohols **3.11a** which was further purified by column chromatography (60-120 mesh silica gel, EtOAc/pet. ether 3:7 as eluent) to afford pure **3.11a** (1.455 g, 77%) as a viscous liquid.

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 3.57 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, Ar-OC*H*$_3$), 4.00-4.20 (m, 1H, H-4), 4.43-4.60 (m, 2H, *H*-3, *H*-5), 4.69-4.98 (m, 2H, *H*-6), 6.87-6.93 (m, 2H, Ar), 7.30-7.35 (m, 2H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 55.5, 58.2, 60.6, 61.0, 63.0, 63.4, 64.3, 67.9, 77.2, 82.4, 83.9, 114.6, 114.8, 119.6, 120.6, 129.1, 157.1, 163.5

MS: (*m/z*) = 297 (M+1)

Anal. Calcd. for **$C_{13}H_{16}N_2O_6$:** C, 52.70; H, 5.44; N, 9.46%

Found C, 52.84; H, 5.57; N, 9.43%.

3.6.10b: (3*R*,4*R*)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-benzyl)-azetidin-2-one (3.11b):

Following a general procedure as for **3.04a-b**, treatment of *trans*-4-formyl azetidin-2-one **3.10b** (3.40 g, 13.65 mmol) with nitromethane (35 mL) in presence of Et_3N (0.29 mL, 2.05 mmol) gave inseparable diastereomeric mixture of nitroalcohols **3.11b** which was further purified by column chromatography (60-120 mesh silica gel, EtOAc/pet. ether 4:6 as eluent) to afford pure **3.11b** (3.471 g, 82%) as a colourless viscous liquid.

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 3.38-3.65 (m, 4H, -OC*H*$_3$, *H*-5), 3.79 (s, 3H, Ar-OC*H*$_3$), 4.08-4.72 (m, 6H, *H*-3, *H*-4, -NC*H*$_2$, *H*-6), 6.84-6.94 (m, 2H, Ar), 7.16-7.26 (m, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 44.0, 45.0, 55.2, 57.7, 57.9, 59.9, 60.2, 64.9, 69.1, 77.5, 77.7, 82.6, 84.3, 114.4, 114.5, 126.6, 126.9, 129.5, 129.6, 159.3, 166.7, 166.9

MS: (*m/z*) = 311 (M+1)

Anal. Calcd. for **$C_{14}H_{18}N_2O_6$:** C, 54.18; H, 5.86; N, 9.03%

Found C, 54.23; H, 5.77; N, 9.18%.

3.6.10c: (3*R*,4*R*)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-benzyl)-azetidin-2-one (3.11c):

Following a general procedure as for **3.04a-b**, treatment of *trans*-4-formyl azetidin-2-one **3.10c** (3.10 g, 14.15 mmol) with nitromethane (30 mL) in presence of Et_3N (0.30 mL, 2.13 mmol) gave crude inseparable diastereomeric mixture of nitroalcohols **3.11c** which was further column purified (60-120 mesh silica, EtOAc/pet. ether 4:6 as eluent) to afford pure **3.11c** (3.372 g, 85%) as a colourless viscous liquid.

IR ($CHCl_3$): υ_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): 3.42-3.64 (m, 4H, -OC*H*$_3$, *H*-5), 4.31-4.77 (m, 6H, -NC*H*$_2$, H-4, H-3, H-6), 7.25-7.46 (m, 5H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 44.5, 45.6, 57.8, 57.9, 60.0, 60.2, 64.7, 69.1, 77.5, 77.7, 82.7, 84.3, 128.1, 128.2, 129.0, 129.2, 134.6, 135.0, 166.8, 167.0

MS: (*m/z*) = 281 (M+1)

Anal. Calcd. for **$C_{13}H_{16}N_2O_5$:** C, 55.71; H, 5.75; N, 9.99%

Found C, 55.56; H, 6.03; N, 10.11%.

3.6.11a: (3*R*,4*R*)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-vinyl)-azetidine-2-one (3.12a):

Following the general procedure as for **3.05a-b**, acetylation of diasteromeric mixture of nitro alcohols **3.11a** (1.40 g, 4.73 mmol) with acetic anhydride (15 mL), followed by elimination gave the nitro alkene **3.12a** (1.144 g, 87%).

$[\alpha]^{30}_D$ = -162.0 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1764 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.64 (s, 3H, -OC*H*$_3$), 3.84 (s, 3H, Ar-OC*H*$_3$), 4.60-4.70 (m, 2H, *H*-4, *H*-3), 6.94 (d, *J* = 9.0 Hz, 2H, Ar), 7.17 (d, *J* = 13.5 Hz, 1H, *H*-6), 7.30 (d, *J* = 9.0 Hz, 2H, Ar), 7.44 (dd, *J* = 6.7 Hz, 13.5 Hz, 1H, *H*-5).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 55.5, 56.6, 58.4, 89.0, 114.7, 118.6, 129.4, 136.6, 141.5, 157.0, 161.7

MS: (*m/z*) = 279 (M+1)

Anal. Calcd. for **$C_{13}H_{14}N_2O_5$:** C, 56.11; H, 5.07; N, 10.07%

Found C, 56.27; H, 5.15; N, 10.22%.

3.6.11b: (3*R*,4*R*)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-vinyl)-azetidine-2-one (3.12b):

Following the general procedure as for **3.05a-b**, acetylation of diasteromeric mixture of nitro alcohols **3.11b** (3.400 g, 10.97 mmol) with acetic anhydride (35 mL), followed by elimination gave the crude nitro alkene **3.12b**. The crude nitroalkene **3.12b** was purified by column chromatography (60-120 mesh silica, EtOAc/pet. ether 35:65 as eluent) to get pure **3.12b** (2.594 g, 81%) as a pale yellow viscous liquid.

$[\alpha]^{30}_D = -23.3$ (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1763 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.49 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, Ar-OC*H*$_3$), 3.98 (dd, *J* = 1.5 Hz, 7.2 Hz, 1H, *H*-4), 4.08 (d, *J* = 14.8 Hz, 1H, -NC*H*$_a$H$_b$), 4.43 (d, *J* = 1.5 Hz, 1H, *H*-3), 4.63 (d, *J* = 14.8 Hz, 1H, -NCH$_a$*H*$_b$), 6.85-7.20 (m, 6H, Ar, *H*-5, *H*-6).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 44.7, 55.3, 55.9, 58.2, 89.2, 114.5, 125.9, 129.9, 136.9, 141.1, 159.6, 165.2

MS: (*m/z*) = 293 (M+1)

Anal. Calcd. for **$C_{14}H_{16}N_2O_5$:** C, 57.52; H, 5.53; N, 9.58%

Found C, 57.73; H, 5.43; N, 9.76%.

3.6.11c: (3*R*,4*R*)-1-Benzyl-3-methoxy-4-(2-nitro-vinyl)-azetidine-2-one (3.12c):

Following the general procedure as for **3.05a-b**, acetylation of diasteromeric mixture of nitro alcohols **3.11c** (3.30 g, 11.78 mmol) with acetic anhydride (30 mL), followed by elimination gave the crude nitro alkene **3.12c**, which was further purified by column chromatography (60-120 mesh silica, EtOAc/pet. ether 3:7 as eluent) to get pure **3.12c** (2.315 g, 75%) as a pale yellow viscous liquid.

$[\alpha]^{30}_D = -53.3$ (*c* 0.6, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1767 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.50 (s, 3H, -OCH_3), 4.02 (dd, *J* = 1.5 Hz, 7.2 Hz, 1H, *H*-4), 4.13 (d, *J* = 14.8 Hz, 1H, -NCH_aH$_b$), 4.46 (d, *J* = 1.5 Hz, 1H, *H*-3) 4.70 (d, *J* = 14.8 Hz, 1H, -NCH$_a$$H_b$), 6.92-7.42 (m, 7H, Ar, *H*-5, *H*-6).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 45.2, 56.0, 58.2, 89.4, 128.4, 128.5, 129.1, 134.0, 136.8, 141.2, 165.2

MS: (*m/z*) = 263 (M+1)

Anal. Calcd. for **$C_{13}H_{14}N_2O_4$:** C, 59.54; H, 5.38; N, 10.68%

Found C, 59.75; H, 5.41; N, 10.55%.

3.6.12a: (3*R*,4*R*)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-ethyl)-azetidin-2-one (3.13a):

Following the general procedure, as for **3.06a-b**, double bond of nitroalkene **3.12a** (1.100g, 3.96 mmol) was reduced by using tributyltinhydride (1.171 mL, 4.35 mmol) to gave crude nitroalkane which was further purified by column chromatography (EtOAc/pet. ether 3:7 as eluent) to get pure **3.13a** (0.644 g, 60%) as a gum.

$[\alpha]^{30}_D$ = +14.9 (*c* 1.34, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1754 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.09-2.32 (m, 1H, H_a-5), 2.74-2.90 (m, 1H, H_b-5), 3.57 (s, 3H, -OCH_3), 3.80 (s, 3H, Ar-OCH_3), 4.03-4.11 (m, 1H, *H*-4), 4.35 (d, *J* = 1.6 Hz, 1H, *H*-3), 4.49-4.58 (m, 2H), 6.91 (d, *J* = 9.0 Hz, 2H, Ar), 7.29 (d, *J* = 9.0 Hz, 2H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 27.3, 55.3, 56.7, 57.7, 71.2, 87.0, 114.5, 119.2, 129.0, 156.7, 162.6

MS: (*m/z*) = 281 (M+1)

Anal. Calcd. for **$C_{13}H_{16}N_2O_5$:** C, 55.71; H, 5.75; N, 9.99%

Found C, 55.92; H, 5.85; N, 10.23%.

3.6.12b: (3*R*,4*R*)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-ethyl)-azetidin-2-one (3.13b):

Following the general procedure, as for **3.06a-b**, double bond of nitroalkene **3.12b** (2.500 g, 8.56 mmol) was reduced by using tributyltinhydride (2.53 mL, 9.42 mmol) to

gave crude nitroalkane which was further purified by column chromatography (EtOAc/pet. ether 3:7 as eluent) to get pure **3.13b** (1.560 g, 62%) as a viscous liquid.

$[\alpha]^{30}_{D}$ = +63.3 (*c* 0.60, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.04-2.45 (m, 2H, *H*-5), 3.40-3.60 (m, 4H, H-4, -OCH_3), 3.81 (s, 3H, Ar-OCH_3), 4.15 (d, *J* = 15.2 Hz, 1H, -NC$H_a$$H_b$), 4.20-4.36 (m, 3H, *H*-3, *H*-6), 4.55 (d, *J* = 15.2 Hz, 1H, -NCH$_a$$H_b$), 6.89 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 28.5, 44.0, 55.3, 56.6, 57.9, 71.6, 87.5, 114.4, 126.8, 129.5, 159.4, 166.1

MS: (*m/z*) = 295 (M+1)

Anal. Calcd. for **$C_{14}H_{18}N_2O_5$:** C, 57.12; H, 6.18; N, 9.52%

Found C, 57.47; H, 6.40; N, 9.57%.

3.6.12c: (3*R*,4*R*)-1-Benzyl-3-methoxy-4-(2-nitro-ethyl)-azetidin-2-one (3.13c):

Following the general procedure, as for **3.06a-b**, double bond of nitroalkene **3.12c** (2.21 g, 8.43 mmol) was reduced by using tributyltinhydride (2.495 ml, 9.28 mmol) to gave nitroalkane **3.13c**, which was further purified by column chromatography (EtOAc/pet ether 4:6 as eluent) to get pure **3.13c** (1.113 g, 50%) as a colourless viscous liquid.

$[\alpha]^{30}_{D}$ = +70.0 (*c* 0.80, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1759 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07-2.39 (m, 2H, *H*-5), 3.45-3.51 (m, 4H, -OCH_3, *H*-4), 4.18-4.35 (m, 4H, *H*-3, *H*-6, -NC$H_a$$H_b$), 4.61 (d, *J* = 15.1 Hz, 1H, -NCH$_a$$H_b$), 7.23-7.40 (m, 5H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 28.4, 44.6, 56.8, 57.9, 71.5, 87.6, 128.1, 128.2, 129.1, 134.8, 166.1

MS: (*m/z*) = 265 (M+1)

Anal. Calcd. for **$C_{13}H_{16}N_2O_4$:** C, 59.08; H, 6.10; N, 10.60%

Found C, 58.87; H, 6.32; N, 10.42%.

3.6.13a: (2*R*,3*R*)-2-Methoxy-3-(4-methoxy-phenylamino)-5-nitro-pentanoic acid methyl ester (3.14a):

Following the general procedure as for **3.07a-b**, nitro alkane **3.13a** (0.600 g, 2.14 mmol) was stirred in methanolic HCl (20%; 10 mL) for 12 h to get the nitro ester **3.14a** as yellow viscous liquid (0.635 g, 95%).

$[\alpha]^{30}_{D}$ = +19.2 (*c* 0.52, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1749 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10-2.23 (m, 2H, *H*-4), 3.40 (s, 3H, -OC*H*$_3$), 3.77 (s, 3H, -COOC*H*$_3$), 3.79 (s, 3H, Ar-OC*H*$_3$), 3.79-3.95 (m, 1H, *H*-3), 3.97 (d, *J* = 3.1 Hz, 1H, *H*-2), 4.45-4.72 (m, 2H, *H*-5), 6.70 (d, *J* = 9.0 Hz, 2H, Ar), 6.82 (d, *J* = 9.0 Hz, 2H, Ar).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ 27.6, 51.9, 54.7, 55.4, 59.0, 72.4, 79.9, 115.0, 116.6, 139.9, 153.3, 171.2

MS: (*m/z*) = 313 (M+1)

Anal. Calcd. for **$C_{14}H_{20}N_2O_6$:** C, 53.84; H, 6.45; N, 8.97%

Found C, 53.81; H, 6.63; N, 8.90%.

3.6.13b: (2*R*,3*R*)-2-Methoxy-3-(4-methoxy-benzylamino)-5-nitro-pentanoic acid methyl ester (3.14b):

Following the general procedure as for **3.07a-b**, nitro alkane **3.13b** (1.50 g, 5.10 mmol) was stirred in methanolic HCl (20%; 15 mL) for 12 h to get the nitro ester **3.14b** as yellow viscous liquid (1.563 g, 94%)

$[\alpha]^{30}_{D}$ = +42.9 (*c* 0.7, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.94-2.06 (m, 2H, *H*-4), 2.92-3.02 (m, 1H, *H*-3), 3.45 (s, 3H, -OC*H*$_3$), 3.63 (d, *J* = 12.9 Hz, 1H, -NC*H*$_a$H$_b$), 3.75-3.87 (m, 7H, -NCH$_a$*H*$_b$, -COOC*H*$_3$, Ar-OC*H*$_3$), 4.06 (d, *J* = 3.3 Hz, 1H, *H*-2), 4.40-4.62 (m, 2H, *H*-5), 6.87 (d, *J* = 8.6 Hz, 2H, Ar), 7.24 (d, *J* = 8.6 Hz, 2H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 27.9, 50.5, 52.1, 55.3, 56.4, 59.1, 72.8, 79.4, 113.8, 129.2, 131.8, 158.8, 171.8

MS: (*m/z*) = 327 (M+1)

Anal. Calcd. for **$C_{15}H_{22}N_2O_6$:** C, 55.19; H, 6.81; N, 8.58%

Found C, 55.44; H, 6.83; N, 8.76%.

3.6.13c: (2*R*,3*R*)-3-Benzylamino-2-methoxy-5-nitro-pentanoic acid methyl ester (3.14c):

Following the general procedure as for **3.07a-b**, nitro alkane **3.13c** (1.050 g, 3.98 mmol) was stirred in methanolic HCl (20%; 10 mL) for 12 h to get the nitro ester **3.14c** as yellow viscous liquid (1.153 g, 98%).

$[\alpha]^{30}_{D}$ = +42.5 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1743 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98-2.08 (m, 2H, *H*-4), 2.31 (bs, 1H, -N*H*) 2.97-3.06 (m, 1H, *H*-3), 3.45 (s, 3H, -OCH_3), 3.69-3.79 (m, 4H, -NC$H_a$$H_b$Ph, -COOC$H_3$) 3.90 (d, *J* = 13.1 Hz, -NC*H*aHbPh), 4.08 (d, *J* = 3.1 Hz, 1H, *H*-2), 4.44-4.61 (m, 2H, *H*-5), 7.26-7.37 (m, 5H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 27.8, 51.1, 52.1, 56.5, 59.1, 72.7, 79.3, 127.4, 128.2, 128.5, 139.3, 171.6.

MS: (*m/z*) = 297 (M+1)

Anal. Calcd. for **$C_{14}H_{20}N_2O_5$:** C, 56.75; H, 6.80; N, 9.45%

Found C, 56.83; H, 6.92; N, 9.63%.

3.6.14a: (3*R*,4*R*)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine-2-one (3.15a):

Following the general procedure as for **3.08a-b**, nitro ester **3.14a** (0.60 g, 1.92 mmol) was treated with 10% Pd/C (115 mg) and ammonium formate (0.606 g, 9.62 mmol) at room temperature for 5 h to gave the crude 4-aminopiperidin-2-one, which was further purified by flash column chromatography (EtOAc/pet. ether 6:4 as eluent) to get pure **3.15a** (0.322 g, 67%) as a gummy solid.

$[\alpha]^{30}_{D}$ = +38.2 (*c* 0.55, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1651 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00-2.28 (m, 2H, *H*-5), 3.56 (s, 3H, -OCH_3), 3.58-3.73 (m, 3H, *H*-4, *H*-6), 3.75 (s, 3H, Ar-OCH_3), 3.90 (d, *J* = 3.5 Hz, 1H, *H*-3), 6.65 (d, *J* = 9.0 Hz, 2H, Ar), 6.80 (d, *J* = 9.0 Hz, 2H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 23.3, 47.2, 51.7, 55.6, 59.3, 77.3, 114.9, 116.2, 139.5, 153.1, 162.9

MS: (*m/z*) = 251 (M+1)

Anal. Calcd. for **$C_{13}H_{18}N_2O_3$:** C, 62.38; H, 7.25; N, 11.19%

Found C, 62.32; H, 7.33; N, 11.47%.

3.6.14b: (3*R*,4*R*)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine-2-one (3.15b):

Following the general procedure as for **3.08a-b**, nitro ester **3.14b** (1.500 g, 4.60 mmol) was treated with 10% Pd/C (276 mg) and ammonium formate (1.450 g, 23.00 mmole) at room temperature for 5 h to gave the 4-aminopiperidin-2-one **3.15b**, which was further purified by flash column chromatography (acetone/pet. ether 7:3 as eluent) to get pure **3.15b** (0.741 g, 61%) as a gummy solid.

$[\alpha]^{30}_D$ = +48.0 (*c* 0.50, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1650 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84-2.02 (m, 1H, H_a-5), 2.04-2.24 (m, 1H, H_b-5), 3.07-3.17 (m, 1H, *H*-4), 3.46-3.52 (m, 1H, *H*-6), 3.55 (s, 3H, -OCH_3), 3.67-3.79 (m, 3H, *H*-6, -NCH_2), 3.80 (s, 3H, Ar-OCH_3), 3.87 (d, *J* = 3.5 Hz, 1H, *H*-3), 3.95-4.15 (bs, 2H, 2x N-*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar), 7.24 (d, *J* = 8.6 Hz, 2H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 23.3, 46.0, 49.9, 53.1, 55.3, 59.3, 77.3, 113.9, 129.3, 131.4, 158.8, 164.3

MS: (*m/z*) = 265 (M+1)

Anal. Calcd. for **$C_{14}H_{20}N_2O_3$:** C, 63.60; H, 7.64; N, 10.60%

Found C, 63.85; H, 7.77; N, 10.55%.

3.6.14c: (3*R*,4*R*)-4-Benzylamino-3-methoxy-piperidine-2-one (3.15c):

Following the general procedure as for **3.08a-b**, nitro ester **3.14c** (1.100 g, 3.716 mmol) was treated with 10% Pd/C (225 mg) and ammonium formate (1.170g, 18.58 mmol) at room temperature for 3 h to gave the 4-aminopiperidin-2-one **3.15c**, which was further purified by flash column chromatography (acetone/pet. ether 7:3 as eluent) to get pure **3.15c** (0.478 g, 55%) as a gummy solid.

$[\alpha]^{30}_D$ = +36.8 (*c* 0.68, MeOH)

IR ($CHCl_3$): υ_{max} 1655 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02-2.33 (m, 2H, *H*-5), 3.22-3.30 (m, 1H, *H*-4), 3.53 (s, 3H, -OCH_3), 3.64-3.80 (m, 2H, *H*-6), 3.90-4.09 (m, 3H, *H*-3, -NCH_2), 7.28-7.40 (m, 5H, Ar), 7.50 (bs, 1H, -CON*H*).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ 22.2, 47.0, 49.6, 52.7, 59.3, 76.3, 128.3, 128.8, 128.9, 135.3, 163.0

MS: (*m/z*) = 235 (M+1)

Anal. Calcd. for **$C_{13}H_{18}N_2O_2$:** C, 66.64; H, 7.74; N, 11.96%

Found C, 66.53; H, 7.92; N, 11.67%.

3.6.15a: (3*S*,4*R*)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine (3.16a):

Following the general procedure as for **3.09a-b**, reduction of 4-amino piperidin-2-one **3.15a** (0.250 g, 1.00 mmol) using BH_3:DMS (10.0mM, 0.11 mL 10% excess) gave 4-amino piperidine **3.16a**, which was further purified by flash column chromatography (EtOAc/pet. ether 8:2 as eluent) to get pure **3.16a** (0.123 g, 52%).

$[\alpha]^{30}_D$ = +12.5 (*c* 0.72, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 3215, 3368 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72-2.04 (m, 2H, *H*-5), 2.69-2.85 (m, 2H, *H*-6), 3.25-3.45 (m, 5H, *H*-2, -OCH_3), 3.57-3.70 (m, 2H, *H*-4, *H*-3), 3.74 (s, 3H, Ar-OCH_3), 6.62 (d, *J* = 7.8 Hz, 2H, Ar), 6.78 (d, *J* = 7.8 Hz, 2H, Ar), 7.63 (bs, 1H, Ar-N*H*).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 25.6, 52.9, 55.6, 55.9, 56.9, 57.0, 76.0, 114.9, 116.3, 140.2, 152.9

MS: (*m/z*) = 237 (M+1)

Anal. Calcd. for **$C_{13}H_{20}N_2O_2$:** C, 66.07; H, 8.53; N, 11.85%

Found C, 66.24; H, 8.47; N, 12.03%.

3.6.15b: (3*S*,4*R*)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine (3.16b):

Following the general procedure as for **3.09a-b**, reduction of 4-amino piperidin-2-one **3.15b** (0.700 g, 2.65 mmol) using BH_3:DMS (10.0mM, 0.29 mL 10% excess) gave crude 4-amino piperidine, which was further purified by column chromatography (EtOAc/pet. ether 9:1 as eluent) to afford pure **3.16b** (0.331 g, 50%).

$[\alpha]^{30}_D$ = +18.0 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 3257, 3328 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60-1.99 (m, 3H, *H*-5, H_a-2), 2.05 (bs, 1H, -N*H*), 2.40-2.78 (m, 3H, *H*-6, *H*-2), 3.18-3.26 (m, 1H, *H*-4), 3.36 (bs, 1H, -N*H*), 3.42 (s, 3H, -OCH_3), 3.47-3.58 (m, 1H, *H*-3), 3.73-3.87 (m, 5H, Ar-OCH_3, -NCH_2), 6.88 (d, *J* = 8.7 Hz, 2H, Ar), 7.26 (d, *J* = 8.7 Hz, 2H, Ar).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 26.5, 49.1, 52.1, 53.4, 54.3, 55.3, 57.5, 73.9, 114.0, 129.5, 130.5, 159.0

MS: (*m/z*) = 251 (M+1)

Anal. Calcd. for **$C_{14}H_{22}N_2O_2$:** C, 67.17; H, 8.86; N, 11.19%

Found C, 67.34; H, 8.92; N, 11.27%.

3.6.15c: (3*S*,4*R*)-4-Benzylamino-3-methoxy-piperidine (3.16c):

Following the general procedure as for **3.09a-b**, reduction of 4-amino piperidin-2-one **3.15c** (0.410 g, 1.752 mmol) using BH_3:DMS (10.0mM, 0.192 mL 10% excess) gave 4-amino piperidine **3.16c**, which was further purified by flash column chromatography (CH_2Cl_2/MeOH 95:5 as eluent) to gave pure **3.16c** (0.188 g, 49%).

$[\alpha]^{30}_D$ = +11.2 (*c* 0.72, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 3211, 3319 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-1.95 (m, 2H, *H*-5), 2.35-2.70 (m, 2H, *H*-6), 2.80-3.45 (m, 6H, *H*-2, -N*H*, -OCH_3), 3.50-3.90 (m, 4H, *H*-4, *H*-3, -NCH_2), 4.34 (bs, 1H, -N*H*), 7.20-7.33 (m, 5H, Ar).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 26.6, 50.3, 55.0, 56.5, 56.9, 57.4, 75.9, 127.1, 128.1, 128.4, 139.6

MS: (*m/z*) = 221 (M+1)

Anal. Calcd. for **$C_{13}H_{20}N_2O$:** C, 70.87; H, 9.15; N, 12.72%

Found C, 71.12; H, 9.32; N, 12.95%.

3.6.16: 1-(3-bromopropoxy)-4-fluorobenzene:

To a solution of fluorophenol (2.24 g, 20 mmol) in dry acetone (30 mL), anhydrous K_2CO_3 (4.14 g, 30 mmol) was added followed by the addition of 1,3 dibromo propane (0.20 mL, 20 mmol). The reaction mixture was refluxed for 6 h. Allowed to come to room

temperature filtered through whatmann filter paper. Filtrate obtained were concentrated under reduced pressure to gave crude compound which was purified by flash column chromatography (EtOAc/pet. ether 1:99 as eluent) to gave pure **3.17** (2.982 g, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29-2.34 (m, 2H, -C*H*$_2$-CH$_2$-Br), 3.61 (t, *J* = 7.5 Hz, 2H, -CH$_2$-C*H*$_2$-Br), 4.08 (t, *J* = 7.5 Hz, 2H, -OC*H*$_2$), 6.84-6.87 (m, 2H, Ar), 6.97-7.00 (m, 2H, Ar).

3.6.17: (3*R*,4*S*)-2-(3-(4-fluorophenoxy)propoxy)-3-methoxy-N-(4-methoxyphenyl)-3,4,5,6-tetrahydropyridin-4-amine (3.18):

To a stirred solution of 4-amino piperdin-2-one **3.08a** (0.250 g, 1 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C, Boc_2O (0.23 mL, 1 mmol) was added followed by the addition of Et_3N (0.15 mL, 1.1 mmol). The reaction mixture was allowed to stirr at room temperature for 30 min. After completion of reaction (TLC) quenched with addition of water (2 mL), organic layer was dried over anhydrous Na_2SO_4, concentrated under *vacuo* to gave Boc protected compound. Sodium hydride (44 mg, 1.1 mmol) washed with pet ether (2 x 2 mL), anhydrous THF (5 mL) was added to it. To this slurry a solution of Boc protected compound in THF (10 mL) was added at 0 °C, allowed to stir for 30 min. Bromo compound **3.17** (0.256 g, 1.1 mmol) in THF (5 mL) was added to this solution at 0 °C and then allowed to stir at room temperature for 15 min. Refluxed for 12 h, after completion of reaction (TLC) quenched with sat. solution of NH_4Cl (2 mL) at 0 °C. THF was removed under *vacuo*, resulting residue was extracted with CH_2Cl_2 (2 x 15 mL), dried over anhydrous Na_2SO_4, concentrated under *vacuo* to gave oxime ether **3.18**, which was further purified by column chromatography (60-120 mesh silica, EtOAc/ pet. ether 25: 75 as eluent) to gave pure **3.18** (0.281 g, 70 %).

$[\alpha]^{30}_D$ = +27.9 (*c* 0.43, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 1672 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.95-2.95 (m, 3H, *H*-8, *H*$_a$-5), 2.35-2.45 (m, 1H, *H*$_b$-5), 3.49-3.60 (m, 3H, *H*-6, *H*-4), 3.64 (s, 3H, -OC*H*$_3$), 3.77 (s, 3H, Ar-OC*H*$_3$), 3.82-3.87 (m, 1H, *H*-3), 4.08 (t, *J* = 6.2 Hz, 2H, *H*-7), 4.14 (t, J = 6.2 Hz, 2H, *H*-9), 6.75-7.00 (m, 8H, Ar).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 24.3, 28.3, 45.9, 55.6, 55.7, 59.7, 65.1, 70.4, 80.2, 115.0, 115.6, 115.7, 115.9, 156.4, 158.3, 165.9

MS: (*m/z*) = 403 (M+1).

Anal. Calcd. for **$C_{22}H_{27}N_2O_4F$:** C, 65.66; H, 6.76; N, 6.96%

Found C, 65.93; H, 6.54; N, 6.87%.

3.6.18: (3*S*,4*S*)-2-(3-(4-fluorophenoxy)propyl)-3-methoxy-N-(4-methoxyphenyl)piperidin-4-amine (3.20):

4-amino piperidine **3.09a** (0.236 mg, 1 mmol) was dissolved in anhydrous DMF (5 mL), Et_3N (0.15 mL, 1.1 mmol) was added to it, allowed to stirr this solution for 10 min. To this solution bromo compound **3.17** (0.256 g, 1.1 mmol) in DMF (3 mL) was added dropwise and allowed to stir for 12 h at room temperature. DMF was removed under *vacuo* at 30 °C residue obtained was purified by flash column chromatography (CH_2Cl_2/MeOH 9:1 as eluent) to get pure **3.20** (0.155g, 40%).

$[\alpha]^{30}_D$ = +11.1 (*c* 0.36, $CHCl_3$)

IR ($CHCl_3$): υ_{max} 3369 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05-2.45 (m, 4H, *H*-5, *H*-8), 3.05-3.40 (m, 2H, *H*-6), 3.44 (s, 3H, -OCH_3), 3.46-3.70 (m, 3H, *H*-7, H_a-2), 3.71 (s, 3H, Ar-OCH_3), 3.72-3.92 (m, 3H, H_b-2, *H*-4, *H*-3), 4.02 (t, *J* = 6.2 Hz, 2H, *H*-9), 6.73-7.00 (m, 8H, Ar).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ 22.9, 24.8, 52.1, 55.7, 58.3, 62.2, 63.7, 65.6, 65.9, 76.9, 114.8, 115.4, 115.6, 115.9, 141.1, 152.5

MS: (*m/z*) = 389 (M+1)

Anal. Calcd. for **$C_{22}H_{29}N_2O_3F$:** C, 68.02; H, 7.52; N, 7.21%

Found C, 68.23; H, 7.27; N, 7.33%.

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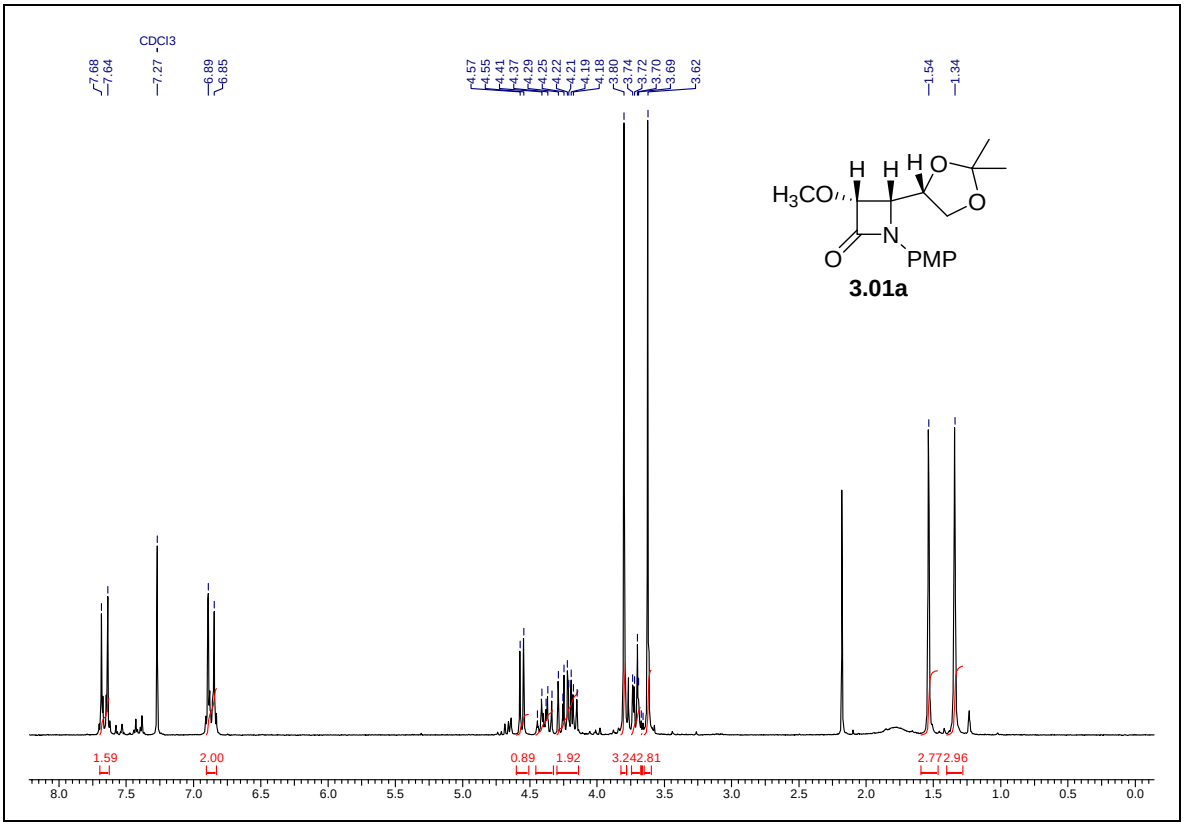
Chapter III

Spectra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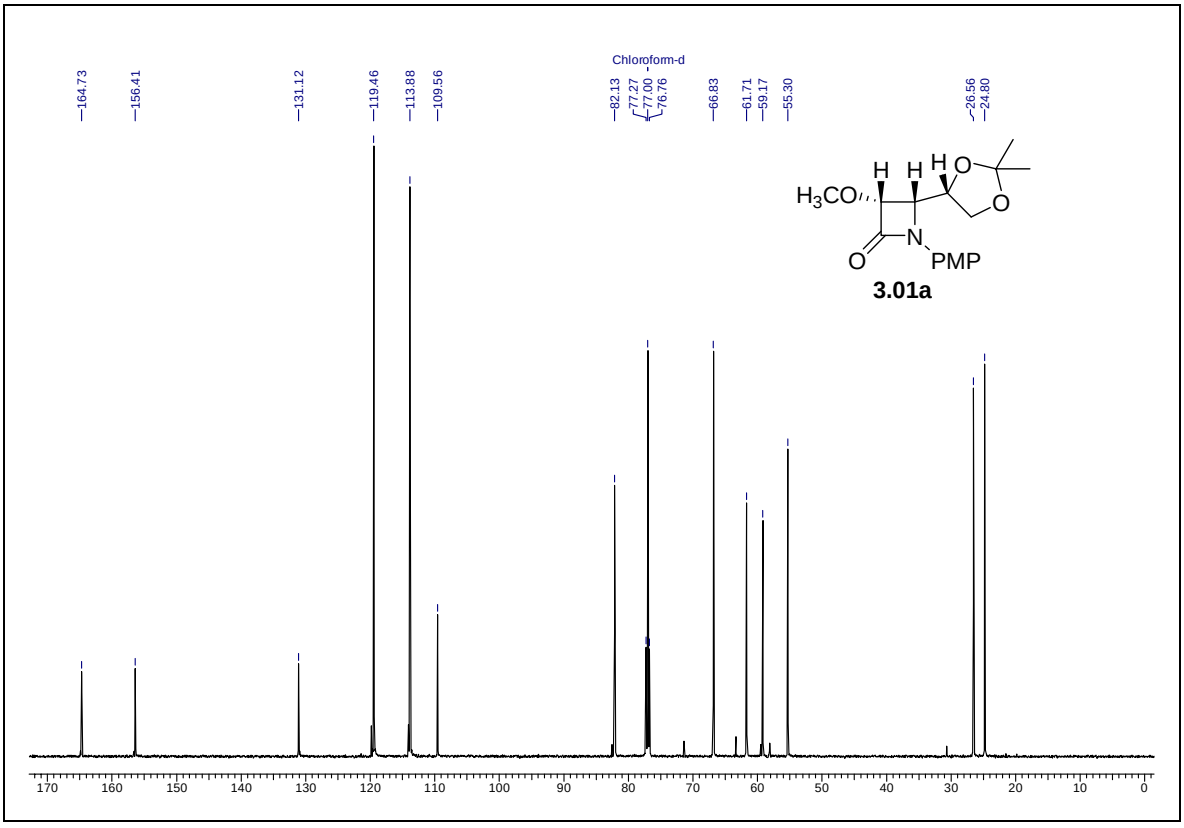
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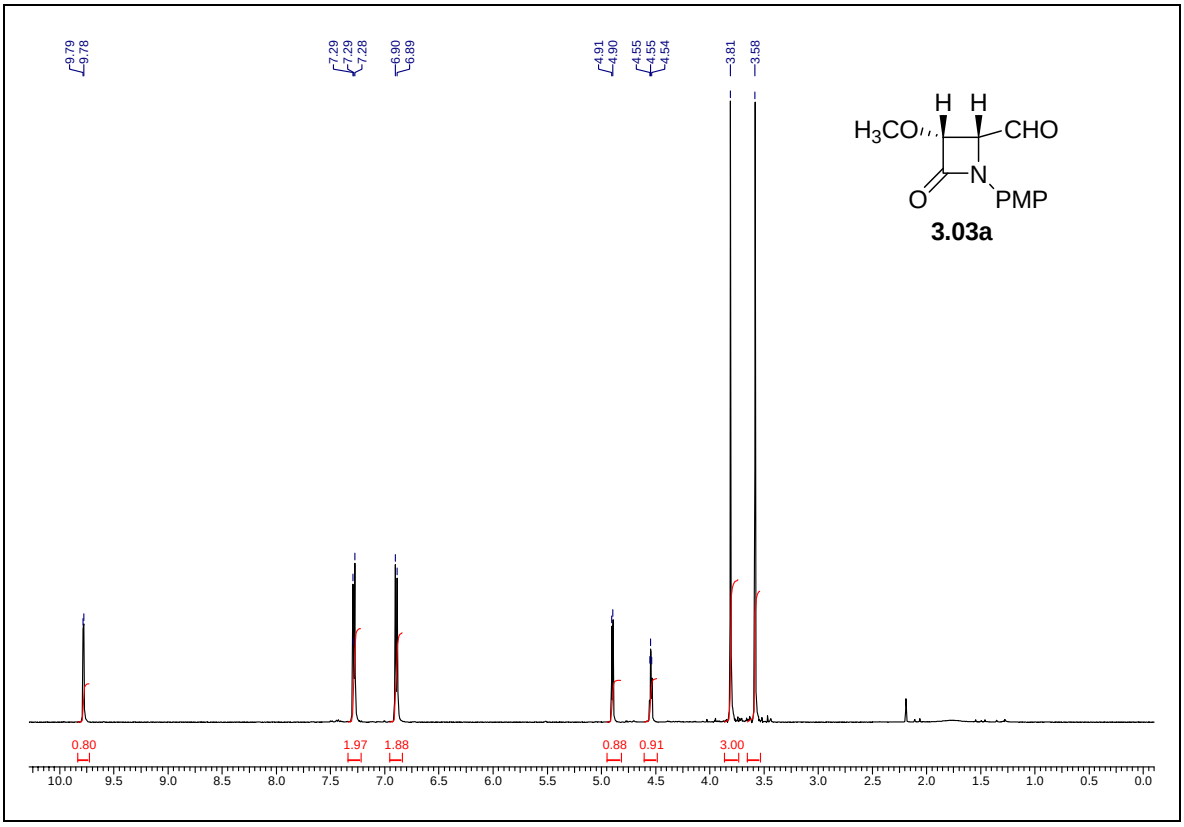
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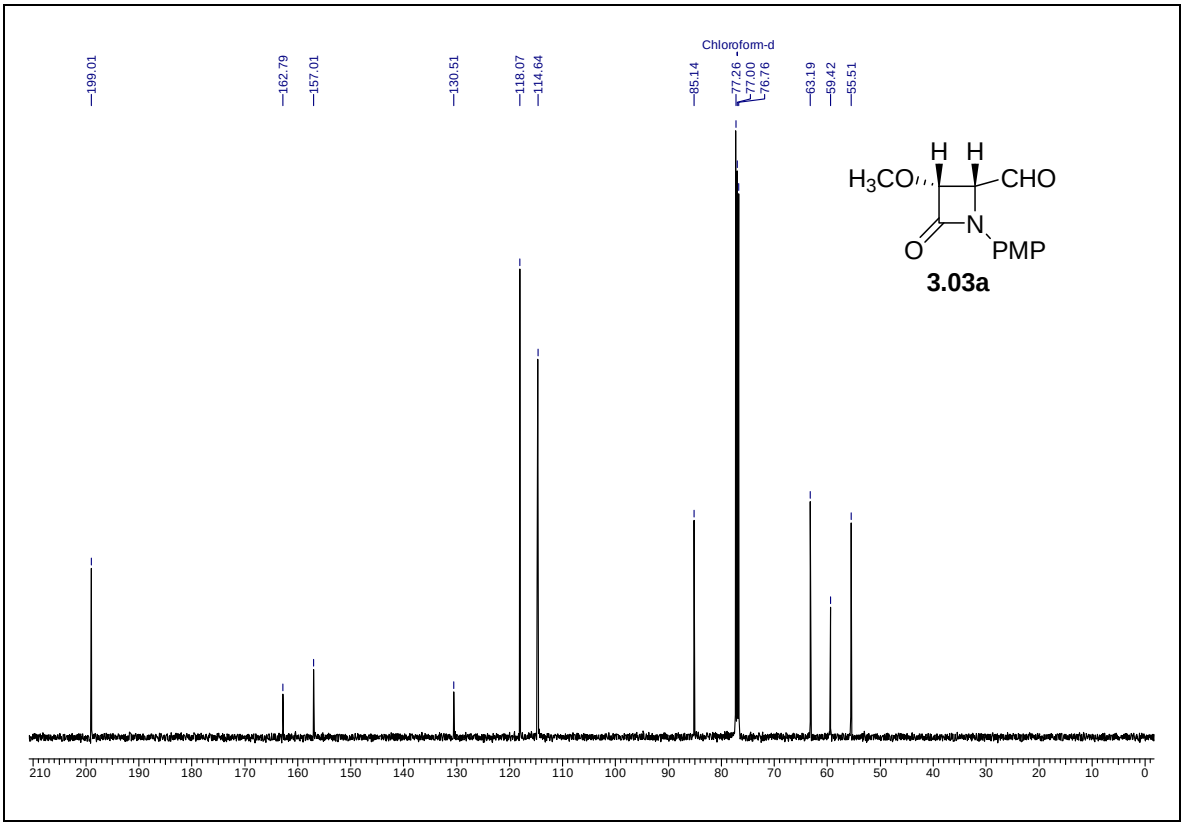
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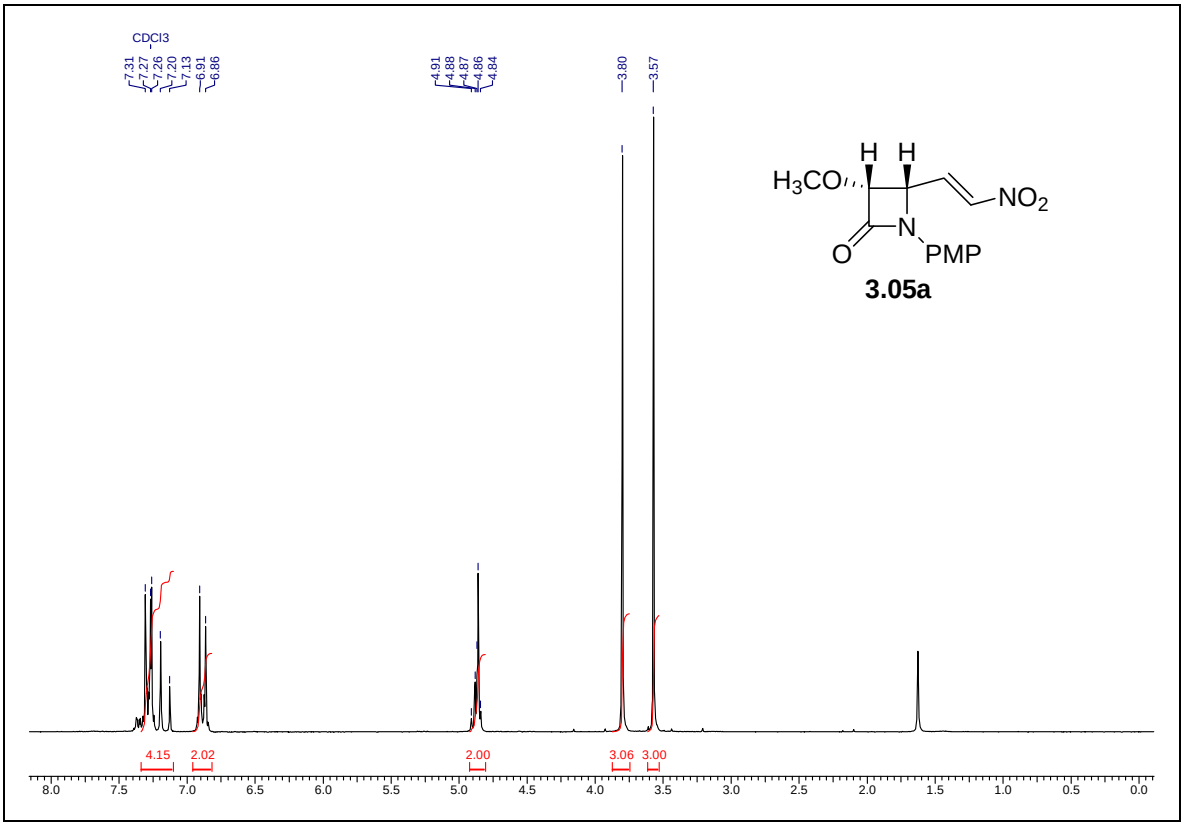
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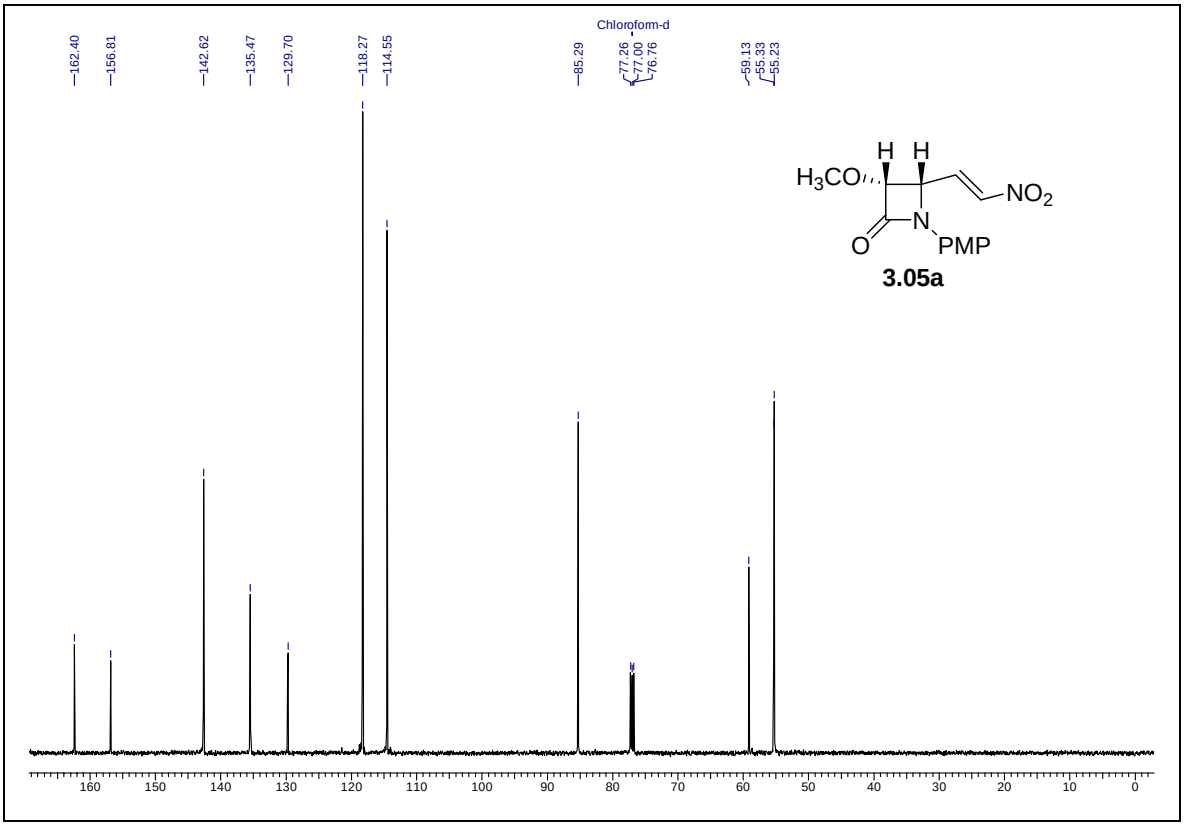
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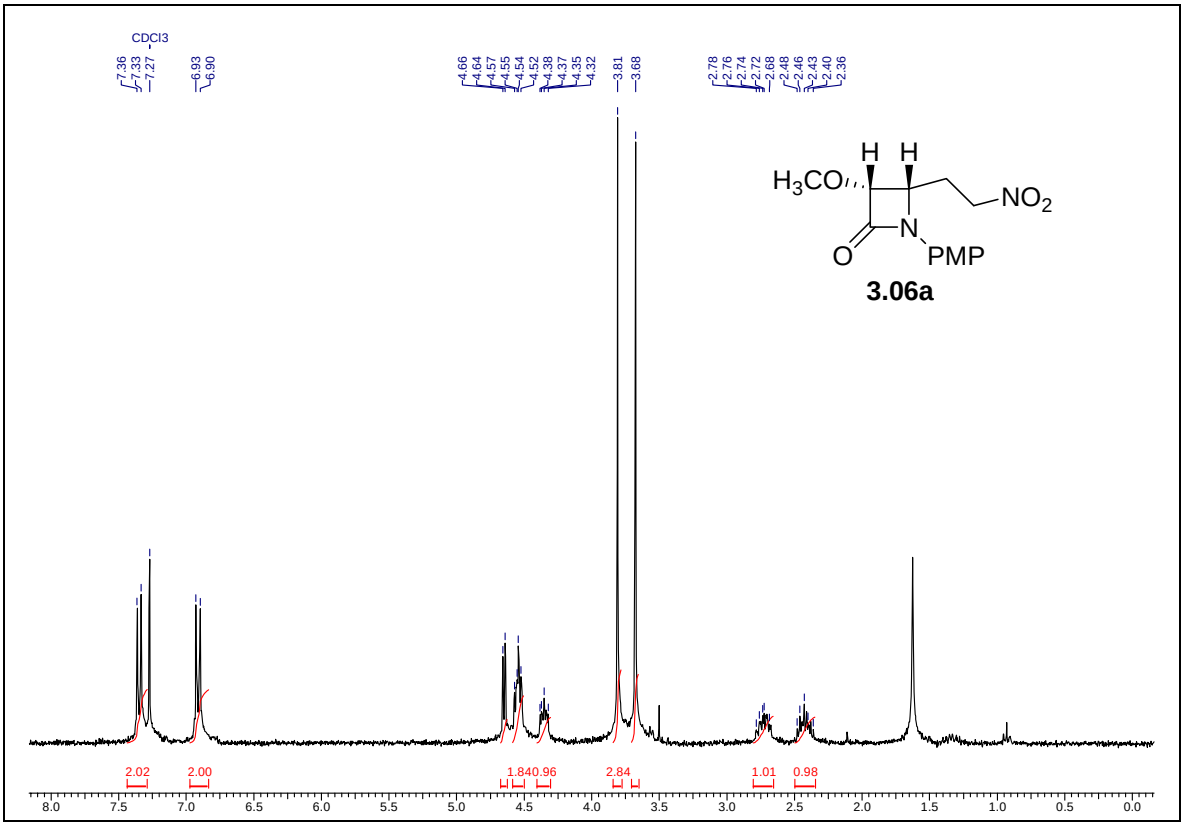
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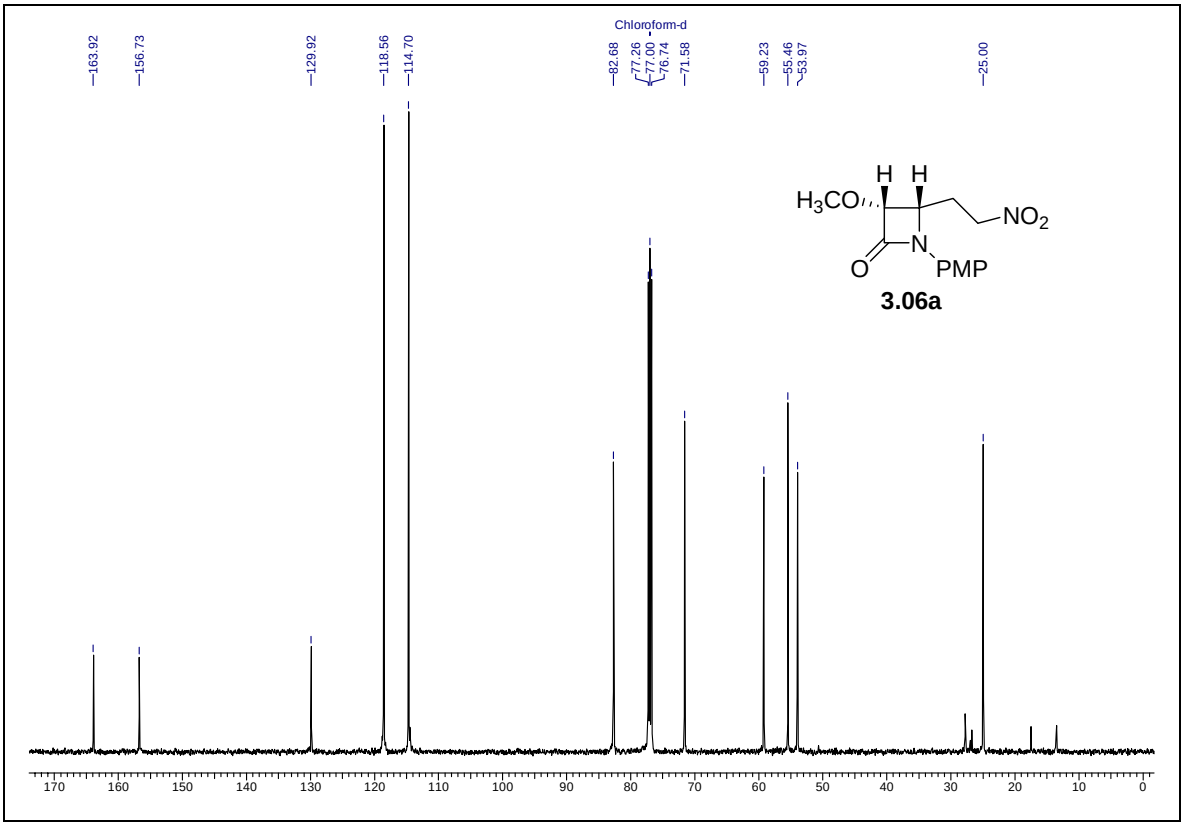
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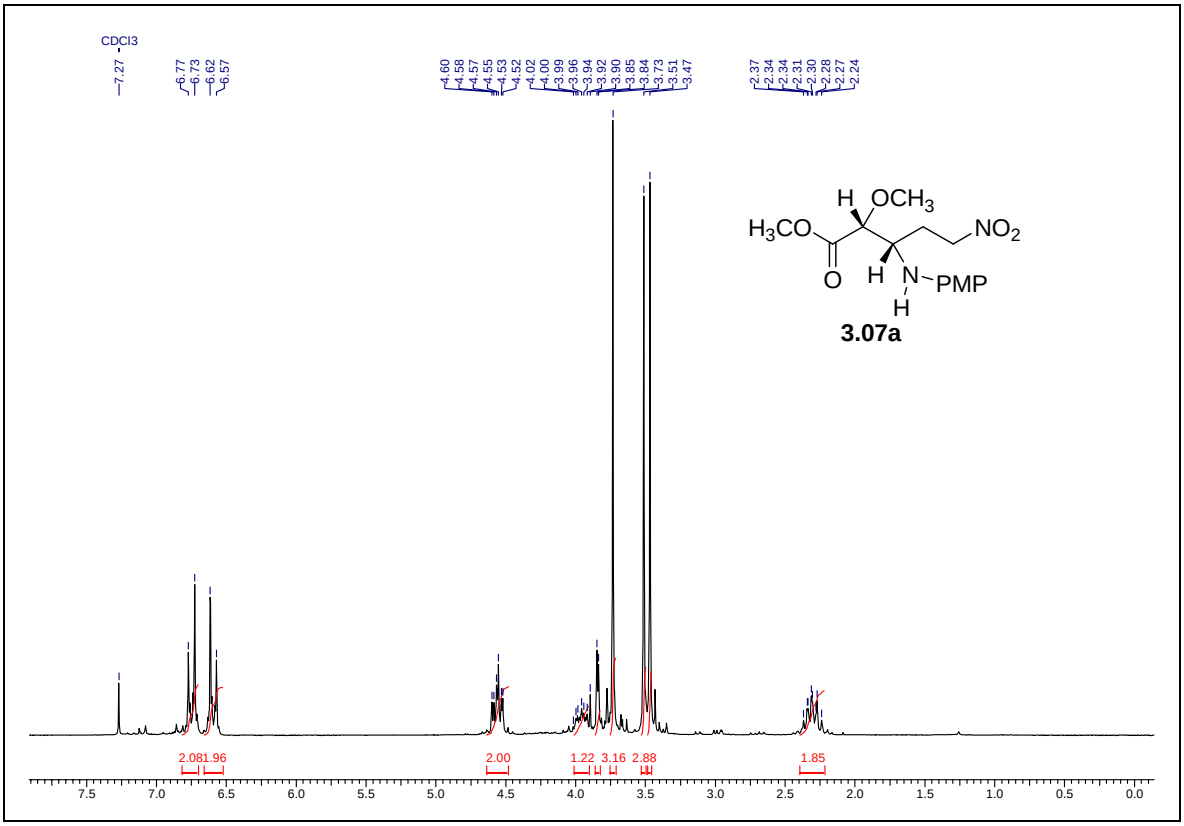
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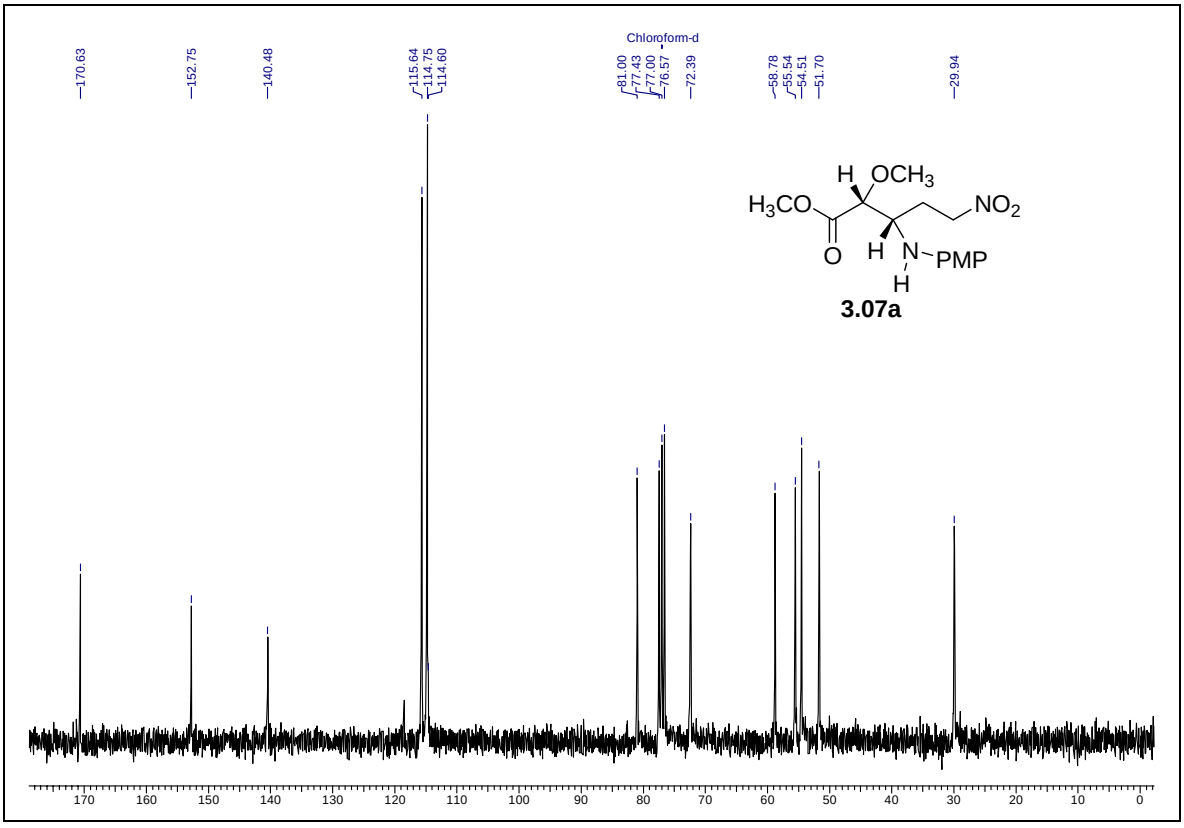
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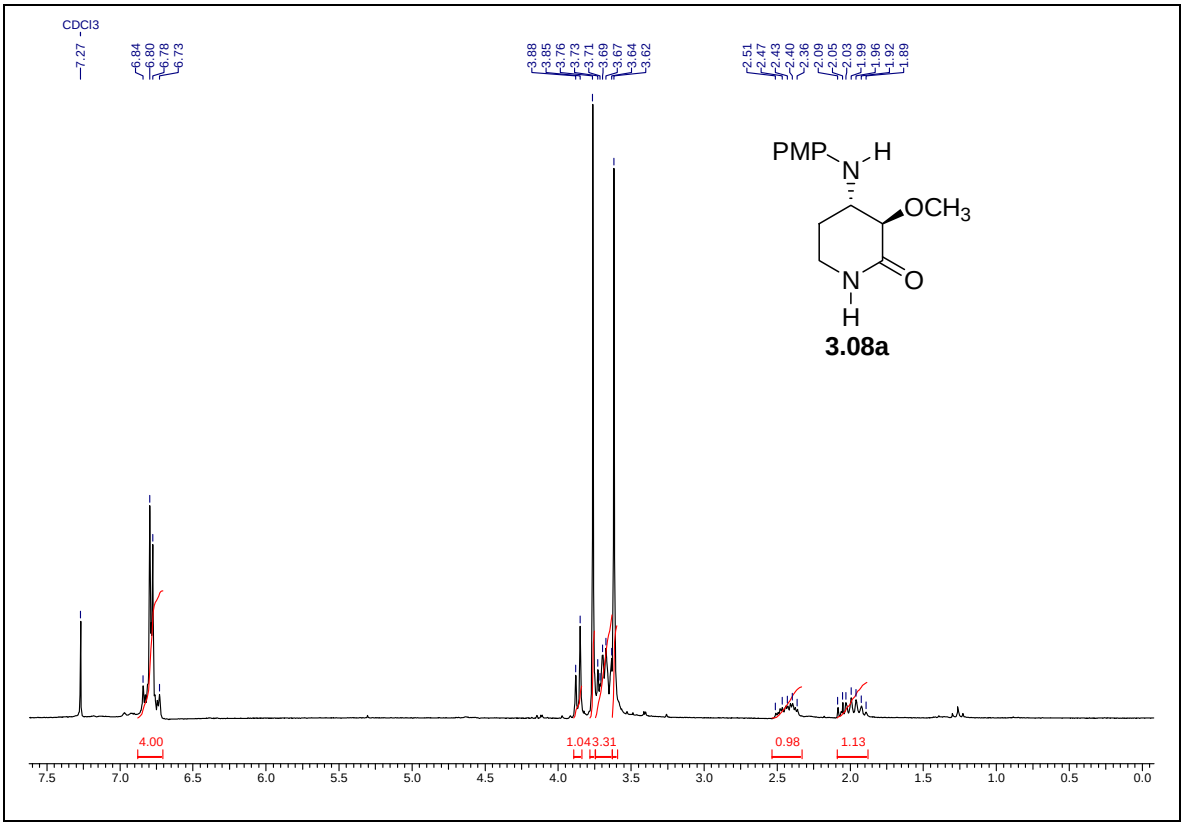
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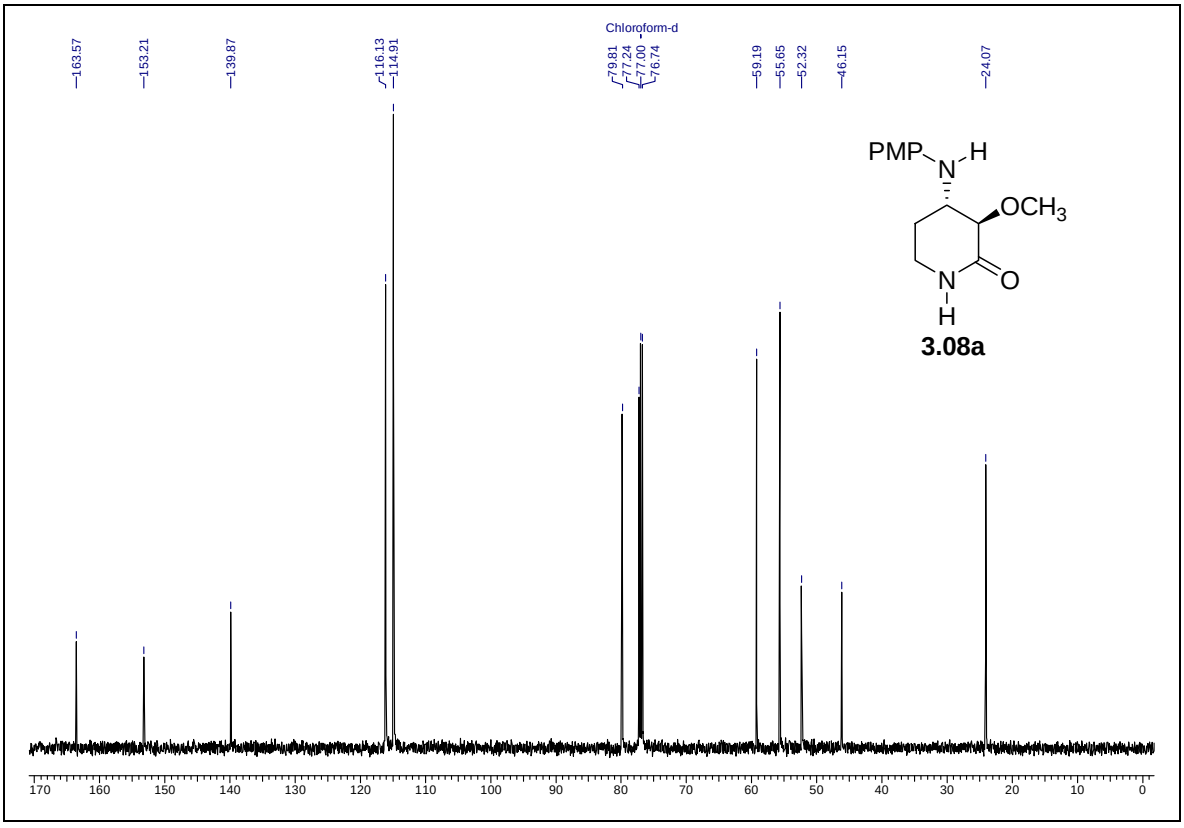
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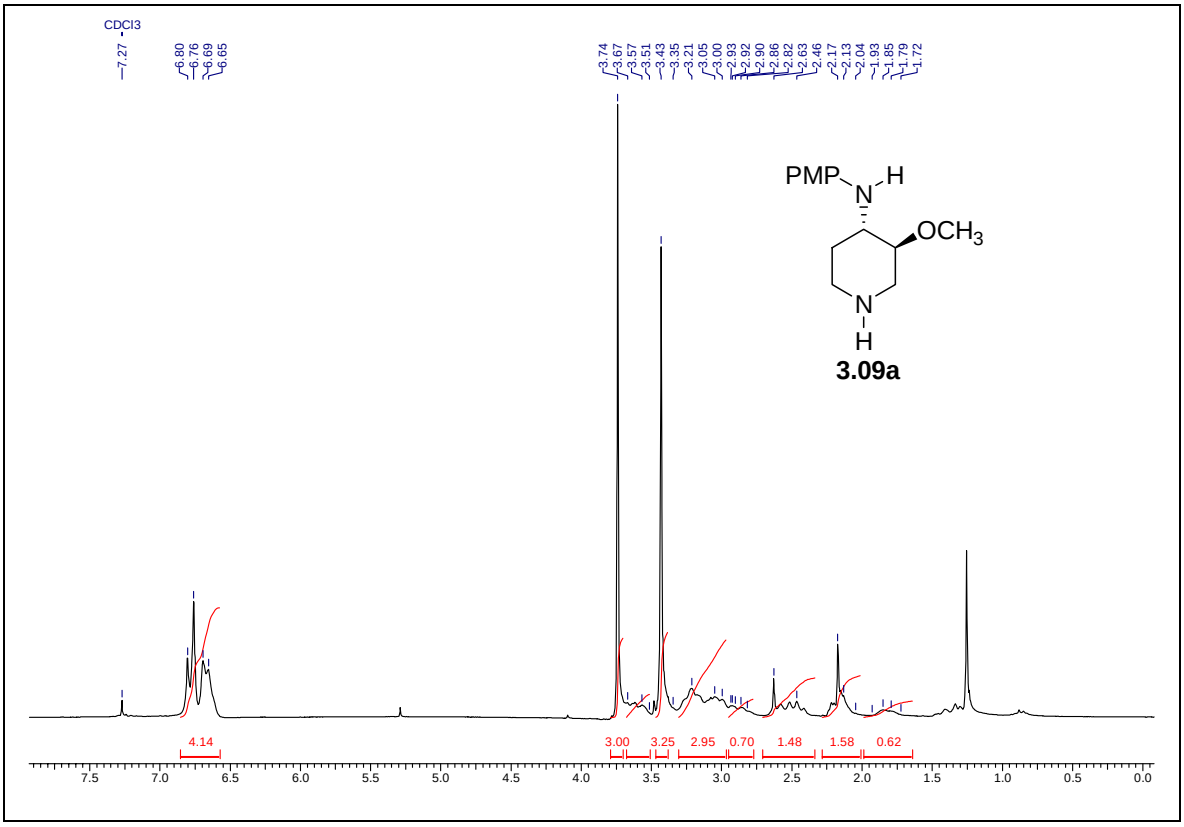
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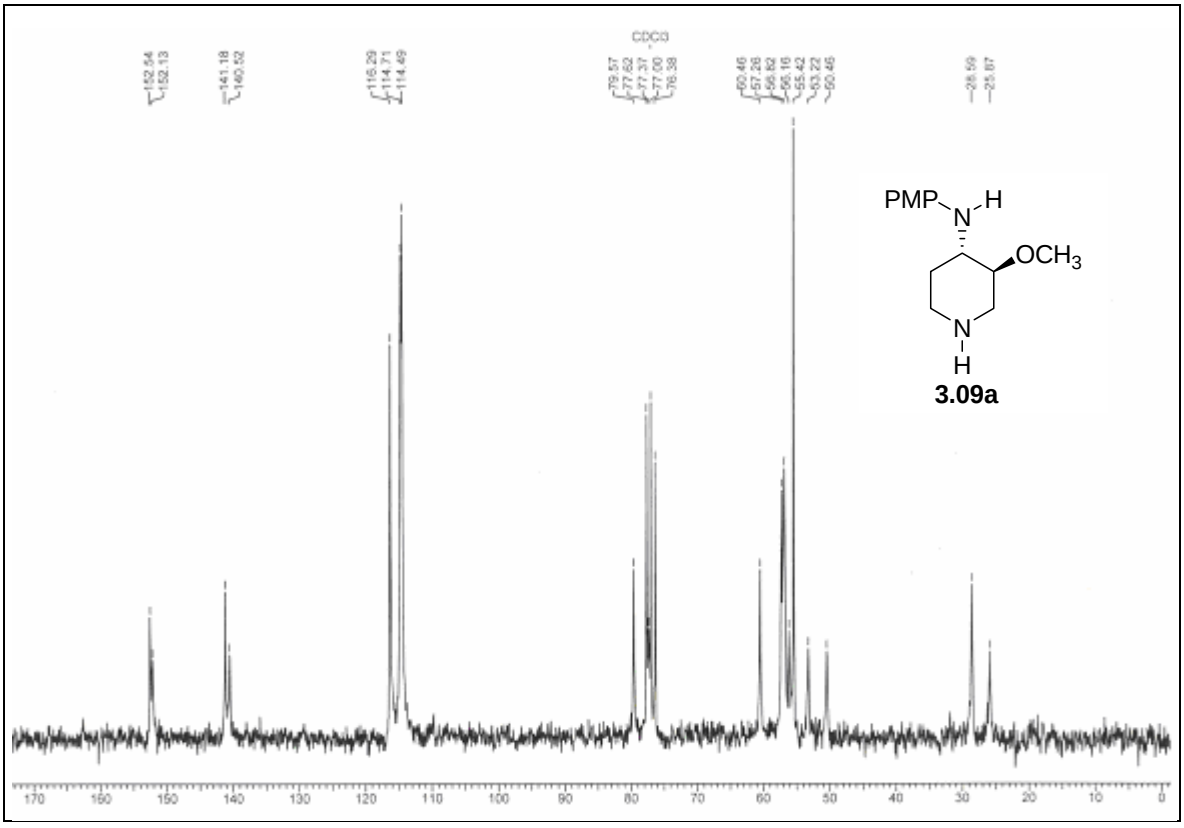
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OCH3
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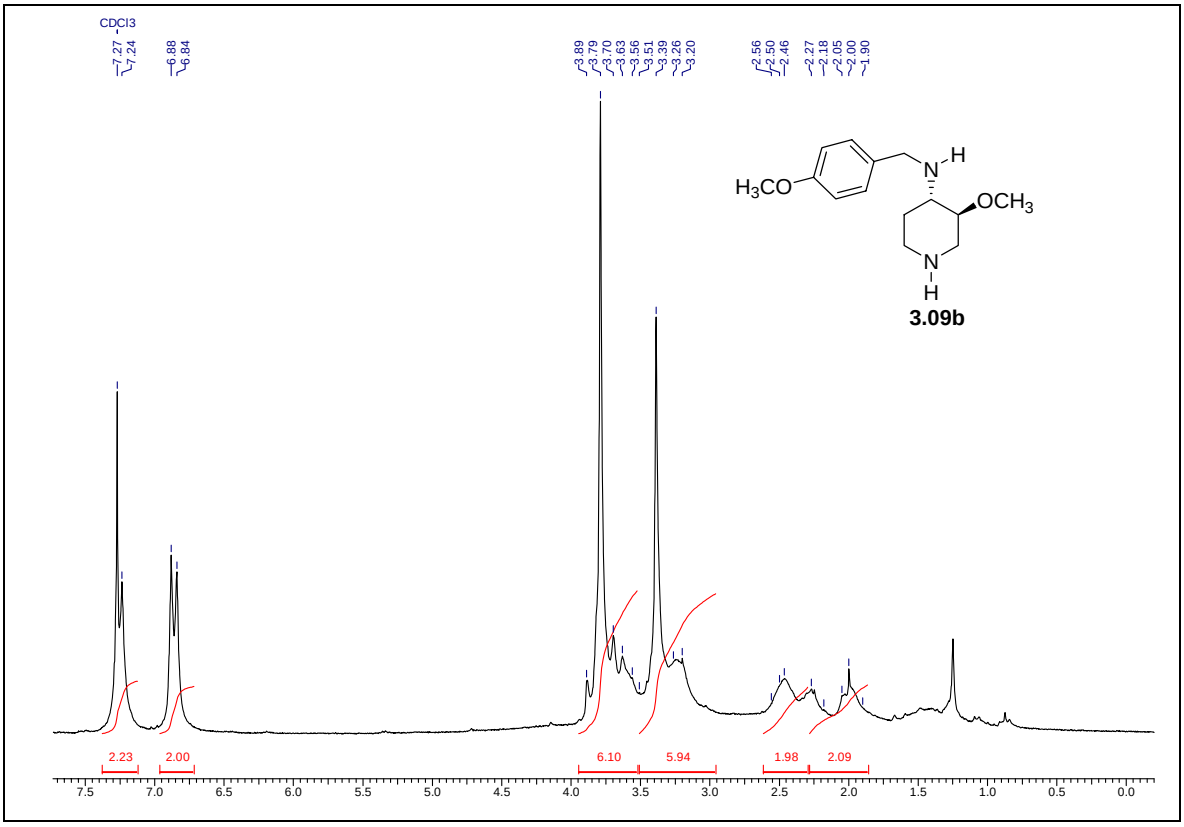
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2.46
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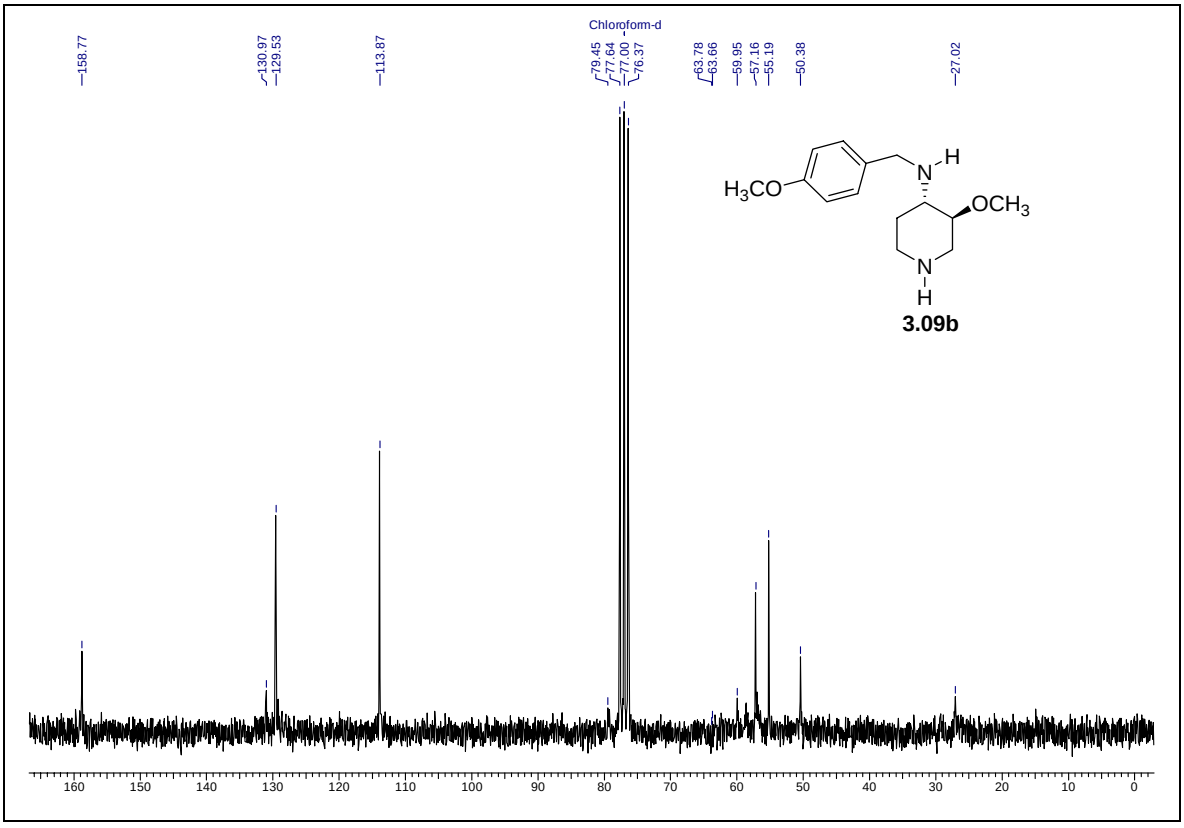
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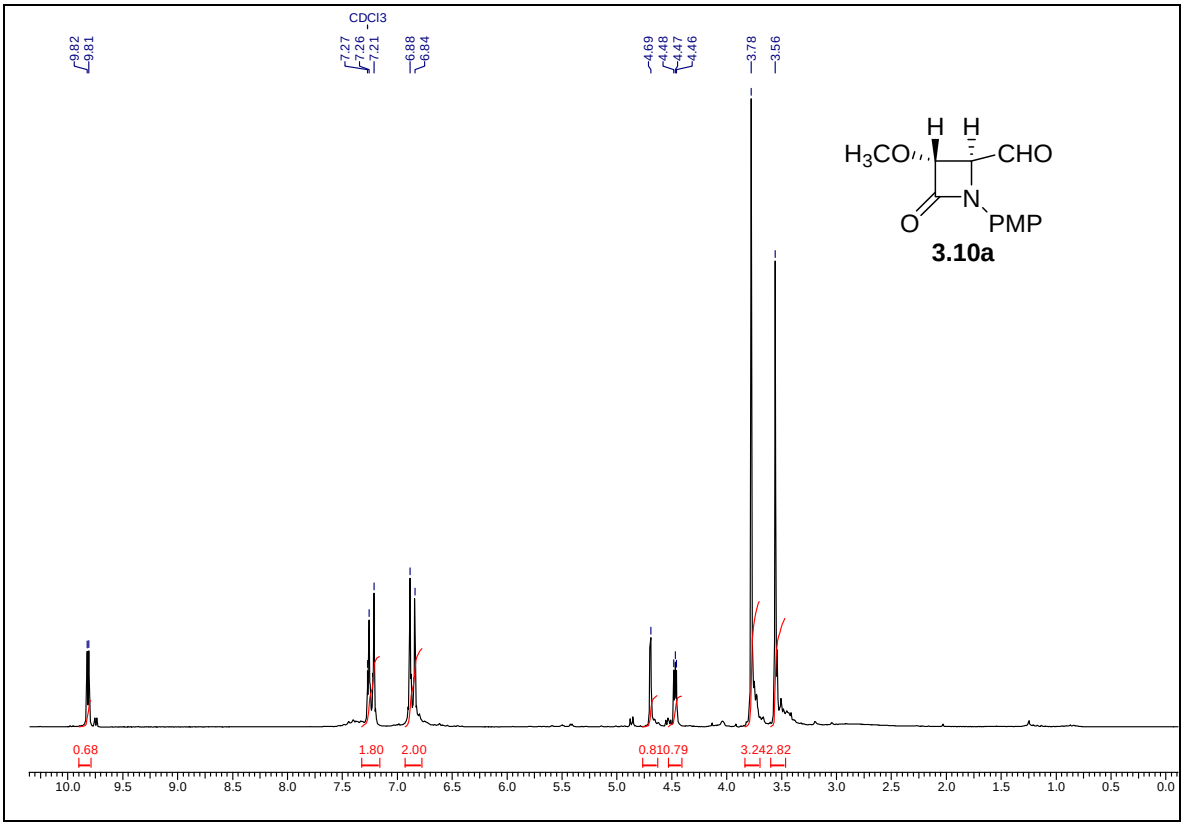
H
3.09b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CHO
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O
PMP
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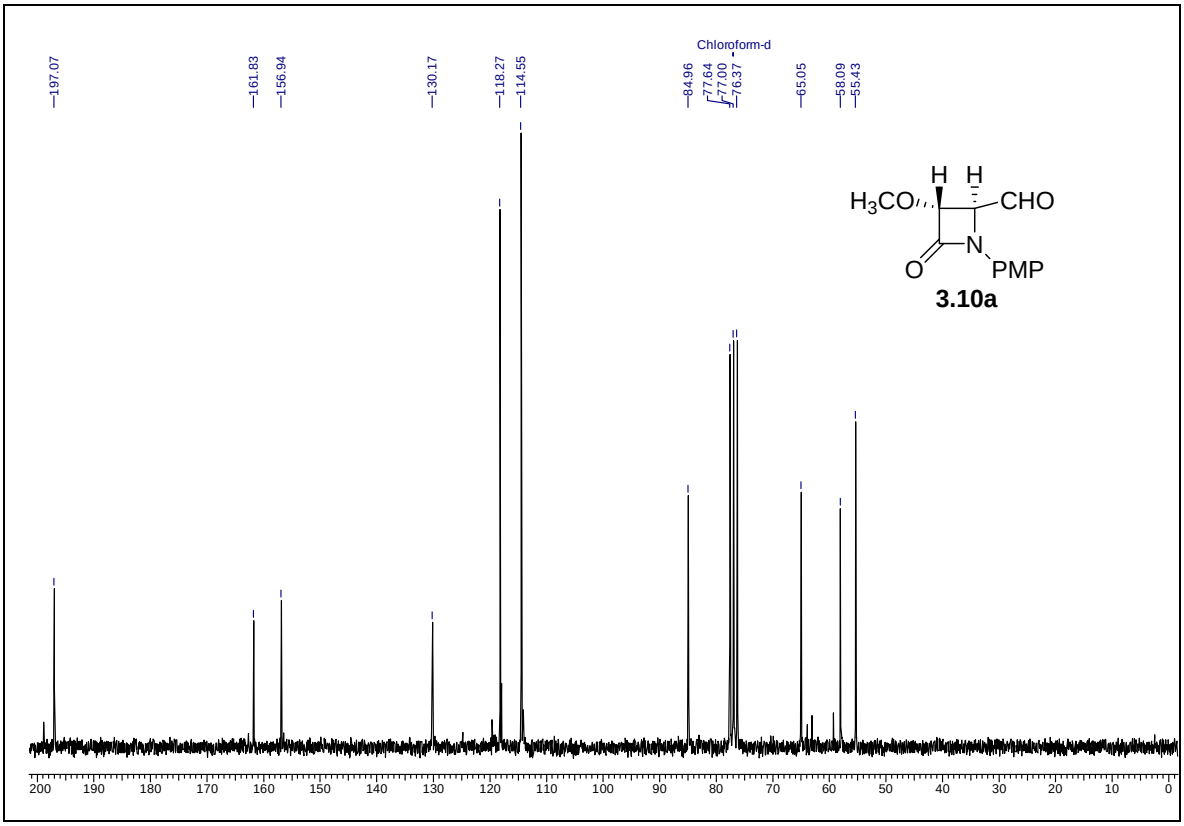
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CHO
N
O
PMP
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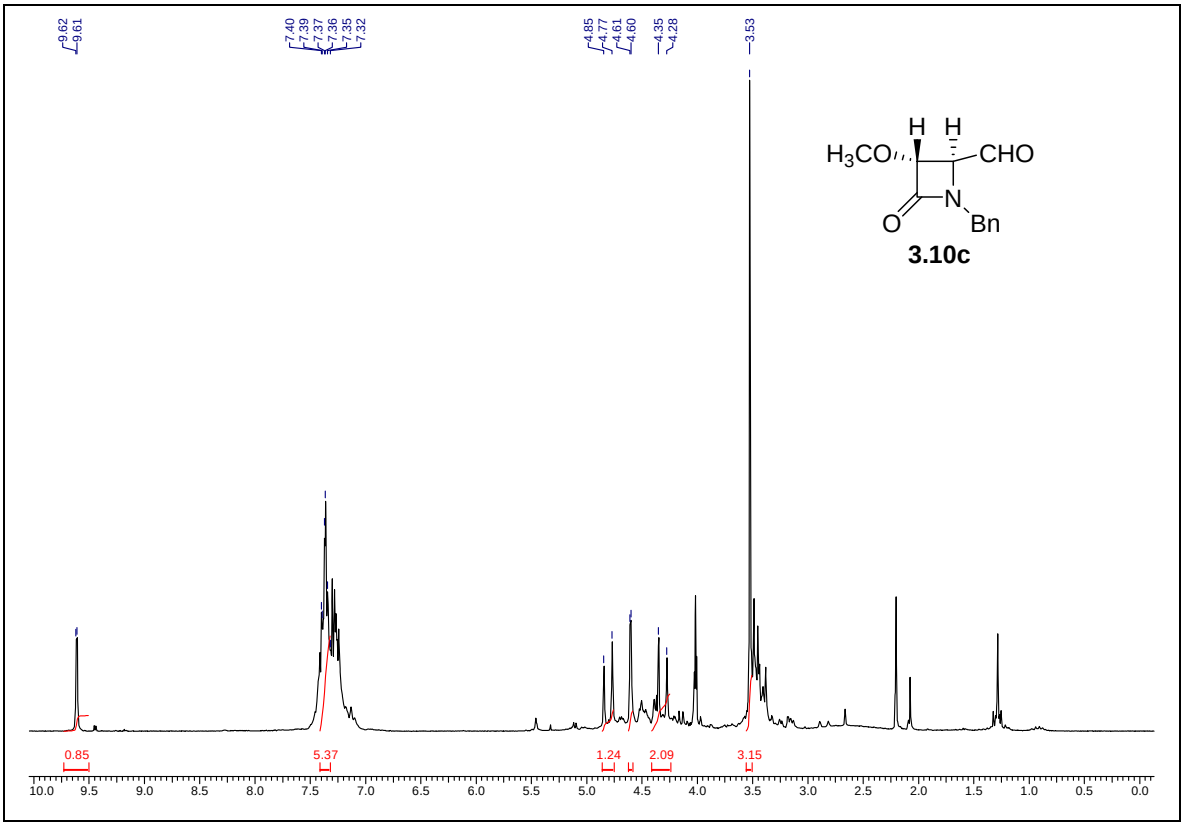
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4.35
4.28
3.53
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H
H3CO
CHO
O
N
Bn
3.10c
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5.37
1.24
2.09
3.15
10.0
9.5
9.0
8.5
8.0
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7.0
6.5
6.0
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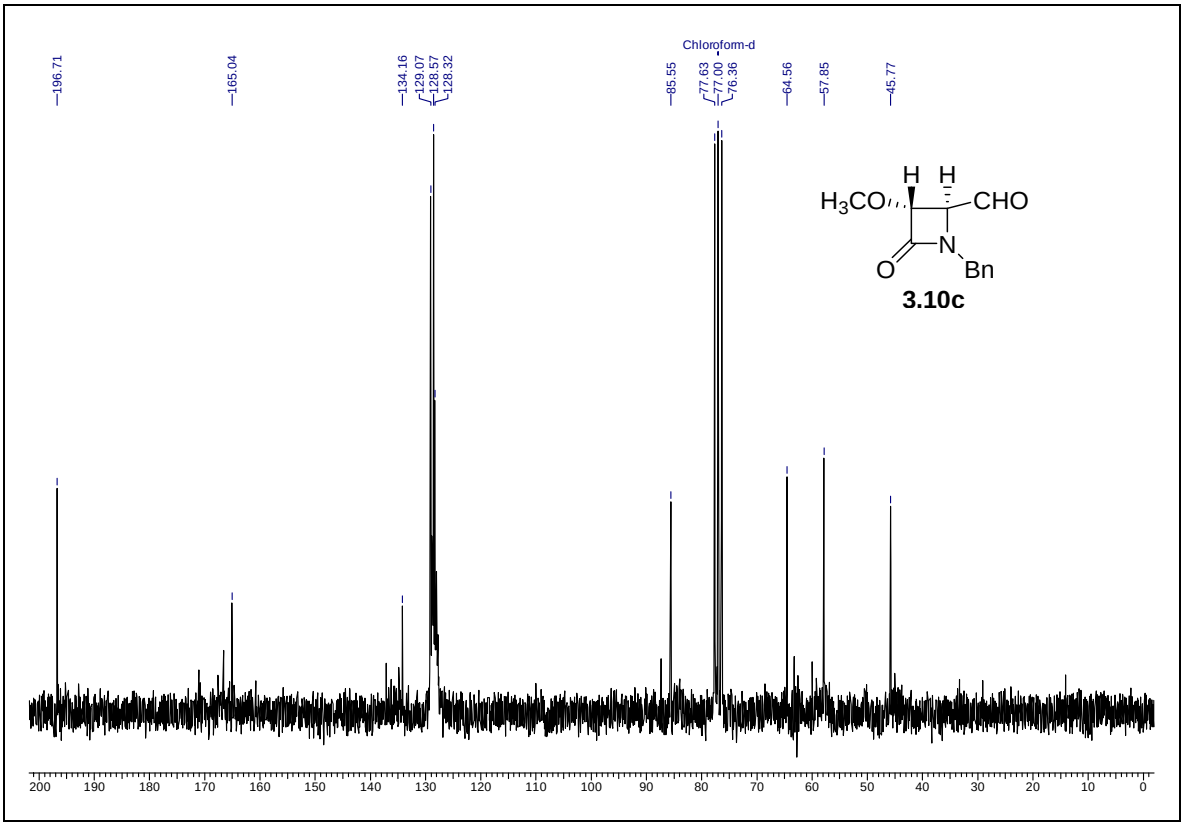
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H
H3CO
CHO
O
N
Bn
3.10c
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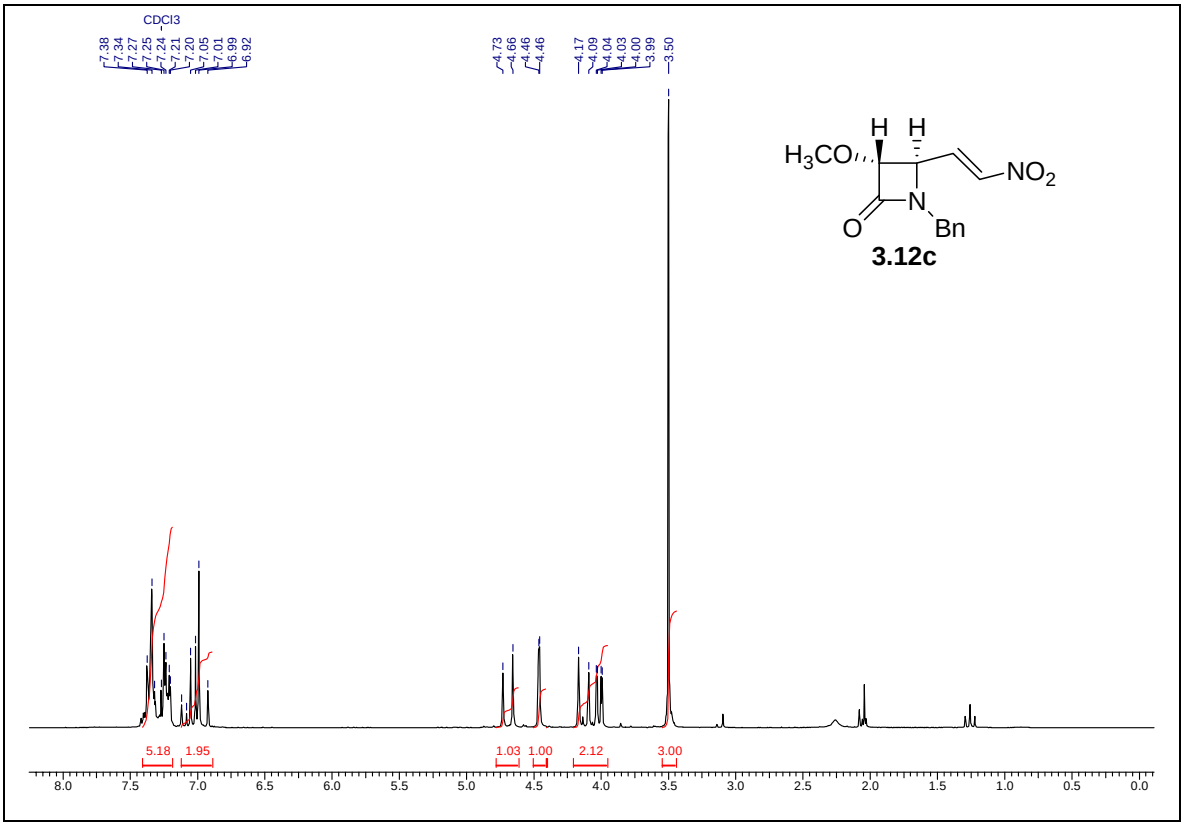
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4.46
4.46
4.17
4.09
4.04
4.03
4.00
3.99
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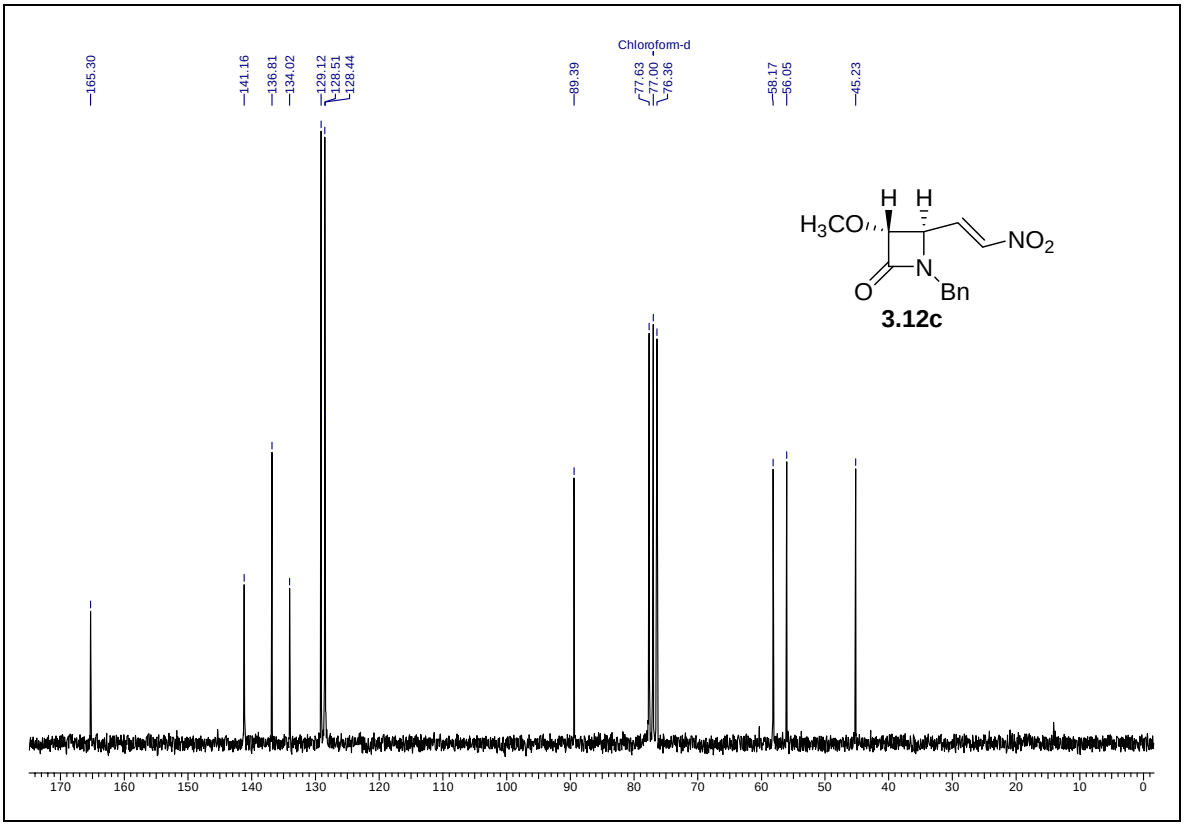
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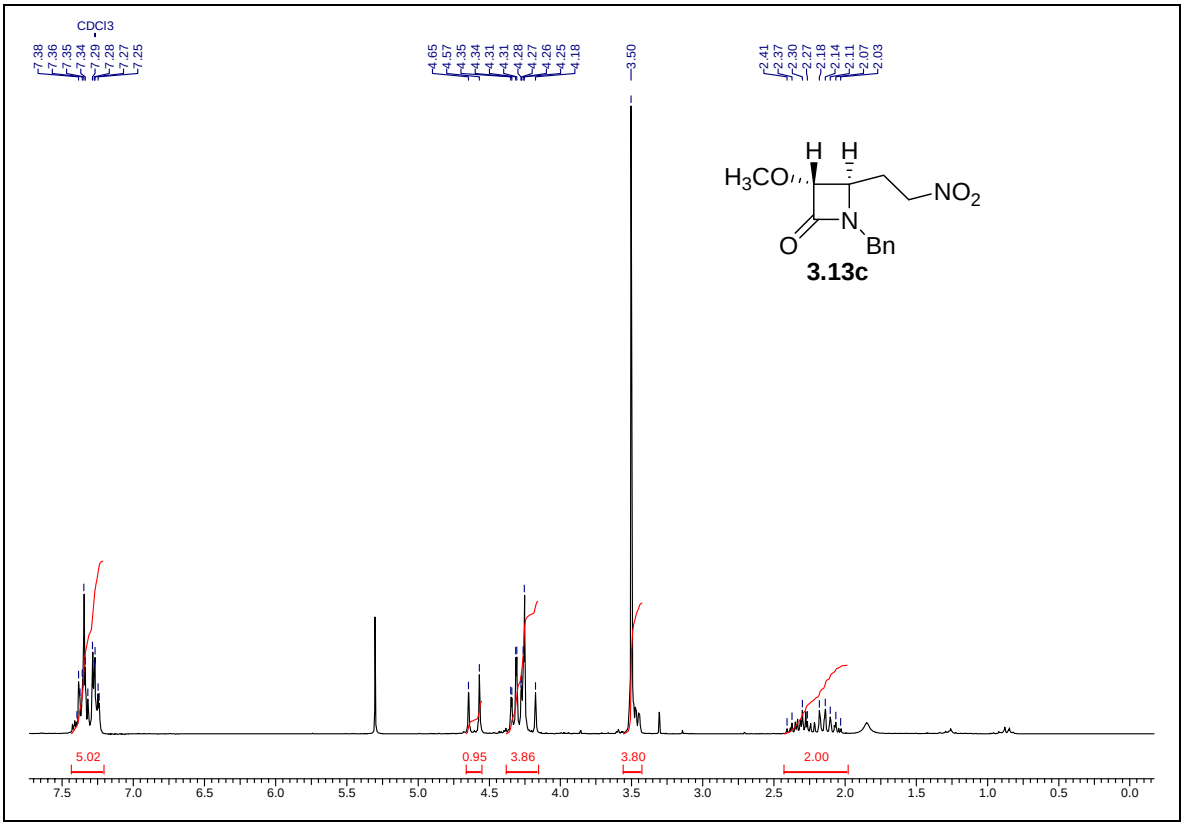
H3CO
NO2
N
O
Bn
3.12c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2.18
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2.11
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Bn
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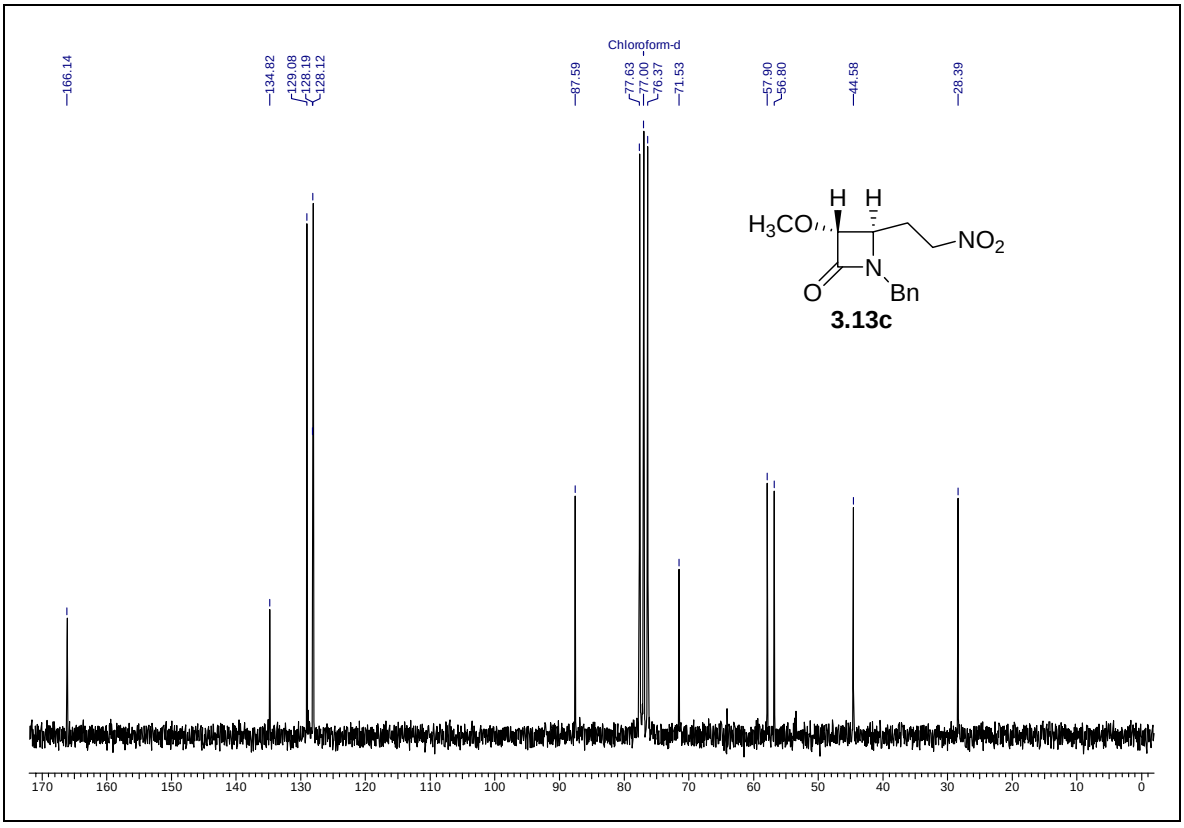
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NO2
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O
Bn
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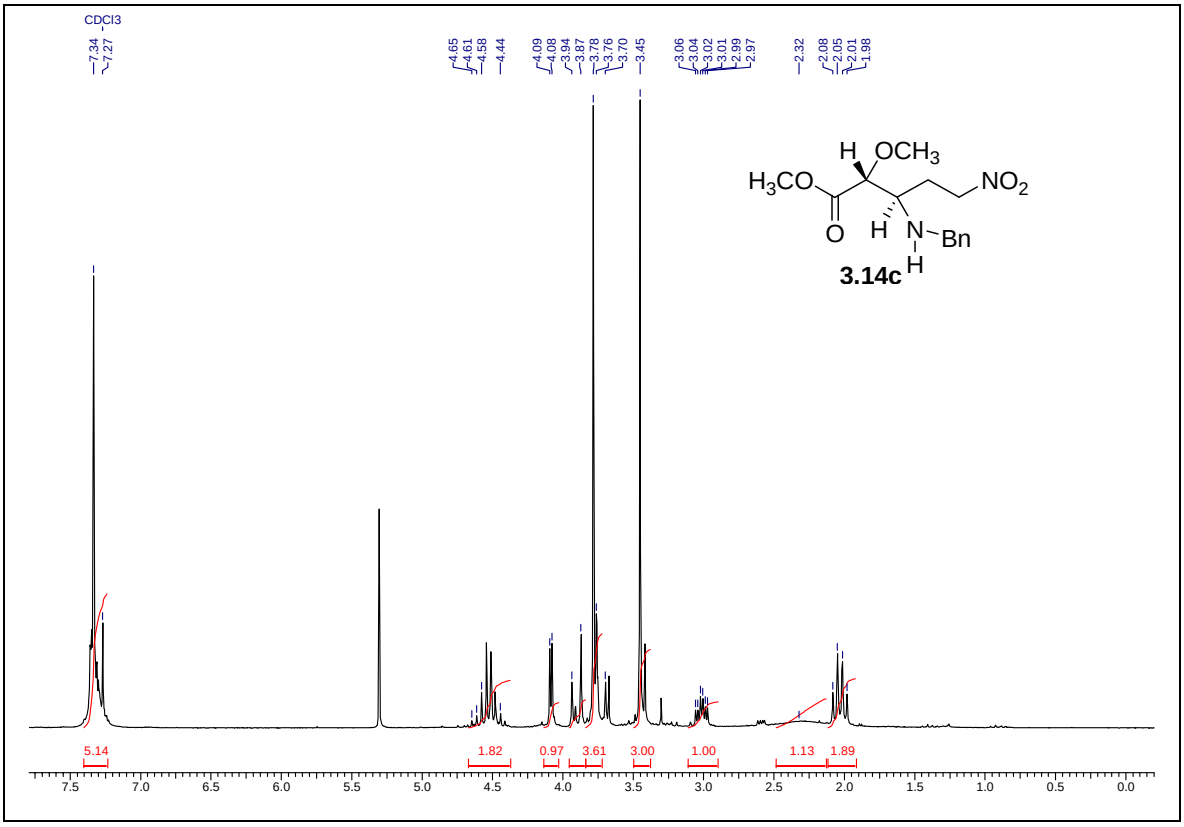
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3.70
3.45
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3.04
3.02
3.01
2.99
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2.32
2.08
2.05
2.01
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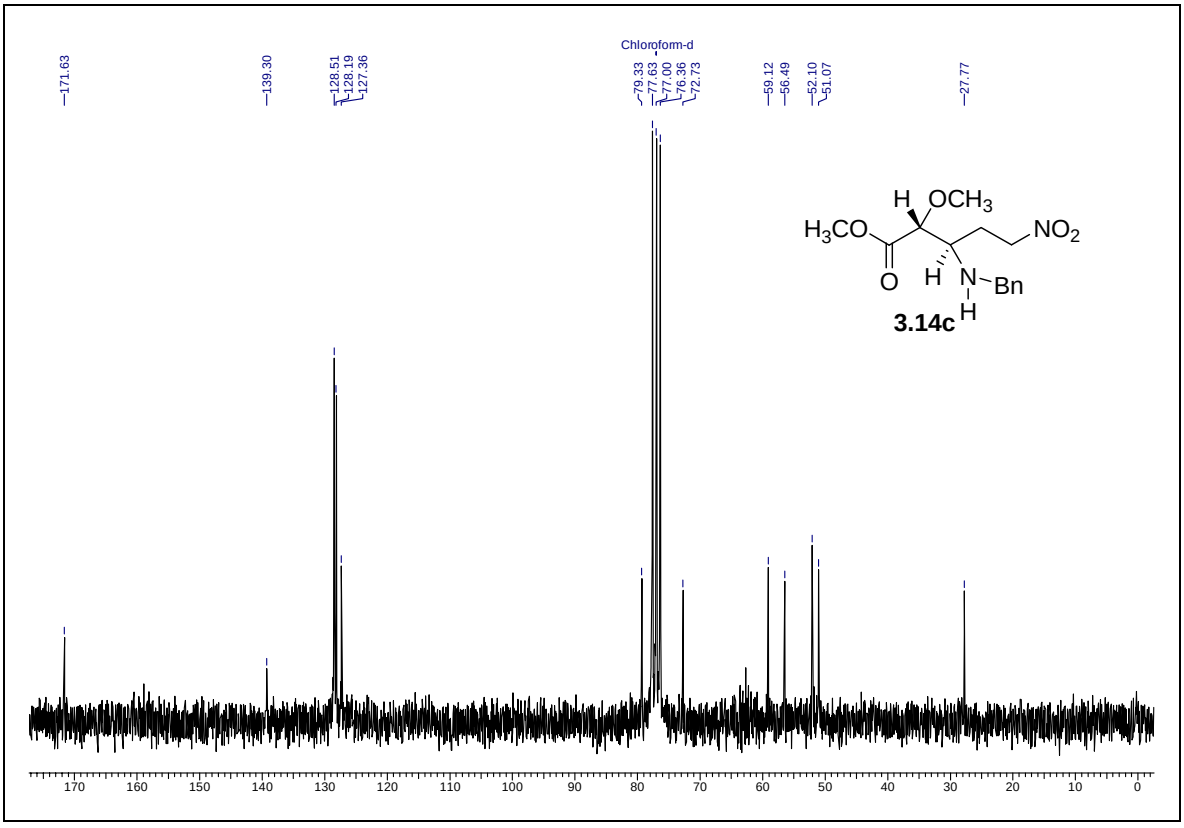
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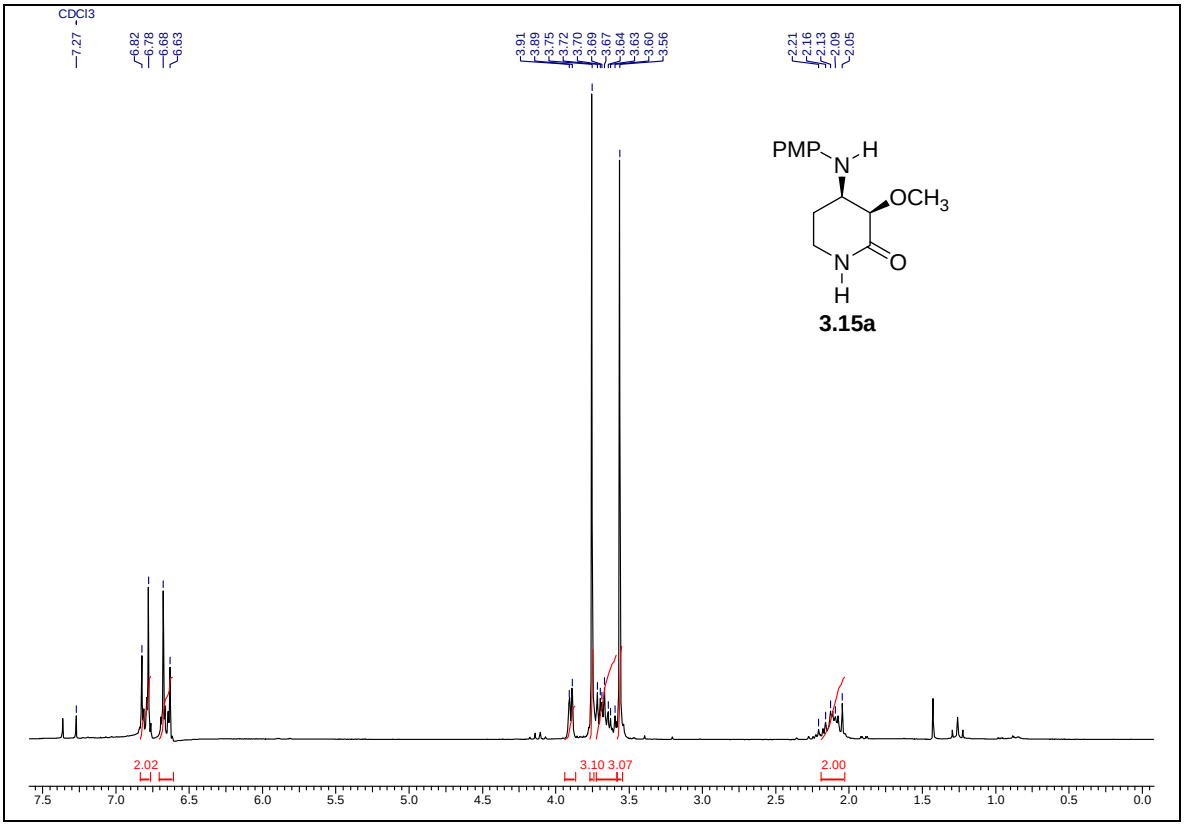
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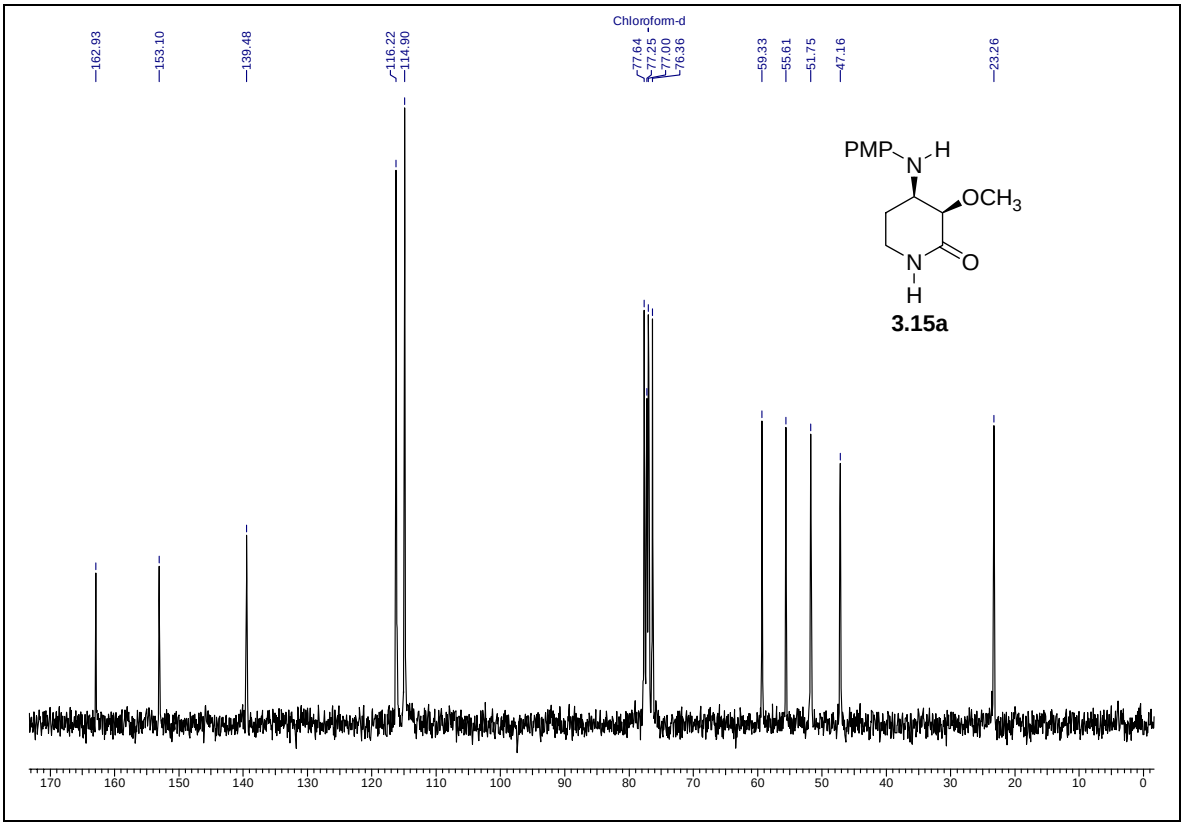
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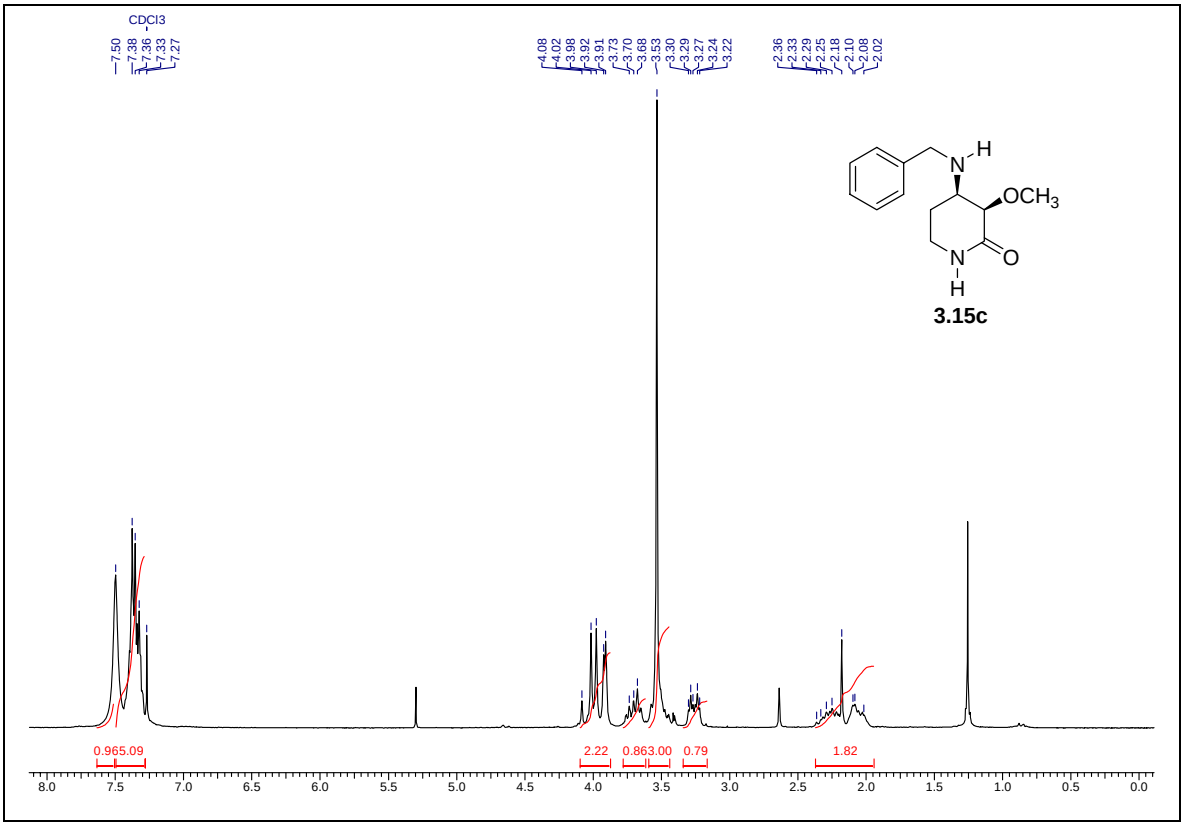
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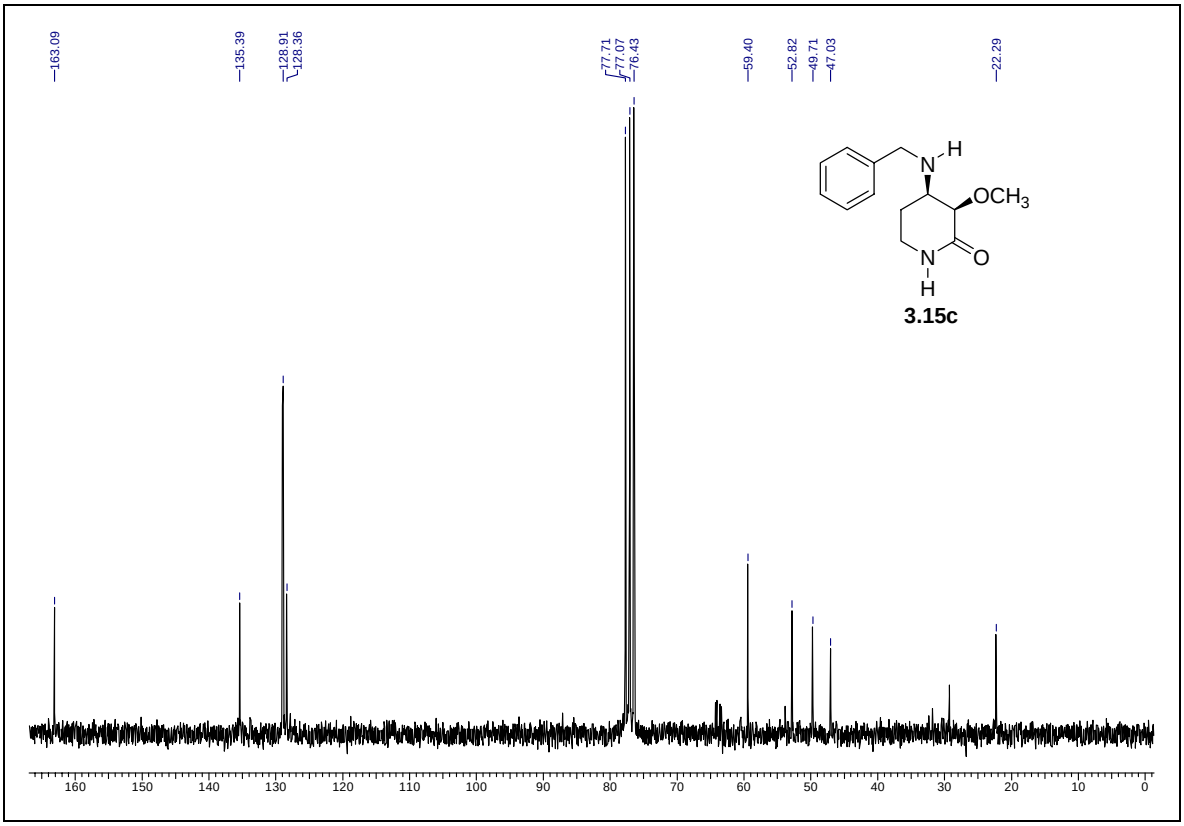
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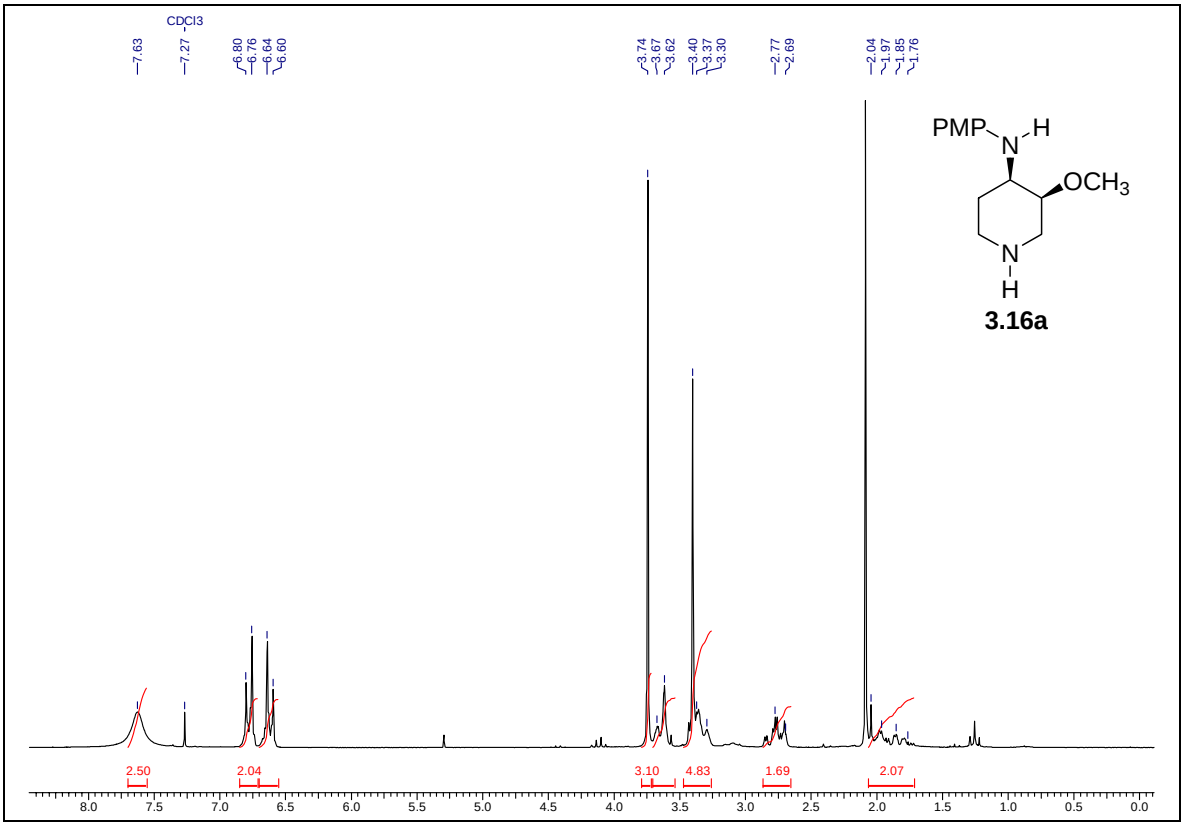
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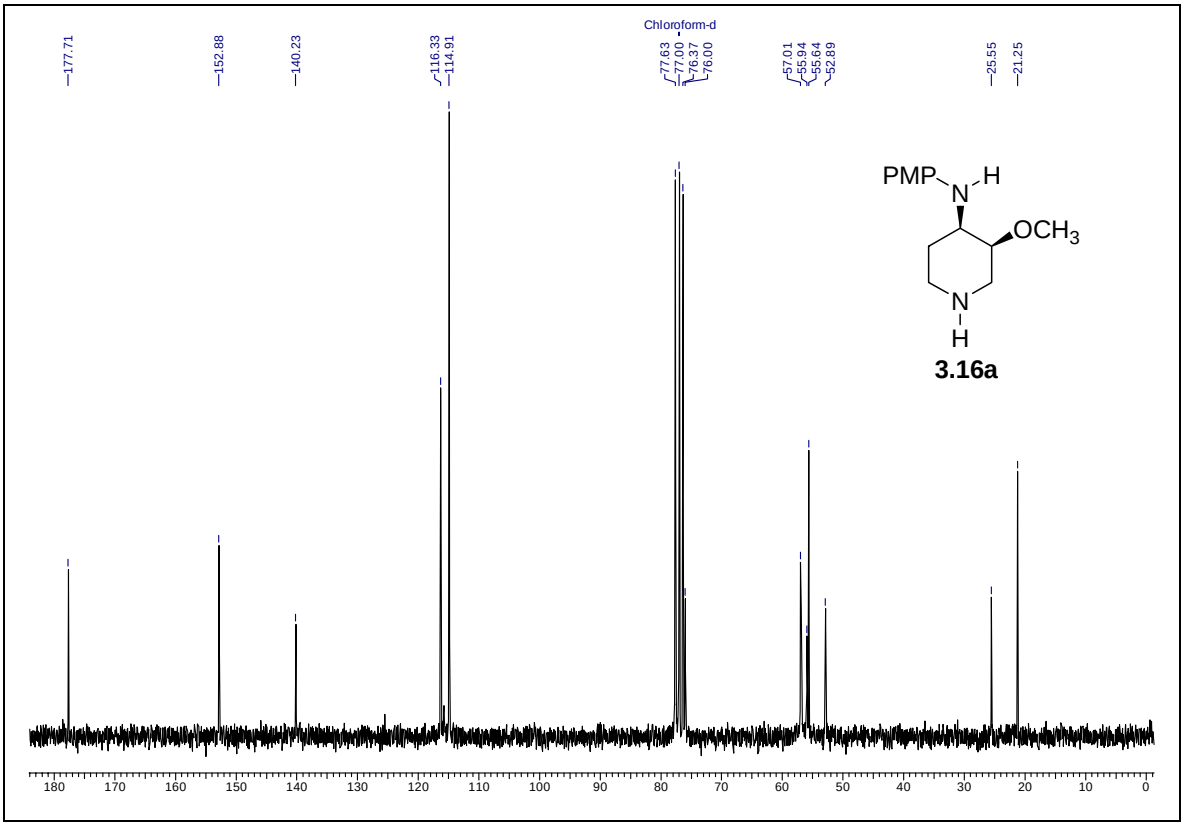
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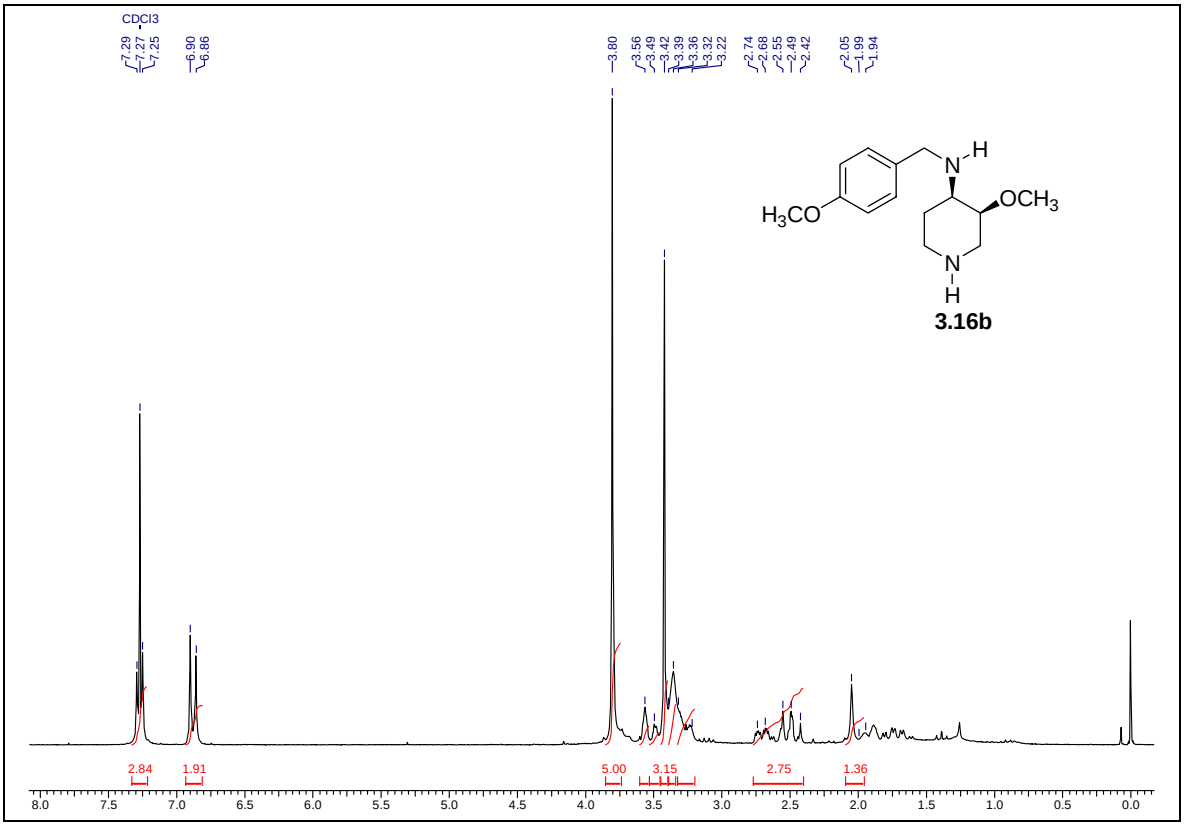
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OCH3
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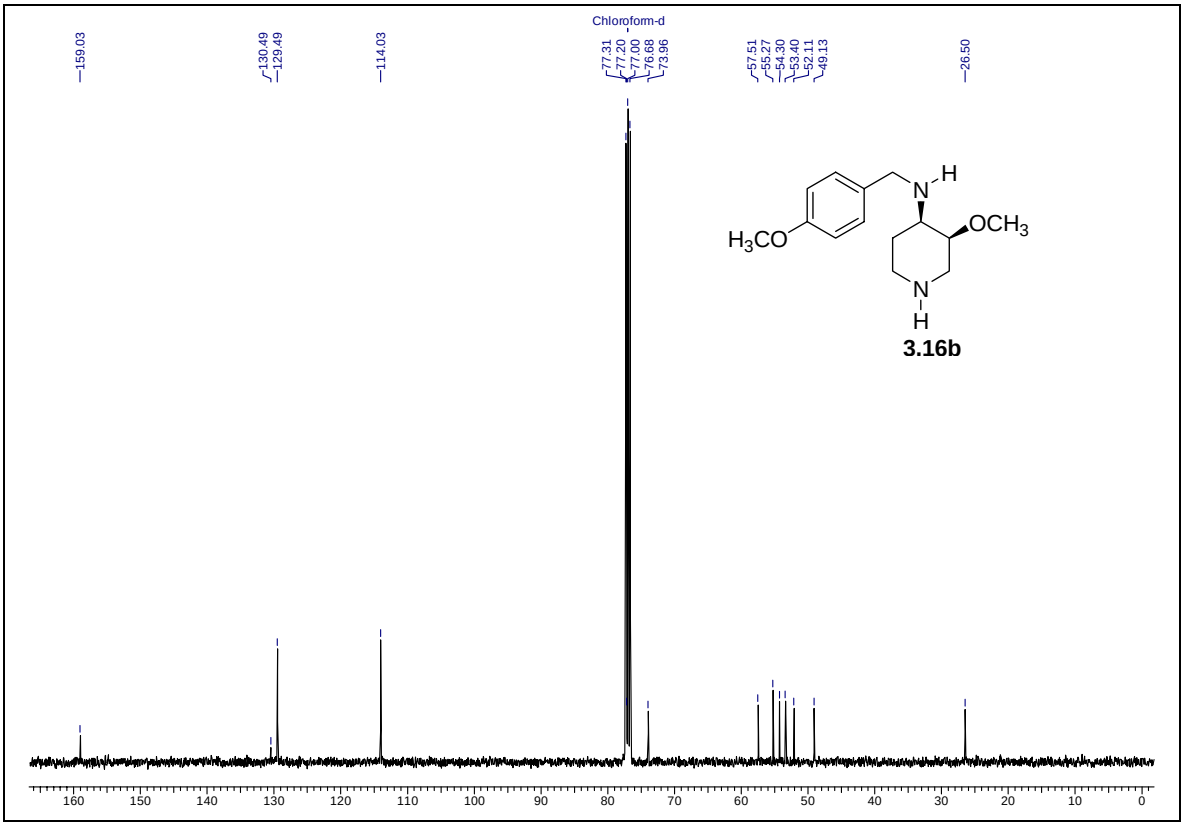
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26.50
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H
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OCH3
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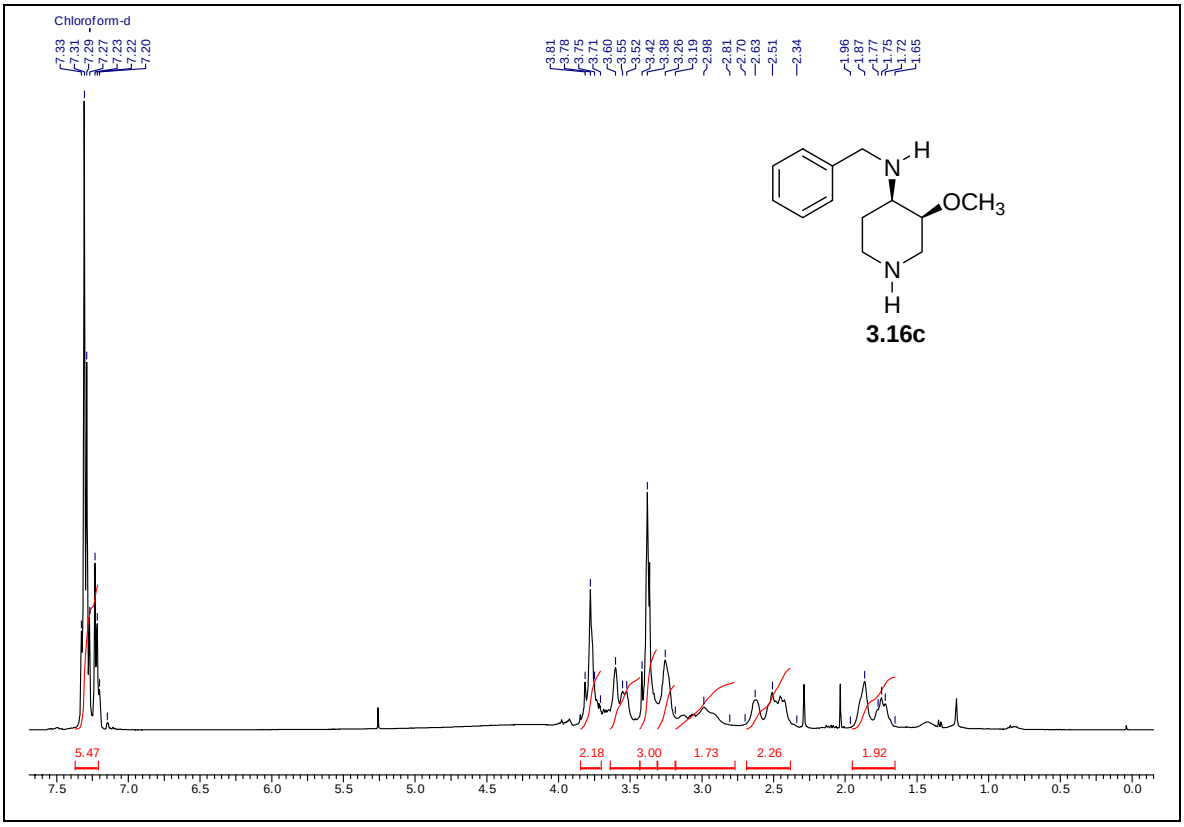
3.16b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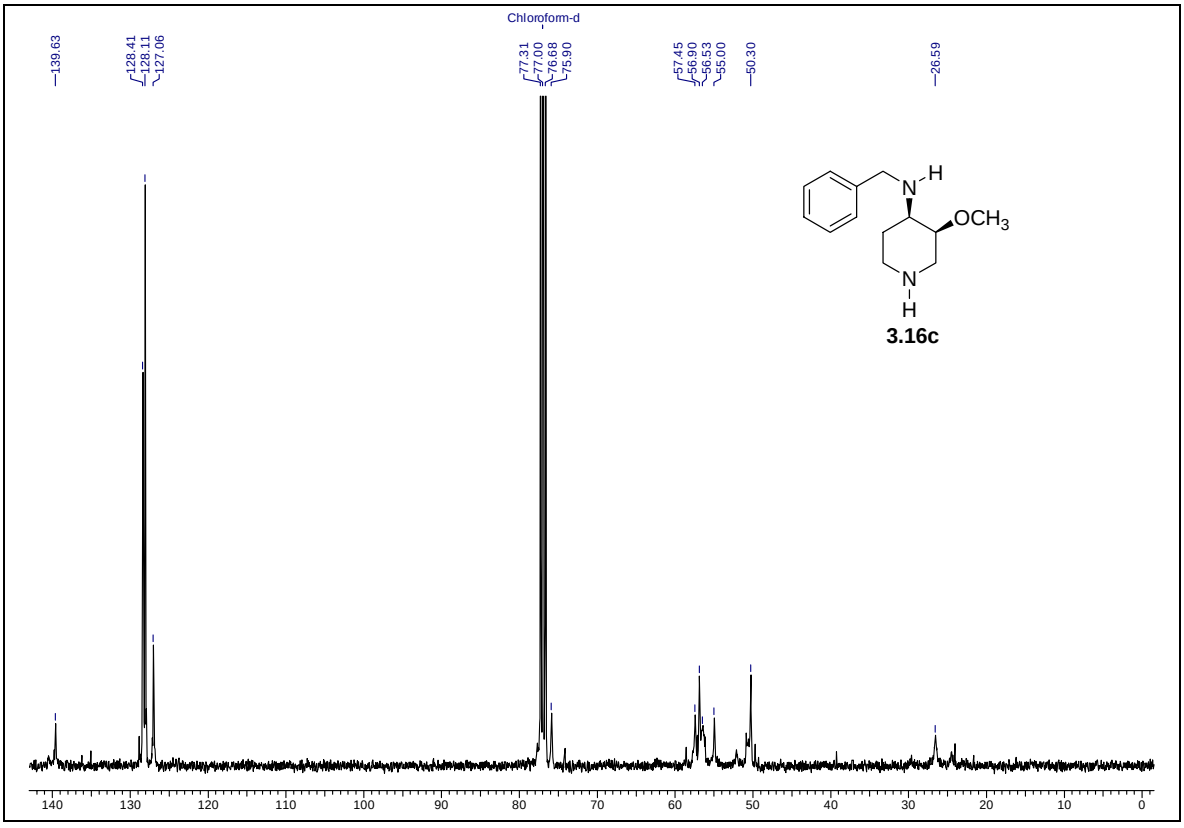
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26.59
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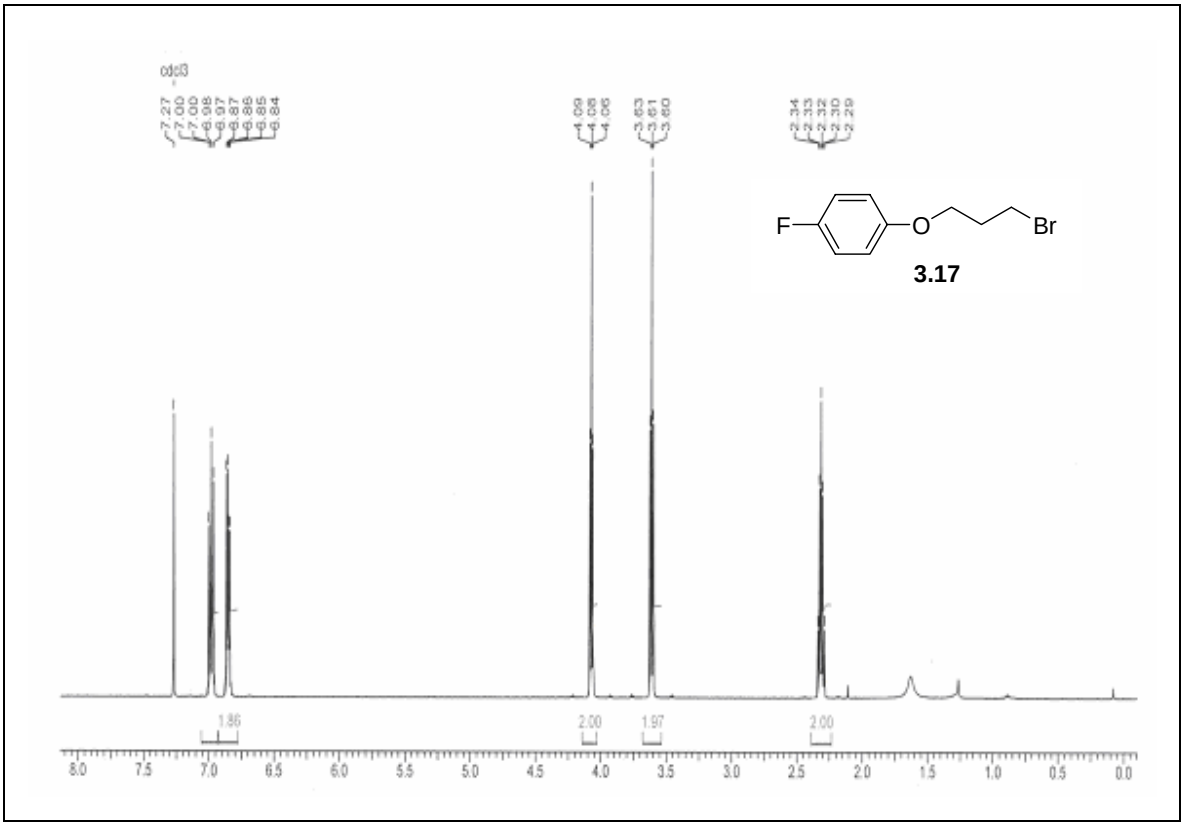
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2.0
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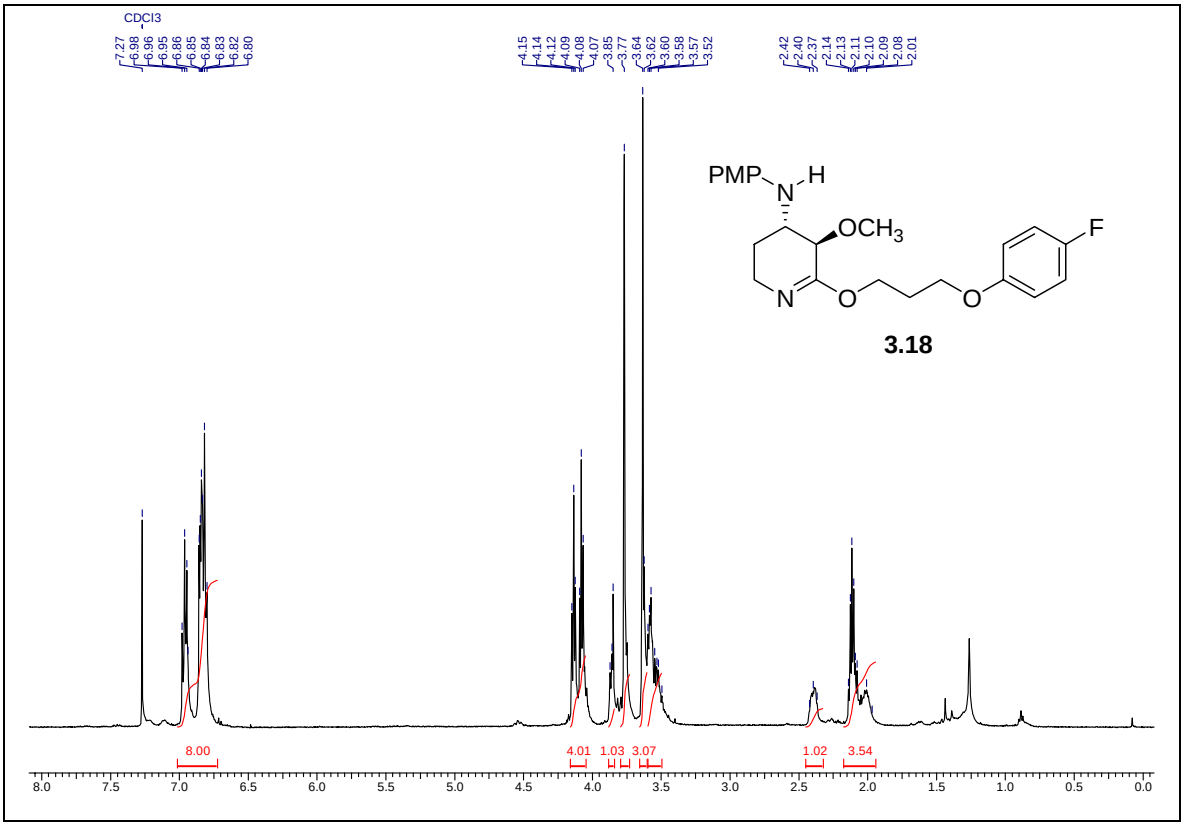
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3.77
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3.60
3.58
3.57
3.52
2.42
2.40
2.37
2.14
2.13
2.11
2.10
2.09
2.08
2.01
PMP
N
H
OCH3
F
N
O
O
8.00
4.01
1.03
3.07
1.02
3.54
8.0
7.5
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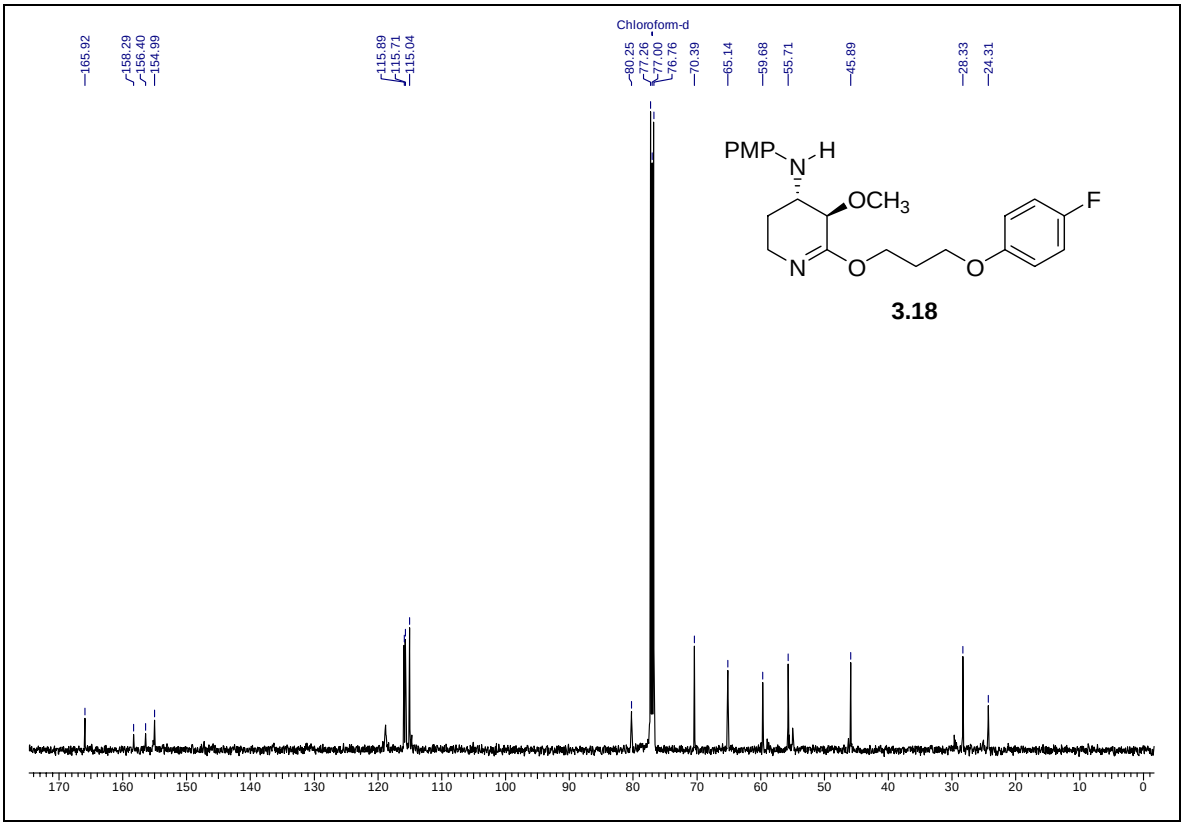
3.18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55.71
45.89
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PMP
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OCH3
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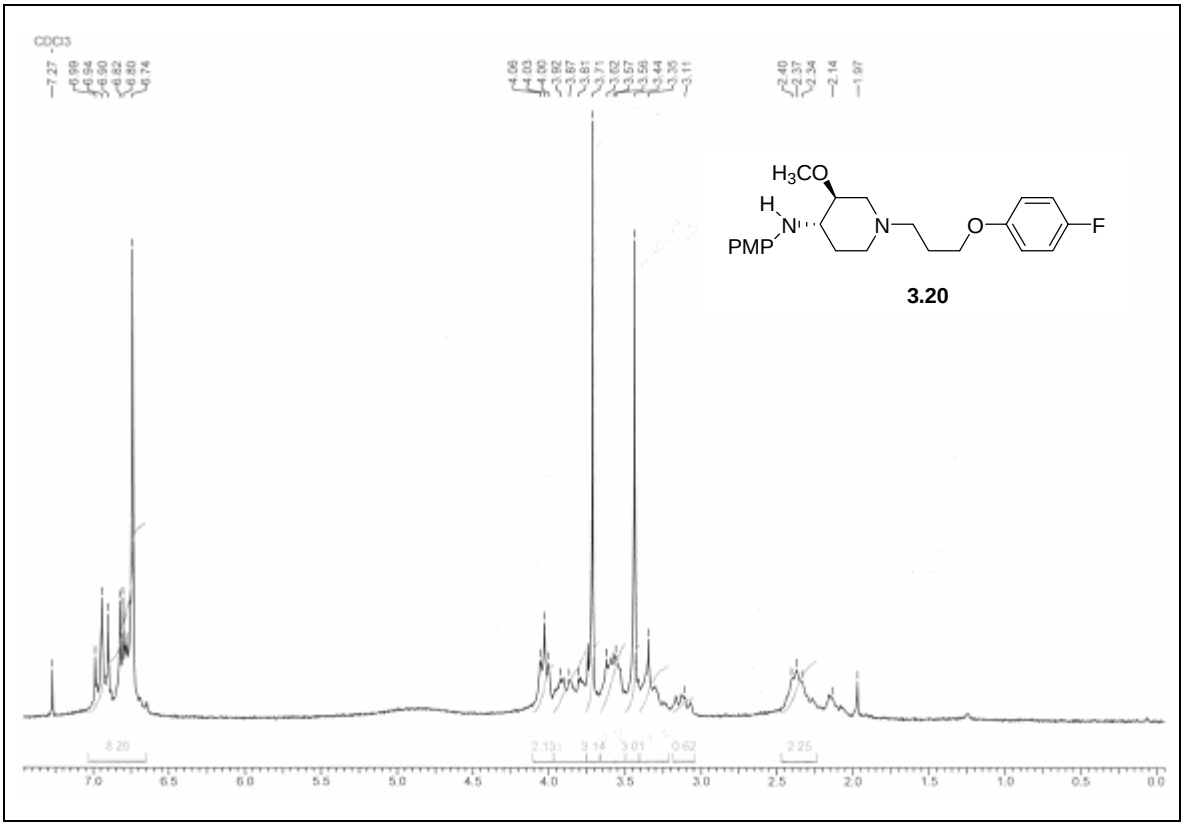
3.18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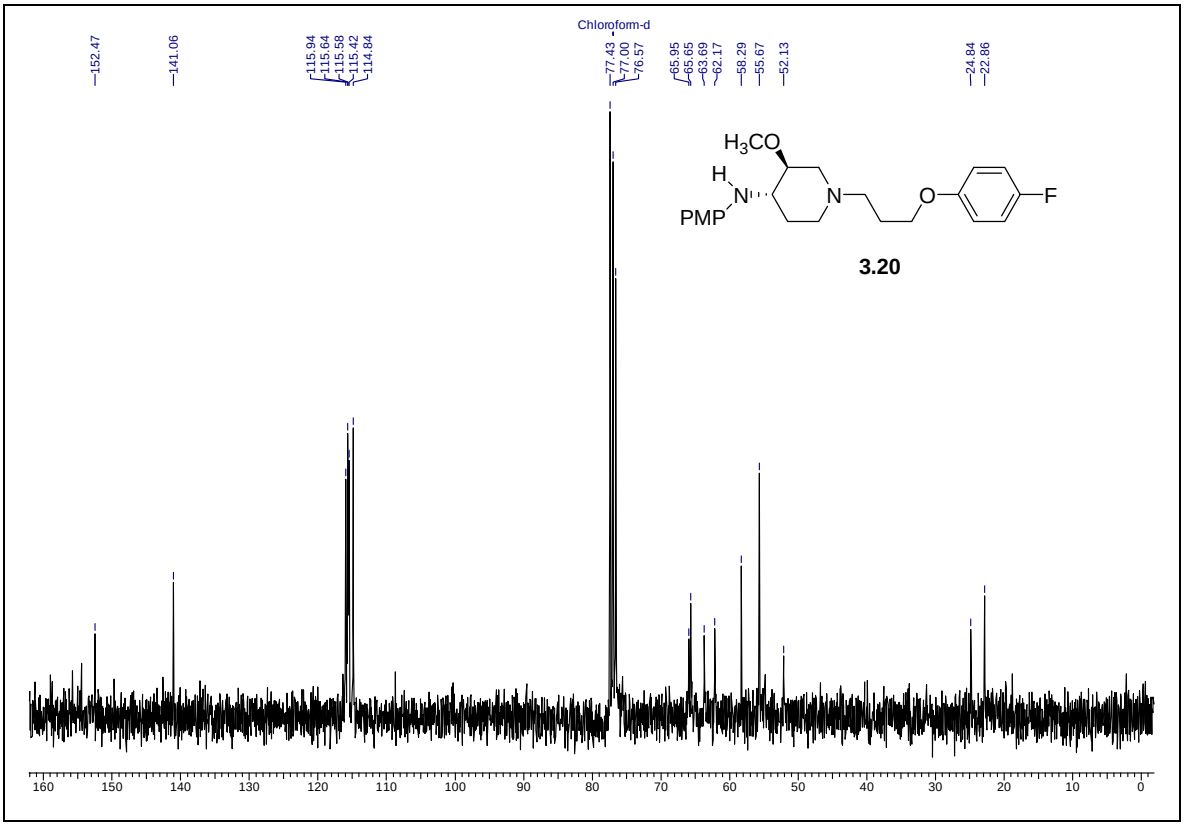
H
N
PMP
N
O
F
3.20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H
N
PMP
N
O
F
3.20

Chapter IV

Stereoselective synthesis of new β-lactam derivatives from D-glucose derived chiral pools.

4.1 Introduction:

Carbohydrates have been extensively exploited as chiral source in asymmetric organic synthesis. This is mainly because they have well defined multiple stereocentres and also they are available in large quantities in optically pure form. Application of carbohydrate derived chiral auxillaries for asymmetric synthesis of β-lactams is a recently developed area. We have been working in this area for the last couple of years and it has been found that D-glucose derived chiral aldehyde, a chiral imine precursor showed high levels of stereoselectivity in formation of azetidin-2-ones in [2+2] cycloaddition reaction with ketenes.[1] The carbohydrate derived chiral pools have been used in the synthesis of antibiotic such as thienamycin and its analogues.[2,3,4] The fused bicyclic and polycyclic structural frameworks with β-lactam unit represent important substructures in many antibiotics. Therefore, asymmetric synthesis of fused bicyclic/polycyclic β-lactams using D-glucose was the major objective of this research. With this goal in mind we decided to synthesize new β-lactam derivatives from D-glucose and further use them as synthons for the synthesis of polycyclic β-lactams.

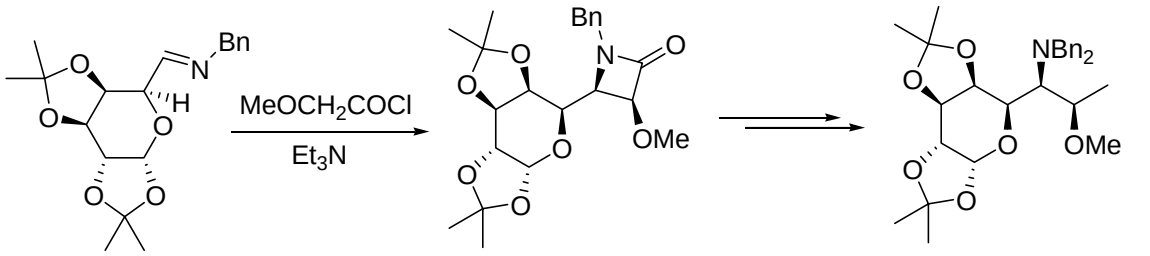
4.2: Background for the present work:

Carbohydrates and related polyhydroxy compounds have attracted considerable attention and increasing interest as chiral starting materials in the ex-chiral pool synthesis of chiral drugs and natural products.[5] The use of carbohydrates in the asymmetric synthesis of β-lactams has become well established and considerable amount of work has been done on sugar derived imines for β-lactam ring construction.

Bose and Manhas[6] have reported successful utilization of chiral imines derived from carbohydrates in the asymmetric Staudinger reaction. They synthesized different chiral auxiliaries derived from sugars and employed them as chiral imine components. These chiral imines proved to be very efficient, providing a high level of diastereoselectivity (de >90%) in all cases. They have mainly used these β-lactams as chiral synthons rather than as a chiral pool and have utilized the carbohydrate skeleton for the synthesis of important natural products.

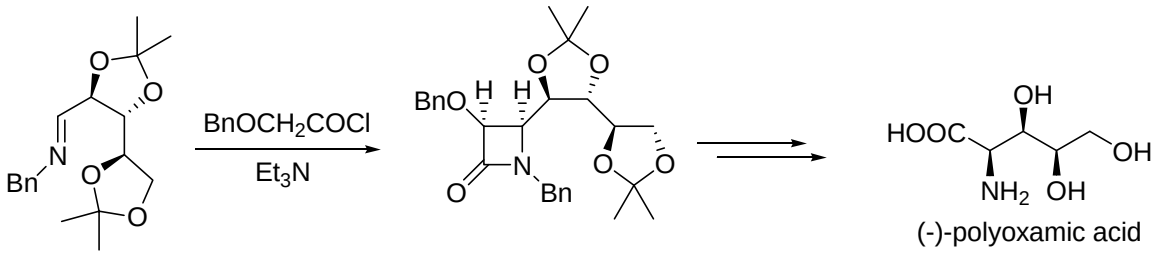
A single *cis*-diastereomer was obtained from the reaction of D-galactopyranose derived chiral imine and methoxy-ketene. On further synthetic transformation this isomer was converted into 6-*epi*-lincosamine[7] (Scheme 4.01)

Scheme 4.01



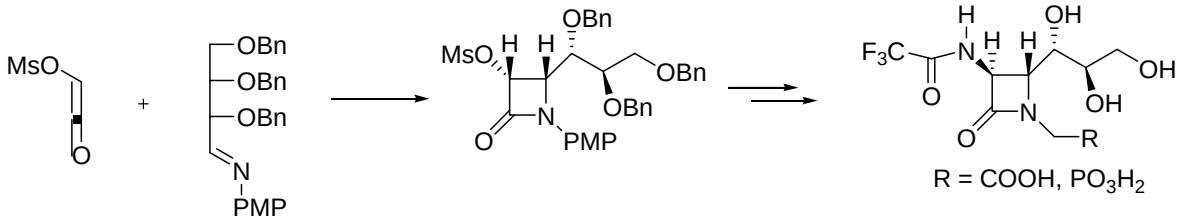
Similarly, the cycloaddition reaction of benzyloxyketene with the imine provided *cis*-β-lactams with complete control of diastereoselectivity. On further chemical transformations it was possible to synthesize (-)-polyoxamic acid, an antipode of natural (+)-polyoxamic acid[8] (Scheme 4.02).

Scheme 4.02



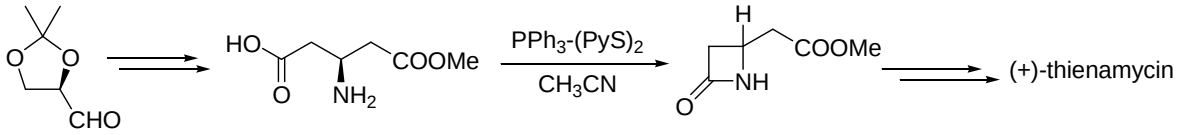
Recently, Stortz et al. have reported the use of D-erythrose derived imines for the synthesis of 2,3-dideoxy-D-mannonic acid derivatives[9] (Scheme 4.03).

Scheme 4.03



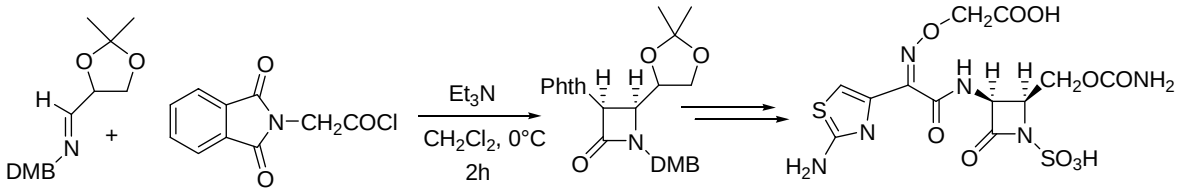
The (*R*)-glyceraldehyde acetonide prepared from D-mannitol has been converted into a β-amino ester, which on cyclization with 2,2'-dipyridyl disulphide and triphenylphosphine gave 3-unsubstituted β-lactam. This β-lactam has been converted into (+)-thienamycin antibiotic in several steps[2] (Scheme 4.04).

Scheme 4.04



The imine derived from L-(-)-glyceraldehyde and 2,4-dimethoxybenzylamine underwent Staudinger reaction with phthalimidoacetyl chloride to afford the corresponding 3-Phth substituted β-lactam, which is a key intermediate in the synthesis of carumonam antibiotics[10] (Scheme 4.05).

Scheme 4.05



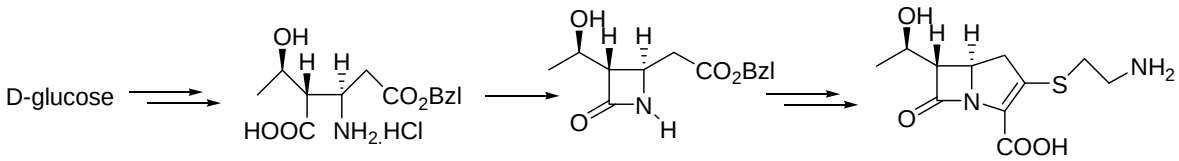
DMB = 2,4-dimethoxybenzyl

Phth = phthalimido

carumonam AMA 1080

The β-amino acid derived from D-glucose, on cyclization in the presence of DCC gave β-lactam, which was further converted into (+)-thienamycin antibiotic in several steps[3] (Scheme 4.06)

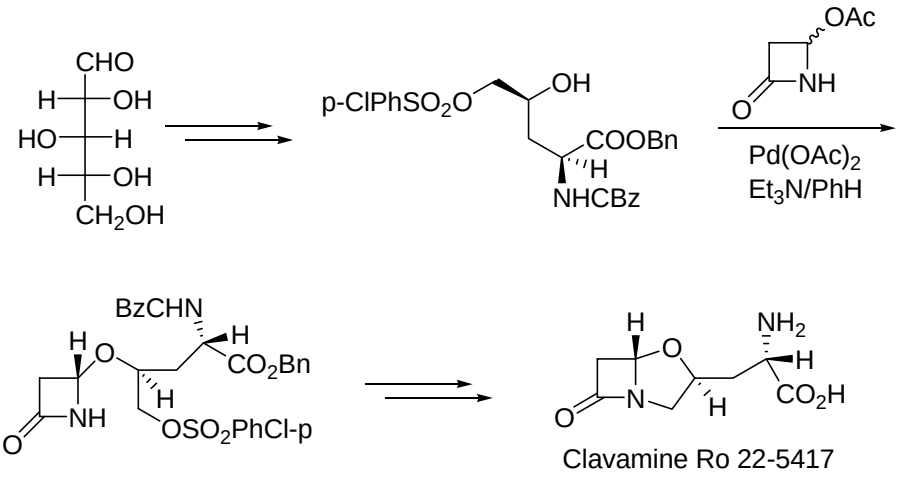
Scheme 4.06



(+)-thienamycin

A chiral amino alcohol derived from D-xylose was coupled with racemic 4-acetyloxy-*N*-unsubstiuted-β-lactam in the presence of palladium acetate–Et_3N to give diastereomeric 70:30 mixture of β-lactams in 65% yield. The major isomer has been converted to the antibiotic clavamine Ro 22-5417[11] (Scheme 4.07).

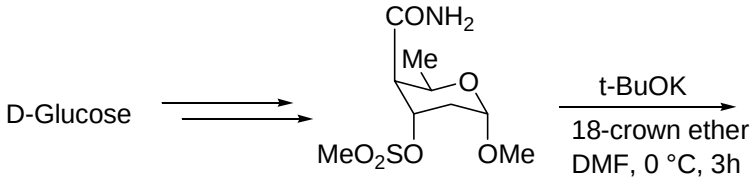
Scheme 4.07

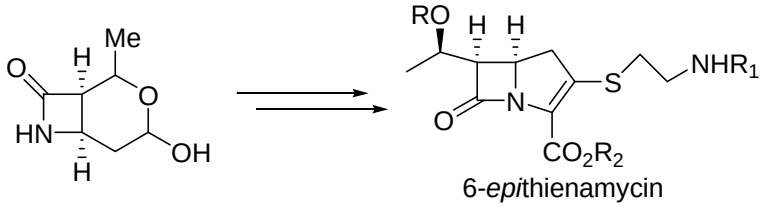


Clavamine Ro 22-5417

The amide derived from D-glucose has been cyclized in the presence of potassium *tert*-butoxide, to give bicyclic β-lactams in 45% yield. This bicyclic β-lactam has been transformed into 6-*epi*thienamycin in a multi-step process[4] (Scheme 4.08).

Scheme 4.08

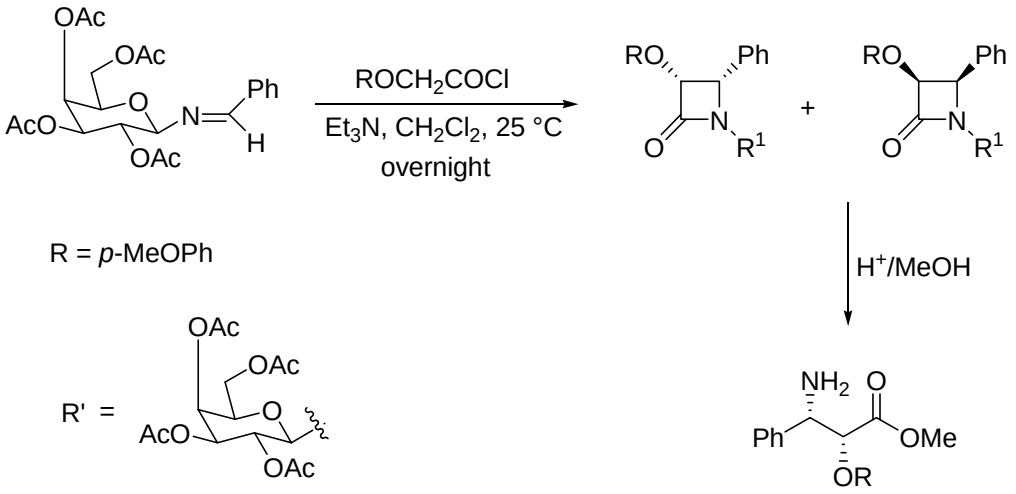




6-*epi*thienamycin

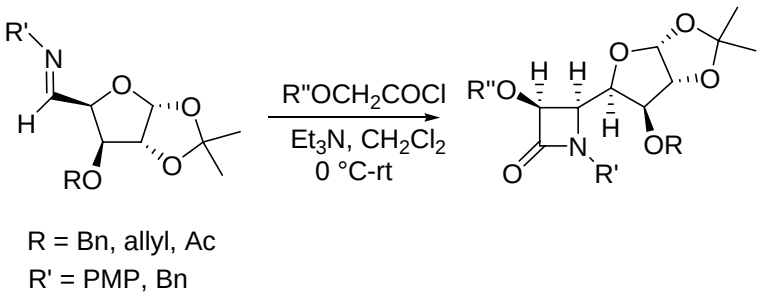
Georg et al. have used the chiral imine derived from 2,3,4,6-tetra-*O*-acetyl-β-D-galactose amine for disatereoselective synthesis of β-lactams. They obtained a 60:40 diastereomeric mixture of β-lactams in 90% yield. The α-isomer is transformed to β-amino ester, which is used as a building block for the synthesis of side chain of anticancer agent taxol[12] (Scheme 4.09).

Scheme 4.09



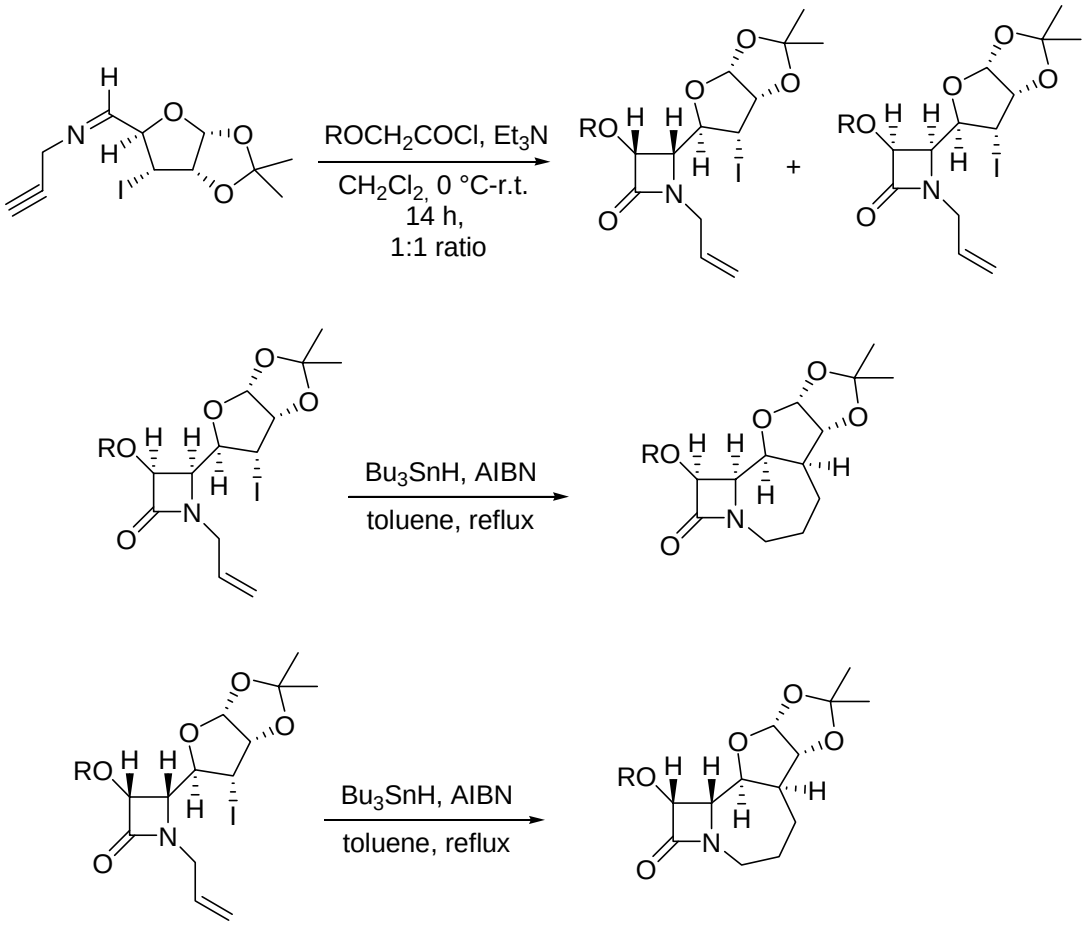
Arun et al.[1] have employed a D-glucose derived chiral aldehyde for the diastereospecific synthesis of *cis*-β-lactams in good yield using asymmetric Staudinger reaction (Scheme 4.10).

Scheme 4.10



Recently Jayanthi et al.[13] have converted D-glucose diacetonide derived iodo substituted imine into diastereomeric mixture of β-lactams. The α-diastereomer gave tetracyclic β-lactam in 20-30% yield by *endo-dig* mode of radical cyclization and the other β-diastereomer provied tetracyclic β-lactam in 30-40% yield by *exo-dig* mode of radical cyclization (Scheme 4.11).

Scheme 4.11



4.3: Present Work:

Carbohydrate derived chiral auxiliary have immense importance for the synthesis of β-lactams. As discussed in background for the present work some of these β-lactams have transformed into polycyclic β-lactams and new class of thienamycin. Therefore we have also decided to transform β-lactam derived from D-glucose diacetonide, to serve as a synthon for synthesis of polycyclic β-lactams and new class of carbapenems.

4.4: Results and Discussion:

4.4a: Synthesis of mono-*O*-alkylated–3-substituted azetidin-2-ones:

The cheaply available D-glucose (**4.01**), was converted to the corresponding glucose diacetonide derivative **4.02** on treatment with anhydrous $CuSO_4$ and catalytic amount of sulphuric acid in dry acetone.[14] The diacetonide formation could lead to the formation of two products, namely, the five-membered furanose and the six-membered pyranose. Formation of the former is favoured because in the furanoid form, glucose offers two suitably disposed vicinal diols for condensation. Also, fusion of a five membered acetal to a furanoid ring causes less strain as against a similar fusion to a pyranoid ring. The β-forms can be eliminated due to the *anti* conformation of the two-hydroxyl groups.

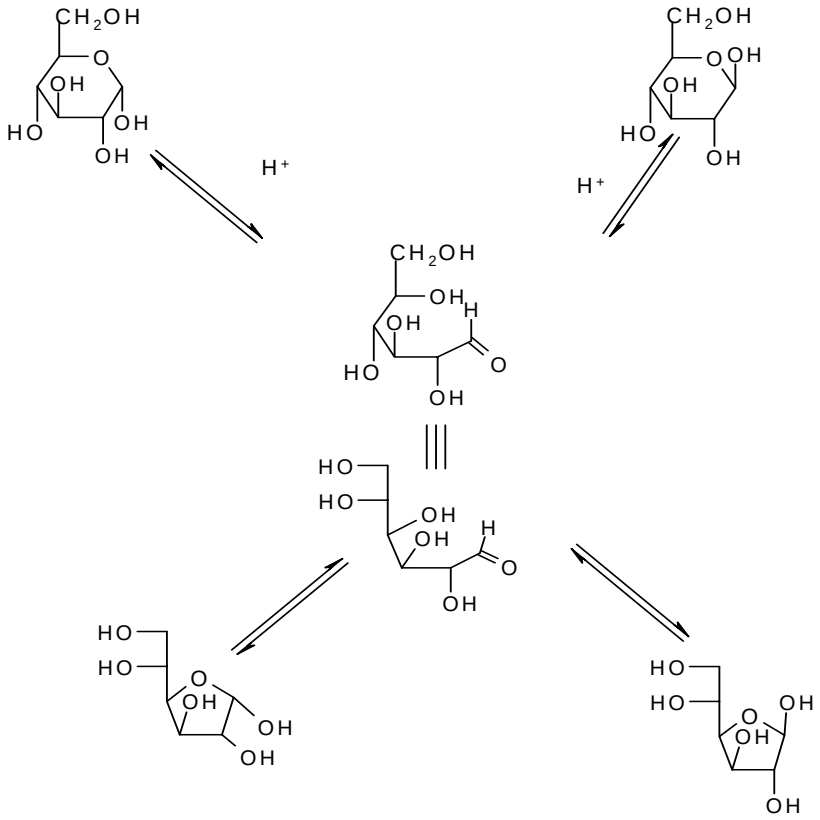
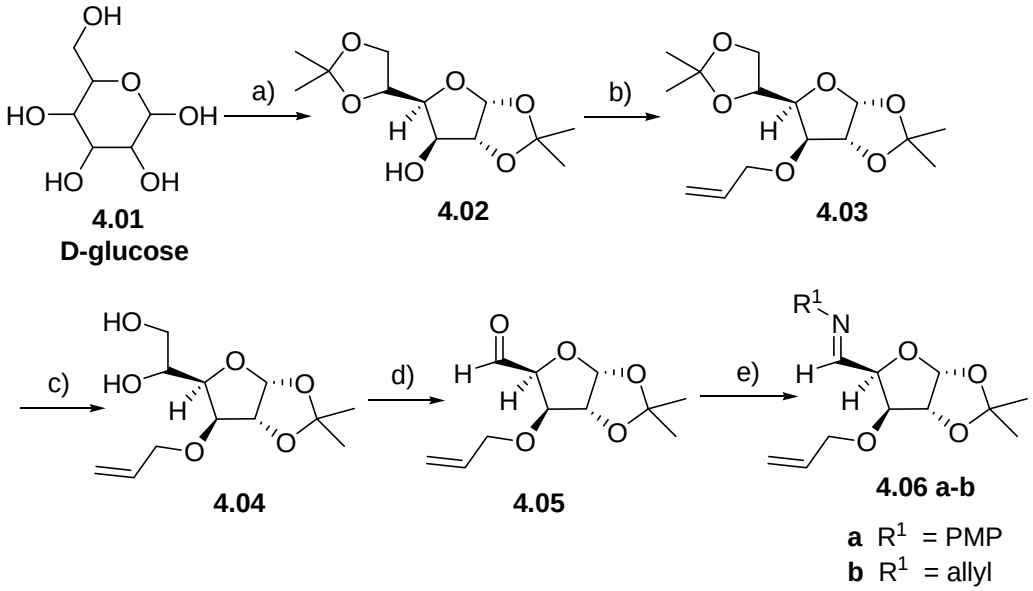


Figure 1

The glucose diacetonide **4.02** on alkylation using allyl bromide and NaOH as a base in CH_2Cl_2 for 24 h gave *O*-allyl glucose diacetonide **4.03** in 90% yield.[1,15] Selective deprotection of the primary acetonide moiety using 75% AcOH in water at 75 °C for 3 h afforded diol **4.04**. The diol **4.04** on oxidative cleavage using 0.65 M aqueous solution of

$NaIO_4$ and silica gel[16] provided the desired *O*-allyl aldehyde **4.05** in 93% yield (Scheme 4.12).

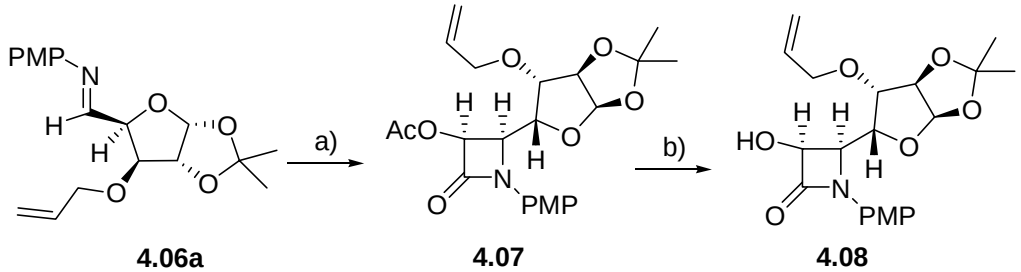
Scheme 4.12



Reagents and conditions: a) $CuSO_4$, acetone, H_2SO_4, 48 h, 50%; b) aq. NaOH, Allyl bromide, TBAB, CH_2Cl_2, 24 h, 90%; c) 75% AcOH in H_2O, 75 °C, 3 h, 84%; d) 0.65 M $NaIO_4$, CH_2Cl_2, 30 min 1.5 h, 93%; e) R^1-NH_2, CH_2Cl_2, anhyd. $MgSO_4$, 6 h.

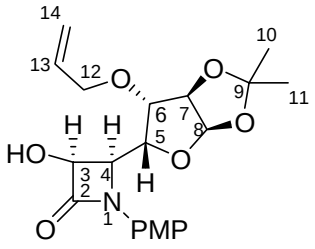
The *O*-allyl aldehyde **4.05** on treatment with *p*-anisidine in presence of anhydrous $MgSO_4$ converted to imine **4.06a** which on Staudinger reaction with acetoxy acetyl chloride in the presence of excess Et_3N gave stereoselectively 3-acetoxy azetidin-2-one **4.07** in 79% yield. The stereochemistry of this azetidin-2-one has been previously established on the basis of X-ray analysis.[1] 3-Acetoxy azetidin-2-one **4.07** on hydrolysis of the acetoxy functional group using saturated sodium bicarbonate in methanol gave 3-hydroxy azetidin-2-one **4.08** in 82% yield (Scheme 4.13).

Scheme 4.13



Reagents and conditions: a) $AcOCH_2COCl$, Et_3N, 0 °C-r. t., 12 h, 79%; b) aq. $NaHCO_3$, MeOH, r. t., 82%

The structure of **4.08** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **4.08** showed a sharp peak at 1728 cm^{-1} for azetidin-2-one amide carbonyl and broad peak at 3371 cm^{-1} for hydroxy group.



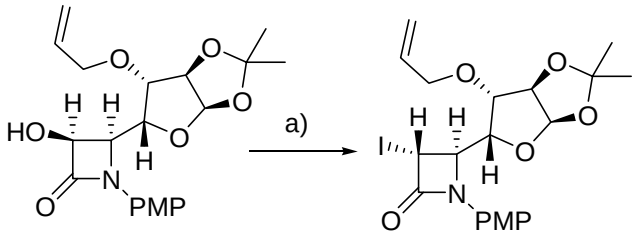
4.08

The ^{1}H NMR spectrum of **4.08** showed singlets at 1.32 and 1.45 ppm corresponds to acetonide methyl group protons. A broad singlet at 2.05 ppm assigned for hydroxy group. A singlet at 3.78 ppm corresponds to –OCH_3 protons of PMP group. A multiplet at 4.01-4.23 ppm integrating for two protons assigned for H-12 allylic methylene proton. A doublet at 4.33 ppm (J = 2.4 Hz) corresponds to H-5 methine proton. The H-4 β-lactam proton, H-6 and H-7 methine protons appears as a multiplet from 4.52-4.61 ppm integrating for three protons. The H-3 methine proton seen as a multiplet from 5.03-5.06 ppm. The H-14 vinylic proton appears as a multiplet from 5.22-5.38 ppm integrating for two protons. A multiplet from 5.85-5.96 ppm corresponds to H-13 vinylic proton. A doublet for anomeric H-8 proton appears at 6.03 ppm (J = 4.1 Hz). The doublets of PMP group appeared at 6.83 ppm and 7.62 ppm (J = 9.1 Hz).

The ^{13}C NMR spectrum of **4.08** showed a peak at 167.5 ppm corresponding to azetidin-2-one carbonyl. The aromatic quaternary carbon appeared at 156.2, 133.9 ppm. The C-13 vinylic carbon assigned at 130.8 ppm. Remaining aromatic carbons appeared at 119.6 and 113.6 ppm. The vinylic carbon C-14 appeared at 117.2 ppm. The quaternary carbon C-9 seen at 111.3 ppm. The anomeric carbon C-8 resonated at 104.5 ppm. The C-7 and C-6 carbons assigned at 82.3 and 82.1 ppm respectively. The C-3 carbon seen at 81.0 ppm. The C-12 carbon appears at 74.3 ppm. The C-5 carbon assigned at 70.8 ppm. The C-4 carbon and Ar-OCH_3 carbon appears at 59.8 and 55.0 ppm respectively. The acetonide methyl groups seen at 26.4 and 26.0 ppm. The mass spectrum of **4.08** gave M+1 peak at m/z 392, also supporting the structure of the compound. Specific rotation for 4.08 were found to be $[\alpha]_D^{25}$ = -147.3 (*c* 1.48, $CHCl_3$).

3-Hydroxy azetidin-2-one **4.08** on treatment with triphenyl phosphine, iodine, and imidazole in toluene as a solvent gave 3-iodo azetidin-2-one **4.09**.[17] The crude product on flash column chromatography (EtOAc/pet. ether 15:85 as eluent) gave pure **4.09** in 75% yield (Scheme 4.14).

Scheme 4.14

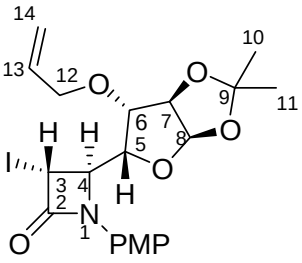


4.08 **4.09**

Reagents and conditions: a) PPh_3, I_2, Imidazole, toluene, reflux, 18 h, 66%.

The structure of **4.09** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **4.09** showed a sharp peak at 1753 cm^{-1} for azetidin-2-one amide carbonyl.

The ^{1}H NMR spectrum of **4.09** showed singlets at 1.31 and 1.43 ppm corresponds to acetonide methyl group protons. A singlet at 3.79 ppm corresponds to $-OCH_3$ protons of PMP group. The H-6 proton appears as a doublet at 3.92 ppm (J = 3.3 Hz). A multiplet at 4.08-4.16 ppm integrating for two protons assigned for H-12 allylic methylene protons. A doublet of doublet at 4.30 ppm (J = 3.4 Hz, 3.2 Hz) assigned for H-7 proton. A multiplet from 4.52-4.63 ppm appears for H-4 and H-5 protons. The H-3 methine proton seen as a doublet at 4.74 ppm (J = 2.1 Hz, indicating *trans* geometry for H-3 and H-4 protons). The H-14 vinylic proton appears as a multiplet from 5.20-5.41 ppm integrating for two protons. A multiplet from 5.91-6.14 ppm corresponds to H-13 vinylic proton. A doublet for anomeric H-8 proton appears at 6.04 ppm (J = 3.9 Hz). The doublets of PMP group appeared at 6.86 ppm and 7.60 ppm (J = 9.2 Hz).



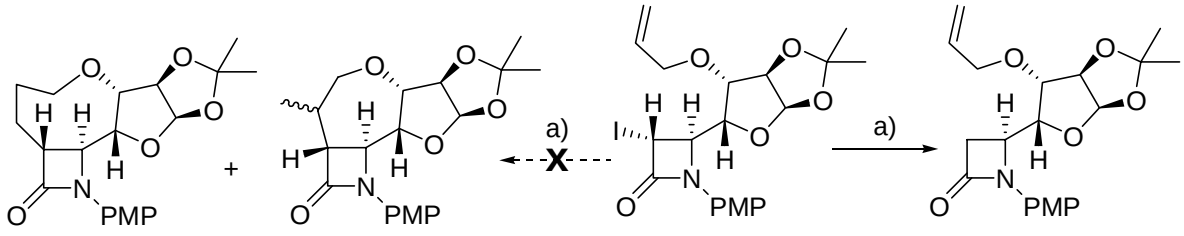
4.09

The ^{13}C NMR spectrum of **4.09** showed a peak at 161.5 ppm corresponding to azetidin-2-one carbonyl. The aromatic quaternary carbon appeared at 156.2, 131.2 ppm. The C-13 vinylic carbon assigned at 133.4 ppm. Remaining aromatic carbons appeared at 119.3 and 114.2 ppm. The vinylic carbon C-14 appeared at 119.0 ppm. The quaternary carbon C-9 seen at 111.9 ppm. The anomeric carbon C-8 resonated at 105.6 ppm. The C-7 and C-6 carbons assigned at 82.7 and 81.7 ppm respectively. The C-5 carbon seen at 81.1 ppm. The C-12 carbon appears at 71.2 ppm. The C-4 carbon seen at 63.5 ppm. The Ar-OCH_3 carbon appears at 55.4 ppm respectively. The acetonide methyl groups seen at 26.7 and 26.1 ppm. The C-3 methine carbon seen at 14.9 ppm.

The mass spectrum of **4.09** gave M+1 peak at m/z 502, also supporting the structure of the compound. Specific rotation for **4.09** were found to be $[\alpha]_D^{25}$ = -24.2 (*c* 1.24, $CHCl_3$).

3-Iodo azetidin-2-one **4.09** on treatment with a solution of tributyltin hydride and a catalytic amount of AIBN[18] in refluxing toluene gave 3-unsubstituted azetidin-2-one **4.10** instead of desired cyclized mixture **4.11** and **4.12** of products in 70% yield (Scheme 4.15). The crude product was purified by flash column chromatography (EtOAc/pet. ether 25:75 as eluent) to get the pure product **4.10**.

Scheme 4.15

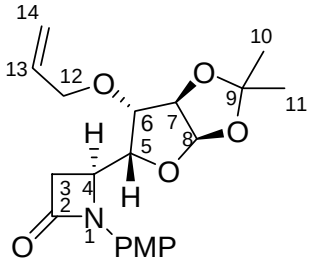


4.12 **4.11** **4.09** **4.10**

Reagents and conditions: a) Bu_3SnH, AIBN, toluene, reflux, 6 h, 70%.

The structure of **4.10** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **4.10** showed a sharp peak at 1747 cm^{-1} for azetidin-2-one amide carbonyl.

The ^{1}H NMR spectrum of **4.10** showed singlets at 1.31 and 1.44 ppm corresponds to acetonide methyl group protons. Two sets of multiplets for H-3 methylene protons were seen at 2.71-2.79 ppm and 3.19-3.29 ppm. A singlet at 3.77 ppm corresponds to $-OCH_3$ protons of PMP group. A multiplet at 3.86-3.98 ppm integrating for two protons corresponds to H-12 allylic methylene protons. A multiplet at 4.12-4.23 ppm integrating for one proton assigned for H-4 methine proton. A multiplet at 4.30-4.34 ppm integrating for two protons assigned for H-5 and H-6 methine protons. A doublet at 4.57 ppm (*J* = 3.9 Hz) corresponds to H-7 methine proton. The H-14 vinylic protons appear as a multiplet from 5.22-5.37 ppm integrating for two protons. A multiplet from 5.75-5.97 ppm corresponds to H-13 olefinic proton. A doublet for anomeric H-8 proton appears at 6.04



4.10

ppm (J = 3.9 Hz). The doublets of PMP group appeared at 6.85 ppm and 7.62 ppm (J = 9.2 Hz).

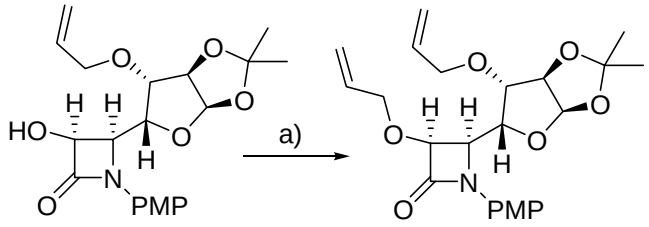
The ^{13}C NMR spectrum of **4.10** showed a peak at 163.7 ppm corresponding to azetidin-2-one carbonyl. The aromatic quaternary carbon appeared at 156.0, 131.9 ppm. The C-13 olefinic carbon assigned at 133.3 ppm. Remaining aromatic carbons appeared at 118.9 and 114.0 ppm. The vinylic carbon C-14 appeared at 118.5 ppm. The quaternary carbon C-9 seen at 111.7 ppm. The anomeric carbon C-8 resonated at 105.7 ppm. The C-7 and C-6 carbons assigned at 82.9 and 82.8 ppm respectively. The C-5 carbon seen at 81.2 ppm. The C-12 carbon appears at 70.9 ppm. The Ar-OCH_3 carbon appears at 55.4 ppm respectively. The C-4 and C-3 carbon seen at 51.6 ppm and 39.4 ppm respectively. The acetonide methyl groups seen at 26.6 and 26.1 ppm.

The mass spectrum of **4.10** gave M+1 peak at m/z 376, also supporting the structure of the compound. Specific rotation for **4.10** were found to be $[\alpha]_D^{25}$ = -152.6 (*c* 0.76, $CHCl_3$).

4.4b: Synthesis of *O-O'*, *O-C* and *O-N* dialkylated–3-substituted azetidin-2-ones for polycyclic β-lactam:

O-Allylation of 3-hydroxy azetidin-2-one **4.08** using allyl bromide, NaH as a base and TBAI as PTC in dry THF gave 3-*O*-allyl azetidin-2-one **4.13**. The crude product was further purified by flash column chromatography (EtOAc/pet. ether 2:8 as eluent) to get pure **4.11** in 91% yield (Scheme 4.16).

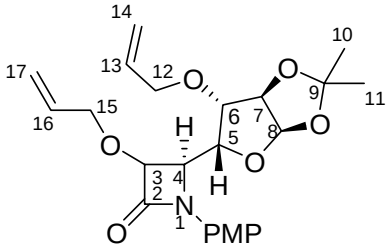
Scheme 4.16



Reagents and conditions: a) NaH, allyl bromide, TBAI, THF.

The structure of **4.13** was established by IR, ^1H NMR and ^{13}C NMR spectral data. IR spectrum of **4.13** showed a sharp peak at 1745 cm^{-1} for azetidin-2-one amide carbonyl.

The ^{1}H NMR spectrum of **4.13** showed singlets at 1.31 and 1.45 ppm corresponds to acetonide methyl group protons. A singlet at 3.78 ppm corresponds to –OC*H*$_3$ protons of PMP group. A multiplet at 3.92-4.26 ppm integrating for three protons corresponds to H-12 allylic methylene protons and H-6 methine proton. A doublet at 4.28 ppm (J = 2.9 Hz) assigned for H-5 proton. A multiplet at 4.40-4.48 ppm integrating for three protons corresponds to H-15 allylic methylene protons and H-4 methine proton. A doublet at 4.60 ppm (J = 3.9 Hz) assigned for H-7 methine proton. A doublet at 4.76 ppm (J = 5.2 Hz) assigned for H-3 methine proton. The H-14 and H-17 vinylic protons appear as a multiplet from 5.19-5.41 ppm integrating for four protons. A multiplet from 5.81-5.98 ppm corresponds to H-13 and H-16 olefinic protons. A doublet for anomeric H-8 proton appears at 6.02 ppm (J = 3.9 Hz). The doublets of PMP group appeared at 6.85 ppm and 7.62 ppm (J = 9.2 Hz).



4.13

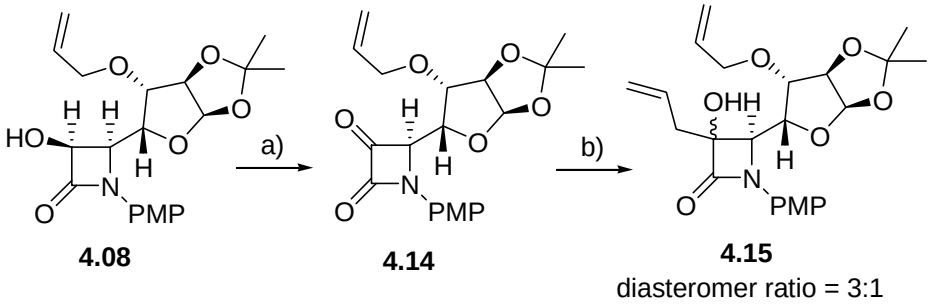
The ^{13}C NMR spectrum of **4.13** showed a peak at 165.1 ppm corresponding to azetidin-2-one carbonyl. The aromatic quaternary carbon appeared at 156.3, 131.3 ppm. The C-13 and C-16 olefinic carbons assigned at 133.9 ppm and 133.5 ppm. Remaining aromatic carbons appeared at 119.6 ppm and 113.9 ppm. The vinylic carbons C-14 and C-17 appeared at 118.0 ppm and 117.4 ppm. The quaternary carbon C-9 seen at 111.6 ppm. The anomeric carbon C-8 resonated at 104.8 ppm. The C-7 and C-6 carbons assigned at 82.9 ppm and 81.9 ppm respectively. The C-5 carbon seen at 81.5 ppm. The C-3 carbon seen at 80.1 ppm. The C-12 and C-15 carbons appears at 72.2 ppm and 70.8 ppm. The C-4 carbon seen at 58.7 ppm. The Ar-OCH_3 carbon appears at 55.4 ppm respectively. The acetonide methyl groups seen at 26.7 ppm and 26.2 ppm.

The mass spectrum of **4.13** gave M+1 peak at m/z 432, also supporting the structure of the compound. Specific rotation for **4.13** were found to be $[\alpha]_D^{25}$ = -206.7 (*c* 0.60, $CHCl_3$)

3-Hydroxy azetidin-2-one **4.08** on oxidation with iodoxo benzoic acid (IBX)[19] in EtOAc gave 3-keto azetidin-2-one **4.14** in quantitative yield. Ketone **4.14** on Grignard reaction with allyl magnesium bromide at 0 °C in dry THF as a solvent furnished 3-allyl 3-

hydroxy azetidin-2-one **4.15** in 3:1 diasteromeric ratio which were difficult to separate by column chromatography (Scheme 4.17).

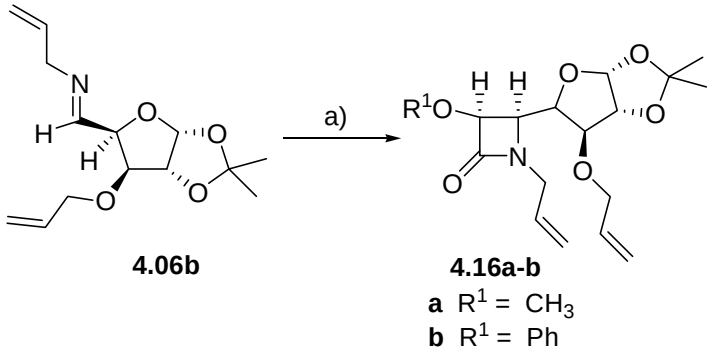
Scheme 4.17



Reagents and conditions: a) IBX, EtOAc, reflux 6 h; b) allyl magnesium bromide, THF, 0 °C, 30 min., 70%.

The *O*-allyl aldehyde **4.05** on treatment with allyl amine in presence of anhydrous $MgSO_4$ converted to imine **4.06b** which on Staudinger reaction with ketene obtained from acid chloride (methoxy acetyl chloride, phenoxy acetyl chloride) in the presence of excess Et_3N gave stereoselectively azetidin-2-one **4.16a-b** in good yield[1] (Scheme 4.18).

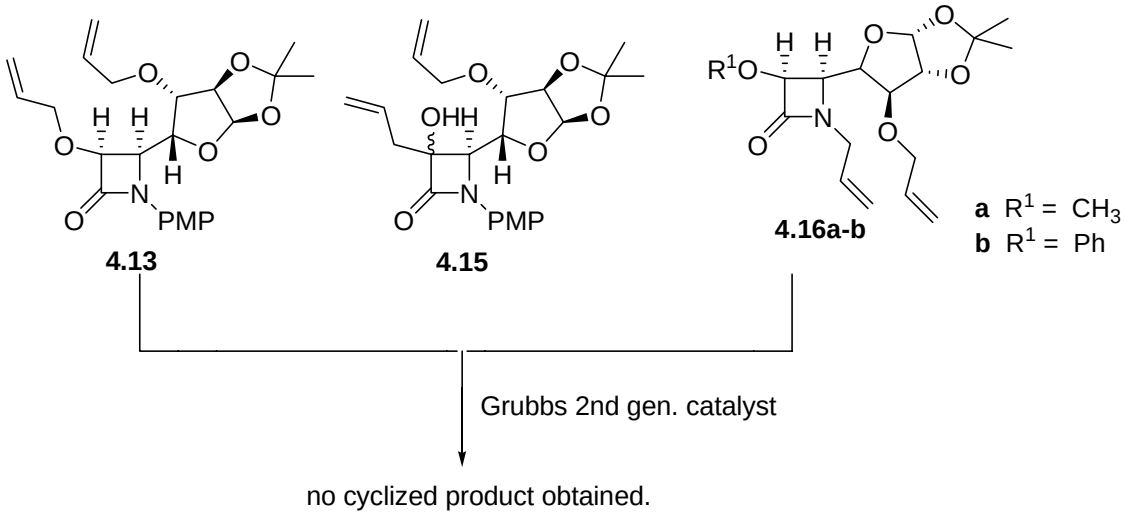
Scheme 4.18



Reagents and conditions: a) Et_3N, R^1OCH_2COCl, CH_2Cl_2, 0 °C-r. t., 12-14 h, 75%.

A dilute solution of azetidin-2-ones **4.13, 4.15, 4.16a-b** in dry CH_2Cl_2 on treatment with Grubbs 2nd generation catalyst (10 mol%) resulted in a recovery of starting material at room temperature, whereas in refluxing CH_2Cl_2 or toluene resulted in complex reaction mixture instead of cyclized product by ring closing metathesis (Scheme 4.19).

Scheme 4.19

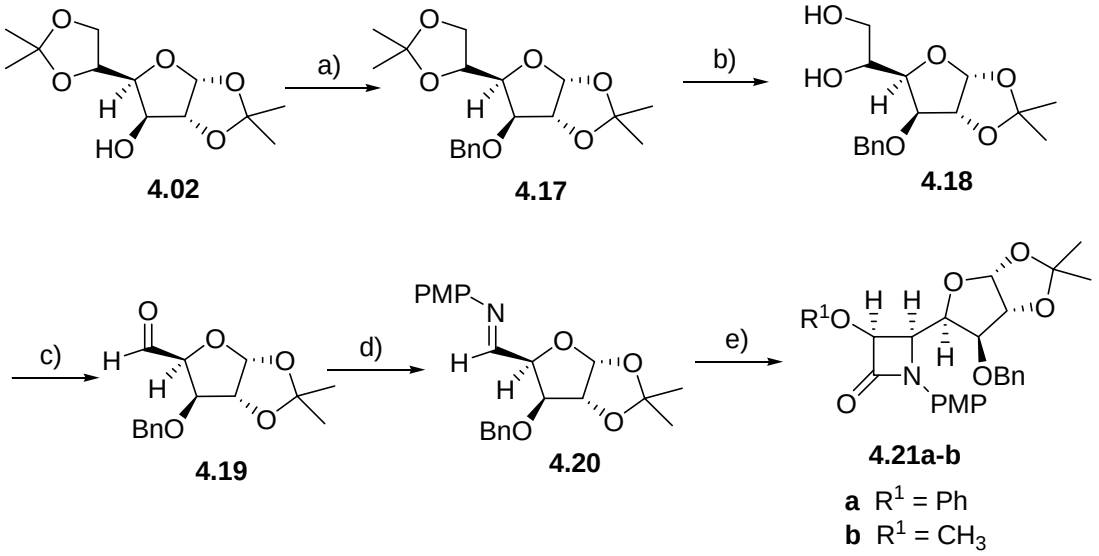


Model study of these diallylated compound suggests that both the allyl groups are projecting away from each other because of which ring closing metathesis were found to be cumbersome.

4.4c: Synthesis of 3-substituted azetidin-2-ones for new class of polycyclic carbapenem derivatives:

Glucose diacetonide **4.02** on benzylation using NaH as a base gave *O*-benzyl protected glucose diacetonide **4.17** in 90% yield. Selective deprotection of the primary acetonide moiety using 75% AcOH in water at 75 °C for 3 h gave diol **4.18** in 84% yield which on oxidative cleavage using 0.65M $NaIO_4$ on silica gel gave O-benzyl protected aldehyde **4.19** in 80% yield. Aldehyde **4.19** on treatment with *p*-anisidine using anhydrous $MgSO_4$ gave imine **4.20**. Imine **4.20** obtained on Staudinger reaction with ketene obtained from acid chlorides (phenoxy, methoxy) in presence of excess Et_3N gave stereoselectively azetidin-2-one **4.21a-b** in good yield (Scheme 4.20).

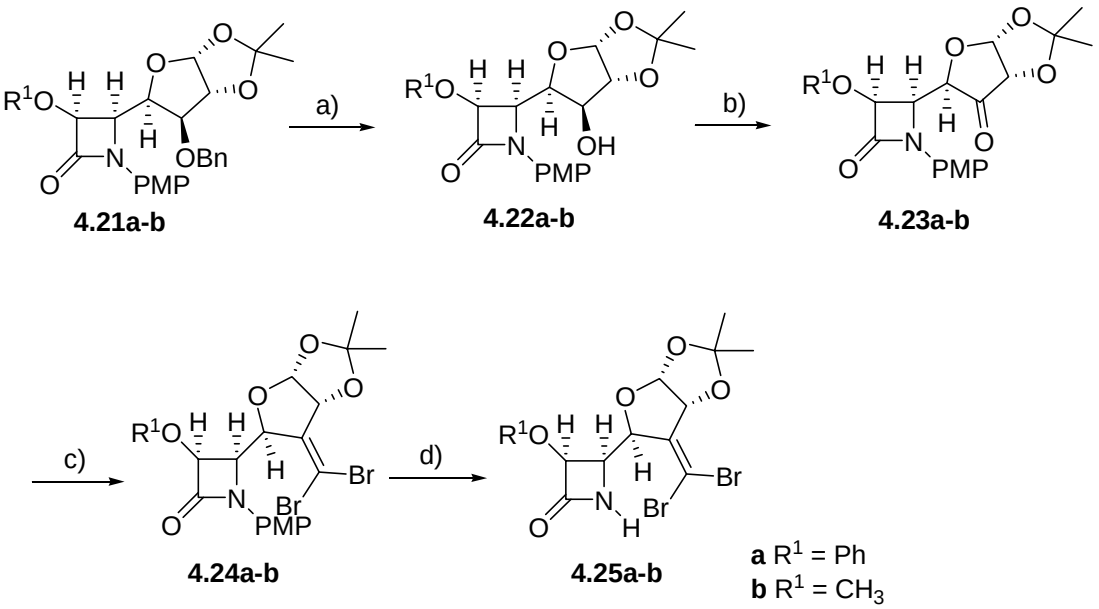
Scheme 4.20



Reagents and conditions: a) NaH, BnBr, THF, TBAI, 2.5 h, 90%; b) 75% AcOH in H_2O, 75 °C, 3 h, 84%; c) $NaIO_4$, acetone/H_2O 0 °C, 1.5 h, 80%; d) PMP-NH_2, CH_2Cl_2, anhyd. $MgSO_4$, 6 h; e) R^1OCH_2COCl, Et_3N, 0 °C-r. t., 12 h, 80%.

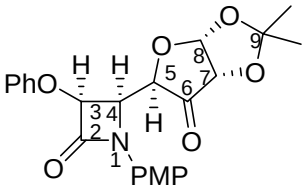
Azetidin-2-one **4.21a** on catalytic hydrogenation using Pd/C (10%) gave 6-hydroxy-β-lactam **4.22a** which on iodoxobenzoic acid (IBX) oxidation afforded ketone **4.23a** in quantitative yield (Scheme 4.21).

Scheme 4.21



Reagents and conditions: a) H_2, EtOAc, 50 psi, 24 h, 90%; b) IBX, CH_3CN, Acetonitrile, reflux 6 h; c) PPh_3, CBr_4, toluene, 80 °C, 12 h, 70%; d) CAN, CH_3CN-H_2O, 60%.

The structure of **4.23a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **4.23a** showed a sharp peaks at 1745 cm^{-1} and 1705 cm^{-1} for azetidin-2-one amide carbonyl and ketone carbonyl respectively.



4.23a

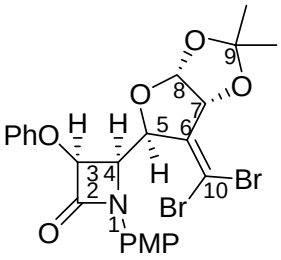
The ^{1}H NMR spectrum of **4.23a** showed singlets at 1.35 and 1.43 ppm corresponds to acetonide methyl group protons. A singlet at 3.81 ppm seen for –OCH_3 protons of PMP group. A doublet of doublet at 4.13 ppm (J = 4.3 Hz, 1.0 Hz) assigned for H-7 methine proton. A doublet of doublet at 4.77 ppm (J = 2.9 Hz, 1.0 Hz) appeared for H-5 methine proton. A doublet of doublet at 4.86 ppm (J = 4.8 Hz, 2.9 Hz) seen for H-4 methine proton. The H-3 methine proton seen as a doublet at 5.45 ppm (J = 4.8 Hz). A doublet at 5.68 ppm (J = 4.3 Hz) assigned for H-8 proton. The doublets of PMP group appeared at 6.91 ppm and 7.12 ppm (J = 9.1 Hz). Remaining aromatic protons appeared as a multiplet at 7.26-7.40 ppm integrating for five protons.

The ^{13}C NMR spectrum of **4.23a** showed a peaks at 208.3 ppm and 162.2 ppm corresponding to ketone carbonyl and azetidin-2-one carbonyl respectively. The aromatic quaternary carbons appeared at 157.1, 129.3 ppm. Remaining aromatic carbons appeared at 129.8, 123.2, 119.9, 116.1, 114.7 ppm. The quaternary carbon C-9 seen at 114.3 ppm. The C-8, C-7 and C-5 carbon resonated at 103.4, 80.1, 76.5 ppm respectively. The C-3 carbon seen at 73.7 ppm. The C-4 carbon and Ar-OCH_3 carbon appears at 58.5 and 55.5 ppm respectively. The acetonide methyl groups seen at 27.5 and 27.1 ppm. The mass spectrum of **4.23a** gave M+1 peak at m/z 426, also supporting the structure of the compound. Specific rotation for **4.23a** were found to be $[\alpha]_D^{25}$ = +22.2 (*c* 0.36, $CHCl_3$).

The 6-keto azetidin-2-one **4.23a** on reaction with triphenylphosphine and carbon tetrabromide[19] in toluene as a solvent at 80 °C gave **4.24a**. The crude product was further purified by column chromatography (EtOAc/pet. ether 15:85 as eluent) to afford pure vinylic dibromo azetidin-2-one **4.24a** in 63% yield (Scheme 4.21).

The structure of **4.24a** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectrum of **4.24a** showed a sharp peak at 1758 cm^{-1} for azetidin-2-one amide carbonyl.

The ^{1}H NMR spectrum of **4.24a** showed singlets at 1.35 and 1.40 ppm corresponds to acetonide methyl group protons. A singlet at 3.83 ppm seen for –OCH_3 protons of PMP group. A doublet of doublet at 4.13 ppm (J = 1.5 Hz, 4.4 Hz) assigned for H-7 methine proton. A doublet at 5.10 ppm (J = 1.5 Hz) appeared for H-5 methine proton. A doublet 5.14 ppm (J = 5.2 Hz) seen for H-4 methine proton. The H-3 methine proton seen as a doublet at 5.38 ppm (J = 5.2 Hz). A doublet at 5.68 ppm (J = 4.4 Hz) assigned for H-8 proton. One of the doublets of PMP group appeared at 6.93 ppm (J = 9.1 Hz). Remaining aromatic protons appeared as a multiplet at 7.02-7.40 ppm integrating for seven protons.



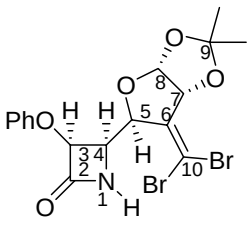
4.24a

The ^{13}C NMR spectrum of **4.24a** showed a peak at 163.0 ppm corresponding to azetidin-2-one carbonyl. The aromatic quaternary carbons appeared at 157.4, 156.6, 129.1 ppm. The C-6 olefinic carbon appeared at 145.9 ppm. Remaining aromatic carbons appeared at 129.5, 122.4, 119.5, 115.6, 114.6 ppm. The quaternary carbon C-9 seen at 113.3 ppm. The C-8 carbon resonated at 106.3 ppm. The C-10 olefinic carbon appeared at 88.6 ppm. The C-7 and C-5 carbon seen at 82.3, 79.0 ppm respectively. The C-3 and C-4 carbon seen at 78.7 ppm and 57.8 ppm respectively. The Ar-OCH_3 carbon appears at 55.3 ppm. The acetonide methyl groups seen at 27.3 and 27.2 ppm. The mass spectrum of **4.24a** gave M+1 peak at m/z 582, also supporting the structure of the compound. Specific rotation for **4.24a** were found to be $[\alpha]_D^{25}$ = +112.0 (*c* 0.5, $CHCl_3$).

PMP group from azetidin-2-one **4.24a** was deprotected to get N-unsubstituted β-lactam **4.25a** by using cerric ammonium nitrate (CAN)[20] oxidation. The crude product was purified by flash column chromatography (EtOAc/pet. ether 3:7 as eluent) to get pure **4.23a** in 83% yield.

The structure of **4.25a** was studied by COSY and NOESY 2D NMR techniques. The IR spectrum of **4.25a** showed a sharp peak at 1770 cm^{-1} for azetidin-2-one amide carbonyl.

The ^{1}H NMR spectrum of **4.25a** showed singlets at 1.44 and 1.47 ppm corresponds to acetonide methyl group protons. A doublet of doublet at 4.48 ppm (J = 5.0 Hz, 1.5 Hz) assigned for H-4 methine proton. A multiplet at 5.07 ppm appeared for H-5 proton. A doublet of doublet at 5.10 ppm (J = 4.2 Hz, 1.2 Hz) assigned for H-7 methine proton. A doublet 5.28 ppm (J = 5.1 Hz) appeared for H-3 methine proton. A doublet at 6.10 ppm (J = 4.2 Hz) assigned for H-8 proton. Aromatic protons appeared as a multiplet at 7.03-7.35 ppm integrating for five protons.



4.25a

The ^{13}C NMR of **4.25a** showed a peak at 168.1 ppm corresponding to azetidin-2-one carbonyl. The aromatic quaternary carbon appeared at 157.5 ppm. The C-6 olefinic carbon appeared at 144.8 ppm. Remaining aromatic carbons appeared at 129.7, 122.5, 115.7 ppm. The quaternary carbon C-9 seen at 113.5 ppm. The C-8 carbon resonated at 106.0 ppm. The C-10 olefinic carbon appeared at 89.1 ppm. The C-7 and C-5 carbon assigned at 82.9, 80.6 ppm respectively. The C-3 and C-4 carbon seen at 80.1 ppm and 55.5 ppm respectively. The acetonide methyl groups seen at 27.5 and 27.3 ppm.

COSY experiment was carried out for **4.25a** to further confirm the bond connectivities (Figure 2). The anomeric proton H-8 showed a strong interaction with H-7. The H-5 proton showed interaction with H-4 proton which in turn is connection with the H-3 proton.

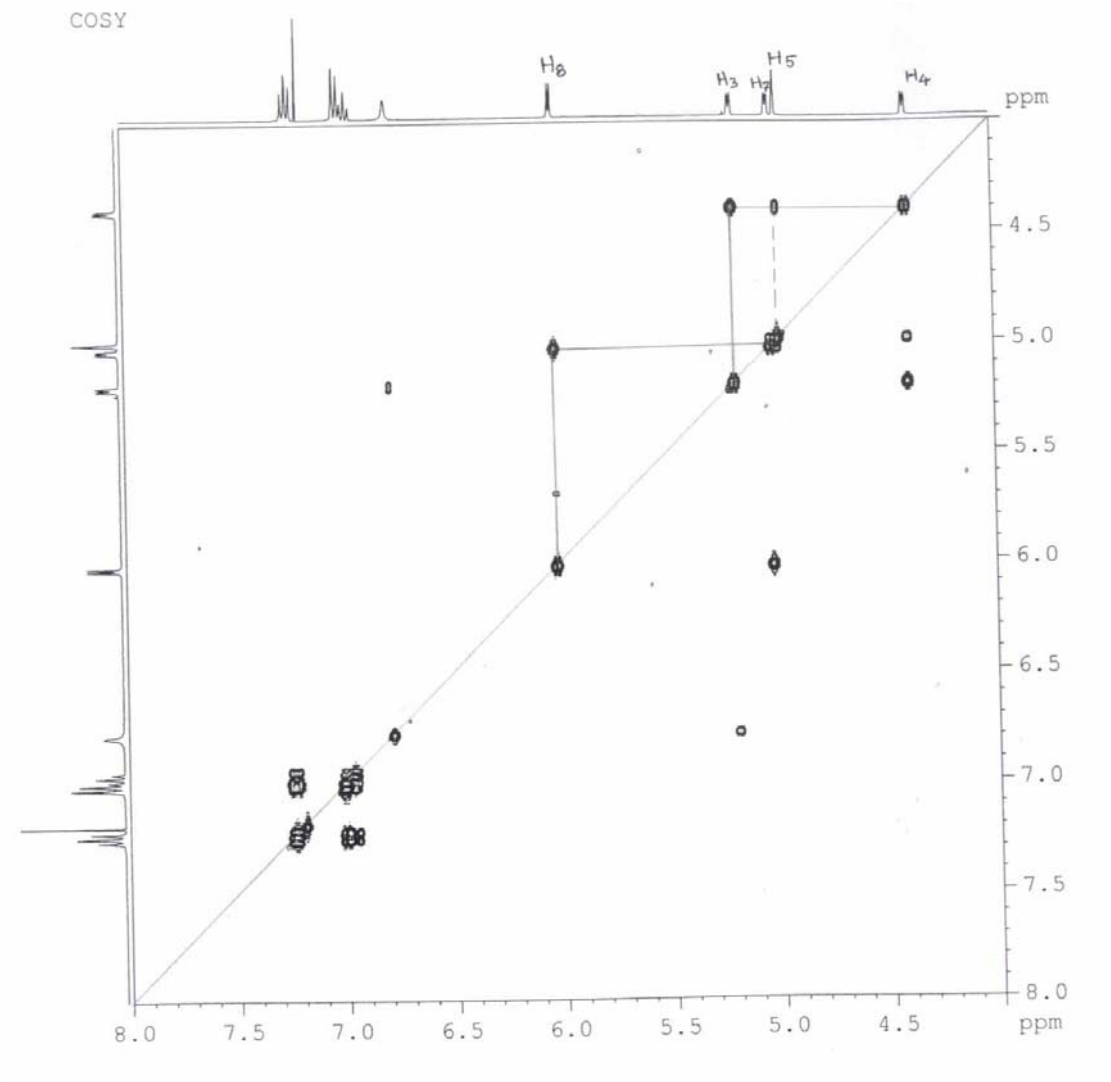


Figure 2: COSY 2D NMR spectrum of **4.25a**

proton	ppm	*J*	^{1}H-^{1}H connectivity
H-8	6.10 (d)	4.2 Hz	H-7
H-7	5.10 (dd)	4.2 Hz, 1.2 Hz	H-8, H-5
H-5	5.07 (m)	--	H-4, H-7
H-4	4.48(dd)	5.0 Hz, 1.5 Hz	H-3, H-5
H-3	5.28(d)	5.1 Hz	H-4

The NOESY spectrum of **4.25a** also showed connectivity of anomeric proton H-8 with H-7 proton. H-3 proton showed connectivity with H-4 proton which further showed connectivity with H-5 proton.

The mass spectrum of **4.25a** gave M+1 peak at m/z 476, also supporting the structure of the compound.

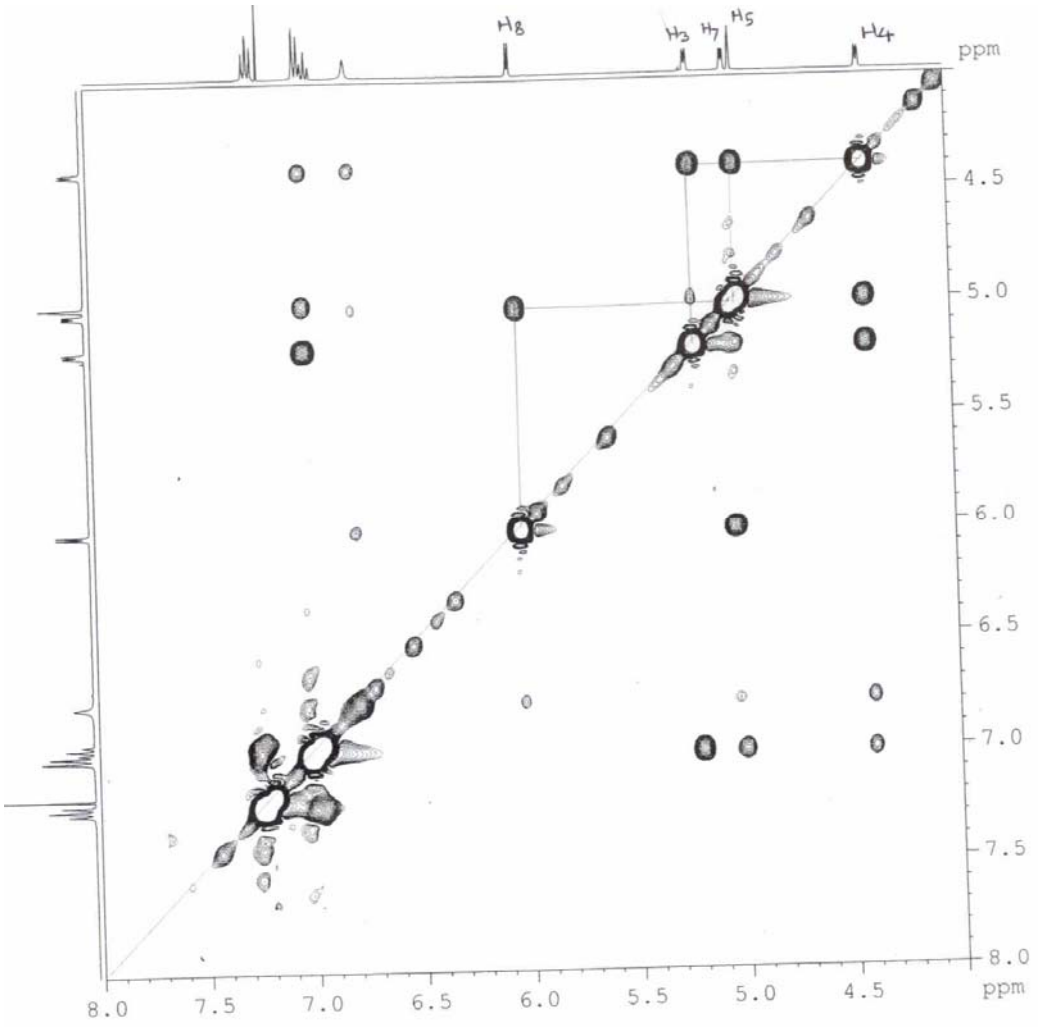
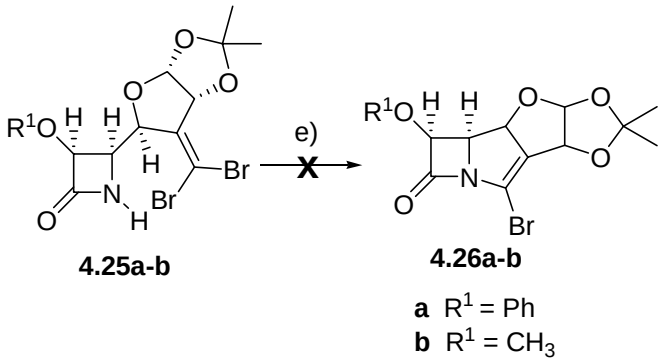


Figure 3: NOESY 2D NMR spectrum of **4.25a**

By Following a similar synthetic sequence (Scheme 4.21) N-unsubstituted β-lactam **4.25b** was also synthesized.

Kozawa et al.[21] have used Buchwald method of C-N bond-formation by using vinyl halide and β-lactam nitrogen in the presence of $Pd(OAc)_2$, DPEphos and K_2CO_3 in the synthesis of 3-alkoxy carbonyl-1β-methylcarbapenem antibiotic. We also tried these reaction conditions in the cyclization reaction to convert vinylic dibromo azetidin-2-one **4.25a-b** to carbapenem **4.26a-b**. However, we did not get the desired product instead we got a complex mixture of products, which were difficult to separate by column chromatography. We used different bases like Cs_2CO_3, K_3PO_4 to convert vinylic dibromo azetidin-2-one **4.25a-b** to the desired carbapenem **4.26a-b**, it also resulted in a complex mixture of products. Lautens M. et al.[22] has converted ortho-gem-dihalovinylanilines to 2-substituted indoles using tandem intramolecular Pd catalyzed C-N (Buchwald-Hartwig amination) and intermolecular C-C bond (Suzuki-Miyaura coupling) formation using $Pd(OAc)_2$, S-Phos, $PhB(OH)_2$, K_3PO_4 (Method E). Similar reaction conditions were used for **4.25a-b,** however, we got a complex inseparable mixture of products.

Scheme 4.22



4.25a-b **4.26a-b**

a $R^1 = Ph$
b $R^1 = CH_3$

Reagents and conditions: a) $Pd(OAc)_2$, ligand, base, toluene, 100 °C.

All our efforts to convert vinylic dibromo azetidin-2-ones **4.25a-b** to cyclized product **4.26a-b**, either by Buchwald-Hartwig C-N bond forming reaction (Scheme 4.22) or by using Cu catalyst were found to be unfruitful. Different conditions tried for this reaction are summarized in Table 2.

Table 2: Conditions tried for cyclization using Buchwalds C-N bond forming reaction

Run	substrate	Base	Ligand	Method	Time
1	**4.25a**	K_2CO_3	DPEphos	A & B	22 h
2	**4.25a**	Cs_2CO_3	DPEphos	A & B	18 h
3	**4.25a**	K_3PO_4	DPEphos	A & B	22 h
4	**4.25a**	K_3PO_4	Binap	B	20 h
5	**4.25a**	K_2CO_3	S-phos	B	20 h
6	**4.25a**	Cs_2CO_3	S-Phos	B	20 h
7	**4.25b**	K_3PO_4	S-phos	A & B	20 h
8	**4.25b**	Na-acetate	S-phos	B	22 h
9	**4.25b**	K_3PO_4	S-phos	C	5 min
10	**4.25b**	K_3PO_4	DPEphos	D	24 h
11	**4.25a**	K_3PO_4	S-phos	D&E	6 h
12	**4.25a**	E_3N	S-phos	D	22 h

Method A: A toluene solution of substrate, 10 mol % of $Pd(OAc)_2$, 15 mol % of ligand, and base (2.0 equivalent) were heated at 100 °C.

Method B: A toluene solution of substrate, 10 mol % of $Pd(OAc)_2$, and 15 mol % ligand were heated at 100 °C for 2 min and was added to a suspension of base (2.0 equivalent) in toluene. Then the toluene solution was heated at 100 °C.

Method C: A DMF solution of substrate, 10 mol % $Pd(OAc)_2$, 15 mol % ligand and base (2.0 equivalents) was irridiated in MW at 70 P for 5 min.

Method D: A toluene solution of substrate, $Pd(OAc)_2$, ligand and ClCOOEt, base was added stirred at room temperature for 5 min then heated at 80 °C for 6 h.

Method E: A solution of $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) in toluene added to a flask containing substrate(1 mmol), $PhB(OH)_2$ (1.5 mmol), and K_3PO_4 (5 mmol) and heated at 90 °C for 6 h.

Method F: $Pd(OAc)_2$, Acetonitrile, K_2CO_3, reflux, 14 h.

Method G: 10% Pd/C, PPh_3, CuI, Et_3N, dioxane, 80 °C.

Method H: 10mol% CuI, NaH, THF, r. t., 12 h.

Method I: Cu, DMF, 80 °C, 3 h.

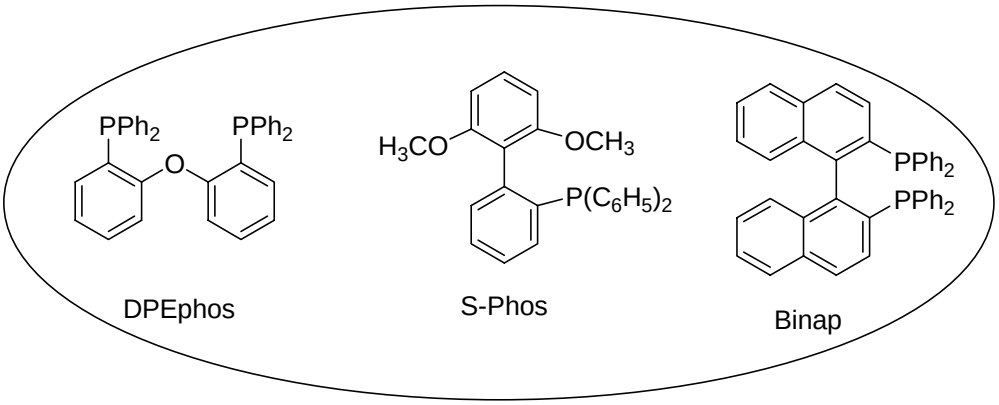


Figure 4: Structures of ligands tried for C-N bond forming reaction.

The success of Pd catalyzed C-N bond forming reaction depends on the combination of ligand, catalyst and base used. However in our case we got complex mixture of products which were difficult to separate by column chromatography. Our efforts towards C-N bond forming reaction using Cu catalyst was unsuccessful and we did not get the desired product, instead we got unreacted starting material back.

4.5 Conclusion:

In conclusion, we have synthesized new β-lactam derivatives from D-glucose diacetonide derived β-lactams, for synthesis of polycyclic β-lactams and carbapenems. Efforts to convert these β-lactams to polycyclic β-lactams and carbapenem derivatives are in progress.

4.6: Experimental:

4.6.1: 1,2;5,6-Di-*O*-isopropylidene-α-glucofuranose(4.02):

A suspension of anhydrous D-glucose **4.01** (28.0 g, 155.40 mmol), anhydrous cupric sulphate (28.2 g, 176.70 mmol) and conc. H_2SO_4 (2 mL) in dry acetone (600 mL) was stirred at room temperature for 48 h. The reaction mixture was then neutralized with potassium carbonate (200 g) and stirred overnight. The reaction mixture was filtered through a Buchner funnel and the acetone layer was dried over Na_2SO_4 and evaporated *in vacuo*. The resulting solid recrystallized from hot cyclohexane to give pure white crystalline glucose diacetonide **4.02** in yield (20.0 g, 50%) as a white solid.

m.p. 109-110 °C

IR ($CHCl_3$): ν_{max} 3429 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 2.33 (bs, 1H), 3.98-4.40 (m, 5H), 4.54 (d, *J* = 3.6 Hz, 1H), 5.95 (d, *J* = 3.6 Hz, 1H).

4.6.2: 3-*O*-Allyl-1,2;5,6 di-O-isopropylidene –α-D-glucofuranose (4.03):

To a solution of the diacetonide **4.02** (10 g, 0.038 mol) and allyl bromide (5 mL, 0.057 mol) in CH_2Cl_2 (100 mL) was added 50% aqueous NaOH solution (50 mL) and the mixture stirred vigorously. TBAB (catalytic) was then added to this mixture and the stirring continued till the disappearance of the starting material, as indicated by TLC. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2. The combined organic layers washed with water, dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The product containing residual PTC was chromatographed over silica (60-120 mesh) using EtOAc/pet. ether (1:4). Removal of solvents under reduced pressure afforded the **4.03** as an oil (11g, 95%).

4.6.3: 3-*O*-Allyl-1,2-O-isopropylidene–α-D-glucofuranose (4.04):

3-O-allyl-1,2;5,6 di-O-isopropylidene–α-D-glucofuranose **4.03** (10 g, 0.033 mol) was dissolved in 40 mL of aqueous acetic acid (75%v/v) and heated to 75 °C for 3 hrs. The solvents were removed under reduced pressure. Resulting mass was dissolved in CH_2Cl_2 and washed with H_2O, saturated $NaHCO_3$ solution, and saturated brine solution, dried over

Na_2SO_4 and concentrated to get **4.04** (7.1 g, 81%) of the diol as viscous oil which was used as such for the next reaction without further purification.

4.6.4: Synthesis of 3-O-allyl-1,2-O-isopropylidene –α-D-glucofuranose aldehyde (4.05):

To a vigorously stirred suspension of chromatographic grade silica gel (54 g) in CH_2Cl_2 (250mL) in 500 mL flask was added a 0.65 M aqueous solution of $NaIO_4$ (54 mL) dropwise with stirring. Diol **4.04** (7.0 g, 26.92 mmol) in CH_2Cl_2 (50 mL) was then added and the reaction was monitored by TLC until disappearance of the starting material (30 min). The mixture was filtered through Buchner funnel, dried over Na_2SO_4 and concentrated to give pure aldehyde **4.05** in quantitative yield (5.71 g, 93%) which was then used as such for imine formation.

4.6.5: General procedure for Synthesis of imine 4.06a-b:

To a solution of amine (*p*-anisidine, allyl amine) (one equivalent) in CH_2Cl_2 and anhydrous $MgSO_4$ (one equivalent) a solution of aldehyde **4.05** (1.1 equivalent) in CH_2Cl_2 were added at room temperature. The reaction mixture was stirred for 6 to 7 h and filtered through a sintered glass crucible. The filtrate was concentrated and the resulting imine **4.06a-b** (quantitative yield) was used as such for the β-lactam formation.

4.6.6: Synthesis of 3-acetoxy β-lactam 4.07:

A solution of the acetoxyacetyl chloride (3.20 mL, 29.72 mmol), in CH_2Cl_2 (20 mL) was added to a solution of imine **4.06a** (6.60 g, 19.81 mmol) and Et_3N (12.40 mL, 89.20 mmol) in CH_2Cl_2 (40 mL) at 0 °C. It was then allowed to warm to room temperature and stirred for a further 15 h. The reaction mixture was washed with H_2O (25mL), sat. $NaHCO_3$ solution (25 mL) and saturated brine (20 mL). The organic layer was then dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to give a crude 3-acetoxy β-lactam **4.07** which on flash column chromatography (EtOAc/pet. ether 3:7 as eluent) gave (6.80 g, 79% yield) as a viscous oil.

$[\alpha]_D^{25}$ = -148.5 (*c* 1.32, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H, C*H*$_3$), 1.46 (s, 3H, C*H*$_3$), 2.20 (s, 3H, -COC*H*$_3$), 3.78 (s, 3H, Ar-OC*H*$_3$), 3.80-3.93 (m, 2H, *H*-12), 4.08-4.17 (m, 1H, *H*-6), 4.43 (dd, *J* = 3.4 Hz, 3.4 Hz, 1H, H-5), 4.57-4.67 (m, 2H, *H*-7, *H*-4), 5.20-5.35 (m, 2H, *H*-14), 5.74-5.94 (m, 1H, *H*-13), 6.01 (d, *J* = 3.9 Hz, 1H, *H*-8), 6.15 (d, *J* = 5.6 Hz, 1H, *H*-3), 6.85 (d, *J* = 9.2 Hz, 2H, Ar), 7,65 (d, *J* = 9.2 Hz, 2H, Ar),

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.8, 26.2, 26.7, 55.4, 58.1, 70.9, 73.0, 80.9, 81.6, 82.3, 104.8, 111.8, 113.9, 118.4, 119.8, 131.0, 133.5, 156.7, 162.1, 168.7.

MS: m/z = 434 (M+1)

Anal. Calcd. for **$C_{22}H_{27}NO_8$:** C, 60.96; H, 6.28; N, 3.23%

Found C, 61.25; H, 6.22; N, 3.33%.

4.6.7: Synthesis of 3-hydroxy β-lactam 4.08:

Acetoxy β-lactam **4.07** (6.50 g, 15.0 mmol) was dissolved in methanol (70 mL) followed by addition of saturated $NaHCO_3$ (26 mL) and stirred at room temperature for 2 h. The solvent was distilled off under reduced pressure and the crude material was extracted with CH_2Cl_2 (2 x 30 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (60-120 mesh silica, EtOAc/pet. ether 4:6 as eluent) to furnish hydroxy β-lactam **4.08** (4.82 g, 82%) as a gum.

$[\alpha]_D^{25}$ = -147.3 (*c* 1.48, $CHCl_3$).

IR ($CHCl_3$): ν_{max} 1728, 3371 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H,-C*H*$_3$), 1.45 (s, 3H, -C*H*$_3$), 2.05 (bs, 1H, -OH), 3.78 (s, 3H, Ar-OC*H*$_3$), 4.01-4.23 (m, 2H, *H*-12), 4.33 (d, *J* = 2.4 Hz, 1H, *H* -5), 4.52-4.61 (m, 3 H, *H*-4, *H*-6, *H*-7), 5.03-5.06 (m, 1H, *H*-3), 5.20-5.38 (m, 2H, *H*-14), 5.85-5.96 (m, 1H, *H*-13), 6.03 (d, *J* = 4.1 Hz, 1H, *H*-8), 6.83 (d, *J* = 9.1 Hz, 2H, Ar), 7.62 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 26.4, 55.0, 59.8, 70.8, 74.3, 81.0, 82.1, 82.3, 104.5, 111.3, 113.6, 117.2, 119.6, 130.8, 133.9, 156.2, 167.5.

MS: m/z = 392 (M+1)

Anal. Calcd. for **$C_{20}H_{25}NO_7$:** C, 61.37; H, 6.44; N, 3.58%

Found C, 61.65; H, 6.57; N, 3.63%

4.6.8: Synthesis of 3-iodo β-lactam (4.09):

A mixture of hydroxy β-lactam **4.08** (1.30 g, 3.32 mmol), triphenyl phosphine (2.62 g, 9.97 mmol) and imidazole (0.68 g, 9.97 mmol) in toluene was heated under reflux for 10 minutes to make the solution homogeneous. Iodine (1.69 g, 6.65 mmol) was added to the solution and refluxed for a further 14 h with stirring. The reaction mixture was cooled and filtered. Filtrate was concnentrated *in vacuo* and the residue was chromatographed (60-120 mesh silica, EtOAc/pet. ether, 15:85 as eluent) to afford **4.09** (1.10 g, 66%) as oil.

$[\alpha]_D^{25}$ = -24.19 (*c* 1.24, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1753 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H, -C*H*$_3$), 1.43 (s, 3H, -C*H*$_3$), 3.79 (s, 3H, Ar-OC*H*$_3$), 3.92 (d, *J* = 3.3 Hz, 1H, *H*-6), 4.08-4.16 (m, 2H, *H*-12), 4.30 (dd, *J* = 3.4 Hz, 3.2 Hz 1H, *H*-7), 4.52-4.63 (m, 2 H, *H*-4, *H*-5), 4.74 (d, *J* = 2.1 Hz, 1H, *H*-3), 5.20-5.41 (m, 2H, *H*-14), 5.91-6.14 (m, 1H, *H*-13), 6.04 (d, *J* = 3.9 Hz, 1H, *H*-8), 6.86 (d, *J* = 9.2 Hz, 2H, Ar), 7,60 (d, *J* = 9.2 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.9, 26.1, 26.7, 55.4, 63.5, 71.2, 81.1, 81.7, 82.7, 105.6, 111.9, 114.2, 119.0, 119.3, 131.2, 133.4, 156.6, 161.5.

MS: m/z = 502 (M+1).

Anal. Calcd. for **$C_{20}H_{24}NO_6I$:** C, 47.92; H, 4.83; N, 2.79%

Found C, 47.74; H, 4.95; N, 2.80%

4.6.9: Attempted radical cyclization of 3-iodo-O-allyl β-lactam 4.09:

3-Iodo β-lactam **4.09** (0.250 g, 0.5 mmol) was dissolved in dry toluene (50 mL), degassed and heated under reflux for 30 minutes. A solution of Bu_3SnH (0.20 mL, 0.75 mmole) and AIBN (17 mg, 0.2 mmol) in toluene (25 mL) was added through a syringe pump over a period of 3 h to the iodo β-lactam under reflux condition. The reaction mixture was refluxed for further 3 h. After completion of reaction (TLC) the solvent was removed under reduced pressure. The crude reaction mixture was purified by column chromatography (230-400 mesh silica gel, EtOAc/pet. ether 25:75 as eluent) to gave reduced product **4.10** (0.125 g, 67%) as oil.

$[\alpha]_D^{25}$ = -152.63 (*c* 0.76, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3), 2.71-2.79 (m, 1H, H_a-3), 3.19-3.29 (m, 1H, H_b-3), 3.77 (s, 3H, Ar-OCH_3), 3.86-3.98 (m, 2H, *H*-12), 4.12-4.23 (m, 1H, *H*-4), 4.30-4.34 (m, 2H, *H*-5, *H*-6), 4.57 (d, *J* = 3.9 Hz, 1H, *H*-7), 5.22-5.37 (m, 2H, *H*-14), 5.75-5.97 (m, 1H, *H*-13), 6.04 (d, *J* = 3.9 Hz, 1H, *H*-8), 6.85 (d, *J* = 9.2 Hz, 2H, Ar), 7,62 (d, *J* = 9.2 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.6, 39.4, 51.6, 55.4, 70.9, 81.2, 82.8, 82.9, 105.7, 111.7, 114.0, 118.5, 118.9, 131.9, 133.3, 156.0, 163.7.

MS: m/z = 376 (M+1).

Anal. **Calcd**. for **$C_{20}H_{25}NO_6$**: C, 63.99; H, 6.71; N, 3.73%

Found C, 63.87; H, 6.75; N, 3.89%

4.6.10: Synthesis of 3-O-allyl β-lactam 4.13:

Sodium hydride (66 mg, 1.65 mmole) was washed with pet. ether (2 x 2 mL). To a suspension of sodium hydride in THF (2 mL) at 0 °C, 3-hydroxy β-lactam **4.08** (0.430 g, 1.10 mmol) in THF (10 mL) was added dropwise. After stirring for 30 min allyl bromide (0.104 mL, 1.21 mmol) in THF (3 mL) was added dropwise to the reaction mixture. Tetrabutyl ammonium iodide (25 mg) was added and the reaction mixture stirred at room temperature for 3 h. Reaction mixture was quenched with Sat. NH_4Cl (2 mL) at 0 °C. THF was evaporated under reduced pressure and resulting residue was extracted with CH_2Cl_2 (2 x 10 mL). Dichloromethane was removed under reduced pressure to get crude **4.13**, which is further purified by flash column chromatography (EtOAc/pet. ether, 2:8 as eluent) to afford pure **4.13** (0.430 g, 91%) as a thick liquid.

$[\alpha]_D^{25}$ = -206.7 (*c* 0.60, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1745 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3), 3.78 (s, 3H, Ar-OCH_3), 3.92-4.26 (m, 3H, *H*-12, *H*-6), 4.28 (d, *J* = 2.9 Hz, 1H, *H*-5), 4.40-4.48 (m, 3H, *H*-15, *H*-4), 4.60 (d, *J* = 3.9 Hz, 1H, *H*-7), 4.76 (d, *J* = 5.2 Hz, 1H, *H*-3), 5.19-5.41 (m, 4H, 2 x -CH=CH_2), 5.81-5.98 (m, 2H, 2 x -C*H*=CH_2), 6.02 (d, *J* = 3.9 Hz, 1H, *H*-8), 6.84 (d, *J* = 9.2 Hz, 2H, Ar), 7,66 (d, *J* = 9.2 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 26.7, 55.4, 58.7, 70.8, 72.2, 80.1, 81.5, 81.9, 82.9, 104.8, 111.6, 113.9, 117.4, 118.0, 119.6, 131.3, 133.5, 133.9, 156.3, 165.1.

MS: m/z = 432 (M+1).

Anal. Calcd. for **$C_{23}H_{29}NO_7$:** C, 64.02; H, 6.77; N, 3.25%

Found C, 64.26; H, 6.98; N, 3.33%.

4.6.11: Synthesis of 3-keto β-lactam 4.14:

3-Hydroxy β-lactam **4.08** (1.96 g, 5 mmol) was dissolved in EtOAc (50 mL). iodoxo benzoic acid (IBX) (2.12 g, 7.5 mmol) was added in one portion to the above reaction mixture and refluxed for 7 h. Allowed to come to room temperature filtered through celite bed using sintered funnel. Filtrate obtained was evaporated under reduced pressure to get 3-keto β-lactam **4.14** (1.8 g, 92% yield) as a fluppy solid which is used as such for next reaction.

$[\alpha]_D^{25}$ = -111.0 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1759 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 3H, -C*H*$_3$), 1.42 (s, 3H, -C*H*$_3$), 3.77 (s, 3H, Ar-OC*H*$_3$), 3.99 (d, *J* = 3.2 Hz, 1H, *H*-6), 4.10-4.19 (m, 2H), 4.46 (dd, *J* = 3.2 Hz, 3.2 Hz, 1H, H-5), 4.59 (d, *J* = 3.8 Hz, 1H, *H*-7), 4.98 (d, *J* = 7.6 Hz, 1H, *H*-4), 5.20-5.36 (m, 2H, *H*-14) 5.86-6.01 (m, 1H, *H*-13), 6.03 (d, *J* = 3.8 Hz, 1H, *H*-8), 6.94 (d, *J* = 9.1 Hz, 2H, Ar), 7,75 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.6, 55.4, 71.4, 71.5, 79.2, 81.5, 82.1, 105.3, 112.0, 114.5, 118.5, 119.7, 130.4, 133.4, 157.9, 159.9, 190.2.

MS: m/z = 390 (M+1).

Anal. Calcd. for **$C_{20}H_{25}NO_6$:** C, 61.69; H, 5.95; N, 3.60%

Found C, 61.77; H, 6.04; N, 3.76%.

4.6.12: Synthesis of 3-hydroxy 3-allyl β-lactam 4.15:

To a stirred solution of 3-keto β-lactam **4.14** (0.4 g, 1.03 mmol) in THF (15mL) at 0 °C was added allyl magnesium bromide (1.545 mmol) which was generated from activated Mg metal and allyl magnesium bromide in dry THF at 0 °C. After completion of reaction (TLC) excess Grignard reagent was quenched using sat. NH_4Cl solution (5 mL). Solvents were removed *in vacuo* and resulting residue was extracted with EtOAc (2 x 15 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude reaction mixture

was purified by flash column chromatography (EtOAc/pet. ether, 3:7 as eluent) to afford an inseperable diasteromeric mixture of 3-hydroxy 3-allyl β-lactam **4.15** (0.310 g, 70%) in 3:1 ratio as viscous liquid.

$[\alpha]_D^{25}$ = -100.0 (*c* 0.26, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1716 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29, 1.31 (s, 3H, -C*H*$_3$), 1.42, 1.44 (s, 3H, -C*H*$_3$), 2.58-2.76 (m, 2H, -C*H*$_2$-CH=CH2), 3.75, 3.77 (s, 3H, Ar-OC*H*$_3$), 4.00-4.22 (m, 3H, -O*H*, OC*H*$_2$-CH=CH$_2$), 4.31-4.41 (m, 2H, *H*-4, *H*-6), 4.47-4.58 (m, 1H, *H*-5), 4.60 (d, *J* = 3.9 Hz, 1H, *H*-7), 5.11-5.43 (m, 4H, 2 x -CH=C*H*$_2$), 5.71-5.98 (m, 2H, 2 x -C*H*=CH$_2$), 6.02 (d, *J* = 3.8 Hz, 1H, *H*-8), 6.76-6.84 (m, 2H, Ar), 7.53-7.62 (m, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3, 26.7, 40.4, 55.4, 63.1, 70.8, 81.3, 81.8, 82.9, 83.0, 104.8, 111.6, 113.9, 117.9, 119.9, 120.6, 121.3, 130.8, 131.1, 133.8, 156.5, 168.2.

MS: m/z = 432 (M+1).

Anal. Calcd. for **$C_{23}H_{29}NO_7$:** C, 64.02; H, 6.77; N, 3.25%

Found C, 64.35; H, 6.52; N, 3.43%

4.6.13: General procedure for synthesis of *N*-allyl-*O*-allyl β-lactams 4.16a-b:

A solution of the acid chlorides (1.5 mmol) in CH_2Cl_2 (10 mL) were added to a solution of the imine **4.06b** (1 mmol) and Et_3N (4.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After the addition was completed the reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The reaction mixture was then washed with water (1 x 10 mL), sat. $NaHCO_3$ solution (15 mL), saturated brine solution (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated to give the β-lactams **4.16a-b**, which were then purified by column chromatography (silica gel 60-120 mesh) to get the pure β-lactams.

4.6.13a: Synthesis of *N*-allyl-*O*-allyl β-lactams 4.16a:

Following a general procedure, imine **4.06b** (0.267 g, 1 mmol) on reaction with methoxy acetyl chloride (0.14 mL, 1.5 mmol) in presence of Et_3N (0.63 mL, 4.5 mmol) gave **4.16a**. The crude product was purified by flash column chromatography (EtOAc/pet. ether, 3:7 as eluent) to afford pure β-lactam **4.16a** as a viscous liquid (0.22 g, 65%).

$[\alpha]_D^{25}$ = -208.5 (*c* 0.70, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1747cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H, -C*H*$_3$), 1.48 (s, 3H, -C*H*$_3$), 3.56 (s, 3H, -OC*H*$_3$), 3.67-3.95 (m, 2H, NC*H*$_2$-CH=CH$_2$), 3.95-4.05 (m, 2H, OC*H*$_2$-CH=CH$_2$), 4.07 (d, *J* = 3.4 Hz, 1H, *H*-6), 4.11-4.16 (m, 1H, *H*-4), 4.28 (dd, *J* = 3.4 Hz, 3.4 Hz, 1H, *H*-5), 4.48 (d, *J* = 5.0 Hz, 1H, *H*-3), 4.53 (d, *J* = 3.8 Hz, 1H, *H*-7), 5.13-5.32 (m, 4H, 2 x -CH=C*H*$_2$), 5.68-5.89 (m, 2H, 2 x -C*H*=CH$_2$), 5.93 (d, *J* = 3.8 Hz, 1H, *H*-8).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 26.8, 43.6, 56.6, 59.1, 70.9, 81.5, 82.1, 82.3, 83.0, 104.9, 111.6, 117.5, 118.3, 131.4, 133.8, 167.2.

MS: m/z = 340 (M+1).

Anal. Calcd. for **$C_{17}H_{25}NO_6$**: C, 60.16; H, 7.42; N, 4.13%

Found C, 60.27; H, 7.18; N, 4.03%

4.6.13b: Synthesis of *N*-allyl-*O*-allyl β-lactams 4.16b:

Following a general procedure, imine **4.06b** (0.267 g, 1 mmol) on reaction with phenoxy acetyl chloride (0.21 mL, 1.5 mmol) in presence of Et_3N (0.63 mL, 4.5 mmol) gave crude **4.16b**. The crude product was purified by flash column chromatography (EtOAc/pet. ether, 25:75) to afford pure β-lactam **4.16b** as a thick liquid (0.280 g, 70%).

$[\alpha]_D^{25}$ = -206.2 (*c* 0.65, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1759cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H, -C*H*$_3$), 1.52 (s, 3H, -C*H*$_3$), 3.69-3.90 (m, 2H, NC*H*$_2$-CH=CH$_2$), 3.98-4.11 (m, 2H, OC*H*$_2$-CH=CH$_2$), 4.13-4.18 (m, 1H, *H*-6), 4.23 (d, *J* = 5.0 Hz, 1H, *H*-4), 4.48 (dd, *J* = 3.4 Hz, 3.4 Hz, 1H, *H*-5), 4.57 (d, *J* = 3.8 Hz, 1H, *H*-7), 5.09-5.26 (m, 4H, 2 x -CH=C*H*$_2$), 5.31 (d, *J* = 4.9 Hz, 1H, *H*-3), 5.66-5.93 (m, 2H, 2 x -C*H*=CH$_2$), 5.97 (d, *J* = 3.8 Hz, 1H, *H*-8), 6.90-7.35 (m, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3, 26.9, 44.0, 56.6, 70.7, 79.9, 81.5, 82.1, 82.2, 105.0, 111.8, 115.6, 117.6, 118.7, 122.3, 129.6, 131.3, 133.7, 157.5, 165.6.

MS: m/z = 402 (M+1).

Anal. Calcd. for **$C_{22}H_{27}NO_6$**: C, 65.82; H, 6.78; N, 3.49%

Found C, 65.89; H, 6.97; N, 3.63%.

4.6.14: 3-*O*-Benzyl-1,2;5,6 di-*O*-isopropylidene-α-D-glucofuranose (4.17):

Sodium hydride (2.32 g, 56 mmol) was washed with pet. ether (2 x 20 mL) To a suspension of sodium hydride in THF (20 mL) at 0 °C, solution of the glucose diacetonide **4.02** (10 g, 0.038 mol) in THF (40 mL) was added dropwise. After stirring for 30 min, benzyl bromide (4.6 mL, 0.038 mol) in THF (30 mL) was added dropwise to the reaction mixture. Tetrabutyl ammonium iodide (0.712 g, 1.92 mmol) was added and the reaction mixture stirred at room temperature for 2.5 h. The reaction mixture was poured into 20 mL of ice-cold water. THF was evaporated and the resulting reaction mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* to give a thick liquid which was further purified by column chromatography (silica gel 60-120 mesh, EtOAc/pet. ether, 2:8 as eluent) to give **4.17** (12.10 g, 90%).

4.6.15: 3-*O*-Benzyl-1,2-*O*-isopropylidene–α-D-glucofuranose (4.18):

3-O-benzyl-1,2;5,6 di-O-isopropylidene–α-D-glucofuranose **4.17** (10 g, 28.57 mmol) was dissolved in 40 mL of aqueous acetic acid (75%v/v) and heated to 75 °C for 3 hrs. The solvents were removed under reduced pressure. Resulting mass was dissolved in CH_2Cl_2 and washed with H_2O (1 x 10 mL), saturated $NaHCO_3$ solution (1 x 10 mL), and saturated brine solution (1 x 10 mL), dried over Na_2SO_4 and concentrated to get diol **4.18** (7.1 g, 81%) as a viscous oil which was used as such for the next reaction without further purification.

4.6.16: Synthesis of 3-O-allyl-1,2 -O-isopropylidene–α-D-glucofuranose aldehyde (4.19):

To a vigorously stirred suspension of chromatographic grade silica gel (52 g) in CH_2Cl_2 (250mL) in 500 mL flask was added a 0.65 M aqueous solution of $NaIO_4$ (52 mL) dropwise with stirring. Diol **4.18** (8.0 g, 25.80 mmol) in CH_2Cl_2 (50 mL) was then added and the reaction was monitored by TLC until disappearance of the starting material (30 min). The mixture was filtered through Buchner funnel washed with water, dried over Na_2SO_4 and concentrated to give pure aldehyde **4.19** (6.75 g, 94%) as viscous liquid which was then used as such for imine formation.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H, -C*H*$_3$), 1.48 (s, 3H, -C*H*$_3$), 4.35 (d, *J* = 3.7 Hz, 1H, *H*-2), 4.49 (d, *J* = 11.8 Hz, 1H, -OC*H*$_a$H$_b$Ph), 4.57-4.61 (m, 2H, -OCH$_a$*H*$_b$Ph, *H*-3),

4.65 (d, *J* = 3.3 Hz, 1H, *H*-1), 6.13 (d, *J* = 3.5 Hz, 1H, *H*-4), 7.21-7.40 (m, 5H, Ar), 9.68 (d, *J* = 1.7 Hz, 1H, -C*H*O)

4.6.17: Procedure for synthesis of imine 4.20:

To a solution of *p*-anisidine (2.417 g, 19.62 mmol) in CH_2Cl_2 and anhydrous $MgSO_4$ (2.354 g, 19.62 mmol) a solution of aldehyde (6.0 g, 21.58 mmol) in CH_2Cl_2 were added at room temperature. The reaction mixture was stirred for 6 to 7 h and filtered through a sintered glass crucible. The filtrate was concentrated to get imine **4.20** (quantitative yield) which was used as such for the β-lactam formation.

4.6.18 General procedure for synthesis of β-lactam 4.21a-b:

A solution of the acid chloride (phenoxy acetyl chloride, methoxy acetyl chloride) (1.5 mmol) in CH_2Cl_2 (10 mL) were added to a solution of the imine **4.20** (1 mmol) and Et_3N (4.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After the addition was completed the reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The reaction mixture was then washed with water (10 mL), sat. $NaHCO_3$ solution (15 mL), sat. brine solution (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated to give the crude β-lactams **4.21a-b**, which were purified by column chromatography (silica gel 60-120 mesh).

4.6.18a: Synthesis of β-lactam 4.21a:

Following a general procedure, imine **4.20** (4.0 g, 10.44 mmol) on reaction with phenoxy acetyl chloride (2.16 mL, 15.66 mmol) in presence of Et_3N (6.55 mL, 47.0 mmol) gave crude β-lactam **4.21a**, which was purified by column chromatography (EtOAc/pet. ether 15:85 as eluent) to get a pure **4.21a** as a white crystalline solid (3.7 g, 68%).

m.p. 148 °C

$[\alpha]_D^{25}$ = -258.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): ν_{max} 1749 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H, -C*H*$_3$), 1.50 (s, 3H, -C*H*$_3$), 3.80 (s, 3H, -Ar-OC*H*$_3$), 4.30 (d, *J* = 11.5 Hz, 1H, -OC*H*$_a$H$_b$Ph), 4.44 (d, *J* = 3.1 Hz, 1H, *H*-6), 4.60-4.77 (m,

4H, -OCH$_a$$H_b$Ph, *H*-4, *H*-5, *H*-8), 5.31 (d, *J* = 5.3 Hz, *H*-3), 6.07 (d, *J* = 3.9 Hz, 1H, *H*-8), 6.86 (d, *J* = 9.1 Hz, 2H, Ar), 7.00-7.35 (m, 10 H, Ar), 7.70 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (50 MHz, CDCl$_3$): δ 26.3, 26.8, 55.4, 58.4, 71.9, 79.1, 81.4, 81.8, 83.1, 104.9, 111.8, 113.9, 115.6, 119.8, 122.4, 127.6, 128.0, 128.5, 129.6, 131.1, 137.1, 156.5, 157.3, 163.4.

MS: m/z = 518 (M+1)

Anal. Calcd. for **$C_{22}H_{27}NO_8$:** C, 69.62; H, 6.04; N, 2.71%

Found C, 69.83; H, 6.32; N, 2.95%.

4.6.18b: Synthesis of β-lactam 4.21b:

Following a general procedure, imine **4.20** (4.0 g, 10.44 mmol) on reaction with methoxy acetyl chloride (1.43 mL, 15.66 mmol) in presence of Et_3N (6.51 mL, 47.0 mmol) gave crude **4.21b**, which was purified by column chromatography (EtOAc/pet. ether, 2:8 as eluent) to get a pure **4.21b** as white crystalline solid (3.5 g, 73%) as a viscous liquid.

$[\alpha]_D^{25}$ = -215.60 (*c* 1.0, $CHCl_3$)

IR (CHCl$_3$): ν_{max} 1743 cm^{-1}

^{1}H NMR (200 MHz, CDCl$_3$): δ 1.32 (s, 3H, C*H*$_3$), 1.46 (s, 3H, C*H*$_3$), 3.47 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, -OC*H*$_3$), 4.32 (d, *J* = 3.2 Hz, 1H, *H*-6), 4.37-4.55 (m, 4H, *H*-3, *H*-4, *H*-5, -OH$_a$$H_b$Ph), 4.65 (d, *J* = 3.9 Hz, 1H, *H*-7), 4.72 (d, *J* = 11.6 Hz, -O*H*$_a$H$_b$Ph), 6.04 (d, *J* = 3.9 Hz, 1H, *H*-8), 6.83 (d, *J* = 9.1 Hz, 2H, Ar), 7.31-7.39 (m, 5H, Ar), 7.65 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (50 MHz, CDCl$_3$): δ 26.1, 26.7, 55.3, 58.3, 58.9, 71.8, 81.2, 81.8, 82.0, 82.5, 104.8, 111.6, 113.8, 119.5, 127.8, 128.1, 128.5, 131.2, 137.3, 156.2, 165.1.

MS: m/z = 456 (M+1)

Anal. Calcd. for **$C_{22}H_{27}NO_8$:** C, 65.92; H, 6.42; N, 3.08%

Found C, 66.12; H, 6.63; N, 3.37%.

4.6.19: General procedure for synthesis of 6-hydroxy β-lactams 4.22a-b:

Compound **4.21a-b** (5 mmol) was dissolved in EtOAc (30 mL) and Pd/C (10%) (500 mg) was added to it. The mixture was hydrogenated at 60 Psi of H_2 in a parr hydrogenator for 24 h at room temperature. After completion of reaction catalyst was

removed by filtration through Celite and washed with EtOAc and the solvent was distilled off under reduced pressure to afford 6-hydroxy β-lactams **4.22a-b** in quantitative yield as a white solid.

4.6.19a: Synthesis of 3-phenoxy substituted 6-hydroxy β-lactam 4.22a:

Following a general procedure, 3-phenoxy substituted 6-hydroxy β-lactam **4.22a** (2.0 g, 93%) was obtained as a white solid.

m.p. 160-162 °C

$[\alpha]_D^{25}$ = -220.0 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1743, 3400 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 3H, -C*H*$_3$), 1.47 (s, 3H, -C*H*$_3$), 1.96 (bs, 1H, -O*H*), 3.79 (s, 3H, Ar-OC*H*$_3$), 4.49-4.65 (m, 4 H, *H*-4, *H*-5, *H*-6, *H*-7), 5.41 (d, *J* = 5.3 Hz, 1H, *H*-3), 6.04 (d, *J* = 3.8 Hz, 1H, *H*-8), 6.87 (d, *J* = 9.1 Hz, 2H, Ar), 7.00-7.37 (m, 5H, Ar), 7.69 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 26.7, 55.4, 58.9, 75.6, 79.2, 81.6, 85.6, 104.6, 111.9, 114.0, 115.7, 119.8, 122.6, 129.7, 131.0, 156.6, 157.6, 163.4.

MS: m/z = 428 (M+1)

Anal. Calcd. for **$C_{23}H_{25}NO_7$:** C, 64.63; H, 5.90; N, 3.28%

Found C, 64.85; H, 5.97; N, 3.43%.

4.6.19b: Synthesis of 3-methoxy substituted hydroxy β-lactam (4.22b):

Following a general procedure 3-methoxy substituted 6-hydroxy β-lactam **4.22b** (1.64 g, 90%) was obtained as a white solid.

m.p. 178-180 °C

$[\alpha]_D^{25}$ = -210.0 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1747, 3475 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 3H, -C*H*$_3$), 1.44 (s, 3H, -C*H*$_3$), 1.99 (bs, 1H, -O*H*), 3.68 (s, 3H, -OC*H*$_3$), 3.78 (s, 3H, Ar-OC*H*$_3$), 4.34-4.58 (m, 4 H, *H*-4, *H*-5, *H*-6, *H*-7), 4.69 (d, *J* = 5.2 Hz, 1H, *H*-3), 6.03 (d, *J* = 3.6 Hz, 1H, *H*-8), 6.85 (d, *J* = 9.1 Hz, 2H, Ar), 7.65 (d, *J* = 9.1 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 26.7, 55.4, 59.0, 59.4, 75.4, 81.6, 82.2, 85.5, 104.5, 111.7, 119.7, 131.0, 156.5, 157.6, 165.0.

MS: m/z = 366 (M+1)

Anal. Calcd. for **$C_{18}H_{23}NO_7$:** C, 59.17; H, 6.34; N, 3.83 %

Found: C, 59.37; H, 6.44; N, 3.80 %.

4.6.20: General procedure for synthesis of 6-keto β-lactam 4.23a-b:

6-Hydroxy β-lactams **4.22a-b** (4 mmol) was dissolved in acetonitrile (40 mL). Iodoxo benzoic acid (IBX) (6 mmol) was added to it. Reaction mixture was refluxed for 7 h, allowed to come to room temperature and filtered through Celite, concentrated under reduced pressure to afford 6-keto β-lactam **4.23a-b** (85-90%) which were pure enough for next reaction.

Data for Compound **4.23a:**

m.p. 176-177 °C

$[\alpha]_D^{25}$ = +22.2 (*c* 0.36, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1745, 1705 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H, C*H*$_3$), 1.43 (s, 3H, C*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$), 4.13 (dd, *J* = 4.3 Hz, 1.0 Hz, 1H, *H*-7), 4.77 (dd, *J* = 2.9 Hz, 1.0 Hz, 1H, *H*-5), 4.86 (dd, *J* = 4.8 Hz, 2.9 Hz, 1H, *H*-4), 5.45 (d, *J* = 4.8 Hz, 1H, *H*-3), 5.68 (d, *J* = 4.3 Hz, 1H, *H*-8), 6.91 (d, *J* = 9.1 Hz, 2H, Ar), 7.12 (d, *J* = 9.1 Hz, 2H, Ar), 7.26-7.40 (m, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.1, 27.5, 55.5, 58.5, 73.7, 76.5, 80.1, 103.4, 114.3, 114.7, 116.1, 119.9, 123.2, 129.3, 129.8, 157.1, 162.2, 208.3.

MS: m/z = 426 (M+1)

Anal. Calcd. for **$C_{23}H_{23}NO_7$:** C, 64.93; H, 5.45; N, 3.29%

Found: C, 64.77; H, 5.37; N, 3.41%.

Data for Compound **4.23b:**

$[\alpha]_D^{25}$ = -40.0 (*c* 0.4, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1747 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 3H, -C*H*$_3$), 1.45 (s, 3H, -C*H*$_3$), 3.63 (s, 3H, -OC*H*$_3$), 3.79 (s, 3H, Ar-OC*H*$_3$), 4.22 (d, *J* = 4.3 Hz, 1H, *H*-7), 4.58-4.74 (m, 3H, *H*-3, *H*-4, *H*-5), 5.91(d, *J* = 4.3 Hz, 1H, *H*-8), 6.88 (d, *J* = 9.0 Hz, 2H, Ar), 7.30 (d, *J* = 9.0 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.1, 27.6, 55.4, 58.1, 59.1, 73.4, 76.4, 82.1, 103.6, 114.2, 114.5, 119.5, 129.5, 156.8, 163.5, 207.5.

MS: m/z = 364 (M+1)

Anal. Calcd. for **$C_{18}H_{21}NO_7$:** C, 59.50; H, 5.83; N, 3.85%

Found C, 59.67; H, 6.02; N, 3.97%.

4.6.21: General procedure for synthesis of vinylic dibromo compounds 4.24a-b:

To a flame dried two neck round bottom flask of 100 mL, a solution of ketone **4.23a-b** (3 mmol) in dry toluene (40 mL) was added. To this solution PPh_3 (3.94 g, 15 mmol) in dry toluene (15 mL) was added followed by the slow addition of CBr_4 (2.50 g, 7.5 mmol) in dry toluene (15 mL). This reaction mixture was allowed to stir at room temperature for 10 min and then heated at 80 °C for 12 h. Allowed to cool to room temperature filtered, concentrated *in vacuo* to give crude **4.24a-b**, which on purification by column chromatography (silica gel 60-120 mesh) gave pure compound **4.24a-b**.

4.6.21a: Synthesis of 3-phenoxy-vinyl-dibromo compound 4.24a:

By following a general procedure keto β-lactam **4.23a** (1.28 g, 3 mmol) converted to compound **4.24a**, which on column chromatography (silica gel 60-120 mesh, EtOAc/pet. ether; 15:85 as eluent) gave pure compound **4.24a** (1.12 g, 63%) as a pale yellow solid.

m.p. 134-135 °C

$[\alpha]_D^{25}$ = +112.0 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1758 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H, -C*H*$_3$), 1.40 (s, 3H, -C*H*$_3$), 3.83 (s, 3H, ArOC*H*$_3$), 4.13 (dd, *J* = 1.5 Hz, 4.4 Hz, 1H, *H*-7), 5.10 (d, *J* = 1.5 Hz, 1H, *H*-5), 5.14 (d, *J* = 5.2 Hz, 1H, *H*-4), 5.38 (d, *J* = 5.2 Hz, 1H, *H*-3), 5.68 (d, *J* = 4.4 Hz, 1H, *H*-8), 6.93 (d, *J* = 9.1 Hz, 2H, Ar), 7.02-7.40 (m, 7H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.2, 27.3, 55.3, 57.8, 78.7, 79.0, 82.3, 88.6, 106.3, 113.3, 114.6, 115.6, 119.5, 122.4, 128.1, 129.1, 129.5, 145.9, 156.6, 157.4, 163.0.

MS: m/z = 582 (M+1)

Anal. Calcd. for **$C_{24}H_{23}NO_6Br_2$:** C, 49.59; H, 3.99; N, 2.41%

Found C, 49.72; H, 4.27; N, 2.53%.

4.6.21b: Synthesis of 3-methoxy-vinyl-dibromo compound (4.24b):

By following a general procedure keto β-lactam **4.23b** (1.10 g, 3 mmol) converted to compound **4.24b**, which on column chromatography (silica gel 60-120 mesh, EtOAc/pet. ether, 2:8 as eluent) gave pure compound **4.24b** (0.932 g, 60%) as a pale yellow solid.

m.p. 128-130 °C

$[\alpha]_D^{25}$ = +115.1 (*c* 1.06, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1755 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H, C*H*$_3$), 1.44 (s, 3H, C*H*$_3$), 3.68 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, Ar-OC*H*$_3$), 4.14 (dd, *J* = 1.5 Hz, 4.4 Hz, 1H, *H*-7), 4.66 (d, *J* = 5.2 Hz, 1H, *H*-4), 4.90 (d, *J* = 5.2 Hz, 1H, *H*-3), 5.09 (m, 1H, *H*-5), 5.63 (d, *J* = 4.4 Hz, 1H, *H*-8), 6.89 (d, *J* = 9.0 Hz, 2H, Ar), 7.28 (d, *J* = 9.0 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.4, 27.5, 55.4, 57.6, 59.8, 79.1, 82.4, 82.7, 88.4, 106.3, 113.5, 114.6, 119.5, 129.4, 146.3, 156.6, 165.0.

MS: m/z = 520 (M+1)

Anal. Calcd. for **$C_{19}H_{21}NO_6Br_2$:** C, 43.95; H, 4.08; N, 2.70%

Found C, 43.68; H, 4.15; N, 2.66%.

4.6.22: Synthesis of N-unsubstituted β-lactam 4.25a:

A solution of **4.24a** (1.0 g, 1.72 mmol) in acetonitrile (30 mL) was cooled to 0 °C and treated with a solution of CAN (2.83 g, 5.17 mmol) in water (24 mL) over 3 min. The reaction mixture was stirred at 0 °C for 25 min and diluted with water (120 mL). The mixture was extracted with EtOAc (3 x 25 mL). The organic extracts were washed with 5% $NaHCO_3$ (2 x 30 mL) and the aqueous extracts back washed with EtOAc (20 mL). The combined organic layer was washed with 10% sodium sulfite (until the aqueous layer remained colourless), 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, evaporated under reduced pressure to yield the crude product **4.25a** which was then purified by flash column chromatography on silica gel (EtOAc/pet. ether 3:7 as eluent) to get pure **4.25a** (0.680 g, 83%) as a moisture sensitive white solid.

$[\alpha]_D^{25}$ = +93.4 (*c* 0.57, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1770 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 4.48 (dd, *J* = 5Hz, 1.5 Hz, 1H, *H*-4), 5.07 (m, 1H, *H*-5), 5.10 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H, *H*-7), 5.28 (d, *J* = 5.1 Hz, 1H, *H*-3), 6.10 (d, *J* = 4.2 Hz, 1H, *H*-8), 6.87 (bs, 1H, N-H), 7.03-7.11 (m, 3H, Ar), 7.29-7.35 (m, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.3, 27.5, 55.5, 80.1, 80.6, 82.9, 89.1, 106.0, 113.5, 115.7, 122.5, 129.7, 144.8, 157.5, 168.1.

MS: m/z = 476 (M+1)

Anal. Calcd. for **$C_{17}H_{17}NO_5Br_2$:** C, 42.97; H, 3.61; N, 2.95 %

Found: C, 42.75; H, 3.83; N, 2.83 %.

4.6.23: Synthesis of N-unsubstituted β-lactam 4.25b:

A solution of **4.24b** (0.80 g, 1.54 mmol) in acetonitrile (25 mL) was cooled to 0 °C and treated with a solution of CAN (2.54 g, 4.63 mmol) in water (22 mL) over 3 min. The reaction mixture was stirred at 0 °C for 25 min and diluted with water (110 mL). Following the similar workup procedure as for compound **4.25a** we get crude product **4.25b** which was then purified by flash column chromatography on silica gel (30% EtOAc/pet. ether as eluent) to get pure **4.25b** (0.478 g, 75%) as a white solid.

m.p. 188-190 °C (dec.)

IR (Nujol): 1767cm^{-1}

$[\alpha]_D^{25}$ = +88.0 (*c* 0.5, $CHCl_3$)

^{1}H NMR (200 MHz, Acetone-d_6): δ 1.39 (s, 3H, C*H*$_3$), 1.44 (s, 3H, C*H*$_3$), 3.53 (s, 3H, -OC*H*$_3$), 4.28 (dd, *J* = 5.1 Hz, 1.4 Hz, 1H, *H*-4), 4.62 (dd, *J* = 5.0 Hz 1.9 Hz, 1H, *H*-3), 5.06 (t, *J* = 1.4 Hz, 1H, *H*-5), 5.14 (dd, *J* = 4.4 Hz, 1.7 Hz, 1H, *H*-7), 6.03 (d, *J* = 4.4 Hz, 1H, *H*-8), 7.31 (bs, 1H, -CON*H*).

^{13}C NMR (50 MHz, Acetone-d_6): δ 27.4, 27.5, 55.4, 57.6, 59.8, 79.1, 82.4, 82.7, 88.4, 106.3, 113.5, 114.6, 119.5, 129.4, 146.3, 156.6, 165.0.

MS: m/z = 414 (M+1)

Anal. Calcd. for **$C_{12}H_{15}NO_5Br_2$:** C, 34.89; H, 3.66; N, 3.39%

Found C, 34.95; H, 3.72; N, 3.67%.

4.6.24: Typical procedure for C-N bond forming reaction: (Run 1 table 2 method B)

To a suspension of $Pd(OAc)_2$ (2.5 mg, 0.0111mmol), DPEphos (8.9 mg, 0.0165 mmol) in toluene (0.5 mL) was added a solution of **4.25a** (52.3 mg, 0.110 mmol) in toluene (2.5 mL) at 0 °C followed by degassed, and the mixture was stirred at 100 °C for 2 min. To a suspension of K_2CO_3 (30.4 mg, 0.220 mmol) in toluene (1 mL) was added the mixture at 0 °C followed by degassed, and the mixture was stirred at 100 °C for 22 h. After removal of the solvent, resulting residue was column chromatographed to separate product from catalyst and base used, which gave an inseparable mixture of unidentified products.

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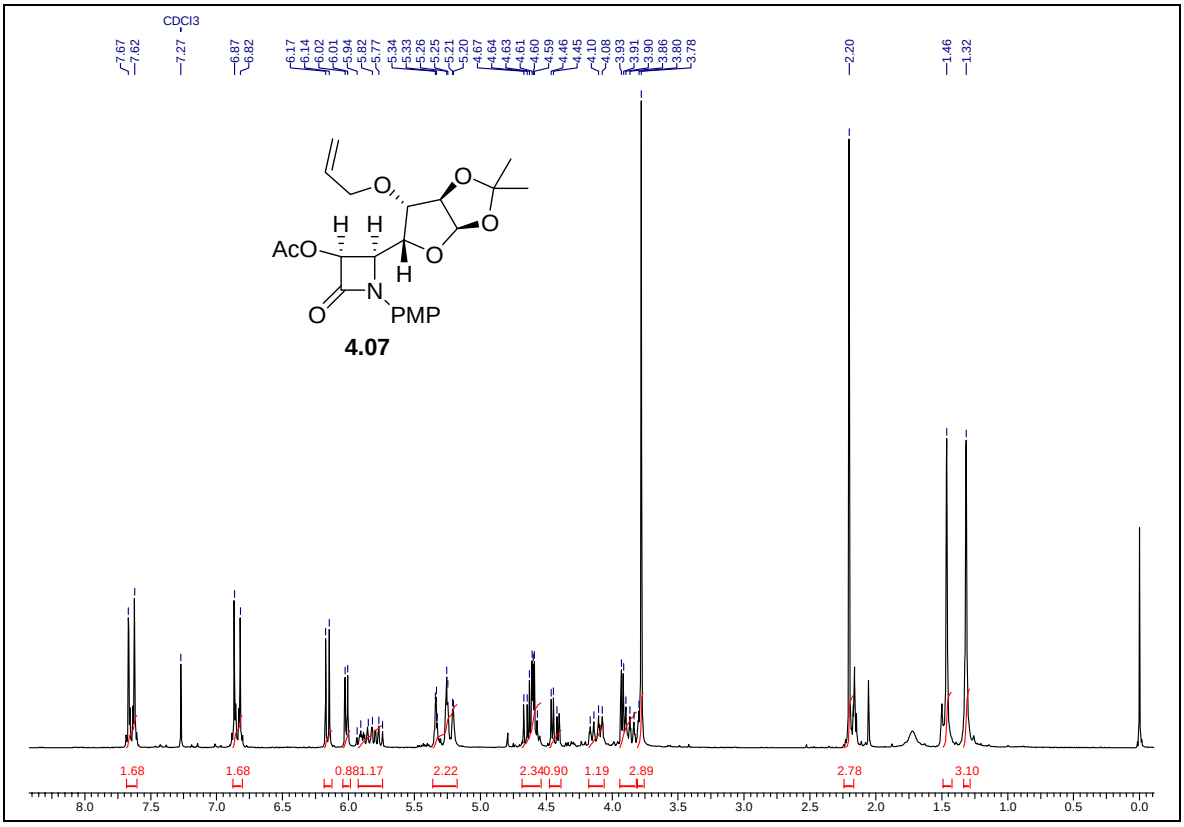
Chapter IV

Spectra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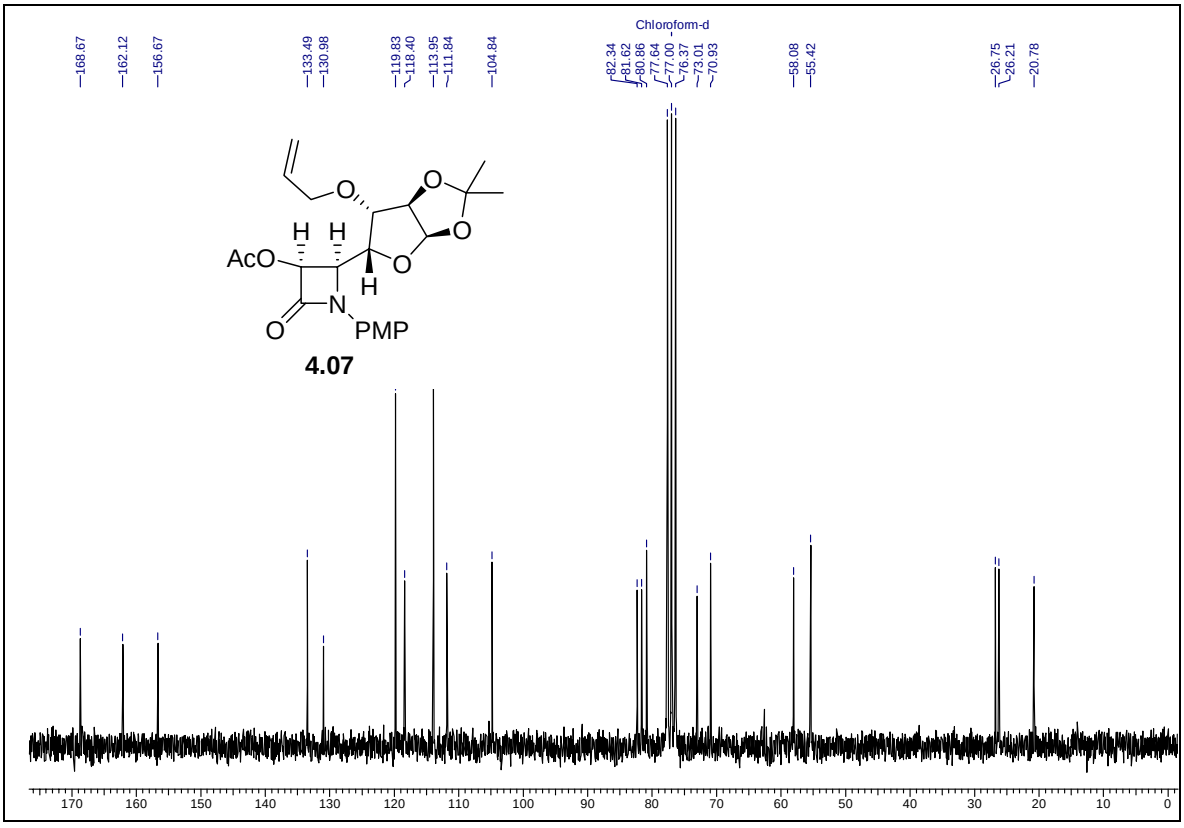
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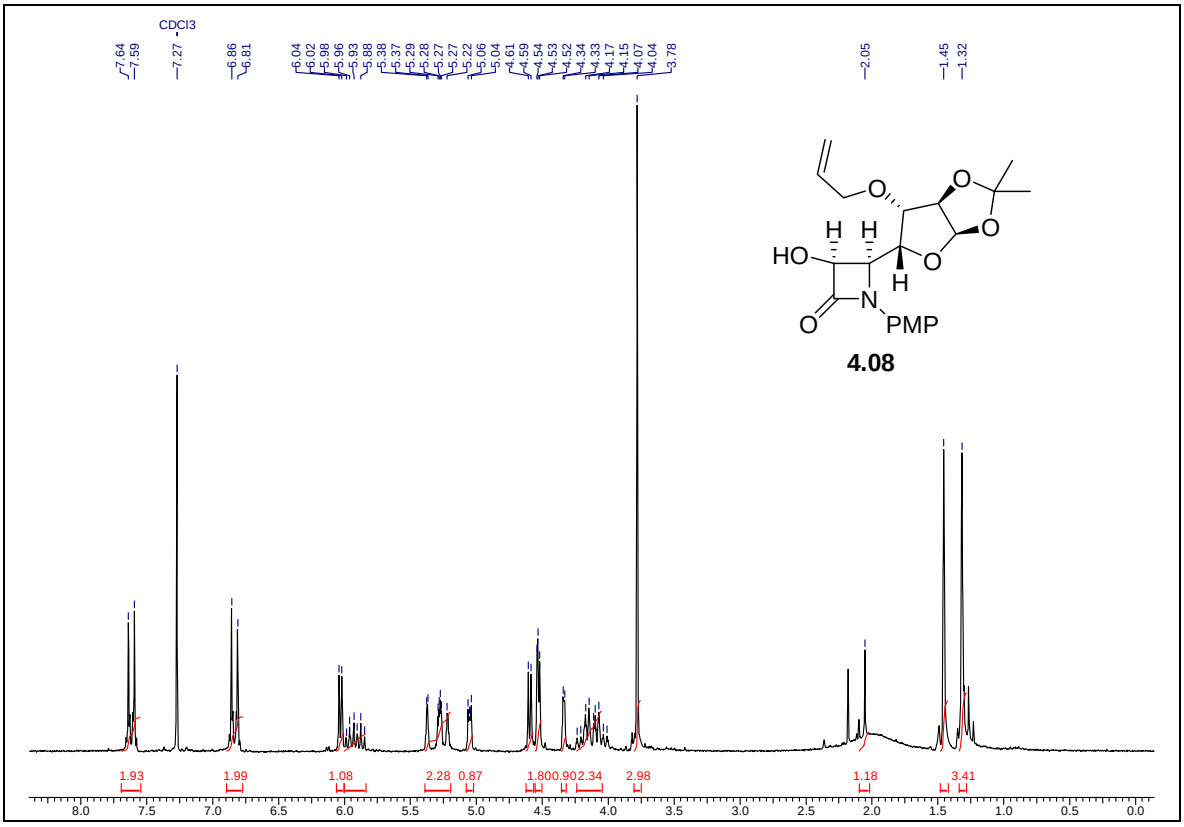
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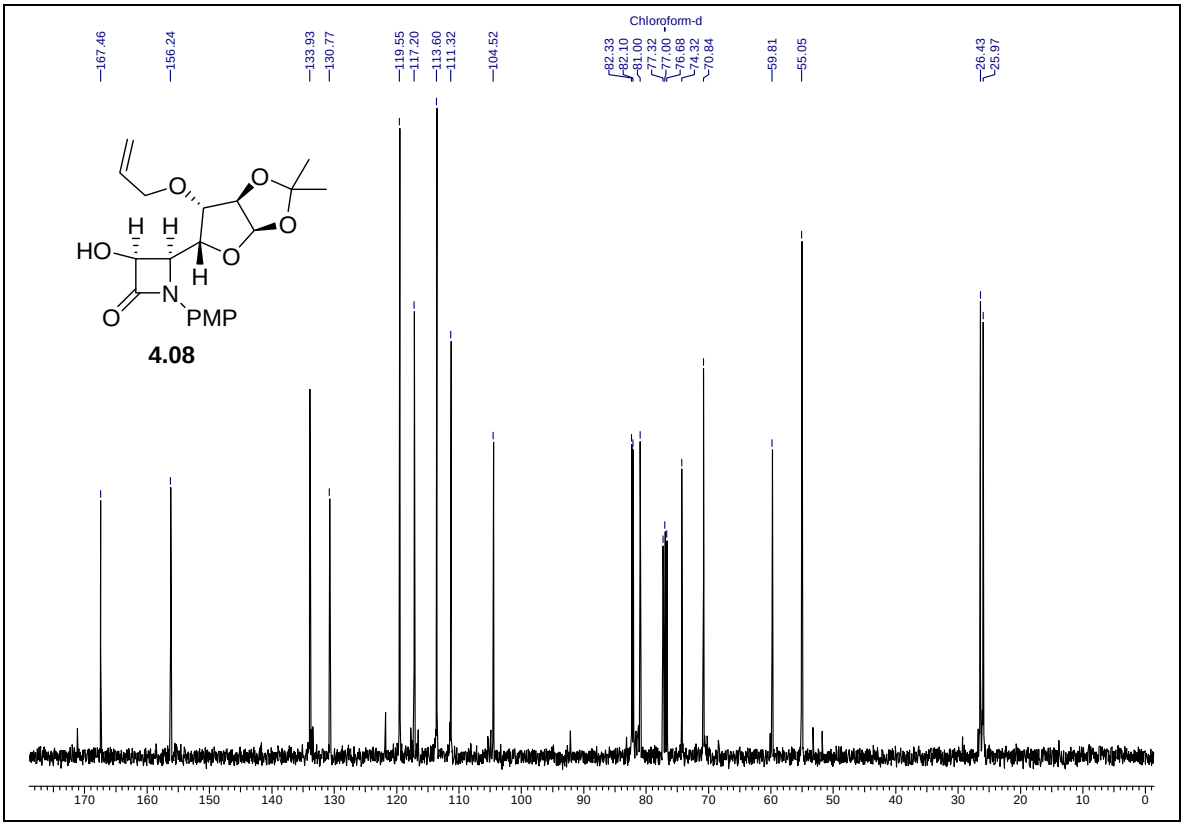
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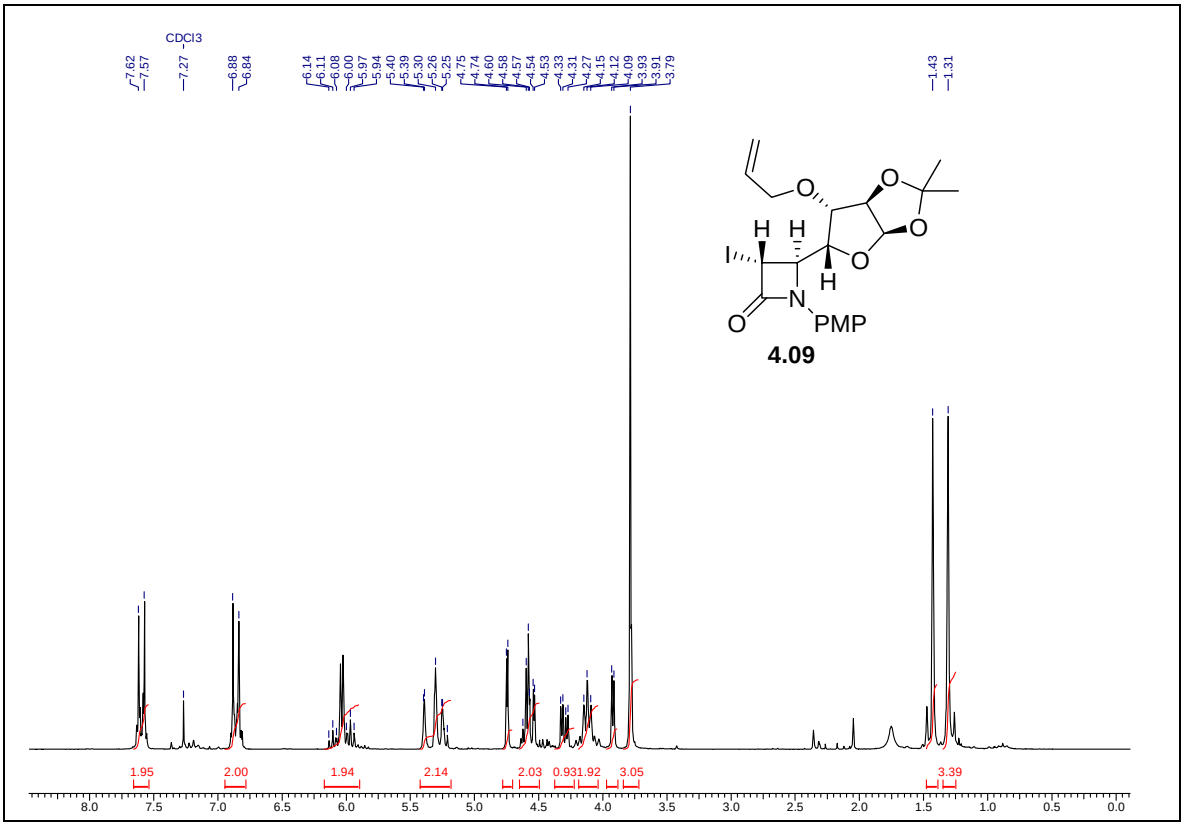
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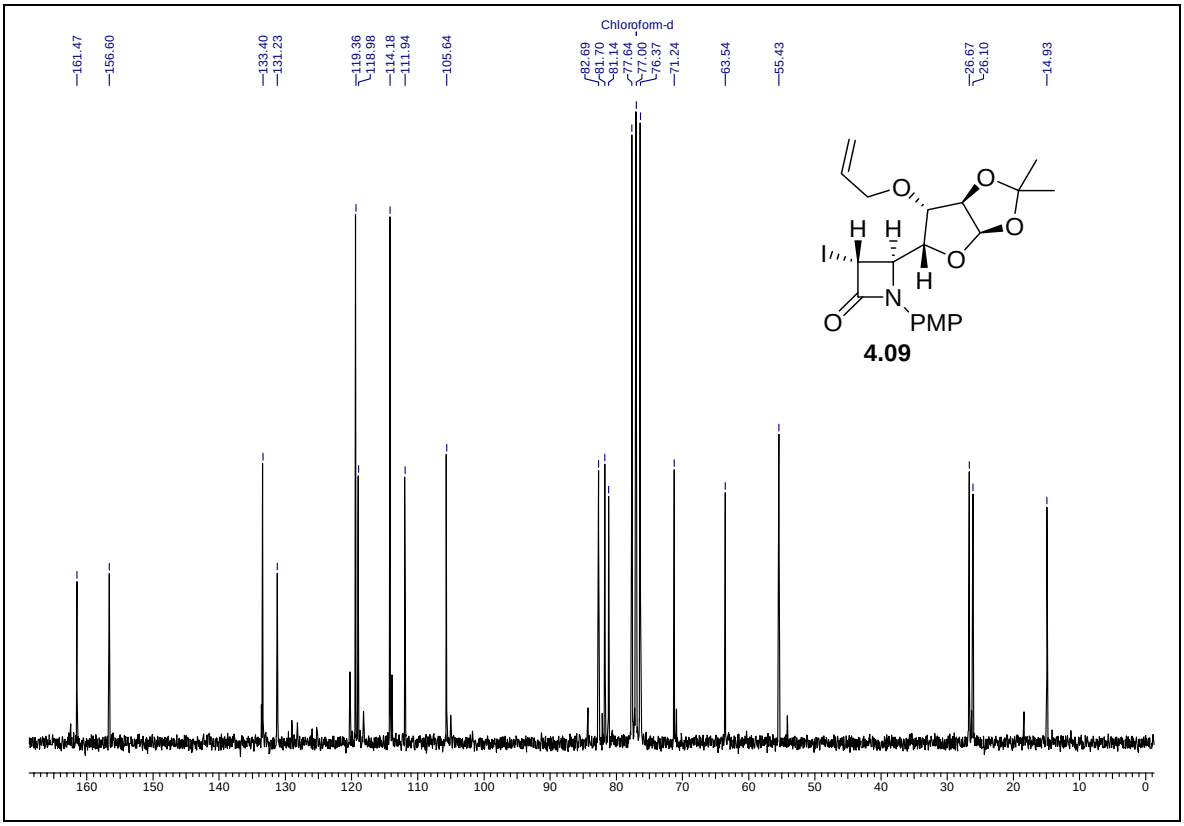
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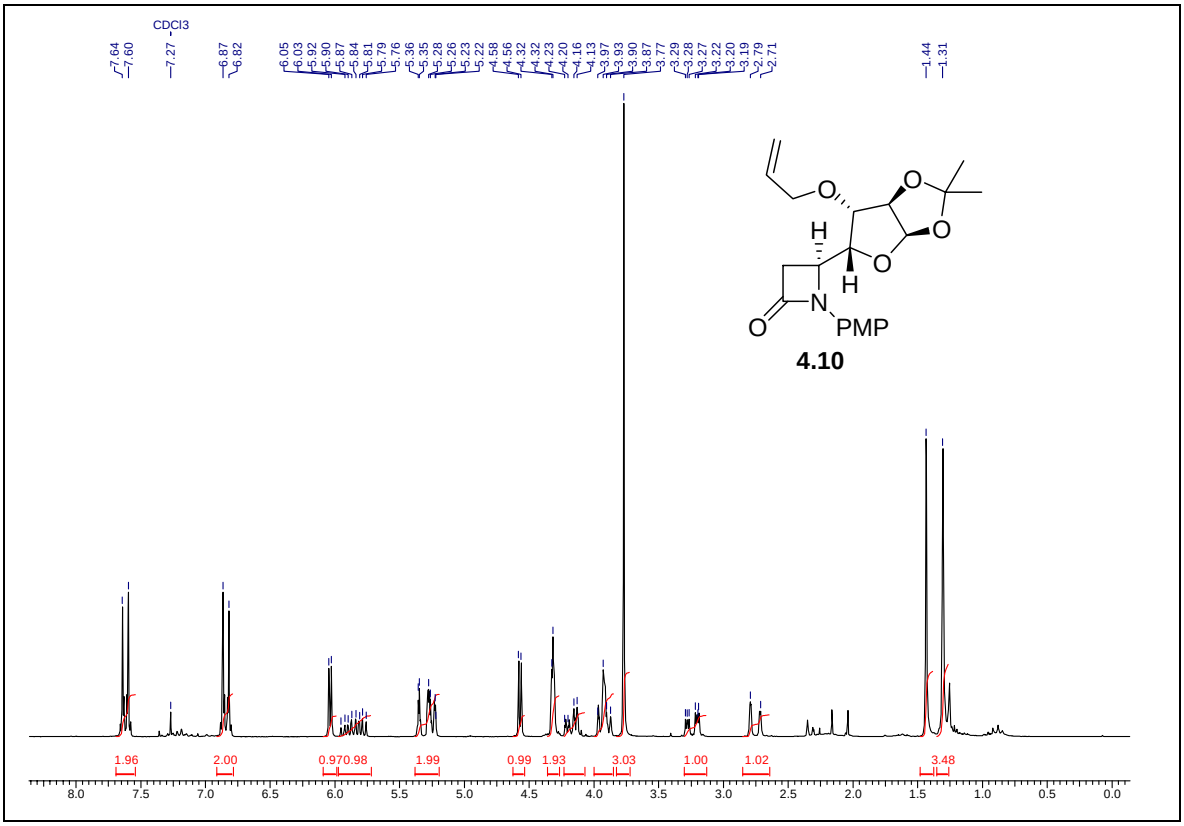
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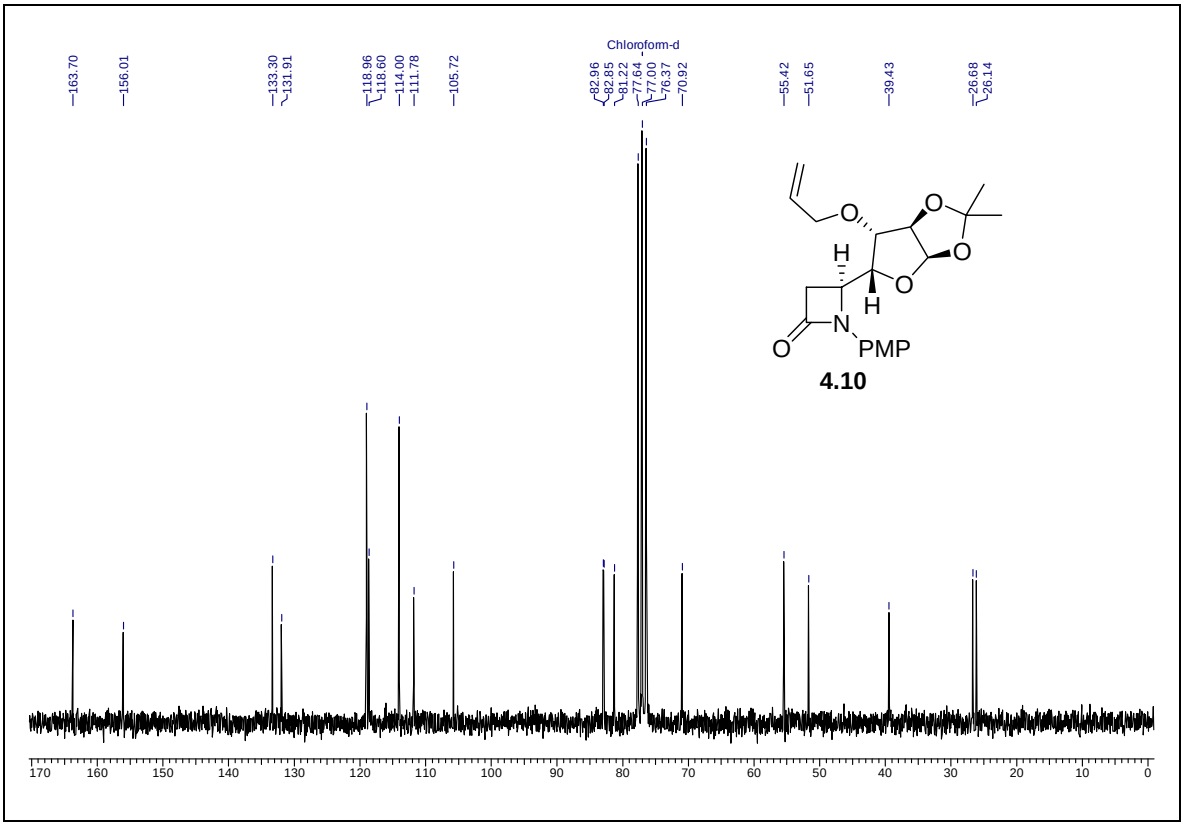
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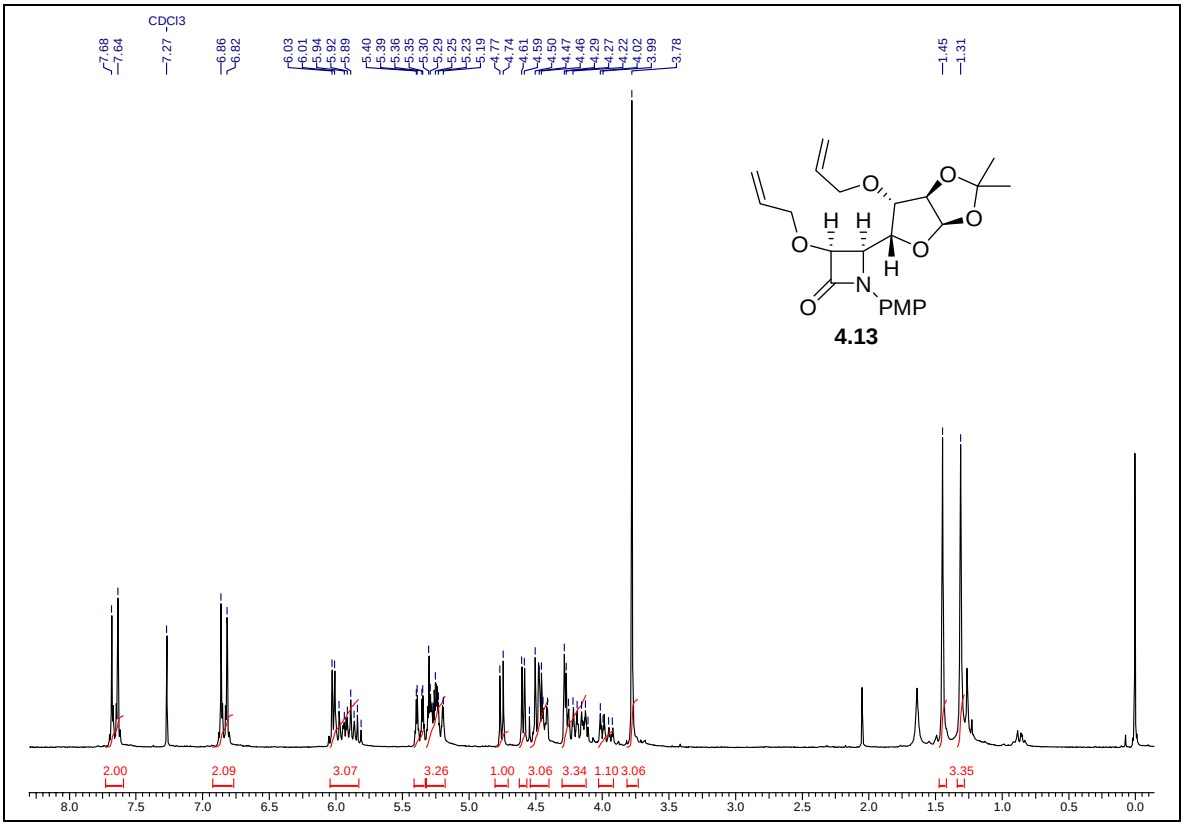
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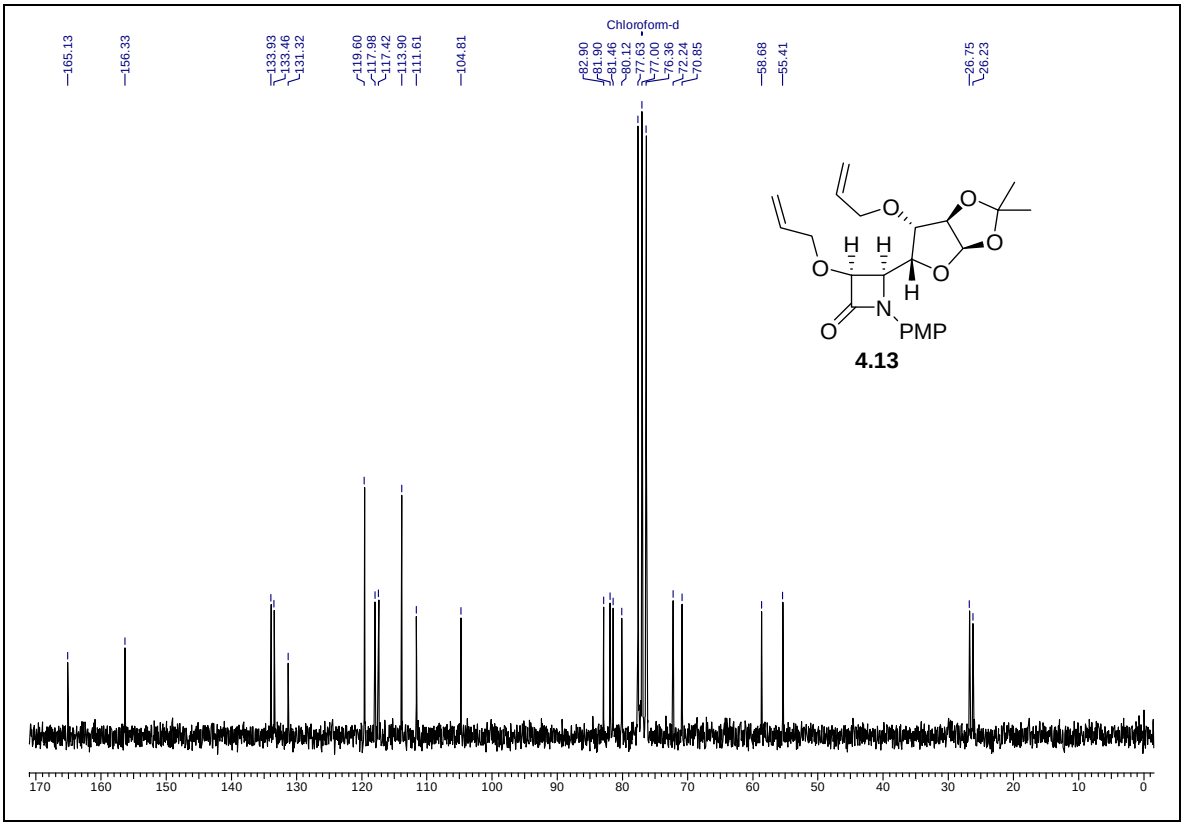
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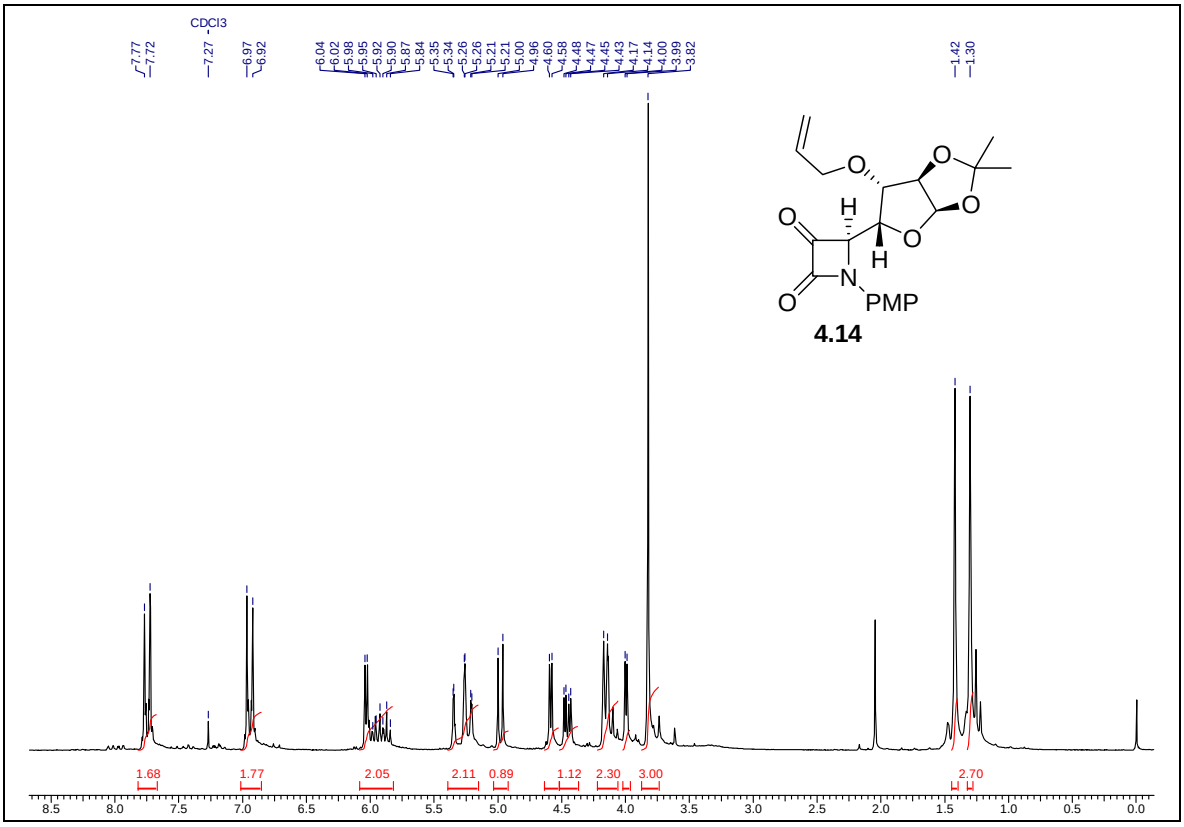
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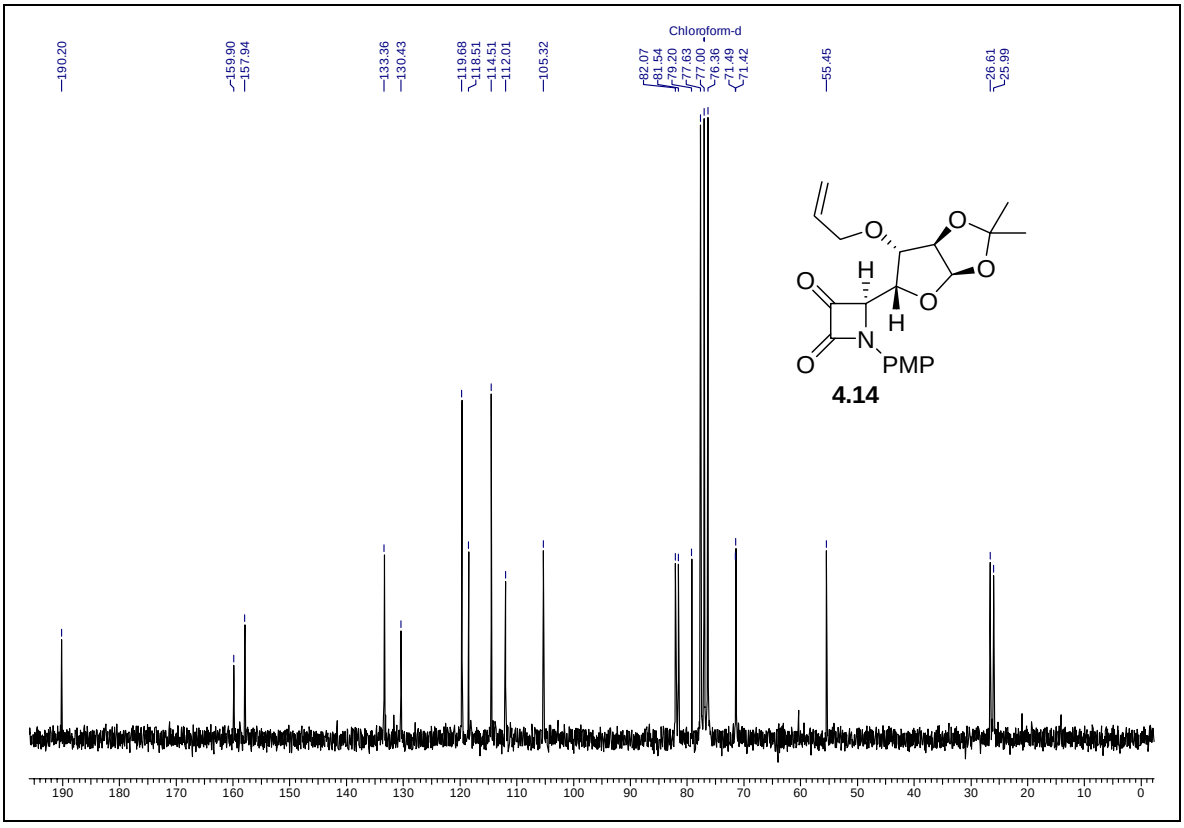
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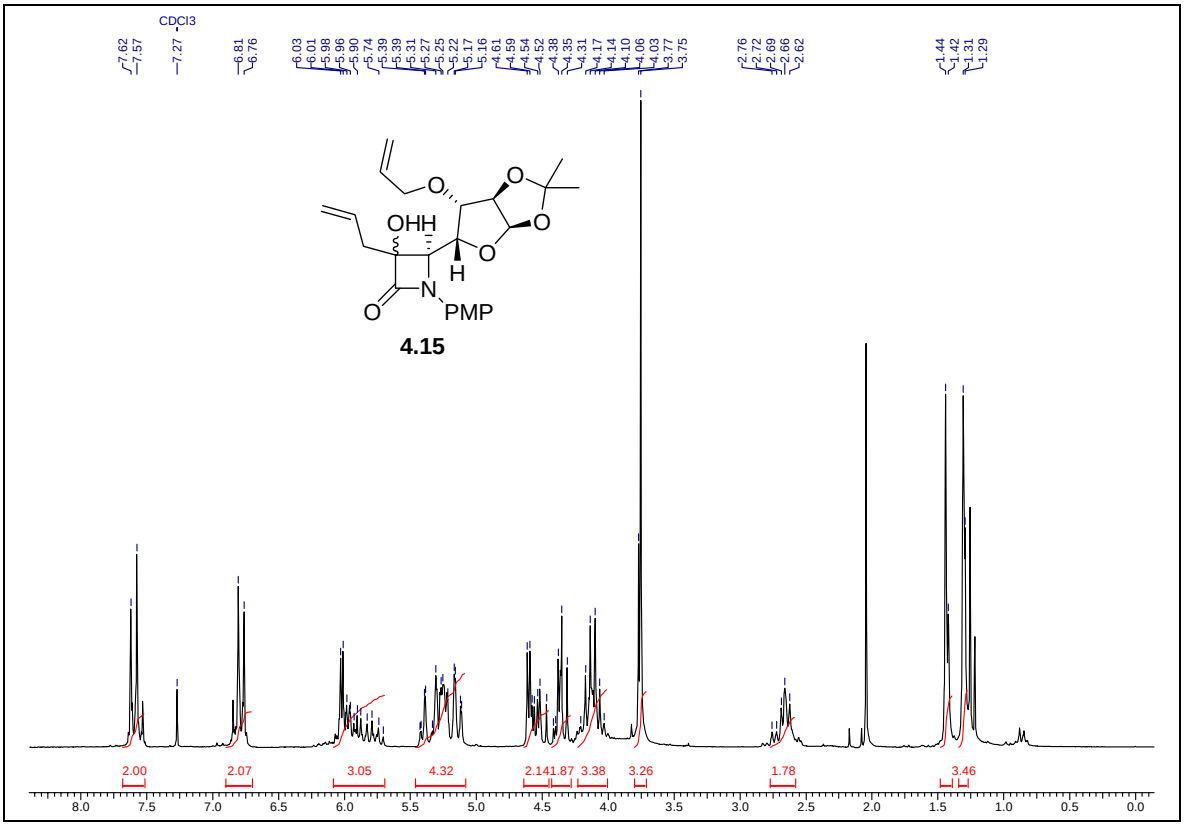
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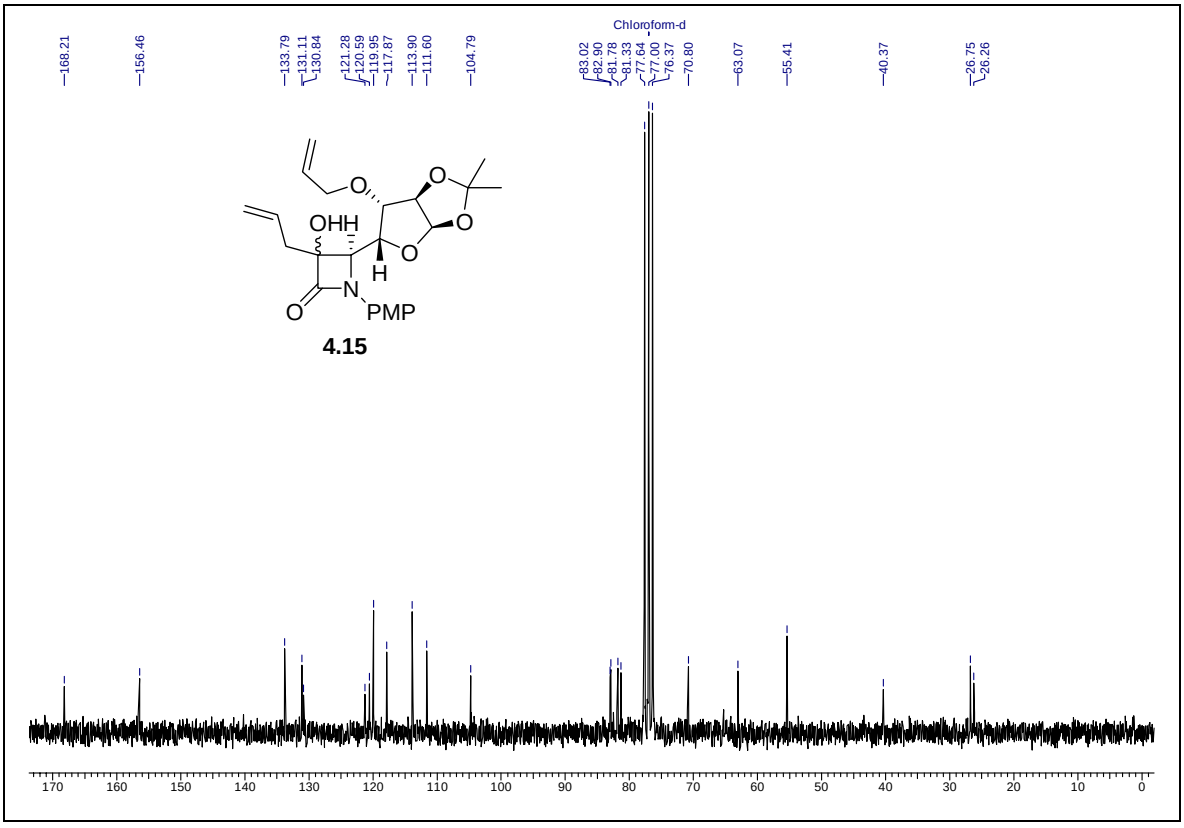
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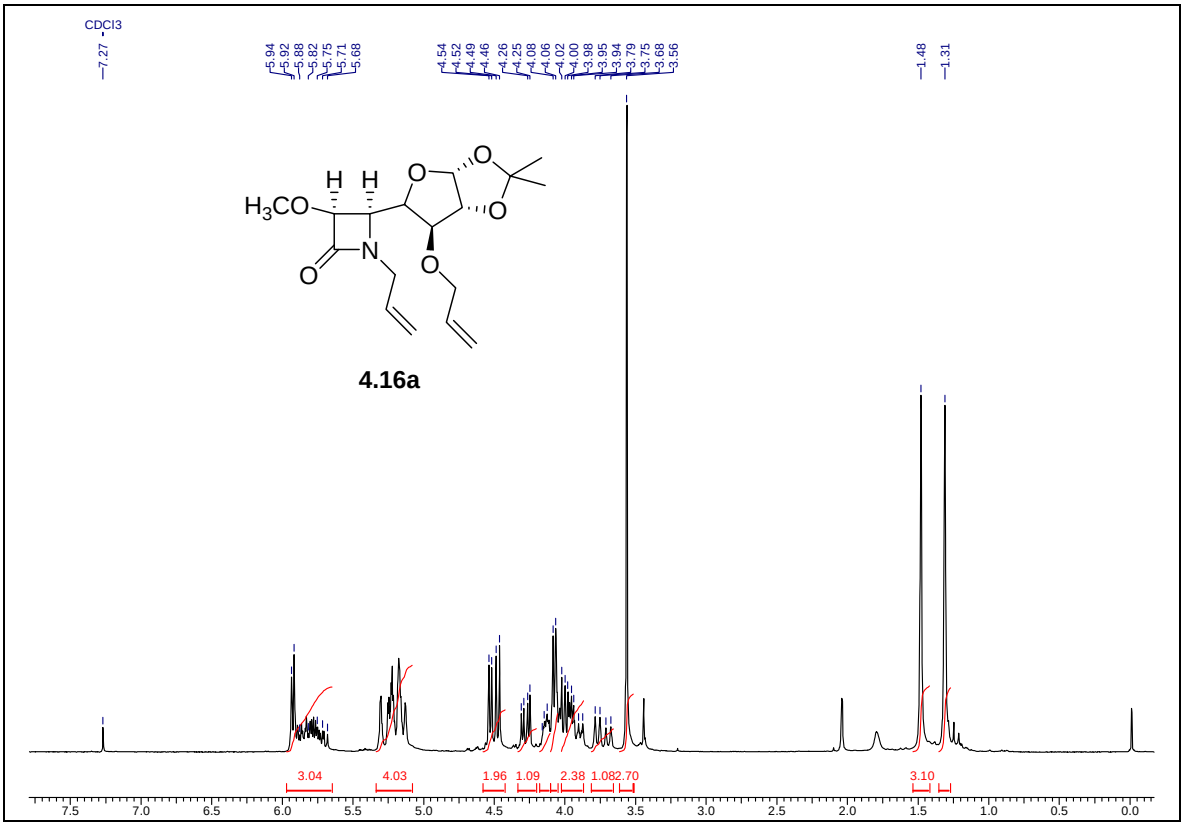
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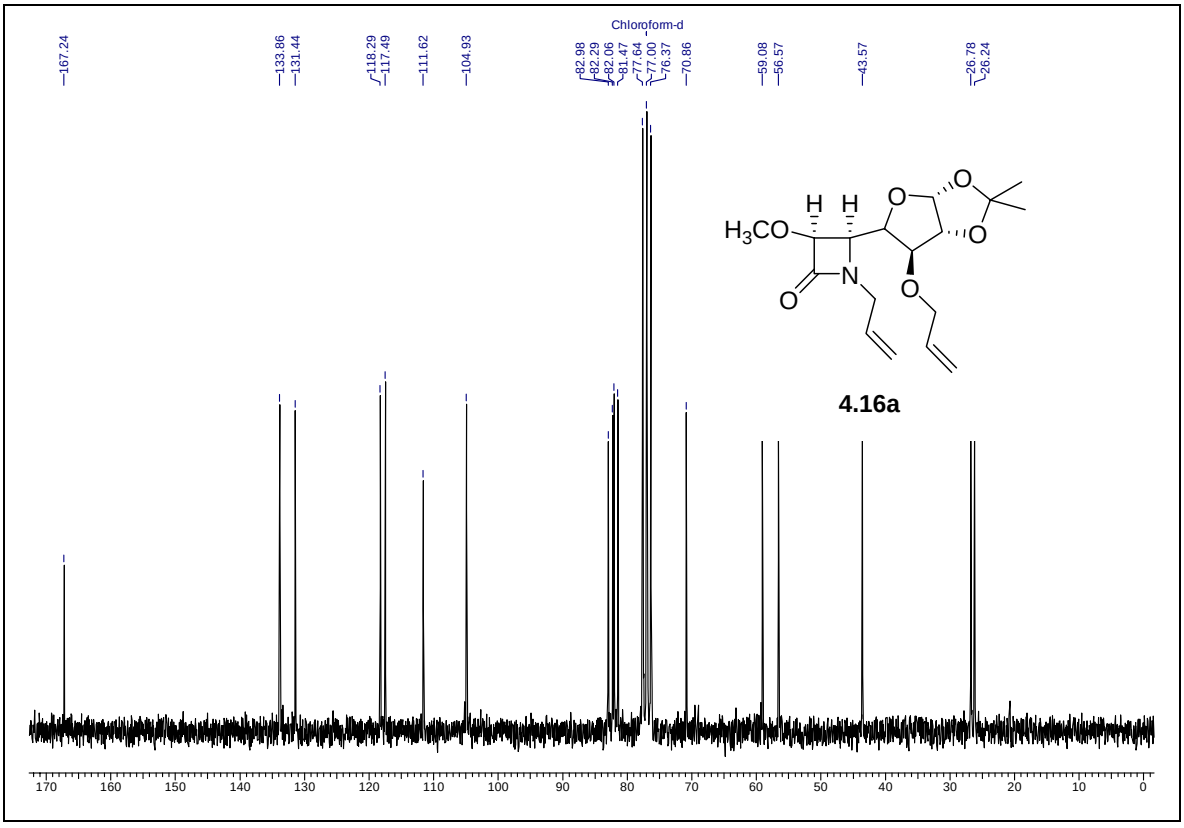
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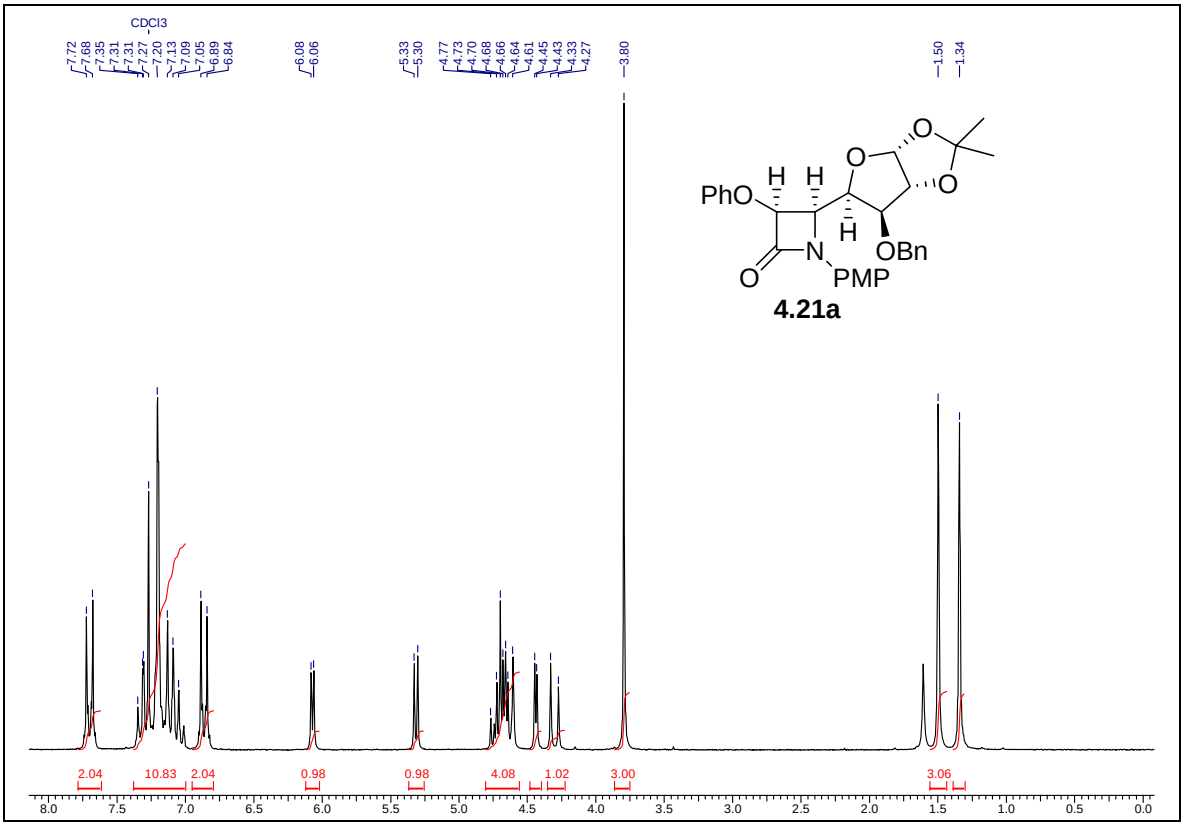
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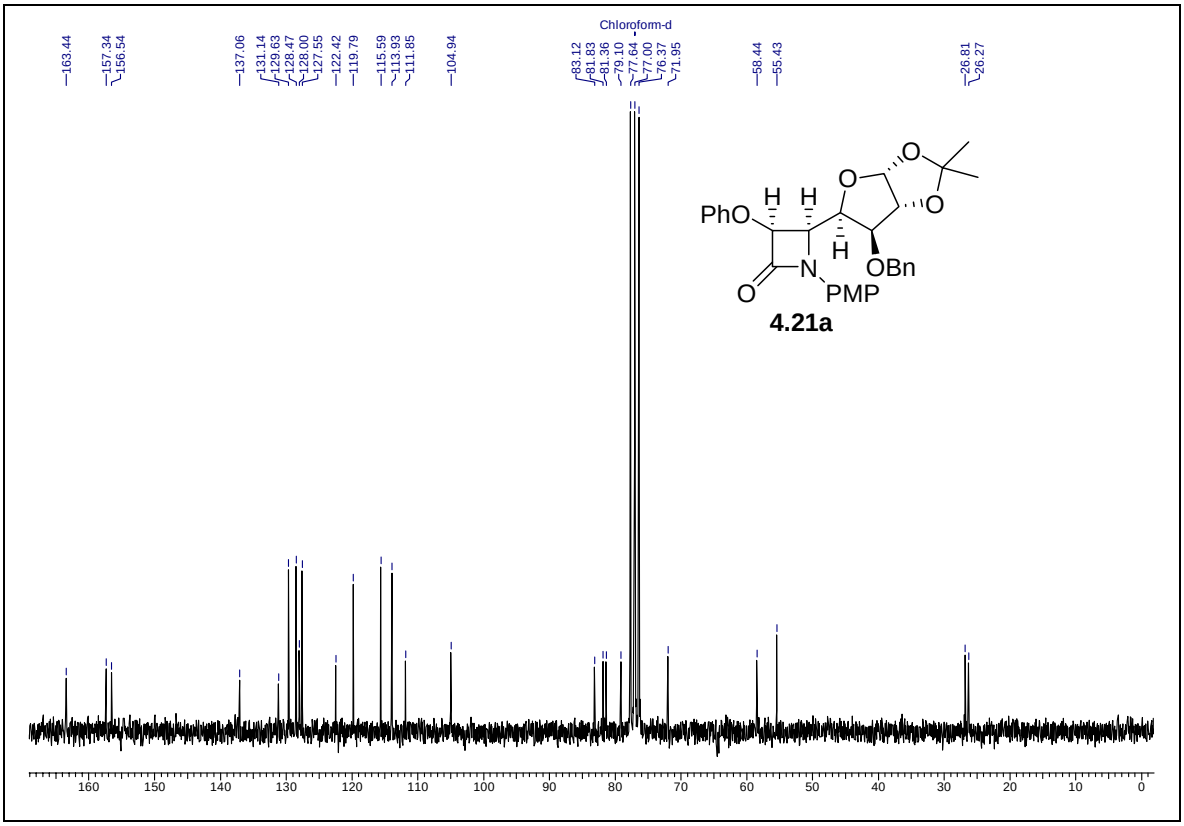
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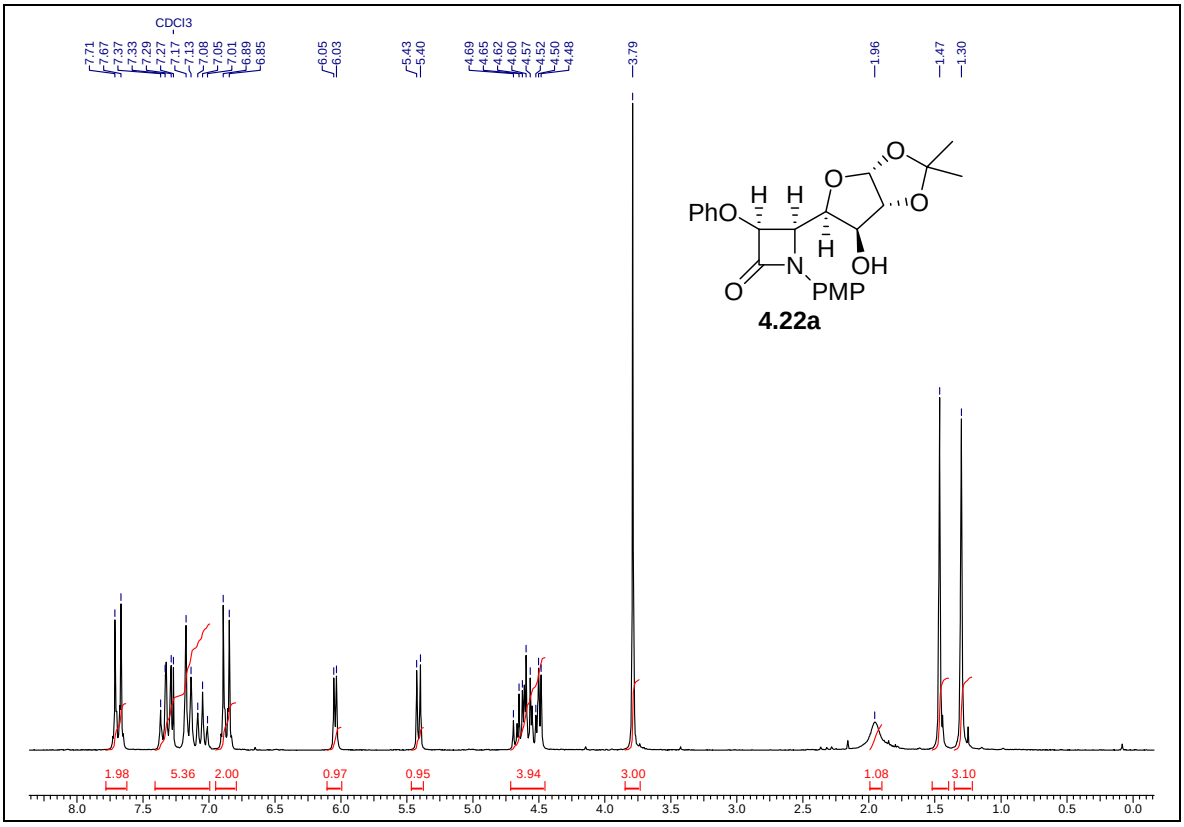
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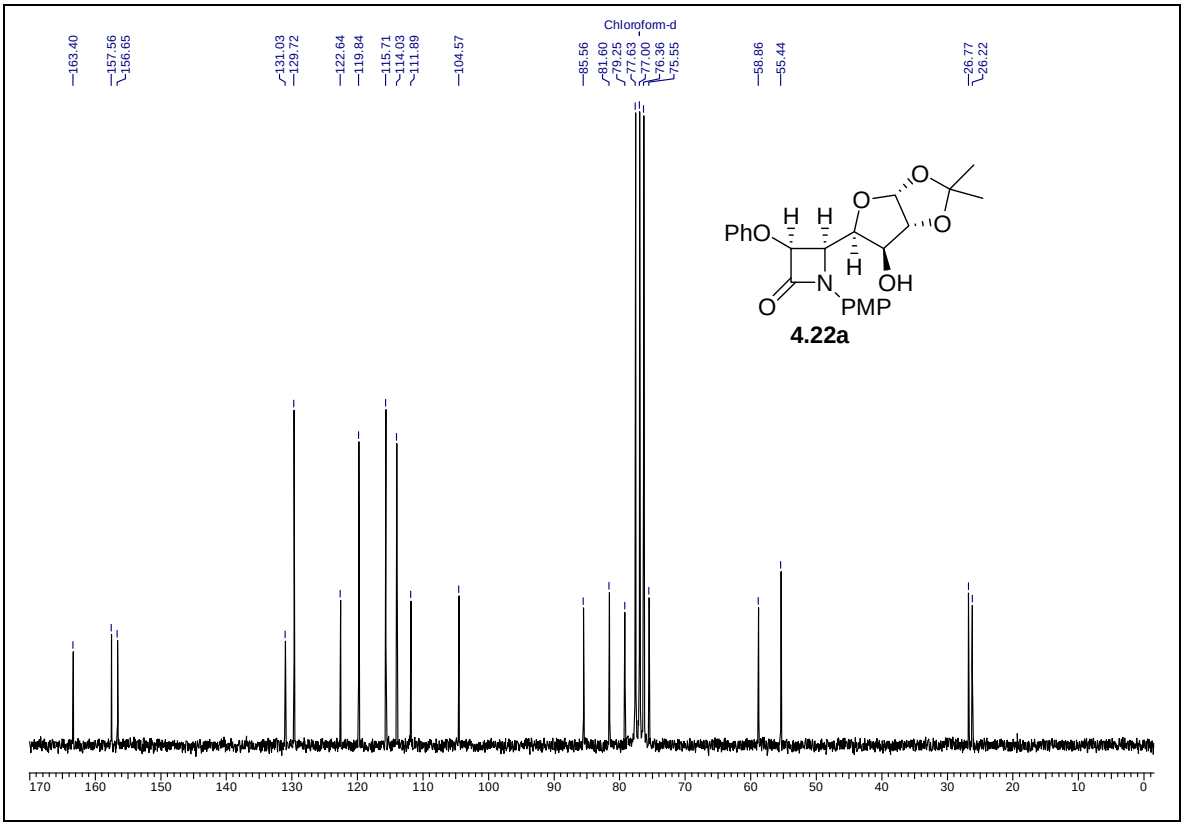
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79.25
77.63
77.00
76.36
75.55
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O
H
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PMP
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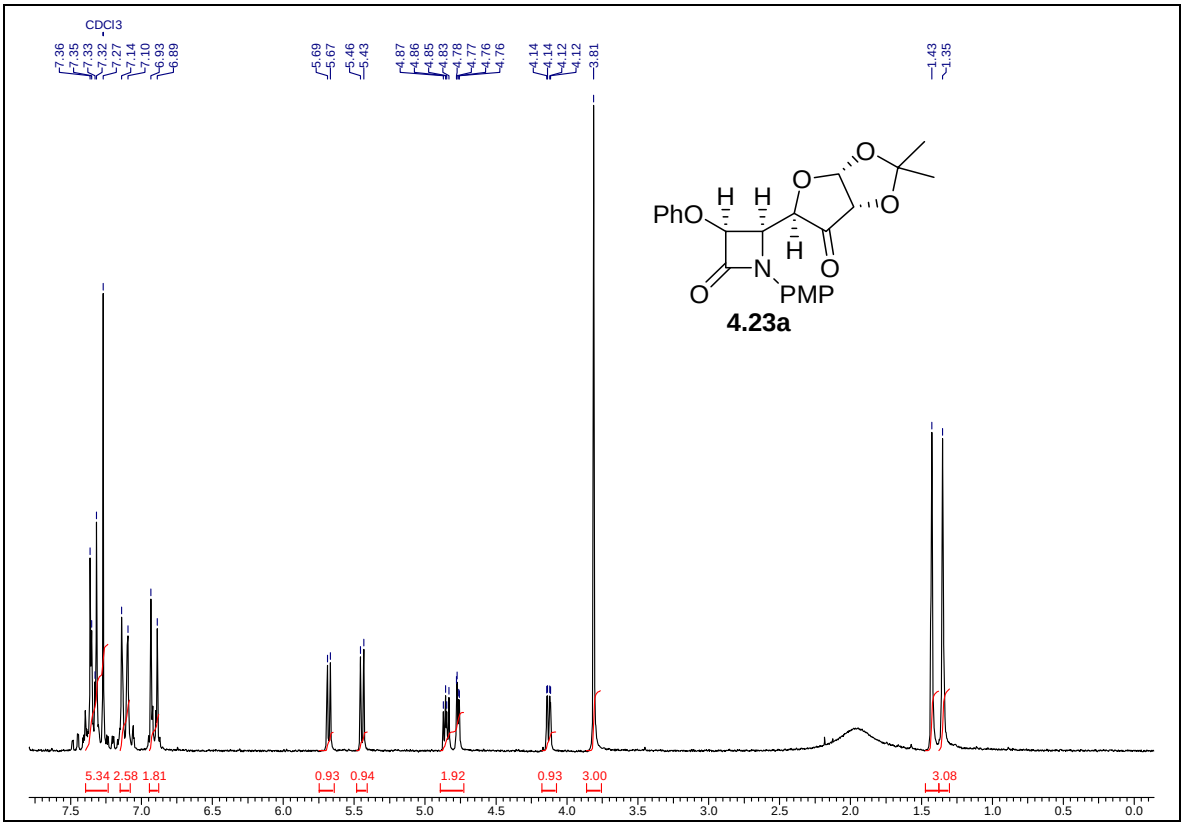
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4.85
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4.78
4.77
4.76
4.76
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4.14
4.12
4.12
3.81
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PhO
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H
O
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O
H
O
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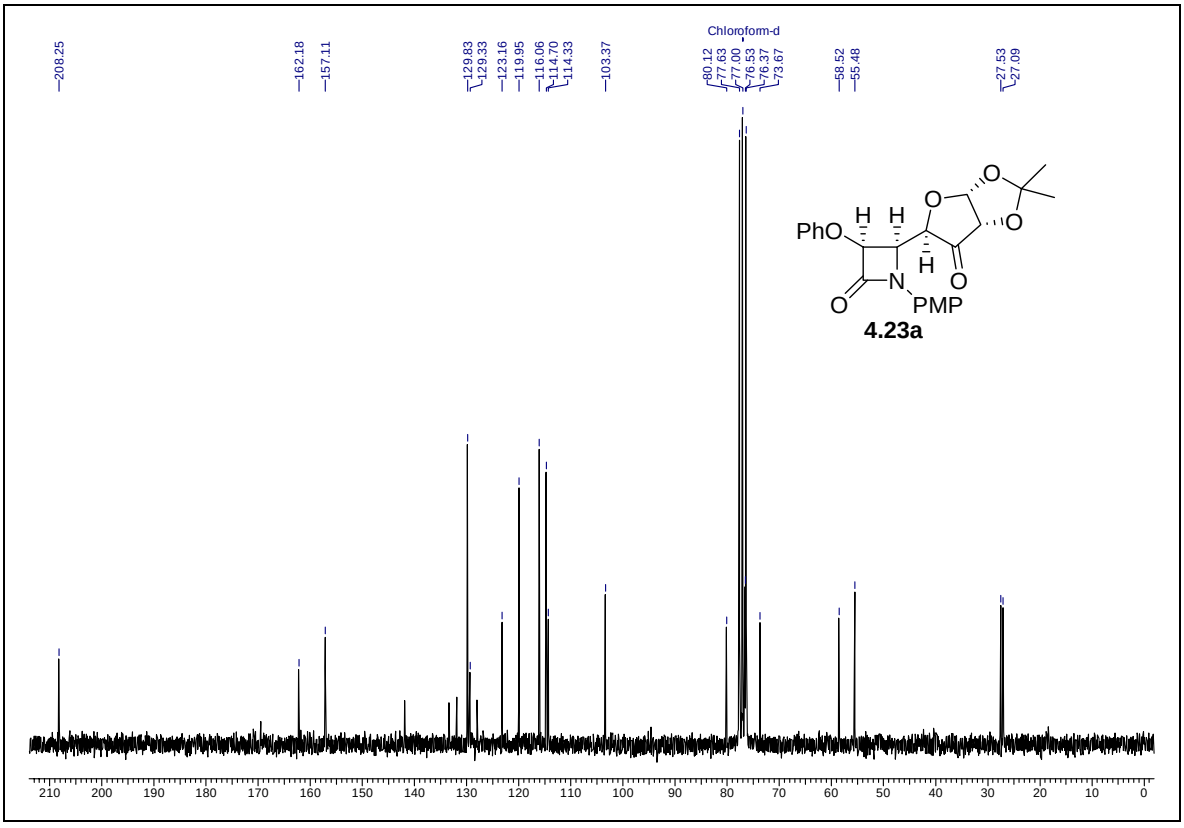
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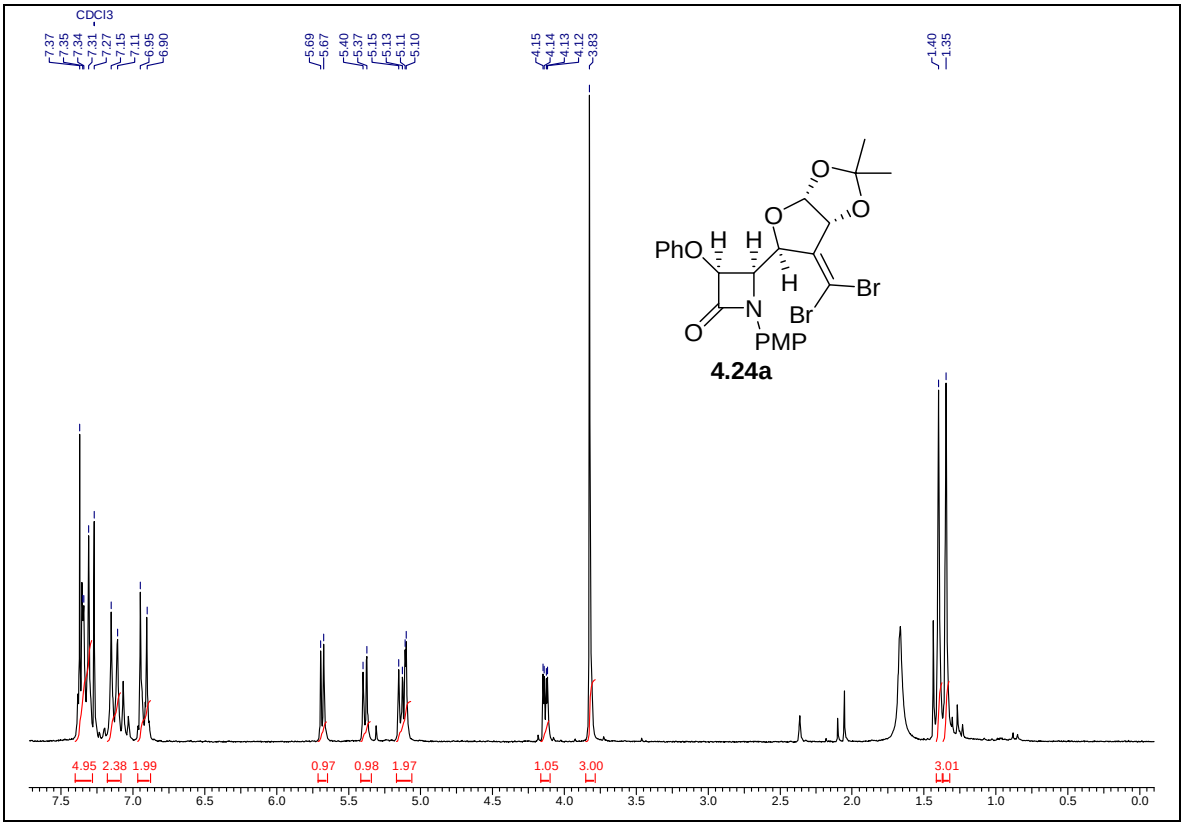
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5.15
5.13
5.11
5.10
4.15
4.14
4.13
4.12
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1.40
1.35
PhO
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H
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Br
N
PMP
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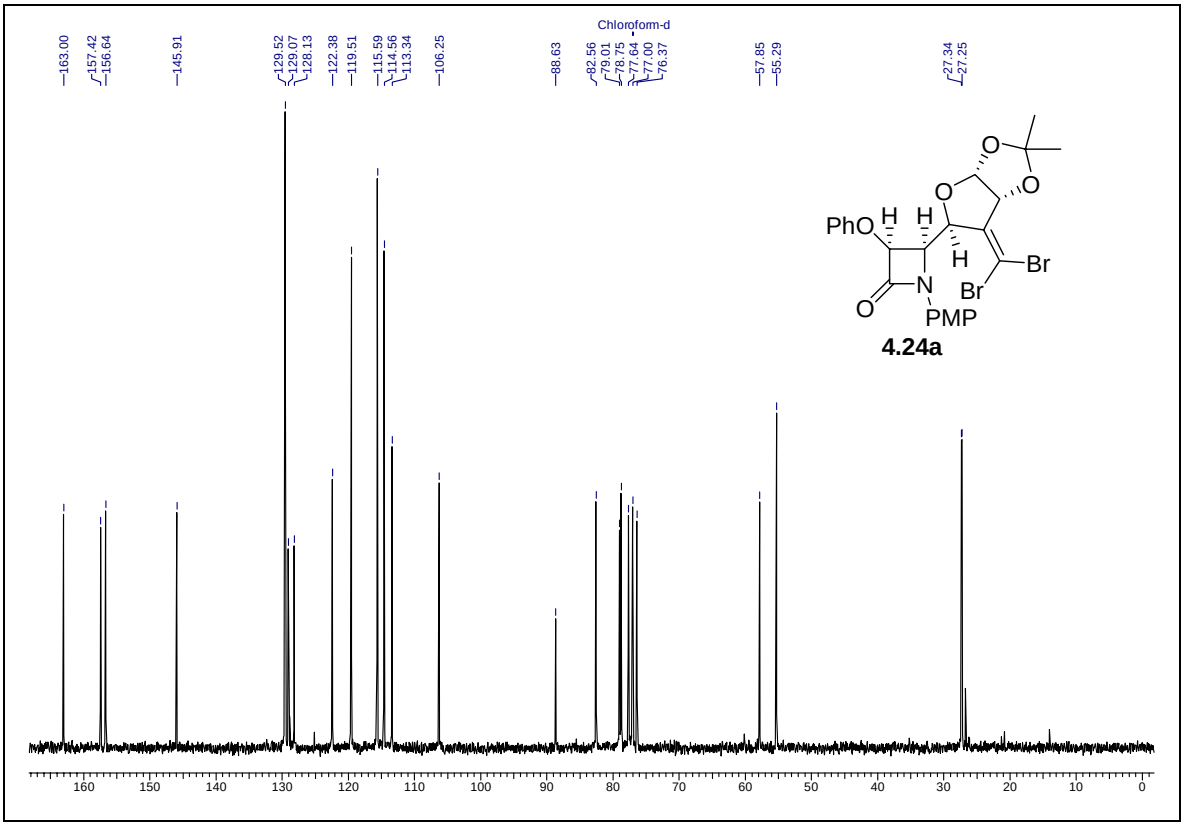
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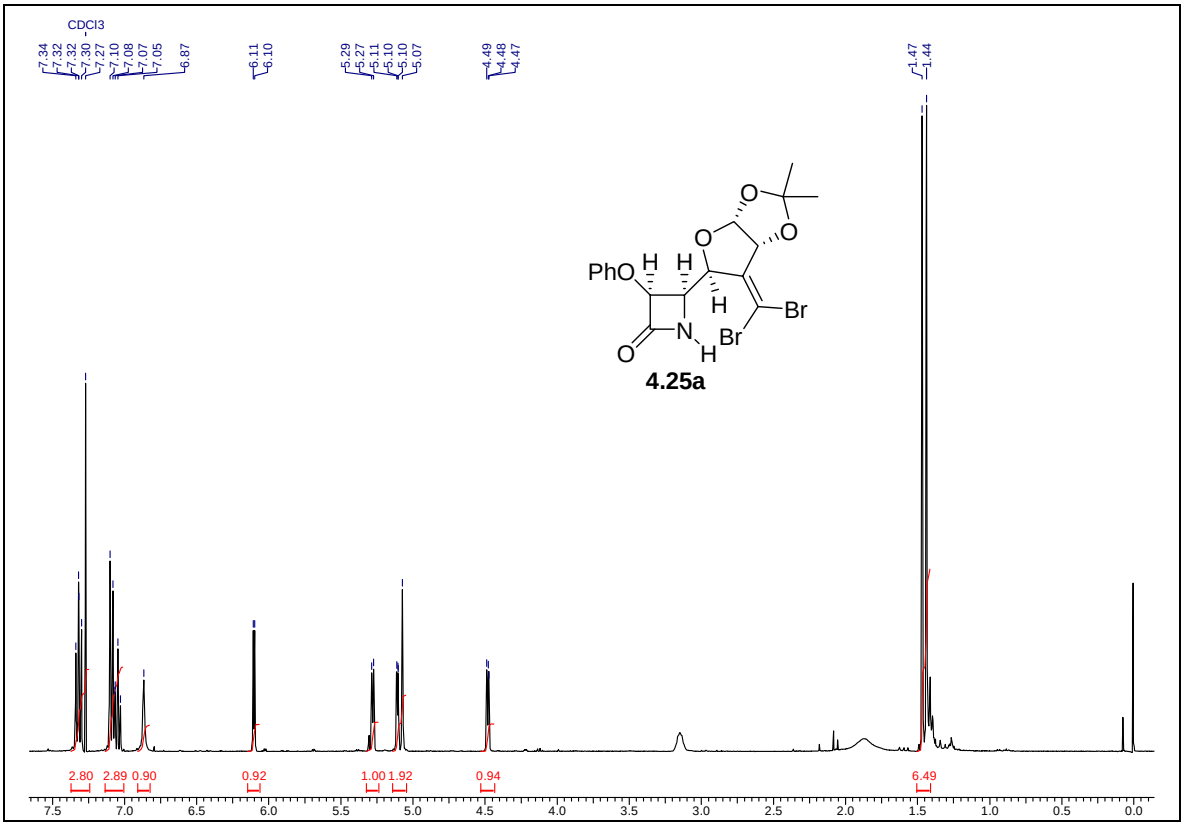
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6.10
5.29
5.27
5.11
5.10
5.10
5.07
4.49
4.48
4.47
1.47
1.44
PhO
H
H
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Br
Br
N
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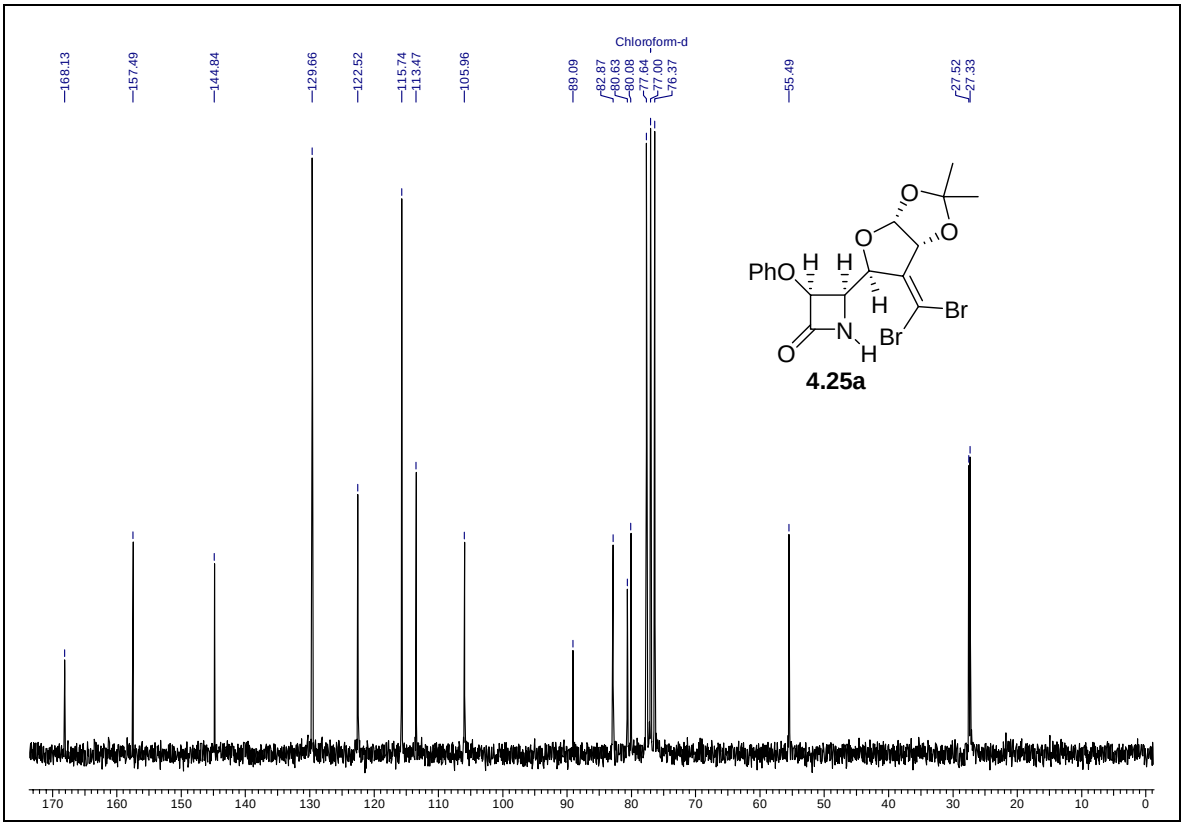
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77.64
77.00
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27.33
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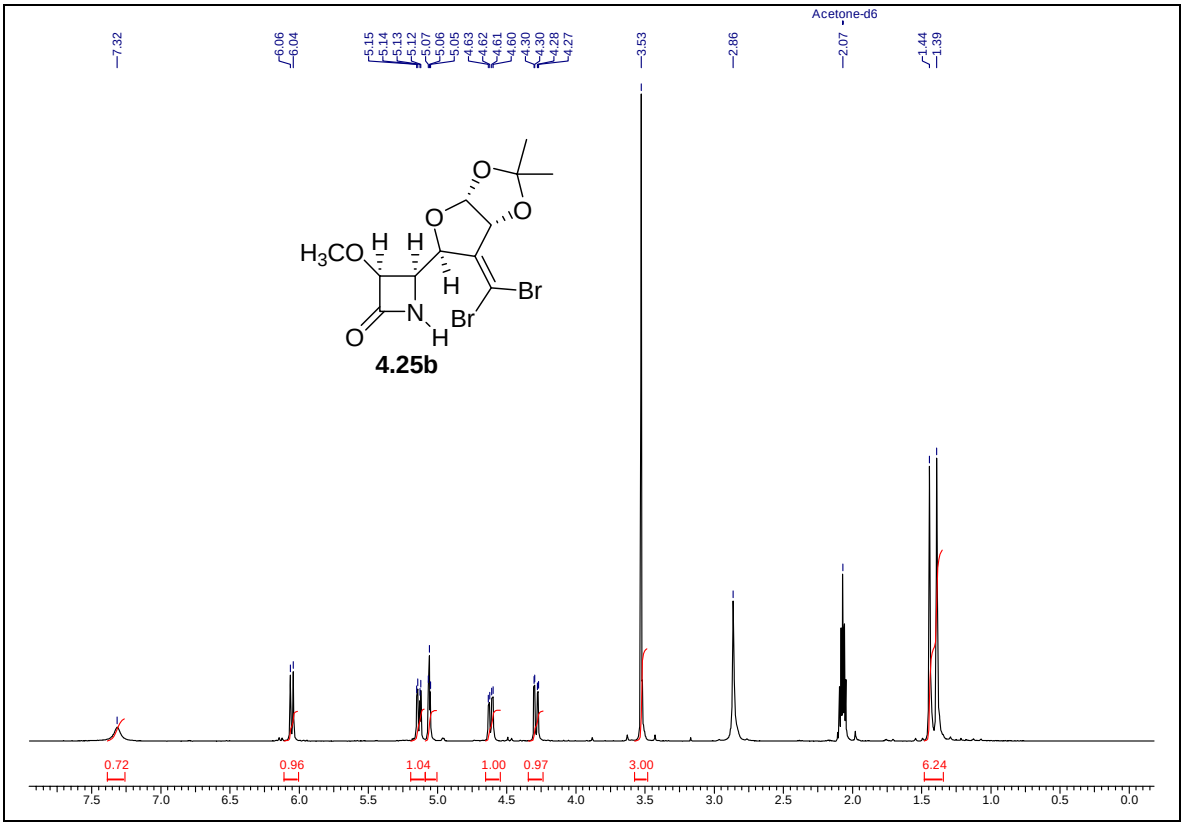
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4.30
4.28
4.27
3.53
2.86
2.07
1.44
1.39
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N
H
Br
O
4.25b
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0.96
1.04
1.00
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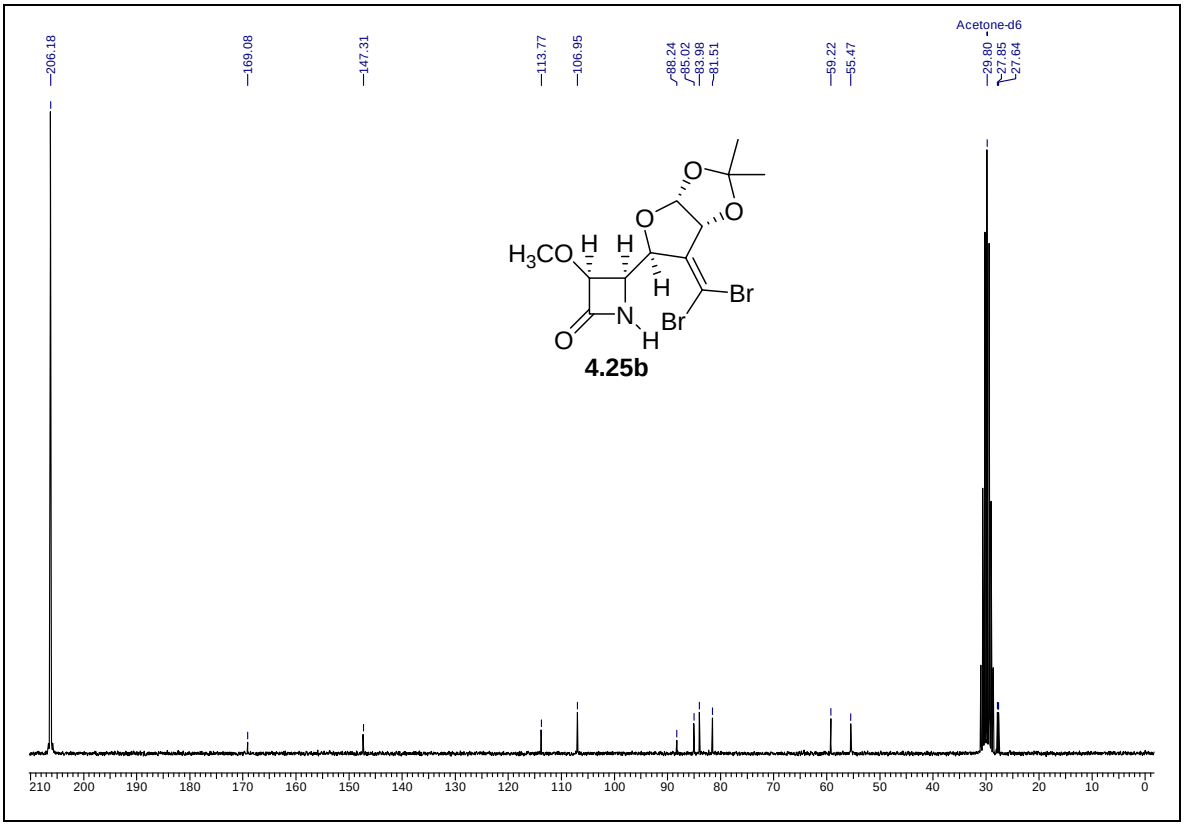
Acetone-d6
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106.95
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85.02
83.98
81.51
59.22
55.47
29.80
27.85
27.64
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O
O
H3CO
H
H
H
Br
N
H
Br
O
4.25b
210
200
190
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170
160
150
140
130
120
110
100
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List of Publications:

1. 4-Formyl azetidin-2-ones synthon for the synthesis of (2*R*,3*S*) and (2*S*,3*R*)-3-amino-2-hydroxy decanoic acid (AHDA).
   Shirode N. M.; Deshmukh A. R. A. S. *Tetrahedron* **2006**, 62, 4615-4621.

2. Microwave assisted rapid synthesis of 4-amino-3,4-dihydroquinolin-2-ones from azetidin-2-ones.
   Shirode N. M.; Kulkarni K. C.; Gumaste V. K.; Deshmukh A. R. A. S. *Arkivoc* **2005** (i) 53-64.

3. 4-Formylazetidin-2-ones, synthon for the synthesis of an important intermediate of (3*S*,4*R*)-Cisapride **Shirode N. M.**; Deshmukh A. R. A. S. (Manuscript under process).

4. Transformations of D-glucose derived azetidin-2-ones for synthesis of new class of carbapenems.
   Shirode N. M.; Deshmukh A. R. A. S. (Manuscript under process).

Erratum