TOTAL SYNTHESES OF β-LACTONE CONTAINING NATURAL PRODUCTS: TOTAL SYNTHESIS OF BELACTOSIN C AND SYNTHETIC STUDIES TOWARD SPONGIOLACTONE

A Dissertation

by

SUNG WOOK CHO

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

December 2008

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	Daniel A. Singleton
	Francois Gabbai
	Dong-Hyun Hong
Head of Department,	David Russell

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ABSTRACT

Total Syntheses of β-Lactone Containing Natural Products: Total Synthesis of Belactosin C and Synthetic Studies toward Spongiolactone. (December 2008)

Sung Wook Cho, B.S., Sogang University, Korea; M.S., Sogang University, Korea

Chair of Advisory Committee: Dr. Daniel Romo

The recently isolated bacterial metabolites, belactosins A-C from a fermentation broth of *Streptomyces* sp. UCK14, uniquely contain a β-lactone dipeptide motif and exhibit anticancer activities. The enantioselective synthesis of (-)-belactosin C and derivatives was accomplished in a concise manner employing the tandem, Mukaiyama aldol-lactonizaton (TMAL) process and test their bioactivities. . One approach involved a distal double diastereoselective TMAL reaction with a dipeptide glyoxamide, whereas a second approach involved amide coupling of a dipeptide with a β-lactone carboxylic acid, obtained via the TMAL process employing a chiral silyl ketene acetal. Enzymatic assays showed that the belactosins act as the dual inhibitors of the proteasome and the thioesterase domain of fatty acid synthase.

Spongiolactone which uniquely contains a cyclopentyl-fused β-lactone was isolated in 1986 from *Spongi-onellagracilis* No biological activity have been reported for this compound; however, the acylating potential of the resident β-lactone warrants screening for potential activity. After many setbacks in the synthesis of spongiolactone, significant progress has been made. Importantly, NCAL process also enabled a concise

construction of [3.2.0]-bicyclo β-lactone, which is the key structure in the spongiolactone synthesis and only a few steps remained to complete the synthesis.

DEDICATION

To my wife and son

ACKNOWLEDGEMENTS

First, I would like to thank my advisor and the committee chair, Prof. Romo for his thoughtful guidance and generous support throughout my graduate career. I would like to thank my committee members, Prof. Singleton, Prof. Gabbai and Prof. Hong for helpful suggestion and valuable instruction.

Thanks also go to all of the former and current Romo group members for making my time at Texas A&M University a great experience.

Great thanks to my family for their encouragement and pray, especially to my wife and son for their patience and love.

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CHAPTER I

INTRODUCTION: THE SYNTHESES OF β-LACTONE CONTAINING NATURAL PRODUCTS

β-lactones are useful synthetic intermediates since they are masked aldol products with inherent reactivity making them useful synthons in natural and unnatural product synthesis.[1] However, there are relatively few enantioselective methods for β-lactone synthesis. Recent studies including those emanating from our group have begun to address this paucity of methods. Furthermore, the total syntheses of β-lactone containing natural products have only recently begun to appear.

In this review chapter, recent syntheses of β-lactone containing natural products since 1995, when this topic was last reviewed will be described. In addition, β-lactone containing natural products that have been isolated but not yet synthesized will also be described.

A. Previously Synthesized a β-Lactone Containing Natural Products

To date there are several reports about various natural products syntheses containing β-lactone including lipstatin **1.1**, (–)-panclicin D[2] **1.2**,[3] tetrahydrolipstatin(orlistat) **1.3**,[4] valilactone **1.4**, ebelactone A **1.5**,[5] norcadiolactone **1.6**, vibralactone **1.7**, omuralide **1.8**,

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This dissertation follows the style and format of *Journal of the American Chemical Society*.

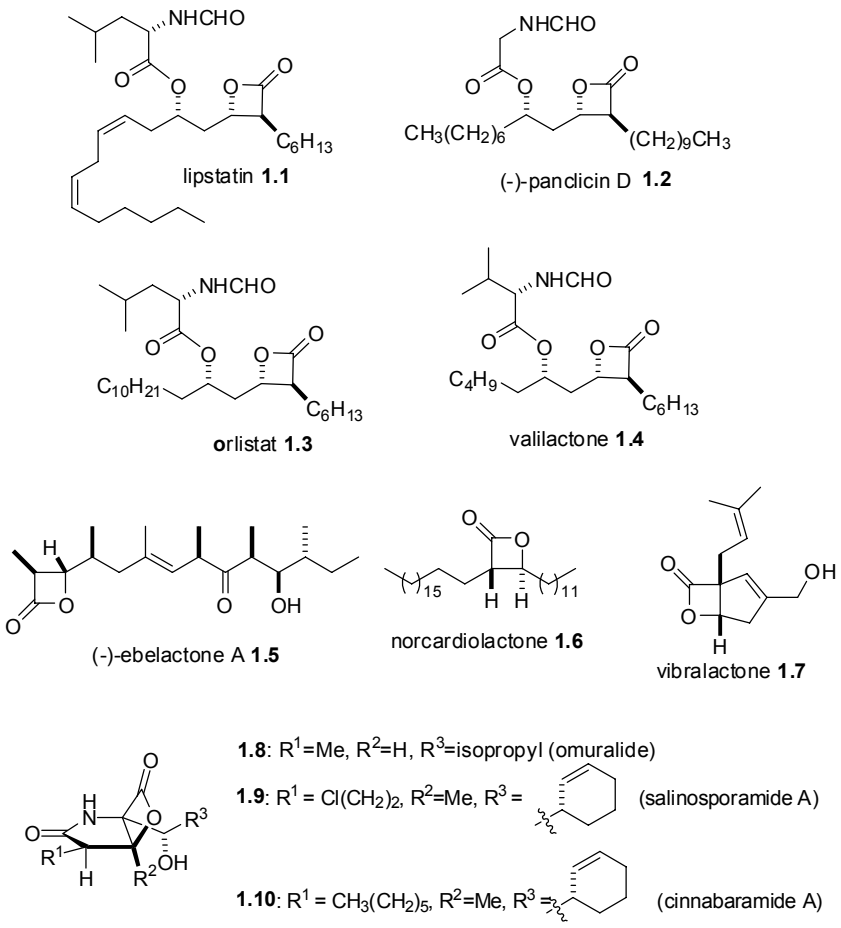


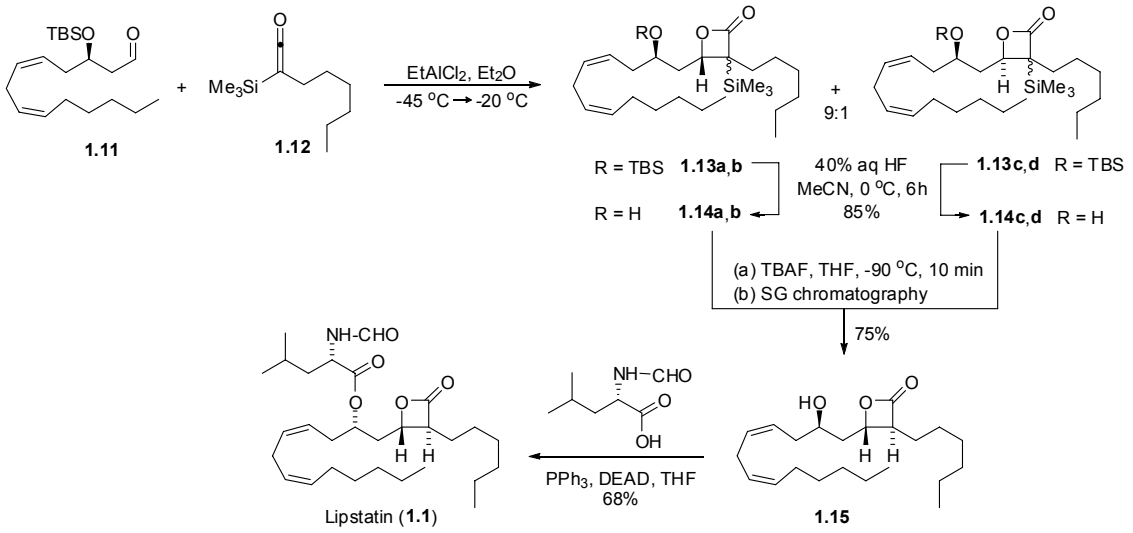
Figure 1.1. Previously Synthesized Natural Products Containing a β-Lactone

salinosporamide A **1.9** and cinnabaramide A **1.10**,[6] (Figure 1.1).

Lipstatin **1.1** was isolated from *Streptomyces toxytricini*, and the structure of lipstatin **1.1** was determined by a combination of spectroscopic and chemical methods,[7] and later confirmed by chemical synthesis.[8] Lipstatin **1.1** features two linear carbon chains of six and thirteen atoms, respectively, affixed to a β-lactone ring. Structural analysis revealed a striking similarity between lipstatin and esterastin. Also ebelactone **1.5**, valilactone **1.4** and the panclicins have similar structures. The total synthesis of

lipstatin **1.1** from (*S*)-*N*-formyl-leucine and dimethyl-(*S*)-(−)-malate was described (Scheme 1.1). The diastereoselective Lewis acid-catalyzed [2 + 2] cycloaddition with silylketene **1.12** and dienal **1.11** delivered a mixture of four diastereomers **1.13a-d**. *O*-desilylation with HF followed by *C*-desilylation using TBAF delivered 2-oxetanone **1.15**, which was isolated by column chromatography on silica gel. Finally, esterfication of the hydroxyl-2-oxetenone **1.15** with (*S*)-*N*-formylleucine under Misunobu condition delivered (-) lipstatin **1.1**.

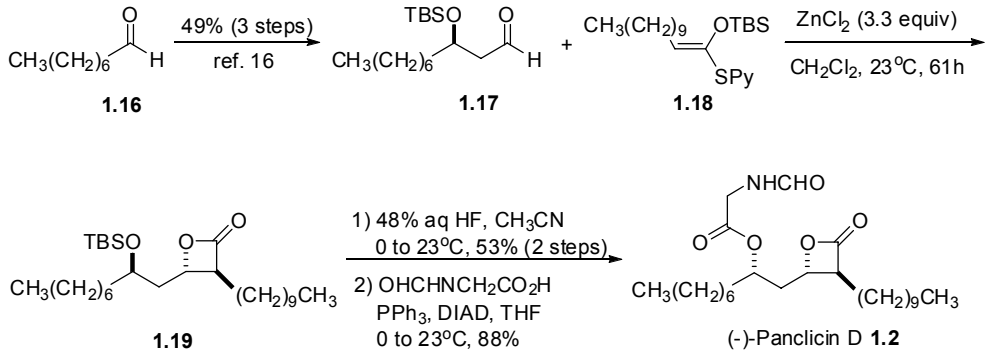
Scheme 1.1



Panclicins are novel pancreatic lipase inhibitors isolated from *Streptomyces* sp. NR 0619. Panclicins structures contain a β-lactone with two alkyl chains, one of which has *N*-formylalanyloxy or *N*-formylglycyloxy substituent. (−)-Panclicin D **1.2** synthesis was reported in 1997 by our group using a substrate controlled diastereoselective tandem Mukaiyama aldol lactonization (TMAL) process (Scheme 1.2). The TMAL process

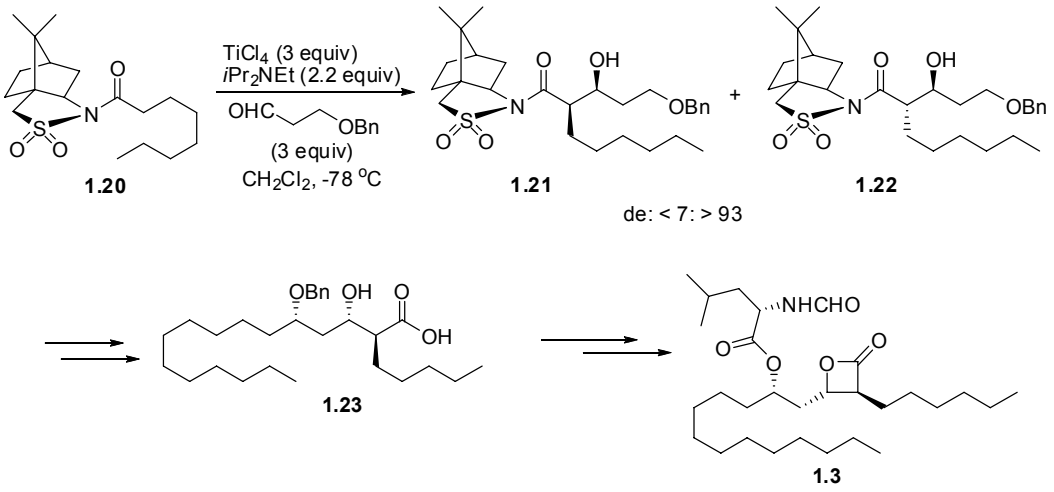
using ketene acetal **1.18** and β-Silyloxy aldehyde **1.17** delivered the required β-lactone **1.19** with good diastereoselectivity. The synthesis was completed by silyl deprotection with aqueous HF followed by inversion of the corresponding alcohol using Mitsunobu conditions to give (−)-panclicin D **1.2** in 20% overall yield from *n*-octanal **1.16**.

Scheme 1.2



Tetrahydrolipstatin **1.3**, a reduced form of lipstatin, is an inhibitor of the thioesterase domain of fatty acid synthase (FAS), an enzyme associated with tumor cell proliferation.[9] Due to the significant activity of tetrahydrolipstatin **1.3**, a number of approaches have been reported for their synthesis.[10] Recently, Kumaraswamy reported the total synthesis of (-)-tetrhydrolipstatin using a directed aldol reaction with Oppolzer's sultam as the key step (Scheme 1.3). Acylsultam **1.20** was treated with $TiCl_4$, and the sultam enolate was quenched with benyloxypropanal to deliver aldol adduct **1.21** (4:5,<7:>93). After several steps, β-hydroxy acid **1.23** underwent lactonization with BOPCl to furnish the β-lactone in 75% yield. After debenzylation, DCC coupling with (*S*)-*N*-formylleucine delivered Tetrahydrolipstatin **1.3**

Scheme 1.3



Our group also reported a convergent, "second generation" strategy toward (–)–panclicin D derivatives that delivered easy access to Tetrahydrolipstatin (orlistat), valilactone and several congeners (Figure 1.2). Biological testing including inhibition studies of thioesterase domain of fatty acid synthase (FAS) were reported for orlistat and its derivatives.

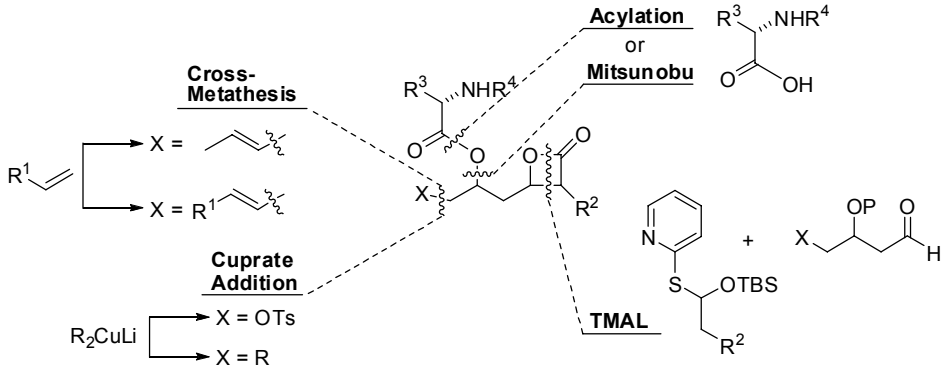


Figure 1.2 Second Generation Strategy to Orlistat

Ebelactone A **1.5** is known to inhibitor esterases, lipases, and *N*-formylmethionone aminopeptidases located on the cellular membrane of various kinds of cells. In 1990, Paterson reported the total synthesis of ebelactone A, relying on aldol condensations and a Claisen rearrangement. However, it's linear nature of the synthesis and poor diastereoselectivity for the aldol reaction were drawbacks. Recently, Mandal reported ebelactone A synthesis using a subsequent Suzuki-Miyuara cross-coupling reaction (Figure 1.3)

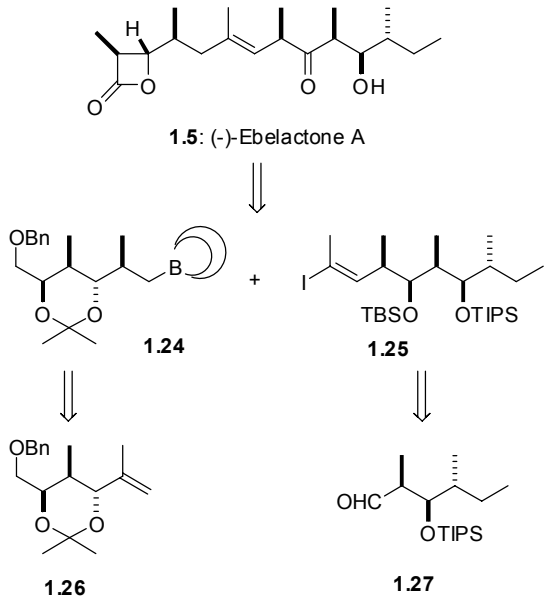
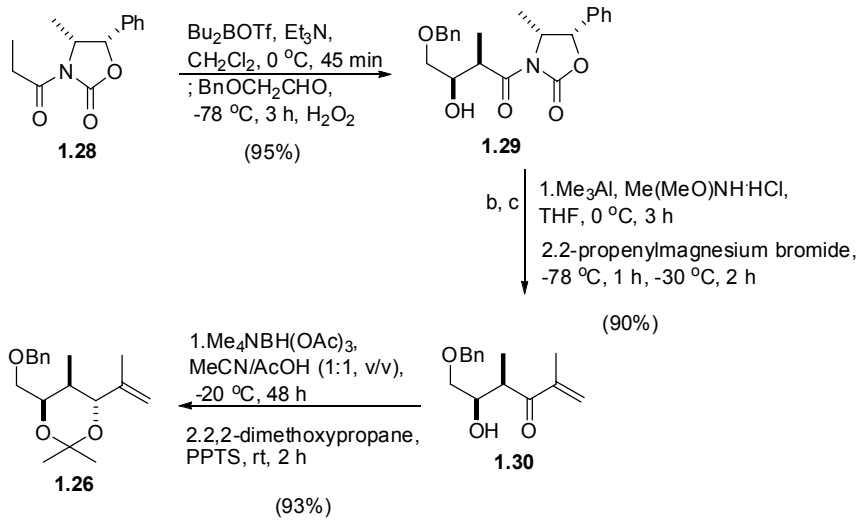


Figure 1.3 Retrosynthesis of ebelactone A

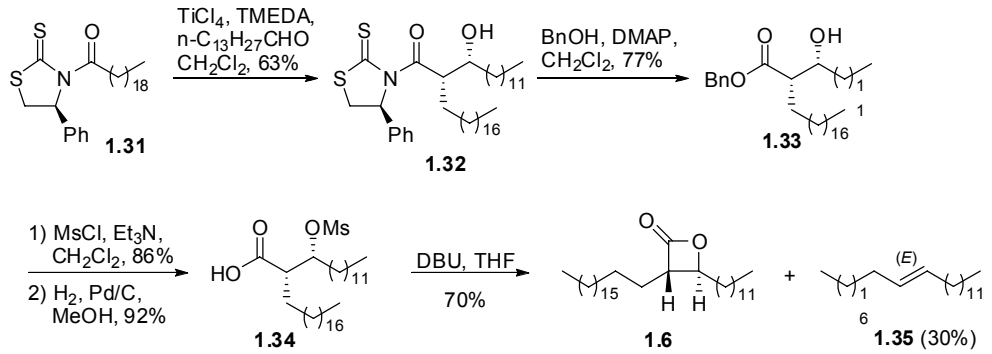
The masked β-lactone was synthesized by an Evan's *syn*-aldol reaction between *N*-propyl oxazolidinone **1.28** and α-benzyloxyacetaldehyde to afford the *syn*-aldol product **1.29** in 95% yield as a single diastereomer (Scheme 1.4).

Scheme 1.4



Norcardiolactone **1.6** is a simple β-lactone isolated by Mikami in 1999 from pathogenic Nocardia strains. During preliminary tests, it showed moderate narrow spectrum activity against gram-positive bacteria. Norcardiolactone **1.6** was synthesized by using a Crimmin's asymmetric aldolization (Scheme 1.5).

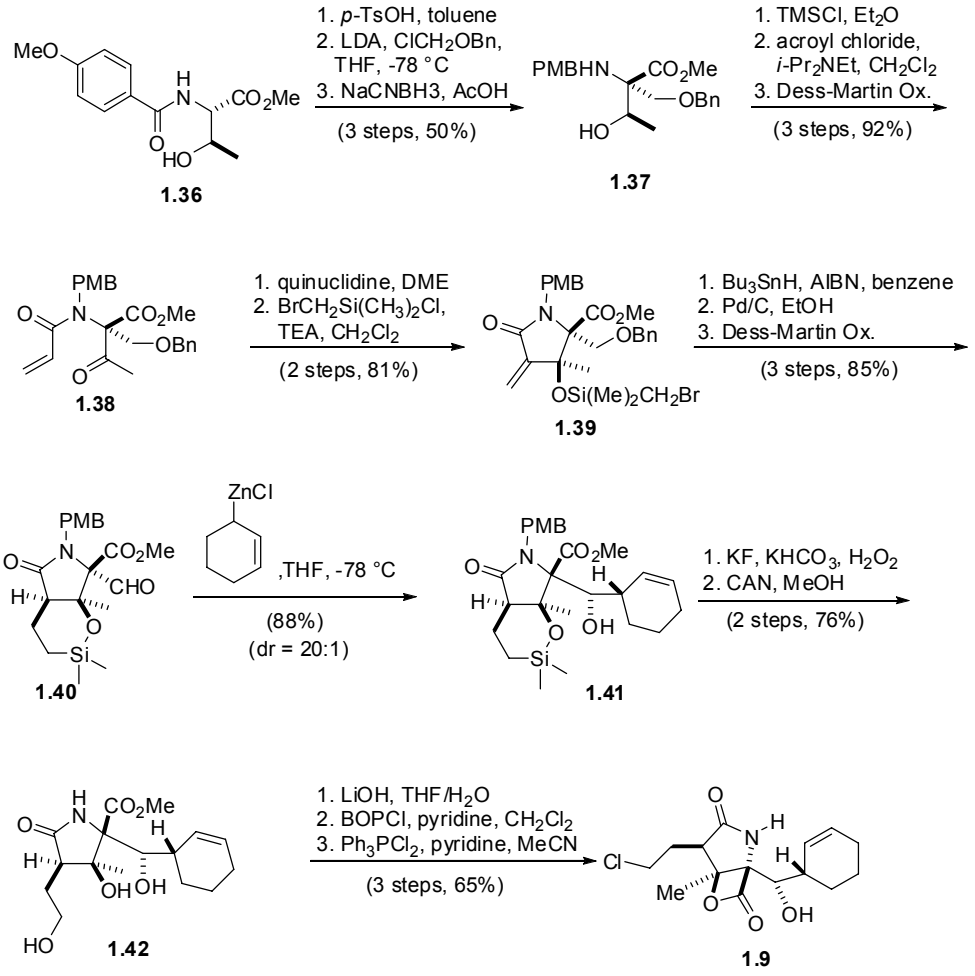
Scheme 1.5



Omuralide, salinosporamide A and their derivatives are "hot" molecules as they show potent proteasome inhibition ability with high target specificity. The synthetic efforts toward these have been reviewed recently.[11]

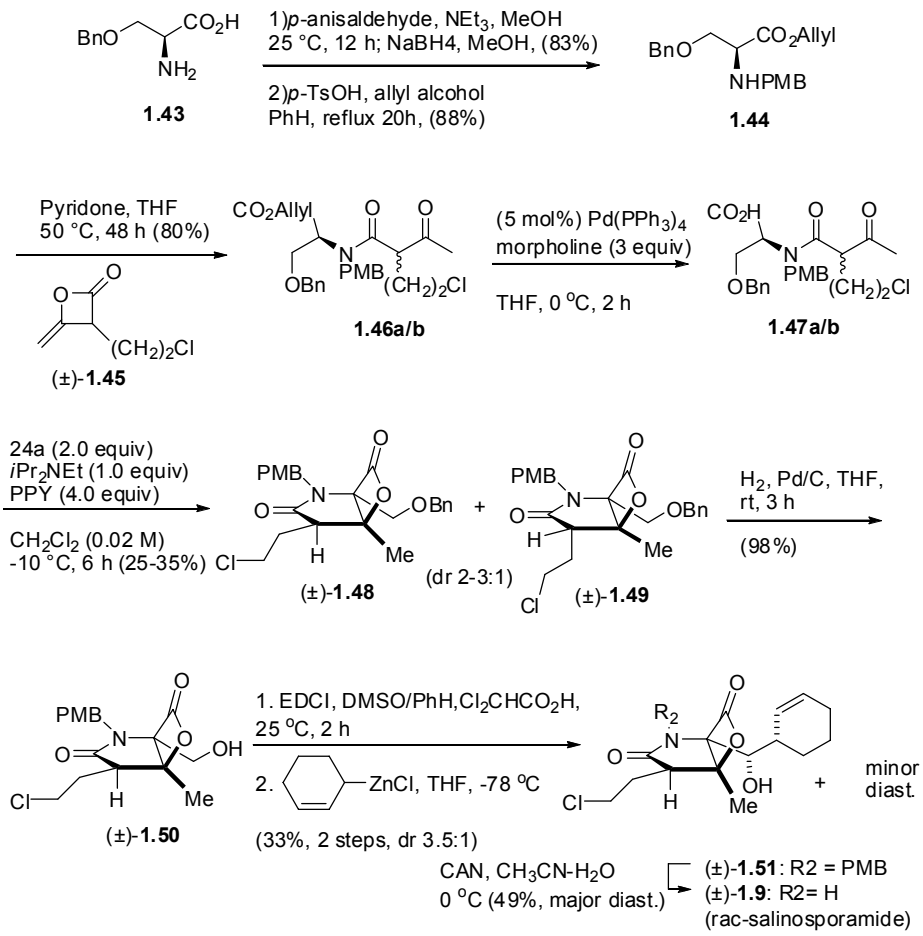
The first total synthesis of salinosporamide A (**1.9**) was also described by Corey (Scheme 1.6).[12] After cyclization of the amide **1.36**, an oxazoline allowing for alkylation and subsequent reduction with $NaBH_3CN$ delivered threonine derivative **1.37**. Transient TMS silylation of **1.37** followed by acylation with acryloyl chloride and Dess-Martin oxidation provided keto amide **1.38**. Cyclization of **1.38** by an intramolecular Baylis-Hillman reaction using quinuclidine led to a γ-lactam (dr 9:1) and subsequent silylation provided ether **1.39**. Radical cyclization with tributyltin hydride delivered a bicyclic compound which was subjected to hydrogenolysis of the benzyl ether and oxidation to give aldehyde **1.40**. An organozinc reagent was utilized to install the remaining two stereocenters in a highly diastereoselective fashion. After further manipulations, salinosporamide A (**1.9**) was obtained by saponification, β-lactone formation with BOPCl, and chlorination in 13% overall yield and a longest linear sequence of 17 steps.

Scheme 1.6


1. p-TsOH, toluene
2. LDA, ClCH2OBn, THF, -78 °C
3. NaCNBH3, AcOH
(3 steps, 50%)
1. TMSCl, Et2O
2. acroyl chloride, i-Pr2NEt, CH2Cl2
3. Dess-Martin Ox.
(3 steps, 92%)
1. quinuclidine, DME
2. BrCH2Si(CH3)2Cl, TEA, CH2Cl2
(2 steps, 81%)
1. Bu3SnH, AIBN, benzene
2. Pd/C, EtOH
3. Dess-Martin Ox.
(3 steps, 85%)
ZnCl
,THF, -78 °C
(88%)
(dr = 20:1)
1. KF, KHCO3, H2O2
2. CAN, MeOH
(2 steps, 76%)
1. LiOH, THF/H2O
2. BOPCl, pyridine, CH2Cl2
3. Ph3PCl2, pyridine, MeCN
(3 steps, 65%)
1.36
1.37
1.38
1.39
1.40
1.41
1.42
1.9

Recently, our group reported the total synthesis of salinosporamide A and cinnabaramide A using the NCAL reaction as a key step (Scheme 1.7). Reductive amination of *O*-benzyl-*L*-serine **1.43** with *p*-anisaldehyde following the esterification provided (*S*)-*N*-PMB serine allyl ester **1.45**. The PMB allyl ester **1.45** was coupled with hetero-ketene dimer **1.46**, to provide keto acids **1.47a/b** following Pd-mediated ester deprotection. The key bis-cyclization proceeded in 25-35% yield with a diastereomeric ratio of 2-3:1 for β-lactones **1.48** and **1.49**, which favored that found in salinosporamide. Deprotection of the benzyl ether enabled enrichment of the major diastereomer **1.50** to 6:1 upon purification. Modified Moffatt oxidation[13] using 1-(1,3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI)[14] and dichloroacetic acid[15] provided the corresponding aldehydes with a diastereomeric ratio of 14:1, which was carried forward directly to the next step. Applying the method developed by Corey for side chain attachment to the aldehyde using a zinc reagent generated *in situ* gave alcohols **1.51** in 33% yield (2 steps, dr = 3.5:1). Finally, deprotection of the PMB group provided *rac*-salinosporamide A **1.9** diastereomerically pure in 49% yield.

Scheme 1.7

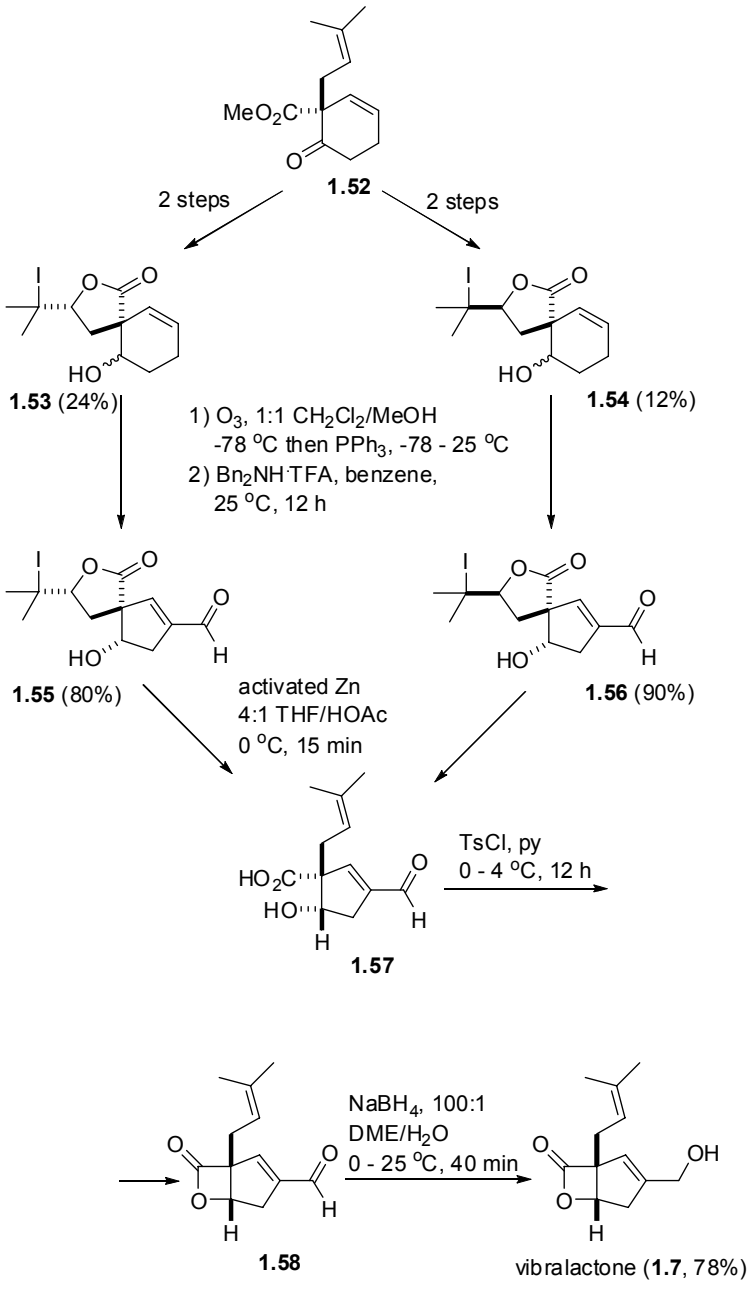

1)p-anisaldehyde, NEt3, MeOH
25 °C, 12 h; NaBH4, MeOH, (83%)
2)p-TsOH, allyl alcohol
PhH, reflux 20h, (88%)
1.43
1.44
Pyridone, THF
50 °C, 48 h (80%)
(±)-1.45
1.46a/b
(5 mol%) Pd(PPh3)4
morpholine (3 equiv)
THF, 0 °C, 2 h
1.47a/b
24a (2.0 equiv)
iPr2NEt (1.0 equiv)
PPY (4.0 equiv)
CH2Cl2 (0.02 M)
-10 °C, 6 h (25-35%)
(±)-1.48
(dr 2-3:1)
(±)-1.49
H2, Pd/C, THF,
rt, 3 h
(98%)
(±)-1.50
1. EDCI, DMSO/PhH,Cl2CHCO2H,
25 °C, 2 h
2. ZnCl, THF, -78 °C
(33%, 2 steps, dr 3.5:1)
minor
diast.
CAN, CH3CN-H2O
0 °C (49%, major diast.)
(±)-1.51: R2 = PMB
(±)-1.9: R2= H
(rac-salinosporamide)

Recently Liu reported the isolation of the fused β-lactone vibralactone **1.7** from cultures of the Basidiomycete *Boreostereum vibrans*. They assigned the structure by detailed spectroscopic analysis, and the absolute stereochemistry was assigned by computational methods.

Vibratone covalently but reversibly modifies the active site serine of the enzyme via acylation by the β-lactone. The first total synthesis of vibratone was completed by Snide in 2007 (Scheme 1.8).

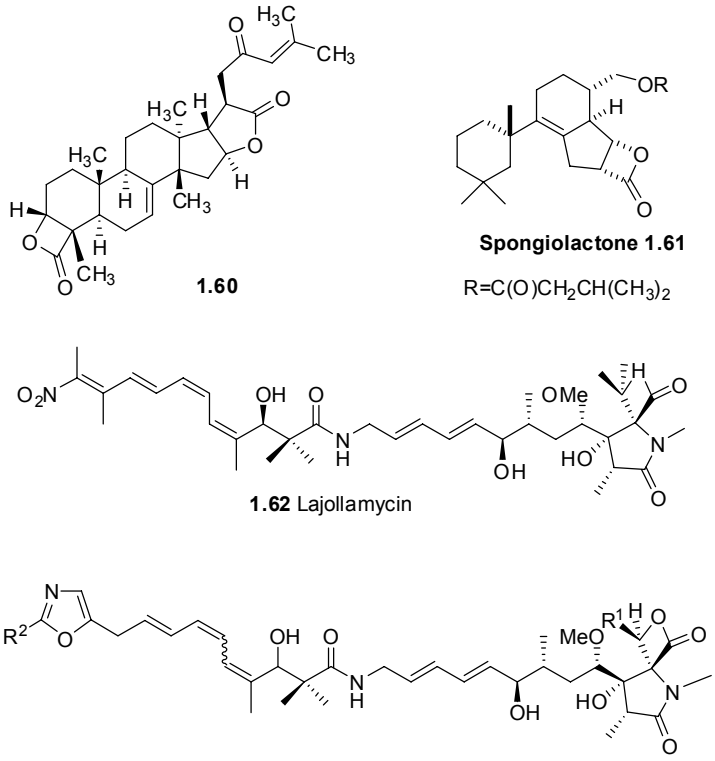
The starting carboxylate was obtained from reductive alkylation of 2-methoxybenzoate with prenyl bromide and further hydrolysis. The cyclopentenal spiro-lactone **1.55** was delivered after a series of standard manipulations via several steps. Zinc mediated retro-iodolactonization delivered aldehyde **1.57** with moderate yield and subsequent intramolecular esterfication with TFA completed β-lactone **1.58**. Finally reduction of the aldehyde **1.58** by $NaBH_4$ delivered vibralactone **1.7** with 78% yield.

Scheme 1.8


MeO2C
O
1.52
2 steps
2 steps
I
O
O
HO
1.53 (24%)
1.54 (12%)
1) O3, 1:1 CH2Cl2/MeOH
-78 °C then PPh3, -78 - 25 °C
2) Bn2NH·TFA, benzene,
25 °C, 12 h
H
1.55 (80%)
1.56 (90%)
activated Zn
4:1 THF/HOAc
0 °C, 15 min
HO2C
1.57
TsCl, py
0 - 4 °C, 12 h
NaBH4, 100:1
DME/H2O
0 - 25 °C, 40 min
OH
1.58
vibralactone (1.7, 78%)

B. Recently Isolated β-Lactone Containing Natural Products and Synthetic Derivatives

Several β-lactone containing natural products have interesting biologically great activity such as Verbanaceae **1.60**, Oxazolomycin**1.63** and lajollamycin **1.62** have not synthesized yet (Figure 1.4).



1.63a Oxazolomycin A: R^1 = H, R^2 = H; 4'*Z*,6'*Z*, 8'*E*
1.63b Oxazolomycin B: R^1 = H, R^2 = H; 4'*E*,6'*E*, 8'*E*
1.63c Oxazolomycin C: R^1 = H, R^2 = H; 4'*Z*,6'*E*, 8'*E*
1.63d 16-Metyloxazolomycin: R^1 = Me, R^2 = H; 4'*Z*,6'*Z*, 8'*E*
1.63e Curromycin A: R^1 = CH_3OCH_2, R^2 = Me; 4'*Z*,6'*Z*, 8'*E*
1.63f Curromycin B: R^1 = Me, R^2 = Me; 4'*Z*,6'*Z*, 8'*E*

Figure 1.4 Recently Isolated Natural Products Containing β-Lactone and Synthetic Derivatives

In 1998, O'Neill reported *Lantana camara* L. (verbanaceae). *Lantana camara* L. (verbanaceae), commonly known as wild sage, is a flowering shrub indigenous to tropical America and Africa.[16] Methanolic extract **1.60** prepared from the leaves of *Lantana camara* have been found to inhibit human thrombin.[17] Analysis of the HRMS and 1D and 2D NMR data for extract led to the structure proposed. An X-ray crystal structure confirmed the proposed structure.

Diterpene isovalerate ester, spongiolactone **1.61**, was isolated from *Spongionella gracilis* as part of a targeted re-isolation of larger quantities of the gracilin family of compounds for screening in a variety in unspecified bioassays. Although spongiolactone **1.61** possesses a heavily rearranged carbon skeleton, it is still thought to originate from a spongian diterpene.[18] Neither a synthesis nor the biological activity has been reported for this compound.

Over the past two decades a large number of complex bioactive natural products containing β-lactones and methylene-interrupted oxazolyl-triene motif have been isolated from strains of *Streptomyces* sp. Oxazolomycin A **1.63a**,[19] isolated in 1985, is the parent of this class of antibiotics, which also includes oxazolomycins B **1.63b** and C **1.63c**,[20] curromycins A **1.63e** and B **1.63f**,[21] 16-methyloxazolomycin **1.63d**,[22] and lajollamycin **1.62**.[23] These compounds are structurally novel antibiotic and antiviral agents, whose bioactivity has been proposed to arise from their protonophoric properties. There are no syntheses reported to the best of our knowledge, although there are a number of groups that have established strategies for the synthesis of core components, including the middle component,[24] and the left-hand portion.[25]

CHAPTER II

TOTAL SYNTHESIS OF BELACTOSIN C AND DERIVATIVES*

A. Isolation and Biological Activity of the Belactosins

The recently isolated bacterial metabolites, belactosins A-C from a fermentation broth of *Streptomyces* sp. UCK14, uniquely contain a β-lactone dipeptide motif and exhibit anticancer activities[26] that has been subsequently attributed to regulation of the ubiquitin-proteasome pathway through inhibition of the 20S proteasome (Figure 2.1).[27] The proteasome, an intracellular proteolytic system, shows the peptidase profile of chymotrypsin, trypsin, and peptidyglutamyl-peptide protease.[28] Belactosins A and C possess the greatest inhibitory activity toward chymotrypsin of the rabbit 20S proteasome (IC_{50} = 0.21 μM), whereas when the β-lactone moiety is absent as in belactosin B there is greatly reduced activity (>10 μM). In addition, degradation studies of belactosin A suggested that the β-lactone moiety was indeed responsible for the observed antiproliferative activity.[2]

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* Reproduced in part from Cho, S. W.; Romo, D. "Total Synthesis of Belactosin C and Congeners via the Tandem Mukaiyama Aldol-Lactonization Process", *Org. Lett*. **2007**, *9*, 1537. Published work copyright 2007 American Chemical Society.

A benzyl ester derivative KF33955, which is presumably more cell permeable exhibited greater growth inhibitory activity toward HeLa S3 cells than both belactosins A and C (IC_{50} = 0.46 μM vs 51 and 200 μM, respectively).

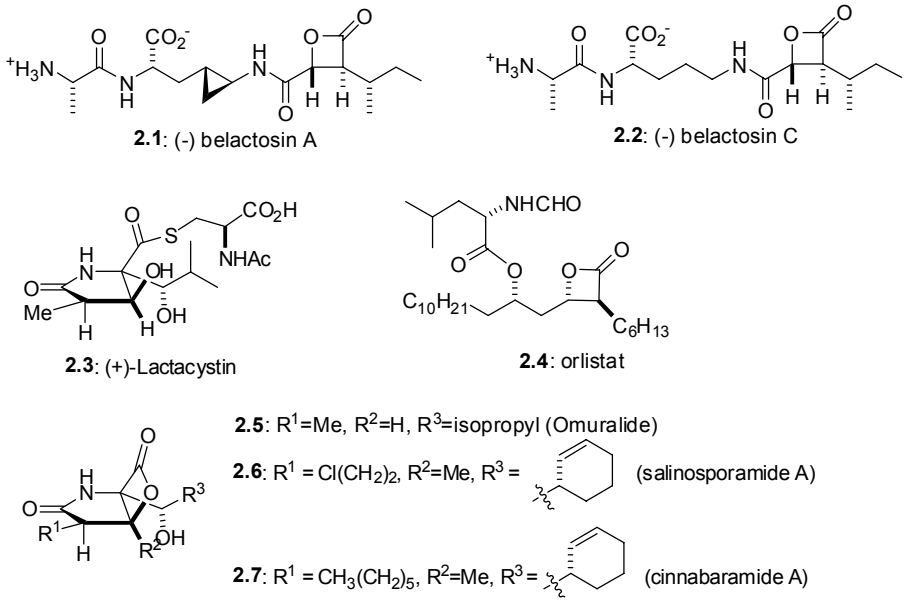


Figure 2.1 Structure of Belactosin A and C and Other β-Lactones: Inhibitors of the Proteasome and Thioesterase Domain of Fatty Acid Synthase

A recent X-ray study of *N*-CBz-*O*-Bn homobelactosin C bound to the yeast 20S proteasome revealed that the *N*-terminal γ-threonine residue in the catalytic pocket of the proteasome is acylated by the β-lactone moiety, and the orientation differs from omuralide a β-lactone-containing proteasome inhibitor (Figure 2.2).[29]

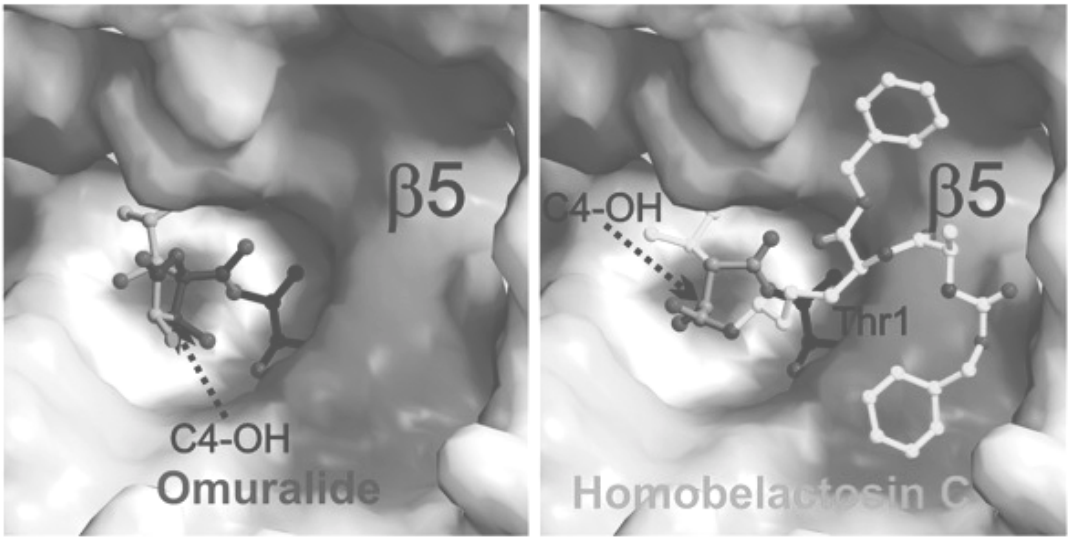


Figure 2.2 Surface Representation of the Chymotryptic-like Active Site in Complex with Omuralide (*Left*) and Homobelactosin C (*Right*), Covalently Bound to Thr-1 (depicted in white). (Reproduced from ref.20)

Proteasome inhibitors are also of high interest as research tools. Since the proteasome is a protein complex in eukaryotic cells that degrades certain proteins, inhibition of its activity can induce cell death in cancer cells or disrupt major cell signaling cascades. These compounds may also have potential usefulness for treatment of malaria, cancer, inflammation and infectious diseases. We have reported other β-lactone containing compounds such as tetrahydrolipstatin (orlistat **1.5**) and derivatives that act as inhibitors of the thioesterase domain of fatty acid synthase (FAS-TE), a reduced form of the natural product lipstatin is an antiobesity agent marketed under the tradename of Xenical that was recently approved by the FDA as the first over-the-counter weight-loss medication (Figure 2.1). The mechanism of inhibition involves

covalent but reversible modification of the active site serine via acylation by the β-lactone. Therefore Belactosin C may be a feasible inhibitor of the FAS-TE even though there is no currently reported activity.

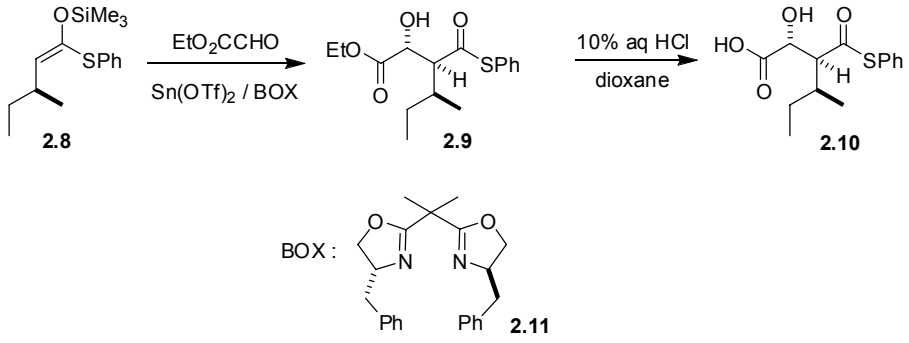
B. Previous Syntheses of Belactosins

To date five total syntheses of belactosin A and C and their derivatives have been reported[30] including ours along with several studies regarding fragment syntheses.[31]

De Meijere has since reported progress toward belactosin C[32] along with studies by Kumaraswamy reporting two different synthetic method for belactosin C and derivatives, whereas, Armstrong has reported the synthesis of the belactosin A[33].

In 2004, De Meijere utilized a chiral BOX ligand **2.11** to make the β-lactone which required several steps to make (Scheme 2.1).

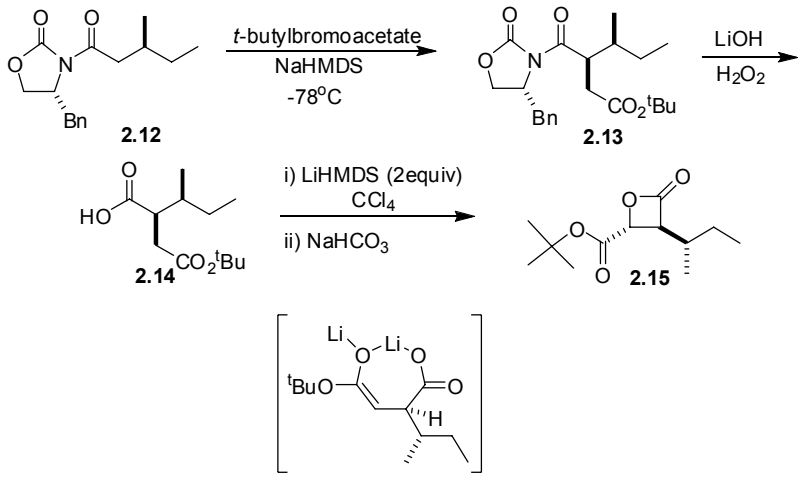
Scheme 2.1



A (*Z*)-silylketene acetal was employed in the Mukaiyama-type aldol reaction with ethyl glyoxalate, using $Sn(OTf)_2$/BOX as the catalytic system. This reaction gave a high enantioselectivty (99% ee) and diastereoselectivity (*syn* : *anti*> 40: 1).

Almost same time, Armstrong used a chiral oxazoline to install the chiral β-lactone (Scheme 1.2). The key chlorination step was prepared by prior conversion to the dianion using LiHMDS followed by treatment with carbon tetrachloride. Lactonization was achieved as described by Barlaam,[34] and the excellent diastereoselectivity presumably came from a cyclic transition state presenting the less hindered site of the enolate to the chlorinating reagent.

Scheme 2.2



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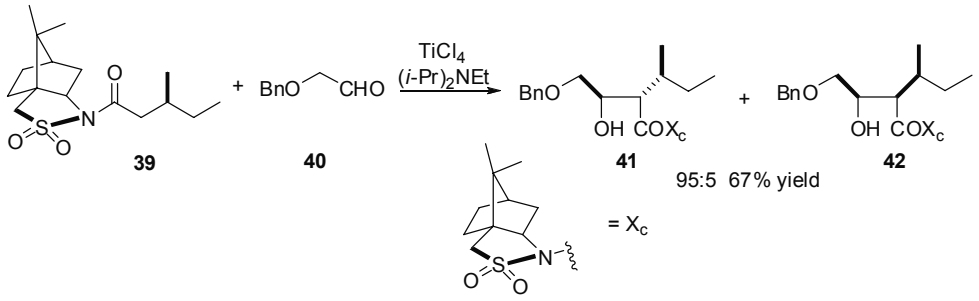
More recently, Kumaraswamy has reported belactosin C synthesis using Oppolzer's sultam directed aldol reaction as a key step (Scheme 2.3)

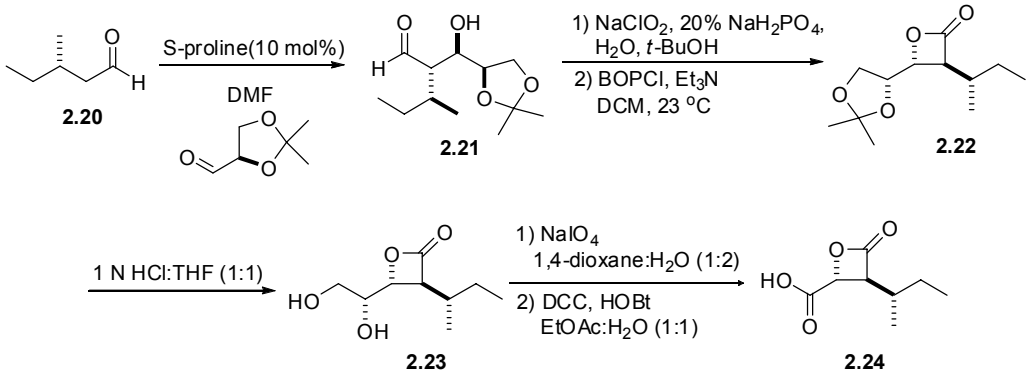
Scheme 2.3



The Oppolzer's sultam directed aldol reaction was achieved by using two equiv. $TiCl_4$ and the anti isomer was obtained exclusively through an open transition state as proposed by Oppolzar.

Kumaraswamy reported another synthesis of belactosin C using a proline catalyzed crossed-aldol reaction, which delivered the chirality from catalytic *S*-proline (Scheme 2.4).[35]

Scheme 2.4

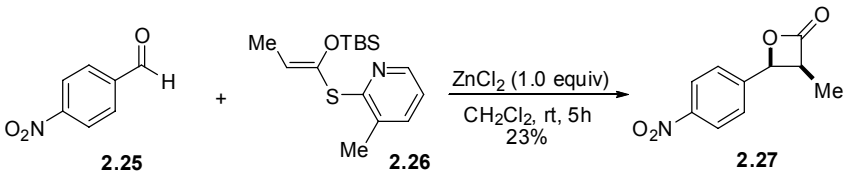


Belactosins A and C possess a *trans*-β-lactone moiety as a key structural feature. Although new methods for the synthesis of β-lactones have drawn great interest in recent years due to their great versatility and utility in natural product synthesis,[36] as we discussed here, relatively few methods exist for the synthesis of these compounds in optically pure form.[37] We have developed diastereoselective and enantioselective methods for the preparation of β-lactones employing chiral Lewis-acid catalyzed [2+2] cycloadditions of ketenes and aldehydes, a tandem Mukaiyama aldol-lactonization (TMAL) process and a nucleophile catalyzed aldol lactonization (NCAL) of aldehydeacids. In case of TMAL delivers *trans* β-lactones in one step sequence.

C. The Tandem Mukaiyama Aldol-Lactonization (TMAL) Process

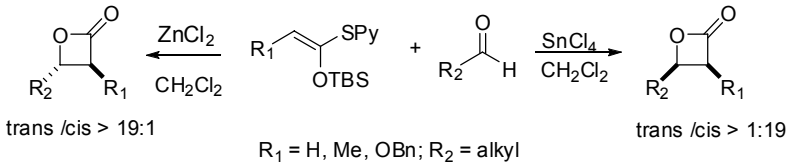
The TMAL process builds on Hirai's initial discovery[38] where a single β-lactone, 4-(*p*-nitrophenyl)-3-methyl oxetan-2-one **2.27** was prepared in 23% yield with high *cis* diasteroselectivity (Scheme 2.5).

Scheme 2.5



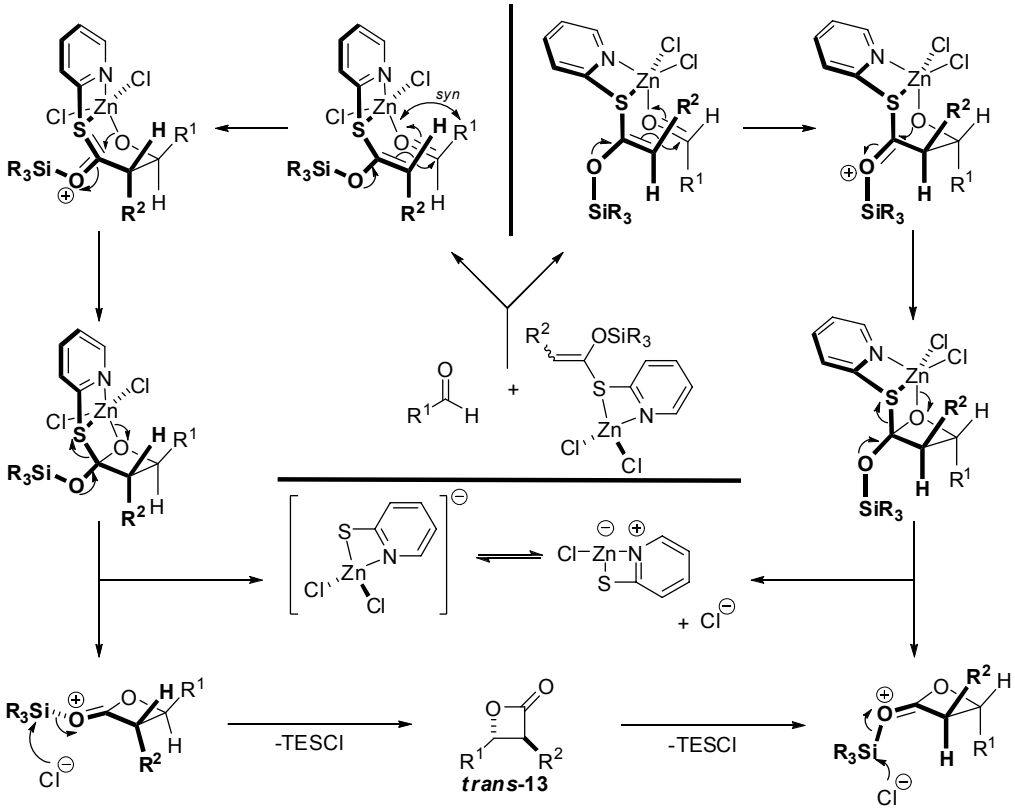
During our investigation of the TMAL reaction we discovered a new TMAL process which provide *trans* β-lactones exclusively major diastereomer (Scheme 2.6).

Scheme 2.6



In the course of optimization of various reaction parameters, several important were found. The thiopyridine moiety of ketene acetal was crucial to the success of this reaction. Second, $ZnCl_2$ is the only Lewis acid to deliver *trans*-β-lactones in the TMAL process so far. Finally, the steric bulk of the silyl group of ketene acetal was found to play an important role in the outcome of the TMAL process. we found that less bulky silyl groups increase the yield of β-lactones as previously observed. Based on our observations, we proposed mechanism in the TMAL reactions (Scheme 2.7)

Scheme 2.7

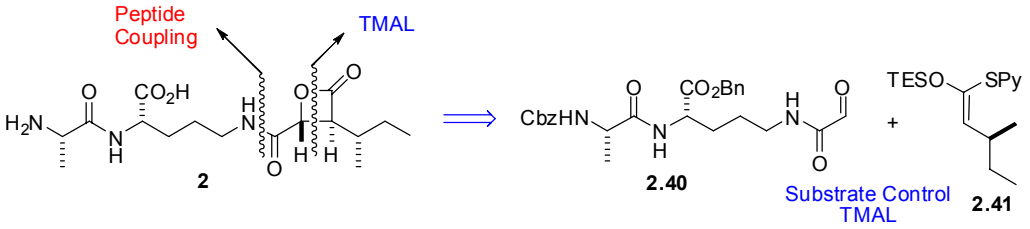


Our group and others[39] have used this method to prepare various β-lactones including natural products such as (–)-panclicin D,[40a,c] tetrahydrolipstatin/orlistat,[4a,41] (–)-grandinolide,[42] and okinonellin B,[43] the latter two targets being accessed via β-lactone intermediates obtained by the TMAL process

D. Retrosynthetic Analysis of Belactosin C

In general, the published syntheses of belactosins require multiple steps to construct the key β-lactone nucleus involving a late-stage lactonization step. We were attracted to the possibility of the direct construction of belactosin and derivatives *via* the TMAL process using a chiral silyl ketene acetal and the requisite glyoxamide dipeptide (strategy A, Figure 2.3). This strategy would enable rapid SAR studies of these enzyme inhibitors toward the proteasome and possibly other cellular proteins. Although this reaction would constitute a double diastereoselective process, a high degree of diastereoselectivity was not assured given the distance between stereogenic centers. Therefore, an alternative strategy would employ chiral glyoxamides[11] bearing cleavable chiral auxiliaries to impart higher diastereoselectivity *via* double diastereodifferentiation due to the greater proximity of the resident stereogenic centers (strategy B, Figure 3). The resulting β-lactone carboxylic acid **2.24** and simpler β-lactone acids could then be coupled to the protected *orn-ala* dipeptide and variations structure-activity studies.

A. Double Diastereoselective (Distal) : Ketene Acetal-Based



B. Double Diastereoselective (Proximal) : Glyoxal-Chiral Auxiliary-Based

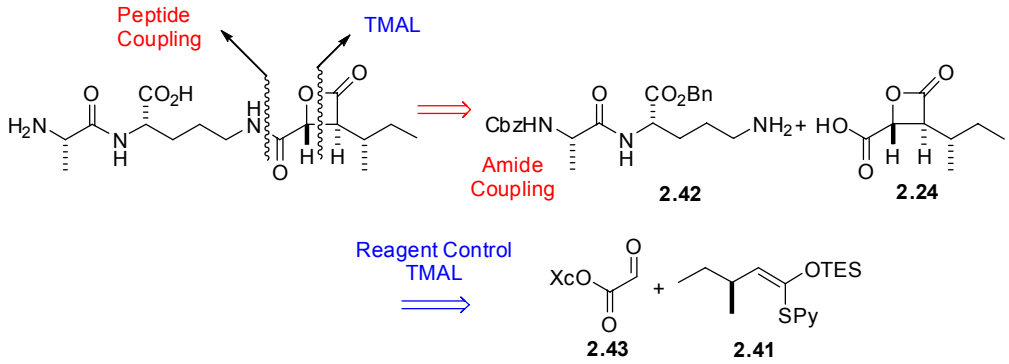
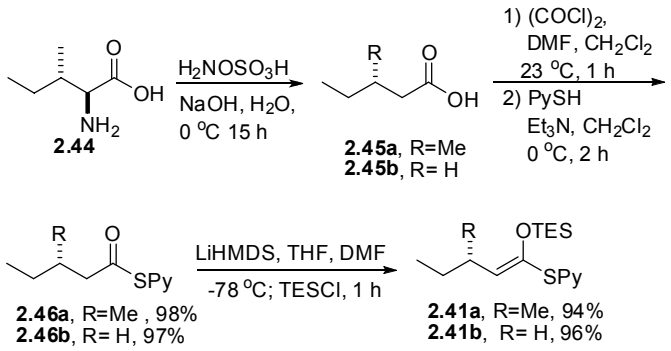


Figure 2.3 Retrosyntheses of Belactosin C Employing Double Diastereoselection

E. Synthesis of Peptide & Ketene Acetal Fragment

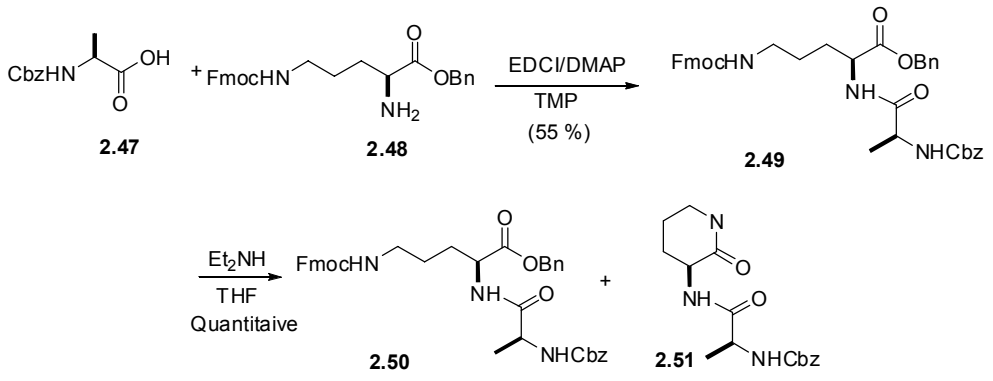
The synthesis of the required chiral silyl ketene acetal **2.41** commenced with the known hydrodeamination[44] of L-isoleucine **2.44** with hydroxylamine-*O*-sulfonic acid followed by conversion to thioester **46a** *via* the acid chloride (Scheme 2.8).[45] Conversion to the silyl ketene acetal (*E*/*Z*, ~9:1) was accomplished using procedures described previously.[5] An identical route was employed to prepare the achiral silyl ketene acetal **2.41b**.

Scheme 2.8



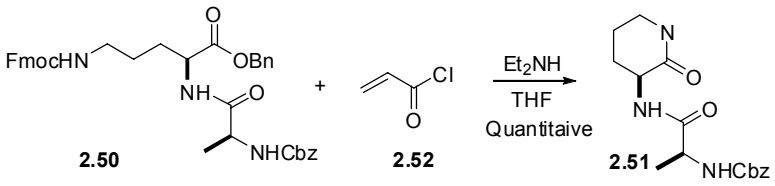
After ketene acetal **2.41a/b** in hand, we started the peptitide fragment synthesis from the Cbz-alanine **2.48** (Scheme 2.9). EDCI coupling with Cbz-alanine **2.48** and Fmoc-ornithine **2.49** delivered dipeptide **2.50** in moderate yield. However, Fmoc deprotection conditions with various bases and solvents did not give the desired free amine **2.51** but the cyclic amide **2.52**.

Scheme 2.9



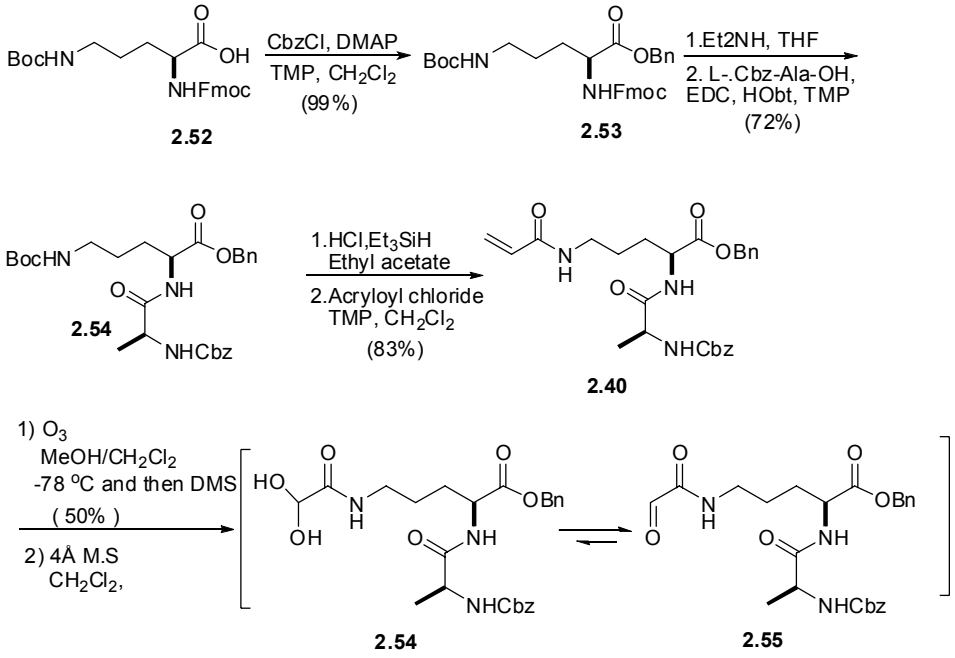
To prevent intramolecular cyclization, we tried *in-situ* capturing with acyloyl chloride but we did not get any success (Scheme 2.10).

Scheme 2.10



Therefore we need to change the protection groups with Boc to change this deprotection step. Benzylation of the diprotected ornithine **2.52** with Cbz-Cl gave the benzyl ester **2.53**, which, after removal of the Fmoc group with Et_2NH, was coupled with Cbz-Ala-OH (Scheme 2.11). Acylation with acryloyl chloride provided amide **2.40** which was converted *via* ozonolysis to a mixture of the desired glyoxamide **2.56** and its corresponding hydrate mixture after purification by flash column chromatography. Stirring the mixture with 4 Å molecular sieves enabled dehydration to deliver the desired glyoxamide **2.56** and checked by H-NMR. Glyoxamide **1** which was treated after 24 h stirring 4 Å molecular sieves in CH_2Cl_2 was suitable for the subsequent TMAL process.

Scheme 2.11

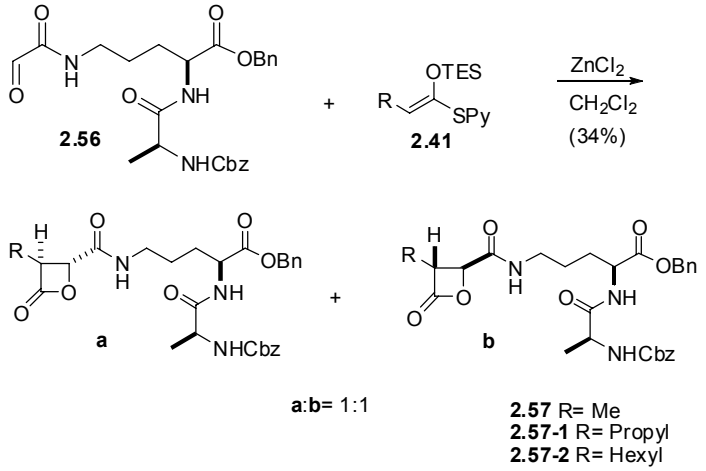


F. Synthesis of the β-Lactone

1. Synthesis Using a Double Diastereoselective (Distal) TMAL

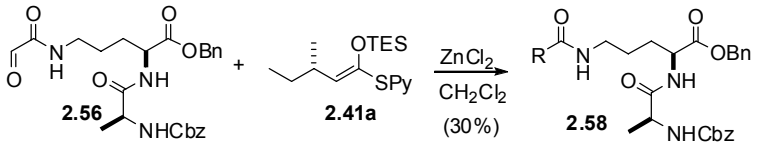
With chiral and achiral ketene acetals **2.41a**/**b** and glyoxamide dipeptide **2.57** in hand, we set out to study the inherent diastereoselectivity, if any, imparted by the dipeptide on the configuration of the β-lactone generated. On the basis of previous studies of the $ZnCl_2$-mediated TMAL process, we expected exclusive formation of *trans*-β-lactone. Indeed, treatment of aldehyde **2.56** with ketene acetal **2.41b** under standard TMAL conditions gave exclusively *trans*-β-lactones **2.57-1a**/**b** albeit in low yield. On the basis of ^{13}C NMR, the ratio of diastereomers **2.57-1a**/**b** was ~1:1 (Scheme 2.12). As expected, the stereogenic centers of the dipeptide are too distal to impart any inherent bias on the diastereoselectivity.

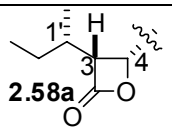
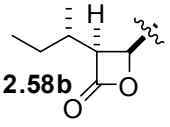
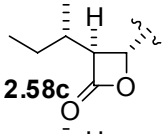
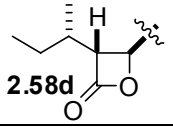
Scheme 2.12



However when chiral ketene acetal **2.41a** was employed, this led to the formation of four diastereomers including *cis*-β-lactones with a slight preference for *trans*-diastereomers (Scheme 2.13). In this case, the stereogenic center of the ketene acetal clearly does impact the diastereoselectivity but not in a favorable manner. After careful purification, the *cis*-(**2.58a/2.58b**) and *trans*-(**2.58c/2.58d**) diastereomers could be separated; however, the two *trans*-diastereomers were inseparable.

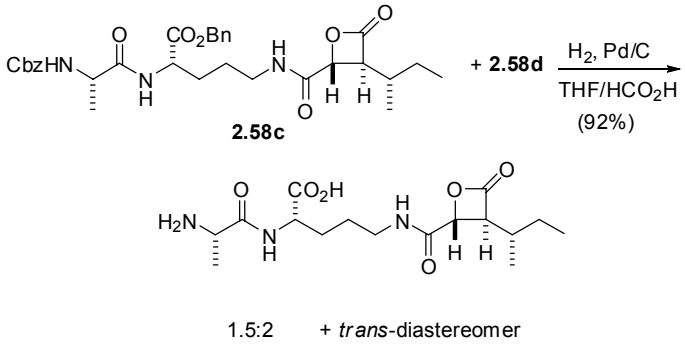
Scheme 2.13



product	R	ratio	$J_{3,4}$ (Hz)	$J_{3,1'}$ (Hz)
C3-epimer	 **2.58a**	1	7.5	10.0
C4-epimer	 **2.58b**	1	6.5	8.5
belactosin C	 **2.58c**	1.5	4.5	8.0
C3,4-epimer	 **2.58d**	2	4.5	8.5

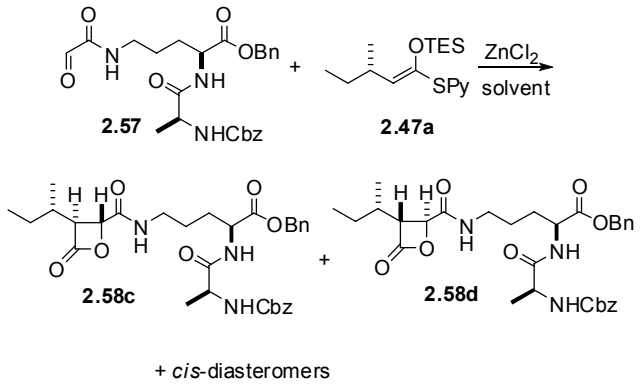
The *trans* diastereomers were deprotected by hydrogenolysis with H_2/Pd with retention of the 1.5:2 ratios of diastereomers which was not more separable (Scheme 2.14).

Scheme 2.14



Alternative reaction conditions were explored in order to increase the diastereoselectivity (Table 2.1). Most solvents did not give the desired β-lactones except THF. The TMAL reaction in THF had not reported, but it proceeded in this reaction. Although, we could obtain exclusively the desired *trans*- β-lactone diastereomers, the yield was below 1%. THF gave the desired *trans*-β-lactones while also increasing the ratio of desired *trans*-β-lactone diastereomers from 1.2: 1 to 3:1.

Table 2.1 TMAL Reaction with Various Solvents

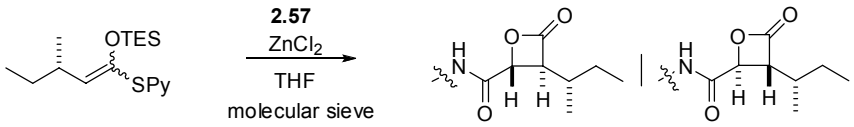


solvent	cis:trans	yield (%)
CH_2Cl_2	2 : 3.5	30
CH_3CN	0	0
Toluene	0	No reaction
THF	0 : 100	Trace

The ratio (3:1) of the products matched the *E/Z* ratio (3:1) of the ketene acetal (Scheme 2.15). Therefore, we decided to examine the relationship between the

diastereomeric ratio of the product of TMAL reaction and the *E/Z* ratio of ketene acetal. Indeed, with exclusively *E*-ketene acetal (17:1) we obtained the desired protected belactosin C in a ratio of 8:1 implying that the *E*–ketene acetal led to the desired diastereomer. However, the yield of this TMAL reaction was poor, which necessitated the use of alternate reaction conditions.

Scheme 2.15



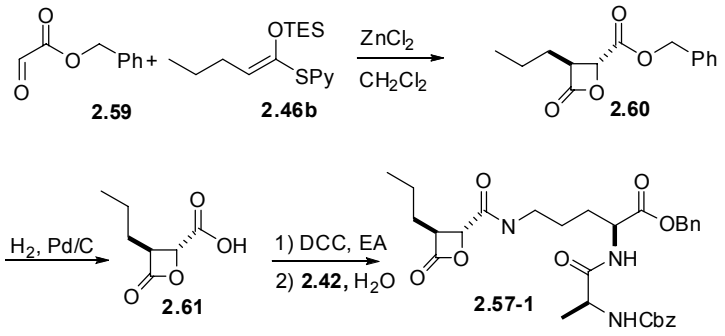
(*Z*)-**2.47**/(*E*)-**2.47**	**2.58c**	**2.58d**
3:1	3	1
17:1	8	1

2. Synthesis Using a Double Diastereoselective (Proximal) TMAL

We next studied the TMAL reactions of glyoxylate esters including those bearing a chiral auxiliary, which could be readily deprotected and then coupled to a number of dipeptides. Carefully examination of the chiral auxiliary candidates required easy approachable synthesis and deprotection by hydrogenolysis, due to the somewhat labile β-lactone moiety that would be present.[46]

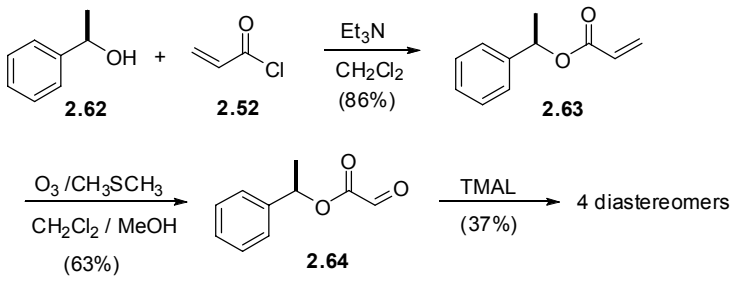
For model study of incorporating the desired functionality, benzylglyoxylate was prepared using same reaction sequence from benzyl alcohol and the TMAL reaction. The benzyl group was deprotected by H_2/Pd and to give β-lactone acid, which was subsequently coupled with dipeptide to give the products (Scheme 2.16).

Scheme 2.16



We then selected a few chiral auxiliary candidates and initiated the synthesis. (*R*)-phenethyl alcohol was selected as a chiral auxiliary since it can be obtained easily and efficiently. However, this auxiliary did not give any significant increase in the diastereoselectivity and just gave 4 diastereomers (Scheme 2.17).

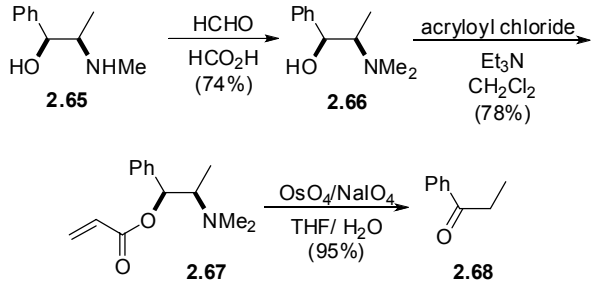
Scheme 2.17



Lately, we examined the possibility of chiral ephedrine derivatives as auxiliaries. We expected the coordination of Zn, *N*- and *O*- and these rigid conformations would fix the transition state arrangement, which would lead to high diastereoselectivity

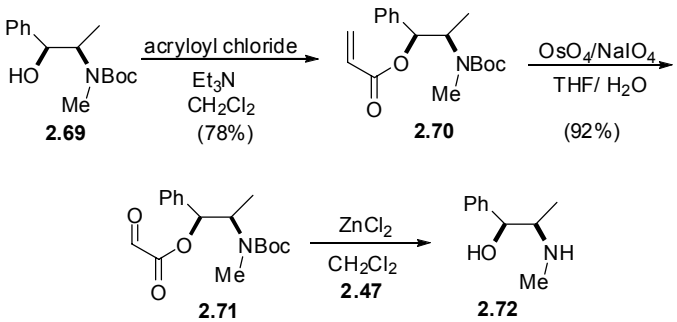
Based on this assumption, we began the synthesis of new auxiliary from ephedrine. *N*-methylation was achieved by formylation and subsequent treatment with acryloyl chloride to give acrylate **2.67**. Oxidative cleavage of acrylate **2.67** was expected to give the glyoxylate. However, only ketone **2.68** was observed (Scheme 2.18), presumably arised from the oxidation of the amine to the *N*-oxide with intramolecular elimination.

Scheme 2.18



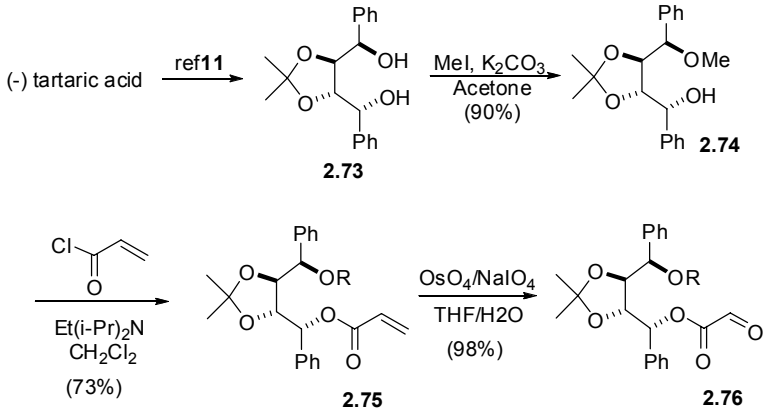
To avoid the formation of ketone **2.68**, the amine was protected with Boc to obtain the desired glyoxylate **2.71** in 92% yield. The TMAL reaction failed with glyoxylate **2.71** since the Boc protecting group was unstable in the reaction conditions (Scheme 2.19).

Scheme 2.19



Therefore, other auxiliaries were used for the asymmetric TMAL reaction protocol. Finally, we elected to study a variant of the known tartrate-derived auxiliaries that would fit our criteria and also possessing C-2 symmetry. The synthesis commenced with known diol **2.74**, available in four steps from (−)-*L*-dimethyl tartrate.[47] Monoprotection of diol **2.74** proceeded efficiently, and subsequent acylation with acryloyl chloride and oxidative cleavage of the double bond provided chiral glyoxylate **2.76** (Scheme 2.20).

Scheme 2.20



Application of the TMAL process with chiral glyoxylate **2.76** delivered an equimolar mixture of *cis*- and *trans*-β-lactones in 73% yield; however, greater selectivity for one *trans*-diastereomer was obtained (**2.77a**/**2.77b** = 1:5, Scheme 2.22). Furthermore, the purification was greatly simplified in the presence of the chiral auxiliary enabling separation of the *trans*-diastereomers by simple column chromatography.

From the purified *cis*-diastereomers, X-ray crystal structure analysis was obtained as

shown in Figure 2.4.

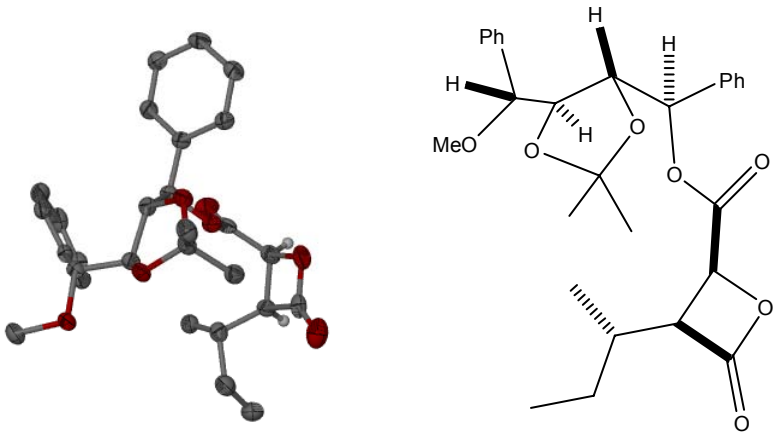


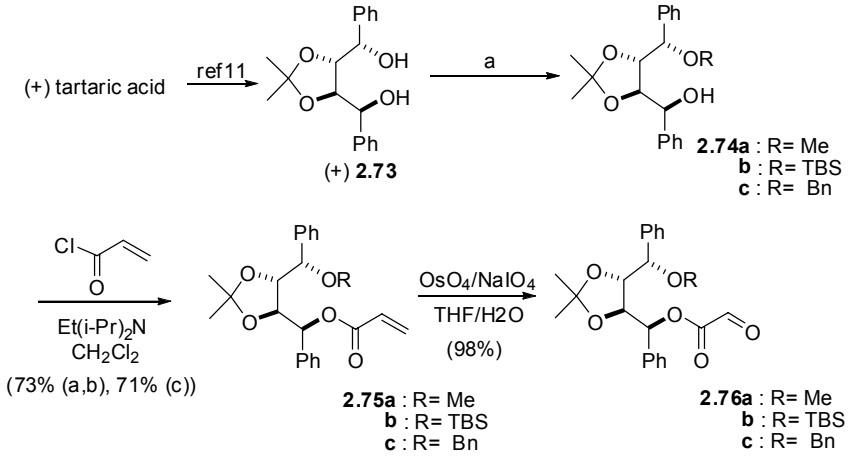
Figure 2.4. X-ray Crystal Structure of cis-β-Lactone Diastereomer **2.77** (some hydrogen atoms omitted for clarity)

To determine if this was the matched or mismatched case for the required *trans*-diastereomer, the enantiomeric glyoxylate ester *ent*-**2.76** was prepared (Scheme 2.21) and utilized in the TMAL reaction.

However, this was the mismatched case as the diastereoselectivity of **2.78-1 a**/**b** decreased to 1.5:1.

Other derivatives were prepared with this method in order to test their bioactivities (Scheme2.21).

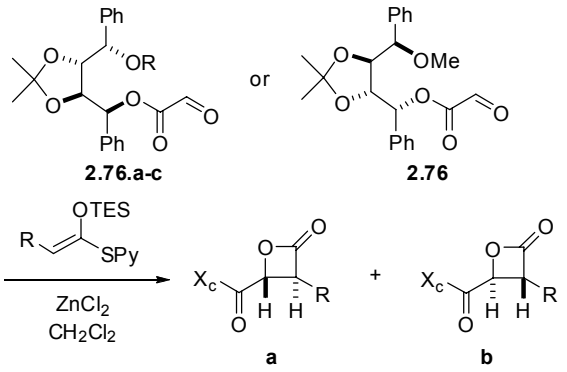
Scheme 2.21

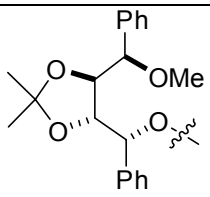
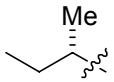
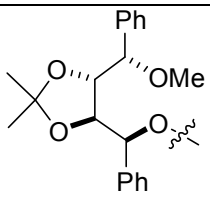
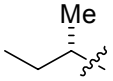
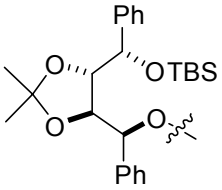
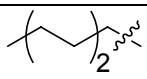
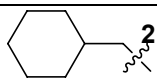
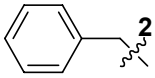
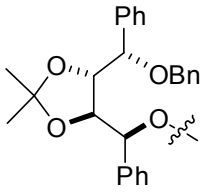
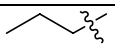


a) **2.74a**: MeI, K_2CO_3, Acetone (90%) ; **2.74b**:TBSCl, imidazole, DMF (45%)
2.74c : BnBr, Et_3N, Acetone (94%)

However, with many different ketene acetals, high diastereoselectivity could not be achieved in resulting inseparable mixtures (Scheme 2.22).

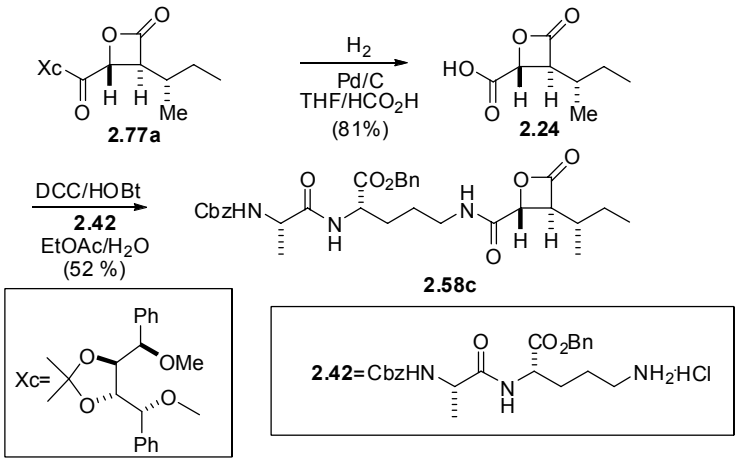
Scheme 2.22



entry	Xc	R	% yield [a]	**a:b** [b]
1		 **2.77**	73	1:5
2		 **2.78-1**	71	1.5:1
3		 **2.79-1**	60	1.1:1
4		 **2.79-2**	43	1.2:1
5		 **2.79-3**	53	1:1
7		Me **2.80-1**	53	1:1
8		 **2.80-2**	70	1.1:1

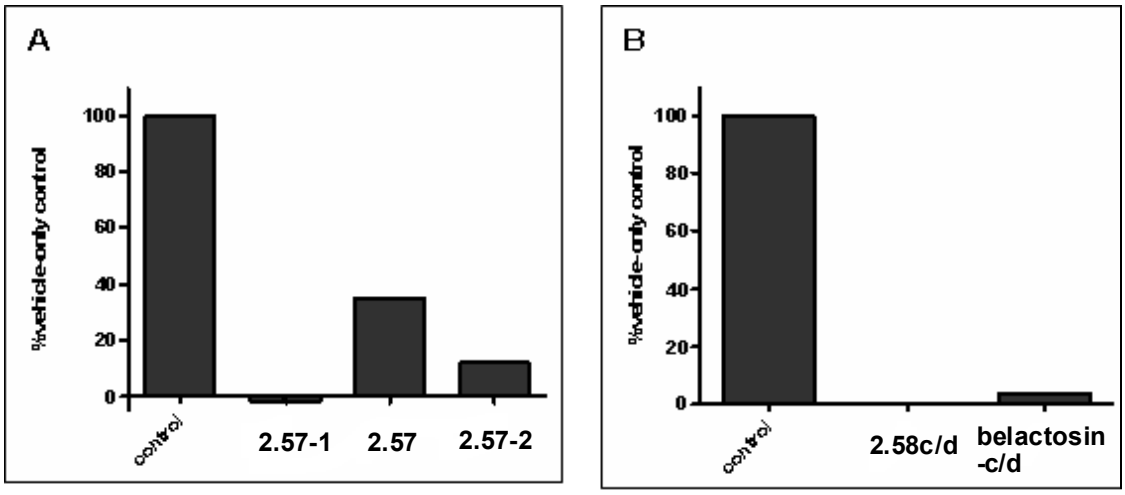
Cleavage of the chiral auxiliary by hydrogenolysis of ester **15a** gave β-lactone acid (-)-**3,** which could be correlated to the same compound reported by Kumaraswamy ($[\alpha]_D$ -3.1; lit. ($[\alpha]_D$ -3.0).[34] Subsequent coupling with protected dipeptide **7** generated protected belactosin C **10c,** and deprotection by the method of Armstrong[33] gave belactosin C in diastereomerically pure form with the spectral data correlated well with those previously reported (Scheme 2.23).[34]

Scheme 2.23



G. Dual Inhibitors of the Proteasome and Fatty Acid Synthase

Inhibition of the enzymatic activity for both the proteasome and fatty acid synthase were saved for several belactosin derivatives by our collaborators at the Burnham Medical Research Institute in La Jolla, CA (Prof. Jeff Smith, Robyn Richardson).

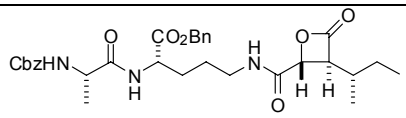
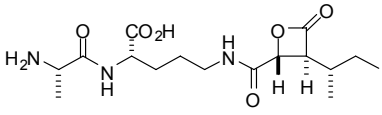
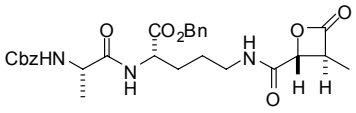
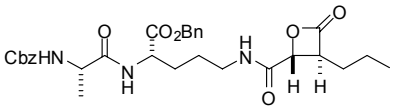
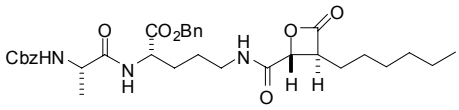


Inhibition of the 20S Proteasome by Novel Belactosin Derivatives.

Figure 2.5 Novel Belactosin Derivatives Inhibit the Turnover of a Fluorogenic Substrate by the 20S Proteasome

The 20S proteasome (5 nM) was incubated with (A) 1.25 μM or (B) 50 μM test compound and 100 μM suc-LLVY-AMC substrate. Fluorescence measurements were taken every ten minutes at 380/460 nm. Results shown are the average of (A) triplicate or (B) duplicate data points.

Table 2.2 Inhibition of the Fatty Acid Synthase Thioesterase Domain by Belactosin C and Derivatives

entry	Belactosin derivatives	FASTE IC_{50} (μM)	95% CI (μM)
1	 (1.3:1 dr)	0.17	0.13 - 0.21
2	 (1.3:1 dr)	26.55	20.48 - 34.42
3	 (1:1 dr)	3.98	3.35 - 4.61
4	 (1:1 dr)	2.86	1.11 - 4.60
5	 (1:1 dr)	0.16	0.13 - 0.19

Novel belactosin derivatives inhibit the turnover of a fluorogenic substrate by fatty acid synthase thioesterase. The thioesterase (230 nM) was incubated with a range of test compound concentrations (100 μM to 0.16 μM) and 120 μM 4-MU-heptanoate substrate. Fluorescence measurements were taken every five minutes at 350/450 nm.

Results shown are the calculated IC_{50} value and corresponding 95% confidence intervals from a dose-response curve fit of the data in triplicate.

H. Conclusion

The enantioselective synthesis of (-)-belactosin C and derivatives was accomplished in a concise manner employing the tandem, Mukaiyama aldol-lactonizaton (TMAL) process and test their bioactivities. One approach involved a distal double diastereoselective TMAL reaction with a dipeptide glyoxamide, whereas a second approach involved amide coupling of a dipeptide with a β-lactone carboxylic acid, obtained via the TMAL process employing a chiral silyl ketene acetal. Notable improvements in diastereoselectivity were achieved in a proximal double diastereoselective TMAL process. Enzymatic assays showed that the belactosins act as the dual inhibitors of the proteasome and the thioesterase domain of fatty acid synthase.

CHAPTER III

SYNTHETIC STUDIES TOWARD SPONGIOLACTONE

A. Isolation and Background

Spongiolactone **3.2** which contains a cyclopentyl-fused β-lactone was isolated in 1986 from *Spongionellagracilis* (Figure 3.1). The name *spongio* reflects the origin of the early examples of this class of diterpene in the dictyoceratid sponge genus *Spongia.*[48] The term spongian diterpene was first coined by Murphy and co-workers in 1979.[1] In tandem with the ongoing discovery of a plethora of related metabolites possessing the same basic spongian diterpene skeleton **3.1**, a wide variety of biological activities associated with this group of compounds have been reported.[49] The diterpene isovalerate ester, spongiolactone **3.2**, was isolated from *Spongionella gracilis* as part of a targeted re-isolation of large quantities of the gracilin family of compounds for screening in a variety of bioassays. Although **3.2** possesses a heavily rearranged carbon skeleton, it clearly originates from related biosynthetic pathway leading to spongian diterpenes.[50]

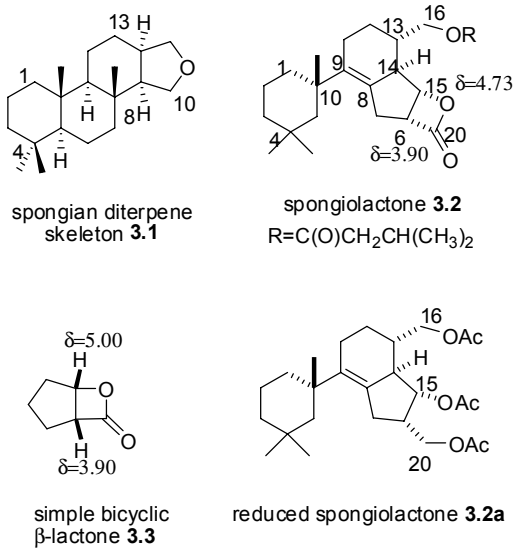


Figure 3.1 Structure of Spongian Diterpene Skeleton, Spongiolactone, and a Known Simple Bizcyclic-β-Lactone

Spongiolactone **3.2** was isolated as an optically active colorless oil ($[\alpha]_D$ +67.6, C=1.7, $CHCl_3$), and the IR spectrum showed two carbonyl absorptions at 1830 cm^{-1}, typical of a β-lactone, and 1730 cm^{-1} attributed to an ester.

Additional evidence for the structure was furnished by LAH reduction of **3.2** followed by acetylation which afforded the expected triacetate **3.2ab**, whose structure was assigned on consideration of its spectral data, ($[\alpha]_D$ -10.3, C=0.4, $CHCl_3$).

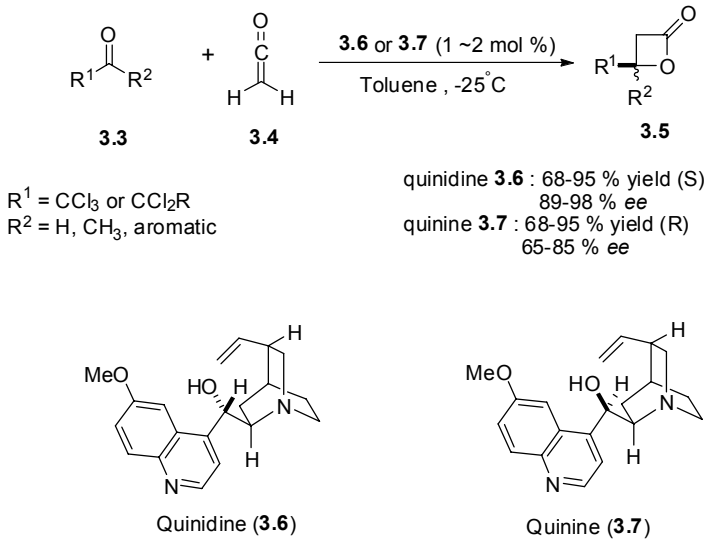
No biological activity has been reported for this compound; however, the acylating potential of the resident β-lactone warrants screening for potential bioactivity. Comparison of a related, simpler bicyclic β-lactone with ^{1}H-NMR data reported for the natural product verifies assignment of this region of the natural product.

B. The Nucleophile-Catalyzed Aldol Lactonization (NCAL) Reaction

New methods for the synthesis of β-lactones have drawn great interest in recent years because of the great versatility and utility exhibited by these strained heterocycles in natural product synthesis.[51] However, relatively few methods exist for the synthesis of these compounds in optically pure form.[52]Our group has developed diastereoselective and enantioselective methods for the preparation of β-lactones employing chiral Lewis-acid catalyzed [2+2] cycloadditions of ketenes and aldehydes, a tandem Mukaiyama aldol-lactonization (TMAL) process and an intramolecular nucleophile catalyzed aldol lactonization (NCAL) employing both aldehydes and ketoacids. The NCAL reaction is based on a several report by Wynberg for the enantioselective synthesis of β-lactones using cinchona alkaloid catalysts.[53]

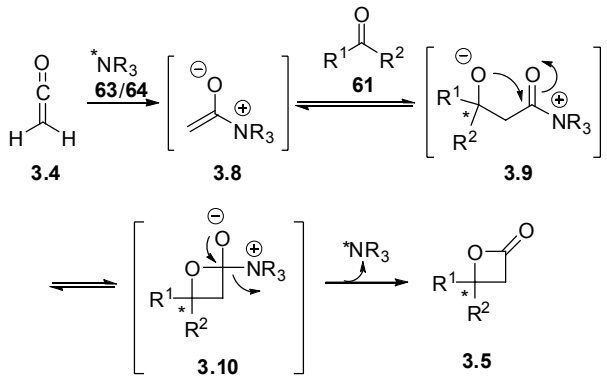
Wynberg found that cinchona alkaloids afforded excellent asymmetric induction in an intramolecular NCAL reaction (Scheme 3.1).[54] The drawback of this initial method is the requirement of a ketene generator and the necessity of at least two chlorine substituents on the carbon adjacent to the carbonyl in ketone and aldehyde substrates **3**.**3**.

Scheme 3.1



The mechanism for this reaction was proposed by Wynberg (Scheme 3.2). Initial attack of ketene **3.4** by the chiral amine **3.6**/**3.7** forms the neutral ammonium enolate intermediate **3.8**.

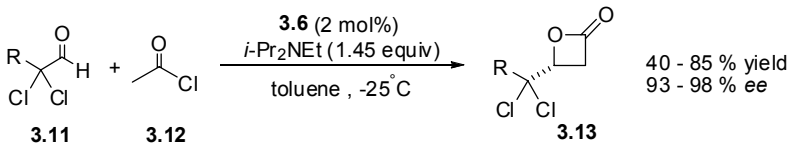
Scheme 3.2



After enolate formation, the resulting enolate **3.8** undergoes an aldol reaction with aldehyde **3.3** to form aldolate **3.7**, followed by cyclization to form oxetane **3.10**. Finally, elimination gives the final chiral β-lactone **3.5**, thus regenerating the catalyst. A possible reason why this method works only with highly activated aldehydes is that the ammonium enolate intermediate **3.8** is not reactive enough to carry out the methodology reaction with unactivated aldehydes.

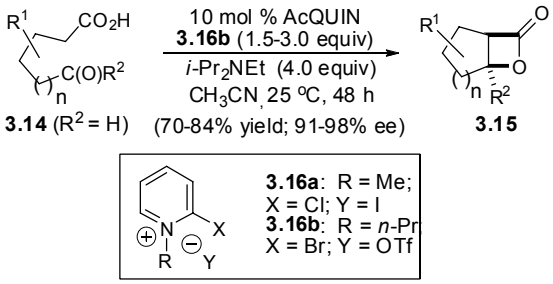
Wynberg's work helped pioneer further explorations in this. Our group later reported that *in situ* generated ketene from acetyl chloride and Hunig's base delivered similar yields and selectivities compared to Wynberg's method, which was performed with a ketene generator.[55] However, highly electrophilic carbonyl compounds remained a prerequisite for the formation of β-lactones (Scheme 3.3).

Scheme 3.3



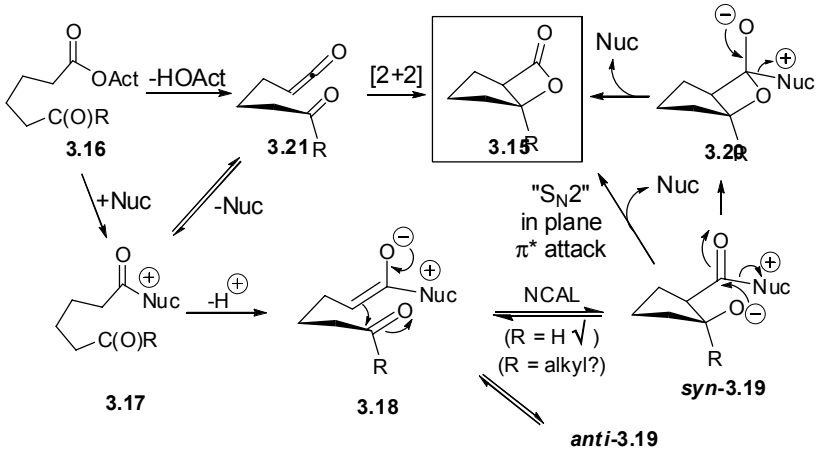
After an aggressive effort overcome limitations of the activated aldehydes, our group finally found that unactivated, non-α-chlorinated, aliphatic aldehydes participated as electrophiles in the NCAL reaction when it was run in an intramolecular fashion (Scheme 3.4).[56] Mukaiyama's reagent, effectively activated the aldehyde acid substrates **3.14** *in-situ.*

Scheme 3.4



The primary mechanistic pathway for this process with aldehyde acid substrates enabled an asymmetric organocatalyzed variant via an ammonium enolate **3.18**, which is not possible via a [2+2] cycloaddition pathway (Scheme 3.5). A few years later, we expanded the reaction scope to induce ketone substrates **3.14** (R^2 = alkyl). The nucleophile-promoted process reaction was facile and proceeded at ambient temperature. The extension to keto-acid substrates significantly expanded the scope of this process allowing access to bicyclic and tricyclic systems bearing masked tertiary alcohols and a reactive β-lactone moiety.[57]

Scheme 3.5



Building on Wynberg's proposed mechanism, our group suggested that the activated acid **3.16** reacts with the cinchona alkaloid catalyst to produce an acyl ammonium **3.17**, which is cab be deprotonated to form ammonium enolate **3.18**. Intramolecular aldol lactonization of the ammonium enolate **3.18** furnishes β-lactone **3.20** with the recovery of the catalyst.

C. Retrosynthetic Analysis

The strategy to be employed for the β-lactone toward spogiolactone will involve application of the NCAL process as one of the final steps in the synthesis (Figure 3.2). Importantly, this application will allow us to investigate the possibility of double asymmetric synthesis in a more complex setting. Thus, the relative stereochemistry obtained with Et_3N, *O*-AcQD, and *O*-AcQN as nucleophilic catalysts will be compared. The key intermediate aldehyde acid **3.23** can be obtained from TBS enol ether **3.24** by oxidative cleavage. TBS enol ether **3.24** will be prepared from triflate **3.26** through the

Heck coupling and finally, the decaline system of triflate **3.26** will be constructed from 1, 3-cyclohexadienone **3.28** *via* several steps.

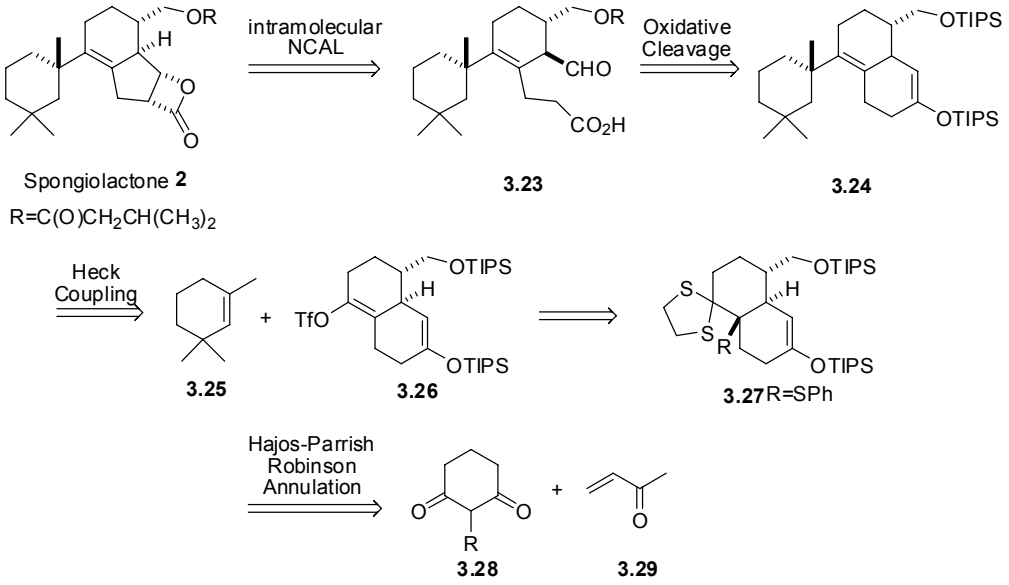


Figure 3.2 Retrosynthetic Analysis of Spongiolactone

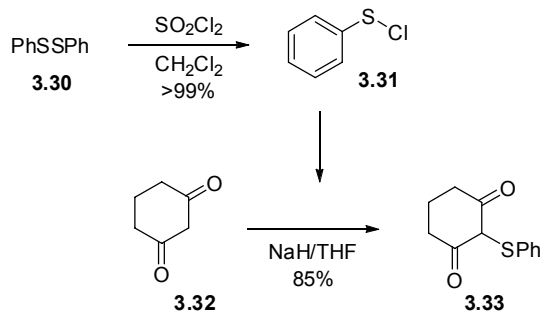
D. Synthesis of the α -Substituted Cyclohexenone Core

1. The Hajos-Parrish Procedure

Synthesis of the decalin system **3.27** began with the application of the Hajos-Parrish procedure.[58] In order to install the thiophenyl group on the central carbon (C2), thiophenylchloride **3.31** was prepared with diphenyldithian **3.30** and thionyl chloride in quantitative yield. The thiophenylchloride **3.31** was used after evaporating solvent and remained thionyl chloride without further purification. The thiophenyl group was installed in the presence of sodium hydride and thiophenylchloride **3.31** to provide **3.33**

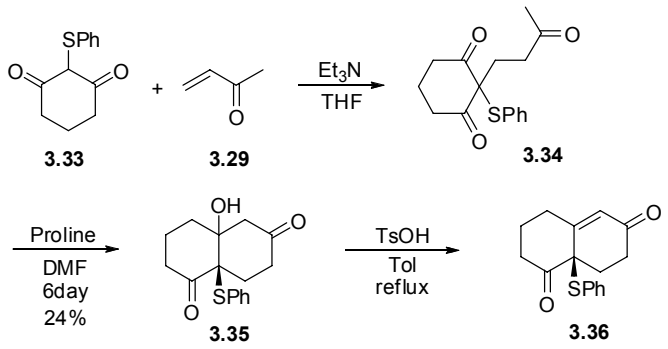
in moderate yield. The thiophenyl substituent was utilized to serve two purposes. 1) to give good stereoselectivity since the Hajos-Parrish procedure generally needs an alkyl group on the central carbon (C2) so the thiophenyl group was installed as a replacement (Scheme 3.6). 2) Also, the thiophenyl group, and it provides steric bulk useful in later steps can be easily removed.

Scheme 3.6



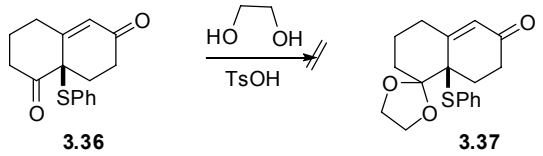
Following the Hajos-Parrish procedure, methyl vinyl ketone was used to get triketone with Et_3N as a base. The decaline alcohol **3.36** when the cyclization was carried out with (-)-proline. Either spongiolactone would be prepared using (*L*)-proline or (*D*)-proline. Since the absolute configuration of spongiolactone remains unknown.. Dehydration occurred with catalytic TsOH at reflux to give **3.36** with quantitative yield. The decaline **3.37** matched with reported results and showed good enantiomericpurity.[48]

Scheme 3.7



After the successful decaline **3.36** synthesis, we began elaboration with ketone protection using ethylene glycol and tosic acid (Scheme 3.8). Although ketone protection is usually usual reaction to chemist, this was detrimental to this substrate **3.36**. A variety of reaction conditions such as TsOH/Dean-Stark, TsOH/Molecular-Sieve, H_2SO_4, Ethylene glycol TMS ether/TMSOTf were screened and all led to decomposition of the sulfur moiety.

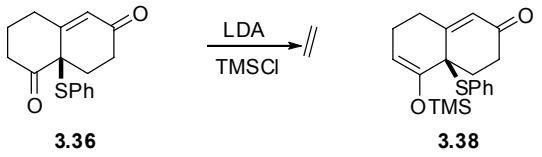
Scheme 3.8



Faced with these difficulties, the protecting group was changed to TMSCl (Scheme 3.9). Milder reaction conditions may give compound **3.38** without decomposition. However, with various bases the phenyl sulfuryl group was easily

decomposed.

Scheme 3.9

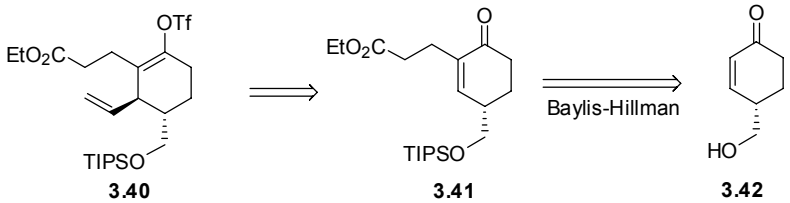


3.36 **3.38**

Although the Hajos-Parrish procedure is an most interesting challenge, due to the difficulties encountered in the mono protection of the ketone, this route was eventually abandoned and to pursue a more feasible strategy to construct first key intermediate

2. Michael Addition/Enolate Trapping Strategy

After considering several strategies, a Michael addition/ enolate trappings strategy was pursued. Michael addition of vinyl cuprate to the cyclohexenone **3.41** and subsequent enolate trapping with an electrophile such as triflate could afford our key intermediate **3.40**. The triflate would then be used in a Heck reaction to provide coupling adduct.



3.40 **3.41** **3.42**

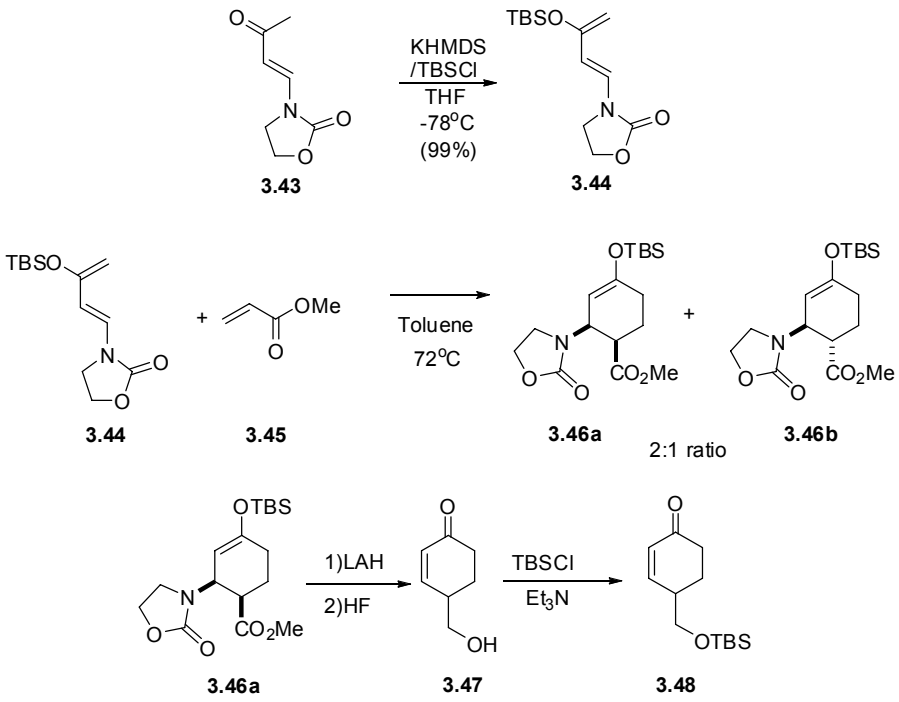
Figure 3.3 Michael Addition/Enolate Trapping Strategy

The ethyl ester **3.41** can be prepared from cyclohexenone **3.42** by the Baylis-Hillman reaction. Finally, the cyclohexenone **3.42** will be constructed from 3-butyne-2-ol *via* several steps.

The Diels-Alder reaction also continues to play a crucial role in the synthesis of complex molecules.[59] Rawal reported a racemic and asymmetric substituted cyclohexenone **3.48** synthesis using the Diels-Alder reaction with achiral and chiral 1-(2-oxazolidinon-3yl)-3-siloxy-1,3-butadienes.[60] Although Rawal's protocol reported chiral cyclohexenone **3.48**, we decided to begin the full synthetic route from racemic cyclohexenone **3.48** toward spongiolactone and then complete the asymmetric synthesis later.

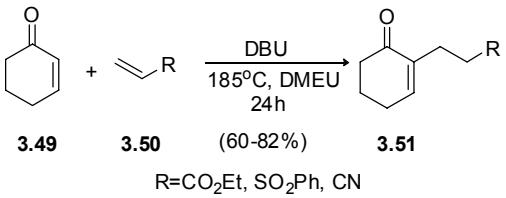
Racemic cyclohexenone **3.48** was prepared by Rawal's protocol without any problem on milligram scale (Scheme 3.10). However, we were quickly disappointed as we attempted scale-up of the Diels-Alder reaction giving only minimal amounts of the desired product **3.46**. Unfortunately, it required much effort to find optimal scale up conditions without success. The maximum reaction conditions for the Diels-Alder reaction in our lab was 3g scale. The exact problem encountered upon scale-up remains elusive.

Scheme 3.10

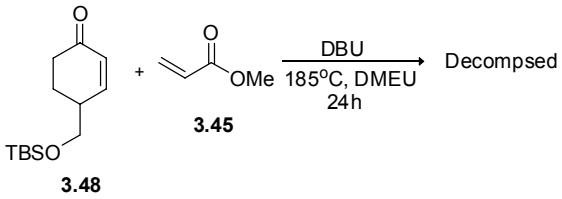


Even though the scale-up was a problem, the desired cyclohexenone **3.48** was in hand. Therefore, the α-alkylation of α,β-unsaturated ketones **3.48**, an important transformation in our synthesis, was explored with the Bayliss-Hillman process.[61] While various methods for the α-functionalization of α,β-unsaturated enones have been developed using a stepwise approach, a direct method for facile introduction of an alkyl group was required rather harsh conditions; sealed tube at 185°C in DMF or 1,3-dimethyl-2-imidazolidinone (DMEU) as reported by Hwu (Scheme 3.11).[62]

Scheme 3.11

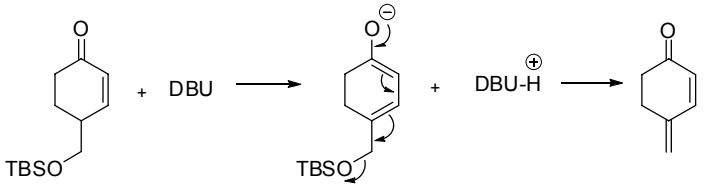


Even with the high temperatures, the reaction pathway was still attractive. Therefore we attempted to utilize Hwu's method to install α-alkyl group without success. The strict high temperature requirements of the α-alkylation in DMEU led complex molecules to decompose and not obtain any of the α-alkylation product. Instead a complex mixture of desilanolated compound resulted.



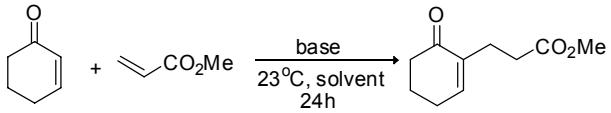
Based on Hwu's experiment and suggested mechanism, we assumed that the high temperature accelerated elimination of the silanoxide after double enolate formation leading to dienone **3.52** (Scheme 3.12).

Scheme 3.12



Therefore we re-examined Hwu's conditions carefully as we required mild temperatures. Milder conditions for direct α-alkylation has been developed and were tested in our group. Many combinations of bases and solvents were tested at room temperature (Table 3.1)

Table 3.1 α-Alkylation Reaction Conditions



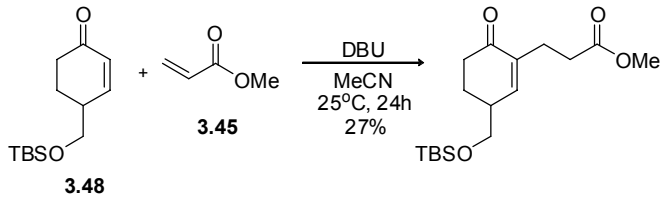
3.49 **3.50** **3.51**

entry	solvent	base	yield
1	DMF	DBU	1% <
2	DMF	DMAP	0
3	MeOH	NaOMe	Trace
4	THF	DBU	0
5	THF	DABCO	0
6	CH_3CN	DBU	80%
7	Toluene	DBU	0

Most conditions did not provide the desired outcome; however, use of acetonitrile gave the desired product at room temperatre. Hwu reported 55% yield in acetonitrile with DBU(0.2 equiv.) at 185 ^oC. Unexpectedly, α-alkylation conducted in acetonitrile with DBU (1.0 equiv.) at room temperature afforded the α-alkylation product in 80%

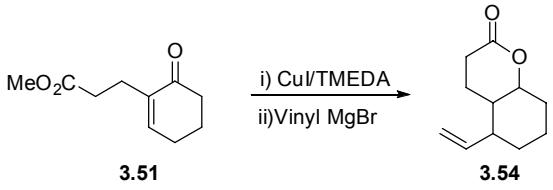
yield. We then tried the α-alkylation of our key intermediate **3.53** (Scheme 3.13) and were able to obtain the desired product **3.53** on small scale (10 mg). However, the same by-product **3.52** was obtained on large scale. Further optimization of there reaction condition are required to use this protocol in our synthesis. However, this protocol is useful to construct α-alkylation of various enones.

Scheme 3.13



After the minor success of the •α-alkylation reaction, our goal was to find conditions for cuprate addition and enolate capture with the triflate. Model studies were conducted to evaluate various reaction methods. Most cases intra-molecular cyclization was occurred to delivered cyclic ester after Michael addition (Scheme 3.14).

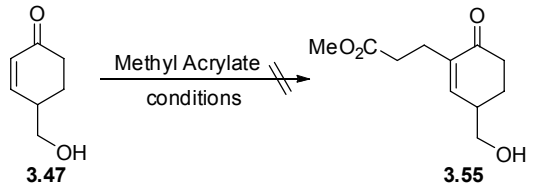
Scheme 3.14



For the problem at hand in model compound and α,β-unsaturated ketones **3.53** formation, it came to our attention that another α,β-unsaturated ketones with bulkier ester would solve the problem.

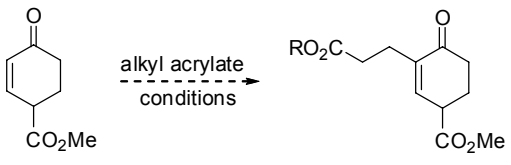
4-Hydroxymethyl cyclohex-2-enone **3.47** was investigated (Scheme 3.15). As expected the base deprotonated the hydroxyl proton and the resulting oxygen anion was not a good leaving group. decomposition reaction would be prevented based on our suggested mechanism. Reaction conditions for including Hwu's method were explored without success. In most reactions, the same decomposition product **3.51** was obtained.

Scheme 3.15



3.47 **3.55**

Alternatively, 4-Methyloxylcarbonyl cyclohex-2-enone **3.56** was selected to prevent side reactions (Figure 3.4). Even if proton abstraction of C-1 occurs, the intermediate should be stable, this preventing the side reaction from occurring.



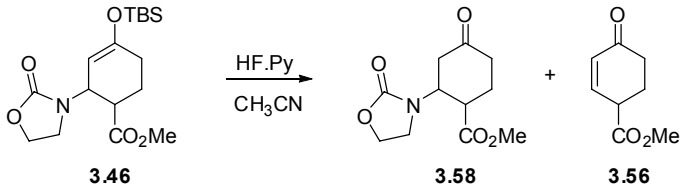
3.56 **3.57**

Figure 3.4. α-Alkylation Reaction with Methyl ester

Based on this hypothesis, we started to make 4-methyloxylcabonyl cylclohex-2-enone **3.56** from intermediate **3.46** (Scheme 3.16). However, TBS deprotection with HF/pyridine delivered only cyclohexanone **3.58** through this route. The poor leaving group ability of the methyl ester **3.46** at least partially stems from lack of the hydrogen bonding comparing to the previous reaction with the hydroxyl group, implying that a leaving group with hydrogen bonding character is required.

After many attempts to make cyclohexenone **3.59** invariably failed, we pursued an alternate route.

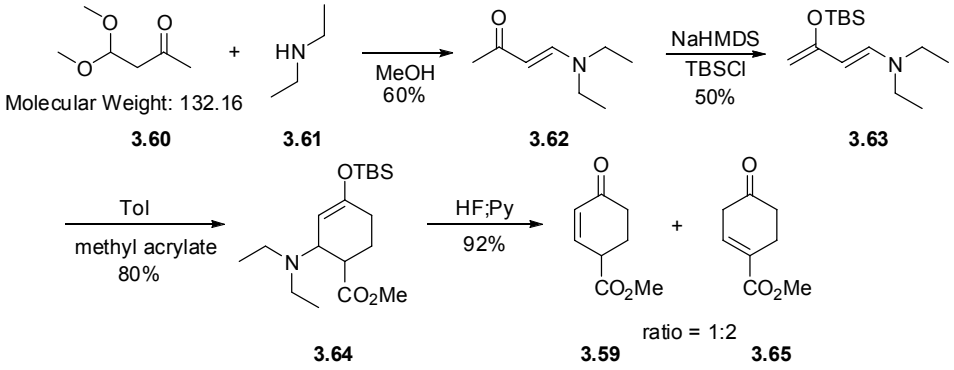
Scheme 3.16



3.46 **3.58** **3.56**

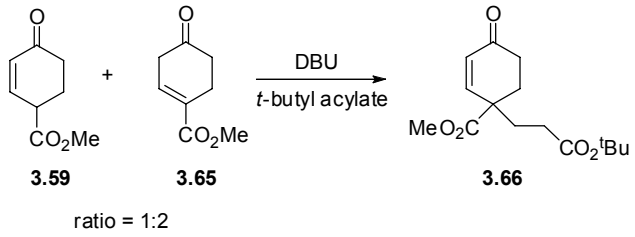
We finally succeeded in making cyclohexenone **3.59** via 4steps (Scheme 3.17).

Scheme 3.17



Not surprisingly, cyclohexenone **3.59** was obtained along with olefin isomer **3.65**. The α-alkylation reaction was tried since this substrate offered the same transition state after proton abstraction. Indeed, the reaction worked without decomposition. However, the product was not α-alkylated but γ-alkylated (Scheme 3.18).

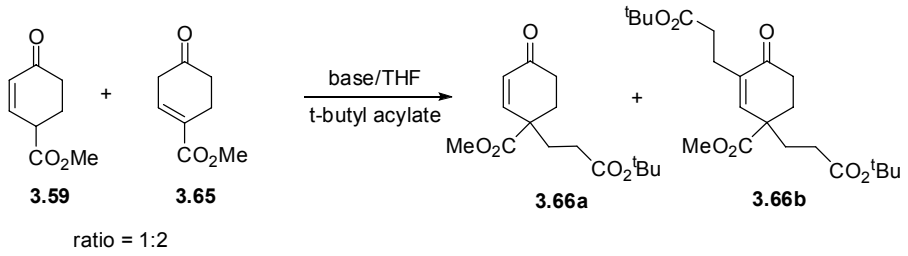
Scheme 3.18



Although the C-3 position has electronically the more charge density than the C-1 position, only C-1 alkylated product **3.66** was obtained. DBU-H+ could be blocking the ketone at the C-3 position. Therefore various bases such as LiHMDS, NaHMDS, KHMDS, NaH, LDA and LDA/HMPA were screened and all led to mixture of γ-alkylation **3.66a** and α,γ-dialkylated products **3.66b**. Although alkylation of Hagemann's

ester (ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate) has been reported 5:5 ratio of products at C-3: C-1, the desired product was not obtained (Table 3.2).

Table 3.2 Approached α-Alkylation

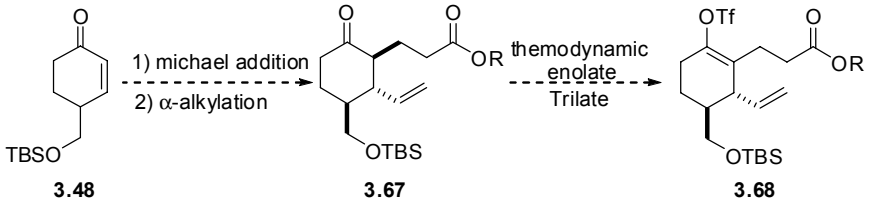


entry	base	products (**3.66a**:**3.66b**)
1	LiHMDS	10:1
2	NaHMDS	8:2
3	KHMDS	8:2
4	NaH	8:2
5	LDA	100:0
6	LDA/HMPA	100:0

Although the α-alkylation route is more concise route, this route was eventually modified as we sought for a more productive strategy.

Michael addition to α,β-unsaturated ketone, electophile capturing is a well known strategy (Scheme 3.19). Though formation of a thermodynamically controlled enolate would not be entirely selective, each triflate could be separable upon further reaction.

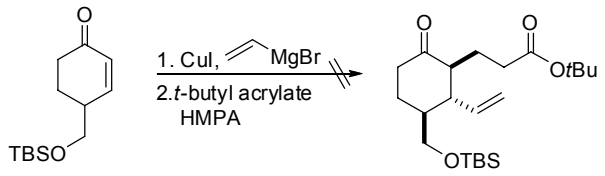
Scheme 3.19



3.48 **3.67** **3.68**

Based on the revised strategy, Michael addition and acrylate capturing was tried with various reaction conditions without success (Scheme 3.20). Most reactions was stopped after Michael addition using vinyl cuprate. Therefore we attempted the sequence in a stepwise fashion.

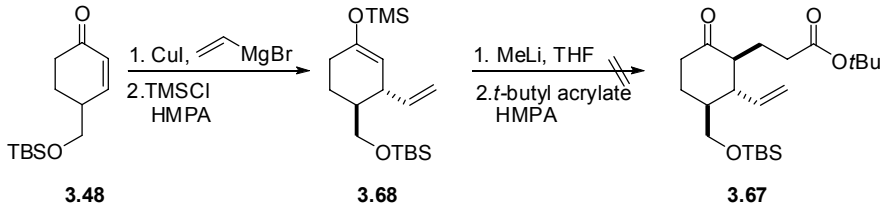
Scheme 3.20



3.48 **3.67**

First, the TMS enol ether **3.68** was synthesized by Michael addition followed by TMS capture with TMSCl/HMPA (Scheme 3.21). *In-situ* TMS deprotection using MeLi with acrylate did not furnish. Usually, electrophile of this reaction type is aldehydes or alky halides.

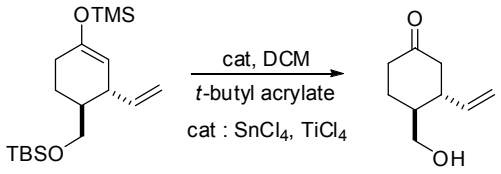
Scheme 3.21



3.48 **3.68** **3.67**

Therefore alkyl bromide was used but it led only to decomposition. In order to increase the electrophilicity of the acrylate, metal reagents were used in conjunction. Nonetheless, some examples were known with methyl acrylate, our reaction did not work with either $SnCl_4$ or $TiCl_4$ giving only the desilated compound **3.69**. The known reaction have less hindrance at the β–position, which is presumably the underlying cause for the ineffectiveness in our system. Since *t*-butyl ester did not led to a productive pathway**,** alternative pathway were pursued.

Scheme 3.22



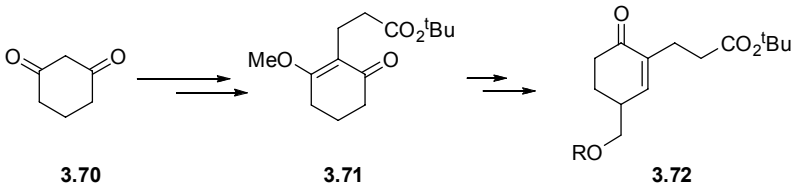
3.68 **3.69**

After careful consideration, the Dahn-Hauser protocol may be useful in preparing the key intermediate **3.72** (Scheme 3.23). This protocol would deliver the racemic synthesis for spongiolactone. After completion of racemic synthesis, we will move forward to asymmetric synthesis.

3. Stork/Danheiser Strategy

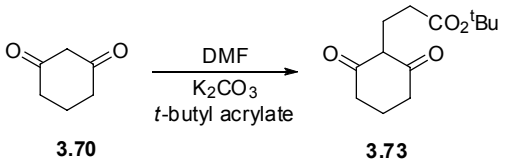
Based on the Stock-Danheiser protocol, the synthesis of *t*-butyl ester **3.72** was planned (Scheme 3.23).

Scheme 3.23

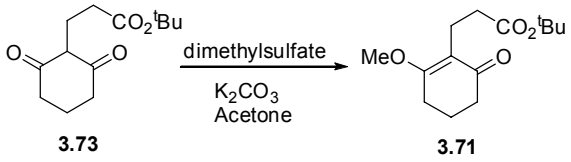


Although many alkyl group installation methods were reported, *t*-butyl acrylate was unknown to the best of our knowledge. Low activity of *t*-butyl acrylate may be the reason. After careful optimization K_2CO_3 as a base in DMF/reflux delivered the desired *t*-butyl ester **3.73** in moderate yield.

Scheme 3.24



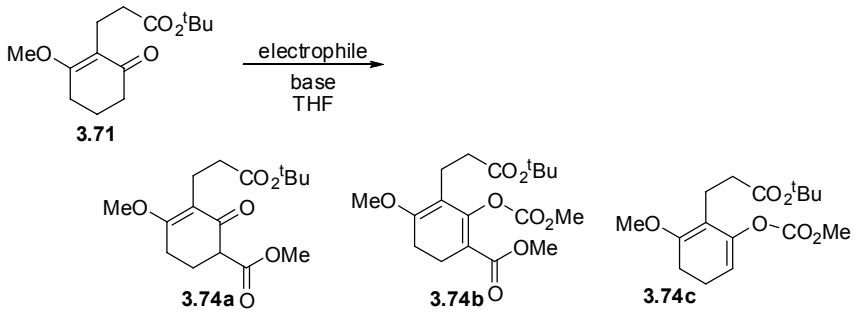
The ketone in *t*-butyl ester **3.74** was then methylated after enol formation in the presence of dimethyl sulfate and K_2CO_3, which gave methyl enolate **3.71**. The reaction was accomplished in quantitative yield.



3.73 **3.71**

Finally the α-hydroxymethyl group was needed to construct key intermediate. Therefore methyl ester was selected and reaction conditions were carefully investigated (Table 3.3). In case of chloromethylester as a electrophile, anhydride formation was the major, where the cyanomethylester delivered the desired product **3.74a** exclusively.

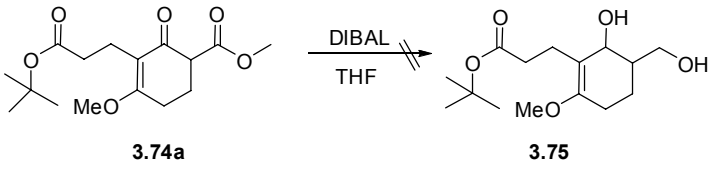
Table 3.3 Methyl Ester Formation



entry	electrophile	base	products
1	$ClCO_2Me$	LiHMDS	**2c**
2	$ClCO_2Me$	LiHMDS/HMPA	**2b** + **2c**
3	$ClCO_2Me$	LDA	**2c**
4	$ClCO_2Me$	LDA/HMPA	**2b** + **2c**
5	$CNCO_2Me$	LDA	**2b** + **2c**
6	$CNCO_2Me$	LDA/HMPA	**2a**

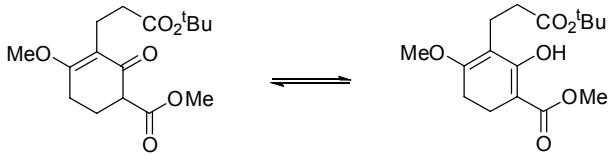
With the desired methyl ester **3.74a** in hand, reduction with 3equiv. DIBAL in THF was tried (Scheme 3.25). Upon comparison of the reactivity and steric effect of three carbonyl groups, we expect the reduction of only the methyl ester and ketone. Unfortunately many adducts were produced and none of the desired compound was obtained.

Scheme 3.25



The messy reaction is most likely due to the tautomerization of starting α-keto ester (Scheme 3.26). This effectivity reduced similar the reactivity of the **3.74** as a electrophile when DIBAL was attached providing electrophilicities of each of the carbonyl functionalities present.

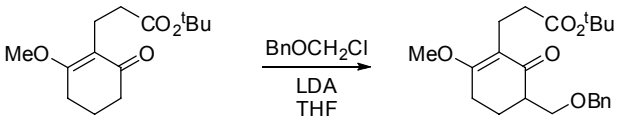
Scheme 3.26



3.74a **3.74d**

An *in situ* hydroxyl methyl installation method was discovered after many trials with the benzyloxy chloromethyl ether (Scheme 3.27). Indeed benzyloxy chloromethyl ether gave the desired hydroxyl methyl group in-situ in the benzyl protected form.

Scheme 3.27

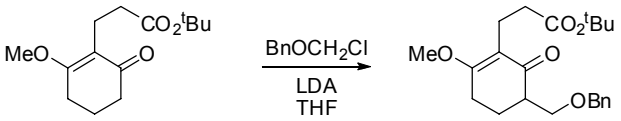


3.73 **3.76**

Although the desired compound was provided, the yield needed improvement. The yield was increased to 78% by changing the reaction temperature (Table 3.4). The key

parameter in this reaction was reaction temperature, -20 °C-25 °C in order to have good productivity. When the temperature dropped below -25 °C or raised above -20 °C the yield was significantly suffered giving half the product.

Table 3.4 Benzyl Ether Formation Conditions

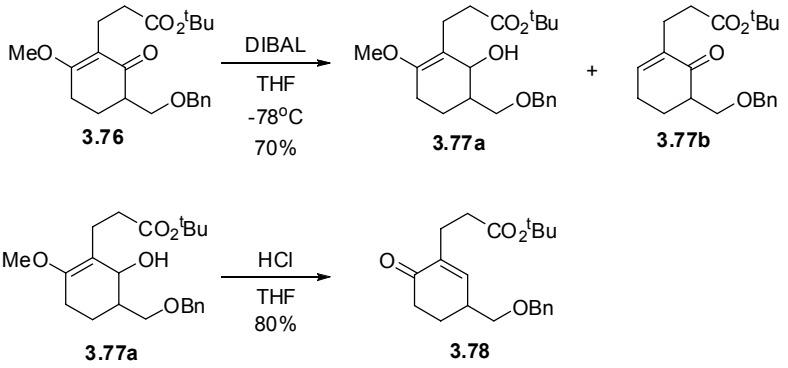


3.73 **3.76**

entry	temperature (°C)	yield (%)
1	-78	0
2	-43	43
3	-20	78
4	0	31

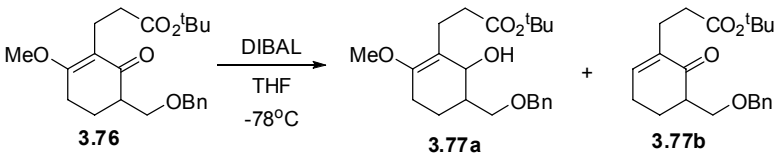
After successful optimization of the reaction, we moved forward to the key synthetic intermediate. The reduction of ketone **3.76** with DIBAL and acid hydrolysis of the reduced compound **3.77a** with aqueous HCl delivered our desired key intermediate **3.78** was obtained (Scheme 3.28). DIBAL reduction condition, we obtained 70% desired product **3.77a** as 3:1 ratio of *cis*:*trans* and 30% 1,4-addition product **3.77b**, which may be due to the steric hindrance of starting enone.

Scheme 3.28



The yield could be increased by blocking the 1,4 addition of hydride, and many substrates and additives were not promising. Surprisingly, the key solution for this reaction was amount of solvent. When the doubled, 1,4 addition decreased from 2:1 to 3:1. Tripling the amount of THF gave only the desired product, which gave the desired key intermediate **3.78** after just acidic work-up using 1-*N* HCl solution (Table 3.6).

Table 3.5 Optimization for Reduction

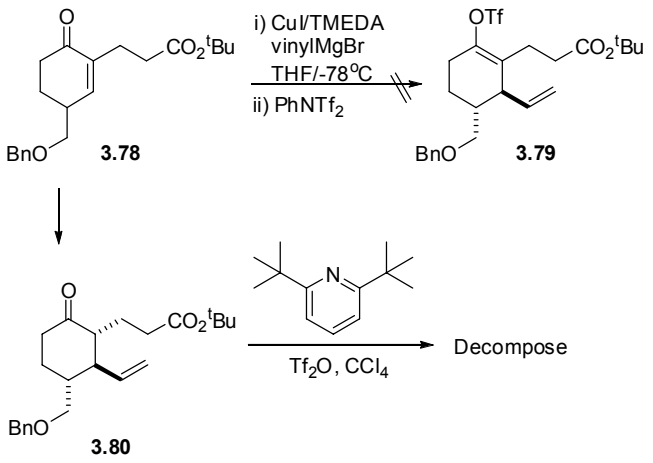


entry	THF/(100mg)	**53:53-1**
1	5 ml	2:1
2	10 ml	3:1
3	15 ml	15:1

Manipulation of the key developed intermediate **3.77a** through a Michael type vinyl addition and triflate capturing was tried. However, we could not obtain the desired

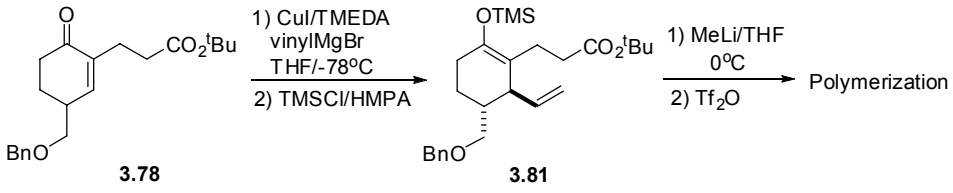
triflate **3.79** but the ketone **3.80**. Therefore, thermodynamic controlled enolate formation and triflate capturing without success (Scheme 3.29). Most adducts of the reaction was not identified and starting ketone **3.80** was recovered.

Scheme 3.29



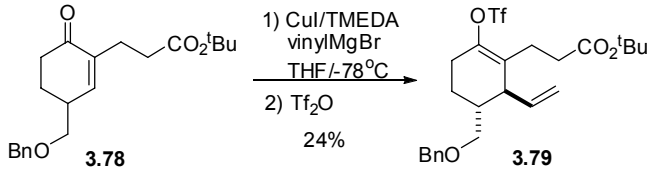
The general method to make triflate **3.79** is a stepwise method *via* enolate capturing with TMSCl and subsequent TMS deprotection and enolate capturing with $PhN(Tf)_2$. Upon subjection to this reaction sequence the desired triflate **3.79** was not provided (Scheme 3.30). The major polymerization problem was in the reaction.

Scheme 3.30



However, triflic anhydride delivered the desired triflate **3.79** with 24 % yield, but further optimization attempts were futile.

Scheme 3.31



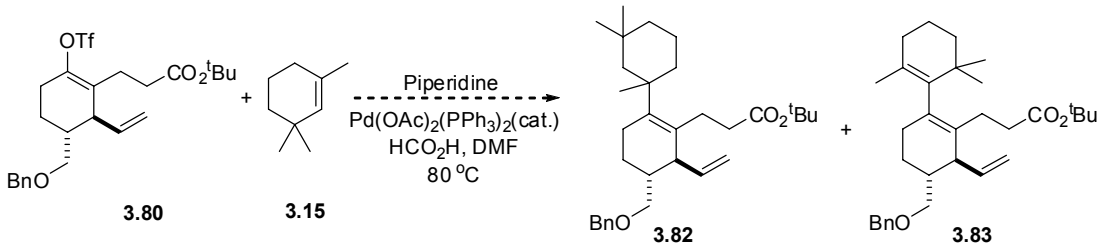
Although the product was obtained in low yield, the desired key intermediate **3.79** could be tested in the Heck reaction.

E. Annulation of the Substituted Cyclohexene

1. Heck Reaction Strategy

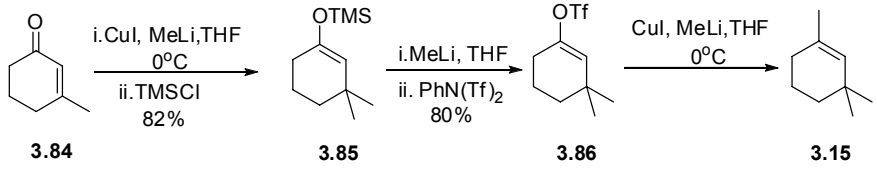
Based on our original plan, the Heck reaction would be used as a key step for the annulation of the triflate **3.80** (Scheme 3.32). Heck reactions typically construct C-C bond at the least substituted carbon of the alkene. Therefore, the product of Heck reaction would be ketone **3.38**.

Scheme 3.32

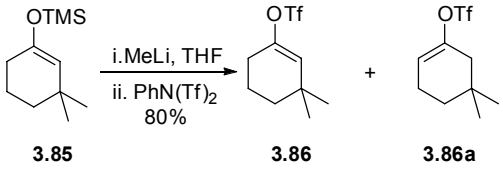


However, the *gem*-dimethyl group of the alkene will divert this reaction to the more substituted carbon to furnish the desired ketone **3.82**. Therefore, we started the synthesis of the cyclohexene **3.15** for the Heck coupling (Scheme 3.33).

Scheme 3.33

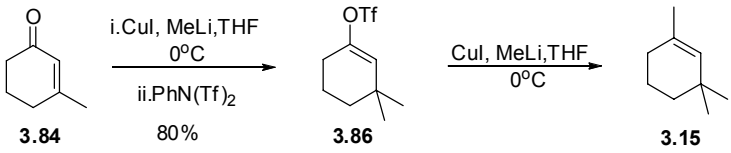


1-methyl-3,3-dimethyl cylclohex-1-ene **3.15**[63] was prepared by modified reported procedure. First, methylcuprate addition to-methyl-2-clohexenone **3.84** and capture with TMSCl delivered silylenol ether **3.85** in 82% yield. The silylenol ether **3.85** was transformed into vinyl triflate **3.86** with $PhN(Tf)_2$ followed by methylcuprate addition to triflate **3.86** to deliver the desired key intermediate **3.15**. However, during the vinyl triflate transformation of silylenol ether **3.85**, isomerization of olefin occurred affording a mixture of products.



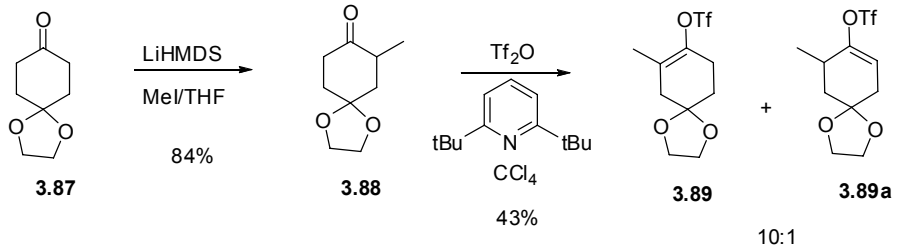
After pursuing several unsuccessful trials, it became apparent our attention that an *in-situ* triflate capturing was promising (Scheme 3.34). After methylcuprate addition to-methyl-2-clohexenone **3.84** and triflate capturing with $PhN(Tf)_2$ delivered enol triflate **3.86** was delivered in 80 % yield.

Scheme 3.34



With the desired cyclohexene **3.15** in hand, we tested the Heck reaction on a model system first. The synthesis of model enol triflate was pursued starting with the commercially available hexanone **3.87** (Scheme 3.35). Ketone **3.87** was methylated with LiHMDS/MeI in good yield. Treatment with triflic anhydride and a hindered pyridine base provided a mixture of enol triflate **3.89** in 10:1 ratio. The major thermodynamically controlled triflate **3.89** was separated from the minor **3.89a** readily.

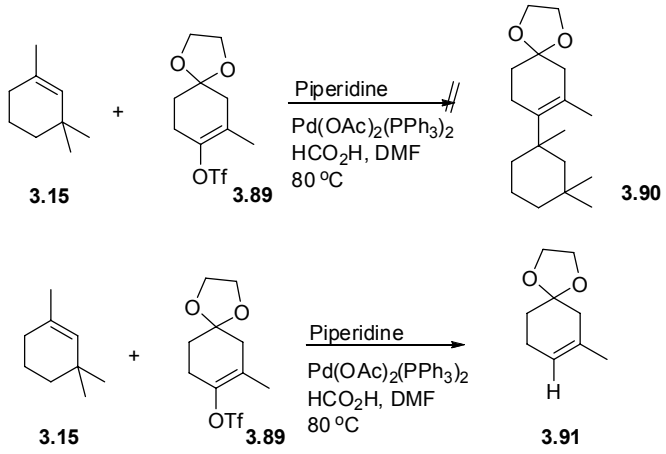
Scheme 3.35



3.87 **3.88** **3.89** **3.89a**

With both trflate and olefin in hand, the model Heck reaction was carried out (Scheme 3.36). However, planned Heck coupling under a variety of conditions giving only the reduced compound **15.**

Scheme 3.36



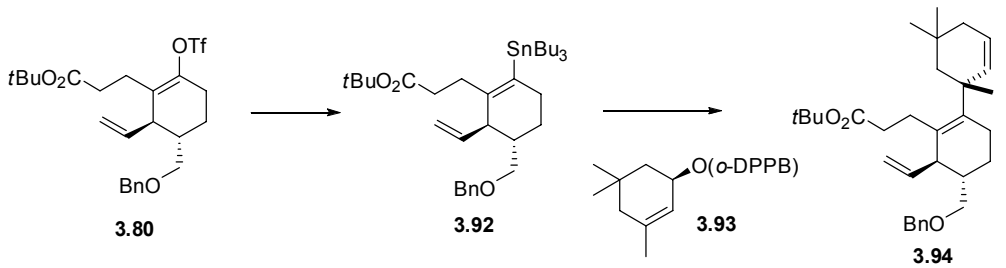
3.15 **3.89** **3.90**

3.15 **3.89** **3.91**

The Heck coupling was challenging reaction in our strategy is a challengeable and interesting reaction, our incapability to find suitable Heck coupling condition, this route was eventually abandoned and a more feasible strategy was pursued.

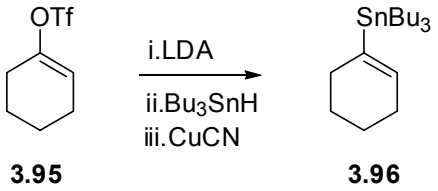
2. S_N2' Strategy

A S_N2' reaction using metals such as zinc, copper and magnesium with proper electrophiles have shown to provide access to such intermediates. Therefore, the S_N2' reaction was further explored toward the key intermediate **3.94** (Scheme 3.37).



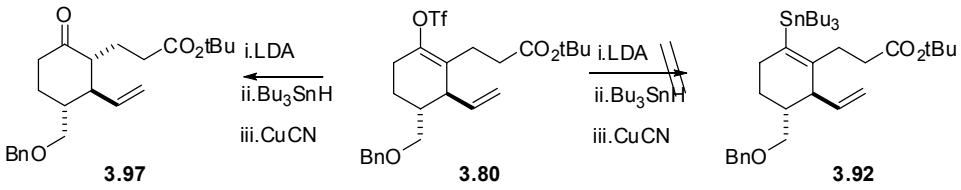
Limited quantities and scale-up problems of triflate **3.80** urged us a model study initially. After selecting a simple α-substituted triflate, the triflate **3.95** was continued to alkyl stannane **3.96** (Scheme 3.38).

Scheme 3.38



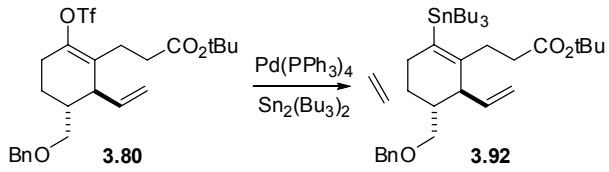
However, the success in the model study did not prove useful in the real system (Scheme 3.39). Attempts to couple triflate **3.80** with cuprate reagent, shown effective in sterically hindered settings, resulted in hydrolysis of the triflate **3.97**. The steric hindrance of α-alkyl group was the problem cause since it blocked the approach of cuprate reagent and gave the ketone **3.97**.

Scheme 3.39



Indeed, the bulky α ethyl *t*-butyl ester was also problematic in installing another bulky alkyl tin group place of the triflate **3.80**. Reaction conditions using Pd (0) were also unsuccessful despite the promising result in the model study (Scheme 3.40).

Scheme 3.40



3. Addition/Dehydration Strategy

Due to the difficulties encountered in the synthesis of the vinyl tin reagent **3.92**, this route was eventually abandoned to establish a productive strategy. Allyzinc addition to the ketone **3.97** could be useful in constructing the quaternary carbon center in an asymmetric fashion based on work by Knochel[64] (Figure 3.5).

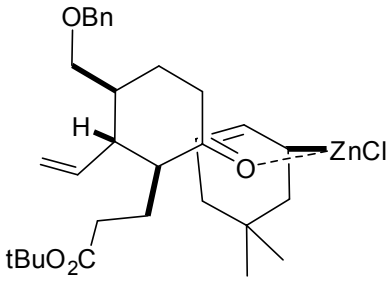
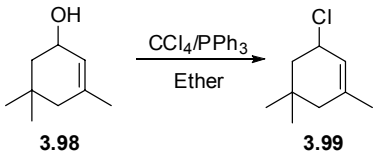


Figure 3.5 Allyzinc Addition to the Ketone **3.97**

Therefore we set out to explore the allyl zinc addition reaction in the context of spongiolactone synthesis. The allyl zinc reagent required either the allyl chloride or allyl phosphate. Therefore, allyl chloride **3.99** synthesis began from allyl alcohol **3.98** with tetrachloromethane and triphenyl phosphate (Scheme 3.41). The reaction proceeded smoothly, but the desired allyl chloride **3.99** was not separable after much effort. The crude product was not stable even at low temperature, so we screened different reagent methods without success.

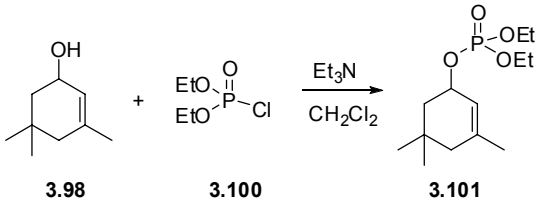
Scheme 3.41



In light of the purification problem, the phosphate intermediate **3.101** may give increased stability. The phosphate was prepared by treatment with diethyl

chlorophospahtem **3.100** and triethyl amine but the phosphate was unstable to silica gel chromatography (Scheme 3.42).

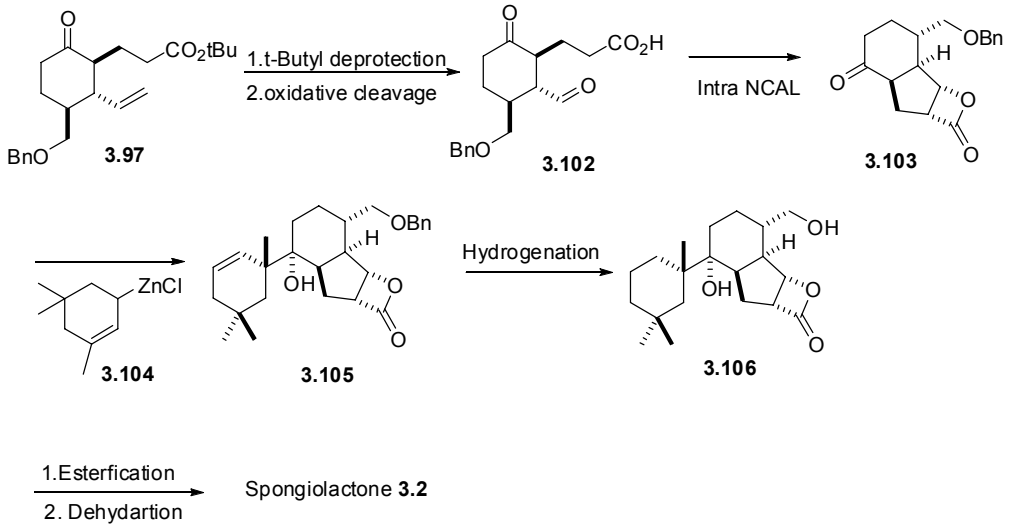
Scheme 3.42



F. Construction of the [3.2.0] Bicyclo β-Lactone via a Diastereoselective NCAL Reaction

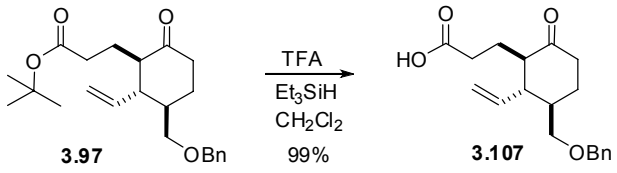
We then turned to the construction of the [3.2.0] bicyclo β-lactone. Due to the inherent problems with the bulky α ethyl *t*-butyl ester was still problematic, if we could construct desired β-lactone first, we can shorten the reaction scheme and make the scheme more favorable manner from ketone **3.97** (Scheme 3.39).

Scheme 3.43



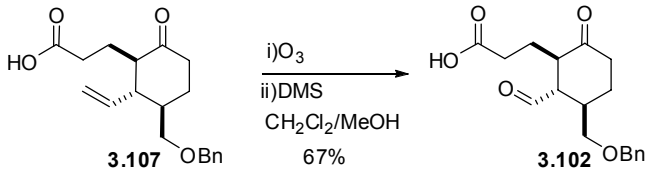
Based on the revised strategy, the first *t*-butyl deprotection of ketone **3.97** using TFA/triethyl silane delivered acid **3.102** in almost quantitative yield (Scheme 3.44).

Scheme 3.44



Oxidative cleavage using $OsO_4/NaIO_4$ the previously described oxidative cleavage conditions proved detrimental to aldehyde **3.102** preparation. The reaction did not give any of the desired aldehyde **3.102**. Therefore Ozonolysis reaction using dimethyl sulfide as a quenching reagent delivered the desired aldehyde **3.102** in moderate yield (Scheme 3.45). Based on H^1 NMR, the relative stereochemistry of cyclohexanone **3.102** was confirmed (*j* value of aldehyde was 10Hz).

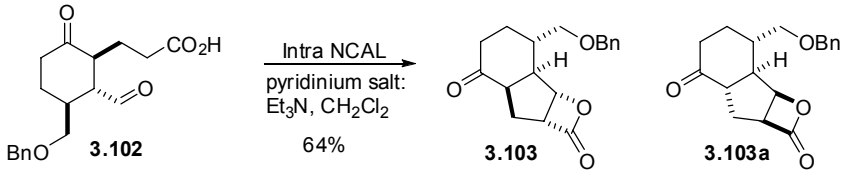
Scheme 3.45



The success of the aldehyde acid **3.102** synthesis, permitted further studies on the NCAL reaction. Although the NCAL reaction had never been attempted in such a complex setting before, pleasingly, it did not require much effort to find optimal

conditions for the NCAL reaction (Scheme 3.46). The NCAL reaction using aldehyde acid **3.102** provided β-lactone **3.103(**or **3.103a)** in excellent yield as an one single diastereomer.

Scheme 3.46



Even though we assumed a moderately diastereoselective NCAL reaction based on steric effect, it was encouraging that β-lactone formed as a single diastereomer. nOe experiments was used to confirm the β-lactone configuration. Although nOe analysis did not provide unambiguous evidence for the stereochemical assignment, it did confirm that there is no correlation between H2 and H4 (Figure 3.6), showing only existing relation ship between H2 and H1/H3/H9. Therefore we could assume that we have the desired diastereomer **3.103**.

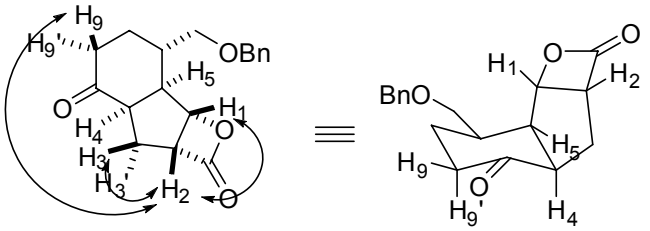
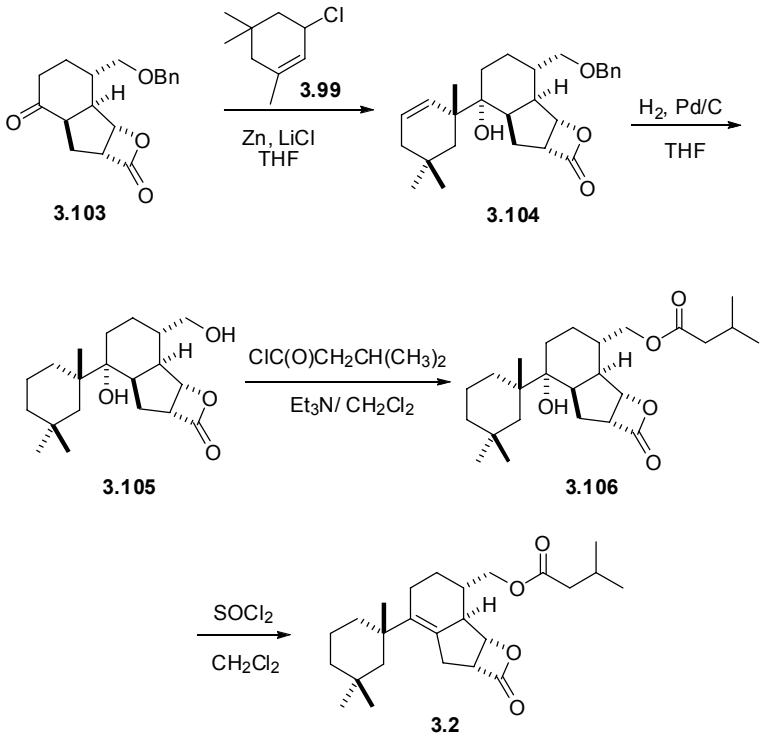


Figure 3.6 Tentative Structure Analysis by nOe

G. Projected Completion of the Synthesis: Proposed Endgames

The completion of the spongiolactone synthesis remains significant progress has been made and only a few steps remained (scheme 3.47). Allyl zinc addition could deliver the desired diastereomer **31** as expected from the transition state arrangement (Figure3.6). Hydrogenation with H_2, Pd/C will provide the reduced with olefin and simultaneous deprotection of the benzyl group. Esterfication with 3-methyl propionyl chloride and Et_3N would provide the primary ester over the tertiary alcohol. Finally, completion of spongiolactone would occur after dehydration using thionyl chloride.

Scheme 3.47

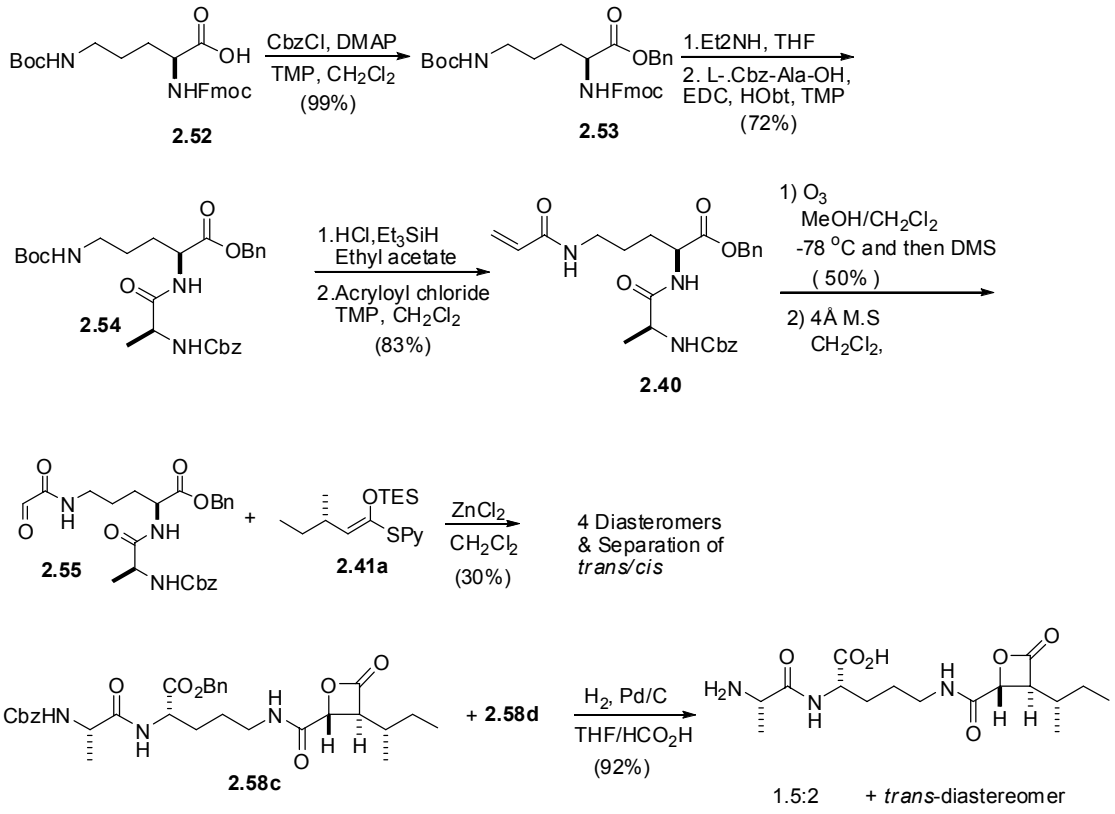


CHAPTER IV

CONCLUSIONS

The recently isolated bacterial metabolites, belactosins A-C from a fermentation broth of *Streptomyces* sp. UCK14, uniquely contain a β-lactone dipeptide motif and exhibit anticancer activities.

The TMAL process enabled a concise synthesis of (−)-belactosin C and derivatives employing a double diastereoselective process with chiral ketene acetals and a dipeptide glyoxamide or a novel tartrate-derived chiral glyoxylate. This strategy is unique in that the pharmacophoric β-lactone moiety of these proteasome inhibitors is constructed in a single step via the TMAL process leading to concise approaches to these novel proteasome inhibitors. Further biological evaluation of these and other belactosin derivatives including diastereomers and other structural derivatives showed that belactosins act as the dual inhibitors of the proteasome and the thioesterase domain of fatty acid synthase.

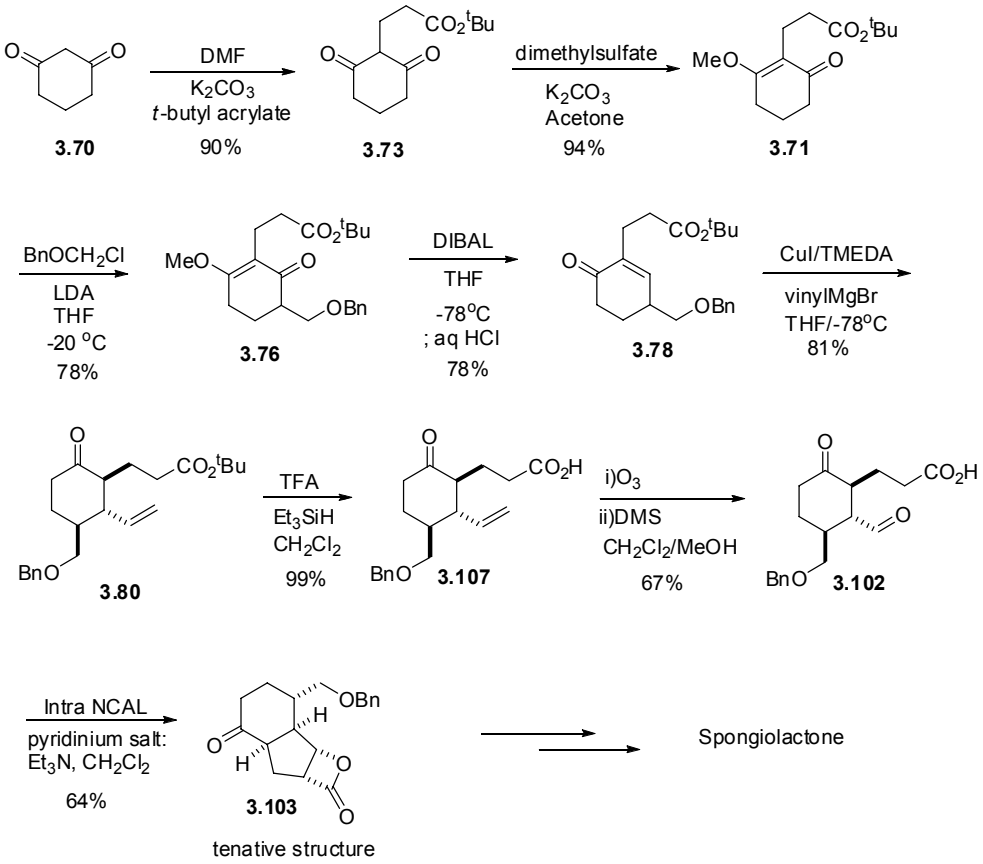

BocHN
OH
NHFmoc
2.52
CbzCl, DMAP
TMP, CH2Cl2
(99%)
BocHN
OBn
NHFmoc
2.53
1.Et2NH, THF
2. L-.Cbz-Ala-OH,
EDC, HObt, TMP
(72%)
BocHN
OBn
NH
2.54
NHCbz
1.HCl,Et3SiH
Ethyl acetate
2.Acryloyl chloride
TMP, CH2Cl2
(83%)
OBn
NH
NHCbz
2.40
1) O3
MeOH/CH2Cl2
-78 °C and then DMS
(50%)
2) 4Å M.S
CH2Cl2,
OBn
NH
2.55
NHCbz
OTES
SPy
2.41a
ZnCl2
CH2Cl2
(30%)
4 Diasteromers
& Separation of
trans/cis
CbzHN
CO2Bn
2.58c
+ 2.58d
H2, Pd/C
THF/HCO2H
(92%)
H2N
CO2H
1.5:2
+ trans-diastereomer

Spongiolactone which uniquely contains a cyclopentyl-fused β-lactone was isolated in 1986 from *Spongi-onellagracilis.* No synthesis has been reported for this compound. After many setbacks in the synthesis of spongiolactone, significant progress has been made. Based on Stork/Danheiser protocol, we could complete the synthesis of intermediate **3.78** via several steps from 1, 3-cyclohexanedione.

After several manipulations such as Michael type addition with vinylcuprate, t-butyl deprotection with TFA and ozonolysis, synthesis of key intermediate **3.102** was completed for NCAL reaction.

Importantly, NCAL process using aldehyde acid **3.102** also enabled a concise construction of [3.2.0]-bicyclo β-lactone as a single diastereomer with 64% yield and we could assume that we have the desired diastereomer **3.103** based on nOe experiment.

This compound is the key structure in the racemic spongiolactone synthesis and several step remained to complete the synthesis.



3.70 **3.73** **3.71** **3.76** **3.78** **3.80** **3.107** **3.102** **3.103**

CHAPTER V

EXPERIMENTAL PROCEDURE

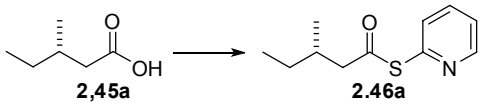
General

All reactions were carried out under nitrogen atmosphere in oven-dried (120 °C) glassware unless noted otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled immediately prior to use from sodium metal/benzophenone ketyl. Methylene chloride (CH_2Cl_2, EM Science) and benzene (EM Science) were distilled from calcium hydride prior to use. Methanol (MeOH, EM Science) was distilled from magnesium methoxide. *N*,*N*-dimethylformide (DMF) was distilled from calcium hydride and stored over 4Å molecular sieves. Triethylamine (Et_3N, EM Science), diisopropylamine (Acros) and pyridine (EM Science) were distilled from calcium hydride immediately prior to use. The molarities indicated for organolithium reagents were established by titration with 2,6-di-tert-butyl-4-methylphenol and 1,10-phenanthroline as indicator. All other commercially obtained reagents were used as received.

Optical rotations were measured with a JASCO DIP-360 digital polarimeter. All optical rotation measurements were made at 23 °C in a 10 millimeter cell (length); concentration *c* is reported in g/100mL. Infrared spectra were recorded with a Nicolet Impact 410 FTIR and a Bruker VERTEX 27 FTIR spectrometer.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Unity Inova500 and Inova300 spectrometer. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to tetramethylsilane (TMS, 0.00 ppm) or residual $CHCl_3$ (7.27 ppm). ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), bs (broad singlet), sext (sextet), apparent (app), dd (doublet of doublets). Unless indicated otherwise, deuterochloroform ($CDCl_3$) served as an internal standard (77.3 ppm) for all ^{13}C spectra. Flash column chromatography was performed using 60Å Silica Gel (Baker, 230-400 mesh) as a stationary phase as described by Still.[65] Mass spectra were obtained on a VG analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer at the center for Chemical Characterization and Analysis (Texas A&M). Enantiomeric excess (ee) was determined by GC (Hewlett-Packard 5880A gas chromatography) analysis using a 2,3-di-OAc-6-TBS β-CD column. Thin layer chromatography (TLC) was performed using glass-backed silica gel 60F254 (Merck, 250 μm thickness).

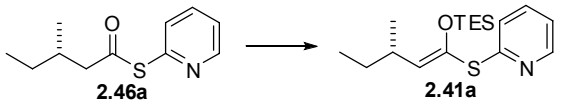
(*S*)-S-pyridin-2-yl 3-methylpentanethioate 2.46a



2,45a 2.46a

To a stirred solution of acid **2.45a** (1.24 g, 10.7 mmol) in CH_2Cl_2 (30 mL) was added oxalyl chloride (1.38 mL, 16.0 mmol) at 25 °C, and the reaction mixture was stirred for 2 h at 25 °C. The solvent was then evaporated under reduced pressure. To a stirred solution of the residual oil diluted with CH_2Cl_2 (20 mL) was added 2-thiopyridine (1.42 g, 12.8 mmol) in CH_2Cl_2 (20 mL) followed by Et_3N (2.98 mL, 21.3 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 25 °C and then quenched with 1*N* HCl (30 mL) and neutralized by washing with saturated $NaHCO_3$ solution (30 mL x 2). The organic layers were combined and evaporated, and the resulting yellow oil was purified by flash chromatography on SiO_2 (20% EtOAc/Hexanes) to afford thioester **2.46a** (2.19 g, 98 %) as a colorless liquid: $[\alpha]_D^{20}$ +8.2 (c=0.027, $CHCl_3$). IR (thin film) 2953, 1702, 1440, 1418 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.64 (m , 1H), 7.75 (m , 1H), 7.64 (m , 1H), 7.31 (m , 1H), 2.73 (dd, *J*= 6.3, 14.7 Hz, 1H), 2.54 (dd, *J*= 7.8, 14.7 Hz, 1H), 1.96-2.10 (m, 1H), 1.42-1.49 (m, 1H), 1.29-1.35 (m, 1H), 0.97 (d, *J*= 6.3 Hz, 3H), 0.91 (t, *J*= 7.8 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 151.9, 150.5, 137.4, 130.4, 123.7, 51.3, 32.8, 29.5, 19.4, 11.5; LRMS (ESI) Calcd. for $C_{11}H_{16}NOS[M+H]^+$: 210.0953. Found : 210.0967.(6.63 ppm)

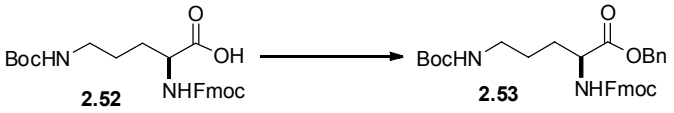
(*S*,*E*)-2-(3-methyl-1-(triethylsilyloxy)pent-1-enylthio)pyridine 2.41a



2.46a **2.41a**

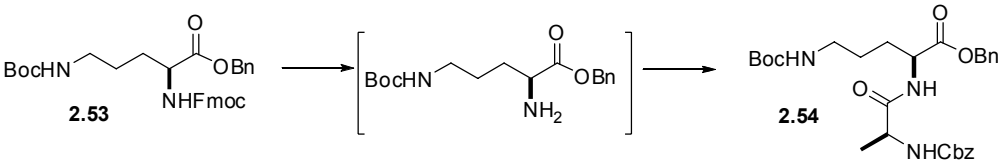
To a stirred solution of thioester **2.46a** (8.00 g, 35.8 mmol), DMF (3.14 g, 43.0 mmol) and Et_3N (6.04g, 43.0 mmol) in CH_2Cl_2 (240 mL) was added LiHMDS (1.0M, 82.6 mL, 82.6 mmol) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and then TESCl (12.02 mL, 71.6 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred for an additional 2 h at −78 °C and then quenched with pH 7 buffer solution (40 mL x 2). The organic layer was separated, dried over Na_2SO_4 and evaporated. The resulting yellowish oil was purified by flash chromatography on SiO_2 (10% EtOAc/Hexanes) to afford ketene acetal **2.41a** (11.1 g, 96%) as a yellow oil : IR (thin film) cm^{-1}; 2950, 2873, 1624, 1568 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (m, 1H), 7.53 (m, 1H), 7.32 (m, 1H), 6.97 (m, 1H), 5.18 (d, *J*= 9.6, 1H), 2.58 (m, 1H), 1.33-1.40 (m, 2H), 1.00 (d, *J*= 6.6 Hz, 3H), 0.93 (t, *J*= 7.5 Hz, 3H), 0.84-0.89 (m, 9H), 0.60-0.68 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 149.6, 138.7, 136.8, 130.5, 122.3, 121.5, 119.9, 33.5, 30.1, 20.4, 12.3, 6.8; LRMS (ESI) Calcd. for $C_{17}H_{29}NOSSiLi[M+Li]^+$: 330.1899. Found : 330.1939 (12.11ppm)

Fmoc-Ori(Boc)-OBn 2.53



To a stirred solution of Fmoc-Orn(Boc)-OH **2.52** (35.0 g, 77.00 mmol) and DMAP (1.0 g, 0.77 mmol) in CH_2Cl(350 mL), at 0 ^oC was added DIPEA (20.12 mL, 115.51 mmol). To the resulting solution, was added CbzCl (13.25 mL, 92.41 mmol) at 0 ^oC. The mixture was stirred at 0 ^oC for 4 h, then washed with 1*N* HCl(100 mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (33% EtOAc/Hexanes) to afford benzyl ester **2.53** (45.0 g, 100%) as a colorless solid. All spectroscopic data for this compound matched that reported previously[30b]

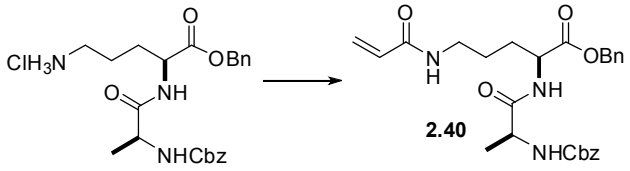
Dipeptide 2.54



To a stirred solution of benzyl ester **2.53** (41 g, 75.33 mmol) in THF (200 mL), was added Et_2NH (49 mL, 376.66 mmol) at room temperature. The reaction mixture was stirred for 12 h at 23 ^oC. The volatiles were evaporated and the residue was passed through a short pad of SiO_2 flushing with 100% EtOAc to separate non-polar impurities. The organics were evaporated to afford the free primary amine (21.47 g, 88%) as a white solid. The resulting solid was taken up in CH_2Cl_2(200 mL) and used directly in the next step.

To a stirred solution of Cbz-ala (17.77 g, 79.65 mmol) and HObt (9.87 g, 73.01 mmol) in CH_2Cl_2 (100 mL), was added EDCI (13.96 g, 73.01 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. To the solution of the free amine was added TMP (20.63 g, 146.03 mmol), and the resulting suspension was added to the stirred reaction mixture. This was left to attain room temperature for 24 h and then was quenched by water, washed with 1*N* HCl (100 mL x 3) , and neutralized by concentrated $NaHCO_3$ solution (100 mL x 2). The organic layer was separated and evaporated to give a crude residue, that residue was purified by flash chromatography on SiO_2 (40% EtOAc/Hexanes) to afford dipeptide **2.54** (28.0 g, 84%) as a white solid. All spectroscopic data for this compound matched that reported previously[30b]

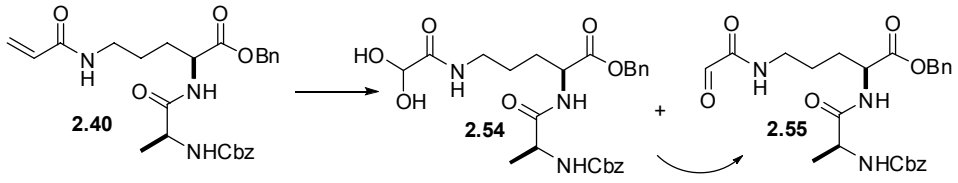
(5*S*, 8*S*)-benzyl 5-methyl-3, 6, 13-trioxo-1-phenyl-2-oxa-4, 7, 12-triazapentadec-14-ene-8-carboxylate 2.40



To a stirred solution of amine salt (25.00 g, 53.89 mmol) and TMP (22.74 g, 134.7 mmol) in CH_2Cl_2 (300 mL) was added acryloyl chloride (5.25 g, 64.7 mmol) at 0 °C. The reaction mixture was stirred for 4 h at 0 °C and then quenched by slow addition of 1*N* HCl (100 mL) and neutralized by washing with saturated $NaHCO_3$ solution (100 mL x 2). The organic layer was separated and evaporated to give a crude solid, that was triturated with pentane to give the acrylamide peptide **2.40** (24.0 g, 93%). : IR (thin film) 2937, 1796, 1728, 1665 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.43 (m, 10H),

6.99 (s, 1H), 6.26 (d, *J*= 4.2 Hz, 1H), 6.04 (dd, *J*= 9.9, 16.6 Hz, 2H), 5.12 (m, 2H), 4.60 (m, 1H), 4.28 (m, 1H), 3.27 (m, 2H), 1.82-1.96 (m, 1H), 1.61-1.73 (m, 1H), 1.42-1.58 (m, 2H), 1.41 (d, *J*= 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 171.7(2), 165.8, 136.1, 135.1, 130.8, 128.7, 128.6(2), 128.5(2), 128.4(2), 128.2(2), 128.0, 126.5, 67.4, 67.1, 52.1, 50.6, 38.7, 29.4, 25.4, 18.5; LRMS (ESI) Calcd. for $C_{26}H_{32}N_3O_6[M+H]^+$: 482.2291 Found :482.26 (64ppm)

(5*S*,8*S*)-benzyl 5-methyl-3,6,13,14-tetraoxo-1-phenyl-2-oxa-4,7,12-triazatetradecane-8-carboxylate 2.55

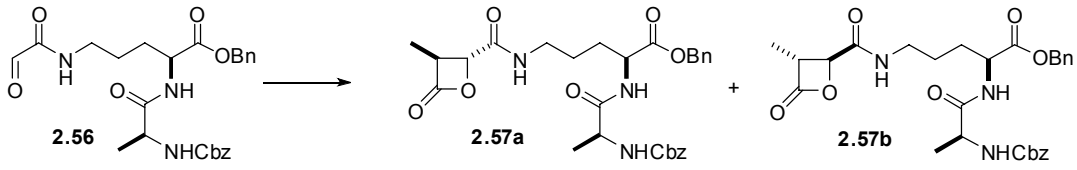


Ozone was bubbled through a stirred solution of acrylamide **2.40** (5.0 g, 10.4 mmol) in CH_2Cl_2 (200 mL) and MeOH (1 mL) at −78 °C until the blue color persisted, and the remaining ozone was removed by bubbling nitrogen through the solution. Dimethyl sulfide (3.1 mL, 41.6 mmol) was added and the mixture was left to attain 23 °C while stirring for 12 h. The solvent was evaporated under reduced vacuum and the resulting oil was purified by flash chromatography on SiO_2 (50% CH_2Cl_2/acetone) to afford a mixture of hydrate **2.54** and glyoxylate **2.55** (3.0 g, 60%) as a white solid. This resulting mixture was dissolved into CH_2Cl_2 with 4 Å MS and stirred for 24 h at 23 °C to give glyoxylate **2.55**. The resulting glyoxylate **2.55** was used directly in the next step without further purification.

Representative Procedure for TMAL Reaction under Normal Conditions (RP 1)

Anhydrous $ZnCl_2$ (1.2-2.0 equiv) was freshly fused under vacuum at ~0.5 mmHg and after cooling to ambient temperature, CH_2Cl_2 (appropriate volume to make final concentration of aldehyde in CH_2Cl_2 ~0.2 M) was added. The aldehyde (1.0 equiv) was then added neat or as a solution in CH_2Cl_2 at 25 °C followed by thiopyridylketene acetal (1.1-1.2 equiv). The suspension was stirred for the indicated time, and then quenched with pH7 buffer and filtered through a celite pad. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product which was purified by flash chromatography

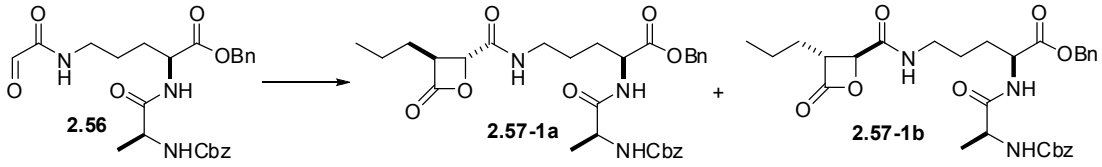
(5*S*,8*S*)-benzyl 5-methyl-3,6,13-trioxo-13-(4-oxo-3-methyloxetan-2-yl)-1-phenyl-2-oxa-4,7,12-triazatridecane-8-carboxylate 2.57



The β-lactone **2.57a/b** (31.0 mg, 34%) as a mixture of diastereomers was prepared from glyoxylate **2.56** (23.7 mg, 0.15 mmol) and ketene acetal (5.3 mg, 0.18 mmol) according to RP 1 as a white solid. IR (thin film) 3298 , 2940, 1831, 1730, 1656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.41 (m, 10H), 6.70 (bs, 1H), 6.58 (bs, 1H), 5.36 (m, 1H), 5.12-5.24 (m, 4H), 4.85 (d, *J*= 7.0 Hz, 1H), 4.63 (m, 1H), 4.26 (m, 1H), 4.00 (q, *J*= 7.0 Hz, 1H), 3.25-3.31 (m, 2H), 1.90 (bs, 2H), 1.80-1.40 (m, 3H), 1.39 (d, *J*= 7.0 Hz,

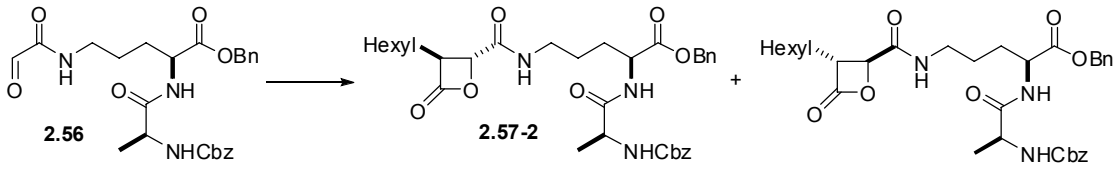
3H), 1.27 (d, *J*= 8.0 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.8, 169.7, 166.7, 156.2, 136.4, 135.2, 128.9(2), 128.9(2), 128.8(2), 128.7, 128.5(2), 128.3, 71.8, 67.6, 67.2, 52.0, 50.7, 50.2, 38.6, 29.6, 25.4, 18.6, 9.8; HRMS (ESI) Calcd. for $C_{28}H_{34}N_3O_8[M+H]^+$: 540.2346. Found : 540.2324 (4.07ppm)

(5*S*,8*S*)-benzyl 5-methyl-3,6,13-trioxo-13-(4-oxo-3-propyloxetan-2-yl)-1-phenyl-2-oxa-4,7,12-triazatridecane-8-carboxylate 2.57-1



β-Lactone **2.57-1a/b** (63.0 mg, 34%) as a mixture of diastereomers was prepared from glyoxylate **2.56** (96.7 mg, 0.30 mmol) and ketene acetal **2.41b** (11.6 mg, 0.36 mmol) according to RP 1 as a white solid: IR (thin film) 3308, 1838, 1724, 1661 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.41 (m, 10H), 6.74 (bs, 1H), 6.57(bs, 1H), 5.38 (s, 1H), 5.12-5.24 (m, 4H), 4.63 (q, *J*= 5.0 Hz, 1H), 4.51 (d, *J*= 4.5 Hz, 1H), 4.25 (m, 1H), 3.65 (m, 1H), 3.27 (m, 2H), 1.88 (m, 2H), 1.78-1.42 (m, 4H), 1.40 (d, *J*= 7.0 Hz, 3H), 0.98 (t, *J*= 7.5 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.8, 169.6, 167.9, 156.0, 136.3, 135.2, 128.9, 128.9(2), 128.8(2), 128.7(2), 128.5(2), 128.3, 73.0, 67.6, 67.3, 57.8, 52.0, 50.8, 38.6, 30.3, 29.6, 25.4, 20.1, 18.4, 13.8; HRMS (ESI) Calcd. for $C_{30}H_{38}N_3O_8[M+H]^+$: 568.2659. Found : 568.2683 (4.22ppm)

(5*S*,8*S*)-benzyl 5-methyl-3,6,13-trioxo-13-(4-oxo-3-hexyloxetan-2-yl)-1-phenyl-2-oxa-4,7,12-triazatridecane-8-carboxylate 2.57-2



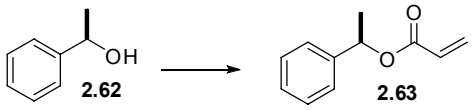
The β-lactone **2.57** (24.0 mg, 31%) as a mixture of diastereomers was prepared from glyoxylate **2.56** (36.7 mg, 0.10 mmol) and ketene acetal (4.6 mg, 0.12 mmol) according to RP 1 as a white solid. IR (thin film) 3291, 2923, 1836, 1713, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.41 (m, 10H), 6.72 (bs, 1H), 6.63(bs, 1H), 5.41 (bs, 1H), 5.09-5.24 (m, 4H), 4.61 (m, 1H), 4.49 (t, *J*= 3.5 Hz, 1H), 4.27 (m, 1H), 3.61 (m, 1H), 3.25 (m, 2H), 1.79-1.89 (m, 3H), 1.63-1.67 (m, 2H), 1.48-1.53 (m, 3H), 1.23-1.47 (m, 5H), 1.40 (d, *J*= 7.0 Hz, 3H), 0.88-0.97 (m, 4H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.8, 169.7, 168.3, 156.3, 137.3, 135.2, 128.9, 128.9(2), 128.8(2), 128.6(2), 128.4, 128.2(2), 73.0, 67.7, 67.3, 58.0, 52.0, 50.7, 38.6, 31.6, 29.8, 29.5, 28.9, 28.3, 26.6, 25.3, 22.7, 14.2; LRMS (ESI) Calcd. for $C_{33}H_{44}N_3O_8[M+H]^+$: 610.3128. Found : 610.3177 (8.02ppm)

Representative Procedure for Acrylate Formation under Normal Conditions (RP 2)

To a stirred solution of alcohol (1 equiv) and Et_3N (1.25 equiv) in CH_2Cl_2 (0.4M) was added acryloyl chloride (1.2 equiv) at 0 °C. The reaction mixture was stirred for 4 h

at 0 °C and then quenched by slow additional 1*N* HCl and neutralized by washing with saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product which was purified by flash chromatography.

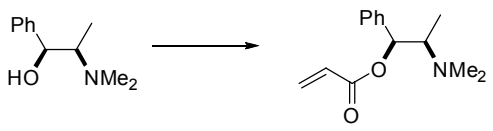
Acrylate 2.63



The acrylate **2.63** (2.01 g, 98%) was prepared from alcohol **2.62** (1.50 g, 12.28 mmol) and acryloyl chloride (1.19 mL, 14.73 mmol) according to RP 2 and was isolated as a liquid following purification by column chromatography (10% EtOAc/hexanes).

IR (thin film) 2985, 1721 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.41 (m, 5H), 6.47 (d, *J*= 17.4 Hz, 1H), 6.17 (dd, *J*= 10.5, 27.6 Hz, 1H), 6.01 (q, *J*= 6.6 Hz, 1H), 5.85 (d, *J*= 10.5 Hz, 1H), 1.62 (d, *J*= 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 141.8, 131.0, 129.0, 128.8, 128.2, 126.3, 72.7, 22.5; LRMS (CI) Calcd. for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0916. Found:177.1 (47.4ppm)

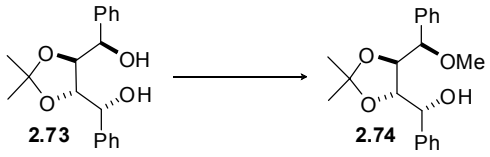
Acrylate 2.67



The acrylate **2.67** (4.46 g, 78%) was prepared from alcohol **2.66** (4.40 g, 24.55 mmol) and acryloyl chloride (2.38 mL, 29.45 mmol) according to RP 2 and was isolated as a white solid following purification by column chromatography (25% EtOAc/hexanes).

IR (thin film) 2974, 2940, 1728, 1407 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.37 (m, 5H), 6.47 (d, *J*= 17.0 Hz, 1H), 6.22 (dd, *J*= 10.5, 17.0 Hz, 1H), 6.02 (d, *J*= 5.0 Hz, 1H), 5.89 (d, *J*= 10.5 Hz, 1H), 2.95 (m, 1H), 2.33 (s, 6H), 1.11 (d, *J*= 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 139.9, 131.0, 128.6, 128.2, 127.5, 126.2, 75.4, 63.8, 41.4, 9.; HRMS (ESI) Calcd. for $C_{14}H_{20}NO_2[M+H]^+$: 234.1494. Found :234.1484 (4.27ppm)

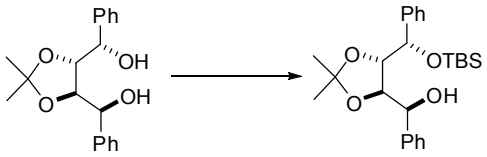
Mono alcohol 2.74



To a stirred solution of diol **2.73** (4.0 g, 12.7 mmol) and K_2CO_3 (5.3 g, 38.2 mmol) in acetone (100 mL) was added MeI (7.9 g, 127.2 mmol) at 25 °C. The reaction was refluxed for 24 h and then cooled to 25 °C. The reaction mixture was filtered and evaporated to give a crude compound. The crude compound was purified by flash chromatography (25% EtOAc/hexanes) to give liquid (3.8 g, 90%). : $[\alpha]_D^{20}$ −11.9 (c = 0.16, $CHCl_3$); IR (thin film) 3446 , 2984, 2937 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11-7.40 (m, 10H), 4.26 (dd, *J*= 6.5, 7.5 Hz, 1H), 4.04 (dd, *J*= 4.0, 7.5 Hz, 1H), 3.94

(d, *J*= 6.5 Hz, 1H), 3.87 (dd, *J*= 3.5, 7.5 Hz, 1H), 3.24 (s, 3H), 3.01 (d, *J*= 7.5 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 137.6, 128.9, 128.9, 128.6, 128.1, 128.0, 126.7, 110.4, 85.0, 81.4, 80.7, 72.9, 57.1, 27.7, 27.6; HRMS (ESI) Calcd. for $C_{20}H_{24}O_4Li$ $[M+Li]^+$: 335.1835. Found : 335.1844 (2.69ppm)

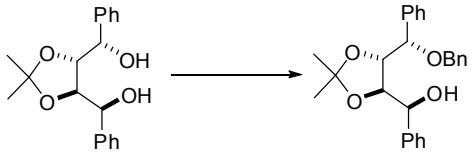
TBS ether 2.74b



To a stirred solution of diol **2.73** (0.37 g, 1.16 mmol) in THF (10 mL) was added 1.6M MeLi (0.73 mL, 1.16 mmol) at −78 °C. The mixture was allowed to reach 25 °C and stirred for 30 min and then TBSCl (0.17g, 1.16 mmol) in THF(3 mL) was added at 25 °C. The reaction mixture was quenched by slow addition of 1*N* HCl (10mL) and washed with saturated $NaHCO_3$ (10mL x 2) solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product. The resulting yellowish oil was purified by flash chromatography (16% EtOAc/hexanes) on SiO_2 to afford TBS ether **2.74b** (0.49 g, 99%). : $[\alpha]_D^{20}$ + 58.4 (c = 0.43, $CHCl_3$); IR (thin film) 3406 , 2912 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.40 (m, 10H), 4.44 (d, *J*= 4.5 Hz, 1H), 4.37 (dd, *J*= 4.0, 7.5 Hz, 1H), 4.12 (dd, *J*= 5.0, 8.0 Hz, 1H), 4.07 (dd, *J*= 4.0, 7.5 Hz, 1H), 3.01 (d, *J*= 7.5 Hz, 1H), 1.41 (s, 3H), 1.26 (s, 3H), 0.90 (s, 9H), 0.01 (s, 3H), -0.16 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 140.6, 128.6, 128.2, 128.0, 128.0,

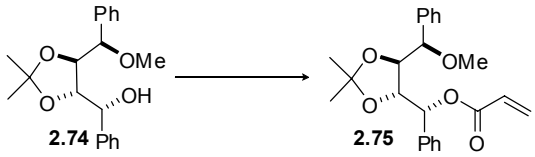
127.7, 126.8, 110.2, 81.6, 80.8, 75.4, 73.6, 27.8, 27.4, 26.1, 18.5, 14.4 ; HRMS (ESI) Calcd. for $C_{25}H_{36}O_4SiLi$ $[M+Li]^+$: 435.2543. Found : 435.2547 (0.91ppm)

Benzyl ether 2.74c



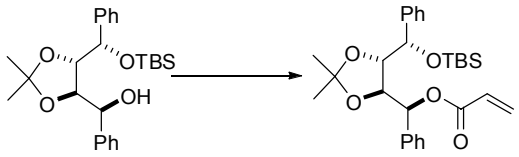
To a stirred solution of diol **2.73** (0.34 g, 1.08 mmol) and K_2CO_3 (0.53 g, 3.82 mmol) in acetone (10 mL) was added BnBr (0.14 g, 1.19 mmol) at 25 °C. The reaction was refluxed for 15 h and then cooled to 25 °C. The reaction mixture was quenched with 1*N* HCl (50 mL), and washed with saturated $NaHCO_3$ solution (50 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product. The resulting crude oil was purified by flash chromatography on SiO_2 to afford TBS ether **2.74c** (0.41 g, 94%). The crude compound was purified by flash chromatography (20% EtOAc/hexanes). : $[\alpha]_D^{20}$ +54.4 (c = 0.62, $CHCl_3$); IR (thin film) 3452 , 3025, 1985, 2873 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.09-7.37 (m, 15H), 4.56 (d, *J*= 12.0 Hz, 1H), 4.21-4.21 (m, 2H), 4.01-4.11 (m, 2H), 4.05 (d, *J*= 6.0 Hz, 1H), 2.88 (d, *J*= 6.5 Hz, 1H), 1.48 (s, 3H), 1.35 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 137.8, 128.5, 128.4, 128.3, 128.3, 128.0, 127.8, 127.7, 127.6, 126.5, 81.0, 80.9, 80.5, 3.3, 70.3, 27.6, 27.1; LRMS (ESI) Calcd. for $C_{26}H_{28}O_4Li$ $[M+Li]^+$: 411.2148. Found : 411.2123 (6.08ppm)

Acrylate 2.75



To a stirred solution of alcohol **2.74** (16.01 g, 28.7 mmol) and Hunig's base (6.02 g, 34.5 mmol) in CH_2Cl_2 (300 mL) was added acryloyl chloride (2.79 g, 34.5 mmol) at 0 °C. The reaction mixture was stirred for 12 h at 25 °C and then quenched with 1*N* HCl (100 mL), and washed with saturated $NaHCO_3$ solution (100 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product, which was purified by flash chromatography (10% EtOAc/hexanes) give a white solid **2.75** (10.1 g, 83%) : $[\alpha]_D^{20}$ −15.4 (c=0.25, $CHCl_3$); IR (thin film) 2978 , 2925, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11-7.41 (m, 10H), 6.46 (dd, *J*= 1.5, 17.4 Hz, 1H), 6.17 (dd, *J*= 10.5, 20.1 Hz, 1H), 5.87 (dd, *J*= 1.5, 10.5 Hz, 1H), 5.03 (d, *J*= 3.9 Hz, 1H), 4.16 (m, 2H), 3.86 (d, *J*= 6.0 Hz, 1H), 3.22 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 137.6, 137..4, 131.5, 129.0, 128.9, 128.6, 128.5, 128.0, 127.4, 110.9, 84.9, 80.7, 80.0, 75.1, 57.0, 27.9, 27.5; LRMS (ESI) Calcd. for $C_{23}H_{26}O_5Li$ $[M+Li]^+$: 389.1940. Found : 389.1974 (8.73ppm)

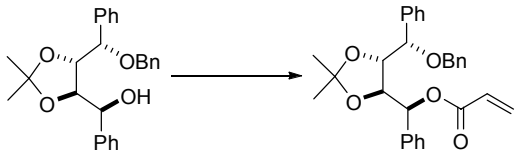
Acrylate 2.75b



The acrylate **2.75b** (0.32 g , 73%) was prepared from free alcohol **2.74b** (0.40g, 0,93 mmol) and acryloyl chloride (0.090 mL, 1.20 mmol) according to RP 2 as a white solid following purification by column chromatography (10% EtOAc/hexanes).

$[\alpha]_D^{20}$ + 69.1 (c=0.75, $CHCl_3$); IR (thin film) 2933, 2855, 1732, 1403 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19-7.40 (m, 10H), 6.48 (dd, *J*= 2.5, 28.5 Hz, 1H), 6.23 (dd, *J*= 17.5, 28.5 Hz, 1H), 5.88 (dd, *J*= 2.5, 17.5 Hz, 1H), 5.53 (d, *J*= 8.0 Hz, 1H), 4.31 (t, *J*= 6.5 Hz, 1H), 4.28 (dd, *J*= 8.0, 12.0 Hz, 1H), 4.07 (dd, *J*= 7.5, 12.5 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 0.93 (s, 9H), 0.02 (s, 3H), -1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 140.9, 137.7, 131.5, 129.7, 128.7, 128.6, 128.3, 128.1, 127.6, 110.7, 81.9, 79.6, 76.1, 75.5, 27.8, 27.5, 26.1, 18.5, 14.4; HRMS (ESI) Calcd. for $C_{28}H_{38}O_5SiLi$ $[M+Li]^+$: 489.2649. Found : 489.2641 (1.6ppm).

Acrylate 2.75c



The acrylate **2.75c** (0.42 g, 72%) was prepared from free alcohol **2.74c** (0.51 g, 1.26 mmol) and acryloyl chloride (0.15 mL, 1.89 mmol) according to RP 2 as a white solid following purification by column chromatography (8% EtOAc/hexanes).

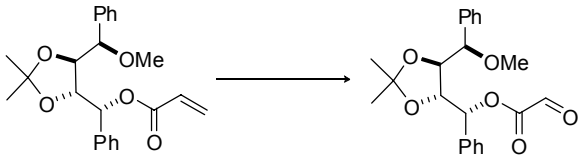
$[\alpha]_D^{20}$ + 51.1 (c=0.14, $CHCl_3$); IR (thin film) 3446 , 2984, 1720, 1403 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04-7.60 (m, 15H), 6.45 (dd, *J*= 1.0, 17.5 Hz, 1H), 6.18 (ddd, *J*= 1.5, 10.5, 17.5 Hz, 1H), 5.86 (dd, *J*= 1.5, 10.5 Hz, 1H), 5.30 (dd, *J*= 2.5, 5.0 Hz, 1H), 4.52 (d, *J*= 12.0 Hz, 1H) 4.28-4.30 (m, 1H), 4.16 (dd, *J*= 1.5, 14.0 Hz, 1H), 4.10-4.12 (m, 1H), 3.86 (dd, *J*= 3.0, 5.0 Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 138.2, 137.9, 137.3, 131.6, 128.9, 128.7, 128.6, 128.6, 128.5, 128.2, 128.1, 127.8, 127.5, 111.1, 81.0, 80.9, 79.7, 76.0, 70.5, 27.7; HRMS (ESI) Calcd. for $C_{29}H_{30}O_5Li$ $[M+Li]^+$: 465.2253. Found : 465.2267. (3.01ppm)

Representative Procedure for Oxidative Cleavage under Normal Conditions (RP 3)

To a stirred solution of acrylate (2.70 g, 7.06 mmol) in THF /H_2O(6/4, 100 mL) was added OsO_4 (0.05 equiv) and $NaIO_4$ (4equiv) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then water was added and the mixture was extracted with Et_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product, which was purified by flash chromatography to afford a mixture of hydrate and desired glyoxylate. The resulting mixture of hydrate and

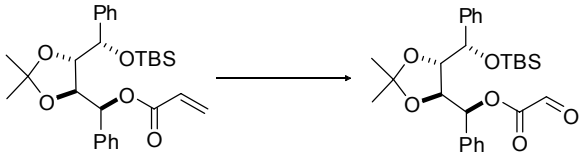
glyoxylate was dissolved into CH_2Cl_2 with 4 Å MS and stirred for 24 h at 23 °C to give glyoxylate. The resulting glyoxylate was used directly in the next step without further purification.

Glyoxylate 2.76



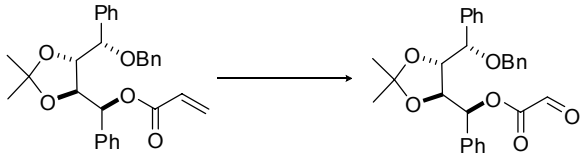
The glyoxylate **2.76 (**2.67 g, 98%) was prepared from acrylate **2.75** (2.70 g, 7.06 mmol), using OsO_4 (0.03 g, 0.35 mmol) and $NaIO_4$ (8.39 g, 28.2 mmol) according to RP 3 and was isolated as a white solid following purification by column chromatography (50% EtOAc/hexanes):

Glyoxylate 2.76b



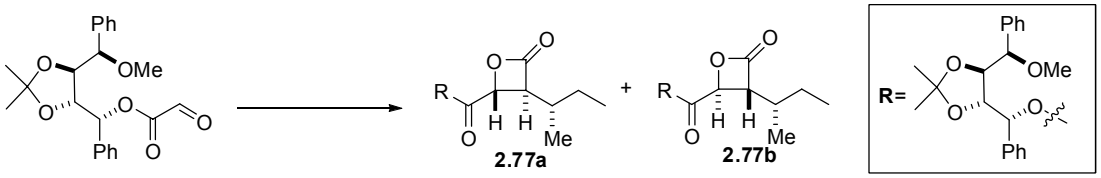
The glyoxylate **2.76b (**0.98 g, 98%) was prepared from acrylate **2.75b** (1.0 g, 2.07 mmol), using OsO_4 (0.01 g, 0.12 mmol) and $NaIO_4$ (2.51 g, 8.46 mmol) according to RP 3 and was isolated as a white solid following purification by column chromatography (50% EtOAc/hexanes).

Glyoxylate 2.76c



The glyoxylate **2.76c (**0.99 g, 98%) was prepared from acrylate **2.75c** (1.0 g, 2.18 mmol), using OsO_4 (0.03 g, 0.35 mmol) and $NaIO_4$ (8.4 g, 28.2 mmol) according to RP 3 and was isolated as a white solid following purification by column chromatography (100% EtOAc).

β-Lactone 15

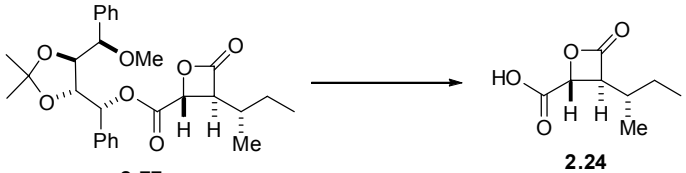


The β-lactone **2.77a** (5.0 mg, 5%) was prepared from glyoxylate **2.76** (79.7 mg, 0.20 mmol) according to RP 1 and was isolated as a white solid: $[\alpha]_D^{20}$ −71.2 (c=0.38, EtOAc); IR (thin film) 2917 , 1843, 1733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14-7.37 (m, 10H), 5.20 (d, *J*= 5.5 Hz, 1H), 4.67 (d, *J*= 4.5 Hz, 1H), 4.19 (dd, *J*= 6.0, 7.5 Hz, 1H), 4.03 (dd, *J*= 6.0, 6.0 Hz, 1H), 3.69 (d, 5.5 Hz, 1H), 3.65 (dd, *J*= 4.5, 7.5 Hz, 1H), 3.16(s, 3H), 2.00 (m, 1H), 1.62 (m, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.33 (m, 1H), 1.07 (d, 7.0 Hz, 3H), 0.92 (t, 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 167.6, 137.5, 136.1, 129.2, 128.9, 128.5, 127.8, 127.7, 111.0, 84.2, 80.8, 79.4, 69.3, 62.9, 57.1, 33.8, 27.8, 27.5, 27.0, 16.6, 11.2; HRMS (ESI) Calcd. for $C_{28}H_{34}O_7Na$ $[M+Na]^+$: 505.2202. Found :

505.2212.(1.97ppm)

The β-lactone **2.77b** (30.0 mg, 30%) was prepared from glyoxylate **2.76** (79.7 mg, 0.20 mmol) according to RP 1 and was isolated as a white solid: $[\alpha]_D^{20}$ −51.6 (c=0.56, EtOAc). IR (thin film) 2917 , 1843, 1733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16-7.39 (m, 10H), 5.17 (d, *J*= 5.5 Hz, 1H), 4.68 (d, *J*= 4.5 Hz, 1H), 4.19 (dd, *J*= 5.0, 6.5 Hz, 1H), 4.06 (dd, *J*= 6.0, 6.0 Hz, 1H), 3.75 (d, 6.0 Hz, 1H), 3.49 (dd, *J*= 4.5, 9.0 Hz, 1H), 3.16(s, 3H), 1.98 (m, 1H), 1.59 (m, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 1.22 (m, 1H), 1.10 (d, 7.0 Hz, 3H), 0.94 (t, 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 167.5, 137.4, 136.1, 129.2, 129.0, 128.9, 128.9, 127.9,127.6, 111.1, 84.5, 80.9, 79.5, 77.1, 70.3, 63.4, 57.1, 34.4, 27.9, 27.6, 27.5, 16.4, 11.1; HRMS (ESI) Calcd. for $C_{28}H_{34}O_7Na$ $[M+Na]^+$: 505.2202 Found : 505.2214 (1.98ppm)

β-lactone acid 2.24

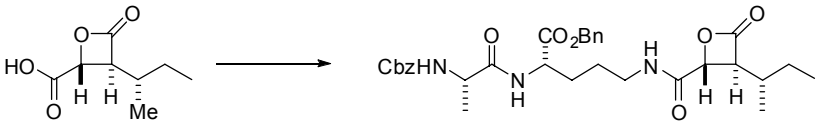


2.77a **2.24**

To a solution of β-lactone **2.77a** (80.3 mg, 0.16 mmol) in THF (3.0 mL) was added Pd/C and HCO_2H (2.0 mL). The mixture was stirred under an atmosphere of H_2 (rubber balloon) for 17 h. The catalyst was filtered off through a pad of cotton wool and the solvent was removed under reduced pressure to give an oily liquid, which was purified by flash chromatography give β-lactone acid **2.24** (21.2 mg, 77%) was obtained as an

oily liquid: $[\alpha]_D^{20}$ +3.1 (c = 0.59, $CHCl_3$). All other data matched that previously reported.[30c]

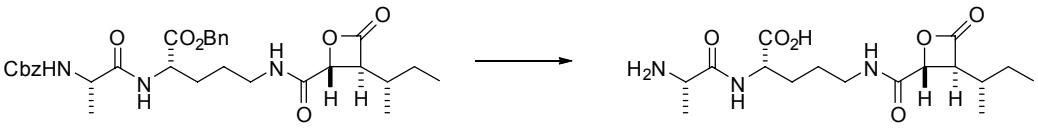
N-CBZ-O-Bn protected belactosin C 2.58c



2.24 **2.58c**

Coupling of dipeptide **2.42** (34.8 mg, 0.075 mmol) and β-lactone acid **2.24** (15.2 mg, 0.088 mmol) was accomplished according to the published procedure [10c] employing DCC (24.8 mg, 0.12 mmol) and HOBT (16.2 mg, 0.12 mmol) in 1.0 mL EtOAc/H_2O (1:1 ratio) to provide amide **2.58c** (23.4 mg, 53%) as a colorless solid: $[\alpha]_D^{20}$ +3.2 (c = 0.72, $CHCl_3$). All other data matched that previously reported.[30b]

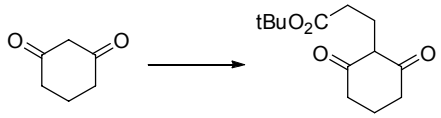
(–)-Belactosin C



Deprotection of N-CBZ-O-Bn belactosin C **2.58c** (6.3 mg, 0.01 mmol) was accomplished by the method of Armstrong[10a] employing Pd/C (1 mg) in 5 mLTHF/HCO_2H (3:2) for 15 h to provide belactosin C (2.9 mg, 81%) as a glassy solid following purification by column chromatography(5% MeOH/$CHCl_3$): $[\alpha]_D^{20}$ –8.1 (c = 0.92, H_2O). ^1H NMR (500 MHz, $CDCl_3$) δ 4.92 (d, *J*= 4.5 Hz, 1H), 4.19 (dd, *J*= 5.0, 6.5 Hz, 1H), 3.84 (dd, *J*= 4.5, 7.5 Hz, 1H), 3.30 (t, *J*= 7.0 Hz, 2H), 2.00-2.09 (m, 1H), 1.77-

1.83 (m, 1H), 1.65-1.74 (m, 1H), 1.51-1.61 (m, 2H), 1.49-1.59 (m, 1H), 1.32 (m, 1H), 1.03 (d, 7.0 Hz, 3H), 0.92 (t, 7.5 Hz, 3H): All other data matched that previously reported. [30b]

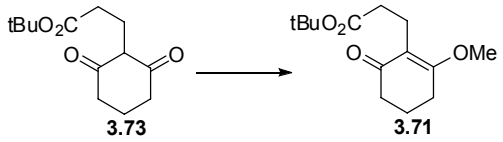
t-Butyl ester 3.73



3.70 **3.73**

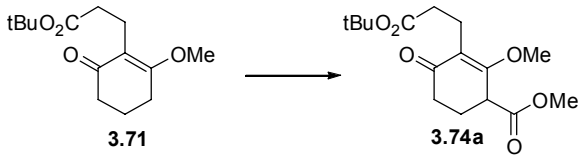
To a stirred solution of 60% NaH (0.42 g, 10.70 mmol) in DMF (20 mL) was added diketone **3.70** (1.0 g, 8.92 mmol) and *t*-butyl acrylate (1.44 g, 9.81 mmol) at 25 °C. The reaction was heated to 85 °C for 24 h and then cooled to 25 °C. The reaction mixture was quenched with 1*N* HCl (50 mL), neutralized by washing with saturated $NaHCO_3$ solution (50 mL x 2). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product. The resulting crude oil was purified by flash chromatography on SiO_2 (15% EtOAc/hexanes) to afford *t*-butyl ester **3.73** (3.8 g, 90%).; IR (thin film) 1723, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 2.45-2.48 (m, 6H), 2.34 (t, *J*= 6.5 Hz, 2H), 1.92 (q, *J*= 6.5 Hz, 2H), 1.45 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 178.2, 173.7, 115.0, 82.7, 36.9, 34.6, 29.6, 28.3(3), 20.7, 16.9; LRMS (APCI) Calcd. for $C_{13}H_{21}O_4[M+H]^+$: 241.1440. Found : 241 (597ppm)

Vinylogous methyl ester 3.71



To a stirred solution of diketone **3.73** (1.0 g, 4.16 mmol) and K_2CO_3 (1.13 g, 4.99 mmol) in acetone (20 mL) was added dimethyl sulfate (0.39 g, 4.16 mmol) at 23 °C. The reaction was stirred for 12 h at 23 °C. The reaction mixture was quenched with water (20 mL) and extracted by ethyl acetate (20 mL x 2). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product. The resulting solid was purified by flash chromatography on SiO_2 (15% EtOAc/hexanes) to afford enol ether **3.71** (0.98 g, 94%) ; IR (thin film) 2980,1724, 1642, 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 2.52-2.62 (m, 4H), 2.22-2.38 (m, 4H), 1.96-2.04 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 173.3, 172.6, 118.2, 79.9, 55.4, 36.5, 34.5, 28.4(3), 25.1, 21.1, 18.1; HRMS (ESI) Calcd. for $C_{14}H_{22}O_4Li$ $[M+Li]^+$: 261.1678. Found : 261.1681 (1.1 ppm)

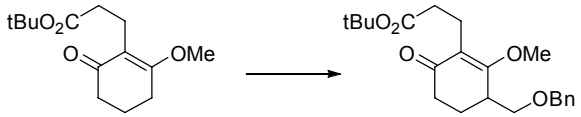
Diester 3.74a



To a stirred solution of hexenone **3.71** (120 mg, 0.47 mmol) in THF (5 mL) at −78 °C was added 1.0M LiHMDS (0.47 mL, 0.47 mmol). After stirring at −78 °C for 30 min, methyl cyanoformate (0.04 mL, 0.52 mmol) was added and the reaction was stirred at 23

°C for 12 h. The reaction mixture was quenched with pH 7 buffer (20mL) and extracted with ethyl ether (20 mL x 2). The combined organic layer was evaporated to give a crude oil that was purified by flash chromatography on SiO_2 (30% EtOAc/Hexanes) to afford methyl ester **3.74a** (91 mg, 61%) : IR (thin film) 2696, 2949, 1723, 1643, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.75 (s, 3H), 3.32-3.38 (m, 1H), 2.76-2.82 (m, 1H), 2.55 (q, *J*= 8.0 Hz, 3H), 2.30-2.50 (m, 1H), 2.25 (t, *J*= 8.5 Hz, 3H), 1.43 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 173.1, 172.5, 117.5, 80.1, 55.5, 52.5, 51.6, 34.3, 31.2, 28.3(3), 23.5, 23.4, 18.3; LRMS (ESI) Calcd. for $C_{16}H_{25}O_6$ $[M+H]^+$: 313.1651. Found : 313.1734 (26.5 ppm)

Benzyl ether 3.76

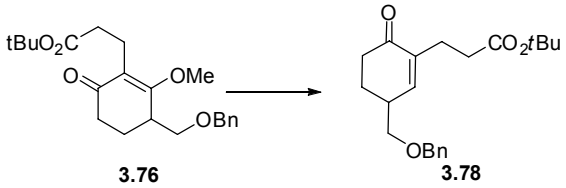


3.73 **3.76**

To a stirred solution of diisopropyl amine (0.27 mL, 1.95 mmol) in THF (5 mL) was added 2.45 M *n*-BuLi (0.83 mL, 2.03 mmol) at −78 °C. After stirring at 0 °C for 30min, the solution was cooled to −78 °C and then cyclohexenone **3.73** (0.45 g, 1.77 mmol) in THF (5 mL) was added. After stirring at −78 °C for 30 min, benzyl chlormethyl ether (0.31 mL, 0.52 mmol) was added to the reaction mixture, and stirring was continued for 12 h at −20 °C. The reaction mixture was then quenched with pH 7 buffer (20 mL) and extracted by ethyl ether (20 mL x 2). The combined organic layer was evaporated to give a crude oil, which was purified by flash chromatography on SiO_2 (30% EtOAc/hexanes)

to afford benzyl ether **3.76** (0.45 g, 78%) ; IR (thin film) 1725, 1683, 1606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.40 (m, 5H), 4.53 (AB, *J*= 12.0 Hz, 2H), 3.90 (dd, *J*= 4.0, 10.0 Hz, 1H), 3.81 (s, 3H), 3.57 (dd, *J*= 9.0, 10.0 Hz, 1H), 2.66 (dt, *J*= 5.0, 17.5 Hz, 1H), 2.47-2.57 (m, 4H), 1.82-1.90 (m, 1H), 1.43 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 173.3, 172.4, 138.7, 128.6(2), 127.9, 127.8(2), 117.9, 79.9, 73.4, 70.0, 55.3, 45.2, 34.5, 28.4(3), 24.3, 24.1, 18.2; HRMS (ESI) $C_{22}H_{30}O_5Li$ $[M+Li]^+$: 381.2253. Found : 381.2262 (2.36 ppm)

Cyclohexenone 3.78

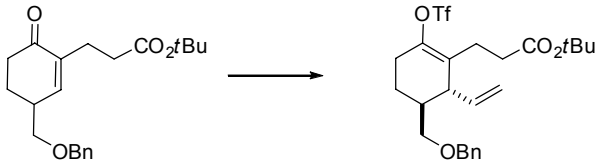


3.76 **3.78**

To a stirred solution of benzyl ether **3.76** (0.14 g, 0.37 mmol) in THF (15 mL) was added DIBAL (0.07 mL, 0.37 mmol) at −78 °C. After stirring at −78 °C for 1 h, The reaction mixture was quenched with Rochelle salt solution (20 mL) and stirred for an additional 2 h while allowing to reach ambient temperature. Water (20 mL) was then added, the mixture extracted with ethyl ether (20 mL x 2). The organic layer was combined, washed with 1*N* HCl (20mL x 5) and then evaporated to give the crude product as a yellow oil. The resulting yellowish crude compound was purified by flash chromatography on SiO_2 (15% EtOAc/hexanes) to afford cyclohexenone **3.78** (0.45 g, 78%) ; IR (thin film) 2978, 2863, 1726, 1673, 1365 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.37 (m, 5H), 6.71 (s, 1H), 4.55 (AB, *J*= 12.0, 2H), 3.44 (dd, *J*= 2.0, 6.5 Hz, 2H),

2.64-2.70 (m, 1H), 2.44-2.60 (m, 3H), 2.34-2.37 (m, 3H), 2.08-2.18 (m, 1H), 1.70-1.80 (m, 1H), 1.42 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 172.6, 147.2, 138.7, 138.2, 128.7(2), 128.0, 127.9(2), 80.4, 73.5, 72.9, 37.5, 37.3, 34.6, 28.4(3), 26.3, 25.7 ; HRMS (ESI) $C_{21}H_{28}O_4Li$ $[M+Li]^+$: 351.2148. Found : 351.2145 (0.8 ppm)

Enol triflate 3.79

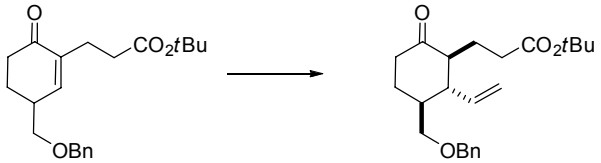


3.78 **3.79**

To a stirred solution of CuI (82 mg, 0.43 mmol) in THF (5 mL) was added TMEDA (0.065 mL, 0.43 mmol) at 0 °C. After stirring at 0 °C for 10 min, the reaction mixture was cooled to −78 °C and then 1M vinyl magnesium bromide (0.87 mL, 0.87 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min and then enone **3.78** (100 mg, 0.29 mmol) in THF (1mL) was added to the reaction mixture. After stirring at −78 °C for 2 h, Tf_2O (0.15 mL, 0.87 mmol) was added. After stirring at −78 °C for 2 h, the reaction mixture was quenched with 1*N* HCl (10 mL), extracted with Et_2O (20 mL x 2), and washed with saturated $NaHCO_3$ solution (10 mL x 2). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product. The resulting yellowish oil was purified by flash chromatography on SiO_2 (15% EtOAc/hexanes) to afford triflate **3.79** (33 mg, 23%) as a colorless oil : IR (thin film) 3437 , 1717, 1634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 5.80-5.89 (m, 1H), 5.31 (d, *J*= 11.5 Hz, 1H), 5.18 (d, *J*= 17.0 Hz, 1H), 4.45 (d, *J*= 3.5 Hz, 2H), 3.34-

3.50 (m, 3H), 2.27-2.58 (m, 5H), 2.11-2.24 (m, 3H), 1.60-1.78 (m, 1H), 1.45 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 138.5, 135.6, 128.6(2), 127.9, 127.8(2), 120.2, 95.0, 80.6, 73.5, 73.4, 72.1, 53.5, 37.8, 36.5, 32.8, 32.3, 29.9, 29.0, 28.4(3); LRMS (ESI) Calcd. for $C_{24}H_{32}F_3O_6S$ $[M+H]^+$: 505.1872. Found : 505.1409 (91.6 ppm)

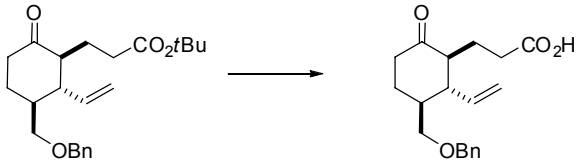
Cyclohexanone 3.80



To a stirred solution of CuI (82 mg, 0.43 mmol) in THF (5 mL) was added TMEDA (0.065 mL, 0.43 mmol) at 0 °C. After stirring for 10 min, the reaction mixture was cooled to −78 °C and then 1M vinyl magnesium bromide (0.87 mL, 0.87 mmol) was added. The reaction was stirred for 30 min and then enone **3.78** (100 mg, 0.29 mmol) in THF (1 mL) was added to the reaction mixture. After stirring at −78 °C for 2 h, the reaction mixture was quenched with pH 7 buffer (20 mL) and extracted with Et_2O (20 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product. The resulting yellow oil was purified by flash chromatography on SiO_2 (20% EtOAc/hexanes) to afford cyclohexanone **3.80** (87 mg, 81%) : IR (thin film) 2968 , 2851, 1728, 1700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5H), 5.55 (dt, *J*= 10.0, 17.0 Hz, 1H), 5.16 (dd, *J*= 1.0, 10.0 Hz, 1H), 5.02 (d, *J*= 17.0 Hz, 1H), 4.47 (AB, *J*= 12.0 Hz, 2H), 3.56 (dd, *J*= 3.0, 9.0 Hz, 1H), 3.30 (dd, *J*= 7.0, 9.0 Hz, 1H), 2.26-2.45 (m, 5H), 2.05-2.20 (m, 2H), 1.90-1.96 (m, 1H), 1.75-1.80 (m, 2H), 1.63-

1.76 (m, 1H), 1.44 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 173.4, 139.3, 138.7, 128.6(2), 127.8, 127.8(2), 117.9, 80.2, 73.4, 72.7, 52.3, 51.9, 41.7, 41.5, 33.3, 30.5, 28.4(3), 22.2 ; LRMS (ESI) Calcd. for $C_{23}H_{32}O_4Li$ $[M+Li]^+$: 379.2461. Found : 379.2423 (10.01 ppm)

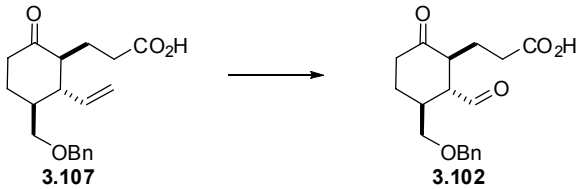
Acid 3.107



3.80 **3.107**

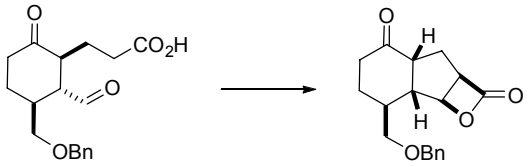
To a stirred solution of ester **3.80** (110 mg, 0.29 mmol) and Et_3SiH (0.62 mL, 0.62 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.067 mL, 0.59 mmol) at 0 °C. After stirring at 25 °C for 16 h, the reaction mixture was evaporated to give a crude oil. The resulting yellow oil was purified by flash chromatography on SiO_2 (25% EtOAc/hexanes) to afford acid **3.102** (92 mg, 96%) : IR (thin film) 2931, 2867, 1711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 5.55 (dt, *J*= 10.0, 17.0 Hz, 1H), 5.16 (dd, *J*= 1.5, 10.0 Hz, 1H), 5.03 (dd, *J*= 1.5, 17.0 Hz, 1H), 4.47 (AB, *J*= 12.0 Hz, 2H), 3.56 (dd, *J*= 3.5, 9.0 Hz, 1H), 3.32 (dd, *J*= 6.5, 9.5 Hz, 1H), 2.45-2.48 (m, 1H), 2.42-2.46 (m, 2H), 2.29-2.35 (m, 3H), 2.09-2.13 (m, 1H),1.81-1.98 (m, 1H), 1.80-1.89 (m, 2H),1.61-1.70 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2, 178.9, 138.8, 138.3, 128.3(2), 127.6, 127.5(2), 117.8, 73.1, 72.3, 51.9, 51.5, 41.4, 41.2, 31.4, 30.2, 21.6 ; HRMS (ESI) Calcd. for $C_{19}H_{25}O_4[M+H]^+$: 317.1753. Found : 317.1742 (3.47ppm)

Acid aldehyde 3.102



Ozone was bubbled through a stirred solution of acid **3.107** (90 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) and MeOH (0.1 mL) at −78 °C until the blue color persisted, and the remaining ozone was removed by bubbling nitrogen through the solution. Excess dimethyl sulfide (1.0 mL) was added and the mixture was warmed to 25 °C for 12 h. The solvent was evaporated under reduced pressure and the resulting oil was purified by flash chromatography on SiO_2 (50% EtOAc/hexanes) to afford aldehyde acid **3.102** (63 mg, 67%) as a colorless oil: IR (thin film) 3446 , 2931, 2860, 1711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.20-7.40 (m, 5H), 4.46 (AB, *J*= 12.0 Hz, 2H), 3.45-3.51 (m, 1H), 3.30-3.37 (m, 1H), 2.75 (t, *J*= 10.0 Hz, 1H), 2.33-2.58 (m, 7H), 2.12-2.21 (bd, *J*= 13.0 Hz, 1H), 1.85-1.94 (m, 1H), 1.55-1.69 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 200.5, 178.7, 137.5, 128.4(2), 127.8, 127.7(2), 73.2, 72.4, 58.9, 46.6, 40.4, 31.5, 38.6, 29.1, 21.9; LRMS (ESI) Calcd. for $C_{18}H_{21}O_5$ $[M-H]^+$: 317.1389. Found: 317.1322 (21.13 ppm)

NCAL Reaction



3.102 **3.103**

To a slurry of Mukaiyama's reagent (109 mg, 0.31 mmol) and triethy amine (0.09 mL, 0.63 mmol) in CH_2Cl_2(2 mL)at 23 ^oC was added via syringe pump a solution of aldehyde-acid **3.102** (50 mg, 0.15 mmol) in 1.0 mL of CH_2Cl_2 over 1 h at 23 ^oC. After the addition was complete, the reaction was stirred for an additional 48 h. The solvent was then removed *in vacuo*, and the dark red residue was purified by flash chromatography on SiO_2 (50 % EtOAc/hexanes) to afford β-lactone **3.103** (32 mg, 71%) as a white solid: IR (thin film) 2940, 2896, 1825, 1711 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) 7.26-7.40 (m, 5H), 5.07 (dd, *J*= 3.5, 3.5 Hz, 1H), 4.55 (dd, *J*= 4.0, 16.0 Hz, 2H), 3.92 (dd, *J*= 3.5, 8.0 Hz, 1H), 3.54-3.66 (m, 2H), 2.79-2.85 (m, 1H), 2.45-2.48 (m, 2H), 2.33-2.38 (m, 1H), 2.16-2.20 (m, 2H), 1.85-1.91 (m, 1H), 1.69-1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209, 170.6, 138.0, 128.4(2), 127.8, 127.5(2), 75.9, 73.2, 71.7, 54.3, 51.8, 50.1, 40.5, 36.9, 30.3, 24.6; HRMS (ESI) Calcd. for $C_{18}H_{20}O_4Li[M+Li]^+$: 307.1522. Found: 307.1507 (4.88ppm)

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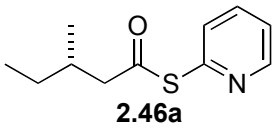
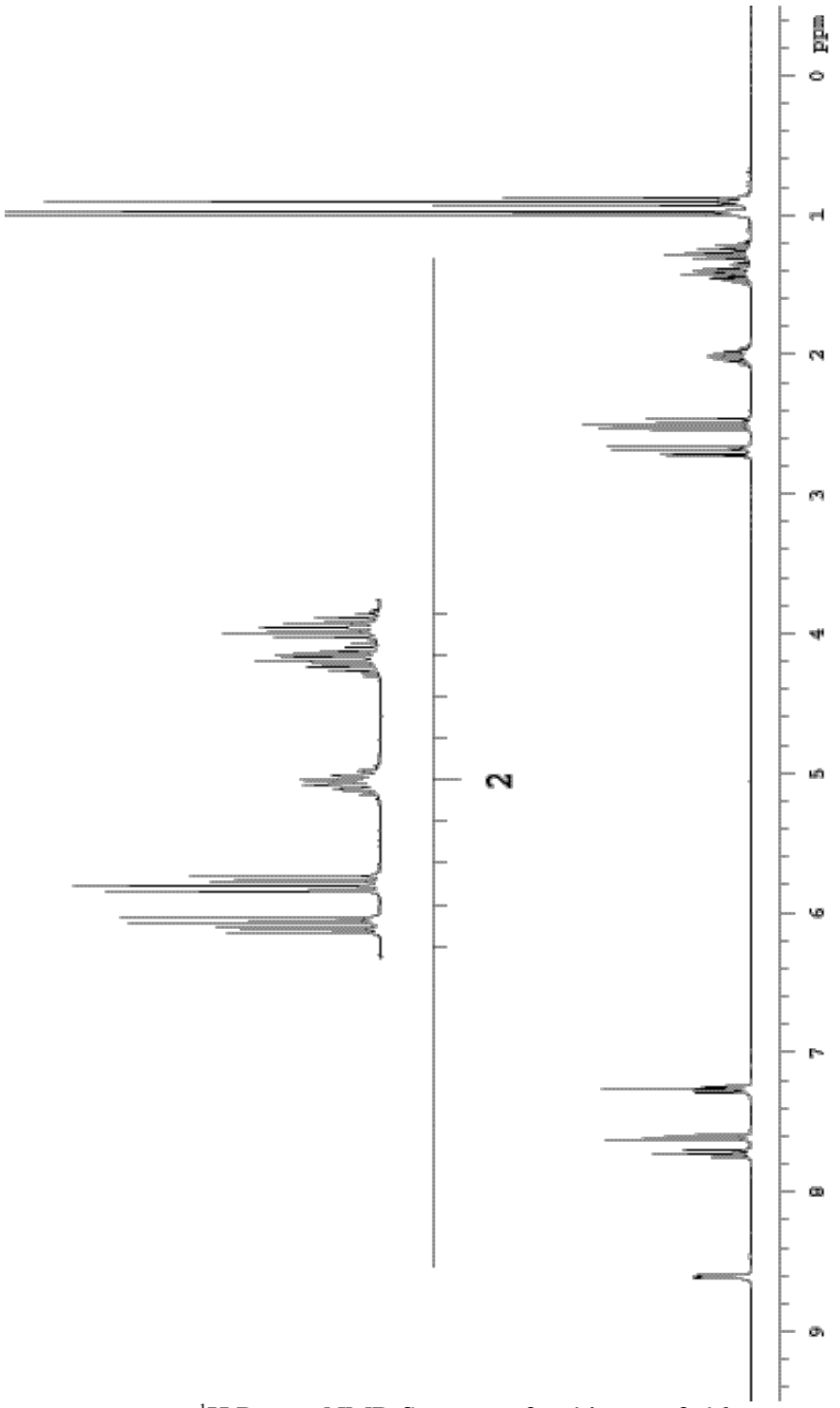
APPENDIX

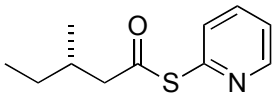
SELECTED SPECTRAL DATA



2.46a



^{1}H Proton NMR Spectrum for thioester **2.46a**



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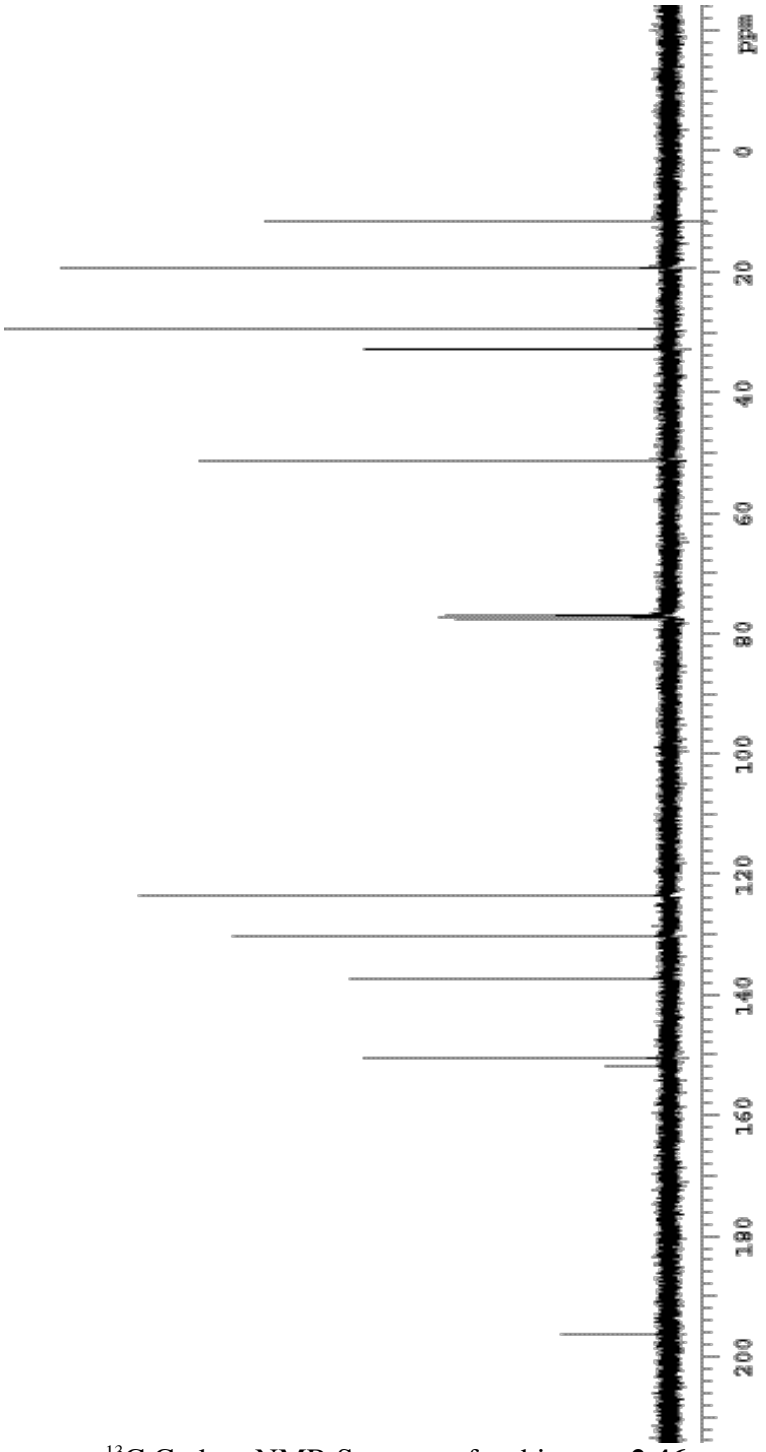

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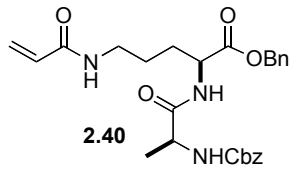
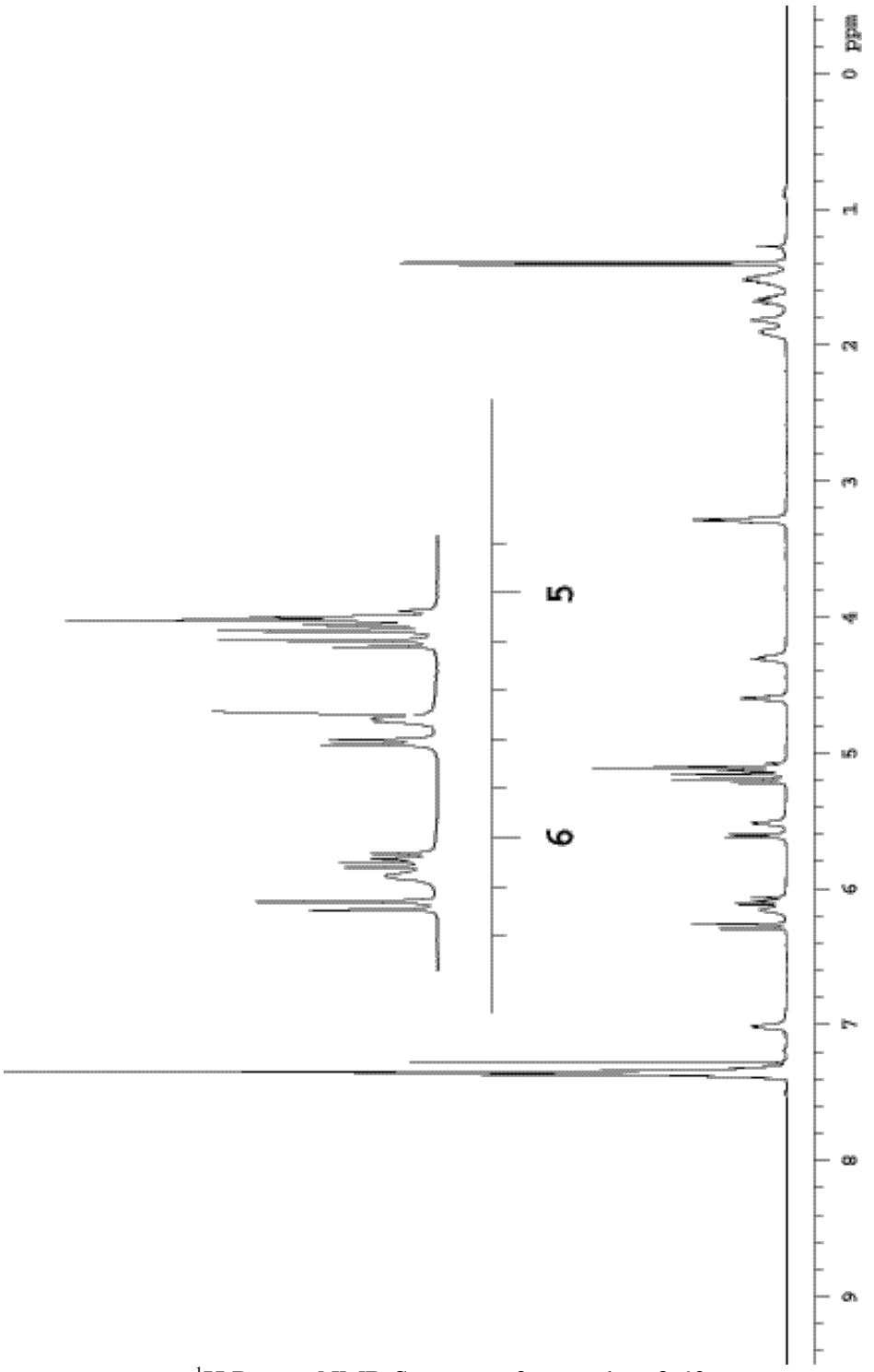


2.40



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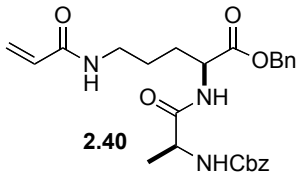

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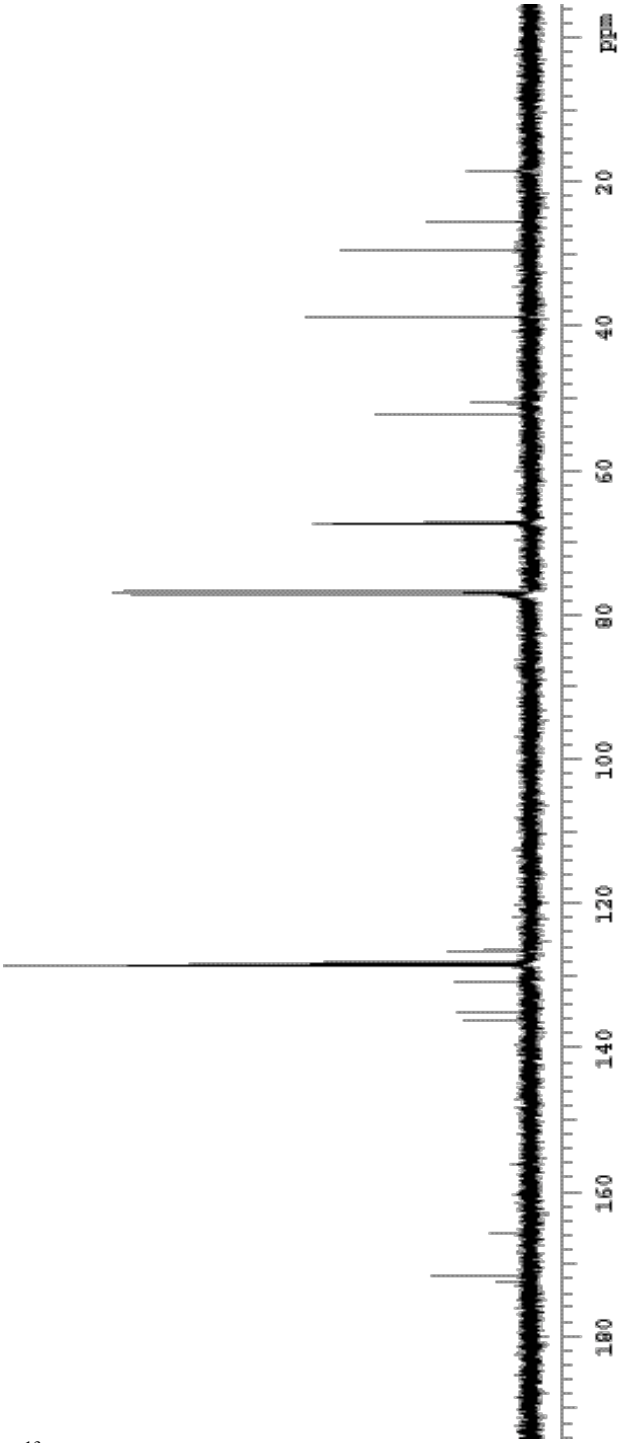

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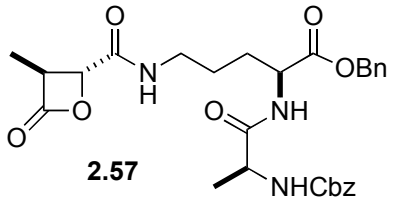

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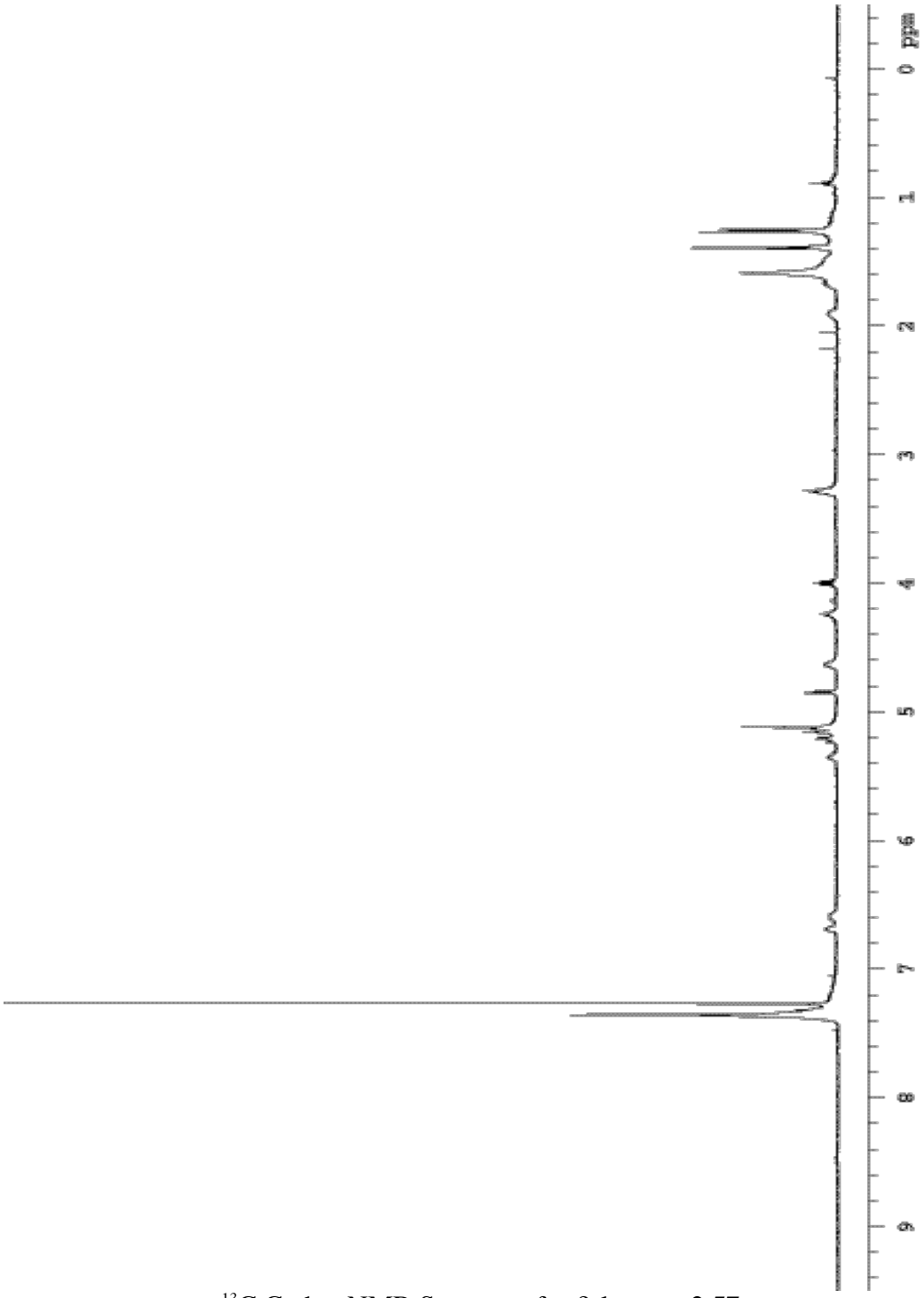
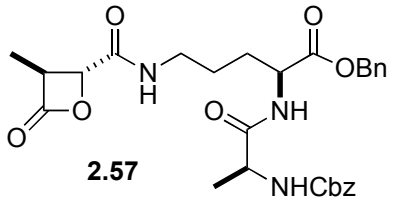
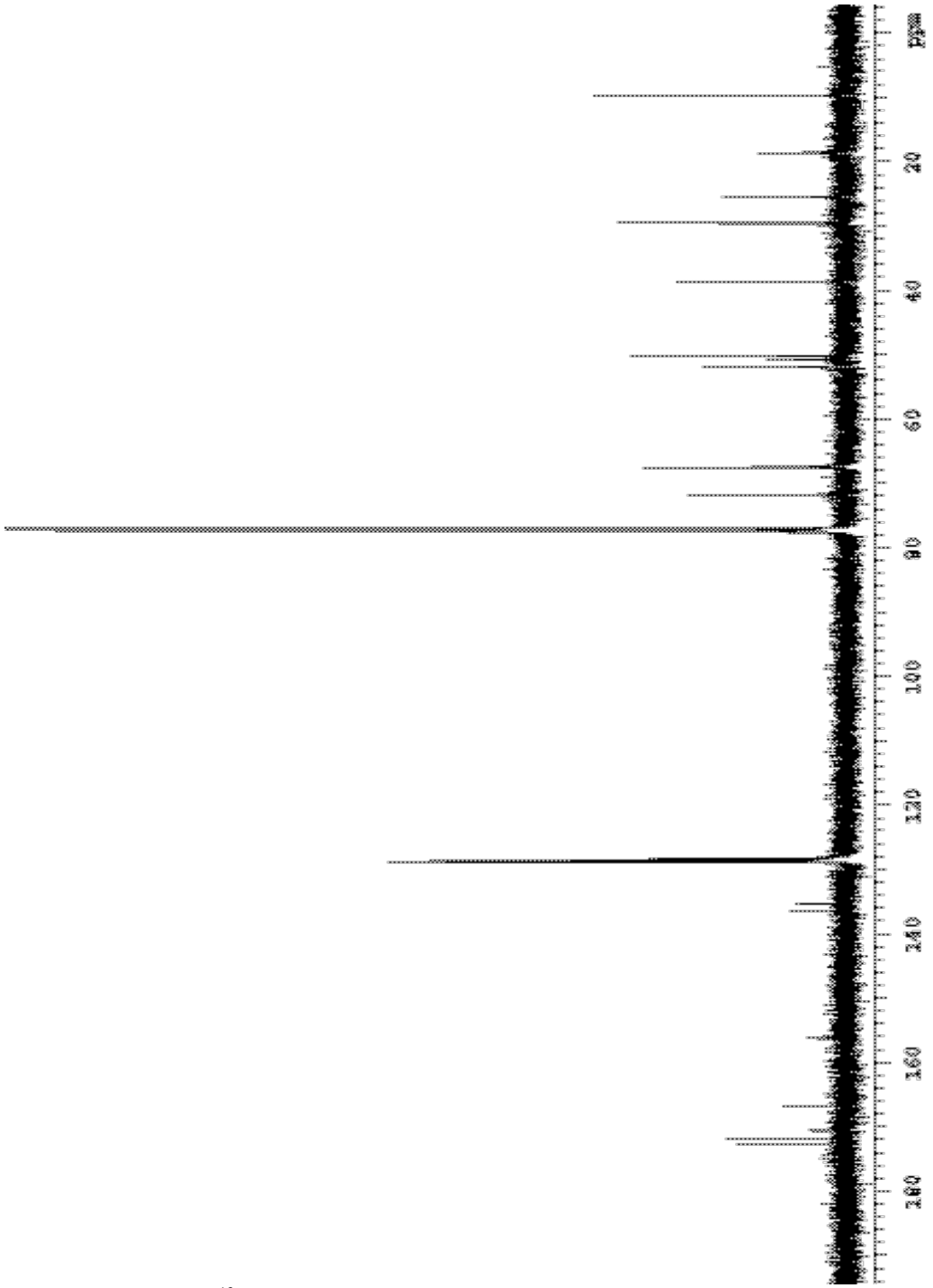


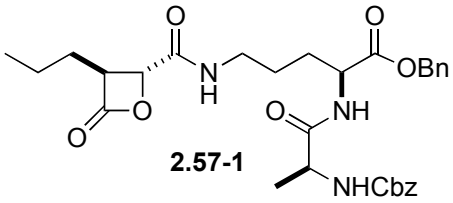
^{13}C CarbonNMR Spectrum for β-lactone **2.57**



2.57



^{13}C Carbon NMR Spectrum for β-lactone **2.57**



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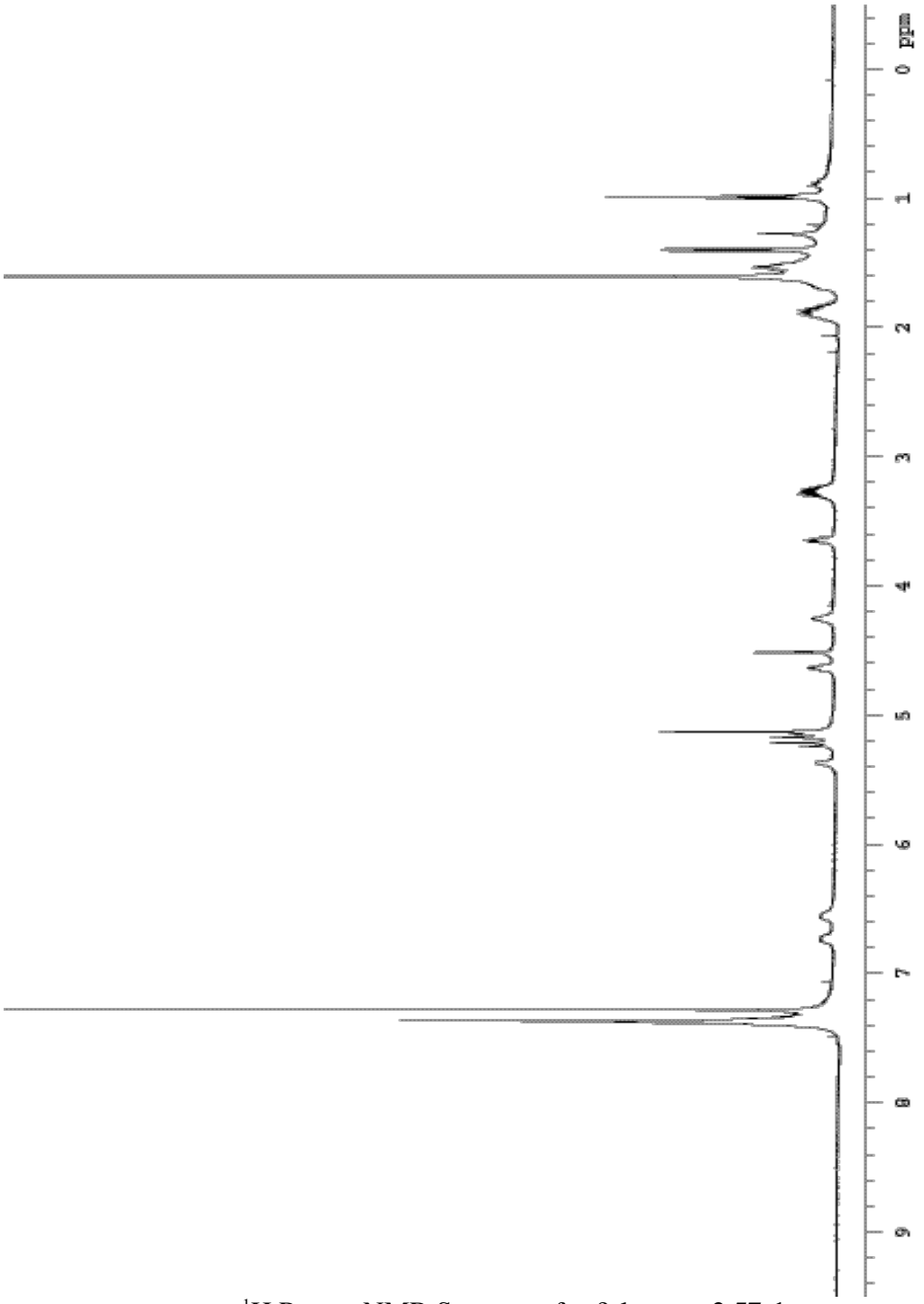
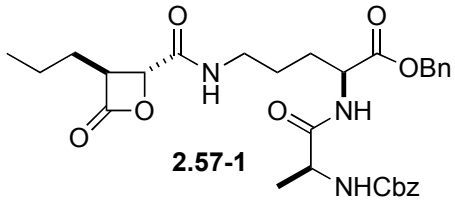
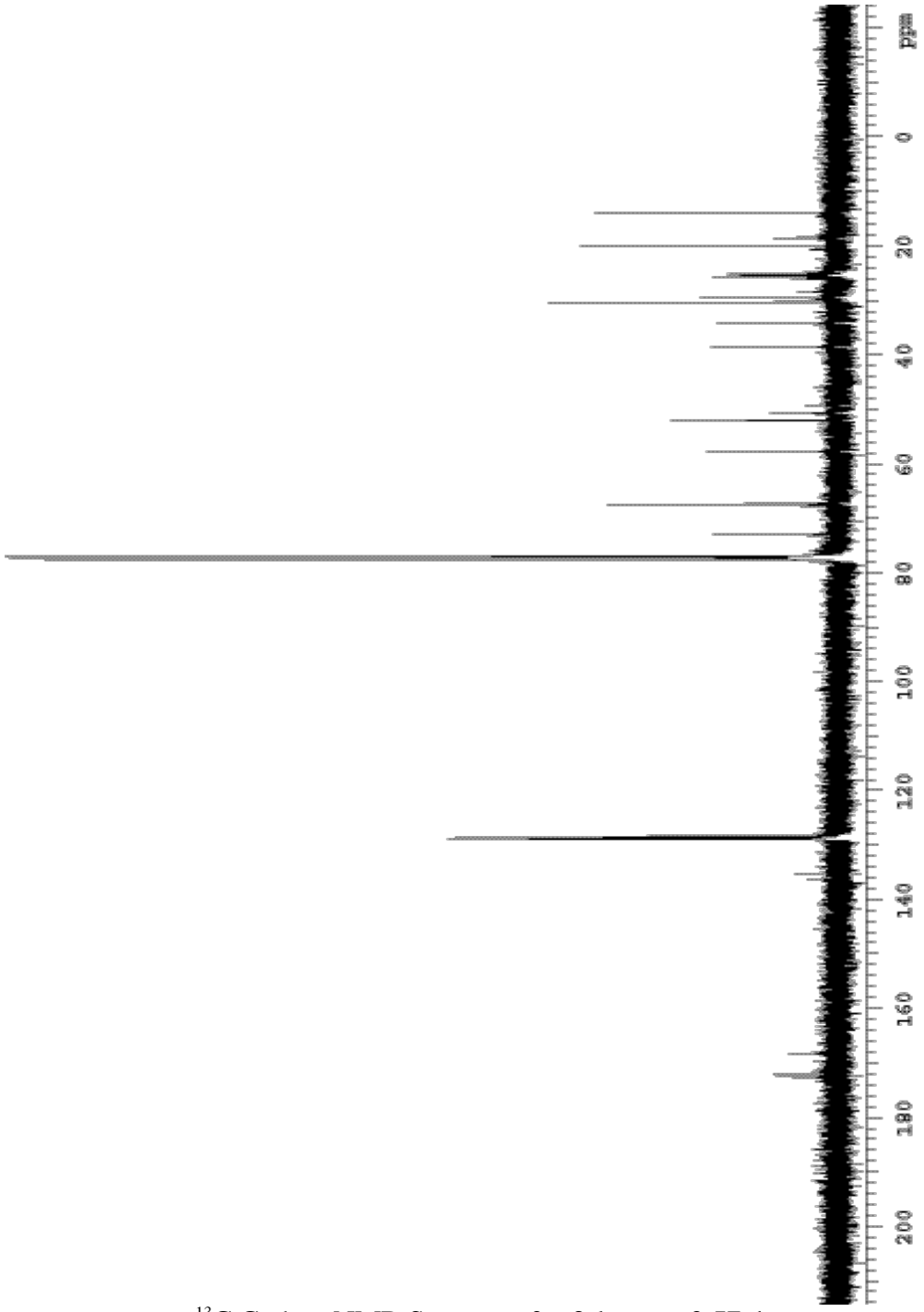


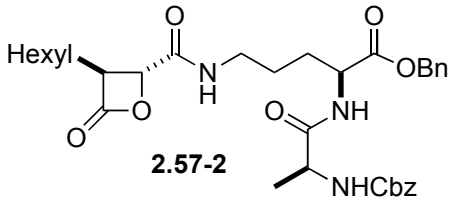
^{1}H Proton NMR Spectrum for β-lactone **2.57-1**



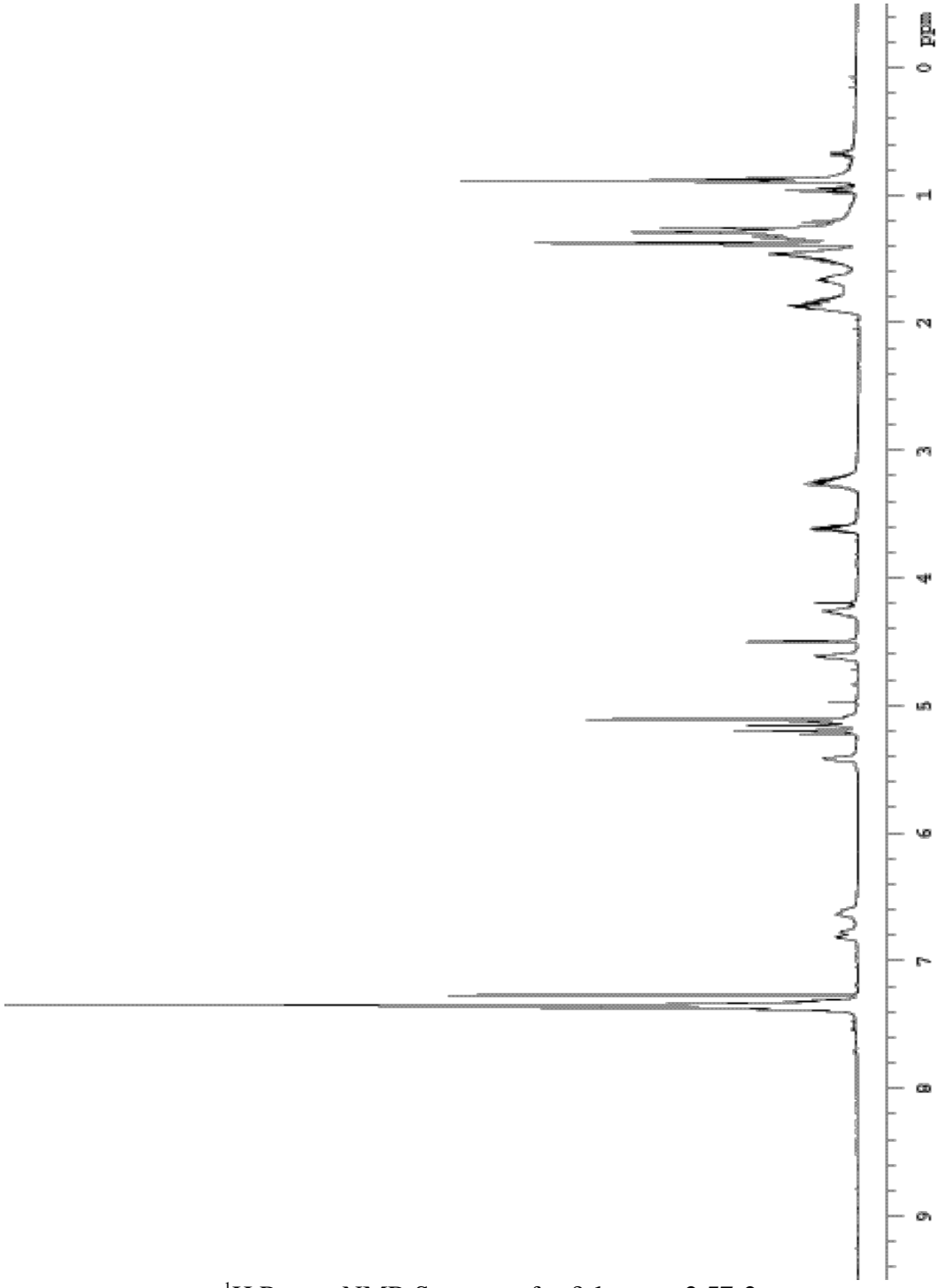
2.57-1



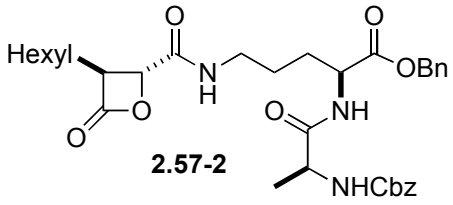
^{13}C Carbon NMR Spectrum for β-lactone **2.57-1**



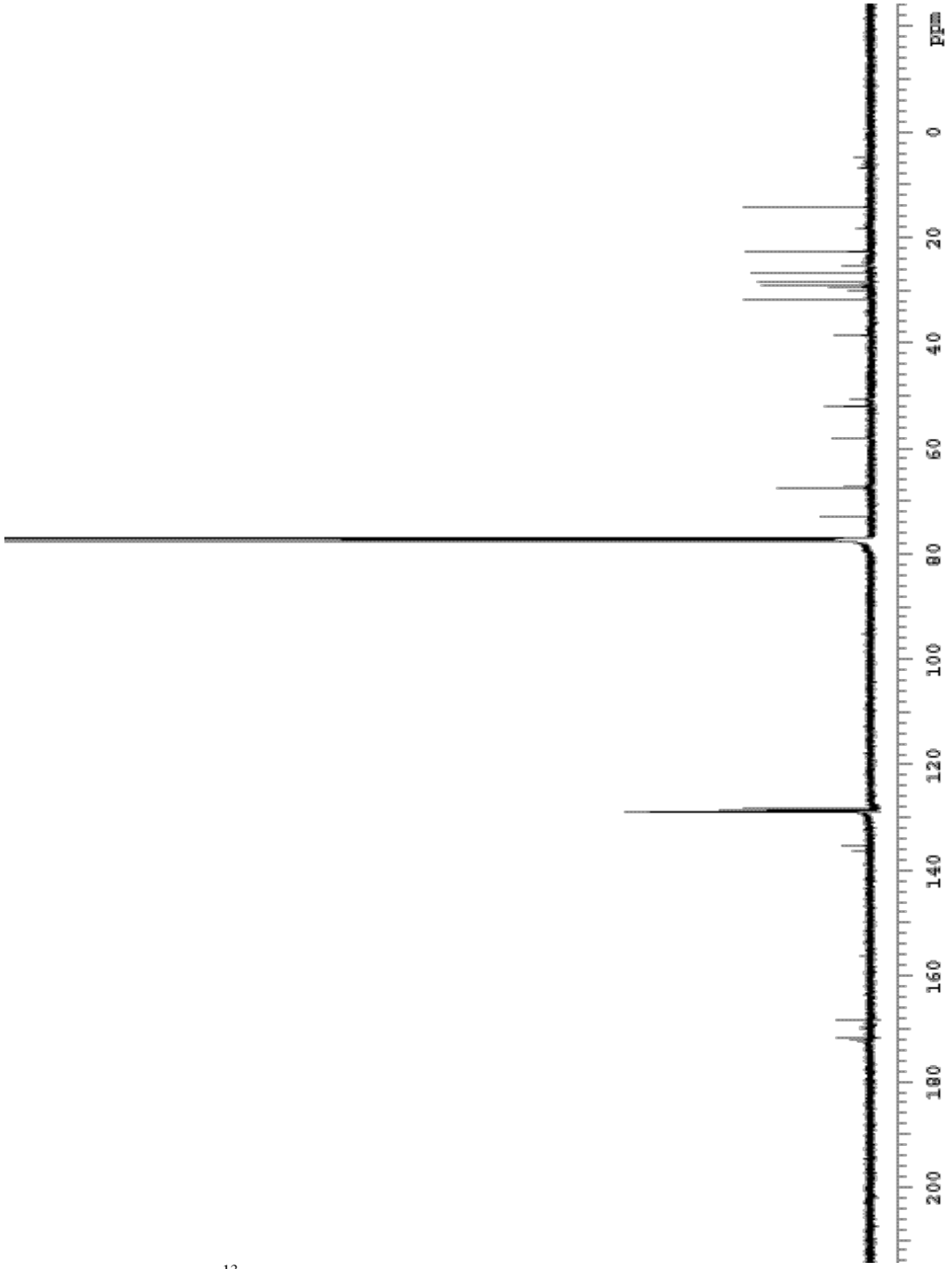
2.57-2



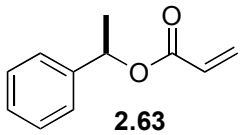
^{1}H Proton NMR Spectrum for β-lactone **2.57-2**



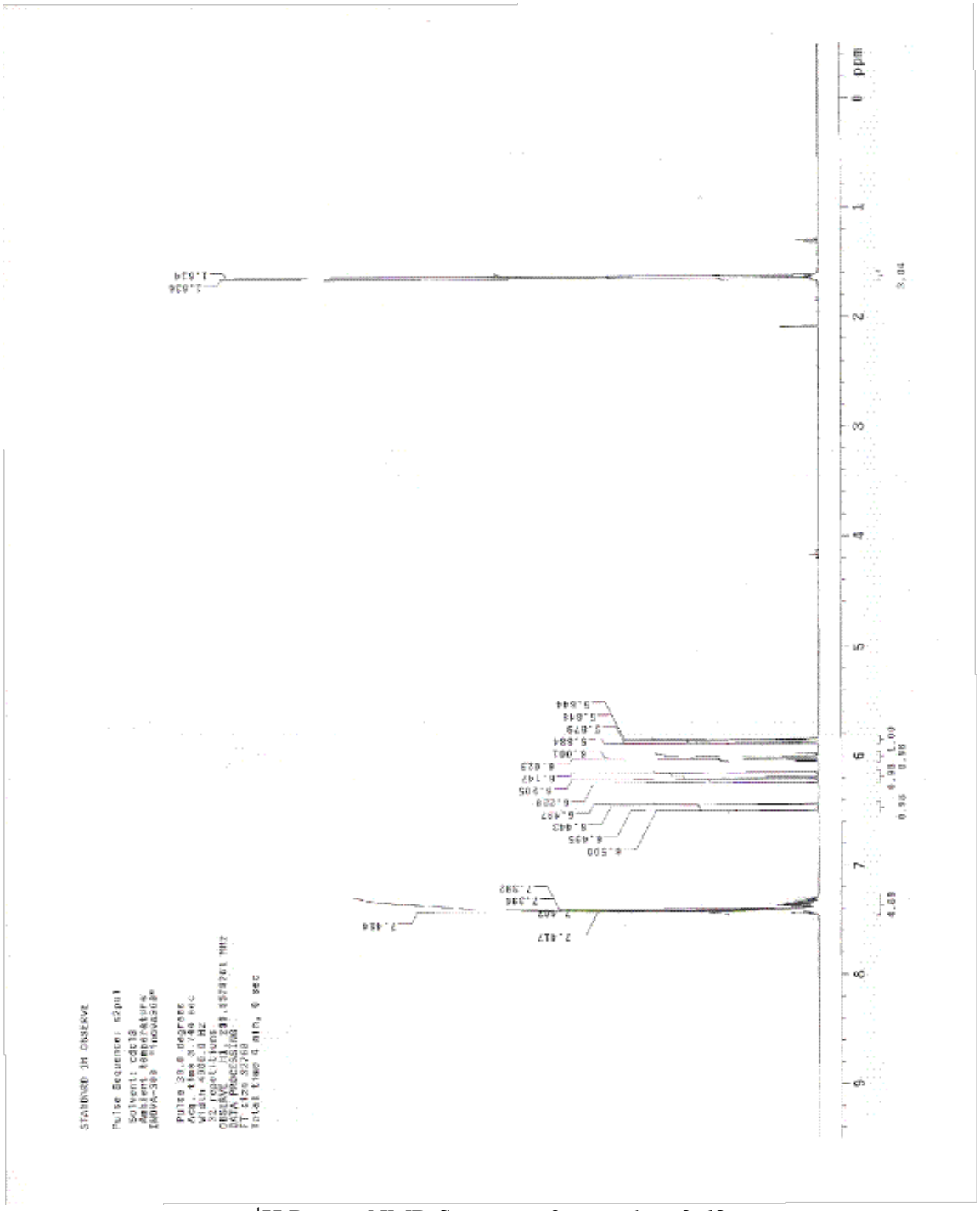
2.57-2



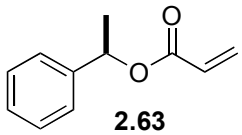
^{13}C Carbon NMR Spectrum for β-lactone **2.57-2**



2.63



^{1}H Proton NMR Spectrum for acrylate **2.63**



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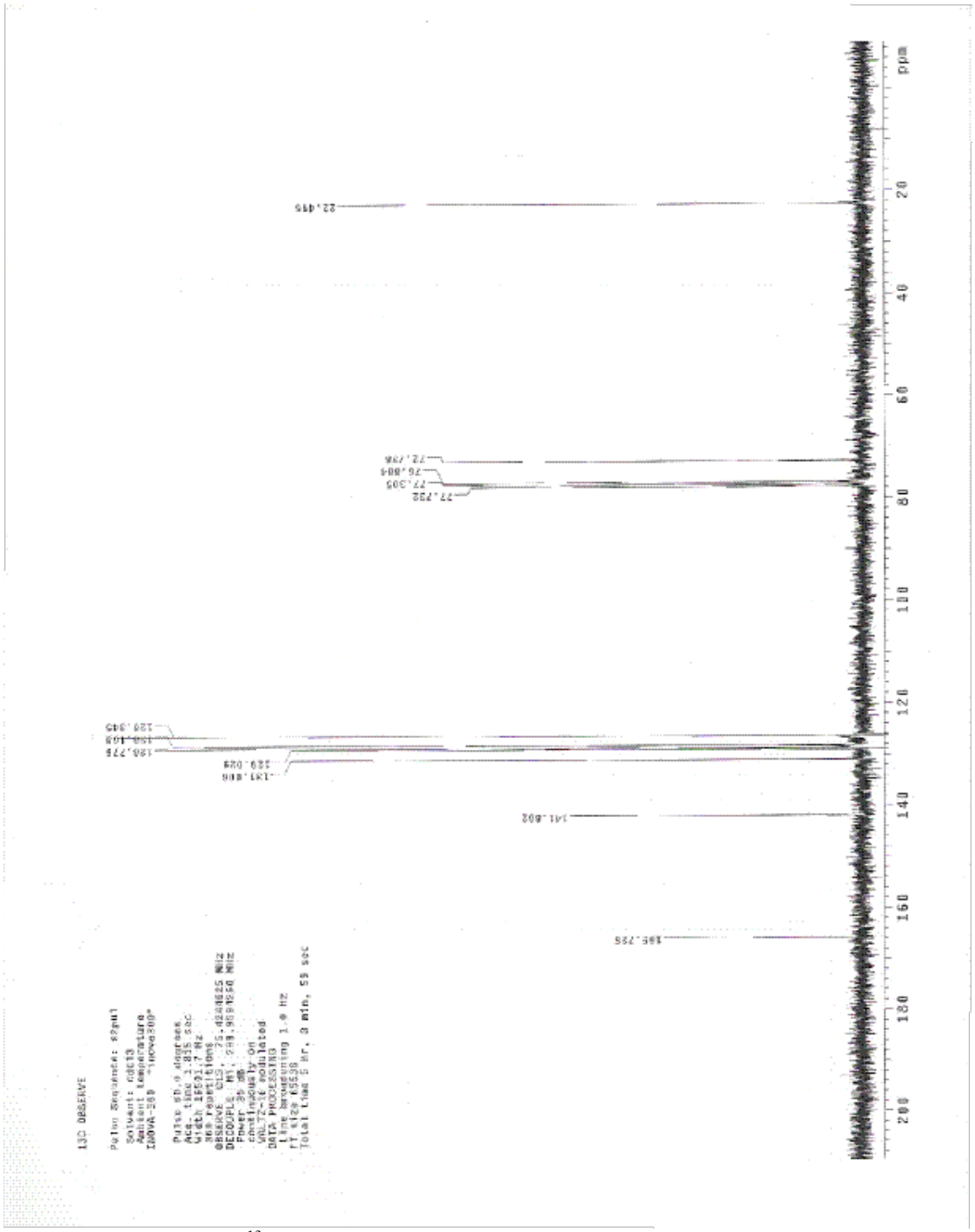
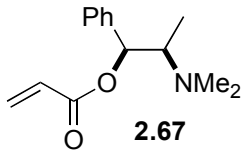


^{13}C Carbon NMR Spectrum for acrylate **2.63**



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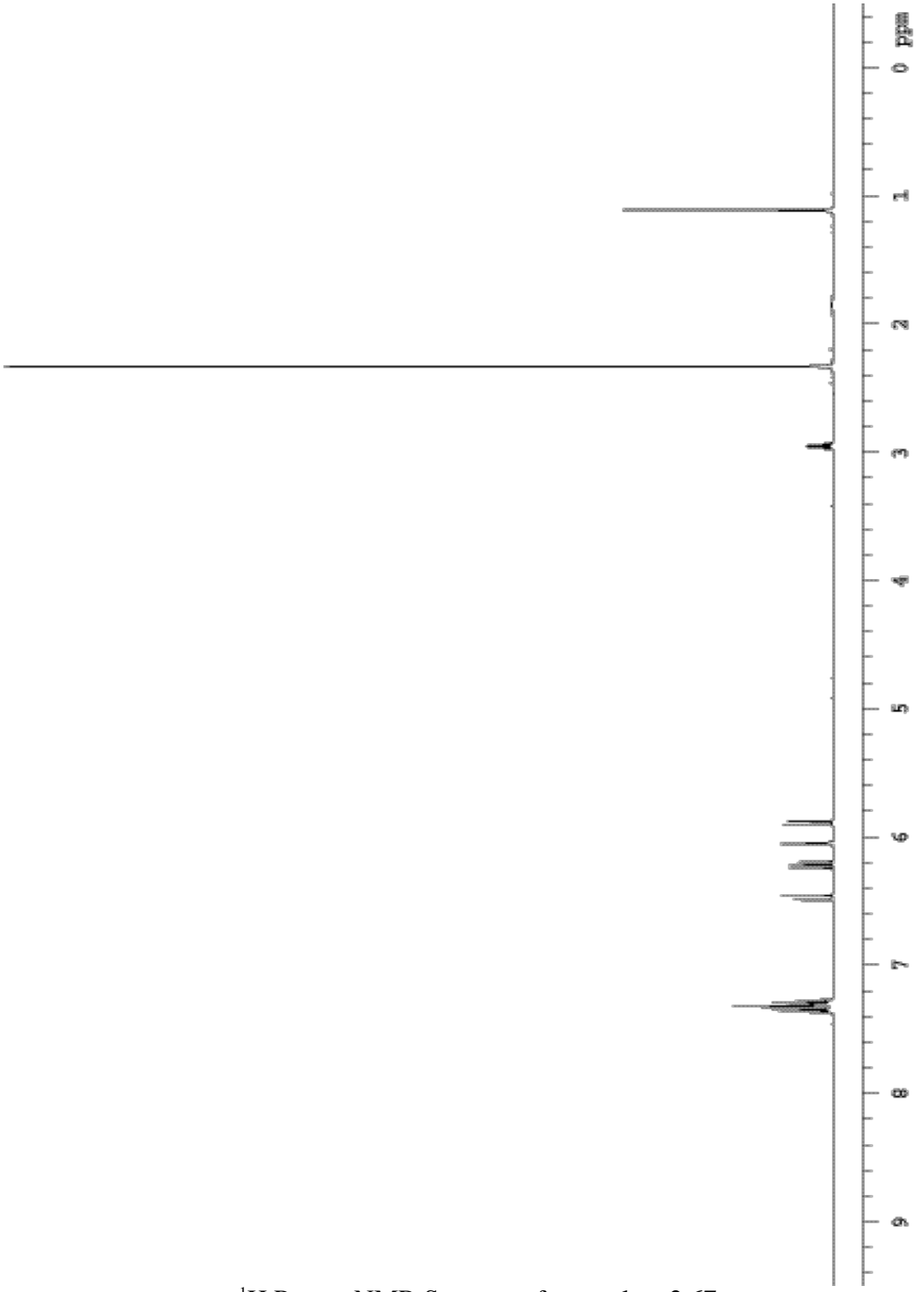
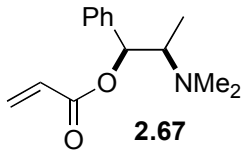


^{1}H Proton NMR Spectrum for acrylate **2.67**



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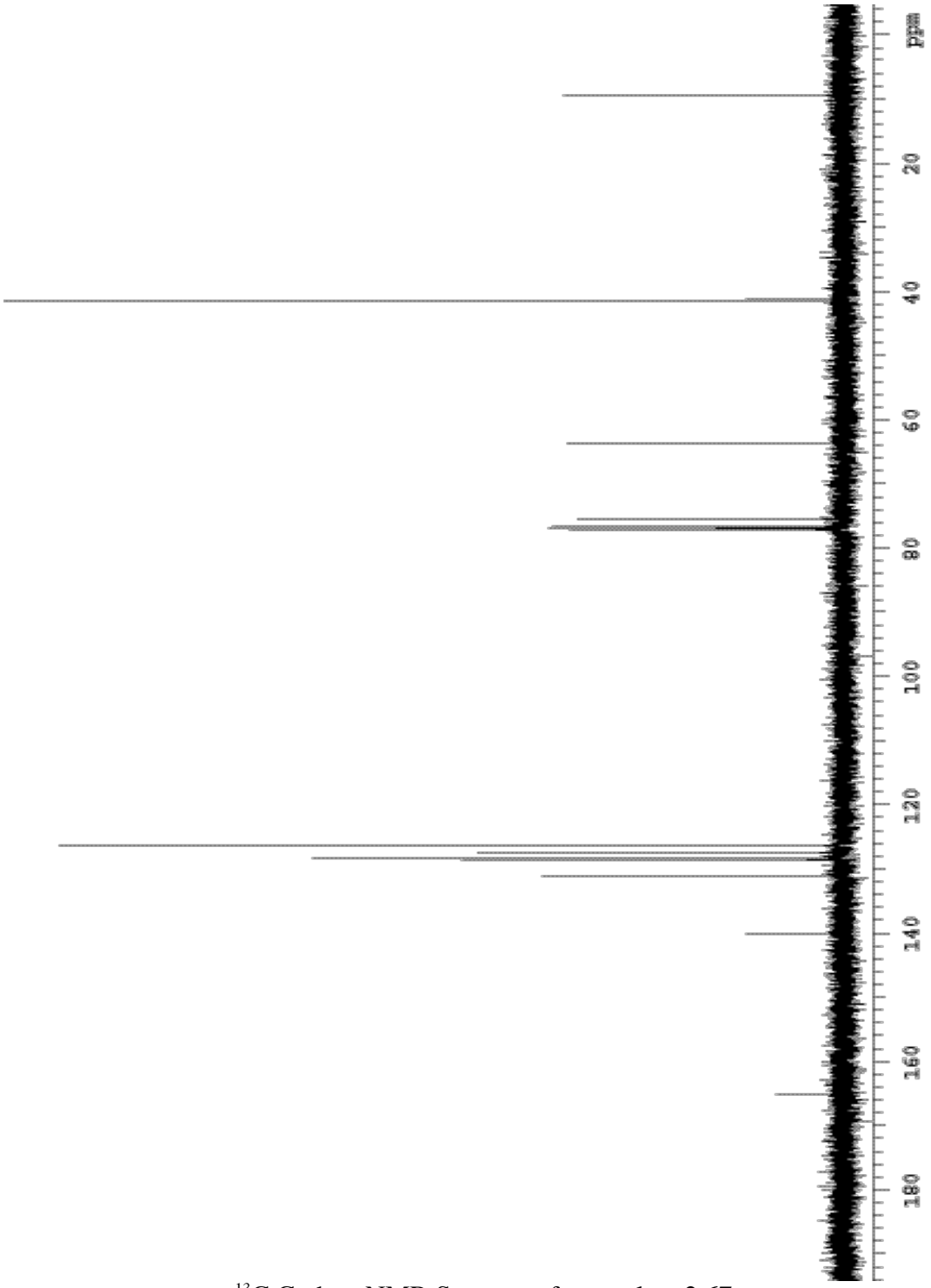
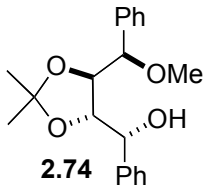
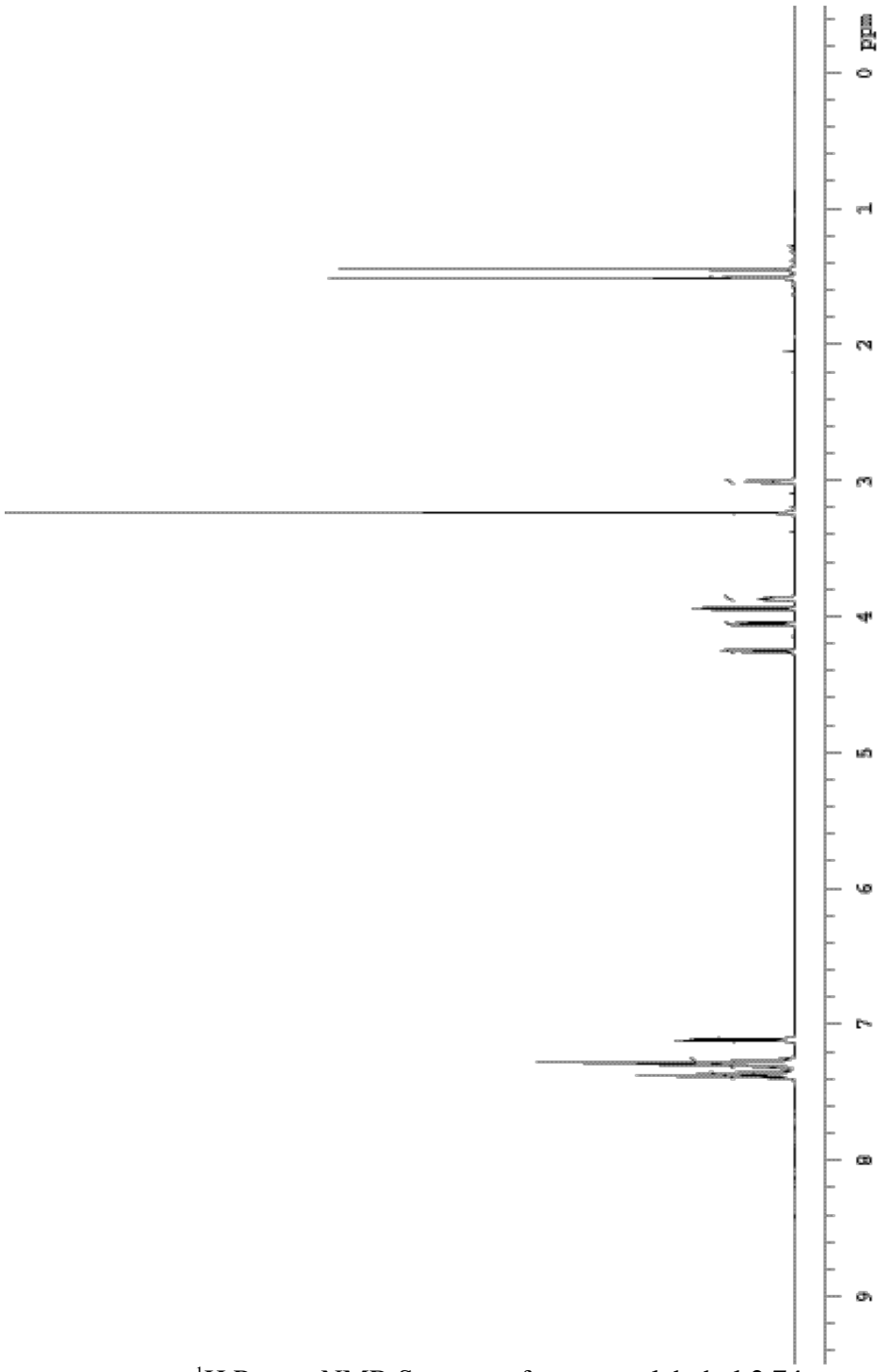


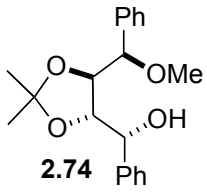
^{13}C Carbon NMR Spectrum for acrylate **2.67**



2.74



^{1}H Proton NMR Spectrum for mono alchohol **2.74**



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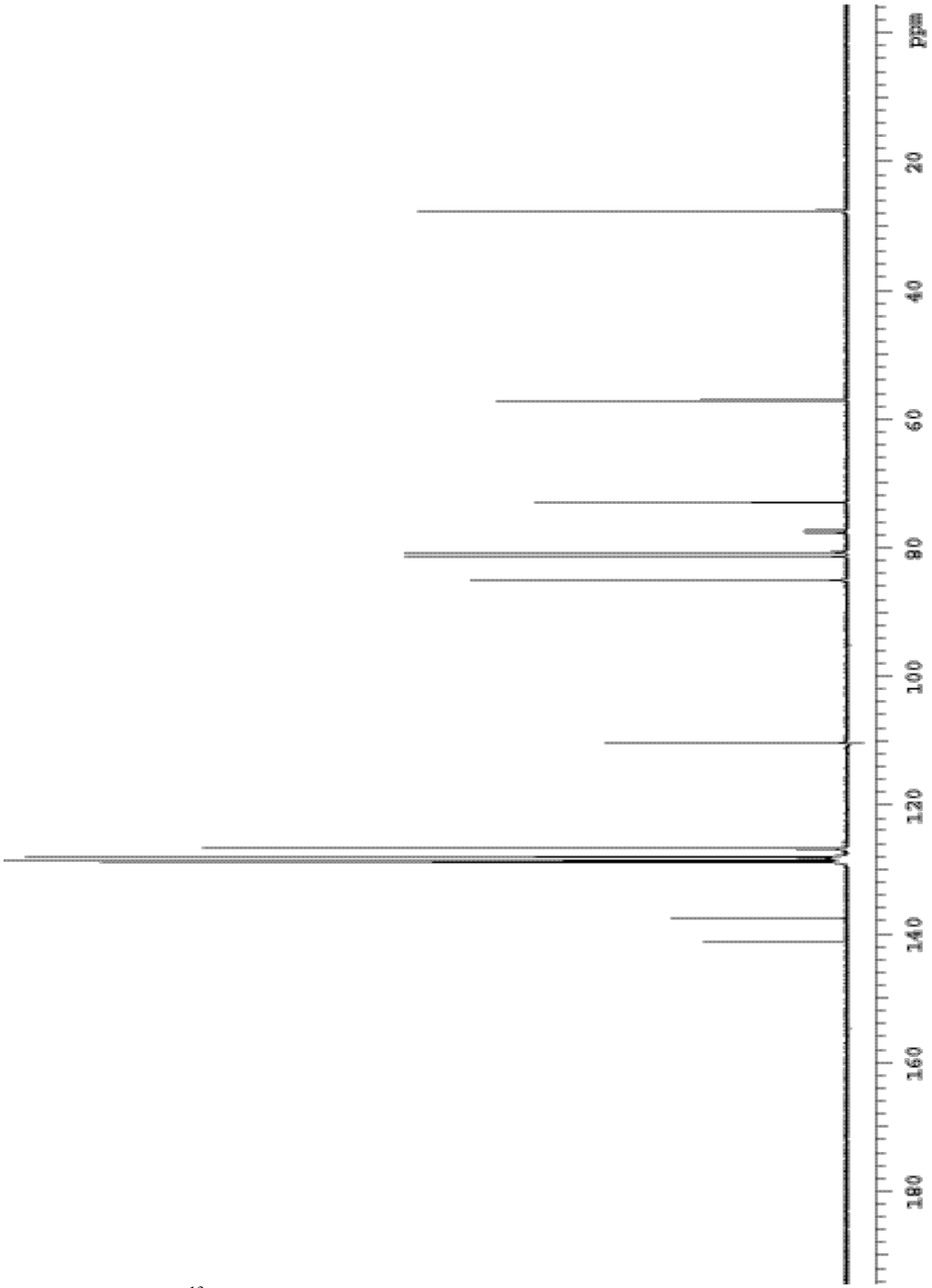
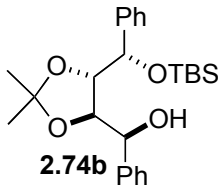
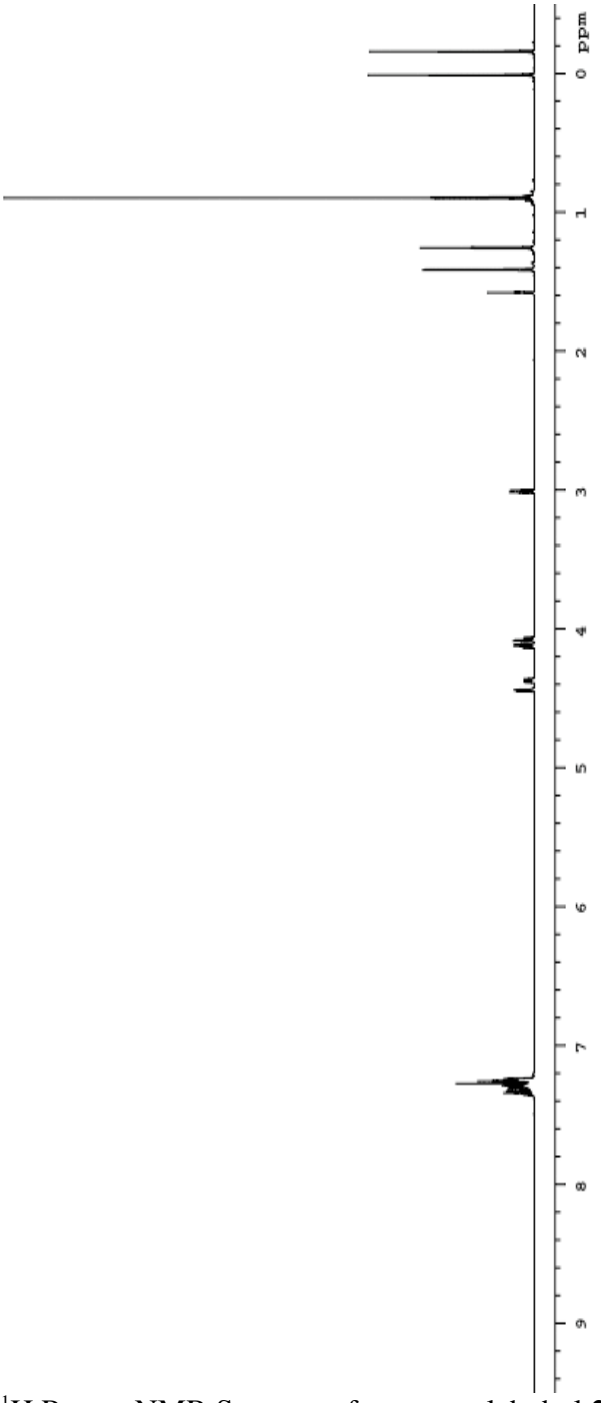


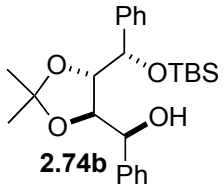
^{13}C Carbon NMR Spectrum for mono alchohol **2.74**



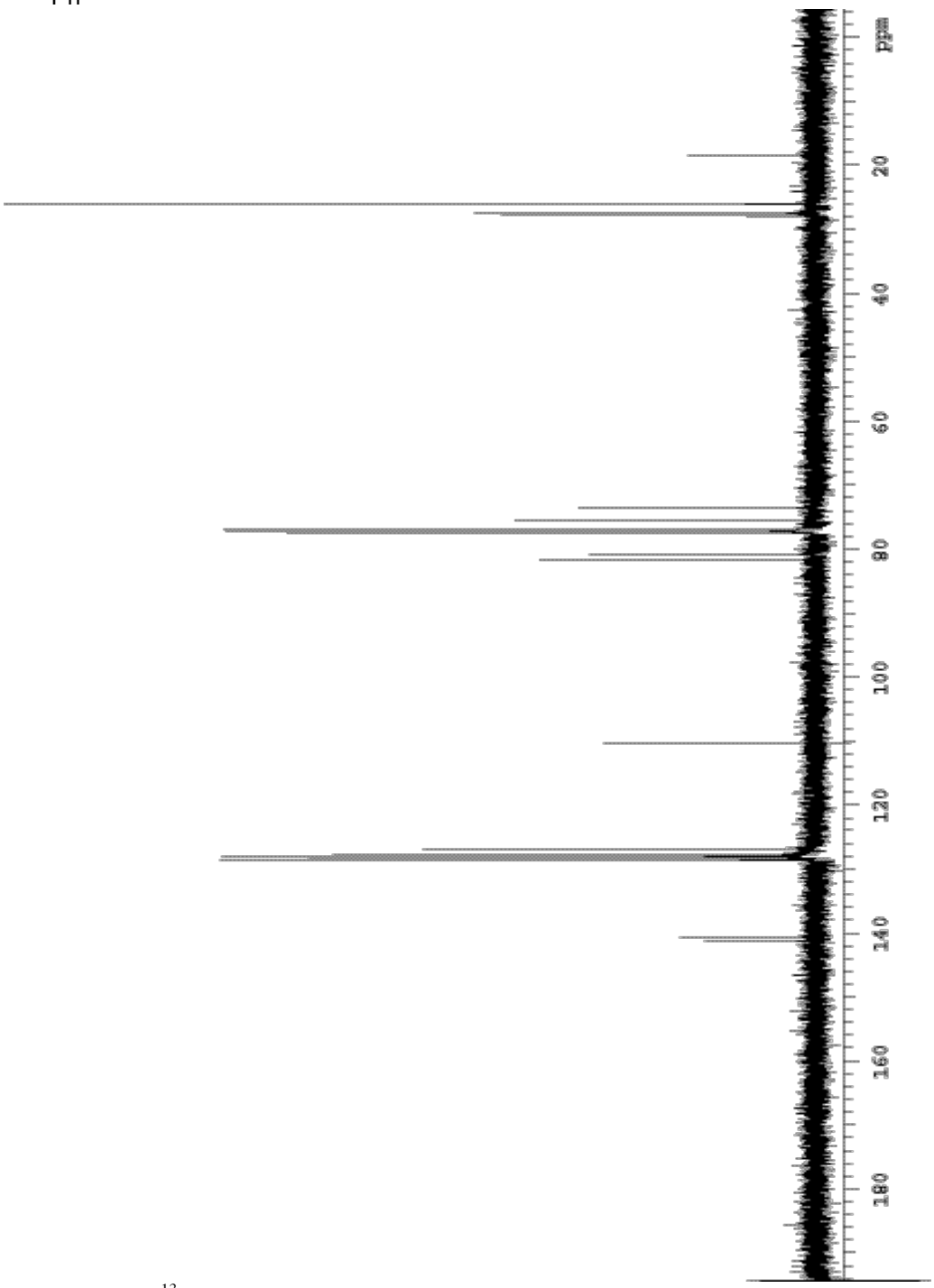
2.74b



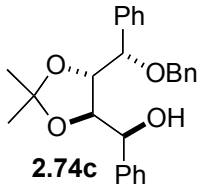
^{1}H Proton NMR Spectrum for mono alchohol **2.74b**



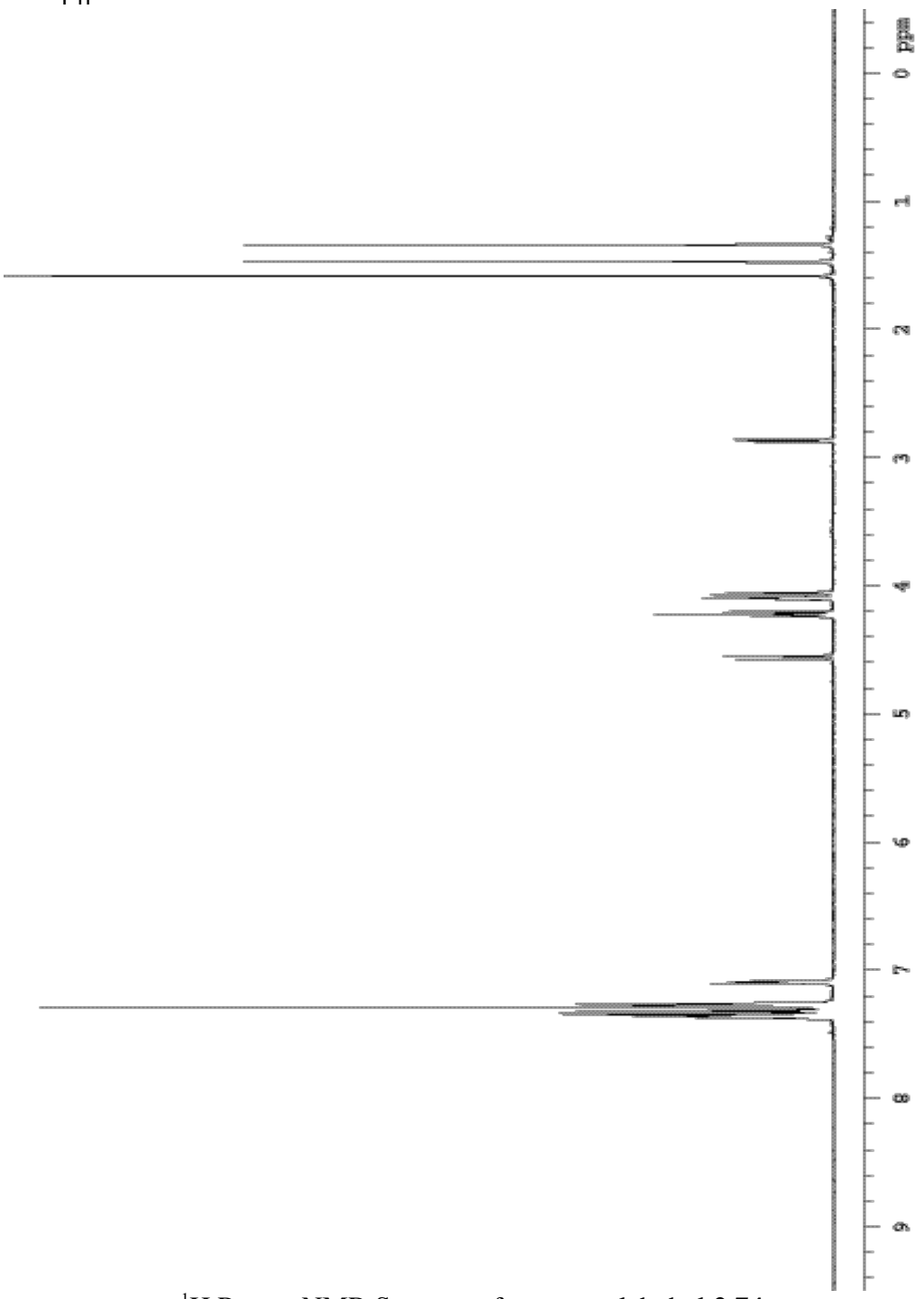
2.74b



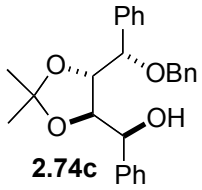
^{13}C Carbon NMR Spectrum for mono alchohol **2.74b**



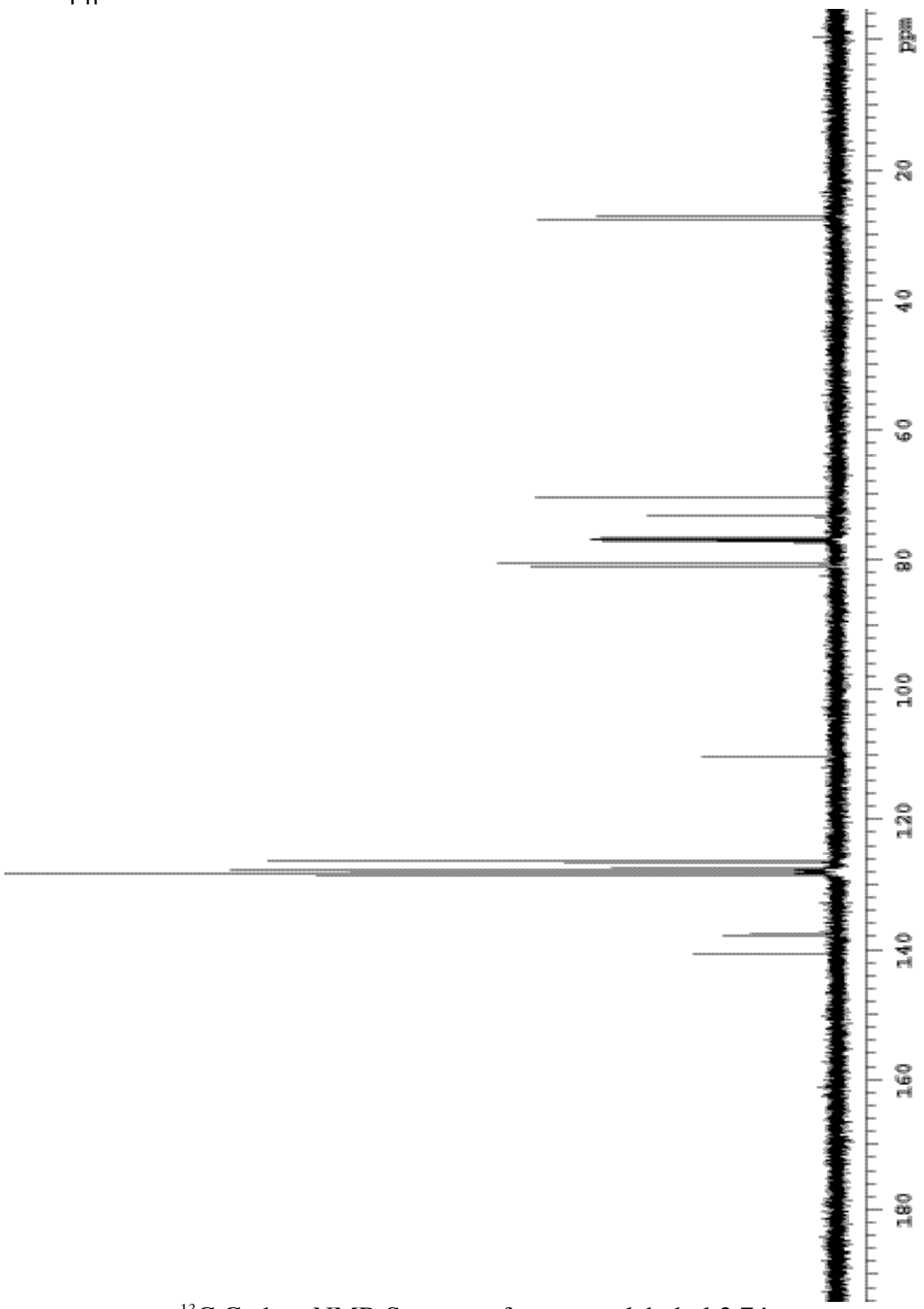
2.74c



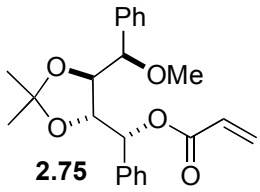
^{1}H Proton NMR Spectrum for mono alchohol **2.74c**



2.74c



^{13}C Carbon NMR Spectrum for mono alchohol **2.74c**



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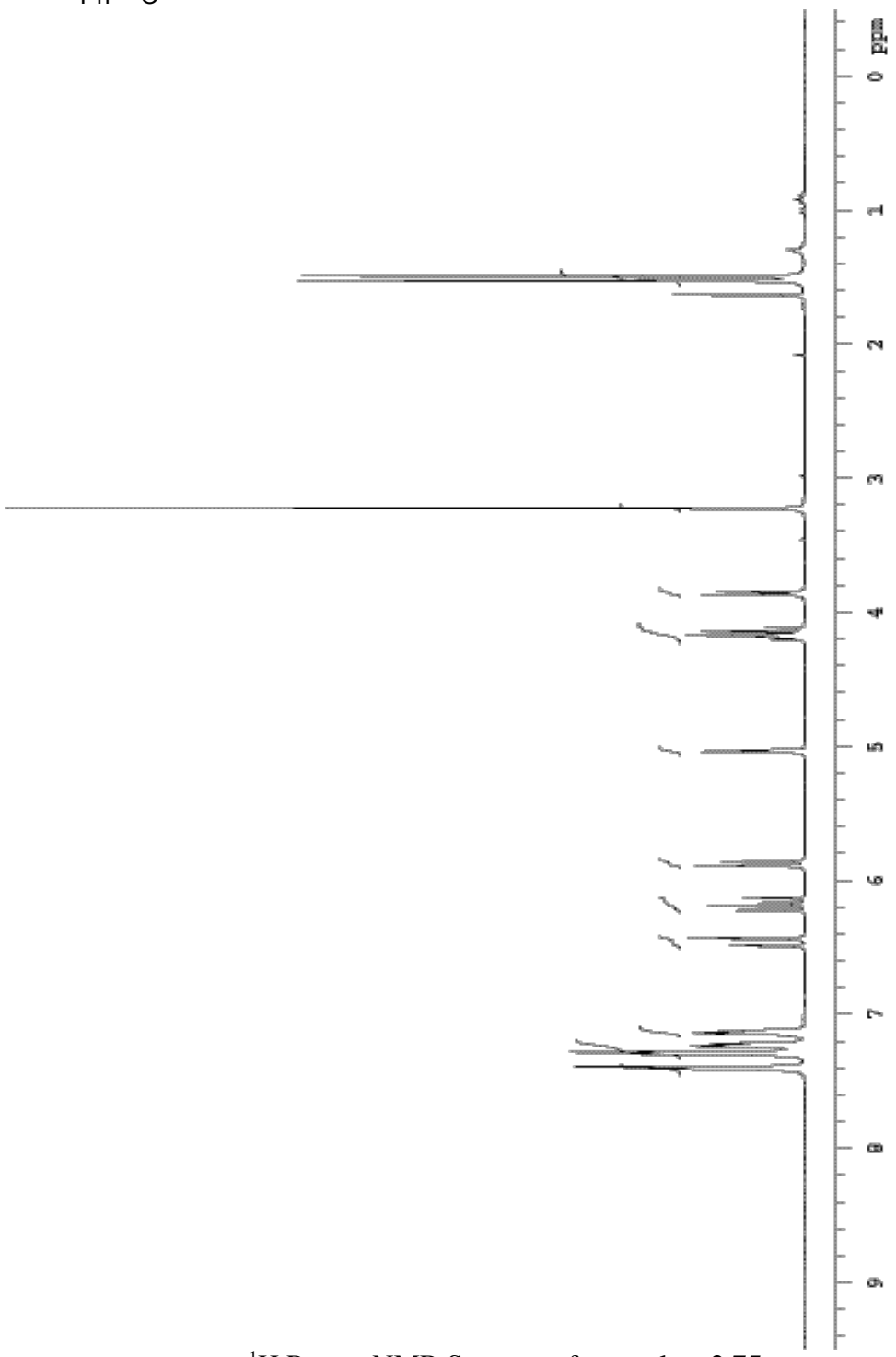
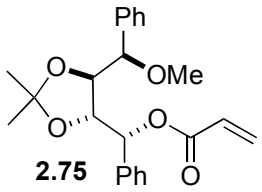


^{1}H Proton NMR Spectrum for acrylate **2.75**



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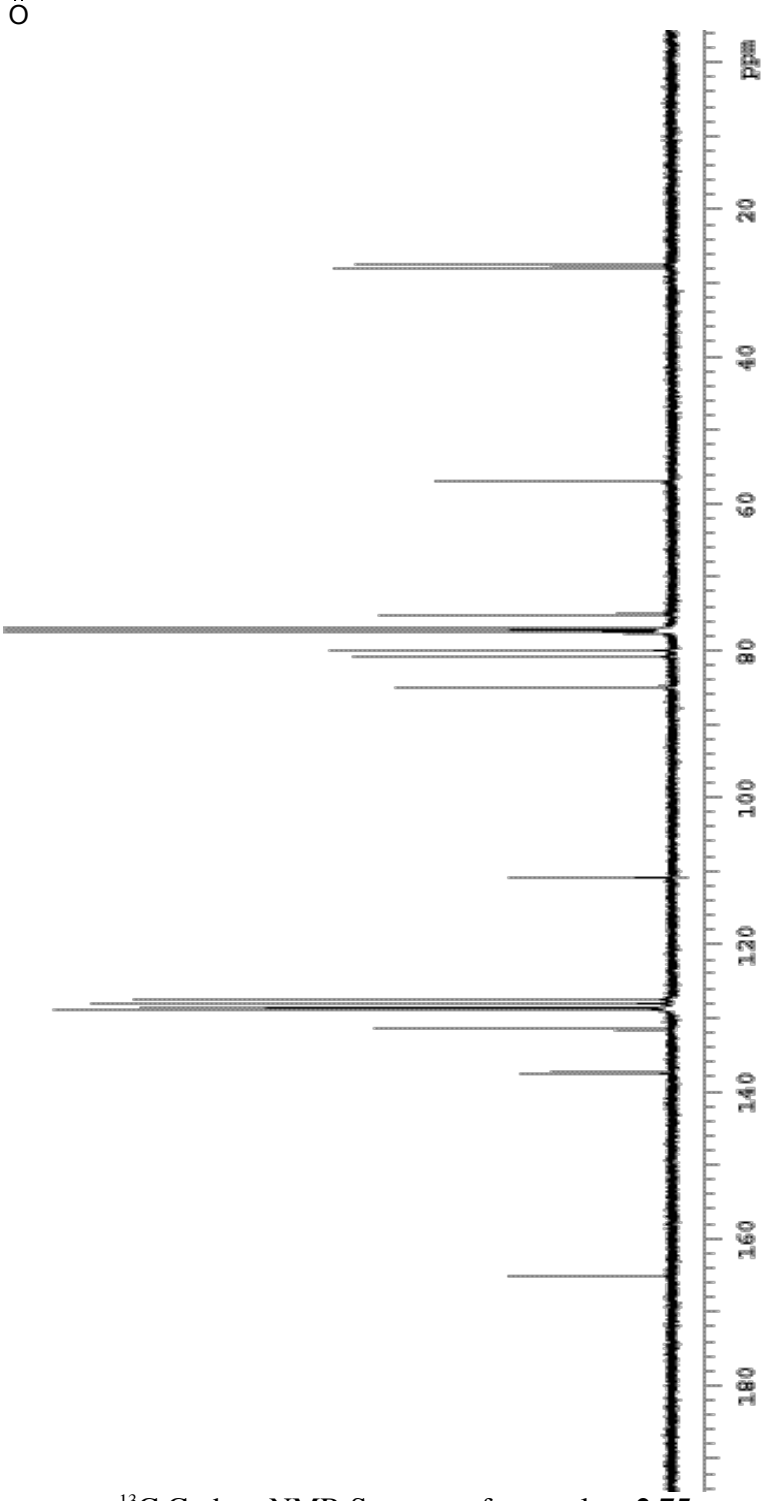
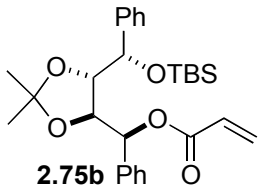
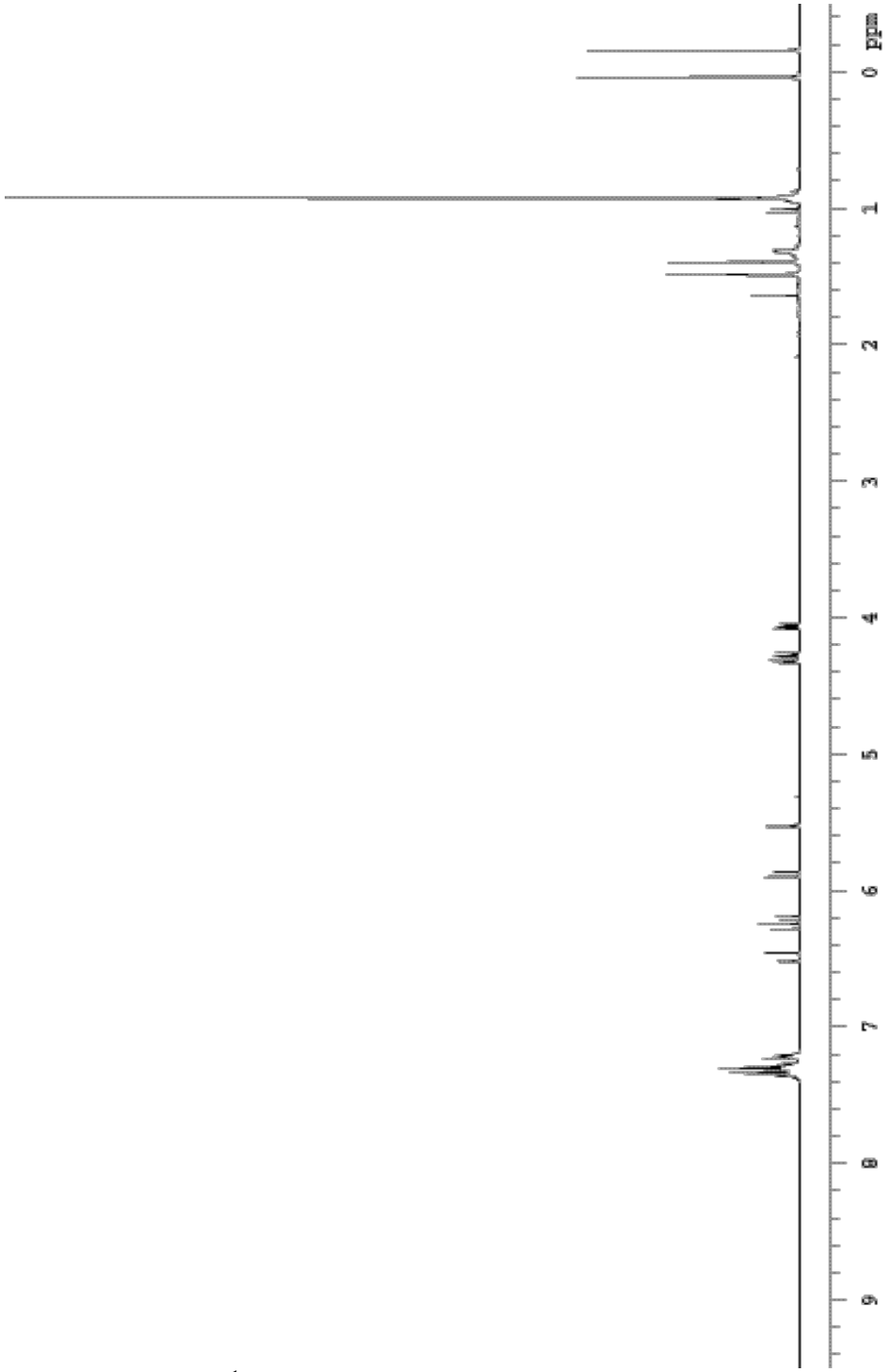


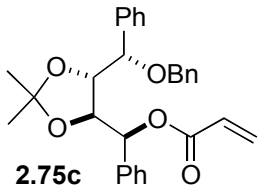
^{13}C Carbon NMR Spectrum for acrylate **2.75**



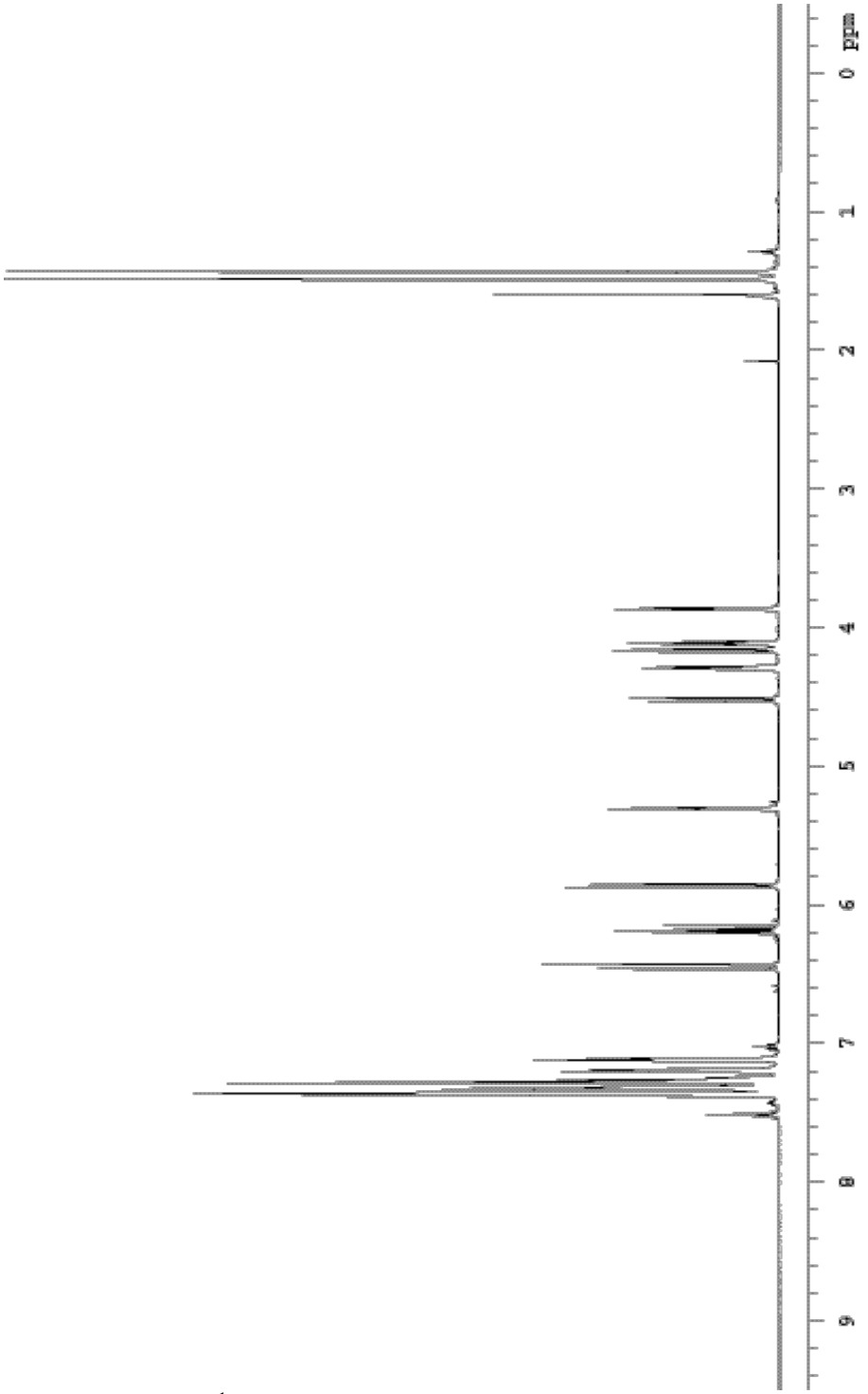
2.75b



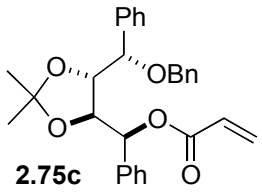
^{1}H Proton NMR Spectrum for acrylate **2.75b**



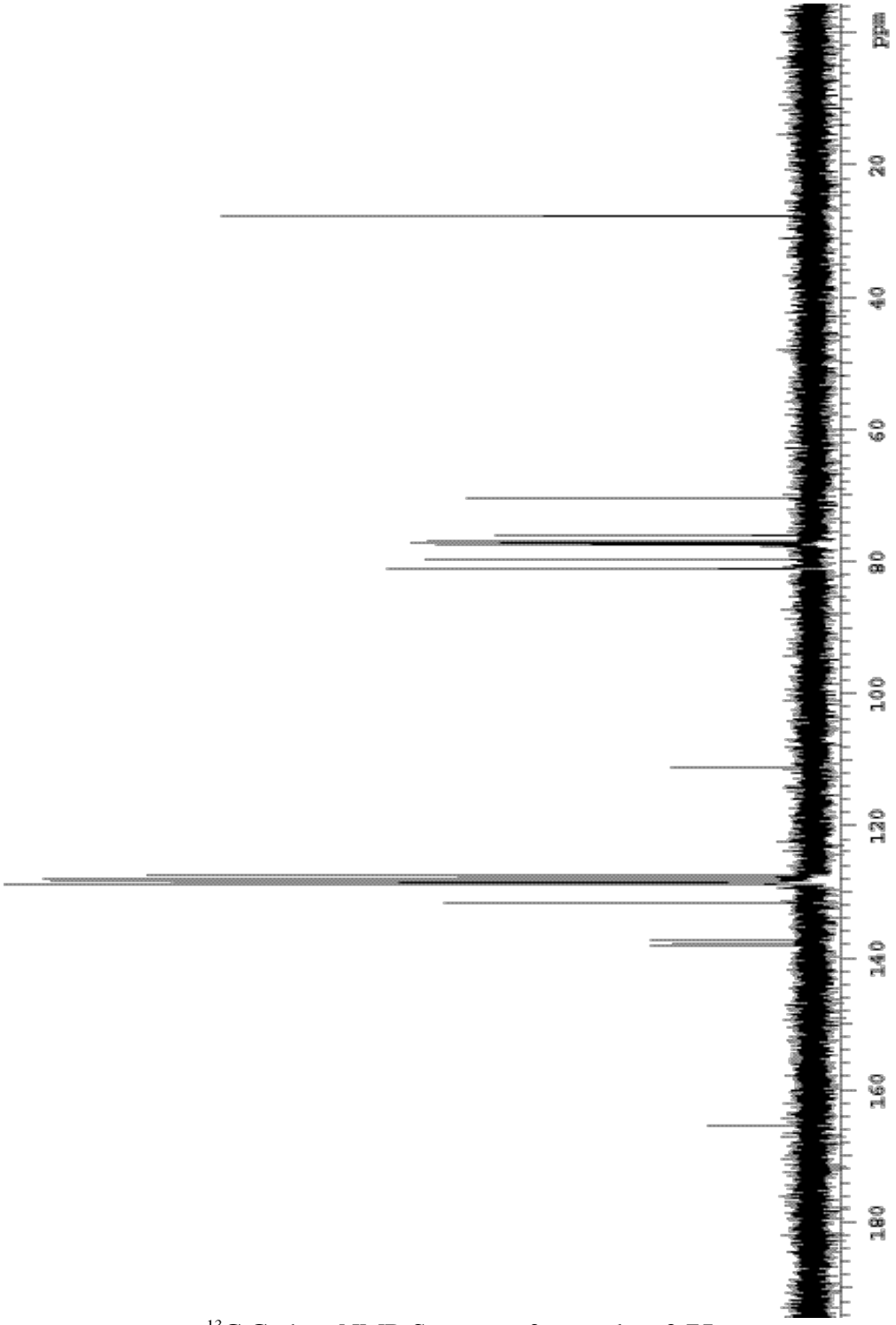
2.75c



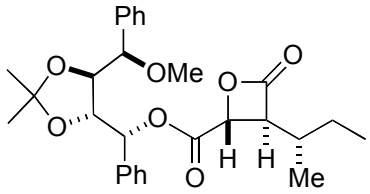
^{1}H Proton NMR Spectrum for acrylate **2.75c**



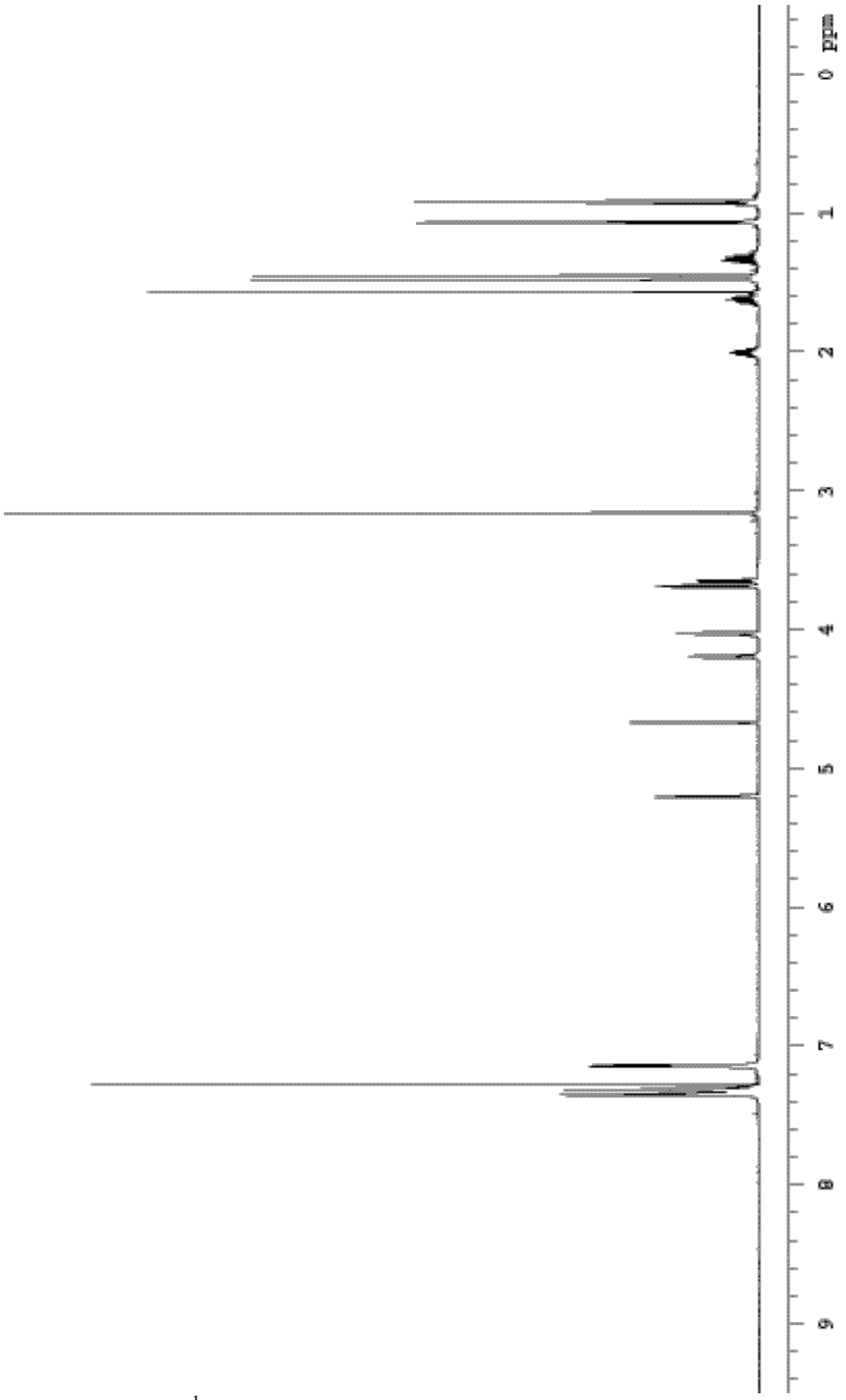
2.75c



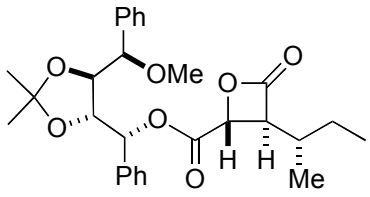
^{13}C Carbon NMR Spectrum for acrylate **2.75c**



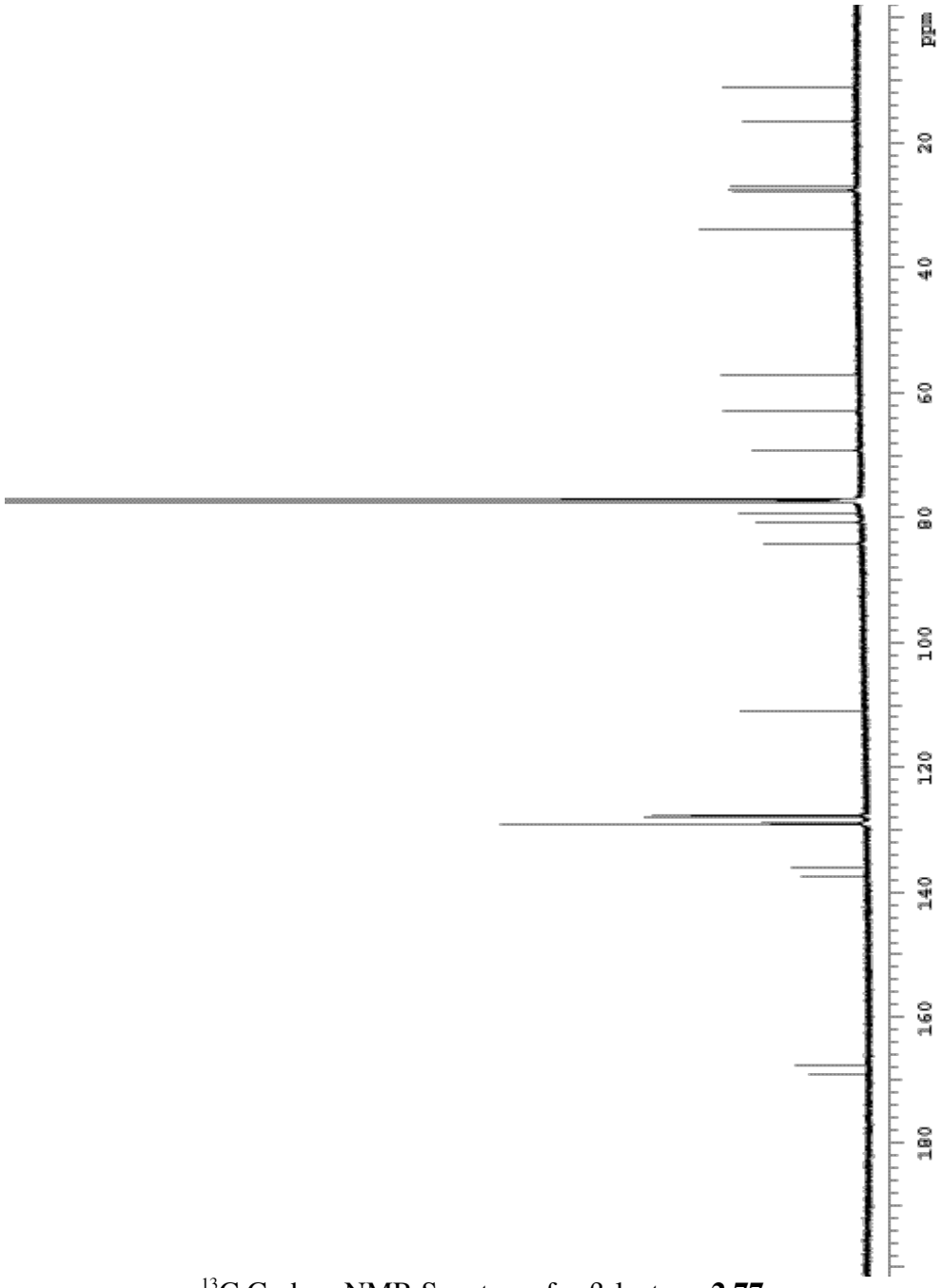
2.77a



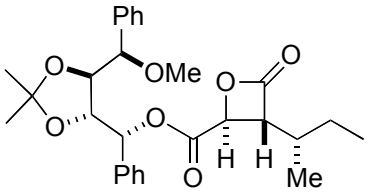
^{1}H Proton NMR Spectrum for β-lactone **2.77a**



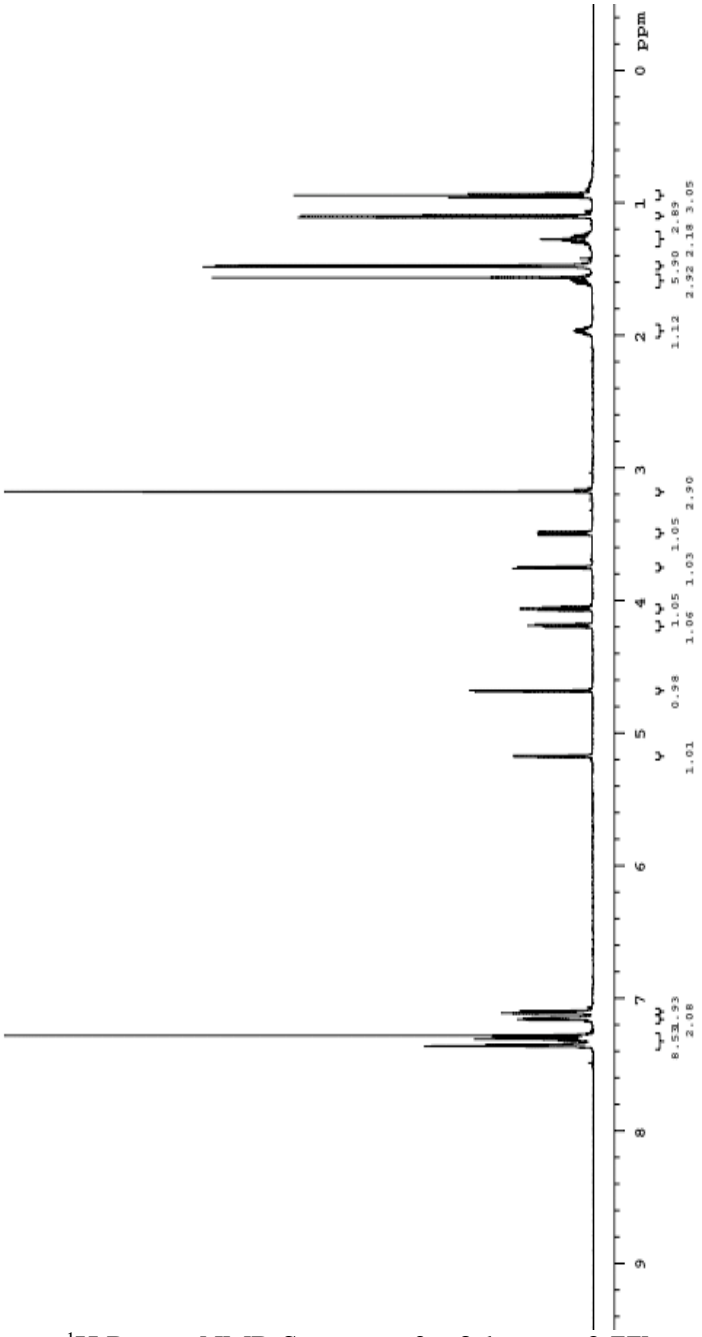
2.77a



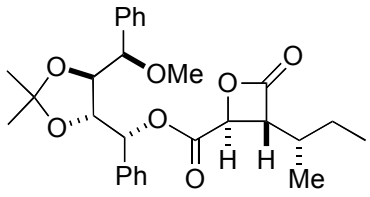
^{13}C Carbon NMR Spectrum for β-lactone **2.77a**



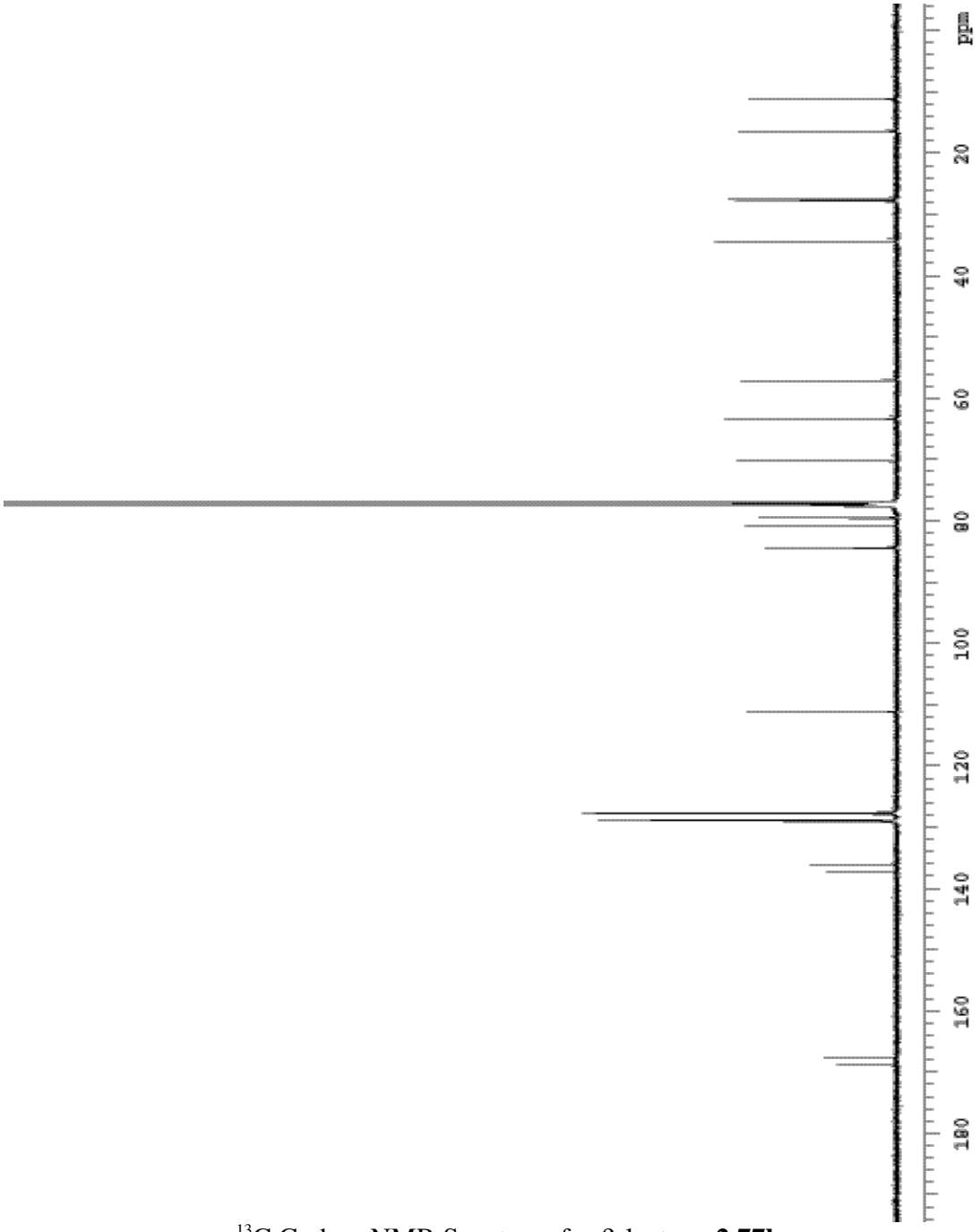
2.77b



^{1}H Proton NMR Spectrum for β-lactone **2.77b**

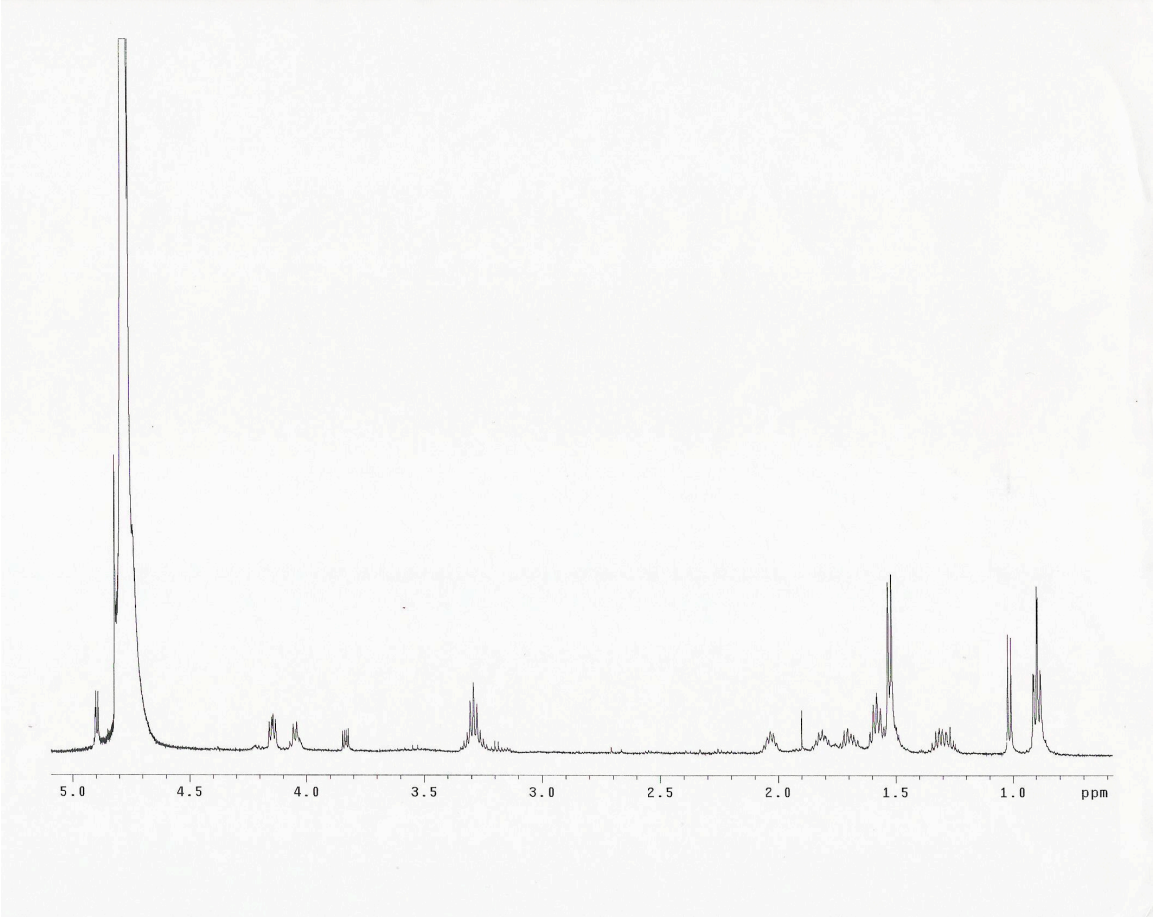


2.77b

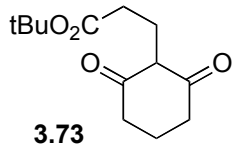


^{13}C Carbon NMR Spectrum for β-lactone **2.77b**

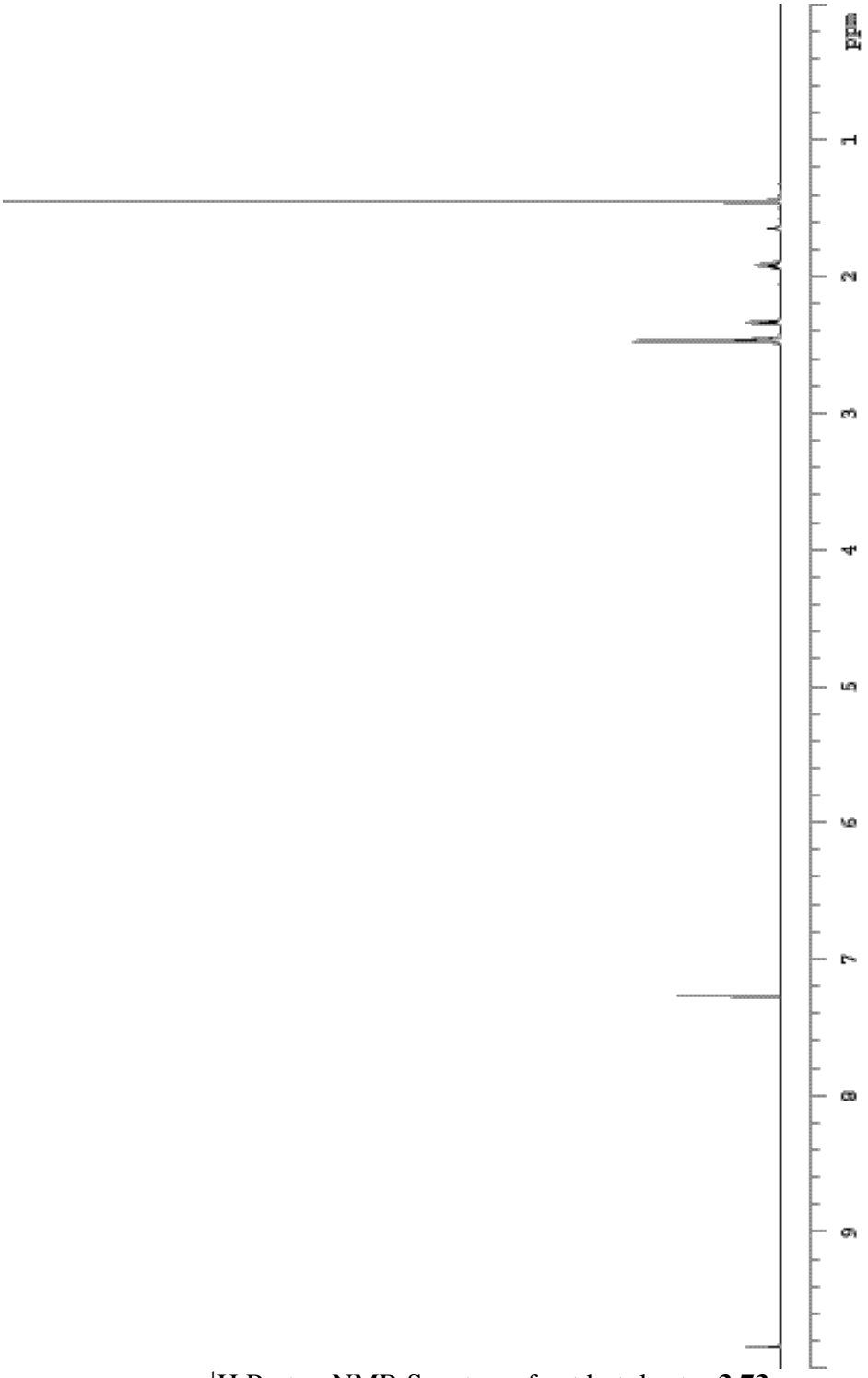
Belactosin C



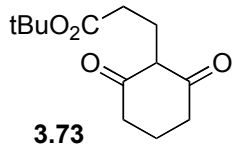
^{1}H Proton NMR Spectrum for Belactosin C



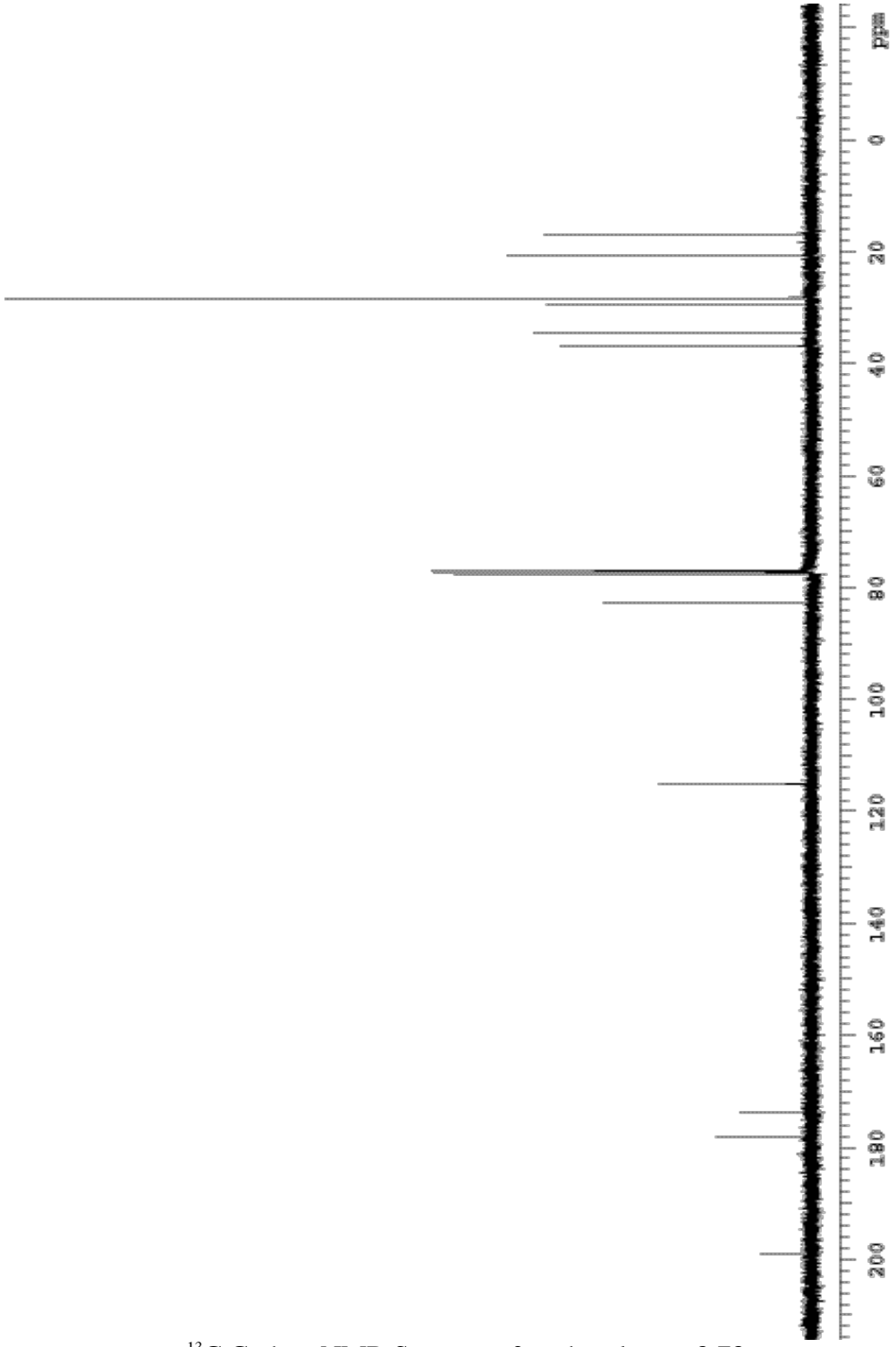
3.73



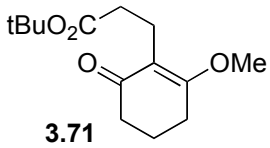
^{1}H Proton NMR Spectrum for *t*-butyl ester **3.73**



3.73



^{13}C Carbon NMR Spectrum for *t*-butyl ester **3.73**



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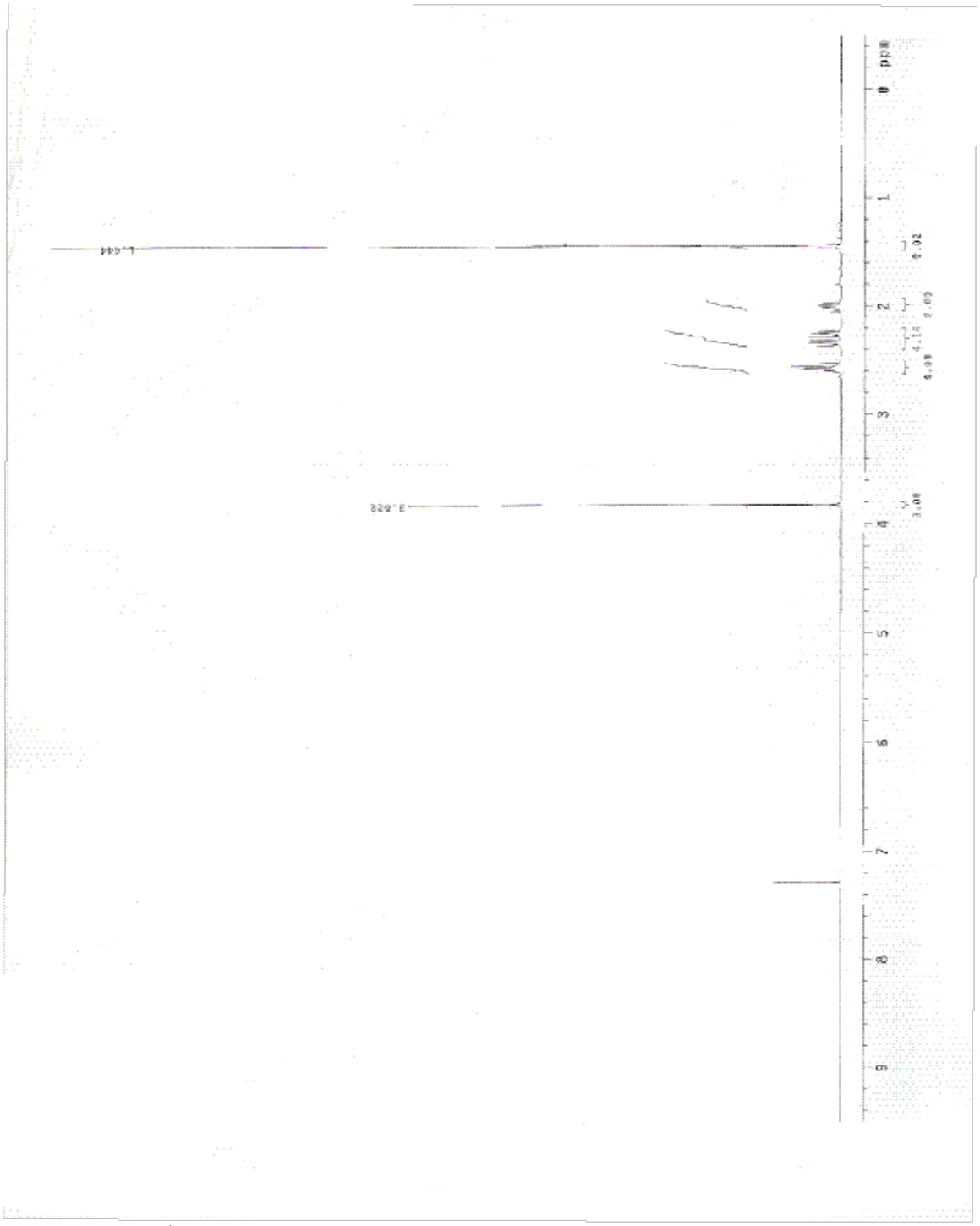
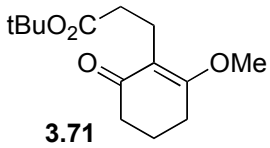
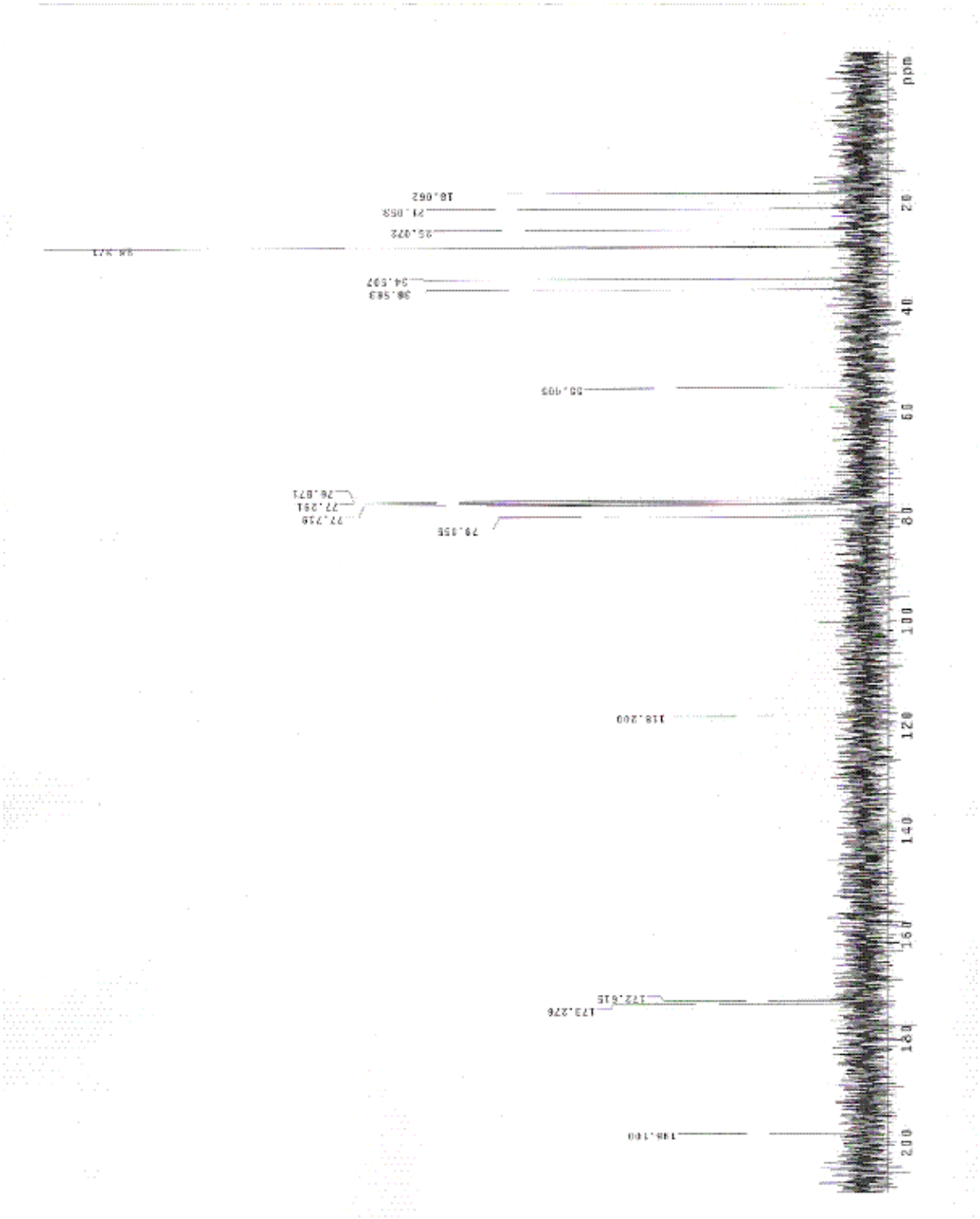


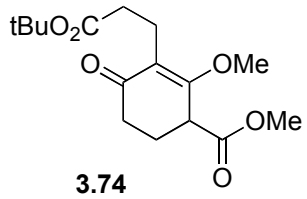
^{1}H Proton NMR Spectrum for vinylogous methyl ether **3.71**



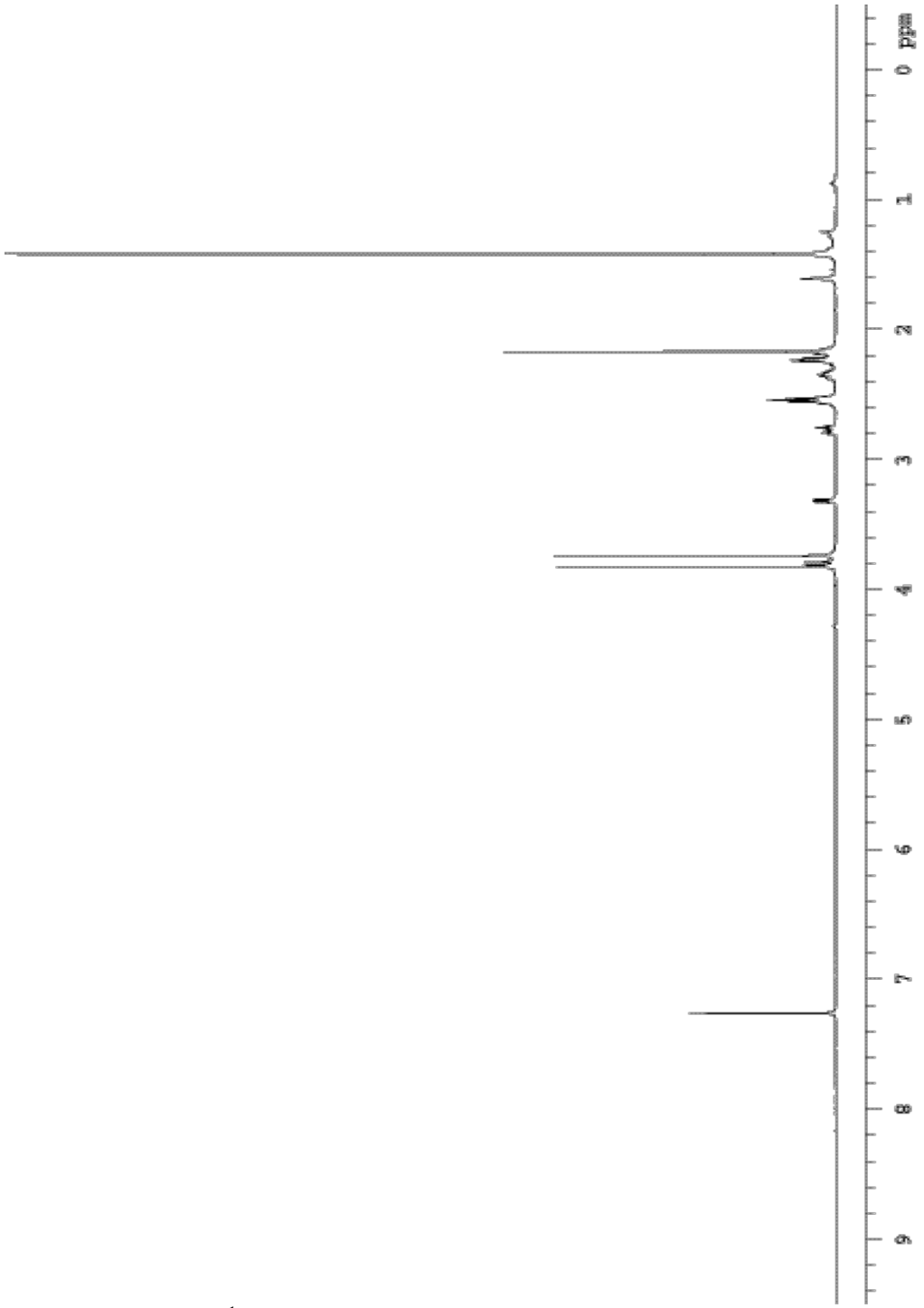
3.71



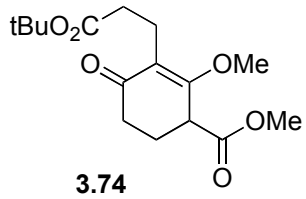
^{13}C Carbon NMR Spectrum for vinylogous methyl ether **3.71**



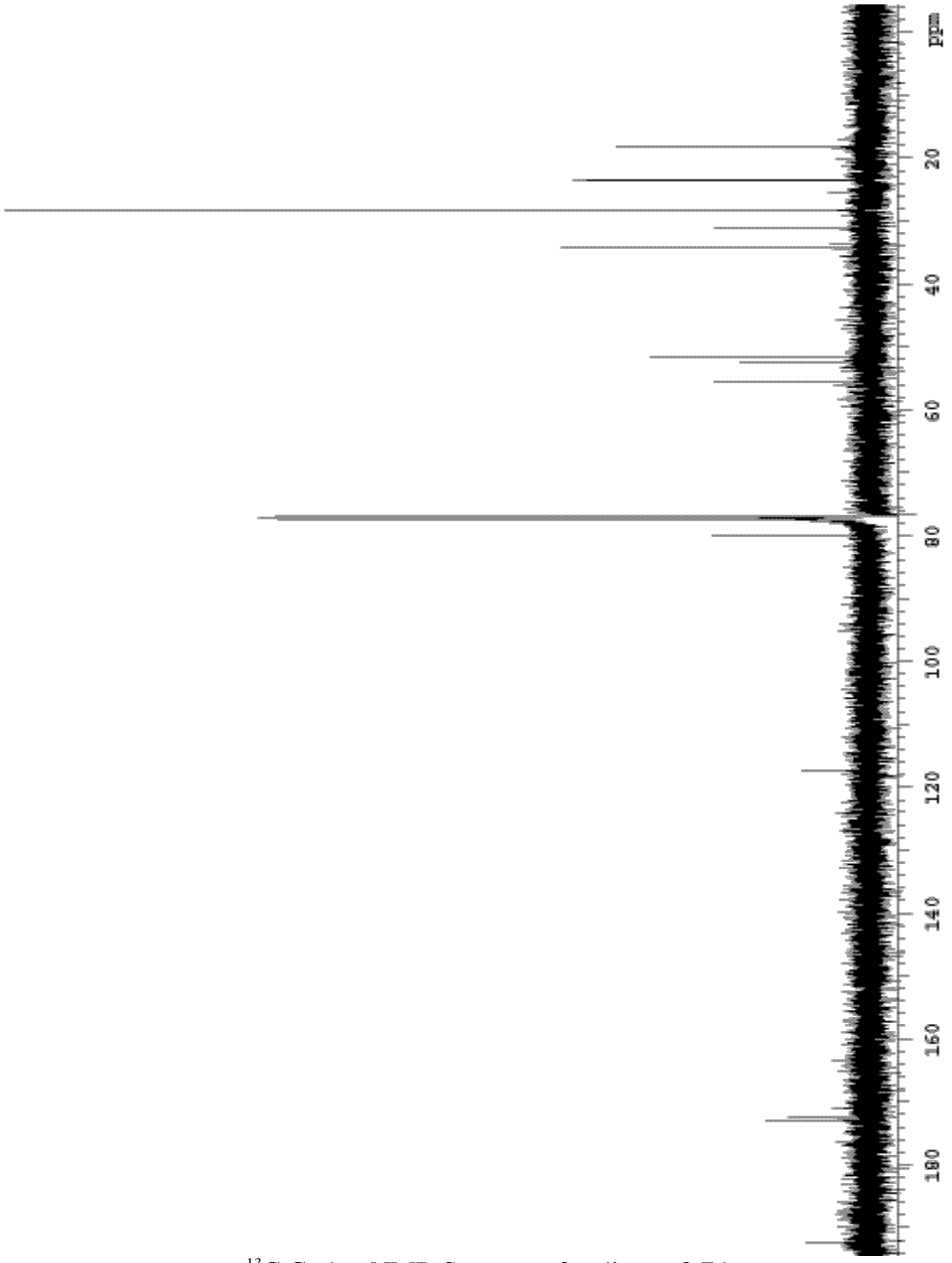
3.74



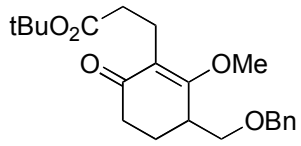
^{1}H Proton NMR Spectrum for diester **3.74a**



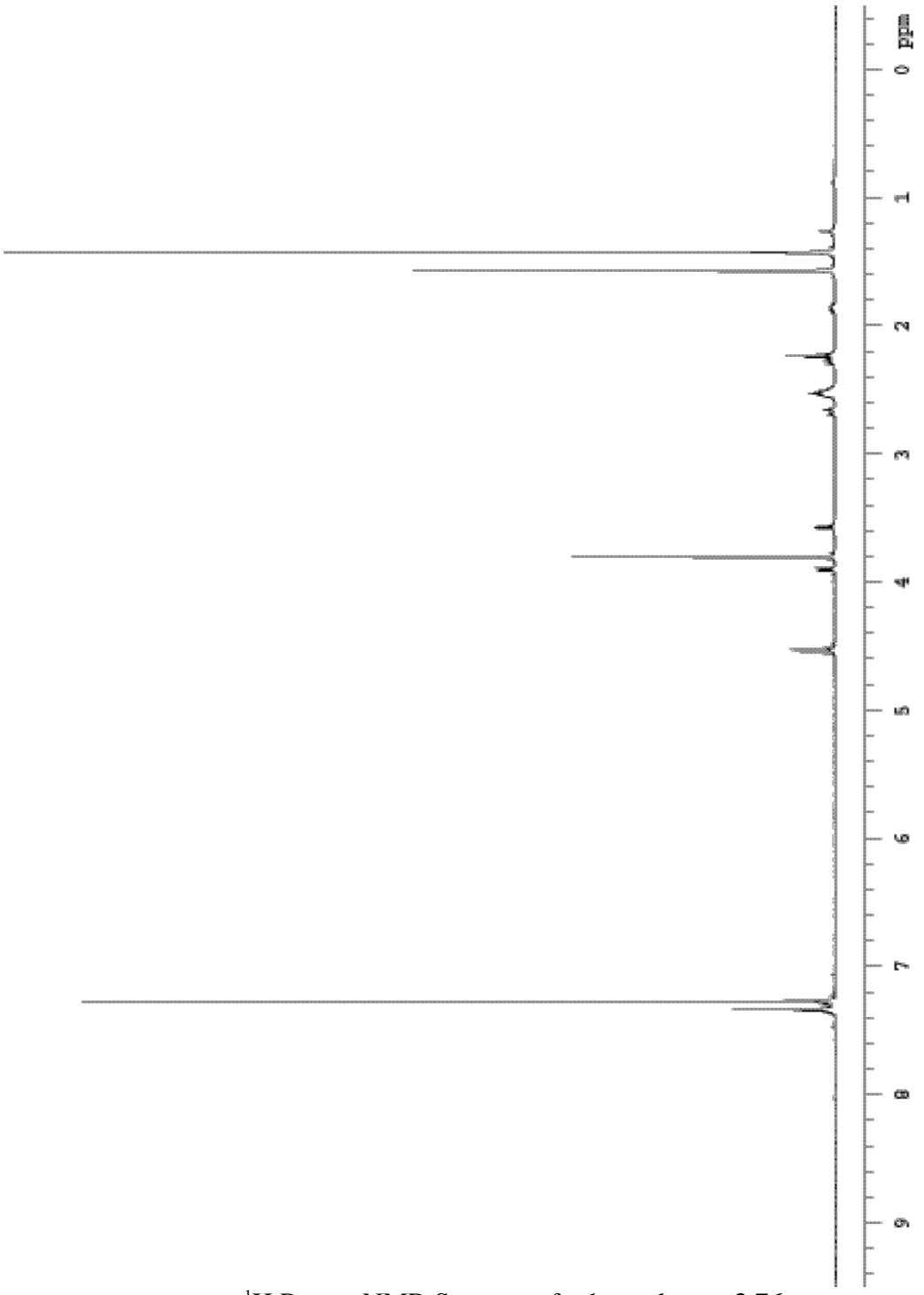
3.74



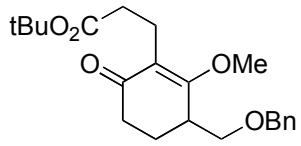
^{13}C CarbonNMR Spectrum for diester **3.74a**



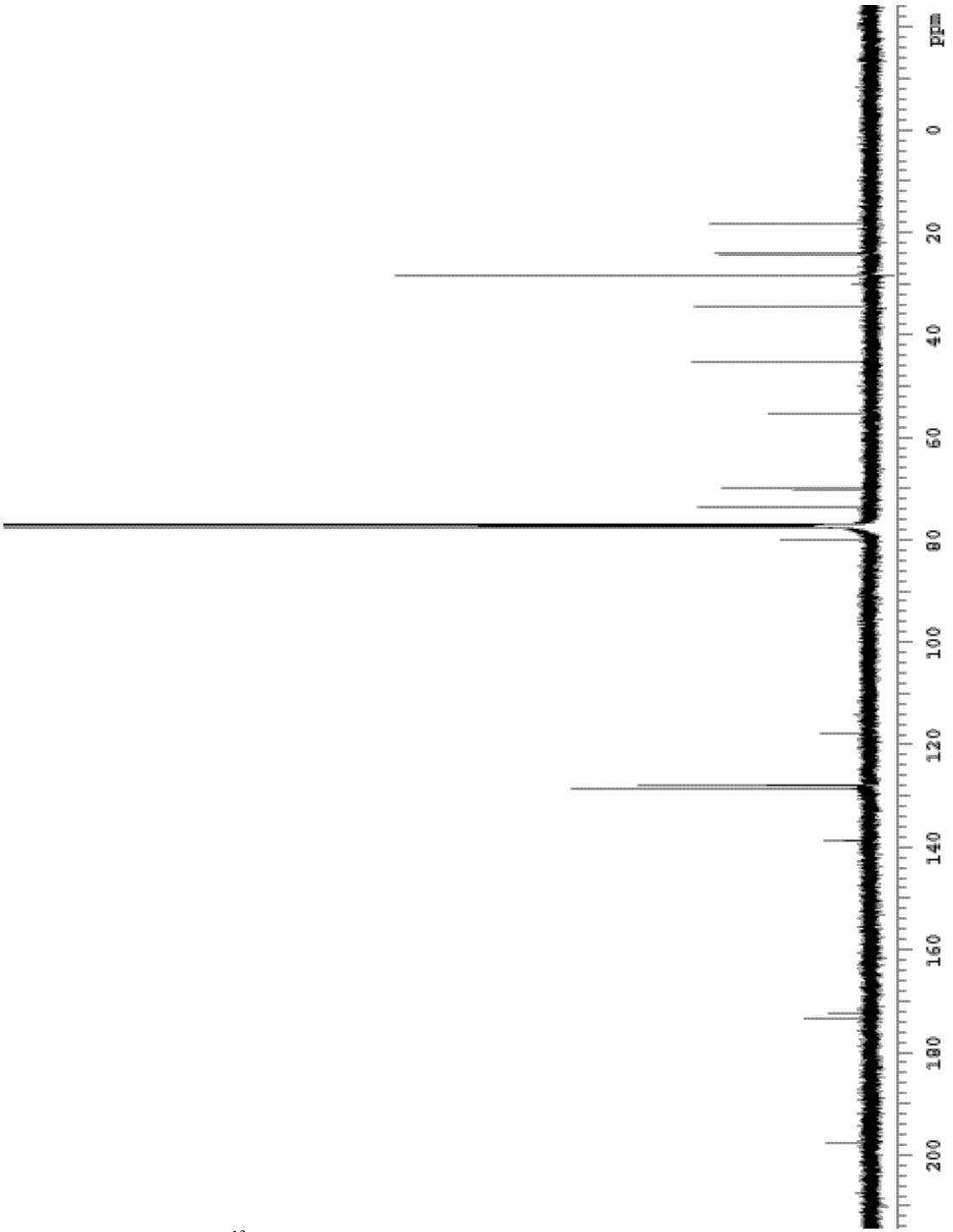
3.76



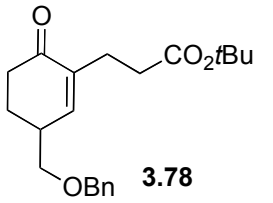
^{1}H Proton NMR Spectrum for benzyl ester **3.76**



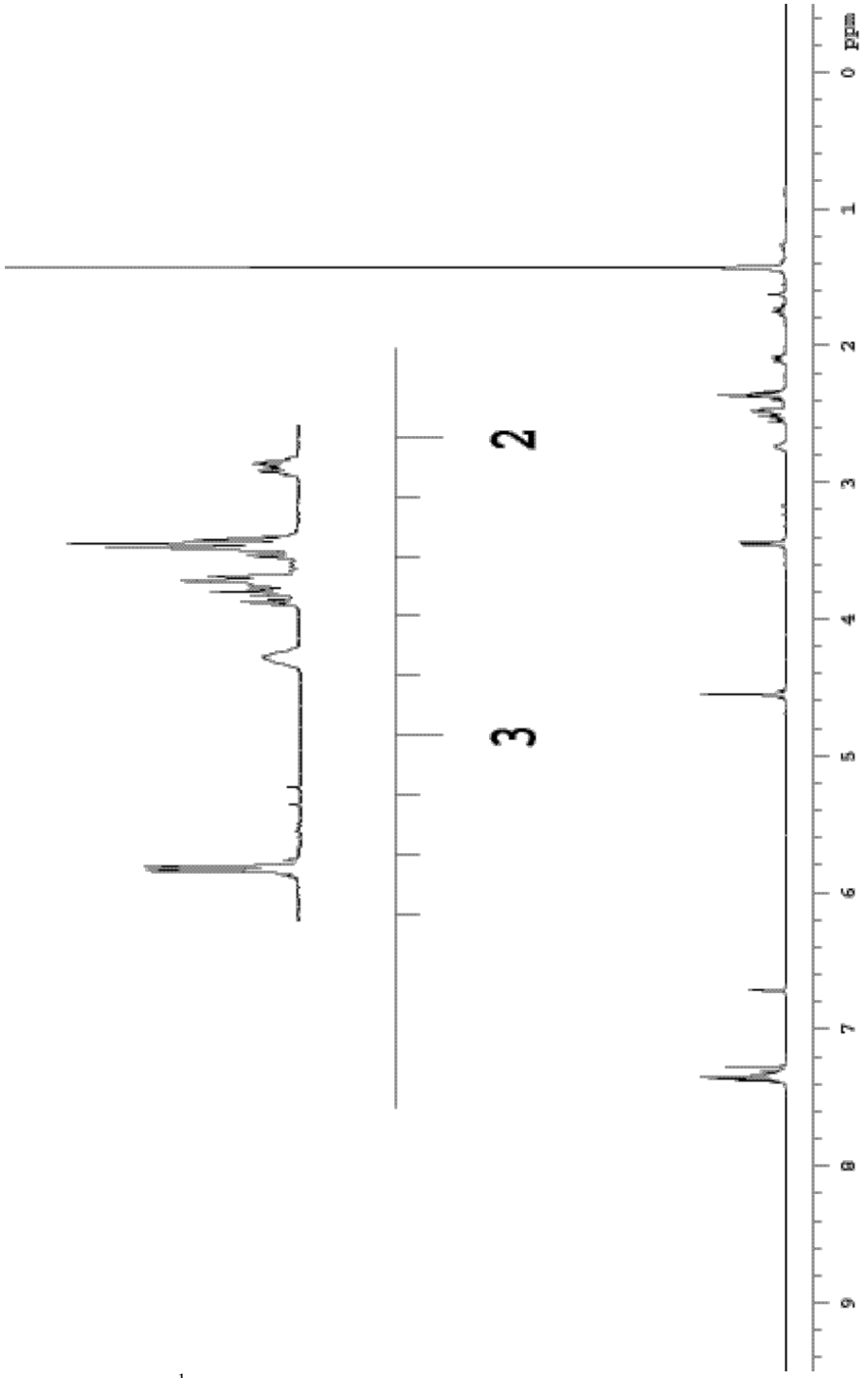
3.76



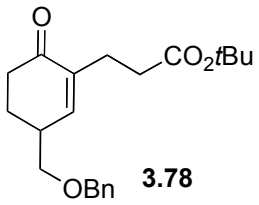
^{13}C CarbonNMR Spectrum for benzyl ester **3.76**



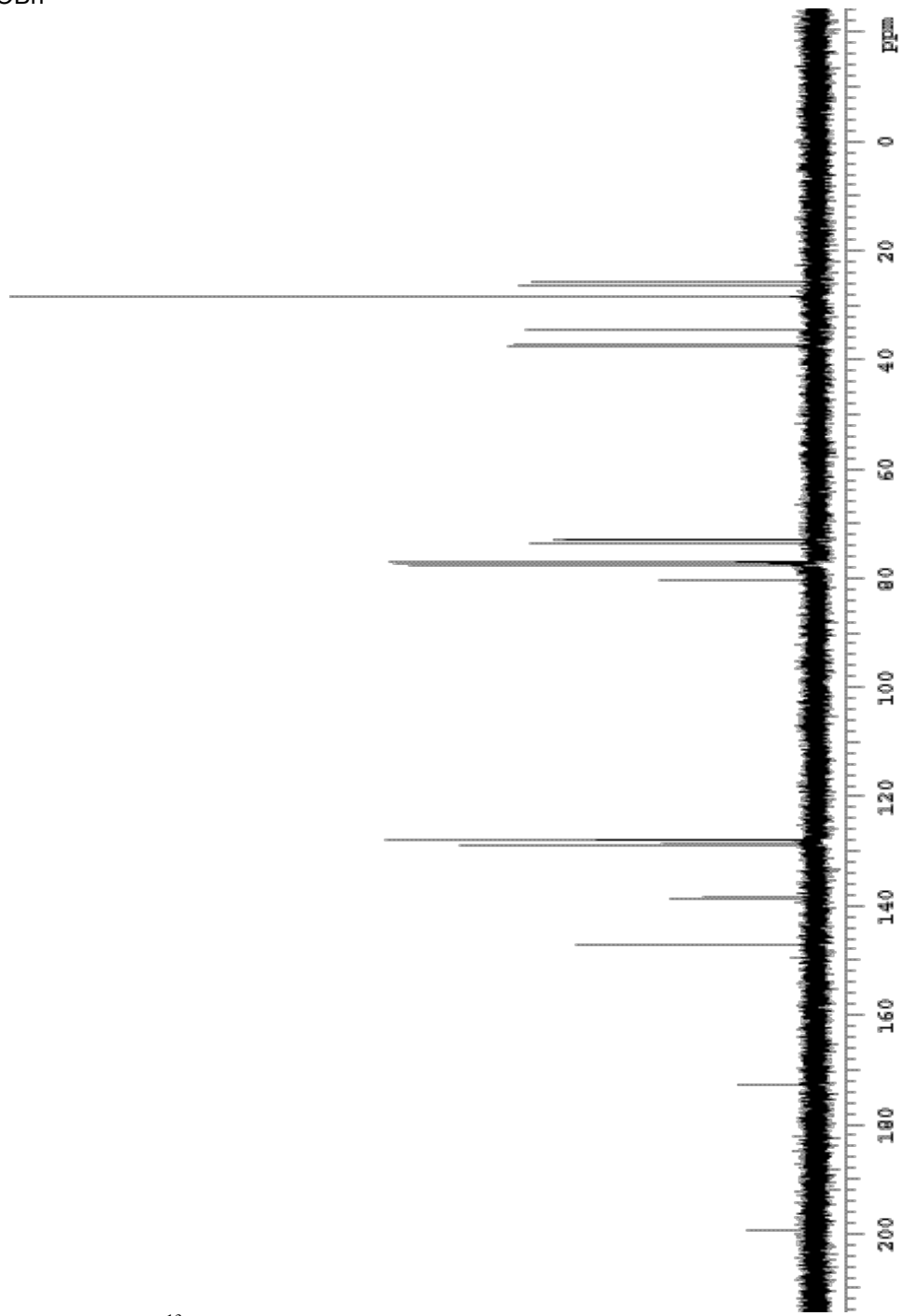
3.78



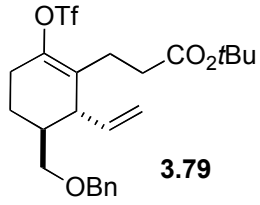
^{1}H Proton NMR Spectrum for cyclohexenone **3.78**



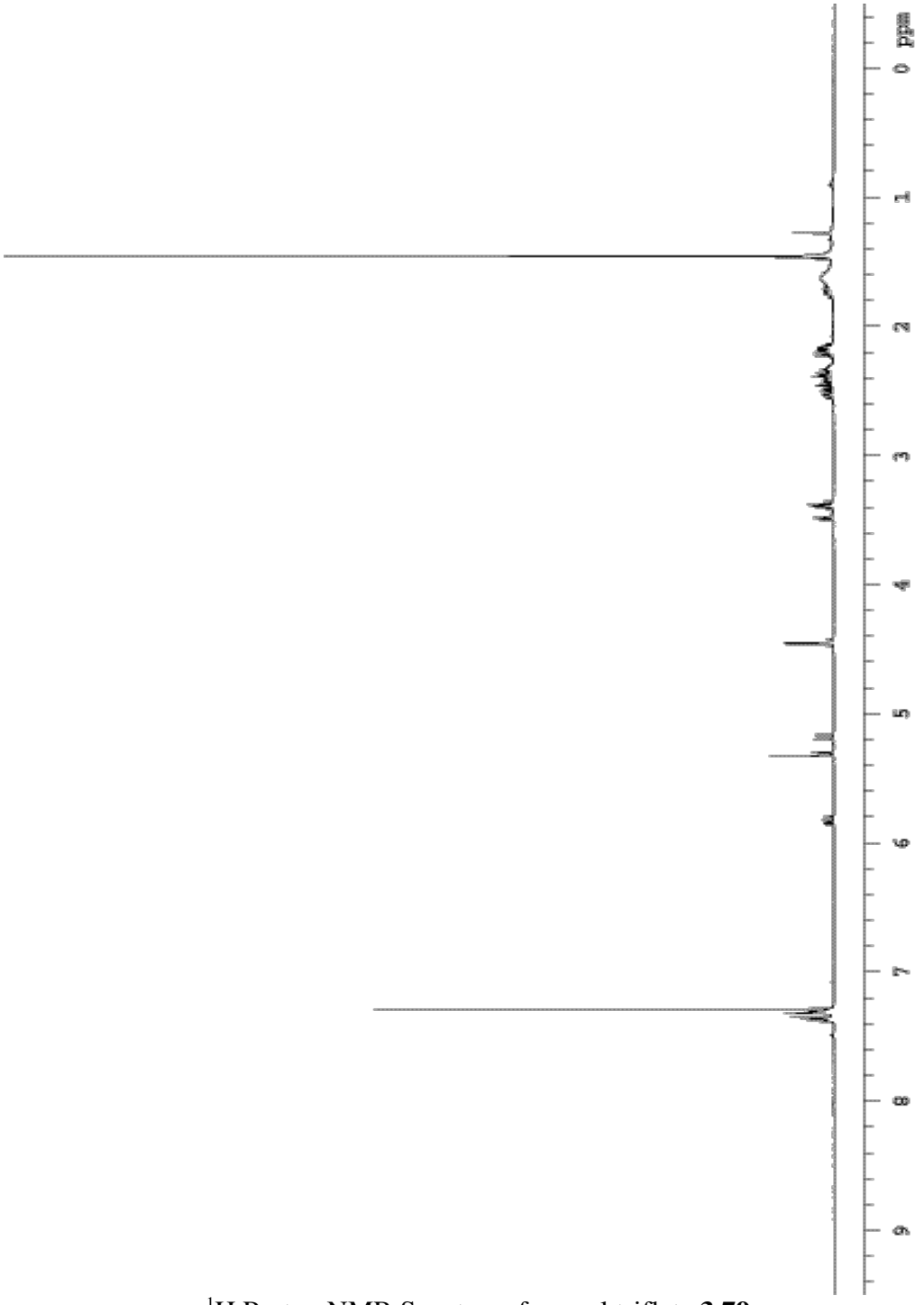
3.78



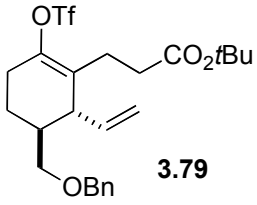
^{13}C Carbon NMR Spectrum for cyclohexenone **3.78**



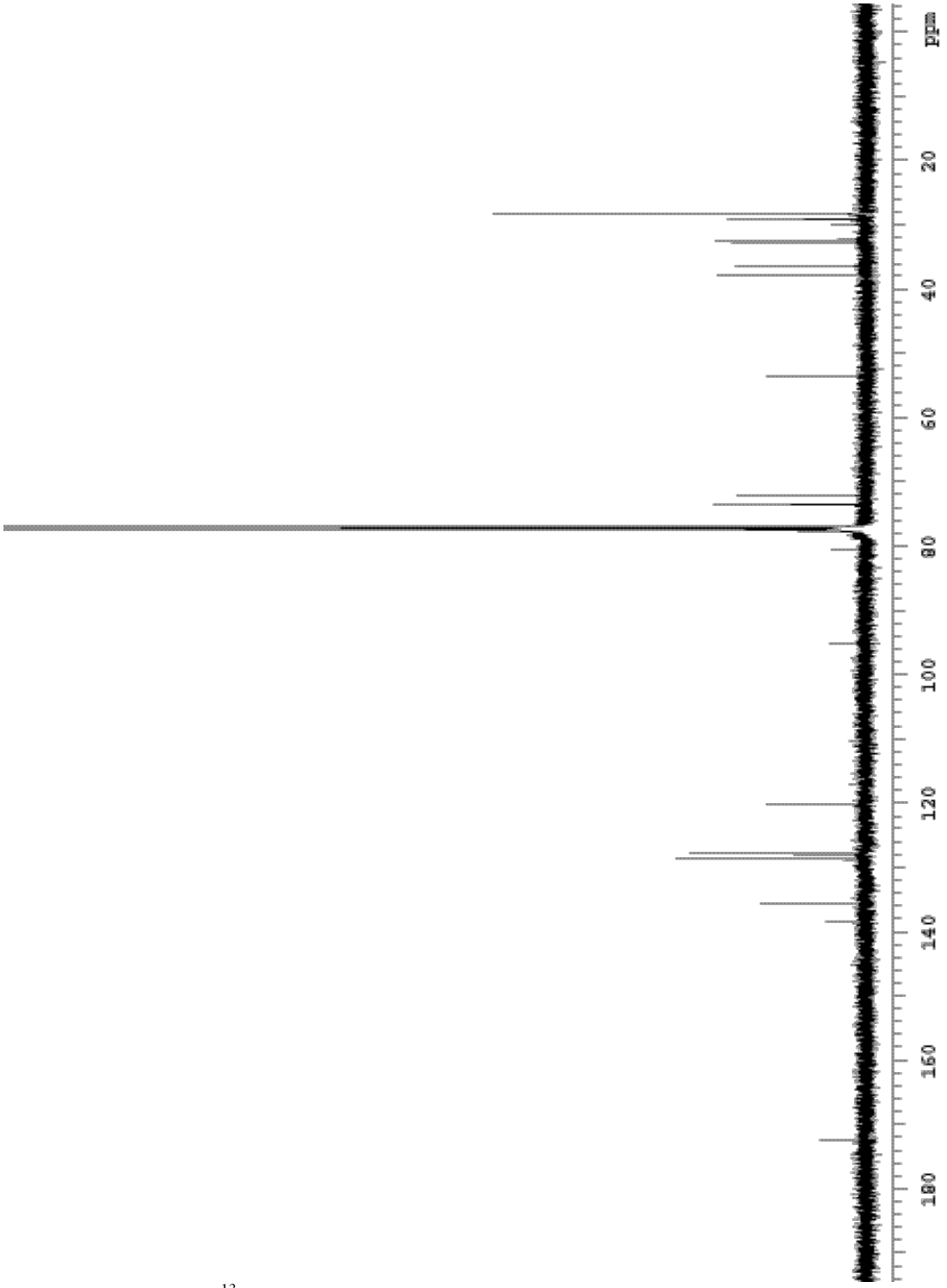
3.79



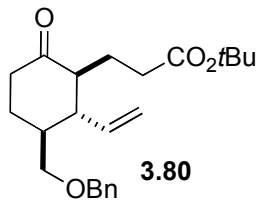
^{1}H Proton NMR Spectrum for enol triflate **3.79**



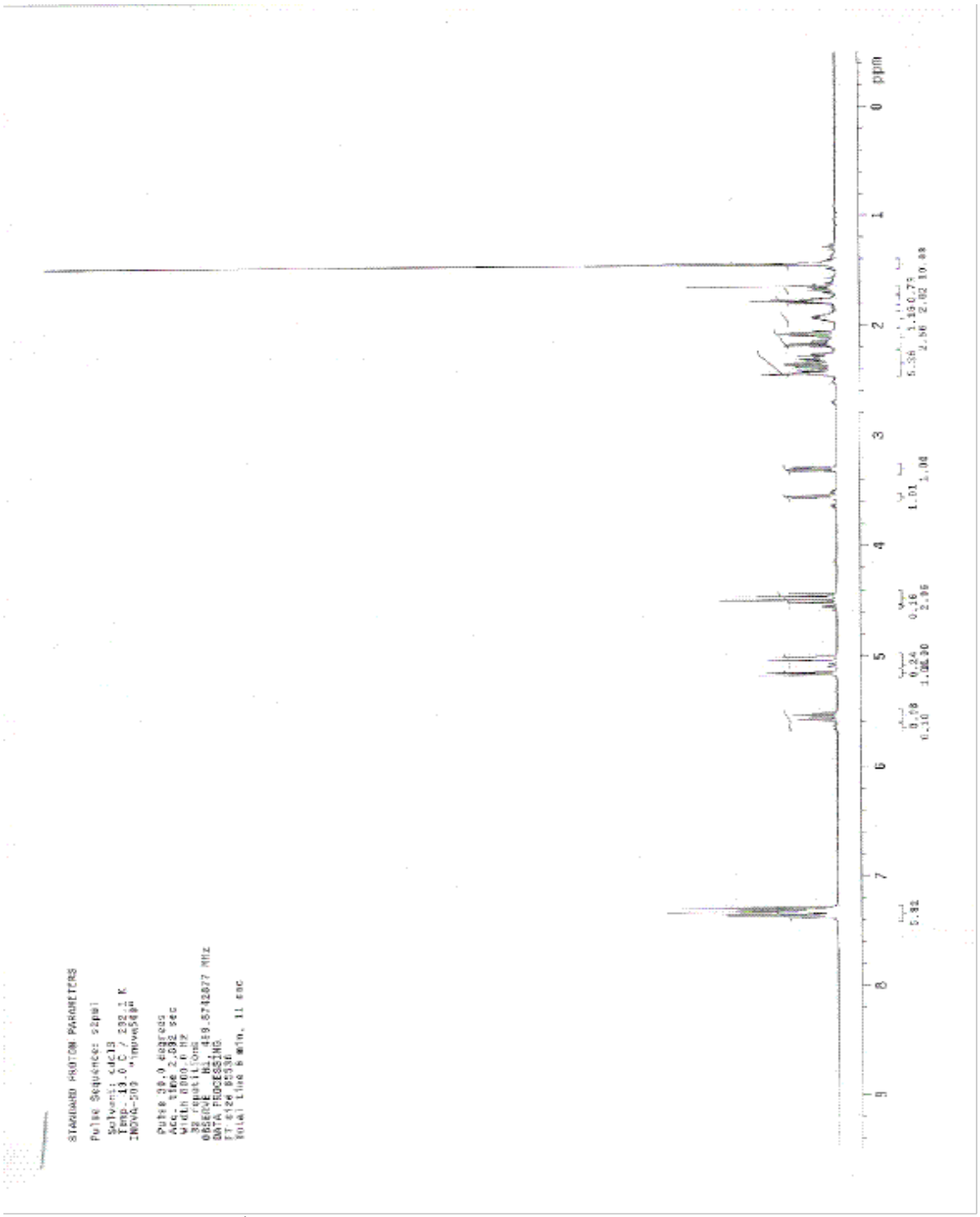
3.79



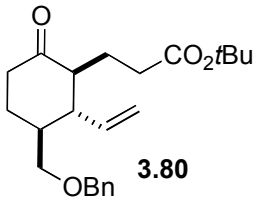
^{13}C Carbon NMR Spectrum for enol triflate **3.79**



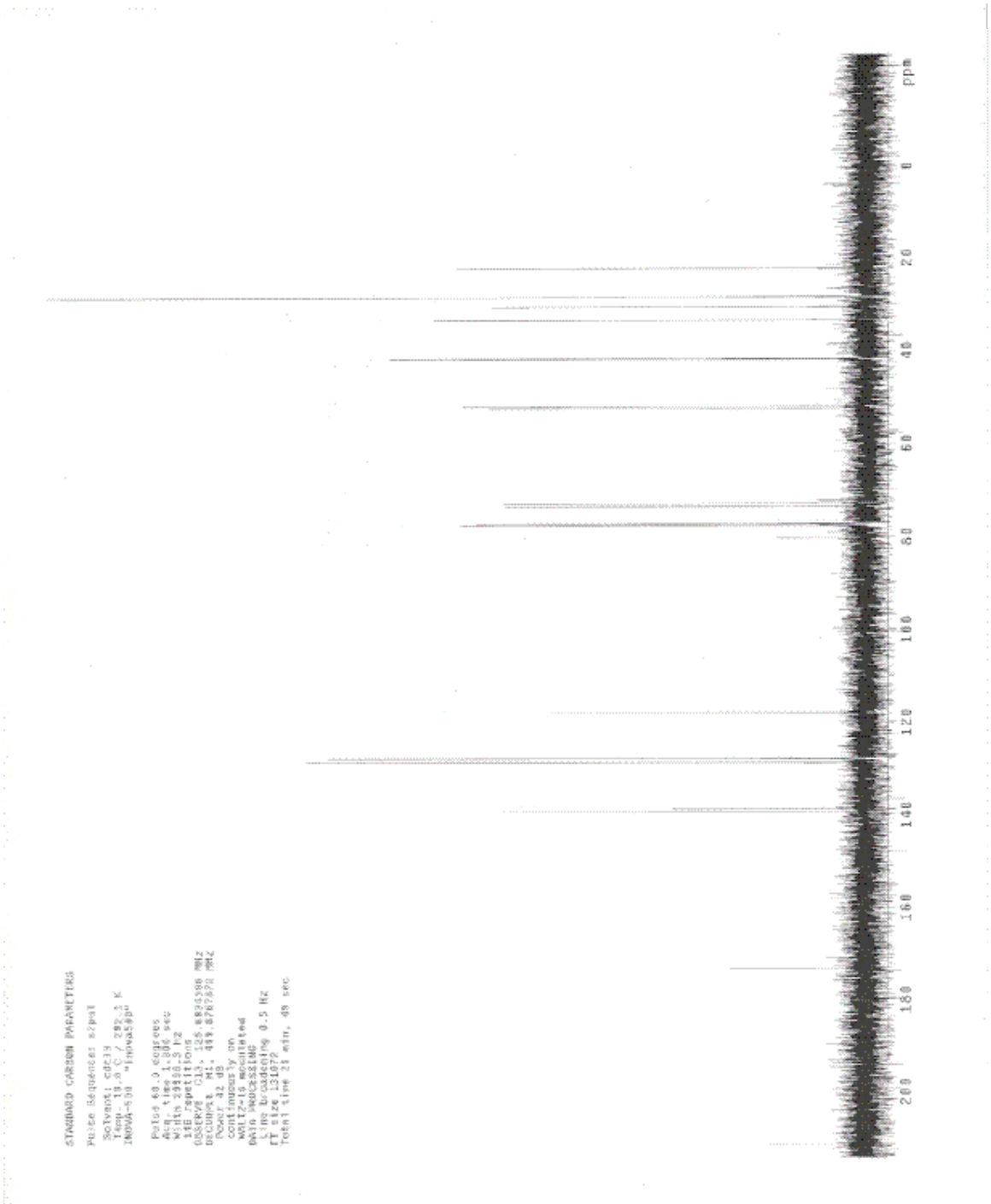
3.80



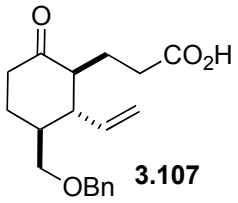
^{1}H Proton NMR Spectrum for butyl ester **3.80**



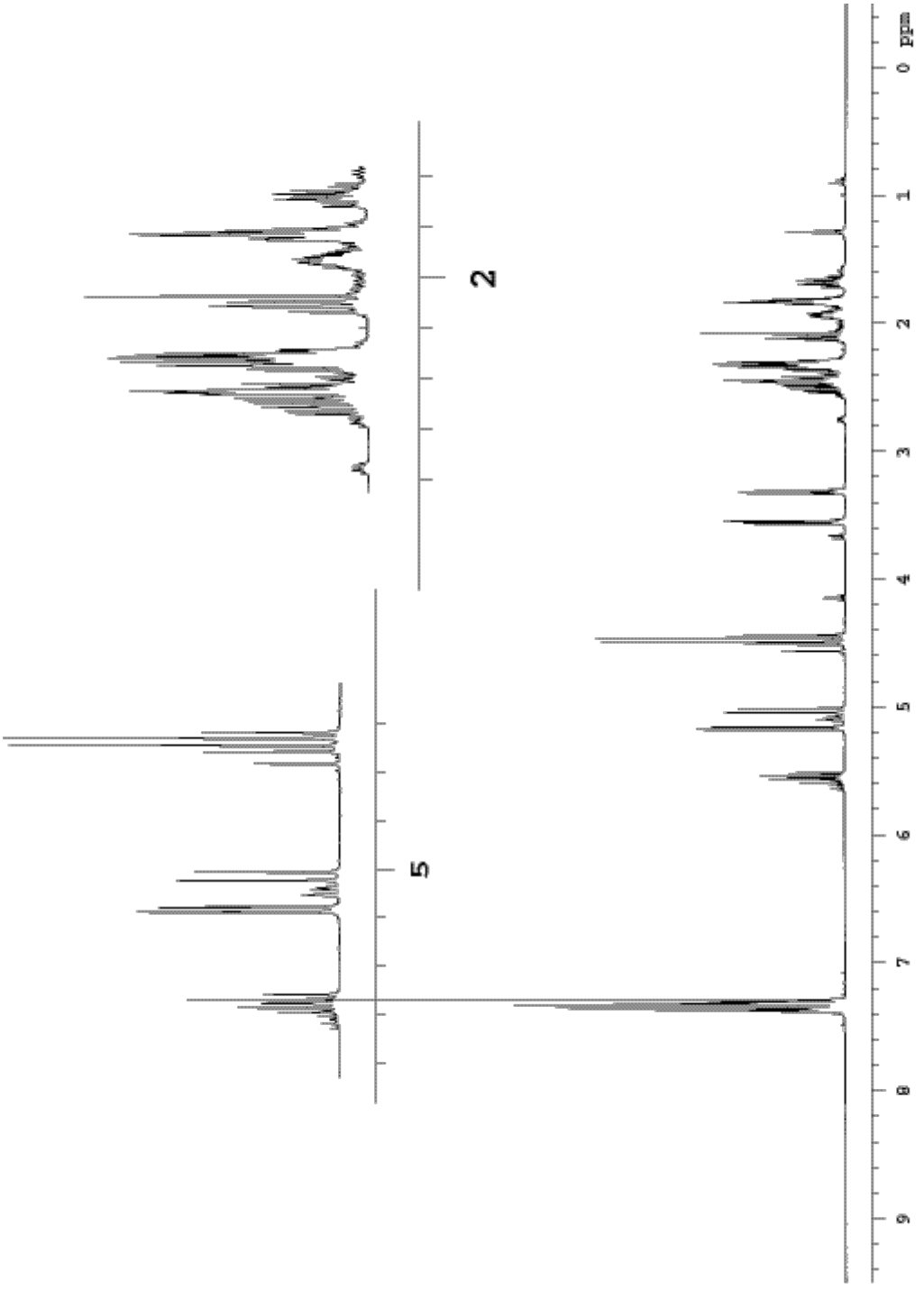
3.80



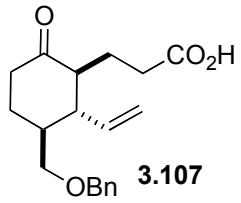
^{13}C Carbon NMR Spectrum for butyl ester **3.80**



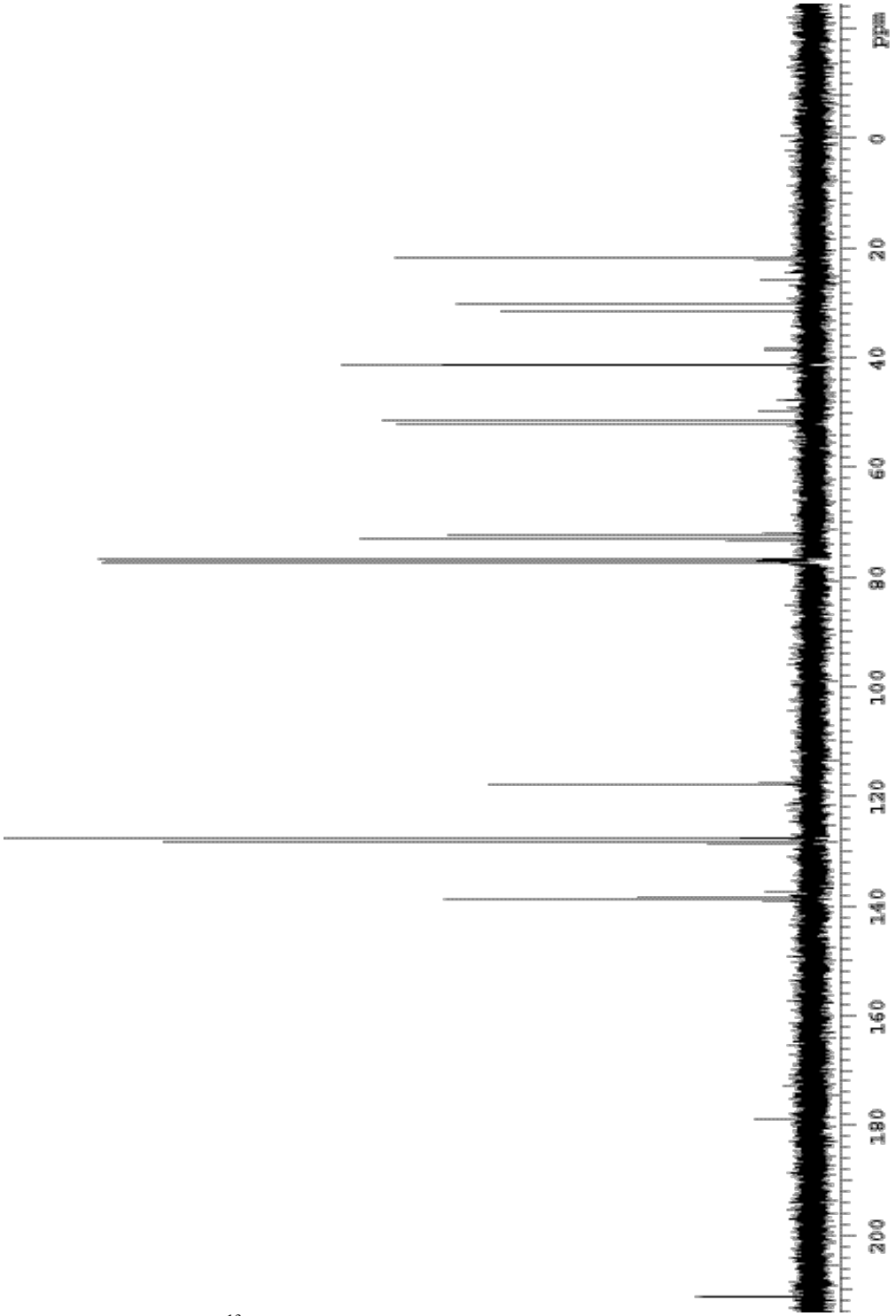
3.107



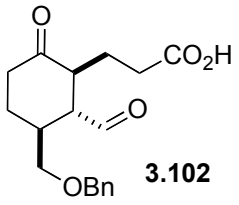
^{1}H Proton NMR Spectrum for acid **3.107**



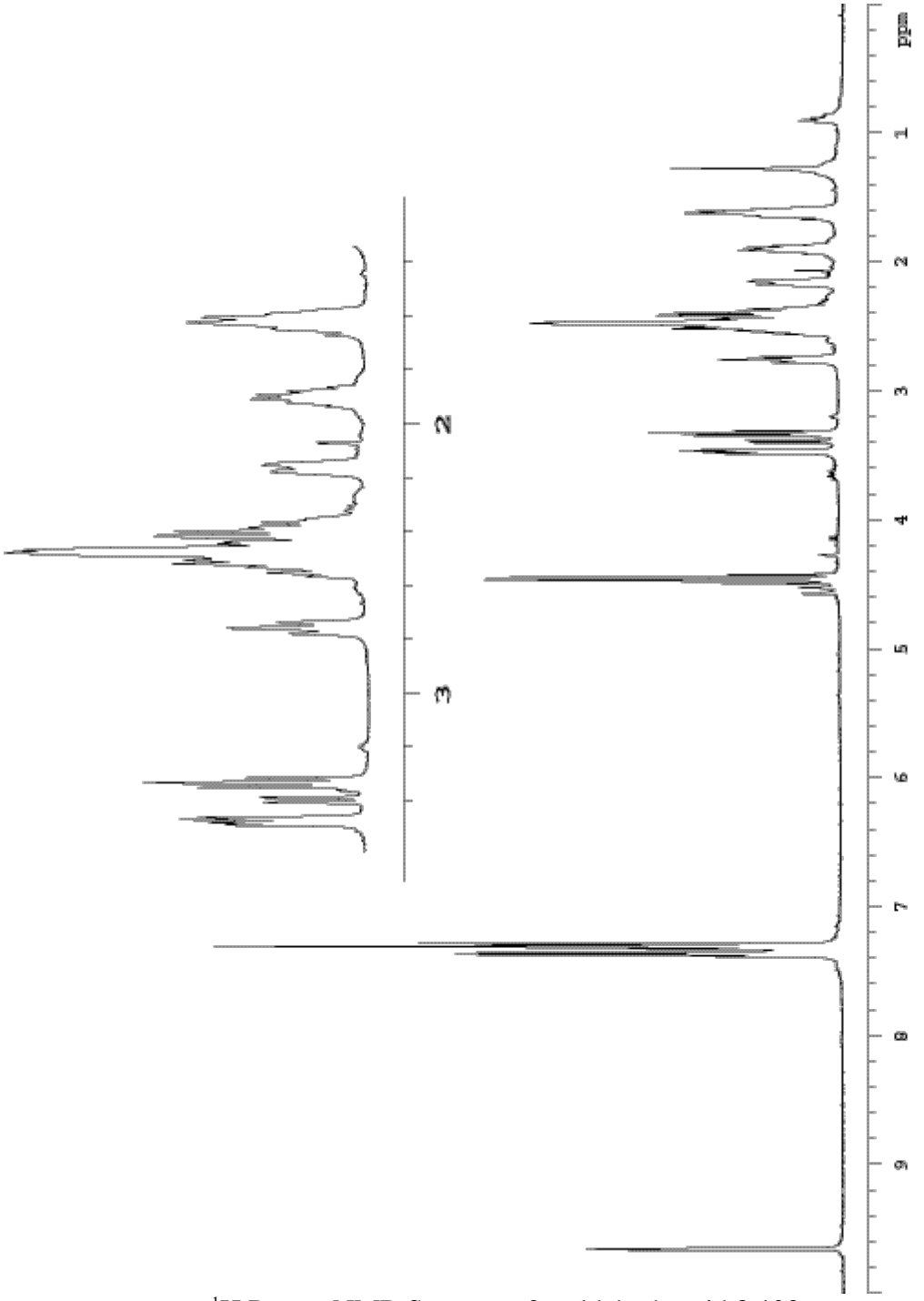
3.107



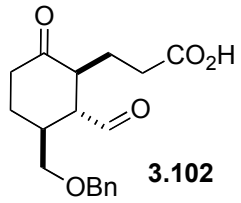
^{13}C Carbon NMR Spectrum for acid **3.107**



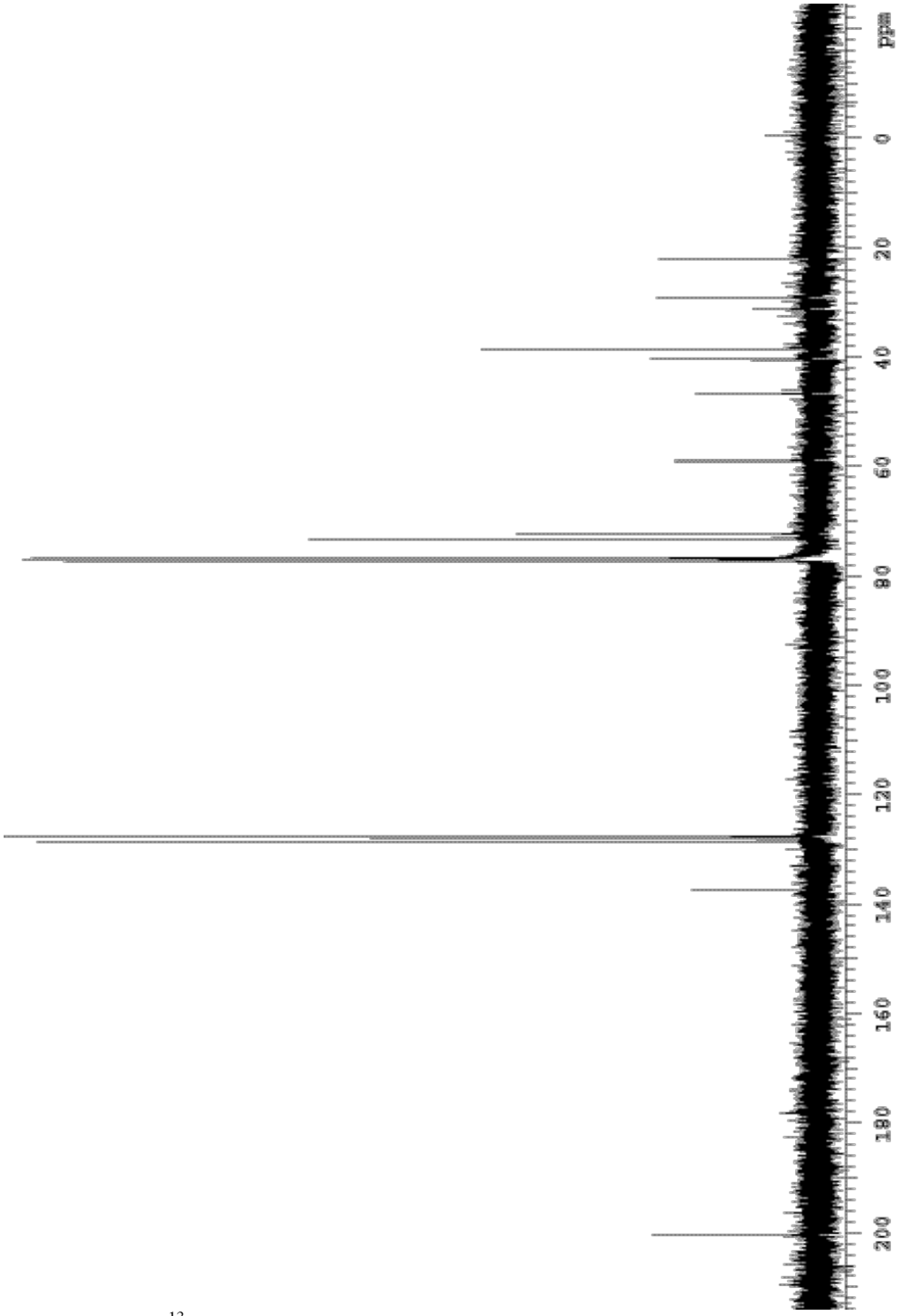
3.102



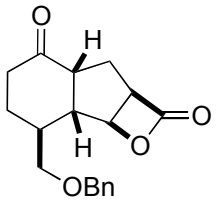
^{1}H Proton NMR Spectrum for aldehyde acid **3.102**

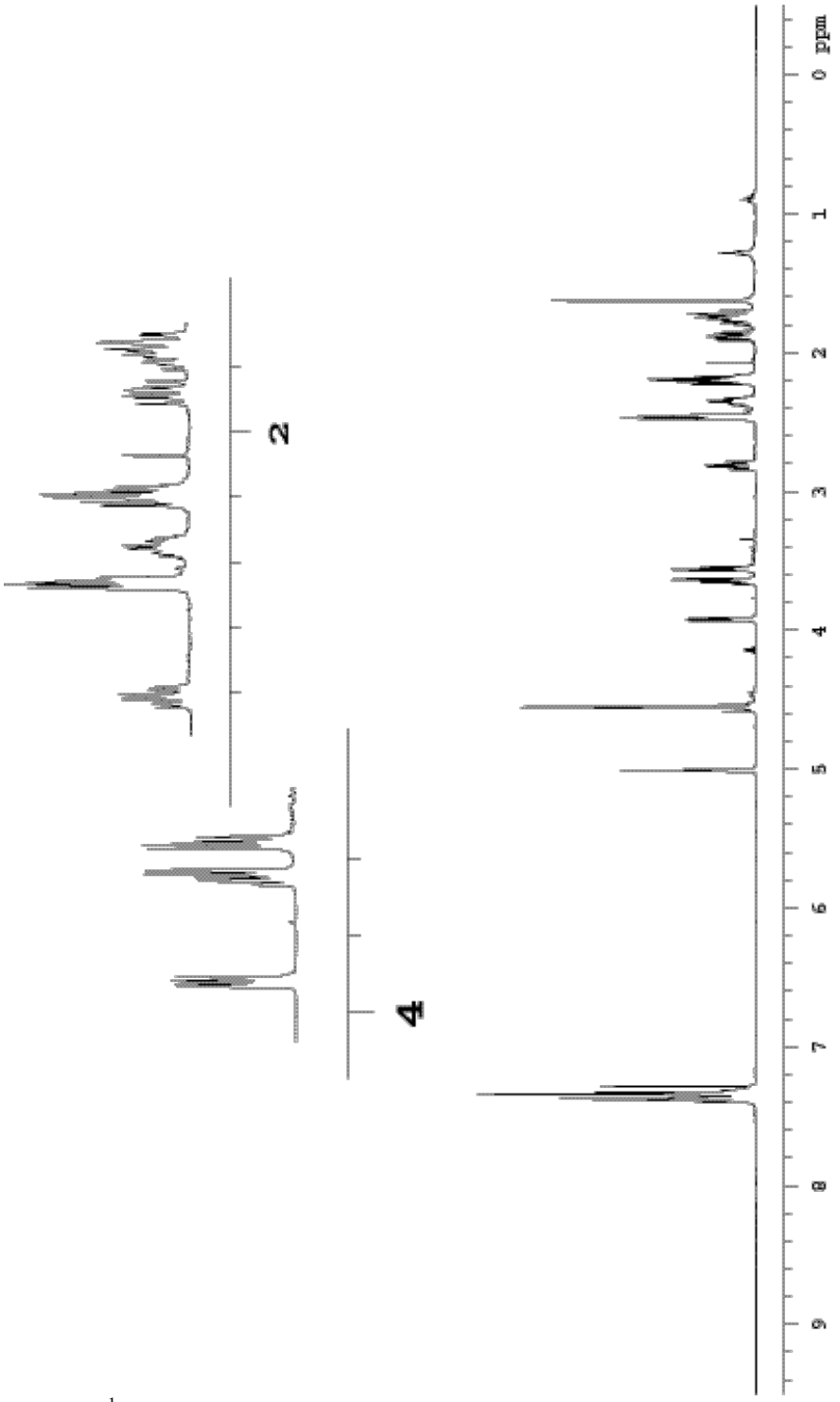


3.102

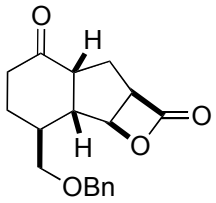


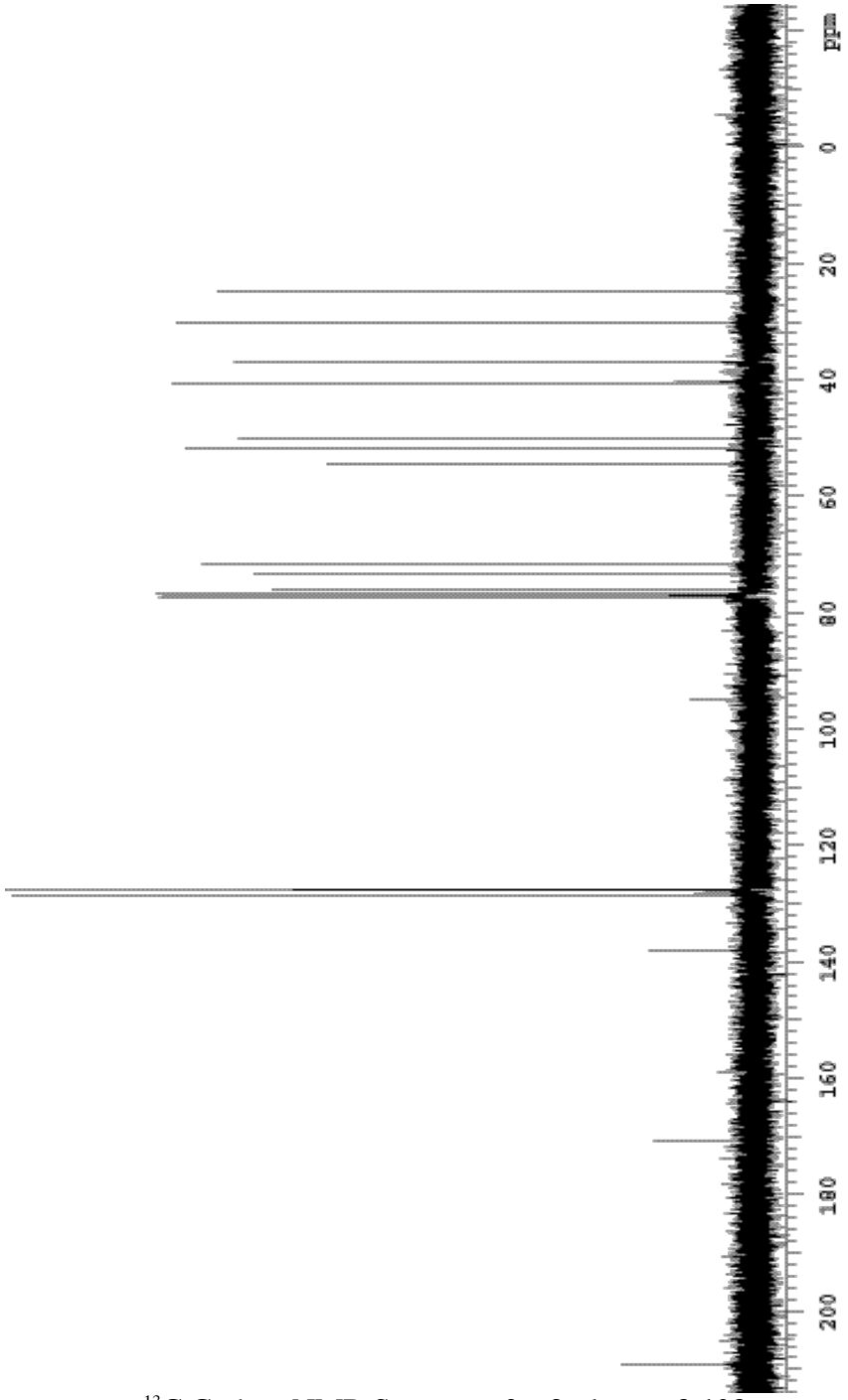
^{13}C Carbon NMR Spectrum for aldehyde acid **3.102**





^{1}H Proton NMR Spectrum for β-alctone **3.103**





^{13}C Carbon NMR Spectrum for β-alctone **3.103**

VITA

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