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Studies in Rhodium Catalyzed Intramolecular C-H Insertion of Amino Acid Derived α-Diazo-α- (substituted)acetamides and its Application to the Total Synthesis of clasto-Lactacystin β-Lactone

David L. Flanigan Jr.
University of South Florida

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Studies in Rhodium Catalyzed Intramolecular C-H Insertion of Amino Acid Derived α-Diazo-α-(substituted)acetamides and its Application to the Total Synthesis of clasto-Lactacystin β-Lactone

by

David L. Flanigan Jr.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy
Department of Chemistry
College of Arts and Sciences
University of South Florida

Major Professor: Kyung Woon Jung, Ph.D.
Edward Turos, Ph.D.
Kirpal S. Bisht, Ph.D.
Julie P. Harmon, Ph.D.

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May 24, 2003

Keywords: γ-lactam, natural product, C-H activation, aldol, proteasome inhibitor

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For Liz, Bren and Kristen
Acknowledgments

First, I need to thank God for providing me with the ability to succeed in this field, without Him none of this is possible.

Liz, you help me to realize my own potential and never underestimate my ability. Thank you for always believing in me and putting up with my “nonsense.” Bren, you constantly bring a smile to my face despite hard days of failure and nothing has changed. My family, both immediate and extended, have been supportive in countless ways. They have been friends, hosts, sources of joy and voices of reason (and not :). They have assisted with financial issues and furnished houses. Obviously, they have played an extraordinary part in making my life happier and easier and to them I am forever grateful.

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<td>1,2-DCE</td>
<td>1,2-dichloroethane</td>
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<td>AD-mix</td>
<td>asymmetric dihydroxylation mix</td>
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<td>de</td>
<td>diastereomeric excess</td>
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<td>DIPEA</td>
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<td>HONH₂·HCl</td>
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<td>Imid</td>
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<td>IPA</td>
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<td>i-PrCHO</td>
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<td>i-PrMgBr</td>
<td>isopropylmagnesium bromide</td>
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<tr>
<td>Jones Reagent</td>
<td>H₂CrO₄ solution</td>
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KMnO$_4$ potassium permanganate
LAH lithium aluminum hydride
LDA lithium diisopropylamide
LHMDS lithium bis(trimethylsilyl)amide
LiBH$_4$ lithium borohydride
LiBr lithium bromide
LiOH lithium hydroxide
LiOOH lithium peroxide
M molarity
$m$-CPBA 3-chloroperoxybenzoic acid
Me methyl
Me$_2$AlCl dimethylaluminum chloride
Me$_2$CO acetone
Me$_3$OBF$_4$ trimethyloxonium tetrafluoroborate
MeCN acetonitrile
MeI iodomethane
MeNH$_2$ methylamine
MeOH methanol
(MeSO$_2$)$_2$O methanesulfonic anhydride
MHz megahertz
MgI$_2$ magnesium iodide
mL milliliter
MnO$_2$ manganese dioxide
xi
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<td>nuclear magnetic resonance</td>
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<tr>
<td>N-PMBGlyME</td>
<td>N-PMB-glycine methyl ester</td>
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<tr>
<td>O₃</td>
<td>ozone</td>
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OsO₄       osmium tetroxide
P₂O₅       phosphorous pentoxide
p-ABSA     4-acetamidobenzenesulfonyl azide
Pd(OH)₂/C  palladium hydroxide on carbon
Pd(Ph₃P)₄  tetrakis(triphenylphosphine)palladium(0)
Pd/C       palladium on carbon
Ph         phenyl
PhCH₃      toluene
PhSCH₂CO₂H  (phenylthio)acetic acid
PhSeBr     phenylselenyl bromide
PhSO₂Na    benzenesulfonic acid sodium salt
PivCl      pivaloyl chloride
PLE        porcine liver esterase
PMA        phosphomolybdic acid
PMB        4-methoxy benzyl
pyr        pyridine
Rh₂(cap)₄  rhodium (II) caprolactamate dimer
Rh₂(OAc)₄  rhodium (II) acetate dimer
SnCl₄      tin (IV) chloride
SOCl₂      thionyl chloride
TBAF       tetrabutylammonium fluoride
TBSCl      t-butyldimethylsilyl chloride

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<td>TBSOTf</td>
<td>t-butyl(dimethyl)silyl trifluoromethanesulfonate</td>
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<td>TBTU</td>
<td>2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate</td>
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<td>t-Bu</td>
<td>tert-butyl</td>
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<tr>
<td>TEA</td>
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<td>TEMPO</td>
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Studies in Rhodium Catalyzed Intramolecular C-H Insertion of Amino Acid Derived \( \alpha \)-Diazo-\( \alpha \)-(substituted)acetamides and its Application to the Total Synthesis of \textit{clasto}-Lactacystin \( \beta \)-Lactone

David L. Flanigan Jr.

ABSTRACT

Lactacystin is a microbial metabolite isolated by Omura that exhibits neurotrophic activity in neuroblastoma cell lines. Lactacystin and especially its \( \beta \)-lactone analog are the first examples of non-polypeptide small molecules capable of specifically inhibiting the 20S proteasome. Various asymmetric total syntheses of lactacystin and its analogs have been reported. The total synthesis of \textit{clasto}-lactacystin \( \beta \)-lactone is achieved using L-serine methyl ester as the starting material and the sole source of stereochemical induction. The success of this synthesis hinges on two featured transformations. The first key step involves formation of the \( \gamma \)-lactam core via rhodium (II) catalyzed intramolecular C-H insertion of the \( \alpha \)-diazo-\( \alpha \)-(phenylsulfonyl)acetamide intermediate. The methodology for this transformation has been developed and applied to the synthesis of highly functionalized stereogenic \( \gamma \)-lactams from natural \( \alpha \)-amino acids. Three control elements that govern \( \gamma \)-lactam formation are described. This step is highlighted by the
simultaneous creation of two stereogenic centers of the \( \gamma \)-lactam core. The second key step involves the late stage aldol coupling for quaternary carbon formation and installation of the hydroxyisobutyl group. In all previously reported syntheses, this is the very first aspect which is addressed. The stereochemical outcome of this step is directed by the chiral environment of the enolate itself. Various attempts to achieve selectivity are explored and reported. Completion of the synthesis of clasto-lactacystin \( \beta \)-lactone requires 17 steps with an overall yield of 10%. Some general attempts for optimizing the synthetic scheme are discussed as well as the future direction of this research.
Chapter One

Introduction

1.1 Background

Lactacystin (1) is a *Streptomyces* metabolite that was isolated and identified by Ōmura and initially reported in 1991.\(^1\) It has been found to be an affector of neurite outgrowth in mouse neuroblastoma cell line Neuro 2A.\(^2\) The scientific community was excited by the discovery of the first non-protein microbial metabolite to exhibit neurotrophic activity and three total syntheses of the new agent were reported over the next 3 years.\(^3-5\) Corey reported that inhibition of the cell cycle of Neuro 2A and MG-63 human osteosarcoma cells past the G\(_1\) phase occurs upon treatment with lactacystin and related analogs 2-5 (Figure 1-2).\(^6\) The specific cellular target was identified by Schreiber

![Figure 1-1. Schematic Diagram of the 20S Proteasome Upon Inhibition by Lactacystin](image-url)
as the 20S proteasome using tritium-labeled lactacystin analogs.\textsuperscript{7} The 20S proteasome is the catalytic core of the 26S proteasome responsible for the degradation of denatured and misfolded proteins. It is also instrumental in the degradation of regulatory proteins in charge of cellular growth and metabolism.\textsuperscript{8} Specifically it is known to exhibit chymotrypsin-like, trypsin-like and peptidylglutamyl-peptide hydrolyzing (PGPH) activities toward small peptides.\textsuperscript{7} The 20S proteasome is an arrangement of four stacked rings (\(\alpha\)- and \(\beta\)-units) consisting of seven protein subunits each (28 total protein subunits) reminiscent of a cylinder (Figure 1-1). Two threonine residues present on the \(\beta\)-units of the 20S proteasome are responsible for much of its catalytic activity.\textsuperscript{9} Lactacystin and its analogs have shown to affect these sites by irreversibly acylating the \(N\)-terminus of the threonine residues rendering them inactive.\textsuperscript{7} Schreiber’s data is confirmed by X-ray crystallographic analysis of the 20S proteasome deactivated by lactacystin.\textsuperscript{10,11}

\textbf{1.2 Kinetic Inhibition Studies}

Extensive studies concerning the structural requirements for biological activity of the \(\gamma\)-lactam were performed. The obvious alteration points for lactacystin were the C-7 methyl, the hydroxyisobutyl group and variations of the \(N\)-acytelycysteine side chain. Schreiber’s initial report of the activity of lactacystin toward the 20S proteasome included a limited structural activity study of lactacystin (1) and related \(\beta\)-lactone 2, dihydroxy acid 3, 6-deoxy 5, 6-\textit{epi}, 7-\textit{epi}-lactacystin and \textit{des}-hydroxybutyl lactacystin analogs 4 (Figure 1-2).\textsuperscript{6} Kinetic inhibition data shows that the \(\gamma\)-lactam core and stereochemistry thereof are requirements for activity of the molecule. The dramatic
increase in kinetic inhibition of the $\beta$-lactone intermediate implies that the electrophilic nature of the carbonyl governs the rate of inhibition. For instance, the dihydroxy acid analog exhibits no activity presumably based on the absence of electrophilic character of the carboxyl moiety. The $\beta$-lactone exhibits activity that is 15-fold more than that of lactacystin based on the increased electrophilicity of the lactone carbonyl as opposed to the carbonyl of the thioester. Smith preformed studies on analogs of the N-acetylcysteine side chain of lactacystin. Variations of the carboxylate function as well as deletion of the amide function had little effect on the activity of the analogs thus corroborating Schreiber’s presumption that the presence and reactivity of the C-4 carbonyl is crucial. Corey’s efforts toward elucidation of the ideal affector molecule focused on optimization of the C-7 alkyl and hydroxyisobutyl substituents of the more potent $\beta$-lactone. Analogs prepared with variations to the hydroxyisobutyl substituent involved exchange of the isopropyl portion of the side chain for simple alkyls and unsaturated moieties and
specifically 9-deoxy, 9-epi and 9-keto groups (Figure 1-3). Ultimately, the hydroxyisobutyl side chain proved to be necessary for sufficient inhibition, that which was 10-fold greater than the most active analog. Eventually, X-ray studies revealed that the isopropyl group of the hydroxyisobutyl side chain binds was bound by a hydrophobic pocket of the lactacystin-labeled proteasome subunit. Conversely, C-7 analogs of the β-

![Chemical structures](image)

Figure 1-3. Kinetic Inhibition Studies of β-Lactone Analogs

lactone showed remarkable increase of inhibition when the methyl was exchanged for ethyl-, n-Bu and especially i-Pr alkyl substituents. Inhibition rates more than doubled with the introduction of longer alkyl chains. The 7-epi analog resulted in a decrease in activity reinforcing the notion that the original stereochemistry of the molecule is a requirement.

1.3 Outlook

As the first non-protein neurotrophic factor and proteasome inhibitor, lactacystin has garnered much attention from both the physical and life sciences. The effects this small molecule exerts on living systems makes it a valuable research tool for exploration
of protein biochemistry and molecular biology. As Corey’s structure-activity project was submitted for publication, Adams was completing work that reported the synthesis of a highly active analog of lactacystin.\textsuperscript{15} A complimentary set of data supported Corey’s results and a $\beta$-lactone incorporating an $n$-Pr C-7 substituent (PS-519) was the highlight of Adams’ report. PS-519 went on to preclinical development by Millennium Pharmaceuticals for treatment of ischemia-reperfusion injury in stroke and myocardial infarction. The biosynthesis of lactacystin has been studied\textsuperscript{16} and more than 10 total syntheses of lactacystin and various analogs have been reported throughout the last decade.
Chapter Two
Previous Syntheses

Newly discovered molecules usually generate interest throughout the synthetic community, particularly when they have novel structural scaffolds. Few synthetic targets, though, have demanded as much attention as lactacystin. Discovered by Omura in 1991 while screening thousands of soil samples for differentiation of the Neuro 2A cell line, lactacystin’s structure was elucidated using $^1$H and $^{13}$C NMR techniques. The absolute stereochemistry was determined using single-crystal X-ray analysis. The positive identification of lactacystin as a potential neurotrophic factor, its appeal as a synthetic target and its scant supply made the $\gamma$-lactam an extremely hot target for total synthesis.

2.1 Corey’s First Total Synthesis of Lactacystin

One year after Omura’s initial report, Corey published the first total synthesis of lactacystin. Starting with $N$-benzyl protected serine methyl ester, the amine and hydroxyl functionalities were simultaneously protected as the oxazolidine (10) resulting in a 9:1 ratio of diastereomers (Scheme 2-1). Aldol coupling of 10 with isobutyraldehyde utilizing the lithium bromide-lithium enolate complex yielded diastereomerically pure 11
with a 51% yield after recrystallization. The significance of this transformation lies in the control by which the eventual C-5 and C-9 stereocenters are formed. These seemingly simple transformations take advantage of the stereogenic environment indigenous to the enolate itself which controls the conformation of the enolate and facial approach of the aldehyde under non-chelated conditions resulting in formation of the quaternary C-5 center. With the C-5 and C-9 stereocenters established, the focus turned to the formation of the remaining stereocenters of the lactam ring. The oxazolidine was opened up under acidic conditions and the resulting primary hydroxyl was protected as silyl ether 12. Again, simultaneous protection of the amine and hydroxyl functionalities with paraformaldehyde resulted in an oxazolidine system (13) with diminished stereochemical bias. The methyl ester was reduced to the primary alcohol and oxidized back to the aldehyde (14) using LiBH₄/MeOH and Swern conditions respectively. Intermediate 14 served as the key fragment and electrophile for the second aldol coupling. Pirrung-Heathcock¹⁷ anti-aldol conditions resulted in a mixture of diastereomers with 78% yield of a 1.5:1 favorable ratio. These results were obviously disappointing and an alternative
aldol coupling using Braun’s chiral controller/Cp₂ZrCl enolate conditions,¹⁸ in light of
good diastereoselection, were not practical for gram scale reactions. Moreover, desired
product 15 and the product resulting from attack on the opposite face of the aldehyde
were not easily separable by column chromatography. Catalytic hydrogenation of 15
resulted in a tandem debenzylolation/cyclization sequence yielding the bicyclic γ-lactam
(16) with C-6 and C-7 stereochemistry intact (Scheme 2-2). Deprotection of the primary
hydroxyl yielded the diol intermediate. To avoid oxidation of both hydroxyls, selective
oxidation of the primary hydroxyl was achieved using a two-step process. Swern
oxidation selectively oxidized the primary hydroxyl to the aldehyde followed by mild
sodium hypochlorite oxidation to yield acid 17. Deprotection of the N/O acetal yielded
dihydroxy acid 3. The first total synthesis of 1 was completed by coupling the N-
acetylcysteine allyl ester with the acid functionality of 3 using BOPCl and subsequent
deallylation with triethylammonium formate and Pd(0). Corey’s total synthesis of
lactacystin was a 15 step protocol with an overall yield of 6%, featuring two
diastereoselective aldol couplings, the second which suffered from mediocre selectivity. Another notable feature of the synthesis is the evolution of the stereochemical elements of lactacystin from serine without the use of asymmetric methodologies.

2.2 Corey’s Extended Methodology

Eventually, a follow-up to Corey’s lactacystin synthesis reported numerous improvements over the first, most notably of which was a superior methodology for the diastereoselective anti-aldol coupling as an alternative to the Pirrung-Heathcock conditions. A novel magnesium-catalyzed doubly diastereoselective anti-aldol coupling of aldehyde 14 and the tert-butyldimethylsilyl enol ether of methyl propioniate under Mukiyama conditions resulted in a 90% yield of 15B with no evidence of the corresponding diastereomer (Figure 2-1). Though Mukiyama-type open transition state

![Chelate Model for the Double Diastereoselective Mukiyama Aldol Coupling](image-url)
aldol couplings typically occur antiperiplanar, the steric repulsions illustrated above make the synclinal transition state a much more energetically favorable arrangement.

### 2.3 Smith’s Total Synthesis of Lactacystin

Six months later a collaboration between Smith and Ōmura resulted in the second total synthesis of lactacystin (1). Touted as an easily accessible route to 1 and a variety of analogs, this 10-step protocol was efficient and high yielding. Starting from the previously prepared unnatural amino acid 2R,3S-β-hydroxyisoleucine methyl ester (18), oxazoline derivative 19 was prepared using methyl benzimidate (Scheme 2-3).

Utilization of this starting material circumvented the installation of the crucial and synthetically challenging hydroxyisobutyl side chain. A stereoselective hydroxymethylation of the oxazoline using LHMDS/formaldehyde resulted in 20 with excellent yield and diastereoselectivity (>98% de). This transformation installs the C-5
quaternary center with outstanding diastereocontrol. A two-step procedure including Moffatt oxidation of primary alcohol 20 to the corresponding aldehyde followed by Brown’s asymmetric allylation20 resulted in simultaneous formation of the C-6 hydroxyl and C-7 methyl substituents of 21 in good yield. Ozonolysis and selective oxidation of the resulting aldehyde yielded acid 22. Activation of the acid functionality using AcOH enabled spontaneous $\gamma$-lactam formation upon debenzylation of the oxazoline. Saponification of the ester moiety resulted in known intermediate 3. The synthesis was then completed utilizing Corey’s two-step protocol for esterification and deallylation. The highlights of the synthesis are the stereoselective hydroxymethylation and the asymmetric anti-allylation steps resulting in a 13% overall yield. The authors also implied that the synthesis is designed in such a way as to allow for minor modifications of the protocol providing analogs for further study.

Eventually, a full account of Smith and Ōmura’s work including analog synthesis and biological assay data was published.12 The versatility for analog synthesis lay in the ability of the authors to obtain the unnatural amino acid in all four isomeric forms. Sharpless’ asymmetric epoxidation21 provided the initial stereochemical differentiation from which the remainder of the synthesis evolves. The bioassay studies focused on analogs of the N-acetyl cysteine side chain. Though a more active analog was not discovered, the authors state that a less cytotoxic yet more specific agent (8) was the ultimate target.
2.4 Corey’s Expanded Studies

Corey’s intense interest in lactacystin was evident during 1993 when three simultaneous accounts of lactacystin analog syntheses were reported.\textsuperscript{22} Perhaps the most significant feature of these reports was the transformation of the dihydroxy acid (3) to the $\beta$-lactone (2) using BOPCl as the activator for the lactonization. Initially, intermediate 3 was part of an alternate, higher yielding sequence for incorporation of the $N$-acetyl cysteine side chain. Lactonization of 3 occurred readily and nucleophilic substitution with the thiol containing side-chain was also an efficient process. These analogs, in addition to a few others, were the subject of Corey’s structure activity relationship and biological assay studies that identified \textit{clasto}-lactacystin $\beta$-lactone (2) as the most potent lactacystin analog known.\textsuperscript{6}

2.5 Baldwin’s Total Synthesis of Lactacystin

The first two total syntheses of lactacystin had similar strategies. Both syntheses utilize variations of Seebach’s oxazolidine/oxazoline alkylation protocol\textsuperscript{23} for formation of the C-5 quaternary center. The critical hydroxyisobutyl side chain was the very first structural and stereochemical issue addressed. Upon installation, the side chain was protected along with the amino functionality as a chiral oxazolidine/oxazoline from which the stereochemistry of the $\gamma$-lactam is derived.

Baldwin’s synthesis of 1 employed a chiral bicyclic $\gamma$-lactam derived from (R)-
glutamate (23) for stereochemical induction (Scheme 2-4). A sequence of methylation, selenation and oxidation yielded the $\alpha,\beta$-unsaturated $\gamma$-lactam (24). Aromatization to siloxypyrrrole 25 provided a key intermediate which was eventually utilized as the silyl enol ether in a Mukiyama type aldol coupling. Using isobutyraldehyde as the electrophile and SnCl4 as the Lewis acid, the aldol coupling proceeded in only mediocre yield with a favorable 9:1 ratio of 26 and its C-9 epimer. Upon formation of the quaternary center, the secondary hydroxyl was protected through acetylation. Syn-dihydroxylation of the unsaturated lactam using osmylation proceeded stereoselectively via substrate control in good yield. Removal of the tertiary hydroxyl of the diol using Barton’s cyclic thiocarbonate radical methodology25 occurred in excellent yield, however, the resultant product was approximately a 1:1 ratio of C-6 epimers. Exposure to 0.5N NaOH resulted in a significant increase of the desired diastereomer (27), although substantial amounts of starting material (10%), epi-27 (10%) and elimination (5%) persisted. Cleavage of the hemiacetal using hydrogenation resulted in a mixture of epimers at C-3 (formerly C-6).
The one-pot global protection was achieved by sequential addition of triethylysilylchloride and acetic anhydride/pyridine to mask the primary and secondary hydroxyls respectively. Deprotection of the silyl ether and oxidation using chromic acid yielded the carboxylic acid which was saponified with NaOH to yield 3. The synthesis of 1 was completed using Corey’s method of direct addition of the N-acetylcysteine sidechain. Baldwin’s synthesis utilized a unique route and was similar to Corey’s first synthesis in that he relied on the stereochemical nature of the starting amino acid for stereochemical induction, thus using no asymmetric methods. Drawbacks of the synthetic route were the low yields of the aldol coupling and the occurrence of diastereomeric mixtures in no less than three steps of the synthesis. Overall, Baldwin’s synthesis of 1 was achieved in 20 steps with a 4.3% overall yield.

2.6 Chida’s Total Synthesis of Lactacystin

Chida’s total synthesis of 1 was novel in the sense that the three previous reports started with amino acid derivatives. In this particular synthesis D-glucose serves as the starting material and the stereogenic template. The primary and secondary hydroxyls of the previously prepared 3-deoxy-1,2-O-isopropylidene-3-C-methyl-α-D-allofuranose (28) were benzylated and oxidized, respectively, to the protected ketone (Scheme 2-5). The Wittig reaction resulted in an inseparable mixture of (E)- and (Z)-isomers (29) in a 1:1 ratio. Reduction of the ester and reaction with trichloroacetonitrile gave the Overman rearrangement substrate, trichloroacetimidate 30. The rearrangement was preformed in a sealed tube by heating 30 to 150 °C in toluene for 89 hours to give terminal olefin 31.
The reaction gave a 60% yield of a mixture of C-5 epimers in a favorable 5:1 ratio. Hydrolysis of the acetonide and oxidative cleavage of the diol affected formation of the hemiaminal. Subsequent chromic acid oxidation gave the γ-lactam which, upon treatment with NaBH₄, was completely deprotected yielding 32. A sequence of reactions including protection of the secondary hydroxyl of 32, deprotection and oxidation of the benzyl ether to the aldehyde and addition of isopropylmagnesium bromide resulted in a complex mixture of C-9 epimers and reduced primary alcohol. Chromatographic separation of the mixture enabled recycling of the reduced product back into the sequence. The undesired C-9 epimer was subject to Moffatt oxidation and selectively reduced to yield desired alcohol 33. Desilylation, ozonolysis and selective oxidation using sodium chlorite provided the common intermediate 3. As was the case with the other syntheses, Chida also finished the synthesis of 1 using Corey’s protocol. The novelty of this synthesis, in
addition to starting with D-glucose, lies in the formation of the C-5 quaternary center via Overman rearrangement. The three previous syntheses formed the C-5 quaternary center via stereoselective aldol coupling. The shortcomings of the protocol are evident not only in the poor selectivity of the Wittig reaction and the Overman rearrangement, but especially in the necessity of a sealed tube for the latter transformation. The rearrangement, particularly, put an original twist on the protocol but renderd it impractical.

2.7 Corey’s Second Total Synthesis of Lactacystin

Corey eventually published a new, shorter, more efficient synthesis of \(1\) employing a unique strategy for controlling diastereoselectivity utilizing a blocking group.\(^{14}\) This report featured an expedient construction of the \(\gamma\)-lactam moiety and installation of the isopropyl side-chain later in the synthesis to facilitate lipophilic group analog synthesis. The effectiveness of the blocking group itself relied on three requirements; (a) it had to be readily reducible, (b) it had to be sufficiently bulky to control the stereochemistry of the hydroxymethylation of the \(\beta\)-keto ester and (c) it had to facilitate a scalable enantioselective process. The methylsulfide blocking group was installed by thioalkylation of dimethyl methylmalonate giving the methylsulfanyl derivative \(34\) (Scheme 2-6). An enantioselective hydrolysis using porcine liver esterase gave the stereogenic monoester \(35\) in 62\% yield and 95\% \(ee\) after recrystallization. Exposure of the carboxylic acid to oxalyl chloride provided the stereogenic acid chloride which readily coupled with \(N\)-PMB-glycine methyl ester. Subsequent Dieckmann cyclization resulted in the cyclic \(\beta\)-keto ester in a 1:1 ratio of diastereomers \(36\). At this
point in the synthetic route the methylsulfide blocking group was intact, the γ-lactam skeleton was formed and the α-carbon of the β-keto ester was primed for aldol coupling. Enolization using DBU and addition of formaldehyde resulted in a 9:1 ratio of diastereomers which underwent stereoselective reduction of the keto moiety yielding 37 with a 95% yield and 99% ee. The effectiveness of the methylsulfide blocking group was showcased in the two previous transformations for its ability to control selectivity through the stereogenic environment of the substrate alone without external asymmetric induction. Simultaneous protection and selective deprotection of the primary hydroxyl resulted in a silyl ether protected secondary hydroxyl and an oxidizable primary hydroxyl group. Diastereoselective desulfurization using Raney nickel resulted in a 10:1 ratio of epimers at the C-3 center. Dess-Martin oxidation of the primary alcohol to the aldehyde 38 set the system up for nucleophilic addition of the isopropyl side-chain or other nucleophiles leading to potential analogs. Grignard and organolithium additions of the isopropyl group proceeded slowly and resulted in the retro-aldol cleavage product. The
use of 2-propenyl Grignard reagent in conjunction with TMSCl as an anion trap was efficient and the reaction occurred stereospecifically to give secondary alcohol \textbf{39} in high yield with no trace of retro-aldol cleavage. Corey proposed that the stereocontrol is a result of the steric blocking that exists when Mg\(^{2+}\) chelates the 1,3-dicarbonyl system. The completion of the synthesis involved hydrogenation of the isopropenyl group, desilylation of the secondary hydroxyl group and hydrolysis of the ester moiety yielding dihydroxy acid \textbf{40}. As in previous work, BOPCl was used to affect lactonization and ceric ammonium nitrate oxidation of the \(N\)-PMB group yields \(\beta\)-lactone \textbf{2}. This protocol touts its applicability from an economic standpoint as well as its efficiency of synthetic steps and isolation of pure products. An additional point is the versatility it lends to analog synthesis for bioassay studies.

\textbf{2.8 Kang’s First Formal Synthesis of Lactacystin}

Shortly after Corey’s second generation synthesis, Kang reported two novel routes\textsuperscript{28} to \textbf{1}, both employing an intramolecular mercurioamidation of an allylic trichloroacetimidate.\textsuperscript{29} The first protocol started with the base promoted ring opening of Sharpless epoxide \textbf{41}\textsuperscript{30} followed by functionalization of the primary hydroxyl as the trichloroacetimidate (\textbf{42}) using trichloroacetonitrile and DBU (Scheme 2-7). Treatment of \textbf{42} with mercuric trifluoroacetate and K\(_2\)CO\(_3\) resulted in mercuration of the olefin and concomitant oxazoline formation via intramolecular mercurioamidation. Workup using TEMPO and LiBH\(_4\) gave the masked hydroxyl \textbf{43}. Routine protection of the secondary hydroxyl, deprotection of the primary hydroxyl and sequential oxidation gave oxazoline \textbf{44}. Reflux under acidic conditions followed by addition of zinc initiated oxazoline
hydrolysis, concomitant γ-lactam cyclization and cleavage of the TEMPO group.

Protection of the cis- primary and secondary hydroxyls as the acetonide occurred selectively (7:1) over the gem-hydroxymethyl groups presumably based on the cyclization of the fused 5,6-system (45) as opposed to the spiro system. Swern oxidation of the persisting primary hydroxymethyl group to the aldehyde and Grignard addition of

\[ \text{HO-OTBDPS} \quad \text{NH} \quad \text{Cl}_3\text{C-NH} \quad \text{OTBDPS} \quad \text{OH} \quad \text{Cl}_3\text{C} \quad \text{TEMPO} \quad \text{CO}_2\text{H} \quad \text{OMOM} \quad \text{Cl}_3\text{C} \quad \text{TEMPO} \quad \text{NH} \quad \text{O} \quad \text{O} \quad \text{OH} \quad \text{OH} \quad \text{NH} \quad \text{O} \quad \text{OH} \]

\[ \text{i) LDA, THF} \quad \text{ii) Cl}_3\text{CCN, DBU} \]
\[ \text{i) Hg(O}_2\text{CCF}_3\text{)}_2 \quad \text{ii) TEMPO, LiBH}_4 \]
\[ \text{i) MOMCl, DIPEA} \quad \text{ii) TBAF, THF} \quad \text{iii) Swern Ox.} \quad \text{iv) K MnO}_4 \]

\[ \text{CO}_2\text{H} \quad \text{OH} \]

^iPrMgBr resulted in a disappointing 1:1 ratio of C-9 epimers. Serendipitously, it was realized that with addition of excess Grignard reagent to the ester analog, the reduced desired product 46 was obtained exclusively. Intermediate 46 was the previously known trihydroxy intermediate of Baldwin’s synthesis, thus completing the first formal synthesis utilizing Kang’s intramolecular mercurioamidation methodology.

2.9 Kang’s Second Formal Synthesis of Lactacystin

The second simultaneous report involved a completely original route to 1. The key step in the synthesis was, again, the intramolecular mercurioamidation of an allylic trichloroacetimidate. This time the functionality of the latent lactam is installed
throughout the first part of the synthesis and the key step was the endgame to 1. The Sharpless epoxide 47 was subjected to base promoted ring opening and the resulting allylic and secondary alcohols were selectively oxidized and benzoylated respectively (Scheme 2-8). Stereoselective crotylboration of $\alpha,\beta$-unsaturated aldehyde 48 provided alcohol 49 in a 50:1 diastereomeric ratio. The resultant secondary alcohol was protected as the MOM ether and the terminal olefin was oxidized to the aldehyde. Exposure of the aldehyde to hydroxylamine hydrochloride resulted in the oxime and upon treatment with methanesulfonic anhydride and DBU the latent nitrile (50) was unmasked. Hydrolysis of the benzoyl protecting group and functionalization with trichloroacetonitrile resulted in trichloroacetimidate 51. The key step of this synthesis is initiated by addition of mercuric acetate to the olefin of 51. Spontaneous cyclization to the oxazoline gives a mixture of separable diastereomers, the desired mercurate in 64%. As in the previous synthesis problematic oxidative demercuration issues were circumvented by exposing the oxazoline to LiBH$_4$/TEMPO providing 52. Exposure to 6$N$ HCl followed by AcOH
hydrolyzes the oxazoline, initiates cyclization and removes the TEMPO group resulting in the known triol 46. Overall, both of Kang’s syntheses of 1 rely on Sharpless asymmetric epoxidation early in the synthetic scheme and utilize the intramolecular mercurioamidation of a trichloroacetimidate to set up a zinc promoted cyclization to the γ-lactam.

2.10 Adams’ Total Synthesis of Lactacystin Analog PS-519

Lastly, Adams’ team at LeukoSite conducted an independent synthesis and structure activity study of 2 and its analogs. Confirming and building upon Corey’s data, Adams found that increasing the bulk of the C-7 alkyl substituent the activity increases 2-fold. Ultimately, the group settled on the n-propyl C-7 substituent/β-lactone combination to give them the best activity and labeled the experimental compound PS-519. The novelty of this synthesis lies in the use of a semi-convergent route. All other syntheses to date have been strictly linear routes based on the compact nature of 1 and 2. The key step of the synthesis is the convergence of a stereogenic aldehyde and a trans-oxazoline via a

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**Scheme 2-B. Synthesis of the trans-Oxazoline Coupling Partner**

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doubly diastereoselective aldol coupling. The construction of the oxazoline fragment begins with Sharpless’ asymmetric dihydroxylation\textsuperscript{31} of the Wittig product of isobutyraldehyde and methyl-triphenylphoranylideneacetate (53). The quantitative conversion to diol 54 occurred with only 77\% ee but was improved to >99\% ee after recrystalization. Upon addition of trimethyl orthobenzoate the diol was tied up as the cyclic orthoester and subsequently opened with the addition of acetyl bromide resulting in the bromohydrin 55. Azide 56 is the product of bromide displacement and hydrogenation yields amine 57. Refluxing in toluene with toluenesulfonic acid provided stereogenic

![Scheme 2-10. Synthesis of the α-Alkyl-β-formyl Amide Coupling Partner](image)

oxazoline 58 that would ultimately provide the hydroxyisobutyl and C-5 portions of PS-519. The coupling partner of 58 is a chiral α-alkyl-β-formyl amide that will provide the chelation control for the doubly diastereoselective aldol coupling. The coupling fragment is derived from acyloxazolidinone 59 (Scheme 2-10). Alkylation of the titanium enolate using benzyloxymethyl chloride gave oxazolidinone 60 which, after peroxide hydrolysis, yields the carboxylic acid 61. Transformation of the acid to the diethyl amide 62 was achieved using triethylamine and TBTU to add diethylamine. Hydrogenolysis of the benzyl ether yielded the hydroxy amide (63) which, upon exposure to Dess-Martin
oxidation conditions resulted in the $\alpha$-alkyl-$\beta$-formyl amide (64) coupling partner. After exploring a multitude of conditions for the aldol coupling of 58 and 64, it was determined that enolization of the oxazoline and sequential addition of dimethylaluminum chloride followed by the aldehyde gave the 6S alcohol (65) exclusively. The stereochemical rationale was explained using the transition state model shown in Figure 2-2. Chelation of the 1,3-dicarbonyl system of 64 by the Lewis acid requires the $n$-propyl substituent to adopt a si-face blocking position. This leaves only approach from the re-face possible in anti-Felkin-Ahn-Eisenstein fashion. While the stereochemistry of C-6 was a direct result of the chelation model, the C-5 stereochemistry is purely based on steric bias of the isopropyl substituent of the oxazoline. Apart from obtaining alcohol 65 exclusively, the significance of this transformation lies in the use of a dialkylaluminum chloride as a
bidentate Lewis acid as opposed to its typical utility as a monodentate coordinator. With alcohol 65 in hand, three routine transformations remained to complete the synthesis of PS-519 (Scheme 2-11). As seen in previous syntheses, hydrogenolysis of the oxazoline initiates spontaneous cyclization to the γ-lactam 66 which was recrystallized and structurally confirmed using X-ray diffraction analysis. Saponification of the methyl ester using NaOH yielded dihydroxy acid 67 which was then activated by conversion to the mixed anhydride using isopropenyl chloroformate. Subsequent cyclization resulted in β-lactone 9, an analog of the highly potent β-lactone 2. Adam’s synthesis of 9 was also applied to the total synthesis of 2 using a parallel method with only slight variations in starting material preparation. This particular synthesis is highlighted by a semi-convergent protocol requiring 10 operations resulting in a 20% overall yield of 9 starting from readily available oxazoline 58.

Overall, lactacystin (1) and its various analogs have garnered much attention based not only on the pharmacological significance of the target but on the synthetic challenges they present. The syntheses above are the premier works preformed on this family of molecules and do not include the many unsuccessful attempts or works in progress that have not yet been reported.
Chapter Three

Stereogenic γ-Lactams via Rhodium Catalyzed Intramolecular C-H Insertion

Of the many natural products that possess γ-lactam cores, lactacystin (1) and its intermediates are quite possibly the most outstanding in terms of biological activity, structural originality and synthetic appeal. The β-lactone (2) is particularly intriguing based on its bicyclic [3.2.0] arrangement, four contiguous stereogenic centers (one a quaternary center) and high concentration of heteroatoms. Considering the methodologies we developed, 2 appeared to be an ideal synthetic target for its validation. In all previous syntheses of 1 and its analogs the strategy is to asymmetrically functionalize a linear molecule followed by formation of the γ-lactam by nucleophilic addition of an amine moiety to an activated ester. Our proposed synthesis involved γ-lactam formation via rhodium catalyzed intramolecular C-H insertion followed by stereoselective functionalization of the γ-lactam core.

3.1 C-H Insertion of the Acyclic System

Our first tier of this methodology originated from our discovery of rhodium catalyzed intramolecular C-H insertion of α-diazo-α-(phenylsulfonyl)acetamides to give γ-lactams
regio- and stereoselectively. Previous work showed that this general transformation, when applied to $\alpha$-amino acid derivatives, typically resulted in mixtures of $\beta$- and $\gamma$-lactam regioisomers. Padwa and Wee reported that the ratios of the regioisomers could be affected by the electronic nature of the carbenoid $\alpha$-substituent. Our model system utilizes an $\alpha$-phenylsulfonyl substituent for alteration of the electron density of the metallocarbenoid and also exerts a steric effect for enhancement of regio- and stereoselectivity. The showcase example of this transformation from the $\alpha$-diazo-$\alpha$-(phenylsulfonyl)acetamide to the trans-$\gamma$-lactam is shown in Scheme 3-1. Reflux conditions using rhodium acetate dimer provide the $\gamma$-lactams exclusively in excellent yield with no $\beta$-lactam or aromatic cycloaddition side products. Rationalization of the regio- and stereochemical selectivity is shown in Scheme 3-2. The first control element of this transformation is the conformational effect. Rhodium carbenoid 70 can adopt the s-cis and the s-trans conformations. The s-cis conformer is favored due to the severe nonbonded interaction between the $t$-butyl substituent and the rhodium ligands that exist in the s-trans conformer. As a result of the conformational effect, two possible transition states exist through which insertion can occur. Reaction via 5-membered transition state 71 and 6-membered transition state 72 would yield $\beta$-lactam 73 and $\gamma$-lactam 74 respectively. Padwa and Doyle performed similar transformations using the $\alpha$-acetyl
substituent with various rhodium catalysts. All attempts resulted in mixtures of \( \beta \)- and \( \gamma \)-lactam with no ratio of regioisomers exceeding 3:7 respectively. In the same report it was proposed that when a catalyst with an electron donating ligand is used the rhodium carbenoid is stabilized thus proceeding through a late transition state. As shown by the results, when the \( \alpha \)-phenylsulfonyl substituent is incorporated into the insertion precursor we achieve complete selectivity for the \( \gamma \)-lactam. Presumably, the \( \alpha \)-phenylsulfonyl substituent lends further stabilization to the carbenoid allowing the cyclization to occur via 6-membered transition state exploiting the stereoelectronic effect. Also explained by the transition state is the \( trans \)- geometry at C-3 and C-4. For insertion to occur the carbon-rhodium “bond” and the target C-H bond must be arranged parallel to each other. Two conformations exist since insertion is occurring at a methylene center. The more favorable conformation in this case is that in which the C4/C5 bond is oriented so that the phenyl substituent is in the pseudoequitorial position resulting in \( trans-\gamma \)-lactam 74. The outstanding selectivity of this transformation makes it an attractive method of
constructing γ-lactams.

3.2 C-H Insertion of the Cyclic System

In an attempt to expand the general applicability of this methodology we considered utilizing amino acids as highly versatile, stereogenic substrates. To our surprise an extensive literature search revealed that previous attempts using amino acids as C-H insertion substrates were unsatisfactory due to poor regio- and stereoselectivities and side reactions. With an original approach, our methodology was modified to accommodate amino acid derived precursors for the synthesis of highly functionalized chiral γ-

![Scheme 3-3. Synthesis Stereogenic γ-Lactams From α-Amino Acid Precursors](image)

Synthesis of the prototype phenylalanine derived α-diazo-α-(phenylsulfonyl)acetamide 77 began with esterification of the acid function of (L)-phenylalanine followed by amide coupling using (phenylthio)acetic acid resulting in amide 75 (Scheme 3-3). Reduction of the methyl ester using LiBH₄ generated in situ gave the primary alcohol. With protection of the alcohol and amide moieties as our focus, we sought to simultaneously tie-up both functional groups as acetonide 76. In toluene, the
alcohol was refluxed with 2,2-DMP and catalytic TsOH. A Dean-Starke apparatus was instrumental in water removal. This particular transformation was quite disappointing based on the inconsistency of product yield and side reactions that occurred. After a tedious purification using silica gel column the phenylsulfide was completely oxidized to the phenylsulfone using multiple equivalents of m-CPBA. Finally, the α-position was activated for carbenoid formation by installation of a diazo group using Davies’ p-ABSA reagent and DBU yielding 77. Intramolecular C-H insertion occurs efficiently under reflux in methylene chloride with a catalytic amount of rhodium acetate dimer. This transformation provides the trans-γ-lactam 78, as a single diastereomer, in excellent yield without formation of β-lactam or aromatic cycloaddition products. The regio- and stereoselectivity of this cyclization is explained using a modified transition state theory congruent to our aforementioned acyclic system and control elements previously discussed (Scheme 3-4). Metallocarbenoid 79 adopts the favorable s-cis conformation as dictated by the conformational effect. Based on the severe nonbonded interaction

![Scheme 3-4. Conformational and Stereochemical Effects on C-H Insertion of α-Amino Acid Derivatives](image-url)
between the rhodium ligands and the gem-dimethyl moiety of the acetonide, *s-trans*-79 is the unfavorable conformation. Insertion then occurs via the 6-membered transition state (81) as directed by the stereoelectronic effect and proven by the absence of β-lactam formation. The *trans*-stereochemistry of the γ-lactam is established by the preference of the C-4 substituent to orient itself in the pseudoequatorial position, thus relieving the 1,3-diaxial interaction present in transition state 80. The profound significance of the conformational effect is exemplified by attempting to perform C-H insertion on an analog of 77 that has a formaldehyde derived acetal (82) in place of the acetonide (Scheme 3-5). The *s-trans* 83 conformation of the amide is more favored in the presence of the methylene group. In this case, the typical insertion center is oriented away from the rhodium carbenoid, therefore, no insertion occurs.

Intramolecular C-H insertion of the (L)-phenylalanine derivative resulted in γ-lactam 78 as a single enantiomer whose stereochemistry was governed by the existing stereocenter of the original amino acid. The stereochemistry of the γ-lactam (78) was confirmed by X-ray crystallographic analysis. Ultimately, two new stereocenters are formed in a single synthetic operation providing highly versatile, functionalized, stereogenic γ-lactams selectively.

Scheme 3-5. Conformational Requirements for Intramolecular C-H insertion
3.3 C-H Insertion of Amino Acid Derived α-Diazo-α-(phenylsulfonyl)acetamides

With a highly effective protocol for converting (L)-phenylalanine into a highly functionalized stereogenic γ-lactam in hand, we decided to apply it to a series of α-amino acids. It is well established that the trend for preference of C-H insertion to occur at a particular center is methine>methylene>methyl. The electron deficient carbenoid carbon complexes with the most electron rich C-H bond via the 6-membered transition state and insertion immediately ensues. The substrates were specifically chosen to examine our stereoelectronic and substituent effect hypotheses by containing multiple insertion sites and varying degrees of electron donating and withdrawing substituents, respectively.

Table 3-1 shows the results of C-H insertion on α-amino acid derived α-diazo substrates with various alkyl substituents and multiple potential insertion centers. In most cases the γ-lactam was formed exclusively and in high yield. Entries 1 and 2 are perfect examples of the influence that the stereoelectronic effect has on the course of the reaction. With

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>reactant</th>
<th>yield (%)</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>84(^a)</td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>86(^a)</td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>(^t)Pr</td>
<td>88(^b)</td>
<td>87(^c)</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>90(^a)</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)CO(_2)Me</td>
<td>92</td>
<td>64</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>4-(MeO)Ph</td>
<td>94(^d)</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>77(^d)</td>
<td>91</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\) Starting with the corresponding racemic α-amino acid. \(^b\) Rh\(_2\)(pfb)\(_4\) was used. \(^c\) γ-lactam was also obtained (6%). \(^d\) Starting with 4-methoxtyrosine.

Table 3-1. C-H Insertion of α-Diazo Substrates at the Methylene Position
two electronically similar methylene centers present on the ethyl (84) and propyl (86) alkyl chains as the possible insertion sites, the stereoelectronic effect dictates the formation of the γ-lactam in favor of the β- and δ-lactams. Entry 3 shows the preference for insertion to occur at a methine center. Though insertion at the methylene center of the isobutyl (88) side chain provides the γ-lactam in high yield, six percent of δ-lactam is formed as well. In comparison, the only difference that exists between the analogs is the presence of a methine center in 88 as opposed to an additional methylene center in 86. In the case of 86 no δ-lactam is formed and it can be concluded that the stereoelectronic effect dictates γ-lactam formation exclusively. However, the preference for insertion at a methine center is significant enough to provide the δ-lactam, albeit as the minor product.

The goal of entries 4 and 6 were to compare the results of insertion on analogs of our showcase example (entry 7). Presumably, the facile conversion of 77 to 78 was enhanced by the phenyl substituent directly adjacent to the methylene center. Incorporation of an additional methylene center to the insertion precursor (90) had no effect on the transformation and only γ-lactam was formed. In an attempt to enhance the transformation of 77 to 78, a tyrosine analog with an electron donating 4-methoxy substituent was derived (94). No appreciable improvement was noticed in the reaction in light of the modest increase in electron density. α-Diazo amide 92 is an (L)-glutamic acid derivative that possesses an electron withdrawing carbomethoxy group. This reaction proceeded with only a moderate yield as a result of the decreased reactivity of the insertion center. This particular reaction was intriguing since there was no β-lactam, δ-lactam or ylide formation detected and no starting material recovered. The γ-lactam was
the only product recovered and the other side products were indecipherable. A series of analogs with potential methyl and methine insertion centers were also subject to our methodology (Table 3-2). α-Diazo amide 96 derived from (L)-alanine underwent intramolecular C-H insertion to yield γ-lactam 97 exclusively, though only in moderate yield. Insertion into the methyl C-H is an unfavorable process especially in the presence of a methine center from which the β-lactam would form. This example corroborates the strong influence that the stereoelectronic effect exerts on this transformation. In entries 2 and 3 both insertion precursors possess methine centers from which the γ-lactam, via C-H insertion, will potentially form. C-H insertion of α-diazo amides 98, an (L)-valine derivative, and 100, an (L)-isoleucine derivative, both proceeded with excellent yield and result in exclusive γ-lactam formation (99 and 101 respectively) as anticipated. Disastereomeric mixtures were formed in both cases. This is a result of the substituents at the methine centers having no significant steric bias (two methyls in the case of (L)-valine and a methyl and an ethyl in the case of (L)-isoleucine) to achieve a particular conformation at the insertion center. A point of note is that upon desulfonation of 101 using Na(Hg) a single diastereomer (102) was recovered which suggests that the insertion

![Chemical structure](image)

**Table 3-2. C-H Insertion of α-Diazo Substrates at Methyl and Methine Positions**

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>reactant</th>
<th>yield (%)</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>96</td>
<td>67</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Me</td>
<td>98</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>Me</td>
<td>100</td>
<td>93</td>
<td>101</td>
</tr>
</tbody>
</table>
proceeds with complete retention of configuration of the inserton center. In light of the success of methylene insertion we attempted insertion of electronically activated methylene centers. A set of α-amino acid derivatives that were suitable for this transformation were those of (L)-serine (103) and two different (L)-threonine analogs (105 and 107) (Table 3-3). We anticipated an enhancement in efficiency of insertion into the methylene C-H adjacent to a heteroatom due to electronic inductive effects. As expected, the efficiency of insertions were improved as yields were comparable with data from methine C-H insertions. Entries 1 and 2, which possessed essentially identical insertion sites, both proceeded with excellent yield and resulted in exclusive trans-γ-lactam formation. The alternate (L)-threonine derivative 107 also underwent C-H insertion in high yield but resulted in a diastereomeric mixture of γ-lactams at the C-3

---

Table 3-3. C-H Insertion of α-Diazo Substrates at Electron Rich Methylene Positions

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>reactant</th>
<th>yield (%)</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>103</td>
<td>97</td>
<td>104</td>
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<td>2</td>
<td>H</td>
<td>Me</td>
<td>105</td>
<td>94</td>
<td>106</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>H</td>
<td>107</td>
<td>92</td>
<td>108</td>
</tr>
</tbody>
</table>

Scheme 3-6. Functionalized Stereogenic γ-Lactams are Versatile Synthetic Intermediates

from methine C-H insertions. Entries 1 and 2, which possessed essentially identical insertion sites, both proceeded with excellent yield and resulted in exclusive trans-γ-lactam formation. The alternate (L)-threonine derivative 107 also underwent C-H insertion in high yield but resulted in a diastereomeric mixture of γ-lactams at the C-3
position as experienced previously with the (L)-valine and (L)-isoleucine derivatives. Presumably, the steric bias of the methyl group rivals that of the \textit{tert}-butyldimethylsilyl ether since the bulk of the substitution on the silicon is one oxygen atom removed from the reaction center. Nevertheless, insertion at the chiral center of the side-chain of (L)-threonine results in retention of configuration. Moreover, the success of insertion at the methylene position adjacent to a heteroatom adds a degree of functionality to the \(\gamma\)-lactam. An intriguing point and an impetus for further pursuit and application of this methodology is the striking resemblance that \(\gamma\)-lactams 104 and 108 have with synthetic targets 1 and 109, and it is, therefore, anticipated that they will be valuable synthetic intermediates (Scheme 3-6). In general this methodology is useful for the synthesis of highly functionalized \(\gamma\)-lactams from stereogenic \(\alpha\)-amino acids. In one synthetic operation, two additional chiral centers are formed in a stereoselective fashion and result in \(\gamma\)-lactams that are functionalized at each carbon center.

### 3.4 C-H Insertion of \(\alpha\)-Diazo-\(\alpha\)-(substituted)acetamides

The success of C-H insertion of \(\alpha\)-amino acid derivatives encouraged us to explore alternate pathways for diversified functionality and a streamlined synthetic sequence. Our initial route for construction of the \(\alpha\)-diazo-\(\alpha\)-(phenylsulfonyl)acetamides derived from \(\alpha\)-amino acids was relatively costly, suffered from yield inconsistency and required multiple laborious purification steps. Particularly, the acetonide formation step, which involved tying-up the amide nitrogen and the primary alcohol, was impetuously
inconsistent. Side products, incomplete cyclizations and a rather formidable flash column purification rendered this process impractical. An improved sequence that was one synthetic operation shorter, utilized commodity reagents and required no purification, until after the diazotransfer step, was formulated. The new protocol called for the reduction of the (L)-phenylalanine using lithium aluminum hydride to provide the corresponding amino alcohol (Scheme 3-7). The Fischer protocol was utilized to complex and precipitate the unreacted LAH as a means of filtering the product and avoiding the use of aqueous work-up procedures. A superior procedure for acetonide formation involved refluxing the amino alcohol in a 1:1 mixture of 1,2-DCE and acetone with the addition of Na₂SO₄ as a water scavenger. This reaction was complete in less than one hour and simple filtration of the solids followed by evaporation of the solvent provided acetonide 110 cleanly in near quantitative yield. This improved protocol also provided options for functionalization of this system. The secondary amine, in this case, could be
easily acylated using a variety of reagents. Toward obtaining our \(\alpha\)-diazo-\(\alpha\)-(phenylsulfonyl)acetamide intermediate, a three-step procedure consisting of \(N\)-acylation using bromoacetyl bromide followed by bromide displacement with benzenesulfonic acid sodium salt proceeded cleanly and in very good yield providing the known phenylsulfonyl intermediate (77). With our goal of highlighting the profound effect that the \(\alpha\)-phenylsulfonyl substituent plays in \(\gamma\)-lactam formation via C-H insertion, a series of \(\alpha\)-diazoacetamide analogs with \(\alpha\)-substituents of varying electron-withdrawing capacities were prepared. The three variations used to contrast to the \(\alpha\)-phenylsulfonyl

![Chemical structure](attachment:image.png)

Table 3-4. C-H Insertion of \(\alpha\)-Diazo Substrates with Varied \(\alpha\)-Substituents

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>(R)</th>
<th>78 (%) yield</th>
<th>78-lactam</th>
<th>78-lactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhSO(_2)</td>
<td>78</td>
<td>84</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>EtO(_2)C</td>
<td>114</td>
<td>93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>MeCO</td>
<td>115</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>-</td>
<td>91</td>
<td>116</td>
<td>116</td>
</tr>
</tbody>
</table>

substituent were the \(\alpha\)-ethoxycarbonyl, \(\alpha\)-acetyl and, simply, \(\alpha\)-diazo substituents (Table 3-4). Our improved protocol for synthesis of the \(\alpha\)-substituted acetamides was applied and construction of the three analogs was possible from acetonide 110. \(N\)-acylation using ethyl-4-chloroacetoacetate and diketene afforded the \(\alpha\)-ethoxycarbonyl 111 and \(\alpha\)-acetyl 112 acetamides respectively in high yield with no need for purification. Diazotransfer of both 111 and 112, although occurring at a decreased rate as compared to the \(\alpha\)-phenylsulfonyl acetamides, proceeds in very high yield. Analog 113, which possessed a proton as the \(\alpha\)-substituent, is a product of base promoted decarbonylation of 112 using
LiOH in aqueous media. In anticipation of consistent results with previous reports which showed poor stereo- and regioselectivities, we were surprised to find that \textit{trans}-\(\gamma\)-lactam formation was the exclusive product of C-H insertion with exception to the \(\alpha\)-diazo substrate 113. Cyclization of 111 and 112 occurred efficiently and in very high yield providing chiral \(\gamma\)-lactams 114 and 115 with functionality that is more versatile than the phenylsulfone substituent. \(\alpha\)-Diazo substrate 113, when subjected to insertion conditions, resulted in aromatic cycloaddition yielding cycloheptatriene 116. The latter result was not at all surprising and is, in fact, quite common when aromatic systems are in the presence of carbenes. The peculiar aspect of this data is the complete selectivity of the transformations. We expected a certain degree of \(\beta\)-lactam formation and obtained exclusively \(\gamma\)-lactam. In the case of the \(\alpha\)-Diazo substrate 113, we expected a mixture of products including \(\gamma\)-lactam, but recovered the aromatic cycloaddition product exclusively. The obvious explanation for this data is the absence of an electron-withdrawing \(\alpha\)-substituent. Padwa and Doyle have shown, using competition experiments, that the rhodium catalyst ligands play a major role in reaction preference.\textsuperscript{35e} Therefore, in an attempt to switch the preference in reactivity from aromatic cycloaddition to \(\gamma\)-lactam formation, we used the rhodium caprolactamate catalyst which has a more electron donating ligand. Under these conditions the reaction yielded mostly
aromatic cycloaddition product 116 along with a minor product that was eventually elucidated as the norcaradiene tautomer (117) of the major product (Scheme 3-8). Two explanations for the persistence of aromatic cycloaddition in the absence of an $\alpha$-substituent have appeared in the literature. Wee suggests that the electronic differences of the $\alpha$-substituents dictate the reaction pathway and, in the case of the $\alpha$-diazo substrate, preference for aromatic cycloaddition dominates.\textsuperscript{35d} Padwa and Doyle reason that conformational influences of the $\alpha$-substituents (other than $\alpha$-diazo, of course) inhibit the approach of the phenyl group to the reactive carbene center.\textsuperscript{35e} This theory is further corroborated by the fact that highly electron rich phenyl rings, as in the case of dimethoxy phenyl groups, do not undergo aromatic cycloaddition despite their increased vulnerability to carbene attack.\textsuperscript{40}

Overall, our methodology is an improvement over previous methodologies based on the regio- and stereoselectivities obtained from C-H insertion. It was originally assumed
that the $\alpha$-phenylsulfonyl group was responsible for the selectivity of the methodology, and it is most definitely the case with our initial, acyclic example. Clearly, it is not the only factor in play since comparable success was observed in the presence of the $\alpha$-ethoxycarbonyl and $\alpha$-acetyl substituents. Our latest rationalization is that the acetonide moiety present in all of the amino acid derived systems must play a significant role in lending a degree of conformational constraint to the transition state of the transformation. The aromatic cycloaddition product is not observed when electron withdrawing groups are present and the unfavored 5-membered transition state (119) required for $\beta$-lactam formation would experience severe non-bonded interactions. With this particular system used for C-H insertion of $\alpha$-amino acid derivatives $\gamma$-lactams are the only likely product (Scheme 3-9).

At this point the phenyl group had participated in the reaction and had a substantial
influence on the results. To dispel any skepticism about the success of this project we applied the same methodology to an amino acid system that included an \( n \)-propyl side chain. In this case multiple equivalent insertion sites were available without the influence of the phenyl group. We initiated this leg of the project with the racemic, unnatural amino acid norvaline. The improved protocol for synthesis of the C-H insertion precursors was applied to the construction of the norvaline analogs (Scheme 3-10). Reduction of the amino acid with LAH followed by acetonide formation yielded versatile intermediate \( 123 \). Next, the diversification using the various \( N \)-acylation conditions was carried out followed by diazo transfer resulting in insertion precursors \( 86, 124 \) and \( 125 \). Deacylation of \( 125 \) using aqueous LiOH provided \( \alpha \)-diazo substrate \( 126 \). Exposure of the diazosubstrates to the standard C-H insertion conditions yielded \( \gamma \)-lactams in all cases (Table 3-5). In the case of the \( \alpha \)-phenylsulfonyl \( (86) \), \( \alpha \)-methoxycarbonyl \( (124) \), and \( \alpha \)-acetyl \( (125) \) compounds, insertion occurred with complete regio- and stereoselectivity. Yields were all very good and no minor products were detected. On the other hand, \( \alpha \)-diazo substrate \( 126 \) formed a mixture of products with very good yield but, in only a 2:1 ratio which were separated and identified as the \( \delta \) and \( \gamma \)-lactams respectively.

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>( R )</th>
<th>( \gamma )-lactam</th>
<th>yield (%)</th>
<th>( \delta )-lactam</th>
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<tr>
<td>1</td>
<td>86</td>
<td>PhSO(_2)</td>
<td>87</td>
<td>91</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>124</td>
<td>MeO(_2)C</td>
<td>127</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>MeCO</td>
<td>128</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>126</td>
<td>H</td>
<td>129</td>
<td>84(^a)</td>
<td>130</td>
</tr>
</tbody>
</table>

\(^a\) Product ratio was 2:1 favoring the \( \delta \)-lactam

Table 3-5. C-H Insertion of \( \alpha \)-Diazo Norvaline Derivatives
3.5 C-H Insertion of a Conformationally Constrained Cyclic System

An additional series of analogs were prepared that had a varied cyclic system incorporated into the insertion precursors (scheme 3-11). The N,O-acetonide that was utilized throughout all of the previous work was replaced with an N,N'-acetonide in which both nitrogens were of the secondary amide type. The goal was to probe the effects of a more rigid cyclic system on the course of insertion. The replacement of an sp³ hybridized center with an sp² hybridized center would provide the increase in rigidity we sought. Starting from (L)-phenylalanine, esterification followed by amide formation using methylamine resulted in the α-amino amide, which, upon exposure to refluxing acetone/1,2-DCE in the presence of Na₂SO₄, was transformed to the N,N'-acetonide 131. Acylation followed by diazo transfer using conditions previously delineated achieved construction of the α-phenylsulfonyl-, α-ethoxycarbonyl- and α-acetyl-diazo substrates 132, 133 and 134 respectively. Our typical C-H insertion conditions yielded γ-lactams in

\[
\text{Scheme 3-11. Synthesis of N,N'-Acetonide Substrates with Varied } \alpha\text{-Substituents}
\]
all cases in excellent yield, regio- and stereoselectively (Table 3-6). In general, a 2-6% increase in yield of C-H insertion of the N,N’-acetonide analogs over the N,O-acetonide system was obtained. This was attributed to the increase in rigidity of the N,N’-acetonide system over the N,O-acetonide and the marginal boost in conformational constraint that it lends to the transition state of the transformation.

After an extensive review of the literature, there seems to be no clear-cut rationalization concerning the effects of α-substituents on C-H insertion. Conversely, extensive work has been done describing the diversity of this chemistry when the catalyst ligands are varied. The presently accepted transition state theory for C-H insertion implies that the selectivity of the reaction depends on the electrophilicity of the carbenoid itself. Highly electrophilic, more reactive carbenes proceed via an early transition state resulting in decreased selectivity. Therefore, greater selectivity can be achieved by using a less reactive carbenoid system, namely the carbene intermediate from rhodium acetate or any other catalyst ligand that is not electron withdrawing in nature. One would then assume that electron withdrawing α-substituents would increase the reactivity of the carbene and make the C-H insertion process less selective, but this is just not the case.

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>R</th>
<th>γ-lactam</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>PhSO₂</td>
<td>135</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>133</td>
<td>MeO₂C</td>
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<tr>
<td>3</td>
<td>134</td>
<td>MeCO</td>
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<td>99</td>
</tr>
</tbody>
</table>

Table 3-6. C-H Insertion of Conformationally Constrained N,N'-Acetonide Substrates with Varied α-Substituents
seen in our initial acyclic example of C-H insertion of $\alpha$-diazo-$\alpha$-(phenylsulfonyl)acetamides, the excellent regioselectivity is a result of the electron withdrawing $\alpha$-phenylsulfonyl substituent. It is clear that the selectivity of the amino acid methodology is not based solely on the mitigating effects of the $\alpha$-phenylsulfonyl substituent since excellent selectivity is achieved with other $\alpha$-substituents as well. The conformational constraints exerted by the acetonide moiety must, therefore, influence the regioselectivity and most likely enhance the overall success of the transformation. The premise that the acetonide moiety plays a significant role in this transformation is corroborated by an alternate cyclic system that was used. The increased rigidity of the $N,N'$-acetonide system does result in an increase in the efficiency of the transformation. Overall, carbenoid insertions are complex transformations that have various possible reaction pathways and outcomes that can be tuned by variation of catalyst ligands and $\alpha$-substituents. What we have elaborated is the formation of $\gamma$-lacams in a regio- and stereoselective manner from $\alpha$-amino acids utilizing a variety of $\alpha$-substituents. The utility of this methodology is directly applied to natural product synthesis of $\gamma$-lactam containing targets.
Chapter Four

Jung’s Total Synthesis of clasto-Lactacystin β-Lactone

Early on in the development of our rhodium catalyzed intramolecular C-H insertion methodology, we discovered just how promising and effective this transformation was. The applicability of our initial, acyclic methodology was profoundly broadened by its adaptation to accommodate α-amino acids as starting materials. Using only the α-amino acid as the source of stereogenic bias, γ-lactams were synthesized regio- and stereoselectively yielding a single enantiomer. Two additional stereocenters were formed simultaneously as dictated by the original stereocenter of the starting material and the three control elements delineated in chapter three. Immediately, we turned our full attention to the total synthesis of clasto-Lactacystin β-Lactone (2).

4.1 Retrosynthetic Analysis of clasto-Lactacystin β-Lactone

We had taken notice that application of this methodology to (L)-serine yielded a highly functionalized γ-lactam that possessed many of the characteristics of 2. Retrosynthetically, we envisioned an expedient route to the target molecule featuring two key steps (Scheme 4-1). β-Lactone 2 is readily available via lactonization of the cis-
arranged, masked hydroxyl and acid functionalities of intermediate 138. The alcohol
derivative of 138 is the product of the second key step of the synthesis, namely a
quaternary carbon-forming late stage aldol-coupling of the iminoether 139 and
isobutyraldehyde. The iminoether is derived from γ-lactam 140. The bicyclic γ-lactam is

![Scheme 4-1](image)

a product of our rhodium catalyzed intramolecular C-H insertion of α-amino acid derived
α-diazo-α-(phenylsulfonyl)acetamides methodology which is the first key step in the
synthetic route. The α-diazo insertion precursor 143 is efficiently derived from (L)-
serine.

### 4.2 First Generation Synthesis of the Bicyclic γ-Lactam Intermediate

Our initial endeavor into the synthesis of 2 began with the natural α-amino acid
(L)-serine (Scheme 4-2). Esterification of the amino acid was conducted by bubbling HCl
gas into a methanolic suspension of (L)-serine. (Phenylthio)acetic acid was then
dissolved in methylene chloride and activated using the carbodiimide reagent DCC.
Addition of the HCl salt of serine methyl ester and triethylamine resulted in amide-coupling of amide 142. The primary alcohol and the amide nitrogen were then simultaneously protected as the acetonide by refluxing 142 in toluene with 2,2-DMP and p-TsOH yielding ester 143 (Scheme 4-3). For this transformation to occur effectively, removal of water using a Dean-Starke trap was required to yield the desired products. This particular reaction provided inconsistent results due to extensive side-product formation and incomplete cyclizations. The impracticality of this transformation was compounded by the necessity of a tedious purification via flash column chromatography. Nevertheless, the ester function of the recovered phenylsulfide (143) was reduced to the primary alcohol 144 using LiBH₄ generated in situ from excess equivalents of NaBH₄ and LiCl in a 1:1 solution of THF and methanol. Protection of the hydroxyl as the silyl ether 145 using TBSCl and imidazole in DMF occurred in high yield. Complete oxidation of phenylsulfide 145 using excess m-CPBA yielded phenylsulfone 146 in nearly quantitative yield (Scheme 4-4). Diazo transfer using p-ABSA and DBU provided
the $\alpha$-diazo-$\alpha$-(phenylsulfonyl)acetamide insertion precursor 103. Our standard conditions for rhodium catalyzed intramolecular C-H insertion were carried out and the trans-bicyclic $\gamma$-lactam 104 was the sole product of the transformation. As one of the key steps of the synthetic route to 2, the $\gamma$-lactam was produced in 97% yield as a single enantiomer. This highly effective methodology provides $\gamma$-lactams with two additional stereocenters in one synthetic operation in a regio- and stereoselective manner.

4.3 Functionalization of the $\gamma$-Lactam Core

The goal of the next leg of the synthesis was to functionalize the $\gamma$-lactam at the C-3 and C-5 positions. Meyers has shown that alkylation of bicyclic systems typically occur on the $\beta$-face (convex face in this case) of the molecule. In our bicyclic system the C-3 position is highly activated for alkylation. Methylation of this center using iodomethane and sodium hydride in DMF occurred at 0 °C. Elimination of the protected
secondary C-4 hydroxyl substituent was a competing pathway that was ultimately inhibited by performing the reaction at -20 °C (Scheme 4-5). The methylation of the bicyclic system occurred stereoselectively in nearly quantitative yield (147). This particular reaction benefits from the concave/convex nature of the bicyclic γ-lactam. We then turned our attention to hydrolysis of the acetonide followed by oxidation of the resulting primary alcohol in preparation for the aldol coupling of the hydroxyisobutyl side-chain. To circumvent reactivity issues with the silyl ether protecting group throughout the remainder of the synthesis, the protected secondary hydroxyl 147 was unmasked using TBAF and reprotected as the benzyl ether 149. Subsequent hydrolysis via reflux in methanol and catalytic p-TsOH yielded the primary alcohol 150 which was then oxidized using Jones reagent to acid 151 (Scheme 4-6). Methylation of the carboxylic acid using iodomethane and DBU provided the ester functionality at the C-5 position of 152, which would prove integral in the aldol coupling of the hydroxyisobutyl side-chain. At this point in the synthesis a multitude of conditions to achieve aldol
coupling of the ester with isobutyraldehyde were tried. Various benzyl, carbonate and carbamate \(N\)-protecting groups along with numerous C-4 hydroxyl protecting groups were employed to direct the reactivity toward enolization of the C-5 position (Scheme 4-7). All attempts at aldol coupling of the ester and isobutyraldehyde and/or formaldehyde using amide bases were unsuccessful resulting in elimination products or no reaction altogether.

A complete reevaluation of our proposed synthesis followed the unsuccessful attempts to achieve the second key-step aldol coupling. The synthetic route to the bicyclic \(\gamma\)-lactam had a few shortcomings, namely inconsistencies of the acetonide forming step and the amide coupling reaction (not to mention cost of the acid reagent). It had also been a consequence of the proposed synthetic route that the natural amino acid would ultimately yield the enantiomer of the natural product, thus requiring the use of the much less economically feasible (D)-serine as the starting material to obtain the correct enantiomer. This synthesis would eventually benefit from the discovery of the synthetically superior second generation route to \(\alpha\)-diazo-\(\alpha\)-(phenylsulfonyl) acetamides applied to our earlier methodologies in chapter 3.

### 4.4 Second Generation Synthesis of the Bicyclic \(\gamma\)-Lactam Intermediate

Additional concerns that we had were the lack of significant stereochemical bias to affect the aldol-coupling selectively. Originally, the bulky silyl ether was used anticipating a need for stereochemical induction. Eventually, this group proved to be incompatible with subsequent steps of the synthesis. It had been exchanged for other alkyl ethers such as benzyl and methyl although the effectiveness of both toward
induction of stereogenic differentiation at the aldol step were ineffective based on the
distal orientation of the phenyl ring and the size of the methyl group, respectively. We
settled on using a tert-butyl ether based on its steric presence, resiliency to most
conditions and its facile introduction and cleavage. The HCl salt of (L)-serine methyl
ester was subject to the ether forming conditions using liquefied isobutylene and p-TsOH

\[ \text{HCl(g), MeOH, } \Delta \text{ ii) isobutylene, p-TsOH, CH}_2\text{Cl}_2 \]

in methylene chloride (Scheme 4-8). Initially, this transformation required three days to
complete. However, our endeavors into the realm of process chemistry provided us with
optimized conditions for this etherification providing the tert-butyl ether 153.
Dehydration of the p-toluenesulfonic acid monohydrate shortened the reaction time to 24

\[ \text{Me}_2\text{CO/1,2-DCE Na}_2\text{SO}_4, \Delta \]

hours and eliminated the need for a closed, pressurized system. Reduction of the ester
using LAH at 0 °C provided amino alcohol 154 cleanly and in high yield. The acetonide
formation (155) was achieved using the conditions from the previous methodologies and
occurred in nearly quantitative yield. N-Acylation using bromoacetyl bromide proceeded
readily but suffered from mediocre yield and required flash column chromatography for
purification of the bromide (156) (Scheme 4-9). Once again, we were dissatisfied with the means by which the bromide was recovered and the yield of the product. We replaced the acid bromide with its chloride analog and a much cleaner reaction ensued with improved yield. Recovery of chloride 157 consisted of simple recrystallization. Displacement of the chloride with benzenesulfinic acid sodium salt occurred readily and sulfone 158 was purified by recrystallization. Diazot transfer to the α-position of the amide occurred readily using p-ABSA and DBU in acetonitrile providing the α-diazo-α-(phenylsulfonyl)acetamide C-H insertion precursor 159 which was also purified by recrystallization. Application of our standard C-H insertion conditions yielded bicyclic γ-

![Scheme 4-10. γ-Lactam Formton via Rhodium Catalyzed Intramolecular C-H Insertion](image)

lactam 160 in high yield regio- and stereoselectively (Scheme 4-10).

At this point in the synthetic scheme significant improvements over the first generation synthesis were evident by the requirement of less synthetic operations to the γ-lactam intermediate, product availability from the natural amino acid, incorporation of the tert-butyl ether which protects the hydroxyl function and will lend stereochemical bias to further transformations. Nowhere were the benefits of our experience in process chemistry more apparent than in the techniques used for purification throughout the first leg of the synthesis. The first generation synthetic route called for flash column purification of six intermediates. Our second generation synthesis of the bicyclic γ-lactam
calls for only one flash column purification directly following the insertion step. This enabled us to scale-up $\gamma$-lactam production without concern for costly and time consuming flash column purifications.

4.5 Stereoselective Functionalization of the Bicyclic $\gamma$-Lactam

With the bicyclic $\gamma$-lactam in hand, functionalization of the C-3 and C-5 centers became the focus of the next leg of the synthesis. Stereoselective methylation of the C-3 center occurred readily using NaH and iodomethane in DMF resulting in alkylated bicyclic $\gamma$-lactam 161 in nearly quantitative yield (Scheme 4-11). We were confident that methylation at the C-3 center occurred from the $\beta$-face (the convex face) of the $\gamma$-lactam based on x-ray crystal data obtained from the product of an analogous transformation involving the phenylalanine derivative 78. Though, without irrefutable evidence we were forced to consider the possibility of $\alpha$- and $\beta$-alkylated products. Following methylation, reduction of the phenylsulfone group using 10% Na(Hg) in methanol occurred readily resulting in an equal mixture of C-3 epimers 162 and epi-162. This result was not at all surprising as we somewhat anticipated a degree of diastereoselection based on the single electron transfer mechanism through which this reaction proceeded. We did expect a more favorable ratio resulting from the stereochemical and steric bias of the $\gamma$-lactam.
itself. An alternate route involving reduction of the phenylsulfone group prior to methylation was explored (Scheme 4-12). The $\alpha$-methylene product (163) of Na(Hg) reduction was methylated using LHMDS and iodomethane resulting in the C-3 methylated $\gamma$-lactam with complete diastereoselectivity. Moreover, the original methylation-reduction conditions were optimized to yield the desired epimer (162) in a diastereoselective manner as well.\(^1\) Despite the ambiguity of the C-3 epimers, both were carried through the synthesis separately. A one-pot procedure for the hydrolysis of the \textit{N,O}-acetonide and subsequent oxidation of the resultant primary alcohol was devised (Scheme 4-13). Essentially, simple Jones oxidation conditions are sufficiently acidic to effect hydrolysis of the acetonide moiety and oxidation of the acid (164 and \textit{epi-164}) promptly follows. Methylation of the acid using trimethyl orthoformate in methanol with catalytic sulfuric acid resulted in methyl esters 165 and \textit{epi-165}. Again, numerous attempts at forming the quaternary center via aldol coupling of \textit{N}-protected methyl esters were unsuccessful resulting in elimination products and recovered starting materials. In
an attempt to activate the C-5 center the amide function was converted to the iminoether (166 and epi-166) using Meerwein’s salt in methylene chloride. Addition of iminoether 166 and epi-166 to LDA in THF at -78 °C resulted in enolization of the ester.

Isobutyraldehyde was added after 10 minutes followed by saturated ammonium chloride solution which resulted in formation of the quaternary C-5 center of 167. Upon purification of the products it was revealed that the aldol-coupling of the iminoether product derived from the reduction-methylation protocol yielded a single isomer (epi-167) as a crystalline solid. The methylation-reduction iminoether intermediate (166) provided a 2:1 mixture of diastereomers as an oil (Scheme 4-15). X-ray crystal analysis of epi-167 revealed that the quaternary center had indeed formed selectively with the correct stereochemistry at the C-5 quaternary center and the C-9 center as well.

Unfortunately, the C-3 center which remained ambiguous until this point was shown to
be alkylated from the $\alpha$-face establishing absolute 3S stereochemistry. Epimerization of the C-3 methyl center was unsuccessful and this leg of the project was, therefore, discontinued.

Although, not the results we were hoping for, this data proved invaluable for elucidation of the absolute stereochemistry of the C-3 centers of the bicyclic methylated compounds 162 and epi-162 and displayed a new and efficient option for stereoselective C-3 alkylation of bicyclic $\gamma$-lactams. The diastereomeric mixture ($167\,5R,\,9S$ & $167\,5S$) resulting from aldol coupling of the 3R epimer (166) was now the focus and elucidation of the absolute stereochemistry was our goal.

4.6 Elucidation of Aldol Stereoselectivity

Throughout the course of the aldol coupling two new stereocenters are formed. In this case the C-5 and the C-9 stereocenters were those in question. Based on the selectivity of the aldol coupling of epi-166 we felt confident that the tert-butyl ether “blocking group” was performing its function. A simple test to distinguish which center had formed selectively was to oxidize the secondary diastereomeric alcohols ($167\,5R,\,9S$ & $167\,5S$) to ketones (Scheme 4-16). Obviously, if C-9 was the nonselectively-formed center, the product of oxidation would be a single isomer. Interestingly, oxidation of the mixture using TPAP/NMO conditions resulted in oxidation of one of the diastereomers and left the other unreacted as the secondary alcohol, a piece of data which would become useful later in the synthesis. Exposure of the mixture to Dess-Martin oxidation conditions yielded two different ketone products ($168R & S$), thus confirming
diastereomers at the C-5 center. This result proved that our inclusion of a bulky ether substituent failed to induce selectivity for the aldol coupling reaction. Various conditions were used to improve the selectivity of the second key-step of the synthesis with no success. The best selectivity that could be achieved was a 2:1 ratio of $167 R$ & $S$ diastereomers respectively.

An alternate route for formation of the quaternary carbon center which holds promise is acylation of iminoether 166 under the same conditions using isobutyrylchloride (Scheme 4-17). Ketone 168S is recovered as a 10:1 diastereomeric mixture that matches spectral data from that previously generated in the oxidation of the $167 5R, 9S$ & $167 5S$ mixture. Reduction of the ketone (168S) at this and the two ensuing
deprotected intermediates resulted in perfect selectivity for 9R secondary alcohol 167 5R, 9R. This alternate route may eventually prove successful under the selectivity inducing reduction conditions or inversion of the selectively formed C-9 center itself.

4.7 Rationalization for Aldol Coupling Stereoselectivity

With our first successful aldol transformation from *epi*-166 in hand, we were excited by the high degree of selectivity we experienced. Unfortunately, the same degree of selectivity was not obtained for the reaction of 166. Initially, we were confounded by the complete lack of stereoselectivity for the latter aldol transformation. The tert-butyl ether, which was intended to act as a blocking group, was effective in the case of *epi*-166 but rather ineffective as in the case of 166. Assuming that the aldol coupling would proceed through a 6-membered transition state, we expected the highly populated face of enolate of 166 present with a methyl at C-3 and *t*-butyl ether at C-4 would only reinforce the bias for facial-selectivity during the transformation (Figure 4-1). Therefore, approach of the aldehyde would be more likely to occur from the α-face of the enolate as in 166α. Our conclusion and explanation for the results we obtained are based on the conformation of the enolate substituents in their minimized energy states (Figure 4-2).
MM2 calculations using Chem 3D Pro 7.0 show that when the C-3 methyl is on the $\alpha$-face of the enolate, the tert-butyl ether can adopt a position which is more facially blocking as determined by the dihedral angle of 72° ($^t\text{BuO-C-C=C}$). When the C-3 methyl is on the $\beta$-face of the enolate, a steric repulsion exists between the two substituents disallowing the blockage of the $\beta$-face by the tert-butyl ether evidenced by the dihedral angle of 51°. Obviously, steric consequences of the overpopulated $\beta$-face of the enolate had a profoundly detrimental effect on this transformation.

4.8 Endgame for the Total Synthesis of clasto-Lactacystin $\beta$-Lactone

The 2:1 mixture of diastereomers (167 5$R$, 9$S$ & 167 5$S$) was carried forward through the deprotection stage of the synthesis using anhydrous TFA for cleavage of the tert-butyl protecting group yielding a mixture of diols (169 5$R$, 9$S$/169 5$S$). Exposure of the diols to 1% HCl in methanol resulted in the known amide 170 5$R$, 9$S$ as a mixture of
diastereomers with 170 5S. The major component of the resulting mixture was identical to the 1H NMR spectral data reported by Adam’s and Smith for the amide 169 5R, 9S. This data was useful by confirming that aldol product 167 5R, 9S was formed with a favorable yet mediocre ratio. Combined with the results of oxidation of the aldol diastereomers, we were able to distinguish the stereochemical configuration of the product of the acylation methodology and declare it a viable alternative to the aldol coupling.

Completion of the synthesis of the β-lactone 2 was accomplished using Adams’ method of basic hydrolysis of the methyl ester to the dihydroxy acid followed by activation to the mixed anhydride which spontaneously lactonized resulting in 2 as a single isomer. The corresponding diastereomer was most likely hydrolyzed but was not fit for lactonization based on the trans-arrangement of the hydroxyl and carboxylic acid substituents and subsequently lost during work-up of 2. The synthetic β-lactone 2 was identical spectroscopically to reported data and an x-ray crystal analysis confirmed the absolute stereochemistry of the final product. The total synthesis of 2 was accomplished in 17 steps with a 10% overall yield.

Made obvious by the elegant and elaborate syntheses highlighted above, lactacystin (1) and its analogs have been intensely pursued by some of the most
prestigious and successful synthetic groups in recent years. Moreover, it is a perfect example of the significant role natural product synthesis plays in the scientific community. Seldom do we experience the discovery of a natural target that possesses such novel biological activity and specificity. Because of scant supply, the only practical means of obtaining material for further research is through total synthesis.
Chapter Five

Experimental Data

All experiments were carried out under nitrogen atmosphere using oven dried glassware (or flame dried when necessary). All chemicals were purchased from Aldrich Chemical Co. and/or Acros Organics and used without further purification unless otherwise noted. Methylene chloride was distilled over calcium hydride. THF and diethyl ether were distilled over sodium metal. Proton nuclear magnetic resonance (250 MHz) and $^{13}$C (63 MHz) spectra were recorded at room temperature in CDCl$_3$ unless otherwise noted. All chemical shifts are reported as $\delta$ relative to CHCl$_3$ ($\delta_H$ 7.26 ppm) and CDCl$_3$ ($\delta_C$ 77.0 ppm) as internal standards, respectively, using a Bruker DPX 250 spectrometer. Infrared spectra were recorded using a Nicolet Magna FTIR 550 spectrometer and are reported in reciprocal centimeters (cm$^{-1}$). Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA. Thin layer chromatography (TLC) was performed on EMD precoated silica plates with silica gel 60 Å, 250 μm thickness. Visualization of TLC was accomplished using a UV lamp (254 nm), iodine or charring solutions (ninhydrin and PMA). Flash column chromatography was performed on Whatman Purasil 60 Å (230-400 mesh) silica gel.
Thionyl chloride (3.65 mL, 50 mmol) was added drop wise to a solution of (L)-phenylalanine (7.6 g, 46 mmol) in methanol (60 mL) at 0 °C, and the mixture was heated under reflux 1 h. The solvent was evaporated to give (L)-phenylalanine methyl ester, hydrochloride as white solid. To a solution of (L)-phenylalanine methyl ester hydrochloride (46 mmol), phenylthioacetic acid (8.5 g, 51 mmol) and imidazole (4.1 g, 60 mmol) in DMF (50 mL, C = 1.0 M), was slowly added N,N’-diisopropylcarbodiimide (8 mL, 51 mmol) at 0 °C. The mixture was stirred briefly at 0 °C and then at r.t. for 12 h. After filtration of the precipitate, the filtrate was diluted with EtOAc and the organic layer was washed twice with water and dried over Na₂SO₄. After evaporation of solvent, the resulting residue was recrystallized with hexanes-EtOAc to afford desired product 75 (15 g, 97%) as white solid: ¹H NMR (250 MHz, CDCl₃) δ 7.31-7.18 (m, 10 H), 6.95 (m, 1 H), 4.85 (m, 1 H), 3.68 (s, 3 H), 3.61 (s, 2 H), 3.06 (d, 2 H, J = 5.9 Hz), ¹³C NMR (62.5 MHz, CDCl₃) δ 171.4, 167.7, 135.5, 134.5, 129.2, 129.1, 128.6, 128.3, 127.1, 126.7, 53.3, 52.3, 37.7, 37.4; IR (thin film, cm⁻¹) 1744, 1676, 1512, 1265.
Preparation of Alcohol 75A

To a solution of phenylthioacetylmide methyl ester 75 (10 g, 30 mmol) in THF-MeOH (150 ml, C = 0.2 M, 1:1 vol. ratio), were slowly added NaBH₄ (3.4 g, 90 mmol) followed by LiCl (3.7 g, 90 mmol) at 0 °C. The resulting mixture was stirred for 1 h at r.t., and the solvent was evaporated. The residue was partitioned with EtOAc and brine, and the organic layer was dried over Na₂SO₄ and concentrated. The resulting residue was recrystallized with hexanes-EtOAc to afford primary alcohol 75A (8.6 g, 95%) as white solid: ¹H NMR (250 MHz, CDCl₃) δ 7.31-7.10 (m, 10 H), 7.03 (br d, 1 H), 4.14 (m, 1 H), 3.66 and 3.56 (ABq, 2 H, J = 17.1 Hz), 3.53 (m, 2 H), 2.79 (m, 2 H), 2.14 (t, 1 H, J = 5.7 Hz); ¹³C NMR (62.5 MHz, CDCl₃) δ 168.3, 137.1, 135, 129.3, 129.1, 128.1, 126.7, 64.1, 53.1, 37.5, 36.8; IR (thin film, cm⁻¹) 3290, 1661, 1540, 1265.
Preparation of Acetonide 76

Primary alcohol 77A (6 g, 20 mmol) is added to a mixture of 2,2-dimethoxypropane (4.8 mL, 40 mmol), and catalytic p-toluenesulfonic acid in toluene (70 ml, C = 0.3 M). The solution is heated under reflux for 1 hr using a Dean-Starke apparatus for the removal of water. The reaction mixture was poured into saturated NaHCO₃ and extracted with EtOAc. The combined organic layer was washed with brine, then dried over Na₂SO₄, filtered and concentrated to give crude product as an oil, which was chromatographed to afford acetonide 76 (4.8 g, 70 %): ¹H NMR (250 MHz, CDCl₃) δ 7.52-7.11 (m, 10 H), 4.04 (m, 1 H), 3.79 (m, 2 H), 3.48 and 3.40 (ABq, 2 H, J = 13.7 Hz), 2.89 (m, 2 H), 2.05 (s, 3 H), 1.47 (s, 3 H); ¹³C NMR (62.5 MHz, CDCl₃) δ 165.3, 137.2, 134.7, 131.1, 129.2, 129.0, 127.3, 127.1, 95.8, 66.9, 59.4, 40.7, 38.9, 26.9, 22.7; IR (thin film, cm⁻¹) 1652, 1496, 1265.
Preparation of Phenylsulfone 77

To a solution of phenylthioacetamide 76 (3.7 g, 10.8 mmol) in dry CH₂Cl₂ (54 mL, C = 0.2 M) \( m \)-CPBA (6.7 g, 27 mmol) was slowly added and stirred for 1 hr at 0 °C. The reaction mixture was poured into 1 N NaOH, and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated yielding pure phenylsulfofone 76A: \(^1\)H NMR (250 MHz, CDCl₃) \( \delta \) 7.84-7.50 (5 m, 5 H), 7.36-7.17 (m, 5 H), 4.39 (m, 1 H), 4.01 (dd, 1H, \( J = 5.0, 8.9 \) Hz), 3.87 (d, 1H, \( J = 8.9 \) Hz), 3.81 and 3.41 (ABq, 2 H, \( J = 13.8 \) Hz), 2.93 (m, 2 H), 1.71 (s, 3H), 1.51 (s, 3 H); \(^1\)C NMR (62.5 MHz, CDCl₃) \( \delta \) 158.3, 138.7, 137.0, 134.2, 129.4, 129.2, 129.0, 128.4, 127.3, 96.1, 67.5, 61.7, 60.0, 40.8, 26.6, 22.5; IR (thin film, cm⁻¹) 1738, 1373, 1245, 1046.

General Preparation of \( \alpha \)-Diazo-\( \alpha \)-(phenylsulfonyl)acetamides.

To a mixture of a \( \alpha \)-(phenylsulfonyl)acetamide (5.0 mmol) and \( p \)-acetamidobenzenesulfonyl azide (1.3 g, 5.5 mmol) in dry CH₃CN (25 mL, C = 0.2 M), was slowly added DBU (1.64 mL, 11 mmol) at 0 °C. The resulting mixture was stirred for 1 hr at 0 °C, and the solvent was evaporated. The residue was diluted with Et₂O, and the mixture was washed successively with 1 N NaOH, water, and brine. The yellow organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was
chromatographed to give \(\alpha\)-diazo-\(\alpha\)-(phenylsulfonyl)acetamide.

\[
\begin{align*}
\text{77: } & \quad ^1\text{H NMR (250 MHz, CDCl}_3\text{)} \delta 7.96-7.51 \text{ (m, 5 H)}, 7.35-7.17 \text{ (m, 5 H), 4.39 (m, 1 H), 3.85 (d, 2 H, } J = 3.6 \text{ Hz)}, 3.08 \text{ (dd, 1 H, } J = 5.3, 13.5 \text{ Hz)}, 2.81 \text{ (dd, 1 H, } J = 9.3, 13.5 \text{ Hz)}, 1.69 \text{ (s, 3 H)}, 1.34 \text{ (s, 3 H)}; ^{13}\text{C NMR (62.5 MHz, CDCl}_3\text{)} \delta 153.9, 141.9, 136.5, 133.9, 129.4, 129.2, 128.8, 127.5, 127.1, 96.7, 74.8, 67.1, 58.7, 40.0, 26.9, 23.4; \\
& \quad \text{IR (thin film, cm}^{-1}\text{)} 2086, 1734, 1641, 1371, 1265, 1047.
\end{align*}
\]

\[
\begin{align*}
\text{84: } & \quad ^1\text{H NMR (250 MHz, CDCl}_3\text{)} \delta 8.03-7.53 \text{ (m, 5 H), 4.01 (dd, 1 H, } J = 5.0, 9.0 \text{ Hz)}, 3.82 \text{ (dd, 1 H, } J = 2.5, 9.0 \text{ Hz)}, 3.79 - 3.73 \text{ (m, 1 H)}, 1.75-1.65 \text{ (m, 2 H)} 1.64 \text{ (s, 3 H)}, 1.42 \text{ (s, 3 H)}, 0.91 \text{ (t, 3 H, } J = 7.4 \text{ Hz}); ^{13}\text{C NMR (62.5 MHz, CDCl}_3\text{)} \delta 153.8, 142.0, 133.8, 129.1, 127.8, 96.6, 74.3, 67.3, 58.6, 26.9, 26.2, 23.6, 10.1; \text{IR (thin film, cm}^{-1}\text{)} 1696, 1419, 1367, 1304, 1141, 1080, 1026.
\end{align*}
\]
**86:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.02-7.53 (m, 5 H), 4.0 (m, 1 H), 3.83 (m, 2 H), 1.64 (m, 2 H) 1.61 (s, 3 H), 1.41 (s, 3 H), 1.31 (m, 2 H), 0.96 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 153.6, 141.9, 133.7, 129.0, 127.7, 96.4, 74.1, 67.6, 57.2, 36.1, 26.2, 23.5, 19.1, 13.8; IR (thin film, cm$^{-1}$) 2089, 1638, 1388, 1153, 1085.

**88:** $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 8.01-7.55 (m, 5 H), 4.06 - 3.95 (m, 2 H), 3.81 (dd, 1 H, $J$ = 2.7, 6.1 Hz) 1.63 (s, 3 H), 1.41 (s, 3 H), 0.97 (d, 3 H, $J$ = 3.5 Hz), 0.96 (d, 3 H, $J$ = 3.8 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 153.5, 141.9, 133.8, 129.0, 127.6, 96.1, 73.6, 67.8, 56.2, 43.1, 26.3, 25.5, 23.6, 21.3; IR (thin film, cm$^{-1}$) 2092, 1645, 1388, 1266, 1155, 1084.
90: $^1$H NMR (250 MHz, CDCl$_3$) δ 8.02-7.52 (m, 5 H), 7.36 - 7.18 (m, 5 H), 4.02 (dd, 1 H, $J = 5.7$, 8.7 Hz), 3.88 (d, 1 H, $J = 8.7$ Hz), 3.82 (m, 1 H), 2.74-2.50 (m, 2 H), 2.02 (m, 2 H), 1.63 (s, 3 H), 1.41 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 153.7, 142.0, 140.0, 133.8, 129.1, 128.8, 128.3, 127.8, 126.5, 96.5, 74.0, 67.5, 56.8, 35.8, 32.3, 26.4, 23.7; IR (thin film, cm$^{-1}$) 2102, 1617, 1374, 1308, 1142, 1083.

92: $^1$H NMR (250 MHz, CDCl$_3$) δ 8.0-7.54 (m, 5 H), 4.08-3.97 (m, 1 H), 3.81 (d, 1 H, $J = 9.0$ Hz), 3.73 (s, 3 H), 2.36 (m, 2 H), 1.99 (m, 2 H), 1.64 (s, 3 H), 1.39 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 172.4, 153.9, 141.8, 133.8, 129.1, 127.6, 96.4, 74.3, 67.3, 56.5, 51.9, 30.0, 29.0, 26.6, 23.4; IR (thin film, cm$^{-1}$) 2096, 1730, 1630, 1391, 1317, 1147, 1080.
**94:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.98-7.57 (m, 5 H), 7.13 (d, 2 H, $J = 8.5$ Hz), 6.88 (d, 1 H, $J = 8.5$ Hz), 4.27 (m, 1 H), 3.87 (d, 2 H, $J = 3.2$ Hz), 3.8 (s, 3 H), 3.03 (dd, 1 H, $J = 5.0$, 13.0 Hz), 2.79 (dd, 1 H, $J = 8.9$, 13.0 Hz), 1.69 (s, 3 H), 1.36 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 158.6, 154, 141.8, 133.9, 130.5, 129.3, 128.4, 127.5, 114.3, 96.7, 74.8, 67.2, 59.1, 55.2, 39.3, 26.9, 23.4; IR (thin film, cm$^{-1}$) 2087, 1623, 1512, 1363, 1244, 1150, 1083.

**96:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.0-7.51 (m, 5 H), 4.09-3.94 (m, 2 H), 3.68 (dd, 1 H, $J = 3.0$, 8.5 Hz), 1.60 (s, 3 H), 1.40 (s, 3 H), 1.26 (d, 3 H, $J = 6.1$ Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 153.7, 142.0, 133.8, 129.1, 127.7, 96.7, 74.2, 69.9, 52.8, 26.2, 23.8, 20.1; IR (thin film, cm$^{-1}$) 2097, 1641, 1257, 1156.
98: \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 8.0-7.51 (m, 5 H), 3.95-3.79 (m, 3 H), 2.10 (m, 1 H), 1.64 (s, 3 H), 1.40 (s, 3 H), 0.95 (d, 3 H, \(J = 7.0\) Hz), 0.90 (d, 3 H, \(J = 6.7\) Hz); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) 154.5, 142.0, 133.8, 129.2, 127.6, 96.6, 74.8, 64.9, 62.3, 30.0, 25.9, 23.6, 19.1, 16.8; IR (thin film, cm\(^{-1}\)) 2097, 1641, 1268, 1048.

100: \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 8.01-7.26 (m, 5 H), 3.98-3.82 (m, 3 H), 1.85 (m, 1 H), 1.61 (s, 3 H), 1.41 (s, 3 H), 1.4 - 1.0 (m, 2 H), 0.95 (t, 2 H, \(J = 7.2\) Hz), 0.85 (d, 3 H, \(J = 6.8\) Hz); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) 154.4, 141.9, 133.8, 129.1, 127.6, 96.6, 74.5, 64.5, 61.0, 36.3, 26.2, 25.3, 23.9, 13.3, 12.1; IR (thin film, cm\(^{-1}\)) 2097, 1641, 1257, 1156.
103: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.0-7.53 (m, 5 H), 3.98 (m, 3 H), 3.62 (m, 2 H), 1.58 (s, 3 H), 1.41 (s, 3 H), 0.86 (s, 9 H), 0.059 (s, 6 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 154.1, 142.1, 133.7, 129.0, 127.8, 96.8, 74.6, 65.9, 62.7, 58.2, 26.5, 25.7, 23.5, 18.2, -5.58, IR (thin film, cm$^{-1}$) 2092, 1634, 1448, 1378, 1261, 1155, 1087.

105: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.0-7.53 (m, 5 H), 4.24 (dq, 1 H, $J$ = 6.3, 6.3 Hz), 3.92 (dd, 1 H, $J$ = 5.5, 10.0 Hz), 3.73 (dd, 1 H, $J$ = 2.5, 10.0 Hz), 3.55 (m, 1 H), 1.56 (s, 3 H), 1.42 (s, 3 H), 1.36 (d, 3 H, $J$ = 6.1 Hz), 0.89 (s, 9 H), 0.092 (s, 3 H), 0.082 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 154.9, 141.9, 133.8, 129.1, 127.5, 96.4, 75.5, 73.7, 64.6, 61.0, 60.2, 25.7, 25.6, 24.5, 20.9, 19.1, 18.2, 14.1, -5.68, -5.79; IR (thin film, cm$^{-1}$) 2090, 1646, 1344, 1253, 1154, 1086.
General Procedure for Rhodium Catalyzed Intramolecular C-H Insertion

To a solution of an α-diazo-α-(phenylsulfonyl)acetamide (1 mmol) in dry CH$_2$Cl$_2$ (20 mL), was added Rh$_2$(OAc)$_4$ (11 mg, 2.5 mol%). The mixture was refluxed for 12 h under N$_2$, cooled to r.t., and concentrated. The residue was chromatographed to give pure γ-lactam.

78: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.93-7.49 (m, 5 H), 7.35-7.23 (m, 5 H), 4.50 (d, 1 H, $J$ = 9.1 Hz), 4.14-4.05. (m, 2 H), 3.88 (dd, 1 H, $J$ = 6.2, 9.1 Hz), 3.68 (dd, 1 H, $J$ = 7.9, 8.0 Hz), 1.65 (s, 3 H), 1.45 (s, 3 H); 13C NMR (62.5 MHz, CDCl$_3$) $\delta$; IR (thin film, cm$^{-1}$) 1734, 1373, 1266, 1246, 1046.

85: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.01-7.54 (5 H, m) 4.12 (dd, 1 H, $J$ = 5.5, 8.5 Hz), 4.00 (d, 1 H, $J$ = 9.9 Hz), 3.73 (m, 1 H), 3.48 (dd, 1 H, $J$ = 8.5, 9.0 Hz), 2.81 (m, 1 H), 1.51 (s, 3 H), 1.42 (d, 3 H, $J$ = 6.7 Hz), 1.38 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 161.7, 137.8, 134.1, 129.8, 128.8, 92.4, 76.2, 68.8, 64.9, 34.1, 26.4, 23.5, 18.7; IR (thin film, cm$^{-1}$) 1734, 1373, 1266, 1246, 1046.
film, cm\(^{-1}\) 1696, 1419, 1367, 1304, 1142, 1080, 1023.

**87:** \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 8.01-7.54 (5 H, m), 4.10 (dd, 1 H, \(J = 4.1, 8.6\) Hz), 4.05 (d, 1 H, \(J = 9.6\) Hz), 3.77 (m, 1 H), 3.51 (dd, 1 H, \(J = 8.6, 9.0\) Hz), 2.68 (m, 1 H), 2.2 (m, 1 H), 1.54 (s, 3 H), 1.40 (s, 3 H), 0.97 (t, 3 H, \(J = 7.4\) Hz); \(^13\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) 161.6, 137.7, 134.0, 129.7, 128.7, 91.9, 74.7, 69.4, 63.6, 40.2, 26.4, 26.3, 23.3, 11.6; IR (thin film, cm\(^{-1}\)) 1698, 1416, 1306, 1142, 1082, 1028.

**89:** \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 8.03-7.58 (5 H, m), 4.16 (d, 1 H, \(J = 8.2\) Hz), 4.07 (dd, 1 H, \(J = 5.5, 7.9\) Hz), 3.87 (m, 1 H), 3.59 (dd, 1 H, \(J = 7.9, 9.3\) Hz) 2.79 (1H, m), 2.22 (m, 1 H), 1.62 (s, 3H), 1.45 (s, 3H), 1.05 (d, 3 H, \(J = 6.7\) Hz), 1.04 (d, 3 H, \(J = 6.9\) Hz); \(^13\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) 162.4, 137.9, 134.1, 129.7, 128.8, 92.4, 72.7, 69.6, 59.9, 42.3, 29.1, 26.9, 23.4, 20.6, 17.5; IR (thin film, cm\(^{-1}\)) 1706, 1407, 1309, 1266, 1150, 1085.
91: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.08-7.50 (5 H, m), 7.37-7.21 (m, 5 H), 4.22 (d, 1 H, $J = 10.2$ Hz), 3.78 (m, 1 H), 3.55 (dd, 1 H, $J = 3.9, 13.3$ Hz) 3.21-3.01 (m, 2 H), 2.70 (dd, 1 H, $J = 11.6, 13.0$ Hz), 1.45 (s, 3H), 1.35 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 161.2, 137.8, 134.2, 129.8, 129, 128.9, 128.7, 127.2, 91.9, 74.3, 68.9, 63.1, 41.8, 38.9, 26.3, 23.4; IR (thin film, cm$^{-1}$) 1694, 1316, 1308, 1145, 1083, 1025.

93: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.03-7.26 (5 H, m), 4.23-4.16 (m, 2 H), 3.81 (m, 1 H), 3.72 (s, 3 H), 3.58 (dd, 1 H, $J = 9.0, 9.1$ Hz), 3.24 (dd, 1 H, $J = 3.3, 17.2$ Hz), 3.09 (m, 1 H), 2.67 (dd, 1 H, $J = 10.5, 17.2$ Hz), 1.49 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 171.6, 160.9, 137.1, 134.3, 129.9, 128.8, 92.1, 73.5, 69.9, 63.8, 52.0, 36.7, 35.3, 26.4, 23.3; IR (thin film, cm$^{-1}$) 1734, 1705, 1281, 1143, 1080, 1036.
95: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.95-7.50 (m, 5 H, 7.19 (d, 2 H, $J = 8.6$ Hz), 6.89 (d, 1 H, $J = 8.6$ Hz), 4.46 (d, 1 H, $J = 8.6$ Hz), 4.16-4.07 (m, 2 H), 3.86 (m, 1 H), 3.81 (s, 3 H), 3.70 (m, 1 H), 1.66 (s, 3 H), 1.46 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 161.7, 159.2, 137.7, 134.1, 130.7, 129.7, 128.8, 128.5, 114.6, 92.9, 69.0, 65.9, 55.3, 42.8, 26.7, 23.5; IR (thin film, cm$^{-1}$) 1711, 1365, 1217.

97: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.0-7.34 (m, 5 H), 3.42-4.02 (m, 3 H), 3.39 (m, 1 H), 2.89-2.17 (m, 2 H), 1.56 and 1.53 (s, 3H), 1.38 (s, 3 H); IR (thin film, cm$^{-1}$) 1700, 1405, 1310, 1265, 1150, 1085, 1039.

99: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.06-7.49 (m, 5 H), 4.49 and 3.78 (m, 3 H), 4.07 and 3.54 (s, 1 H), 1.60 and 1.59 (s, 3 H), 1.50 (s, 3 H), 1.43 and 1.42 (s, 3 H), 1.32
and 1.11 (s, 3 H); IR (thin film, cm\(^{-1}\)) 1701, 1448, 1393, 1147, 1058, 1214, 1085, 1036.

101: \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta 8.10-7.53\) (m, 5 H), 4.56 and 3.80 (m, 3 H), 4.12 and 3.61 (s, 1 H), 2.30 (m, 1 H), 1.63 and 1.52 (s, 3 H), 1.47 (s, 3 H), 1.37 and 1.11 (s, 3 H), 0.94 and 0.91 (t, 3 H, \(J = 7.5\) Hz); IR (thin film, cm\(^{-1}\)) 1706, 1422, 1369, 1265, 1150, 1084.

104: \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta 8.01-7.55\) (m, 5 H), 4.83 (dd, 1 H, \(J = 4.8, 6.7\) Hz), 4.26 (d, 1 H, \(J = 6.8\) Hz), 4.17 (dd, 1 H, \(J = 5.8, 8.2\) Hz), 3.97 (ddd, 1 H, \(J = 4.8, 5.8, 8.4\) Hz), 3.60 (dd, 1 H, \(J = 8.4, 8.4\) Hz), 1.57 (s, 3 H), 1.41 (s, 3 H), 0.91 (s, 9 H), 0.24 (s, 3 H), 0.17 (s, 3 H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta 160.7, 138.1, 134.1, 129.6, 128.8, 92.7, 77.8, 69.3, 67.6, 66.8, 26.6, 25.6, 23.4, 17.9, -4.85, -5.15\); IR (thin film, cm\(^{-1}\)) 1713, 1447, 1371, 1265, 1153, 1082.
106: $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.97-7.54 (m, 5 H), 4.85 (dd, 1 H, $J = 3.5$, 4.8 Hz), 4.12 (d, 1 H, $J = 4.8$ Hz), 3.82 (m, 1 H), 3.51 (dd, 1 H, $J = 3.5$, 9.3 Hz), 1.59 (s, 3 H), 1.43 (s, 3 H), 1.35 (d, 3 H, $J = 6.0$ Hz), 0.91 (s, 9 H), 0.27 (s, 3 H), 0.23 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 161.5, 137.9, 134.2, 129.6, 129.2, 128.8, 92.5, 79.2, 74.4, 73.8, 67.0, 27.5, 25.6, 23.6, 17.9, 16.8, -4.51, -5.17; IR (thin film, cm$^{-1}$) 1718, 1310, 1250, 1151, 1083.

Preparation of $\gamma$-lactam 105

To a solution of $\gamma$-lactam 101 (62 mg, 0.18 mmol) and anhydrous disodium hydrogen phosphate (104 mg, 0.72 mmol) in 2 mL of methanol cooled to the 0 °C was added pulverized 10% sodium amalgam (168 mg). The mixture was stirred for 30 min., poured into water and extracted with ether. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was chromatographed to give the reduced $\gamma$-lactam in 83% yield as a single isomer: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 3.94 (dd, 1 H, $J = 6.2$, 8.7 Hz).
Hz), 3.85 (dd, 1 H, J = 6.2, 8.5 Hz), 3.68 (dd, 1 H, J = 8.5, 8.7 Hz), 2.87 and 1.94 (ABq, 2 H, J = 16 Hz) 1.62 (s, 3 H), 1.44 (s, 3 H), 0.99 (s, 3 H), 0.84 (t, 3 H, J = 7.4 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 170.0, 90.3, 68.6, 63.8, 51.4, 40.6, 32.8, 26.0, 23.4, 19.0, 9.5; IR (thin film, cm$^{-1}$) 1700.

**General Preparation of $\alpha$-Amino Acid Derived N,O-Acetonides**

To a suspension of LAH (3.8 g, 100 mmol) and 250 mL of anhydrous THF (0.2 M) cooled to 0 °C was slowly added 50 mmol of $\alpha$-amino acid. The entire suspension was then refluxed under N$_2$ atmosphere for 8 hrs. The reaction mixture was cooled to 0 °C and, while stirring, 3.8 mL of water was added via dropping funnel. It was followed by 3.8 mL of 20% NaOH and 7.6 mL of water. The entire solution was then stirred for an additional half hour and filtered through a sintered glass funnel with a celite pad. The filter cake was rinsed with a portion of anhydrous THF and the filtrate was then evaporated yielding the crude amino alcohol. The crude product was then combined with 250 mL of a 1:1 mixture of acetone and 1,2-DCE and 10 grams of anhydrous Na$_2$SO$_4$ and refluxed under N$_2$ atmosphere for 1 hr. The solution was then cooled to r.t. and filtered through a sintered glass funnel with a pad of celite. The filter cake was rinsed with a portion of acetone and the filtrate was evaporated yielding the crude acetonide.
110: $^1$H NMR (250 MHz, CDCl$_3$) δ 7.33-7.19 (m, 5 H), 3.87 (dd, 1 H, $J = 7.1, 7.4$ Hz), 3.69 (m, 1 H), 3.39 (dd, 1 H, $J = 7.7, 7.8$ Hz), 3.00 (dd, 1 H, $J = 5.8, 13.6$ Hz), 2.72 (dd, 1 H, $J = 7.8, 13.6$ Hz) 1.44 (s, 3 H), 1.31 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 137.7, 128.3, 128.1, 126.0, 94.6, 69.7, 58.6, 39.0, 27.3, 26.1.

**General Preparation of α-Amino Acid Derived N,N’-Acetonides**

Thionyl chloride (3.65 mL, 50 mmol) was added drop wise to a solution of (L)-phenylalanine (7.6 g, 46 mmol) in methanol (60 mL) at 0 °C, and the mixture was heated under reflux 1 h. The solvent was evaporated to give (L)-phenylalanine methyl ester hydrochloride as white solid. The solid was then redissolved in MeOH and methylamine was added and stirred for 4 hrs. The solvent was evaporated and the residue was dissolved in EtOAc and neutralized with 1 N HCl. The organic solution was dried and concentrated yielding crude aminoamide. The crude product was then combined with 250 mL of a 1:1 mixture of acetone and 1,2-DCE and 10 grams of anhydrous Na$_2$SO$_4$ and refluxed under N$_2$ atmosphere for 1 hr. The solution was then cooled to r.t. and filtered through a sintered glass funnel with a pad of celite. The filter cake was rinsed with a portion of acetone and the filtrate was evaporated yielding the crude acetonide.
**131**: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.25-7.00 (m, 5 H), 3.64 (dd, 1 H, $J = 4.5, 7.6$ Hz), 2.98, (dd, 2 H, $J = 4.4, 14.1$ Hz), 2.57 (s, 3 H), 1.09 (s, 3 H), 0.99 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) 172.7, 136.6, 128.9, 127.9, 126.1, 75.0, 58.6, 36.6, 26.5, 24.5.

**General Preparation of $\alpha$-Diazoo-$\alpha$-(ethoxycarbonyl)acetamides**

To a solution of crude acetonide (10 mmol) in anhydrous THF (50 mL) and TEA (0.153 mL, 11 mmol) at 0 °C was added methyl-3-chloro-3-oxopropionate (0.118 mL, 11 mmol) and stirred under N$_2$ atmosphere for 1 hr. The reaction mixture was evaporated and the residue was diluted with EtOAc and washed with water, dried and concentrated. The crude product was then diluted with MeCN (50 mL) and p-ABSA (360 mg, 15 mmol) added. The solution was cooled to 0 °C, DBU was added drop wise and the mixture was stirred for 12 hrs. The reaction mixture was then evaporated, the residue dissolved in equal parts EtOAc and water and the organic phase was then washed with water twice, dried and concentrated. The red-brown residue was purified by flash column and the pale yellow product was recovered as an oil.
**111:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.12-6.92 (m, 5 H), 3.99 (q, 2 H, $J$ = 7.2 Hz), 3.78 (m, 1 H), 3.77 (dd, 1 H, 5.0, 8.5 Hz), 3.62 (d, 1 H, $J$ = 8.5 Hz), 2.78 (dd, 1 H, $J$ = 7.9, 12.9 Hz), 2.57 (dd, 1 H, $J$ = 6.8, 13.1 Hz), 1.78 (s, 3 H), 1.31 (s, 3 H), 1.06 (t, 3 H, $J$ = 7.0 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) 161.8, 157.2, 137.5, 129.1, 128.4, 126.7, 96.2, 68.3, 67.8, 60.8, 58.6, 40.7, 27.4, 23.0, 14.2.

**124:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.15 (ddd, 1 H, $J$ = 2.3, 5.8, 13.9 Hz), 3.88 (dd, 1 H, $J$ = 5.8, 8.6 Hz), 3.65 (s, 3 H), 3.67 - 3.61 (m, 1 H), 1.53 (s, 3 H), 1.43 (m, 2 H), 1.36 (s, 3 H), 1.12 (m, 2 H), 0.75 (t, 3 H, $J$ = 7.3 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) 162.5, 156.8, 95.9, 67.7, 67.5, 57.0, 52.1, 36.3, 26.7, 23.3, 19.2, 13.6.
133: \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 7.26-6.94 (m, 5 H), 4.97 (t, 1 H, \(J = 4.5\) Hz), 3.66 (s, 3 H), 3.04 (d, 2 H, \(J = 4.6\) Hz), 2.63 (s, 3 H), 1.43 (s, 3 H), 0.87 (s, 3 H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)) 167.0, 161.2, 158.1, 135.6, 129.2, 128.1, 126.7, 80.0, 68.4, 59.6, 51.8, 37.3, 23.8, 23.0, 22.7.

**General Preparation of \(\alpha\)-Diamo-\(\alpha\)-(acetyl)acetamides**

To a solution of acetonide (10 mmol) in anhydrous THF (50 mL) at 0 °C was added diketene (0.848 mL, 11 mmol) and stirred under N\(_2\) atmosphere for 1 hr. The reaction mixture was evaporated and the residue was diluted with EtOAc and washed with water, dried and concentrated. The crude product was then diluted with MeCN (50 mL) and \(p\)-ABSA (360 mg, 15 mmol) added. The solution was cooled to 0 °C, DBU was added drop wise and the mixture was stirred for 12 hrs. The reaction mixture was then evaporated, the residue dissolved in equal parts EtOAc and water and the organic phase was then washed with water twice, dried and concentrated. The red-brown residue was purified by flash column and the pale yellow product was recovered as an oil.
**112:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.37-7.12 (m, 5 H), 4.34-4.25 (m, 1 H) 4.30 (dd, 1 H, $J$ = 6.3, 13.2 Hz), 3.87 (d, 1 H, $J$ = 8.8 Hz), 2.98 (dd, 1 H, $J$ = 8.5, 13.3 Hz), 2.81 (dd, 1 H, $J$ = 6.3, 13.4 Hz), 2.12 (s, 1 H), 1.85 (s, 1 H), 1.53 (s, 1 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 186.9, 156.6, 137.0, 128.8, 128.3, 126.6, 96.1, 67.8, 58.4, 40.6, 27.0, 26.2, 22.8.

**125:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 3.88 (dd, 1 H, $J$ = 5.6, 8.6 Hz), 3.73 (m, 1 H), 3.62 (dd, 1 H, $J$ = 2.7, 8.7 Hz), 2.16 (s, 3 H), 1.49 (s, 3 H), 1.41 (m, 2 H), 1.35 (s, 3 H), 1.08 (m, 1 H); 0.72 (t, 3 H, $J$ = 7.3 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 188.9, 156.3, 95.9, 74.3, 67.7, 57.1, 36.2, 27.1, 26.3, 23.4, 19.1, 13.6.
**134:** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.31-7.06 (m, 5 H), 4.74 (t, 1 H, $J = 4.5$ Hz), 3.14 (d, 2 H, $J = 4.8$ Hz), 2.77 (s, 3 H), 2.24 (s, 3 H), 1.56 (s, 3 H), 1.05 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 186.8, 166.8, 157.8, 135.5, 129.1, 128.2, 126.8, 80.0, 59.6, 53.1, 37.6, 26.4, 23.9, 23.0, 22.7.

**General Preparation of $\alpha$-Diazooacetamides.**

To a mixture of 5:1 water/MeCN (13.3 mL) was added the $\alpha$-diazoo-$\alpha$-(acetyl)acetamide (10 mmol) followed by LiOH (1.47 g, 35 mmol). The reaction mixture was then stirred at r.t. for 20 hrs. The solvent was evaporated and the residue dissolved in EtOAc. The organic solution was then washed with water twice and dried. Flash column chromatography was used for purification of the product.
113: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.37-7.19 (m, 5 H), 4.83 (s, 1 H), 3.87 (s, 2 H), 3.70 (m, 1 H), 3.02 (dd, 1 H, $J = 2.0$, 12.8 Hz), 2.82 (dd, 1 H, $J = 10.3$, 13.1 Hz), 1.73 (s, 3 H), 1.58 (s, 3 H).

126: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.76 (s, 1 H), 3.80 (dd, 1 H, $J = 5.3$, 8.9 Hz), 3.67 (d, 1 H, 8.8 Hz), 3.36 (m, 1 H), 1.51 (s, 3 H), 1.46 (m, 2 H), 1.40 (s, 3 H), 1.18 (m, 2 H), 0.83 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 161.8, 95.2, 66.8, 57.2, 47.9, 35.8, 26.9, 23.3, 19.5, 13.7.

114: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.30 (m, 1 H), 4.25 (q, 2 H, $J = 7.6$ Hz), 4.16 (dd, 1 H, $J = 5.8$, 8.1 Hz), 4.04 (d, 1 H, $J = 11.9$ Hz), 3.83 (dd, 1 H, $J = 8.6$, 12.6 Hz),
3.77 (t, 1H, $J = 8.6$ Hz), 1.71 (s, 3 H), 1.50 (s, 3 H), 1.25 (t, 3 H, $J = 7.6$ Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 168.5, 165.1, 137.4, 129.1, 127.8, 127.0, 92.1, 69.0, 65.1, 61.7, 60.9, 48.7, 26.5, 23.7, 14.1.

$^{115}$: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.36-7.20 (m, 5 H), 4.27 (m, 1 H), 4.19 (m, 1 H), 4.13 (m, 1 H), 3.90 (dd, 1 H, $J = 8.6$, 11.1 Hz) 3.67 (t, 1 H, $J = 8.6$ Hz) 2.39 (s, 3 H), 1.65 (s, 3 H), 1.51 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 202.2, 165.3, 138.3, 129.0, 127.6, 127.3, 91.9, 69.2, 67.4, 64.7, 45.4, 31.1, 26.6, 23.7.

$^{116}$: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 6.58 (m, 2 H), 6.27 (d, 2 H, $J = 9.1$ Hz), 6.07 (s, 1 H), 5.12 (dd, 1 H, $J = 5.4$, 9.0 Hz), 4.20 (dd, 1 H, $J = 5.1$, 7.5 Hz), 3.70 (m, 2 H), 2.76 (dd, 1 H, $J = 2.0$, 14.8 Hz), 2.47 (m, 2 H), 1.68 (s, 3 H), 1.62 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 168.1, 131.7, 130.4, 129.9, 127.2, 121.4, 119.4, 94.9, 69.1, 57.0, 47.7, 34.7, 25.4, 24.0.
128: $^1$H NMR (250 MHz, CDCl₃) $\delta$ 4.08 (dd, 1 H, $J = 5.6$, $8.2$ Hz), 3.74 (m, 1 H), 3.60 (d, 1 H, $J = 11.0$ Hz), 3.48 (t, 1 H, $J = 9.1$ Hz), 2.54 (m, 1 H), 2.37 (s, 3 H), 1.54 (s, 3 H), 1.41 (s, 3 H), 1.33 (m, 1 H), 0.81 (t, 3 H, $J = 4.3$ Hz); $^{13}$C NMR (62.5 MHz, CDCl₃) $\delta$ 203.0, 166.0, 91.3, 69.5, 66.3, 64.1, 42.0, 30.8, 26.5, 25.3, 23.6, 12.1.

127: $^1$H NMR (250 MHz, CDCl₃) $\delta$ 3.99 (dd, 1 H, $J = 5.8$, $8.3$ Hz), 3.71 (m, 1 H), 3.64 (s, 3 H), 3.46 (dd, 1 H, $J = 8.8$, $8.8$ Hz), 3.40 (d, 1 H, $J = 11.3$ Hz), 2.38 (qt, 1 H, $J = 2.5$, $8.5$ Hz), 1.49 (s, 3 H), 1.44 (m, 2 H), 1.30 (s, 3 H), 0.73 (t, 3 H, $J = 7.3$ Hz); $^{13}$C NMR (62.5 MHz, CDCl₃) $\delta$ 169.5, 165.7, 91.3, 69.1, 64.4, 60.0, 52.4, 45.3, 26.3, 25.0, 23.5, 11.8.
**135**: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.90-7.44 (m, 5 H), 7.29-7.23 (m, 5 H), 4.51 (d, 1 H, $J = 9.1$ Hz), 4.14 (m, 2 H), 2.80 (s, 3 H), 1.78 (s, 3 H), 1.46 (s, 3 H).

**136**: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.45-7.13 (m, 5 H), 4.30 (d, 1 H, $J = 9.2$ Hz), 4.10 (dd, 1 H, $J = 9.2, 10.5$ Hz), 3.95 (d, 1 H, $J = 11.7$ Hz), 3.74 (s, 3 H), 2.82 (s, 3 H), 1.84 (s, 3 H), 1.47 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 168.7, 167.6, 167.2, 136.7, 128.9, 127.7, 127.5, 76.9, 63.1, 58.0, 52.8, 47.8, 24.6, 24.5, 23.2.

**137**: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.39-7.24 (m, 5 H), 4.30 (d, 1 H, $J = 9.0$ Hz), 4.13 (d, 1 H, $J = 10.7, 33.0$ Hz), 4.11 (d, 1 H, $J = 13.1$ Hz), 2.80 (s, 3 H), 2.39 (s, 3 H), 1.79 (s, 3 H), 1.48 (s, 3 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 201.3, 167.5, 167.0, 137.1, 128.4, 128.2, 127.2, 127.1, 76.4, 64.0, 62.3, 44.7, 30.7, 24.1, 22.7.
Preparation of O^t-Bu-(L)-Serine Methyl Ester

Thionyl chloride (38 mL, 0.53 mol) was added to a solution of (L)-serine (50 g, 0.48 mol) in MeOH (0.5 L) at 0 °C and the resulting mixture was refluxed for 2 hours. After concentration, the residue was solidified from ether to give (L)-serine methyl ester HCl salt as white solid. Liquid isobutylene (200 mL) was added to a mixture of (L)-serine methyl ester HCl salt (20 g, 0.12 mol), p-TsOH (40 g, 0.12 mol) and CH₂Cl₂ (400 mL) in a thick-walled, well-stoppered flask at −78°C and the resulting mixture was stirred for 72 hours at room temperature. After degassing, the reaction mixture was concentrated and the residue was diluted with EtOAc, washed with saturated NaHCO₃, dried over anhydrous Na₂SO₄, and concentrated to afford 153, which was used for the next step without further purification: ^1H NMR (250 MHz, CDCl₃) δ 3.72 (s, 3 H), 3.59 (br s, 3 H), 1.82 (br s, 2 H, NH₂), 1.15 (s, 9 H); ^13C NMR (62.5 MHz, CDCl₃) δ 173.9, 72.4, 63.5, 54.7, 51.3, 26.9.
Preparation of Amino Alcohol 154

A solution of 153 (24 g, 0.14 mol) in anhydrous THF was added to the mixture of lithium aluminum hydride (31 g, 0.27 mol) in THF (450 mL) at 0 °C. The resulting reaction mixture was stirred for 8 hrs. at room temperature and quenched by successive addition of water (30 mL)-20% NaOH (30 mL)-water (60 mL). The precipitate was filtered and washed with THF. The filtrate was dried and concentrated to give amino alcohol 154 as an oil, which was used for the next step without further purification: $^1$H NMR (250 MHz, CDCl$_3$) δ 3.58 (m, 2 H), 3.39 (d, 2 H, $J = 5.3$ Hz), 3.00 (m, 1 H), 1.19 (s, 9 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 72.6, 64.5, 64.3, 51.9, 26.9.
Preparation of $N,O$-Acetonide 155

\[
\begin{array}{c}
\text{NH}_2 \\
\text{O} \\
\text{t-Bu}
\end{array}
\xrightarrow{\text{Me}_2\text{CO/1,2-DCE, Na}_2\text{SO}_4, \Delta}
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{t-Bu}
\end{array}
\]

The mixture of the amino alcohol 154 (12 g, 80 mmol), acetone (200 mL), and anhydrous Na$_2$SO$_4$ (68 g, 0.48 mol) in 1,2-dichloroethane (200 mL) was refluxed with stirring for 2 hrs. The reaction mixture was filtered and concentrated to give acetonide intermediate 155.

Preparation of $N$-Acylated $N,O$-Acetonides 156 and 157

\[
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{t-Bu}
\end{array}
\xrightarrow{X \cdot \text{TEA, CH}_2\text{Cl}_2}
\begin{array}{c}
\text{X} \\
\text{O} \\
\text{Bu}
\end{array}
\]

Bromoacetyl bromide or chloroacetyl chloride (80 mmol) was added to a mixture of acetonide 155 (15 g, 80 mmol) and TEA (17 mL, 160 mmol) in CH$_2$Cl$_2$ (160 mL) at 0 °C. After stirring for 4 hrs. at room temperature, the reaction mixture was washed with water, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and evaporated to give the corresponding $\alpha$-haloamide 156/157, which was used for the next step without further purification. For
compound 156: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.32 (ABq, 1 H, $J_{AB} = 10.7$ Hz), 4.10 (m, 1 H), 4.00 (m, 1 H), 3.83 (d, 1 H, $J = 9.7$ Hz), 3.79 (ABq, 1 H, $J_{AB} = 10.7$ Hz), 3.43 (d, 2 H, $J = 7.0$ Hz), 1.66 (s, 3 H), 1.53 (s, 3 H), 1.18 (s, 9 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 164.7, 95.6, 73.7, 65.7, 63.5, 58.0, 29.8, 27.3, 26.9, 22.0; IR (thin film, cm$^{-1}$) 2976, 1648, 1415, 1365, 726, 705. Anal. Calcd. for C$_{12}$H$_{22}$BrNO$_3$: C, 46.76; H, 7.19; N, 4.54. Found: C, 46.29; H, 7.21; N, 4.58, 161:

**Preparation of $\alpha$-Phenylsulfonylacetamide 158**

PhSO$_2$Na (84 mmol) was added to a solution of haloacetyl amide 156/157 (80 mmol) in DMF (160 mL) at room temperature. After stirring for 6 hrs, the reaction mixture was diluted with EtOAc, washed with water twice, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography to give $\alpha$-phenylsulfonyl acetamide 158: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.90-7.52 (m, 5 H), 5.10 (ABq, 1 H, $J_{AB} = 14.0$ Hz), 4.47 (m, 1 H), 4.04 (ABX, 1 H, $J_{AB} = 9.2$ Hz, $J_{AX} = 5.3$ Hz), 3.91 (ABq, 1 H, $J_{AB} = 14.0$ Hz), 3.77 (ABX, 1 H, $J_{AB} = 9.2$ Hz, $J_{AX} = 0$ Hz), 3.42 (d, 2 H, $J = 7.3$ Hz), 1.57 (s, 3 H), 1.49 (s, 3 H), 1.15 (s, 9 H); IR (thin film, cm$^{-1}$) 2980, 1651, 1423, 1366, 1320, 1157, 741. Anal. Calcd. for C$_{18}$H$_{27}$NO$_5$S: C, 58.51; H, 7.37; N, 3.79;
S, 8.68. Found: C, 58.41; H, 7.20; N, 3.81; S, 8.72.

**Preparation of α-Diazo-α-(phenylsulfonyl)acetamide 163.**

![Chemical structure](image)

To a solution of α-phenylsulfonylacetamide 158 (6.8 g, 18 mmol) in acetonitrile (90 mL) was added p-ABSA (5.2 g, 21 mmol) followed by DBU (6.8 mL, 45 mmol). The reaction mixture was stirred for 1 hr. at 0 °C. After evaporation of acetonitrile the residue was diluted with EtOAc. The organic layers were washed with water twice, dried over Na₂SO₄ and then evaporated. The residue was purified by column chromatography to give α-diazo-α-(phenylsulfonyl)acetamide 159 as yellow solid: ¹H NMR (250 MHz, CDCl₃) δ 8.02 (d, 2 H, J = 7.1 Hz), 7.57 (m, 3 H), 3.99-3.91 (m, 3 H), 3.37 (m, 2 H), 1.59 (s, 3 H), 1.41 (s, 3 H), 1.16 (s, 9 H); ¹³C NMR (62.5 MHz, CDCl₃) δ 154.2, 142.2, 133.6, 129.0, 127.7, 96.8, 74.7, 73.5, 66.3, 61.9, 57.1, 27.2, 26.6, 23.5; IR (thin film, cm⁻¹) 2976, 2092, 1628, 1395, 1267, 1150, 1085, 745.
Preparation of γ-Lactam 160

To a solution of the α-diazo-α-(phenylsulfonyl)acetamide 159 (6.0 g, 15 mmol) in dry CH₂Cl₂ (300 mL, C = 0.05 M) was added catalytic amount of Rh₂(OAc)₄ (66 mg, 0.15 mmol). The mixture was refluxed with stirring for 12 hrs. under N₂, cooled to room temperature, and was then concentrated. The residue was purified by column chromatography to give γ-lactam 160 as a single isomer: ¹H NMR (250 MHz, CDCl₃) δ 7.95 (d, 2 H, J = 7.3 Hz), 7.67-7.51 (m, 3 H), 4.69 (dd, 1 H, J = 3.75, 6.0 Hz), 4.25 (d, 1 H, J = 6.0 Hz), 4.14 (ABX, 1 H, Jₐₙ = 8.9 Hz, Jₐₓ = 5.8 Hz), 3.96 (m, 1 H), 3.62 (ABX, Jₐₙ = 8.9 Hz, Jₓₓ = 8.0 Hz), 1.58 (s, 3 H), 1.39 (s, 3 H), 1.25 (s, 9 H); ¹³C NMR (62.5 MHz, CDCl₃) δ 161.1, 138.1, 134.1, 129.5, 128.7, 92.9, 76.9, 76.1, 67.6, 67.4, 67.3, 28.3, 26.9, 23.4; IR (thin film, cm⁻¹) 2977, 1705, 1401, 1321, 1266, 1153, 1080, 889, 840, 737. Anal. Calcd. for C₁₈H₂₅NO₅S: C, 58.83; H, 6.86; N, 3.81; S, 8.73. Found: C, 58.80; H, 6.78; N, 3.98; S, 8.68.
Preparation of α-Methylated γ-Lactam 161

Mel (2.6 mL, 42 mmol) was added to a mixture of γ-lactam 160 (5.0 g, 14 mmol) and NaH (1.1 g, 28 mmol) in DMF (28 mL) at 0 °C. After stirring for 1 hour at 0 °C, the reaction was quenched with saturated NH₄Cl, extracted with EtOAc, dried over Na₂SO₄ and concentrated to give methylated γ-lactam 161: ¹H NMR (250 MHz, CDCl₃) δ 7.90-7.51 (m, 5 H), 4.84 (d, 1 H, J = 4.0 Hz), 4.18 (ABX, 1 H, Jₐb = 8.7 Hz, Jₐₓ = 5.3 Hz), 3.92 (m, 1 H), 3.79 (ABX, 1 H, Jₐb = 8.7 Hz, Jₖₓ = 7.7 Hz), 1.68 (s, 3 H), 1.51 (s, 3 H), 1.47 (s, 3 H), 1.28 (s, 9 H); ¹³C NMR (62.5 MHz, CDCl₃) δ 165.6, 135.6, 134.0, 131.3, 128.2, 92.6, 78.9, 76.0, 67.6, 67.5, 67.4, 28.4, 26.9, 23.2, 14.6; IR (thin film, cm⁻¹) 2979, 1707, 1405, 1306, 1265, 1189, 1151, 1114, 742. Anal. Calcd. for C₁₉H₂₇NO₅S: C, 59.82; H, 7.13; N, 3.67; S, 8.41. Found:  C, 59.87; H, 7.00; N, 3.73; S, 8.42.
Preparation of Reduced $\gamma$-Lactam 161

10% Sodium amalgam (12 g) was added to a solution of $\alpha$-methylated $\gamma$-lactam 161 (5.0 g, 13 mmol) and anhydrous disodium hydrogen phosphate (11 g) in dry methanol (250 mL) at 0 °C. The mixture was stirred for 2 hrs., quenched with water, and extracted twice with ether. The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated to give 162: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.14 (m, 1 H), 4.03 (m, 2 H), 3.58 (br t, 1 H), 2.67 (m, 1 H), 1.66 (s, 3 H), 1.44 (s, 3 H), 1.23 (d, 3 H, $J$ = 7.5 Hz), 1.17 (s, 9 H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 173.2, 91.5, 74.2, 72.5, 68.2, 64.8, 48.9, 28.0, 26.5, 23.7, 11.0; IR (thin film, cm$^{-1}$) 2983, 1699, 1456, 1402, 1364, 1263, 1191, 1101, 1039, 745. Anal. Calcd. for C$_{13}$H$_{23}$NO$_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.19; H, 9.59; N, 3.79.
Preparation of Carboxylic Acid 164

=[H_2CrO_4]_{Me_2CO} \rightarrow [O\_H\_t-\text{BuO}CO_2H]_{164}

Jones reagent (1.0 M, 103 mL, 103 mmol) was added to a solution of 162 (4.2 g, 17 mmol) in acetone (340 mL) at 0 °C and the resulting mixture was stirred for 2 hrs. at that temperature. The reaction was quenched with IPA, extracted three times with CH_2Cl_2, dried over Na_2SO_4 and concentrated to give carboxylic acid 164, which was used for the next step without further purification.

Preparation of Methyl Ester 165

=[NH_2O\_t-\text{BuO}CO_2H]_{164} \rightarrow [O\_H\_t-\text{BuO}CO_2Me]_{165}

A mixture of the carboxylic acid 164 and trimethyl orthoformate (19 mL, 170 mmol) in methanol (340 mL) containing a catalytic amount of sulfuric acid (2-3 drops) was stirred for 4 hours at room temperature. The reaction mixture was neutralized by addition of solid NaHCO_3 and evaporated. The residue was diluted with water, extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated and purified by column chromatography.
to afford **165**: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.91 (br s, 1 H), 4.36 (br d, 1 H, $J = 7.0$ Hz), 4.04 (br s, 1 H), 3.77 (s, 3 H), 2.50 (dq, 1 H, $J = 7.0$ Hz, 7.3 Hz), 1.23 (s, 9 H), 1.13 (d, 3 H, $J = 7.3$ Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 179.4, 171.3, 74.9, 73.0, 63.2, 52.4, 39.8, 27.9, 8.8. Anal. Calcd. for C$_{11}$H$_{19}$NO$_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 56.71; H, 8.31; N, 5.93.

**Preparation of Iminoether 166**

To a mixture of **165** (2.6 g, 11 mmol) and 4 Å molecular sieve in dry CH$_2$Cl$_2$ (110 mL) was added a solution of trimethyloxonium tetrafluoroborate (4.8 g, 31 mmol) in CH$_2$Cl$_2$ (60 mL) at 0 °C. The reaction mixture was stirred for 3 hrs., filtered and poured into an aqueous solution of K$_2$CO$_3$. The aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic layers were dried over Na$_2$SO$_4$, concentrated and chromatographed to give **166**: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.38 (dd, 1 H, $J = 4.3$, 7.3 Hz), 4.29 (d, 1 H, $J = 4.3$ Hz), 3.89 (s, 3 H), 3.74 (s, 3 H), 2.79 (dq, 1 H, $J = 7.3$ Hz, 7.3 Hz), 1.25 (s, 9 H), 1.08 (d, 3 H, $J = 7.3$ Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 176.7, 173.0, 75.2, 74.4, 74.0, 55.3, 52.0, 42.0, 28.0, 10.0; Anal. Calcd. for C$_{12}$H$_{21}$NO$_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.65; H, 8.75; N, 5.77.
Preparation of α-Methylene γ-Lactam.

10% Sodium amalgam (7.8 g) was added to a solution of γ-lactam 160 (3.0 g, 8.4 mmol) and anhydrous disodium hydrogen phosphate (7.0 g) in dry methanol (160 mL) at 0 °C. The mixture was stirred for 2 hrs., concentrated, diluted with water and extracted with ether twice. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed to give reduced γ-lactam 163. ¹H NMR (250 MHz, CDCl₃) δ 4.09 (m, 3 H), 3.54 (dd, 1 H, J = 7.1, 7.9 Hz), 2.73 (m, 2 H), 1.62 (s, 3 H), 1.42 (s, 3 H), 1.14 (s, 9 H).

Preparation of α-Methylated γ-Lactam epi-162

To a solution of reduced γ-lactam 163 (250 mg, 1.0 mmol) in THF (5.0 mL) was added a solution of LHMDS in THF (1.2 mmol) at -78°C. After stirring for 15 min at that temperature, MeI (11 µL, 1.2 mmol) was added to the reaction mixture, which was
further stirred for 30 min. and quenched with saturated NH₄Cl. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was chromatographed to give *epi-162*: ¹H NMR (250 MHz, CDCl₃) δ 4.15 (dd, 1 H, *J* = 5.7, 8.2 Hz), 3.96 (m, 1 H), 3.55 (m, 2 H), 2.78 (dq, 1 H, *J* = 7.1, 9.7 Hz), 1.62 (s, 3 H), 1.46 (s, 3 H), 1.19 (d, 3 H, *J* = 7.1 Hz), 1.17 (s, 9 H).

**Preparation of Carboxylic Acid *epi-164***

![Chemical structures](image)

Following the same procedures for the preparation of *164*, *epi-164* was obtained from *epi-162* in a 56% yield: ¹H NMR (250 MHz, CDCl₃) δ 6.2 (br s, 1 H), 4.1 (d, 1 H, *J* = 3.0 Hz), 4.0 (br s, 1 H), 3.77 (s, 3 H), 2.34 (dq, 1 H, *J* = 3.0, 7.6 Hz), 1.21 (d, 3 H, *J* = 7.6 Hz), 1.21 (s, 9 H).
Preparation of Methyl Ester \textit{epi}-165

\[
\text{epi-164} \xrightarrow{\text{TMOF}} \text{MeOH, H}_2\text{SO}_4 \xrightarrow{} \text{epi-165}
\]

Following the same procedures for the preparation of 165, \textit{epi}-165 was obtained from \textit{epi}-164 in a 70% yield: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 6.23 (s, 1 H), 4.04 (m, 2 H), 3.77 (s, 3 H), 2.34 (qd, 1 H, $J$ = 3.0, 7.8 Hz), 1.21 (m, 12 H).

Preparation of Iminoether \textit{epi}-166

\[
\text{epi-165} \xrightarrow{\text{Me}_3\text{O·BF}_4} \text{CH}_2\text{Cl}_2 \xrightarrow{} \text{epi-166}
\]

Following the same procedures for the preparation of 166, \textit{epi}-166 was obtained from \textit{epi}-165 in a 70% yield: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.29 (d, 1 H, $J$ = 3.2 Hz), 4.09 (dd, 1 H, $J$ = 3.3, 3.6 Hz), 3.83 (s, 3 H), 3.75 (s, 3 H), 2.65 (m, 1 H), 1.22 (d, 3 H, $J$ = 7.6 Hz), 1.18 (s, 9 H).
Preparation of Aldol Coupling Product *epi*-167

To a solution of iminoether *epi*-166 (250 mg, 1.0 mmol) in THF (5.0 mL) was added a solution of LDA in THF (1.2 mmol) at -78 °C. After stirring for 15 min. at that temperature, isobutyraldehyde (11 µL, 1.2 mmol) was added to the reaction mixture, which was further stirred for 30 min. and quenched with saturated NH₄Cl. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was chromatographed to give aldol product *epi*-167 as a single isomer: \(^1\)H NMR (250 MHz, CDCl₃) δ 4.22 (d, 1 H, \(J = 4.1 \) Hz), 3.94 (dd, 1 H, \(J = 3.4, 11.1 \) Hz), 3.85 (s, 3 H), 3.69 (s, 3 H), 2.64 (m, 1 H), 1.95 (m, 1 H), 1.23 (d, 3 H, 7.4 Hz), 1.15 (s, 9 H), 1.00 (d, 6 H, \(J = 6.8 \) Hz).
Preparation of Aldol Coupling Products 167 5R, 9S / 167 5S

Following the same procedure for epi-167, aldol reaction of 166 afforded an inseparable mixture 167 5R, 9S and 167 5S in 70% yield. 167 5R, 9S: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.64 (d, 1 H, $J = 8.67$ Hz), 3.95 (dd, 1 H, $J = 3.0, 10.9$ Hz), 3.85 (s, 3 H), 3.67 (s, 3 H), 2.68 (m, 1 H), 1.92 (m, 1 H), 1.15 (s, 9 H), 1.07 (d, 3 H, $J = 7.6$ Hz), 1.01 (d, 3 H, $J = 6.76$ Hz), 0.99 (d, 3 H, $J = 6.7$ Hz). 167 5S: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.36 (d, 1 H, $J = 9.5$ Hz), 4.08 (dd, 1 H, $J = 3.4, 5.5$ Hz), 3.87 (s, 3 H), 3.70 (s, 3 H), 3.23 (d, 1 H, $J = 3.4$ Hz), 2.73 (m, 1 H), 1.85 (m, 1 H), 1.22 (s, 9 H), 1.11 (d, 3 H, $J = 7.5$ Hz), 1.04 (d, 3 H, $J = 6.7$ Hz), 0.94 (d, 3 H, $J = 6.9$ Hz).
Preparation of \( \beta \)-Keto Esters 172R and 172S.

The mixture of \( \beta \)-keto esters 167 5R, 9S and 167 5S were dissolved in CH\(_2\)Cl\(_2\) and cooled to 0 °C. Excess DMP solution was added and the reaction was quenched after 5 min. using saturated sodium bicarbonate solution. The organic solution was washed with water, dried and concentrated. The products were separated using flash column chromatography. 168 5R: \(^1\)H NMR (250 MHz, CDCl\(_3\)) \( \delta \) 5.10 (d, 1 H, \( J = 8.5 \) Hz), 3.86 (s, 3 H), 3.74 (s, 3 H), 3.06 (m, 1 H), 2.71 (m, 1 H), 1.15 (s, 9 H + 3 H), 1.11 (d, 3 H, \( J = 7.6 \) Hz), 1.08 (d, 3 H, \( J = 6.8 \) Hz). 168 5S: \(^1\)H NMR (250 MHz, CDCl\(_3\)) \( \delta \) 5.11 (d, 1 H, \( J = 8.0 \) Hz), 3.90 (s, 3 H), 3.75 (s, 3 H), 2.87 (m, 2 H), 1.15 (s, 9 H + 3 H), 1.09 (d, 3 H, \( J = 7.8 \) Hz), 1.04 (d, 3 H, \( J = 6.8 \) Hz).

A solution of aldol products $167\, 5R$, $9S$ and $167\, 5S$ (160 mg, 0.51 mmol) in trifluoroacetic acid (2.5 mL) was stirred for 1 hr. at room temperature. After concentration, the crude diol compounds were dissolved in a solution of 1% HCl in EtOH. The mixture was stirred for 1 hour, concentrated, diluted with EtOAc, washed with saturated NaHCO$_3$ and dried over Na$_2$SO$_4$. After concentration, the residue was chromatographed to afford an inseparable mixture of dihydroxy $\gamma$-lactams $169\, 5R$, $9S$ and $169\, 5S$. $169\, 5R$, $9S$: $^1$H NMR (250 MHz, CD$_3$OD) $\delta$ 4.43 (d, 1 H, $J = 6.0$ Hz), 3.90 (d, 1 H, $J = 7.3$ Hz), 3.72 (s, 3 H), 2.94 (m, 1 H), 1.65 (m, 1 H), 1.06 (d, 3 H, $J = 7.6$ Hz), 0.97 (d, 3 H, $J = 6.6$ Hz), 0.83 (d, 3 H, $J = 6.8$ Hz). $169\, 5S$: $^1$H NMR (250 MHz, CD$_3$OD) $\delta$ 4.61 (d, 1 H, $J = 5.8$ Hz), 3.95 (d, 1 H, $J = 5.1$ Hz), 3.74 (s, 3 H), 2.48 (m, 1 H), 1.76 (m, 1 H), 1.10, (d, 3 H, $J = 7.3$ Hz), 1.01 (d, 3 H, $J = 6.8$ Hz), 0.93 (d, 3 H, $J = 6.68$ Hz).

Preparation of clasto-Lactacycstn $\beta$-Lactone 2

A mixture of dihydroxy $\gamma$-lactams $169\, 5S$ & $169\, 5R$, $9S$ in 0.1 N NaOH/EtOH solution was stirred for 4 hrs. at r.t. The reaction mixture was neutralized with saturated NH$_4$Cl and concentrated to give a mixture of dihydroxy acids. To the mixture of dihydroxy acids and TEA in THF was added isopropenyl chloroformate at 0 °C and
stirred for 1 hour. The reaction mixture was diluted with water, extracted with CH₂Cl₂, dried over anhydrous. Na₂SO₄, concentrated and purified by column chromatography to afford 2. ¹H NMR (250 MHz, Pyridine d₅) δ 10.47 (s, 1 H), 7.87 (d, 1 H, J = 6.8 Hz), 5.69 (d, 1 H, J = 6.1 Hz), 4.36 (dd, 1 H, J = 3.7, 6.8 Hz), 3.06 (m, 1 H), 2.12 (m, 1 H), 1.48 (d, 3 H, J = 7.5 Hz), 1.13 (d, 3 H, J = 6.9 Hz), 1.02 (d, 3 H, J = 6.7 Hz).
References


6 Fenteany, G.; Standaert, R. F.; Reichard, G. A.; Corey, E. J.; Schreiber, S. L.

7 Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L.


9 Dick, L. R.; Cruikshank, A. A.; Grenier, L.; Melandri, F. D.; Nunes, S. L.; Stein,

10 Groll, M.; Ditzel, L.; Löwe, J.; Stock, D.; Bochtler, M.; Bartunik, H. D.; Huber,

12 Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Ōmura, S.; Sprengeler, P. A.; Smith, A.


21 Gao, Y.; Hanson, R.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B.


Ultra dilute conditions were required for this reduction to occur diastereoselectively. Originally, using a 0.05M methanol solution resulted in a mixture of epimers. Further diluting the concentration to 0.025M provides the $\beta$-methyl product selectively.
Appendices
Appendix A: Selected $^1$H NMR and $^{13}$C NMR Spectra
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Appendix A: (Continued)
Table 1. Crystal data and structure refinement for (2) bdm1.

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<tr>
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<tr>
<td>Wavelength</td>
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</tr>
<tr>
<td>Crystal system</td>
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<tr>
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<tr>
<td>α</td>
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<tr>
<td>b</td>
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</tr>
<tr>
<td>β</td>
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</tr>
<tr>
<td>c</td>
<td>18.2095(16) Å</td>
</tr>
<tr>
<td>γ</td>
<td>90°</td>
</tr>
<tr>
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<tr>
<td>Density (calculated)</td>
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<td>F(000)</td>
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### Table 7. Crystal data and structure refinement for (epi-167) df01m.

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<td>Wavelength</td>
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<td>Crystal system</td>
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<tr>
<td>Space group</td>
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<tr>
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<td>Largest diff. peak and hole</td>
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Appendix B: (Continued)

*epi*-167