The Pennsylvania State University
The Graduate School
Eberly College of Science

TOTAL SYNTHESSES OF (-)-SECU’AMAMINE A
AND (±)-COMMUNESIN F

A Dissertation in
Chemistry
by
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Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

August 2010
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ABSTRACT

In part I, a convergent stereoselective total synthesis of the novel *Securinega* alkaloid (-)-secu’amamine A (9) was described. The synthesis requires 15 steps starting from aldehyde 34 and proceeds in approximately 9% overall yield. Key steps include a stereoselective conjugate addition of amino enedione 86 to afford indolizidine 91 as the major product and a tandem aldol/lactonization of diketoester 92 to produce tetracyclic γ-lactone 93.

In part II, a stereoselective total synthesis of the heptacyclic alkaloid communesin F (8) was achieved in racemic form in 30 steps from the known enol triflate 147 and commercially available o-nitrobenzeneboronic acid. Key transformations in the sequence include an intramolecular Heck cyclization of a tetrasubstituted alkene to generate a tetracycle with a quaternary carbon center, a reductive cyclization of an N-Boc aniline onto an oxindole moiety to form the pentacyclic framework containing the lower aminal, a stereoselective lactam C-allylation to introduce the second quaternary carbon center, and an azide reduction/translactamization cascade eventually leading to the upper aminal functionality.
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ACKNOWLEDGEMENTS

I would first like to express my greatest gratitude to my advisor Professor Steven M. Weinreb for his scientific guidance and continuous support throughout my graduate studies. His extensive knowledge in the field and enthusiasm for science have always made me feel it is an honor to be one of his students.

I would also like to thank Prof. Raymond L. Funk, Prof. Przemyslaw Maslak and Prof. Ryan J. Elias for their service as my committee members. I thank Dr. Alan Benesi and Dr. Bernie O’Hare for their help with the NMR spectroscopy.

I would like to acknowledge the past and present Weinreb group members, with whom working in the lab is a pleasure. I truly enjoy the friendly atmosphere of the group.

I also thank my parents and sisters for their unconditional love and support. Most of all, I thank my wife Min, for her love, encouragement and understanding over these many years. To them, I dedicate this thesis.
Part I: Total Synthesis of the *Securinega* Alkaloid (-)-Secu’amamine A

Chapter 1. Introduction and Background

The *Securinega* alkaloids are a relatively small family of natural products isolated from the Euphorbiaceae family of plants, especially members of the *Securinega* and *Phyllanthus* genera.\(^1,2\) Most *Securinega* alkaloids have a 6-azabicyclo[3.2.1]octene system (rings B and C), which is fused to a butenolide (ring D) and either a piperidine or pyrrolidine (ring A), forming a rather complex and intriguing molecular framework (Figure 1). (-)-Securinine (1), the most abundant *Securinega* alkaloid, was isolated from the leaves of *Securinega suffruticosa*.\(^3\) In addition, (-)-allosecurinine (2), the C-2 epimer of (-)-securinine, was also isolated in minor amount from the same plant, and later from a *Phyllanthus* species.\(^1,2\) Interestingly, virosecurinine (3), the antipodal compound of (-)-securinine is also naturally occurring, and discovered from *Securinega virosa*. Moreover, (-)-norsecurinine (4), which incorporates a pyrrolidine A-ring instead of the piperidine ring present in the securinine-type of alkaloids, and the partially saturated (+)-dihydronorsecurinine (5) have also been described.\(^1,2\)

In addition to the typical securinine/norsecurinine type of structures, there are also several *Securinega* alkaloids that show significant skeletal variations, as is the case with (+)-phyllantidine (6)\(^4\), (+)-nirurine (7)\(^5\) and the structurally related securinol A (8)\(^6\) (Figure 1). (+)-Phyllantidine (6), isolated from *Phyllanthus discoides* and *Securinega suffruticosa*, has a tetrahydro-1,2-oxazine ring, which is an uncommon structural motif in natural products. Interestingly, phyllantidine is believed to be derived biogenetically from virosecurinine (2) and, in fact, can be prepared by peracid or ozone oxidation of this
alkaloid via a Meisenheimer rearrangement. (+)-Nirurine (7), isolated from Phyllanthus niruri, has an oxygen bridge between the A and B-rings, and incorporates an azabicyclo[2.2.2]octane framework. Securinol A (8), which is structurally related to nirurine (7), was isolated from Securinega suffruticosa, and has a unique quinolizidine skeleton embedded in the azabicyclo[2.2.2]octane skeleton.

In 2003, Ohsaki and coworkers reported a structurally novel Securinega alkaloid, (-)-secu'amamine A (9), isolated from Securinega suffruticosa var. amamiensis (Figure 2).\textsuperscript{7} The structure and relative stereochemistry of (-)-secu'amamine A were elucidated by spectroscopic data and its absolute configuration was assigned on the basis of the OMe-mandelate method. Different from the common 6-azabicyclo[3.2.1]octene B/C ring system of the Securinega alkaloids, the skeleton of 9 incorporates an azabicyclo[3.3.1]nonene system (rings B and C) fused to a butenolide (ring D) and a pyrrolidine (ring A). Although
the stereochemistry of the indolizidine moiety (AB-ring) was not initially addressed, we have determined that the \textit{trans}-fused invertomer shown in 9 is thermodynamically preferred (\textit{vide infra}).

In 2007 and 2009, the same group which discovered secu’amamine A (9) reported six additional alkaloids isolated in minor quantities from \textit{Securinega suffruticosa} var. \textit{amamiensis} and named the metabolites secu'amamines B-G (10-14)\textsuperscript{9} (Figure 2), although their structures are more closely related to other types of \textit{Securinega} alkaloids. More specifically, the skeleton and stereochemistry of secu'amamine B (10) and C (11) resembles that of allosecurine (2) and securine (1), respectively, except for the absence of C14/15 double bond and the presence of methoxy substitution in 10 and 11. Secu'amamine D (12) compares to \textit{ent}-phyllanthine (\textit{ent}-6) except for the extra C4 methoxy group. Secu’amamine E (13) is closely related to \textit{ent}-securinol A (\textit{ent}-8). Secu’amamines F and G (14-15) have the same structure as secu’amamine E except for the presence of an extra piperidine ring, and are assigned to be stable atropisomers around bond C13 and C1’.
Recently, Magnus and Padilla proposed that secu'amamine A (9) is derived biogenetically from allosecurinine (2). Thus, as illustrated in Scheme 1, a biological oxidation of allosecurinine would produce 3-β-hydroxyallosecurinine (16) (an alkaloid currently unknown). Subsequent cyclization would give the aziridinium ion intermediate 17, which is then ring-opened by water to afford the rearranged alkaloid 9.
The Magnus group also conducted some simple model experiments to support the involvement of an aziridinium ion in the rearrangement of 16 into 9, which is the key idea of their proposal. In one of their model studies, a deuterium labeled indolizidine 18 was prepared, possessing A and B rings of the 3β-hydroxyallosecurinine (16) (Scheme 2). They then studied nucleophilic substitution of the p-nitrobenzoate moiety of 18 by an acetate anion. If the substitution reaction does involve formation of the aziridinium ion 19, the highly strained three-membered ring can be opened by the nucleophile at either carbon atom (paths a and b) to give a mixture of products with the deuterium label residing at different positions of the bicyclic ring system. Indeed, when 18 was treated with sodium acetate in acetic acid at reflux, it was converted into a mixture of 20 and 21 as evidenced by two distinct deuterium peaks in the 2H NMR spectrum, which is consistent with the intermediacy of the aziridinium ion 19.

Scheme 2

The Securinega alkaloids exhibit a wide range of biological activity,² and several of the plants that produce these compounds have been used for many years in traditional Chinese folk medicine.⁴ Securinine (1), for instance, has been shown to be a γ-aminobutyric acid (GABA) receptor antagonist, and has also been found to be a stimulant of the central nervous system (CNS).¹¹ In addition, securinine (1) is also an antimalarial, an antibacterial agent, cytotoxic and causes apoptosis in leukemia cells.¹² Some Securinega
alkaloids have been sporadically used in the clinic for diseases such as poliomyelitis, ALS, and chronic aplastic anemia.

The *Securinega* alkaloids have drawn increasing interest from the synthetic community due to the challenges in preparing their complex ring systems, as well as the known biological activity of some family members. A number of elegant syntheses of these alkaloids have been reported. This area of synthesis has recently been thoroughly reviewed. Most of the total syntheses completed so far have focused primarily on securinine and norsecurinine-type alkaloids, with only a few exceptions. In 1992, Magnus and coworkers reported the first, and to date only total synthesis of racemic nirurine (7). In 2008, we completed the first and thus far only total synthesis of (-)-secu’amamine A (9), which is discussed in the following sections.

**Chapter 2. Results and Discussion**

**2.1. Retrosynthetic Analysis**

For consistency and clarity, the structure of (-)-secu’amamine A (9) and related intermediate will be drawn with a *trans*-fused indolizidine moiety even though we were not aware of this during the original planning of the synthesis (*vide infra*). As depicted in Scheme 3, (-)-secu’amamine A (9) could be derived via double bond introduction at C12/13 from *γ*-lactone 22 through stereoselective enolate selenation from the least hindered face, followed by oxidation and *syn* selenoxide elimination. The C14/15 double bond of 22 should be accessible from the ketone functional handle of 23. We hoped to synthesize the tetracycle 23 via a novel cascade cyclization sequence. Thus, the *γ*-lactone functionality of 23 could be formed via lactonization of hydroxy ester 24, which would be
derived from an intramolecular aldol reaction of diketoester 25. It should be noted that intramolecular aldol reaction of compound 25 might produce a mixture of stereoisomers at C13 but only the axial isomer 24 as shown can undergo ring closure to form tetracyclic $\gamma$-lactone 23. However, we expected that the C13 equatorial isomer could epimerize under the reaction conditions and therefore eventually lead to lactone 23. Ring flip and nitrogen lone pair inversion of intermediate 26 should give rise to the corresponding C9 axial conformer 25, which is imperative for further reactions to occur. The C9-N bond of 26 was anticipated to be formed through an intramolecular conjugate addition from amino enone intermediate 27, via the reactive conformation shown. This conformation should be favorable since it puts the electronegative OP group adjacent to the ketone in a pseudo-axial position, thus lowering the dipole-dipole repulsion (vide infra). A hydrogen bond between the NH and the protected hydroxyl group may also help stabilize this conformation. This step will set the C-2,3,9 relative and absolute stereochemistry of the alkaloid. In the synthetic direction, the steps from 27 to 24 should all be reversible, but the final lactonization step to form tetracycle 23 should drive the overall process to completion.

**Scheme 3**

Intermediate 27 would be formed upon removal of the N-trityl group of 28 under acidic conditions, followed by basification (Scheme 4). Diketone 28 could be accessed by
cleavage of the thioketal moiety of 29. (E)-α,β-Unsaturated ketone 29 could be synthesized from a Wittig reaction between aldehyde 30 and the known phosphonium ylide 31.\(^{15}\) Aldehyde 30 would be derived from 32 through hydroxyl deprotection followed by oxidation. The bis-protected diol 32 could be obtained via a stereoselective addition of the dithiane anion 33 to the known (R)-N-tritylprolinal (34).\(^{16}\)

**Scheme 4**

2.2. Addition of Dithiane Anions to (S)-N-Tritylprolinal (ent-34)

The starting material leading to (R)-N-tritylprolinal (34) is D-proline ($99.80 for 5 g from Sigma-Aldrich), which is much more expensive than its enantiomer L-proline ($44.50 for 100 g). Thus, we decided to initially investigate the synthesis with L-proline rather than D-proline, so that the final product in this sequence would actually be the (+)-enantiomer of natural (-)-secu'amamine A. Once the reaction sequence had been worked out, we could effect the same route with the more expensive D-proline. (S)-N-Tritylprolinal (ent-34) was thus synthesized in four steps from L-proline following a literature protocol (Scheme 5).\(^{17}\)
It has been documented that additions of nucleophiles such as organolithium and Grignard reagents to (S)-N-tritylprolinal (ent-34) generally proceed with high diastereoselectivity, affording the syn amino alcohol 35 as the major isomer. It is believed that the trityl group tends to adopt an orientation anti to the carbonyl moiety of ent-34 as suggested by both NOE studies and PM3 calculations (Scheme 6). In such a conformation, the stereoselectivity of addition of nucleophiles can be rationalized based on a Felkin-Anh transition state model. One might expect the metal ion can coordinate with the aldehyde oxygen and the α-nitrogen, thus inducing a chelation-controlled addition. However, the reaction of ent-34 with allyltrimethylsilane in the presence of BF₃·Et₂O (a monodentate Lewis acid) also exhibits high syn stereoselectivity (d.r. > 98/2), which strongly suggests a nonchelated transition state. Any organometallic chelation to nitrogen is probably prevented by the bulky trityl group due to steric hindrance.

As depicted in the retrosynthetic analysis (Scheme 4), we planned on using a dithiane anion as the nucleophile. The advantage of introducing a dithiane group in the synthesis lies in its ability to eventually be hydrolyzed to a ketone functional group. However, instead of starting with a 2-alkyl-1,3-dithiane anion like 33, we decided to
prepare a simple anion from the readily available 1,3-dithiane so that we could quickly test
the key nucleophilic addition. Once the desired adduct was obtained, we might be able to
again alkylate the dithiane moiety to arrive at the desired compound 32. Thus, dithiane
anion 36 was generated by treating commercially available 1,3-dithiane with \( n\)-BuLi at low
temperature (Scheme 7). Upon addition of 36 to the aldehyde \( \text{ent-34} \), the desired adduct 37
was produced as a mixture of two diastereomeric compounds in a ratio of 8:1. Although a
dithiane anion had never been used previously in an addition to aldehyde \( \text{ent-34} \), the major
product was tentatively assigned to be the desired \( \text{syn} \) diastereomer by analogy with earlier
additions. After screening different solvent systems and stationary phase materials for
column chromatography, all efforts to separate the two diastereomers of 37 failed.
Conversion of the hydroxyl group of 37 into its MOM ether afforded 38 in good yield, but
still as a mixture of two chromatographically inseparable diastereomers.

In view of the separation difficulties encountered in this sequence, we planned to
alkylate the mixture of dithiane compounds 38, hoping to separate the diastereomers
afterwards. Thus, compound 38 was treated with \( n\)-BuLi at \(-78\) °C. However, subsequent
reaction with ethylene oxide did not provide the desired dialkylated dithiane 39 (Scheme 8).
It was found, however, that an E1cB elimination process leading to the alkenyl compound
40 took place within five minutes after the \( n\)-BuLi was added, rendering it impractical to
obtain 39 through this route.
An alternative access to the dialkylated dithiane intermediate 39 would be to alkylate the 1,3-dithiane first and then add the resulting 2-alkyl-1,3-dithiane anion to aldehyde ent-34. A model study was first carried out using commercially available 2-methyl-1,3-dithiane (41) (Scheme 9). Exposure of 41 to n-BuLi followed by reaction with ent-34 did not generate the desired adduct 42, and only the unreacted aldehyde was recovered. However, with the addition of HMPA as a co-solvent, the desired alcohol 42 was formed in good yield as a pair of chromatographically separable diastereomers, albeit with low diastereoselectivity.

Encouraged by the results with the model system, we embarked on the synthesis of the real system. Ring opening of ethylene oxide with the 1,3-dithiane anion 36 afforded the known dithiane-derived alcohol 43 (Scheme 10). Subsequent MOM protection of the hydroxyl group gave 30, which was then lithiated with n-BuLi in the presence of HMPA, followed by reaction with ent-34 to give the desired adduct 45 in good overall yield. The major isomer of 45 was tentatively assigned to be the desired syn diastereomer. As in the
model system, the two diastereomers of 45 are chromatographically separable, but the
diastereoselectivity is again poor.

We have also tried to replace the N-trityl group of ent-34 with an N-Boc protecting
group, with the hope of improving the diastereoselectivity of the dithiane addition. Thus
the known (S)-N-Boc-prolinal (46) was prepared according to literature procedures19 as
shown in Scheme 11. However, lithiation of the mono-alkylated dithiane 44 with the aid of
either HMPA or DMPU, followed by addition to the aldehyde 46, provided only trace
amount of the desired adduct 47 as detected by mass spectrometry (Scheme 12).
2.3. Revision of the Retrosynthetic Plan

In view of the problems associated with the dithiane chemistry, we needed to therefore revise the original retrosynthetic approach. As shown in Scheme 13, we believed diketone 28 could be produced by selectively cleaving the more electron-rich exo-methylene group of 48. The \( \alpha,\beta \)-unsaturated ketone 48 would be synthesized via a Wittig reaction of aldehyde 49 and known phosphonium ylide 31. Aldehyde 49 could be derived from TBS-ether 50 via desilylation and alcohol oxidation. The bis-protected diol 50 would be formed through a stereoselective addition of the Grignard reagent prepared from known vinyl bromide 51\textsuperscript{20} to aldehyde 34, followed by suitable protection of the resulting hydroxyl group.

2.4. Addition of Vinyl Grignard Reagents to \((S)-N\)-Tritylprolinal (\textit{ent}-34)

Grignard reagent formation from the known vinyl bromide 51\textsuperscript{20} (preparation shown in Scheme 14), followed by addition to aldehyde \textit{ent}-34 afforded alcohol 52 as a single diastereomer in high yield. Although we expected that adduct 52 had the desired \textit{syn} relative stereochemistry as shown, this supposition needed to be conclusively proven. To this end, the trityl group of 52 was removed with acetic acid in methanol (Scheme 14).
Neutralization of the reaction mixture with triethylamine, followed by addition of methyl chloroformate delivered the desired methyl carbamate 53. Treatment of 53 with sodium hydride in THF effected cyclization to give the desired bicyclic compound 54. A strong NOE correlation between H2 and H3 of 54 confirmed the relative configuration at C2/3 of adduct 52.

**Scheme 14**

2.5. Synthetic Studies of the Methyl Ether Substrate

To proceed with our synthesis, the C3 secondary alcohol moiety of 52 needed to be protected. For simplicity at this point, alcohol 52 was transformed into its methyl ether 55 (Scheme 15), although we expected that some other type of protection may eventually be necessary if the methyl ether proved difficult to cleave. The labile trityl group of 55 was replaced with a more stable Boc substituent to afford 56 in good yield. Removal of the TBDPS group with TBAF proceeded cleanly to generate alcohol 57. Dess-Martin oxidation then converted 57 into aldehyde 58, which was found to be quite unstable and decomposed on chromatography on either silica gel or basic alumina. Therefore, the crude aldehyde 58 was not purified but was directly combined with the known phosphonium
ylide 31 (prepared in three steps from levulinic acid as depicted in Scheme 16) to furnish α,β-unsaturated ketone 59 in good overall yield.

**Scheme 15**

With 59 in hand, the next objective in the synthesis involved oxidative cleavage of the exo-methylene group to give the requisite diketoester for the key cascade cyclization process outlined in Scheme 3. Examples in the literature have shown that electron rich alkenes are more prone to cleavage by ozone than are conjugated alkenes.21 In our case, however, ozonolysis of 59 only yielded a complex mixture of products, rather than the desired diketoester 60 (Scheme 17). Oxidative cleavage of the exo-methylene moiety of 59 using the Johnson-Lemieux method also failed.
Another option to access diketoester 60 would be to utilize an earlier intermediate 57 (cf. Scheme 15) and effect *exo*-methylene cleavage of this compound. To our delight, the desired hydroxy ketone 61 was obtained in good yield by cleaving the *exo*-methylene compound 57 with ozone (Scheme 18). However, transformation of alcohol 61 to the desired β-keto aldehyde 62 was tried under Swern or DMP oxidation conditions, but to no avail. Attempts to mask the ketone moiety of 61 as the dimethyl ketal 63 prior to alcohol oxidation also failed. Instead, loss of the *N*-Boc group was observed after prolonged reaction time and at high temperature.

In view of the difficulties in preparing diketoester 60, we decided to delay the cleavage of the *exo*-methylene group of 59 and execute the intramolecular conjugate addition first. Thus, treatment of 59 with TFA/DCM removed the *N*-Boc group, generating the corresponding TFA amine salt (Scheme 19). Subsequent addition of saturated aqueous NaHCO₃ solution at room temperature to this salt yielded the free amine intermediate.
which underwent an intramolecular Michael addition \textit{in situ} to afford a 1:1 mixture of diastereomeric indolizidines 64 and 65 in good total yield. The C9 axial isomer 64 possesses the relative stereochemistry required for secu’amamine A. The configurations and conformations of 64 and 65 were established to be as shown by HMQC, HMBC, COSY and NOESY-NMR experiments.

The isomeric ratio of 64 and 65 was found to be highly dependent on the specific reaction conditions used to neutralize the TFA amine salt. Some representative results of the intramolecular Michael reaction carried out under a variety of reaction conditions are presented in Table 1. Thus, simply by addition of aqueous NaHCO$_3$ solution to the TFA amine salt at 0 °C, the ratio increased to 3:1 in favor of formation of the desired diastereomer 64 (Table 1, Entry 1). An alternative way to remove the $N$-Boc protecting group involved initial conversion to the O-TBS carbamate as described by Ohfune and coworkers$^{22}$ (Entry 2). Subsequent addition of TBAF at -78 °C did promote the Michael addition, but generated a 1:1 diastereomeric mixture of 64 and 65 (Table 1, Entry 2). When Hunig’s base (iPr$_2$NEt) was added to the TFA salt at ambient temperature, a 1:1 mixture of isomers 64 and 65 was again obtained (Table 1, Entry 3), whereas a much enhanced selectivity was achieved at -78 °C, with the formation of isomers 64 and 65 at a ratio of 8:1 (Table 1, Entry 4).
Table 1. Reaction Conditions and Product Distribution for the aza-Michael Addition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product Ratio (64 : 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1) TFA, DCM</td>
<td>3:1</td>
</tr>
<tr>
<td></td>
<td>2) aq NaHCO₃, 0 °C</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1) TBSOTf, 2,6-lutidine, DCM</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td>2) TBAF, -78 °C to rt</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1) TFA, DCM</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td>2) DIPEA, DCM</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1) TFA, DCM</td>
<td>8:1</td>
</tr>
<tr>
<td></td>
<td>2) DIPEA, DCM, -78 °C to rt</td>
<td></td>
</tr>
</tbody>
</table>

The interconversion of isomers 64 and 65 was also explored. An NMR sample containing a 5:1 mixture of 64 and 65 on standing in CDCl₃ for ten days at room temperature decreased to 3:1, and after 20 days the ratio became 1:1 (Scheme 20). This observation suggests that isomers 64 and 65 are interconvertable, presumably via a reversible Michael process involving the free amine intermediate 66 (Scheme 21). Refluxing a mixture containing a 1:3 mixture of isomers 64 and 65 in toluene in the presence of Hunig’s base did not change the ratio at all after 36 hours (Scheme 22). Interestingly, if the C9 axial isomer 64 is absorbed onto dry basic alumina and allowed to stand at room temperature overnight, it isomerizes completely to the C9 equatorial isomer 65 in moderate yield (Scheme 23). In contrast, exposure of the pure isomer 65 to the same reaction conditions results in no change. Thus, it seems that 65 is the thermodynamically more stable product.
On the basis of the above observations, the aza-Michael addition of 64 carried out at -78 °C appears to be under kinetic control. It seems reasonable that 64 arises from cyclization of the free amine derived from carbamate 59 via conformation 66a, leading initially to the intermediate cis-indolizidine 67. This compound can undergo conformational isomerization to 68, followed by nitrogen lone pair inversion, to produce trans-indolizidine 64. Direct formation of 64 via a transition state resembling the conformation of 64 would be less likely, since it requires putting the α,β-unsaturated side chain in a pseudo-axial position in the developing six-membered ring. The isomeric cyclization product 65 could form directly via amino enone conformation 66b. Our rationale for the conjugate addition to occur primarily via conformer 66a to afford 64 as the major kinetic product is based upon the known conformational preferences of acyclic allylic ethers. Thus, work by Gung and others has shown that the allylic hydrogen in such systems prefers to be eclipsed (in plane) with the double bond as is the case in
conformation 66a. An in plane C-O bond, as in the alternative conformer 66b, is generally disfavored. In addition, a hydrogen bond between the NH and the pseudo-axial methoxy group may also stabilize conformer 66a relative to 66b.

In order to carry out the key intramolecular aldol reaction outlined in the retrosynthetic plan, the exo-methylene moiety of 64 needed to be converted into a ketone. Oxidative cleavage of 64 was attempted via ozonolysis or by RuCl₃/NaIO₄ oxidation but only led to unrecognizable products. Dihydroxylation of 64 using 5 mol% osmium tetroxide, followed by diol cleavage with NaIO₄, did effect the desired double bond cleavage, but provided a 1:1 mixture of diketones 69 and 70 in moderate yield (Scheme 25). It is apparent that C9 isomerization takes place at some point during the two-step process. We reasoned that speeding the reaction process should help to minimize formation of the undesired isomerized ketone 70. Gratifyingly, a one-pot oxidation of 64 using 25 mol% of osmium tetroxide and sodium periodate delivered the desired ketone 69 without noticeable formation of the isomerized product 70. The configuration and conformation of 70 were elucidated by HMQC, HMBC, COSY and NOESY-NMR experiments.
With the desired diketoester 69 prepared, we were pleased to find that exposure of this compound to sodium methoxide in methanol at room temperature afforded the desired tetracyclic lactone 71 in 70% yield. The structure of \( \gamma \)-lactone 71 was initially assigned on the basis of HMQC, HMBC, COSY and NOESY-NMR data, and later confirmed by an X-ray crystal structure analysis. In the crystal of 71, the indolizidine ring is clearly trans-fused, and the cyclohexanone adopts a boat conformation (Figure 3).
Before we proceeded further with 71, we decided to test if the methyl ether moiety could be cleaved at this stage. Unfortunately, subjection of methyl ether 71 to various demethylation conditions did not produce the desired alcohol 72 (Scheme 27).

2.6. Studies of a Benzyl Ether-Protected Substrate

Since the methyl ether protecting group turned out to be difficult to cleave, different C3 hydroxyl protection had to be applied and a benzyl group seemed to be an appropriate candidate. Thus, the previously prepared alcohol 52 was converted to benzyl ether 73 using NaH and BnBr (Scheme 28). The reaction conditions for this step shown in the scheme are unoptimized, and the low yield resulted from incomplete conversion of starting material. To continue the synthesis, the silyl protecting group of 73 was cleaved with TBAF to give the primary alcohol 74. Removal of the trityl group of 74, followed by
Boc protection of the resulting amine, generated 75 in good overall yield. It should be noted that in the current reaction sequence to 75, desilylation was performed prior to installing the N-Boc group, opposite to the way we prepared the analogous methyl ether substrate 57 (cf. Scheme 15). This sequence was preferred because of easier separation of product 75 and the TrOH generated during removal of the trityl group from 74. Analogous to the methyl ether counterpart 57, Dess-Martin oxidation of 75 formed an unstable aldehyde, which was combined directly with phosphonium ylide 31 to afford 77 in moderate overall yield. Following the previously established conditions, removal of the N-Boc group of 77 with TFA gave an amine salt which was subsequently treated with Hunig’s base at -78 °C to afford a mixture of indolizidine isomers 78 and 79 at a ratio of 6:1. Thus, the selectivity of the aza-Michael addition step for 77 is slightly lower than for the methyl ether substrate 59 (8:1).

Scheme 28
With indolizidine 78 in hand, oxidative double bond cleavage was tried multiple times using the previously established conditions for the methyl ether substrate 64 (cf. Scheme 25). Instead of the desired ketone 80, however, a complex mixture of compounds was formed here. This failure does appear surprising since the only difference between substrates 78 and 64 is the benzyl protecting group, which somehow dramatically influences the reaction outcome.

![Scheme 29](image)

### 2.7. Studies of a MOM Ether Substrate and Completion of the Total Synthesis

Having learned a lesson from explorations of the methyl ether and benzyl ether substrates, we realized that the choice of the C3 hydroxyl protecting group is critical. Therefore, we decided to utilize a MOM protecting group, which we expected to behave much like a methyl group, but can be removed under milder conditions. The anticipated chemistry did work well with the MOM ether substrate and led to a total synthesis of secu’amamine A (vide infra). It might be noted that the antipodal unnatural (+)-secu’amamine A was initially prepared because we started with L-proline instead of the required D-proline. Eventually, we synthesized (-)-secu’amamine A commencing with D-proline. For clarity and to avoid redundancy, only the reaction sequence involving the correct enantiomeric series is presented since both enantiomers are identical in terms of chemical reactivity and spectral data.
Thus, starting with D-proline, ent-52 was prepared following exactly the same synthetic route to access 52. This alcohol was then protected as the MOM ether 81 using MOMBr (Scheme 30). Following a similar sequence developed in the benzyl ether series (cf. Scheme 28), removal of the silyl group of 81 with TBAF gave 82, and subsequent replacement of the N-trityl group with a Boc substituent generated carbamate alcohol 83.

### Scheme 30

As depicted in Scheme 31, Dess-Martin oxidation of the primary alcohol 83 led to an unstable aldehyde 84, which without purification reacted with the phosphonium ylide 31, providing the (E)-enone 85 in only 37% overall yield. However, replacement of ylide 31 with the more reactive phosphonate anion derived from the known phosphonate 86 greatly improved the reaction efficiency, affording enone 85 in 70% overall yield.

### Scheme 31
The Boc group of carbamate 85 was next removed with TFA in DCM. Upon careful addition of Hunig’s base to the TFA solution containing the amine salt at -78 °C, a mixture of indolizidines 90 and 91 was formed in 1:5 ratio, with the major product 91 as the desired stereoisomer in good combined yield (Scheme 32). The configuration and conformation of these compounds were determined to be as shown by HMQC, HMBC, COSY and NOESY-NMR experiments. Similar to what was observed for the methyl ether substrates, it was also found that, when the major isomer 91 was adsorbed onto dry basic alumina and allowed to remain at room temperature overnight, it was transformed completely to the minor isomer 90. Thus, the aza-Michael cyclization again appears to be under kinetic control. As illustrated in Scheme 32, the selective formation of 91 over 90 can also be rationalized via a process analogous to the one proposed for the aza-Michael cyclization of the methyl ether substrate 59 (cf. Scheme 24)

To continue the synthesis, the exo-methylene group of indolizidine 91 was first oxidatively cleaved to give ketone 92 (Scheme 33). Exposure of diketoester 92 to sodium methoxide in methanol at room temperature afforded the desired tetracyclic lactone 93 in 75% yield along with a small amount of a polar compound which is assigned to be
epimeric hydroxy ester 94. Resubjection of 94 to NaOMe/MeOH for a longer period of
time produced lactone 93 in high yield, strongly supporting its structural assignment. In
hindsight, we believe an analogous epimeric hydroxy ester must have been produced
during reaction of the methyl ether substrate 69 with NaOMe (cf. Scheme 26). At that time, this minor compound might have been overlooked due to its high polarity.

To complete the total synthesis, ketone 93 was first converted to enol triflate 95 which was subjected to palladium-mediated reduction, generating alkene lactone 96 (Scheme 34). Selenation of the γ-lactone moiety of 96 occurred stereoselectively from the
least hindered face to produce 97, which upon periodate oxidation underwent syn-
elimination to give diene lactone 98. Finally, cleavage of MOM ether with MeOH/HCl yielded (-)-secu’amamine A (9) having proton and carbon NMR spectra identical to those of authentic material. In addition, the observed optical rotation of synthetic 9 was in good
accord with that of the natural alkaloid, thereby confirming the original assignment of
absolute configuration.

It is worth mentioning that the stereochemistry of the indolizidine moiety was not
initially addressed by Ohsaki and coworkers due to overlap of proton NMR signals in
CDCl₃, rendering it difficult to elucidate NOE correlations of protons at C2 and C6. We
have found that if the ¹H NMR spectrum of 9 is recorded in deuteriobenzene, the proton
peaks of C-2/6 are sufficiently dispersed to allow NOE analysis, which indicates that the
indolizidine is trans-fused. We have also been able to obtain an X-ray crystal structure of synthetic 9 which confirms these conclusions (Figure 4).

**Scheme 34**

![Scheme 34]

**Figure 4.** ORTEP Structure of (-)-secu’amamine A (9)

2.8. Concluding Remarks

In summary, we have accomplished a convergent stereoselective total synthesis of the novel Securinega alkaloid (-)- secu’amamine A (9) using D-proline as the chiral source. The synthesis requires 15 steps starting from aldehyde 34 and proceeds in approximately 9% overall yield. Key steps include a stereoselective conjugate addition of amino enedione 86
to afford indolizidine 91 as the major product and a tandem aldol/lactonization of diketoester 92 to produce tetracyclic γ-lactone 93.

Chapter 3. Experimental Section

General Methods. All non-aqueous reactions were carried out in oven- or flame-dried glassware under an argon atmosphere. All chemicals were purchased from commercial vendors and used as is, unless otherwise specified. Anhydrous tetrahydrofuran (THF) and dichloromethane (DCM) were obtained from a solvent purification system (Glass Contour). Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 250 µm EMD 60 F254 precoated silica gel plates. Flash column chromatography was performed using EMD silica gel 60 (230-400 mesh). 1H and 13C NMR spectral data were recorded on Bruker DPX-300, CDPX-300, or DRX 400 MHz spectrometers. Chemical shifts are reported relative to chloroform (δ 7.24), dichloromethane (δ 5.32), benzene (δ 7.15) for 1H NMR and chloroform (δ 77.0), dichloromethane (δ 53.8), benzene (δ 128.0) for 13C NMR. Optical rotations were measured on a Rudoph Research Analytical Autopol II digital polarimeter.
Synthesis of Alcohol 37. To a solution of 1,3-dithiane (429 mg, 3.57 mmol) in THF (40 mL) at -78 °C, was added \( n \)-BuLi (2.5 M in hexanes, 1.3 mL, 3.25 mmol). The reaction mixture was stirred at -78 °C for 3 h before a solution of aldehyde \textit{ent-34} (975 mg, 2.86 mmol) in THF (50 mL) was slowly added. The mixture was stirred at this temperature for another 4 h and quenched by addition of H2O. The aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na2SO4 and concentrated. The residue obtained was purified by flash column chromatography on silica gel (Et3N/hexanes/EtOAc, 0.1/9/1) to provide alcohol 37 as a 8:1 mixture of two inseparable diastereomers (1.200 g, 91%). \(^1\)H NMR (300 MHz, CDCl3) \( \delta \) 7.44 (d, \( J = 7.4 \) Hz, 6H), 7.09 (t, \( J = 7.2 \) Hz, 6H), 7.00 (d, \( J = 7.1 \) Hz, 3H), 4.25 (dd, \( J = 10.2, 2.0 \) Hz, 1H), 3.96-3.88 (m, 1H), 3.22(d, \( J = 10.2 \) Hz, 1H), 3.17-3.13 (m, 1H), 3.02 (br s, 1H), 2.91-2.84 (m, 1H), 2.75-2.66 (m, 1H), 2.43-2.35 (m, 1H), 2.14-2.01 (m, 2H), 1.75-1.65 (m, 2H), 1.39-1.30 (m, 1H), 1.17-0.98 (m, 2H), 0.06–0.10 (m, 1H); LRMS-ES (m/z): \([M + H]^+\) caled for C9H17NOS2, 219.1; found, 219.2.

Synthesis of MOM Ether 38. To a solution of the alcohol 37 (856 mg, 1.85 mmol) in DCM (20 mL) at rt was added DIPEA (1.3 mL, 7.46 mmol) followed by MOMCl (1.4
mL, 18.43 mmol). The reaction mixture was stirred at rt for 12 h before addition of aqueous NaHCO₃. The aqueous mixture was then extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue obtained was purified by flash column chromatography on silica gel (Et₃N/hexanes/EtOAc, 0.1/5/1) to provide MOM ether 37 as a 8:1 mixture of two inseparable diastereomers (842 mg, 90%).

\[ ^{1}H\text{ NMR (300 MHz, CDCl}_3\) \delta 7.42 (d, } J = 8.4 \text{ Hz, 6H), 7.10 (t, } J = 7.2 \text{ Hz, 6H), 6.99 (t, } J = 7.2 \text{ Hz, 3H), 5.34 (d, } J = 6.3 \text{ Hz, 1H), 4.84 (d, } J = 6.2 \text{ Hz, 1H), 4.33 (dd, } J = 9.1, 1.6 \text{ Hz, 1H), 3.93-3.89 (m, 1H), 3.50 (s, 3H), 3.10-2.97 (m, 1H), 2.88-2.80 (m, 1H), 2.75-2.66 (m, 1H), 2.56-2.44 (m, 1H), 2.30-2.20 (m, 1H), 2.10-2.02 (m, 1H), 1.84-1.73 (m, 1H), 1.70-1.62 (m, 1H), 1.50-1.40 (m, 1H), 1.24-1.13 (m, 1H), 1.00-0.90 (m, 1H), 0.03-0.06 (m, 1H); ^{13}C\text{ NMR (75 MHz, CDCl}_3\) \delta 145.4, 130.2, 128.3, 128.1, 128.0, 127.7, 126.5, 98.5, 81.5, 79.1, 63.7, 57.6, 52.3, 49.3, 28.4, 26.1, 25.8, 25.6.]

**Synthesis of Dithioketene Acetal 40.** To a solution of MOM ether 38 (101 mg, 0.20 mmol) in THF (10 mL) at -78 °C, was added n-BuLi (2.5 M in hexanes, 0.12 mL, 0.30 mmol). The reaction mixture was stirred at -78 °C for 5 min and it was quenched with aqueous NaHCO₃. The aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (Et₃N/hexanes/EtOAc, 0.1/9/1) to provide alkene 40 (82 mg, 92%).

\[ ^{1}H\text{ NMR (300 MHz, CDCl}_3\) \delta 7.51 (d, } J = 7.2 \text{ Hz, 6H), 7.17 (t, } J = 7.1 \text{ Hz, 6H), 7.09-7.04 (m, 3H), 6.23 (d, } J = 8.9 \text{ Hz, 1H), 4.18 (td, } J = 8.4, 3.6 \text{ Hz, 1H), 3.20-3.12 (m, 1H), 2.85-2.76 (m, 1H), 2.71-2.63 (m, 2H), 2.43 (t, } J = 6.1 \text{ Hz, 2H), 2.03-1.94 (m, 2H),} \]
1.42-1.31 (m, 1H), 1.12-1.03 (m, 1H), 0.98-0.86 (m, 1H), 0.83-0.69 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.7, 141.9, 129.7, 127.2, 126.1, 121.6, 58.9, 49.7, 32.6, 30.6, 29.7, 25.4, 24.3; LRMS-ES (m/z): \([M + H]^+\) calcd for C\(_9\)H\(_{15}\)NS\(_2\), 201.1; found, 201.1.

**Synthesis of Alcohol 42.** To a solution of 2-methyl-1,3-dithiane 41 (59 mg, 0.44 mmol) in THF (5 mL) and HMPA (0.5 mL) at -78 °C, was added \(n\)-BuLi (2.5 M in hexanes, 0.15 mL, 0.38 mmol). The reaction mixture was stirred at -78 °C for 2 h before a solution of aldehyde ent-34 (100 mg, 0.29 mmol) in THF (5 mL) was slowly added. The mixture was stirred at this temperature for another 1.5 h and diluted with H\(_2\)O. The aqueous mixture was extracted with EtOAc. The combined organic layers were washed with brine for four times, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et\(_3\)N/EtOAc/hexanes, 0.1/2/5) to provide alcohol 42 as a 2.5:1 mixture of two separable diastereomers (103 mg, 75%) and only the major isomer was characterized.

Major isomer of 42: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.55-7.46 (m, 6H), 7.19-7.08 (m, 9H), 3.63 (t, \(J = 7.4\) Hz, 1H), 3.13-3.01 (m, 2H), 2.98-2.94 (m, 1H), 2.87-2.69 (m, 3H), 1.94-1.88 (m, 2H), 1.44 (s, 3H), 1.40-1.30 (m, 2H), 0.83-0.78 (m, 1H), 0.53-0.46 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 129.9, 127.5, 127.3, 126.3, 125.8, 78.7, 77.9, 61.8, 52.3, 49.8, 32.6, 29.5, 26.7, 26.5, 24.9, 23.8, 23.3; LRMS-ES (m/z): \([M + H]^+\) calcd for C\(_{10}\)H\(_{19}\)NOS\(_2\), 233.1; found, 233.1.
Synthesis of Monoalkylated Dithiane 44. To a solution of alcohol 43 (707 mg, 4.30 mmol) in DCM (20 mL) at rt was added DIPEA (6.0 mL, 34.44 mmol) followed by MOMCl (1.96 mL, 25.80 mmol). The mixture was stirred at rt for 12 h. The mixture was concentrated under reduced pressure and the residue obtained was subjected to silica gel chromatography (EtOAc/hexanes, 1/4) to give dithiane 44 (878 mg, 98%). ¹H NMR (300 MHz, CDCl₃) δ 4.60 (s, 2H), 4.19 (t, J = 7.2 Hz, 1H), 3.67 (t, J = 6.2 Hz, 2H), 3.34 (s, 3H), 2.91-2.76 (m, 4H), 2.13-2.07 (m, 1H), 2.04, 1.99 (ABq, J = 6.2 Hz, 2H), 1.91-1.79 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 96.4, 63.8, 55.3, 44.0, 35.5, 30.1, 26.0.

Synthesis of Alcohol 45. To a solution of dithiane 44 (532 mg, 2.55 mmol) in THF (25 mL) and HMPA (1 mL) at -78 °C, was added n-BuLi (2.5 M in hexanes, 0.87 mL, 2.13 mmol). The reaction mixture was stirred at -78 °C for 1 h before a solution of aldehyde ent-34 (291 mg, 0.85 mmol) in THF (15 mL) was slowly added. The mixture was then allowed to gradually warm to rt and was stirred for another 12 h. The mixture was diluted with H₂O and the aqueous phase was extracted with Et₂O. The combined organic layers were washed with brine five times, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et₃N/EtOAc/hexanes,
0.1/1/6) to provide alcohol 45 as a 2:1 mixture of separable diastereomers (328 mg, 70%). Only the major isomer was characterized.

Major isomer of 45: 1H NMR (300 MHz, CDCl₃) δ 7.65-7.53 (m, 6H), 7.28-7.13 (m, 9H), 4.65-4.61 (m, 2H), 3.94-3.88 (m, 2H), 3.86-3.80 (m, 1H), 3.58 (d, J = 5.7 Hz, 1H), 3.37 (s, 3H), 3.25-3.17 (m, 1H), 3.15-3.10 (m, 1H), 3.01-2.97 (m, 1H), 2.94-2.90 (m, 1H), 2.84-2.75 (m, 2H), 2.44-2.36 (m, 1H), 2.11-2.04 (m, 1H), 1.97-1.90 (m, 2H), 1.53-1.39 (m, 2H), 1.01-0.90 (m, 1H), 0.64-0.57 (m, 1H); 13C NMR (75 MHz, CDCl₃) δ 129.7, 127.6, 126.3, 96.3, 78.7, 78.1, 64.9, 62.1, 55.3, 55.1, 49.9, 35.6, 32.6, 26.7, 26.4, 24.6, 23.4; LRMS-ES (m/z): [M + H]⁺ calcd for C₃₃H₄⁹NO₃S₂, 550.2; found, 550.1.

**Synthesis of Alcohol 52.** Magnesium turnings (5.991 g, 246.54 mmol) were flame dried, cooled under argon and then immersed in THF (20 mL). Two drops of 1,2-dibromoethane were added to the mixture which was then heated at reflux for 15 min. The heating was stopped and a solution of vinyl bromide 51 (24.000 g, 61.63 mmol) in THF (50 mL) was added dropwise via an addition funnel to maintain a gentle reflux. After the addition was complete, the reaction mixture was stirred further at reflux for 30 min and then cooled to rt.

The resulting Grignard reagent was added via cannula to a solution of the aldehyde ent-34 (14.028 g, 41.088 mmol) in THF (50 mL) at -78 °C. The reaction mixture was stirred for 4 h at -78 °C and then quenched by the addition of saturated aqueous NH₄Cl (5 mL). The solution was diluted with EtOAc and H₂O. The aqueous phase was saturated
with NaCl and the organic phase was separated. The aqueous layer was further extracted with EtOAc. The combined organic phases were dried over MgSO₄ and concentrated \textit{in vacuo}. Purification of the residue via flash chromatography on silica gel (hexanes/EtOAc/Et₃N, 9.5/0.5/0.1) afforded the desired alcohol 13 (25.449 g, 95%) as a white foam. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.74 (d, \(J = 6.6\) Hz, 4H), 7.64 (d, \(J = 7.8\) Hz, 6H), 7.54-7.45 (m, 6H), 7.39-7.21 (m, 9H), 5.23 (s, 1H), 4.91 (s, 1H), 4.45 (s, 1H), 3.71-3.67 (m, 1H), 3.63 (t, \(J = 7.1\) Hz, 2H), 3.36-3.27 (m, 2H), 3.14-3.07 (m, 1H), 2.21-2.11 (m, 1H), 2.02-1.95 (m, 1H), 1.70-1.59 (m, 1H), 1.43-1.35 (m, 1H), 1.14 (s, 9H), 1.08-1.01 (m, 1H), 0.39-0.26 (m, 1H); \(^1^3\)C NMR (75 MHz, CDCl₃) \(\delta\) 145.4, 144.5, 135.5, 135.4, 133.8, 129.7, 129.5, 127.5, 127.4, 126.2, 110.2, 78.0, 75.6, 62.6, 62.4, 52.9, 36.2, 26.8, 25.2, 24.8, 19.1; HRMS-ES (\(m/z\)): [M + H]\(^+\) calcd for C₄₄H₅₀NO₂Si, 652.3611; found, 652.3618.

\[\text{Synthesis of Methyl Carbamate 53.} \]

To a solution \(N\)-trityl alcohol 52 (95 mg, 0.15 mmol) in MeOH (10 mL) and DCM (1.5 mL) was added glacial AcOH (0.4 mL). After the mixture was stirred at rt for 2 h, Et₃N (1 mL) was added followed by ClCO₂Me (0.1 mL, 1.29 mmol). The reaction mixture was stirred for an additional 12 h at rt and the solvent was removed under reduced pressure. Purification of the residue via flash chromatography on silica gel (EtOAc/hexanes, 1/4) afforded methyl carbamate 53 (46 mg, 67%) as a colorless oil. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.71-7.68 (m, 4H), 7.45-7.40 (m, 6H), 5.12 (s, 1H), 4.95 (s, 1H), 4.45 (br s, 0.6H), 4.34 (br s, 0.4H), 4.04 (br s, 0.6H), 3.88-3.49 (br m,
6H), 3.37 (br s, 1H), 3.24 (br s, 0.6H), 2.70 (br s, 0.3H), 2.45 (br s, 1H), 2.30 (br s, 1H),
1.97 (br, 2H), 1.76 (br, 2H), 1.07 (s, 9H).

**Synthesis of Bicycle 54.** To a suspension of NaH (20 mg, 60% dispersion in
mineral oil, 0.50 mmol) in THF (6 mL) was added a solution of alcohol 53 (46 mg, 0.098
mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred at rt for 5 h before the
addition of H2O. The aqueous mixture was extracted with EtOAc. The combined organic
layers were dried over Na2SO4 and concentrated. The residue was purified by flash column
chromatography on silica gel (Et3N/EtOAc/hexanes, 0.15/1/9) to provide methyl ether 54
(34 mg, 80%). 1H NMR (300 MHz, CDCl3) δ 7.65-7.62 (m, 4H), 7.42-7.35 (m, 6H), 5.24
(s, 1H), 5.11 (d, J = 7.7 Hz, 1H), 5.00 (s, 1H), 3.85-3.80 (m, 1H), 3.77 (t, J = 6.7 Hz, 2H),
3.67-3.58 (m, 1H), 3.17-3.09 (m, 1H), 2.29-2.22 (m, 1H), 2.12-2.05 (m, 1H), 2.00-1.90 (m,
1H), 1.84-1.73 (m, 1H), 1.59-1.50 (m, 1H), 1.36-1.24 (m, 1H), 1.02 (s, 9H); 13C NMR (75
MHz, CDCl3) δ 161.2, 139.9, 135.54, 135.53, 133.40, 133.37, 129.8, 127.7, 112.3, 77.2,
62.8, 62.5, 45.9, 35.9, 26.8, 25.6, 24.9, 19.1; [M + H]+ calcd for C26H34NO3Si, 436.2;
found, 436.3.

**Synthesis of Methyl Ether 55.** To a suspension of NaH (33 mg, 60% dispersion in
mineral oil, 0.83 mmol) in THF (5 mL) was added a solution of alcohol 52 (300 mg, 0.46
mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and MeI (0.12 mL, 1.84 mmol) was added at this temperature. The reaction mixture was warmed to rt and further stirred for 12 h before the addition of H₂O. The aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (Et₃N/EtOAc/hexanes, 0.15/1/12) to provide methyl ether 55 (275 mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.94-7.85 (m, 10H), 7.63-7.59 (m, 5H), 7.45-7.32 (m, 10H), 5.26 (s, 1H), 5.05 (s, 1H), 4.43 (s, 1H), 3.93-3.82 (m, 2H), 3.70 (s, 3H), 3.68-3.60 (m, 2H), 3.27-3.22 (m, 1H), 2.24-2.18 (m, 1H), 2.10-2.02 (m, 1H), 1.90-1.82 (br, 1H), 1.60-1.50 (br, 1H), 1.33 (s, 9H), 1.20-1.13 (br, 1H), 1.00-0.92 (br, 1H), 0.60-0.50 (br, 1H); LRMS-ES (m/z): [M + H]⁺ calcd for C₂₆H₃₇NO₂Si, 423.3; found, 423.3.

**Synthesis of N-Boc Carbamate 56.** To a solution of pyrrolidine 55 (1.350 g, 2.04 mmol) in MeOH (40 mL) was added glacial AcOH (0.20 mL). After the mixture was stirred at rt for 2 h, DIPEA (1.24 mL) was added followed by (Boc)₂O (1.330 g, 6.09 mmol). The reaction mixture was stirred for an additional 12 h at rt and the solvent was removed under reduced pressure. Purification of the residue via flash chromatography on silica gel (EtOAc/hexanes, 1/16 then 1/4) afforded N-Boc carbamate 56 (900 mg, 84%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.65 (m, 4H), 7.37-7.27 (m, 6H), 5.05 (s, 1H), 4.91 (s, 1H), 4.06 (s, 0.4H), 3.85-3.73 (br m, 3.6H), 3.54-3.50 (br, 0.6H), 3.40-3.36
(br, 0.4H), 3.35-3.30 (br, 1H), 3.19 (s, 3H), 2.40-2.30 (br, 2H), 2.00-1.90 (br, 2H), 1.78-1.64 (br, 2H), 1.45 (s, 9H), 1.02 (s, 9H).

**Synthesis of Alcohol 57.** To a solution of silyl ether 56 (156 mg, 0.30 mmol) in THF (10 mL) was added TBAF (1 M solution in THF, 0.45 mL, 0.45 mmol) at rt. After 12 h at rt, the reaction mixture was diluted with saturated aqueous NH₄Cl, and then EtOAc and H₂O. Solid NaCl was added to saturate the aqueous phase and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by silica gel flash chromatography (hexanes/EtOAc 1/1) to give the alcohol 57 (81 mg, 95%).

$^1$H NMR (400 MHz, CDCl₃) $\delta$ 4.96-4.87 (br m, 2H), 3.80-3.74 (br m, 1H), 3.67-3.57 (br m, 3H), 3.43-3.34 (br m, 1.4H), 3.25-3.12 (br m, 1.6H), 3.08 (s, 3H), 2.30-2.05 (br m, 2H), 1.89-1.70 (m, 2H), 1.63-1.50 (m, 2H), 1.36-1.25 (br m, 9H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 155.0, 154.2, 143.5, 143.2, 113.0, 112.6, 84.8, 84.5, 79.4, 60.9, 60.0, 59.1, 58.6, 58.0, 57.4, 46.8, 35.9, 34.3, 28.4, 25.6, 25.4, 23.7.

**Synthesis of Aldehyde 58.** To a solution of the carbamate alcohol 57 (960 mg, 3.36 mmol) in DCM (25 mL) was added Dess-Martin periodinane (1.567 g, 3.70 mmol). After 2 h, saturated aqueous NaHCO₃ (10 mL) and 10% aqueous Na₂S₂O₃ solution (10 mL) were added to the reaction mixture. The organic phase was separated and the aqueous
phase was extracted with DCM. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated \textit{in vacuo} to give a pale yellow oil. The aldehyde obtained was unstable and decomposed during chromatographic purification and therefore was used in crude form.

**Synthesis of Enone 59.** To a solution of the phosphonium ylide \textbf{31} (2.624 g, 6.72 mmol) in DCM (20 mL), was added a solution of the crude aldehyde \textbf{58} (3.36 mmol) in DCM (40 mL). The reaction mixture was heated at reflux and stirred for 12 h before the solvent was removed under vacuum. The crude residue was chromatographed on silica gel (EtOAc/hexanes 1/5 then 1/4) to give the enone \textbf{59} (970 mg, 73% based on carbamate alcohol \textbf{57}). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.90-6.76 (br, 1H), 6.11 (d, $J$ = 15.9 Hz, 1H), 5.07 (d, $J$ = 29.5 Hz, 1H), 4.88 (d, $J$ = 24.5 Hz, 1H), 3.82 (s, 2H), 3.59 (s, 3H), 3.35-3.20 (br, 2H), 3.17 (s, 3H), 2.90-2.80 (m, 3H), 2.56-2.53 (m, 2H), 1.90-1.80 (br, 2H), 1.70-1.60 (br, 2H), 1.17 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 198.0, 197.7, 173.3, 154.6, 154.2, 145.1, 144.3, 143.9, 143.1, 131.4, 131.2, 113.5, 84.7, 84.4, 79.5, 79.0, 59.1, 58.7, 58.0, 57.6, 51.7, 46.9, 35.2, 34.8, 34.6, 34.4, 28.6, 28.5, 27.7, 25.5, 25.3, 24.1, 23.6; $[M + H]^+$ calcd for C$_{21}$H$_{34}$NO$_6$, 396.2; found, 396.3.
Synthesis of Hydroxy Ketone 61. A solution of alcohol 57 (57 mg, 0.30 mmol) in DCM (6 mL) was cooled to –78 °C and a stream of oxygen containing ozone (v/v about 1%) was bubbled through the mixture for 30 min before Me₂S (0.30 mL) was added. The reaction mixture was then allowed to warm to rt and was stirred for another 12 h. The solvent was evaporated in vacuo and the residue was purified by silica gel flash chromatography (hexanes/EtOAc 1/1) to give hydroxy ketone 61 (70 mg, 82%). ¹H NMR (400 MHz, CDCl₃) δ 4.08-4.02 (br, 1H), 3.97-3.90 (br, 1H), 3.88-3.80 (br, 1H), 3.73 (d, J = 6.3 Hz, 1H), 3.40-3.30 (br, 2H), 3.35 (s, 3H), 3.10-3.02 (br, 1H), 3.00-2.95 (br, 1H), 2.76-2.73 (br, 0.5H), 2.65-2.56 (br, 1H), 2.37-2.32 (br, 0.2H), 1.96-1.75 (br, 3H), 1.50-1.40 (br, 9H); LRMS-ES (m/z): [M + Na]⁺ calcd for C₁₄H₂₅NO₅Na, 310.2; found, 310.2.

Synthesis of Indolizidines 64 and 65. To a solution of the enone 59 (200 mg, 0.51 mmol) in DCM (10 mL) was added TFA (1 mL, 13.4 mmol). After the reaction mixture was stirred for 6 h at rt, the solvent was removed under reduced pressure and the resulting residue was evacuated under high vacuum for 1 h. The residue was then dissolved in DCM (30 mL) and cooled to -78 °C. DIPEA (2 mL, 11.5 mmol) was diluted with DCM (10 mL) and slowly added along the inner wall of the flask. After 4 h at this temperature, the
mixture was warmed to rt and the solvent was removed in vacuo. Purification of the residue by silica gel chromatography (Et₃N/EtOAc/hexanes, 0.1/6/4) afforded the major cyclization product 64 (106 mg, 71%) and the minor isomer 65 (13 mg, 9%).

Major isomer 64: 1H NMR (400 MHz, CDCl₃) δ 5.06 (s, 1H), 4.84 (s, 1H), 3.65 (s, 3H), 3.63-3.56 (br, 1H), 3.44 (s, 3H), 3.30-3.25 (br, 1H), 2.90-2.83 (br, 1H), 2.72-2.68 (m, 2H), 2.60-2.46 (br m, 6H), 2.43-2.35 (br, 1H), 2.15 (d, J = 13.4 Hz, 1H), 2.05-1.95 (br, 1H), 1.88-1.80 (br, 1H), 1.75-1.57 (br, 2H); 13C NMR (75 MHz, CDCl₃) δ 208.8, 173.5, 143.5, 114.3, 108.7, 85.1, 62.4, 59.3, 52.2, 51.8, 49.5, 38.6, 38.3, 37.9, 29.3, 28.0, 21.8; LRMS-ES (m/z): [M + H]^+ calcd for C₁₆H₂₆NO₄, 296.2; found, 296.2.

Minor isomer 65: 1H NMR (400 MHz, CDCl₃) δ 4.96 (s, 1H), 4.82 (s, 1H), 3.63 (s, 3H), 3.43 (s, 3H), 3.31 (d, J = 9.2 Hz, 1H), 3.00 (td, J = 8.5, 2.3 Hz, 1H), 2.77 (dd, J = 16.1, 4.8 Hz, 1H), 2.74-2.68 (m, 2H), 2.63-2.55 (m, 1H), 2.56-2.53 (m, 2H), 2.42 (dd, J = 16.1, 7.7 Hz, 1H), 2.36 (dd, J = 13.2, 3.0 Hz, 1H), 2.08-2.00 (m, 2H), 1.97-1.89 (m, 2H), 1.82-1.66 (m, 2H), 1.63-1.54 (m, 1H); 13C NMR (75 MHz, CDCl₃) δ 206.8, 173.0, 145.0, 106.1, 85.0, 69.4, 59.0, 58.4, 51.7, 51.0, 47.8, 40.1, 37.9, 28.7, 27.5, 21.0; LRMS-ES (m/z): [M + H]^+ calcd for C₁₆H₂₆NO₄, 296.2; found, 296.2.

Isomerization of Indolizidine 64 to 65. To a solution of the major conjugate addition product 64 (10.0 mg, 0.0461 mmol) in DCM (5 mL) was added basic alumina (EMD Chemicals TLC/GL AL OX60 F254, 1.00 g). The heterogenous mixture was stirred for 5 min and the solvent was removed in vacuo. The remaining solid was evacuated under high vacuum. After 12 h at rt, the alumina was washed with 10% MeOH in EtOAc and filtered. The filtrate was concentrated and the residue was purified by silica gel
chromatography (Et$_3$N/EtOAc/hexanes, 0.1/6/4) to afford the minor conjugate addition product 65 (6 mg, 60%).

**Synthesis of Diketoesters 69 and 70.** To a solution of the major indolizidine 64 (125 mg, 0.42 mmol) in THF (15 mL) and H$_2$O (5 mL) was added OsO$_4$ (0.13 mL, 4 wt% solution in water, 0.02 mmol) and NMO (248 mg, 2.11 mmol). The mixture was stirred at rt for 12 h and then a solution of NaIO$_4$ (271 mg, 1.27 mmol) in H$_2$O (3 mL) was added. The mixture was further stirred at rt for 4 h. The cloudy aqueous solution was diluted with H$_2$O and extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by silica gel chromatography (hexanes/EtOAc/Et$_3$N, 4/6/0.1) to give compounds 69 (37 mg, 30%) and 70 (38 mg, 30%).

**Diketoester 69:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.94-3.88 (m, 1H), 3.61 (s, 3H), 3.47 (d, $J = 9.2$ Hz, 1H), 3.43 (s, 3H), 2.95-2.90 (m, 1H), 2.84-2.78 (m, 2H), 2.71-2.63 (m, 3H), 2.60-2.55 (m, 1H), 2.54-2.46 (m, 2H), 2.38 (dd, $J = 16.5$, 8.7 Hz, 1H), 2.18 (dd, $J = 13.2$, 2.0 Hz, 1H), 2.10-2.03 (m, 1H), 1.94-1.86 (m, 1H), 1.84-1.71 (m, 2H); LRMS-ES (m/z): [M + H]$^+$ calcd for C$_{15}$H$_{24}$NO$_5$, 298.2; found, 298.2.

**Diketoester 70:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.59 (s, 3H), 3.51 (d, $J = 10.1$ Hz, 1H), 3.42 (s, 3H), 3.00 (td, $J = 8.6$, 2.5 Hz, 1H), 2.93-2.86 (m, 1H), 2.78 (dd, $J = 16.5$, 5.0 Hz, 1H), 2.68-2.63 (m, 2H), 2.52-2.43 (m, 3H), 2.38 (dd, $J = 13.8$, 3.2 Hz, 1H), 2.31-2.21 (m, 2H), 2.16-2.09 (m, 1H), 2.07-1.98 (m, 1H), 1.87-1.70 (m, 2H), 1.66-1.57 (m, 1H), $^{13}$C
NMR (75 MHz, CDCl₃) δ 206.3, 205.7, 172.8, 87.4, 68.0, 59.1, 56.2, 51.6, 50.4, 47.7, 45.6, 37.6, 29.2, 27.4, 21.5; LRMS-ES (m/z): [M + H]⁺ calcd for C₁₅H₂₄NO₅, 298.2; found, 298.2.

**Synthesis of Tetracyclic γ-Lactone 71.** To a solution of diketoester 69 (30 mg, 0.10 mmol) in MeOH (7 mL) was added NaOMe (5 mg, 0.09 mmol). The solution was stirred for 12 h at rt and then quenched with saturated aqueous NH₄Cl (0.2 mL). The methanol solvent was removed under reduced pressure. The cloudy aqueous solution was diluted with H₂O and extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and concentrated. Purification of the residue by chromatography on silica gel (hexanes/EtOAc/Et₃N, 3/7/0.1) yielded lactone 71 (19 mg, 70 %). ¹H NMR (400 MHz, CDCl₃) δ 3.60-3.57 (m, 1H), 3.54 (s, 3H), 3.49 (t, J = 10.3 Hz, 1H), 3.27 (d, J = 9.1 Hz, 1H), 2.95-2.86 (m, 2H), 2.83-2.75 (m, 1H), 2.57 (d, J = 18.2 Hz, 1H), 2.51-2.36 (m, 2H), 2.35-2.29 (m, 1H), 2.28-2.24 (m, 1H), 2.18-2.11 (m, 1H), 2.01-1.91 (m, 1H), 1.85-1.66 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 207.5, 174.0, 87.3, 84.2, 60.9, 59.7, 48.7, 48.5, 47.0, 36.6, 35.5, 29.8, 28.7, 21.6; HRMS-ES (m/z): [M + H]⁺ calcd for C₁₄H₂₀NO₄, 266.1392; found, 266.1404.
Synthesis of Benzyl Ether 73. To a suspension of NaH (60% dispersion in mineral oil, 235 mg, 5.88 mmol) in THF (10 mL) was added a solution of alcohol 52 (932 mg, 1.43 mmol) in THF (20 mL) at rt. The mixture was stirred at rt for 15 min before BnBr (0.35 mL, 2.86 mmol) was added. The reaction mixture was stirred for 12 h at rt and quenched with saturated aqueous NH₄Cl. The aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by chromatography on silica gel (Et₃N/EtOAc/hexanes, 0.2/1/20) to give ether 73 (478 mg, 45%). ¹H NMR (300 MHz, CDCl₃) δ 7.83-7.80 (m, 4H), 7.63-7.54 (m, 16H), 7.31-7.24 (m, 10H), 5.25 (s, 1H), 5.00 (s, 1H), 4.87 (d, J = 12.3 Hz, 1H), 4.70 (s, 1H), 4.55 (d, J = 20.6 Hz, 1H), 3.72 (t, J = 6.5 Hz, 2H), 3.59-3.52 (m, 2H), 3.15-3.10 (m, 1H), 2.20-2.08 (m, 1H), 1.90-1.77 (m, 2H), 1.65-1.55 (m, 1H), 1.22 (s, 9H), 0.94-0.82 (m, 1H), 0.48-0.35 (m, 1H).

Synthesis of Alcohol 74. To a solution of silyl ether 73 (180 mg, 0.24 mmol) in THF (100 mL) was added TBAF (1 M solution in THF, 0.5 mL, 0.50 mmol) at rt. After 12 h at rt, the reaction mixture was diluted with saturated aqueous NH₄Cl and then EtOAc and H₂O. Solid NaCl was added to saturate the aqueous phase and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by
silica gel flash chromatography (Et$_3$N/EtOAc/hexanes, 0.1/3/7) to give 74 (106 mg, 87%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70-7.52 (m, 10H), 7.29-7.19 (m, 10H), 5.24 (s, 1H), 4.98 (s, 1H), 4.83 (d, $J = 12.3$ Hz, 1H), 4.57 (d, $J = 12.3$ Hz, 1H), 4.43 (s, 1H), 3.51-3.44 (m, 4H), 3.10-3.00 (m, 1H), 2.10-1.95 (m, 1H), 1.75-1.60 (m, 2H), 1.55-1.40 (m, 2H), 0.90-0.80 (m, 1H), 0.40-0.35 (m, 1H).

**Synthesis of N-Boc Carbamate 75.** To a solution of N-trityl alcohol 55 (50 mg, 0.10 mmol) in MeOH (5 mL) and DCM (1 mL) was added glacial AcOH (0.3 mL). After the mixture was stirred at rt for 2 h, Et$_3$N (1 mL) was added followed by (Boc)$_2$O (65 mg, 0.30 mmol). The reaction mixture was stirred for an additional 12 h at rt and the solvent was removed under reduced pressure. Purification of the residue via flash chromatography on silica gel (EtOAc/hexanes, 1/2) afforded N-Boc carbamate 75 (29 mg, 81%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38-7.28 (m, 5H), 5.29 (br s, 0.4H), 5.17-5.10 (m, 1.6H), 4.58 (d, $J = 11.9$ Hz, 1H), 4.33-4.27 (m, 1H), 4.17 (br s, 0.4H), 4.03 (br s, 1.2H), 3.86-3.73 (m, 1H), 3.52-3.32 (m, 2H), 2.53-2.27 (m, 2H), 2.12-1.89 (m, 2H), 1.79-1.65 (m, 2H), 1.41 (br s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.9, 154.1, 143.6, 143.2, 138.4, 128.3, 128.2, 127.5, 127.4, 127.3, 113.1, 112.8, 81.8, 81.3, 79.3, 71.2, 71.0, 60.7, 60.1, 59.0, 58.5, 46.9, 46.7, 36.0, 34.7, 28.4, 25.4, 25.2, 23.7. LRMS-ES (m/z): [M + H]$^+$ calcd for C$_{21}$H$_{32}$NO$_4$, 362.2; found, 362.2.
Synthesis of Aldehyde 76. To a solution of the carbamate alcohol 75 (29 mg, 0.080 mmol) in DCM (5 mL) was added Dess-Martin periodinane (41 mg, 0.097 mmol). After 2 h, saturated aqueous NaHCO₃ and 10% aqueous Na₂S₂O₃ solution were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give a pale yellow oil. The aldehyde obtained was unstable to chromatographic purification and therefore was used in crude form.

Synthesis of Enone 77. To a solution of the phosphonium ylide 31 (160 mg, 0.41 mmol) in DCM (10 mL), was added a solution of the crude aldehyde 58 (0.08 mmol) in DCM (10 mL). The reaction mixture was heated at reflux and stirred for 12 h before the solvent was removed under vacuum. The crude residue was purified by silica gel flash chromatography (EtOAc/hexanes, 1/4) to give enone 77 (26 mg, 69% based on carbamate alcohol 76). ¹H NMR (300 MHz, CDCl₃) δ7.38-7.29 (m, 5H), 7.02-6.84 (m, 1H), 6.22 (d, J = 16.0 Hz, 1H), 5.27 (d, J = 25.3 Hz, 1H), 5.03 (d, J = 18.3 Hz, 1H), 4.60-4.56 (m, 1H), 4.33-4.29 (m, 1H), 4.17 (br s, 1H), 4.08-3.80 (m, 1H), 3.71 (s, 3H), 3.50-3.30 (m, 2H), 3.05-2.90 (m, 3H), 2.69-2.63 (m, 2H), 2.14-1.90 (m, 2H), 1.80-1.70 (m, 2H), 1.42 (s, 9H).
Synthesis of Indolizidines 78. To a solution of the enone 77 (110 mg, 0.23 mmol) in DCM (5 mL) was added TFA (0.3 mL, 3.89 mmol). After the reaction mixture was stirred for 6 h at rt, the solvent was removed under reduced pressure and the resulting residue was evacuated under high vacuum for 1 h. The residue was then dissolved in DCM (15 mL) and cooled to -78 °C. DIPEA (0.6 mL, 3.44 mmol) was diluted with DCM (5 mL) and slowly added along the inner wall of the flask. After 4 h at this temperature, the mixture was warmed to rt and the solvent was removed in vacuo. Purification of the residue by silica gel chromatography (Et₃N/EtOAc/hexanes, 0.1/6/4) afforded the major conjugate addition product 78 (56 mg, 65%) and the minor isomer 79 (10 mg, 11%). Only the major isomer 78 was characterized. ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.24 (m, 5H), 5.18 (s, 1H), 4.87 (d, J = 1.5 Hz, 1H), 4.73, 4.46 (ABq, J = 11.6 Hz, 2H), 3.65 (s, 3H), 3.63-3.56 (m, 1H), 3.52 (d, J = 8.9 Hz, 1H), 2.84 (td, J = 8.7, 3.8 Hz, 1H), 2.73-2.68 (m, 2H), 2.57-2.49 (m, 4H), 2.46-2.41 (m, 2H), 2.17 (dd, J = 13.3, 1.9 Hz, 1H), 2.00-1.95 (m, 1H), 1.77-1.62 (m, 3H), 1.54-1.48 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 208.4, 173.2, 143.3, 138.3, 128.3, 128.0, 127.7, 108.7, 82.3, 72.6, 61.9, 51.8, 51.4, 49.0, 38.2, 37.7, 37.5, 28.9, 27.6, 21.3; LRMS-ES (m/z): [M + H]⁺ calcd for C₂₂H₃₀NO₄, 372.2; found, 372.2.
Synthesis of N-Trityl Ester 99. To a solution of D-proline (15.000 g, 130.30 mmol) in methanol (150 mL) was slowly added thionyl chloride (19 mL, 260.5 mmol) at 0 °C. The reaction mixture was stirred for an additional 12 h at rt before the solvent and other volatile compounds were removed in vacuo. The resulting oil was dissolved in CHCl₃ (200 mL), and Et₃N (55 mL, 394.6 mmol) was added followed by trityl chloride (34.500 g, 123.80 mmol). The reaction mixture was stirred for 12 h at rt and hydrolyzed with a 2:1 mixture of saturated aqueous NH₄Cl solution and NH₄OH (28% in water). The aqueous layer was extracted with DCM. The combined organic extracts were dried over MgSO₄ and concentrated. The solid obtained was dissolved in THF and filtered. The filtrate was concentrated under reduced pressure. After recrystallization of the residue from Et₂O, ester 99 (40.600 g, 84%) was obtained as a slightly yellow solid: \([\alpha]_D^{20} = +40.1\) (c 2.74, CHCl₃); \(^1\)H NMR (300 MHz, CDCl₃) δ 7.62-7.59 (m, 6H), 7.33-7.27 (m, 6H), 7.22-7.16 (m, 3H), 3.97 (dd, J = 8.9, 2.5 Hz, 1H), 3.73 (s, 3H), 3.50-3.46 (m, 1H), 2.92-2.89 (m, 1H), 1.70-1.50 (m, 2H), 1.14-0.95 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 177.1, 144.7, 129.2, 127.6, 126.1, 77.4, 62.7, 51.5, 49.9, 31.2, 24.2; HRMS-ES (m/z): \([M + Na]^+\) calcd for C₂₅H₂₅NO₂Na, 394.1783; found, 394.1793.
Synthesis of N-Trityl Alcohol 100. A solution of ester 99 (39.000 g, 105.00 mmol) in dry THF (150 mL) was added slowly via an addition funnel to a slurry of LiAlH₄ (3.190 g, 84.00 mmol) in dry THF (50 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to rt and stirred for 12 h. The reaction mixture was cooled to 0 °C and then carefully quenched with water (3.2 mL), 15% aqueous NaOH (3.2 mL), and water (9.6 mL). After being stirred for 30 min, the mixture was diluted with EtOAc, filtered through Celite and the phases were separated. The aqueous phase was saturated with solid NaCl and extracted with EtOAc. The combined organic phases were dried over MgSO₄, and concentrated to yield the title compound as a white foam (34.260 g, 95%), which was used without further purification. For analytical purposes, alcohol 100 was purified by flash column chromatography on silica gel (hexanes/EtOAc/Et₃N, 9/1/0.1) to give a white foam: \( [\alpha]_{D}^{20} = -37.7 \) (c 2.17, CHCl₃); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.65-7.62 (m, 6H), 7.34-7.28 (m, 6H), 7.25-7.22 (m, 3H), 3.70-3.66 (m, 1H), 3.62 (d, \( J = 7.1 \) Hz, 1H), 3.57-3.54 (m, 1H), 3.27-3.24 (m, 1H), 3.10-3.04 (m, 1H), 2.40 (br s, 1H), 1.48-1.44 (m, 2H), 1.10-1.02 (m, 1H), 0.70-0.63 (m, 1H); \(^1\)C NMR (75 MHz, CDCl₃) \( \delta \) 145.0, 129.5, 127.5, 126.1, 77.6, 65.7, 61.1, 50.9, 29.0, 24.1; HRMS-ES (m/z): [M + Na]⁺ calcd for C₂₄H₂₅NONa, 366.1834; found, 366.1824.
**Synthesis of N-Trityl Aldehyde 34.** To a solution of (COCl)$_2$ (13 mL, 148.5 mmol) in DCM (120 mL) cooled to -78 °C was added dropwise a solution of DMSO (17.6 mL, 247.5 mmol) in DCM (70 mL) via an addition funnel. After the addition was complete, the reaction mixture was stirred for 30 min before a solution of the alcohol 100 (34.000 g, 99.00 mmol) in DCM (90 mL) was added dropwise at -78 °C. After stirring the mixture for 1.5 h at this temperature, Et$_3$N (55.2 mL, 396.0 mmol) was added. The reaction mixture was further stirred for 1.5 h at -78 °C and then quenched with a 2:1 mixture of a saturated aqueous NH$_4$Cl solution and NH$_4$OH (28% in water). The layers were separated, and the aqueous layer was extracted with DCM. The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The solid obtained was dissolved in THF and filtered. The filtrate was concentrated *in vacuo* to give, after recrystallization from ether, the aldehyde 34 (30.400 g, 90%) as a pale yellow solid: $\left[\alpha\right]_{D}^{20} = +12.5$ (c 2.55, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.77 (d, $J = 2.8$ Hz, 1H), 7.50-7.47 (m, 6H), 7.21-7.16 (m, 6H), 7.12-7.07 (m, 3H), 3.71-3.65 (m, 1H), 3.24-3.16 (m, 1H), 2.88-2.80 (m, 1H), 1.55-1.47 (m, 1H), 1.38-1.30 (m, 1H), 1.07-1.00 (m, 1H), 0.74-0.69 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 204.4, 144.4, 129.4, 127.7, 126.4, 76.9, 50.5, 28.0, 24.2; HRMS-ES (m/z): [M + Na]$^+$ calcd for C$_{24}$H$_{23}$NONa, 364.1677; found, 364.1657.
Synthesis of Alcohol ent-52. Magnesium turnings (5.991 g, 246.54 mmol) were flame dried, cooled under argon and then immersed in THF (20 mL). Two drops of 1,2-dibromoethane were added to the mixture which was then heated at reflux for 15 min. The heating was stopped and a solution of vinyl bromide 51 (24.000 g, 61.63 mmol) in THF (50 mL) was added dropwise via an addition funnel to maintain a gentle reflux. After the addition was complete, the reaction mixture was stirred at reflux for 30 min and then cooled to rt.

The resulting Grignard reagent was added via cannula to a solution of the aldehyde 34 (14.028 g, 41.09 mmol) in THF (50 mL) at -78 °C. The mixture was stirred for 4 h at -78 °C and then quenched by the addition of saturated aqueous NH₄Cl (5 mL). The solution was diluted with EtOAc and H₂O. The aqueous phase was saturated with solid NaCl and the organic phase was separated. The aqueous layer was further extracted with EtOAc. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. Purification of the residue via flash chromatography on silica gel (Et₃N/EtOAc/hexanes, 0.1/0.5/9.5) afforded the desired alcohol ent-52 (25.449 g, 95%) as a white foam: [α]D²⁰ = +24.5 (c 5.88, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, J = 6.6 Hz, 4H), 7.64 (d, J = 7.8 Hz, 6H), 7.54-7.45 (m, 6H), 7.39-7.21 (m, 9H), 5.23 (s, 1H), 4.91 (s, 1H), 4.45 (s, 1H), 3.71-3.67 (m, 1H), 3.63 (t, J = 7.1 Hz, 2H), 3.36-3.27 (m, 2H), 3.14-3.07 (m, 1H), 2.21-2.11 (m, 1H), 2.02-1.95 (m, 1H), 1.70-1.59 (m, 1H), 1.43-1.35 (m, 1H), 1.14 (s, 9H), 1.08-1.01 (m, 1H), 0.39-0.26 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 145.4, 144.5, 135.5, 135.4, 133.8, 129.7,
129.5, 127.5, 127.4, 126.2, 110.2, 78.0, 75.6, 62.6, 62.4, 52.9, 36.2, 26.8, 25.2, 24.8, 19.1;

HRMS-ES (m/z): [M + H]⁺ calcd for C₄₄H₅₀NO₂Si, 652.3611; found, 652.3618.

Synthesis of MOM Ether 81. To a solution of the alcohol ent-52 (25.000 g, 38.35 mmol) in DCM (200 mL) at rt was added DIPEA (33.4 mL, 191.9 mmol) followed by MOMBr (12.5 mL, 153.4 mmol). The reaction mixture was then heated at 50 °C and stirred for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in THF and filtered. The filtrate was then concentrated and the resulting oil was subjected to silica gel chromatography (hexanes/EtOAc/Et₃N, 8/2/0.1) to give the title compound (24.000 g, 90%) as a pale yellow oil: [α]D²⁰ = +38.8 (c 5.73 , CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.71 (m, 4H), 7.67 (d, J = 7.2 Hz, 6H), 7.52-7.47 (m, 6H), 7.30 (t, J = 7.6 Hz, 6H), 7.21 (t, J = 7.2 Hz, 3H), 5.08 (s, 1H), 4.90 (d, J = 6.5 Hz, 1H), 4.87 (s, 1H), 4.81 (d, J = 6.5 Hz, 1H), 4.77 (s, 1H), 3.72 (s, 3H), 3.64 (t, J = 7.0 Hz, 2H), 3.56 (d, J = 8.1 Hz, 1H), 3.49-3.36 (m, 1H), 3.13-3.05 (m, 1H), 1.97-1.90 (m, 1H), 1.83-1.72 (m, 1H), 1.71-1.64 (m, 1H), 1.47-1.38 (m, 1H), 1.13 (s, 9H), 0.88-0.77 (m, 1H), 0.34-0.22 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 145.4, 144.2, 135.54, 135.51, 134.0, 133.9, 130.0, 129.5, 127.6, 127.5, 126.0, 111.5, 95.0, 82.7, 78.4, 62.8, 62.1, 55.8, 51.8, 36.2, 26.8, 25.3, 24.1, 19.2; HRMS-ES (m/z): [M + H]⁺ calcd for C₄₆H₅₄NO₅Si, 696.3873; found, 696.3914.
Synthesis of Alcohol 82. To a solution of silyl ether 81 (23.000 g, 33.05 mmol) in THF (100 mL) was added TBAF (1 M solution in THF, 49.6 mL, 49.6 mmol) at rt. After 12 h at rt, the reaction mixture was diluted with saturated aqueous NH₄Cl (60 mL) and then EtOAc and H₂O. Solid NaCl was added to saturate the aqueous phase and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The crude material was purified by silica gel flash chromatography (Et₃N/EtOAc/hexanes, 0.1/1/9) to give the title compound (14.370 g, 95%) as a slightly yellow oil: \([\alpha]_D^{20} = +28.4 \text{ (c 9.5, CHCl}_3\); \(^1\)H NMR (300 MHz, CD₂Cl₂) \(\delta\) 7.64-7.59 (m, 6H), 7.31-7.25 (m, 6H), 7.22-7.13 (m, 3H), 5.08 (t, \(J = 1.6\) Hz, 1H), 4.90 (d, \(J = 0.8\) Hz, 1H), 4.87 (d, \(J = 6.5\) Hz, 1H), 4.73 (d, \(J = 6.6\) Hz, 1H), 4.68 (s, 1H), 3.61 (s, 3H), 3.50-3.46 (m, 3H), 3.42-3.32 (m, 1H), 3.06-2.98 (m, 1H), 1.99-1.89 (m, 1H), 1.68-1.58 (m, 3H), 1.40-1.29 (m, 1H), 0.77-0.69 (m, 1H), 0.32-0.22 (m, 1H); \(^{13}\)C NMR (75 MHz, CD₂Cl₂) \(\delta\) 145.8, 145.2, 130.1, 127.9, 126.4, 112.5, 95.8, 83.0, 78.8, 63.2, 61.1, 56.1, 52.1, 37.2, 25.7, 24.4; HRMS-ES (m/z): \([M + H]^+\) calced for C₃₀H₃₆NO₃, 458.2695; found, 458.2722.

Synthesis of Carbamate Alcohol 83. To a solution of alcohol 82 (14.150 g, 30.92 mmol) in MeOH (200 mL) was added glacial AcOH (14 mL). After the mixture was
stirred at rt for 12 h, Et₂N (40 mL) was added followed by (Boc)₂O (10.120 g, 46.38 mmol). The reaction mixture was stirred for an additional 6 h at rt and the solvent was removed under reduced pressure. Purification of the residue via flash chromatography on silica gel (Et₃N/EtOAc/hexanes, 0.1/4/6) afforded alcohol 83 (8.680 g, 89%) as a colorless oil: [α]D²⁰ = +125.2 (c 6.15, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.16 (s, 0.5 H), 5.07 (s, 0.5 H), 5.00 (s, 1H), 4.51 (d, J = 6.7 Hz, 1H), 4.45 (d, J = 6.6 Hz, 1H), 4.32 (d, J = 5.0 Hz, 0.5 H), 3.94 (br s, 0.5 H), 3.82-3.70 (m, 3H), 3.45 (m, 0.5 H), 3.34 (m, 0.5 H), 3.29 (s, 1.5 H), 3.26 (m, 1H), 3.25 (s, 1.5 H), 2.91 (br s, 0.5 H), 2.44-2.35 (m, 0.5 H), 2.31-2.16 (m, 1.5 H), 2.07-1.93 (m, 2H), 1.71-1.66 (m, 2H), 1.45 (s, 4.5 H), 1.38 (s, 4.5 H); ¹³C NMR (75 MHz, CDCl₃) δ 154.4, 153.9, 143.4, 143.2, 112.7, 112.2, 94.3, 94.2, 79.3, 79.0, 77.8, 77.3, 60.5, 60.1, 58.3, 58.2, 55.4, 55.2, 55.0, 46.9, 46.8, 36.0, 35.4, 28.2, 24.8, 24.7, 23.8, 23.5; HRMS-ES (m/z): [M + H]⁺ calcd for C₁₆H₃₀NO₅, 316.2124; found, 316.2108.

**Synthesis of Aldehyde 84.** To a solution of the carbamate alcohol 83 (6.200 g, 19.660 mmol) in DCM (200 mL) was added NaHCO₃ (7.430 g, 88.470 mmol) followed by Dess-Martin periodinane (12.50 g, 29.49 mmol). After 4 h, 10% aqueous Na₂S₂O₅ solution (200 mL) was added to the reaction mixture. After the solids had dissolved, the mixture was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give a pale yellow oil. The aldehyde obtained was unstable to chromatographic purification and therefore was used in crude form.
Synthesis of (E)-Enone 85. To a suspension of NaH (60% dispersion in mineral oil, 1.415 g, 35.39 mmol) in THF (15 mL) was slowly added a solution of the phosphonate 31 (9.364 g, 39.32 mmol) in THF (50 mL) at rt. After 45 min at rt, a solution of the crude aldehyde 84 (6.161 g, 19.66 mmol) in THF (40 mL) was added. The reaction mixture was stirred for 1.5 h and quenched with saturated aqueous NH₄Cl (5 mL). The resulting cloudy solution was diluted with EtOAc and H₂O. The aqueous phase was saturated with NaCl and the organic phase was separated. The aqueous phase was then extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was chromatographed on silica gel to give enone 85 (5.851 g, 70% based on carbamate alcohol 83) as a pale yellow oil: [α]²⁰D = +87.5 (c 6.40, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.93-6.71 (m, 1H), 6.17 (d, J = 15.9 Hz, 1H), 5.20 (d, J = 26.3 Hz, 1H), 4.95 (d, J = 19.2 Hz, 1H), 4.54-4.45 (m, 3H), 3.93 (br s, 0.5H), 3.79 (br s, 0.5H), 3.67 (s, 3H), 3.54 (br s, 0.5H), 3.39 (br s, 0.5H), 3.32 (s, 2H), 3.30 (s, 2H), 3.08-3.02 (m, 0.5H), 2.95-2.88 (m, 3.5H), 2.65-2.59 (m, 2H), 2.01-1.95 (m, 2H), 1.76-1.69 (m, 2H), 1.48 (s, 4.5H), 1.45 (s, 4.5H); ¹³C NMR (75 MHz, CDCl₃) δ 198.0, 197.6, 173.2, 154.4, 154.0, 144.6, 143.8, 143.8, 143.2, 131.4, 131.3, 113.6, 94.6, 94.3, 79.6, 79.0, 78.2, 77.7, 58.6, 58.5, 55.44, 55.36, 51.7, 47.0, 35.6, 35.3, 34.6, 34.4, 28.4, 27.7, 27.6, 25.2, 24.8, 24.2, 23.7; HRMS-ES (m/z): [M + H]⁺ calcd for C₂₂H₃₆NO₇, 426.2492; found, 426.2468.
Synthesis of Indolizidines 90 and 91. To a solution of the enone \(85\) (71 mg, 0.17 mmol) in DCM (6 mL) was added TFA (0.26 mL, 3.34 mmol). After the reaction mixture was stirred for 6 h at rt, the solvent was removed under reduced pressure and the residue was evacuated under high vacuum for 1 h. The residue was then dissolved in DCM (10 mL) and cooled to -78 °C. DIPEA (0.29 mL, 1.67 mmol) was slowly added along the inner wall of the flask. After 4 h at this temperature, the mixture was warmed to rt and the solvent was removed \textit{in vacuo}. Purification of the residue by silica gel chromatography (Et\(_3\)N/EtOAc/hexanes, 0.1/6/4) afforded the major conjugate addition product \(91\) (32 mg, 59 %) and the minor isomer \(90\) (6 mg, 11%).

Major isomer \(91\) (pale yellow oil): \([\alpha]_{D}^{20} = +86.9 \text{ (c 3.50, CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.02 (s, 1H), 4.80 (d, \(J = 1.6\) Hz, 1H), 4.64 (dd, \(J = 17.9, 6.8\) Hz, 2H), 3.71 (d, \(J = 8.9\) Hz, 1H), 3.63 (s, 3H), 3.56 (dd, \(J = 12.4\) Hz, 5.8 Hz, 1H), 3.37 (s, 3H), 2.85 (td, \(J = 8.8, 3.6\) Hz, 1H), 2.71-2.66 (m, 2H), 2.55-2.45 (m, 6H), 2.39 (dd, \(J = 16.0, 7.2\) Hz, 1H), 2.13 (dd, \(J = 13.3, 1.9\) Hz, 1H), 2.02-1.93 (m, 1H), 1.85-1.76 (m, 1H), 1.72-1.56 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 208.3, 173.1, 143.5, 108.7, 95.7, 79.9, 61.6, 55.8, 51.7, 51.3, 49.1, 38.1, 37.6, 37.5, 28.9, 27.6, 21.3; HRMS-ES (\(m/z\)): [M + H]\(^+\) calcd for C\(_{17}\)H\(_{28}\)NO\(_5\), 326.1907; found, 326.1946.

Minor isomer \(90\) (pale yellow oil): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.91 (d, \(J = 1.6\) Hz, 1H), 4.78 (d, \(J = 1.7\) Hz, 1H), 4.66 (dd, \(J = 11.4, 6.7\) Hz, 2H), 3.79 (d, \(J = 9.0\) Hz, 1H),
3.64 (s, 3H), 3.37 (s, 3H), 3.02 (td, \( J = 8.3, 2.3 \) Hz, 1H), 2.82-2.69 (m, 3H), 2.64-2.53 (m, 3H), 2.48-2.35 (m, 2H), 2.09-1.90 (m, 4H), 1.79-1.60 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 207.3, 173.5, 145.9, 107.0, 96.4, 80.5, 69.7, 58.8, 56.2, 52.2, 51.7, 48.3, 40.6, 38.4, 29.3, 28.0, 21.4; HRMS-ES (m/z): [M + H]+ calcd for C\(_{17}\)H\(_{28}\)NO\(_5\), 326.1907; found, 326.1964.

**Isomerization of Indolizidines 91 to 90.** To a solution of the major conjugate addition product 91 (15 mg, 0.046 mmol) in DCM (5 mL) was added basic alumina (EMD Chemicals TLC/GL AL OX60 F254, 2.000 g). The heterogenous mixture was stirred for 5 min and the solvent was removed *in vacuo*. The remaining solid was evacuated under high vacuum. After 12 h at rt, the alumina was washed with 10% isopropanol in CHCl\(_3\) and filtered. The elutant was concentrated and the residue was purified by silica gel chromatography (Et\(_3\)N/EtOAc/hexanes, 0.1/6/4) to afford the minor conjugate addition product 90 (12 mg, 80%).

![Structure of 92](image)

**Synthesis of Diketoester 92.** To a solution of the major indolizidine 91 (36 mg, 0.11 mmol) in THF (6 mL) and H\(_2\)O (2 mL) at 0 °C was added OsO\(_4\) (4 wt% solution in water, 0.21 mL, 0.033 mmol). After the mixture was stirred for 15 min at this temperature, a solution of NaIO\(_4\) (119 mg, 0.56 mmol) in H\(_2\)O (3 mL), and a solution of NMO (65 mg, 0.56 mmol) in H\(_2\)O (3 mL) were added. The reaction mixture was stirred for another 5 h at 0 °C. The mixture was then partitioned between EtOAc and H\(_2\)O and the aqueous phase was saturated with solid NaCl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na\(_2\)SO\(_4\) and
concentrated. The residue was purified by silica gel chromatography (Et$_3$N/EtOAc/hexanes, 0.1/6/4) to give compound 92 (23 mg, 63%) as a colorless oil: $[\alpha]_{D}^{20} = +88.4$ (c 1.90, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.71 (d, $J = 7.0$ Hz, 1H), 4.62 (d, $J = 7.0$ Hz, 1H), 3.98-3.89 (m, 1H), 3.95 (d, $J = 9.4$ Hz, 1H), 3.62 (s, 3H), 3.36 (s, 3H), 2.98-2.86 (m, 2H), 2.81 (dd, $J = 13.4$, 6.4 Hz, 1H), 2.74-2.61 (m, 3H), 2.60-2.48 (m, 3H), 2.39 (dd, $J = 16.5$, 8.7 Hz, 1H), 2.20 (dd, $J = 13.3$, 2.0 Hz, 1H), 2.13-2.04 (m, 1H), 1.96-1.87 (m, 1H), 1.85-1.73 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.6, 206.9, 172.9, 96.1, 81.0, 62.4, 55.9, 52.9, 51.8, 49.4, 43.5, 40.8, 38.0, 30.0, 27.5, 22.1; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{16}$H$_{26}$NO$_6$, 328.1760; found, 328.1779.

Synthesis of Tetracyclic γ-Lactone 93 and Hydroxy ester 94. To a solution of diketoester 92 (95 mg, 0.29 mmol) in MeOH (20 mL) was added NaOMe (24 mg, 0.44 mmol). The solution was stirred for 12 h at rt and then quenched with saturated aqueous NH$_4$Cl (1 mL). The methanol solvent was removed under reduced pressure. The cloudy aqueous solution was diluted with H$_2$O and extracted with 15% isopropanol in CHCl$_3$. The combined organic phases were dried over Na$_2$SO$_4$ and concentrated. Purification of the residue by chromatography on silica gel (Et$_3$N/EtOAc/hexanes, 0.1/7/3) yielded lactone 93 (64 mg, 75 %) as a colorless oil: $[\alpha]_{D}^{20} = +12.6$ (c 1.90, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.74 (d, $J = 6.8$ Hz, 1H), 4.61 (d, $J = 6.8$ Hz, 1H), 3.64 (d, $J = 9.1$ Hz, 1H), 3.58-3.53 (m, 1H), 3.47 (t, $J = 10.6$ Hz, 1H), 3.34 (s, 3H), 2.91-2.68 (m, 3H), 2.55 (d, $J = 18.3$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.6, 206.9, 172.9, 96.1, 81.0, 62.4, 55.9, 52.9, 51.8, 49.4, 43.5, 40.8, 38.0, 30.0, 27.5, 22.1; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{16}$H$_{26}$NO$_6$, 328.1760; found, 328.1779.
Hz, 1H), 2.48-2.33 (m, 3H), 2.26-2.19 (m, 1H), 2.11-2.03 (m, 1H), 1.93-1.84 (m, 1H),
1.81-1.67 (m, 3H); \[^{13}\text{C}\] NMR (75 MHz, CDCl\(_3\)) \(\delta\) 207.4, 173.9, 97.4, 86.8, 79.9, 59.4, 56.1,
48.8, 48.7, 47.1, 36.6, 35.5, 29.8, 28.6, 21.5; HRMS-ES (m/z): \([\text{M} + \text{H}]^+\) calcd for
C\(_{15}\)H\(_{22}\)NO\(_5\), 296.1498; found, 296.1515.

By further elution of the silica gel column with EtOAc/isopropanol/Et\(_3\)N
(9.5/0.5/0.1), hydroxy ester 94 (14 mg, 15%) was obtained as a pale yellow oil: \(^1\text{H}\) NMR
(400 MHz, CDCl\(_3\)) \(\delta\) 4.73 (d, \(J = 5.9\) Hz, 1H), 4.46 (d, \(J = 5.9\) Hz, 1H), 4.34 (s, 1H), 3.67
(s, 3H), 3.45 (d, \(J = 2.8\) Hz, 1H), 3.41 (s, 3H), 3.22 (d, \(J = 9.8\) Hz, 1H), 3.15 (dd, \(J = 10.1,
2.7\) Hz, 1H), 2.93 (dd, \(J = 16.8, 10.1\) Hz, 1H), 2.82 (td, \(J = 8.1, 4.1\) Hz, 1H), 2.78 (dt, \(J =
16.5, 2.0\) Hz, 1H), 2.69 (dd, \(J = 16.8, 2.9\) Hz, 1H), 2.67-2.61 (m, 1H), 2.36-2.27 (m, 2H),
2.19 (dd, \(J = 12.9, 2.7\) Hz, 1H), 2.13 (dt, \(J = 12.1, 3.0\) Hz 1H), 1.93-1.83 (m, 1H), 1.85-1.75
(m, 1H), 1.72-1.63 (m, 1H), 1.46-1.39 (m, 1H); \[^{13}\text{C}\] NMR (75 MHz, CDCl\(_3\)) \(\delta\) 208.3, 174.2,
98.7, 89.6, 73.8, 59.4, 58.6, 56.1, 51.7, 50.7, 48.4, 41.0, 40.4, 29.4, 28.5, 21.3; HRMS-ES
(m/z): \([\text{M} + \text{H}]^+\) calcd for C\(_{16}\)H\(_{26}\)NO\(_6\), 328.1760; found, 328.1756.

**Transformation of Hydroxy Ester 94 to Lactone 93.** To a solution of hydroxy
ester 94 (6 mg, 0.031 mmol) in MeOH (5 mL) was added NaOMe (20 mg, 0.37 mmol).
After stirring the mixture for 36 h at rt, the reaction was quenched with saturated aqueous
NH\(_4\)Cl (1 mL). The solvent was removed under reduced pressure and the aqueous solution
was diluted with H\(_2\)O and extracted with 15% isopropanol in CHCl\(_3\). The combined
organic phases were dried over Na\(_2\)SO\(_4\) and concentrated. Purification of the residue by
chromatography on silica gel (Et\(_3\)N/EtOAc/hexanes, 0.1/7/3) yielded lactone 93 (5 mg,
90%).
Synthesis of Enol Triflate 95. A solution of ketone 93 (95 mg, 0.32 mmol) in THF (10 mL) was added dropwise to a solution of KHMDS (0.5 M in toluene, 1.29 mL, 0.65 mmol) in THF (2 mL) at -78 °C. After 1 h at this temperature, a solution of N-phenyltriflimide (138 mg, 0.39 mmol) in THF (2 mL) was added slowly to the mixture. The reaction mixture was stirred at -78 °C for another 12 h and then quenched with saturated aqueous NH₄Cl (1 mL). The solution was diluted with EtOAc and H₂O and the aqueous phase was saturated with NaCl. The organic phase was then separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (Et₃N/EtOAc/hexanes, 0.1/4/6) to give enol triflate 95 (117 mg, 85%) as a colorless oil: 

\[ \left[ \alpha \right]_{D}^{20} = -10.7 \ (c \ 3.55, \ CHCl_3); \ \] ¹H NMR (400 MHz, CDCl₃) δ 5.93 (d, J = 6.4 Hz, 1H), 4.74 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 3.79-3.75 (m, 1H), 3.64 (d, J = 9.5 Hz, 1H), 3.54 (t, J = 10.5 Hz, 1H), 3.36 (s, 3H), 2.91 (dd, J = 8.4, 2.7 Hz, 1H), 2.85 (dd, J = 17.8, 9.6 Hz, 1H), 2.63 (dd, J = 17.6, 11.9 Hz, 1H), 2.38 (dd, J = 16.5, 8.3 Hz, 1H), 2.32-2.24 (m, 1H), 2.08 (dd, J = 12.4, 3.1 Hz, 1H), 2.05-1.99 (m, 1H), 1.91-1.83 (m, 1H), 1.79 (dd, J = 12.3, 3.0 Hz, 1H), 1.77-1.68 (m, 1H), 1.67-1.58 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 149.7, 124.8, 120.6, 116.3, 115.4, 112.1, 97.3, 85.9, 78.8, 58.8, 56.0, 49.5, 48.6, 37.2, 32.9, 33.8, 27.8, 21.8; HRMS-ES (m/z): [M + H]⁺ calcd for C₁₆H₂₁NO₅SF₃, 428.0991; found, 428.0967.
Synthesis of Alkene 96. To a solution of enol triflate 95 (71 mg, 0.17 mmol), DIPEA (0.12 mL, 0.69 mmol), Pd(OAc)$_2$ (0.4 mg, 0.002 mmol) and PPh$_3$ (1.0 mg, 0.004 mmol) in DMF (1.5 mL) was added formic acid (22.9 mg, 0.498 mmol). The solution was stirred at 60 °C for 1 h. During this period, the mixture became black. After cooling, the mixture was diluted with EtOAc and washed with brine. The organic phase was dried over Na$_2$SO$_4$ and concentrated. The residue was purified by silica gel column chromatography (Et$_3$N/EtOAc/hexanes, 0.1/7/3) to give alkene 96 (44 mg, 95%) as a colorless oil:

$[\alpha]_{D}^{20} = -104.4$ (c 0.90, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.99 (dd, $J = 9.7$ Hz, 3.7 Hz, 1H), 5.82-5.78 (m, 1H), 4.75 (d, $J = 6.7$ Hz, 1H), 4.60 (d, $J = 6.7$ Hz, 1H), 3.61 (d, $J = 9.4$ Hz, 1H), 3.57 (dd, $J = 5.7$, 2.9 Hz, 1H), 3.34 (s, 3H), 3.20-3.09 (m, 1H), 2.88 (td, $J = 8.5$, 3.0 Hz, 1H), 2.73 (dd, $J = 17.4$, 9.3 Hz, 1H), 2.42-2.21 (m, 3H), 2.01 (dd, $J = 12.3$, 2.8 Hz, 1H), 1.96-1.95 (m, 1H), 1.89-1.81 (m, 1H), 1.75 (dd, $J = 12.0$, 3.0 Hz, 1H), 1.71-1.57 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.0, 130.8, 124.4, 97.5, 85.7, 79.8, 58.8, 55.9, 50.8, 48.5, 34.9, 34.7, 33.7, 27.7, 21.8; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{16}$H$_{22}$NO$_4$, 280.1549; found, 280.1552.
**Synthesis of Selenide 97.** To a solution of the lactone 96 (21 mg, 0.075 mmol) in THF (3 mL) at -78 °C was added LDA (2.0 M in heptane/THF/ethylbenzene, 0.15 mL, 0.30 mmol). After stirring the mixture for 1 h at this temperature, a solution of PhSeCl (29 mg, 0.15 mmol) in THF (2 mL) was slowly added. The reaction mixture was stirred at -78 °C for another 12 h and then quenched with saturated aqueous NH₄Cl (1 mL). The mixture was diluted with EtOAc and H₂O, and solid NaCl was then added to saturate the aqueous phase. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated. The residue was subjected to silica gel column chromatography (Et₃N/EtOAc/hexanes, 0.1/7/3) to provide the selenide (28 mg, 86%) as a colorless oil: $[\alpha]_D^{20} = -127.1$ (c 1.40, CHCl₃); $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.72-7.68 (m, 2H), 7.38-7.26 (m, 3H), 6.06 (dd, $J = 9.7$, 3.7 Hz, 1H), 5.84 (ddd, $J = 9.6$, 5.7 Hz, 1.8 Hz, 1H), 4.48 (d, $J = 6.8$ Hz, 1H), 4.15 (d, $J = 6.8$ Hz, 1H), 3.63 (d, $J = 12.1$ Hz, 1H), 3.57 (dt, $J = 6.0$, 3.0 Hz, 1H), 3.50 (d, $J = 9.5$ Hz, 1H), 3.20 (s, 3H), 3.06 (ddd, $J = 12.1$, 3.7, 2.0 Hz, 1H), 2.86 (td, $J = 8.5$, 3.2 Hz, 1H), 2.36 (dd, $J = 16.4$, 8.6 Hz, 1H), 2.16 (td, $J = 8.8$ Hz, 6.4 Hz, 1H), 1.99 (dd, $J = 12.1$, 2.9 Hz, 1H), 1.94-1.88 (m, 1H), 1.82-1.76 (m, 1H), 1.68 (dd, $J = 11.9$, 3.0 Hz, 1H), 1.64-1.52 (m, 2H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 173.8, 136.7, 129.5, 129.2, 129.0, 125.9, 125.0, 97.0, 84.7, 79.5, 58.8, 55.7, 51.0, 48.5, 44.1, 41.3, 34.0, 27.7, 21.8; HRMS-ES (m/z): [M + H]$^+$ calcd for C₂₁H₂₆NO₄Se, 436.1027; found, 436.1019.
Synthesis of Diene Lactone 98. To a solution of selenide 97 (28 mg, 0.065 mmol) in MeOH (8 mL) and H₂O (4 mL) was added NaHCO₃ (11 mg, 0.13 mmol) followed by NaIO₄ (69 mg, 0.32 mmol) at rt. The reaction mixture was stirred for 1 h at this temperature and then methanol was removed in vacuo. The resulting cloudy solution was diluted with H₂O and EtOAc. The aqueous phase was saturated with solid NaCl and the organic phase was separated. The aqueous layer was subsequently extracted with EtOAc and 15% isopropanol in CHCl₃. The combined organic extracts were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude material obtained was purified by silica gel column chromatography (Et₃N/EtOAc/hexanes, 0.1/7/3) to yield diene lactone 98 (15 mg, 84%) as a colorless oil: [α]₂⁰D = −468.6 (c 0.70, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 6.77 (d, J = 9.5 Hz, 1H), 6.14 (dd, J = 9.5, 5.5 Hz, 1H), 5.83 (s, 1H), 4.75 (d, J = 6.9 Hz, 1H), 4.56 (d, J = 7.0 Hz, 1H), 3.88 (dd, J = 5.5, 2.8 Hz, 1H), 3.62 (d, J = 9.6 Hz, 1H), 3.33 (s, 3H), 2.98 (td, J = 8.6, 3.3 Hz, 1H), 2.54-2.43 (m, 2H), 2.33 (dd, J = 11.6, 2.8 Hz, 1H), 2.10-1.98 (m, 1H), 1.97 (dd, J = 11.6, 3.2 Hz, 1H), 1.91-1.84 (m, 1H), 1.74-1.65 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 162.0, 133.5, 124.3, 114.3, 98.1, 86.7, 80.4, 59.1, 56.2, 51.9, 48.5, 37.5, 28.2, 22.1; HRMS-ES (m/z): [M + H]⁺ calcd for C₂₁H₂₀NO₄, 278.1392; found, 278.1385.
Synthesis of (-)-Secu'amamine A (9). To a solution of diene lactone 98 (14 mg, 0.050 mmol) in MeOH (6 mL) was added conc. HCl (0.6 mL). The reaction mixture was then stirred for 5 h at 60 °C. After cooling the mixture to rt, saturated aqueous NaHCO$_3$ (3 mL) was added and methanol was removed under reduced pressure. The resulting cloudy solution was then diluted with H$_2$O and 15% isopropanol in CHCl$_3$. The aqueous phase was saturated with solid NaCl, and the organic phase was separated. The aqueous layer was extracted with 15% isopropanol in CHCl$_3$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Purification of the residue via silica gel column chromatography (hexanes/EtOAc/Et$_3$N, 1/9/0.1) gave (-)-secu’amamine A (9) (11 mg, 93 %) as a colorless oil: $[\alpha]_{D}^{20} = -511.3$ (c 0.15, CHCl$_3$); reported rotation: $[\alpha]_{D}^{20} = -479$ (c 0.15, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 6.76 (d, $J = 9.6$ Hz, 1H), 6.16 (dd, $J = 9.5$, 5.6 Hz, 1H), 5.83 (s, 1H), 3.90 (dt, $J = 5.5$, 2.8 Hz, 1H), 3.70 (d, $J = 9.6$ Hz, 1H), 2.98 (td, $J = 8.6$, 3.7 Hz, 1H), 2.68 (br s, 1H), 2.60-2.47 (m, 2H), 2.34 (dd, $J = 11.6$, 2.8 Hz, 1H), 2.09-2.03 (m, 1H), 1.98 (dd, $J = 11.6$, 3.2 Hz, 1H), 1.94-1.86 (m, 1H), 1.78-1.72 (m, 1H), 1.68-1.60 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.4, 162.1, 134.0, 124.3, 114.1, 87.1, 74.8, 59.5, 52.1, 48.6, 36.9, 28.2, 22.2; HRMS-ES (m/z): [M + H]$^+$ calcd for C$_{13}$H$_{16}$NO$_3$, 234.1130; found, 234.1150.

NMR Data for (-)-Secu’amamine A (9) in Deuteriobenzene: $^1$H NMR (C$_6$D$_6$, 400 MHz) δ 6.07 (d, $J = 9.5$ Hz, 1H), 5.54 (s, 1H), 5.43 (dd, $J = 9.5$, 5.6 Hz, 1H), 3.50 (d, $J = 9.6$ Hz, 1H), 3.18 (dt, $J = 5.5$, 3.0 Hz, 1H), 2.90 (br s, 1H), 2.53 (td, $J = 8.3$, 3.7 Hz, 1H),
2.38 (dt, $J = 9.5, 7.0$ Hz, 1H), 2.13 (td, $J = 8.5, 7.1$ Hz, 1H), 2.05 (dd, $J = 11.4, 2.8$ Hz, 1H),
1.96-1.88 (m, 1H), 1.65-1.54 (m, 1H), 1.52 (dd, $J = 11.4, 3.9$ Hz, 1H), 1.49-1.42 (m, 1H),
1.40-1.34 (m, 1H); $^{13}$C NMR (C$_6$D$_6$, 75 MHz) $\delta$ 172.3, 162.0, 133.5, 124.2, 114.8, 87.0,
75.4, 60.1, 52.3, 48.8, 37.1, 28.9, 22.8.
References:


Chapter 1. Introduction and Background

1.1. Isolation and Biological Activity of the Communesins and Structurally Related Metabolite Perophoramidine

In 1993 Numata and coworkers isolated two unique polycyclic fungal metabolites, communesins A (1) and B (5), from a strain of *Penicillium* found growing on the marine alga *Enteromorpha intestinalis* (Figure 1).\(^1\) It was noted by Mantle and coworkers in 2006 that communesins A and B had been isolated under the names commindolines B and A, respectively, from *Penicillium commune* in the laboratories of Pfizer, UK prior to the publication of Numata et al.\(^2\) Both communesins A (1) and B (5) incorporate a densely functionalized heptacyclic framework bearing two contiguous all-carbon quaternary centers (C7, C8), two aminal functional groups (C6, C9), and an epoxide moiety. The
relative stereochemistry of communesins A and B (except for C21) was elucidated by NOE studies, while the absolute configuration of these compounds was not assigned at that time.

In 2003, Hemscheidt and coworkers reported an alkaloid, nomofungin (9) (Figure 1), which was isolated from the fermentation broth of an unidentified fungus derived from the bark of Ficus microcarpa L. growing on the Manoa campus of the University of Hawaii. The alkaloid was named nomofungin because the fungus sample producing this alkaloid died after isolation of the metabolite. The compound was initially proposed to have an N,O-acetal in the southern part of the molecule, rather than the aminal of communesin B (5). However, it was later found independently by both Stoltz and Funk that this assignment was incorrect, and that nomofungin is actually communesin B (5). After this interesting finding, the communesin natural products started to receive attention, as reflected by the volume of research papers published since 2003 (vide infra). Although Hemscheidt et al. retracted the nomofungin structure in a later publication, their work served to establish the configuration at C21 of 5 using Murata’s J-based NMR method. The researchers also established the absolute configuration of the molecule to be 6R, 7R, 8R, 9S, 11S, 21R utilizing the exciton chirality method.

In recent years, several other communesin derivatives have also been reported (Figure 1). Communesins C (6) and D (7), along with communesin B, were isolated from a Penicillium fungus derived from the sponge Axinella verrucosa. Communesins E (2) and F (8), together with communesins A, B and D, were isolated from the fermentation broth of okara (the insoluble residue of whole soybeans) with Penicillium espansum Link MK-57. Communesin G (3) and H (4) were isolated from Penicillium rivulum Frisvad. As displayed in Figure 1, all of these communesins (A-H) have the same heptacyclic backbone
with two vicinal quaternary carbons and two aminal groups. These compounds differ only in the substituents at N15 and N16, except for communesin F, which has a double bond between C21 and C22, instead of an epoxide. Most recently, the existence of several new communesin derivatives have been suggested on the basis of mass spectrometry data from an extract of marine-derived *Penicilium expansum*, although the exact structures of these metabolites have not yet been determined.\textsuperscript{10}

The communesins have been shown to have a variety of biological activities. Communesins A and B were found to be cytotoxic against P-388 lymphoid leukemia cells with moderate to potent activity ($ED_{50} = 3.5 \, \mu\text{g/mL}$ and $0.45 \, \mu\text{g/mL}$, respectively).\textsuperscript{1} In addition, communesin B has cytotoxic activity against LoVo and KB cells.\textsuperscript{3} Communesins B, C and D were found to exhibit moderate antiproliferative activity against several leukemia cell lines.\textsuperscript{7} Communesins A, B, E, D and F show insecticidal activity against the third instar larvae of silkworms with $LD_{50}$ values of 150, 5, 80, 300 and 80 $\mu\text{g/g}$, respectively.\textsuperscript{8}

Perophoramidine (10), a natural product similar in structure and biosynthetic origin (*vide infra*) to the communesins, was isolated in 2002 by Ireland and coworkers from the tropical colonial ascidian *Perophora namei* collected in the Philippines (Figure 2).\textsuperscript{11} Perophoramidine has a hexacyclic skeleton consisting of A to E rings resembling those of the communesins, while the metabolite lacks the azepine G ring. Similar to the communesins, perophoramidine also has adjacent quaternary carbon centers (C4, C20), but the relative stereochemistry of these two stereogenic centers was assigned as *trans*, in stark contrast to the *cis*-related quaternary carbons of the communesins. Interestingly, perophoramidine has *bis*-amidine rather than the *bis*-aminal functionality as seen in the
communesins. A unique feature of perophoramidine lies in the three halogen atoms around the aromatic rings. The absolute stereochemistry of 10 has not yet been established. Perophoramidine was shown to have cytotoxicity against the HCT116 colon carcinoma cell line (IC$_{50}$ = 60 µM).

**Figure 2. Structure of Perophoramidine**

1.2. Biosynthetic Considerations of the Communesins and Perophoramidine

About 50 years before the actual isolation of the communesins and perophoramidine, the hexacyclic skeleton (i.e. A to F-rings) of these compounds had been forseen independently by both Robinson$^{12}$ and Woodward$^{13}$ during their studies of the plant-derived *Calycanthaceous* alkaloids. In the biogenetic pathway proposed by these investigators for the formation of the known alkaloid calycanthine 16 (Scheme 1), it was postulated that oxidative dimerization of *N*-methyltryptamine (11) would give an indolenine dimer 12, which after hydrolysis should generate a hypothetical tetra-amino bis-aldehyde 14. Interestingly, besides the calycanthine skeleton 16, aminal formation from the indolenine dimer 12 or the amino aldehyde 14 would furnish another four possible isomers (13, 15, 17 and 18) which were unknown compound types at that time. Remarkably, except for 13, structural motifs 15,$^{14}$ 17$^{15}$ and 18 are all now represented by natural products isolated since then. In particular, the skeleton 18 is incorporated in the ring framework of
the communesins and perophoramidine, which implies a biosynthetic relationship between the communesins and the *Calycanthaceous* alkaloids.\textsuperscript{16}

![Scheme 1](image-url)

More specifically, dimerization of tryptamine 19 should produce both the C\textsubscript{2}-symmetric isomer 20 and the *meso* isomer 22 (Scheme 2). By the same process described in Scheme 1, isomers 20 and 22 would generate hexyclic intermediates 21 and 23 possessing *cis* and *trans* vicinal quaternary carbons, respectively. The hexacycle 21 with the *cis*-related vicinal quaternary carbons would lead to the communesins, while 23 with the *trans* quaternary centers would lead to perophoramidine.
Mantle and coworkers have provided some experimental evidence for the putative biogenetic pathway outlined above for the communesins. On the basis of labeling studies, these researchers proposed that biosynthesis of the communesins commences with decarboxylation of tryptophan (24) to give tryptamine (19), which, in the presence of dimerase and methylase, furnishes 25 (Scheme 3). This process presumably involves oxidative dimerization of 19 to form 20. The C₂-symmetric indolenine dimer 20 then leads to intermediate 25 through hydrolysis, recyclization and methylation. Although it remains unclear how 25 is transformed into communesin A (1), a biosynthetic sequence including N-acylation, C-prenylation and olefin epoxidation could possibly be involved.
Analogous to the tryptamine dimerization pathway, Stoltz and coworkers have proposed that oxidative combination of the known *Penicillium* fungal alkaloid aurantioclavine (26) with tryptamine (19) would give an indolenine intermediate 27 (Scheme 4). Hydrolysis of the indolenine, followed by aminal formation, could produce the heptacyclic compound 28 which would be transformed to the communesins.

**Scheme 4**

![Scheme 4](image)

Despite the remarkable simplicity of the dimerization-based biosynthetic approaches outlined above, it is, however, impractical to directly adapt them to laboratory syntheses of the communesins and perophor amidine due to the expected lack of stereochemical control in the dimerization event. In 2003, Stoltz and coworkers proposed an alternative communesin biosynthetic pathway relying on a hetero Diels-Alder reaction to install the *cis*-vicinal quaternary centers of this family of alkaloids (Scheme 5). This pathway requires formation of a heterodiene like *N*-acyl-aza-*ortho*-xylylene 29, which could possibly be derived from tryptamine (19) via a biological oxidation. This electron deficient diene 29 can then react with aurantioclavine (26) in an *exo* mode through an inverse-demand Diels-Alder reaction to generate the highly strained bridged lactam 30. The highly twisted lactam should be readily opened by the appended primary amine to
produce the spirolactam 31. Reductive cyclization of the secondary amine in the G-ring on the lactam would provide hepacycle 28, which should eventually lead to the different communesins.

To investigate the feasibility of the hetero Diels-Alder step in this hypothetical biosynthetic route, a heterodiene 33, generated in situ from the precursor 32, was reacted with indole 34, the N-Boc-1-methyl derivative of (±)-aurantioclivine (Scheme 6). The desired intermolecular Diels-Alder cycloaddition proceeded smoothly, furnishing the pentacycle 35 bearing the C, D, E, F, and G-rings of the communesins in high yield. However, this reaction showed no diastereoselectivity with regard to C11.
Also relying on a strategy involving a hetero Diels-Alder addition, Funk and coworkers proposed a related biosynthetic route for the communesins through a cycloaddition of a prenylated N-methyl tryptamine 36 and the oxidized tryptamine 29 (Scheme 7). An *exo* mode of addition here would form adduct 37 with the vicinal carbon centers possessing the communesin stereochemistry. Translactamization of the bridged lactam 37 would then give spirolactam 38 which would lead to various communesins. It should also be noted that an *endo* mode addition of 36 and 29 would result in the perophoramidine stereochemistry. This type of hetero Diels-Alder reaction served as the pivotal step in Funk’s total synthesis of (±)-perophoramidine (*vide infra*).17

![Scheme 6](image)

![Scheme 7](image)

1.3. Synthetic Approaches to the Communesins and Perophoramidine by Other Research Groups

The intriguing structures of the communesins and perophoramidine, as well as the promising biological activity of these alkaloids, have elicited synthetic effort from several research groups. The primary challenges to synthesize these alkaloids are to construct the
vicinal quaternary centers and the two aminal/amidine functionalities. Different strategies to address these problems have been investigated by several groups in a number of publications including model studies and total syntheses of the communesins and perophoramidine. The Funk and Adlington groups have been working on an intramolecular hetero Diels-Alder addition strategy to construct the polycyclic framework and the vicinal quaternary centers of the communesins.\(^5,18,19\) The Qin group developed a novel intramolecular cyclopropanation/ring opening sequence to form a pentacycle and one quaternary stereocenter of the communesins,\(^20\) and accomplished the first total synthesis of (±)-communesin F.\(^21\) Regarding the synthesis of perophoramidine, the Funk group achieved the first assembly of this molecule using an intermolecular hetero Diels-Alder reaction as a key step.\(^17\) Rainier disclosed an approach to the unnatural dehaloperophoramidine showcasing a cyclization strategy involving 2-thioindole derivatives.\(^22\)

**1.3.1. Funk’s Intramolecular Diels-Alder Addition Approach to the Communesins**

Complementary to Stoltz’s intermolecular Diels-Alder approach to the core ring system of the communesins as described in Scheme 6, Funk and Crawley made use of an intramolecular hetero Diels-Alder reaction to access the pentacycle and one of the quaternary centers of the communesins.\(^5,18\) In one of their model studies, an aziridine 39 was used as the Diels-Alder cycloaddition precursor (Scheme 8).\(^18\) Treatment of 39 with fluoride induced removal of the Teoc group and triggered opening of the aziridine ring to form the putative \textit{aza-ortho-}xylylene intermediate 40. Cycloaddition of the diene moiety of 40 with the tethered indole double bond proceeded in an \textit{endo} fashion to give pentacyclic adduct 41. Gold (I) catalyzed intramolecular hydroamination of 41 installed the azepine
G-ring, providing a hexacycle 42 with the B, C, D, E, F, and G rings and one quaternary center of the communesins. Moreover, it was expected that the alkene moiety of 42 would provide a handle for the introduction of the C21 epoxide substituent, and the methyl ester could be used to install the pyrrolidine A ring of the communesins.

1.3.2. Adlington’s Intramolecular Diels-Alder Reaction Strategy for the Communesins

As discussed in the previous sections, the idea of using hetero Diels-Alder reactions to access the core ring system of the communesins has been examined by both Stoltz (intermolecular reaction) and Funk (intramolecular addition). In both cases, one of the two vicinal quaternary centers was formed during the Diels-Alder addition. Adlington and George proposed that by having a properly substituted substrate, the two vicinal quaternary centers could be formed simultaneously via an intramolecular hetero Diels-Alder reaction. Thus, they prepared amino alcohol 43 as the Diels-Alder precursor (Scheme 9). Treatment of 43 with CDI formed the activated carbamate intermediate 44. Subsequent
loss of carbon dioxide and imidazole anion presumably gave rise to a stabilized allylic carbocation 45. Intramolecular attack of C3 of indole on the carbocation center would give a spirocyclic indolenium ion, which could be trapped by the neighboring NHBoc moiety to afford product 47 possessing the two vicinal quaternary centers as a single isomer, albeit in only moderate yield. Alternatively, formation of the pentacycle 47 can be rationalized by invoking a hetero Diels-Alder pathway. Thus, loss of a proton from the cationic intermediate 45 would give a hetero diene aza-ortho-xylyene 46. This reactive species could undergo a [4+2]-cycloaddition with the indole double bond to give 47. Unfortunately, the relative stereochemistry of the two vicinal quaternary carbons in 47 is opposite to that present in the communesins. Therefore, extra steps are necessary to correct this issue if this strategy were to be used for a total synthesis of the communesins.

Scheme 9
1.3.3. Qin’s Total Synthesis of (±)-Communesin F

In 2007, Qin and coworkers completed the first total synthesis of a communesin alkaloid in the form of racemic communesin F (8).\textsuperscript{21} Their synthesis commenced with the known 4-bromotryptophol (48) and several straightforward steps led to 49 (Scheme 10). The key step involved a Cu(I)-catalyzed intramolecular cyclopropanation of the diazoester 49 to form a stable azido cyclopropane 50. Reduction of the azide moiety of 50 with PBU\textsubscript{3} in aqueous THF initiated ring opening of the cyclopropane, presumably generating an iminium ion intermediate 51. Spontaneous cyclization of the pendant aniline upon the iminium ion moiety furnished the pentacycle 52 in good yield as a single stereoisomer. Aminal protection then provided methyl carbamate 53. Interestingly, it was found that the configuration at C9 of \textit{trans}-fused lactone 53 could be easily inverted to form the \textit{cis}-isomer 54 by treatment with DMAP in DCM, whereas in the previous step the presence of DMAP in chloroform did not cause any inversion. However, the stereochemistry at C9 is inconsequential to subsequent lactone enolate formation. To install the second quaternary center, lactone 54 was alkylated following the lactone allylation protocol previously used by the Weinreb group in some model studies.\textsuperscript{23} Thus exposure of the lactone 54 to NaH and allyl bromide in DMF at 0 °C furnished the O-allyl intermediate 55, which is similar to what had been observed by the Weinreb group.\textsuperscript{24} Increase of the reaction temperature to 65 °C promoted a Claisen rearrangement, delivering the desired C-allyl product 56 with the allyl group being transferred from the less hindered convex face of the molecule.
To complete the synthesis, lactone 56 was converted to spiro γ-lactam 57 via a series of straightforward transformations (Scheme 11). A microwave-assisted Heck reaction then converted the aryl bromide moiety of bromide 57 to a tertiary allylic alcohol, which upon treatment with PPTS, undergoes an intramolecular allylic substitution to form the azepine G-ring of hexacycle 58 stereoselectively. To facilitate B-ring formation, the spiro lactam moiety of 58 was first converted to the ethyl imidate 59 using Meerwein’s reagent. Removal of the Boc group of imidate 59 liberated the secondary amine which was heated with silica gel in MeOH to effect cyclization onto the ethyl imidate moiety, providing the heptacyclic amidine 60. The methoxy carbonyl group on the southern aminal of 60 was removed at this point. Subsequent reduction of the northern amidine moiety with NaBH₄ formed the aminal which without isolation was acylated to give (±)-communesin F (8).
1.3.4. Funk’s Total Synthesis of (±)-Perophoramidine

The first, and thus far only, total synthesis of perophoramidine was completed in 2004 in racemic form by Funk and Fuchs.\(^\text{17}\) Their synthesis relied on an intermolecular hetero Diels-Alder reaction to construct the trans-vicinal quaternary carbon centers found in perophoramidine (Scheme 12). Thus, 3-bromo-2-oxindole 62 was transformed \textit{in situ} to a hetero diene \textit{N}-acyl-aza-ortho-xylylene 63, which was trapped with 3-alkylindole 61, in a Diels-Alder cycloaddition to give indolenine 65 in high yield and with excellent diastereoselectivity (89%, \(\text{dr} > 20:1\)). The reaction presumably occurs through an \textit{endo} [4+2]-cycloaddition pathway, initially affording a highly strained lactam 64, which undergoes rapid ring opening and proton transfer to give lactam 65. To activate the lactam moiety of 65 for ring opening, the lactam was converted to an \textit{N}-Boc imide. Reduction of the azide moiety initiated a cascade process involving translactamization and cyclization of the resulting NHBoc moiety onto the indolenine to provide the pentacyclic aminal 66. Treatment of 66 with NCS in the presence of AcOH successfully delivered the dichlorinated product 67. Direct introduction of the northern amidine functionality from an
N-methyl derivative of spiro lactam 67 proved to be problematic. Therefore, a less direct route was required. Compound 67 was converted to the six-membered cyclic imidate 68 in several steps. Removal of the nosyl group formed the secondary amine which cyclized onto the imidate moiety to form amidine 69. Oxidation of the lower aminal of 69 then gave (±)-perorphoramidine (10).

Scheme 12
1.3.5. Rainier’s Synthesis of Dehaloperophoramidine

In 2006, Rainier and coworkers described a synthesis of unnatural (±)-dehaloperophoramidine (75) (Scheme 13).\textsuperscript{22} Their strategy features an intramolecular enamine alkylation of a 2-thioindole derivative to form a spiro indolenine, thereby installing one of the quaternary carbon centers. Thus, reduction of 70 provided the corresponding α-hydroxy amide which, upon mesylation, cyclized \textit{in situ} to give spiro lactam 71 as a 1:1 mixture of diastereomers. The existence of 71 as a diastereomeric mixture turns out to be inconsequential. Treatment of the mixture with DBU gave the pentacyclic amidine 72 as a single stereoisomer in 79% overall yield from 70. The presence of DBU presumably caused interconversion between the two isomers and one cyclized to form the pentacycle 72. Enolate formation of the lactam 72, followed by alkylation, afforded 73 having the desired relative configuration required in perophoramidine. It is worth pointing out that in Qin’s synthesis of (±)-communesin F, alkylation of lactone 54 with a lower aminal moiety gave the allylated product with opposite relative stereochemistry as compared to alkylation of lactam 72. The presence of a southern amidine moiety in 72 changes the conformation of the pentacycle and thus switches the facial selectivity of the alkylation process. After several steps, lactam 73 was transformed to imidate 74, a compound quite similar to Funk’s late stage intermediate 68. Removal of the Boc group of 74 with TFA led to cyclization of the resulting amine onto the imidate, introducing the upper bicyclic amidine functionality. Interestingly, if C12 remains as an amidine instead of an aminal as shown in 74, the same type of cyclization does not occur. Hydrolysis of the methyl carbamate, followed by oxidation of the resulting aminal, provided (±)-dehaloperophoramidine (75).
1.4. Previous Synthetic Studies on Perophoramidine and the Communesins in the Weinreb Group

1.4.1. Heck/Carbonylation Cascade Strategy

The Weinreb group was among the first to work on syntheses of perophoramidine and the communesins.\textsuperscript{23,24} Initial investigations were directed towards developing a synthetic route to perophoramidine. The strategy involved a halogen-selective tandem Heck reaction/carbonylation and a diastereoselective C-allylation to introduce the two vicinal quaternary carbon centers of perophoramidine. In one example studied, compound 76 was exposed to Heck/carbonylation conditions to give oxindole 77 in good yield (Scheme 14). Desilylation of 77 and subsequent acid catalyzed lactonization at elevated temperature formed spiro lactone 78. Treatment of 78 with NaH and allyl bromide in DMF at 70 °C gave the allylated product 79 as a single diastereomer. The stereochemistry of the alkylated lactone was initially determined to be as shown in 81, possessing perophoramidine relative configuration at the two vicinal quaternary centers.\textsuperscript{23} However, this assignment turned out to be incorrect because an NOE signal was misinterpreted.\textsuperscript{24}
Lactone 79 was converted into amide 80 by treatment with the aluminum amide derived from ammonium chloride and trimethylaluminum. An X-ray analysis was performed on 80, confirming that the allylated lactone 79 in fact has the communesin stereochemistry.\textsuperscript{24}

Since the key lactone alkylation of a substrate like 78 intended for a perophoramidine synthesis actually produced a compound with the communesin relative configuration, this result suggested that it might be possible to adapt the chemistry outlined above to a synthesis of the communesins simply by varying the substitution pattern in the two aromatic rings. Thus, Heck substrate 82, bearing functional groups in the C and F rings suitable for a communesin synthesis, was prepared and subjected to Heck/carbonylation reaction conditions (Scheme 15).\textsuperscript{24} After substantial optimization, the best result attained was formation of equal amounts of 83 and 84 in low yield along with a
small quantity of ester 85. Under most other experimental conditions, the Heck/carbonylation sequence led to the reduced compound 84 as the major or sole product rather than the desired ester 83. Related examples of reductive Heck reactions are preceded in the literature. For example, during a study of intramolecular Heck reactions of nitroolefin substrates, Denmark and coworkers observed a similar tendency for the formation of the reduced Heck products.25

Therefore, to prevent the reductive Heck reaction from occurring, it seemed necessary to avoid the presence of the electron withdrawn nitro group in the C-ring during the Heck/carbonylation event. Thus, a new substrate 86 bearing a PMP-protected hydroxymethyl group in the aromatic C-ring was prepared.24 From this substrate, the required C-ring nitrogen would be installed via a Curtius rearrangement at a late stage. Compound 86 underwent smooth tandem Heck cyclization/carbonylation to produce the desired lactam ester 87 as a single stereoisomer (Scheme 16). Desilylation of 87 with TBAF followed by cyclization led to lactone 88 as a 2:1 mixture of diastereomers. It was
discovered at this stage that the enolate of lactone 88 does not actually undergo a direct C-alkylation, but rather, treatment with sodium hydride in DMF along with allyl iodide at room temperature afforded the chromatographically isolable ketene acetal 89 in 57% yield. Heating ketene acetal 89 at 130 °C in either DMF or toluene initiated a Claisen rearrangement, producing a separable mixture of diastereomeric C-allylation products 90 and 91, albeit with poor diastereoselectivity in both cases. In hindsight, it was believed that the alkylation process described in Scheme 14 also involves an initial O-allylation and a concomitant thermal Claisen rearrangement, although the ketene acetal intermediate was not isolated in that case.

In view of the disappointing stereochemical outcome in the rearrangement of 89, it was decided to examine the influence of different substituents at the C12a position on the
level of stereoselectivity of the lactone alkylation. One example commenced with Heck substrate 92 which contains a carbamoyl-protected phenol in the F-ring.\textsuperscript{24} The tandem Heck cyclization/carbonylation of this substrate proceeded cleanly to generate the requisite lactam ester 93 as a single diastereomer (Scheme 17). Removal of the MOM protecting group of 93 with methanolic HCl followed by cyclization gave the desired spiro lactone 94. As expected, O-allylation of the spiro lactone 94 gave ketene acetal 95. Heating 95 in DMF at 110 °C led to a mixture of stereoisomers 96 and 97 in a ratio of 2.3:1, showing no improvement over the system in Scheme 16. Gratifyingly, however, a synthetically useful 9.8:1 mixture of 96 and 97 was obtained by heating ketene acetal 95 in toluene.

\textbf{Scheme 17}
1.4.2. Intramolecular Heck Cyclization of Tetrasubstituted Alkenes

The chemistry outlined in the preceding sections has shown some success towards syntheses of the communesins. However, the efficiency of the Heck/carbonylation and the lactone alkylation steps depend highly on the substituents in the two aromatic rings. In addition, the reproducibility of large-scale Heck/carbonylation reactions was often an issue under the conditions carefully optimized for small scale reactions. These problems hindered further development of this methodology into a viable synthetic route to the communesins.

In view of these problems, a new strategy was explored involving an intramolecular Heck reaction of a tetrasubstituted alkene such as 98 to form a spirocyclic enamine derivative 99 having the C7 quaternary carbon (Scheme 18). Since the tetrahydropyridine ring of 98 already incorporates C9 of the communesins, a carbonylation of the Heck intermediate is not necessary, thus bypassing a problematic step. Moreover, the Heck cyclization product 99 possesses an enamine functionality which might be utilized as a handle to introduce the second (C8) quaternary center. It should be noted that examples of intramolecular Heck reactions of tetrasubstituted double bonds are relatively uncommon and their application in natural product synthesis is rare. In the following sections, the reactions of two Heck substrates with different C12a substituents (X = CH₂OSiR₃ and Br) will be presented.
1.4.2.1. The TBS-Protected C-12a Hydroxymethyl Substrate

Heck substrate 100 possessing a TBS-protected hydroxymethyl at the C12a position was prepared via chemistry as described below in Scheme 34.\textsuperscript{26,28} Subjection of 100 to the Heck reaction conditions shown in Scheme 19 produced the desired spirocyclic enamides 101. Catalytic hydrogenation of the nitro group followed by treatment of the resulting amine with (Boc)\textsubscript{2}O furnished N-Boc aniline 102 in good overall yield. Exposure of 102 to alane-dimethylethylamine complex effected partial reduction of the lactam, and \textit{in situ} cyclization of the appended NHBoc moiety to produce the desired pentacyclic Boc-protected aminal 103 as a single stereoisomer in good yield.\textsuperscript{29} The cyclization step is probably under thermodynamic control, stereoselectively generating the more stable C6/7 \textit{cis}-isomer 103 possessing a 5,6-fused E/D ring system embedded in the pentacycle. To introduce the C8 quaternary carbon, an enamine alkylation approach was then investigated. Thus, enamide 103 was treated with excess \textit{n}-butyllithium at low temperature, generating the cup-shaped lithio enamine intermediate 104.\textsuperscript{30} Subsequent alkylation of 104 with allyl iodide occurred from the less congested convex face to form 105 having the communnesin relative stereochemistry at the two vicinal quaternary carbons, along with a small amount of the \textit{N}-allyl enamine 106.
With pentacyclic imine 105 in hand, it was envisioned that the heptacyclic framework of the communesins could be constructed through initial formation of the northern aminal A/B-ring system. Subsequent installation of an appropriate side chain using the hydroxymethyl handle in the F ring would finally lead to construction of the azepine G-ring. Toward this goal, oxidative cleavage of the allyl group was necessary. Prior to this operation, it was decided to convert the sensitive imine functionality to an \( \alpha \)-ethoxycarbamate, which would not only mask the imine but also provide a convenient functional handle to facilitate later formation of the northern aminal. Thus, compound 105 was treated with diethyl pyrocarbonate in EtOH, providing the desired \( \alpha \)-ethoxycarbamate 107 as a mixture of diastereomers together with a significant amount of aldehyde 108 (Scheme 20). Formation of this aldehyde seems surprising at first glance. However, inspection of models revealed that there is a close proximity between the siloxymethyl
group at C12a and the electrophilic N-acyliminium ion functionality in the intermediate leading to 107. Thus, intramolecular hydride transfer between these two sites is facile, resulting in formation of aldehyde 108. It turns out that N,O-acetal 107 also tends to rearrange to the aldehyde 108 during purification. Thus, the crude product mixture of 107 and 108 was carried through to the next steps. A straightforward three step sequence involving dihydroxylation, oxidative cleavage, and reduction provided the desired alcohol 109 in 45% yield based on imine 105. Diol 110 derived from aldehyde 108 was also isolated in 30% yield. In an attempt to continue the synthesis, alcohol 109 was first converted to the corresponding azide under Mitsunobu conditions. This azide was then reduced by catalytic hydrogenation, and the resulting amine was protected in a one-pot reaction to afford carbamate 111. Unfortunately, it was not possible to cyclize pentacycle 111 to hexacycle 112 bearing the desired northern aminal under various reaction conditions. Instead, under acidic conditions, hydride migration from the C11 methylene group occurred to give an aldehyde by-product analogous to 108.
1.4.2.2. The C12a Brominated Substrate

It was apparent that the major issue associated with the siloxymethyl series of compounds is formation of the undesired aldehyde by-products like 108 due to intramolecular hydride transfers. A solution to this problem would be to substitute the C12a position with a bromine, which will entirely eliminate the possibility of this hydride migration. In addition, the C12a bromine substituent can also serve as a versatile functional handle for the introduction of an appropriate side chain for G-ring construction. As discussed above, in Qin’s total synthesis of (±)-communesin F, a C12a bromine group was utilized to install an allylic alcohol side chain via a Heck reaction (cf. Scheme 11).21
Therefore, Heck substrate 113 was prepared and exposed to the optimized experimental conditions shown in Scheme 21 to yield the desired product 114 and a pentacyclic by-product 115 as a 6.7:1 mixture in 51% total yield, along with 40% of recovered starting material. Increasing the reaction temperature or allowing the reaction to proceed longer did lead to consumption of more starting material but dramatically increased the amount of the pentacyclic by-product. The pentacycle 115 arises from an intramolecular Heck arylation of aryl bromide 114. The desired Heck product 114 was then converted to α-ethoxy carbamate 116 in a route analogous to the one used for the TBS-protected hydroxymethyl substrate (cf. Scheme 20). To our surprise, dihydroxylation of alkene 116 followed by oxidative diol cleavage with periodate did not give rise to the desired aldehyde. Instead, hexacyclic acetal 117 was produced in 46% overall yield as a mixture of epimers. This acetal could be hydrolyzed to the hemiacetal 118 in good yield. However, several attempts to achieve reductive aminations of lactol 118 were unsuccessful.
Chapter 2. Results and Discussion

I took over the communesin project from my colleague Jae Hong Seo after he graduated in 2008.\textsuperscript{28} As discussed above, Dr. Seo successfully prepared hexacyclic hemiacetal 118 which already bears the communesin AB ring system incorporating an $N,O$-acetal rather than the desired aminal. It was still very attractive to attempt to apply a reductive amination sequence to 118 to install the desired northern aminal functionality. Dr. Seo did try a few reductive amination conditions without much much success, although the availability of 118 was limited at that time. Our initial plan therefore was to accumulate more of the hemiacetal 118 and try other methods to effect this transformation. However, we soon realized that the two-step sequence to form the cyclic acetal 117 from 116 is problematic. First, the sequence is not a clean transformation due to the formation of several byproducts that are hard to separate by column chromatography. Second, the yield of 117 was irreproducible and usually less than 20%. Therefore, we decided to make a major revision to our synthetic plan to develop a more efficient approach to the communesins.

2.1. Revised Retrosynthetic Route for the C-12a Brominated Seires

Retrosynthetically, (±)-communesin F (8) could be derived from spiro lactam 119 via cyclization of the secondary amine moiety onto the A-ring lactam (Scheme 22). The azepine-G ring of 119 could be formed from tertiary allylic alcohol 120 via an intramolecular allylic substitution as had been shown to work for a similar substrate in Qin’s communesin F synthesis.\textsuperscript{21} The allylic alcohol side chain of 120 could be introduced from the C12a bromide functional handle of 121. Spirolactam 121 would be derived from lactam 122 via an azide reduction/tranlactamization sequence. Lactam 122 should be
derived from $N,O$-acetal 116 which had been prepared from the corresponding imine in our previous work. The $N,O$-acetal functionality of 116 is not compatible with oxidative double bond cleavage conditions as evidenced by the low yields obtained in related reactions. Thus, we believed that converting the labile $N,O$-acetal 116 to a more stable lactam prior to oxidative double bond cleavage would solve this problem.

It should also be noted that we have made a major adjustment in this new retrosynthetic plan in terms of the ring forming sequence to access the heptacyclic framework of the communesins. Previously, since we established a viable route to prepare a pentacycle like $\alpha$-ethoxycarbamate 116 possessing the B, C, D, E and F rings of the communesins, we had been exploring a route to build the A-ring onto a pre-existing B-ring to form the northern aminal, and the azepine G-ring would be installed after formation of the A-ring. Thus, the previous ring forming sequence can be described as B $\rightarrow$ A $\rightarrow$ G. Due to the difficulties to access intermediate 118, we decided to adopt a ring forming sequence like that reported by Qin et al. in their total synthesis of (±)-communesin F.$^{21}$ Thus, the
current plan would involve formation of the A-ring spirolactam of 121 at the expense of the B-ring lactam of 122. Reformation of B-ring would be necessary after construction of the azepine G-ring. The revised ring forming sequence is thus B → A → G → B as illustrated in Scheme 22.

2.1.1. Synthesis of a Brominated Lactam Substrate

With N,O-acetal 116 already in hand, the most direct way to convert this compound to a lactam would be hydrolysis of the N,O-acetal moiety to a hemiaminal and oxidation of the resulting hydroxyl group. Thus, hydrolysis of the N,O-acetal 116 using PPTS in wet chloroform yielded the desired hemiaminal 123 in moderate yield (Scheme 23). Oxidation of hemiaminal 123 to lactam 124 turned out to be problematic. Different oxidation methods including Dess-Martin, Swern and Jones oxidations were tried, but to no avail. This failure is presumably due to the congested environment of the hydroxyl group in the cup-shaped molecule 123, with the convex face now shielded by the allyl chain.

Scheme 23

In view of the oxidation problem, we considered the possibility of producing a lactam from an intermediate before 116, and the enamine 128 (Scheme 25) seemed to be a competent candidate for this purpose. A literature search revealed that reaction of cyclic N-methyl enamine 125 with cyanogen azide efficiently produced cyanogen amidine 126 which was then hydrolyzed under acidic conditions to give lactam 127 in moderate yield.32
Cyanogen azide is notorious for explosiveness due to its high nitrogen content, and thus has found limited use in organic synthesis. However, the mild reaction conditions needed to convert enamine 125 to the stable cyanogen amidine intermediate 126 prompted us to try this reaction. Thus, a dilute solution of cyanogen azide in acetonitrile was prepared and carefully manipulated according to literature procedures. Gratifyingly, addition of this NCN₃ solution to enamine 128 provided cyanogen amidine 130 as a single stereoisomer in nearly quantitative yield (Scheme 25). The structure and stereochemistry of 130 were established by HMQC, HMBC and NOESY-NMR experiments, although the orientation of the cyano group could not be determined via NMR techniques. This transformation presumably occurs via an initial [3+2]-dipolar cycloaddition of the enamine to afford adduct 129, which upon evolution of N₂ gas and 1,2-hydrogen shift gave 130. Basic hydrolysis of the imine moiety of 130 then provided the desired lactam 131 in moderate yield. The structure and stereochemistry of lactam 131 were confirmed by HMQC, HMBC and NOESY-NMR data.
2.1.2. Alkylation of the Brominated Lactam Substrate

With lactam 131 in hand, we planned to next install the second quaternary center via a lactam enolate alkylation process. However, it was necessary to first protect the lactam NH to prevent undesired N-alkylation. A Boc group was thus installed onto the lactam to give N-Boc imide 132 in high yield (Scheme 26).

With the N-protected lactam 132 in hand, treatment with LDA followed by addition of 1-azido-2-iodoethane did not provide the desired alkylation product 133 (Scheme 27). Addition of freshly distilled HMPA as a cosolvent was not helpful. Moreover, treatment of N-Boc lactam 132 with potassium t-butoxide followed by addition of freshly prepared nitroethylene did not give the desired conjugate addition product (Scheme 28). Instead, C8 epimerized lactam 134 was isolated as the major product, along with a small amount of lactam 131 resulted from loss of the Boc group from the starting material.
After some experimentation, it was discovered that enolization of lactam \textbf{132} with potassium \textit{t}-butoxide, followed by addition of allyl iodide delivered the desired \textit{C}-allyl lactam \textbf{136} in moderate yield with the desired \textit{C7/8} relative stereochemistry required for the communesins (Scheme 29). Compound \textbf{136} exists as a mixture of carbamate rotamers with broadened $^1$H NMR peaks, which makes it difficult to conduct 2D NMR studies. The structure and stereochemistry of \textbf{136} was eventually deducted by 2D NMR analysis of its derivative \textbf{137} with the \textit{N}-Boc group removed (\textit{vide infra}). Analogous to previous enamine alkylation processes (cf. Scheme 19), the lactam alkylation proceeds via attack of the allyl iodide from the least hindered convex face of lactam enolate \textbf{135}. It is worth noting that the choice of base for the enolate formation is critical. Other strong bases including LiHMDS, KHMDS, LDA and NaH did not give the desired product \textbf{136}. 

\textbf{Scheme 29}
2.1.3. Azide Reduction/Translactamization Cascade with the C-12a Brominated Substrates

With the desired C-allyl compound 136 now in hand, the remaining tasks included oxidative cleavage of the terminal alkene and introduction of an azide functionality. We soon realized that the Boc group on the lactam nitrogen of 136 had to be removed for this purpose. For substrate 136 with the upper Boc group, the double bond dihydroxylation step was not clean, showing multiple spots on TLC analysis. The cleavage reaction is presumably complicated by ring opening of the N-Boc lactam by the adjacent diol initially formed. Loss of the upper Boc group from 132 in the presence of potassium t-butoxide (cf. Scheme 28) hinted that the N-Boc group of the lactam is susceptible to cleavage by base. Thus, a simple basic hydrolysis removed the upper Boc group of 136, cleanly producing 137 in high yield. As noted above, the structure and stereochemistry of lactam 137 were established by HMQC, HMBC and NOESY-NMR experiments. As expected, dihydroxylation of substrate 137 was now a clean transformation. Subsequent oxidative cleavage of the diol, aldehyde reduction, mesylation of the resulting hydroxyl group and azidation delivered the desired azide 122 in excellent overall yield without purification of intermediates.

The next objective in the synthesis was to reduce the azide moiety and initiate an in situ B-ring lactam opening by the resulting primary amine to form a spiro A-ring lactam.
To this end, lactam 122 was activated with a methoxycarbonyl group to provide methyl carbamate 138 (Scheme 31). However, subjection of 138 to either catalytic hydrogenation or Staudinger reduction conditions using trimethyl phosphine at 70 °C did not produce the desired spiro lactam 139.

Alternatively, lactam 122 was activated with a highly electron withdrawing nosyl (p-nitrobenzenesulfonyl) group to give substrate 140 (Scheme 32). Exposure of 140 to the same azide reduction conditions used previously did form the desired spiro lactam 141 in reasonable yield. Before moving forward with 141, we decided to test if the nosyl group could be easily removed. However nosyl deprotection of 141 under Fukuyama’s conditions was problematic. Instead of the desired amine 142, starting material was usually recovered. Harsher conditions or extended reaction times only resulted in decomposition.
2.2. Retrosynthetic Analysis of the BOM-protected C-12a Hydroxymethyl Series

As presented in the preceding section, the azide reduction/translactamization cascade for the C12a brominated substrate was successful only with the N-nosyl lactam 140. However, removal of the nosyl group from spiro lactam 141 turned out to be problematic. The C-12a bromine substituent was chosen only to avoid the undesired hydride transfer issue encountered with the O-protected hydroxymethyl substrate during formation of the α-ethoxycarbamate intermediate 107 (cf. Scheme 20). This series lose its advantage since an N-acyliminium ion is no longer involved in the synthesis. In addition, the key Heck cyclization reaction of the brominated substrate 113 to form 114 is not efficient even under carefully optimized conditions (cf. Scheme 21). In view of the problems associated with the C12a brominated substrate, we decided to revisit the O-protected C-12a hydroxymethyl series since we believed that the chemistry we worked out during exploration of the bromo series should readily apply to the protected hydroxymethyl substrates. However, we decided that different hydroxyl protection other than the previously utilized TBS group needed to be used since the silyl-ether would probably be lost under some of the hydrolysis conditions needed in various steps of the planned synthesis. A BOM group seemed to be appropriate in terms of stability and ease of installation and removal. We thus proposed a retrosynthetic route utilizing a BOM-protected hydroxymethyl substrate.
Therefore, in the retrosynthetic direction, communesin F (8) could be derived from amide 119 via cyclization of the amine moiety onto the A-ring lactam (Scheme 33). The azepine G-ring of 119 could be constructed from 143 via an intramolecular aza-Michael addition of the NHBoc moiety to the enone side chain. The enone side chain of 143 could be introduced from aldehyde 144. Aldehyde 144 would be derived from BOM-ether 145 via deprotection and benzyl alcohol oxidation. Spirolactam 145 could be derived from lactam 146 via an azide reduction/translactamization cascade. Pentacycle 146 would be prepared via a route like that used to make its C-12a brominated counterpart 122.

2.2.1. Total Synthesis of (±)-Communesin F

Using methodology previously developed by Seo to prepare substrates 100 and 113, our synthesis commenced with the known enol triflate 147 which was coupled with 2-nitrobenzeneboronic acid in a Suzuki-Miyaura reaction to afford the arylated product 148 in nearly quantitative yield (Scheme 34). Basic hydrolysis of ester 148 gave the acid 149 which was transformed to the acid chloride and then coupled with readily
prepared iodo aniline 150 (see Scheme 35 for preparation) to yield amide 151 in good overall yield. At this point, the benzyl group of 151 was replaced by an ethoxy carbonyl group using ethyl chloroformate.37 The resulting amide 152 was alkylated to form the N-methyl amide 153. We were pleased to find that tetrasubstituted alkene 153 underwent a clean intramolecular Heck reaction to afford tetracyclic enamide 154 in high yield bearing the C-7 quaternary center of the communesins. After some experimentation, it was found that catalytic hydrogenation of 154 at 40 atm using 5% Pt/C afforded an unstable aniline which was immediately protected as the Boc derivative 155. Lactam 155 was then treated with alane-dimethylethylamine complex to effect a reductive cyclization, yielding the pentacyclic aminal 156 with the requisite stereochemistry at C-6/7 as determined by 2D NMR studies.
Enamide 156 was then hydrolyzed to the corresponding enamine, which was immediately reacted with in situ generated cyanogen azide to afford N-cyanoamidine 157 in excellent overall yield (Scheme 36). The structure and stereochemistry of lactam 157 were elucidated by HMQC, HMBC and NOESY-NMR experiments. Basic hydrolysis of amidine 157 gave lactam 158. Subsequent acylation afforded N-Boc lactam 159 in high yield as a 3:1 mixture of C8 epimers, which is of no consequence to the next step.
Following the similar conditions used to alkylate the brominated compound 132, alkylation of N-Boc lactam 159 could be effected by treatment with potassium t-butoxide at low temperature, followed by addition of allyl iodide to afford the desired product 160 as a single C-8 stereoisomer in high yield. Analogous to the alkylation of the brominated substrate 132, alkylation of lactam 159 also proceeded stereoselectively via attack of the allyl iodide from the least hindered convex face of lactam enolate. Basic hydrolysis removed the Boc group on the lactam nitrogen of 160 to provide 161 in high yield. Similar to the brominated compound 136, 160 also exists as a mixture of rotamers displaying broadened 1H NMR peaks. The structure and stereochemistry of 160 was in fact based on 161 whose structure and stereochemistry were determined by 2D NMR studies. In order to prepare for construction of the upper aminal, 161 was manipulated via a straightforward three-step sequence to form mesylate 162 in high overall yield. Subsequent azidation gave azide 146.
The B-ring lactam of 146 was then acylated with (Boc)₂O to provide N-Boc imide 163 (Scheme 37). Exposure of 163 to PMe₃ in aqueous THF at 70 °C proceeded smoothly to produce the azide reduction/translactamization product 164 in good yield. This result is in stark contrast to the case of C-12a brominated compound 138, which did not undergo this kind of cascade process under the same reaction conditions. Apparently, for some unknown reason, the substituent at the C12a position dramatically influences the reactivity of the N-acyl lactam in this step. Hydrogenolysis of the BOM group was achieved with Pearlman’s catalyst (Pd(OH)₂) to produce the benzylic alcohol 165. However, attempts to oxidize this alcohol to aldehyde 166 were fruitless using either Dess-Martin or TPAP oxidation. In one experiment, oxidation of alcohol 165 with TPAP was carried out in deuterated methylene chloride and monitored by NMR spectroscopy. Although the ¹H
NMR spectrum clearly indicated formation of an aldehyde proton peak within five minutes after addition of TPAP, we could never isolate the desired aldehyde 166.

We suspected that the adjacent NHBoc group might be attacking the initially formed aldehyde to form a hemiaminal. To circumvent this problem, it was necessary to change the reaction sequence. Thus, instead of carrying out the alcohol oxidation after the trans lactamization, we now decided to form the aldehyde and use it to install the requisite side chain before trans lactamization. Toward this goal, hydrogenolysis of the BOM group of mesylate 162 using Pearlman’s catalyst gave the desired alcohol which was converted to aldehyde 167 via Dess-Martin oxidation in good overall yield (Scheme 38). Displacement of the mesylate with sodium azide gave azide aldehyde 168 in moderate yield.

In an effort to improve the overall yield of azide 168 from intermediate 162, an alternative route was developed (Scheme 39). Thus, hydrogenolysis of the BOM group of 162 gave the benzylic alcohol which was silylated to give TBS-ether 169 in good yield over two steps. Azidation of 169 was carried out with LiN₃ in DMF to produce azide 170 in 76% yield. Removal of the TBS group with TBAF afforded the alcohol 171 in excellent yield. Oxidation of 171 with Dess-Martin reagent furnished aldehyde 168 in good yield. The overall yield of 168 following this longer route is 60% over 5 steps, which is higher than the 46% yield obtained when using the three step sequence described in Scheme 37.

With the aldehyde 168 in hand, our plan was to install an α,β-unsaturated carbonyl side chain as a handle to assemble the azepine G-ring. To our surprise, aldehyde 168 was found to be unreactive in Wadsworth-Emmons-Horner or Wittig condensations. Treatment of the aldehyde 168 with various stabilized phosphonium ylides or more reactive phosphonate anions did not produce the desired products even using excess amounts of reagents and elevated temperatures (Scheme 40).
Alternatively, the lactam nitrogen of 168 was protected with a Boc group, affording 172 in good yield (Scheme 41). However, treatment of the protected species 172 with the same phosphonium ylides or phosphonate anions still did not produce any of the desired homologated products.

We then investigated installing the enone side chain via a simple aldol reaction. Thus, upon stirring a solution of aldehyde 168 in acetone with aqueous sodium hydroxide for one hour at room temperature, a polar new spot was detected by TLC, presumably indicating formation of the β-hydroxy carbonyl compound. Stirring the mixture at 60 °C then promoted the dehydration process, affording the desired (E)-enone 173 in 93% yield (Scheme 42).
The B-ring lactam of 173 was then acylated to give N-Boc imide 174 in good yield (Scheme 43). It should be noted that the amount of base used in this reaction had to be carefully controlled to avoid undesired C-acylation of the methyl ketone. Subsequent azide reduction and in situ translactamization proceeded uneventfully to give the desired spiro lactam 175 in high yield.

With enone 175 in hand, we were ready to explore formation of the azepine G-ring of 176 via an intramolecular aza-Michael addition. Towards this end, enone 175 was subjected to a variety of basic or acidic conditions (Scheme 44). However, under basic conditions, starting material was usually recovered. Under acidic conditions, 175 quickly decomposed to unidentifiable compounds.
Another option to construct the azepine G-ring would be to convert the enone to a tertiary allylic alcohol and then effect an intramolecular allylic substitution. In an early example of this process, Hegedus and coworkers showed that tertiary allylic alcohol 177 could be cyclized to tricycle 178 possessing an azepine ring under acid catalysis (Scheme 45). In Qin’s synthesis of (±)-communesin F, an analogous acid catalyzed allylic cyclization was also used to construct the azepine G-ring (cf. Scheme 11).

Thus, the unsaturated ketone 175 was first treated with methyllithium at low temperature to produce allylic alcohol 179 in 73% yield (Scheme 46). Applying the same conditions as used in Qin’s work, exposure of 179 to a catalytic amount of PPTS in chloroform at room temperature led to hexacycle 180 in 62% yield with the formation of the G-ring having the requisite configuration at C-11. The stereochemical outcome of this cyclization is not surprising. Inspection of models reveals that the isopentenol side chain tends to point away from the lactam A-ring in order to minimize steric interactions. Thus, attack of the NHBoc group to the isopentenol side chain occurred through the preferred
conformation shown in 179 to provide 180 with the communesin configuration at C11. In addition, a small amount of the diene 181 resulting from dehydration of starting alcohol 179 was produced, similar to what was observed in the work of Qin et al.21

To complete the synthesis, it was now necessary to form the northern aminal. Toward this end, $\gamma$-lactam 180 was treated with commercially available triethylloxonium fluoroborate and DIEA in methylene chloride in order to form the corresponding ethyl imidate, similar to the conditions reported by Qin et al. Although this reaction produced some of the desired compound, a substantial amount of an unidentified byproduct was formed. Alternatively, the use of trimethylloxonium fluoroborate in the presence of Hunig’s base cleanly generated the desired methyl imidate 182 (Scheme 47). The upper Boc protecting group was found to be much more labile towards acid than the one on the southern aminal. Thus, selective removal of the upper Boc group of 182 was achieved with 5% TFA in DCM. Subsequent basification of the acidic reaction mixture gave the heptacyclic amidine 183. Although Qin et al. have reported that it was necessary to stir an analogous amine with silica gel at 50 °C in order to effect cyclization to the amidine, we observed that simple neutralization of the azepine TFA salt at room temperature was sufficient to produce 183. Reduction of this amidine with sodium borohydride in a mixture of acetic acid and acetic anhydride as done by Qin delivered the hydride stereoselectively
from the least congested back face of 183, and in situ acylation of the resulting aminal yielded the N-acetyl aminal. The crude N-acetyl aminal obtained was next treated with 40% TFA in DCM to remove the Boc protecting group on the lower aminal, affording racemic communesin F (8) which has proton and carbon NMR spectra identical to those reported by the Qin group for the natural product.\textsuperscript{21,39}

\textbf{2.3. Concluding Remarks}

In summary, we have achieved a stereoselective total synthesis of the heptacyclic alkaloid communesin F (8) in racemic form in 30 steps from the known enol triflate 147 and commercially available o-nitrobenzeneboronic acid. Key transformations in the sequence include an intramolecular Heck cyclization of a tetrasubstituted alkene to generate a tetracycle with a quaternary carbon center, a reductive cyclization of an \(N\)-Boc aniline onto an oxindole moiety to form the pentacyclic framework containing the lower aminal, a stereoselective lactam C-allylation to introduce the second quaternary carbon center, and an azide reduction/translactamization cascade eventually leading to the upper aminal functionality.
Chapter 3. Experimental Section

**General Methods.** All non-aqueous reactions were carried out in oven- or flame-dried glassware under an argon atmosphere. All chemicals were purchased from commercial vendors and used as is, unless otherwise specified. Anhydrous tetrahydrofuran (THF) and dichloromethane (DCM) were obtained from a solvent purification system (Glass Contour). Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 250 µm EMD 60 F254 precoated silica gel plates. Preparative TLC was performed with 500 µm EMD 60 F254 precoated silica gel plates. Flash column chromatography was performed using EMD silica gel 60 (230-400 mesh). High-pressure hydrogenation was carried out in a Parr Instrument Series 4680 pressure vessel. $^1$H and $^{13}$C NMR spectral data were recorded on Bruker DPX-300, CDPX-300, or DRX 400 MHz spectrometers. Chemical shifts are reported relative to chloroform (δ 7.24), acetonitrile (δ 1.93) for $^1$H NMR and chloroform (δ 77.0), acetonitrile (δ 1.3) for $^{13}$C NMR.
**Synthesis of Hemiaminal 123.** To a solution of N,O-acetal 116 (10.0 mg, 0.016 mmol) in CDCl₃ (5 mL) containing a small amount of H₂O (10 µL) was added PPTS (0.8 mg, 0.0032 mmol). The reaction mixture was stirred at rt for 12 h. The solvent was removed *in vacuo* and the residue was purified by preparative TLC on silica gel (hexanes/EtOAc, 2/1) to give the hemiaminal 123 (6.0 mg, 64%). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J = 7.7 Hz, 1H), 7.65-7.63 (br, 2H), 7.12-7.05 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 5.80 (br s, 1H), 5.33 (1H), 5.04-4.90 (m, 1H), 4.85 (d, J = 9.5 Hz, 1H), 4.75 (d, J = 9.5 Hz, 1H), 4.44 (br s, 1H), δ 4.10-4.00 (br, 2H), 3.75-3.60 (br, 1H), 2.89 (s, 3H), δ 2.85-2.80 (br, 1H), 2.60-2.50 (br m, 1H), 1.61 (s, 9H), 1.33-1.20 (m, 3H). LRMS-ES (m/z): [M + H]⁺ calcd for C₃₀H₃₇BrN₃O₅, 598.2; found, 598.3.

**Preparation of Cyanogen Azide.** To a solution of cyanogen bromide (536 mg, 5.06 mmol) in CH₃CN (10.0 mL) was added NaN₃ (339 mg, 5.22 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h to give a solution of NCN₃ in CH₃CN (0.50 M) which can be stored at 0 °C for several weeks without noticeable decomposition.
**Synthesis of N-Cyanoamidine 130.** To a solution of the enamine 128 (21.0 mg, 0.045 mmol) in MeCN (5.0 mL) was added NCN$_3$ (0.1 mL, 0.5 M in MeCN, 0.05 mmol, freshly prepared). The solution was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 2/3) to give the cyanoamidine 130 (22.0 mg, 98%). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$ 7.25-7.20 (br, 2H), 7.14 (d, $J = 7.4$ Hz, 1H), 7.07-7.02 (m, 1H), 6.79 (t, $J = 7.9$ Hz, 1H), 6.60 (dd, $J = 0.6, 8.0$ Hz, 1H), 6.11 (br s, 1H), 6.04 (d, $J = 7.5$ Hz, 1H), 4.71 (s, 1H), 3.90-3.82 (m, 1H), 3.69-3.63 (m, 1H), 3.16-3.05 (m, 1H), 2.76 (s, 3H), 2.07 (dd, $J = 4.8, 14.3$ Hz, 1H), 1.46 (s, 9H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$ 172.8, 153.6, 152.8, 137.1, 133.0, 131.1, 130.0, 128.6, 126.9, 126.7, 126.3, 121.6, 118.8, 116.3, 104.0, 82.3, 78.8, 55.5, 44.8, 39.7, 30.2, 29.9, 28.6, 28.5. LRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{25}$H$_{27}$BrN$_5$O$_2$, 508.1; found, 508.3.

**Synthesis of Lactam 131.** To a solution of cyanoamidine 130 (433 mg, 0.852 mmol) in EtOH (50 mL) was added 1 N aqueous KOH solution (50 mL, 50 mmol). The
mixture was stirred at 94 °C for 12 h and then cooled to rt. After removal of EtOH *in vacuo*, the cloudy aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc/Et₃N, 1/1/0.02) to give the lactam 131 (265 mg, 64%).

1H NMR (300 MHz, CDCl₃) δ 7.17-7.09 (m, 3H), 7.02-6.96 (m, 1H), 6.72 (t, *J* = 8.0 Hz, 1H), 6.62 (br s, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.12 (brs, 1H), 5.96 (d, *J* = 7.8 Hz, 1H), 4.54 (s, 1H), 3.84-3.80 (br m, 1H), 3.44-3.40 (br m, 1H), 3.07 (td, *J* = 6.0, 13.5 Hz, 1H), 2.73 (s, 3H), 1.91 (dd, *J* = 3.7, 13.9 Hz, 1H), 1.42 (s, 9H); 13C NMR (75 MHz, CDCl₃) δ 170.7, 153.4, 151.9, 136.1, 132.4, 130.1, 129.7, 127.4, 126.9, 125.9, 121.1, 118.2, 103.2, 81.3, 78.5, 55.4, 46.1, 37.9, 29.6, 28.8, 28.1, 24.6. LRMS-ES (m/z): [M + H]⁺ calcd for C₂₄H₂₇BrN₃O₃, 484.1; found, 484.3.

**Synthesis of N-Boc Lactam 132.** To a solution of lactam 131 (125 mg, 0.26 mmol) in THF (10 mL) was added LiHMDS (0.4 mL, 1.0 M in THF, 0.40 mmol). The mixture was stirred at rt for 10 min and (Boc)₂O (62 mg, 0.28 mmol) was added. The reaction mixture was stirred at rt for another 10 min and quenched with aqueous saturated NaHCO₃. The mixture was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7/3) to give N-Boc lactam 132 (142 mg, 94%).

1H NMR (300 MHz, CDCl₃) δ 7.17-7.11 (m, 3H), 7.02-6.97 (m, 1H), 6.73 (t, *J* = 7.9
Hz, 1H), 6.57 (dd, J = 0.8, 8.0 Hz, 1H), 6.10 (br s, 1H), 5.98 (d, J = 7.4 Hz, 1H), 4.71 (s, 1H), 4.03-3.97 (m, 2H), 3.17-3.06 (m, 1H), 2.73 (s, 3H), 2.05 (dt, J = 3.5, 14.3 Hz, 1H), 1.46 (s, 9H), 1.40 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 169.4, 153.1, 152.0, 136.2, 132.2, 130.3, 129.7, 127.7, 126.7, 126.0, 121.2, 118.3, 103.4, 92.2, 83.2, 81.6, 79.4, 56.3, 48.9, 42.1, 30.2, 29.7, 28.4, 28.1, 27.9, 23.8; LRMS-ES (m/z): [M + H]+ calcd for C29H35BrN3O5, 584.2; found, 584.2.

Synthesis of Epimerized N-Boc Lactam 134. To a solution of N-Boc lactam 132 (20.0 mg, 0.034 mmol) in THF (5.0 mL) was added a solution of KOT-Bu (4.2 mg, 0.037 mmol) in THF (1.0 mL) at rt, followed by the addition of nitroethylene (0.17 mL, 1.0 M in benzene, 0.17 mmol). The reaction mixture was stirred for 1.5 h at rt before aqueous saturated NaHCO3 was added. The mixture was diluted with H2O and extracted with EtOAc. The combined organic layers were dried over Na2SO4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1) to give the epimerized lactam 134 (11.6 mg, 52%). 1H NMR (400 MHz, CDCl3) δ 8.27 (d, J = 5.1 Hz, 1H), 7.09-7.01 (m, 3H), 6.73 (t, J = 8.0 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.13 (d, J = 7.6 Hz, 1H), 5.86 (br s, 1H), 4.29-4.23 (m, 1H), 3.89-3.83 (m, 1H), 3.70-3.60 (m, 1H), 2.93 (s, 3H), 2.52-2.46 (m, 1H), 2.41-2.36 (m, 1H), 1.60 (s, 9H), 1.46 (s, 9H); LRMS-ES (m/z): [M + H]+ calcd for C29H35BrN3O5, 584.2; found, 584.2.
Synthesis of Allylated N-Boc Lactam 136. To a solution of N-Boc lactam 132 (65 mg, 0.11 mmol) in THF (6.0 mL) was added a solution of KOt-Bu (14 mg, 0.12 mmol) in THF (0.5 mL) dropwise at rt, followed by the addition of allyl iodide (0.15 mL, 1.0 M in THF, 0.15 mmol). The reaction mixture was stirred at rt for 30 min before aqueous saturated NaHCO₃ was added. The mixture was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 4/1) to give the C-allyl lactam 136 (47 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, J = 6.2 Hz, 1H), 7.43 (d, J = 6.2 Hz, 1.3H), 7.10-6.90 (m, 7H), 6.75-6.65 (m, 2.6H), 6.60-6.47 (m, 2H), 6.19 (d, J = 7.7 Hz, 1H), 6.03 (d, J = 7.7 Hz, 1.3H), 5.62 (br s, 1H), 5.70-5.60 (br, 2H), 5.60-5.50 (m, 1.3H), 5.10-5.00 (m, 2.5H), 4.90-4.80 (m, 2H), 4.45-4.40 (m, 1H), 4.30-4.20 (m, 3H), 3.90-3.80 (m, 2.3H), 3.70-3.60 (m, 2H), 3.15-3.00 (m, 1H), 2.93 (s, 3H), 2.85 (s, 3.9H), 2.70-2.55 (m, 1H), 2.40-2.30 (m, 1.3H), 2.15-2.00 (m, 2.6H), 1.52 (s, 9H), 1.37 (s, 12 H); LRMS-ES (m/z): [M + H]⁺ calcd for C₃₂H₃₉BrN₅O₅, 624.2; found, 624.3.
Synthesis of NH Lactam 137. To a solution of the N-Boc lactam 136 (20.0 mg, 0.032 mmol) in EtOH (4.0 mL) was added 1 N aqueous KOH solution (0.2 mL, 0.20 mmol). The mixture was stirred at 80 °C for 13 h and then cooled to rt. After removal of EtOH \textit{in vacuo}, the cloudy aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc, 7/3) to give the NH- lactam 137 (15.0 mg, 91%). \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 8.42 (t, \(J = 4.0\) Hz, 1H), 6.92 (br, 3H), 6.71(t, \(J = 7.9\) Hz, 1H), 6.53 (d, \(J = 7.9\) Hz, 1H), 6.21 (d, \(J = 7.7\) Hz, 1H), 5.81-5.76 (m, 1H), 5.66 (s, 1H), 5.64 (s, 1H), 4.88-4.82 (m, 2H), 3.59 (td, \(J = 4.0, 12.9\) Hz, 1H), 3.35-3.32 (m, 1H), 2.94 (s, 3H), 2.85 (d, \(J = 5.2\) Hz, 2H), 2.61 (td, \(J = 5.5, 13.2\) Hz, 1H), 2.07-2.02 (m, 1H), 1.44 (s, 9H); \(^1\)C NMR (75 MHz, CDCl₃) \(\delta\) 174.2, 154.7, 154.2, 152.7, 138.1, 134.4, 132.3, 130.6, 129.5, 128.0, 126.2, 126.0, 124.0, 123.8, 118.7, 116.9, 105.5, 82.9, 81.5, 59.5, 48.6, 41.0, 40.0, 31.3, 29.5, 28.2; LRMS-ES (\(m/z\)): [M + H]⁺ calcd for C₂₇H₃₁BrN₃O₃, 524.2; found, 524.3.
Synthesis of Azide 122. To a solution of allyl lactam 137 (57 mg, 0.11 mmol) in THF (7 mL) and H₂O (3.5 mL) was added OsO₄ (0.14 mL, 4 wt% solution in water, 0.022 mmol) and NMO (64 mg, 0.55 mmol). The mixture was stirred at rt for 12 h and then a solution of NaIO₄ (117 mg, 0.55 mmol) in H₂O (1.0 mL) was added. The mixture was stirred further at rt for 2 h. The cloudy aqueous solution was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The resulting aldehyde was not purified and was used directly in the next step.

To a solution of the crude aldehyde in EtOH (6 mL) was added NaBH₄ (8.0 mg, 0.21 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous NH₄Cl. After removal of EtOH in vacuo, the residue was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The alcohol was not purified and was used directly in the next step.

To a solution of the above alcohol in DCM (5 mL) was added Et₃N (60 µL, 0.43 mmol) and MsCl (17 µL, 0.22 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous NaHCO₃. The mixture was diluted with H₂O and extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The mesylate was not purified and was used directly in the next step.
To a solution of the crude mesylate in DMF (3.0 mL) was added NaN₃ (100 mg, 1.54 mmol). The reaction mixture was stirred at 90 °C for 15 h and diluted with H₂O. The aqueous phase was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 3/2) to give the azide 122 (49 mg, 81% from 137). ¹H NMR (300 MHz, CDCl₃) δ 8.39 (d, J = 7.1 Hz, 1H), 6.98-6.89 (m, 3H), 6.71 (t, J = 7.9 Hz, 1H), 6.53 (dd, J = 0.9, 8.0 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 5.84 (s, 1H), 5.59 (s, 1H), 3.74-3.54 (m, 2H), 3.38-3.31 (m, 1H), 2.93 (s, 3H), 2.87-2.77 (m, 1H), 2.52 (td, J = 5.7, 13.4 Hz, 1H), 2.32-2.23 (m, 2H), 2.11-2.05 (m, 1H), 1.44 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 174.6, 154.1, 152.9, 138.3, 130.9, 129.8, 129.7, 127.8, 126.5, 126.4, 124.2, 123.8, 118.6, 105.5, 83.1, 81.8, 67.9, 59.9, 48.9, 46.6, 39.9, 35.5, 31.2, 29.6, 29.4, 28.1; LRMS-ES (m/z): [M + H]⁺ calcd for C₂₆H₃₀BrN₆O₃, 553.2; found, 553.1.

**Synthesis of Methyl Carbamate 138.** To a solution of lactam 122 (12.0 mg, 0.022 mmol) in THF (3.0 mL) was added LiHMDS (33 µL, 1.0 M in THF, 0.033 mmol) and ClCOOMe (2 µL, 0.026 mmol). The reaction mixture was stirred at rt for 30 min and quenched with aqueous saturated NaHCO₃. The mixture was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc, 7/3) to give methyl carbamate 138 (10.0 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, J = 7.2 Hz,
1H), 6.98-6.94 (m, 3H), 6.72 (t, J = 7.8 Hz, 1H), 6.51 (d, J = 7.9 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 5.59 (s, 1H), 4.03-3.99 (m, 1H), 3.92 (s, 3H), 3.88-3.81 (m, 1H), 3.55-3.48 (m, 1H), 2.92 (s, 3H), 2.85-2.78 (m, 1H), 2.53 (td, J = 5.7, 14.1 Hz, 1H), 2.35-2.30 (m, 2H), 2.15 (d, J = 14.1 Hz, 1H), 1.44 (s, 9H); LRMS-ES (m/z): [M + H]$^+$ calcd for C$_{28}$H$_{32}$BrN$_6$O$_5$, 611.2; found, 611.2.

**Synthesis of N-Nosyl Lactam 140.** To a solution of lactam 122 (5.0 mg, 0.009 mmol) in THF (3.0 mL) was added LiHMDS (24 µL, 1.0 M in THF, 0.024 mmol) and NsCl (5.0 mg, 0.023 mmol). The reaction mixture was stirred at rt for 10 min and quenched with aqueous saturated NaHCO$_3$. The mixture was diluted with H$_2$O and extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc, 3/2) to give N-nosyl lactam 140 (4.6 mg, 69%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.42-8.38 (m, 2H), 8.33-8.29 (m, 2H), 8.05 (d, J = 8.9 Hz, 1H), 6.99-6.85 (m, 3H), 6.71 (t, J = 8.0 Hz, 1H), 6.38 (dd, J = 0.9, 8.0 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 5.59 (s, 1H), 4.58-4.53 (m, 1H), 3.84-3.73 (m, 1H), 3.30-3.20 (m, 1H), 2.91 (s, 3H), 2.76-2.60 (m, 2H), 2.31-2.15 (m, 3H), 1.42 (s, 9H); LRMS-ES (m/z): [M + H]$^+$ calcd for C$_{32}$H$_{33}$BrN$_7$O$_7$S, 738.1; found, 738.1.
**Synthesis of Spiro Lactam 141.** To a solution of the N-nosyl lactam 140 (4.6 mg, 0.0062 mmol) in THF (2.0 mL) and H₂O (0.4 mL) was added PMe₃ (60 µL, 1.0 M in THF, 0.06 mmol). The reaction mixture was stirred at 70 °C for 36 h and then cooled to rt. The solvent was evaporated and the residue was purified by preparative TLC (hexanes/EtOAc, 1/3) to give the spiro-γ-lactam 141 (2.7 mg, 60%). ¹H NMR (300 MHz, CDCl₃) δ 8.30 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.70-7.67 (m, 1H), 7.57-7.50 (m, 1H), 7.40-7.35 (m, 1H), 7.20-7.10 (m, 1H), 7.15-7.10 (m, 1H), 6.74 (t, J = 7.9 Hz, 1H), 6.58 (d, J = 7.9 Hz, 1H), 6.50 (s, 1H), 5.93 (d, J = 7.7 Hz, 1H), 5.87 (s, 1H), 5.42-5.35 (m, 1H), 4.21-4.18 (m, 1H), 3.30-3.20 (m, 1H), 3.10-2.95 (m, 2H), 2.90-2.75 (m, 2H), 2.40 (s, 3H), 2.35-2.30 (m, 2H), 1.53 (s, 9H); LRMS-ES (m/z): [M - H]⁻ calcd for C₃₂H₃₃BrN₅O₇S, 710.1; found, 710.3.

**Synthesis of Ester 148.** To a solution of triflate 147 (763 mg, 1.94 mmol) and 2-nitrobenzeneboronic acid (356 mg, 2.13 mmol) in DME (11.0 mL) and water (3.7 mL) were added Pd(PPh₃)₄ (45 mg, 0.039 mmol) and Na₂CO₃ (617 mg, 5.82 mmol). The reaction mixture was stirred at 80 °C for 1 h and then cooled to rt. The solution was diluted
with H₂O and extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/3) to give arylated compound 148 (697 mg, 98%). ¹H NMR (300 MHz, CDCl₃) δ 8.03 (dd, J = 1.2, 8.2 Hz, 1H), 7.57 (ddd, J = 0.8, 7.6, 7.6 Hz, 1H), 7.46-7.39 (m, 3H), 7.36-7.26 (m, 3H), 7.19 (dd, J = 1.3, 7.6 Hz, 1H), 3.87 (q, J = 7.2 Hz, 2H), 3.73 (q, J = 12.7 Hz, 2H), 3.48, 3.22 (ABq, J = 17.9 Hz, 2H), 2.83 (t, J = 5.8 Hz, 2H), 2.60 (m, 2H), 0.88 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 148.3, 144.7, 138.2, 137.1, 133.5, 130.1, 129.4, 128.8, 128.4, 127.7, 125.1, 124.6, 61.8, 60.7, 58.6, 49.2, 26.0, 14.0; HRMS-ES (m/z): [M + H]⁺ calcd for C₂₁H₂₃N₂O₄, 367.1658; found, 367.1651.

Synthesis Carboxylic Acid 149. To a solution of ester 148 (18.23 g, 49.75 mmol) in MeOH (260 mL) and water (108 mL) was added LiOH·H₂O (10.45 g, 249.05 mmol). The reaction mixture was stirred at 50 °C for 12 h before MeOH was removed under reduced pressure. The resulting aqueous solution was acidified with 1 N HCl to pH 5-6 and extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (MeOH/DCM, 1/10) to give the carboxylic acid 149 (16.48 g, 86%). ¹H NMR (300 MHz, CDCl₃) δ 12.6 (br s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.1 Hz, 1H), 7.33-7.26 (m, 6H), 7.13 (d, J = 7.2 Hz, 1H), 4.03-3.90 (m, 2H), 3.73-3.51 (m, 2H), 3.00 (br s, 1H), 2.78
(br s, 1H), 2.47 (br S, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.4, 148.5, 136.6, 135.6, 133.8, 131.8, 130.9, 130.7, 129.4, 129.3, 128.7, 127.3, 124.2, 58.6, 54.5, 46.6, 23.3; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{19}$H$_{19}$N$_2$O$_4$, 339.1345; found, 339.1325.

**Synthesis of BOM Ether 184.** To a solution of (2-iodo-3-nitrophenyl)methanol (263 mg, 0.94 mmol) in THF (5.0 mL) was added TBAI (70 mg, 0.19 mmol), DIPEA (0.25 mL, 1.41 mmol) and BOMCl (0.13 mL, 0.94 mmol). The reaction mixture was heated at 70 °C for 14 h and then quenched by the addition of saturated aqueous NaHCO$_3$. The solution was then extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/4) to give the BOM ether 184 (232 mg, 62%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.67 (d, $J = 7.6$ Hz, 1H), 7.58 (dd, $J = 1.5$, 7.9 Hz, 1H), 7.49 (d, $J = 7.7$ Hz, 1H), 7.45-7.32 (m, 5H), 4.98 (s, 2H), 4.74 (s, 2H), 4.72 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.7, 143.8, 137.4, 131.0, 128.8, 128.4, 127.8, 127.7, 123.3, 94.4, 88.7, 73.9, 69.9; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{15}$H$_{15}$NO$_4$I, 400.0046; found, 400.0039.
Synthesis of Aniline 150. To a solution of nitrobenzene 184 (3.16 g, 7.92 mmol) in EtOH (50.0 mL) was added ion powder (2.21 g, 39.59 mmol) and glacial AcOH (6.8 mL). The reaction mixture was heated at 60 °C for 12 h and then cooled to rt. The mixture was filtered and the filtrate was concentrated. The residue was diluted with EtOAc and H2O and basified with solid Na2CO3·H2O. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1) to provide the iodoaniline 150 (2.22 g, 76%). 1H NMR (300 MHz, CDCl3) δ 7.49-7.31 (m, 5H), 7.16 (br m, 1H), 6.89 (d, J = 7.4 Hz, 1H), 6.77 (br s, 1H), 4.94 (s, 2H), 4.74 (s, 2H), 4.69 (s, 2H); 13C NMR (75 MHz, CDCl3) δ 146.5, 141.0, 137.7, 128.8, 128.4, 127.9, 127.6, 119.2, 114.3, 94.2, 88.4, 74.2, 69.6; HRMS-ES (m/z): [M + H]+ calcd for C15H17NO2I, 370.0304; found, 370.0295.

Synthesis of Amide 151. The acid 149 (11.33 g, 38.49 mmol) was dissolved in SOCl2 (25.0 mL) and the solution was refluxed for 3 h. Excess SOCl2 was distilled off and the residue was dried under high vacuum and then dissolved in DCM (30.0 mL). To a stirred solution of aniline 150 (9.16 g, 24.80 mmol) and DIPEA (17.3 mL, 99.31 mmol) in
DCM (50.0 mL) was added the above acid chloride solution dropwise at rt. The reaction mixture was further stirred at rt for 12 h, and was diluted with DCM and saturated aqueous NaHCO₃. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7/3) to give the amide 151 (14.88 g, 87% based on aniline 150). ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.85 (s, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.47-7.31 (m, 12H), 7.28-7.18 (m, 2H), 4.91 (s, 2H), 4.70 (s, 2H), 4.63 (s, 2H), 3.76 (br d, J = 5.5 Hz, 2H), 3.36, 3.14 (ABq, J = 16.9 Hz, 2H), 2.97-2.77 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 166.1, 147.6, 140.7, 137.9, 137.4, 137.3, 134.8, 133.5, 130.6, 129.3, 128.65, 128.59, 128.3, 128.13, 128.09, 127.6, 127.4, 127.0, 124.8, 124.4, 121.4, 94.01, 93.94, 73.9, 69.4, 61.1, 56.6, 48.5, 26.2; HRMS-ES (m/z): [M + H]⁺ calcd for C₃₄H₃₃N₃O₅I, 690.1465; found, 690.1472.

**Synthesis of Ethyl Carbamate 152.** To a stirred solution of amide 151 (3.13 g, 4.54 mmol) in DCM (35.0 mL) was added ClCO₂Et (0.52 mL, 5.45 mmol) dropwise at 0 °C. After the addition was complete, the ice bath was removed and the mixture was stirred at rt for 12 h before saturated aqueous NaHCO₃ was added. The layers were separated. The aqueous layer was extracted with DCM and the combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on
silica gel (hexanes/EtOAc/DCM, 5/3/2) to provide carbamate 152 (2.92 g, 96%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 7.9$ Hz, 1H), 7.81 (dd, $J = 1.3$, 7.8 Hz, 1H), 7.73 (s, 1H), 7.63-7.58 (m, 1H), 7.47-7.27 (m, 7H), 7.24-7.14 (m, 2H), 4.86 (s, 2H), 4.65 (s, 2H), 4.58 (s, 2H), 4.41-4.09 (br m, 2H), 4.22 (q, $J = 7.0$ Hz, 2H), 3.87-3.75 (br m, 2H), 2.85-2.68 (br m, 2H), 1.45-1.29 (br m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.7, 154.9, 147.6, 140.8, 137.7, 137.3, 133.8, 133.6, 130.7, 129.1, 128.4, 128.2, 127.6, 127.5, 125.1, 124.7, 121.5, 94.3, 94.0, 73.9, 69.4, 61.4, 47.1, 39.5, 25.8, 14.4; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{30}$H$_{31}$N$_3$O$_7$I, 672.1207; found, 672.1226.

**Synthesis of N-Methyl Amide 153.** To a suspension of NaH (192 mg, 60% dispersion in mineral oil, 4.79 mmol) in THF (10.0 mL) was added a solution of amide 152 (2.92 g, 4.35 mmol) in THF (30.0 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and MeI (0.33 mL, 5.22 mmol) was added at this temperature. The reaction mixture was warmed to rt and further stirred for 12 h before the addition of saturated aqueous NaHCO$_3$. The aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue obtained was purified by flash column chromatography on silica gel (hexanes/EtOAc, 3/2) to provide methylated amide 153 (2.74 g, 92%). $^1$H NMR (300 MHz, CD$_3$CN) $\delta$ 8.07 (dd, $J = 1.1$, 8.1 Hz, 1H), 7.76-7.73 (m, 1H), 7.62-7.56 (m, 1.7H), 7.47-7.44 (br m, 1H), 7.40-7.29 (m, 6H), 7.02 (br s, 0.2H), 6.40 (br s, 0.3H), 4.93 (s, 0.7H), 4.87 (s, 1.3H), 4.69 (s, 1.2H), 4.64 (s, 1.3H), 4.59 (s, 1.3H), 4.40 (br
s, 1H), 4.20 (q, J = 7.1 Hz, 1.5H), 4.11-4.00 (m, 1H), 3.86-3.72 (m, 1.3H), 3.45 (br s, 0.3H), 3.11 (s, 2H), 2.99 (s, 0.3H), 2.92 (s, 0.8H), 2.87 (s, 0.3H), 2.58 (s, 1.3H), 2.26 (s, 0.6H), 1.30 (t, J = 6.9 Hz, 2H), 1.17 (t, J = 7.1 Hz, 1H); 13C NMR (75 MHz, CD3CN, 65 °C) δ 170.0, 156.6, 150.2, 147.0, 144.2, 139.7, 134.9, 134.2, 133.3, 132.0, 130.7, 130.6, 129.6, 129.3, 129.1, 128.8, 128.6, 126.1, 125.6, 103.1, 96.0, 75.3, 71.0, 62.5, 49.0, 48.1, 41.1, 39.0, 37.7, 27.2, 15.3; HRMS-ES (m/z): [M + H]+ calcd for C31H33N3O7I, 686.1363; found, 686.1371.

**Synthesis of Tetracyclic Enamide 154.** To a solution of N-methyl amide 153 (2.21 g, 3.23 mmol) in DMA (56.0 mL) were added Pd(OAc)2 (145 mg, 0.65 mmol), PPh3 (339 mg, 1.29 mmol), n-Bu4NBr (2.08 g, 6.45 mmol) and K2CO3 (892 mg, 6.48 mmol). The mixture was stirred at 150 °C for 25 min, then cooled to rt and was diluted with H2O. The aqueous solution was extracted with EtOAc. The combined organic extracts were dried over Na2SO4 and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/2) to provide 154 (1.88 g, 90%). 1H NMR (300 MHz, CD3CN, 65 °C) δ 7.53-7.49 (m, 2H), 7.40-7.30 (m, 6H), 7.28-7.21 (m, 2H), 7.00 (d, J = 7.9 Hz, 1H), 6.80-6.84 (m, 2H), 4.85-4.80 (m, 2H), 4.36 (d, J = 11.9 Hz, 1H), 4.31, 4.26 (ABq, J = 7.1 Hz, 2H), 4.07-3.99 (m, 2H), 3.23 (s, 3H), 2.64-2.53 (m, 1H), 1.98-1.89 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CD3CN, 65 °C) δ 178.8, 154.5, 150.9, 145.2, 139.7, 136.3, 132.6, 132.4, 132.15, 132.11, 130.1, 129.6, 129.4, 129.0, 128.8,
125.2, 124.9, 110.4, 109.1, 95.8, 70.9, 66.7, 63.8, 50.5, 38.9, 31.5, 27.5, 15.0; HRMS-ES (m/z): [M + H]$^+$ calcd for C$_{31}$H$_{32}$N$_3$O$_7$, 558.2240; found, 558.2238.

**Synthesis of N-Boc Aniline 155.** To a beaker containing a solution of the Heck product 154 (1.71 g, 3.07 mmol) in toluene (30.0 mL) was added 5% platinum on carbon (514 mg). The beaker was then transferred into a Parr high-pressure reaction vessel and flushed with H$_2$. The hydrogen pressure was increased to 40 atm, and the reaction mixture was stirred at rt for 14 h. The pressure was released and the suspension was filtered through a pad of Celite. The solvent was removed to give the aniline which decomposed on standing and therefore was used immediately in crude form.

To a solution of the freshly prepared crude aniline in THF (90.0 mL) and H$_2$O (30.0 mL) were added K$_2$CO$_3$ (8.49 g, 61.43 mmol) and (Boc)$_2$O (10.05 g, 46.05 mmol). The mixture was stirred at 60 °C for 20 h. The aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/4) to provide N-Boc aniline 155 (1.68 g, 87% for 2 steps). $^1$H NMR (300 MHz, CD$_3$CN, 65 °C) $\delta$ 7.72 (d, $J = 8.9$ Hz, 1H), 7.43-7.26 (m, 7H), 7.21 (s, 1H), 7.15-7.08 (m, 2H), 6.80-6.71 (m, 3H), 4.94, 4.91 (ABq, $J = 6.7$ Hz, 2H), 4.82, 4.73 (ABq, $J = 11.6$ Hz, 2H), 4.70 (s, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 4.17-4.01 (m, 2H), 3.11 (s, 3H), 2.71-2.60 (m, 1H), 2.10-1.99 (m, 1H), 1.55 (s, 9H), 1.31 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_3$CN, 65 °C) $\delta$
180.1, 154.7, 154.5, 145.1, 139.6, 138.6, 136.1, 131.8, 131.7, 129.99, 129.94, 129.6, 129.1, 
129.0, 128.8, 125.1, 123.7, 122.9, 112.0, 109.2, 96.1, 80.9, 71.1, 67.0, 63.5, 51.8, 39.3, 
32.1, 29.0, 27.4, 15.1; HRMS-ES (m/z): $[\text{M + H}]^+$ calcd for C$_{36}$H$_{42}$N$_3$O$_7$, 628.3023; found, 
628.3022.

**Synthesis of Pentacyclic Aminal 156.** To a solution of N-Boc aniline 155 (302 mg, 
0.48 mmol) in THF (15.0 mL) was added AlH$_3$·Me$_2$NEt (1.44 mL, 0.5 M in toluene, 0.72 
mmol) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred for 4 h before 
saturated aqueous Na$_2$SO$_4$ was added. The aqueous mixture was extracted with EtOAc. 
The combined organic phases were dried over Na$_2$SO$_4$ and concentrated. The residue was 
purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/9) to give the 
aminal 156 (250 mg, 74%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42-7.29 (m, 6H), 7.19 (dd, $J$ = 
1.4, 7.3 Hz, 2H), 7.05 (br m, 1H), 6.97 (t, $J$ = 7.8 Hz, 2H), 6.56 (d, $J$ = 7.7 Hz, 1H), 6.24 (d, 
$J$ = 7.8 Hz, 1H), 5.82 (s, 1H), 4.84 (s, 2H), 4.74-4.65 (m, 3H), 4.50 (d, $J$ = 11.6 Hz, 1H), 
4.31-4.15 (m, 3H), 3.51 (br s, 1H), 3.00 (s, 3H), 2.50-2.35 (m, 2H), 1.53 (s, 9H), 7.1 (t, $J$ = 
1.35 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_3$CN, 65 °C) $\delta$ 154.3, 154.0, 151.8, 139.2,139.0, 
134.4, 134.1, 130.4, 128.83, 128.76, 128.2, 127.9, 126.8, 125.7, 125.1, 124.5, 118.7, 116.8, 
104.9, 94.9, 85.6, 81.5, 69.9, 65.5, 62.6, 52.0, 40.5, 34.6, 30.5, 28.0, 14.3; HRMS-ES (m/z): 
$[\text{M + H}]^+$ calcd for C$_{36}$H$_{42}$N$_3$O$_6$, 612.3074; found, 612.3055.
Synthesis of N-Cyanoamidine 157. To a solution of enamide 156 (202 mg, 0.33 mmol) in EtOH (10.0 mL) was added 1 N aqueous KOH aqueous solution (10.0 mL, 10.0 mmol). The mixture was stirred at 94 °C for 3 h and then cooled to rt. After removal of EtOH in vacuo, the cloudy aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Since the resulting enamine was unstable and decomposed during chromatographic purification, it was not purified, but used directly in the next step.

To a solution of the crude enamine in MeCN (15.0 mL) was added NCN₃ (1.0 mL, 0.5 M in MeCN, 0.50 mmol, freshly prepared). The solution was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 2/3) to give the cyanoamidine 157 (178 mg, 93%). ¹H NMR (300 MHz, CDCl₃) δ 7.68 (br s, 1H), 7.44-7.29 (m, 5H), 7.20 (d, J = 3.0 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 7.06-7.00 (m, 1H), 6.96 (d, J = 7.7 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 6.09 (d, J = 8.0 Hz, 1H), 6.07 (s, 1H), 4.92, 4.89 (ABq, J = 6.9 Hz, 2H), 4.81, 4.63 (ABq, J = 11.7 Hz, 2H), 4.74 (s, 2H), 4.34 (s, 1H), 3.87-3.84 (m, 1H), 3.55-3.51 (m, 1H), 2.78 (s, 3H), 2.75-2.64 (m, 1H), 2.12 (dd, J = 3.5, 14.3 Hz, 1H), 1.51 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 172.3, 150.1, 150.6, 137.5, 136.4, 132.8, 132.3, 129.8, 129.1, 128.5, 127.8, 127.6, 127.5, 125.9, 125.7, 119.5, 116.3, 104.5, 93.3, 81.6, 78.8, 69.8, 65.9,
53.9, 46.8, 39.1, 30.5, 29.9, 28.1; HRMS-ES (m/z): [M + H]$^+$ calcd for C$_{34}$H$_{38}$N$_5$O$_4$, 580.2924; found, 580.2918.

**Synthesis of Lactam 158.** To a solution of cyanoamidine 157 (178 mg, 0.33 mmol) in EtOH (15.0 mL) was added 1 N aqueous KOH solution (15.0 mL, 15.0 mmol). The mixture was stirred at 94 °C for 12 h and then cooled to rt. After removal of EtOH in vacuo, the cloudy aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/1) to give the lactam 158 (102 mg, 60%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.45-7.29 (m, 5H), 7.19-7.16 (m, 3H), 7.05-6.95 (m, 2H), 6.58 (d, $J$ = 7.6 Hz, 1H), 6.44 (br s, 1H), 6.13 (s, 1H), 6.09 (d, $J$ = 7.9 Hz, 1H), 4.92, 4.89 (ABq, $J$ = 6.9 Hz, 2H), 4.83, 4.72 (ABq, $J$ = 11.6 Hz, 2H), 4.78 (s, 2H), 4.17 (s, 1H), 3.86 (t, $J$ = 11.7 Hz, 1H), 3.39-3.35 (m, 1H), 2.79 (s, 3H), 2.75-2.69 (m, 1H), 2.08-2.01 (m, 1H), 1.49 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.7, 153.4, 150.5, 137.6, 136.3, 132.8, 132.5, 129.9, 128.7, 128.4, 128.3, 127.7, 127.6, 127.2, 125.6, 119.1, 104.3, 93.4, 81.1, 79.1, 69.6, 65.7, 54.6, 49.1, 38.2, 31.5, 30.0, 28.1; HRMS-ES (m/z): [M + H]$^+$ calcd for C$_{33}$H$_{38}$N$_3$O$_5$, 556.2811; found, 556.2820.
Synthesis of \(N\)-Boc Lactams 159a and 159b. To a solution of lactam 158 (343 mg, 0.62 mmol) in THF (15.0 mL) was added LiHMDS (0.93 mL, 1.0 M in THF, 0.93 mmol). The mixture was stirred at rt for 10 min and (Boc)_2O (141 mg, 0.65 mmol) was added. The reaction mixture was stirred at rt for another 10 min and quenched with aqueous saturated NaHCO_3. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7/3) to give the \(N\)-Boc lactams 159a and 159b as a 1:3 mixture of epimers (384 mg, 95%). For analytical purposes, the mixture was carefully purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1 then 7/3) to give pure 159a and 159b.

159a: \(^1\)H NMR (300 MHz, CDCl_3) \(\delta\) 8.31 (d, \(J = 5.7\) Hz, 1H), 7.44-7.37 (m, 4H), 7.35-7.31 (m, 1H), 7.02-6.98 (m, 3H), 6.92 (t, \(J = 7.8\) Hz, 1H), 6.46 (d, \(J = 7.7\) Hz, 1H), 6.20 (d, \(J = 7.8\) Hz, 1H), 5.90 (s, 1H), 4.84, 4.80 (ABq, \(J = 6.8\) Hz, 2H), 4.69, 4.61 (ABq, \(J = 12.0\) Hz, 2H), 4.50, 4.42 (ABq, \(J = 11.7\) Hz, 2H), 4.36-4.33 (m, 1H), 3.87 (s, 1H), 3.83-3.77 (m, 1H), 2.97 (s, 3H), 2.52-2.37 (m, 2H), 1.60 (s, 9H), 1.49 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl_3) \(\delta\) 169.4, 154.2, 152.1, 151.4, 138.1, 137.8, 133.0, 130.6, 128.6, 128.4, 128.3, 128.1, 127.8, 127.5, 126.1, 125.8, 125.2, 119.4, 105.2, 93.7, 84.9, 83.3, 81.2, 69.2, 66.8, 56.6, 45.2, 42.7, 34.5, 30.7, 28.1, 28.0; HRMS-ES (m/z): [M + H]\(^+\) calcd for C_{38}H_{46}N_{3}O_{7}, 656.3336; found, 656.3320.
159b: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42-7.38 (m, 4H), 7.35-7.32 (m, 1H), 7.28 (br s, 1H), 7.19-7.12 (m, 2H), 7.03-6.94 (m, 2H), 6.56 (d, $J = 5.7$ Hz, 1H), 6.10 (s, 1H), 6.09 (d, $J = 5.9$ Hz, 1H), 4.91, 4.88 (ABq, $J = 5.1$ Hz, 2H), 4.82, 4.69 (ABq, $J = 8.8$ Hz, 2H), 4.73 (d, $J = 1.4$ Hz, 2H), 4.35 (s, 1H), 4.10-4.04 (m, 1H), 3.96-3.93 (m, 1H), 2.84-2.76 (m, 1H), 2.78 (s, 3H), 2.17 (d, $J = 10.6$ Hz, 1H), 1.52 (s, 9H), 1.49 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.3, 152.8, 150.4, 137.5, 136.2, 132.6, 132.1, 129.7, 128.7, 128.3, 128.0, 127.63, 127.57, 127.3, 125.7, 125.5, 119.2, 104.4, 93.2, 82.8, 81.2, 79.7, 69.6, 65.7, 55.2, 51.6, 42.2, 32.3, 29.9, 28.0, 27.7; HRMS-ES (m/z): [M + H]$^+$ calcd for C$_{38}$H$_{46}$N$_3$O$_7$, 656.3336; found, 656.3344.

Synthesis of C- Allyl Lactam 160. To a solution of N-Boc lactams 159a and 159b (207 mg, 0.32 mmol) in THF (20.0 mL) was added a solution of KOt-Bu (42 mg, 0.38 mmol) in THF (1.5 mL) dropwise at -78 °C, followed immediately by the addition of allyl iodide (0.48 mL, 1.0 M in THF, 0.48 mmol). The dry ice-acetone bath was removed and the mixture was warmed to rt and stirred for 40 min before aqueous saturated NaHCO$_3$ was added. The mixture was diluted with H$_2$O and extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1 then 7/3) to give the C-allyl lactam 160 (191 mg, 87%). $^1$H NMR (300 MHz, CD$_3$CN, 65 °C) δ 8.31 (dd, $J = 1.6$, 7.7 Hz, 0.8H), 7.44-7.31 (m, 10H), 7.24(d, $J = 9.0$ Hz, 1H), 7.10-7.03 (m, 2H), 6.98-6.88 (m,
5H), 6.53 (d, J = 7.9 Hz, 1.8H), 6.36 (dd, J = 1.0, 7.8 Hz, 0.8H), 6.21 (d, J = 7.8 Hz, 1H),
5.75 (s, 1H), 5.70 (s, 1H), 5.64-5.55 (m, 1.8H), 5.13-5.03 (m, 2H), 4.93-4.83 (m, 4H),
4.80-4.75 (m, 2H), 4.67-4.52 (m, 5.8H), 4.35-4.17 (m, 4.8H), 3.84-3.77 (m, 0.8H), 3.73-
3.62 (m, 0.8H), 3.13-3.02 (m, 1.7H), 3.00 (s, 2.8H), 2.93 (s, 3H), 2.91-2.84 (m, 1H), 2.70
(td, J = 5.7, 13.7 Hz, 1H), 2.26 (s, 2.3H), 2.25-2.12 (m, 2H), 1.93-1.88 (m, 1H), 1.58 (s,
9H), 1.55 (s, 9H), 1.51 (s, 15H); 13C NMR (75 MHz, CD3CN, 65 °C) δ 173.0, 155.3, 155.2,
155.1, 154.4, 152.6, 152.3, 146.4, 140.3, 139.9, 139.8, 139.6, 135.4, 135.3, 134.8, 134.4,
130.7, 130.4, 130.0, 129.7, 129.6, 129.5, 129.1, 128.8, 128.7, 128.6, 127.6, 127.4, 127.3,
125.9, 125.2, 120.3, 118.8, 118.7, 118.4, 107.4, 106.2, 105.3, 96.0, 95.8, 86.5, 84.6, 84.0,
82.8, 82.6, 82.1, 70.94, 70.88, 70.7, 68.1, 66.1, 60.8, 55.9, 52.4, 45.1, 40.7, 37.4, 32.1, 31.1,
30.9, 28.92, 28.89, 28.8, 28.7; HRMS-ES (m/z): [M + H]+ calcd for C41H50N3O7, 696.3349;
found, 696.3651.

**Synthesis of NH-Lactam 161.** To a solution of the N-Boc lactam 160 (191 mg,
0.27 mmol) in EtOH (28.0 mL) was added 1 N aqueous KOH solution (2.8 mL, 2.8 mmol).
The mixture was stirred at 80 °C for 13 h and then cooled to rt. After removal of EtOH in
*vacuo*, the cloudy aqueous solution was extracted with EtOAc. The combined organic
layers were dried over Na2SO4 and concentrated. The residue was purified by flash column
chromatography on silica gel (hexanes/EtOAc, 7/3 then 1/1) to give the NH lactam 161
(155 mg, 94%). 1H NMR (300 MHz, CDCl3) δ 8.27-8.22 (m, 1H), 7.40-7.24 (m, 5H), 6.97-
6.82 (m, 4H), 6.53 (dd, \( J = 7.8, 0.8 \) Hz, 1H), 6.26 (dd, \( J = 7.8, 0.9 \) Hz, 1H), 6.25 (s, 1H), 5.88-5.74 (m, 1H), 5.63 (s, 1H), 4.88-4.81 (m, 2H), 4.84, 4.77 (ABq, \( J = 6.7 \) Hz, 2H), 4.70, 4.61 (ABq, \( J = 11.9 \) Hz, 2H), 4.51 (d, \( J = 12.1 \) Hz, 1H), 4.24 (d, \( J = 12.1 \) Hz, 1H), 3.49 (td, \( J = 4.5, 12.8 \) Hz, 1H), 3.25-3.18 (m, 1H), 2.97 (s, 3H), 2.85 (d, \( J = 7.0 \) Hz, 2H), 2.54 (td, \( J = 6.0, 13.4 \) Hz, 1H), 1.95 (dd, \( J = 13.5, 4.2 \) Hz, 1H), 1.45 (s, 9H); \(^{13}\text{C NMR} (75 \text{ MHz, CDCl}_3) \delta 173.4, 154.1, 150.8, 138.5, 137.8, 134.4, 133.8, 132.7, 128.8, 128.4, 128.3, 127.8, 127.6, 126.8, 126.3, 125.9, 124.0, 119.4, 116.9, 106.1, 94.2, 83.1, 81.2, 69.6, 66.6, 58.6, 48.7, 40.6, 39.3, 31.4, 28.4, 28.1; HRMS-ES \((m/z)\): [M + H]\(^+\) calcd for C\(_{36}\)H\(_{42}\)N\(_3\)O\(_5\), 596.3124; found, 596.3136.

**Synthesis of Mesylate 162.** To a solution of allyl lactam 161 (155 mg, 0.26 mmol) in THF (9.0 mL) and H\(_2\)O (3.0 mL) was added OsO\(_4\) (0.33 mL, 4 wt% solution in water, 0.052 mmol) and NMO (152 mg, 1.30 mmol). The mixture was stirred at rt for 12 h and then a solution of NaIO\(_4\) (278 mg) in H\(_2\)O (3.0 mL) was added. The mixture was further stirred at rt for 2 h. The cloudy aqueous solution was diluted with H\(_2\)O and extracted with EtOAc. The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated. The resulting aldehyde obtained was not purified and was used directly in the next step.

To a solution of the crude aldehyde in EtOH (20.0 mL) was added NaBH\(_4\) (25 mg, 0.66 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous NH\(_4\)Cl. After removal of EtOH in vacuo, the residue was
diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The alcohol obtained was not purified and was used directly in the next step.

To a solution of the above alcohol in DCM (10.0 mL) was added Et₃N (0.18 mL, 1.29 mmol) and MsCl (61 µL, 0.78 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous NaHCO₃. The mixture was diluted with H₂O and extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc/Et₃N, 2/3/0.1 then 3/7/0.1) to give the mesylate 162 (147 mg, 83% for 3 steps). 

\[ ^1H \text{ NMR (300 MHz, CDCl}_3) \delta 8.18 (d, J = 7.4 \text{ Hz, 1H}), 7.39-7.28 (m, 5H), 6.97-6.85 (m, 4H), 6.52 (d, J = 7.7 \text{ Hz, 1H}), 6.25 (d, J = 7.3 \text{ Hz, 1H}), 5.82 (s, 1H), 5.58 (s, 1H), 4.81, 4.76 (ABq, J = 6.7 \text{ Hz, 2H}), 4.68, 4.61 (ABq, J = 11.8 \text{ Hz, 2H}), 4.51-4.43 (m, 1H), 4.44 (d, J = 12.0 \text{ Hz, 1H}), 4.14 (d, J = 12.1 \text{ Hz, 1H}), 3.50 (td, J = 4.4, 12.5 \text{ Hz, 1H}), 3.24-3.18 (m, 1H), 2.95 (s, 3H), 2.72 (s, 3H), 2.53-2.38 (m, 3H), 2.01 (dd, J = 3.8, 13.3 \text{ Hz, 1H}), 1.45 (s, 9H); \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3) \delta 173.2, 150.9, 138.9, 137.8, 133.8, 130.8, 128.6, 128.5, 127.8, 127.2, 126.8, 126.2, 124.4, 119.7, 106.4, 94.1, 83.2, 82.0, 69.7, 68.1, 66.6, 59.0, 46.5, 39.4, 36.7, 34.5, 31.4, 28.3, 28.1; \]

HRMS-ES (m/z): [M + H]⁺ calcd for C₃₆H₄₄N₃O₈S, 678.2849; found, 678.2849.
Synthesis of Azide 146. To a solution of the mesylate 162 (20 mg, 0.030 mmol) in DMF (1.5 mL) was added NaN₃ (50 mg, 0.77 mmol). The reaction mixture was stirred at 90 °C for 12 h and diluted with H₂O. The aqueous mixture was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative TLC (hexanes/EtOAc, 1/1) to give the azide 146 (16 mg, 87%).

¹H NMR (300 MHz, CDCl₃) δ 8.17 (d, J = 7.5 Hz, 1H), 7.37-7.28 (m, 5H), 6.97-6.83 (m, 4H), 6.51 (d, J = 7.6 Hz, 1H), 6.25 (d, J = 7.7 Hz, 1H), 6.16 (s, 1H), 5.58 (s, 1H), 4.81, 4.75 (ABq, J = 6.7 Hz, 2H), 4.68, 4.60 (ABq, J = 11.9 Hz, 2H), 4.43 (d, J = 12.0 Hz, 1H), 4.18 (d, J = 11.9 Hz, 1H), 3.64-3.50 (m, 2H), 3.30-3.20 (m, 1H), 2.95 (s, 3H), 2.90-2.80 (m, 1H), 2.46-2.40 (m, 1H), 2.34-2.26 (m, 2H), 2.05-1.95 (m, 1H), 1.44 (s, 9H); LRMS-ES (m/z): [M + H]+ calcd for C₃₅H₄₁N₆O₅, 625.3; found, 625.4.

Synthesis of N-Boc Lactam 163. To a solution of lactam 146 (65 mg, 0.104 mmol) in THF (10.0 mL) was added LiHMDS (0.16 mL, 1.0 M in THF, 0.16 mmol) and (Boc)₂O (23 mg, 0.105 mmol). The reaction mixture was stirred at rt for 10 min and quenched with
aqueous saturated NaHCO₃. The mixture was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 4/1) to give N-Boc lactam 163 (69 mg, 92%). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, J = 7.4 Hz, 1H), 7.43-7.32 (m, 5H), 7.03-6.93 (m, 4H), 6.68 (d, J = 7.6 Hz, 1H), 6.28 (d, J = 7.7 Hz, 1H), 5.63 (s, 1H), 4.77 (s, 2H), 4.71, 4.60 (ABq, J = 12.1 Hz, 2H), 4.29, 4.23 (ABq, J = 12.2 Hz, 2H), 3.90-3.80 (m, 2H), 3.57-3.50 (m, 1H), 2.99 (s, 3H), 2.90-2.84 (m, 1H), 2.60-2.50 (m, 1H), 2.45-2.34 (m, 2H), 2.10-2.04 (m, 1H), 1.56 (s, 9H), 1.48 (s, 9H); LRMS-ES (m/z): [M + H]⁺ calcd for C₄₀H₄₉N₆O₇, 725.4; found, 725.6.

**Synthesis of Spiro Lactam 164.** To a solution of the N-Boc lactam 163 (12 mg, 0.017 mmol) in THF (5.0 mL) and H₂O (1.0 mL) was added PMe₃ (50 µL, 1.0 M in THF, 0.05 mmol). The reaction mixture was stirred at 70 °C for 12 h and then cooled to rt. After removal of THF *in vacuo*, the cloudy aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc, 1/1) to give the spiro-γ-lactam 164 (10 mg, 86%). ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.26 (m, 6H), 7.14-7.09 (m, 1H), 6.92 (t, J = 7.6 Hz, 2H), 6.58 (d, J = 7.3 Hz, 1H), 6.23 (s, 1H), 6.01 (s, 1H), 5.90 (d, J = 7.2 Hz, 1H), 4.82, 4.79 (ABq, J = 6.6 Hz, 2H), 4.68, 4.62 (ABq, J = 11.8 Hz, 2H), 4.53 (s, 2H), 3.25-3.16 (m, 3H), 3.00-2.90 (m, 1H), 2.85-2.70 (m, 1H), 2.55 (s, 3H), 2.45-2.40 (m, 1H), 2.35-
2.30 (m, 1H), 1.49 (s, 9H), 1.35 (s, 9H); LRMS-ES (m/z): [M + H]$^+$ calcd for C$_{40}$H$_{51}$N$_4$O$_7$, 699.4; found, 699.6.

**Synthesis of Alcohol 165.** To a solution of BOM ether 164 (29 mg, 0.041 mmol) in EtOAc (5.0 mL) was added Pearlman’s catalyst (25 mg). After stirring under an atmosphere of hydrogen for 12 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc, 1/3) to give the corresponding alcohol 165 (17 mg, 68%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 (br, 1H), 7.13 (br, 3H), 6.95 (br, 2H), 6.74 (br, 1H), 5.97 (br s, 1H), 5.88 (d, $J = 7.4$ Hz, 1H), 4.79 (br, 1H), 4.49 (br, 2H), 3.42 (br, 1H), 3.27 (br, 1H), 2.96 (br, 3H), 2.54 (s, 3H), 2.31 (br, 1H), 1.96 (br, 1H), 1.49 (s, 9H), 1.40 (s, 9H); LRMS-ES (m/z): [M + H]$^+$ calcd for C$_{32}$H$_{43}$N$_4$O$_6$, 579.3; found, 579.4.

**Synthesis of Aldehyde 167.** To a solution of BOM ether 162 (49 mg, 0.072 mmol) in THF (5.0 mL) was added Pearlman’s catalyst (50 mg). After stirring under an atmosphere of hydrogen for 14 h, the reaction mixture was filtered through a pad of Celite
and concentrated to give the corresponding alcohol which was not purified but used directly in the next step.

To a solution of the benzyl alcohol in DCM (5.0 mL) was added Dess-Martin periodinane (35 mg, 0.083 mmol). The reaction was stirred at rt for 15 min and quenched by the addition of 10% aqueous Na₂S₂O₅ solution. The aqueous mixture was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/3) to give the aldehyde 167 (30 mg, 75% for 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 10.08 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.06-6.88 (m, 4H), 6.78 (dd, J = 1.0, 7.8 Hz, 1H), 6.50 (dd, J = 1.0, 7.9 Hz, 1H), 6.25 (s, 1H), 5.70 (s, 1H), 4.55-4.46 (m, 1H), 4.03-3.92 (m, 1H), 3.41-3.32 (m, 1H), 3.17 (td, J = 4.5, 12.8 Hz, 1H), 3.01 (s, 3H), 2.74 (s, 3H), 2.60-2.49 (m, 3H), 1.96 (dd, J = 4.4, 13.8 Hz, 1H), 1.47 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 193.2, 172.6, 154.0, 151.1, 138.8, 134.6, 130.8, 130.0, 129.2, 127.6, 127.1, 126.2, 125.0, 117.4, 111.3, 82.6, 82.3, 67.9, 59.7, 46.8, 38.8, 36.7, 34.5, 31.2, 28.0, 27.9; HRMS-ES (m/z): [M + H]⁺ calcd for C₂₈H₃₄N₃O₇S, 556.2117; found, 556.2133.

**Synthesis of Azide 168.** To a solution of the mesylate 167 (25 mg, 0.045 mmol) in DMF (1.5 mL) was added NaN₃ (50 mg, 0.77 mmol). The reaction mixture was stirred at 90 °C for 2 h and diluted with H₂O. The aqueous mixture was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue
was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/1) to give the azide 168 (14 mg, 61%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.10 (s, 1H), 8.11 (dd, $J$ = 2.5, 7.6 Hz, 1H), 7.05-6.94 (m, 4H), 6.77 (dd, $J$ = 1.1, 7.8 Hz, 1H), 6.49 (dd, $J$ = 1.0, 7.9 Hz, 1H), 6.14 (s, 1H), 5.70 (s, 1H), 3.72-3.63 (m, 1H), 3.38-3.32 (m, 1H), 3.17 (td, $J$ = 4.7, 12.9 Hz, 1H), 3.00 (s, 3H), 2.92-2.82 (m, 1H), 2.55 (td, $J$ = 6.1, 13.3 Hz, 1H), 2.33 (t, $J$ = 8.8 Hz, 2H), 1.95 (dd, $J$ = 4.5, 13.8 Hz, 1H), 1.45 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 193.4, 172.8, 154.0, 151.1, 138.6, 134.7, 131.2, 130.1, 129.1, 127.5, 126.9, 126.3, 125.1, 117.3, 111.1, 82.7, 82.0, 59.8, 48.7, 47.2, 38.8, 35.1, 31.1, 28.1, 28.0; HRMS-ES (m/z): [M + H]$^+$ calcd for C$_{27}$H$_{31}$N$_6$O$_4$, 503.2407; found, 503.2418.

**Synthesis of TBS Ether 169.** To a solution of BOM ether 162 (320 mg, 0.47 mmol) in THF (10.0 mL) was added Pearlman’s catalyst (320 mg). After stirring under an atmosphere of hydrogen for 12 h, the reaction mixture was filtered through a pad of Celite and concentrated to give the corresponding alcohol which was not purified but used directly in the next step.

To a solution of the crude alcohol in DCM (70 mL) was added imidazole (78 mg, 1.15 mmol) and TBSCl (130 mg, 0.86 mmol). After stirring at rt for 4 h, the reaction mixture was quenched with aqueous NaHCO$_3$ and extracted with DCM. The organic layers were combined, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/1) to give TBS ether 169 (275 mg,
87%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.19 (d, $J$ = 6.9 Hz, 1H), 6.97-6.86 (m, 4H), 6.59 (d, $J$ = 7.5 Hz, 1H), 6.23 (d, $J$ = 7.1 Hz, 1H), 5.77 (d, $J$ = 2.5 Hz, 1H), 5.57 (s, 1H), 4.52-4.46 (m, 1H), 4.47 (d, $J$ = 13.0 Hz, 1H), 4.18 (d, $J$ = 12.9 Hz, 1H), 3.97-3.88 (m, 1H), 3.52 (td, $J$ = 4.3, 12.6 Hz, 1H), 3.34-3.28 (m, 1H), 2.95 (s, 3H), 2.72 (s, 3H), 2.60-2.41 (m, 3H), 2.05-2.00 (m, 1H), 1.45 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.1, 154.1, 150.6, 138.9, 137.0, 130.7, 128.5, 127.2, 126.8, 126.4, 126.0, 124.3, 118.4, 105.8, 83.1, 81.9, 68.1, 62.1, 58.9, 46.4, 39.6, 36.6, 34.6, 31.3, 28.6, 28.1, 25.9, 18.2, -5.17, -5.21; LRMS-ES (m/z): [M + H]$^+$ calcd for C$_{34}$H$_{50}$N$_3$O$_7$SSi, 672.3; found, 672.5.

**Synthesis of Azide 170.** To a solution of the mesylate 169 (32 mg, 0.048 mmol) in DMF (1.5 mL) was added LiN$_3$ (235 mg, 20% wt in H$_2$O, 0.96 mmol). The reaction mixture was stirred at 90 °C for 4 h and diluted with H$_2$O. The aqueous mixture was extracted with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified via preparative TLC (hexanes/EtOAc, 1/1) to give the azide 170 (23 mg, 78%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.19 (d, $J$ = 7.0 Hz, 1H), 6.97-6.86 (m, 4H), 6.60 (d, $J$ = 7.6 Hz, 1H), 6.22 (d, $J$ = 7.5 Hz, 1H), 5.92 (d, $J$ = 2.4 Hz, 1H), 5.57 (s, 1H), 4.49 (d, $J$ = 13.0 Hz, 1H), 4.19 (d, $J$ = 13.0 Hz, 1H), 3.66-3.46 (m, 2H), 3.34-3.28 (m, 1H), 2.95 (s, 3H), 2.89-2.79 (m, 1H), 2.51-2.42 (m, 1H), 2.30 (t, $J$ = 8.8 Hz, 2H), 2.05-1.99 (m, 1H), 1.44 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR
(75 MHz, CDCl₃) δ 173.7, 154.2, 150.7, 138.7, 137.1, 131.1, 128.5, 127.1, 126.6, 126.5, 126.1, 124.4, 118.2, 105.8, 83.3, 81.7, 62.1, 59.0, 48.9, 46.9, 39.6, 35.2, 31.9, 31.3, 28.7, 28.1, 25.9, 18.3, -5.18, -5.19; LRMS-ES (m/z): [M + H]+ calcd for C₃₃H₄₇N₆O₄Si, 619.3; found, 619.5.

**Synthesis of Alcohol 171.** To a solution of TBS ether 170 (206 mg, 0.33 mmol) in THF (25 mL) was added TBAF (1 M solution in THF, 0.67 mL, 0.67 mmol) at rt. After 12 h at rt, the reaction mixture was diluted with saturated aqueous NH₄Cl and then EtOAc and H₂O. Solid NaCl was added to saturate the aqueous phase and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by silica gel flash chromatography (hexanes/EtOAc, 1/2) to give the benzyl alcohol 171 (164 mg, 98%). ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, J = 6.8 Hz, 1H), 7.18 (s, 1H), 6.97-6.84 (m, 4H), 6.58 (d, J = 7.4 Hz, 1H), 6.24 (d, J = 7.4 Hz, 1H), 5.59 (s, 1H), 4.46, 4.26 (ABq, J = 12.7 Hz, 2H), 3.69-3.59 (m, 1H), 3.49 (td, J = 4.4, 12.9 Hz, 1H), 3.35-3.25 (m, 1H), 2.95 (s, 3H), 2.90-2.80 (m, 1H), 2.46 (td, J = 6.0, 13.4 Hz, 1H), 2.31 (t, J = 8.5 Hz, 2H), 2.03-1.98 (m, 1H), 1.44 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 174.3, 154.0, 150.8, 138.9, 136.7, 131.4, 128.7, 127.3, 127.2, 126.6, 125.9, 124.3, 119.0, 106.1, 83.2, 81.7, 61.6, 59.1, 48.9,
46.7, 39.3, 35.0, 31.3, 28.3, 28.1; LRMS-ES (m/z): [M + H]+ calcd for C_{27}H_{33}N_{6}O_{4}, 505.3; found, 505.3.

**Synthesis of N-Boc Lactam 172.** To a solution of lactam 168 (10.0 mg, 0.020 mmol) in THF (5 mL) was added LiHMDS (22 µL, 1.0 M in THF, 0.022 mmol) and (Boc)_{2}O (7.0 mg, 0.032 mmol). The reaction mixture was stirred at rt for 10 min and quenched with aqueous saturated NaHCO_{3}. The mixture was diluted with H_{2}O and extracted with EtOAc. The combined organic layers were dried over Na_{2}SO_{4} and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc, 2/1), to give N-Boc lactam 172 (10.0 mg, 85%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 9.84 (s, 1H), 8.07 (d, \(J = 7.9\) Hz, 1H), 7.12 (t, \(J = 7.7\) Hz, 1H), 6.98-6.93 (m, 3H), 6.88 (d, \(J = 7.8\) Hz, 1H), 6.57 (d, \(J = 7.9\) Hz, 1H), 5.73 (s, 1H), 4.00-3.90 (m, 1H), 3.65-3.60 (m, 1H), 3.50-3.45 (m, 1H), 3.05 (s, 3H), 2.95-2.85 (m, 1H), 2.70-2.60 (m, 1H), 2.50-2.40 (m, 1H), 2.15-2.05 (m, 1H), 1.62 (s, 9H), 1.25 (s, 9H); LRMS-ES (m/z): [M + H]+ calcd for C_{32}H_{39}N_{6}O_{6}, 603.3; found, 603.3.
Synthesis of (E)-α,β-Unsaturated Ketone 173. To a solution of the aldehyde 168 (130 mg, 0.26 mmol) in acetone (20.0 mL) was added 10% aqueous NaOH solution (2.4 mL). The reaction mixture was stirred at 60 °C for 3 h and then cooled to rt. After removal of acetone in vacuo, the cloudy aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/1) to give the (E)-α,β-unsaturated ketone 173 (130 mg, 93%). ¹H NMR (300 MHz, CDCl₃) δ 8.35 (dd, J = 2.0, 6.6 Hz, 1H), 7.59 (d, J = 16.0 Hz, 1H), 6.98-6.91 (m, 4H), 6.35 (t, J = 7.9 Hz, 2H), 6.20 (d, J = 16.0 Hz, 1H), 5.74 (s, 1H), 5.63 (s, 1H), 3.66-3.59 (m, 1H), 3.29-3.26 (m, 1H), 3.16 (td, J = 4.4, 12.7 Hz, 1H), 3.00 (s, 3H), 2.89-2.82 (m, 1H), 2.55-2.44 (m, 1H), 2.49 (s, 3H), 2.31 (t, J = 8.6 Hz, 2H), 2.02-1.95 (m, 1H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 199.9, 173.2, 154.0, 151.1, 145.1, 138.8, 132.7, 131.5, 131.2, 129.1, 128.6, 127.4, 126.9, 125.9, 124.7, 118.6, 107.8, 82.6, 81.9, 58.9, 48.8, 46.5, 39.4, 35.2, 31.1, 28.8, 28.1, 26.5; HRMS-ES (m/z): [M + H]⁺ calcd for C₃₀H₃₅N₆O₄, 543.2720; found, 543.2720.
Synthesis of N-Boc Lactam 174. To a solution of lactam 173 (130 mg, 0.24 mmol) in THF (40.0 mL) was added LiHMDS (0.26 mL, 1.0 M in THF, 0.26 mmol) and (Boc)$_2$O (63 mg, 0.29 mmol). The reaction mixture was stirred at rt for 10 min and quenched with aqueous saturated NaHCO$_3$. The mixture was diluted with H$_2$O and extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1, 3/1 then 1/1) to give N-Boc lactam 174 (125 mg, 81%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.34 (d, $J = 7.2$ Hz, 1H), 7.42 (d, $J = 16.0$ Hz, 1H), 6.97-6.88 (m, 4H), 6.32 (t, $J = 7.2$ Hz, 2H), 6.21 (d, $J = 16.0$ Hz, 1H), 5.61 (s, 1H), 3.63 (dd, $J = 4.0$, 13.3 Hz, 1H), 3.52-3.38 (m, 2H), 2.95 (s, 3H), 2.91-2.81 (m, 1H), 2.51 (td, $J = 5.6$, 13.6 Hz, 1H), 2.37 (s, 3H), 2.37-2.30 (m, 2H), 2.01-1.96 (m, 1H), 1.48 (s, 9H), 1.43 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 198.9, 171.5, 153.9, 152.8, 150.8, 143.2, 138.5, 133.1, 132.7, 131.1, 129.2, 128.4, 127.5, 127.0, 125.5, 124.9, 118.7, 107.7, 83.9, 82.4, 81.9, 59.0, 48.4, 48.2, 44.0, 34.2, 31.0, 29.4, 28.0, 27.6, 26.4; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{35}$H$_{43}$N$_6$O$_6$, 643.3244; found, 643.3247.
Synthesis of Spiro-γ-Lactam 175. To a solution of the N-Boc lactam 174 (140 mg, 0.22 mmol) in THF (60.0 mL) and H₂O (12.0 mL) was added PMe₃ (2.0 mL, 1.0 M in THF, 2.0 mmol). The reaction mixture was stirred at 70 °C for 13 h and then cooled to rt. After removal of THF *in vacuo*, the cloudy aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/3) to give the spiro-γ-lactam 175 (118 mg, 88%). ¹H NMR (300 MHz, CDCl₃) δ 8.29 (br s, 0.5H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.20 (br s, 0.8H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.98-6.93 (m, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.04 (s, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 4.66 (s, 0.8H), 3.44-3.38 (m, 1H), 3.21 (t, *J* = 9.7 Hz, 1H), 2.99-2.92 (m, 2H), 2.78 (br s, 2H), 2.37 (s, 3H), 2.42-2.37 (br m, 1H), 2.05-1.98 (m, 1H), 1.52 (s, 9H), 1.35 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 199.5, 176.0, 155.4, 153.8, 151.6, 143.5, 137.5, 136.9, 134.1, 129.3, 126.7, 125.9, 125.4, 125.3, 114.5, 105.6, 82.3, 81.6, 79.2, 62.1, 52.8, 40.1, 37.7, 35.5, 34.6, 30.0, 28.3, 28.2, 27.4; HRMS-ES (*m/z*): [M + H]⁺ calcd for C₃₅H₄₅N₄O₆, 617.3339; found, 617.3342.
Synthesis of Allylic Alcohol 179. To a solution of the spiro-γ-lactam 175 (113 mg, 0.18 mmol) in THF (30.0 mL) was added MeLi (0.57 mL, 1.6 M in Et₂O, 0.91 mmol) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 15 min and then quenched with saturated aqueous NaHCO₃. After removal of THF in vacuo, the residue was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc) to give the allylic alcohol 179 (85 mg, 73%). ¹H NMR (300 MHz, CDCl₃) δ 7.45 (d, J = 7.5 Hz, 1H), 7.27 (br s, 0.8H), 7.21 (br s, 0.6H), 7.12 (td, J = 1.2, 7.4 Hz, 1H), 6.99-6.89 (m, 2H), 6.85 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.10 (d, J = 11.2 Hz, 1H), 5.90 (s, 0.7H), 5.87 (d, J = 7.8 Hz, 1H), 4.80 (br s, 0.8H), 4.27 (br s, 0.8H), 3.46-3.40 (m, 1H), 3.24 (t, J = 9.7 Hz, 1H), 3.09 (br s, 1H), 2.99-2.91 (m, 1H), 2.83-2.79 (m, 1H), 2.72-2.64 (br m, 1H), 2.47 (s, 3H), 2.18-2.06 (m, 1H), 1.92-1.84 (m, 1H), 1.51 (s, 9H), 1.41 (s, 3H), 1.37 (s, 9H), 1.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 155.7, 153.9, 15.08, 138.9, 138.3, 137.6, 137.1, 129.0, 126.4, 126.1, 125.2, 124.9, 123.4, 114.7, 103.7, 82.8, 81.3, 79.6, 70.5, 60.4, 52.8, 40.1, 38.1, 35.4, 35.1, 30.7, 30.0, 28.8, 28.4, 28.3; HRMS-ES (m/z): [M + H]⁺ calcd for C₃₆H₄₉N₄O₆, 633.3652; found, 633.3647.
Synthesis of Hexacyclic Compound 180 and Diene 181. To a solution of the allylic alcohol 179 (83 mg, 0.13 mmol) in CHCl₃ (20.0 mL) was added PPTS (3.3 mg, 0.013 mmol). The reaction mixture was stirred at rt for 1.5 h. After removal of CHCl₃ in vacuo, the residue was purified by flash column chromatography on silica gel (hexanes/acetone, 5/1) to give the hexacycle 180 (51 mg, 62%) and diene 181 (20 mg, 24%).

Hexacycle 180: ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.32 (br m, 1H), 7.26-7.23 (br m, 1H), 7.13 (t, J = 7.7 Hz, 1H), 6.92 (td, J = 1.3, 7.7 Hz, 1H), 6.88 (t, J = 7.9 Hz, 1H), 6.28 (br d, J = 6.7 Hz, 1H), 5.98 (br s, 1H), 5.89 (d, J = 7.6 Hz, 1H), 5.84 (s, 1H), 5.55 (br s, 1H), 5.10 (br s, 1H), 3.91 (br s, 1H), 3.47 (br d, J = 9.0 Hz, 1H), 3.14-2.90 (m, 4H), 2.45 (s, 3H), 2.14-2.09 (br m, 1H), 1.98-1.92 (br m, 1H), 1.84 (s, 3H), 1.75 (s, 3H), 1.51 (s, 9H), 1.48 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 174.3, 156.2, 153.5, 150.6, 139.3, 137.3, 133.3, 128.8, 126.4, 125.9, 125.1, 125.0, 124.3, 116.9, 103.2, 89.5, 81.2, 79.6, 61.2, 59.7, 52.3, 41.0, 39.2, 36.1, 30.7, 28.6, 28.4, 25.6, 18.9; HRMS-ES (m/z): [M + H]⁺ calcd for C₃₆H₄₇N₄O₅, 615.3546; found, 615.3560.

Diene 181: ¹H NMR (300 MHz, CDCl₃) δ 7.49 (d, J = 7.7 Hz, 1H), 7.45 (br s, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.97 (td, J = 1.4, 7.8 Hz, 1H), 6.88 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 14.6 Hz, 1H), 6.74 (d, J = 7.3 Hz, 1H), 6.61 (d, J = 15.8 Hz, 1H), 5.97 (s, 1H), 5.88 (d, J = 7.6 Hz, 1H), 4.96 (s, 1H), 4.85 (s, 1H), 4.42 (br s, 1H), 3.48-3.42 (m, 1H), 3.26 (t, J = 9.8
1H, 3.01-2.94 (m, 2H), 2.82 (br s, 1H), 2.52 (s, 3H), 2.46-2.37 (m, 1H), 2.03-1.86 (m, 1H), 1.91 (s, 3H), 1.53 (s, 9H), 1.38 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.8, 155.4, 151.3, 142.3, 138.2, 137.2, 131.5, 129.1, 128.2, 126.6, 126.1, 125.3, 125.1, 123.5, 116.7, 114.4, 103.9, 82.9, 81.4, 79.2, 61.5, 52.7, 40.1, 37.8, 35.2, 30.6, 28.4, 28.3, 19.2; HRMS-ES ($m/z$): [M + H]$^+$ calcd for C$_{36}$H$_{47}$N$_4$O$_5$, 615.3546; found, 615.3554.

**Synthesis of Imidate 182.** To a solution of the lactam 180 (12.0 mg, 0.020 mmol) in DCM (10.0 mL) was added DIPEA (34 µL, 0.20 mmol) and Me$_3$OBF$_4$ (29 mg, 0.20 mmol). The reaction mixture was stirred at rt for 30 min and quenched with saturated aqueous NaHCO$_3$. The solution was diluted with H$_2$O and extracted with DCM. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by preparative TLC (hexanes/acetone, 2/1) to give the imidate 182 (10.5 mg, 86%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.25 (d, $J = 5.4$ Hz, 1H), 7.13 (td, $J = 1.4$, 7.5 Hz, 1H), 6.95-6.89 (m, 2H), 6.77 (d, $J = 7.8$ Hz, 1H), 6.33 (br s, 1H), 5.96 (d, $J = 6.8$ Hz, 1H), 5.68 (s, 1H), 5.18 (br s, 1H), 3.92-3.65 (m, 4H), 3.78 (s, 3H), 3.48-3.36 (br m, 1H), 3.26-3.14 (br m, 1H), 2.98-2.73 (br m, 2H), 2.38 (s, 3H), 2.24-2.15 (m, 1H), 1.84 (s, 3H), 1.74 (s, 3H), 1.51 (s, 9H), 1.50 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.1, 155.8, 153.5, 150.7, 140.3, 136.8, 128.4, 126.3, 125.0, 124.9, 124.8, 124.5, 116.9, 103.5, 81.4, 80.2, 59.1, 57.9,
55.6, 51.1, 40.1, 38.4, 31.2, 29.7, 28.5, 28.4, 25.7, 18.8; HRMS-ES (m/z): [M + H]$^+$ calcld for C$_{37}$H$_{49}$N$_4$O$_5$, 629.3703; found, 629.3723.

**Synthesis of Amidine 183.** To a solution of the imidate 182 (13.0 mg, 0.021 mmol) in DCM (5.0 mL) was added TFA (0.25 mL). The reaction mixture was stirred at rt for 45 min and quenched with saturated aqueous NaHCO$_3$. The solution was extracted with DCM. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by preparative TLC (hexanes/acetone, 2/1) to give the amidine 183 (9.0 mg, 88%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.07-6.96 (m, 2H), 7.05 (dd, $J$ = 1.4, 7.4 Hz, 1H), 6.86 (t, $J$ = 8.5 Hz, 1H), 6.78 (t, $J$ = 7.7 Hz, 1H), 6.05 (dd, $J$ = 7.9, 12.9 Hz, 2H), 5.79 (br s, 0.6H), 5.61 (br s, 0.4H), 5.36-5.31 (m, 1H), 4.81 (d, $J$ = 8.7 Hz, 1H), 3.83-3.73 (m, 2H), 3.36-3.29 (m, 1H), 3.26-3.18 (m, 1H), 2.90 (s, 3H), 2.87-2.77 (m, 1H), 2.29-2.20 (m, 1H), 2.07-2.00 (m, 1H), 1.85 (br s, 1H), 1.78 (s, 3H), 1.71 (s, 3H), 1.42 (br s, 5H), 1.23 (s, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 180.0, 154.0, 149.6, 137.7, 136.6, 134.3, 130.2, 129.7, 128.5, 127.5, 126.6, 124.6, 123.9, 121.9, 116.9, 104.3, 81.0, 79.1, 60.1, 58.6, 54.9, 54.8, 45.5, 38.3, 30.4, 28.3, 27.0, 25.7, 18.6; HRMS-ES (m/z): [M + H]$^+$ calcld for C$_{31}$H$_{37}$N$_4$O$_2$, 497.2917; found, 497.2918.
Synthesis of (±)-Communesin F (8). To a solution of the amidine 183 (14.0 mg, 0.028 mmol) in glacial acetic acid (0.8 mL) and acetic anhydride (0.8 mL) was added NaBH₄ (90 mg, 2.38 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and quenched with saturated aqueous Na₂CO₃. The aqueous solution was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The resulting N-acetyl aminal was not purified and was used directly in the next step.

To a solution of the N-acetyl aminal in DCM (5.0 mL) was added TFA (2.0 mL). The reaction mixture was stirred at rt for 12 h and quenched with saturated aqueous Na₂CO₃. The aqueous solution was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/acetone, 5/1 then 2/1) to give (±)-communesin F (8, 8.2 mg, 66% for 2 steps).

As described by the Qin group, (±)-communesin F exists as two amide rotamers at a ratio of 2.6: 1 in CDCl₃ as shown by its ¹H NMR spectrum. Only the NMR data for the major rotamer is listed:

Major Rotamer of 8: ¹H NMR (300 MHz, CDCl₃) δ 6.98 (d, J = 1.7, 7.7 Hz, 1H), 6.80 (t, J = 7.7 Hz, 1H), 6.72-6.64 (m, 3H), 6.06 (d, J = 7.7 Hz, 1H), 5.84 (d, J = 7.6 Hz, 1H), 5.21 (br d, J = 8.9 Hz, 1H), 5.09 (s, 1H), 5.03 (d, J = 8.8 Hz, 1H), 4.64 (s, 1H), 3.83 (dd, J = 8.8, 11.4 Hz, 1H), 3.76 (br s, 0.5H), 3.34-3.27 (m, 1H), 3.25-3.17 (m, 1H), 3.04-
2.96 (m, 1H), 2.80 (s, 3H), 2.75-2.70 (m, 1H), 2.38 (s, 3H), 2.30-2.18 (m, 2H), 1.97-1.91 (m, 1H), 1.83 (d, J = 1.2 Hz, 3H), 1.76 (d, J = 1.1 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.6, 150.1, 142.7, 140.6, 136.1, 132.7, 131.3, 128.3, 127.3, 124.6, 123.2, 120.6, 117.0, 114.7, 100.7, 82.6, 79.5, 64.4, 51.8, 51.2, 44.2, 37.8, 36.2, 30.8, 29.6, 26.0, 22.6, 18.5;

HRMS-ES (m/z): [M + H]$^+$ calcd for C$_{28}$H$_{33}$N$_4$O, 441.2654; found, 441.2635.
References:


Vita

Peng Liu

Peng Liu was born and brought up in China. He attended University of Science and Technology of China in 1999 and got his undergraduate degree in chemistry in 2004. He then enrolled in the Pennsylvania State University as a graduate student to continue his study in chemistry. At Penn State, he joined Prof. Steven M. Weinreb’s research group and completed the total syntheses of (-)-secu’amamine A and (±)-communesin F. He passed his Ph.D. defense on June 24, 2010 and will take a postdoc position in Harvard University with Professor E.J. Corey.