CHAPTER ONE: STUDIES DIRECTED TOWARDS A TOTAL SYNTHESIS OF
THE CHARTELLAMIDES

CHAPTER TWO: STUDIES DIRECTED TOWARDS A TOTAL SYNTHESIS OF
THE CHARTELLINES

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Abstract

Chapter 1

In work directed towards a total synthesis of the chartellamides, several strategies were investigated to construct the pentacyclic core of this marine alkaloid with the correct relative stereochemistry at C9,20.

The first approach involved intermolecular addition of aryl Grignard reagents to \textit{in situ} generated $N$-acyliminium ions. Thus, $N$-acyl hemiaminals 77a-c were synthesized from the addition of alkyl Grignards to the carbonyl of $\gamma$-lactam 76. Unfortunately, \textit{in situ} formation of $N$-acyliminium ion 81 from $N$-acyl hemiaminals 77a-c, followed by addition of aryl Grignard 82 did not give the desired C9 addition product 80.

Alternatively, an intramolecular cyclization approach towards diastereoselectively forming the C9,20 adjacent quaternary centers was examined. Cyclization precursor 117 was synthesized from $\gamma$-lactam 84 in five steps \textit{via} addition of a lithio acetylide to the C9 carbonyl group of sulfonamide 115 followed by a Meyer-Schuster rearrangement of the resulting hemiaminal 116. However, attempts to cyclize arylbromide 117 using either radical or reductive Heck conditions resulted in ring opening of the $\beta$-lactam to form undesired indole products 119 or 122, respectively.

Finally, a novel method for the construction of the bromoenamide moiety of the chartellamides was developed based on an extension of the known copper catalyzed coupling of amides with vinylhalides. In this study, haloenamides were constructed both inter- and intramolecularly \textit{via} a halogen-selective N-vinylation reaction.
Chapter 2

In work directed towards a total synthesis of the marine alkaloids chartelline A-C (1-3), a model system was explored to probe the formation of the 10-membered macrocycle via RCM. After an initial model study demonstrated that ketone enolates add effectively to the carbonyl of activated N-acyl γ-lactams, the requisite ketoimidazole 292 was synthesized from known aldehyde imidazole 259 in 4 steps and 50% overall yield. However, addition of the enolate of ketoimidazole 292 to the C12 carbonyl of N-acyl γ-lactam 293 resulted in formation of vinylogous amide 297 rather than the desired hemiaminal 295.

An alternative route was therefore examined in which the bond between C11 and C12 would be formed via the addition of a metallated (Z)-alkene to the activated carbonyl group. Simple model reactions between the metallated alkene of vinyliodide 310 and γ-lactams 96 and 76 gave hemiaminals 311 and 312, respectively. After this successful model study the requisite iodovinylimidazole 302 was synthesized from either alcohol imidazole 314 or alkynyl imidazole 262. Unfortunately, formation of the metallated anion of 302 followed by addition of N-acyl γ-lactam 231 resulted in formation of alkynememial 263 rather than the desired alkene hemiaminal 310.

We next turned to an alternative approach in which the chloroenamide moiety of the chartellines would first be constructed and then the macrocycle would be closed via either the intramolecular addition of a ketone enolate or a metallated (Z)-alkene to the activated C12 γ-lactam carbonyl moiety. Thus, ketoimidazole 317 and related imidazoles 324, 325, 330 were synthesized through functional group manipulations of aldehyde imidazole 259 or isobutenyl imidazole 281. Unfortunately, coupling of these imidazoles,
which contained the C9-C11 functionality found in the chartellines, with \( \text{NH-\( \beta \)-lactams} \) 260, 316, or 334 did not give any of the desired haloenamide products. Fortunately, imidazoles 247, 370, and 403, containing the C9,10 functionality of the chartellines, were found to couple with \( \text{NH-\( \beta \)-lactams} \) to form the desired chloroenamide products. Efforts are being made to utilize these chloroenamide products to construct the 10-membered macrocycle towards completion of a total synthesis of the chartellines.
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Chapter 1

Studies Directed Towards a Total Synthesis of the Chartellamides

Part 1

Introduction and Background

1.1 Isolation and Structural Identification of the Chartellines, Chartellamides and Securamines

Chartellines A (1), B (2), C (3) and methoxydechlorochartelline A (4) belong to a small group of highly halogenated β-lactam alkaloids isolated by Christophersen and coworkers from the marine bryozoan *Chartella papyracea* collected in the North Sea (Figure 1).\(^1\) Compound 4 is most likely an artifact of the isolation procedure and can be formed from chartelline A (1) by reaction with methanol/sodium methoxide solution at room temperature (*vide infra*). In addition to the chartellines, two biogenetically related compounds, the chartellamides A (5) and B (6), were isolated during the 1980's.\(^2\) Several congenic alkaloids in which the β-lactam moiety has rearranged into a γ-lactam (i.e. securamines A (7), B (8), C (11), D (12), E (13), F (14) and G (15)) were isolated from *Securiflustra securifrons*.\(^3\) Their structures were determined by a combination of NMR and mass spectrometry analysis. The relative configurations of securamines C-G were established through extensive NMR NOE experiments, but this methodology was unable
to establish the relative configurations of securamines A and B. The absolute configuration of all the securamines is at present unknown. The relative configurations of securamines A and B are difficult to determine because in DMSO solution 7 and 8 are in equilibrium with the macrocyclic indoles, securine A (9) and B (10), respectively. It is not clear whether the securines are natural products, as they have not been directly isolated from the marine bryozoans.

**Figure 1.** Alkaloids isolated from *Chartella papyracea* and *Securiflustra securifrons*
Chartelline A (1) was the first member of this family of metabolites to be fully characterized (Figure 2). The molecule is composed of a unique highly halogenated pentacyclic core, containing a spiro-β-lactam and 10-membered hetero macroring. X-ray analysis of 1 indicated that the macrocyclic ring adopts a rigid "tub-like" conformation in which the indolenine system is parallel to the imidazole ring and nearly perpendicular to the spiro-β-lactam. In this conformation there is very little conjugation between the indolenine and the lower alkene, or between the β-lactam and the haloenamide double bond. The absolute configuration of C20 was established to be $S$ at a better than 99.5% significance level according to Hamilton's $R$-factor test.\(^4\) Chartelline A (1) can exist in two tautomeric forms because of proton exchange between the N5 and N7 positions of the 2-bromoimidazole moiety. In the crystalline form the N-7-H tautomer is preferred. In contrast, when chartelline A (1) is in solution the N-5-H tautomer predominates, as determined by NMR analysis.

![Figure 2. X-ray structure of chartelline A (1)](image)

The structural assignments of the chartellamides are based on NMR NOE experiments (Figure 3).\(^2\) The CD curves of both 5 and 6 are nearly superimposable and
thus they probably have the same absolute configuration. Based on the known C20 configuration of chartelline A (1) the chartellamides are proposed to have the (9S, 11R, 12R, 20S) configuration. Interestingly, the stereochemical assignment of the chartellamides is based on the lack of an NOE enhancement between the C21 protons and the C10 protons, "strongly indicating that the two rings are trans with respect to the plane."\(^2\) This configuration would create a very strained, fairly flat molecule as depicted in Figure 3. Alternatively, the C9,20 stereocenter could be cis with respect to the β-lactam nitrogen and the imidazole ring. This structure 5b, would have more of a cup shape and the six-membered ring containing the nitrogen of the indoline and nitrogen of the imidazole would be in a chair conformation. We believe that based on the inconclusive nature of the NMR NOE experiments there is some question as to the true structure of the chartellamides, and further studies are warranted.
Figure 3. Possible stereostructures of the chartellamides
1.2 Biological Activity of the Chartelline Class of Marine Alkaloids

None of these marine alkaloids have shown significant biological activity. Chartelline A (1) is inactive against gram positive and negative bacteria, as well as molds. In addition, 1 is inactive against leukemia screen 3PS31 at a dose level of 5.60 mg/kg and had ED$_{50}$ values of 31 and 29 µg/mL in \textit{in vitro} PS and KB tests, respectively.\textsuperscript{1b}

1.3 Proposed Biosynthesis of the Chartelline, Chartellamide and Securamine Alkaloids

In Nature, the chartelline, chartellamide and securamine alkaloids are purported to be derived from the securines (Figure 4).\textsuperscript{1,3} The chartellines are proposed to be formed \textit{via} path a through an oxidative cyclization of the amide nitrogen of the securines onto the indole C3 position. Similarly, following path b, C3 protonation of the indole followed by attack of the amide onto the indole C2 position would form the securamine structures. In turn, the securines are most likely derived from one isoprene unit 18, tryptophan (16) and histidine (17). It is unclear as to whether the chartellamides are derived directly from the securines or \textit{via} some other pathway. There have been no experimental studies on the biosynthesis of this group of alkaloids.
The Christophersen group has proposed that methoxydechlorochartelline A (4) is an artifact of the isolation procedure and is formed directly from chartelline A (1). They prepared methoxydechlorochartelline A (4), in 80% yield, by refluxing chartellamide A (1) in a solution of methoxide in methanol. The Sorensen group has envisioned this transformation to proceed via elimination of chloride ion from chartelline A (1) to give allene intermediate 19 (Scheme 1). Addition of methoxide ion to allene 19 affords methoxydechlorochartelline A (4).
An alternative mechanism for this transformation is attack of methoxide at C3 of chartellamide A (1) resulting in ring opening of the β-lactam to form indole 20 (Scheme 2). Cyclization of indole anion 20 via $S_N2'$ attack on the nitrogen would give methoxydechlorochartelline A (4) after protonation. Some support for this type of mechanism can be found in the cyclization work of Isobe in which an indole anion is cyclized onto an activated nitrogen to give an indolenine β-lactam (see, Chapter 2, Section 1.1.1, pg. 74). Additionally, our work has demonstrated that the β-lactam can ring open under Brønsted acidic (see, Chapter 1, Section 2.3, pg. 23), Lewis acidic and basic conditions (see, Chapter 1, Section 2.4, pg. 34).
1.4 Synthetic Approaches to the Chartellamides

These metabolites present a formidable synthetic challenge not only due to their extensive halogenation patterns but also because of their unprecedented heterocyclic arrays including a spiro-β-lactam, macrocyclic haloenamide and adjacent quaternary centers at C9,20. However, there are no published reports of synthetic work on the chartellamides (5/6) except for our preliminary study in this area.6 In addition, a model system for the synthesis of the pentacyclic core of the chartellamides has been explored by the Sorensen group and is described in an unpublished thesis.5

1.4.1. Sorensen's Synthetic Approach to the Pentacyclic Core of the Chartellamides

The Sorensen group has investigated an interesting approach towards synthesis of the chartellamides via use of a photoinduced electron transfer (PET)7,8 reaction for the construction of the pentacyclic core.5 The cyclization precursors were prepared by N-acylation of the bromohistidin derivative with indoleacetic acid (21a) or 2-prenyl-indoleacetic acid (21b), followed by hydrolysis of the resultant esters 22a,b with lithium

Scheme 3
hydroxide in methanol to give carboxylic acid salts 23a,b (Scheme 3). A variety of other indole / imidazole derivatives similar to 23 were formed by varying the halogen on the imidazole and substitution on the indole ring.

Cyclization precursors 23a,b were subjected to PET conditions in order to effect carbon-carbon bond formation. The optimized conditions resulted in conversion of bromoimidazole 23a into four isolable products (Scheme 4). Lactam 24 and dehalogenated product 25 were formed along with some of the desired biaryl coupling products 26 and 27. No stereochemical information was given as to the relationship between the β-lactam nitrogen and imidazole moieties in 27. Subjection of prenyl compound 23b to the PET conditions did not give the desired cyclization product.

Sorensen proposed that mechanistically the PET reaction of 23a begin with photolysis of the electron-rich indole promoting electron transfer to the pendant electron-deficient bromoimidazole moiety to afford radical cation / radial anion intermediate 28.
Coupling of diradical 28 at the C2 position of the indole followed by expulsion of bromide ion would give iminium ion 30. It is proposed that π-stacking of the iminium and imidazole subunits facilitated the cyclization by placing the two radicals in close proximity, as illustrated in conformer 29. Finally, attack of the amide nitrogen onto the indole 3-position of iminium 30 would then form pentacycle 27.

Scheme 5

1.5 Previous Synthetic Studies on the Chartellamides in the Weinreb Group

Pinder and Weinreb recently reported model studies towards the synthesis of chartellamides A (5) and B (6), and tested the feasibility of forming the unique pentacyclic core of the molecule with the desired relative stereochemistry at C9,20. Retrosynthetically, the lower two rings of the chartellamides would be formed at the end of the synthesis from pentacycle 31 (Scheme 6). It was hoped that addition of an allyl nucleophile to an N-acyliminium ion derived from 32 would give pentacycle 31 in which
the two adjacent quaternary carbons at C9,20 would be trans with respect to the β-lactam nitrogen and imidazole ring. β-Lactam 32 would result from a Staudinger [2+2] cyclization of imine 33 with a ketene. Functional group manipulation of vinyl imidazole 34 would give imine 33. Finally, addition product 34 could result from addition of metallated imidazole 36 to dibromoisatin derivative 35.

Scheme 6

An initial model study was developed to test the viability of this synthetic approach to the chartellamides in which a simple benzene ring was employed as an imidazole surrogate. The synthesis began with the addition of 2-lithiostyrene to the lactam carbonyl group of isatin ketal derivative 37 to afford adduct 38 (Scheme 7). Subsequent O-methylation of aminal 38 and functional group manipulation of the vinyl moiety generated ketal azide 40 in four steps. Selective hydrolysis of the ketal functionality of 40 could be achieved in the presence of the acid labile BOC group to give...
a keto azide, which was cyclized via an aza-Wittig reaction to yield the desired seven-membered ring imine \( \text{41} \). Staudinger [2+2] cycloaddition of imine \( \text{41} \) with excess chloroketene, generated in situ from chloroacetyl chloride and triethylamine, gave chloro-\( \beta \)-lactam \( \text{42} \) as a single stereoisomer as well as dichloride \( \text{43} \) as a separable 2:1 mixture.\(^9\)

**Scheme 7**

![Scheme 7](image)

Treatment of chloride \( \text{42} \) with Raney-nickel effected dechlorination to form pentacyclic lactam \( \text{44} \) (Scheme 8). In situ formation of \( N \)-acyliminium ion \( \text{45} \) from pentacycle \( \text{44} \), followed by addition of allylmagnesium bromide, gave BOC-deprotected allylation product \( \text{46} \) as a single diastereomer. Additionally, pentacycle \( \text{42} \) was subjected to the allylation procedure to give chloride \( \text{48} \), which was characterized by X-ray crystallography. Pentacycle \( \text{46} \) was then formed via removal of the chloride from \( \beta \)-lactam \( \text{48} \). Unfortunately, the relative stereochemistry between C9,20 of \( \text{46} \) was found to be cis with respect to the nitrogen of the \( \beta \)-lactam and the aryl group, opposite to that proposed for chartellamide A (5).
Scheme 8

$N$-Acyliminium ion 45 is believed to exist in a conformation in which the ethano bridge of the 7-membered ring blocks Grignard addition from one face of the molecule. As illustrated in Figure 5, blocking the back face of the molecule would lead to exclusive addition from the front face, thus giving the undesired diastereomer 46 in which the nitrogen of the $\beta$-lactam and the aryl ring are cis.

**Figure 5.** Ethylene bridge blocking one face of $N$-acyliminium 45 from attack by a nucleophile
2.1 Synthetic Approaches to $\beta$-Lactam Subunit 35 and Imidazole Subunit 36

2.1.1 Initial Studies on the Formation of $\beta$-Lactam 35

While the above feasibility study was in progress (see Section 1.5), initial research was begun into the synthesis of halogenated dibromoisatin 35 necessary for the formation of addition product 34 in our original retrosynthesis (see Scheme 6). This study began with formation of known 4,6-dibromoisatin (53), which was synthesized in 5 steps using a modified literature procedure (Scheme 9). Starting from $p$-nitroaniline (49), dibromination in glacial acetic acid followed by reductive deamination yielded 3,5-dibromonitrobenzene (50). Reduction of the nitro group of 50 with iron and hydrochloric acid afforded 51.

Scheme 9
acid followed by condensation of the resultant aniline 51 with chloral and hydroxylamine sulfate generated dibromo oxime 52. Acid-catalyzed cyclization of oxime 52 gave the desired halogenated isatin 53.

To continue the synthesis of β-lactam subunit 35, ketalization of 4,6 dibromoisatin (53) by standard procedures cleanly afforded either dimethoxy derivative 54 or cyclic ketal 55 (Scheme 10). Protection of γ-lactams 54 or 55 with di-tert-butylidicarbonate (BOC₂O) gave N-BOC derivatives 35 and 56, respectively.

Scheme 10

2.1.2 Addition of Imidazoles 60 and 58 to γ-Lactam 37

A model study was explored to investigate the reactivity of metallated imidazoles in addition reactions with the carbonyl of isatin derivatives, as would be necessary for the formation of addition product 34 in the originally proposed synthesis of the chartellamides (see Scheme 6). The known diiodoimidazole 58 was formed via treatment
of imidazole (57) with iodine and potassium iodide,\textsuperscript{13} followed by BOM protection (Scheme 11).\textsuperscript{14} This protecting group strategy was employed at an early stage to alleviate future potential regioselectivity complications associated with nitrogen protection of unsymmetrical imidazoles.\textsuperscript{15} BOM-diiodoimidazole 58 was subjected to a regioselective lithium-halogen exchange at the more reactive 5-position,\textsuperscript{16} which after aqueous workup yielded 4-iodoimidazole 59.\textsuperscript{17} Under standard Stille conditions 4-iodoimidazole 59 was coupled with vinyltributyltin to give 4-vinylimidazole 60.\textsuperscript{18} However, addition of the 2,5-lithiodianion 61 of vinylimidazole 60 to isatin derivative 37 did not give any of the desired addition product 63.\textsuperscript{19} We hoped to block the 2-position of the imidazole through the formation of the 2-trimethylsilyl imidazole 62. Unfortunately,

\textbf{Scheme 11}
treatment of vinylimidazole 60 with n-butyllithium and TMSCl failed to produce the desired adduct 62. However, treatment of BOM-diiodoimidazole 58 with ethylmagnesium bromide gave imidazole-5-ylmagnesium bromide, which added to the activated γ-lactam of isatin derivative 37 to form adduct 64, in low yield.

2.2 Revised Retrosynthetic Analysis of the Chartellamides

2.2.1 Revised Retrosynthetic Analysis

As the previous model study gave the undesired relative stereochemistry between the β-lactam nitrogen and the aryl ring (see Scheme 8), a revised retrosynthesis was devised to install the requisite trans relationship at the C9,20 stereocenters. Breaking the indicated bonds in 5/6 would give pentacycle 65 containing an α,β-unsaturated ester moiety (Scheme 12). Synthetically, conversion of 65 into 5/6 could result from a stereoselective intramolecular bromoamination reaction. Ester 65 would come from aldehyde 66 utilizing a Still-Gennari olefination. Bromo enamide 66 would result from a novel intramolecular halogen-selective N-vinylation of β-lactam 67 (vide infra). Conversion of silyl alkyne 68 to dihaloalkene 67 can be achieved via deprotection of the alkyne followed by dihalogenation of the resultant terminal acetylene. Finally, deprotection of the β-lactam would afford cyclization precursor 67. Addition product 68 was anticipated to be formed from an intermolecular addition of metallated imidazole 69 to in situ generated N-acyliminium ion 70. Intermediate 70 in turn would be prepared by
addition of allylmagnesium bromide (73) to γ-lactam 72, followed by Lewis acid mediated formation of the $N$-acyliminium ion 70 from $N$-acyl hemiaminal 71.

Scheme 12

In order to address the structural intricacies of chartellamides A (5) and B (6) and ensure formation of the desired C9,20 stereochemistry, our strategy was to reverse the order of addition of the aryl and allyl nucleophiles compared to the previous model study (see Scheme 8). It was hoped that aryl Grignard ($\text{Nu}^-$) addition to the alkyl-substituted $N$-acyliminium ion 70 would occur opposite to the bulky $p$-methoxyphenyl (PMP) protecting group on the β-lactam nitrogen and give the desired trans product 68 (Figure 6).
Figure 6. PMP protecting group blocking the back face of the molecule from attack

2.2.2 Model Studies on the Addition of Aryl Grignards to N-Acyliminium Ion 70

The initial efforts to establish the correct relative C9,20 stereochemistry found in the chartellamides were centered on modeling the conversion of hemiaminal 71 to addition product 68 via an intermolecular addition of metallated nucleophiles to an in situ generated N-acyliminimum ion (see Scheme 12). In the model system simple lactam derivatives were used in place of the actual bis-lactam 72, and simple aryl Grignard reagents were employed as metallated imidazole surrogates.

Lin and Weinreb had previously prepared BOC-protected γ-lactam 76 in their studies directed toward the synthesis of the chartellines, which would be used as a model for 72 in this study (Scheme 13). Thus, reaction of isatin (74) with p-anisidine and a catalytic amount of acetic acid in ethanol furnished a PMP-imine, which underwent cycloaddition with chloroketene, generated in situ from chloroacetyl chloride, to afford chloro-β-lactam 75 as a mixture of diastereomers. Free radical dechlorination of chloro-
β-lactam 75, followed by BOC protection of the γ-lactam moiety produced the desired bis-lactam 76.

Scheme 13

A series of alkyl Grignards were added to the carbonyl of N-BOC-lactam 76 to give adducts 77a-c in good yield as mixtures of diastereomers (Scheme 14). Unfortunately, numerous attempts to form indolenines 78 from hemiaminals 77a-c under both thermal and acidic conditions did not result in any of the desired compounds. In situ generation of N-acyliminium ion 81 from hemiaminals 77b,c and subsequent addition of aryl Grignard 82 did not lead to the desired addition product 80 and only the starting materials were recovered. Interestingly, subjecting N-acyl hemiaminal 77a to the same reaction procedure resulted in formation of elimination product 83a.

It was felt that the alcohol of the hemiaminal may not be a good leaving group for in situ formation of N-acyliminium compound 81 (Scheme 14), methoxy derivatives 79b-c were formed to facilitate the elimination. However, attempts to O-methylate allyl derivative 77a resulted in formation of elimination product 83b. Unfortunately, similar results to the hemiaminal series were seen when methoxy derivatives 79b-c were used in the N-acyliminium / aryl Grignard addition sequence. The major compounds isolated in these reactions were hemiaminals 77b-c, indicating that the N-acyliminium ion 81 was
being formed and then hydrated during the aqueous work up. It may be that the 2-position of the aminal derivative is too sterically hindered to allow for intermolecular nucleophilic addition. Addition of the smaller allyl Grignard (73) to the in situ generated N-acyliminium of 77a or 79b also did not lead to any of the desired addition products, providing support for this supposition.

Scheme 14

Due to the difficulties in removing the BOC protecting group from addition products 77a-c to form indolenine 78, a Cbz protecting group, readily removed via catalytic hydrogenation, was used. Thus, γ-lactam 84 was reacted with CbzCl in the presence of triethylamine to give the Cbz-γ-lactam (Scheme 15). Addition of ethylmagnesium bromide to the activated γ-lactam carbonyl group gave N-acyl hemiaminal 85 along with 57% of Cbz cleaved product 84. The Cbz group in 85 was
then removed by hydrogenation\textsuperscript{25} to afford \textit{NH}-hemianimal 86 in good yield. Unfortunately, treatment of \textit{NH}-hemiaminal 86 with BF\textsubscript{3}·Et\textsubscript{2}O did not yield any of the desired indolenine 87, with only starting material recovered.

Scheme 15

2.3 Revised Retrosynthesis of the Chartellamides

2.3.1 Revised Retrosynthesis: Intramolecular Radical or Reductive Heck Cyclization

As the formation of an indolenine or activated indolenine derivative and selective Grignard addition was unsuccessful, an alternative approach was proposed for the formation of the C9,20 adjacent quaternary centers, as outlined in Scheme 16. It was thought that tethering an arylhalide to the \(\gamma\)-lactam would allow for a diastereoselective intramolecular cyclization onto the \(\beta\)-position of vinylogous amide 89, affording pentacycle 88 with the desired relative stereogenicity between C9,20. Therefore, cyclization of arylhalide to the vinylogous amide of 89 \textit{via} a radical or reductive Heck cyclization should afford the desired product 88. We believed the desired relative stereochemistry should result from attack of the aryl group at the \(\beta\)-position of the
vinyllogous amide from the face opposite the bulky PMP protecting group on the β-lactam nitrogen. Conformer 89a, in which the PMP protecting group and the aryl halide are on opposite sides of the vinyllogous amide, illustrates this point. Vinyllogous amide 89 would come from N-acylation of vinyllogous amide 90, which in turn would be prepared by a Meyer-Schuster rearrangement of alcohol 91.

Scheme 16

A number of groups have demonstrated the synthetic utility of intramolecular cyclizations for the formation of quaternary centers via radical and reductive Heck methods. Intramolecular radical cyclizations using aryl halides and vinyllogous amides have been reported, including some involving the formation of quaternary carbon centers. Additionally, intramolecular reductive Heck reactions have been employed effectively using enamine, enone and vinyllogous amide substrates. It is important to
note that in the large majority of literature examples the intramolecular cyclizations proceed via a 5-exo process in preference to the 6-endo mode. This fact is illustrated in the examples found in Scheme 17. Radical cyclization of aryl bromide 92 onto the β-position of the vinylogous amide moiety proceeded via a 5-exo-trig process to give tricycle 93. Similarly, the reductive Heck reaction of aryl bromide 94 resulted in cyclization to afford tricycle 95 as a single diastereomer.

Scheme 17

2.3.2 Synthesis of the Intramolecular Cyclization Precursor

A Meyer-Schuster rearrangement similar to the one proposed in our retrosynthesis (see Scheme 16) has previously been used by Lin and Weinreb in their model studies on the chartellines (Scheme 18). Addition of a lithio acetylide to the carbonyl of BOC-protected γ-lactam 96 afforded adduct 97 as a mixture of diastereomers.
Reaction of \( N \)-acyl hemiaminal 97 with tetrabutylammonium perrhenate (\( \text{Bu}_4\text{NReO}_4 \)) resulted in a Meyer-Schuster rearrangement to give vinylogous amide 101. Mechanistically, this reaction is believed to proceed via initial reaction of hemiaminal 97 with perrhenic acid, generated in situ, to give alkynyl perrhenate 98, which rearranges to allenyl perrhenate 99 via a six-membered ring transition state. Allene 99 is then hydrolyzed to afford allenic alcohol 100, which subsequently undergoes tautomerization to yield vinylogous amide 101.26

Scheme 18

By analogy with the above method, vinylogous amides 90a-c, necessary for conducting the intramolecular cyclization model study, were formed. Thus, addition of 1-lithio alkynes to the carbonyl of \( N \)-BOC-\( \gamma \)-lactam 76 gave hemiaminals 91a-c (Scheme 19). Two methods were used to effect the desired Meyer-Schuster rearrangement. Treatment of hemiaminal 91a with trifluoroacetic acid (TFA) resulted in formation of
NH-vinyllogous amide 90a. Exposure of hemiaminals 91b-c to Bu₄ReO₄ and p-toluenesulfonic acid (p-TsOH) effected Meyer-Schuster rearrangements to give vinlylogous amides 90b-c. It should be noted that the products 90a-c are the result of concomitant BOC removal during the Meyer-Schuster rearrangement.

Scheme 19

The synthesis of the intramolecular cyclization precursor was continued via the attempted via N-acylation of γ-lactams 90a-c. Numerous attempts at N-acylation of vinlylogous amides 90a-c with o-halogen-substituted benzoic and phenylacetic acid derivatives to form products 102 or 103 were unsuccessful (for selected examples see Table 1). Only the starting vinlylogous amide was recovered from these attempted acylations.

Table 1. Attempted N-acylation of vinlylogous amides 90a-c.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Sub.</th>
<th>Acylating Group</th>
<th>Reagents/Solvents</th>
<th>Temp.</th>
<th>Time</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90c</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>DMAP, DCC DCM</td>
<td>rt</td>
<td>overnight</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>90a / 90c</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>DMAP, Et₃N DCM</td>
<td>rt</td>
<td>overnight</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>90a</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(a) LiHMDS, THF, (b) NaH, DMF, (c) Et₃N, DBU, toluene</td>
<td>rt</td>
<td>overnight</td>
<td>(a) S.M.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rt</td>
<td>overnight</td>
<td>(b) S.M.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reflux</td>
<td></td>
<td>(c) S.M</td>
</tr>
<tr>
<td>4</td>
<td>90a</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>NaH, THF</td>
<td>rt</td>
<td>overnight</td>
<td>S.M.</td>
</tr>
<tr>
<td>5</td>
<td>90b</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(a) pyridine, (b) DMAP, Et₃N DCM</td>
<td>rt</td>
<td>overnight</td>
<td>(a) S.M.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rt</td>
<td></td>
<td>(b) S.M.</td>
</tr>
<tr>
<td>6</td>
<td>90b</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>18-crown - 6, NaHMDS, DMAP THF</td>
<td>0 °C → rt</td>
<td>overnight</td>
<td>S.M.</td>
</tr>
<tr>
<td>7</td>
<td>90b</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>KH, THF</td>
<td>0 °C → rt</td>
<td>3 h</td>
<td>S.M.</td>
</tr>
</tbody>
</table>

These results were somewhat unexpected as related vinylogous amides are known to acylate on nitrogen. Additionally, to probe the reactivity of this system, vinylogous amide 90b was treated with BOC₂O, Et₃N and DMAP to cleanly afford N-BOC vinylogous amide 104 in good yield (Scheme 20). Use of these conditions, however, with a benzoyl acid chloride did not afford any of the desired acylated products (see Table 1, entry 2).

**Scheme 20**

![Scheme 20 Diagram](image8)
To circumvent these problems, we employed a strategy involving an initial N-acylation or N-alkylation of β-lactam 84 followed by addition of the lithio acetylide to the γ-lactam carbonyl and Meyer-Schuster rearrangement of the resultant hemiaminal. Thus, N-acylation of γ-lactam 84 with acid chloride 105 readily afforded iodide 106 (Scheme 21). Unfortunately, addition of the lithio acetylide of 1-pentyne to the carbonyl of N-acyl γ-lactam 106 resulted in formation of deacylated γ-lactam 84.

To determine the degree of activation necessary to allow for addition of alkynyl nucleophiles to the lactam carbonyl, enamide 108 was formed by condensation of amide 83 and aldehyde 107 (Scheme 21). Addition of the lithioacetylide of ethoxyacetylene to enamide 108 did not afford the desired addition product 109 and only starting material was recovered. The enamide fails to significantly activate the amide carbonyl group for nucleophilic addition.

Scheme 21
Alternatively, the use of a sulfonyl group attached to the γ-lactam to act as a tether for the intramolecular cyclization was explored. A similar strategy was employed by Herradon et al. in the synthesis of γ-amino-α,β-unsaturated esters (Scheme 22).36 In this method, Heck reaction of sulfonamide 110 afforded tricycle 111 in excellent yield via a 6-exo-trig cyclization.

Scheme 22

Our study began with N-nosylation of isatin derivative 84 with sulfonyl chloride 112, followed by catalytic hydrogenation of nitro compound 113 to give aniline 114 (Scheme 23). Sandmeyer diazotisation of aniline 114 furnished aryl bromide 115.
Addition of the lithium acetylide derived from 1-pentyne to γ-lactam 115 gave N-sulfonyl hemiaminal 116 as a mixture of diastereomers. Subjection of N-sulfonyl hemiaminal 116 to Meyer-Schuster rearrangement catalyzed by Bu₄ReO₄ using a minimum amount of p-TsOH gave vinylogous amide substrate 117. Use of increased amounts of p-TsOH resulted in concomitant cleavage of the sulfonyl group.

2.3.3 Attempted Intramolecular Cyclizations of Aryl Bromide 117

With model cyclization precursor 117 in hand, methods were explored to form pentacyclic system 118 with the desired relative stereochemistry between C9,20 via either radical or reductive Heck methods. As noted above, we believed that the desired relative stereochemistry should result from 5-exo attack of the aryl group at the β-position of the vinylogous amide opposite to the bulky PMP protecting group on the β-

Scheme 24
lactam nitrogen (see Scheme 16). However, it was found that treatment of bromide 117 with AIBN and (TMS)\(_3\)SiH resulted in formation of ring-opened product 119 (Scheme 24). This compound is most likely the result of initial \(6\)-endo cyclization of the aryl radical formed from bromide 117 onto the \(\alpha\)-position of the vinylogous amide to give the more stable tertiary radical 120. Homolytic cleavage of the C-N bond of radical 120 then affords amidyl radical 121, which upon hydrogen atom abstraction, presumably from (TMS)\(_3\)SiH, gives undesired indole 119.

Alternatively, a reductive Heck cyclization of bromide 117 was also investigated. Treatment of bromide 117 with Pd (0) and formic acid under reductive Heck conditions gave indole 122 in which concomitant debromination and ring opening occurred without cyclization (Scheme 25). To probe the reactivity of vinylogous amides towards palladium catalyzed coupling reaction several intermolecular Heck reactions were examined. Reaction of BOC protected vinylogous amide 123 and aryl halides 124 and 125 under reductive Heck conditions did not give any of the desired coupled products

Scheme 25
Interestingly, the ring opened indole derivative 127 was the major product observed, similar to the ring-opened compound 122 obtained by the intramolecular reductive Heck reaction of vinylogous amide 117.

A possible mechanism for the formation of the observed indole product 127 is outlined in Scheme 26. Formation of $\pi$-allylpalladium intermediate 128 from vinylogous amide 123 could occur with concomitant ring opening of the $\beta$-lactam via insertion of the palladium into the vinylogous amide double bond. Similar formation of $\pi$-allylpalladium species have been observed with vinyl cyclobutylamines$^{37}$ and vinyl epoxides.$^{38}$ Protonation of the amide nitrogen and formation of the $\eta^1$ complex would give C-bound enolate 129. Formation of the $O$-bound enolate 130 followed by protonolysis would give indole 127. A similar mechanism is plausible for the formation of indole 122 from intramolecular Heck substrate 117.

Scheme 26
2.4 Studies on the Construction of the Adjacent C9,20 Stereocenters via an Intermolecular Cuprate Addition to the β-Position of a Vinylogous Amide

In order to overcome the problems associated with the N-acyliminium and intramolecular cyclization methods, an alternative intermolecular addition strategy using Meyer-Schuster scaffold 133 was investigated towards synthesis of the chartellamides. Retrosynthetically, the chartellamides could be formed from α,β-unsaturated ester 65, which in turn could be derived from aldehyde 66 (Scheme 27). Functional group manipulation of ester 131 would afford aldehyde 66. Finally, ester 131 would result from addition of metallated imidazole 69 to the β-position of vinylogous amide 133, followed by conversion of the resultant alkyne 132 into the iodobromoalkene moiety. We believed that the bulky PMP protecting group on the β-lactam would block one face from addition and the desired trans relationship between the β-lactam nitrogen and imidazole would be achieved.

Scheme 27
Honda et al. recently reported the diastereoselective 1,4-addition of an alkyl Grignard to BOC-protected vinylogous amide 134 to give substituted carbamate 135 via attack at the β-position (Scheme 28). In this example, addition occurred from the less hindered face of the molecule due to the ester group blocking one face of the vinylogous amide from attack of the cuprate, as illustrated in conformer 134a.

**Scheme 28**

A model system was first investigated to test the feasibility of forming the adjacent C9,20 quaternary centers of the chartellamides with the desired relative stereochemistry via an intermolecular cuprate conjugate addition. Addition of the lithio acetylide derived from 1-pentyne was added to the activated carbonyl group of N-tosyl γ-lactam 136 to give hemiaminal 137 (Scheme 29). Meyer-Schuster rearrangement of hemiaminal 137 catalyzed by Bu₄NReO₄ and p-TsOH afforded vinylogous amide 138. However, attempted addition of the cuprate derived from phenylmagnesium bromide to vinylogous amide 138 gave only tryptamine derivative 139 in good yield. This result is reflective of the rather unstable nature of the β-lactam / vinylogous amide compounds in general as the strained β-lactam tends to ring open when possible to give an indole.
2.5 Studies on the Construction of the Haloenamide Moiety of the Chartellamides via a Vinylhalide / β-Lactam Coupling Strategy

2.5.1 Introduction and Background of β-Lactam / Vinylhalide Couplings

The feasibility of forming the β-bromoenamide functionality of the chartellamides via an intra- or intermolecular halogen-selective N-vinylation reaction was also examined (see Chapter 2, Section 2.4, pg. 106 for a discussion of the application of this methodology to the chartellines). This model system was pursued to study synthesis of the bond between N1 and C2 of the chartellamide (Scheme 30). Enamide 140 could result from an intermolecular coupling of iodobromoalkene 141 with NH-β-lactam 142. Alternatively, β-Bromoenamide 143 could result from an intramolecular halogen-selective copper catalyzed coupling of β-lactam 67. By developing this method we
hoped to achieve a degree of flexibility in our approach towards the chartellamides, as well as develop a general procedure for the synthesis of β-haloenamides.

Scheme 30

A substantial amount of research has recently focused on the formation of stereochemically well-defined enamides\textsuperscript{40} and enamide-containing natural products\textsuperscript{41} utilizing the copper-catalyzed coupling of amides and vinyl halides. Buchwald et al. have shown that iodo- and bromoalkenes, such as 145 and 147, can be coupled with amides under copper (I) iodide / \(N, N'\)-dimethylethylenediamine catalysis to give N-vinylation products (Scheme 31).\textsuperscript{42} In addition to being a relatively mild and generally high yielding process, the double bond geometry of the vinyl halide is maintained in the product, making this process potentially amenable to formation of the enamide moiety in the chartellines, chartellamides and securamines. For example, coupling of primary amide 144 with (Z)-vinyl iodide 145 gave (Z)-enamide 146 in excellent yield and with
complete retention of the olefin geometry. Conversely, coupling of amide 144 and (E)-alkene 147 afforded (E)-enamide 148 in good yield. However, the coupling is affected by steric hindrance, as acyclic secondary amides are unsuitable for the reaction.

Scheme 31

A significant amount of research has been done to probe the mechanism of the copper catalyzed coupling of amides with vinyl- and aryl halides. The N-vinylation reaction is envisioned to proceed via initial coordination of the copper (I) iodide to amide 149, followed by deprotonation to give copper (I) amidate complex 150 (Figure 7).42 Four-centered ipso-substitution of vinyl iodide 151 on copper (I) amidate 150 would then afford enamide 152 and regenerate copper catalyst 153.43 At high base concentrations, there is an excess of deprotonated amide that impedes the reaction, probably through the formation of cuprate complex 154. To keep the base concentration low, an inorganic base that is only slightly soluble in organic solvents, such as cesium carbonate, is generally used.44 Extensive kinetic studies carried out by the Buchwald group on the related Goldberg reaction (i.e. amidation of aryl iodides) have shown that the rate of the reaction is dependent on the concentration of both the diamine ligand and the amide.45
The N-vinylation methodology developed by Buchwald was recently expanded to the intramolecular vinylation of amides to form lactams.\textsuperscript{46} In this report Li and coworkers were able to form 5, 6, and 7 membered lactams. For example, lactam 156 was formed \textit{via} an intramolecular N-vinylation reaction of (Z)-iodoalkene 155 (Scheme 32). Unfortunately, the synthesis of similar 8 and larger membered rings was not possible, due to competing dimer formation.

\textbf{Scheme 32}
2.5.2 Intermolecular β-Haloenamide Formation via Direct Copper-Promoted Coupling

A model study was explored to investigate the formation of the haloenamide linkage found in the chartellamides via either an inter- or intramolecular halogen-selective N-vinylation reaction. During the course of our research on the construction of β-haloenamides via Buchwald's N-vinylation method, a single example of a closely related process was described by the Isobe group. It was found that β-lactam 157 coupled with vinyliodide 158 under Buchwald conditions to give enamides 159 and 160, as a 5:1 mixture (Scheme 33).

Scheme 33

We initially investigated the possibility of expanding Buchwald's method to the coupling of 1,2-bromoiodo- and 1,2-chloroiodoalkenes with amides in both an inter- and intramolecular fashion. This research is also discussed later as it pertains to the synthesis of the chartellines (Chapter 2, Section 2.4, pg. 106). To begin the intermolecular coupling study, the requisite mixed dihaloalkenes were synthesized. 1-Bromo-2-iodovinylbenzene (162) was prepared by reaction of phenylacetylene (161) with copper bromide and iodine at 0 °C (Scheme 34).
The copper (I) iodide catalyzed intermolecular coupling reaction of mixed dihaloalkenes was then studied using Buchwald's experimental conditions. Notably, known chloroiodoalkene 158 was found to couple with NH-γ-lactam 163 to afford β-chloroenamide 164 in 92% yield (Scheme 35). In contrast, reaction of iodobromoalkene

Scheme 35
with \( NH-\gamma \)-lactam \( 163 \) gave \( \beta \)-bromoamidine \( 165 \) in much lower yield. Acetamide \( 166 \) coupled in low yield with mixed dihaloalkene \( 162 \) to give \( \beta \)-bromoamidine \( 167 \). Encouragingly, \( NH-\gamma \)-lactam \( 168 \) reacted with bromoiodoalkene \( 162 \) to give \( \beta \)-bromoamidine \( 169 \) in moderate yield. Importantly, none of the iodoalkene products corresponding to enamide \( 160 \) were observed in our reactions, in contrast to the report of Isobe et al. (see Scheme 33).47

2.5.3 Intramolecular \( \beta \)-Chloroamidine Formation via Direct Copper-Promoted Coupling

A model system was also briefly investigated to study the feasibility of forming the haloamidine functionality of the chartellamides via an intramolecular N-vinylation reaction (see Scheme 30, eq. b). Thus, cyclization precursor \( 172 \) was prepared via a DCC mediated esterification49 of pyroglutamic acid \( 170 \) with known \( (2E)\)-2-chloro-3-iodopropenol \( 171 \) (Scheme 36).50 Amide \( 172 \) was subjected to Buchwald's conditions to afford seven-membered bicycle \( 173 \) in 46% yield. Iodobromination of alkyne \( 174 \), formed via esterification of \( 170 \), resulted in 3-bromo-2-iodoalkene \( 175 \) with the undesired halogen regiochemistry. Additionally, dibromoalkene \( 176 \) was formed from alkyne \( 174 \). However, subjection of dibromoalkene \( 176 \) to Buchwald's conditions failed to give any of the desired coupled product \( 177 \), despite the fact that vinyl bromides have been used extensively in this process.40-42 Unfortunately, the inability to form the requisite \( (2E)\)-2-bromo-3-iodopropenol or effect regioselective iodobromination of an alkyl acetylene...
discouraged any investigation of the intramolecular cyclization of the corresponding iodobromo derivative utilizing this scaffold.

**Scheme 36**

2.6 Studies on Construction of the 7-Membered Ring Enamide Moiety *via* an Intramolecular RCM

In addition to an intramolecular N-vinylation reaction to form the 7-membered ring, a ring closing metathesis (RCM) strategy was investigated towards formation of the dehaloenamide 178 from diene 179 (Scheme 37).
There have been no published reports of the construction of 7-membered ring enamide heterocycles using RCM, although the method has proven useful for the synthesis of 5- and 6-membered ring enamides. For example, Overman and coworkers have shown that diene 180 reacts to give cyclic enamide 182 when subjected to standard Grubbs RCM conditions (Scheme 38).

A model study was used to investigate the use of a RCM reaction to form 7-membered ring enamide systems. Our study began with a DCC mediated coupling of pyroglutamic acid (170) with allyl alcohol to give ester 183. N-Vinylation of lactam 183 was effected by reaction with (4,7-diphenyl-1,10-phenanthroline) palladium (II) trifluoroacetate complex, (DPP)-Pd(OCOCF$_3$)$_2$, and butyl vinyl ether (BVE) to form diene 184 (Scheme 39). Subjection of diene 187 to standard RCM protocols using Grubbs' second generation catalyst 181 failed to give any of the desired bicycle 186, with only starting material recovered. Martin et. al. reported that incorporation of a phenyl
substituent on one of the alkenes in a RCM reaction forced the metallocarbene to initially form on the terminal olefin. After the metathesis, the more stable Grubbs' II catalyst 181 is regenerated rather than the fragile methylidene derivative 187. Therefore, phenyl enamide 185 was synthesized by condensation of lactam 183 with phenyl acetaldehyde and subjected to the RCM conditions. Unfortunately, diene 185 also did not cyclize to enamide 186 and only starting material was recovered.

Scheme 39

2.7 Conclusion

In conclusion, a number of strategies were investigated leading towards a total synthesis of the chartellamides. Intermolecular addition of aryl Grignards to in situ generated alkyl N-acyliminium ions did not result in the desired coupled product. Additionally, intramolecular radical or reductive Heck cyclizations of vinylogous amide
substrates resulted in concomitant $\beta$-lactam ring opening to form 2,3-disubstituted indoles. Attempted intermolecular cuprate additions to the $\beta$-position of vinylogous amides also give $\beta$-lactam ring opened indole products. A novel method for the intra- and intermolecular halogen-selective N-vinylation of amides and lactams was developed to allow for facile synthesis of the haloenamide moiety of the chartellamides. Due to these problems, and the uncertainties surrounding the stereostructure of the chartellamides discussed in the introduction (see Section 1.1), this project was terminated.
Part 3

Experimental Section

General Methods. All non-aqueous reactions were carried out under a positive pressure of dry argon or nitrogen. Air and moisture sensitive liquid reagents were added via a dry cannula or syringe. $^1$H and $^{13}$C spectra were recorded on Bruker DPX-300, CDPX-300, AMX-360 or DRX-400 MHz spectrometers. Flash chromatography was performed on EM Science silica gel 60 (230-400 mesh). Analytical and preparative TLC were performed on EM Science silica gel 60 PF$_{254}$. THF, benzene and ether were either dried over and distilled from sodium / benzophenone ketyl or used directly after passing through activated alumina columns. DCM, toluene, MeOH and DMF were distilled from CaH$_2$ or used directly after passing through activated alumina columns.

1,3-Dibromo-5-nitrobenzene (50). To a stirred solution of 4-nitroaniline (20.0 g, 0.15 mol) in acetic acid (300 mL) at reflux was added dropwise via an addition funnel a solution of bromine (50.9 g, 0.32 mol) in acetic acid (150 mL). Water (15 mL) was added when the bright yellow precipitate became too thick to stir (~ 50 % of Br$_2$ added). The resulting solution was stirred for 1 h and was cooled to rt. The solution was poured into a solution of sodium bisulfate (4.0 g) in ice water (1 L). The resulting solid was filtered and washed with cold water. The solid was dissolved in acetone, dried over MgSO$_4$ and the solvent removed under reduced pressure to yield 2,6-dibromo-4-nitroaniline (42.6 g, 99%) which was used without further purification. $^1$H NMR (300
MHz, acetone-d$_6$) $\delta$ 8.21 (s, 2H), 6.04-6.07 (bs, 2H); LRMS-APCI $m/z$ (relative intensity) 297 (MH$^+$).

To a stirred solution of the above 2,6-dibromo-4-nitroaniline (42.6 g, 0.14 mol) in EtOH (900 mL) at rt was added conc. H$_2$SO$_4$ (60 mL). The temperature was raised to reflux and NaNO$_2$ (24.7 g, 0.36 mol) was added portionwise. The solution was stirred at reflux for 30 min. The resulting solution was cooled in an ice bath and filtered. The filtrate was washed with cold water (500 mL), dissolved in EtOAc (1 L) and dried over MgSO$_4$. The solvent was removed under reduced pressure to give 1,3-dibromo-5-nitrobenzene (50, 28.6 g, 71%) which was used without further purification (yellow solid). $^1$H NMR (300 MHz, acetone-d$_6$) $\delta$ 8.40 (m, 2H), 8.26 (m, 1H).

3,5-Dibromoaniline (51). To a stirred solution of 1,3-dibromo-5-nitrobenzene (50, 28.6 g, 0.10 mol) in EtOH:H$_2$O (5:1, 550 mL) at rt were added conc. HCl (40 mL) followed by portion-wise addition of iron powder (22.8 g, 0.41 mol). The mixture was heated at 100 °C for 1 h. The solution was cooled in an ice bath, filtered through a pad of Celite and the solvent was removed under reduced pressure to yield 3,5-dibromoaniline (51, 20.0 g, 77%), which was used in the next step without purification. $^1$H NMR (300 MHz, acetone-d$_6$) $\delta$ 7.93 (m, 2H), 7.73 (m, 1H); LRMS-APCI $m/z$ (relative intensity) 252 (MH$^+$).

$N$-(3,5-Dibromophenyl)-2-hydroxyiminoacetamide (52). To a stirred solution of crude 3,5-dibromoaniline (51, 36.40 g, 0.145 mol) in H$_2$O:EtOH (3:1 800 mL) at rt were added chloral hydrate (28.78 g, 0.174 mol),
hydroxylamine sulfate (35.70 g, 0.218 mol), sodium sulfate decahydrate (200 g, 0.62 mol) and conc. HCl (50 mL). The solution was heated at 80 °C for 3.5 h. The resulting solution was cooled in an ice bath and the resulting solid was isolated by filtration. The solid was washed with cold H₂O and dried over silica gel in a desiccator to yield N-(3,5-dibromophenyl)-2-hydroxyiminoacetamide (52, 25.4 g, 54%), which was used in the next step without further purification. "H NMR (300 MHz, acetone-d₆) δ 8.22 (bs, 1H), 7.89 (bs, 1H), 7.75 (m, 2H), 7.57 (s, 1H), 7.44 (m, 1H); LRMS-APCI m/z (relative intensity) 323 (MH⁺).

**4,6-Dibromo-1H-indole-2,3-dione (53).** A stirred solution of N-(3,5-dibromophenyl)-2-hydroxyiminoacetamide (52, 0.25 g, 0.0008 mol) in 86% aqueous H₂SO₄ (50 mL) was heated at 60 to 110 °C for a period of 2 h. The resulting red solution was poured onto ice and the precipitate was collected via filtration. The solid was dried in a desiccator over silica gel to yield 4,6-dibromo-1H-indole-2,3-dione (53, 0.21 g, 88%), which was used in the next step without further purification. IR (cm⁻¹): 3251, 1774, 1733, 1599, 1567; "H NMR (300 MHz, acetone-d₆) δ 7.45 (m, 1H), 7.20 (m, 1H); LRMS-APCI m/z (relative intensity) 305.9 (MH⁺); HRMS-APCI: [M-H]⁻ calcd for C₈H₂NO₂Br₂, 301.84468; found, 301.84333.

**4,6-Dibromo-3,3-dimethoxy-1,3-dihydroindol-2-one (54).** To a stirred solution of 4,6-dibromo-1H-indole-2,3-dione (53, 0.20 g, 0.00065 mol) in dry MeOH (12 mL) at rt was added conc. H₂SO₄ (0.30 mL). The solution was heated at 80 °C overnight. The resulting solution was cooled to rt. Solid NaHCO₃ (1.0 g) was
added and the solvent was removed under reduced pressure. DCM (50 mL) and H₂O (30 mL) were added. The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure to give 4,6-dibromo-3,3-dimethoxy-1,3-dihydroindol-2-one (54, 0.18 g, 79%). ¹H NMR (300 MHz, acetone-d₆) δ 8.14 (m, 1H), 7.61 (m, 1H), 4.51-4.46 (m, 4H), 1.61 (s, 9H).

**4,6-Dibromo-3,3-dimethoxy-2-oxo-2,3-dihydroindole (55).** To a stirred solution of 4,6-dibromo-1H-indole-2,3-dione (53, 5.00 g, 0.0164 mol) in benzene (175 mL) at rt were added p-TsOH (10 mg) and ethylene glycol (1.12 g, 0.018 mol). The solution was heated at reflux overnight with a Dean-Stark apparatus. The resulting solution was cooled to rt, poured into cold water and the solid precipitate was collected. To the benzene:H₂O solution was added solid NaCl (5.0 g) and the mixture was extracted with ether (2 x 200 mL). The organic extracts and the filtered precipitate were combined, dried over MgSO₄ and the solvent was removed under reduced pressure to yield crude 4,6-dibromo-3,3-dimethoxy-2-oxo-2,3-dihydroindole (55, 5.72 g, 100%) which was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 7.36 (m, 1H), 6.99 (m, 1H), 4.43-4.29 (m, 4H); ¹³C NMR (100 MHz, DMSO-d₆) δ 173.9, 146.2, 128.2, 125.4, 122.3, 119.9, 113.1, 102.2, 66.5; HRMS (C₁₀H₇Br₂NO₃) calcd 364.9136 (M⁺NH₄), found 364.9130.

**4,6-Dibromo-3,3-dimethoxy-2-oxo-2,3-dihydroindole-1-carboxylic Acid tert-Butyl Ester (56).** To a stirred solution of 4,6-dibromo-3,3-dimethoxy-2-oxo-2,3-dihydroindole (55, 5.7 g, 0.016 mol) in dry DCM (100 mL) at rt were added 4-
dimethylaminopyridine (2.0 g, 0.016 mol), triethylamine (2.3 mL, 0.016 mol) and di-tert-
butyldicarbonate (4.28 g, 0.020 mol). The resulting solution was stirred overnight at rt. 
Brine (100 mL) and DCM (200 mL) were added. The organic layer was dried over 
MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by 
flash column chromatography on silica gel (DCM) to afford 4,6-dibromo-3,3-dimethoxy-
2-oxo-2,3-dihydroindole-1-carboxylic acid tert-butyl ester (56, 570 mg, 8%).$^1$H NMR 
(300 MHz, acetone-d$_6$) $\delta$ 8.01 (s, 1H), 7.48 (s, 1H), 4.40-4.29 (m, 4H), 1.48 (s, 9H); $^{13}$C 
NMR (75 MHz, acetone-d$_6$) $\delta$ 170.9, 149.6, 144.9, 132.3, 126.7, 122.6, 121.1, 119.1, 
102.7, 86.1, 68.1, 28.4.

2-(3-Benzylxoyethyl-5-iodo-3H-imidazol-4-yl)-2-hydroxy-3,3-dimethoxy-2,3-dihydroindole-
1-carboxylic Acid tert-Butyl Ester (64). To a 
stirred solution of 1-benzylxoyethyl-4,5-diiodo-1H-imidazole (58, 264 mg, 0.6 mmol) 
in dry toluene (20 mL) at rt was added dropwise a solution of ethylmagnesium bromide 
(0.19 mL, 3 M in diethyl ether, 0.57 mmol) and the resulting mixture was stirred for 1 h. 
A solution of 3,3-dimethoxy-2-oxo-2,3-dihydroindole-1-carboxylic acid tert-butyl ester 
(37, 85 mg, 0.3 mmol) in dry toluene (3 mL) was added dropwise and the resulting 
mixture was stirred at rt for 3 h. Saturated aqueous NH$_4$Cl (50 mL) and EtOAc (100 mL) 
were added. The organic layer was washed with brine and dried over MgSO$_4$. The 
solvent was removed under reduced pressure and the residue was purified by flash 
column chromatography on silica gel (2:1 hexanes:EtOAc) to give 2-(3-
benzylxoyethyl-5-iodo-3H-imidazol-4-yl)-2-hydroxy-3,3-dimethoxy-2,3-dihydro-
indole-1-carboxylic acid tert-butyl ester (64, 31 mg, 17%). $^1$H NMR (400 MHz, CDCl$_3$)
δ 7.63 (s, 1H) 7.35-7.15 (m, 9H), 5.35 (s, 2H), 4.37 (s, 2H), 3.46 (s, 3H), 3.07 (s, 3H), 1.36 (s, 9H); LRMS-APCI m/z (relative intensity) 608 (MH⁺, 100).

Preparation of Allyl-N-BOC-β-lactam 77a. To a stirred solution of N-BOC-β-lactam 76 (110 mg, 0.28 mmol) in diethyl ether (10 mL) at -78 °C was added dropwise a solution of allylmagnesium bromide (0.56 mL, 1 M in diethyl ether, 0.56 mmol) and the resulting mixture was stirred at -78 °C for 2 h. Saturated aqueous NH₄Cl (30 mL) and EtOAc (50 mL) were added. The organic layer was washed with brine (50 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 hexanes:EtOAc) to give allyl-N-BOC-β-lactam 77a (105 mg, 86%). ¹H NMR (300 MHz, CDCl₃) δ 7.55 (bs, 1H), 7.34-7.31 (m, 2H), 7.15-7.12 (m, 2H), 7.07-7.02 (m, 1H), 6.68-6.63 (m, 2H), 5.42-5.33 (m, 1H), 5.07-4.91 (m, 2H), 3.72 (d, J = 15.2 Hz, 1H), 3.36 (d, J = 15.2 Hz, 1H), 3.63 (s, 3H), 3.21-3.17 (m, 1H), 2.81-2.73 (m, 1H), 1.63 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 165.7, 158.1, 133.1, 132.7, 128.9, 126.0, 125.3, 122.4, 121.7, 116.8, 115.7, 85.6, 71.0, 57.3, 46.7, 45.6, 30.4; LRMS-APCI m/z (relative intensity) 436 (MH⁺, 70).

Preparation of Vinyl-N-BOC-β-lactam 77b. To a stirred solution of N-BOC-β-lactam 76 (96 mg, 0.24 mmol) in dry THF (7 mL) at -78 °C was added dropwise a solution of vinylmagnesium bromide (0.5 mL, 1 M in diethyl ether, 0.5 mmol) and the resulting mixture was stirred at -78 °C for 2 h. Saturated aqueous NH₄Cl (20 mL) and EtOAc (50 mL) were added. The organic layer was washed
with brine (30 mL) and dried over MgSO₄ to quantitatively give vinyl-\(\text{N-BOC}\)-\(\beta\)-lactam \(\text{77b}\) as a 2:1 mixture of diastereomers, which was used in the next step without purification. \(^{1}\)H NMR (300 MHz, CDCl₃) \(\delta \) 7.82-7.79 (m, 1H), 7.41-7.27 (m, 1H), 7.22-7.19 (m, 1H), 7.11-7.07 (m, 1H), 6.96-6.93 (m, 2H), 6.69-6.65 (m, 2H), 6.01-5.86 (m, 1H), 5.63-5.20 (m, 2H), 4.39 (bs, 1H), 3.91 (d, \(J = \) 15.9 Hz, 0.6H), 3.49 (d, \(J = \) 15.4 Hz, 0.4H), 3.25 (d, \(J = \) 15.9 Hz, 0.6H), 3.21 (d, \(J = \) 15.4 Hz, 0.4H), 2.03 (s, 1H), 1.52 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta \) 167.1, 158.4, 144.7, 133.4, 126.4, 126.3, 126.3, 121.6, 119.0, 117.6, 116.5, 116.2, 96.3, 86.0, 72.9, 62.7, 57.7, 47.1, 30.8; LRMS-APCI \(m/z\) (relative intensity) 423 (MH\(^{+}\), 100).

**Preparation of Methoxylactam 79b.** To a stirred solution of the above vinylaminal \(\text{77b}\) (100 mg, 0.24 mmol) in dry THF (10 mL) at 0 °C, sodium hydride (10 mg, 60% dispersion in mineral oil, 0.35 mol) was added portionwise. The reaction mixture was stirred at rt for 30 min and cooled to 0 °C. Methyl iodide (45 \(\mu\)L, 0.72 mmol) was added and the reaction mixture was stirred at rt overnight. Ether (50 mL) and water (50 mL) were added. The organic layer was washed with brine (30 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3:1 hexanes:EtOAc) to give methoxylactam \(\text{79b}\) (105 mg, 100% from \(\text{N-BOC-}\beta\)-lactam \(\text{76}\)). \(^{1}\)H NMR (300 MHz, CDCl₃) \(\delta \) 7.90-7.87 (m, 1H), 7.43-7.38 (m, 2H), 7.14-7.09 (m, 1H), 6.98-6.93 (m, 2H), 6.69-6.64 (m, 2H), 5.84-5.75 (m, 1H), 5.56 (m, 1H), 5.28 (m, 1H), 3.74 (s, 3H), 3.61 (d, \(J = \) 10.7 Hz, 1H), 3.32 (d, \(J = \) 10.7 Hz, 1H), 3.24 (s, 3H), 1.53 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta \) 164.2, 155.9, 151.6, 143.3, 132.7, 131.0, 130.8,
Preparation of \(N\)-Cbz-\(\beta\)-lactam 86. To a stirred solution of \(N\)-\(H\)-\(\beta\)-lactam 84 (225 mg, 0.76 mmol) in dry THF (10 mL) at 0 °C were added triethylamine (118 \(\mu\)L, 0.92 mmol) and benzyl chloroformate (131 \(\mu\)L, 0.92 mmol) and the resulting mixture was stirred at rt for 2 h. Brine (30 mL) and EtOAc (50 mL) were added. The organic layer was dried over MgSO\(_4\), the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (CH\(_2\)Cl\(_2\)) to give \(N\)-Cbz-\(\beta\)-lactam (461 mg, 61%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.98–7.96 (m, 1H), 7.44–7.36 (m, 2H), 7.34–7.28 (m, 5H), 7.17–7.15 (m, 1H), 6.90–6.87 (m, 2H), 6.64–6.61 (m, 2H), 5.43–5.38 (m, 3H), 3.60 (s, 3H), 3.51 (d, \(J\) = 14.6 Hz, 1H), 3.21 (d, \(J\) = 14.6 Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.6, 160.6, 155.0, 148.6, 137.6, 132.8, 129.5, 128.1, 127.1, 127.0, 126.5, 124.2, 122.2, 121.7, 116.9, 114.4, 112.9, 67.5, 58.7, 53.7, 49.3; LRMS-APCI \(m/z\) (relative intensity) 429 (MH\(^+\), 95).

Preparation of Ethyl-\(N\)-\(H\)-\(\beta\)-lactam 86. To a stirred solution of the above \(N\)-Cbz-\(\beta\)-lactam (41 mg, 0.096 mmol) in dry ether (5 mL) at -78 °C was added dropwise a solution of ethylmagnesium bromide (64 \(\mu\)L, 3 M in diethyl ether, 192 mmol) and the resulting mixture was stirred at -78 °C for 4 h. Saturated aqueous NH\(_2\)Cl (15 mL) and EtOAc (20 mL) were added. The organic layer was washed with brine and dried over MgSO\(_4\). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (CH\(_2\)Cl\(_2\)) to give ethyl- \(N\)-Cbz-\(\beta\)-lactam 85.
Argon was bubbled through a stirred solution of the above ethyl-N-Cbz-β-lactam 85 (20 mg, 0.044 mmol) in methanol (3 mL) at rt for 30 min. The reaction vessel was charged with 10% Pd/C (8 mg, 0.063 mmol), placed under an atmosphere of H₂ and stirred at rt for 1 h. The mixture was filtered through a pad of Celite (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (CH₂Cl₂) to give ethyl-N-H-β-lactam 86 (10 mg, 31% from N-Cbz-β-lactam).

1H NMR (300 MHz, CDCl₃) δ 8.12 (bs, 1H), 7.59-7.54 (m, 1H), 7.30-7.22 (m, 1H), 7.18-7.04 (m, 4H), 6.72-6.67 (m, 2H), 3.79 (s, 2H), 3.72 (s, 3H), 2.76 (q, J = 7.6 Hz, 2H), 1.54 (bs, 1H), 1.22 (t, J = 3.3 Hz, 3H); 13C NMR (75 MHz, CDCl₃) δ 170.0, 156.8, 139.7, 135.7, 131.0, 128.4, 122.3, 120.6, 118.2, 114.3, 111.0, 103.9, 55.7, 33.3, 19.8, 14.4; LRMS-APCI m/z (relative intensity) 325 (MH⁺, 100).

Preparation of Pentynyl-N-BOC-β-lactam 91b. To a stirred solution of 1-pentyne (0.18 mL, 1.8 mmol) in dry THF (10 mL) at -78 °C was added dropwise a solution of n-BuLi (0.76 mL, 2.4 M in hexanes, 1.8 mmol) and the resulting mixture was stirred at rt for 15 min followed by cooling to -78 °C. A solution of N-BOC-β-lactam 76 (580 mg, 1.7 mmol) in dry THF (20 mL) at -78 °C was added and the mixture was stirred at -78 °C for 4 h. Saturated aqueous NH₄Cl (50 mL) and EtOAc (50 mL) were added. The organic layer was washed with brine (30 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 hexanes:EtOAc) to give pentynyl-N-BOC-β-lactam 91b as a 2:1 mixture of diastereomers (680 mg, 100%). 1H NMR (400 MHz, CDCl₃) δ 7.65 (bs, 1H), 7.28-7.23 (m, 2H), 7.08–7.06 (m, 1H), 7.02-
6.99 (m, 3H), 6.60-6.57 (m, 2H), 4.01 (d, J = 15.7 Hz, 0.6H), 3.91 (d, J = 15.5 Hz, 0.4H), 3.33 (d, J = 15.5 Hz, 0.4H), 3.13 (d, J = 15.7 Hz, 0.6H), 3.60 (s, 3H), 1.74 (t, J = 7.0 Hz, 2H), 1.56 (s, 9H), 1.03-1.01 (m, 2H), 0.63 (t, J = 7.3 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\) ) \(\delta\) 163.5, 155.0, 130.0, 129.9, 122.9, 122.8, 118.9, 113.9, 113.8, 112.7, 112.6, 88.2, 86.7, 82.6, 70.1, 54.3, 45.1, 27.2, 20.6, 19.9, 19.4, 12.4.

**Preparation of Alkyne Alcohol 91c.** To a stirred solution of ethynyl ether (0.18 mL, 40% in hexanes, 0.72 mmol) in dry THF (10 mL) at -78 °C was added dropwise a solution of \(n\)-BuLi (0.34 mL, 2.1 M in hexanes, 0.72 mmol) and the resulting mixture was stirred for 30 min at -78 °C. The solution was added to a solution of \(N\)-BOC-\(\beta\)-lactam 76 (260 mg, 0.65 mmol) in dry THF (5 mL) at -78 °C. Stirring was continued at -78 °C for 4 h and saturated aqueous NH\(_4\)Cl (30 mL) and EtOAc (50 mL) were added. The organic layer was washed with brine (30 mL) and dried over MgSO\(_4\). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give alkyne alcohol 91c as a mixture of diastereomers (300 mg, 98%). \(^1\)H NMR (300 MHz, CDCl\(_3\) ) \(\delta\) 7.93-7.90 (m, 1H), 7.39-7.30 (m, 2H), 7.16-7.10 (m, 1H), 6.91-6.86 (m, 2H), 6.64-6.59 (m, 2H), 4.19-4.17 (m, 0.4H), 3.99-3.97 (m, 0.6H), 3.57 (s, 3H), 3.47 (d, J = 14.6 Hz, 1H), 3.17 (d, J = 14.6 Hz, 1H), 1.51 (s, 9H), 1.13 (t, J = 7.1 Hz, 0.6H), 1.06 (t, J = 7.1 Hz, 0.4H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\) ) \(\delta\) 172.5, 162.4, 156.8, 148.9, 139.9, 131.2, 130.0, 125.6, 123.9, 123.5, 118.8, 118.7, 116.1, 114.6, 114.3, 85.4, 60.5, 55.5, 51.0, 28.4, 28.1, 14.3.
Preparation of Vinylogous Amide 90b. To a stirred solution of pentynyl-N-BOC-β-lactam 91b (575 mg, 1.24 mmol) in dry DCM (40 mL) at rt was added p-toluenesulfonic acid (120 mg, 0.62 mmol) and tetrabutylammonium perrhenate (120 mg, 0.25 mmol). The resulting mixture was stirred at rt for 4 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was stirred at rt for 5 min. DCM (50 mL) was added, the organic layer was washed with brine (30 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3:1 hexanes:EtOAc) to give vinylogous amide 91b (329 mg, 74%). ¹H NMR (300 MHz, CDCl₃) δ 10.6 (bs, 1H), 7.10-7.03 (m, 2H), 6.78-6.70 (m, 4H), 6.44-6.41 (m, 2H), 5.42 (s, 1H), 3.41 (s, 3H), 3.20 (ABq, J = 39.0, 15.0 Hz, 2H), 2.13-2.08 (m, 2H), 1.42-1.32 (m, 2H), 0.63 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 201.2, 163.2, 160.5, 156.6, 144.4, 131.1, 130.2, 126.2, 123.6, 122.9, 118.6, 114.7, 111.0, 93.1, 64.7, 55.6, 54.5, 45.1, 28.6, 19.0, 14.2.

Preparation of Vinylogous Amide 90c. To a stirred solution of alkyne 91c (160 mg, 0.35 mmol) in dry DCM (20 mL) at rt were added p-toluenesulfonic acid (8.6 mg, 0.045 mmol) and tetrabutylammonium perrhenate (35 mg, 0.070 mmol) and the resulting mixture was stirred at rt for 4 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was stirred at rt for 5 min. DCM (50 mL) was added and the organic layer was washed with brine (30 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (8:1 DCM:EtOAc) to give vinylogous amide 90c (69 mg, 55%). ¹H
NMR (300 MHz, CDCl$_3$) δ 9.54 (bs, 1H), 7.26-7.19 (m, 2H), 6.96-6.93 (m, 2H), 6.89-6.84 (m, 2H), 6.66-6.63 (m, 2H), 5.12 (s, 1H), 4.11-4.06 (m, 2H), 3.63 (s, 3H), 3.43 (d, $J$ = 15 Hz, 1H), 3.30 (d, $J$ = 15 Hz, 1H), 1.20 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.6, 161.9, 159.5, 155.3, 142.9, 129.8, 128.9, 124.9, 122.4, 121.1, 117.4, 113.4, 109.0, 83.1, 63.2, 58.8, 54.4, 53.8, 13.4.

**Preparation of N-BOC Vinylogous Amide 104.** To a stirred solution of vinylogous amide 90b (217 mg, 0.46 mmol) in dry DCM (10 mL) at rt were added 4-dimethylaminopyridine (17 mg, 0.14 mmol), triethylamine (0.07 mL, 0.55 mmol) and di-tert-butyldicarbonate (0.13 mL, 0.55 mmol). The resulting mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3:2 hexanes:EtOAc) to give N-BOC vinylogous amide 104 (160 mg, 76%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.73-7.71 (m, 1H), 7.29-7.26 (m, 3H), 7.10-7.04 (m, 1H), 6.88-6.85 (m, 2H), 6.61-6.58 (m, 2H), 4.11 (d, $J$ = 14.0 Hz, 1H), 3.61 (s, 3H), 3.13 (d, $J$ = 14.0 Hz, 1H), 2.17-2.12 (m, 1H), 1.97-1.90 (m, 1H), 1.61 (s, 9H), 1.30-1.25 (m, 2H), 0.61 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 199.9, 164.6, 156.3, 151.4, 149.5, 141.0, 130.7, 130.6, 130.1, 125.6, 125.8, 122.8, 118.9, 117.1, 115.3, 114.6, 85.3, 64.2, 56.3, 55.9, 46.7, 28.8, 18.2, 14.8, 14.2.

**Preparation of Aryliodide 106.** To a stirred solution of NH-$\beta$-lactam 84 (189 mg, 0.64 mmol) in dry DCM (10 mL) at rt were added 4-dimethylaminopyridine (130 mg, 1.1 mmol) and triethylamine (1.0 mL,
0.77 mmol) and the resulting solution was stirred at rt for 10 min. 2-Iodobenzoyl chloride (300 mg, 1.2 mmol) was added and the mixture was stirred at rt for 10 min. DCM (30 mL) and water (30 mL) were added. The organic layer was washed with brine (20 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 hexanes:EtOAc) to give aryliodide 106 (250 mg, 75%). ¹H NMR (300 MHz, CDCl₃) δ 8.32 (m, 1H), 7.73 (m, 1H), 7.53–7.23 (m, 5H), 7.10-7.05 (m, 2H), 6.92-6.89 (m, 2H), 6.63-6.60 (m, 2H), 3.59 (s, 3H), 3.56 (d, J = 14.7 Hz, 1H), 3.32 (d, J = 14.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 173.9, 168.5, 162.4, 157.2, 141.6, 139.9, 139.4, 132.0, 131.7, 130.0, 128.8, 128.4, 127.1, 124.9, 123.9, 119.3, 117.4, 91.7, 60.9, 55.8, 51.7.

Preparation of N-Nosyl-β-lactam 113. To a stirred solution of NH-β-lactam 84 (810 mg, 2.75 mmol) in dry THF (30 mL) at rt were added 4-dimethylaminopyridine (100 mg, 0.82 mmol), triethylamine (0.39 mL, 3.0 mmol) and 2-nitrobenzenesulfonyl chloride (112, 850 mg, 3.9 mmol). The resulting mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3:2 hexanes:EtOAc) to give N-nosyl-β-lactam 113 (1.3 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 8.43 (m, 1H), 7.82-7.79 (m, 1H), 7.73-7.68 (m, 3H), 7.43-7.34 (m, 2H), 7.24-7.20 (m, 1H), 6.81-6.78 (m, 2H), 6.47-6.44 (m, 2H), 3.53 (s, 3H), 3.42 (d, J = 14.9, 1H), 3.23 (d, J = 14.9 Hz, 1H), 1.69-1.59 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 160.9, 155.6, 146.8, 138.6, 135.0, 133.9, 131.5, 130.6, 129.6, 128.6, 125.2, 123.8, 122.8, 122.3, 117.3, 114.5, 113.4, 59.0, 54.4, 49.5.
**Preparation of Aniline 114.** Nitrogen was bubbled through a solution of N-nosyl-β-lactam 113 (150 mg, 0.31 mmol) in MeOH:DCM (5:2, 7 mL) at rt for 30 min. 10% Pd/C (18 mg, 0.014 mmol) was added and the solution was placed under an atmosphere of H₂. The solution was stirred at rt overnight. The mixture was filtered through a pad of Celite (EtOAc) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3:2 hexanes:EtOAc) to give aniline 114 (90 mg, 65%). ¹H NMR (300 MHz, CDCl₃) δ 7.81-7.74 (m, 2H), 7.36-7.13 (m, 4H), 6.71-6.68 (m, 2H), 6.66-6.61 (m, 2H), 6.50-6.47 (m, 2H), 5.12 (bs, 2H), 3.59 (s, 3H), 3.45 (d, J = 14.8, 1H), 3.17 (d, J = 14.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 173.9, 162.4, 156.9, 147.7, 139.9, 136.6, 131.8, 130.7, 129.9, 126.2, 124.3, 123.9, 118.6, 118.2, 117.9, 117.5, 114.8, 114.7, 60.6, 55.7, 50.9.

**Preparation of Bromide 115.** To a stirred solution of aniline 114 (64 mg, 0.14 mmol) in dry MeCN (5 mL) at rt was added copper (II) bromide (38 mg, 0.17 mmol) and t-butylnitrite (18 mg, 0.17 mmol). The solution was heated at 65 °C for 1 h. The resulting mixture was cooled to rt and aqueous sodium bicarbonate (20 mL) and EtOAc (25 mL) were added. The organic layer dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) to give bromide 115 (50 mg, 71%). ¹H NMR (300 MHz, CDCl₃) δ 8.36-8.33 (m, 1H), 8.03-8.00 (m, 1H), 7.63-7.60 (m, 1H), 7.48-7.40 (m, 3H), 7.40-7.36 (m, 1H), 7.33-7.19 (m, 1H), 6.85-6.82 (m, 2H), 6.61-6.58 (m, 2H), 3.62
(s, 3H), 3.43 (d, J = 14.8, 1H), 3.23 (d, J = 14.8 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.8, 162.1, 157.1, 140.6, 137.4, 135.9, 135.6, 134.6, 131.6, 129.8, 126.2, 124.1, 123.8, 121.0, 118.9, 115.9, 114.8, 60.3, 55.8, 51.1; LRMS-ES$^+$ m/z (relative intensity) 608 (M$^+$Na, 60).

**Preparation of Alkyne 116.** To a stirred solution of 1-pentyne (0.02 mL, 0.22 mmol) in dry THF (3 mL) at -78 °C was added dropwise a solution of n-BuLi (0.1 mL, 2.1 M in hexanes, 0.21 mmol) and the resulting mixture was stirred at -78 °C for 15 min. The solution was added to a solution of bromide 115 (58 mg, 1.7 mmol) in dry THF (7 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 4 h. Saturated aqueous NH$_4$Cl (25 mL) and EtOAc (25 mL) were added. The organic layer was washed with brine (20 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (9:1 DCM:EtOAc) to give alkyne 116 (48 mg, 75%). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.00 (bs, 1H), 8.18-8.15 (m, 1H), 7.63-7.61 (m, 1H), 7.51-7.49 (m, 2H), 7.41-7.39 (m, 1H), 7.35-7.29 (m, 1H), 7.16-7.13 (m, 1H), 7.00-6.90 (m, 1H), 6.80-6.73 (4H), 3.85 (d, J = 15.3 Hz, 1H), 3.70 (s, 3H), 3.62 (d, J = 15.3 Hz, 1H), 2.10 (t, J = 7.1 Hz, 2H), 1.87-1.77 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.3, 160.0, 158.9, 141.9, 135.7, 135.4, 134.0, 131.2, 130.9, 129.8, 129.1, 128.6, 128.4, 123.8, 121.9, 120.6, 114.3, 90.9, 88.9, 71.6, 70.6, 55.8, 47.0, 21.0, 14.5.

**Preparation of Vinylogous Amide 117.** To a stirred solution of alkyne 116 (395 mg, 0.68 mmol) in dry DCM (25 mL) at rt were
added p-toluenesulfonic acid (17 mg, 0.09 mmol) and tetrabutylammonium perrhenate (69 mg, 0.14 mmol). The resulting mixture was stirred at rt overnight. Saturated aqueous sodium bicarbonate (25 mL) was added and the mixture was stirred at rt for 5 min. DCM (50 mL) was added, the organic layer was washed with brine (30 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give vinylogous amide 117 (280 mg, 71%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.13-8.11 (m, 1H), 7.69-7.67 (m, 1H), 7.62-7.60 (m, 1H), 7.42-7.36 (m, 2H), 7.27-7.22 (m, 2H), 7.27-6.87 (m, 1H), 6.85-6.83 (m, 2H), 6.64 (s, 1H), 6.59-6.56 (2H), 3.69 (d, $J = 14.0$ Hz, 1H), 3.58 (s, 3H), 3.03 (d, $J = 14.0$ Hz, 1H), 2.08-2.00 (m, 1H), 1.88-1.80 (m, 1H), 1.16-1.13 (m, 2H), 0.53 (t, $J = 7.4$, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.4, 163.6, 156.2, 148.9, 141.3, 136.8, 136.4, 135.6, 134.0, 130.7, 130.0, 129.4, 127.9, 126.2, 122.8, 120.6, 118.7, 116.9, 115.3, 114.5, 64.6, 56.1, 55.7, 46.2, 17.8, 13.8.

**Preparation of Indole 119.** To a stirred solution of vinylogous amide 117 (94 mg, 0.16 mmol) in dry benzene (3.0 mL) at rt were added AIBN (2.7 mg, 0.016 mmol) and tris(trimethylsilyl)silane (48 mg, 0.19 mmol). The resulting solution was refluxed for 2 h and cooled to rt. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) to give indole 119 (25 mg, 31%) as well as the starting vinylogous amide 117 (45 mg, 48%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.72 (bs, 1H), 7.92-7.85 (m, 2H), 7.53-7.44 (m, 4H), 7.39-7.36 (m, 2H), 7.17-7.07 (m, 2H), 4.88 (s, 1H), 3.60 (s, 2H), 3.56 (s, 3H), 2.30-2.22 (m, 1H), 1.45-1.37 (m, 1H), 0.65 (t, $J = 7.4$, 3H); $^{13}$C NMR and
DEPT-135 (75 MHz, CDCl$_3$) δ 205.9, 168.0, 156.5, 154.5, 138.1, 135.1, 134.3, 133.9, 131.9, 131.4, 129.4, 128.3, 125.9, 124.2, 124.0, 121.8, 120.0, 115.4, 114.3, 113.8, 55.8, 53.0, 43.5, 34.5, 17.0, 13.7.

**Preparation of N-Benzylsulfonylindole 122.** To a stirred solution of vinylogous amide 117 (40 mg, 0.069 mmol) in dry DMF (1.5 mL) at rt were added tetrakis(triphenylphosphine) palladium (0) (8 mg, 0.0069 mmol), piperidine (26 mg, 0.31 mmol) and formic acid (14 mg, 0.30 mmol). The mixture was heated at 75 °C overnight and cooled to rt. DCM (15 mL) and brine (15 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) to give N-benzylsulfonylindole 122 (28 mg, 80%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.54 (bs, 1H), 7.91-7.89 (m, 1H), 7.66-7.62 (m, 2H), 7.51-7.40 (m, 4H), 7.34-7.28 (m, 2H), 7.22-7.16 (m, 2H), 6.75-6.70 (m, 2H), 4.14 (s, 2H), 3.67 (s, 3H), 3.58 (s, 2H), 2.71 (t, J = 14.6 Hz, 2H), 1.69-1.59 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 209.1, 167.7, 156.4, 139.0, 136.6, 134.3, 132.1, 131.5, 129.7, 126.8, 125.9, 124.6, 121.5, 119.7, 119.0, 114.8, 114.2, 55.8, 45.2, 40.4, 34.7, 17.3, 14.0.

**Preparation of N-BOC-indole 127.** To a stirred solution of vinylogous amide 123 (63 mg, 0.14 mmol) in dry DMF (0.5 mL) were added 1-benzyloxymethyl-4-iodo-1$H$-imidazole (125, 87 mg, 0.41 mmol), tetrakis(triphenylphosphine) palladium (0) (16 mg, 0.014 mmol), piperidine (40 mg, 0.48 mmol) and formic acid (18 mg, 0.41 mmol). The mixture was heated at 75 °C overnight and cooled
to rt. DCM (10 mL) and brine (10 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (3:2 hexanes:EtOAc) to give N-BOC-indole 127 (48 mg, 74%). \(^1\)H NMR (300 MHz, CDCl₃) \(δ\) 8.30 (bs, 1H), 7.89-7.87 (m, 1H), 7.49-7.43 (m, 1H), 7.41-7.40 (m, 2H), 7.23-7.16 (m, 2H), 6.71-6.68 (m, 2H), 4.08 (s, 2H), 3.65 (s, 3H), 3.64 (s, 2H), 2.65 (t, \(J = 8.1\) Hz, 2H), 1.67-1.53 (m, 11H), 0.88 (t, \(J = 7.4\) Hz, 3H); \(^1\)C NMR (75 MHz, CDCl₃) \(δ\) 209.1, 168.3, 156.3, 151.0, 135.7, 132.7, 132.0, 129.4, 125.1, 123.5, 121.7, 119.0, 116.1, 115.8, 114.2, 84.9, 55.8, 45.1, 41.0, 34.0, 28.6, 17.4, 14.1.

Preparation of N-Tosyl Vinylogous Amide 138. To a stirred solution of 1-pentyne (0.18 mL, 1.8 mmol) in dry THF (20 mL) at -78 °C was added dropwise a solution of n-BuLi (0.75 mL, 2.25 M in hexanes, 1.68 mmol) and the resulting mixture was stirred at -78 °C for 30 min. This solution was added to a solution of N-tosyl-β-lactam 136 (540 mg, 1.2 mmol) in dry THF (40 mL) at -78 °C. The mixture was stirred at -78 °C for 4 h and saturated aqueous NH₄Cl (50 mL) and EtOAc (50 mL) were added. The organic layer was washed with brine (30 mL) and dried over MgSO₄. The solvent was removed under reduced pressure to give crude alkyne 137, which was used without further purification.

To a stirred solution of the above aminal (290 mg, 0.56 mmol) in dry DCM (20 mL) at rt were added \(p\)-toluenesulfonic acid (14 mg, 0.07 mmol) and tetra-butylammonium perrhenate (55 mg, 0.11 mmol). The resulting mixture was stirred at rt overnight. Saturated aqueous sodium bicarbonate (25 mL) was added, the mixture was stirred at rt for 5 min and DCM (50 mL) was added. The organic layer was washed with
brine (30 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 hexanes:EtOAc) to give N-tosyl vinylogous amide 138 (250 mg, 40% from 136). ¹H NMR (300 MHz, CDCl₃) δ 7.85-7.82 (m, 1H), 7.39-7.34 (m, 3H), 7.11-7.09 (m, 4H), 6.97 (s, 1H), 6.72-6.69 (m, 2H), 6.52-6.49 (m, 2H), 3.56 (s, 3H), 3.13-3.09 (d, J = 14.1, 1H), 2.45-2.40 (d, J = 14.1, 1H), 2.26 (s, 3H), 2.15-2.05 (m, 1H), 2.02-1.83 (m, 1H), 1.07-0.82 (m, 2H), 0.60 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 199.4, 163.5, 156.2, 149.1, 146.0, 140.5, 133.9, 131.2, 131.0, 130.1, 130.0, 127.6, 127.2, 122.7, 119.4, 118.7, 118.5, 114.4, 64.5, 60.8, 55.7, 44.2, 26.4, 22.5, 14.1.

Preparation of N-Tosylindole 139. To a stirred solution of copper (II) bromide dimethyl sulfide complex (72 mg, 0.35 mmol) in dry THF (5 mL) at -78 °C was added phenylmagnesium bromide in THF (0.46 mL, 1 M) and the resulting solution was stirred at -78 °C for 1 h. Boron trifluoride etherate (50 mg, 0.35 mmol) was added and the mixture was stirred at -78 °C for 5 min. A solution of N-tosyl vinylogous amide 138 (60 mg, 0.11 mmol) in dry THF (1 mL) was added and the resulting solution was stirred at -78 °C overnight. The solution was warmed to rt and stirred for an additional 4 h. Saturated aqueous NH₄Cl (50 mL) and EtOAc (50 mL) were added. The organic layer was washed with brine (30 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) to give N-tosylindole 139 (40 mg, 70%). ¹H NMR (360 MHz, CDCl₃) δ 8.38 (bs, 1H), 7.76-7.74 (m, 1H), 7.39-7.36 (m, 2H), 7.34-7.32 (m, 1H), 7.28-7.26 (m, 2H), 7.06-7.02 (m, 2H), 6.95-6.93 (m, 2H), 6.58-
6.56 (m, 2H), 3.98 (s, 2H), 3.52 (s, 3H), 3.42 (s, 2H), 2.57 (t, \( J = 14.9 \) Hz, 2H), 2.08 (s, 3H), 1.47-1.43 (m, 2H), 0.73 (t, \( J = 14.7 \), 3H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \( \delta \) 209.2, 167.8, 156.4, 145.5, 136.0, 131.5, 130.29, 129.7, 126.8, 125.8, 124.4, 121.5, 119.6, 118.7, 114.9, 114.2, 55.8, 43.1, 40.3, 34.7, 25.8, 22.6, 14.5.

**1-Bromo-2-iodovinylbenzene (162).** To a stirred mixture of copper (II) bromide (1.3 g, 9.8 mmol) and iodine (2.5 g, 9.8 mmol) in dry acetonitrile (20 mL) at 0 °C was added phenylacetylene (161, 0.22 mL, 2.0 mmol) and the resulting mixture was stirred at 0 °C for 1 h. Saturated aqueous sodium thiosulfate (75 mL) and EtOAc (100 mL) were added. The organic layer was washed with brine (30 ml) and dried over MgSO\(_4\). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give 1-bromo-2-iodovinylbenzene (162) as a yellow oil (600 mg, 100%). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 7.37–7.35 (m, 2H), 7.29-7.25 (m, 4H), 6.89 (s, 1H); \(^{13}\)C NMR and DEPT-135 (90 MHz, CDCl\(_3\)) \( \delta \) 139.8, 129.8, 129.5, 128.8, 122.5, 75.7.

**1-(2-Chloro-2-phenylvinyl)-pyrrolidin-2-one (164).** A resealable Schlenk tube was charged with copper (I) iodide (36 mg, 0.19 mmol), cesium carbonate (470 mg, 1.4 mmol) and pyrrolidinone (163, 100 mg, 1.2 mmol), evacuated and filled with argon. \( N,N' \)-Dimethylethylenediamine (40 \( \mu \)L, 0.38 mmol), 1-chloro-2-iodovinylbenzene (158, 300 mg, 0.96 mmol) and dry THF (1 mL) were added under argon. The Schlenk tube was sealed, heated at 70 °C for 40 h and cooled to rt. The resultant mixture was filtered through a pad of Celite (EtOAc). EtOAc (25 mL) and
water (25 mL) were added. The organic layer was washed with brine (20 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give 1-(2-chloro-2-phenylvinyl)-pyrrolidin-2-one (164) as a white solid (195 mg, 92%). ¹H NMR (300 MHz, CDCl₃) δ 7.27 (bs, 5H), 7.14 (s, 1H), 2.88 (t, J = 6.9 Hz, 2H), 2.28 (t, J = 7.9 Hz, 2H), 1.79 (q, J = 7.4 Hz, 2H); ¹³C NMR and DEPT-135 (75 MHz, CDCl₃) δ 173.9, 135.7, 128.7, 128.3, 127.3, 122.3, 118.4, 46.9, 29.3, 17.8; LRMS-APCI m/z (relative intensity) 222 (MH⁺, 100), 186 (40); HRMS-APCI: [M+H]⁺ calcd for C₁₂H₁₂ClNO, 222.0607; found, 222.0698.

1-(2-Bromo-2-phenylvinyl)-pyrrolidin-2-one (165). A resealable Schlenk tube was charged with copper (I) iodide (11 mg, 0.06 mmol), cesium carbonate (550 mg, 1.7 mmol) and pyrrolidinone (163, 110 mg, 1.3 mmol), evacuated and filled with argon. N,N'-Dimethylethylenediamine (12 µL, 0.13 mmol), 1-bromo-2-iodovinylbenzene (162, 340 mg, 1.1 mmol) and dry THF (1 mL) were added under argon. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of Celite (EtOAc). EtOAc (25 mL) and water (25 mL) were added. The organic layer was washed with brine (20 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 hexanes:EtOAc) to give 1-(2-bromo-2-phenylvinyl)-pyrrolidin-2-one (165, 61 mg, 21%). ¹H NMR (300 MHz, CDCl₃) δ 7.32–7.25 (m, 5H), 7.22 (s, 1H), 2.86 (t, J = 6.9 Hz, 2H), 2.29 (t, J = 7.8 Hz, 2H), 1.79 (q, J = 7.0 Hz, 2H); ¹³C NMR and DEPT-135 (75 MHz, CDCl₃) δ 174.8, 141.7, 130.2,
129.9, 128.3, 125.9, 107.8, 48.0, 30.3, 18.9; LRMS-APCI \textit{m/z} (relative intensity) 266 (MH$^+$, 100); HRMS-APCI: [M+H]$^+$ calcd for C$_{12}$H$_{12}$BrNO, 266.0102; found, 266.0164.

\textbf{N-(2-Bromo-2-phenylvinyl)-acetamide (167).} A resealable Schlenk tube was charged with copper (I) iodide (19 mg, 0.10 mmol), cesium carbonate (490 mg, 1.5 mmol) and acetamide (166, 71 mg, 1.2 mmol), evacuated and filled with argon. \textit{N,N}-Dimethylethylenediamine (22 \textmu L, 0.20 mmol), 1-bromo-2-iodovinylbenzene (162, 308 mg, 1.0 mmol) and dry THF (1 mL) were added under argon. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting bright blue mixture was filtered through a pad of Celite (EtOAc). EtOAc (25 mL) and water (25 mL) were added. The organic layer was washed with brine (20 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give \textit{N}-(2-bromo-2-phenylvinyl)-acetamide (167, 53 mg, 22%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.58–7.41 (m, 4H), 7.28-7.18 (m, 3H), 2.10 (s, 3H); $^{13}$C NMR and DEPT-135 (75 MHz, CDCl$_3$) $\delta$ 167.8, 137.2, 128.9, 128.6, 127.3, 122.0, 23.8; LRMS-APCI \textit{m/z} (relative intensity) 240 (MH$^+$, 55), 200 (85), 198 (100), 192 (95); HRMS-APCI: [M+H]$^+$ calcd for C$_{10}$H$_{10}$BrNO, 239.9946; found, 240.0017.

\begin{center}
\includegraphics[width=0.2\textwidth]{image1}
\end{center}

\textbf{Preparation of \textit{\beta}-Bromoenamide 169.} A resealable Schlenk tube was charged with copper (I) iodide (1.7 mg, 0.009 mmol), cesium carbonate (88 mg, 0.27 mmol) and \textit{NH-\gamma}-lactam 168 (60 mg, 0.21 mmol), evacuated and filled with argon. \textit{N,N'}-Dimethylethylenediamine (2 \textmu L, 0.018
mmol), 1-bromo-2-iodovinylbenzene (162, 55 mg, 0.18 mmol) and dry THF (5 mL) were added under argon. The Schlenk tube was sealed, heated at 50 °C overnight and cooled to rt. The resultant mixture was filtered through a pad of Celite (EtOAc). EtOAc (25 mL) and water (25 mL) were added. The organic layer was washed with brine (20 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give β-bromoenamide 169 (32 mg, 39%). ^1H NMR (360 MHz, CDCl₃) δ 7.48–7.35 (m, 1H), 7.15-7.09 (m, 2H), 7.02–6.82 (m, 3H), 6.98 (s, 1H), 6.89-6.84 (m, 1H), 6.75-6.73 (m, 1H), 6.68-6.64 (m, 1H), 3.39-3.32 (m, 1H), 3.07-2.96 (m, 1H), 1.58 (s, 9H).

5-Oxopyrrolidine-2-carboxylic Acid 2-Chloro-3-iodoallyl Ester (172). To a stirred solution of 2-pyrrolidine-5-carboxylic acid (170, 160 mg, 1.25 mmol) in dry DCM (25 mL) at rt was added 4-dimethylaminopyridine (31 mg, 0.25 mmol) followed by 1,3-dicyclohexylcarbodiimide (1.9 mL, 1.9 mmol) and 2-chloro-3-iodoprop-2-en-1-ol (171, 110 mg, 0.51 mmol), and the resulting solution was stirred at rt for 2 d. The mixture was filtered through a pad of silica gel (EtOAc) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc) to give 5-oxopyrrolidine-2-carboxylic acid 2-chloro-3-iodoallyl ester (172, 140 mg, 84%). ^1H NMR (300 MHz, CDCl₃) δ 7.00 (bs, 1H), 6.66 (s, 1H), 4.91 (q, J = 12.9, 24.3 Hz, 2H), 4.30-4.26 (m, 1H), 2.46-2.24 (m, 4H); ^13C NMR and DEPT-135 (75 MHz, CDCl₃) δ 176.5, 169.7, 129.1, 76.5, 65.4, 53.6, 27.4, 23.1; LRMS-APCI m/z (relative intensity) 330 (MH⁺, 100); HRMS-APCI: [M+H]⁺ calcd for C₈H₉ClINO₃, 329.5194; found, 329.9361.
4-Chloro-9,9a-dihydro-3H,8H-pyrrolo[2,1-c]oxazepine-1,7-dione (173). A resealable Schlenk tube was charged with copper (I) iodide (3 mg, 0.014 mmol), cesium carbonate (46 mg, 0.14 mmol) and 5-oxopyrrolidine-2-carboxylic acid 2-chloro-3-iodoallyl ester (172, 31 mg, 0.09 mmol), evacuated and filled with argon. N,N'-Dimethylethlyenediamine (4 µL, 0.03 mmol) and dry THF (2 mL) were added under argon. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting bright blue mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (EtOAc) to give 4-chloro-9,9a-dihydro-3H,8H-pyrrolo[2,1-c]oxazepine-1,7-dione (173, 8 mg, 46%). ^1H NMR (300 MHz, CDCl₃) δ 6.26 (s, 1H), 5.11 (d, J = 12.9 Hz, 1H), 4.45 (d, J = 12.9 Hz, 1H), 4.38-4.3 (m, 1H), 2.60-2.27 (m, 4H); ^13C NMR and DEPT-135 (75 MHz, CDCl₃) δ 174.0, 170.0, 126.3, 125.9, 64.0, 61.2, 29.5, 22.4.

5-Oxopyrrolidine-2-carboxylic Acid Prop-2-ynyl Ester (174). To a stirred solution of 2-pyrrolidinine-5-carboxylic acid (170) (260 mg, 2.0 mmol) in propargyl alcohol (1.4 mL, 24 mmol) at 0 °C was added dimethylformamide (0.04 mL) followed by thionyl chloride (0.58 mL, 8.0 mmol). The resulting mixture was stirred at rt for 15 h. The thionyl chloride was then removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc) to give 5-oxopyrrolidine-2-carboxylic acid prop-2-ynyl ester (174) (233 mg, 70%). ^1H NMR (300 MHz, CDCl₃) δ 7.74 (bs, 1H), 4.69 (bs, 2H), 4.26–4.23 (m, 1H), 2.54-2.14 (m, 4H), 1.97 (s, 1H); ^13C NMR and DEPT-135 (75 MHz, CDCl₃) δ 178.9, 171.9, 77.1, 76.0, 55.7, 53.1, 29.5, 24.9;
LRMS-APCI \( m/z \) (relative intensity) 168 (MH\(^+\), 100); HRMS-APCI: [M+H]\(^+\) calcd for C\(_8\)H\(_9\)NO\(_3\), 168.0582; found, 168.0671.

5-Oxopyrrolidine-2-carboxylic Acid 3-Bromo-2-iodoallyl Ester (175). To a stirred solution of 5-oxopyrrolidine-2-carboxylic acid prop-2-ynyl ester (174, 70 mg, 0.42 mmol) in dry acetonitrile (3 mL) at rt were added copper (II) bromide (470 mg, 2.1 mmol) and iodine (530 mg, 2.1 mmol). The resulting mixture was heated under reflux for 5 h and cooled to rt. Saturated aqueous sodium thiosulfate (50 mL) and EtOAc (50 mL) were added. The organic layer was washed with brine (30 mL) and dried over MgSO\(_4\). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give 5-oxopyrrolidine-2-carboxylic acid 3-bromo-2-iodoallyl ester (175, 102 mg, 65%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.90–6.86 (m, 1H), 6.82 (bs, 1H), 4.88–4.84 (m, 2H), 4.30–4.26 (m, H), 2.47–2.26 (m, 4H); \(^13\)C NMR and DEPT-135 (75 MHz, CDCl\(_3\)) \( \delta \) 178.5, 171.7, 111.4, 93.8, 67.7, 55.8, 29.6, 25.2; LRMS-APCI \( m/z \) (relative intensity) 374 (MH\(^+\), 100), 186 (40); HRMS-APCI: [M+H]\(^+\) calcd for C\(_8\)H\(_9\)BrINO\(_3\), 373.8811; found, 373.8890.

5-Oxopyrrolidine-2-carboxylic Acid 2,3-Dibromoallyl Ester (176). To a stirred solution of 5-oxopyrrolidine-2-carboxylic acid prop-2-ynyl ester (174, 150 mg, 0.88 mmol) in glacial acetic acid (5 mL) at 65 °C was added bromine (160 mg, 0.97 mmol) and the resulting solution was stirred at 65 °C for 1 h. The mixture was poured into cold saturated aqueous sodium thiosulfate solution (20 mL). DCM (25 mL) and water (10 mL) were added. The organic layer was dried over MgSO\(_4\), the solvent
was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give 5-oxopyrrolidine-2-carboxylic acid 2,3-dibromoallyl ester (176) as a clear oil (120 mg, 49%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.01 (bs, 1H), 6.67 (s, 1H), 5.01-4.90 (m, 2H), 4.30-4.26 (m, 1H), 2.46-2.23 (m, 4H); $^{13}$C NMR and DEPT-135 (75 MHz, CDCl$_3$) δ 176.8, 169.9, 117.2, 106.4, 63.5, 53.9, 27.6, 23.3.

**5-Oxopyrrolidine-2-carboxylic Acid Allyl Ester (183).** To a stirred solution of 2-pyrrolidine-5-carboxylic acid (170, 1.0 g, 7.7 mmol) in dry DCM (120 mL) at rt was added 4-dimethylaminopyridine (200 mg, 1.5 mmol) followed by 1,3-dicyclohexylcarbodiimide (12 mL, 12 mmol), and allyl alcohol (490 mg, 8.5 mmol) and the resulting solution was stirred at rt for 2 d. The mixture was filtered through a pad of silica gel (EtOAc) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc) to give 5-oxopyrrolidine-2-carboxylic acid allyl ester (183, 990 mg, 77%).$^1$H NMR (300 MHz, CDCl$_3$) δ 7.43 (bs, 1H), 5.85-5.76 (m, 1H), 5.26-5.14 (m, 2H), 4.55-4.53 (m, 2H), 4.21-4.16 (m, 1H), 2.38-2.10 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 178.9, 172.3, 131.8, 119.2, 66.3, 55.9, 29.7, 25.1.

**5-Oxo-1-vinylpyrroldine-2-carboxylic Acid Allyl Ester (184).** To a stirred solution of 5-oxopyrrolidine-2-carboxylic acid allyl ester (183, 340 mg, 2.0 mmol) in butyl vinyl ether (2.6 mL, 20 mmol) at rt was added palladium (II) trifluoroacetate (33 mg, 0.1 mmol) and 4,7-diphenylphenanthroline (33 mg, 0.1 mmol).
The resulting solution was heated at 75 °C for 3 h with an 18 gauge needle through the septum to act as a purge. The mixture was cooled to rt and purified by flash column chromatography on silica gel (CH₂Cl₂) to give 5-oxo-1-vinylpyrrolidine-2-carboxylic acid allyl ester (184, 360 mg, 95%). \[ ^1H \text{NMR (360 MHz, CDCl}_3) \delta 7.06-6.99 \text{ (m, 1H), 5.90-5.81 \text{ (m, 1H), 5.33-5.23 \text{ (m, 2H), 4.64-4.62 \text{ (m, 2H), 4.45-4.27 \text{ (m, 2H), 2.60-2.41 \text{ (m, 1H), 2.40-2.34 \text{ (m, 2H), 2.15-2.13 \text{ (m, 1H); ^13C \text{NMR and DEPT 135 (75 MHz, CDCl}_3) \delta 173.6, 171.2, 131.5, 128.7, 119.5, 95.2, 66.4, 58.1, 30.0, 23.1.} \]

**5-Oxo-1-styrylpyrrolidine-2-carboxylic Acid Allyl Ester (185).** To a stirred solution of 5-oxopyrrolidine-2-carboxylic acid allyl ester (183) (130 mg, 0.77 mmol) in toluene (15 mL) at rt were added a catalytic amount of \( p \)-toluenesulfonic acid and phenylacetaldehyde (280 mg, 2.3 mmol). The solution was heated at reflux overnight with a Dean-Stark apparatus. The resulting mixture was cooled to rt and aqueous sodium bicarbonate (40 mL) and EtOAc (40 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give 5-oxo-1-styrylpyrrolidine-2-carboxylic acid allyl ester (185, 155 mg, 74%). \[ ^1H \text{NMR (300 MHz, CDCl}_3) \delta 7.41-7.18 \text{ (m, 11H), 7.14-6.93 \text{ (m, 2H), 6.67-6.63 \text{ (m, 2H), 3.62 \text{ (s, 3H), 3.53 \text{ (d, } J = 14.6 \text{ Hz, 1H), 3.25 \text{ (d, } J = 14.6 \text{ Hz, 1H).} \]

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Chapter 2

Studies Directed Towards a Total Synthesis of the Chartellines

Part 1

Introduction and Background

1.1 Synthetic Approaches to the Chartellines

Due to the novel structures of the chartellines (1-3) there has been considerable research directed towards their synthesis. These metabolites present a formidable synthetic challenge due to their extensive halogenation as well as unprecedented spiro-β-lactam, macrocyclic β-chloroenamide and α,β-unsaturated indolenine moieties. In 2001, our group reported the first synthetic studies on the chartellines.\textsuperscript{14a} Some initial research on the synthesis of the β-lactam and enamide moieties has also been published by the Isobe group.\textsuperscript{47,56,57,58} Recently, the Baran group has reported the first total synthesis of any member of this family of marine natural products by synthesizing chartelline C (3).\textsuperscript{59,60} Additionally, the Magnus group has conducted some preliminary investigations on the synthesis of the chartellines.\textsuperscript{61}

1.1.1 Isobe's Synthetic Approaches to the Spiro-β-Lactam and Enamide Moieties of the Chartellines
Isobe and coworkers have developed two methods for the formation of the spirom-β-lactam moiety of the chartellines as well as two approaches for the formation of the enamide functionality. Their first method for the synthesis of the spiro-β-lactam moiety found in the chartellines began with the condensation of isatin (188) with p-anisidine, which gave PMP imine 189 (Scheme 40). Condensation of imine 189 with the silylketene acetal of ethyl acetate afforded β-amino ester 190. Functional group manipulation of this ester gave amino acid 191. Finally, treatment of amino acid 191 with tris(2-oxo-3-benzoxazolinyl)phosphine oxide (192) and triethylamine in refluxing acetonitrile furnished NH-β-lactam 193 in good yield.

A second, biogenetically inspired method for the formation of the β-lactam moiety developed by the Isobe group involved an intramolecular nucleophilic substitution onto an activated amide nitrogen by the C3 position of the indole. Thus, BOC protection of the nitrogen of indole 194 followed by saponification of the ester gave carboxylic acid.
195, which was then converted to \( N \)-methylhydroxamic acid 196 via an activated hydroxysuccinimide ester (Scheme 41). Treatment of hydroxamic acid 196 with nosyl chloride followed by BOC deprotection gave \( NH \)-indole 197. Treatment of this indole with lithium hexamethyldisilazide (LiHMDS) in THF at -78 °C, followed by warming to room temperature, yielded the desired \( N \)-methyl \( \beta \)-lactam indolenine 198 in good yield, via the mechanism depicted below.

**Scheme 41**

The Isobe group has also examined the formation of the chartelline enamide moiety via \( N \)-acylation of oxime derivatives with an acid chloride. Thus, reaction of acid chloride 199 with model oxime ether 200 in refluxing dichloromethane in the presence of molecular sieves afforded hydroxy enamide 201 in fair yield (Scheme 42). Deallylation of (E)-enamide 201 to hydroxy enamide 202 was accomplished in the presence of a palladium (0) catalyst and morpholine. Isobe also coupled imidazole oxime ether 203 with indole acid chloride 199 to give exclusively (E)-enamide 204 in 39%
yield. This method may provide a viable route to the chartellines when used in tandem with Isobe's β-lactam formation methodology (see Scheme 41) if the enamide formation can be accomplished in an intramolecular fashion to give the requisite (Z)-enamide.

Scheme 42

1.1.2 Baran’s Total Synthesis of Chartelline C (3)

Baran and coworkers recently reported the first total synthesis\(^5\) of chartelline C (3) based upon extensive prior work on a model system.\(^6\) The first key connection in their synthesis began with the halogen-selective Heck-Sonogashira\(^6\) coupling of advanced 2-iodoindole 205 and alkynyl imidazole 206 intermediates to give 2-ethynyl indole 207 (Scheme 43). \textit{syn}-Reduction of alkyne 207 followed by removal of the TBS group from the alcohol and subsequent 1° alcohol oxidation gave aldehyde ester 208. Saponification of ester 208 followed by intermolecular BOP-Cl mediated coupling between the resultant acid and amine 209 yielded amide aldehyde 210. Enamide
formation was accomplished via an intramolecular Horner-Wadsworth-Emmons (HWE) reaction of amidoaldehyde 210, which after treatment of the resultant macrocycle with bromine gave tribromide 211. Finally, thermal BOC removal from indole 211 followed by a key ring contraction of the macrocycle, chlorination and subsequent decarboxylation of the ester completed the total synthesis of (+/-)-chartelline C (3).

Scheme 43

The penultimate step of Baran's synthesis involved a key ring contraction step in which the spiro-β-lactam moiety was installed (211 to 3, Scheme 43). To rationalize this transformation, Baran has proposed that BOC deprotection of indole 211 followed by bromination of the NH-indole initially gives bromoindolenine intermediate 212 (Scheme 44). Nucleophilic attack of the pendant amide onto the C2 position of indolenine 212 affords dearomatized 2H-indole intermediate 213. A 1,5 shift of the γ-lactam nitrogen in intermediate 213 results in rearomatization of the benzene ring and formation of β-
lactam 214. Treatment of 214 with brine to install the C3 chlorine and thermal
decarboxylation of the ester then affords (+/-)-chartelline C (3). The three dimensional
structure of the chartellines probably promotes this unprecedented ring contraction (i.e.
the \(\pi\)-stacking of the indolenine and imidazole rings as well as the parallel alkene and
enamide functionalities).\(^{66}\)

\[\text{Scheme 44}\]

\[\text{1.1.3 Magnus' Approach to a Coupled Indole - Imidazole Moiety of Chartelline C (3)}\]

Recently the Magus group reported a model study towards the synthesis of
chartelline C (3, Scheme 45).\(^{61}\) The synthesis began with the coupling of 2,6-
dibromoindole 215 with alkyne 216 under Sonogashira conditions to afford 2-alkynyl
indole 217. Alkyne 217 was then reduced with Adam's catalyst to give (Z)-alkene 218.
Deprotection of acetonide 218 followed by oxidation of the resulting diol gave ketone
219. Formation of the imidazole ring from diketone 219 yielded imidazole-indole 220.
At this point the research project was ended due to the similarity between this route and Baran's completed total synthesis of chartelline C (3).

**Scheme 45**

1.2 Previous Synthetic Studies on the Chartellines in the Weinreb Group

1.2.1 Initial Retrosynthetic Analysis for the Synthesis of Chartelline A (1)

The initial retrosynthetic analysis developed by the Weinreb group for the synthesis of the chartellines involved as key steps a macrocyclodehydration to form the enamide moiety and addition of a lithioacetylide to the carbonyl of a γ-lactam to couple the N-acyloxindole and alkynyl imidazole moieties. Retrosynthetically, chartelline A (1) could come from chlorination of the enamide and reduction of the vinylogous amide of pentacycle 221 (Scheme 7). Enamide 221 would come from cyclodehydration of NH-β-lactam aldehyde 222 forming the N1-C2 bond. Vinylogous amide 222 results from a
Meyer-Schuster rearrangement\textsuperscript{26} of hemiaminal 223 followed by functional group manipulations of the acetonide moiety to form the aldehyde. Finally, the C11,12 bond of $N$-acyl hemiaminal 223 could be formed from selective addition of the lithioacetylide derived from alkynyl imidazole 225 to the activated C9 carbonyl of $N$-acyl $\gamma$-lactam 224. Both 224 and 225 should be available from commercially available starting materials (i.e. 5-nitroisatin (227) and histidine (226), respectively). For clarity, the chartelline A (1) numbering system is utilized throughout when referring to bond connection / disconnections, as well as to indicate the position of functional groups.

\textbf{Scheme 46}

\textit{1.2.2 Synthesis of Tribromo-$\beta$-lactam 224}

A significant amount of work was done by the Weinreb group on model systems relevant to the synthesis of the chartellines.\textsuperscript{14a-c} The initial focus of the research was on
the formation of a spiro-β-lactam moiety like 224 and probing its reactivity. Based on this initial work, a synthesis of a tribromo spiro-β-lactam synthon for chartelline A (1) was developed (Scheme 47). Condensation of 5-nitroisatin (226) with p-anisidine resulted in an imine that was subjected to a Staudinger [2+2] cycloaddition with in situ generated chloroketene to afford chloro β-lactam 228 as a mixture of diastereomers. BOC protection of NH-γ-lactam 228 followed by a two-step reduction / dechlorination sequence of the nitro and chloro moieties proceeded cleanly to afford amine 230. Bromination of 230 with tetrabutylammonium tribromide, followed by subjection of the aniline to the Doyle modification of the Sandmeyer reaction, yielded tribromo β-lactam 231. Finally, removal of the PMP protecting group from β-lactam 231 gave the desired tribromo NH-β-lactam 224.

Scheme 47
A synthesis of the substituted imidazoles, required for our approach towards the chartellines, which allowed for regioselective incorporation of a variety of different functional groups was also examined. Towards this end, \textit{NH}-imidazole 232, easily prepared from histidine (227),\textsuperscript{68} was first BOM-protected to give a regioisomeric mixture of products 233 and then the ester enolate was dimethylated to give dimethyl ester 234 (Scheme 48).\textsuperscript{14c} Refluxing ester 234 in THF with a catalytic amount of BOM-Cl resulted in complete conversion to C8-substituted imidazole 236, as determined by NOE analysis. We believe that this transformation proceeds through di-BOM cationic intermediate 235, which breaks down to give the thermodynamically more stable N5-BOM product 236.\textsuperscript{14} Regioselective bromination of imidazole 236 at C4 followed by Stille coupling of the resulting bromoimidazole 237 with allyltributyltin gave C4-allylimidazole 238.

Scheme 48
Dihydroxylation of allylimidazole 238 followed by formation of the acetonide and C6-bromination of acetonide imidazole 239 yielded 6-bromoimidazole 240. Finally, DIBAL-H reduction of ester 240 formed aldehyde 241, which was converted to alkyne 225 using the Ohira modification of the Gilbert-Seyferth reaction.

1.2.4 Coupling of the β-Lactam (224) and Imidazole (225) Subunits

After the syntheses of both the β-lactam (214) and imidazole (225) fragments were completed, their coupling and subsequent formation of the macrocycle of chartelline A (1) was examined. Thus, deprotonation of two equivalents of alkyne 225, followed by reaction with one equivalent of N-BOC-γ-lactam 224 gave coupled products 223 as a

Scheme 49
single regioisomer, but as a mixture of diastereomers (Scheme 49).\textsuperscript{14c} Cleavage of acetonide 223 with TFA proceeded smoothly to give diol 242. Diol 242 was cleaved to aldehyde 243, which reacted with \( p \)-TsOH to give an unstable bright yellow solid believed to be cyclization compound 244 instead of the desired 10-membered ring enamide 222. The formation of vinylogous amide 244 most likely occurs via intramolecular aldol-type condensation of enamide 243. In this reaction the more stable conjugated 7-membered ring is preferentially formed over the rather strained 10-membered macrocycle in intermediate 222. Compound 244 was bis-BOC protected to give the stable vinylogous imide 245, which was used for characterization purposes.\textsuperscript{71}

\textbf{1.2.5 Revised Retrosynthesis of Chartelline A (1): \( N \)-Vinylation Methodology}

In light of the unsuccessful cyclodehydration step, Weinreb and Sun explored an alternative strategy for the total synthesis of chartelline A (1). This approach sought to take advantage of a lithioacetylilide addition to the carbonyl of a tribromo bis-lactam derivative in conjunction with a Buchwald type \( N \)-vinylation reaction to form the \( \beta \)-chloroenamide moiety. To provide flexibility in this approach, two routes were examined for making the key connections (Scheme 50). In one sequence, chartelline A (1) could be formed from an intramolecular cyclization of alkyne 246 to form the C11,12 bond, followed by functional group manipulations (path a). Alkyne 246 in turn could come from a halogen-selective \( N \)-vinylation reaction between \( NH \)-\( \beta \)-lactam 224 and iodovinylimidazole 247 to form the N1-C2 bond, followed by functional group manipulation of the ester moiety. Conversely, initial addition of the lithioacetylide of
alkyne imidazole 249 to the carbonyl of N-acyl γ-lactam 224, followed by functional
group manipulations and intramolecular N-vinylation of the NH-β-lactam of iodoalkene
248 to form the N1-C2 bond was also envisioned to lead to 1 (path b).

Scheme 50

The scope, limitations and mechanism of amide / lactam N-vinylation reactions
with haloalkenes was discussed in detail in Chapter 1, Section 2.5, pg. 36. Thus, a model
system was constructed to test the feasibility of using this methodology for the
stereocontrolled formation of β-chloroenamides of the chartelline type. Coupling of β-
lactam 250 with iodovinylimidazole 251 using modified Buchwald conditions gave the
desired β-chloroenamide 252 in excellent yield as a single geometric and regioisomer
(Scheme 51). Interestingly, use of N-BOC-γ-lactam 224 in the coupling reaction with
iodoalkene 251 gave chloroenamide 253 in which the BOC group was lost. It is
important to reiterate that the Weinreb group has never observed any compound
corresponding to the product of vinyl chloride coupling that was obtained by the Isobe
group (i.e. compound 160, Chapter 1: Section 2.5.2, Scheme 33, pg. 40).
1.2.6 Synthesis of Imidazoles 247 and 249

In order to further investigate the synthesis of the chartellines based on the revised retrosynthesis in Scheme 50, synthetic routes to dihalovinylimidazoles 247 and 249 were devised. Thus, known allylimidazole 254 was converted into ester 255 via a three-step procedure (Scheme 52). Iodoimidazole 255 was then coupled with TMS-acetylene under Sonogashira conditions to afford TMS-alkyne imidazole 256. Dimethylation of the enolate of ester 256, followed by removal of the TMS group from the acetylene with TBAF gave terminal alkyne imidazole 257. Iodochlorination of alkyne imidazole 257 with iodine and copper (II) chloride yield the desired mixed dihaloalkene 247.

Scheme 52
In addition to dihalovinylimidazole ester 247, dialkynyl imidazole 249 was also formed to study the intramolecular N-vinylation strategy towards the chartellines (Scheme 53, path b). Thus, bromination of imidazole 255 at C6, followed by halogen-selective Sonogashira reaction of 4-iodoimidazole 256 with TBS-acetylene gave TBS-alkyne imidazole 257. Dimethylation of the enolate of ester imidazole 257, followed by reduction and oxidation of the resulting ester 258 afforded aldehyde imidazole 259. Finally, using the Ohira modification of the Gilbert-Seyferth reagent, 69 aldehyde 259 was converted to dialkyne imidaazole 249, which was suitably substituted for coupling with N-BOC-γ-lactam 231.

Scheme 53

1.2.7 Cul Catalyzed Coupling of β-Lactam 260 and Imidazole Subunits 247 and 249

Sun and Weinreb initially studied the halogen-selective intermolecular N-vinylation reaction of β-lactam 260 with iodochlorovinylimidazole 247 to form the β-chloroenamide moiety of 1 (see Scheme 50, path a). Model studies had indicated that BOM or SEM protecting groups on the γ-lactam were compatible with the N-vinylation
conditions, and therefore $\beta$-lactam 260 was used in this study. Reaction of iodochlorovinylimidazole 247 with $NH$-$\beta$-lactam 260 under Buchwald conditions gave haloenamide 261 in moderate yield based on recovered imidazole starting material (Scheme 54).\textsuperscript{14d} Unfortunately, it was not possible to convert ester 261 to the desired BOC-alkyne imidazole 246 under a variety of conditions.\textsuperscript{72}

**Scheme 54**

In light of the inability to elaborate the ester moiety of enamide 261 to the desired alkyne 246, the alternative intermolecular alkyne / $N$-acyl $\gamma$-lactam addition strategy was investigated (see Scheme 50, path b). During model work on the intermolecular $\beta$-lactam N-vinylation reaction it was found that a bromine at the C6 position of the imidazole is incompatible with the Buchwald coupling procedure. Therefore, the C6-bromine of imidazole 249 was removed via lithium halogen exchange, followed by aqueous quenching, to give alkyne imidazole 262 (Scheme 55).\textsuperscript{14c} Addition of the lithium acetylide derived from alkyne 262 to $N$-BOC-$\gamma$-lactam 231 yielded hemiaminal 263 as a mixture of diastereomers. After unsuccessful cyclization attempts via an intramolecular
N-vinylation reaction on various derivatives of N-acyl hemiaminal 263, including iodoalkene 268 (see Scheme 50), it was decided to investigate the macrocyclization of a vinylogous amide intermediate. Thus, subjection of hemiaminal 263 to tetrabutylammonium perrhenate effected a Meyer-Schuster rearrangement to give a NH-vinylogous amide. Previous model work had demonstrated that the N-tosyl protecting group on the tribromo-γ-lactam is stable under the N-vinylation conditions. Thus, removal of the silyl protecting group from the alkyne followed by N-tosylation of the NH-γ-lactam afforded terminal alkyne 264. Treatment of alkyne 264 with iodine and copper (II) chloride gave (E)-iodoalkene 265 as a 1:1 mixture of BOM regioisomers. PMP-β-Lactam 265 was deprotected with CAN to yield cyclization precursor 266. A number of conditions were then tried to initiate the desired intramolecular N-vinylation of NH-β-lactam 266, but unfortunately none afforded any of the desired pentacycle 267.

Scheme 55
In summary, an array of methods were explored by Weinreb, Sun and Lin towards the synthesis of the chartellines. The key bond disconnections and the main routes that were studied are summarized in Figure 1 and Scheme 56. Both inter- and intramolecular N-vinylation reactions as well as cyclodehydration routes were examined to form the upper enamide moiety (disconnection between N1-C2). The common theme to these routes is the addition of an alkynyl nucleophile to the activated C12 carbonyl group of a γ-lactam derivative, generally followed by a Meyer-Schuster rearrangement (connection between C11-C12). Additionally, an RCM route towards formation of the upper enamide moiety was examined (disconnection between C2-C3). Analysis of the structural motifs found in Scheme 56 shows that the majority of the substrates contained either an sp² stereocenter or a hemiaminal-alkyne at C12 of the chartellines. It is believed that these moieties inhibit the formation of the macrocyclic ring as the reactive partners are too far apart to form the desired bonds. Additionally, there is considerable ring strain that must be overcome for the macrocyclization of these substrates to proceed, as observed in the attempted cyclodehydration of aldehyde 243 (cf. Scheme 49). We assume that the inflexibility of the substrates, as well as significant steric hindrance and ring strain, contributed to the inability to form the macrocyclic core of the chartellines via the approaches outlined below.

![chartelline A (1)](image)

**Figure 1.** Key bond disconnections
Additionally, as illustrated in Figure 2, even if the hemiaminal-alkyne system was flexible enough to allow for an intramolecular N-vinylation reaction, cyclization could only occur through the diastereomer in which the β-lactam nitrogen and alcohol moieties
are trans (i.e. 248a). In the cis diastereomer 248b, the vinyl iodide and β-lactam nitrogen are on opposite sides of the planar oxindole derivative, precluding cyclization.

![trans and cis addition products 248](image)

**Figure 2.** trans vs. cis addition products 248
Part 2

Results and Discussion

2.1 Retrosynthetic Analysis

Based on the previous work by Sun and Lin (see Section 1.2) a new retrosynthetic analysis towards the chartellines (1-3) was devised as illustrated in Scheme 57. Although the basic disconnections are similar to the previous work (i.e. breaking the molecule at the N1-C2 and C11-C12 bonds) we expected that this new approach would allow increased conformational flexibility in the macrocyclization substrate. We believed that in the previous routes explored, the alkyne or vinylogous amide at C10-12 of the intermediates caused significant ring strain in the macrocyclization step, which inhibited formation of the 10-membered ring. Additionally, we felt that due to a combination of steric, stereoelectronic and ring strain difficulties an intramolecular addition of an alkyne nucleophile to the carbonyl of an activated C12 γ-lactam would also be problematic. Our new approach aimed to alleviate some of these problems by forming an sp\(^3\) center at C12. Thus, retrosynthetic chartelline A (1) could come from reduction of ketone 270 followed by dehydration of the resulting alcohol indolenine. β-Chloroenamide 270 could come from RCM of diene 271, followed by C3 chlorination of the resulting enamide. It seemed possible that the BOC group would be lost from γ-lactam 271 under these conditions with concomitant dehydration of the resulting hemiaminal to generate the indolenine moiety. Diene 271 would result from intermolecular addition of the enolate
of ketoimidazole 273 to the N-acyl γ-lactam carbonyl in 272. Imidazole ketone 273 could be derived from imidazole ester 258, previously synthesized in our laboratory.¹⁴

Scheme 57

2.2 Studies on the Coupling of Methyl Ketone 273 and N-BOC-γ-Lactam 272

2.2.1 Background and Model Studies on the Addition of Ketone Enolates to Activated γ-Lactams

Prior to undertaking a synthesis of the requisite imidazole subunit 273, a model system was explored to test whether a ketone enolate will add selectively to the carbonyl group of an activated γ-lactam in the presence of a β-lactam. Ketone enolates are known to add both intra- and intermolecularly to N-activated lactams,⁷³ although no examples have been reported for their addition to oxindole derivatives. Thus, in a preliminary experiment, it was found that addition of the lithium enolate derived from pinacolone to
known bis-lactam $96^{14b}$ was selective for the $N$-BOC-$\gamma$-lactam and cleanly afforded either hemiaminal $274$ or vinylogous amide $275$, depending on the reaction work-up conditions (Scheme 58).

**Scheme 58**

2.2.2 **Synthesis of Imidazole Subunit 273**

Having demonstrated the feasibility of adding a ketone enolate to bis-lactam $274$, a route for formation of the requisite ketoimidazole $273$ was developed based on manipulations of known diiodoimidazole $58$ (cf. Scheme 11).$^{13}$ Diiodoimidazole $58$ can be selectively functionalized at the C8-position through metal halogen exchange, followed by addition of allyl bromide to give allylimidazole $254$ (Scheme 20).$^{17}$ However, Wacker oxidation$^{74}$ of allylimidazole $254$ failed to give the desired ketone $276$. Additionally, metal halogen exchange of diiodoimidazole $58$, followed by addition of propylene oxide did not install the desired three-carbon moiety at C8 of the imidazole.$^{75}$ Formation of the C8 monocuprate of diiodoimidazole $58$, followed by reaction with known bromoallene $278^{76}$ did not give the desired addition product $279$, even though the analogous addition of phenylmagnesium bromide to bromoallene $278$ is known.$^{77}$
Alkene 281 could be formed using a combination of Knochel's procedure\textsuperscript{78} for selective cuprate formation and Lindell's method for aryl allylation.\textsuperscript{16} Thus, the cuprate derived from diiodoimidazole 58 was successfully coupled with 3-bromo-2-methylpropene (280) to give alkene 281. Alkene 281 was converted to ketone 276 either \textit{via} a Johnson-Lemieux oxidative cleavage or by treatment with ruthenium trichloride and sodium periodate.\textsuperscript{79} Additionally, it was found that addition of the cuprate derived from diiodoimidazole 58 to 1-bromo-3-methyl-2-butene (282) did not give the expected S\textsubscript{N}2' addition product 284,\textsuperscript{80} but rather afforded alkene 283 derived from an S\textsubscript{N}2 pathway.

\textbf{Scheme 59}

\(\text{Scheme 59}\)

\[\begin{align*}
\text{58} & \xrightarrow{n\text{-BuLi}, \text{CuCN-2LiCl, THF, -20 °C}} \text{254} \quad \text{PdCl}_2, \text{CuCl, DMF:H}_2\text{O, rt} \quad \text{276} \\
\text{73\%} & \quad \text{277} \\
\text{278} & \xrightarrow{n\text{-BuLi or EtMgBr, THF, -78 °C}} \quad \text{279} \\
\text{CuLiBr, n-BuLi, THF, -78 °C} & \quad \text{278} \\
\text{279} & \xrightarrow{\text{OsO}_4, \text{NMO, H}_2\text{O:Mg}_2\text{CO, NaI}_{2} \text{O}_2, 60\%} \quad \text{281} \\
\text{280} & \xrightarrow{n\text{-BuLi, CuCN-2LiCl, THF, -20 °C}} \quad \text{281} \\
\text{93\%} & \quad \text{276} \\
\text{282} & \xrightarrow{n\text{-BuLi, CuCN-2LiCl, THF, -20 °C}} \quad \text{283} \quad \text{284} \\
\text{75\%} & \quad \text{observed} \quad \text{desired}
\end{align*}\]
The dialkylation of a variety of carbonyl-substituted imidazoles was also probed in order to install the requisite gem-dimethyl functionality found in the natural product (Scheme 60). For example, attempted methylation of ketone 276 with methyl iodide, 18-crown-6 and either potassium t-butoxide or sodium hydride as base resulted in formation of enol ether 285. Additionally, conversion of ketone 276 to vinyl imidazole 286, followed by attempted C-methylation with potassium t-butoxide / methyl iodide did not give any of the desired product 287. Alternatively, methylation of ketovinylimidazole 286 using sodium hydride as base gave exclusively the methylated enol ether 288.

Scheme 60

In light of the difficulties in synthesizing imidazole 273 from ketone 276 an alternative route was examined based on functional group modification of the previously prepared aldehyde 259.14e Thus, addition of methylmagnesium chloride to known aldehyde 259 gave alcohol imidazole 289 that was then oxidized with Dess-Martin periodinane to afford ketoimidazole 290 (Scheme 61). Removal of the silyl protecting
group from alkyne 290, followed by Lindlar reduction of the resulting terminal alkyne yielded the desired ketovinylimidazole 273 in good overall yield.

Scheme 61

2.2.3 Coupling of Imidazole 273 and β-Lactam 293 Subunits

With the requisite ketone 273 and the previously prepared γ-lactam 293 components in hand, procedures for their coupling to form the core of 3 followed by an intramolecular RCM process were examined. Thus, ketoimidazole 273 was treated with LDA to form enolate 292, which subsequently reacted with the activated carbonyl of γ-lactam 293 and then the reaction was work-up under neutral conditions (Scheme 62). However, when the crude product mixture was subjected to Grubbs second generation metathesis catalyst, none of the desired hemiaminal 295 or indolenine 296 were isolated. Attempts to first purify the crude adduct 294 via preparative TLC resulted in formation of vinylogous amide 297 along with recovered ketonimidazole 273.
To reduce the steric bulk at the β-position of the enamide, the styryl moiety was changed to a simple vinyl group. The requisite vinyl lactam 298 was formed from NH-β-lactam 168 (cf. Scheme 35) utilizing the method of Stahl (Scheme 63). Unfortunately, reaction of ketoimidazole 273 with the caronyl of γ-lactam 298 under the conditions used for the model study in Scheme 58 did not give any of the desired coupled product 299.

Scheme 63
2.3 Studies on Construction of the 10-Membered Ring via Initial Addition of a Metallated (Z)-Alkene to the γ-Lactam Carbonyl

2.3.1 Background and Model Studies on the Addition of Metallated (Z)-Alkenes to Activated Lactams

In light of the above unsuccessful RCM study, an alternative synthetic route towards the chartellines was explored which relied on the initial formation of the C11-C12 bond via the addition of a (Z)-vinyl anion to the activated carbonyl of a γ-lactam. Retrosynthetically, a late stage imidazole C6-bromination of pentacycle 300 was envisioned to give chartelline A (1, Scheme 64). Chloroenamide 300 could be accessed via an intramolecular N-vinylation reaction of haloalkene 301 (see Chapter 1, Section 2.5, pg. 36 for a detailed description of this methodology and its application in the synthesis of the chartellamides). Addition of the metallated compound from (Z)-vinyl

Scheme 64
iodide 302 to N-BOC-γ-lactam 231 should give the desired hemiaminal 301 after functional group manipulation of the alkyne and deprotection of the β-lactam nitrogen. Imidazole 302 would in turn be synthesized from previously prepared aldehyde 303.\textsuperscript{14c}

There are very few examples of the intermolecular addition of (Z)-vinyl organometallics to the carbonyl of activated lactams. However, a number of groups have reported the addition of aryllithium reagents\textsuperscript{81} to N-activated lactams and related compounds, including our previous work on the chartellamides (see Chapter 1, Section 1.5, pg. 11). For example, addition of the aryl Grignard to N-acyl γ-lactam 304 afforded hemiaminal 305, which was subsequently reduced to give tetrasubstituted pyrrolidine 306 (Scheme 65).\textsuperscript{82}

\textbf{Scheme 65}

\begin{center}
\includegraphics[width=\textwidth]{Scheme65.png}
\end{center}

A simple model study was undertaken to evaluate this proposed route to the chartellines in which a phenyl group was used as a surrogate for the imidazole. Thus, vinyl halide 310 was formed via dimethylation of commercially available phenyl acetonitrile (307) and reduction\textsuperscript{83} of the resultant nitrile to aldehyde 308 (Scheme 66). Reaction of aldehyde 308 with the ylid from phosphonium salt 309\textsuperscript{84,85} gave (Z)-vinyl iodide 310 as a single geometric isomer. Addition of the lithoalkene derived from vinyl iodide 310 to the carbonyl of γ-lactams 96 and 76 afforded the desired N-acyl
hemiaminals 311 and 312, respectively, as mixtures of diastereomers. It was found that an increase in steric bulk on the β-lactam nitrogen led to a precipitous drop in the yield of the desired addition product (i.e. butyl vs. PMP). Unfortunately, the use of two equivalents of the vinyl anion and one equivalent of $NH$-$\beta$-lactam 168 did not give any of the desired $NH$-$\beta$-lactam product, despite the fact that it had been found previously that an acetylide anion will add to the tribromo derivative of $N$-BOC-$\gamma$-lactam 168 to give a hemiaminal (see Section 1.2.4, pg. 84).$^{14c}$ Reaction of alcohol 311 with TFA did not effect formation of the desired vinyl imine 313, also in contrast to previous work in our group in which an $\alpha$,$\beta$-unsaturated imine was formed from a similar hemiaminal (see Chapter 1, Section 1.5, pg. 11).$^6$

### Scheme 66

![Scheme 66](image)

**2.3.2 Synthesis of Imidazole 302**

Encouraged by the results of this model study, a synthesis for the requisite C8 substituted imidazole 302 necessary for the formation of the chartellines was developed.
Alcohol 314 was first oxidized to aldehyde 303 and then reacted with the ylid from the commercially available bromotriphenylphosphonium salt to give bromoalkene 315, but as a 1:1 mixture of geometric isomers (Scheme 67). Thus, two additional routes towards the synthesis of (Z)-vinyl iodide 302 were explored. Iododination of alkyne 262 followed by syn reduction of iodoalkyne 316 using α-nitrobenzenesulfonylhydrazide gave vinyl iodide 302 in good yield. Additionally, reaction of aldehyde 303 with the ylid from phosphonium salt 309 afforded exclusively (Z)-vinyl iodide 302. The assignment of the configuration for alkene 302 was determined by analysis of its proton NMR spectrum, which had a coupling constant of 8.2 Hz between the vinyl protons, indicative of a (Z)-alkene.

Scheme 67
2.3.3 Attempted Coupling of Vinyl Iodide 302 and N-BOC-γ-Lactam 231

With the necessary vinyl iodide 302 and activated γ-lactam fragment 231 in hand, their coupling was examined. However, addition of the vinyl lithium reagent derived from iodovinylimidazole 302 to β-lactam 231 gave alkynyl-product 263 instead of the desired alkene 310, along with a significant amount (~50%) of dehaloalkeneimidazole (Scheme 68). Hemiaminal 263 presumably arises from an initial E₂ elimination of vinyl iodide 302 followed by deprotonation of the resultant terminal alkyne to form lithium acetylide 317, which then adds to the carbonyl of γ-lactam 231. The structure of dialkyne 263 was further confirmed via removal of the TBS protecting group from the alkyne to give hemiaminal 318. Compound 263 had previously been synthesized by Sun via addition of the lithioacetylide of alkyne 262 to the carbonyl of γ-lactam 231 (see Scheme 55).¹⁴e

Scheme 68
2.4 **Studies on the Formation of the Haloenamide Moiety via a N-Vinylation Reaction Between a C9-C11-Substituted Dihalovinylimidazole and a NH-β-Lactam**

2.4.1 *Revised Retrosynthesis: Initial Intermolecular β-Lactam N-Vinylation*

Another route that we examined towards the synthesis of the chartellines was the initial formation of the chloroenamide moiety *via* an intermolecular NH-β-lactam vinylation reaction followed by macrocyclization *via* an enolate addition reaction. A potential advantage of this method is that the C9-C11 carbon fragment of the chartellines would be installed in the N-vinylation step and therefore the post-coupling modifications to homologate the C10 position that plagued our previous routes would be circumvented (see Section 1.2.7). This approach is based upon the copper iodide promoted halogen-selective N-vinylation reaction discussed for the synthesis of the chartellamides (see Chapter 1, Section 2.5, pg. 36).\(^{14d}\) Retrosynthetically, chartelline A (1) could come from reduction and dehydration of ketone 319 followed by C6-bromination of the imidazole (Scheme 69). Ketone 319 would result from an intramolecular addition of the enolate of ketone 320 to the N-acyl γ-lactam carbonyl, followed by dehydration of the resulting hemiaminal. Chloroenamide 320 would come from intermolecular N-vinylation of NH-β-lactams 260 or 321 with dihalovinylimidazole 322. Ketoimidazole 322, containing the C9-C11 carbons of the chartellines, would in turn come from known aldehyde imidazole 259.\(^{14e}\)
2.4.2 Synthesis of Dihalovinylimidazole Ketone 322 and Related Derivatives

A route towards the formation of the requisite iodochlorovinylimidazole 322 was developed based on manipulation of aldehyde imidazole 259, previously synthesized by Sun.\textsuperscript{14c} Thus, addition of methylmagnesium chloride to aldehyde 259 yielded bromoalcohol 323 (Scheme 70). Since we knew that a bromine at the C6-position of the imidazole was not compatible with the N-vinylation reaction (see Section 1.2.7), it was removed at this stage of the synthesis. Thus, treatment of the bromoalcohol with \textit{n}-BuLi followed by quenching with saturated aqueous ammonium chloride effected removal of the bromine. Oxidation of the resultant alcohol gave ketone 324. Desilylation of TBS-alkyne 324 with TBAF followed by reaction of the terminal alkyne with copper chloride and iodine using the condition of Uemura\textsuperscript{48} cleanly yielded the desired dihaloketone 322 as a mixture of BOM regioisomers. Although an inconvenience, the mixture of BOM
regioisomers does not affect our synthesis because this protecting group will ultimately be removed.

Scheme 70

To probe the influence of steric effects on the N-vinylation reaction, two other dihalovinylimidazoles bearing the C9,11 carbons were also synthesized. Starting from alcohol 323, desilylation of the silylalkyne followed by TBS protection of the secondary alcohol yielded terminal alkyne 325 (Scheme 71). Subjection of the alkyne to

Scheme 71
the usual iodochlorination conditions afforded dihalide 326. Similarly, deprotected alcohol 327 was formed from alcohol 322 via desilylation and iodochlorination of the alkyne.

Additionally, a didemethyl substrate was synthesized in hopes of minimizing the steric bulk at the C9 position of the imidazole subunit. Thus, iodoimidazole 281 was coupled with TBS-acetylene to give an alkyne imidazole (Scheme 72). Johnson-Lemieux oxidative cleavage of the alkene gave ketone 328. Desilylation of alkyne 328 and reduction of the ketone then gave alcohol 329. TBS protection of alcohol 329 followed by iodochlorination of the terminal alkyne yielded the desired didemethyl imidazole substrate 330.

**Scheme 72**

2.4.3 *Attempted β-Lactam N-Vinylation with Dihalides 322, 326, 327 and 330*

With the requisite imidazole and NH-β-lactam coupling partners in hand, we next examined their coupling via the halogen-selective N-vinylation methodology. However, reaction of tribromo β-lactam 260 with iodochlorovinylimidazole 322 under the usual
coupling conditions did not produce the desired product 331 (Scheme 73). In this case only the starting imidazole 322 was recovered (52% yield), with concomitant decomposition of bis-lactam 260. The problem with this coupling may be that the copper enolate of ketone 322 is formed in situ, thus depleting the copper catalyst. Increasing the amount of copper (I) iodide used to 3 equivalents, however did not give the desired chloroenamide 331.

Scheme 73

To alleviate the possible soft enolization problem associated with ketone 322, the imidazole substrates containing reduced ketone functionality were also examined in the N-vinylation reaction. However, attempted coupling of either the BOM (260) or SEM (321)-protected substrates with TBS-alcohol imidazole 326 did not give any of the desired product 332 (Scheme 74). Additionally, unprotected alcohol imidazole 327 did not react with either of the $NH$-$\beta$-lactam substrates 260 or 321. Moreover, no coupling between debromo $\beta$-lactam 334 and unprotected alcohol imidazole 327 was observed. In all of these attempts the starting imidazoles were recovered, but the $NH$-$\beta$-lactams decomposed under the reaction conditions.
In addition, attempts were made to combine $NH$-β-lactam 260 and didemethyl iodovinylimidazole 330 under the standard coupling conditions (Scheme 75). Unfortunately, none of the desired haloenamide 336 was obtained with only the starting imidazole 330 was recovered. The main problem with these reactions may be the bulky substituent on C8 of the imidazole, which interferes with the couplings.
2.5 **Studies on Introduction of the β-Chloroenamide Moiety via Coupling of a C9,10-Containing Dihalovinylimidazole and a β-Lactam**

2.5.1 *Revised Retrosynthetic Analysis*

Due to the problems encountered in the above study, another method was examined in which the C11 carbon of the chartellines would be installed after the coupling of the substituted imidazole and β-lactam subunits. This approach is based on our previous research, which demonstrated the compatibility of an ester moiety at the C10 position of the imidazole with the N-vinylation methodology (see Section 1.2.7).¹⁴d Retrosynthetically, the C11-C12 bond could be formed via two pathways: (1) intramolecular addition of the enolate of ketone 339 to the γ-lactam carbonyl followed by reduction, deprotection and dehydration or (2) from an intramolecular vinyl lithium addition to the C12 carbonyl group of γ-lactam 338, followed by deprotection and dehydration (Scheme 76). Both of these routes would afford pentacycle 337. Vinyl halide 338 and ketone 339 would arise from copper (I) iodide mediated coupling of NH-β-lactam 341 and iodo vinylimidazole 342. Subsequent one carbon homologation and / or functional group manipulation of the ester or alcohol moiety at C10 would then give vinyl halide 338 or ketone 339. We believed that it would be possible to change the various γ-lactam protecting groups of 340 to the desired N-BOC derivative at some point after the coupling. A variety of protecting groups on both the γ-lactam and imidazole subunits were examined in order to probe functional group compatibility with the N-vinylation reaction, as well as to allow flexibility in post-coupling functional group manipulations.
There are a few literature examples of intramolecular additions of vinyl metals, derived from vinyl halides, to activated lactams.\textsuperscript{90} For example, lithium halogen-exchange of vinyl bromide \textsuperscript{343} gave the corresponding vinyl lithium that subsequently added to the lactam carbonyl to afford hemiaminal \textsuperscript{344}. Hemiaminal \textsuperscript{344} was then reduced with LiAlH\textsubscript{4} to give aminoalkene \textsuperscript{345} (Scheme 77).\textsuperscript{91}
Some of the requisite imidazoles like 342 had been previously synthesized by Sun in approaches to the chartellines (see Scheme 76). In addition to the BOM-protected imidazole derivatives, attempts were made to form a methyl-protected imidazole to probe the steric influence of the N7 protecting group in the N-vinylation reaction. Thus, N-methylation of diiodoimidazole 346 afforded known N-methylimidazole 347 (Scheme 78). Alkylation of N-methylimidazole 347 proceeded smoothly under the standard conditions to give allylimidazole 348. Unfortunately, subjection of allylimidazole 348 to the same three-step sequence previously used in Scheme 52 did not afford any of the desired ester 349. In an alternate sequence towards ester imidazole 349, N-methyl diiodoimidazole 347 was treated with ethylmagnesium bromide to form a C8 metallated imidazole, which upon treatment with ethyl oxalyl chloride gave α-ketoester 350. However, reduction of ketone 350 with triethylsilane in refluxing TFA afforded a separable mixture of alcohol 351 and triethylsilyl alcohol 352 rather than the expected ester 349. Further reduction of alcohol 351 to the desired ester 349 was attempted using

![Scheme 78](image-url)
sodium cyanoborohydride, triphenylphosphine / iodine\textsuperscript{95} and zinc iodide / sodium cyanoborohydride,\textsuperscript{96} but only the starting alcohol was recovered.

2.5.3 Synthesis of Bis-Lactam Subunits 341

A variety of protected bis-lactam derivatives were synthesized in order to examine which protecting groups on the γ-lactam were compatible with the coupling conditions. Thus, SEM-protected γ-lactam 353 was formed from NH-γ-lactam 84 by treatment with SEM-Cl and sodium hydride (Scheme 79). The PMP protecting group was then removed from β-lactam 353 to give crude NH-β-lactam 334. Due to a persistent impurity formed in the ceric ammonium nitrate (CAN) deprotection step which could not be removed, a two step β-lactam N-silylation / desilylation sequence was utilized to provide pure NH-β-lactam 334. Thus, silylation of crude NH-β-lactam 334, followed by column chromatography of the resultant N-silylated compound afforded pure N-silyl-β-lactam. Finally, removal of the N-silyl group with TBAF gave pure SEM-γ-lactam 334 as a white solid.

Scheme 79

\[
\begin{align*}
\text{84} & \xrightarrow{\text{NaH, SEMCI, THF, 0 °C - rt}} 62\% \quad \text{353} \\
\text{353} & \xrightarrow{\text{CAN, MeCN, 0 °C - rt}} \text{334 (96\%)} \\
\text{334} & \xrightarrow{\text{1. TBSCl, Et3N, DCM, rt \quad 98\% (2 steps), 2. TBAF, THF, 0 °C, 92\%}} \text{334}
\end{align*}
\]
The previously synthesized\textsuperscript{14} BOM (354) and BOC (168)-protected \(\gamma\)-lactams were also prepared in pure form via a similar silylation sequence to give the clean \(NH-\beta\)-lactams in good overall yield (Scheme 80), thus minimizing the impurities carried on to the copper (I) promoted N-vinylation reaction.

\textbf{Scheme 80}

\begin{center}
\includegraphics[width=\textwidth]{scheme80}
\end{center}

In order to probe the affect of steric bulk on the \(\gamma\)-lactam with regard to the N-vinylation reaction, a relatively small \(N\)-methyl group was used to protect the \(\gamma\)-lactam. Thus, treatment of \(NH-\gamma\)-lactam 84 with sodium hydride and iodomethane gave \(N\)-methyl derivative 357 (Scheme 81). Removal of the PMP group from \(\beta\)-lactam 357, followed by use of the silylation / desilylation protocol yielded the pure \(NH-\beta\)-lactam 358.

\textbf{Scheme 81}

\begin{center}
\includegraphics[width=\textwidth]{scheme81}
\end{center}
Attempts were also made to synthesize the methyl carbamate-protected γ-lactam derivative 363 to reduce the steric bulk on the nitrogen compared to N-BOC compound 168. Thus, reaction of NH-γ-lactam 84 with sodium hydride and methyl chloroformate afforded protected lactam 360 (Scheme 82). However, deprotection of β-lactam 360 with CAN, followed by the usual silylation sequence gave only a small amount of the desired NH-β-lactam 361. Alternatively, formation of d bis-NH-lactam 363,14b followed by selective TBS protection of the β-lactam gave exclusively TBS-β-lactam 364 and none of the bis-TBS compound 365. N-Acylation of γ-lactam 364 afforded lactam 362. Desilylation of γ-lactam 362 with TBAF did not give any of the desired product.

Scheme 82

2.5.4 Coupling of Imidazoles 342 and β-Lactams 341

With the requisite C9,10-containing imidazole and NH-β-lactam substrates in hand, their copper-promoted coupling was investigated. Similar to the previously
described model systems (see Scheme 54),\textsuperscript{14d} iodovinylimidazole 247 and the SEM (334) and BOM (354)-protected γ-lactams coupled under the standard conditions to give β-chloroenamides 366 and 367, respectively, along with a significant amount of the starting imidazoles (Scheme 83). The poor yields are probably a result of decomposition of the β-lactam starting materials under the reaction conditions. Unfortunately, attempted reduction of ester 367 with LiEt$_3$BH\textsuperscript{97} did not yield any of the desired alcohol 368.\textsuperscript{98} Reaction of ester 367 with methylmagnesium chloride did not give addition product 369.

**Scheme 83**

Due to the inability to modify the ester functionality in 366 and 367, coupling of the C10 alcohol imidazole 370\textsuperscript{99} with a NH-β-lactam was investigated. Previous studies by Sun had shown that the O-acyl and O-silyl protected analogs of imidazole alcohol 370...
do not couple with the tribromo derivative of β-lactam 334 under the standard conditions. In contrast, unprotected alcohol 370 did combine effectively with the SEM (334) and BOM (354)-protected γ-lactams to give haloenamides 371 and 373, respectively, in moderate yields (Scheme 84). Unfortunately, when alcohol 371 was subjected to Dess-Martin, Swern or PCC oxidation procedures, none of the desired aldehyde 372 was observed, with only starting material recovered. Similarly, subjection of BOM-lactam 373 to Dess-Martin or PCC oxidation did not afford aldehyde 374.

Scheme 84

We next sought to probe what influence steric bulk on the γ-lactam nitrogen may have on the β-lactam N-vinylation reaction. Thus, attempts were made to couple the N-methyl-γ-lactam 358 and previously prepared N-tosyl-γ-lactam (375) with alcohol imidazole 370 (Scheme 85). Unfortunately, neither of these reactions gave any of the
desired products 376, with only the starting imidazole 370 recovered, but the β-lactam was consumed under the reaction conditions.

Scheme 85

In an attempt to overcome the problems associated with the oxidation of the C10 alcohol in the SEM (371) and BOM (373) substrates, the coupling of \(N\)-BOC-\(γ\)-lactam 168 with dihalovinylimidazole 370 was also examined. Thus, \(NH\)-β-lactam 168 and iodovinylimidazole 370 were combined under the standard conditions to give BOC protected haloenamide 377 in 20% yield (Scheme 86). Dess-Martin oxidation of alcohol 377 gave a small amount of aldehyde 378. Small scale Wittig reactions utilizing phosphonium salt 309 were attempted with aldehyde 378, but none of the desired vinyl iodide 379 was obtained. Scale up of the coupling reaction resulted only in BOC transfer from the \(γ\)-lactam of 168 to the alcohol of imidazole 370 to yield \(O\)-BOC-imidazole 380 with concomitant decomposition of β-lactam 168. All attempts to improve the desired coupling of 168 with 370 proved unsuccessful, and this route was therefore abandoned.
2.6 Deprotection of N-BOM- and N-SEM-γ-Lactams 371 and 373

Based on the fact that we were able to oxidize alcohol 377 to aldehyde 378 in the BOC protected series (cf. Scheme 86), we decided to examine the possibility of first removing the SEM- or BOM-γ-lactam protecting group and then attempting oxidation of the C10 alcohol. We hoped that the C10 alcohol would be easier to oxidize in an unprotected γ-lactam compound as there would be no γ-nitrogen protecting group to interfere with the reaction. A model β-lactam was first explored to test the deprotection procedures. Thus, haloenamide 381 was synthesized via the N-vinylation of β-lactam 334 with iodoalkene 251 (Scheme 87). Treatment of haloenamide 381 with BF3·OEt formed methylol 382 that was subsequently reacted with potassium carbonate101 to give NH-γ-lactam 383 in excellent overall yield.
Unfortunately, numerous attempts at applying these SEM removal conditions to alcohol enamide 371 gave only a trace amount of the desired product 384 as observed by mass spectral analysis (Scheme 88). Although the reaction seemed to proceed smoothly by TLC analysis, NH-γ-lactam alcohol imidazole 384, could not be isolated from the reaction medium, probably due to its high polarity. Moreover, TBAF or TFA 102 did not effect conversion of SEM derivative 371 to the desired NH-γ-lactam 384 with the starting materials recovered or decomposed, respectively.
Removal of the BOM moiety from the γ-lactam nitrogen was also examined. For example, treatment of simple BOM-γ-lactam 385 with boron tribromide, followed by potassium carbonate, gave NH-γ-lactam 84 in moderate yield (Scheme 89). Unfortunately, when alcohol imidazole 373 was treated under the same conditions, only a trace of the bis-NH-compound 386 was observed via mass spectral analysis. Treatment of N-BOM-β-chloroenamide 373 with aluminum trichloride also did not give the desired deprotected compound 386.

Scheme 89

To overcome the isolation problems associated with BOM-imidazoles 384 and 386, we also examined utilizing a p-methoxybenzyl (PMB) group to protect N7 of the imidazole. We hoped that the PMB group would survive the Lewis acid conditions used to remove the SEM and BOM-protecting groups from the γ-lactam. We also believed that the NH-γ-lactam product containing the PMB group would be easier to isolate due to its increased hydrophobicity. Therefore, in a sequence similar to the one previously
developed by Sun,\textsuperscript{14e} diiodoimidazole \textbf{346} was protected by reaction with PMB-Cl and anhydrous sodium carbonate in dry DMF to give PMB imidazole \textbf{387} (Scheme 90).\textsuperscript{105} Regioselective allylation of diiodoimidazole \textbf{387} afforded allylimidazole \textbf{388}. Subjection of allylimidazole \textbf{388} to a three step oxidative cleavage, oxidation, esterification reaction sequence yielded ester imidazole \textbf{390} in low overall yield. Similar overall yields were observed when using either trimethylsilyl diazomethane\textsuperscript{106} or sulfuric acid for the esterification of acid \textbf{389} in this sequence (this three step sequence was also the bottleneck in the formation of BOM protected imidazole \textbf{255}). Continuing with the synthesis, a Sonogashira reaction of TBS-acetylene with iodoimidazole \textbf{390} followed by dimethylation of the ester enolate gave dimethyl imidazole ester \textbf{392}. Desilylation of TBS-alkyne imidazole \textbf{392}, followed by iodochlorination of terminal alkyne \textbf{393} and DIBAL-H reduction of ester \textbf{394} yielded the desired alcohol imidazole \textbf{395}.

\textbf{Scheme 90}
With alcohol 395 in hand, attempts were made to form β-chloroenamide 396. Thus, the SEM (334) or BOM (354)-protected γ-lactams were reacted with vinyl dihalide 395 under the standard N-vinylation conditions (Scheme 91). Although both of these β-lactam substrates couple with BOM-protected imidazole 370 (cf. Scheme 84), in this case none of the desired haloenamide 396 was isolated. It is possible that the N7-PMB group is sufficiently bulky to prevent the coupling reaction. Due to the inability to synthesize the requisite PMP-haloenamide 396 or isolate the NH-β-lactams 384 or 386, this route was abandoned.

Scheme 91

2.7 Attempted Construction of the 10-Membered Ring via RCM

2.7.1 Synthesis of the Imidazole Moiety

An alternative route that was examined for the synthesis of the chartellines involved an initial intermolecular N-vinylation reaction to connect the NH-β-lactam and iodovinylimidazole subunits, followed by vinylation of the C12 carbonyl and RCM to
form the C11-C10 bond (Scheme 92). Retrosynthetically, chartelline A (1) could result from RCM of diene 397, followed by concomitant loss of the BOC protecting group and dehydration. Diene 397 would result from addition of vinylmagnesium bromide to the γ-lactam carbonyl of 398, followed by C6-bromination. N-Vinylation of β-lactam 224 (cf. Scheme 51) with iodoalkene 399 was envisioned to yield β-chloroenamide 398.

Scheme 92

In order to examine the feasibility of this approach, a simple model system was examined in which the gem-dimethyl substituents at C9 of the imidazole and the bromines on the β-lactam derivative were omitted. The requisite imidazole was formed from iodoimidazole 254,14c which was coupled with TMS-acetylene to give the corresponding alkynylimidazole 400 (Scheme 93). TBAF induced desilylation of imidazole 400 afforded terminal alkynylimidazole 401, which was iodochlorinated to give iodochlorovinylimidazole 402 in quantitative yield.
2.7.2 Copper Iodide Mediated Coupling of Dihalovinylimidazole 402 and β-Lactam 168

The coupling reaction between β-lactam 168 and dihalovinylimidazole 402 gave chloroenamide 403 in modest yield (Scheme 94). Addition of vinylmagnesium bromide to the carbonyl group of N-BOC-γ-lactam 403 proceeded selectively to give a small amount of hemiaminal 404. However, subjection of the aminal to Grubbs second generation catalyst51 failed to give any of the desired macrocycle 405. In addition, TFA

Scheme 94
was added to the RCM reaction of diene 404 in an attempt to generate vinylindolenine 406 in situ. We believed that 406 should exist in a conformation that placed the two alkene moieties in close proximity. Unfortunately, this procedure also did not give any of the desired 10-membered ring 407.

2.8 Conclusions and Future Work

Synthetic efforts towards a total synthesis of racemic chartelline A (1) have been described. An initial model study demonstrated that simple ketone enolates add chemoselectively to the activated γ-lactam carbonyl group of bis-lactam 274. Ketoimidazole 273 was therefore synthesized from aldehyde 259. However, intermolecular reaction of the enolate of ketone 273 with N-BOC-γ-lactam 293 afforded vinylogous amide 297 rather than the desired macrocycle 295 or 296.

We next examined the intermolecular addition of (Z)-vinyllithium reagents to the activated carbonyl of a γ-lactam in an attempt to form the C11-C12 bond of the chartellines. After successful exploration of a model system, vinyl iodide 302 was synthesized from either alkyne 262 or aldehyde 303. Reaction of the (Z)-vinyllithium derived from 302 with the γ-lactam carbonyl group of tribromo bis-lactam 231 gave alkynyl-hemiaminal 263 rather than the desired alkenyl-hemiaminal 310.

As an alternative to initially forming the C11-C12 bond of the chartellines, we also investigated a halogen-selective N-vinylation reaction to first construct the haloenamide moiety. Two model systems were used to probe the steric and electronic limitations of this coupling reaction that varied in the number of carbons and functional
groups attached at C8 of the imidazole. Ketone 322 and its reduced derivatives 326, 327 and 330, which contain C9-C11 of the chartellines, were not suitable coupling partners with a variety of β-lactams under standard N-vinylation conditions. In contrast, ester (247), alcohol (370), and alkene (402) substituted imidazoles reacted with SEM (334), BOM (354) and BOC(168)-protected γ-lactams to form β-chloroenamides in moderate yields.

In view of these promising N-vinylation of NH-β-lactams with iodochloro-vinylimidazoles, it should be possible to find the correct pairing of β-lactam 408 and imidazole 409 protecting groups to give haloenamide 410 (Scheme 95). Deprotection of γ-lactam 410 followed by oxidation of the alcohol should give key aldehyde intermediate 411. Wittig olefination of aldehyde 411 followed by BOC protection of the γ-lactam should yield vinyl iodide 412. Addition of the (Z)-vinylolithium derivative of vinyl iodide 412 to the activated C12 carbonyl of N-acyl γ-lactam 412 followed by dehydration and deprotection should give the desired pentacycle 413. Finally, bromination on C8 of imidazole 413 would afford the chartellines A (1).

Scheme 95
Part 3

Experimental Section

General Method. All non-aqueous reactions were carried out under a positive pressure of dry argon or nitrogen. Air and moisture sensitive liquid reagents were added via a dry cannula or syringe. $^1$H and $^{13}$C spectra were recorded on Bruker DPX-300, CDPX-300, AMX-360 or DRX-400 MHz spectrometers. Flash chromatography was performed on EM Science silica gel 60 (230-400 mesh). Analytical and preparative TLC were performed on EM Science silica gel 60 PF$_{254}$. THF, benzene and ether were either dried over and distilled from sodium/benzophenone ketyl or used directly after passing through activated alumina columns. DCM, toluene, MeOH and DMF were distilled from CaH$_2$ or used directly after passing through activated alumina columns.

Preparation of Hemiaminal 275. To a stirred solution of LDA (0.34 mL, 2 M in THF, 0.67 mmol) at 0 °C was added excess pinacolone and the resulting solution was stirred for 30 min at 0 °C. A solution of N-BOC-$\gamma$-lactam 274 (77 mg, 0.22 mmol) in dry THF (1 mL) was added and the solution was stirred at rt overnight. A pH 7 buffer solution (10 mL) was added, followed by EtOAc (20 mL). The organic layer was dried over Na$_2$SO$_4$, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (4:1 DCM:EtOAc) to give hemiaminal 275 (68 mg, 70%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.50-7.43 (m, 1H), 7.25-7.20 (m, 2), 7.05-7.02 (m, 1H), 3.97 (bs, 1H), 3.57-3.41 (m,
2H), 3.11-2.95 (m, 2H), 2.85-2.65 (m, 2H), 1.52 (s, 9H), 1.10-1.07 (m, 2H), 1.01 (s, 9H),
0.87-0.83 (m, 2H), 0.72-0.67 (m, 3H).

**Preparation of Vinylogous Amide 276.** To a stirred solution of LDA (0.29 mL, 2 M in THF, 0.58 mmol) at 0 °C was added excess pinacolone and the resulting solution was stirred for 30 min at 0 °C. A solution of N-BOC-γ-lactam 274 (67 mg, 0.19 mmol) in dry THF (1 mL) was added and the solution was stirred at rt overnight. The solution was cooled to 0 °C and TFA (1.5 mL) was added and the resulting solution was stirred for 4 h. Saturated aqueous sodium bicarbonate (20 mL) and EtOAc (30 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (4:1 DCM:EtOAc) to give vinylogous amide 276 (65 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ 7.72 (s, 1H), 7.68-7.66 (m, 1H), 7.28-7.22 (m, 2H), 7.12-7.07 (m, 1H), 3.98-3.91 (m, 1H), 3.01-2.94 (m, 2H), 2.60-2.56 (m, 1H), 1.61 (s, 9H), 1.54-1.51 (m, 2H), 1.21-1.11 (m, 11H), 0.86 (bs, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.2, 168.3, 152.4, 151.3, 140.9, 130.7, 130.1, 125.0, 122.7, 116.7, 110.8, 84.9, 64.0, 55.0, 44.7, 41.1, 30.2, 28.5, 27.4, 20.7, 13.9.

**1-Benzzyloxymethyl-4-iodo-5-(2-methylallyl)-1H-imidazole (281).** To a stirred solution of 4,5-diiodoimidazole 58 (630 mg, 1.4 mmol) in dry THF (10 mL) at rt was added dropwise a solution of ethylmagnesium bromide (0.52 mL, 3 M in diethyl ether) and the resulting solution was stirred for 30 min at rt. A solution of CuCN·2LiCl (1.4 mL, 1 M in THF) was then added and the temperature was lowered to
-20 °C. 3-Bromo-2-propene was added dropwise and the solution was stirred at rt for 4 h. Saturated ammonium chloride solution containing 2% ammonium hydroxide (50 mL) was added and the solution was stirred for 30 min. DCM (30 mL) and brine (30 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to give 1-benzyloxymethyl-4-iodo-5-(2-methylallyl)-1H-imidazole (281, 477 mg, 93%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.35 (s, 1H), 7.22-7.11 (m, 5H), 5.10 (s, 2H), 4.66 (s, 1H), 4.39 (s, 1H), 4.27 (s, 2H), 3.23 (s, 2H), 1.57 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.0, 139.8, 136.4, 132.1, 129.1, 128.8, 128.4, 112.6, 87.3, 74.1, 70.3, 33.2, 22.7.

1-(3-Benzylxoymethyl-5-iodo-3H-imidazol-4-yl)-propan-2-one (276). To a stirred solution of isobutenyl imidazole 281 (300 mg, 0.81 mmol) in H$_2$O:acetone (1:2, 18 mL) at rt were added N-methylmorpholine-N-oxide (477 mg, 4.0 mmol) and a solution of osmium tetraoxide (0.51 mL, 2.5% in 2-methyl-2-propanol, 0.04 mmol), and the resulting solution was stirred at rt overnight. The solution was cooled to 0 °C, sodium periodate (433 mg, 2.0 mmol) was added and the solution was stirred at 0 °C for 4 h. EtOAc (50 mL) and saturated aqueous sodium sulfite solution (50 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to give 1-(3-benzyloxymethyl-5-iodo-3H-imidazol-4-yl)-propan-2-one (276, 180 mg, 60%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.36 (s, 1H), 7.22-7.09 (m, 5H), 5.10
(s, 2H), 4.23 (s, 2H), 3.63 (s, 2H), 2.04 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.8, 140.9, 136.1, 129.1, 128.9, 128.6, 128.5, 88.3, 74.8, 70.4, 40.2, 30.1.

1-Benzzyloxymethyl-4-iodo-5-(3-methylbut-2-enyl)-1H-imidazole (283). To a stirred solution of 4,5-diiodoimidazole 58 (725 mg, 1.65 mmol) in dry THF (10 mL) at rt was added dropwise a solution of ethylmagnesium bromide (0.60 mL, 3 M in diethyl ether, 1.8 mmol) and the resulting solution was stirred at rt for 30 min. A solution of CuCN·2LiCl (1.4 mL, 1 M in THF) was added and the temperature was reduced to -20 °C. 4-Bromo-2-methyl-2-butene was added dropwise and the solution was stirred at rt for 4 h. Saturated aqueous ammonium chloride solution containing 2% ammonium hydroxide (50 mL) was then added and the solution was stirred for 30 min. DCM (30 mL) and brine (30 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to give 1-benzyloxymethyl-4-iodo-5-(3-methylbut-2-enyl)-1H-imidazole (283, 472 mg, 75%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.34 (s, 1H), 7.25-7.15 (m, 5H), 5.12 (s, 2H), 4.96-4.92 (m, 1H), 4.31 (s, 2H), 3.27 (d, $J = 6.9$ Hz, 2H), 1.61 (s, 3H), 1.56 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.2, 135.2, 133.1, 127.8, 127.5, 127.4, 127.1, 118.7, 73.1, 69.5, 24.8, 23.2, 17.3.

1-Benzzyloxymethyl-4-iodo-5-(2-methoxy-1-methylpropenyl)-1H-imidazole (285). To a stirred solution of 1-(3-benzyloxymethyl-5-iodo-3H-imidazol-4-yl)-propan-2-one (276, 345 mg, 0.93 mmol) in dry THF (3 mL) at 0 °C was added sodium hydride (85 mg, 60% dispersion in mineral oil, 2.1 mmol), and the
The resulting solution was stirred at rt for 30 min. The solution was cooled to 0 °C, methyl iodide (0.15 mL, 2.3 mmol) was added and the solution was stirred at 0 °C for 4 h. Saturated aqueous ammonium chloride (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to give 1-benzyloxymethyl-4-iodo-5-(2-methoxy-1-methylpropenyl)-1H-imidazole (285, 150 mg, 42%). IR (film) 3395, 2937, 2223, 1711, 1667, 1479 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.49 (s, 1H), 7.27-7.17 (m, 5H), 5.19-5.03 (m, 2H), 4.35-4.34 (m, 2H), 3.57 (s, 3H), 1.71 (s, 3H), 1.62 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.2, 141.8, 139.3, 136.8, 129.0, 128.8, 128.6, 101.4, 86.3, 75.2, 70.7, 56.5, 15.8, 14.5.

1-(3-Benzzyloxymethyl-5-vinyl-3H-imidazol-4-yl)-propan-2-one (286). To a stirred solution of iodoimidazole 276 (190 mg, 0.51 mmol) in dry toluene at rt were added vinyltributylstannane (0.30 mL, 1.0 mmol) and palladium (II) chloride (5 mg, 0.026 mmol), and the resulting solution was refluxed for 3 h. The solution was cooled to rt and filtered through a pad of Celite (DCM). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 to 1 EtOAc:hexanes gradient containing 1% triethylamine) to give 1-(3-benzyloxymethyl-5-vinyl-3H-imidazol-4-yl)-propan-2-one (286, 105 mg, 76%). IR (film) 2906, 1715, 1504, 1360 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.41 (s, 1H), 7.27-7.17 (m, 5H), 6.50-6.42 (m, 1H), 5.87-5.82 (m, 1H), 5.15-5.11 (m, 3H), 4.29 (s, 2H), 3.71 (s, 2H), 2.06 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 204.0, 139.4, 138.2, 128.7, 128.3, 128.0, 126.4, 121.8, 113.5, 73.7, 69.7, 38.1, 29.3.
1-Benzylxoxymethyl-5-(2-methoxypropenyl)-4-vinyl-1H-imidazole (288).

To a stirred solution of 1-(3-benzylxoxymethyl-5-vinyl-3H-imidazol-4-yl)-propan-2-one (286, 28 mg, 0.10 mmol) in dry THF (1 mL) at 0 °C was added sodium hydride (12 mg, 60% dispersion in mineral oil, 0.31 mmol), and the resulting solution was stirred at rt for 30 min. The solution was cooled to 0 °C, methyl iodide (0.02 mL, 0.31 mmol) was added and the solution was stirred at 0 °C for 4 h. Saturated aqueous ammonium chloride (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (4:1 EtOAc:hexanes) to give 1-benzylxoxymethyl-5-(2-methoxy-1-methylpropenyl)-4-vinyl-1H-imidazole (288, 10 mg, 33%). IR (film) 2935, 2359, 1710, 1667, 1497, 1454 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.51 (s, 1H), 7.28-7.19 (m, 5H), 6.42-6.34 (m, 1H), 5.83-5.77 (m, 1H), 5.15-5.03 (m, 3H), 4.37-4.35 (m, 2H), 3.58 (s, 3H), 1.76 (s, 3H), 1.61 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 154.1, 137.5, 137.0, 136.4, 128.6, 128.0, 127.9, 127.8, 111.8, 101.1, 73.4, 69.9, 55.6, 16.0, 14.3.

3-{3-Benzylxoxymethyl-2-bromo-5-[(tert-butyldimethylsilyl)-ethynyl]-3H-imidazol-4-yl}-3-methylbutan-2-ol (289). To a stirred solution of aldehyde imidazole 259 (120 mg, 0.25 mmol) in dry THF (10 mL) at -78 °C was added a solution methylmagnesium chloride (0.09 mL, 3 M in THF, 0.27 mmol) and the resulting solution was stirred at -78 °C for 2 h. Saturated aqueous ammonium chloride (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (4:1 EtOAc:hexanes) to give 3-{3-Benzylxoxymethyl-2-bromo-5-[(tert-butyldimethylsilyl)-ethynyl]-3H-imidazol-4-yl}-3-methylbutan-2-ol (289).
chromatography on silica gel (1:3 EtOAc:hexanes) to give 3-{3-benzyloxymethyl-2-bromo-5-[(tert-butyldimethylsilyl)-ethynyl]-3H-imidazol-4-yl}-3-methylbutan-2-ol (289, 83 mg, 68%). ¹H NMR (300 MHz, CDCl₃) δ 7.16-7.06 (m, 5H), 5.23 (s, 2H), 4.43 (s, 2H), 3.72 (m, 1H), 3.52 (bs, 1H), 1.27 (s, 6H), 0.92 (d, J = 6.4 Hz, 2H), 0.79 (s, 9H), 0.00 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 152.5, 135.0, 126.6, 126.1, 125.4, 117.0, 113.2, 91.9, 72.7, 69.4, 39.4, 24.2, 23.3, 20.0, 15.7, 14.9, -6.6.

3-(3-Benzoxymethyl-2-bromo-5-ethynyl-3H-imidazol-4-yl)-3-methylbutan-2-one (291). To a stirred solution of alcohol imidazole 289 (180 mg, 0.48 mmol) in dry DCM (25 mL) at rt was added Dess Martin periodinane (75 mg, 0.18 mmol) and the resulting solution was stirred at rt for 1 h. Aqueous sodium hydroxide (15%, 30 mL) and DCM (30 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure to give TBS-imidazole 290, which was used in the next step without further purification.

To a stirred solution of crude TBS-imidazole 290 (0.48 mmol) in dry THF (25 mL) at 0 ºC was added a solution of TBAF (0.96 mL, 1 M in THF) and the resulting solution was stirred at 0 ºC for 30 min. Saturated aqueous ammonium chloride (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give 3-(3-benzyloxymethyl-2-bromo-5-ethynyl-3H-imidazol-4-yl)-3-methylbutan-2-one (291, 130 mg, 73% from alcohol 289). ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.17 (m, 5H), 5.27 (s, 2H), 4.46 (s, 2H), 3.54 (s, 1H), 1.89 (s,
3H), 1.37 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 209.4, 151.4, 137.0, 128.9, 128.5, 127.9, 120.3, 114.6, 89.6, 74.8, 71.8, 71.5, 50.5, 26.1, 24.3.

3-(3-Benzzyloxymethyl-2-bromo-5-vinyl-3H-imidazol-4-yl)-3-methylbutan-2-one (273). To a stirred solution of alkyne imidazole 291 (80 mg, 0.21 mmol) in dry THF (20 mL) at rt was added Lindlar catalyst (2.2 mg) and the resulting solution was stirred under an atmosphere of hydrogen for 3 d. The solution was then filtered through a pad of silica gel (EtOAc) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give 3-(3-benzyloxymethyl-2-bromo-5-vinyl-3H-imidazol-4-yl)-3-methylbutan-2-one (273, 79 mg, 100%). $^1$H NMR (360 MHz, CDCl$_3$) δ 7.19-7.12 (m, 5H), 6.29-6.21 (m, 1H), 5.45-5.40 (m, 1H), 5.24-5.20 (m, 3H), 4.48 (s, 2H), 1.84 (s, 3H), 1.32 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 210.5, 143.3, 136.5, 129.2, 128.5, 128.1, 127.6, 123.1, 120.2, 119.7, 74.3, 70.7, 40.8, 25.5, 24.5.

Preparation of Vinylogous Amide 297. To a stirred solution of ketoimidazole 273 (22 mg, 0.059 mmol) in dry THF (0.5 mL) at 0 °C was added LDA (0.03 mL, 2 M in THF, 0.059 mmol) and the resulting solution was stirred at 0 °C for 30 min. A solution of γ-lactam 293 (22 mg, 0.056 mmol) in dry THF (0.5 mL) was added and the resulting solution was stirred at rt overnight. A solution of pH 7 buffer (5 mL) and EtOAc (10 mL) were added. The organic layer was dried over Na$_2$SO$_4$, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (2:1 EtOAc:hexanes) to give vinylogous
amide 297 (5 mg, 14%). $^1$H NMR (360 MHz, CDCl$_3$) δ 7.60-7.58 (m, 1H), 7.32-7.29 (m, 2H), 7.17-7.06 (m, 5H), 7.05-7.04 (m, 2H), 6.97-6.95 (m, 2H), 6.48 (s, 1H), 6.34-6.26 (m, 1H), 5.64 (s, 1H), 5.44-5.39 (m, 2H), 5.25-5.14 (m, 3H), 4.46 (s, 2H), 3.65-3.55 (m, 2H), 1.51 (s, 6H); LRMS-ES+ m/z (relative intensity) 650 (MH$^+$, 10).

**Preparation of N-Vinyl-$\beta$-lactam 298.** To a stirred solution of NH-$\beta$-lactam 168 (55 mg, 0.19 mmol) in butyl vinyl ether (5 mL) at rt was added palladium (II) trifluoroacetate (16 mg, 0.048 mmol) and 4,7-diphenylphenanthroline (16 mg, 0.048 mmol). The resulting solution was then heated at 75 °C for 3 h with an 18 gauge needle through the septum to act as a purge. The mixture was cooled to rt and directly purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to give N-vinyl-$\beta$-lactam 298 (45 mg, 75%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.90-7.87 (m, 1H), 7.41-7.35 (m, 2H), 7.22-7.17 (m, 1H), 6.51-6.43 (m, 1H), 4.24-4.20 (m, 1H), 3.85-3.80 (m, 1H), 3.48 (d, $J = 14.9$ Hz, 1H), 3.17 (d, $J = 14.9$ Hz, 1H), 1.58 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.8, 162.8, 149.7, 140.8, 132.1, 126.4, 125.9, 124.3, 123.4, 116.9, 97.3, 63.7, 60.7, 51.7, 29.0.

**2-Methyl-2-phenylpropionaldehyde (308).** To a stirred solution of 2-methyl-2-phenylpropionitrile (307, 1.7 g, 11.7 mmol) in dry DCM (60 ml) at -78 °C was added a solution of DIBAL-H (14 mL, 1 M in toluene, 14.0 mmol). The resulting solution was warmed to rt and stirred for 1.5 h. Saturated aqueous ammonium chloride (20 mL) was added followed by conc. H$_2$SO$_4$ to pH 2-3. DCM (40 mL) and brine (20 mL) were then added. The organic layer was dried over MgSO$_4$, the solvent
was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give 2-methyl-2-phenylpropionaldehyde (308, 785 mg, 45%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.33 (s, 1H), 7.22-7.19 (m, 2H), 7.14-7.11 (m, 3H), 1.31 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.4, 141.6, 129.3, 127.6, 127.5, 50.8, 22.9.

(3-Iodo-1,1-dimethylallyl)-benzene (310). Phosphonium salt 309 (3.1 g, 5.8 mmol) was dried under vacuum (100 °C, 1 h) and then cooled to rt. Dry THF (15 mL) and a solution of NaHMDS (1.5 mL, 2 M in THF, 3.0 mmol) were added and the resulting solution was stirred at rt for 5 min. The solution was then cooled to -78 °C and DMPU (5.0 mL) was added, followed by a solution of 2-methyl-2-phenylpropionaldehyde (308, 785 mg, 5.3 mmol) in dry THF (5 mL). The resulting solution was stirred at -30 °C for 45 min. Ethyl acetate (20 mL) was added and the solution was filtered through a plug of silica gel (EtOAc). The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give (3-iodo-1,1-dimethylallyl)-benzene (310, 784 mg, 55%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.25-7.19 (m, 4H), 7.17-7.11 (m, 1H), 6.72 (d, $J$ = 8.3 Hz, 1H), 6.19 (d, $J$ = 8.3 Hz, 1H), 1.42 (s, 6H); $^{13}$C NMR and DEPT135 (75 MHz, CDCl$_3$) $\delta$ 149.4, 148.1, 128.7, 127.4, 126.3, 79.3, 42.8, 30.4.

Preparation of Vinyl Addition Product 311. To a stirred solution of (3-iodo-1,1-dimethylallyl)-benzene (310, 140 mg, 0.51 mmol) in dry
THF (2 mL) at -78 °C was added a solution of n-BuLi (0.21 mL, 2.4 M in hexanes, 0.50 mmol) and the resulting solution was stirred at -78 °C for 15 min. A solution of N-NOC-\(\gamma\)-lactam 96 (160 mg, 0.47 mmol) in dry THF (0.5 mL) was then added dropwise and the solution was stirred at -78 °C for 4 h. Saturated aqueous ammonium chloride (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO\(_4\), the solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give vinyl addition product 311 (145 mg, 70%) as a 2:1 mixture of diastereomers. Data for major diastereomer: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.48-7.27 (m, 8H), 7.10-7.06 (m, 1H), 7.22 (d, \(J = 12.5\) Hz, 1H), 6.23 (d, \(J = 12.5\) Hz, 1H), 5.85 (bs, 1H), 3.42 (d, \(J = 14.7\) Hz, 1H), 3.40-3.35 (m, 2H), 2.95 (d, \(J = 14.7\) Hz, 1H), 1.75-1.73 (m, 2H), 1.50 (s, 9H), 1.31-1.28 (m, 2H), 0.95 (t, \(J = 7.3\), 14.6 Hz, 3H) ; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 161.3, 143.1, 135.4, 129.3, 128.1, 126.4, 126.0, 125.8, 125.7, 123.7, 121.7, 114.8, 82.9, 80.8, 68.9, 53.3, 47.4, 44.4, 42.1, 30.8, 30.6, 28.6, 20.6, 13.6; LRMS-ES\(^+\) \(m/z\) (relative intensity) 491 (MH\(^+\), 10), 513 (M+Na, 100), 550 (MH\(^+\)+TMA).

**Preparation of Vinyl Addition Product 312.** To a stirred solution of vinyl iodide 310 (190 mg, 0.70 mmol) in dry THF (5 mL) at -78 °C was added a solution of n-BuLi (0.57 mL, 2.3 M in hexanes, 1.3 mmol) and the resulting solution was stirred at -78 °C for 10 min. A solution of N-NOC-\(\gamma\)-lactam 76 (212 mg, 0.54 mmol) in dry THF (2 mL) was added and the resulting solution was stirred at -78 °C for 4 h. Saturated aqueous ammonium chloride (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO\(_4\), the solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 EtOAc:hexanes)
to give vinyl addition product 312 (35 mg, 12%) as a mixture of diastereomers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26-7.17 (m, 4H), 7.18-7.10 (m, 2H), 7.08-7.05 (m, 2H), 7.02-6.99 (m, 3H), 6.89-6.86 (m, 2H), 6.60-6.57 (m, 2H), 7.58-6.20 (m, 2H), 5.54 (bs, 1H), 3.48 (s, 3H), 3.40-3.35 (m, 1H), 3.09-3.04 (m, 1H), 1.53 (s, 6H), 1.44 (s, 9H); LRMS-ES+ m/z (relative intensity) 563 (M+Na$^+$, 100).

$^{(E,Z)}$-1-Benziloxymethyl-5-(3-bromo-1,1-dimethylallyl)-4-[(tert-butylidemethylsilanyl)-ethynyl]-1H-imidazole (315). To a stirred solution of alcohol imidazole 314 (43 mg, 0.11 mmol) in dry DCM (5 mL) at rt was added Dess-Martin reagent (50 mg, 0.12 mmol), and the resulting solution was stirred at rt for 1 h. Aqueous sodium hydroxide (15%, 10 mL), DCM (15 mL) and brine (10 mL) were then added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure to give the crude aldehyde 303, which was used in the next step without further purification.

The triphenylphosphonium bromide salt (48 mg, 0.11 mmol) was dried under vacuum (100 °C, 1 h) and then cooled to rt. Dry THF (5 mL) and a solution of NaHMDS (0.055 mL, 1 M in THF, 0.055 mmol) were added and the resulting solution was stirred at rt for 5 min. The solution was then cooled to -78 °C and DMPU (0.5 mL) was added, followed by a solution of the above aldehyde 303 (0.10 mmol) in dry THF (2 mL). The resulting solution was stirred for 1 h at -30 °C. Brine (10 mL), ethyl acetate (10 mL) and 10% aqueous Na$_2$CO$_3$ (10 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (2:1 EtOAc:hexanes) to give 1-benziloxymethyl-5-(3-bromo-1,1-dimethylallyl)-4-
[(**tert**-butyldimethylsilyl)-ethynyl]-1*H*-imidazole (315) as a 1:1 mixture of E:Z isomers (14 mg, 30% for two steps). ¹H NMR (360 MHz, CDCl₃) δ 7.38-7.32 (m, 0.5H), 7.28-7.20 (m, 0.5H), 7.17-7.13 (m, 5H), 6.86 (d, *J* = 9.0 Hz, 0.5H), 6.56 (d, *J* = 9.0 Hz, 0.5H), 6.26 (d, *J* = 7.7 Hz, 0.5H), 6.03 (d, *J* = 7.7 Hz, 0.5H), 5.17-5.14 (m, 2H), 4.34-4.28 (m, 2H), 1.69 (s, 6H), 0.80 (s, 9H), 0.00 (s, 6H).

1-Benzyloxymethyl-4-[(**tert**-butyldimethylsilyl)-ethynyl]-5-iodo-1,1-dimethylprop-2-ynyl-1*H*-imidazole (316). To a stirred solution of aldehyde imidazole 262 (25 mg, 0.076 mmol) in dry THF (1 mL) at -78 °C was added a solution of *n*-BuLi (0.04 mL, 2.0 M in hexanes, 0.08 mmol) and the resulting solution was stirred at -78 °C for 30 min. A solution of iodine (23 mg, 0.092 mmol) in dry THF (1 mL) was added over 10 min, until the red color persisted. Saturated aqueous ammonium chloride (10 mL), EtOAc (10 mL) and saturated aqueous Na₂S₂O₃ were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give 1-benzyloxymethyl-4-[(**tert**-butyldimethylsilyl)-ethynyl]-5-(3-iodo-1,1-dimethyl-prop-2-ynyl)-1*H*-imidazole (316, 23 mg, 58%). ¹H NMR (300 MHz, CDCl₃) δ 7.33 (s, 1H), 7.19-7.17 (m, 5H), 5.48 (s, 2H), 4.35 (s, 2H), 1.69 (s, 6H), 0.83 (s, 9H), 0.00 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 140.1, 138.0, 137.4, 130.0, 129.6, 129.2, 122.7, 101.5, 99.4, 97.0, 76.1, 71.6, 34.5, 27.5, 18.1, -3.3.

1-Benzyloxymethyl-4-[(**tert**-butyldimethylsilyl)-ethynyl]-5-(3-iodo-1,1-dimethylallyl)-1*H*-imidazole (302). To a stirred solution of 1-
benzyloxymethyl-4-[(tert-butyldimethylsilyl)-ethynyl]-5-(3-iodo-1,1-dimethylprop-2-ynyl)-1H-imidazole (316, 25 mg, 0.048 mmol) in THF:i-PrOH (1:1, 1 mL) at rt were added triethylamine (10 µL, 0.072 mmol) and o-nitrobenzenesulfonylhydrazine (11 mg, 0.05 mmol), and the resulting solution was stirred at rt overnight. Saturated aqueous sodium bicarbonate (10 mL) and ethyl acetate (10 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (EtOAc) to give 1-benzyloxymethyl-4-[(tert-butyldimethylsilyl)-ethynyl]-5-(3-iodo-1,1-dimethylallyl)-1H-imidazole (302, 18 mg, 73%). ¹H NMR (400 MHz, CDCl₃) δ 7.30 (s, 1H), 7.20-7.10 (m, 5H), 6.58 (d, J = 8.2 Hz, 1H), 6.20 (d, J = 8.2 Hz, 1H), 5.13 (s, 2H), 4.31 (s, 2H), 1.91 (s, 6H), 0.81 (s, 9H), -0.09 (s, 6H); LRMS-APCI m/z (relative intensity) 521 (MH⁺, 100).

**Preparation of Hemiaminal 263.** To a stirred solution of iodovinylimidazole 302 (24 mg, 0.046 mmol) in dry THF (3 mL) at -78 °C was added a solution of n-BuLi (21 µL, 2.1 M in hexanes, 0.046 mmol) and the resulting solution was stirred at -78 °C for 15 min. A solution of N-NOC-γ-lactam 231 (29 mg, 0.046 mmol) in dry THF (1 mL) was then added and the resulting solution was stirred at -78 °C for 4 h. Saturated aqueous ammonium chloride (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (2:1 EtOAc:hexanes) to give hemiaminal 263 (14 mg, 30%). ¹H NMR (300 MHz, CDCl₃) δ 7.36 (bs, 1H), 7.20-7.10 (m, 6H), 7.02-7.01 (m, 2H), 6.58-6.55 (m, 2H), 5.88-5.84 (m, 1H), 5.56 (bs, 1H), 5.36-5.34 (m, 1H), 5.18-5.14 (m, 2H),
3.66-3.65 (m, 1H), 3.57 (s, 3H), 3.53-3.50 (m, 1H), 1.67 (s, 6H) 1.43 (s, 9H), 0.80 (s, 9H), 0.00 (s, 6H); LRMS-ES+ $m/z$ (relative intensity) 1023 (MH$^+$, 100).

**Preparation of Alkyne-Hemiaminal 318.** To a stirred solution of hemiaminal 263 (13 mg, 0.013 mmol) in dry THF at 0 °C was added a solution of TBAF (19 ml, 1 M in THF, 0.019 mmol) and the resulting solution was stirred for 10 min. Saturated aqueous ammonium chloride (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (EtOAc) to give alkyne-hemiaminal 318 (3 mg, 25%) as a mixture of diastereomers. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 (bs, 1H), 7.22-7.13 (m, 6H), 7.09-7.02 (m, 1H), 6.85-6.83 (m, 1H), 6.57-6.55 (m, 1H), 6.48-6.46 (m, 1H), 5.57 (s, 1H), 5.44-5.31 (s, 1H), 4.37-4.27 (m, 2H), 3.56-3.51 (m, 3H), 3.03-2.95 (m, 1H), 2.14 (s, 1H), 1.67 (s, 6H), 1.44 (s, 9H); LRMS-ES+ $m/z$ (relative intensity) 908 (MH$^+$, 100).

**Preparation of Alcohol Imidazole 323.** To a stirred solution of aldehyde imidazole 259 (120 mg, 0.25 mmol) in dry THF (10 mL) at -78 °C was added a solution of methylmagnesium chloride (0.09 mL, 3 M in THF, 0.27 mmol) and the resulting solution was stirred at -78 °C for 2 h. Saturated aqueous ammonium chloride (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (1:3 hexanes:EtOAc) to give alcohol imidazole 323 (83 mg, 68%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.16-7.06 (m, 5H), 5.23 (s, 2H), 4.43 (s, 2H),
3.72-3.70 (m, 1H), 3.52 (bs, 1H), 1.15 (s, 6H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.79 (s, 9H), 0.00 (s, 6H). $^{13}$C (75 MHz, CDCl$_3$) δ 152.5, 135.0, 126.6, 126.1, 125.4, 117.0, 113.2, 103.1, 91.6, 72.7, 69.4, 39.4, 24.2, 23.3, 20.0, 15.7, 14.9, -6.6.

To a stirred solution of bromoimidazole 323 (80 mg, 0.16 mmol) in dry THF (15 mL) at -78 °C was added a solution of n-BuLi (0.15 mL, 2.3 M in hexanes, 0.34 mmol) and the resulting solution was stirred at -78 °C for 5 min. Saturated aqueous ammonium chloride (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure to give an alcohol imidazole, which was used in the next step without further purification. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (s, 1H), 7.15-7.07 (m, 5H), 5.19 (s, 2H), 4.36 (s, 2H), 3.73 (q, $J = 6.4$, 12.8 Hz, 1H), 1.20 (s, 6H), 0.93 (d, $J = 6.4$ Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.3, 137.0, 136.4, 128.9, 128.4, 127.9, 112.1, 104.2, 94.6, 75.1, 74.3, 71.3, 41.2, 26.5, 22.5, 18.0, 17.1, -4.3.

To a stirred solution of the above crude alcohol imidazole in dry DCM (4 mL) at rt was added Dess Martin periodinane (75 mg, 0.18 mmol), and the resulting solution was stirred at rt for 1 h. Aqueous sodium hydroxide (15%, 30 mL) and DCM (30 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to give 3-{3-benzylxymethyl-5-[(tert-butyldimethylsilyl)-ethynyl]-3H-imidazol-4-yl}-3-methylbutan-2-one (324, 54 mg, 82% from bromide 323).
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.40 (s, 1H), 7.18-7.08 (m, 5H), 5.28 (s, 2H), 4.36 (s, 2H), 1.84 (s, 3H), 1.36 (s, 6H), 0.79 (s, 9H), 0.00 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 209.8, 150.4, 137.2, 136.9, 128.9, 128.5, 127.9, 112.7, 105.3, 74.5, 71.4, 50.3, 26.4, 26.1, 24.4, 17.1, -4.4; LRMS-ES+ \(m/z\) (relative intensity) 411 (MH\(^+\), 100) 433 (M+Na\(^+\), 55); HRMS-ES+: [M+H]\(^+\) calcd for C\(_{24}\)H\(_{35}\)N\(_2\)O\(_2\)Si, 411.2468; found, 411.2463.

**Preparation of Iodochlorovinylimidazole 322.** To a stirred of solution of TBS-imidazole 324 (48 mg, 0.11 mmol) in dry THF (3 mL) at 0 °C was added a solution of TBAF (0.22 mL, 1 M in THF, 0.22 mmol), and the resulting solution was stirred at 0 °C for 30 min. Saturated aqueous ammonium chloride (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO\(_4\), the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give a terminal acetylene (28 mg, 86%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.51 (s, 1H), 7.26-7.19 (m, 5H), 5.32 (s, 2H), 4.47 (s, 2H), 3.57 (s, 1H), 1.96 (s, 3H), 1.48 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 209.9, 150.8, 137.5, 136.6, 129.0, 128.6, 128.2, 111.4, 88.7, 74.2, 72.1, 71.2, 50.3, 26.0, 24.3; LRMS-ES+ \(m/z\) (relative intensity) 297 (MH\(^+\), 100) 319 (M+Na\(^+\), 90); HRMS-ES+: [M+H]\(^+\) calcd for C\(_{18}\)H\(_{21}\)N\(_2\)O\(_2\), 297.1603; found, 297.1612.

To a stirred solution of the above alkyne imidazole (25 mg, 0.084 mmol) in dry MeCN (3 mL) at 0 °C were added copper (II) chloride (57 mg, 0.42 mmol) and iodine (106 mg, 0.42 mmol), and the resulting solution was stirred at 0 °C for 1 h. Saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (20 mL) and EtOAc (20 mL) were added. The organic layer was dried...
over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give iodochlorovinylimidazole 317 (36 mg, 93%) as a mixture of BOM regioisomers. ¹H NMR (300 MHz, CDCl₃) δ 7.49 (s, 0.2H), 7.40 (s, 0.8H), 7.18-7.13 (m, 5H), 7.08 (s, 0.2H), 6.99 (s, 0.8H), 5.11-5.00 (m, 2H), 4.37-4.33 (m, 2H), 1.98 (s, 0.75H), 1.90 (s, 2.25H), 1.39 (s, 1.5H), 1.34 (s, 4.5H); ¹³C NMR (75 MHz, CDCl₃) δ 210.6, 144.8, 138.6, 136.7, 129.4, 129.1, 128.8, 126.4, 93.8, 87.6, 74.7, 71.4, 50.9, 26.9, 24.4; LRMS-ES+ m/z (relative intensity) 459 (MH⁺, 100); HRMS-ES+: [M+H]⁺ calcd for C₁₈H₂₁N₂O₂ClI, 459.0336; found, 459.0340.

1-Benzylxymethyl-5-[2-(tert-butylidimethylsilyloxy)-1,1-dimethyl-propyl]-4-ethynyl-1H-imidazole (325). To a stirred solution of TBS-alkyne imidazole 323 (185 mg, 0.45 mmol) in dry THF (25 mL) at rt was added a solution of TBAF (0.87 mL, 1 M in THF, 0.87 mmol), and the resulting solution was stirred at rt for 30 min. Saturated aqueous ammonium chloride (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give a terminal alkyne (134 mg, 100%). ¹H NMR (300 MHz, CDCl₃) δ 7.41 (s, 1H), 7.26-7.19 (m, 5H), 5.28 (s, 2H), 4.45 (s, 2H), 3.83 (q, J = 6.2, 12.4 Hz, 1H) 3.58 (s, 1H), 1.31 (s, 6H), 1.04 (d, J = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 154.7, 136.7, 128.9, 128.5, 128.1, 110.9, 88.0, 75.1, 74.0, 71.1, 60.7, 25.7, 22.5, 18.1.

To a stirred solution of the above alcohol imidazole (130 mg, 0.43 mmol) in dry DMF (10 mL) at rt were added imidazole (92 mg, 1.35 mmol) and TBS-Cl (136 mg, 0.90
mmol), and the resulting solution was stirred at rt overnight. Brine (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give 1-benzzyoxymethyl-5-[2-(tert-butyldimethylsilanyloxy)-1,1-dimethylpropyl]-4-ethynyl-1H-imidazole (325, 155 mg, 87%). ¹H NMR (300 MHz, CDCl₃) δ 7.47 (s, 1H), 7.33-7.23 (m, 5H), 5.31 (s, 2H), 4.48 (s, 2H), 4.18 (q, J = 6.2, 12.4 Hz, 1H), 3.59 (s, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 0.95 (d, J = 6.2 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 3H), -0.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.4, 136.9, 128.9, 128.5, 128.2, 110.8, 87.5, 74.2, 74.1, 73.8, 70.8, 42.4, 26.3, 25.1, 20.9, 19.3, 18.3, -3.7, -4.5.

**Preparation of Dihalovinylimidazole 326.** To a stirred solution of alkyne 325 (150 mg, 0.36 mmol) in dry MeCN (20 mL) at 0 °C were added copper (II) chloride (244 mg, 1.8 mmol) and iodine (456 mg, 1.8 mmol), and the resulting solution was stirred at 0 °C for 1.5 h. Saturated Na₂S₂O₃ (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give dihalovinylimidazole 326 (157 mg, 76%) as a 1:1 mixture of BOM-regioisomers. ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.47 (m, 1H), 7.31-7.23 (m, 5H), 7.06-7.04 (m, 1H), 5.16-5.04 (m, 2H), 4.46-4.37 (m, 2H), 4.35-4.26 (m, 0.5H), 4.16-4.09 (m, 0.5H), 1.29-1.23 (m, 6H), 0.96-0.88 (m, 3H), 0.85-0.80 (m, 9H), 0.02-0.00 (m, 6H); ¹³C NMR and DEPT135 (75 MHz, CDCl₃) δ 148.9, 148.4, 137.5,
Preparation of Iodochlorovinylimidazole 327. To a stirred of solution TBS-imidazole 323 (50 mg, 0.12 mmol) in dry THF (10 mL) at 0 °C was added a solution of TBAF (0.24 mL, 1 M in THF, 0.24 mmol), and the resulting solution was stirred at 0 °C for 30 min. Saturated aqueous ammonium chloride (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure to give the terminal alkyne, which was used in the next step without further purification.

To a stirred solution of the above crude alcohol (0.12 mmol) in dry MeCN (5 mL) at 0 °C were added copper (II) chloride (80 mg, 0.60 mmol) and iodine (150 mg, 0.60 mmol), and the resulting solution was stirred at 0 °C for 1 h. Saturated aqueous Na₂S₂O₃ (20 mL) and EtOAc (20 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give iodochlorovinylimidazole 327 (33 mg, 60%, 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.73 (bs, 1H), 7.33-7.27 (m, 5 H), 7.19 (s, 1H), 5.23-5.13 (m, 2H), 4.49 (s, 2H), 3.85 (bs, 1H), 3.52 (m, 1H), 1.36-1.29 (m, 6H), 0.89 (d, J = 5.8 Hz, 3H); LRMS-ES+ m/z (relative intensity) 461 (MH⁺, 100).

1-{3-Benzyloxyethyl-5-[(tert-butyldimethylsilyl)-ethynyl]-3H-imidazol-4-yl}-propan-2-one (328). To a stirred solution of isobutenyl imidazole 281 (540 mg, 1.5 mmol) in TEA:THF (3:5, 8 mL) at rt were added TBS-
acetylene (1.2 mL, 2.9 mmol), copper (I) iodide (28 mg, 0.15 mmol) and tetrakis(triphenylphosphine) palladium (0) (170 mg, 0.15 mmol), and the resulting solution was stirred at rt for 3 h. EtOAc (50 mL) and brine (50 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give a TBS-acetylene imidazole (560 mg, 100%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (s, 1H), 7.20-7.09 (m, 5H), 5.07 (s, 2H), 4.63 (s, 1H), 4.49 (s, 1H), 4.26 (s, 2H), 3.33 (s, 2H), 1.51 (s, 3H), 0.82 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.3, 137.7, 136.4, 134.5, 129.1, 128.8, 128.7, 128.4, 112.8, 99.0, 95.1, 73.9, 70.2, 32.6, 26.5, 22.3, 17.0, -4.2.

To a stirred solution of the above acetylene imidazole (250 mg, 0.65 mmol) in H$_2$O:acetone (1:2, 15 mL) at rt were added N-methylmorpholine-N-oxide (385 mg, 3.3 mmol) and a solution of osmium tetraoxide (0.20 mL, 4% in H$_2$O, 0.033 mmol), and the resulting solution was stirred at rt overnight. The solution was then cooled to 0 °C, sodium periodate (350 mg, 1.6 mmol) was added and the solution was stirred at 0 °C for 4 h. EtOAc (50 mL) and saturated aqueous sodium sulfite solution (50 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give 1-{{3-benzyloxymethyl-5-[(tert-butyldimethylsilyl)-ethynyl]-3H-imidazol-4-yl}-propan-2-one (328, 150 mg, 60%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28 (s, 1H), 7.19-7.08 (m, 5H), 5.07 (s, 2H), 4.21 (s, 2H), 3.68 (s, 2H), 2.01 (s, 3H), 0.80 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 204.0, 138.1, 136.1, 130.1,
Preparation of Allyl $N$-Methylimidazole 348. To a stirred solution of 4,5-diiodoimidazole (346, 8.0 g, 25.0 mmol) in dry THF (150 mL) at 0 °C was added sodium hydride (900 mg, 60% dispersion in mineral oil, 37.5 mmol), and the resulting solution was stirred at rt for 30 min, then cooled to 0 °C. Methyl iodide (1.9 mL, 30 mmol) was added and the resulting solution was stirred at rt overnight. Saturated aqueous ammonium chloride (200 mL) and EtOAc (400 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure to give diodo-$N$-methylimidazole 347, which was used in the next step without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.60 (s, 1H), 3.68 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.6, 95.9, 83.5, 83.0.

To a stirred solution of the above diiodoimidazole 347 (13.9 g, 41.6 mmol) in dry THF (90 mL) at rt was added dropwise a solution of ethylmagnesium bromide (15.3 mL, 3M in diethyl ether, 5.1 mmol) and the resulting solution was stirred for 30 min at rt. A solution of CuCN·2LiCl (41.6 mL, 1 M in THF, 41.6 mmol) was then added and the temperature was decreased to -20 °C. Allyl bromide (3.8 mL, 43.7 mmol) was then added dropwise and the solution was stirred at rt for 4 h. A solution of saturated ammonium chloride containing 2% ammonium hydroxide (100 mL) was added and the mixture was stirred for 30 min. DCM (300 mL) and brine (100 mL) were added. The organic layer was dried over MgSO$_4$ and the solvent was removed under reduced pressure to give allyl imidazole 348, which was used in the next step without further
purification (5.0 g, 82% from diiodoimidazole 346). \( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.36 (bs, 1H), 5.75-5.66 (m, 1H), 5.04-4.84 (m, 2H), 3.51, (s, 3H), 3.28-3.25 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 133.6, 117.0, 84.3, 68.3, 32.9, 29.2, 25.9.

**Preparation of \( \alpha \)-Keto Ester Imidazole 350.** To a stirred solution of 4,5-diiodoimidazole 347 (560 mg, 1.68 mmol) in dry THF (15 mL) at rt was added dropwise a solution of ethylmagnesium bromide (0.56 mL, 3 M in diethyl ether, 0.19 mmol) and the resulting solution was stirred for 30 min. Ethyl oxalyl chloride (0.23 mL, 2.0 mmol) was added dropwise and the solution was stirred at rt for 1 h. Saturated ammonium chloride (30 mL) and EtOAc (50 mL) were then added. The organic layer was dried over MgSO\(_4\), the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give \( \alpha \)-keto ester imidazole 350 (160 mg, 31%). \( ^1 \)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 7.57 (bs, 1H), 4.32 (q, J = 7.0 Hz, 2H), 3.82 (s, 1H), 1.29 (t, J = 7 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 178.2, 163.2, 145.9, 129.1, 98.4, 63.3, 36.1, 14.1.

**Preparation of \( \alpha \)-Hydroxy Ester Imidazole 351 and \( \alpha \)-Silyl Hydroxy Ester Imidazole 352.** To a stirred solution of \( \alpha \)-keto ester imidazole 350 (1.0 g, 3.2 mmol) in TFA (20 mL) at rt was added triethylsilane (2.1 mL, 13.0 mmol), and the resulting solution was stirred at rt overnight. The solvent was then removed under reduced pressure and saturated aqueous sodium bicarbonate (20 mL) and EtOAc (40 mL) were added. The organic layer was dried over MgSO\(_4\), the solvent was removed under reduced pressure and the residue was purified by
flash column chromatography on silica gel (1:3 hexanes:EtOAc) to give α-hydroxy ester imidazole 351 (558 mg, 56%) and α-silyl hydroxy ester imidazole 352 (305 mg, 22%).

α-Hydroxy ester imidazole 351: $^1$H NMR (360 MHz, CDCl$_3$) δ 7.30 (s, 1H), 5.95 (bs, 1H), 5.32 (s, 1H), 4.22-4.01 (m, 2H), 3.63 (s, 3H), 1.23-1.14 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.5, 141.2, 131.2, 85.7, 66.2, 62.5, 33.6, 14.5. α-Silyl hydroxy ester imidazole 352: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.10 (s, 1H), 5.02 (s, 1H), 3.91-3.86 (m, 2H), 3.44 (s, 3H), 0.95 (t, $J = 7.0$ Hz, 3H), 0.62 (t, $J = 8.0$ Hz, 9H), 0.38-0.30 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.4, 141.4, 131.2, 86.5, 67.9, 62.0, 33.5, 14.4, 6.8, 4.8.

Preparation of N-SEM-γ-Lactam 353. To a stirred solution of $NH$-γ-lactam 84 (350 mg, 1.19 mmol) in dry THF (20 mL) at 0 °C was added NaH (34 mg, 60% dispersion in mineral oil, 1.4 mmol), and the resulting solution was stirred at rt for 30 min then cooled to 0 °C. 2-(Trimethylsilyl)ethoxymethyl chloride (0.25 mL, 1.4 mmol) was then added and the solution was stirred at rt overnight. Water (30 mL) and EtOAc (30 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to give N-SEM γ-lactam 353 (313 mg, 62%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.46-7.43 (m, 2H), 7.24-7.18 (m, 2H), 7.03-7.00 (m, 2H), 6.73-6.71 (m, 2H), 5.35-5.20 (m, 2H), 3.69 (s, 3H), 3.66-3.61 (m, 2H), 3.57 (d, $J = 14.6$ Hz, 1H), 3.36 (d, $J = 14.6$ Hz, 1H), 1.01-0.96 (m, 2H), 0.00 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.5, 163.9, 157.8, 143.5, 132.2, 131.7, 125.6, 125.4, 125.1, 119.6, 115.8, 112.1, 71.1, 67.9, 61.5, 56.6, 50.9, 19.1, 0.00; LRMS-AP+ $m$/z (relative intensity) 425 (MH$^+$, 100).
Preparation of NH-γ-lactam 334. To a stirred solution of N-PMP-β-lactam 353 (1.1 g, 2.6 mmol) in dry MeCN (40 ml) at 0 °C was added a 0 °C solution of ammonium ceric nitrate (4.7 g, 7.8 mmol) in water (32 mL) and the resulting solution was stirred at rt for 30 min. Saturated aqueous Na₂SO₄ (40 mL) and EtOAc (40 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give NH-β-lactam 334 containing an inseparable impurity.

To a stirred solution of the above impure NH-β-lactam 334 (800 mg, 2.5 mmol) in dry DCM (30 mL) at 0 °C were added triethylamine (0.7 mL, 5.0 mmol) and t-butyldimethylsilyl chloride (750 mg, 5.0 mmol), and the resulting solution was stirred at rt for 3 h. Water (50 mL) and DCM (50 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:3 EtOAc:hexanes) to give the N-TBS-β-lactam (1.08 g, 96% from β-lactam 353) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.38 (m, 2H), 7.20-7.11 (m, 2H), 5.23-5.15 (m, 2H), 3.67-3.61 (m, 2H), 3.47 (d, J = 14.9, 1H), 3.23 (d, J = 14.9, 1H), 0.99-0.93 (m, 11H), -0.03 - -0.04 (m, 15H); ¹³C NMR (75 MHz, CDCl₃) δ 177.9, 172.1, 143.3, 131.6, 129.1, 125.0, 124.7, 111.6, 71.3, 67.9, 58.7, 52.4, 27.5, 27.1, 19.3, 0.0, -4.7.

To a stirred solution of the above N-TBS-β-lactam (580 mg, 1.3 mmol) in dry THF (30 mL) at 0 °C was added a solution of TBAF (2.7 mL, 1 M in THF, 2.7 mmol) and the resulting solution was stirred at 0 °C for 30 min. Saturated aqueous ammonium chloride (100 mL) and EtOAc (100 mL) were added. The organic layer was dried over
MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give \(NH\)-\(\beta\)-lactam 334 (381 mg, 92%). \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.47-7.45 (m, 1H), 7.36-7.32 (m, 1H), 7.16-7.14 (m, 1H), 7.06-7.04 (m, 1H), 6.84 (bs, 1H), 5.17-5.06 (m, 2H), 3.58-3.54 (m, 2H), 3.39-3.35 (m, 1H), 3.20-3.16 (m, 1H), 0.91-0.86 (m, 2H), 0.00 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 177.1, 168.0, 143.4, 131.8, 127.7, 125.2, 124.8, 111.6, 71.2, 67.8, 57.5, 52.6, 19.1, 0.0.

**Preparation of \(N\)-Methyl-\(\gamma\)-lactam 357.** To a stirred solution of \(NH\)-\(\gamma\)-lactam 84 (1.00 g, 3.4 mmol) in dry THF (25 mL) at 0 °C was added sodium hydride (165 mg, 60% dispersion in mineral oil, 4.08 mmol), and the resulting solution was stirred at rt for 30 min then cooled to 0 °C. Iodomethane (0.25 mL, 4.08 mmol) was added and the resulting solution was stirred at rt overnight. Saturated aqueous ammonium chloride (20 mL) and EtOAc (20 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give \(N\)-methyl-\(\gamma\)-lactam 357 (650 mg, 62%). \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.27-7.22 (m, 2H), 7.00-6.95 (m, 1H), 6.86-6.80 (m, 3H), 6.55-6.52 (m, 2H), 3.50 (s, 2H), 3.35 (d, \(J = 14.6\) Hz, 1H), 3.17-3.11 (m, 4H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 173.9, 163.0, 156.7, 144.0, 131.2, 130.7, 124.9, 124.0, 123.9, 118.6, 114.8, 109.6, 60.3, 55.7, 49.5, 27.1.

**Preparation of \(NH\)-\(\beta\)-lactam 358.** To a stirred solution of PMP-\(\beta\)-lactam 357 (540 mg, 1.75 mmol) in dry MeCN (30 mL) at 0 °C was added a solution
of ceric ammonium nitrate (3.10 g, 5.25 mmol) in water (23 mL) and the resulting solution was stirred at rt for 30 min. Saturated aqueous Na₂SO₃ (30 mL) and EtOAc (60 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to give NH-β-lactam 358 containing an inseparable impurity.

To a stirred solution of the above impure NH-β-lactam 358 (170 mg, 0.84 mmol) in dry DCM (5 mL) at 0 °C were added triethylamine (0.23 mL, 1.7 mmol) and t-butyldimethylsilyl chloride (250 mg, 1.7 mmol), and the resulting solution was stirred at rt overnight. Water (20 mL) and DCM (20 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc:hexanes) to give TBS-β-lactam 359 (265 mg, 54% from β-lactam 358). ¹H NMR (300 MHz, CDCl₃) δ 7.55-7.50 (m, 2H), 7.30-7.25 (m, 1H), 7.06-7.03 (m, 1H), 3.60 (d, J = 14.9 Hz, 1H), 3.40-3.32 (m, 4H), 1.05 (s, 9H), 0.12 (s, 3H), 0.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 176.3, 171.2, 143.8, 130.6, 128.5, 123.8, 123.5, 109.1, 57.4, 50.6, 26.9, 26.5, 18.2, -5.8, -6.1.

To a stirred solution of TBS-β-lactam 359 (260 mg, 0.82 mmol) in dry THF (10 mL) at 0 °C was added a solution of TBAF (1.6 mL, 1 M in THF, 1.6 mmol) and the resulting solution was stirred at 0 °C for 30 min. Saturated aqueous ammonium chloride (30 mL) and EtOAc (30 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to give N-methyl-γ-lactam 358 (121 mg, 73%). ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.37 (m, 1H), 7.33-7.30 (m, 1H),
7.09-7.04 (m, 1H), 6.82-6.80 (m, 1H), 6.54 (bs, 1H), 3.38-3.32 (m, 1H), 3.18-3.11 (m, 4H).

**Preparation of Methyl Carbamate 360.** To a stirred solution of NH-γ-lactam 84 (780 mg, 2.65 mmol) in dry THF (30 mL) at 0 °C was added sodium hydride (95 mg, 60% dispersion in mineral oil, 3.97 mmol), and the resulting solution was stirred at rt for 30 min, then cooled to 0 °C. Methyl chloroformate (0.41 mL, 2.0 mmol) was added and the resulting solution was stirred at rt overnight. Saturated aqueous ammonium chloride (40 mL) and EtOAc (40 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was quickly purified by flash column chromatography on silica gel (5:1 DCM:EtOAc) to give methyl carbamate-γ-lactam 360 (870 mg, 93%). IR (film) 1765, 1732, 1511 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.90-7.87 (m, 1H), 7.30-7.25 (m, 2H), 7.09-7.07 (m, 1H), 6.79-6.76 (m, 2H), 6.54-6.51 (m, 2H), 3.86 (s, 3H), 3.52 (s, 3H), 3.42 (d, J = 11.7 Hz, 1H), 3.14 (d, J = 11.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 172.7, 162.6, 157.1, 151.4, 131.6, 130.1, 126.3, 124.3, 123.8, 119.0, 116.4, 114.9, 60.8, 55.8, 54.7, 51.3.
**Preparation of Methyl Carbamate-NH-β-lactam 363.** To a stirred solution of PMP-β-lactam 360 (225 mg, 0.64 mmol) in dry MeCN (20 mL) at 0 °C was added a solution of ceric ammonium nitrate (1.1 g, 1.9 mmol) in water (13 mL) and the resulting solution was stirred at rt for 30 min. Saturated aqueous Na$_2$SO$_3$ (30 mL) and EtOAc (60 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give an impure mixture containing N-methyl carbamate-NH-β-lactam 361 (~ 10 mg).

To a stirred solution of the above crude compound in dry DCM (2 mL) at rt were added triethylamine (0.01 mL, 0.08 mmol) and t-butyldimethylsilyl chloride (12 mg, 0.08 mmol) and the resulting solution was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give TBS-β-lactam 362 (3.5 mg).

To a stirred solution of the above TBS-β-lactam 362 (3.0 mg, 0.008 mmol) in dry THF (1 mL) at 0 °C was added a solution of TBAF (0.02 mL, 1 M in THF, 0.02 mmol) and the resulting solution was stirred at 0 °C for 30 min. Saturated aqueous ammonium chloride (5 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give methyl carbamate-γ-lactam 363 (2.5 mg, 1.5% for 3 steps). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.43 (bs, 1H), 7.31-7.25 (m, 2H), 7.08-7.03 (m, 1H), 6.88-6.85 (m, 1H), 3.71 (s, 3H), 3.45 (d, $J$ = 15.8 Hz, 1H), 3.19 (d, $J$ = 15.8 Hz, 1H).
Preparation of N-TBS-β-lactam 365. To a stirred solution of bis-NH-lactam 364 (230 mg, 1.2 mmol) in dry DCM (15 mL) at rt were added triethylamine (0.85 mL, 6.1 mmol) and t-butyldimethylsilyl chloride (920 mg, 6.1 mmol), and the resulting solution was stirred at rt overnight. Water (30 mL) and DCM (40 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc:DCM) to give N-TBS-β-lactam 365 (73 mg, 20%). ¹H NMR (300 MHz, CDCl₃) δ 9.22 (bs, 1H), 7.44-7.42 (m, 1H), 7.40-7.36 (m, 1H), 7.18-7.15 (m, 1H), 7.02-6.99 (m, 1H), 3.55 (d, J = 14.9 Hz, 1H), 3.28 (d, J = 14.9 Hz, 1H), 0.98 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.1, 171.5, 141.1, 130.6, 128.9, 124.1, 123.6, 111.1, 58.0, 50.8, 26.5, 18.3, -5.8.

Preparation of Methyl Carbamate-γ-lactam 362. To a stirred solution of TBS-β-lactam 365 (60 mg, 0.20 mmol) in dry THF (10 mL) at 0 °C was added sodium hydride (12 mg, 60% dispersion in mineral oil, 0.30 mmol), and the resulting solution was stirred at rt for 30 min, then cooled to 0 °C. Methyl chloroformate (0.03 mL, 0.40 mmol) was added and the resulting solution was stirred at rt overnight. Saturated aqueous ammonium chloride (20 mL) and EtOAc (30 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was quickly purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give methyl carbamate-γ-lactam 362 (49 mg, 70%). ¹H NMR (300 MHz, CDCl₃) δ 7.98-7.95 (m, 1H), 7.46-7.43 (m, 2H), 7.30-7.27 (m, 1H), 4.04 (s, 3H), 3.53 (d, J = 14.9 Hz, 1H), 3.21 (d, J = 14.9 Hz, 1H), 0.92 (s, 9H), 0.00 (s, 3H), -0.10
(s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.2, 170.6, 151.5, 139.4, 131.0, 127.6, 125.9, 123.7, 116.0, 57.8, 54.6, 52.6, 26.5, 18.2, -5.7.

Preparation of N-SEM-γ-lactam Ester Imidazole 366. A resealable Schlenk tube was charged with copper (I) iodide (1.4 mg, 0.0074 mmol), cesium carbonate (52 mg, 0.15 mmol) and NH-β-lactam 334 (35 mg, 0.11 mmol), evacuated and filled with nitrogen. Iodochlorovinylimidazole 247 (35 mg, 0.074 mmol) in dry THF (1.0 mL), followed by N,N'-dimethylethlenediamine (1.5 µL, 0.015 mmol), were added under nitrogen. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (2:1 hexanes:EtoAc) to give N-SEM-γ-lactam ester imidazole 366 (13 mg, 18%, 50% BRSM). LRMS-AP+ m/z (relative intensity) 665 (MH$^+$, 100).

Preparation of N-BOM-γ-lactam Ester Imidazole 367. A resealable Schlenk tube was charged with copper (I) iodide (5.0 mg, 0.0074 mmol), cesium carbonate (162 mg, 0.15 mmol) and NH-β-lactam 354 (92 mg, 0.30 mmol), evacuated and filled with nitrogen. Iodochlorovinylimidazole 247 (118 mg, 0.25 mmol) in dry THF (1.0 mL), followed by N,N'-dimethylethlenediamine (5.0 µL, 0.05 mmol), were added under nitrogen. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (2:1 hexanes:EtoAc) to give N-BOM-γ-lactam ester imidazole 367.
(13 mg, 20%, 83% BRSM). $^1$H NMR (360 MHz, CDCl$_3$) δ 7.09-7.06 (m, 12H), 6.90-6.86 (m, 1H), 6.79-6.78 (m, 2H), 6.35 (s, 1H), 5.02 (s, 1H), 4.93-4.71 (m, 3H), 4.51-4.34 (m, 2H), 4.25-4.17 (m, 2H), 3.42 (s, 3H), 3.08 (d, J = 15.0 Hz, 1H), 2.84 (d, J = 15.0 Hz, 1H), 1.48-1.46 (m, 6H); LRMS-ES+ m/z (relative intensity) 655 (MH$^+$, 100), 677 (M+Na$^+$, 60); HRMS-ES+:[M+H]$^+$ calcd for C$_{36}$H$_{36}$N$_4$O$_6$Cl, 655.2323; found 655.2338.

Preparation of $N$-SEM-$\gamma$-lactam Alcohol Imidazole 371. A resealable Schlenk tube was charged with copper (I) iodide (8.5 mg, 0.045 mmol), cesium carbonate (320 mg, 2.0 mmol) and $NH$-$\beta$-lactam 334 (210 mg, 0.67 mmol), evacuated and filled with nitrogen. Iodochlorovinylimidazole 370 (200 mg, 0.45 mmol) in dry THF (3.0 mL), followed by $N,N'$-dimethylethylenediamine (10 µL, 0.09 mmol), were added under nitrogen. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:2 hexanes:EtOAc) to give $N$-SEM-$\gamma$-lactam alcohol imidazole 371 (60 mg, 21%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41 (bs, 1H), 7.31-7.23 (m, 9H), 6.48-6.44 (m, 1H), 5.60-5.35 (m, 2H), 5.17-5.12 (m, 2H), 5.85-5.74 (m, 2H), 4.01-3.97 (m, 2H), 3.62-3.54 (m, 2H), 2.97-2.93 (m, 1H), 2.55-2.45 (m, 1H), 1.30 (s, 2H), 1.01-0.90 (m, 6H), 0.00 (s, 9H); (LRMS-ES+ m/z (relative intensity) 659 (M+Na$^+$, 100).

Preparation of Alcohol Imidazole 373. A resealable Schlenk tube was charged with copper (I) iodide (6.0 mg, 0.034 mmol), cesium carbonate (240 mg, 0.68 mmol) and $NH$-$\beta$-lactam 354 (155 mg, 0.50
mmol), evacuated and filled with argon. Iodochlorovinylimidazole 370 (150 mg, 0.34 mmol) in THF (1.5 mL), followed by \(N,N^\prime\)-dimethylethlenediamine (7.0 \(\mu\)L, 0.068 mmol), were added under nitrogen. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) then repurified by preparative TLC (1:1 DCM:EtOAc) to give alcohol imidazole 373 (59 mg, 28%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.55 (bs, 1H), 7.29-7.09 (m, 14H), 6.30-6.20 (m, 1H), 5.12-5.00 (m, 4H), 4.48-4.39 (m, 4H), 3.79 (s, 2H), 2.85-2.75 (m, 1H), 2.15-2.05 (m, 2H), 1.27 (s, 6H); LRMS-ES+ m/z (relative intensity) 627 (MH\(^+\), 100), 649 (M+Na\(^+\), 10).

**Preparation of Alcohol Imidazole 377.** A resealable Schlenk tube was charged with copper (I) iodide (2.5 mg, 0.013 mmol), cesium carbonate (95 mg, 0.27 mmol) and \(NH\)--\(\beta\)--lactam 168 (60 mg, 0.20 mmol), evacuated and filled with nitrogen. Iodochlorovinylimidazole 370 (60 mg, 0.13 mmol) in dry THF (2.0 mL), followed by \(N,N^\prime\)-dimethylethlenediamine (3.0 \(\mu\)L, 0.026 mmol), were added under nitrogen. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) then repurified by preparative TLC (1:1 DCM:EtOAc) to give alcohol imidazole 377 (16 mg, 20%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.66 (bs, 1H), 7.31-7.22 (m, 9H), 7.02-6.83 (m, 1H), 5.20-5.05 (m, 2H), 4.40 (s, 2H), 3.77 (s, 2H), 2.88 (s, 1H), 2.15-2.05 (m, 2H), 1.27 (s, 6H); LRMS-ES+ m/z (relative intensity) 627 (MH\(^+\), 100), 649 (M+Na\(^+\), 10).
3.80-3.70 (m, 2H), 3.52-3.30 (m, 1H), 3.03-2.97 (m, 1H), 1.45 (s, 9H); LRMS-ES+ m/z (relative intensity) 607 (MH⁺, 100), 629 (MNa⁺, 40).

**Preparation of N-SEM-γ-lactam Imidazole 381.** A resealable Schlenk tube was charged with copper (I) iodide (3.6 mg, 0.019 mmol), cesium carbonate (130 mg, 0.38 mmol) and NH-β-lactam 334 (71 mg, 0.22 mmol), evacuated and filled with nitrogen. Iodochlorovinylimidazole 251 (70 mg, 0.19 mmol) in dry THF (1.0 mL), followed by N,N'-dimethylethylenediamine (4.0 µL, 0.038 mmol), were added under nitrogen. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) to give N-SEM-γ-lactam imidazole 381 (39 mg, 39%). ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.38 (m, 2H), 7.37-7.31 (m, 7H), 7.20-7.09 (m, 2H), 6.16 (s, 1H), 5.32-5.17 (m, 4H), 4.44 (s, 2H), 3.65-3.61 (m, 2H), 3.63 (d, J = 14.8 Hz, 1H), 3.25 (d, J = 14.8 Hz, 1H), 0.98-0.94 (m, 2H), 0.00 (s, 9H); LRMS-ES+ m/z (relative intensity) 565 (MH⁺, 100).

**Preparation of NH-γ-Lactam 383.** To a stirred solution of N-SEM-γ-lactam 381 (3 mg, 0.005 mmol) in dry DCM (3 mL) at 0 °C was added BF₃·OEt (3 µL, 0.021 mmol), and the resulting solution was stirred at rt for 30 min. Saturated aqueous sodium bicarbonate (5 mL) and DCM (5 mL) were added. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give crude methylol 382.
The crude residue was dissolved in 9:1 THF:H₂O (2.2 mL) at rt and K₂CO₃ (14 mg, 0.1 mmol) was added. The solution was stirred at rt for 30 min then H₂O (10 mL) and DCM (10 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (EtOAc) to give NH-γ-lactam 383 (2 mg, 92%). ¹H NMR (300 MHz, CDCl₃) δ 7.53 (bs, 1H), 7.35-7.25 (m, 9H), 6.84 (s, 1H), 5.23-5.11 (m, 2H), 4.45-4.32 (m, 2H), 3.67-3.60 (m, 2H), 3.19-3.15 (m, 2H), 1.18 (s, 6H); LRMS-ES⁺ m/z (relative intensity) 435 (MH⁺, 100), 457 (M+Na⁺, 55).

**Preparation of N-PMB-imidazole 387.** To a stirred solution of 4,5-diodoimidazole (346, 15.5 g, 48.4 mmol) in dry DMF (45 mL) at rt was added anhydrous sodium carbonate (7.6 g, 48.4 mmol), and the resulting solution was stirred at 55 °C for 2 d. The solution was filtered through a pad of Celite (DCM) the solvent was removed under reduced pressure. Brine (100 mL) and DCM (100 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give N-PMB-imidazole 387 (9.2 g, 43%). ¹H NMR (300 MHz, CDCl₃) δ 7.48 (s, 1H), 7.04-7.01 (m, 2H), 6.82-6.79 (m, 2H), 5.00 (s, 2H), 3.73 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 160.1, 141.5, 129.4, 126.9, 114.8, 96.5, 83.0, 55.7, 53.3.

**Preparation of Allyl PMB-imidazole 388.** To a stirred solution of diiodoimidazole 387 (345 mg, 0.55 mmol) in dry THF (5 mL) at rt was added dropwise a solution of ethylmagnesium bromide (0.2 mL, 3M in diethyl ether, 0.67
mmol) and the resulting solution was stirred for 30 min at rt. A solution of CuCN·2LiCl (0.55 mL, 1 M in THF, 0.55 mmol) was then added and the temperature was decreased to -20 °C. Allyl bromide (0.05 mL, 0.58 mmol) was then added dropwise and the solution was stirred at 0 °C for 4 h. A solution of saturated ammonium chloride containing 2% ammonium hydroxide (200 mL) was added and the mixture was stirred for 30 min. DCM (30 mL) and brine (10 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give allyl PMB-imidazole 388 (133 mg, 69%). ¹H NMR (300 MHz, CDCl₃) δ 7.33 (bs, 1H), 6.94-6.91 (m, 2H), 6.80-6.77 (m, 2H), 5.69-5.60 (m, 1H), 5.01-4.84 (m, 4H), 3.71 (s, 3H), 3.17 (d, J = 5.7 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 160.3, 139.9, 134.3, 130.0, 129.3, 128.1, 117.6, 115.2, 85.9, 56.2, 49.9, 29.8.

**Preparation of Ester Imidazole 390. Method 1:** To a stirred solution of allyl PMB-imidazole 388 (100 mg, 0.28 mmol) in dry THF:H₂O (3:1, 2 mL) at rt were added N-methylmorpholine-N-oxide (160 mg, 1.4 mmol) and a solution of OsO₄ (0.04 mL, 0.007 mmol, 4% in H₂O). The resulting solution was stirred at rt overnight and then cooled to 0 °C. NaIO₄ (130 mg, 0.62 mmol) was added and the solution stirred for 4 h at 0 °C. Ethyl acetate (30 mL) and a saturated aqueous solution of Na₂SO₃ (20 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure to give the aldehyde, which was used in the next step without further purification.
To a stirred solution of the above crude aldehyde in acetone (10 mL) at rt was added dropwise Jones reagent (0.28 mL, 2.5 M, 0.11 mmol) until the orange color persisted (~10 min). i-PrOH (10 mL), H₂O (10 mL) and ethyl acetate (30 mL) were then added. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the corresponding acid 389, which was used in the next step without further purification.

To a stirred solution of the above acid in dry MeOH (10 mL) at 0 °C was added TMSCHN₂ (0.56 mL, 1.12 mmol), and the resulting solution was stirred at 0 °C for 10 min. The solvent was removed under reduced pressure in a cold water bath and the residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give ester imidazole 390 (17 mg, 16% over three steps).

**Method 2:** To a stirred solution of allyl PMB-imidazole 388 (6.3 g, 17.8 mmol) in dry THF:H₂O (3:1, 150 mL) at rt were added N-methylmorpholine-N-oxide (10.4 g, 89 mmol) and a solution of OsO₄ (2.7 mL, 0.025 mmol, 4% in H₂O). The resulting solution was stirred at rt overnight and then cooled to 0 °C. NaIO₄ (8.4 mg, 39.2 mmol) was added and the solution was stirred for 4 h at 0 °C. Ethyl acetate (300 mL) and a saturated aqueous Na₂SO₃ (200 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure to give the aldehyde, which was used in the next step without further purification.

To a stirred solution of the above crude aldehyde in acetone (160 mL) at rt was added dropwise Jones reagent (12.6 mL, 2.5 M, 5.0 mmol) until the orange color persisted (~10 min). i-PrOH (20 mL), H₂O (100 mL) and ethyl acetate (200 mL) were then added. The organic layer was dried over MgSO₄ and the solvent was removed under
reduced pressure to give the corresponding acid 389, which was used in the next step without further purification.

To a stirred solution of the above acid in dry MeOH (10 mL) at rt was added H$_2$SO$_4$ (0.5 mL) and the resulting solution was refluxed overnight. The reaction mixture was cooled to rt and saturated aqueous NaHCO$_3$ (100 mL) and DCM (200 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give ester imidazole 390 (1.3 g, 19%, 3 steps). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.36 (s, 1H), 6.95-6.92 (m 2H), 6.78-6.75 (m, 2H), 4.98 (s, 2H), 3.68 (s, 3H), 3.54 (s, 3 H), 3.42 (s, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.7, 159.9, 140.0, 129.1, 127.7, 127.1, 114.8, 87.1, 55.7, 52.8, 49.9, 31.3.

Preparation of TBS-Alkyne Imidazole Ester 391. To a stirred solution of ester imidazole 390 (1.20 g, 3.1 mmol) in TEA:THF (2:1, 30 mL) at rt were added TBS-acetylene (0.87 mL, 4.7 mmol), copper (I) iodide (59 mg, 0.31 mmol) and dichloro-bis-triphenylphosphine palladium (II) (220 mg, 0.31 mmol), and the resulting solution was stirred at rt overnight. EtOAc (50 mL) and saturated aqueous ammonium chloride (50 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give TBS-alkyne imidazole ester 390 (1.23 g, 100%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.20 (s, 1H), 6.87-6.85 (m, 2H), 6.70-6.68 (m, 2H0, 4.88 (s, 2H), 3.61 (s, 3H), 3.48-3.45 (m, 5H), 0.81 (s, 9H), 0.00 (s,
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.6, 159.9, 137.9, 129.7, 128.9, 127.3, 125.0, 
114.7, 98.8, 95.1, 55.5, 52.5, 49.3, 30.1, 26.4, 16.8, -4.5.

**Preparation of Dimethyl Imidazole Ester 392.** To a stirred solution of 
TBS-alkyne imidazole ester 391 (1.20 g, 3.0 mmol) in dry THF (60 mL) at 
-78 °C were added t-BuOK (1.5 g, 12.0 mmol) and 18-crown-6 (160 mg, 0.6 mmol), and 
the resulting solution was stirred at -78 °C for 30 min. Methyl iodide (0.93 mL, 15.0 
mmol) was added and the solution was stirred at -78 °C for 2 h. Saturated aqueous 
ammonium chloride (100 mL) and EtOAc (100 mL) were added. The organic layer was 
dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was 
purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give 
dimethyl imidazole ester 392 (1.23 g, 96%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.03 (s, 1H), 
6.82-6.79 (m, 2H), 6.70-6.68 (m, 2H), 4.67 (s, 2H), 3.62 (s, 3H), 3.33 (s, 3H), 1.58 (s, 6 
H), 0.81 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 176.4, 159.9, 138.8, 136.9, 
128.7, 127.5, 122.0, 114.6, 101.2, 95.1, 55.6, 52.8, 49.0, 43.2, 27.0, 26.6, 17.2, -4.2.

**Preparation of Dihalovinylimidazole 394.** To a stirred solution of TBS-
imidazole 392 (260 mg, 0.61 mmol) in dry THF (10 mL) at 0 °C was 
added a solution of TBAF (1.2 mL, 1 M in THF, 1.2 mmol) and the resulting solution 
was stirred at 0 °C for 30 min. Saturated aqueous ammonium chloride (25 mL) and 
EtOAc (25 mL) were added. The organic layer was dried over MgSO$_4$ and the solvent 
was removed under reduced pressure to give an alkynyl imidazole 393, which was used 
in the next step without further purification.
To a stirred solution of the above crude alkynylimidazole in dry MeCN (30 mL) at 0 °C were added copper (II) chloride (410 mg, 3.05 mmol) and iodine (775 mg, 3.05 mmol), and the resulting solution was stirred at rt overnight. Saturated aqueous Na₂S₂O₃ (50 mL) and EtOAc (100 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 hexanes:EtOAc) to give dihalovinylimidazole 394 (200 mg, 69% for 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.21 (s, 1H), 6.92 (m, 2H), 6.78-6.75 (m, 3H), 4.76 (s, 2H), 3.68 (s, 3H), 3.41 (s, 3H), 1.57 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 176.5, 159.9, 139.1, 135.6, 131.9, 128.9, 127.5, 114.7, 82.0, 55.7, 52.9, 49.0, 42.9, 25.9.

Preparation of Alcohol Imidazole 395. To a stirred solution of ester imidazole 394 (190 mg, 0.4 mmol) in dry DCM (10 mL) at -78 °C was added a solution of DIBAL-H (1.6 mL, 1 M in toluene, 1.6 mmol) and the resulting solution was stirred at -78 °C for 1.5 h. Saturated aqueous ammonium chloride (30 mL) and EtOAc (30 mL) were added and the solution was stirred for 2 h. The solution was decanted and the organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:2 hexanes:EtOAc) to give alcohol imidazole 395 (140 mg, 78%). ¹H NMR (360 MHz, CDCl₃) δ 7.27 (s, 1H), 7.00-6.98 (m, 2H), 6.89-6.84 (m, 3H), 5.32 (s, 1H), 3.80 (s, 3H), 3.71 (s, 2H), 3.17 (bs, 1H), 1.42 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 159.3, 139.7, 136.0, 133.3, 132.3, 128.5, 127.9, 114.4, 81.5, 70.7, 55.3, 50.7, 38.2, 25.0.
Preparation of Allylimidazole 400. To a stirred solution of iodoimidazole 254 (1.05 g, 2.96 mmol) in dry TEA:THF (2:1, 15 mL) at rt were added TMS-acetylene (0.85 mL, 5.9 mmol), copper (I) iodide (56 mg, 0.30 mmol) and bistriphenylphosphine palladium (II) chloride (210 mg, 0.30 mmol), and the resulting solution was stirred at rt overnight. EtOAc (50 mL) and brine (50 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes) to give allylimidazole 400 (747 mg, 78%). ¹H NMR (300 MHz, CDCl₃) δ 7.15 (s, 1H), 7.11-6.99 (m, 5H), 5.66-5.57 (m, 1H), 5.01-4.98 (m, 2H), 4.85-4.77 (m, 2H), 4.12 (s, 2H), 3.28 (d, J = 11.8 Hz, 2H), 0.00 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 137.3, 136.1, 134.2, 133.6, 128.6, 1282., 127.9, 123.6, 116.8, 98.3, 96.2, 73.6, 69.7, 53.6, 28.0, 0.0.

5-Allyl-1-benzyloxymethyl-4-ethynyl-1H-imidazole (401). To a stirred solution of 5-allyl-1-benzyloxymethyl-4-[(trimethysilanyl)-ethynyl]-1H-imidazole (400, 740 mg, 2.2 mmol) in dry THF (40 mL) at 0 °C was added a solution of TBAF (4.5 mL, 1M in THF, 4.5 mmol) and the resulting solution was stirred at 0 °C for 30 min. Saturated aqueous ammonium chloride (100 mL) and EtOAc (100 mL) were added. The organic layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give 5-allyl-1-benzyloxymethyl-4-ethynyl-1H-imidazole (401, 462 mg, 83%). ¹H NMR (300 MHz, CDCl₃) δ 7.33 (s, 1H), 7.30-7.16 (m, 5H), 5.82-5.73 (m, 1H), 5.15 (s, 2H), 5.10-4.89 (m, 2H), 4.32 (s, 2H), 3.46 (d, J = 5.9 Hz, 2H), 3.07 (s, 1H);
Preparation of Iodochlorovinylimidazole 402. To a stirred solution of 5-allyl-1-benzyloxymethyl-4-ethynyl-1H-imidazole (401, 310 mg, 1.2 mmol) in dry MeCN (30 mL) at 0 °C were added copper (II) chloride (250 mg, 1.8 mmol) and iodine (460 mg, 1.8 mmol), and the resulting solution was stirred at rt overnight. Saturated aqueous Na$_2$S$_2$O$_3$ (60 mL) and EtOAc (60 mL) were added. The organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc) to give iodochlorovinylimidazole 402 (497 mg, 100%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.46 (s, 1H), 7.31-7.19 (m, 5H), 6.74 (s, 1H), 5.83-5.76 (m, 1H), 5.21 (s, 2H), 5.05-4.96 (m, 2H), 4.36 (s, 2H), 3.44-3.37 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.0, 136.3, 133.8, 129.6, 129.1, 128.7, 128.5, 128.4 (2C), 117.6, 77.7, 74.0, 70.3, 28.9; LRMS-ES+ m/z (relative intensity) 415 (MH$^+$, 100).

Preparation of Coupled Product 403. A resealable Schlenk tube was charged with copper (I) iodide (1.8 mg, 0.0097 mmol), cesium carbonate (68 mg, 0.19 mmol) and NH-$\beta$-lactam 168 (33 mg, 0.12 mmol), evacuated and filled with nitrogen. Iodochlorovinylimidazole 402 (40 mg, 0.097 mmol) in dry THF (1.0 mL), followed by $N,N'$-dimethylethylenediamine (2.0 µL, 0.019 mmol), were added under nitrogen. The Schlenk tube was sealed, heated at 70 °C overnight and cooled to rt. The resulting mixture was filtered through a pad of silica gel
(EtOAc). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 hexanes:EtOAc) to give coupled product 403 (19 mg, 29%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.19 (m, 10H), 5.77-5.71 (m, 1H), 5.22 (s, 2H), 5.40-4.97 (m, 2H), 4.38 (s, 2H), 3.57-3.51 (m, 2H), 3.44 (s, 2H), 3.03 (s, 1H), 1.57 (s, 9H); LRMS-ES+ m/z (relative intensity) 575 (MH$^+$, 100).
References and Notes


8 For use of PET with indoles, see: Yonemitsu, O.; Cerutti, P.; Witkop, B. J. Am. Chem. Soc. 1966, 88, 3941-3945.


Compound 78b has previously been synthesized in our group, although the reaction was carried out in a NMR tube and the product was never isolated (see ref. 14b).


For a discussion of Isobe's N-vinylation methodology see, Chapter 1, Section 2.5.2


Importantly, this late stage formation of the spiro-β-lactam stands in stark contrast to literature precedent in which similar transformation were shown to not work.\textsuperscript{14b}


Use of a dummy base or less than two equivalents of alkyne \textbf{225} resulted in lower yields.\textsuperscript{14}

This proposed structure / mechanism was further investigated in a study of a model system having a PMP group on the spiro-β-lactam.\textsuperscript{14d}

See Section 2.5.4 for further attempts at the modification of ester \textbf{261}.


The oxidative cleavage of alkene 281 with RuCl\textsubscript{3} did not proceed to completion even after extended reaction times. For example of this process, see: Podeschwa, M.; Plettenburg, O.; vom Brocke, J.; Block, O.; Adelt, S.; Altenback, H., J. Eur. J. Org. Chem. 2003, 1958-1972.


98 Similar reactions with DIBAL-H also did not give any of the desired reduced product (ref. 14).

99 Imidazole 370 was previously synthesized by Sun but never used in an N-vinylation reaction with β-lactams (ref. 14).

100 Sun, C.; Weinreb, S. M. unpublished work, 2005.


VITA

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