STUDIES TOWARDS A TOTAL SYNTHESIS OF ALKALOIDS MANZAMINE A AND CYLINDROSPERMOPSIN AND DEVELOPMENT OF A COMPLEX EXAMPLE OF THE DOWD-BECKWITH REARRANGEMENT

DISSERTATION

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By

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This dissertation describes efforts towards a total synthesis of manzamine A and cylindrospermopsin, and the development of a novel variant of the Dowd rearrangement. Manzamine A is a marine sponge alkaloid with a complex structure and potentially valuable biological activity. This thesis describes an approach to a manzamine A substructure involving an asymmetric Birch reductive alkylation of the amide derived from (L)-prolinol methyl ether and 2-methoxybenzoic acid as a key step. Another key step was projected to be a diastereoselective Keck allylation, however a novel Dowd-Beckwith rearrangement occurred instead, producing a substituted 2-oxabicyclo[3.3.0]octan-3,6-dione in good yield.

A study of the scope and limitations of this process is described herein. This study illustrated that the rearrangement can be efficient and stereoselective, and culminated in a nontrivial synthesis of a bicyclo[3.3.0]octanone containing three contiguous quaternary stereocenters.

Cylindrospermopsin is a highly toxic cyanobacterial guanidinium alkaloid. The work presented herein describes a synthesis of advanced intermediates in a projected synthesis of cylindrospermopsin. Key steps include a Roush crotylation reaction to establish several key stereogenic centers, an intramolecular conjugate addition to form a
piperidine ring, a Curtius rearrangement with internal trapping to provide a hexahydroimidazo[1,5-a]pyridine-3-one, and a Sonogashira coupling to attach the incipient D-ring pyrimidine. Whereas a synthesis was not accomplished, a 14-step synthesis of an intermediate that may serve as a cylindrospermopsin precursor is described.
To my grandfather, Gyuri.
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“It is not yours to finish the task – neither are you free to desist from it” – Pirke Avot 2:16.

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TABLE OF CONTENTS

Abstract...................................................................................................................... ii
Dedication................................................................................................................ iv
Acknowledgements................................................................................................. v
Vita......................................................................................................................... vii
List of Schemes....................................................................................................... xii
List of Figures......................................................................................................... xvi
List of abbreviations............................................................................................. xvii

Chapters:
1. Studies towards a total synthesis of manzamine A................................. 1
   1.1 Introduction................................................................................................... 1
   1.2 The biosynthesis of manzamine A.............................................................. 3
   1.3 Previous synthetic studies towards manzamine A – a brief survey......... 5
      1.3.1 Winkler’s total synthesis of manzamine A....................................... 6
      1.3.2 Martin’s enantioselective total synthesis of manzamine A.......... 9
   1.4 Synthetic studies on manzamine A in the Hart group......................... 12
   1.5 Latest synthetic efforts towards manzamine A................................... 18
      1.5.1 Introduction of the problem............................................................ 18
      1.5.2 Model studies for the first steps.................................................... 20
      1.5.3 Modified synthetic strategy........................................................... 31
      1.5.4 Free ketone strategy......................................................................... 36
      1.5.5 Study of internal acetal formation................................................ 41
      1.5.6 Successful iodolactone synthesis – unexpected allylation results... 43
2. Development of a complex example of the Dowd-Beckwith rearrangement.... 48
2.1 The Dowd rearrangement – a brief introduction ........................................ 48
2.2 Initial observations .................................................................................. 51
2.3 Radical reduction experiments with iodolactone 136 ............................. 52
2.4 Varying substitution patterns .................................................................. 54
   2.4.1 Synthesis of starting materials ....................................................... 54
   2.4.2 Rearrangement studies – radical allylation reactions ..................... 59
   2.4.3 Rearrangement studies – radical reduction reactions ..................... 60
2.5 Conclusions ............................................................................................ 62
3. Studies towards a total synthesis of cylindrospermopsin ............................... 63
   3.1 Introduction .......................................................................................... 63
      3.1.1 Isolation and characterization of cylindrospermopsin ................. 63
      3.1.2 Toxicity of cylindrospermopsin .................................................. 65
      3.1.3 Cylindrospermopsin biosynthesis .............................................. 66
   3.2 Synthetic studies towards cylindrospermopsin ....................................... 67
      3.2.1 Snider’s synthesis of cylindrospermopsin .................................... 67
      3.2.2 Weinreb’s synthesis of cylindrospermopsin ................................. 71
      3.2.3 White group synthesis of 7-epicylindrospermopsin ............... 77
   3.3 Hart group approach to cylindrospermopsin ......................................... 80
      3.3.1 Initial approach ............................................................................ 80
      3.3.2 Ridenour – revised synthetic strategy towards CYN ................... 86
   3.4 Current results ....................................................................................... 91
      3.4.1 Research plan .............................................................................. 91
      3.4.2 Asymmetric synthesis of carboxylic acids of type 234 ............... 92
      3.4.3 Early steps .................................................................................. 93
      3.4.4 Installation of C_{12-14} .............................................................. 96
      3.4.5 Synthesis of an AC ring intermediate towards CYN .................. 98
      3.4.6 Attempted improvement of the 284 → 295 conversion .............. 102
      3.4.7 D ring installation ...................................................................... 107
      3.4.8 Guanidine formation ................................................................. 110
      3.4.9 Conclusions and future directions .............................................. 121
4. Experimental………………………………………………………………….…. 123

List of references………………………………………………………………….… 253
Appendix A – $^1$H and $^{13}$C NMR spectra for selected compounds…………………. 263
<table>
<thead>
<tr>
<th>Scheme</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 The Baldwin – Whitehead Hypothesis</td>
<td>4</td>
</tr>
<tr>
<td>1.2 Winkler’s synthesis of a Manzamine ABCD core unit</td>
<td>7</td>
</tr>
<tr>
<td>1.3 Completion of Winkler’s synthesis of Manzamine A</td>
<td>8</td>
</tr>
<tr>
<td>1.4 Early steps in Martin’s synthesis of Manzamine A</td>
<td>10</td>
</tr>
<tr>
<td>1.5 Martin’s completion of Manzamine A</td>
<td>11</td>
</tr>
<tr>
<td>1.6 Campbell’s Retrosynthetic analysis of Manzamine A</td>
<td>13</td>
</tr>
<tr>
<td>1.7 Synthesis of synthetic intermediate 47</td>
<td>14</td>
</tr>
<tr>
<td>1.8 Campbell’s synthesis of an ABD unit of Manzamine</td>
<td>15</td>
</tr>
<tr>
<td>1.9 Campbell’s synthesis of ABCD units of Manzamine A</td>
<td>16</td>
</tr>
<tr>
<td>1.10 Filippini’s most advanced intermediates</td>
<td>17</td>
</tr>
<tr>
<td>1.11 Ellman-Davis sulfinimine addition chemistry</td>
<td>19</td>
</tr>
<tr>
<td>1.12 A potential solution to stereocontrol at C21</td>
<td>20</td>
</tr>
<tr>
<td>1.13 Schultz’s asymmetric reductive alkylation chemistry</td>
<td>21</td>
</tr>
<tr>
<td>1.14 Planned model studies for the first steps</td>
<td>22</td>
</tr>
<tr>
<td>1.15 Snieckus ortho-metallation pathway to 69</td>
<td>23</td>
</tr>
<tr>
<td>1.16 The Comins <em>ortho</em>-Metallation</td>
<td>24</td>
</tr>
<tr>
<td>1.17 Synthesis of 69 through transmetallation chemistry</td>
<td>25</td>
</tr>
<tr>
<td>1.18 Synthesis of alkylating agent 87</td>
<td>26</td>
</tr>
<tr>
<td>1.19 Reductive alkylation of model compound 69</td>
<td>26</td>
</tr>
<tr>
<td>1.20 Dehydrobromination as a possible side reaction</td>
<td>27</td>
</tr>
<tr>
<td>1.21 Halolactonization attempts on model compound 88</td>
<td>27</td>
</tr>
<tr>
<td>1.22 Attempted dihydroxylation of 88</td>
<td>29</td>
</tr>
<tr>
<td>1.23 Attempted epoxidation of 88</td>
<td>30</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1.24 Modified strategy for the early steps towards Manzamine A</td>
<td>31</td>
</tr>
<tr>
<td>1.25 Revised strategy – early steps</td>
<td>32</td>
</tr>
<tr>
<td>1.26 Initial attempt at ketal formation</td>
<td>33</td>
</tr>
<tr>
<td>1.27 Strategy check</td>
<td>34</td>
</tr>
<tr>
<td>1.28 Synthesis of new alkylating agents</td>
<td>35</td>
</tr>
<tr>
<td>1.29 New reductive alkylations</td>
<td>36</td>
</tr>
<tr>
<td>1.30 Initial attempts at C₄ ketal formation</td>
<td>37</td>
</tr>
<tr>
<td>1.31 Schultz’s work as a precedent for carrying C₄ as the free ketone</td>
<td>38</td>
</tr>
<tr>
<td>1.32 First attempt at adapting Schultz’s strategy</td>
<td>40</td>
</tr>
<tr>
<td>1.33 Study of internal acetal formation</td>
<td>41</td>
</tr>
<tr>
<td>1.34 Jake Freed’s model study of internal acetal use</td>
<td>42</td>
</tr>
<tr>
<td>1.35 Successful synthesis of iodolactone 136, and unexpected results</td>
<td>44</td>
</tr>
<tr>
<td>1.36 Last attempts at C₄ acetal formation</td>
<td>46</td>
</tr>
<tr>
<td>1.37 Protection of C₄ as acetylated alcohol</td>
<td>47</td>
</tr>
<tr>
<td>2.1 Proposed mechanism for the Dowd rearrangement</td>
<td>49</td>
</tr>
<tr>
<td>2.2 Selected examples of the Dowd reaction</td>
<td>50</td>
</tr>
<tr>
<td>2.3 Proposed mechanism for the formation of 138</td>
<td>52</td>
</tr>
<tr>
<td>2.4 Study of concentration effects on the reduction of 136</td>
<td>54</td>
</tr>
<tr>
<td>2.5 Synthesis of rearrangement substrate 167</td>
<td>56</td>
</tr>
<tr>
<td>2.6 Synthesis of carboxylic acid 179</td>
<td>57</td>
</tr>
<tr>
<td>2.7 Synthesis of rearrangement substrate 168</td>
<td>58</td>
</tr>
<tr>
<td>2.8 Allylation studies</td>
<td>60</td>
</tr>
<tr>
<td>2.9 Radical reduction studies</td>
<td>62</td>
</tr>
<tr>
<td>3.1 Proposed biosynthesis of cylindrospermopsin</td>
<td>66</td>
</tr>
<tr>
<td>3.2 Snider’s synthesis of the A ring of cylindrospermopsin</td>
<td>67</td>
</tr>
<tr>
<td>3.3 Snider’s progression to an ACD-ring intermediate to CYN</td>
<td>69</td>
</tr>
<tr>
<td>3.4 Completion of Snider’s synthesis of (±)-190</td>
<td>70</td>
</tr>
<tr>
<td>3.5 Early steps in Weinreb’s synthesis of cylindrospermopsin</td>
<td>72</td>
</tr>
<tr>
<td>3.6 Weinreb’s key step towards cylindrospermopsin</td>
<td>73</td>
</tr>
<tr>
<td>3.7 Weinreb’s construction of the D ring of cylindrospermopsin</td>
<td>74</td>
</tr>
</tbody>
</table>
3.8 Weinreb’s completion of 220 and 7-epicylindrospermopsin………………… 76
3.9 White’s synthesis of an ABD intermediate towards CYN…………………….. 78
3.10 White’s completion of 7-epicylindrospermopsin……………………………. 79
3.11 Hart’s initial retrosynthetic approach to cylindrospermopsin……………….. 80
3.12 Djung’s synthesis of the B ring of cylindrospermopsin…………………….. 81
3.13 Djung’s C7 functionalization………………………………………………… 83
3.14 Installation of C12 and C13………………………………………………… 84
3.15 Amidomercuration of 243………………………………………………… 85
3.16 Revised retrosynthesis of cylindrospermopsin……………………………… 87
3.17 Ridenour’s early steps towards cylindrospermopsin………………………… 88
3.18 Proof of stereochemistry in 253 and 254……………………………………. 89
3.19 Ridenour’s attempt at electrophile-initiated cyclization of the A ring……… 89
3.20 Ridenour’s synthesis of an A ring intermediate…………………………….. 90
3.21 Djung’s enantioselective route to acid 266…………………………………… 93
3.22 Early steps towards an enantioselective synthesis of cylindrospermopsin…. 94
3.23 Synthesis of alkylating agents……………………………………………… 95
3.24 Installation of carbons 12-14………………………………………………… 97
3.25 Suspected asymmetric amplification in the Roush crotylboronation……….. 98
3.26 Synthesis of an AC ring intermediate towards cylindrospermopsin……… 99
3.27 Cyclization of 303…………………………………………………………… 100
3.28 Attempts to double protect nitrogen prior to A ring cyclization…………….. 103
3.29 Further attempts at double nitrogen protection……………………………. 104
3.30 Precedents for olefin metathesis of 284……………………………………… 105
3.31 Olefin metathesis of 284 and 285…………………………………………… 106
3.32 Synthesis of bromopyrimidine 325………………………………………… 108
3.33 Installation of the D ring of cylindrospermopsin……………………………. 109
3.34 Sonogashira coupling of compound 330……………………………………. 109
3.35 Initial guanidine formation attempts………………………………………. 111
3.36 Further attempts towards formation of a guanidine……………………….. 112
3.37 Synthesis of model urea 341………………………………………………… 113
3.38  Protection studies and synthesis of model thiourea 347. .......................... 113
3.39  Model guanidine formation studies. .............................................................. 115
3.40  Synthesis of ureas 357 and 358. ................................................................. 116
3.41  Attempted protection of ureas 357 and 358. ............................................. 119
3.42  Latest advances towards guanidine installation ......................................... 120
3.43  Future directions towards cylindrospermopsin ........................................ 122
LIST OF FIGURES

1.1 Some members of the Manzamine family of alkaloids.............................. 2
1.2 ORTEP drawing of ketal 139................................................................. 46
2.1 Chosen substrates for rearrangement study........................................... 55
3.1 Cylindrospermopsin (CYN) and 7-epi-cylindrospermopsin (ECYN)......... 64
3.2 Most stable conformations of 298 and 305........................................... 101
3.3 Olefin metathesis catalysts................................................................. 105
3.4 Stereochemical comparison of 355 and 356........................................... 118
LIST OF ABBREVIATIONS

Ac = Acetyl
Ar = Aryl
AIBN = Azo-bis(isobutyronitrile)
Bu = Butyl
BOC = t-Butoxycarbonyl
m-CPBA = meta-Chloroperbenzoic acid
DMF = Dimethylformamide
Et = Ethyl
Me = Methyl
Ms = Methanesulfonyl
NBS = N-Bromosuccinimide
NIS = N-Iodosuccinimide
NMO = N-Methylmorpholine oxide
NMR = Nuclear Magnetic Resonance
PG = Protecting Group
Piv = Pivaloyl
Ph = Phenyl
PMB = p-Methoxybenzyl
PMP = p-Methoxyphenyl
RCM = Ring-Closing Metathesis
rt = Room Temperature
SES = 2-(Trimethylsilyl)ethanesulfonfonyl
TBDPS = t-Butyldiphenylsilyl
TBS = t-Butyldimethylsilyl
THF = Tetrahydrofuran
THP = Tetrahydropyranyl
TMEDA = N,N,N',N'-Tetramethylethylenediamine
TMS = Trimethylsilyl
Tr = Trityl
Troc = 2,2,2-Trichloroethylcarbonyl
Ts = Toluenesulfonyl
CHAPTER 1

STUDIES TOWARDS A TOTAL SYNTHESIS OF MANZAMINE A

1.1 Introduction.

The alkaloid manzamine A (1, Figure 1.1) is a marine natural product, isolated in 1986 from the sponge Haliclona sp. by Higa and coworkers off the coast of Manzamo, Japan. The structure of 1 was determined primarily by NMR and X-ray crystallographic studies.

Many manzamine congeners were subsequently isolated from several marine sponge species, including manzamines B (2) and C (3), manzamines E and F, manzamine L, manzamine M, ircinals A (4) and B, ircinols A and B, 12,34-oxamanzamines, keramaphidin B (5), nakadomarin A (6), ma’eganedin A (7), kauluamine, and neo-kauluamine A (8). Ircinal A and keramaphidin B are thought to be biogenetic precursors of manzamine A. Ircinal A can be transformed into manzamine A through a published two-step procedure.

Manzamine A possesses a wide range of biological activity, including significant activity against the growth of mouse leukemia cells (IC$_{50}$ = 0.07µg/mL), as well as antibacterial activity (minimal inhibitory concentration of 6.3 µg/mL against the Staphylococcus Aureus bacterium). Manzamine A and other family members have
also recently shown potent activity against infectious diseases such as malaria, tuberculosis and toxoplasmosis, and activity as anti-inflammatory agents. Most recently, manzamine A was shown to possess insecticidal activity against *S. Litoralis* larvae. 

![Figure 1.1: Some members of the Manzamine family of alkaloids.](image-url)
1.2. The biosynthesis of Manzamine A.

In 1992, Baldwin and Whitehead proposed a hypothesis by which the manzamine alkaloids could be biosynthetically formed from four building blocks: tryptophan, ammonia, a symmetrical C$_{10}$ dialdehyde unit (13), and a C$_3$ acrolein equivalent (Scheme 1.1).$^{21}$ Retrosynthetically from manzamine A (1), removal of the C$_3$ oxygen and the tryptophan unit, and opening of the D ring gives amino aldehyde 9, which can be derived from the reduction-oxidation and hydrolysis of 10. Disconnection of 10 by an intramolecular Diels-Alder reaction gives macrocycle 11, the conjugate base of 12, whose formation can be envisioned from Baldwin’s proposed starting blocks. The subsequent discovery of manzamine-related alkaloids bearing strong resemblance to intermediates in the proposed biosynthesis, such as ircinal A (4) and keramaphidin B (5), reminiscent of 10,$^{10}$ lend additional support to the Baldwin-Whitehead hypothesis. Model studies conducted by the Baldwin group and others indicated that the key Diels-Alder reaction was feasible in a bimolecular fashion.$^{22}$
Scheme 1.1: The Baldwin – Whitehead Hypothesis.
1.3. Previous synthetic studies towards Manzamine A – a brief survey.

Over the years, many groups have turned their attention to the total synthesis of manzamine A. These include Pandit’s synthesis of a complete chiral ABCDE manzamine ring system, cyclization of the D and E ring being accomplished via olefin metathesis. Pandit also accomplished the addition of the β-carboline unit to an ABCE manzamine unit. Nakagawa has described a synthesis of an ABCD core compound, starting with an intermolecular Diels-Alder reaction to form the B ring. Yamamura has published a synthesis of an ABCE subunit. Langlois has applied Zincke-Bradsher chemistry to a synthesis of a Manzamine ABE tricycle. Markó has reported syntheses of structures related to the ABC core of manzamine. Magnus has prepared the ABC manzamine core via Pauson-Khand chemistry. Coldham has attained an ABC subunit via an azomethine ylide dipolar cycloaddition. Overman has synthesized an ABC subunit, via an intramolecular Mannich reaction. Brand’s synthesis of an ABC subunit uses an intramolecular Michael reaction. Clark’s synthesis of an AB fragment employs enyne ring-closing metathesis, and his route to a CE fragment uses carbenoid chemistry. Marazano has described biomimetic studies leading to the synthesis of the ABC ring system of manzamine. Baldwin’s biomimetic studies have provided the core structure of keramaphidin B. A complete review of these efforts will not be presented here. The reader is encouraged to refer to existing reviews for a more detailed account.

Two successful total syntheses of Manzamine A have so far been published, by the Winkler and Martin groups. We will now briefly examine these syntheses.
1.3.1. Winkler’s total synthesis of Manzamine A.

The first published total synthesis of manzamine A was that of Winkler and coworkers, resting on a highly stereoselective tandem intramolecular vinylogous amide photoaddition – retro-Mannich fragmentation transformation, followed by a Mannich cyclization reaction (Scheme 1.2). The starting material for this key reaction sequence (16) was obtained from azocine 14, containing preformed A and D ring units, and ynone 15, whose elongated chain carried the carbon atoms needed for the completion of the B and C rings of the tetracyclic core of manzamine, as well as those needed to close the 13-membered E ring.

The key transformation accomplished the closing of the C and B rings. This strategy gave Winkler access to tetracyclic ABCD compound 21 with a high degree of stereocontrol over 4 contiguous stereocenters. Introduction of C10 then led to intermediate 22. Installation of the C1 – C2 double bond proved difficult. Low regioselectivity was observed as the undesired α,β-unsaturated ester 23 was major and the desired α,β-unsaturated ester 24 was minor (Scheme 1.3). After introduction of the B ring alcohol functionality, the E ring was closed to yield 26, although in low yield. This remains the problematic step in Winkler’s synthesis, although Winkler reports better results with the cyclization of an acetylenic equivalent of 25 (followed by the reduction of the acetylene to the cis-olefin). Ester 26 was then converted to manzamine A (1) in four steps via ircinal A (4).
Scheme 1.2: Winkler’s synthesis of a Manzamine ABCD core unit.

(a) hv; (b) Pyridine, AcOH (20% from 16); (c) TBSCl (87%); (d) LiHMDS, MeOCOCN (90%).
(a) NaBH₄ (90%); (b) MsCl, Et₃N (95%); (c) DBU (90%, 23:24 = 2:1); (d) MCPBA; (e) NaOMe (69% over 2 steps); (f) TBAF (94%); (g) TsCl, Et₃N (96%); (h) TFA (100%); (i) i-Pr₂NEt (12%); (j) DIBAL-H (83%); (k) Dess-Martin periodinane (90%); (l) tryptamine, TFA; (m) DDQ (50% over 2 steps).

Scheme 1.3: Completion of Winkler’s synthesis of Manzamine A.
1.3.2. Martin’s enantioselective total synthesis of Manzamine A.

Most recently published is Martin’s enantioselective total synthesis of manzamine A. Martin’s strategy rests on: (1) a domino Stille coupling - intramolecular [4+2] Diels-Alder cyclization (29 → 30 → 31) to simultaneously form the A and B rings of manzamine from a substrate (27) containing a preexisting 5-membered C ring precursor, and (2) on olefin metathesis chemistry to form the D and E rings.

The critical domino transformation (Scheme 1.4) furnished tricyclic intermediate 31 as a single compound, thus forming three carbon-carbon bonds in one transformation, stereochemistry at the three new centers (confirmed by NOE experiments) being directed by the single stereocenter in 27. Tricyclic intermediate 31 was converted to 33 in several steps, including allylic oxidation of C3, methylation of the side chains to give 32, and addition of 3-buten-1-yllithium to C3 to yield advanced intermediate 33.

Martin’s original strategy called for the simultaneous closing of the D and E rings by olefin metathesis. Experimental observations of disappointing selectivity, however, suggested this would have to be done in a sequential manner (Scheme 1.5).
Scheme 1.4: Early steps in Martin’s synthesis of Manzamine A.
Thus, tetraene 33 underwent ring-closing metathesis to yield triene 34 as a separable 8:1 mixture of Z and E isomers. After elaboration to 35, the D ring was closed in a similar fashion, though in low yield, to yield 36, which was then converted first to ircinal A (4), and then to manzamine A (1), according to Kobayashi’s published protocols.15

Scheme 1.5: Martin’s completion of Manzamine A.
1.4 Synthetic studies on Manzamine A in the Hart group.

The synthesis of manzamine A (1) has been of interest to the Hart research group for several years. One series of efforts, led most notably by Campbell and Filippini, has followed the retrosynthetic approach described in Scheme 1.6.\textsuperscript{39,40} Disconnection of the E ring, to be installed by organometallic addition to a C\textsubscript{3} carbonyl followed by formation of the C\textsubscript{30}-N\textsubscript{1} bond, led to precursor 37. This enone was to be obtained by 1,2- or 1,4- addition of a β-carboline unit to a suitable α,β-unsaturated carbonyl compound of type 38 or 39. The C ring was to be installed by nucleophilic opening of an epoxide, thus revealing precursor 40. The D ring in 40 was to be installed by organometallic addition to a C\textsubscript{21} carbonyl followed by nucleophilic displacement at C\textsubscript{31}, leading back to precursor 41. In this pathway, success would then partially be dependent on obtaining acceptable diastereoselectivity in the organometallic addition to C\textsubscript{21}. 


Scheme 1.6: Campbell’s Retrosynthetic analysis of Manzamine A.

A synthesis of a compound of type 41 was accomplished in 11 steps and 22% overall yield from benzoic acid (Scheme 1.7). Birch reductive alkylation of benzoic acid (42) yielded 43, which was subjected to iodolactonization to form 44. Radical allylation of 44 yielded 45 with good stereoselectivity (the allyl group was installed into the
equatorial position with 96:4 selectivity). Lactone 45 was then further manipulated to yield 47, including a key reductive amination to close the A ring.

Scheme 1.7: Synthesis of synthetic intermediate 47.

Addition of an appropriate alkynyllithium reagent to 47 yielded alcohols 48 and 49 with modest selectivity (Scheme 1.8). The alkyne in 48 was selectively reduced to the corresponding olefin to yield 50 and 51. These epimers proved separable (although undesired isomer 51 proved resistant to inversion at C21). Mitsunobu – type chemistry converted 50 to 52 with retention of stereochemistry at C21 (a result which can be explained through a double inversion mechanism involving neighboring group
participation of the C₆ carbonyl). After suitable protecting group manipulations, the D ring was successfully closed to form azocine 53, the structure of which was confirmed by X-ray crystallography. Azocine 53 was then deprotected and selectively epoxidized to give 54.

Scheme 1.8: Campbell’s synthesis of an ABD unit of Manzamine.
Deprotection of the azocine nitrogen in 54 was accompanied by nucleophilic opening of the epoxide to yield 55. The B-ring of 55 was transformed into enone 56, a structure of type 39 (see Scheme 1.6). Enone 57 (related to 38), was also synthesized from 55 in two steps, although in modest yield (Scheme 1.9).

(a) MOMCl, i-Pr₂NEt, CH₂Cl₂ (95%); (b) CsF, DMF, Δ (72%); (c) Ac₂O, i-Pr₂NEt, CH₂Cl₂ (93%); (d) TMSCl, NaI, CH₃CN (65%); (e) (COCl)₂, DMSO, CH₂Cl₂ (100%); (f) (COCl)₂, DMSO, CH₂Cl₂ (93%); (g) t-BuOK, t-BuOH, C₆H₆ (43%).

Scheme 1.9: Campbell’s synthesis of ABCD units of Manzamine A.
Attention was then turned (by Filippini) to a strategy for the closing of the 13-membered E ring of manzamine A. As implementation of the originally planned organometallic addition to C₃ proved problematic, it was decided to introduce the E ring in two smaller halves, to be later joined by olefin metathesis or Ramberg-Backlund chemistry. From Campbell’s intermediate 53, with appropriate protecting group manipulations, a 5-carbon unit was introduced at N₁ to afford intermediate 56. The C ring of manzamine was then closed, according to the methodology developed by Campbell, to give diol 59.

\[
\begin{align*}
\text{(a) CAN, } 0^\circ\text{C, CH₃CN, H₂O (40%); (b) KH, 18-Crown-6, PhMe; H₂C=CH(CH₂)₃Br; (c) LiOH, MeOH-THF-H₂O (54% over 2 steps); (d) Mo(CO)₆, t-BuOOH, C₆H₆, } \Delta \text{ (50% + 20% bis-epoxide); (e) CsF, DMF, } \Delta \text{ (85%); (f) iodoxybenzoic acid, DMSO (53%); (g) 2-lithio-1,3-dithiane, THF, -78^\circ\text{C (75%); (h) DMSO, (COCl)₂, Et₃N (55%).}
\end{align*}
\]

**Scheme 1.10: Filippini’s most advanced intermediates.**
As efforts towards direct introduction of a fully formed β-carboline unit were unsuccessful, a dithiane acyl anion equivalent was next employed to introduce C_{10}. Thus, selective oxidation of the C_{1} alcohol, addition of the acyl anion equivalent, and oxidation of C_{3} provided 60, the most advanced intermediate prepared by Filippini. Dehydration of 60 to install a C_{1}-C_{2} double bond, however, proved difficult. Were this dehydration to be accomplished, an appropriate organometallic unit would have to be added to C_{3}, followed by closing of the E ring. Lastly, the β-carboline system would have to be elaborated from the dithiane substructure.

1.5. Latest synthetic efforts towards manzamine A.

1.5.1. Introduction of the problem.

The results described in Schemes 1.7-1.10 set the stage for the research to be described in the initial portion of this thesis. The problem with this approach to manzamine A is its failure to provide good stereocontrol at C_{21} relative to stereogenic centers in the perhydroisoquinoline substructure (Scheme 1.8). Furthermore, the undesired stereoisomer (49 and/or 51) proved resistant to attempts at stereochemical inversion, making much of the synthesized material unusable. The research presented in this chapter focuses on the development of a solution to this problem. The potential solution to be pursued has its roots in chemistry developed by the Ellman and Davis
groups. These groups have shown that reaction of sulfinimines, for example 61, with a variety of nucleophiles provide sulfinamides (63 from 61) with high diastereoselectivity (Scheme 1.11). This chemistry has been applied by these groups to the asymmetric synthesis of substituted α- and β-amino acids and amines. The yields are good and the diastereoselectivity is frequently excellent.43

Application of this methodology to the current problem would require an enantioselective synthesis of an aldehyde of type 64 (Scheme 1.12; see also 47 in Scheme 1.8). Conversion of this aldehyde to an appropriate sulfinimine such as 65, followed by addition of an appropriate organometallic reagent, would be expected to provide 66 if the stereochemistry was controlled by the configuration at the sulfinimine sulfur. This compound could then be used to move on toward ABCD units of manzamine A such as those shown in Scheme 1.9.
1.5.2. Model studies for the first steps.

Given this background, our goal was to develop an enantioselective synthesis an aldehyde of type 64. The plan was to use the basic approach outlined in Scheme 1.7, introducing enantioselectivity at the stage of the reductive alkylation (42→43). This was to be accomplished using chemistry developed by the Schultz group. Schultz had shown that reductive alkylation of amide 67 provided 68 in 97% yield with excellent diastereoselectivity (>98%de). The trimethylsilyl substituent in 67 would introduce the required asymmetry, and could easily be replaced with hydrogen, thus providing an easy fit with our previously established methodology.
Before attempting work with homochiral materials, it was decided to investigate this chemistry in a racemic series (Scheme 1.14). Thus the initial goal became the preparation of amide 69, followed by a study of its behavior under reductive alkylation conditions (69→70), and conversion of a compound of type 70 to a perhydroisoquinoline of type 72 using chemistry similar to that described in Scheme 1.7.
Scheme 1.14: Planned model studies for the first steps.

We began work toward amide 69 as shown in Scheme 1.15. Treatment of benzoyl chloride (73) with pyrrolidine provided amide 74 in 90% yield. It was hoped that ortho-metallation of 74 followed by silylation would provide desired amide 69. Unfortunately, following a procedure developed by Snieckus yielded an intractable mixture of compounds. In an effort to reproduce Snieckus’ results, diethylamide 75 was prepared in quantitative yield as outlined in Scheme 1.15. Metallation of 75 followed by treatment of the reaction mixture with trimethylsilyl chloride gave the expected amide 76 (28%) and o-benzoylbenzamide 77 (21%). Apparently ortho-metallated 75 reacts with 75
itself to provide 77. Although the Snieckus group reported that this transformation (75→76) could be accomplished in 70% yield, we were never able to identify conditions that gave more than 30% of 76.

![Chemical structure image]

(a) Pyrrolidine, NaOH, H2O, 5°C → rt (90%); (b) s-BuLi, TMEDA, THF, -78°C; TMSCl, -78°C → rt; (c) Et2NH, NaOH, H2O, 5°C → rt (100%); (d) s-BuLi, TMEDA, THF, -78°C; TMSCl, -78°C → rt (28% 76 + 21% 77).

**Scheme 1.15: Snieckus ortho-metallation pathway to 69.**

We next turned to an approach that, although longer, more closely mimicked Schultz’s approach to amide 67. This approach follows chemistry developed by Comins, as shown in Scheme 1.16. Treatment of benzaldehyde (78) with the lithium amide derived from N,N,N’-trimethylethylene diamine, followed by directed ortho-metallation of
the resulting intermediate, provided presumed intermediate 79. Silylation of this anion and workup with aqueous acid provided aldehyde 80 in 83% overall yield from benzaldehyde. Oxidation of 80 with potassium permanganate provided the desired acid 81 in modest (37%) yield.

\[
\begin{align*}
&\text{CHO} \\
&\text{78} \\
&\text{COOH} \\
&\text{SiMe}_3
\end{align*}
\]

\[
\begin{align*}
&\text{LiO} \\
&\text{Li} \\
&\text{N} \\
&\text{N} \\
&\text{N} \\
&\text{SiMe}_3
\end{align*}
\]

\[
\begin{align*}
&\text{CHO} \\
&\text{SiMe}_3
\end{align*}
\]

(a) \(N,N,N'\)-trimethylethylenediamide, THF, -10°C; \(n\)-BuLi (2eq), THF; (b) TMSCl, then \(\text{H}_3\text{O}^+\) (83% from 78); (c) KMnO₄, acetone-\(\text{H}_2\text{O}\), rt. (37%).

**Scheme 1.16: The Comins ortho-Metallation.**

Whereas the chemistry described in Scheme 1.16 provided an immediate precursor of target amide 69, the disappointing efficiency of this oxidation, combined with operational difficulties involved in carrying out the ortho-metallation and in scaling the synthesis of 81, led us to consider alternate routes to acid 81. We eventually settled on
metal-halogen exchange chemistry, as developed by Benkeser and Krysiak (Scheme 1.17). Sequential treatment of \( o \)-bromobenzoic acid (82) with \( n \)-butyllithium and trimethylsilyl chloride gave 81 in only 18% yield. When \( o \)-iodobenzoic acid (84) was used as starting material, however, the yield increased to a more acceptable 57%. Conversion of 81 to the corresponding acid chloride, followed by reaction with pyrrolidine provided amide 69 in 94% yield. This synthesis was reproducible on a multigram scale and thus became our method of choice for preparation of the starting material for reductive alkylation studies.

(a) \( n \)-BuLi, \( \text{Et}_2\text{O} \), \(-78^\circ\text{C}\), then \( \text{TMSCl, Et}_2\text{O} \) (18% from 82, 57% from 84); (b) \( \text{CCl}_4 \), \( \text{PPh}_3 \), \( \text{CH}_3\text{CN} \), \( \Delta \), then pyrrolidine, \( 5^\circ\text{C} \rightarrow \Delta \) (94%).

Scheme 1.17: Synthesis of 69 through transmetallation chemistry.
With 69 in hand, we turned to the reductive alkylation step (Schemes 1.18-1.20). Following a small modification of the chemistry described in Scheme 1.7, it was decided to use 2-bromoethyl tert-butyl ether (87) as the alkylating agent. This halide was prepared in 40% yield from 2-bromoethanol and isobutylene as shown in Scheme 1.18.

Scheme 1.18: Synthesis of alkylating agent 87.

Attempts to reductively alkylate 69 with 87 were partially successful. Treatment of 69 with potassium in ammonia and 87 using the Schultz protocol provided the desired product 88 in 33% yield along with a 46% yield of reduction product 89 (Scheme 1.19). The formation of 89 suggests the presence of a proton source in the reaction, perhaps alkylation agent 85 undergoing the elimination reaction shown in Scheme 1.20.

Scheme 1.19: Reductive alkylation of model compound 69.
Scheme 1.20: Dehydrobromination as a possible side reaction.

Although the reductive alkylation was not completely satisfactory, sufficient amounts of 88 were obtained to attempt the halolactonization described in Scheme 1.21. Despite exploring several halonium ion sources, the transformation of 88 to 92 was not accomplished.\textsuperscript{49} For example, iodine in aqueous THF returned the starting amide, as did bromonium di-sym(collidine) hexafluorophosphate. N-Bromosuccinimide in aqueous acetic acid and THF gave a complex mixture of products.

(a) I\textsubscript{2}, THF–H\textsubscript{2}O (returns 77% 88); (b) NBS, AcOH, THF–H\textsubscript{2}O (gives complex mixture of products); (c) Bromonium di-sym(collidine) hexafluorophosphate, CHCl\textsubscript{3} (returns 88).

Scheme 1.21: Halolactonization attempts on model compound 88.
The failure of 88 to undergo halolactonization led us to search for an alternate route from 88 to a compound that could function as an equivalent to 92. With this goal in mind, it was hoped that vicinal dihydroxylation of 88 syn to the carboxamide might provide 93, which was expected to undergo lactonization to provide 94 (Scheme 1.22). The secondary hydroxyl group in 94 could then serve as a precursor of the free radical demanded by the chemistry shown in Scheme 1.7. To this end, 88 was submitted to typical dihydroxylation conditions using catalytic osmium tetroxide and either N-methylmorpholine N-oxide or trimethylamine oxide as stoichiometric oxidant. Instead of diol 93, however, dienone 95 was obtained in 29% yield, along with 54% of recovered 88 (Scheme 1.22). We were able to determine that this reaction is indeed catalyzed by osmium tetroxide (for example omission of OsO₄ provided no 95) but did not further investigate the mechanism of this allylic oxidation.
Scheme 1.22: Attempted dihydroxylation of 88.

In view of the failure of dihydroxylation, we attempted epoxidation of the target double bond in 88 under standard conditions.\textsuperscript{51} The reaction showed no selectivity, however, and afforded a mixture of epoxidation products as well as, more unexpectedly, some dienone 95 (Scheme 1.23).
Scheme 1.23: Attempted epoxidation of 88.
1.5.3 Modified synthetic strategy.

In view of the setbacks described above, we turned to a variation of this strategy (Scheme 1.24). It was imagined that replacement of the trimethylsilyl group with a methoxy group would be productive in the following manner: reductive alkylation of 99 would be followed by protection of the resulting enol ether as an acetal (100) which would allow us to carry a masked C₄ ketone functionality. Iodolactonization of 100 followed by allylation (see Scheme 1.7) would provide 101 which contains the C₅ and C₉ functionality needed to construct the A-ring of the manzamine skeleton. The latent C₄ ketone was to ultimately be used to close the C-ring after construction of the D-ring in the manner described above. Furthermore, we decided to proceed directly with the chiral series, using a chiral auxiliary in place of the pyrrolidine ring of model compound 69.

(a) Reductive alkylation; (b) ketal formation; (c) iodolactonization; (d) radical allylation.

Scheme 1.24: Modified strategy for the early steps towards Manzamine A.
Starting material 99 was easily prepared in two steps according to literature procedures (Scheme 1.25). Treatment of o-anisic acid (102) with thionyl chloride provided the corresponding acid chloride, which reacted with (L)-prolinol to provide amide 103 in 96% yield. Methylation of the primary alcohol in 103 using a standard Williamson ether synthesis provided 99 in 99% yield. Reductive alkylation of 99 with 87 then afforded 104 in a modest 44% yield, consistent with the results obtained with 69 (Scheme 1.19). Whereas literature precedent suggests that this alkylation should have provided the diastereomer shown in Scheme 1.25 with high selectivity, the magnitude and sense of asymmetric induction in this reaction was not proven.

Scheme 1.25: Revised strategy – early steps.

(a) SOCl₂, rt; L-prolinol, Et₃N, CH₂Cl₂, 0°C → rt (96%); (b) NaH, MeI, THF, Δ (99%); (c) K, NH₃, THF, t-BuOH; Br(CH₂)₂Or-Bu (87) (44%).
With 104 in hand, ketal formation was attempted (Scheme 1.26). Treatment of 104 with ethylene glycol and phosphorus oxychloride (catalytic) gave only a 2% yield of the expected ketal 105 along with an 18% yield of lactone 106. One may surmise that the \textit{tert}-butyl ether moiety was cleaved under the acidic conditions, and the resulting alcohol attacked the amide carbonyl group affording the unexpected lactone (106). When 104 was treated with phosphorus oxychloride (catalytic) in methanol, lactone 107 was obtained in 55% yield. This lactone could then be converted to 106, albeit in only an unoptimized 25% yield, under the reaction conditions used for its direct formation from 104.

(a) Ethylene glycol, POCl$_3$, C$_6$H$_6$ (2% 105 + 18% 106); (b) POCl$_3$, MeOH, HC(OEt)$_3$ (55%); (c) Ethylene glycol, POCl$_3$, C$_6$H$_6$ (25% 106).

\textbf{Scheme 1.26: Initial attempt at ketal formation.}
It was clear that the use of a tert-butyl protecting group was problematic. To verify the validity of the strategy outlined in Scheme 1.24, it was decided to examine a system where this problem would not be present. Therefore the “strategy check” shown in Scheme 1.27 was performed. Reductive alkylation of 99 with methyl iodide cleanly afforded 108 in 73% yield, consistent with results published by Schultz. Enol ether 108 was then cleanly converted to the corresponding ketal 109 in an unoptimized 43% yield. Finally, 109 underwent iodolactonization upon treatment with N-iodosuccinimide in aqueous tetrahydrofuran to provide 110 in 44% yield. This reaction sequence indicated that the plan delineated in Scheme 1.24 might be useful, once optimized, if the ether cleavage problem could be circumvented.

(a) K, NH₃, t-BuOH, THF; CH₃I (73%); (b) ethylene glycol, POCl₃, C₆H₆ (43%); (c) N-iodosuccinimide, THF–H₂O (44% + 20% recovered 109).

Scheme 1.27: Strategy check.
To prevent the lactone formation reaction observed in the case of 104 (Scheme 1.26), three other protecting groups (methyl, acetyl, pivaloyl) were investigated. 2-Bromoethyl methyl ether (112) was purchased and 2-bromoethyl acetate (113) and 2-bromoethyl pivalate (114) were synthesized (in 68% and 86% yields, respectively) by acylation of 2-bromoethanol (85) (Scheme 1.28).

![Scheme 1.28: Synthesis of new alkylating agents.](image)

Reductive alkylation of 99 with 112 proceeded (much as with 87) to provide 117 in 45% yield (Scheme 1.29). When 113 and 114 were used as alkylating agents, the yields were much better, providing 115 and 116 in 83% and 81% yields respectively. We note that these reactions closely follow reactions reported by Schultz and indicate that an ester performs much better than an ether as a protecting group in the alkylation step. We also note that once again the %de and sense of asymmetric induction were not determined, although the diastereoselectivity of these alkylations appeared high.
(a) K, NH₃, t-BuOH, THF; Br(CH₂)₂OAc (114) (83%); (b) K, NH₃, t-BuOH, THF; Br(CH₂)₂OPiv (113) (81%); (c) K, NH₃, t-BuOH, THF; Br(CH₂)₂OMe (112) (45%).

Scheme 1.29: New reductive alkylations.

1.5.4. Free ketone strategy.

Attempts to convert enol ethers 115-117 to C₄ acetals using a variety of conditions unfortunately were unproductive (Scheme 1.30). For example, application of standard conditions to 117 provided only ketone 119 in 30% yield. Use of 2,2-dimethylpropane-1,3-diol (with enol ether 115) in place of ethylene glycol failed to provide the desired 120. Attempts to prepare the corresponding thioacetal were also
ineffective. For example, treatment of pivalate 116 with ethane-1,2-dithiol and HCl provided the desired thioacetal 121 (30%), ketone 122 (30%) and recovered starting material (20%).

(a) Ethylene glycol, POCl₃, C₆H₆ (30% 119); (b) 2,2-propane-1,3-diol, HCl, THF; (c) HS(CH₂)₂SH, HCl, CHCl₃ (30% 121 + 30% 122 + 20% returned 116).

Scheme 1.30: Initial attempts at C₄ ketal formation.
We speculate that steric hindrance is at least partially responsible for the difficulties associated with installation of a C₄ acetal, although this cannot be the whole story (note preparation of 105 in a poor yield and 109 and 121 in modest yields). Thus it was decided to attempt to carry the required C₄ functionality as an unprotected ketone, following precedent published by the Schultz group. In particular, as part of a total synthesis of (+)-1-deoxylycorine, Schultz carried out the reaction sequence described in Scheme 1.31. Compound 123 was synthesized from 99 by reductive alkylation, followed by deprotection of the alcohol, conversion to the azide, and hydrolysis of the enol ether to the free carbonyl group (Scheme 1.31). Amide 123 was then converted to iodolactone 124, indicating that a free carbonyl at C₄ might be a viable option for our own studies. This gave us hope, and we proceeded as described in Scheme 1.32.

Scheme 1.31: Schultz’s work as a precedent for carrying C₄ as the free ketone.
Hydrolysis of ester 115 using potassium carbonate in aqueous methanol gave alcohol 125 in 75% yield. To our surprise, however, 125 cyclized to internal acetal 126 when exposed to trace amounts of acid (for example CDCl$_3$) and sometimes on silica gel. Similarly, upon attempted acidic hydrolysis, enol ether 115 gave internal hemiacetal 127 in 21% yield as the major product. This material presumably resulted from double deprotection of 115 followed by cyclization. The desired ketoester 128 was obtained, albeit in only 9% yield, along with 45% of recovered starting material. This small amount of ketone (128) was subjected to iodolactonization conditions (N-iodosuccinimide in aqueous THF), producing iodolactone 129 in low (23%) although unoptimized yield. This result provided an encouraging sign that a free ketone precursor might be converted to a useful halolactone intermediate.
The unexpected formation of 126 and 127 showed that a sturdier protecting group than acetate was needed for the alcohol functionality. This suggested the use of 116 as a starting point. Since intermolecular acetal formation had proven unattainable in our early work (for example Scheme 1.30), it was also decided to investigate use of an internal acetal as a protecting group for both the ketone and alcohol functionality.
1.5.5. Study of internal acetal formation.

The latter possibility was pursued as shown in Scheme 1.33. Treatment of enol ether 125 with catalytic HCl in methanol gave a low yield (28%) of 126. When the solvent was changed to chloroform the yield of 126 remained the same (26%) and hemiacetal 127 was also obtained in 15% yield. Both 126 and 127, however, failed to provide the desired iodolactones (130 and 131 respectively) upon treatment with N-iodosuccinimide in aqueous THF. The reason for the failure of these iodolactonizations may be that success would require iodonium ion formation on the sterically hindered concave side of the 2-oxabicyclo[4.3.0]non-6-ene substructure of 126 or 127.

Scheme 1.33: Study of internal acetal formation.
In parallel studies, another student in the Hart group (John Freed) conducted model studies related to those described in Scheme 1.33. Freed converted o-anisic acid (102) to the corresponding \(N\)-acylpyrrolidine, which was taken on to dihydrobenzoic acid 132 (54% overall yield as shown in Scheme 1.34). Ammonolysis of the acetate followed by HCl-promoted acetal formation gave 133 in variable yields. Vicinal dihydroxylation of 133 followed by lactonization (mediated by methanolic HCl) provided hydroxylactone 134 in 47% yield.

\[
\begin{align*}
&\text{CO}_2\text{H} \quad \text{O} \quad \text{OMe} \\
&\text{102} \\
&\text{AcO} \quad \text{O} \quad \text{N} \quad \text{OMe} \\
&\text{132} \\
&\text{HO}^- \quad \text{O} \quad \text{OMe} \\
&\text{O} \quad \text{O} \\
&\text{O} \quad \text{OMe} \\
&\text{134} \\
&\text{a - b} \quad \text{54\%} \\
&\text{c - d} \\
&\text{e - f} \quad \text{28\%} \\
\end{align*}
\]

(a) SOCl\(_2\); Pyrrolidine, Et\(_3\)N (90%); (b) K, NH\(_3\), \(t\)-BuOH, THF; Br(CH\(_2\))\(_2\)OAc (60%); (c) EtNH\(_2\), EtOH; (d) HCl, MeOH (variable yields from 132); (e) OsO\(_4\), NMO, \(t\)-BuOH–acetone–H\(_2\)O (61%); (f) HCl, MeOH, \(\Delta\) (47%).

**Scheme 1.34: Jake Freed’s model study of internal acetal use.**
Although this model study shows that it is possible to obtain a lactone that might be used to move forward toward an aldehyde of type 64 (Scheme 1.12), the difficulties encountered along the way (low and variable yields, sensitive compounds and difficult purifications) led to the abandonment of this line of investigation and our turning to the aforementioned potential of 116 (*vide supra*).

1.5.6. Successful iodolactone synthesis – unexpected allylation results.

Following our results with 115, we turned to pivaloyl-protected compound 116. Enol ether 116 could be hydrolyzed in aqueous methanolic HCl to yield ketone 135 in 86% yield (Scheme 1.35). This was followed by another gratifying result: iodolactonization of 135 under standard conditions provided 136 in 83% yield. Thus, the stage was finally set to proceed with the free radical allylation critical to the synthesis of the target perhydroisoquinoline substructure of manzamine A.
Scheme 1.35: Successful synthesis of iodolactone 136, and unexpected results.

Submission of 136 to standard Keck free radical allylation conditions (allyltri-$n$-butylstannane, AIBN, benzene at reflux) provided a surprise.$^{53}$ A single compound with a molecular formula $\text{C}_{17}\text{H}_{24}\text{O}_{5}$ (by MS) was obtained in 94% yield. Unfortunately this compound turned out not to be the expected allylation product 137. Whereas NMR spectral data were largely consistent with this structure, there were some glaring discrepancies. Most suspicious was the clear insulation of the spin system derived from $\text{C}_{17}\text{H}_{24}\text{O}_{5}$.
the allyl group from the remainder of the molecule by a quaternary center. This was apparent from $^1$H and $^{13}$C NMR 1-dimensional and 2-dimensional (COSY) spectra. It was ultimately determined that structure 138 best fit the spectral data. In addition, X-ray crystallographic analysis of the ketal (139), derived from this compound, confirmed the structure of the allylation product (Figure 1.2). The formation of 138 from 136 can be rationalized by the intervention of a Beckwith-Dowd rearrangement prior to free radical allylation. This result will be discussed in greater detail in Chapter 2 of this thesis.

The formation of 138 from 136 most likely involves initial conversion of the iodide into a free radical and subsequent addition of that radical to the C$_4$ carbonyl group (vide infra). Conversion of the C$_4$ carbonyl group to the corresponding ketal would presumably prevent the addition reaction and allow for the desired allylation. Thus protection of the C$_4$ carbonyl group was examined (Scheme 1.36). These attempts, however, were unsuccessful, even under the popular conditions developed by Noyori (TMSOCH$_2$CH$_2$OTMS, TMSOTf).$^{54}$
Figure 1.2: ORTEP drawing of ketal 139.

Scheme 1.36: Last attempts at C₄ acetal formation.

46
Attempts to mask C₄ carbonyl group by reduction to the corresponding alcohol were more successful (Scheme 1.37). Treatment of 136 with sodium borohydride in aqueous methanol provided alcohol 142 in 35% yield. Protection of the alcohol as an acetate gave 143 in 78% yield. Unfortunately, attempted radical allylation of this substrate failed to provide the desired product 144.

Scheme 1.37: Protection of C₄ as acetylated alcohol.

1.6. Conclusion.

This discouraging result led us to abandon this project and indeed, this approach to manzamine A (1). While it was disappointing to not be able to evaluate the problem and solution set forth in Schemes 1.8 and 1.12, this research did uncover an unusual and unexpected example of the Beckwith-Dowd rearrangement and a new route to highly functionalized 2-oxabicyclo[3.3.0]octan-3,6-diones (see Scheme 1.35). An exploration of the scope and limitations of this process will be the topic of the next chapter of this thesis.
2.1. The Dowd rearrangement – a brief introduction.

This chapter will describe a study of the scope and limitations of an interesting rearrangement discovered during the course of the aforementioned studies directed towards manzamine A and introduced in scheme 1.35. This reaction represents a complex example of the Dowd rearrangement (sometimes referred to as the Beckwith–Dowd rearrangement).55 To place this work in perspective for the reader, a brief introduction to the Dowd rearrangement will be presented here. The reader is referred to a detailed review for a more comprehensive introduction to this topic.56

The Dowd rearrangement involves transformation of a β-keto radical such as 145, to a β-keto radical such as 147, via intermediacy of a cyclopropyloxido radical such as 146 (Scheme 2.1). Many variations of this reaction have been reported where other
functional groups such as alkenes or alkynes, nitriles, or imines play the role of radical acceptor.

Scheme 2.1: Proposed mechanism for the Dowd rearrangement.

Several examples of the Dowd rearrangement, demonstrating the versatility of this reaction, are shown in Scheme 2.2. Ring expansion reactions, such as the conversion of 148 to 149 in the case of a one-carbon expansion (the original reaction published by Dowd), the application of this one-carbon expansion to a synthesis of the carbon skeleton of manicol (150 → 151), and the conversion of heterocyclic substrate 152 to 153 are illustrative. The conversions of 154 to 155 and 156 to 157 (the example originally published by Beckwith) extend this rearrangement to a three-carbon expansion. Tandem ring expansion-annelation reactions, such as the conversion of 158 to 159, have also been reported.
Scheme 2.2: Selected examples of the Dowd reaction.
2.2. Initial observations.

Although the unexpected conversion of 136 to 138 spelled failure for our approach to manzamine A, this efficient reaction seemed interesting in itself, as 138 was produced in excellent yield and as a single isomer. The assigned relative stereochemistry of 138 was supported by NOE difference experiments. For example, irradiation of H₅ showed enhancement of the signal due to H₁ (2.6%), suggesting a cis relationship between these protons (see Scheme 2.3). Irradiation of H₁ also showed an enhancement of the H₁₁ protons (1.8%), while irradiation of either H₁ or H₅ gave rise to no enhancement of the signal for H₉, suggesting a cis relationship between the allyl group and the H₁ and H₅ protons. This stereochemical assignment was further supported by X-ray crystallography of acetal derivative 139 (see Figure 1.2).

Based on the commonly accepted mechanism for the Dowd-Beckwith rearrangement (Scheme 2.1), a mechanism can be proposed for this reaction as outlined in Scheme 2.3. Iodine abstraction by tri-n-butylstannyl radical affords β-keto radical 160. Radical addition to ketone, forming the C₅–C₆ bond, gives cyclopropyloxido radical 161, in which the bicyclic skeleton of 138 is apparent. Fragmentation of the C₄–C₆ bond yields β-keto radical 162. Allylation from the most accessible face of 162 produces 163, which upon fragmentation produces the observed product 138.

To further explore the potential of this novel variant of the Dowd-Beckwith rearrangement, it was decided to carry out a study of radical allylations and reductions of
substrates of type 136 with varying substitution patterns. A description of these studies will be the subject of this chapter.

Scheme 2.3: Proposed mechanism for the formation of 138.
2.3. Radical reduction experiments with iodolactone 136.

We began by examining the behavior of 136 upon treatment with tri-\textit{n}-butylstannane. The purpose of this study was to probe the relative rates of the rearrangement \textit{vs.} reduction of iodolactone 136. Three experiments were carried out under different reaction conditions (Scheme 2.4). When 136 was treated with tri-\textit{n}-butylstannane\textsuperscript{62} (1 equivalent) under dilute conditions (10 mM), a rearrangement similar to that which produced 138 was observed. This reaction gave lactone 164 as a single isomer in moderate (46\%) though unoptimized yield. The relative stereochemistry of 138 was established by NOE difference experiments. Irradiation of H\textsubscript{1} yielded an enhancement of the signals from H\textsubscript{4} and H\textsubscript{5} (2.6\%), but no enhancement of the H\textsubscript{9} methylene signal, suggesting an all-\textit{cis} relationship between H\textsubscript{1}, H\textsubscript{4} and H\textsubscript{5}. When the same reaction was run at higher concentration (1 M, 5 equivalents of \textit{n}-Bu\textsubscript{3}SnH), reduction of the C-I bond took precedence over the rearrangement process, yielding lactone 165 in 74\% yield, in which the C\textsubscript{6} ketone was also reduced to the corresponding alcohol. The C\textsubscript{6} stereochemistry of 165 was established by \textsuperscript{1}H NMR NOE difference experiments: irradiation of H\textsubscript{6} gave rise to no discernible enhancements of either H\textsubscript{1} or H\textsubscript{9}. Under intermediate conditions (10 mM, 5 equivalents of \textit{n}-Bu\textsubscript{3}SnH), a 1.6:1 (68\% combined yield) mixture of 164 and ketone 166 was obtained. The identity of 165 and 166 was further confirmed by the Dess-Martin oxidation of 165 to 166 in 68\% yield.\textsuperscript{63}
2.4. Varying substitution patterns.

2.4.1 Synthesis of starting materials.

We next decided to examine the rearrangement of additional iodolactones structurally related to 136. Compounds 167 and 168 were chosen with an eye on examining increasing substitution at C₁ and C₅, respectively (Figure 2.1). The syntheses...
of \(167\) and \(168\) were carried out from appropriate benzoic acid starting materials in a manner similar to that used to prepare \(136\).

![Substrates chosen for rearrangement study.](image)

Iodolactone \(167\) was synthesized in five steps from 2-bromo-3-methoxytoluene \(169\) (Scheme 2.5). Thus, metal-halogen exchange with \(n\)-butyllithium, followed by quenching of the resulting aryllithium with \(CO_2\), yielded carboxylic acid \(170\) in 72% yield. This acid was converted to amide \(171\) in good yield (90%) via conversion to the corresponding acid chloride followed by treatment with pyrrolidine. Amide \(171\) was then treated with potassium in ammonia followed by iodomethane, to give diene \(172\) in 80% yield. The enol ether functionality in \(172\) was hydrolyzed using aqueous \(HCl\) to furnish ketone \(173\) in 98% yield. Iodolactonization of \(173\) gave the desired substrate \(167\), in excellent yield (95%).
Scheme 2.5: Synthesis of rearrangement substrate 167.

The synthesis of 168 began with the preparation of carboxylic acid 179 from p-methoxybenzyl bromide (174) in five steps (Scheme 2.6) according to a published procedure.\(^6\) Thus, 174 was converted to quaternary ammonium salt 175 (95% yield) by reaction with trimethylamine. Treatment of 175 with sodium amide in refluxing ammonia effected rearrangement to amine 176 (96%), which bears the desired C\(_1\) methyl substituent. Amine 176 was in turn quaternized using excess iodomethane to give
ammonium iodide 177 in 93% yield. Rearrangement of 177 to amine 178, bearing the desired C\textsubscript{1} and C\textsubscript{5} methyl substitution pattern, was accomplished by treatment with sodium amide in good yield (84%). Amine 178 was then oxidized with potassium permanganate to give carboxylic acid 179 in 50% yield.

\begin{align*}
\text{[Br]}_\text{174} & \xrightarrow{\text{a}} 95\% \xrightarrow{\text{I}} \text{[Me\textsubscript{3}N]}_\text{175} \xrightarrow{\text{b}} 96\% \xrightarrow{\text{Me\textsubscript{3}N}} \text{[OMe]}_\text{176} \\
\text{[H\textsubscript{3}C-CO\textsubscript{2}H}_\text{179} & \xrightarrow{\text{c}} 93\% \xrightarrow{\text{I}} \text{[NMe\textsubscript{2}]}_\text{178} \xrightarrow{\text{d}} 84\% \xrightarrow{\text{K}} \text{[H\textsubscript{3}C]}_\text{177}
\end{align*}

(a) NMe\textsubscript{3}, CH\textsubscript{3}CN–H\textsubscript{2}O (95%); (b) NaNH\textsubscript{2}, NH\textsubscript{3}, Δ (96%); (c) CH\textsubscript{3}I, CH\textsubscript{3}CN (93%); (d) NaNH\textsubscript{2}, NH\textsubscript{3}, Δ (84%); (e) KMnO\textsubscript{4}, NaOH, H\textsubscript{2}O (50%).

**Scheme 2.6: Synthesis of carboxylic acid 179.**

Carboxylic acid 179 was then converted to the corresponding amide 180 in 61% yield via reaction of an intermediate acid chloride with pyrrolidine (Scheme 2.7). Amide 180 was subjected to reductive alkylation with potassium in liquid ammonia followed by iodomethane, to provide diene 181 in 64% yield. Hydrolysis of 181 was accomplished
with aqueous HCl in good yield (95%), and resulting ketone 182 was lactonized with iodine to give desired rearrangement substrate 168 in 83% yield.

(a) SOCl₂; pyrrolidine, Et₃N, CH₂Cl₂, 0 °C → rt (61%); (b) K, NH₃, t-BuOH, THF, -78 °C; CH₃I (64%); (c) HCl, THF–H₂O (95%); (d) I₂, THF–H₂O (83%).

Scheme 2.7: Synthesis of rearrangement substrate 168.
2.4.2. Rearrangement studies – radical allylation reactions.

With substrates 167 and 168 in hand, we turned our attention to the study of radical allylation reactions. Under the conditions which initially produced 138 (allyltri-\textit{n}-butylstannane, AIBN, refluxing benzene), 167 and 168 were converted to rearranged allylation products 183 and 184, respectively (Scheme 2.8). Although yields were low (37% and 18% respectively), the rearrangement products were obtained, in each case, as a single stereoisomer. The assignment of relative stereochemistry depicted in Scheme 2.8 was supported by NOE difference experiments. In the case of 183, irradiation of H\textsubscript{5} gave enhancement of the signals due to H\textsubscript{13} (1.0%) and H\textsubscript{11} (0.6%), stronger than that due to H\textsubscript{9} (0.3%). Similarly, irradiation of H\textsubscript{13} showed enhancement of the H\textsubscript{5} signal (1.7%), but no enhancement for H\textsubscript{9}. This suggests an all-\textit{cis} relationship between the C\textsubscript{13} methyl group, H\textsubscript{5}, and the allyl group. In the case of 184, irradiation of H\textsubscript{14} showed enhancement of H\textsubscript{13} (2.3%) and H\textsubscript{11} (0.9%), while irradiation of H\textsubscript{13} showed enhancement at H\textsubscript{14} (1.8%), but very little enhancement at H\textsubscript{9} (0.3%), suggesting the all-\textit{cis} arrangement between C\textsubscript{13}, C\textsubscript{14}, and the allyl group.

These studies show that the rearrangement-allylation under investigation has some generality. The yields seem to be sensitive to steric effects, however, as increased substitution adversely affects the efficiency of the reaction. It is worth noting that compound 183 contains two contiguous quaternary stereocenters, and that compound 184 contains three contiguous quaternary stereocenters.
2.4.3. Rearrangement studies – radical reduction reactions.

Next, we examined the radical reduction of substrates 167 and 168 (Scheme 2.9). The reductions were carried out under dilute (10 mM) conditions, as earlier results on the reduction of 136 (Scheme 2.4) indicated that this would maximize the opportunity for rearrangement. Thus, when 167 was subjected to the radical reduction conditions (tri-n-butylstannane, AIBN, refluxing benzene), a 4:1 mixture of diastereomers 185 and 186 was obtained in 78% yield. Under the same conditions, 168 gave a 9:1 mixture of rearrangement products 187 and 188 in 74% yield. In both cases, the major diastereomer was the one arising from capture of the intermediate rearranged β-keto radical from the most accessible face. Product ratios were determined on the basis of $^1$H NMR
spectroscopy. In all cases, the assignment of relative stereochemistry was supported by $^1$H NMR NOE difference experiments. In the case of 185, irradiation of $H_{10}$ showed enhancement of the signals due to $H_5$ (1.1%) and $H_4$ (1.0%) but only a very weak enhancement of the signal due to $H_9$ (0.1%). This suggested the all-cis arrangement of $H_4$, $H_5$, and $H_{10}$ as shown in Scheme 2.9. In the case of 186, irradiation of $H_9$ gave rise to enhancement of the $H_5$ signal (1.2%) and of the $H_{10}$ signal (0.5%), but irradiation of $H_{10}$ showed no enhancement of the $H_4$ signal, suggesting the all-cis configuration of $H_5$, $H_9$, and $H_{10}$. In the case of 187, irradiation of $H_{10}$ enhanced the signals from $H_{11}$ (1.7%) and $H_4$ (0.9%), but only a very weak enhancement of the signal from $H_9$ (0.2%) was observed, consistent with the all-cis arrangement of $H_{10}$, $H_{11}$, and $H_4$ shown in Scheme 2.9. In the case of 188, irradiation of $H_{11}$ showed enhancement of the signals due to $H_9$ (0.9%) and $H_{10}$ (1.3%), but no enhancement of the signal due to $H_4$, suggesting an all-cis relationship between $H_{10}$, $H_{11}$, and $H_9$.

The higher selectivity observed in the reduction of the more substituted 168 (relative to 167) indicates this process is also somewhat sensitive to steric effects. This correlates with the fact that a single rearranged isomer was obtained from the reduction of 136, which possesses a larger C4 substituent.
2.5. Conclusions.

We have briefly examined the scope of this novel variant of the Dowd-Beckwith rearrangement, and determined some of its limitations. In most cases this reaction proved efficient, although steric effects seemed to adversely affect yields. Most notable is the formation of compound 184, a compound with three contiguous stereocenters, obtained through a nontrivial synthesis pathway.
CHAPTER 3

STUDIES TOWARDS A TOTAL SYNTHESIS OF CYLINDROSPERMOPSIN

3.1. Introduction

3.1.1. Isolation and characterization of cylindrospermopsin.

Cylindrospermopsin\textsuperscript{65} (CYN, Figure 3.1) was originally isolated from the blue alga \textit{Cylindrospermopsis Raciborskii} by Ohtani and Moore in 1992,\textsuperscript{66} and was identified as the causative agent behind a 1979 outbreak of hepatoenteritis on Palm Island, Australia. The structure of cylindrospermopsin, initially based on NMR spectroscopy, UV spectroscopy, and mass spectrometry, was then thought to be 190. The relative stereochemistry was assigned mainly on the basis of \textsuperscript{1}H NMR coupling constants and NOE experiments. However, the absolute configuration of cylindrospermopsin was then unknown. The stereochemistry at C\textsubscript{7} was also in some measure of doubt, as it had been assigned mainly on the basis of the observed 4.0 Hz \textsuperscript{1}H NMR coupling constant between the C\textsubscript{7} and C\textsubscript{8} hydrogens, and on the basis of somewhat unusual chemical shifts for several protons. It was postulated that cylindrospermopsin existed as shown in Figure 3.1 with a hydrogen bond between the guanidine functional group and the enol tautomer of
the uracil ring. This would have explained both the observed chemical shifts and coupling constants.

![Chemical structures](image)

**Figure 3.1: Cylindrospermopsin (CYN) and 7-epi-cylindrospermopsin (ECYN).**

In 2001, however, the relative stereochemistry of CYN was revised by Weinreb and coworkers, who accomplished a total synthesis of racemic cylindrospermopsin and found its structure to correspond to 190 (see below). In the same year, White and coworkers accomplished an asymmetric total synthesis of (-)-ECYN. This allowed them to establish its absolute configuration as shown in Figure 3.1 (190). This also implied that CYN has the absolute configuration shown in Figure 3.1 (189).

CYN was subsequently isolated from *Umezakia Natans* by Ohtani and coworkers in 1994, and from *Aphanizomenon Ovalisporum* by Sukenik and coworkers in 1997. In addition, 7-epicylindrospermopsin 190 (ECYN) was isolated in 2000 from *Aphanizomenon Ovalisporum* by Carmeli and coworkers, and 7-deoxycylindrospermopsin was isolated in 1999 from *Cylindrospermopsis Raciborskii* by Shaw and coworkers.
3.1.2. Toxicity of cylindrospermopsin.

Since the original Palm Island incident, cylindrospermopsin has been linked to several other incidents involving human and animal toxicity. The in vitro toxicity (LD$_{50}$) of cylindrospermopsin in mice has been found to be 52 mg/kg at 24 h, and 32 mg/kg at 7 days, by intraperitoneal injection.$^{72}$ Toxicology studies have shown that cylindrospermopsin affects principally the liver, though other organs, such as the kidney, spleen, thymus, and the heart are also affected.$^{73}$ CYN has shown hepatotoxicity in mice, and its mechanism of action has been shown to involve depletion of glutathione levels in hepatocytes.$^{74}$ There is also evidence that cylindrospermopsin only becomes toxic after activation by the cytochrome P 450, and that its mechanism of action involves inhibition of protein synthesis, possibly through the binding of metabolites to DNA or RNA.$^{75}$ Renal toxicity of CYN in mice has also been shown, as well as toxicity to brine shrimp.$^{76,77}$ Recently, preliminary evidence was presented for in vivo carcinogenic activity of cylindrospermopsin in mice.$^{78}$

The uracil moiety of cylindrospermopsin was shown by Carmeli and coworkers to be required for its toxicity, as a truncated derivative lacking the D ring proved to be nontoxic, as did 5-chlorocylindrospermopsin.$^{79}$ Both derivatives were obtained by treatment of cylindrospermopsin with chlorine. Interestingly, 7-deoxycylindrospermopsin was also found to be nontoxic, indicating that the C$_7$ oxygen was somehow critical for the toxicity of cylindrospermopsin. As a result of its toxicity, several methods have been developed for the detection and removal of cylindrospermopsin present in the water supply.$^{65b}$
3.1.3. Cylindrospermopsin biosynthesis

The biosynthesis of cylindrospermopsin was investigated by Moore and coworkers and can be summarized as shown in Scheme 3.1.\textsuperscript{80} Feeding experiments indicated a polyketide origin, with the proposed starter unit 191, guanidinoacetic acid and five acetate units. The C\textsubscript{13} methyl group appears to originate from S-adenosylmethionine. No evidence is as yet available regarding the mode of construction of the D ring.

![Scheme 3.1: Proposed biosynthesis of cylindrospermopsin.](image-url)

Scheme 3.1: Proposed biosynthesis of cylindrospermopsin.
3.2. Synthetic studies towards cylindrospermopsin.

Cylindrospermopsin’s novel structure and dense and diverse functionality, including a guanidine functional group as part of its tricyclic core and six chiral carbons, make it a challenging and interesting synthetic target. Three total syntheses have been published by Snider, Weinreb, and White as detailed below. Synthetic studies have also been published by Armstrong, Williams, and by Hart. Whereas the Armstrong and Williams approaches will not be described here, studies from the Hart group will be discussed to provide the reader with a perspective of the research described in this thesis.

3.2.1. Snider’s synthesis of cylindrospermopsin.

The Snider group published a total synthesis of racemic cylindrospermopsin in 2000. The synthesis rests on addition of organometallic reagents to a pyridine starting material to stereospecifically generate the A ring of cylindrospermopsin, and nucleophilic displacement on an α-bromoketone to close the B ring.

![Scheme 3.2: Snider’s synthesis of the A ring of cylindrospermopsin.](image-url)
Thus from pyridine 193, containing the C₁₂ oxygen and C₁₃ methyl groups, addition of trimethylsilylethynylmagnesium bromide to C₁₀, followed by stereoelectronically directed axial addition of allylmagnesium bromide to C₁₄, yielded ketone 194 (Scheme 3.2). Upon deprotection of the nitrogen in 194 under acidic conditions, the C₁₃ methyl group equilibrated to the less strained equatorial position. Stereoselective reduction of the C₁₂ carbonyl provided 195 containing the four chiral centers of the A ring of cylindrospermopsin. The stereochemistry was confirmed by analysis of $^1$H NMR coupling constants.

Protection of the nitrogen and oxygen in 195, followed by coupling with an appropriate D-ring aldehyde and protection of the resulting alcohol, led to intermediate 197 as a mixture of C₇ epimers (Scheme 3.3). Selective ozonolysis of the 197 alkene, followed by reductive amination of the resulting aldehyde gave diamine 198. Reduction of the alkyne triple bond and hydrogenolysis of the N-benzyl group gave a diamine, which upon reaction with cyanogen bromide and bis-carbobenzoxylation gave compound 199, containing the guanidine functional group and the C-ring of cylindrospermopsin.
Scheme 3.3: Snider’s progression to an ACD-ring intermediate to CYN.

Deprotection of the C\textsubscript{7} oxygen, followed by selective oxidation of the pseudobenzylic alcohol to the corresponding ketone and protection of the C\textsubscript{12} oxygen as the acetate, gave ketone 200 (Scheme 3.4). This intermediate was brominated \(\alpha\) to the C\textsubscript{7} carbonyl and the guanidine in the resulting bromoketone was deprotected by catalytic hydrogenation. The presumed intermediate guanidine cyclized to yield 201 as a separable 3:2 mixture of C\textsubscript{8} isomers. The stereochemistry in 201 at C\textsubscript{7} was assigned on the basis of \(^1\text{H}\) NMR coupling constants. Upon deprotection and functional group manipulation, 201 was converted to racemic 190. Overall, Snider’s synthesis of (\(\pm\))-190 was accomplished
in 21 steps with an overall yield of 1.0%. Recall that at the time Snider’s studies were carried out, 190 was thought to be the structure of cylindrospermopsin.

(a) TBAF, THF (83%); (b) MnO₂, CH₂Cl₂ (87%); (c) Ac₂O, pyridine (87%); (d) CuBr₂, EtOAc; (e) H₂, Pd(OH)₂/C, MeOH (42% from 200); (f) concentrated HCl, Δ; (g) SO₃•DMF, pyridine, DMF (60-80% from 201).

Scheme 3.4: Completion of Snider’s synthesis of (±)-190.
3.2.2. Weinreb’s synthesis of cylindrospermopsin

Weinreb and coworkers published a total synthesis of cylindrospermopsin in 2002.\textsuperscript{86} This synthesis rests upon a stereospecific intramolecular $N$-sulfinylurea Diels-Alder cycloaddition to install the B ring of cylindrospermopsin, followed by a Grignard ring opening–allylic sulfoxide [2,3]-sigmatropic rearrangement sequence to reach an intermediate possessing appropriate functional groups for installation of the C\textsubscript{7} oxygen and the D ring.

Weinreb’s synthesis started from commercially available 4-methoxypyridine (202). This starting material contains the impending A ring with C\textsubscript{12} oxygen functionality in place (Scheme 3.5). Activation of the pyridine by $N$-acylation followed by Grignard addition to introduce C\textsubscript{15}, and enolate alkylation to introduce the C\textsubscript{13} methyl substituent with the requisite trans stereochemistry, gave enone 203 in 83\% yield. Stereoselective conjugate addition of a vinyl cuprate to 203 introduced C\textsubscript{8} and C\textsubscript{9} with the desired stereochemistry. Stereoselective reduction of the C\textsubscript{12} carbonyl gave the corresponding alcohol, which was protected to yield intermediate 204 in 74\% yield. This intermediate comprised the complete A ring of cylindrospermopsin with all stereocenters set and with functional groups needed for elaboration.
Scheme 3.5: Early steps in Weinreb’s synthesis of cylindrospermopsin.

Tamao oxidation of 204 led to carbamate 205 in 88% overall yield. Elaboration of the vinylic side chain by hydroboration-oxidation and Wittig olefination gave \( \alpha,\beta \)-unsaturated ester 206 in 65% yield. Reduction of the ester to the alcohol was followed by protection as the \( p \)-methoxybenzyl ether. The carbamate ring was hydrolyzed, the resulting alcohol was protected as the benzyl ether, and the amine was converted to the corresponding urea to yield cyclization precursor 207.
Weinreb then moved on to the key hetero-Diels-Alder reaction (Scheme 3.6). Treatment of \(207\) with thionyl chloride produced cycloadduct \(209\) in 81% yield as a single isomer, presumably through N-sulfinylurea \(208\). The structure of \(209\) was confirmed by X-ray crystallography of deprotected alcohol \(210\). Treatment of \(209\) with phenylmagnesium bromide and subsequent sigmatropic rearrangement of the resulting allylic sulfoxide led to alcohol \(211\) in 84% yield.

Cyclic urea \(211\) was converted to \(N,O\)-acetal \(212\) (Scheme 3.7), which was elaborated in several steps to \(\alpha,\beta\)-unsaturated ester \(213\). The D-ring was built by conjugate addition of a protected hydroxylamine into \(213\), yielding \(214\), followed by
treatment with phenyl chloroformate and ammonium hydroxide to yield 215. Dehydration of 215 gave uracil 216.

(a) Me₂C(OMe)₂, CSA, acetone (93%); (b) DDQ, H₂O, CH₂Cl₂ (78%); (c) Dess-Martin periodinane; (d) NaClO₂, t-BuOH, H₂O; (e) i-Pr₂NEt, MeI, DMF (81% over 3 steps); (f) TMSNHTMS, THF, EtOH (82%); (g) PhOCOCl, NEt₃, THF; (h) NH₄OH, i-PrOH (65% over 2 steps); (i) Tf₂O, pyridine, CH₂Cl₂ (73%).

Scheme 3.7: Weinreb’s construction of the D ring of cylindrospermopsin.

Weinreb finally turned to the construction of the C ring of cylindrospermopsin (Scheme 3.8). To that end, the uracil hydroxyl groups in 216 were protected, the C₁₅ oxygen was deprotected (X-ray crystallography of the resulting alcohol 217 provided structure confirmation) and converted to the corresponding azide, and the acetonide was hydrolyzed to yield intermediate 218. The urea was activated with MeOTf, followed by
catalytic hydrogenation of the azide to form the desired guanidine functionality and close the C ring. MOM deprotection afforded a diol which was found to differ from the corresponding intermediate in Snider’s synthesis of cylindrospermopsin. This diol exhibited spectral data which better fit the data for natural 7-epicylindrospermopsin 190 than for cylindrospermopsin 189. Indeed, conversion of the diol to the monosulfate furnished 7-epicylindrospermopsin (190).

When $N,O$-acetal 216 was hydrolyzed, the C7 alcohol was inverted via Mitsunobu chemistry, and the C ring was closed in the same manner described above (Scheme 3.8), diol 220 was obtained. Guanidinium chloride 220 proved to be spectroscopically identical to the penultimate intermediate in Snider’s total synthesis of 190. Weinreb’s stereochemical reassignment of 189 and 190 was confirmed by the X-ray crystallographic analysis of intermediate 219.
Scheme 3.8: Weinreb’s completion of 220 and 7-epicylindrospermopsin.
3.2.3. White group synthesis of 7-epicylindrospermopsin.

In 2002, White and Warren reported a synthesis of cylindrospermopsin that rests on an intramolecular nitrone cycloaddition to form the A ring.\textsuperscript{87} Thus, condensation of hydroxylamine 221 (carrying C\textsubscript{11}–C\textsubscript{15} of cylindrospermopsin) with aldehyde 222 (carrying the D ring in protected form and carbons C\textsubscript{7}–C\textsubscript{10}) produced nitrone 223 (Scheme 3.9) in 60% yield. Nitrone 223 then cyclized upon heating in toluene to afford bicyclic compound 224. Reduction of the N-O bond and removal of the N-BOC group yielded piperidine 225 (68% overall), containing the newly formed A ring of cylindrospermopsin with correct stereochemistry at all centers except for C\textsubscript{12}.

Diamine 225 was then converted to cyclic urea 226 in 85% yield. The C\textsubscript{12} alcohol was then adjusted to the desired cylindrospermopsin configuration by oxidation to the corresponding ketone and stereoselective reduction to yield diol 227 after removal of the benzyl protecting group. The relative stereochemistry of 227 was verified by X-ray crystallography.
Scheme 3.9: White’s synthesis of an ABD intermediate towards CYN.
The primary alcohol of 227 was converted to the corresponding azide (Scheme 3.10), the C12 alcohol was protected, and the urea was O-methylated to give intermediate 228. Reduction of the azide was followed by cyclization to form the C ring of cylindrospermopsin (229). Functional group manipulations then led White to 7-epicylindrospermopsin 190 in a total of 22 steps (longest linear sequence from commercially available materials) with an overall yield of 0.4%. The compared specific rotations for the natural and synthetic materials established the absolute stereochemistry of the cylindrospermopsin alkaloids to be as shown.

(a) (Cl$_3$CO)$_2$CO, THF; NaN$_3$, DMF (49%); (b) TESOTf, Et$_3$N, CH$_2$Cl$_2$ (99%); (c) KHMDS, Me$_3$OBF$_4$, CH$_2$Cl$_2$; (d) Pd/C, H$_2$, MeOH; (e) conc. HCl, Δ (21% over 3 steps); SO$_3$•pyridine, DMF (63%).

Scheme 3.10: White’s completion of 7-epicylindrospermopsin.
3.3. Hart group approach to cylindrospermopsin.

3.3.1. Initial approach.

The initial approach reported by the Hart group is outlined retrosynthetically in Scheme 3.11. Disconnection of the C and A rings led back to intermediate 230. The A ring was to be closed through an electrophile-initiated cyclization. Disconnection of the B ring in 230 suggested precursor 231, the B ring to be closed through an intramolecular conjugate addition into a vinlypyrimidine system. The C7 oxygen was to be installed after cyclization. C12 and C13 were to be installed via Roush crotylboronation chemistry on the aldehyde derived from oxidative cleavage of alkene 232.

Scheme 3.11: Hart’s initial retrosynthetic approach to cylindrospermopsin.
It should be noted at this stage that 190, which was at the time thought to be cylindrospermopsin, was proved in the interim to be 7-epicylindrospermopsin. Thus, Hart’s route became a strategy for the synthesis of 7-epicylindrospermopsin.

Prompted by the results of model studies carried out by Erick Young, which indicated that the proposed formation of the B ring by conjugate addition was feasible, Jane Djung began a synthesis of a racemic 232-like system (Scheme 3.12). Thus, dimethyl malonate 233 was alkylated twice, after which hydrolysis and decarboxylation furnished carboxylic acid 234 in 56% yield. The carboxylic acid functional group was converted to a urea through Curtius rearrangement chemistry, after which the D ring was introduced in protected form by a Sonogashira coupling to yield intermediate 235 (77% from 234). Upon treatment with sodium hydride, 237 cyclized efficiently to yield enamide 236 in 97% yield.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
233 & \quad \rightarrow \quad a-d \\
& \quad 51\% \\
\text{CO}_2\text{H} & \quad \text{CH}_2=\text{CHCH}_2\text{Br} \\
234 & \quad \rightarrow \quad e-i \\
& \quad 77\% \\
\text{NH}_2 & \quad \text{NH} \\
236 & \quad \rightarrow \quad j \\
& \quad 97\% \\
\text{NH}_2 & \quad \text{NH} \\
235 & \\
&
\end{align*}
\]

(a) NaH, THF; H$_2$C=CHCH$_2$Br; (b) NaH, THF; HC≡CCH$_2$Br (57% from 233); (c) NaOH, THF–H$_2$O; (d) Δ (90% over 2 steps); (e) SOCl$_2$; (f) NaN$_3$, acetone–H$_2$O; (g) C$_6$H$_6$, Δ; (h) NH$_3$, THF (86% from 234); (i) PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N, THF, 6-bromo-2,4-dimethoxypyrimidine (90%); (j) NaH, THF (97%).

**Scheme 3.12: Djung’s synthesis of the B ring of Cylindrospermopsin.**
The C₇ oxygen was then introduced by a regioselective oxidation of the enamide double bond in 236 (Scheme 3.13) using dimethyldioxirane (DMD) in methanol. Reduction of the resulting N,O-acetal (237) with sodium borohydride at low pH yielded an inseparable mixture of isomeric alcohols 238 and 239 in a 3.5:1 ratio. Separation of these alcohols, as well as proof of stereochemistry (from NOE experiments and ¹H NMR coupling constants), was accomplished by conversion to the corresponding N,O-acetals 240 and 241. The stereochemical course of the oxidation can be explained by attack of the DMD on the most accessible face of the enamide double bond in 236, followed by hydride delivery to an intermediate acyliminium ion to give the less strained product (possessing equatorial substituents when formed in a chair conformation). The major product of this reaction possesses the relative stereochemistry required for CYN (after Weinreb’s revision of its stereochemistry). Djung also showed that inversion of C₇ stereochemistry in 238/239 was possible through the Mistunobu methodology, and developed an asymmetric synthesis of 234 (see below) that led to the preparation of 241 as a single enantiomer.
Djung next turned to construction of the A-ring. Johnson–Lemieux oxidation of 241 followed by Roush crotylboronation of the resulting aldehyde gave an inseparable mixture of isomeric alcohols 242 and 243 (Scheme 3.14). As before, separation and proof of stereochemistry was achieved for 242 and 243 through conversion to the corresponding cyclic carbamates 244 and 245. The carbamates were then hydrolyzed to the individual alcohols. Although diastereoselection in the crotylboronation was only modest, 243 possessed the correct relative stereochemistry for the cylindrospermopsin alkaloids.

Scheme 3.13: Djung’s C7 functionalization.
With 243 in hand, Djung turned to electrophile-initiated cyclizations to generate the A ring. Several electrophiles (NIS, NBS, PhSeCl) failed to provide cyclization products, but amidomercuration gave the results shown in Scheme 3.15. Unfortunately, the product obtained (246) showed the wrong stereochemistry at C14 for the cylindrospermopsin alkaloids, as determined by NOE experiments and 1H NMR coupling constants.

The stereochemical course of this amidomercuration may reflect thermodynamics. Organomercurial 246 is most likely more stable than its C14 epimer, because the latter would experience allylic strain between the urea oxygen and the C14 mercurymethyl group. Although solutions to this stereochemical problem at C14 were imagined, this pathway was abandoned in favor of more promising strategies.
3.3.2. Ridenour – revised synthetic strategy towards cylindrospermopsin.

The results of Djung’s studies suggested that it might be better to install the C\textsubscript{14}–N bond (closing the A-ring) \textit{before} installing C\textsubscript{16} functionality (closing the B-ring). This would remove the allylic strain between the C\textsubscript{16} functional group and the C\textsubscript{15} substituent, which proved problematic in Djung’s synthesis of advanced intermediate 246. Thus, a new approach to cylindrospermopsin was proposed as outlined retrosynthetically in Scheme 3.16. It was imagined that a compound such as 248 might undergo cyclization via conjugate addition of a C-ring guanidine to an alkynylpyrimidine to provide 247 (after introduction of the C\textsubscript{7} hydroxyl group and other functional group manipulations). Guanidine 248 was to be accessed from piperidine 249, with the D-ring brought in as a protected pyrimidine using a Sonogashira coupling. The A-ring in 249 was to be prepared by an electrophile-initiated cyclization. It was hoped that construction of the N-C\textsubscript{14} bond using an amine nucleophile rather than an amide nucleophile (as in Scheme 3.14) would lead to the required C\textsubscript{14} stereochemistry. These studies were initially undertaken by Sam Ridenour as part of his MS thesis research.
Ridenour began with the synthesis of 250 through known intermediate 234, which was prepared in four steps from dimethyl malonate 233 as described by Djung (Scheme 3.17). Acid 234 was then converted directly to BOC-protected amine 251 in 80% yield using a one-step Curtius rearrangement protocol, and the alkyne in 251 was protected as a TBS ether. The alkene was selectively oxidized using a Johnson-Lemieux reaction to yield aldehyde 252. This aldehyde was submitted to the Roush crotylboronation conditions to yield a mixture of isomeric alcohols 253 (43%) and 254 (42%), which fortuitously proved separable by column chromatography. The relative stereochemistry of 253 and 254 was established by conversion to cyclic carbamates followed by NOE experiments similar to those employed earlier by Djung (Scheme 3.18).
It is noted that because racemic 252 was used in the crotylboronation reaction, 253 and 254 were undoubtedly formed as unequal mixtures of enantiomers.

\[
\begin{align*}
233 & \xrightarrow{\text{a-d}} 36\% \quad 234 & \xrightarrow{\text{e}} 80\% \quad 251 \\
254 (42\%) & + 253 (43\%) & \xrightarrow{\text{f-g}} 64\% \\
\end{align*}
\]

(a) NaH, THF; H₂C=CHCH₂Br; (b) NaH, THF; HC≡CCH₂Br (58% from 233); (c) KOH, THF – MeOH; (d) Δ (62% over 2 steps); (e) DPPA, Et₃N, t-BuOH (80%); (f) n-BuLi, THF; TBSCl, DMPU (87%); (g) OsO₄, NaIO₄, t-BuOH – H₂O (73%); (h) Roush (E)-crotylboronate, molecular sieves, THF, -78ºC (43% 253 + 42% 254).

**Scheme 3.17: Ridenour’s early steps towards cylindrospermopsin.**

Moving forward, carbamate 253 was converted to cyclization substrate 257 by protecting the alcohol and deprotecting the amine functional groups (Scheme 3.19). Unfortunately, 257 did not cyclize in the expected manner.
Scheme 3.18: Proof of stereochemistry in 253 and 254.

Scheme 3.19: Ridenour’s attempt at electrophile-initiated cyclization of the A ring.
Attention was next turned to construction of the A-ring by intramolecular Michael addition of the C\textsubscript{10} amino group to an $\alpha,\beta$-unsaturated ester (Scheme 3.20). Thus, selective Johnson-Lemieux oxidation of alkene \textbf{259}, prepared by protection of \textbf{257}, yielded hemiaminal \textbf{260}, which was immediately olefinated to give \textbf{261} in modest yields. Treatment of \textbf{261} with trifluoroacetic acid gave \textbf{262} in 31\% yield, presumably via an intermediate primary amine. The stereochemistry of \textbf{262} was established by NOE experiments.

(a) OsO$_4$, NaIO$_4$, $t$-BuOH–H$_2$O; (b) Ph$_3$P=CHCO$_2$Et, PhMe, 80°C (46\% from \textbf{259}); (c) TFA, CH$_2$Cl$_2$ (31\%).

\textbf{Scheme 3.20:} Ridenour’s synthesis of an A ring intermediate.
Piperidine 262, possesses the A-ring of cylindrospermopsin with all substituents in place and with the correct relative stereochemistry at all stereogenic centers. In addition, 262 has functional handles for further elaboration. As will be shown, this work served as the foundation upon which the remainder of this thesis was built.

3.4. Current results.

3.4.1. Research plan.

It was at this stage that the author became involved with this effort towards a synthesis of cylindrospermopsin. It was clear that completion of five objectives would be necessary to bring this project to fruition:

1. An enantioselective synthesis of carboxylic acids such as 234 would be needed.

2. The Ridenour approach to piperidine 262 would have to be accomplished in a highly enantioselective manner. It would also have to be scaled up to provide sufficient material for work on the front end of the synthesis.

3. Piperidine 262 would have to be converted to the cyclic guanidine needed for the cylindrospermopsin skeleton.
4. Coupling of the above guanidine with 6-bromo-2,4-dimethoxypyrimidine would have to be accomplished to give a compound of type 248 (Scheme 3.16).

5. The cyclization of alkynylguanidine 248 would have to succeed, and manipulation of the residual functional groups would be necessary.

The remainder of this thesis will describe our progress towards these goals.

3.4.2. Asymmetric synthesis of carboxylic acids of type 234.

As mentioned earlier, Djung had developed an enantioselective route to carboxylic acids of type 234. This rested on an Evans-type asymmetric enolate alkylation for introduction of stereochemistry. It will be useful to recall that White’s establishment of the absolute configuration of cylindrospermopsin was published after one enantiomer was chosen for these studies. Thus Djung’s acid was that which would ultimately provide ent-cylindrospermopsin.

Moving forward, 4-pentenoic acid 263 was coupled with Evans auxiliary (4R,5S)-4-methyl-5-phenyl-oxazolidin-2-one (264) to provide imide 265 in 93% yield. This imide was alkylated with TMS-protected propargyl bromide, and the auxiliary and the TMS protecting group were removed with lithium hydroxide and hydrogen peroxide in aqueous THF to yield carboxylic acid 266 in 63% yield. The enantiomeric excess of 266 was determined to be 80% (corresponding to a 9:1 mixture of enantiomers).
(a) PivCl, Et$_3$N, THF; LiCl, (4R,5S)-4-methyl-5-phenyloxazolidin-2-one 264 (93%); (b) NaHMDS, THF, -78 °C; TMS-C≡C-CH$_2$Br (68%); (c) LiOH, H$_2$O$_2$, THF – H$_2$O (93%).

Scheme 3.21: Djung’s enantioselective route to acid 266.

3.4.3. Early steps.

We began by repeating this work in a manner that would leave a silicon protecting group at the alkyne terminus. The synthesis of 265 developed by Djung was repeated in good yield (86%). Alkylation of 265 with TMS-protected propargyl bromide 277 (synthesized in two steps from propargyl alcohol in 53% overall yield as shown in Scheme 3.23) furnished 267 in 68% yield, consistent with Djung’s studies. Treatment of 267 with lithium hydroxide and hydrogen peroxide gave acid 266 in excellent yields (92%). In accordance with Ridenour’s results, Curtius rearrangement of 266 upon treatment with diphenylphosphoryl azide in $t$-butyl alcohol gave BOC-protected amine 271 in 86% yield. Protection of the alkyne with a TBS group led to carbamate 272 in 79% yield.

To prevent loss of the alkyne protecting group, and eliminate the need for a subsequent reprotction step, alternate alkylation agents were examined. Propargyl...
bromide 278, featuring the desired TBS protecting group, was synthesized in three steps (Scheme 3.23). THP protection of propargyl alcohol (87% yield), followed by TBS protection of the terminal alkyne and subsequent alcohol deprotection with p-toluenesulfonic acid in methanol gave 275 in 56% overall yield. Conversion of the alcohol to bromide 278 was accomplished with bromine in the presence of triphenylphosphine in 83% yield.94

Scheme 3.22: Early steps towards an enantioselective synthesis of cylindrospermopsin.
Alkylation of the enolate derived from 265 with 278 gave 268 in 62% yield, similar to the corresponding alkylation with 277 (Scheme 3.22). As had been hoped, the TBS protecting group withstood the removal of the Evans auxiliary, giving carboxylic acid 270 in 87% yield. Unfortunately, Curtius rearrangement of 270 with DDPA gave markedly lower yields (38%) of protected amine 272, perhaps due to lower solubility of 270 in the solvent system used (t-BuOH). An attempt to alkylate 265 with propargyl bromide 279 also provided disappointing results as 269 was obtained in only 37% yield. The best route to 272 follows the path from 265 to 271 through 267, followed by introduction of the TBS protecting group. This process was scaled to provide 14 g of 272 in a single pass from 28 g of 265.

(a) n-BuLi, THF, -78°C; TMSCl; HCl, H₂O–THF (71%); (b) PBr₃, pyridine, Et₂O (75%, X = TMS); (c) CSA, DHP, CH₂Cl₂, 0°C → rt (87%); (d) n-BuLi, THF; TBSCl, 0°C → rt; p-TsOH, MeOH, rt (56%); (e) Br₂, PPh₃, imidazole, CH₂Cl₂, 0°C (83%, X = TBS); (f) n-BuLi, Et₂O–hexanes; TMSCl, DMPU, -78°C → 10°C.

Scheme 3.23: Synthesis of alkylating agents.
3.4.4. Installation of C_{12}-C_{14}.

With a supply of 272 in hand, we proceeded as shown in Scheme 3.24. Following the methodology originally developed by Djung, alkene 272 was subjected to Johnson-Lemieux oxidation to give aldehyde 280 in 79% yield. Roush asymmetric crotylboronation of 280 gave a 4:1 mixture of diastereoismeric alcohols 281 (69%) and 282 (17%), separable by column chromatography. Given the estimated 80% enantiomeric excess of 280 (from Djung’s studies), and the 4:1 ratio of products obtained from the crotylboronation step, we can estimate enantiomeric excesses using the concept of asymmetric amplification as shown in Scheme 3.25. We assume that the starting aldehyde is introduced as a 9:1 mixture of 280 and its enantiomer 286 (based on Djung’s work). As each enantiomer undergoes crotylboronation, two pairs of diastereomers are produced: 281 and 282 from 280, and 288 and 289 from 286. If we assume the 4:1 selectivity of the crotylboronation is reagent driven, we can predict a 36:9:4:1 ratio for the four alcohols 281, 282, 288, 289. These four alcohols represent two enantiomeric pairs: 281 and 289 on the one hand, 282 and 288 on the other. Thus, we can estimate an enantiomeric excess of approximately 95% (36:1 mixture of enantiomers) for 281 and 38% (9:4 mixture of enantiomers) for 282. Although this prediction must ultimately be supported with experimental data, we nonetheless continued separately with 281 and 282 (Scheme 3.24).
(a) OsO₄, NaIO₄, t-BuOH–H₂O, 0°C, 4 h (79%); (b) Roush (E)-crotylboronate, 4 Å molecular sieves, -78 ºC (69% 281 + 17% 282); (c) PivCl, Et₃N, CH₂Cl₂, rt (33% 283); (d) TBDPSCI, imidazole, DMF, rt 24 h (89% 284); (e) TBDPSCI, imidazole, DMF, rt 24 h (82%).


Alcohol 281 was then protected as TBDPS ether 284 in good (89%) yield and also as the pivalate ester 283, albeit in disappointing 33% yield. Alcohol 282 was similarly protected as TBDPS ether 285 in 82% yield (Scheme 3.24).
3.4.5. Synthesis of an AC ring intermediate towards cylindrospermopsin.

A-ring cyclization precursors 283, 284, and 290 were all subjected to Johnson-Lemieux oxidation to give hemiaminals 291, 292, and 293 respectively (Scheme 3.26). The crude aminals were directly reacted with carbethoxymethylidenetriphenylphosphorane to give α,β-unsaturated esters 294, 295, and 296, respectively.
Scheme 3.26: Synthesis of an AC ring intermediate towards cylindrospermopsin.
The pivalate protected substrate (283) gave unsatisfactory results (modest yields of very impure material) in the olefination step and was thus abandoned. The silyl ether protected substrates (284 and 290), on the other hand, furnished usable material albeit in low yields (30-36%).

Treatment of 296 with trifluoroacetic acid effected removal of the BOC protecting group and concomitant intramolecular Michael addition to yield piperidine 297 as a single isomer, albeit in low (38%) yields. Free alcohol 303 was also sometimes isolated from this reaction, suggesting that loss of the TBS protecting group was part of the problem (Scheme 3.27). When the BOC protecting group was removed from 303, piperidine 304 was obtained as a single isomer in 52% yield.

Scheme 3.27: Cyclization of 303.

Treatment of 295, with a TBDPS protecting group on the C12 oxygen, gave better results in the cyclization (Scheme 3.26) as the protecting group remained intact and piperidine 298 was obtained as a single isomer in excellent (90%) yield.
Throughout these studies, cyclization products in the stereochemical series derived from 281 (Scheme 3.25) were obtained as single isomers, with the desired relative stereochemistry for cylindrospermopsin as verified by $^1$H NMR NOE difference experiments. It is probable that thermodynamics set the A-ring stereochemistry in this cyclization. This is illustrated in Figure 3.2 for the case of 298. This figure shows what we imagine are the most stable conformations of the observed cyclization product (298) and its C$_{14}$ epimer (305). Piperidine 298 has a single axial substituent, making it more stable than epimer 305, which has two axial substituents. We imagine the reversible nature of the intramolecular Michael addition allows for the formation of 298 as the only observed product of the reaction.

![Figure 3.2: Most stable conformations of 298 and 305.](image)

Our next task was the degradation of the C$_{14}$ acetic acid residue to an isocyanates, followed by intramolecular trapping to provide the requisite cyclic urea. Thus, saponification of esters 297 and 298 with KOH in aqueous methanol yielded the corresponding amino acids 299 and 300 in quantitative yields. Treatment of these
amino acids with diphenylphosphoryl azide in tert-butyl alcohol yielded cyclic ureas 301 and 302 (Scheme 3.26). Once again, the TBDPS protecting group afforded better yields than the TBS derivative (63% and 40% respectively). Compound 302 contains the A and C rings of cylindrospermopsin, with the desired relative stereochemistry, and functional handles for further elaboration towards the natural product.

3.4.6. Attempted improvement of the 284 → 295 conversion.

Whereas the chemistry presented above provided 302 in only 12 steps from oxazolidinone 265, it suffered from low yields in the conversion of 284 to 295. It was felt that the lability of hemiaminal 292 may have been responsible in part for the low yields. Thus, tactics that bypass this intermediate were explored. For example, it was imagined that double protection of the C_{10} nitrogen would preclude hemiaminal formation, but still permit generation of 295 or the amino ester precursor of 298. Some failed attempts to accomplish this protection at various stages of the synthesis are shown in Scheme 3.28. For example, attempts to install a SES group on 272 gave at best low yields of protected compound 306. Similar attempts on 290 returned starting material. Attempted TBS protection of 284 under a variety of conditions generally returned only starting material. Attempted BOC protection of 285 also returned starting material. Attempted PMB protection of 285 resulted in loss of the silyl protecting groups and displacement of the t-butoxy group of the BOC protecting group by the resulting free C_{12} alcohol, to yield compound 310 (39%), also bearing a PMB protecting group on nitrogen.
Scheme 3.28: Attempts to double protect nitrogen prior to A ring cyclization.
Given the failure of our efforts to directly introduce a second nitrogen protecting group, the BOC protecting group was removed from compound 285 in quantitative yield upon treatment with TFA (Scheme 3.29) to allow for installation of a bidentate protecting group. Unfortunately, installation of Magnus’s STABASE silyl protecting group failed, returning only starting amine 311. Treatment of 311 with phthalic anhydride yielded singly protected amino acid 313, suggesting steric hindrance may be preventing the desired double protection.

(a) F₃CCOOH, CH₂Cl₂, rt, 24 h (100%); (b) Me₂ClSi(CH₂)₂SiClMe₂, Et₃N, CH₂Cl₂ (returns impure starting material); (c) phthalic anhydride, CHCl₃, 60°C, 48 h (31%).

Scheme 3.29: Further attempts at double nitrogen protection.
Given the failure to effect double nitrogen protection, we attempted to bypass the olefination stage entirely using olefin metathesis to directly convert \( \text{284} \) to \( \text{295} \). This idea rested on a recent publication by Grubbs, who reported olefin cross-metathesis reactions between terminal alkenes and acrylates.\(^{109}\) For example, conversion of \( \text{317} \) to \( \text{318} \) (Scheme 3.30) was catalyzed by second-generation ‘Grubbs’s catalyst’ \( \text{315} \) (Figure 3.3) in 62% yield and excellent isomeric distribution \((E:Z > 20:1)\).

![Figure 3.3: Olefin metathesis catalysts.](image_url)

(a) \( \text{315} \) (5 mol\%), \( \text{H}_2\text{C} = \text{C} (\text{CH}_3) \text{CO}_2\text{Me} \) (0.5 eq), \( \text{CH}_2\text{Cl}_2 \) (62%, \( E:Z > 20:1 \)); (b) \( \text{315} \) (4 mol\%), \( \text{H}_2\text{C} = \text{CHC} \text{O}_2\text{Me} \) (2.5 eq), \( \text{CH}_2\text{Cl}_2 \), \( \Delta \), 3h (100%); (c) \( \text{314} \) (10 mol\%), \( \text{H}_2\text{C} = \text{CHC} \text{O}_2\text{Me} \) (2.4 eq), \( \text{CH}_2\text{Cl}_2 \), \( \Delta \), 1h (66%).

**Scheme 3.30: Precedents for olefin metathesis of 284.**
As a technique check, we converted alkene 319 (available from another project within the Hart group) to $\alpha,\beta$-unsaturated ester 320 in quantitative yield (Scheme 3.30). Only the $E$ isomer of 320 was isolated. It was also verified that the more expensive 315 was required for these reactions. For example, attempts to couple 319 with methyl acrylate using the more affordable first-generation Grubbs’s catalyst (314) failed to produce 320. Instead, dimer 321 was produced in 66% yield.

(a) 315 (4 mol%), H$_2$C=CHCO$_2$Me (3 eq), CH$_2$Cl$_2$, $\Delta$, 24h (5%); (b) 315 (30 mol%), H$_2$C=CHCO$_2$Me (3 eq), CH$_2$Cl$_2$, $\Delta$, 24h (25% with impurities); (c) 315 (1.1 eq), H$_2$C=CHCO$_2$Me (3 eq), CH$_2$Cl$_2$, $\Delta$, 24h (complex mixture); (d) 316 (5 mol%), H$_2$C=CHCO$_2$Et (3 eq), CH$_2$Cl$_2$, rt, 24h (returns 100% 285).

Scheme 3.31: Olefin metathesis of 284 and 285.
When this methodology was applied to 284, however, the results proved disappointing (Scheme 3.31). Although some 295 was isolated, the yields were proportional to the amount of catalyst used. For instance, when 0.04 equivalents of catalyst 315 was used, a 5% yield of 295 was obtained. When 0.25 equivalents of catalyst were used, the yield climbed to 25%, although the purity of the material obtained was less satisfying. It would seem that the catalyst accomplished a single reaction, and was then destroyed – although reasons for this have not been investigated. Unfortunately, when a full equivalent of 315 was used (a solution which would in any case prove onerous given the high cost of 315), a complex mixture of compounds was obtained and no useful 295 was isolated.

Based on a publication by Crowe on olefin metathesis of acrylonitrile catalyzed by Schrock’s catalyst 316, we attempted the metathesis of 285 under Crowe’s conditions (Scheme 3.31).110 Unfortunately, this experiment returned 100% of the starting olefin 285.

3.4.7. D ring installation.

While we were not able to improve the synthesis of 302, the 12-step route was efficient enough to produce gram quantities of the material. Therefore, we turned to installation of the pyrimidine D ring. D-Ring precursor 325 was prepared in two steps from barbituric acid (323) according to published procedures in 41% overall yield (Scheme 3.32).111 The alkyne in 302 was selectively deprotected with TBAF (Scheme 107
3.33), yielding terminal alkyne 326 in 63% yield.\textsuperscript{112} An 18% yield of doubly deprotected alcohol 327 was also isolated. Sonogashira coupling of 326 with bromopyrimidine 325, catalyzed by Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} and copper iodide, yielded advanced ACD-ring intermediate 328 in 59% yield, along with an amount (17%) of dimer byproduct 329.\textsuperscript{113} The formation of 329 was probably due to the running of this coupling reaction on very small scales, making fine control of reaction conditions difficult. Attempts to run this coupling without the copper co-catalyst, generally thought to be responsible for the formation of dimer byproducts, returned starting alkyne 326. Similarly, a coupling attempt in the ionic liquid solvent butylmethylimidazolium hexafluorophosphate only returned starting material.\textsuperscript{114}

![Scheme 3.32: Synthesis of bromopyrimidine 325.](image)

(a) POBr\textsubscript{3}, N,N-dimethylaniline, PhMe, \textdegree{} (75% crude); (b) NaOMe, MeOH, PhMe (55%).
Scheme 3.33: Installation of the D ring of cylindrospermopsin.

The coupling of alcohol 330 with 325 was also examined, but this yielded alkynyl pyrimidine 331, in only 13% yield (Scheme 3.34).

Scheme 3.34: Sonogashira coupling of compound 330.
3.4.8. Guanidine formation.

With 328 in hand, we examined conversion of the urea to the guanidine needed for cylindrospermopsin (Scheme 3.35). Attempted activation of the urea by conversion to the corresponding iminoyl chloride with POCl₃ or (COCl)₂, followed by displacement of the resulting leaving group with ammonia, was not successful. The same was true when Meerwein’s reagent was used to activate the urea.¹¹⁵ Most reactions returned starting urea 328. With phosphorus oxychloride, a compound tentatively assigned the structure of phosphoramid 335 was isolated. Presumably the intermediate alkoxyphosphoryl dichloride 333 was reluctant to undergo nucleophilic acyl substitution to provide 334, and reaction of 333 with ammonia provided 335. Attempts to convert 326 to 336 also met with failure.
Scheme 3.35: Initial guanidine formation attempts.

We next tried to convert 326 to thiourea 337. It was anticipated that 337 would be easier to activate than 326. Unfortunately, treatment of 326 with sulfur transfer agents P$_2$S$_5$ and Lawesson’s reagent failed to give 337, and only complex mixtures of compounds were obtained (Scheme 3.36).$^{116,117}$ Attempted hydrolysis of 326 to produce diamine 338, which might have then been converted to the desired guanidine, resulted in complete loss of material.$^{118}$
(a) Lawesson’s reagent, PhMe, Δ, 5 h (complex mixture); (b) P$_2$S$_5$, xylenes, Δ, 24 h (complex mixture); (c) Ba(OH)$_2$, H$_2$O, Δ, 24 h (no material recovered).

**Scheme 3.36: Further attempts towards formation of a guanidine.**

Given the failure of our initial efforts to introduce the guanidine functionality, it was decided to develop the necessary methodology on urea 341, a simple, easily accessible model system (Scheme 3.37). The synthesis of 341 was accomplished in two steps from commercially available 339. Oxidation of the alcohol with chromic acid, according to a published procedure, gave amino acid 340 in 76% yield.$^{119}$ Acid 340 was then converted to urea 341 in 56% yield using DPPA, the same method used for the conversion of 300 to 302. Our failure to convert 326 to 337 (Scheme 3.36) suggested that the secondary urea nitrogen would likely need to be protected. Toward that end, several protecting group schemes were examined (Scheme 3.38).
Scheme 3.37: Synthesis of model urea 341.

(a) CrO₃, H₂SO₄, H₂O, 0 °C → rt, 3 h (76%); (b) DPPA, Et₃N, t-BuOH, ∆, 24 h (56%).

Scheme 3.38: Protection studies and synthesis of model thiourea 347.

(a) H₃COCH₂Cl, i-Pr₂NEt, CH₂Cl₂, rt, 24 h (10%); (b) Ph₃CCl, Et₃N, CHCl₃, rt, 48 h (52%); (c) Lawesson’s reagent, toluene, ∆, 4 h (complex mixture); (d) NaH, DMF; PMBCl, 0 °C → rt, 3 h (82%); (e) Lawesson’s reagent, toluene, ∆, 24 h (81%).
Attempted methoxymethylation\textsuperscript{120} of \textbf{341} failed to yield any protected urea \textbf{342}, and gave instead a 10\% yield of \textit{N}-formyl urea \textbf{343} (as evidenced by formyl signals in the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra, a carbonyl vibration in the IR spectrum, and confirmed by mass spectroscopy). Treatment of \textbf{341} with trityl chloride provided \textbf{344} in 52\% yield.\textsuperscript{121} However, decomposition occurred when \textbf{344} was treated with Lawesson’s reagent and no thiourea \textbf{345} was obtained. Better results were obtained with the \textit{p}-methoxybenzyl protecting group. Thus, treatment of \textbf{341} with sodium hydride followed by \textit{p}-methoxybenzyl chloride produced \textbf{346} in good (82\%) yield.\textsuperscript{106} Reaction of \textbf{346} with Lawesson’s reagent gave thiourea \textbf{347} in 81\% yield.

With model thiourea \textbf{347} in hand, we turned to the formation of the necessary guanidine functionality (Scheme 3.39). Treatment of thiourea \textbf{347} with methyl triflate followed by ammonia gave guanidine \textbf{348}, obtained as the triflate salt, in 85\% yield.\textsuperscript{122} Deprotection of \textbf{348} was accomplished using neat TFA, affording guanidinium trifluoroacetate \textbf{349} in a modest 38\% yield.\textsuperscript{123}

When the same methodology was used with \textit{N},\textit{N}-dimethylethylenediamine and \textit{n}-hexylamine instead of ammonia, guanidinium triflates \textbf{350} and \textbf{351} were obtained in 86\% and 93\% yields, respectively. Some limitations of this method came to light when use of the less nucleophilic \textit{p}-toluenesulfonamide led to the isolation of the intermediate \textit{S}-methylated thiourea \textbf{353} in 93\% yield, instead of the expected guanidine \textbf{352}. The identity of \textbf{353} was confirmed by synthesis from \textbf{347} in 95\% yield upon treatment with methyl triflate and isolation without intervention of an amine nucleophile.
With the successful development of a methodology for converting ureas of type 341 to the corresponding guanidines, we took the next step towards cylindrospermopsin. Rather than proceeding directly with precious 328, we decided to test our method on cyclic urea 358 (Scheme 3.40). This compound is epimeric to 302 at C12 and C13. As will be seen, this study was not without surprises. Substrate 358 was prepared from 282, the minor product of the Roush crotylboronation of 280 (Scheme 3.25).
Thus, when 285 (prepared by TBDPS protection of 282) was oxidized with catalytic osmium tetroxide and sodium periodate, and the resulting aldehyde was olefinated with the appropriate phosphorane, α,β-unsaturated ester 354 was isolated in variable yields (20-48%). Upon treatment with trifluoroacetic acid, 354 gave a mixture of

Scheme 3.40: Synthesis of ureas 357 and 358.
inseparable epimers 355 and 356 in moderate yields (38-55%) and somewhat variable isomer ratios (1:1-2:1 by $^1$H NMR spectroscopy). When this mixture of amino esters was hydrolyzed to the corresponding amino acid mixture, and this mixture was treated with DPPA under standard conditions, two separable epimeric ureas, 357 and 358, were obtained in 15-25% and 34-36% yields respectively.

The stereochemistry assignments for 357 and 358 were supported by $^1$H NMR NOE difference experiments. In the case of 357, irradiation of H$_{13}$ gave rise to enhancement of the signal of H$_{15}$ (2.3%), but only a weak enhancement of the signal of H$_{14}$ (0.7%). Irradiation at H$_{14}$ showed no enhancement at H$_{10}$ or H$_{12}$. In the case of 358, irradiation of H$_{15}$ showed an enhancement of the signal from H$_{17}$ (3.7%), but only a very weak enhancement of H$_{12}$ (0.2%). Irradiation of H$_{14}$ gave rise to enhancements at H$_{12}$ (2.3%), H$_{13}$ (3.3%), and H$_{10}$ (1.6%), but only weak enhancements at H$_{17}$ (0.7%) and H$_9$ (0.2%).

The stereochemical result in the cyclization of 354 was surprising. It had been expected that piperidine 356 would by far be the major product given that there is only one axial substituent in its most stable conformation, compared to two axial substituents in 355 (Figure 3.4). The cyclization, however, was not nearly as selective as the cyclization of 295 (Scheme 3.26). Recall that this reaction gave only 298 and none of its C$_{14}$ diastereomer 305. The fact that 355 is observed as a significant minor product from 354, while 305 was not observed at all from 295, might be due to C$_{13}$-C$_{14}$ torsional strain in 305 (not present in 355) which further disfavors 305.
When compared to cylindrospermopsin, urea 357 contains the A and C rings, with incorrect relative stereochemistry at C₁₂, C₁₃, and C₁₄, while 358 contains the A and C rings with correct relative stereochemistry at C₁₄ and C₁₀, but incorrect relative stereochemistry at C₁₂ and C₁₃.

With ureas 357 and 358 in hand, we turned to the application of the guanidine installation protocol developed for 341 (Schemes 3.38 and 3.39). Another surprise awaited. When 358 was treated with NaH followed by p-methoxybenzyl chloride in DMF (Scheme 3.41), protected urea 359 was not formed. Instead, the deprotonated urea acquired a formyl group from the DMF, producing a 27% yield of N-formylated urea 360. Similarly, when 357 was submitted to the same reaction conditions, formylation product 362 was produced in 29% yield instead of 361. An attempt to circumvent this
problem by running the protection reaction in THF instead of DMF returned only starting

358.

(a) NaH, DMF; PMBCl, 0°C → rt, 3 h (27% 360 + 61% returned 358); (b) NaH, DMF; PMBCl, 0°C → rt, 3 h (29% 362 + 33% returned 357); (c) NaH, THF; PMBCl, 0°C → rt, 3 h (returns 78% 358).

Scheme 3.41: Attempted protection of ureas 357 and 358.
The results obtained from ureas 357 and 358 indicated that these compounds were inadequate models, although for reasons that are still unclear. Thus, we decided to apply our methodology for guanidine synthesis to the cylindrospermopsin stereochemical series, and returned to urea 302.

Thus, when urea 302 was treated with sodium hydride followed by p-methoxybenzyl chloride (Scheme 3.42), a 68% yield of protected urea 363 was obtained, along with 24% of terminal alkyne 364, resulting from loss of the TBS protecting group. Unfortunately, treatment of 363 with Lawesson’s reagent failed to produce thiourea 366, and only returned decomposition products and 43% of starting 365.

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\text{Scheme 3.42: Latest advances towards guanidine installation.}
\]
**3.4.9. Conclusions and future directions.**

We have presented synthetic studies towards cylindrospermopsin, leading first to ACD-ring intermediate 328. This intermediate, as well as immediate precursor 326 unfortunately failed to lend themselves to installation of the guanidine functionality required for cylindrospermopsin. A model studies was carried out with urea 341, which, when applied to complete substrate 302, allowed for the synthesis of protected urea 363. Unfortunately, our efforts to convert 363 to thiourea 365, then guanidine 366 have been unsuccessful.

It is our opinion that further studies on the conversion of 363 to 365 should be carried out, as it seems possible that this conversion would eventually succeed, and that 365 could likely be converted to guanidine 366. From 366, deprotection of the alkyne and urea functional groups would lead to intermediate 367 (Scheme 3.43). Sonogashira coupling to introduce the D-ring pyrimidine would yield 368, which upon intramolecular conjugate addition would give ABCD-ring intermediate 369. Stereoselective C7 oxidation, per Djung’s precedent, would lead to compound 370, which upon final functional group manipulations could be converted to ent-cylindrospermopsin 371.
Scheme 3.43: Future directions towards cylindrospermopsin.
CHAPTER 4

EXPERIMENTAL SECTION

All melting points were taken with a Thomas – Hoover capillary melting point apparatus, and are uncorrected, as are all boiling points. Nuclear magnetic resonance spectra were recorded on Bruker Avance 250, 400, or 500 MHz spectrometers, and reported in parts per million from internal chloroform on the δ scale. The $^1$H NMR spectra are reported as follows: chemical shift (multiplicity [br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constants in Hz, integration, interpretation). The $^{13}$C NMR spectra are reported as follows: chemical shift (multiplicity [br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet]). Infrared spectra were taken on Perkin-Elmer FT-1600 spectrometers. Electron impact mass spectra were obtained on Kratos MS-25 or Kratos VG70-250s instruments at an ionization energy of 70eV. Electrospray ionization mass spectra were obtained on a Finnigan FTMS-2000 instrument. Combustion analyses were performed by Atlantic MicroLab Inc., Norcross, Georgia.
Solvents and reagents were dried and/or purified prior to use as necessary: benzene, diethyl ether, and tetrahydrofuran were distilled from sodium–benzophenone ketyl; dichloromethane, triethylamine, t-butanol, and methanol were distilled from calcium hydride. Trimethylsilyl chloride was purified by reaction with excess triethylamine, followed by centrifugation. Reactions requiring an inert atmosphere were run under nitrogen. Analytical thin-layer chromatography was conducted using EM Laboratories or Scientific Adsorbents, Inc. 0.25 mm precoated 60F-254 silica gel plates. Flash chromatography was performed over EM Laboratories, ICN, or SAI silica gel (230-400 Mesh). Atmospheric column chromatography was performed over EM Laboratories, ICN, Whatman, or SAI silica gel (70-230 Mesh). All organometallic reagents were titrated prior to use with menthol, using 1,10-phenanthroline as indicator. The order of experimental procedures follows the order of their appearance in the text.

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\text{N-Benzoylpyrrolidine (74).}^{126} \text{ To a stirred solution of 18.34 g (0.46 mol) of NaOH in 100 mL of water were added 18.2 mL (15.5 g; 0.218 mol) of pyrrolidine, in one portion at 5°C, followed by the slow addition of 24.8 mL (30.03 g; 0.214 mol) of benzoyl}
\]
chloride (73), dropwise at 5°C over a 2 h period. The resulting solution was then allowed to warm to room temperature and stirring was continued for 14 h. The opaque, light yellow reaction mixture was extracted with three 30-mL portions of CH₂Cl₂. The combined organic extracts were washed with 30 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 37.15 g of crude product as a yellow oil. The crude product was bulb-to-bulb distilled (100°C @ 0.15 torr), to yield 33.69 g (90%) of amide 74 as a white solid: mp 50-52°C (lit. 45-48°C); IR (KBr) 1611 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.89 (br s, 4H, CH₂), 3.5 (m, 4H, NCH₂), 7.35 (m, 3H, ArH), 7.49 (m, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 25 (br d), 27 (br d), 47 (br t), 49 (br t), 127.3 (d), 128.4 (d), 129.9 (d), 137.4 (s), 169.9 (s).

\[
\begin{align*}
&\text{O} \\
&\text{N} \\
&\text{75} \\
&\text{N} \\
&\text{N-Diethylbenzamide (75).}^{126a,127} \text{ To a stirred solution of 6.16 g (154 mmol) of NaOH in 33 mL of H₂O was added dropwise at 5°C 7.6 mL (5.33 g; 72.8 mmol) of diethylamine in one portion, followed by dropwise addition of 8.2 mL (9.93 g; 70.6 mmol) of benzoyl chloride (73) over a 1 h period. The reaction mixture was then allowed to slowly warm up to room temperature and stirring was continued for 15 h. The bright}
\end{align*}
\]
yellow reaction mixture was extracted with three 15-mL portions of CH$_2$Cl$_2$, and the combined organic layers were washed with 15 mL of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo, to yield 13.23 g of crude product as a fluid yellow oil. The crude product was bulb-to-bulb distilled ($220^\circ$C @ 0.08 torr), to yield 13.05 g (100%) of amide 75 as a yellow oil: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.12 (br s, 3H, CH$_3$), 1.22 (br s, 3H, CH$_3$), 3.25 (br s, 2H, CH$_2$), 3.53 (br s, 2H, CH$_2$), 7.37 (br s, 5H, ArH); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 126.2 (d), 128.3 (d), 129.0 (d), 137.2 (s), 171.2 (s); the aliphatic carbons were not observed due to amide exchange.

![Diagram of 76](image)

$N,N$-Diethyl-2-(trimethylsilyl)benzamide (76). To a stirred mixture of 14.7 mL (19.11 mmol) of s-butyllithium (1.3M in cyclohexane), 2.8 mL (2.1 g; 18.55 mmol) of TMEDA, and 5 mL of THF, at -78$^\circ$C under N$_2$, was added dropwise a solution of 3.07 g (17.33 mmol) of $N,N$-diethylbenzamide (75) in 5 mL of dry THF over 1 h (exotherm observed). The solution was stirred at -78$^\circ$C for 1 h, followed by dropwise addition of 6.7 mL (5.73 g; 52.8 mmol) of trimethylsilyl chloride at -78$^\circ$C over a 45 min period. The resulting red-black reaction mixture was then allowed to slowly warm to room
temperature, and stirring was continued for 15 h. TLC analysis (silica gel; Et₂O–hexanes, 1:1) showed no remaining starting material. To the gray-green reaction mixture was added 60 mL of saturated aqueous NH₄Cl. The organic phase was concentrated in vacuo and the resulting orange residue was extracted with three 50-mL portions of CH₂Cl₂. The combined organic extracts were washed with 50 mL of brine, dried (Na₂SO₄), and concentrated in vacuo. The resulting dark orange oil (3.24 g) was purified by flash chromatography over 160 g of silica gel (Et₂O–hexanes, 10:90 → 100:0), to yield 1.22 g (28%) of 76 as an orange oil along with 518 mg (21%) of impure 77. Data for 76: ¹H NMR (CDCl₃, 400 MHz) δ 0.29 (s, 9H, SiMe₃), 1.1 (br t, J = 6.7 Hz, 3H, CH₃), 1.25 (br t, J = 6.9 Hz, 3H, CH₃), 3.18 (br q, J = 6.9 Hz, 2H, CH₂), 3.56 (br q, J = 6.7 Hz, 2H, CH₂), 7.19 (dd, J = 5.5, 3 Hz, 1H, ArH), 7.34 (m, 2H, ArH), 7.59 (dd, J = 5.7, 3Hz, 1H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ -0.2 (q), 12.8 (q), 13.8 (q), 39.0 (t), 43.5 (t), 125.6 (d), 127.8 (d), 128.4 (d), 135.0 (d), 137.5 (s), 142.8 (s), 172.4 (s); exact mass calcd. for C₁₄H₂₃NOSi m/z 249.1550, found m/z 249.1529.

![CHO SiMe₃ 80]

**o-(Trimethylsilyl)benzaldehyde (80).**⁴⁶ To a stirred solution of 2.95 mL (2.32 g; 22.69 mmol) of N,N,N’-trimethylethylenediamine in 56 mL of dry THF under N₂ at -20°C was added 8.75 mL (21.9 mmol) of n-butyllithium (2.5M in hexanes) dropwise
over a period of 20 min. The solution was stirred at -20°C for 15 min, followed by dropwise addition of 2.1 mL (2.19 g; 20.64 mmol) of benzaldehyde (78) over a 10 min period. The solution was stirred at -20°C for 15 min, followed by dropwise addition of 25.2 mL (63 mmol) of n-butyllithium (2.5M in hexanes) over a 30 min period. The resulting mixture was stirred at -20°C for 15 min and placed in a freezer at -15°C for 24 h. Trimethylsilyl chloride (16.1 mL; 13.78 g; 126.8 mmol) was then added dropwise at -40°C with stirring over a 30 min period, and stirring was continued at -40°C for 30 min. TLC analysis over silica gel (Et$_2$O-hexanes, 10:90) showed no remaining starting material. The reaction mixture was poured with stirring into 500 mL of cold 10% aqueous HCl, and the resulting mixture was extracted with three 200-mL portions of Et$_2$O. The combined organic layers were washed with 200 mL of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo, to yield 4.89 g of crude product as a pale yellow oil. The crude product was purified by flash chromatography over 245 g of silica gel (hexanes-ether 98:2), to yield 3.04 g (83%) of aldehyde 80 as a pale yellow oil [Note: Aldehyde 80 oxidizes readily in the presence of air, to form the corresponding carboxylic acid and formate ester, and should be stored under an inert atmosphere]: $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.36 (s, 9H, SiMe$_3$), 7.58 (m, 2H, ArH), 7.22 (m, 1H, ArH), 7.91 (m, 1H, ArH), 10.15 (s, 1H, CHO).
**o-(Trimethylsilyl)benzoic acid (81).** From 80:**48** To a stirred solution of 295 mg (1.66 mmol) of o-(trimethylsilyl)benzaldehyde (80) in 4.5 mL of acetone and 0.8 mL of distilled water, was added at room temperature 315 mg (1.99 mmol) of KMnO₄. An exothermic reaction was observed and the resulting mixture was stirred at room temperature for 1.5 h. TLC analysis (silica gel; ether – hexanes, 10:90) showed no remaining starting material. The solvent was evaporated in vacuo, and 50 mL of saturated aqueous Na₂SO₃ was added to the residue. The resulting mixture was filtered through Celite, and the dark brown filter cake was rinsed several times with H₂O and CH₂Cl₂. The colorless filtrate was carefully acidified to pH 1 with 10% aqueous HCl. The organic layers were separated, and the aqueous layer was extracted with three 10-mL portions of CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo, to yield 1.255 g of a yellow solid. The solid was ground to a powder and suspended in 50 mL of CH₂Cl₂. The suspension was extracted with four 20-mL portions of 1N aqueous NaOH. The combined aqueous extracts were cooled in an ice water bath and carefully acidified to pH 1 with concentrated aqueous HCl. The resulting fine white precipitate was collected and air-dried to yield 120 mg (37%) of acid 81 as a fine white solid: mp 96-98°C (lit. 97-98.5°C); IR (KBr) 3437, 2962, 1687, 1562, 1413, 1272, 1119, 847, 734 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.37 (s, 9H, TMS), 7.50 (t, J = 7.3 Hz, 1H, ArH), 7.56 (t, J = 7.5 Hz, 1H, ArH), 7.74 (d, J = 7 Hz, 1H, ArH), 8.17 (d, J = 8 Hz, 1H, ArH);
$^{13}$C NMR (CDCl$_3$, 100 MHz) δ 0.3 (q), 128.9 (d), 130.9 (d), 132.4 (d), 134.1 (s), 135.7 (d), 143.8 (s), 173.5 (s). From 2-iodobenoic acid (84): To a stirred suspension of 12.3 g (49.6 mmol) of 2-iodobenoic acid (84) in 50 mL of dry diethyl ether under nitrogen at −70°C was added, dropwise over 1.75 h, a solution of 43 mL (107.5 mmol) of n-butyllithium (2.5 M in hexanes) in 60 mL of dry Et$_2$O. The resulting solution was stirred at -78°C for 30 min, followed by dropwise addition of a solution of 14 mL (3.42 g; 110.3 mmol) of trimethylsilyl chloride in 20 mL of dry Et$_2$O over a 20 min period. The resulting mixture was allowed to slowly warm to room temperature and stirring was continued for 14 h. To the reaction mixture was added 50 mL of 1M aqueous HCl. The aqueous layer was separated and the organic layer was extracted with seven 30-mL portions of 1N NaOH. The combined aqueous layers were cooled in an ice water bath and carefully acidified to pH 1 with concentrated HCl. The resulting white precipitate was collected and air-dried to yield 5.56 g (58%) of acid 81 as an off-white solid: mp 94-96°C.
A solution of 1.164 g (5.99 mmol) of \( \alpha \)-(trimethylsilyl)benzoic acid (81), 1.9 g (7.2 mmol) of triphenylphosphine, and 3 mL (4.78 g; 31.1 mmol) of carbon tetrachloride in 20 mL of anhydrous acetonitrile was heated to reflux for 2 h. The solution was then cooled to 0\(^\circ\)C followed by addition of 1 mL (0.85 g; 12 mmol) of pyrrolidine in one portion. The resulting solution was then heated to reflux for 1 h, cooled to room temperature, diluted with 50 mL of Et\(_2\)O, and washed with 20 mL of brine. The organic phase was dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residual brown oil (3.6 g) was purified by flash chromatography over 180 g of silica gel (hexanes–ether, 60:40), to yield 1.36 g (92%) of amide 69 as a pale yellow oil: IR (neat) 2952, 2875, 3050, 1631, 1413, 1244, 1125, 841, 743 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.28 (s, 9H, SiMe\(_3\)), 1.86 (br s, 2H, CH\(_2\)), 1.95 (br s, 2H, CH\(_2\)), 3.21 (br s, 2H, NCH\(_2\)), 3.63 (br s, 2H, NCH\(_2\)), 7.25 (m, 1H, ArH), 7.35 (m, 2H, ArH), 7.60 (m, 1H, ArH); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) -0.4 (q), 24.6 (t), 26.0 (t), 45.6 (t), 49.2 (t), 125.6 (d), 128.0 (d), 128.6 (d), 135.0 (d), 137.3 (s), 143.5 (s), 171.1 (s); exact mass calcd. for C\(_{14}\)H\(_{21}\)NOSi \(m/z\) 247.1393, found \(m/z\) 247.1399.
2-Bromoethyl tert-butyl ether (87). A mixture of 514.5 g (4.12 mol) of 2-bromoethanol (85) and 4.5 mL (8.28 g; 84.42 mmol) of concentrated H₂SO₄ was vigorously stirred at room temperature under an isobutylene atmosphere (relative pressure of about 2 psi). The reaction was followed by ¹H NMR (dilution of an aliquot with CDCl₃). After 48 h, a significant amount of starting material remained and an additional 4.5 mL (8.28 g; 84.42 mmol) of H₂SO₄ was added. After 72 h only traces of starting material remained visible and the volume of the mixture had increased significantly. The reaction mixture was diluted with 2 L of pentane and the resulting solution was washed with 500-mL portions of saturated aqueous NaHCO₃ until all evolution of CO₂ ceased, followed by one more 500-mL portion of saturated aqueous NaHCO₃. The organic layer was then dried (Na₂SO₄) and concentrated in vacuo, to yield 555 g of the crude product as a yellow liquid. The crude product was distilled under reduced pressure, to yield 325 g of slightly impure 87 as a pale yellow liquid. The distillate was purified by flash chromatography over 1 kg of silica gel (eluted with CH₂Cl₂), to yield 293 g (40%) of ether 87 as a colorless liquid: bp = 72-76 °C @ 45 mmHg (lit.⁹ᵃ 65-67 °C @ 30mmHg); IR (neat) 2973, 2934, 2876, 1470, 1420, 1391, 1364, 1279, 1259, 1235, 1198, 1105, 1075, 1037, 1018, 956, 912, 877, 812, 759, 735, 651, 571 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.22 (s, 9H, CH₃), 3.41 (t, J = 6.6 Hz, 2H, CH₂Br), 3.67 (t, J = 6.6 Hz, 2H, CH₂O); ¹³C NMR (CDCl₃, 100 MHz) δ 27.5 (q), 31.5 (t), 62.3 (t), 73.6 (s); exact mass calcd. for C₆H₁₃⁷⁹BrO m/z 180.0150, found m/z 180.0150.
1,4-Cyclohexadienes **88** and **89**. Into a stirred solution of 1.04 g (4.18 mmol) of \(N\)-(2-trimethylsilyl)pyrrolidine (69) and 396 µL (310 mg; 4.18 mmol) of \(t\)-butanol in 30 mL of anhydrous THF at -78°C under N₂, was condensed approximately 150 mL of NH₃. Potassium metal was added to the mixture in small portions until the reaction sustained a deep blue-black color. The mixture was then stirred for 30 min, followed by addition of 0.552 g (6.35 mmol) of LiBr in one portion. Approximately 2 mL of isoprene was then added dropwise, until the blue-black color reverted to yellow. 2-Bromoethyl \(t\)-butyl ether (87) (3.98 g; 22.0 mmol) was then added over a 5 min period, and the resulting opaque yellow mixture was stirred at -78°C for 2 h. To the reaction was added 1.0 g (21 mmol) of solid NH₄Cl, and the reaction mixture was allowed to slowly warm to room temperature as the ammonia was allowed to evaporate. The residue was partitioned between 30 mL of CH₂Cl₂ and 10 mL of H₂O. The organic phase was washed sequentially with 10 mL of H₂O and 5 mL of saturated aqueous Na₂S₂O₃, dried (Na₂SO₄) and concentrated in vacuo to yield 3.24 g of crude product as a yellow oil. The crude product was purified by flash chromatography over 160 g of silica gel (Et₂O–hexanes, 1:1), to yield 475 mg (32%) of amide **88** as a white solid and 474 mg (46%) of **89** as a pale yellow oil. Data for **88**: mp 89-91°C; IR (KBr): 2968, 2871, 1621, 1401, 1385, 1361, 1250, 1198, 1075, 885, 837, 759 cm⁻¹; \(^1\)H NMR (CDCl₃, 400 MHz) δ 0.09 (s, 9H, 133
SiMe$_3$), 1.15 (s, 9H, tBu), 1.74 (m, 4H, NCH$_2$CH$_2$), 2.10 (m, 2H, CH$_2$CH$_2$OtBu), 2.70 (m, 2H, =CCH$_2$C=), 3.19 (m, 1H, CH$_2$O), 3.29 (m, 1H, CH$_2$O), 3.41 (m, 4H, NCH$_2$), 5.49 (dt, $J = 10.1$, 1.9 Hz, 1H, CH=CHCH$_2$), 5.85 (m, 1H, CH=CHCH$_2$), 6.24 (br, 1H, CH$_2$CH=); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 0.1 (q), 23.3 (t), 26.8 (t), 27.5 (t), 27.7 (q), 38.2 (t), 46.1 (t), 47.9 (t), 49.7 (s), 58.4 (t), 72.5 (s), 123.9 (d), 128.5 (d), 136.2 (d), 137.8 (s), 171.3 (s); exact mass calcd. for C$_{20}$H$_{35}$NO$_2$Si m/z 349.2493, observed m/z 348.2403.

Anal. calcd. for C$_{20}$H$_{35}$NO$_2$Si: C, 68.72; H, 10.09. Found: C, 68.71; H, 10.02. Data for 89: IR (neat): 3316, 2952, 2876, 2811, 1627, 1417, 1339, 1246, 840, 752; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.07 (s, 9H, SiMe$_3$), 1.80-1.94 (m, 4H, NCH$_2$CH$_2$), 2.78 (m, 2H, =CCH$_2$C=), 3.49 (m, 4H, NCH$_2$), 4.03 (m, 1H, =CCHC=), 5.72 (m, 1H, CH=CHCH$_2$), 5.88 (m, 1H, CH=CHCH$_2$), 6.22 (m, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ -1.8 (q), 23.8 (t), 26.4 (t), 27.1 (t), 45.7 (t), 46.8 (t), 45.9 (d), 122.7 (d), 125.9 (d), 134.2 (s), 135.4 (d), 170.8 (s); exact mass calcd. for C$_{14}$H$_{23}$NOSi m/z 249.1550, observed m/z 249.1549.

4-(2~t~-Butoxyethyl)-4-(pyrrolidinylcarbonyl)cyclohexa-2,5-dienone (95). To a stirred solution of 1.00 g (2.87 mmol) of diene 88 in 2.2 mL of acetone, 0.7 mL of H$_2$O,
and 0.43 mL of t-butanol at room temperature was added 1.46 mL (0.057 mmol) of a 1% solution of OsO₄ in H₂O and 482 mg (4.34 mmol) of trimethylamine oxide dihydrate. The mixture was stirred at room temperature for 2 h, after which the mixture was heated to reflux for 3 h. TLC analysis (silica gel; ether–hexanes, 1:1), indicated the reaction had stopped. The mixture was cooled to room temperature, diluted with 90 mL of CH₂Cl₂, saturated with NaCl, dried (Na₂SO₄) and concentrated in vacuo to yield 928 mg of a yellow oil. The crude mixture was purified by flash chromatography over 46 g of silica gel (ether–hexanes, 1:1) to yield 539 mg (54%) of pure starting material as a white solid, and 299 mg (29%) of dienone 95 as an off-white solid: mp 103-109°C; IR (KBr) 3025, 2967, 2879, 1636, 1403, 1078 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.21 (s, 9H, SiMe₃), 1.08 (s, 9H, tBu), 1.75 (br m, 4H, NCH₂CH₂), 2.41 (m, 2H, CH₂CH₂OtBu), 3.10 (m, 4H, NCH₂), 3.44 (m, 1H, CH₂OtBu), 3.52 (m, 1H, CH₂OtBu), 6.48 (dd, J = 10.0, 1.8 Hz, 1H, CH=CHCO), 6.78 (d, J = 1.8 Hz, 1H, CH=CSiMe₃), 6.94 (d, J = 10.0 Hz, 1H, CH=CHCO); ¹³C NMR (CDCl₃, 100 MHz) δ 6.8 (q), 23.2 (t), 26.6 (t), 27.4 (q), 36.7 (t), 45.4 (t), 48.5 (t), 56.2 (s), 56.9 (t), 72.8 (s), 130.0 (d), 139.7 (d), 152.1 (d), 164.5 (s), 166.3 (s), 183.9 (s); exact mass calcd. for C₂₀H₃₃NO₃Si: m/z 363.2231, found m/z 363.2209. Anal. calcd. for C₂₀H₃₃NO₃Si: C, 66.08; H, 9.16. Found: C, 65.85; H, 9.16.
(S)-N-(o-Methoxybenzoyl)-2-hydroxymethylpyrrolidine (103). To 1.37 g (9.03 mmol) of o-anisic acid (102) was added 8.45 mL (13.78 g; 116 mmol) of thionyl chloride in one portion with stirring at room temperature under a nitrogen atmosphere. Gas evolution was observed, and stirring was continued at room temperature under N₂ for 24 h. Excess SOCl₂ was distilled from the reaction mixture over 1 h under reduced pressure, and the crude residue was bulb-to-bulb distilled (80°C @ 0.15 torr), to yield 1.14 g (94%) of o-anisyl chloride as a colorless liquid. To a stirred solution of 0.92 mL (943 mg; 9.32 mmol) of (S)-pyrrolidinemethanol and 1.8 mL (1.307 g; 12.91 mmol) of triethylamine in 25 mL of anhydrous CH₂Cl₂ at 0°C under nitrogen was added a solution of the acid chloride in 10 mL of CH₂Cl₂ over a 30 min period. The reaction mixture was then warmed to room temperature and stirring was continued for 4 h. TLC analysis (silica gel; EtOAc - hexanes, 1:1) showed no remaining starting material. To the reaction mixture was added 50 mL of 5% aqueous HCl, and the resulting solution was extracted with three 50-mL portions of CHCl₃. The combined organic extracts were washed with 50 mL of saturated aqueous NaHCO₃ and 50 mL of brine, dried (Na₂SO₄) and concentrated in vacuo to yield 2.05 g of amide 103 as a colorless oil that crystallized slowly to give a white solid: mp 103-104°C (lit.¹ 100-103 °C); IR (KBr) 3293, 1592,
1496, 1286, 1109, 1052, 814 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.67 (m, 1H, NCHCH$_2$), 1.76 (m, 1H, NCH$_2$CH$_2$), 1.85 (m, 1H, NCH$_2$CH$_2$), 2.16 (m, 1H, NCHCH$_2$), 3.30 (m, 2H, NCH$_2$), 3.71 (dd, $J = 11.4$, 7.44 Hz, 1H, CH$_2$OH), 3.85 (br s, 4H, CH$_3$ and CH$_2$OH), 4.36 (br q, 1H, NCH), 4.50 (br, 1H, OH), 6.93 (d, $J = 8.4$ Hz, 1H, ArH), 7.00 (t, $J = 7.4$ Hz, 1H, ArH), 7.28 (dd, $J = 6.7$, 1.1 Hz, 1H, ArH), 7.36 (td, $J = 7.9$, 1.6 Hz, 1H, ArH); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 24.5 (t), 28.7 (t), 49.3 (t), 55.7 (q), 61.2 (d), 66.8 (br t), 111.2 (d), 121.0 (2C, d + s), 126.8 (s), 127.6 (d), 130.7 (d), 155.0 (s); exact mass calcd. for C$_{13}$H$_{17}$NO$_3$: m/z 235.1209, found m/z 235.1209.

![Chemical Structure](image)

**(S)-N-(o-Methoxybenzoyl)-2-methoxymethylpyrrolidine (99).** To a stirred solution of 2.49 g (10.4 mmol) of alcohol 103 and 2.15 mL (4.90 g; 34.50 mmol) of methyl iodide in 45 mL of anhydrous THF at room temperature under nitrogen was added 813 mg (20.33 mmol) of NaH (60% dispersion in mineral oil). The resulting mixture was heated to reflux for 6 h. TLC analysis (silica gel; EtOAc-hexanes 3:1) showed no remaining starting material. The solution was cooled to room temperature and concentrated in vacuo. The pasty white residue was dissolved in 125 mL of CHCl$_3$ and
the CHCl₃ solution was washed sequentially with 75 mL of 10% aqueous HCl and 75 mL of brine. The organic phase was dried (Na₂SO₄) and concentrated in vacuo to yield 3.05 g of the crude product as a yellow oil. The crude product was purified by flash chromatography over 150 g of silica gel (EtOAc - hexanes 3:1), to yield 2.44 g (94%) of ether 99 as a pale yellow oil: IR (Neat) 2972, 2881, 2836, 1632, 1415, 1248, 1110, 756 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.75 (m, 1H, NCH₂CH₂), 1.90 (m, 1H, NCH₂CH₂), 1.95 (m, 1H, NCHCH₂), 2.01 (m, 1H, NCHCH₂), 3.03 and 3.20 (2 m, 0.4H + 1.6H, NCH₂), 3.09 and 3.41 (2 s, 1H + 2H, CH₂OCH₃), 3.55 (dd, J = 9.7, 6.9 Hz, 1H, CH₂OCH₃), 3.73 (dd, J = 9.4, 3.3 Hz, 1H, CH₂OCH₃), 3.78 and 4.41 (2m, 0.3H + 0.6H, NCH), 3.82 (s, 3H, ArOMe), 6.91 (d, J = 8.3 Hz, 1H, ArH), 6.97 (t, J = 7.3 Hz, 1H, ArH), 7.23 (d, J = 7.4 Hz, 1H, ArH), 7.32 (t, J = 7.2 Hz, 1H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 22.2 (t, NCH₂CH₂), 24.2 (t, NCH₂CH₂), 27.7 (t, NCH₂CH₂), 28.4 (t, NCH₂CH₂), 45.7 (t, CH₂OMe) 48.4 (t, NCH₂), 55.5 (q, ArOCH₃), 55.6 (q, ArOCH₃), 56.2 (d, NCH), 57.2 (d, NCH), 58.7 (q, CH₂OCH₃), 59.1 (q, CH₂OCH₃), 72.3 (t, CH₂OCH₃), 73.4 (t, NCH₂), 111.1 (d, Ar =CH), 120.8 (d, Ar =CH), 127.2 (s, Ar C₆), 127.7 (d, Ar =CH), 130.2 (d, Ar =CH), 155.0 (s, Ar C₆), 155.2 (s, Ar C₆), 167.9 (s, C=O), 168.0 (s, C=O) [Note: split NMR signals are due to the presence of amide rotamers]; exact mass calcd. for C₁₄H₁₉NO₃ m/z 249.1366, found m/z 249.1352.
(2'S,6S)-6-(2- t-Butoxyethyl)-1-methoxy-6-[[2'-(methoxymethyl)-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (104). Into a stirred solution of 2.45 g (9.81 mmol) of amide 99 and 0.94 mL (729 mg; 9.83 mmol) of t-butanol in 50 mL of dry tetrahydrofuran at -78°C under a nitrogen atmosphere, was condensed 600 mL of NH₃. Potassium was added to the resulting solution in small portions until the reaction medium sustained a deep blue-black color. 2-Bromoethyl t-butyl ether (3.79 g, 20.9 mmol) was then added over 5 min and stirring was continued at -78°C for 1 h. To the reaction mixture was added 5 g (93 mmol) of solid NH₄Cl. The resulting mixture was allowed to warm up and the ammonia was allowed to evaporate under a stream of N₂. To the white residue was added 200 mL of brine, and the resulting mixture was extracted with three 200-mL portions of CH₂Cl₂. The combined organic extracts were washed with 200 mL of 10% aqueous Na₂S₂O₃, 200 mL of water, and 200 mL of brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 150 g of silica gel (EtOAc - hexane, 1:1), to yield 1.53 g (44%) of 104 as a yellow oil: IR (Neat) 2972, 2876, 1634, 1400, 1384, 1115, 1074 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.11 (s, 9H, t-Bu), 1.68 (m, 1H, NCH₂CH₂), 1.79 (m, 2H, NCHCH₂), 1.84 (m, 1H, NCH₂CH₂), 1.98 (m, 1H, t-BuOCH₂CH₂), 2.25 (m, 1H, t-BuOCH₂CH₂), 2.82 (m, 2H, =CHCH₂CH=), 3.22 (m, 2H,
NCH$_2$ + CH$_2$OCH$_3$), 3.29 (m, 2H, t-BuO-CH$_2$), 3.30 (s, 3H, CH$_2$OCH$_3$), 3.48 (s, 3H, =COMe), 3.57 (m, 2H, NCH$_2$ + CH$_2$OCH$_3$), 4.27 (m, 1H, N-CH), 4.69 (br t, $J$ = 3.3 Hz, 1H, CH=COMe), 5.41 (br dt, $J$ = 8.1, 1.7 Hz, 1H, CH=CH-CH$_2$), 5.81 (br dt, $J$ = 9.8, 3.1 Hz, 1H, CH=CH-CH$_2$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 24.9 (t), 26.2 (t), 26.7 (t), 27.5 (q), 37.2 (t), 45.8 (t), 50.5 (s), 53.9 (q), 58.0 (d), 58.3 (t), 58.8 (q), 71.9 (t), 72.5 (s), 92.1 (d), 125.5 (d), 126.8 (d), 153.3 (s), 169.8 (s); exact mass calcd. for C$_{20}$H$_{33}$NO$_4$ m/z 351.2411, found m/z 351.2414.

(5S)-6-Methoxy-2-oxaspiro[4.5]deca-6,9-dien-1-one (107). To a stirred solution of 351 mg (1.00 mmol) of amide 104 and 0.33 mL (294 mg; 1.98 mmol) of triethyl orthoformate in 45 mL of anhydrous methanol was added 5 drops of phosphorus oxychloride. The mixture was stirred at room temperature under N$_2$ atmosphere for 12 h, after which TLC analysis (silica gel; EtOAc - hexanes, 1:1) showed no remaining starting material. Solid NaHCO$_3$ was added until CO$_2$ evolution ceased, and the resulting mixture was filtered and concentrated in vacuo to yield 1.28 g of a white paste. The crude product was purified by flash chromatography over 65 g of silica gel (EtOAc – hexanes, 1:3), to yield 100 mg (55%) of lactone 107 as a salmon-colored oil: IR (Neat) 2938, 2834, 1769, 1725 cm$^{-1}$. 

\[ \text{107} \]
1374, 1214, 1169, 1030 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400MHz) \(\delta\) 2.19 (m, 1H, CH\(_2\)CH\(_2\)O), 2.68 (m, 1H, CH\(_2\)CH\(_2\)O), 2.90 (m, 2H, =CHCH\(_2\)CH=), 3.55 (s, 3H, CH\(_3\)), 4.39 (m, 2H, CH\(_2\)O), 4.89 (t, \(J = 3.5\) Hz, 1H, CH=COCH\(_3\)), 5.54 (dt, \(J = 9.8, 2\) Hz, 1H, CH=CHCH\(_2\)), 5.98 (dt, \(J = 9.4, 1.6\) Hz, 1H, CH=CHCH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 26.2 (t), 35.4 (t), 48.1 (s), 54.4 (q), 66.4 (t), 93.4 (d), 125.0 (d), 127.0 (d), 125.4 (s), 177.7 (s); exact mass calcd. for C\(_{10}\)H\(_{12}\)O\(_3\): m/z 180.0787, found m/z 180.0782.

(10S)-1,4,8-Trioxadispiro[4.0.4.4]tetradec-11-en-7-one (106). A mixture of 8 mL of benzene, 2 drops of phosphorus oxychloride, and 1 mL of ethylene glycol was heated to reflux for 1 h. Approximately 6 mL of partly cloudy benzene was collected in a Dean-Stark trap. The mixture was cooled to room temperature, a solution of 55 mg (0.31 mmol) of lactone 107 in 0.5 mL of anhydrous benzene was added in one portion, and stirring was continued at room temperature for 4 h. TLC analysis (silica gel; EtOAc–hexanes, 1:1) showed that no more starting material was being consumed. To the reaction mixture was added 4 mL of saturated aqueous NaHCO\(_3\), 4 mL of H\(_2\)O, and 8 mL of CH\(_2\)Cl\(_2\). The organic layer was separated and the aqueous layer was extracted with two 4-mL portions of CH\(_2\)Cl\(_2\). The combined organic layers were washed with 8 mL of brine,
dried (Na₂SO₄) and concentrated in vacuo to yield 54 mg of a yellow oil. The crude product was purified by flash chromatography over 2.7 g of silica gel (EtOAc–hexanes, 1:1), to yield 16 mg (25%) of ketal 106 as a colorless oil: IR (neat): 3028, 2985, 2894, 1757, 1278, 1180, 1030, 696 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.78 and 2.2-2.4 (2 m, 1H + 3H, =C(CH₂)₂), 2.12 and 2.64 (2 m, 1H + 1H, CH₂CH₂O), 4.06 (m, 4H, OCH₂CH₂O), 4.29 (t, J = 8 Hz, 2H, OCH₂), 5.44 (dt, J = 9.3, 2.0 Hz, 1H, =CH), 5.98 (dt, J = 10.7, 3.7 Hz, 1H, =CHCH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 24.2 (t), 26.9 (t), 31.1 (t), 52.3 (s), 65.0 (t), 65.1 (t), 65.6 (t), 109.0 (s), 126.3 (d), 130.5 (d), 176.7 (s); exact mass calcd. for C₁₁H₁₄O₄ m/z 210.0892, found m/z 210.0884.

(2'S,6S)-6-Methyl-1-methoxy-6-[[2'-(methoxymethyl)pyrrolidinyl]-carbonyl]-1,4-cyclohexadiene (108). Into a stirred solution of 252 mg (1.10 mmol) of amide 99 and 105 µL (1.10 mmol) of t-butanol in 5 mL of dry tetrahydrofuran at -78°C under a nitrogen atmosphere, was condensed 60 mL of NH₃. Potassium (130 mg, 3.35 mmol) was added to the resulting solution in small portions until the reaction medium sustained a deep blue-black color. Methyl iodide (140 µL, 319 mg, 2.25 mmol) was then
added in one portion and stirring was continued at -78°C for 1 h. To the reaction mixture was added 0.5 g (9 mmol) of solid NH₄Cl. The resulting mixture was allowed to warm up and the ammonia was allowed to evaporate under a stream of N₂. To the white residue was added 20 mL of brine, and the resulting mixture was extracted with three 20-mL portions of CH₂Cl₂. The combined organic extracts were washed with 20 mL of 10% aqueous Na₂S₂O₃, 20 mL of water, and 20 mL of brine, dried (Na₂SO₄) and concentrated in vacuo, to yield 249 mg of a yellow oil. The crude product was chromatographed over 12 g of silica gel (EtOAc - hexane, 1:1) to give 214 mg (73%) of 108 as a colorless oil:

\[ \text{1H NMR (CDCl}_3, 400 MHz) \delta 1.42 (s, 3H, CH}_3), 1.7-2.0 (m, 4H, CH}_2), 2.85 (m, 2H, =CHCH}_2), 3.30 (m, 2H, NCH}_2 + CH}_2OCH}_3), 3.34 (s, 3H, CH}_2OCH}_3), 3.51 (s, 3H, =COCH}_3), 3.61 (m, 2H, NCH}_2 + CH}_2OMe), 4.30 (m, 1H, NCH), 4.64 (br t, J = 3.3 Hz, 1H, CH=COMe), 5.49 (br d, J = 9.8 Hz, 1H, =CHCH}_2), 5.74 (dt, J = 9.8, 3.3 Hz, 1H, CH=CHCH}_2). \]

**Acetal 109.** A stirred mixture of 2 mL of ethylene glycol, 2 drops of POCl₃, and 20 mL of benzene was heated to reflux under N₂ for 1.5 h during which 18 mL of partly
cloudy benzene was collected in a Dean-Stark trap. After the mixture was cooled to room temperature, 163 mg (0.61 mmol) of amide 108 was added in one portion as a solution in 1 mL of anhydrous benzene. Stirring was then continued at room temperature for 3 h. TLC analysis (silica gel; EtOAc–hexanes, 1:1) showed no remaining starting material. To the reaction mixture was added 7 mL of saturated aqueous NaHCO₃, 7 mL of H₂O, and 15 mL of CH₂Cl₂. The organic layer was separated and the aqueous layer was extracted with two 15-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried (Na₂SO₄) and concentrated in vacuo, to yield 162 mg of a yellow oil. The crude product was purified by flash chromatography over 8 g of silica gel (EtOAc–hexanes, 1:1), to yield 72 mg (43%) of ketal 109, as a colorless oil: IR (neat): 2969, 2890, 1616, 1399, 1381, 1120, 1094 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.40 (s, 3H, CH₃), 1.65-1.95 (m, 6H, =CHCH₂CH₂ + NCH₂CH₂), 2.16 (m, 1H, =CHCH₂), 2.30 (m, 1H, =CHCH₂), 3.30 (s, 3H, OCH₃), 3.35 (m, 1H, CH₂OCH₃), 3.57 (br d, J = 2.8 Hz, 1H, CH₂OCH₃), 3.62 (m, 1H, NCH₂), 3.69 (m, 1H, NCH₂), 3.81-3.93 (m, 4H, OCH₂CH₂O), 4.27 (m, 1H, NCH), 5.62 (br s, 2H, CH=CH); ¹³C NMR (CDCl₃, 125 MHz) δ 24.1 (t), 24.9 (t), 25.1 (q), 26.4 (t), 29.0 (t), 48.8 (t), 52.7 (s), 58.2 (d), 58.6 (q), 64.7 (t), 64.9 (t), 71.6 (t), 111.2 (s), 123.8 (d), 132.5 (d), 171.3 (s); exact mass calcd. for C₁₆H₂₅NO₄: m/z 295.1785, found m/z 295.1789.
**Iodolactone 110.** To a stirred solution of 60 mg (0.22 mmol) of amide 109 in 2.5 mL of THF and 0.25 mL of H2O was added at room temperature 128 mg (0.57 mmol) of N-iodosuccinimide. The mixture was stirred at room temperature in the absence of light for 60 h. TLC analysis (EtOAc–hexanes, 1:1) showed the reaction had stopped. To the dark brown reaction mixture was added 1.2 mL of saturated aqueous NaHSO3 and stirring was continued for 20 min. The resulting mixture was diluted with 3 mL of Et2O. The organic layer was separated and the aqueous layer was extracted with 2 mL of Et2O. The combined organic layers were washed with 3 mL of brine, dried (Na2SO4) and concentrated in vacuo, to yield 80 mg of a yellow oil. The crude mixture was separated by flash chromatography over 4 g of silica gel (EtOAc-hexanes 3:1), to yield 12 mg (20%) of starting material 109 and 31 mg (44%) of lactone 110 as a white solid: mp 137-139°C; IR (KBr) 2958, 2870, 1779, 1148, 1078 cm⁻¹; ¹H NMR (CDCl3, 400 MHz) δ 1.18 (s, 3H, CH3), 1.90 (m, 2H, (RO)₂CCH2), 2.13 (m, 1H, COOCHCH2), 2.53 (m, 1H, COOCHCH2), 3.85 (m, 1H, O(CH2)2O), 3.99 (m, 2H, O(CH2)2O), 4.12 (m, 1H, O(CH2)2O), 4.16 (dd, J = 5.0, 1.7 Hz, 1H, CHI), 4.73 (t, J = 4.9 Hz, 1H, CHO); ¹³C NMR (CDCl3, 125 MHz) δ 12.8 (q), 23.6 (t), 25.6 (d), 30.2 (t), 51.6 (s), 65.1 (t), 65.4 (t), 78.2 (d), 105.8 (s), 172.4 (s); exact mass calcd. for C₁₀H₁₃IO₄; m/z 323.9859, found m/z 323.9866.
2-Bromoethyl acetate (114).\textsuperscript{131} To a stirred solution of 4.83 g (38.6 mmol) of 2-bromoethanol (85) in 40 mL of anhydrous dichloromethane at room temperature under N\textsubscript{2} was added a solution of 4.2 mL (4.6 g, 64 mmol) of acetyl chloride in 40 mL of anhydrous CH\textsubscript{2}Cl\textsubscript{2}, dropwise over 10 min, followed by addition of 5.4 mL (3.9 g, 39 mmol) of triethylamine via syringe over 2 min. Stirring was continued at room temperature for 3 h. The reaction mixture was diluted with 400 mL of CH\textsubscript{2}Cl\textsubscript{2} and the resulting solution was washed with 400 mL of H\textsubscript{2}O, 400 mL of saturated aqueous NaHCO\textsubscript{3}, 400 mL of H\textsubscript{2}O, dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo, to yield 5.39 g of crude product as a yellow liquid. This material was distilled under reduced pressure to yield 4.40 g (68\%) of ester 114 as a colorless liquid: bp = 77-85 °C @ 45 mmHg (lit.\textsuperscript{132} 79-83 °C @ 45 mmHg); IR (neat): 2971, 1743, 1221 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 2.11 (s, 3H, CH\textsubscript{3}), 3.52 (t, \(J = 6.2\) Hz, 2H, CH\textsubscript{2}Br), 4.39 (t, \(J = 6.2\) Hz, 2H, CH\textsubscript{2}OAc); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 20.7 (t), 28.6 (t), 63.8 (q), 170.5 (s).

2-Bromoethyl pivalate (113).\textsuperscript{99,133} To a stirred solution of 4.20 g (33.6 mmol) of 2-bromoethanol (85) in 40 mL of anhydrous dichloromethane, at room temperature under N\textsubscript{2} was added a solution of 6.25 mL (6.12 g, 50.7 mmol) of trimethylacetyl chloride in 40 mL of anhydrous CH\textsubscript{2}Cl\textsubscript{2}, dropwise over 10 min, followed by addition of
4.7 mL (3.4 g, 34 mmol) of triethylamine, via syringe over a 2 min period. Stirring was continued at room temperature for 3 h. The reaction mixture was diluted with 400 mL of CH₂Cl₂, and the resulting solution was washed with 400 mL of H₂O, 400 mL of saturated aqueous NaHCO₃, 400 mL of H₂O, dried (Na₂SO₄), and concentrated in vacuo, to yield 6.70 g of crude product as a yellow liquid. This material was distilled under reduced pressure, to yield 5.75 g of impure 113 as a pale yellow liquid. This liquid was fractionally distilled under reduced pressure to yield 4.07 g (58%) of ester 113 as a colorless liquid: bp = 94-98 °C @ 45 mmHg (lit. 133-212 °C @ 760 mmHg); IR (neat): 2973, 2874, 1733, 1481, 1283, 1149 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.22 (s, 9H, t-Bu), 3.51 (t, J = 6.0 Hz, 2H, CH₂Br), 4.36 (t, J = 6.0 Hz, 2H, CH₂OAc); ¹³C NMR (CDCl₃, 100 MHz) δ 27.1 (q), 28.9 (t), 38.8 (s), 63.6 (q), 178.0 (s). Some impurities were visible by ¹³C NMR.

(2'S,6S)-6-(2-Acetoxyethyl)-1-methoxy-6-[(2’-(methoxymethyl)pyrrolidinyl)-carbonyl]-1,4-cyclohexadiene (115). Into a stirred solution of 250 mg (1.00 mmol) of amide 99 and 96 µL (74 mg, 1.00 mmol) of t-butanol in 5 mL of dry tetrahydrofuran, at -78°C under nitrogen atmosphere, was condensed 60
mL of NH₃. Potassium (180 mg, 4.7 mmol) was added to the resulting solution in small portions until the reaction medium sustained a deep blue-black color. 2-Bromoethyl acetate (114) (335 mg, 2.00 mmol) was then added in one portion, and stirring was continued at -78°C for 1 h. To the reaction mixture were added 0.6 g (11 mmol) of solid NH₄Cl. The resulting mixture was allowed to warm up and the ammonia was allowed to evaporate under a stream of N₂. To the white residue was added 20 mL of brine, and the resulting mixture was extracted with three 20-mL portions of CH₂Cl₂. The combined organic extracts were washed with 20 mL of 10% aqueous Na₂S₂O₃, 20 mL of water, and 20 mL of brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (EtOAc–hexanes, 1:1) to give 167 mg (49%) of 115 as a colorless oil: IR (Neat) 1737, 1633, 1388, 1240 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.7-1.9 (m, 4H, CH₂), 1.99 (s, 3H, COCH₃), 2.08 (m, 1H, AcOCH₂CH₂), 2.43 (m, 1H, AcOCH₂CH₂), 2.85 (m, 2H, =CHCH₂), 3.24 (m, 1H, NCH₂), 3.32 (m, 1H, CH₂OCH₃), 3.33 (s, 3H, CH₂OCH₃), 3.52 (s, 3H, =COCH₃), 3.59 (m, 2H, NCH₂ + CH₂OMe), 3.99 (m, 2H, CH₂OAc), 4.30 (m, 1H, NCH), 4.76 (dt, J = 9.8 Hz, 1H, CH=COMe), 5.41 (br d, J = 9.8 Hz, 1H, CH=CH₂), 5.88 (dt, J = 9.8, 3.3 Hz, 1H, CH=CH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 21.0 (q), 24.9 (t), 26.3 (t), 26.7 (t), 34.7 (t), 45.9 (t), 50.4 (s), 54.1 (q), 58.2 (d), 58.9 (q), 61.8 (t), 72.0 (t), 92.9 (d), 126.2 (d), 126.3 (d), 152.5 (s), 169.4 (s), 171.1 (s); exact mass calcd. for C₁₈H₂₇NO₅ m/z 337.1890, found m/z 337.1899.
(2'S,6S)-6-(2-Trimethylacetoxyethyl)-1-methoxy-6-[[2-(methoxymethyl)-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (116). Into a stirred solution of 9.01 g (36.14 mmol) of amide 99 and 3.45 mL (2.67 g, 36.1 mmol) of t-butanol in 180 mL of dry tetrahydrofuran, at -78°C under nitrogen atmosphere was condensed 2000 mL of NH₃. Potassium was added to the resulting solution in small portions until the reaction medium sustained a deep blue-black color. 2-Bromoethyl pivalate (113) (15.17 g, 72.6 mmol) was then added in one portion and stirring was continued at -78°C for 1.5 h. To the reaction mixture was added 18 g (336 mmol) of solid NH₄Cl. The resulting mixture was allowed to warm up and the ammonia was allowed to evaporate under a stream of N₂. To the white residue was added 600 mL of brine and the resulting mixture was extracted with three 600-mL portions of CH₂Cl₂. The combined organic extracts were washed with 600 mL of 10% aqueous Na₂S₂O₃, 600 mL of water, and 600 mL of brine, dried (Na₂SO₄) and concentrated in vacuo to yield 18.13 g of a yellow oil. The crude product was chromatographed over 350 g of silica gel (EtOAc–hexanes, 1:1) to give 11.08 g (81%) of 116 as a pale yellow oil: IR (Neat) 1725, 1634, 1397, 1381, 1285, 1164 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.15 (s, 9H, t-Bu), 1.72 (m, 1H, NCH₂CH₂), 1.8-1.9 (m, 3H, NCHCH₂), 2.10 (m, 1H, PivOCH₂CH₂), 2.41 (m, 1H, PivOCH₂CH₂), 2.85 (m, 2H, =CHCH₂), 3.25 (m, 1H, NCH₂), 3.33 (s with underlying m, 4H, CH₂OCH₃ and
150

CH$_2$OCH$_3$), 3.52 (s, 3H, =COCH$_3$), 3.59 (m, 2H, NCH$_2$ + CH$_2$OMe), 3.93 (m, 1H, CH$_2$OPiv), 4.00 (m, 1H, CH$_2$OPiv), 4.29 (m, 1H, NCH), 4.77 (t, $J = 3.3$ Hz, 1H, CH=COMe), 5.43 (dt, $J = 9.8$, 1.9 Hz, 1H, CH=CH-CH$_2$), 5.87 (dt, $J = 9.8$, 3.1 Hz, 1H, CH=CH-CH$_2$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 24.9 (t), 26.3 (t), 26.6 (t), 27.1 (q), 34.6 (t), 38.6 (s), 45.9 (t), 50.4 (s), 54.2 (q), 58.2 (d), 58.9 (q), 61.7 (t), 71.9 (t), 93.0 (d), 126.2 (d, 2C), 152.5 (s), 169.5 (s), 178.6 (s); exact mass calcd. for C$_{21}$H$_{33}$NO$_5$ $m/z$ 379.2360, found $m/z$ 379.2327.

(2’S,6S)-6-(2-Methoxyethyl)-1-methoxy-6-[[2’-(methoxymethyl)-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (117). Into a stirred solution of 256.5 mg (1.03 mmol) of amide 99 and 100 $\mu$L (78 mg, 1.05 mmol) of t-butanol in 5 mL of dry tetrahydrofuran, at -78°C under nitrogen atmosphere was condensed 60 mL of NH$_3$. Potassium (245 mg, 6 mmol) was added to the resulting solution in small portions until the reaction medium sustained a deep blue-black color. 2-Bromoethyl methyl ether (112) (295 mg, 2.12 mmol) was then added in one portion and stirring was continued at -78°C for 1 h. To the reaction mixture were added 0.5 g (10 mmol) of solid NH$_4$Cl. The
resulting mixture was allowed to warm up, and the ammonia was allowed to evaporate under a stream of N₂. To the white residue was added 20 mL of brine and the resulting mixture was extracted with three 20-mL portions of CH₂Cl₂. The combined organic extracts were washed with 20 mL of 10% aqueous Na₂S₂O₃, 20 mL of water, and 20 mL of brine, dried (Na₂SO₄) and concentrated in vacuo to yield 350 mg of an orange oil. The crude product was purified by flash chromatography over 17 g of silica gel (EtOAc-hexanes, 1:1), to yield 144 mg (45%) of the alkylation product 117 as a pale yellow oil: IR (Neat) 3290, 2929, 2876, 2828, 1633, 1381, 1208, 1164 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.75 (m, 1H, NCH₂CH₂), 1.8-1.9 (m, 3H, NCHCH₂), 2.05 (m, 1H, MeOCH₂CH₂), 2.38 (m, 1H, MeOCH₂CH₂), 2.85 (m, 2H, =CHCH₂), 3.2-3.4 (m with 2 s at 3.28 and 3.35, 10H, NCH₂ + CH₂OCH₃ + CH₂OCH₃ + CH₂CH₂OCH₃ + MeOCH₂CH₂), 3.52 (s, 3H, =COCH₃), 3.60 (m, 1H + 1H, NCH₂ + CH₂OCH₃), 4.32 (m, 1H, NCH), 4.74 (t, J = 3.4 Hz, 1H, CH=COMe), 5.44 (dt, J = 9.8, 1.9 Hz, 1H, CH=CH-CH₂), 5.87 (dt, J = 9.8, 3.1 Hz, 1H, CH=CH-CH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 24.9 (t), 26.3 (t), 26.7 (t), 35.5 (t), 46.0 (t), 50.5 (s), 54.1 (q), 58.2 (d), 58.3 (q), 58.9 (q), 69.6 (t), 72.0 (t), 92.4 (d), 125.8 (d), 126.8 (d), 153.2 (s), 169.8 (s); exact mass calcd. for C₁₇H₂₇NO₄ m/z 309.1941, found m/z 309.1800.
2-(2-Methoxyethyl)-2-(2-methoxymethylpyrrolidine-1-carbonyl)cyclohex-3-enone (119). A stirred mixture of 10 mL of benzene, 0.7 mL of ethylene glycol, and 0.6 µL (1.0 mg, 0.007 mmol) of phosphorus oxychloride was refluxed until most of the benzene was collected in a Dean-Stark trap. The mixture was then allowed to cool down to room temperature, followed by addition of a solution of 65 mg (0.21 mmol) of enol ether 117 in 0.5 mL of anhydrous benzene. Stirring was continued at room temperature for 3 days. To the reaction mixture were added 2 mL of saturated aqueous NaHCO₃, 2 mL of water, and 4 mL of CH₂Cl₂. The organic layer was separated, and the aqueous layer was extracted with 2 mL of CH₂Cl₂, and the combined organic layers were washed with 2 mL of brine, dried (Na₂SO₄), and concentrated in vacuo, to yield 68 mg of a yellow oil. The crude product was purified by flash chromatography over 3.5 g of silica gel (EtOAc/hexanes 1:1), to yield 18 mg (29%) of ketone 119 as a colorless oil: IR (neat) 2927, 2892, 1710, 1633, 1400 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.75 (m, 1H, NCH₂CH₂), 1.90 (m, 3H, NCH₂CH₂), 2.05 (dt, J = 14.2, 5.8 Hz, 1H, CH₂CH₂OMe), 2.38 (ddd, J = 14.2, 7.1, 5.9 Hz, 1H, CH₂CH₂OMe), 2.48-2.69 (m, 4H, HC=CH₂CH₂C=O), 3.08 (m, 1H, NCH₂), 3.22 (s, 3H, CH₂OMe), 3.35 (m, 1H, NCH₂), 3.36 (s, 3H, CH₂CH₂OMe), 3.37 (m, 1H, CH₂OMe), 3.40 (m, 1H, CH₂CH₂OMe), 3.54 (m, 1H, CH₂CH₂OMe), 3.63 (br dd, J = 9.2, 2.5 Hz, 1H, CH₂OMe), 4.26 (br m, 1H, NCH), 5.67
(br d, $J = 9.7$ Hz, 1H, H=CHCH$_2$), 6.00 (dt, $J = 9.7, 3.6$ Hz, 1H, H=CHCH$_2$); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 24.9 (t), 26.1 (t), 27.1 (t), 36.8 (t), 37.1 (t), 47.1 (t), 58.4 (d), 58.7 (q), 59.4 (q), 60.5 (s), 69.5 (t), 72.3 (t), 128.5 (d), 129.5 (d), 169.0 (s), 208.1 (s).

[1-(2-Hydroxyethyl)-2-methoxycyclohexa-2,5-dienyl]-(2-methoxymethyl-pyrrolidin-1-yl)methanone (125). To a stirred solution of 340 mg (1.01 mmol) of acetate 115 in 4.5 mL of methanol and 0.5 mL of H$_2$O was added 285 mg (2.06 mmol) of solid potassium carbonate, and the resulting mixture was stirred at room temperature for 1 h. TLC analysis (silica gel; EtOAc) showed no remaining starting acetate. The reaction mixture was diluted with 25 mL of CH$_2$Cl$_2$, washed sequentially with 5 mL of H$_2$O and 5 mL of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo, to yield 254 mg of a pale yellow oil. The crude product was purified by flash chromatography over 13 g of silica gel (EtOAc), to yield 222.3 mg (75%) of alcohol 125 as a colorless oil (note: 125 is acid-sensitive!): IR (neat) 3422, 2932, 2880, 1612, 1406, 1210, 1164 cm$^{-1}$; $^1$H NMR (C$_6$D$_6$, 500 MHz) $\delta$ 1.33 (m, 1H, NCH$_2$CH$_2$), 1.50 (m, 1H, NCHCH$_2$), 1.61 (m, 1H, NCH$_2$CH$_2$), 1.76 (m, 1H, NCHCH$_2$), 2.20 (dt, $J = 14.3, 5.2$ Hz, 1H, CH$_2$CH$_2$OH), 2.34 - 2.56 (m, 2H, =CHCH$_2$CH=), 2.79 (m, 1H, CH$_2$CH$_2$OH), 3.08 (s, 3H, CH$_3$), 3.10 (s, 3H, CH$_3$), 3.10 (m,
1H, NCH₂), 3.46 (m, 1H, NCH₂), 3.50 (dd, J = 9.3, 6.2 Hz, 1H, CH₂OMe), 3.61 (dd, J = 9.3, 3.0 Hz, 1H, CH₂OMe), 3.67 (t, J = 5.1 Hz, 1H, OH), 3.88 (m, 2H, CH₂OH), 4.21 (t, J = 3.4 Hz, 1H, HÇ=COMe), 4.43 (m, 1H, NH), 5.50 (dt, J = 9.9, 3.1 Hz, 1H, HÇ=CHCH₂), 5.60 (dt, J = 9.9, 2.0 Hz, 1H, HÇ=CHCH₂); ¹³C NMR (CD₆, 125 MHz) δ 25.2 (t), 26.5 (t), 26.6 (t), 42.0 (t), 46.4 (t), 51.6 (q), 53.9 (q), 58.7 (d), 58.8 (q), 59.1 (t), 72.4 (t), 91.2 (d), 125.7 (d), 127.0 (d), 155.4 (s), 170.7 (s); exact mass calcd. for C₁₆H₂₅NO₄ + H m/z 296.1862, found m/z 296.1873.

(2-Methoxymethylpyrrolidin-1-yl)-(7a-methoxy-2,3,7,7a-tetrahydro-6H-benzofuran-3a-yl)methanone (126). To a stirred solution of 797 mg (0.27 mmol) of enol ether 125 in 2 mL of methanol was added 1 µL (1.1 mg, 0.014 mmol) of acetyl chloride. The resulting solution was stirred at room temperature for 20 h. TLC analysis (silica gel, EtOAc) indicated that the major part of the starting material remained. A further 2 µL (2.2 mg, 0.028 mmol) of acetyl chloride was added, and stirring was continued for 15 min. TLC analysis did not indicate any further change. The reaction mixture was diluted with 15 mL of CH₂Cl₂, sequentially washed with 5 mL of H₂O and 5 mL of sat. aq. NaHCO₃, dried (Na₂SO₄), and concentrated in vacuo, to yield 93.2 mg of a
pale yellow oil. The crude mixture was separated by flash chromatography over 4.5 g of silica gel (EtOAc/hexanes 3:1), to yield 21.5 mg (28%) of internal acetal 126 as a colorless oil and 36.8 mg (47%) of starting material 125 as a colorless oil. Data for 126:

IR (neat) 2955, 1626, 1399, 1098, 1045 cm⁻¹; ¹H NMR (C₆D₆, 500 MHz) δ 1.33 (m, 1H, CH₂CH₂O), 1.39 (m, 1H, NCH₂CH₂), 1.52 (m, 1H, NCHCH₂), 1.56 (m, 1H, CH₂CH₂O), 1.66 (m, 1H, NCH₂CH₂), 1.80 (m, 1H, NCHCH₂), 1.86 (m, 1H, =CHCH₂), 1.98 (m, 1H, CH₂C(OR)₂), 2.10 (m, 1H, =CHCH₂), 2.13 (m, 1H, CH₂C(OR)₂), 3.13 (m, 1H, NCH₂), 3.14 (s, 3H, CH₃), 3.22 (s, 3H, CH₃), 3.44 (br, 1H, CH₂OMe), 3.56 (br m, 1H, NCH₂), 3.65 (m, 1H, CH₂CH₂O), 3.70 (br, 1H, CH₂OMe), 3.92 (m, 1H, CH₂CH₂O), 4.51 (m, 1H, NCH), 5.41 (dd, J = 9.9, 2.0 Hz, 1H, HC=CHCH₂), 5.54 (ddd, J = 9.8, 5.8, 2.1 Hz, 1H, HC=CHCH₂); ¹³C NMR (C₆D₆, 125 MHz) δ 22.8 (t), 25.0 (br t), 26.6 (t), 27.1 (t), 38.2 (t), 47.8 (t), 48.3 (q), 58.5 (br d), 58.7 (q), 59.7 (s), 65.4 (t), 72.3 (t), 108.0 (s), 126.8 (d), 130.7 (d), 168.3 (s); exact mass calcd. for C₁₆H₂₅NO₄ m/z 295.1785, found m/z 295.1780.

**Internal Hemiacetal 127 and acetic acid 2-[1-(2-Methoxymethylpyrrolidine-1-carbonyl)-6-oxocyclohex-2-enyl]ethyl ester (128).** To a stirred solution of 336 mg (1.00 mmol) of enol ether 115 in 4.7 mL of THF was added 0.3 mL of a 10% aqueous
HCl solution (0.82 mmol HCl), and the resulting solution was stirred at rt for 6 h. The reaction mixture was diluted with 25 mL of Et₂O, washed with 15 mL of H₂O and 15 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 249 mg of a yellow oil. The crude mixture was separated by flash chromatography over 12.5 g of silica gel (EtOAc-hexanes, 50:50) to yield 131 mg (40%) of starting 115, 68 mg (21%) of ketone 128 as a colorless oil, and 24 mg (9%) of hemiacetal 127 as a colorless oil. Data on 128: IR (film) 2970, 1736, 1711, 1635, 1402, 1238 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.75 (m, 1H, NCH₂CH₂), 1.88 (m, 3H, NCH₂CH₂ + NCHCH₂), 1.87 (s, 3H, CH₃CO), 2.10 (m, 1H, CH₂CH₂OAc), 2.38 (m, 1H, CH₂CH₂OAc), 2.53 (m, 1H, CH₂C=O), 2.57 (m, 1H, CH₂C=O), 2.61 (m, 2H, =CHCH₂), 3.07 (m, 1H, NCH₂), 3.35 (s with underlying m, 5H, OCH₃ + NCH₂ + CH₃OMe), 3.61 (dd, J = 9.1, 2.3 Hz, 1H, CH₂OMe), 4.16 (m, 2H, CH₂OAc), 4.25 (br m, 1H, CHN), 5.68 (d, J = 9.7 Hz, 1H, HC=CHCH₂), 6.02 (m, 1H, HC=CHCH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 20.8 (q), 24.5 (t), 25.8 (t), 26.6 (t), 35.3 (t), 36.4 (t), 46.7 (t), 58.0 (d), 59.0 (q), 60.0 (s), 61.4 (t), 71.8 (t), 128.3 (d), 128.8 (d), 167.8 (s), 170.7 (s), 207.3 (s); exact mass calcd. for C₁₇H₂₅NO₅ + H m/z 324.1811, found m/z 324.1782. Data on 127: IR (film) 3414, 2930, 2893, 1597, 1393, 1190, 1098 cm⁻¹; ¹H NMR (C₆D₆, 500 MHz) δ 1.24 (m, 1H, CH₂CH₂O), 1.42 (m, 1H, CH₂CHN), 1.50 (m, 1H, CH₂CH₂N), 1.56 (m, 1H, CH₂CH₂O), 1.70 (m, 1H, CH₂CHN), 1.85 (m, 1H, =CHCH₂), 2.27–2.41 (m, 4H, =CHCH₂CH₂ + CH₂CH₂N + =CHCH₂), 2.98 (m, 2H, CH₂CH₂O), 3.02 (s, 3H, OCH₃), 3.38 (m, 2H, CH₂OCH₃), 3.75 (q, J = 7.8 Hz, 1H, CH₂N), 4.17 (m, 1H, CH₂N), 4.16 (m, 1H, CHN), 5.32 (d, J = 9.9 Hz, 1H, HC=CHCH₂), 5.58 (m, 1H, HC=CHCH₂), 5.85 (s, 1H, OH); ¹³C NMR (C₆D₆, 125 MHz) δ 24.4 (t), 24.9 (t), 26.6 (t),
31.1 (t), 33.1 (t), 47.6 (t), 56.9 (s), 58.3 (d), 58.7 (q), 65.1 (t), 72.2 (t), 104.8 (s), 126.6 (d), 130.1 (d), 173.1 (s); exact mass calcd. for C_{15}H_{23}NO_{4} + Na m/z 304.1525, found m/z 304.1517.

Iodolactone 129. To a stirred solution of 65 mg (0.20 mmol) of ketone 128 in 2.5 mL of THF and 0.25 mL of H_{2}O, in the absence of light, was added a total of 420 mg (1.87 mmol) of N-iodosuccinimide in three 140-mg portions at 24 h intervals. Stirring was continued for another 24 h, at which time TLC analysis (EtOAc-hexanes, 50:50, SiO_{2}, PMA) indicated that all starting 128 had been consumed. The reaction mixture was quenched by addition of 1.5 mL of saturated aqueous NaHSO_{3}, followed by continued stirring for 20 min. The resulting mixture was extracted with two 3-mL portions of Et_{2}O. The combined organic layers were washed with 3 mL of brine, dried (Na_{2}SO_{4}), and concentrated to yield 68 mg of an orange oil. The crude product was purified by flash chromatography over 3.5 g of silica gel (EtOAc-hexanes, 25:75), to yield 16.4 mg (23%) of iodolactone 129 as a pale yellow oil: IR (film) 2966, 1783, 1733, 1729, 1233, 1135, 1052, 953 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 2.04 (s, 3H, Ac), 2.18 (m, 1H, CH\(_2\)CH\(_2\)OAc), 2.34 (m, 1H, CH\(_2\)CH\(_2\)OAc), 2.49 (m, 1H, CH\(_2\)C=O), 2.64–2.74 (m, 3H, CH\(_2\)CH\(_2\)OAc), 2.84–2.94 (m, 3H, CH\(_2\)CH\(_2\)OAc), 3.88 (s, 3H, Ac).
CH$_2$C=O + CH$_2$CH$_2$C=O), 4.18 (m, 2H, CH$_2$OAc), 4.95 (dd, $J = 5.4$, 1.6 Hz, 1H, CHO), 5.03 (br t, $J = 3.4$ Hz, 1H, CHI); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 20.9 (q), 23.5 (d), 23.9 (t), 27.4 (t), 32.8 (t), 59.3 (t), 62.6 (s), 77.5 (d), 169.4 (s), 170.5 (s), 197.0 (s); exact mass calc'd. for C$_{11}$H$_{13}$IO$_5$ m/z 374.9705, found m/z 374.9702.

Internal Acetal 126 + Internal Hemiacetal 127. A solution of 82 mg (0.28 mmol) of alcohol 125 in 2 mL of chloroform was stirred at rt for 4 h. TLC analysis (EtOAc, silica gel, PMA) indicated partial consumption of the starting 125. Gaseous HCl was bubbled into the solution for 5 seconds, and stirring was continued at rt for 5 min. TLC analysis indicated that all starting 125 had been consumed. 0.5 g of solid NaHCO$_3$ was added to the reaction mixture, which was then filtered and concentrated in vacuo, to yield 71.1 mg of a yellow oil. The crude mixture was separated by flash chromatography over 3.5 g of silica gel (EtOAc-hexanes, 75:25), to yield 21.5 mg (26%) of acetal 126 as a colorless oil, and 12.5 mg (15%) of hemiacetal 127 as a colorless oil. Analytical data for 126 and 127 appear earlier in this section.
2-[1-(2-Methoxymethylpyrrolidine-1-carbonyl)-6-oxocyclohex-2-enyl]ethyl 2,2-dimethylpropanoate (135). To a stirred solution of 11.1 g (29.2 mmol) of 116 in 135 mL of THF was added 16 mL of a 10% aqueous HCl solution. The resulting solution was stirred at room temperature under N₂ for 5 days. TLC analysis (silica gel; EtOAc-hexanes 1:1) showed no remaining starting enol ether. The reaction mixture was diluted with 800 mL of CH₂Cl₂, and the resulting mixture was washed with 160 mL of 10% aqueous NaHCO₃ and 160 mL of brine, then dried (Na₂SO₄) and concentrated in vacuo, to yield 10.12 g (86%) of ketone 135 as a pale yellow oil, suitable for use in the next reaction: IR (neat) 1725, 1634 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.15 (s, 9H, Piv), 1.75 (m, 1H, NCH₂CH₂), 1.89 (m, 3H, NCH₂CH₂), 2.12 (m, 1H, PivOCH₂CH₂), 2.39 (m, 1H, PivOCH₂CH₂), 2.53 (m, 1H, CH₂-C=O), 2.61 (m, 3H, CH=CH₆CH₂C=O), 3.05 (m, 1H, NCH₂), 3.31 (m, 2H, NCH₂ + CH₂OMe), 3.36 (s, 3H, CH₃), 3.63 (dd, J = 9.2, 2.6 Hz, 1H, CH₂OMe), 4.16 (t, 2H, CH₂OPiv), 4.26 (br m, 1H, NCH), 5.68 (d, J = 9.3 Hz, 1H, CH=CH₂), 6.02 (dt, J = 9.5, 3.9 Hz, 1H, CH=CH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 24.5 (t), 25.9 (t), 26.7 (t), 27.1 (q), 35.7 (t), 36.6 (t), 38.6 (s), 46.6 (t), 58.0 (d), 59.0 (q), 60.0 (s), 31.4 (t), 71.8 (t), 128.1 (d), 128.9 (d), 162.5 (s), 167.8 (s), 178.3 (s), 207.3 (s); exact mass calcd. for C₂₀H₃₁NO₅ + H m/z 366.2280, found m/z 366.2280.
2,2-Dimethylpropionic acid 2-(8-iodo-2,7-dioxo-6-oxabicyclo[3.2.1]oct-1-yl)-ethyl ester (136). To a stirred solution of 5.14 g (14.06 mmol) of amide 135 in 220 mL of THF and 22 mL of H₂O was added in one portion 22.13 g (87.19 mmol) of I₂. Stirring was continued at room temperature in the absence of light for 5 days. TLC analysis (silica gel; EtOAc/hexanes 1:3) showed no remaining starting amide. To the reaction mixture was added 105 mL of saturated aqueous NaHSO₃, and the resulting mixture was stirred for 20 min as the color gradually turned to yellow. The resulting mixture was diluted with 300 mL of Et₂O, the organic layer was separated, and the aqueous layer was extracted with 160 mL of Et₂O. The combined organic layers were washed with 220 mL of brine, dried (Na₂SO₄), and concentrated in vacuo, to yield 6.24 g of a yellow oil. The crude product was purified by flash chromatography over 300 g of silica gel (EtOAc/hexanes 1:3), to yield 4.58 g (83%) of lactone 136 as a pale yellow oil: IR (neat) 1787, 1727 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.19 (s, 9H, Piv), 2.19 (m, 1H, PivOCH₂CH₂), 2.37 (m, 1H, PivOCH₂CH₂), 2.49 (m, 1H, CH₂-C=O), 2.63-2.75 (m, 2H, CH₂CH₂C=O), 2.71 (m, 1H CH₂C=O), 4.13 (m, 2H, CH₂OPiv), 4.87 (dd, J = 5.4, 1.6 Hz, 1H, CH-I), 5.03 (t, J = 4.7 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 125 MHz) δ 23.3 (d), 23.6 (t), 27.1 (q), 27.5 (t), 32.7 (t), 38.7 (s), 59.7 (t), 62.4 (s), 77.4 (d), 169.3 (s), 178.2 (s), 197.1 (s); exact mass calcd. for C₁₄H₁₉O₅I + Na m/z 417.0175, found m/z 417.0168.
(1R,5R,4S)-4- Allyl-4-(2-pivaloyloxyethyl)-2-oxabicyclo[3.3.0]octan-3,6-dione (138). Nitrogen was bubbled through a stirred solution of 7.70 g (19.53 mmol) of lactone 136 and 12.2 mL (13.0 g, 39.4 mmol) of allyltri-n-butylstannane in 130 mL of benzene, followed by addition of 321 mg (1.95 mmol) of AIBN. The resulting solution was heated to reflux under N₂ atmosphere for 16 h. TLC analysis (silica gel; EtOAc-hexanes, 1:3) indicated that all starting lactone 136 was consumed. The reaction mixture was cooled to room temperature, 105 mL of 17 M aqueous potassium fluoride was added, and stirring was continued for 2 h. The resulting fine white precipitate was removed by filtration and the filter cake was washed with 250 mL of Et₂O. The organic phase was separated and the aqueous phase was extracted with 500 mL of Et₂O. The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo, to yield 25.0 g of a yellow oil. The crude product was purified by flash chromatography over 400 g of silica gel (EtOAc / hexanes 1:3 → 1:2), to yield 5.4 g (94 %) of lactone 138 as a pale yellow oil: IR (neat) 2974, 1770, 1744, 1725, 1285, 1159 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.18 (s, 9H, Piv), 1.93 (m, 1 H, CH₂CH₂OPiv), 1.99 (m, 1 H, CH₂CH₂OPiv), 2.09 (m, 1H, CH₂CH₂C=O), 2.43 (m, 1 H, CH₂CH₂C=O), 2.37 - 2.46 (m, 4 H, CH₂C=O + CH₂CH=), 2.73 (dd, J = 5.5, 0.8 Hz, 1 H, CHC=O), 4.33 (m, 2H, CH₂OPiv), 5.13 (t, J =
5.5 Hz, 1 H, CH-O), 5.23 (m, 2 H, =CH₂), 5.81 (m, 1 H, =CH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \textit{δ} 27.3 (t), 27.6 (q), 31.7 (t), 36.8 (t), 39.0 (s), 42.0 (t), 50.6 (s), 55.4 (d), 60.7 (t), 80.1 (d), 121.3 (t), 131.9 (d), 178.5 (s), 178.7 (s), 214.6 (s); exact mass calcd. for \( \text{C}_{17}\text{H}_{24}\text{O}_{5} + \text{Na} \) \textit{m/z} 331.1521, found \textit{m/z} 331.1522.

Selected NOE difference experiments for lactone \textbf{138}:

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<th>Observed NOE:</th>
<th>Chemical shift (ppm):</th>
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<td>( \text{H}_9 ) (0%)</td>
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\text{H} \\
\end{center} \) \textbf{139}

\( 2\text{-}[3S,3aR,6aR]-\text{Octahydro-2-oxo-3-(2-propenyl)spiro}[4H-cyclopenta[b]-furan-4,2'-[1,3]dioxolan]-3-yl]ethyl \, 2,2\text{-dimethylpropanoate} \) \textbf{(139)}. To a stirred solution of 2 \( \mu \text{L} \) (2.5 mg, 0.01 mmol) of trimethylsilyl triflate in 0.5 mL of anhydrous
dichloromethane at −78°C under N2 was added in one portion 240 µL (202 mg, 0.98 mmol) of bis(trimethylsilyloxy)ethane, followed by the dropwise addition of a solution of 298 mg (0.97 mmol) of ketone 138 in 0.5 mL of anhydrous CH2Cl2 over 2 min. Stirring was continued at −78 °C for 6 h. The reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h. To the reaction mixture was added 0.2 mL of pyridine, followed by pouring into 1.5 mL of 10% aqueous NaHCO3. The resulting mixture was extracted with three 2-mL portions of CH2Cl2, and the combined extracts were dried (Na2SO4) and concentrated in vacuo, to yield 233 mg of a yellow oil. The crude product was purified by flash chromatography over 12 g of silica gel (EtOAc-hexanes, 40:60) to yield 210 mg (62%) of acetal 139 as a white solid. A sample was prepared for X-ray crystallographic analysis by recrystallization from EtOAc-hexanes (1:9): mp 105-106°C; IR (KBr) 2978, 1767, 1721, 1174, 1161, 1147, 999 cm⁻¹; ¹H NMR (CDCl3, 500 MHz) δ 1.19 (s, 9H, Piv), 1.63 (m, 1H, cyclopentane CH2’s), 1.91 (m, 2H, cyclopentane CH2’s), 2.21 (m, 1H, cyclopentane CH2’s), 2.17 (m, 2H, CH2CH2OPiv), 2.37 (m, 2H, allyl CH2), 2.62 (d, J = 6.6 Hz, 1H, CH-C=O), 3.93 (m, 3H, acetal CH2’s), 4.05 (m, 1H, acetal CH2’s), 4.31 (t, J = 7.7 Hz, 2H, CH2OPiv), 4.94 (t, J = 5.5 Hz, 1H, CHO), 5.18 (d, J = 11.0 Hz, 1H, =CH2), 5.20 (d, J = 3.0 Hz, 1H, =CH2), 5.85 (m, 1H, =CH); ¹³C NMR (CDCl3, 125 MHz) δ 27.2 (q), 27.8 (t), 27.9 (t), 34.1 (t), 38.6 (s), 40.3 (t), 47.7 (s), 52.6 (d), 61.0 (t), 64.0 (t), 64.2 (t), 79.4 (d), 115.8 (s), 119.7 (t), 131.9 (d), 178.3 (s); exact mass calcd. for C19H28O6 + Na m/z 375.1784, found m/z 375.1787.
**2,2-Dimethylpropionic acid 2-(2-hydroxy-8-iodo-7-oxo-6-oxabicyclo-[3.2.1]oct-1-yl)ethyl ester (142).** To a stirred solution of 797 mg (2.02 mmol) of ketone 136 in 12 mL of methanol and 1.4 mL of water was added in one portion 84 mg (2.22 mmol) of sodium borohydride. The resulting mixture was stirred at room temperature for 4 h. TLC analysis (silica gel; EtOAc / hexanes 25:75) showed no remaining starting ketone. The reaction mixture was concentrated in vacuo, and the residue was dissolved in 70 mL of EtOAc. The resulting solution was washed with two 20-mL portions of water, dried (Na₂SO₄), and concentrated, to yield 598 mg of a pale yellow oil. The crude product was purified by flash chromatography over 30 g of silica gel (EtOAc / hexanes 33:67), to yield 280.3 mg (35%) of alcohol 142 as a colorless oil: IR (film) 3494, 2968, 1775, 1726, 1284, 1156, 985, 931 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.19 (s, 9H, t-Bu), 1.92 (dd, J = 15.4, 6.3 Hz, 1H, CH₂CHOH), 2.01-2.13 (m, 2H, CH₂CHOH + CH₂CH-O), 2.20 (m, 2H, CH₂CH₂OPiv), 2.38 (br, 1H, OH), 2.57 (m, 1H, CH₂CH-O), 3.86 (d, J = 5.4 Hz, 1H, CH-OH), 4.17 – 4.19 (m, 2H, CH₂OPiv), 4.43 (d, J = 5.3 Hz, 1H, CHI), 4.85 (t, J = 4.8 Hz, 1H, CH-O); ¹³C NMR (CDCl₃, 125 MHz) δ 19.8 (d), 20.7 (t), 26.4 (t), 27.1 (q), 28.1 (t), 38.7 (s), 49.3 (s), 60.1 (t), 69.3 (d), 79.1 (d), 172.4 (s), 178.4 (s); exact mass calcd. for C₁₄H₂₁O₅I + Na m/z 419.0331, found m/z 419.0349.
2,2-Dimethylpropionic acid 2-(2-acetoxy-8-iodo-7-oxo-6-oxa-bicyclo-
[3.2.1]oct-1-yl)ethyl ester (143). To a stirred solution of 215 mg (0.52 mmol) of alcohol
142 in 5 mL of dichloromethane, at 0 ºC under N₂, were added sequentially 51 µL (55
mg, 0.54 mmol) of acetic anhydride, 75 µL (54 mg, 0.54 mmol) of triethylamine, and 7
mg (0.06 mmol) of 4-dimethylaminopyridine. The resulting solution was stirred at 0 ºC
under N₂ for 1 h. TLC analysis (silica gel, EtOAc / hexanes, 50:50) revealed that all
starting alcohol had been consumed. The reaction mixture was partitioned between 5 mL
of CH₂Cl₂ and 5 mL of H₂O. The aqueous layer was separated, and the organic layer was
washed with 5 mL of 1 N aq. HCl, 5 mL of sat. aq. NaHCO₃, dried (Na₂SO₄), and
concentrated, to yield 199 mg of a pale yellow oil. The crude product was purified by
flash chromatography over 10 g of silica gel (EtOAc / hexanes 50:50), to yield 178 mg
(78%) of acetate 143 as a colorless oil: IR (neat) 2969, 1789, 1740, 1731, 1227, 1142 cm⁻¹
¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.19 (s, 9H, Piv), 1.90 (m, 2H, ring CH₂’s), 1.92 (m, 1H,
CH₂CH₂OPiv), 2.03 (m, 1H, ring CH₂’s), 2.16 (s, 3H, Ac), 2.17 (m, 1H, CH₂CH₂OPiv),
2.53 (m, 1H, ring CH₂’s), 4.10 (ddd, J = 11.8, 8.4, 5.3 Hz, 1H, CH₂OPiv), 4.19 (dt, J =
11.8, 5.7 Hz, 1H, CH₂OPiv), 4.50 (d, J = 5.4 Hz, 1H, CH-l), 4.87 (t, J = 5.1 Hz, 1H,
lactone CH-O), 4.93 (d, J = 5.0 Hz, 1H, CH-OAc); ¹³C NMR (CDCl₃, 125 MHz) δ 18.4
(d), 20.8 (t), 21.1 (q), 23.8 (t), 27.1 (q), 27.9 (q), 38.7 (s), 49.4 (s), 59.7 (q), 68.6 (s), 79.0

165
(1R,5R,4S)-4-(2-Pivaloyloxyethyl)-2-oxabicyclo[3.3.0]octan-3,6-dione (164).

Nitrogen was bubbled through a solution of 400 mg (1.01 mmol) of iodolactone 136 in 100 mL of benzene, 18 mg (0.11 mmol) of AIBN was added, and the resulting solution was heated to a gentle reflux under N₂ atmosphere. Tri-n-butylstannane (275 µL, 298 mg, 1.02 mmol) was added over 30 min and the resulting solution was stirred at reflux under N₂ for 2 h. TLC analysis (silica; EtOAc / hexanes 1:1) showed no remaining starting lactone. The reaction mixture was cooled to room temperature and 2 mL of 17 M aqueous KF was added, resulting in formation of a fine white precipitate. Vigorous stirring was continued for 2 h. The resulting mixture was filtered and the filter cake was washed with 10 mL of Et₂O. The aqueous phase was separated and extracted with 2 mL of Et₂O and the combined organic phases were dried (Na₂SO₄) and concentrated in vacuo. The residual yellow oil (523 mg) was purified by flash chromatography over 27 g of silica gel (EtOAc-hexanes, 1:1), to yield 98 mg (36%) of rearranged reduction product 164 as a
yellow oil, as well as 86 mg (32% mass balance) of a 2:1 mixture of 164 and an unidentified compound. Spectral data for 164: IR (neat) 2962, 1760, 1744, 1721, 1180, 1153, 1004 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 1.21 (s, 9H, Piv), 1.99 (m, 1H, CH\(_2\)CH\(_2\)OPiv), 2.12 (m, 1H, CH\(_2\)CH\(_2\)OPiv), 2.15 (m, 1H, CH\(_2\)CH\(_2\)C=O), 2.42 (m, 2H, CH\(_2\)C=O), 2.52 (m, 1H, CH\(_2\)CH\(_2\)C=O), 3.02 (m, 2H, PivO(CH\(_2\))\(_2\)CH + PivO(CH\(_2\))\(_2\)CH-CH), 4.28 (m, 1H, CH\(_2\)OPiv), 4.39 (m, 1H, CH\(_2\)OPiv), 5.17 (t, \(J = 4.3\) Hz, 1H, CH-O); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 25.4 (t), 26.7 (t), 27.2 (q), 36.0 (t), 38.8 (s), 40.7 (d), 49.4 (d), 62.1 (t), 80.7 (d), 176.3 (s), 178.5 (s), 214.1 (s); exact mass calcd. for C\(_{14}\)H\(_{20}\)O\(_5\) + Na m/z 291.1208, found m/z 291.1215.

Selected NOE difference experiments for lactone 164:

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<th>Observed NOE:</th>
<th>Chemical shift (ppm):</th>
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2-[(1R,2R,5R)-2-Hydroxy-7-oxo-6-oxabicyclo[3.2.1]oct-1-yl]ethyl 2,2-dimethylpropanoate (165). Nitrogen was bubbled through a solution of 393 mg (1.00 mmol) of iodolactone 136 in 1 mL of benzene, 1.35 mL (1.46 g, 5.0 mmol) of tri-n-butylstannane and 16 mg (0.10 mmol) of AIBN were added sequentially, and the resulting solution was heated to a gentle reflux under N₂ atmosphere for 2h. TLC analysis (silica; EtOAc-hexanes, 1:3) showed no remaining starting lactone. The reaction mixture was cooled to room temperature and 9 mL of 17 M aqueous KF was added, and stirring was continued for 2 h. The resulting mixture was filtered, and the filter cake was washed with 10 mL of Et₂O. The aqueous phase was separated and extracted with 2 mL of Et₂O, and the combine organic phases were dried (Na₂SO₄) and concentrated in vacuo to yield 1.69 g of a yellow oil, which was purified by flash chromatography over 85 g of silica gel (EtOAc-hexanes, 1:1), to yield 201 mg (74%) of alcohol 165 as a white solid: mp 74-75ºC; IR (KBr) 3424, 2962, 1738, 1725, 1283, 1162 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.19 (s, 9H, Piv), 1.52 (m, 1H, CH₂CHOH), 1.59 (m, 1H, CH₂CH₂CHOH), 1.71 (d, J = 12.0 Hz, 1H, CH₂CH-OOC), 2.09 (m, 1H, CH₂CH₂CHOH), 2.09 (br, 1H, OH), 2.00 (m, 1H, CH₂CH₂OPiv), 2.26 (m, 1H, CH₂CHOH), 2.30 (m, 1H, CH₂CH₂OPiv), 2.36 (ddd, J = 12.0, 6.1, 2.4 Hz, 1H, CH₂CHOOC), 3.76 (dd, J = 10.2, 5.9 Hz, 1H, CHO), 4.17 (m, 2H, CH₂OPiv), 4.74 (t, J = 5.2 Hz, 1H, CHOOC); ¹³C NMR (CDCl₃, 125 MHz) δ 27.1
(q), 28.2 (t), 28.7 (t), 29.0 (t), 38.6 (s), 39.5 (t), 49.9 (s), 60.8 (t), 70.6 (d), 75.0 (d), 177.5 (s), 178.5 (s); exact mass calcd. for C_{14}H_{22}O_{5} + Na m/z 293.1365, found m/z 293.1365.

2-[(1R,5R)-2,7-Dioxo-6-oxabicyclo[3.2.1]oct-1-yl]ethyl 2,2-dimethylpropanoate (166). To a stirred solution of 312 mg (0.73 mmol) of the Dess-Martin periodinane in 5 mL of anhydrous CH_{2}Cl_{2} at 0 °C under N_{2} was added dropwise over 10 min a solution of 101 mg (0.37 mmol) of alcohol 165 in 5 mL of anhydrous CH_{2}Cl_{2}. The resulting solution was allowed to warm to room temperature, and stirring was continued under N_{2} for 3 h. TLC analysis (silica; EtOAc-hexanes, 1:1) revealed no remaining starting alcohol. The reaction mixture was diluted with 8 mL of Et_{2}O, and the resulting solution was washed with 5 mL of a 1:1 mixture of saturated aqueous Na_{2}CO_{3} and saturated aqueous Na_{2}S_{2}O_{3}, then with 5 mL of 2 N aqueous NaOH, dried (Na_{2}SO_{4}), and concentrated in vacuo to yield 113 mg of a pale yellow oil. The crude product was purified by flash chromatography over 6 g of silica gel (EtOAc / hexanes, 1:1) to yield 67 mg (67%) of ketone 166 as a colorless oil: IR (neat): 2973, 1778, 1722 cm⁻¹; \(^1\)H NMR (CDCl₃, 500 MHz) \(\delta\) 1.17 (s, 9H, Piv), 2.04 (m, 1H, \(\text{CH}_2\text{CH}_2\text{C}=\text{O}\)), 2.07 (m, 1H, \(\text{CH}_2\text{CH}_2\text{OPiv}\)), 2.24 (d, \(J = 12.5\) Hz, 1H, \(\text{CH}_2\text{CHO}\)), 2.38 (dt, \(J = 15.1, 5.9\) Hz, 1H, \(\text{CH}_2\text{CH}_2\text{OPiv}\)), 2.46 (m, 1H, \(\text{CH}_2\text{CH}_2\text{C}=\text{O}\)), 2.80 (ddd, \(J = 12.5, 5.9, 2.6\) Hz, 1H, \(\text{CH}_2\text{CH}_2\text{OPiv}\)).
2-Methoxy-5-methylbenzoic acid (170). To a stirred solution of 3.6 mL (5.0 g, 25 mmol) of 2-bromo-3-methoxytoluene (169) in 50 mL of anhydrous ether was added dropwise via syringe, at –78 °C under N₂, 19.2 mL (25 mmol) of a 1.3 M solution of n-butyllithium in hexanes. The resulting solution was stirred at –78 °C for 1 h, and CO₂ was bubbled through it for 45 min. The reaction mixture was quenched with 50 mL of 1 N aqueous HCl, and the resulting mixture was extracted with three 75-mL portions of 1 N aqueous NaOH. The combined basic extracts were carefully acidified with concentrated aqueous HCl in an ice bath, and the resulting cloudy solution was extracted with three 75-mL portions of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to yield 2.711 g (72%) of acid 170, as a light brown solid: mp 65-67 °C (lit. 68-69 °C); ¹H NMR (CDCl₃, 400 MHz) δ 2.34 (s, 3H, CH₃), 4.05 (s, 3H, OCH₃), 6.98 (d, J = 11.4 Hz, 1H, =CH), 7.37 (dd, J = 11.3, 2.2 Hz, 1H, =CH), 7.99 (d, J = 2.2 Hz, 1H, =CH). This material was suitable for use in the next reaction.
**N-(2-Methoxy-5-methylbenzoyl)pyrrolidine (171).** To 2.71 g (16.3 mmol) of 2-methoxy-5-methylbenzoic acid (170) was added with stirring 18 mL (29.4 g, 247 mmol) of thionyl chloride. The resulting solution was stirred at room temperature under N₂ for 24 h. The excess SOCl₂ was removed under house vacuum and the residue was distilled bulb-to-bulb under high vacuum, to yield the corresponding acid chloride as a colorless liquid. To a stirred solution of 1.50 mL (1.28 g, 18.0 mmol) of pyrrolidine and 3.45 mL (2.50 g, 2.47 mmol) of triethylamine in 45 mL of anhydrous CH₂Cl₂, at 0°C under N₂, was added a solution of the distilled acid chloride in 20 mL of anhydrous CH₂Cl₂, dropwise over 30 min. The resulting solution was allowed to warm to room temperature, and stirring was continued for 14 h. To the reaction mixture was added 50 mL of 5% aqueous HCl, and the resulting mixture was extracted with three 50-mL portions of CH₂Cl₂. The combined organic extracts were washed with 50 mL of saturated aqueous NaHCO₃ and 50 mL of brine, dried (Na₂SO₄) and concentrated in vacuo, to yield 3.22 g (90%) of amide 171 as a pale yellow oil: IR (neat) 2966, 2874, 1630, 1438, 1252 cm⁻¹, ¹H NMR (CDCl₃, 400 MHz) δ 1.84 (quintet, J = 6.7 Hz, 2 H, NCH₂CH₂), 1.94 (quintet, J = 6.7 Hz, 2 H, NCH₂CH₂), 2.27 (s, 3 H, CH₃), 3.23 (t, J = 6.8 Hz, 2 H, NCH₂), 3.63 (t, J = 6.8 Hz, 2 H, NCH₂), 3.80 (s, 3 H, OCH₃), 6.79 (d, J = 8.4 Hz, 1 H, =CH),
7.07 (d, J = 2.0 Hz, 1 H, =CH), 7.11 (dd, J = 8.4, 2.0 Hz, 1 H, =CH); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 20.3 (q), 24.5 (t), 25.8 (t), 45.4 (t), 47.5 (t), 55.6 (q), 111.0 (d), 127.2 (s), 128.2 (d), 130.1 (s), 130.5 (d), 153.1 (s), 167.8 (s); exact mass calcd. for C$_{13}$H$_{17}$NO$_2$ + H $m/z$ 220.1337, found $m/z$ 220.1335.

1-(1,5-Dimethyl-2-methoxy-1,4-dihydrobenzoyl)pyrrolidine (172). Into a stirred solution of 3.22 g (14.68 mmol) of amide 171 and 1.40 mL (1.09 g, 14.64 mmol) of $t$-butanol in 75 mL of dry tetrahydrofuran, at -78°C under nitrogen atmosphere was condensed 800 mL of NH$_3$. Potassium was added to the resulting solution in small portions until the reaction medium sustained a deep blue-black color. Methyl iodide (1.85 mL, 4.21 g, 29.7 mmol) was then added over 30 sec and stirring was continued at -78°C for 1.5 h. To the reaction mixture was added 7.7 g (144 mmol) of solid NH$_4$Cl. The resulting mixture was allowed to warm and the ammonia was allowed to evaporate under a stream of N$_2$. To the white residue was added 250 mL of brine and the resulting mixture was extracted with three 250-mL portions of CH$_2$Cl$_2$. The combined organic extracts

![Structure of 172](image-url)
were washed with 250 mL of 10% aqueous Na$_2$S$_2$O$_3$, 250 mL of water, and 250 mL of brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to yield 3.31 g of a yellow oil. The crude product was chromatographed over 165 g of silica gel (EtOAc / hexanes, 1:1) to give 2.75 g (80%) of 172 as a pale yellow oil: IR (neat) 2970, 2930, 1632, 1406, 1237, 1206 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.39 (s, 3 H, CH$_3$), 1.71 (s, 3 H, CH$_3$), 1.77 (m, 4 H, NCH$_2$CH$_2$), 2.73 (m, 2 H, =CCH$_2$CH=), 3.23 (m, 1 H, NCH$_2$), 3.40 (m, 2 H, NCH$_2$), 3.50 (s, 3 H, OCH$_3$), 3.51 (m, 1 H, NCH$_2$), 4.61 (t, $J$ = 3.6 Hz, 1 H, H$_2$CCH=C-OC$_2$H$_5$), 5.17 (q, $J$ = 1.5 Hz, 1 H, H$_3$C-C=CH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 22.3 (q), 23.4 (t), 26.3 (q), 26.9 (t), 31.3 (t), 45.5 (t), 47.5 (t), 48.6 (s), 54.3 (q), 90.5 (d), 123.9 (d), 131.2 (s), 155.7 (s), 170.9 (s); exact mass calcd. for C$_{14}$H$_{21}$NO$_2$ + Na $m/z$ 258.1470, found $m/z$ 258.1450.

![Image of molecule](attachment:image.png)

1-(1,5-Dimethyl-2-oxo-1,2,3,4-tetrahydrobenzoyl)pyrrolidine (173). To a stirred solution of 1.18 g (5.02 mmol) of 172 in 25 mL of THF was added 4 mL of a 10% aqueous HCl solution. The resulting solution was stirred at room temperature under N$_2$ for 24 h. TLC analysis (silica gel; EtOAc/hexanes, 1:1) showed no remaining starting
enol ether. The reaction mixture was diluted with 135 mL of CH$_2$Cl$_2$, and the resulting mixture was washed with 35 mL of 10% aqueous NaHCO$_3$ and 35 mL of brine, then dried (Na$_2$SO$_4$) and concentrated in vacuo, to yield 1.09 g (98%) of ketone 173 as a colorless oil, suitable for use in the next reaction: IR (neat) 2970, 2930, 2878, 1711, 1634, 1409 cm$^{-1}$, $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.43 (s, 3 H, CH$_3$), 1.79 (s, 3 H, CH$_3$), 1.81 (m, 4 H, NCH$_2$CH$_2$), 2.44 (m, 2 H, CH$_2$CH$_2$C=O), 2.55 (m, 1 H, CH$_2$CH$_2$C=O), 2.65 (m, 1 H, CH$_2$CH$_2$C=O), 3.04 (m, 1 H, NCH$_2$), 3.22 (m, 1 H, NCH$_2$), 3.44 (m, 1 H, NCH$_2$), 3.52 (m, 1 H, NCH$_2$), 5.36 (d, $J = 1.0$ Hz, 1 H, =CH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 22.9 (q), 23.5 (t), 24.1 (q), 26.5 (t), 30.7 (t), 35.8 (t), 46.0 (t), 47.3 (t), 57.1 (s), 125.2 (d), 134.8 (s), 169.6 (s), 209.7 (s); exact mass calcd. for C$_{13}$H$_{19}$NO$_2$ + Na m/z 244.1313, found m/z 244.1307.

![Chemical structure](image)

**8-Iodo-1,5-dimethyl-6-oxabicyclo[3.2.1]octane-2,7-dione (167).** To a stirred solution of 1.09 g (4.94 mmol) of amide 173 in 80 mL of THF and 8 mL of H$_2$O was added in one portion 3.81 g (15.0 mmol) of I$_2$. Stirring was continued at room temperature in the absence of light for 15 h. TLC analysis (silica gel; EtOAc/hexanes, 1:3) showed no remaining starting amide. To the reaction mixture was added 38 mL of
saturated aqueous NaHSO₃, and the resulting mixture was stirred for 20 min as the color gradually turned to yellow. The resulting mixture was diluted with 110 mL of Et₂O, the organic layer was separated, and the aqueous layer was extracted with 60 mL of Et₂O. The combined organic layers were washed with 80 mL of brine, dried (Na₂SO₄), and concentrated in vacuo, to yield 1.38 g (95%) of lactone 167 as a yellow oil: IR (neat) 2936, 1764, 1718, 1265, 1215, 1168, 1045, 941, 912 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.30 (s, 3 H, CH₃), 1.63 (s, 3H, CH₃), 2.46 (m, 2 H, CH₂CH₂C=O), 2.66 (m, 2 H, CH₂CH₂C=O), 4.38 (d, J = 2.0 Hz, 1 H, CHI); ¹³C NMR (CDCl₃, 125 MHz) δ 12.8 (q), 22.6 (q), 33.1 (t), 33.3 (t), 35.5 (d), 62.1 (s), 84.7 (s), 170.9 (s), 198.4 (s).

(4-Methoxybenzyl)trimethylammonium iodide (175).⁶⁴ To a stirred solution of 9.95 g (63.5 mmol) of p-methoxybenzyl chloride (174) in 65 mL of CH₃CN was added 15.1 g of a 40% aqueous solution of trimethylamine (6.04 g NMe₃, 102 mmol), and the resulting solution was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo, and the residue was taken up in 400 mL of benzene. The resulting mixture was heated to reflux for 15 h with a Dean-Stark trap to remove H₂O. The remaining benzene was removed in vacuo, to yield 13.06 g (95%) of quaternary ammonium chloride 175: mp 180-185 °C (lit.⁶⁴ 150 °C); ¹H NMR (CDCl₃, 400 MHz) δ
3.39 (s, 9H, NMe₃), 3.83 (s, 3H, OCH₃), 4.95 (s, 2H, CH₂), 6.95 (dt, \( J = 8.7, 3.0 \text{ Hz} \), 2H, \( =\text{CH} \)), 7.56 (dt, \( J = 8.7, 3.0 \text{ Hz} \), 2H, \( =\text{CH} \)).

![Chemical structure of 176](image)

(5-Methoxy-2-methylbenzyl)dimethylamine (176).⁶⁴ To a stirred suspension of 1.56 g (40 mmol) of sodium amide in 80 mL of ammonia, at reflux under \( \text{N}_2 \), was added 4.18 g (19.4 mmol) of solid ammonium iodide 175 over 1 min. The resulting mixture was stirred at reflux for 2 h, followed by addition of 2.25 g (42 mmol) of solid \( \text{NH}_4\text{Cl} \). The ammonia was evaporated, the yellow solid residue was taken up in 100 mL of \( \text{Et}_2\text{O} \), and the resulting mixture was extracted with three 100-mL portions of 10 % aqueous HCl. The combined acidic extracts were basified with solid \( \text{NaOH} \) ion an ice bath, and the resulting solution was extracted with three 100-mL portions of \( \text{CH}_2\text{Cl}_2 \). The combined organic extracts were dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated in vacuo, to yield 3.33 g (96%) of amine 176 as a yellow oil: \(^1\text{H NMR (CDCl}_3, 400 \text{ MHz}) \delta 2.27 \text{ (s, 6H, NMe}_2\text{), 2.29 \text{ (s, 3H, CH}_3\text{), 3.37 \text{ (s, 2H, CH}_2\text{), 3.80 \text{ (s, 3H, OCH}_3\text{), 6.73 \text{ (dd, } J = 8.3, 2.8 \text{ Hz, 1H, ArH), 6.89 \text{ (d, } J = 2.7 \text{ Hz, 1H, ArH), 7.07 \text{ (d, } J = 8.3 \text{ Hz, 1H, ArH).} \)
To a stirred solution of 3.21 g (17.9 mmol) of amine 176 in 15 mL of acetonitrile was added, in one portion, 2.25 mL (5.13 g, 36.1 mmol) of methyl iodide. The resulting solution was stirred at room temperature for 2 h, as a fine cream-colored precipitate formed. The reaction mixture was cooled in an ice bath, and 50 mL of dry Et₂O was added to complete crystallization. The resulting solid was collected by filtration, washed with 20 mL of dry Et₂O, and dried in vacuo to yield 5.33 g (93%) of quaternary ammonium iodide 177 as a light, crystalline pale beige solid: mp 191-193 °C (lit. 64 166-176 °C); ¹H NMR (CDCl₃, 400 MHz) δ 2.47 (s, 2H, CH₃), 3.47 (s, 9H, NMe₃), 3.84 (s, 3H, OCH₃), 4.96 (s, 2H, CH₂), 6.96 (dd, J = 8.4, 2.8 Hz, 1H, ArH), 7.23 (d, J = 8.4 Hz, 1H, ArH), 7.25 (d, J = 2.8 Hz, 1H, ArH).
To a stirred suspension of 2.07 g (53.1 mmol) of sodium amide in 80 mL of ammonia, at reflux under N₂, was added 5.55 g (17.3 mmol) of solid quaternary ammonium salt 177 over 1 min. The resulting mixture was stirred at reflux for 2 h, as its color progressively turned brown, followed by addition of 2.87 g (54 mmol) of solid NH₄Cl. The NH₃ was allowed to evaporate. The yellow residue was taken up in 100 mL of Et₂O, and the resulting mixture was extracted with three 100-mL portions of 10 % aqueous HCl. The combined aqueous extracts were basified with solid NaOH in an ice bath, and the resulting solution was extracted with three 100-mL portions of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to yield 2.80 g (84%) of amine 178 as a yellow liquid: ¹H NMR (CDCl₃, 400 MHz) δ 2.23 (s, 3H, CH₃), 2.26 (s, 6H, NMe₂), 2.30 (s, 3H, CH₃), 3.50 (s, 2H, CH₂), 3.79 (s, 3H, OCH₃), 6.66 (d, J = 8.3 Hz, 1H, ArH), 7.04 (d, J = 8.3 Hz, 1H, ArH).
6-Methoxy-2,3-dimethylbenzoic acid (179). To a stirred dispersion of 2.65 g (13.7 mmol) of amine 178 in 115 mL of 0.5 N aqueous NaOH was added three 2.4 g (15 mmol) portions of KMnO₄ at 1 h intervals. Vigorous stirring was continued at room temperature for 2 h. The reaction mixture was filtered through Celite 545. The filter cake was rinsed with 30 mL of H₂O. The filtrate was carefully acidified with concentrated aqueous HCl in an ice bath, and the resulting solution was extracted with three 100-mL of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo, to yield 1.23 g (50%) of acid 179, with impurities, as a yellow solid: mp 110-155 ºC (lit. 154-156 ºC); ¹H NMR (CDCl₃, 500 MHz) δ 2.21 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 3.87 (s, 3H, OCH₃), 6.73 (d, J = 8.4 Hz, 1H, ArH), 7.17 (d, J = 8.4 Hz, 1H, ArH).

N-(2-Methoxy-5,6-dimethylbenzoyl)pyrrolidine (180). To 1.28 g (7.1 mmol) of 2-methoxy-5,6-dimethylbenzoic acid (179) was added with stirring 8 mL (13 g, 110
mmol) of thionyl chloride. The resulting solution was stirred at room temperature under N₂ for 16 h. The excess SOCl₂ was removed under house vacuum and the residue was distilled bulb-to-bulb under high vacuum, to yield the corresponding acid chloride as a colorless liquid. To a stirred solution of 655 µL (558 mg, 7.85 mmol) of pyrrolidine and 1.50 mL (1.09 g, 10.8 mmol) of triethylamine in 20 mL of anhydrous CH₂Cl₂, at 0°C under N₂, was added a solution of the distilled acid chloride in 10 mL of anhydrous CH₂Cl₂ dropwise over 30 min. The resulting solution was allowed to warm to room temperature and stirring was continued for 4 h. To the reaction mixture was added 25 mL of 5% aqueous HCl and the resulting mixture was extracted with three 25-mL portions of CH₂Cl₂. The combined organic extracts were washed with 25 mL of saturated aqueous NaHCO₃ and 25 mL of brine, dried (Na₂SO₄) and concentrated in vacuo to yield 1.25 g of a yellow oil. The crude product was purified by flash chromatography over 63 g of silica gel (EtOAc), to yield 1.00 g (61%) of amide 180 as a pale yellow solid: mp 78-79°C; IR (KBr) 2954, 2868, 1628, 1439, 1264, 1084, 820 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.87 (m, 2 H, NCH₂CH₂), 1.96 (m, 2 H, NCH₂CH₂), 2.13 (s, 3 H, CH₃), 2.20 (s, 3 H, CH₃), 3.03 (dt, J = 10.4, 6.6 Hz, 1 H, NCH₂), 3.17 (dt, J = 10.6, 6.9 Hz, 1 H, NCH₂), 3.64 (dt, J = 12.1, 7.0 Hz, 1 H, NCH₂), 3.75 (dt, J = 12.1, 7.0 Hz, 1 H, NCH₂), 3.78 (s, 3 H, OCH₃), 6.66 (d, J = 8.4 Hz, 1 H, =CH), 7.06 (d, J = 8.4 Hz, 1 H, =CH); ¹³C NMR (CDCl₃, 125 MHz) δ 16.1 (q), 19.2 (q), 24.7 (t), 25.8 (t), 45.0 (t), 47.2 (t), 55.7 (q), 108.2 (d), 127.6 (s), 129.2 (s), 130.2 (d), 133.5 (s), 153.4 (s), 168.1 (s); exact mass calcd. for C₁₄H₁₉NO₂ + H m/z 234.1494, found m/z 234.1494; Anal. Calcd. for C₁₄H₁₉NO₂: C, 72.06; H, 8.21. Found: C, 71.73; H, 8.11.

180
(R)-1-(1,5,6-Trimethyl-2-methoxy-1,4-dihydrobenzoyl)pyrrolidine (181). 52

Into a stirred solution of 965.3 mg (4.14 mmol) of amide 180 and 400 µL (310 mg, 4.18 mmol) of t-butanol in 17 mL of dry tetrahydrofuran, at -78°C under nitrogen atmosphere was condensed 250 mL of NH₃. Potassium was added to the resulting solution in small portions until the reaction medium sustained a deep blue-black color. Methyl iodide (520 µL, 1.18 g, 8.35 mmol) was then added over 30 sec and stirring was continued at -78°C for 2 h. To the reaction mixture was added 2.25 g (42.1 mmol) of solid NH₄Cl. The resulting mixture was allowed to warm and the ammonia was allowed to evaporate under a stream of N₂. To the white residue was added 100 mL of brine and the resulting mixture was extracted with three 100-mL portions of CH₂Cl₂. The combined organic extracts were washed with 100 mL of 10% aqueous Na₂S₂O₃, 100 mL of water, and 100 mL of brine, dried (Na₂SO₄) and concentrated in vacuo to yield 1.13 g of a yellow oil. The crude product was chromatographed over 56 g of silica gel (EtOAc-hexanes, 2:1) to give 660 mg (64%) of 181 as a pale beige solid: mp 85°C; IR (KBr) 2971, 2875, 1629, 1404 cm⁻¹;$^1$H NMR (CDCl₃, 500 MHz) δ 1.42 (s, 3 H, CH₃), 1.54 (s, 3 H, CH₃), 1.66 (s, 3 H, CH₃), 1.74 (br m, 4 H, NCH₂CH₂), 2.70 (m, 2 H, =CHCH₂C=), 3.26 (br, 2 H, NCH₂), 3.50 (s, 3 H, OCH₃), 3.50 (br m, 2 H, NCH₂), 4.62 (t, $J = 3.6$ Hz, 1 H, =CH); $^{13}$C NMR (CDCl₃,
125 MHz) \( \delta \) 13.8 (q), 18.5 (q), 23.4 (t), 24.3 (q), 27.0 (t), 32.6 (t), 45.5 (t), 47.2 (t), 52.1 (s), 54.4 (q), 90.4 (d), 124.8 (s), 125.9 (s), 155.6 (s), 170.8 (s); exact mass calcd. C\(_{15}\)H\(_{23}\)NO\(_2\) + Na \( m/z \) 272.1626, found \( m/z \) 271.1629.

(R)-1-(1,5,6-Trimethyl-2-oxo-1,2,3,4-tetrahydrobenzoyl)pyrrolidine (182).

To a stirred solution of 607 mg (2.44 mmol) of 181 in 12 mL of THF was added 2 mL of a 10% aqueous HCl solution. The resulting solution was stirred at room temperature under N\(_2\) for 14 h. TLC analysis (silica gel; EtOAc-hexanes, 1:1) showed no remaining starting enol ether. The reaction mixture was diluted with 65 mL of CH\(_2\)Cl\(_2\), and the resulting mixture was washed with 17 mL of 10% aqueous NaHCO\(_3\) and 17 mL of brine, then dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to yield 547 g (95%) of ketone 182 as a colorless oil suitable for use in the next reaction: IR (neat) 2972, 2931, 2874, 1711, 1634, 1410 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 1.47 (s, 3 H, CH\(_3\)), 1.55 (s, 3 H, CH\(_3\)), 1.72 (s, 3 H, CH\(_3\)), 1.77 (m, 4 H, NCH\(_2\)CH\(_2\)), 2.45 (m, 3 H, CH\(_2\)CH\(_2\)C=O), 2.73 (m, 1 H, CH\(_2\)CH\(_2\)C=O), 2.77 (m, 1 H, NCH\(_2\)), 3.05 (m, 1 H, NCH\(_2\)), 3.43 (m, 1 H, NCH\(_2\)), 3.55 (m, 1 H, NCH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 14.4 (q), 19.2 (q), 23.5 (t), 24.2 (q), 26.5
(t), 31.6 (t), 36.0 (t), 45.4 (t), 47.0 (t), 61.1 (s), 127.3 (s), 127.4 (s), 169.2 (s), 210.4 (s); exact mass calcd. for C_{14}H_{21}NO_{2} + Na m/z 258.1470, found m/z 258.1467.

8-Iodo-1,5,8-trimethyl-6-oxabicyclo[3.2.1]octane-2,7-dione (168). To a stirred solution of 515 mg (2.19 mmol) of amide 182 in 40 mL of THF and 4 mL of H\textsubscript{2}O was added in one portion 1.78 g (7.01 mmol) of I\textsubscript{2}. Stirring was continued at room temperature in the absence of light for 6 h. TLC analysis (silica gel; EtOAc-hexanes, 1:1) showed no remaining starting amide. To the reaction mixture was added 20 mL of saturated aqueous NaHSO\textsubscript{3}, and the resulting mixture was stirred for 20 min as the color gradually turned to yellow. The resulting mixture was diluted with 50 mL of Et\textsubscript{2}O, the organic layer was separated, and the aqueous layer was extracted with 25 mL of Et\textsubscript{2}O. The combined organic layers were washed with 40 mL of brine, dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo, to yield 560 mg (83\%) of lactone 168 as a pale yellow powdery solid: mp 104\(^\circ\)C (dec.); IR (KBr) 1771, 1720 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 1.31 (s, 3 H, CH\textsubscript{3}), 1.60 (s, 3 H, CH\textsubscript{3}), 2.00 (s, 3 H, CH\textsubscript{3}), 2.45 (dt, \(J = 17.5, 10.0\) Hz, 1 H, CH\textsubscript{2}CH\textsubscript{2}C=O), 2.55 (dd, \(J = 14.4, 10.1\) Hz, 1 H, CH\textsubscript{2}CH\textsubscript{2}C=O), 2.69 (dd, \(J = 17.6, 8.4\) Hz, 1 H, CH\textsubscript{2}C=O), 2.78 (dt, \(J = 14.3, 8.5\) Hz, 1 H, CH\textsubscript{2}C=O); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125
(1R,5R,4R)-1,4-Dimethyl-4-allyl-2-oxabicyclo[3.3.0]octan-3,6-dione (183).

Nitrogen was bubbled through a stirred solution of 295 mg (1.00 mmol) of lactone 167 and 625 µL (668 mg, 2.02 mmol) of allyltri-n-butylstannane in 8 mL of benzene, followed by addition of 17 mg (0.10 mmol) of AIBN. The resulting solution was heated to reflux under N₂ atmosphere for 16 h. TLC analysis (silica gel; EtOAc-hexanes, 1:3) indicated that all starting lactone 167 was consumed. The reaction mixture was cooled to room temperature, 3 mL of 17 M aqueous potassium fluoride was added, and stirring was continued for 2 h. The resulting fine white precipitate was removed by filtration and the filter cake was washed with 2 mL of Et₂O. The organic phase was separated and the aqueous phase was extracted with 2 mL of Et₂O. The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo, to yield 491 mg of a yellow oil. The crude product was purified by flash chromatography over 25 g of silica gel (EtOAc-hexanes, 1:1), to yield 77.4 mg (37%) of compound 183 as a yellow oil: IR (neat) 2976, 2937, 1767, 1745, 1383, 1261, 1196, 1040, 943 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.18 (s, 3H)
3H, H$_2$C=C-C=O), 1.62 (s, 3H, s, 3H, O-C-CH$_3$), 2.04 + 2.39 (m, 1H + 5H, cyclopentanone CH$_2$’s + allyl CH$_2$), 2.55 (s, 1H, CH-C=O), 5.18 (dq, $J = 13.4, 1.4$ Hz, 1H, =CH$_2$), 5.25 (dt, $J = 10.1, 0.8$ Hz, 1H, =CH$_2$), 5.76 (m, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 20.4 (q), 26.8 (q), 34.8 (t), 38.1 (t), 44.3 (t), 48.1 (s), 59.1 (d), 87.1 (s), 120.7 (t), 132.1 (d), 179.3 (s), 214.1 (s); exact mass calcd. for C$_{12}$H$_{16}$O$_3$ + Na $m/z$ 231.0997, found $m/z$ 231.0994.

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(1R,5R,4R)-1,4,5-Trimethyl-4-allyl-2-oxabicyclo[3.3.0]octan-3,6-dione (184).

Nitrogen was bubbled through a stirred solution of 267 mg (0.87 mmol) of lactone 168 and 540 µL (577 mg, 1.74 mmol) of allyltri-n-butylstannane in 7 mL of benzene, followed by addition of 14 mg (0.085 mmol) of AIBN. The resulting solution was heated to reflux under N₂ atmosphere for 24 h. TLC analysis (silica gel; EtOAc-hexanes, 1:3) indicated that some starting lactone 168 remained. AIBN (57 mg, 0.35 mmol) was added and the resulting solution was heated to reflux under N₂ atmosphere for 24 h. TLC analysis (silica gel; EtOAc-hexanes, 1:3) indicated that all starting lactone 168 was consumed. The reaction mixture was cooled to room temperature, 3 mL of 17 M aqueous potassium fluoride was added, and stirring was continued for 2 h. The resulting fine white precipitate was removed by filtration and the filter cake was washed with 2 mL of Et₂O. The organic phase was separated and the aqueous phase was extracted with 5 mL of Et₂O. The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo, to yield 555 mg of a yellow oil. The crude product was purified by flash chromatography over 28 g of silica gel (EtOAc / hexanes 1:1), to yield 35.4 mg (18%) of compound 184 as a yellow oil: IR (neat) 3076, 2976, 1765, 1742, 1261, 1091, 1045 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.05 (s, 3H, allyl-CCH₃), 1.08 (s, 3H, H₃CCC=O), 1.57 (s, 3H, OCCH₃), 1.77 (m, 1H, CH₂CH₂C=O), 2.26 (dd, J = 14.0, 7.9 Hz, 1H, allyl CH₂), 2.39 (m,
4H, allyl CH₂ + CH₂CH₂C=O + CH₂C=O), 5.12 (dq, J = 16.9, 1.4 Hz, 1H, =CH₂), 5.17 (dd, J = 10.1, 0.6 Hz, 1H, =CH₂), 5.84 (m, 1H, =CH); ¹³C NMR (CDCl₃, 125 MHz) δ 13.0 (q), 19.0 (q), 23.3 (q), 32.5 (t), 36.4 (t), 40.2 (t), 48.1 (s), 58.0 (s), 90.6 (s), 119.4 (t), 132.4 (d), 178.4 (s), 216.4 (s); exact mass calcd. for C₁₃H₁₈O₃ + Na m/z 245.1154, found m/z 245.1147.

Selected NOE difference experiments for lactone 184:

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1,4,5-Trimethyl-2-oxabicyclo[3.3.0]octan-3,6-diones (185 and 186). Nitrogen was bubbled through a solution of 295 mg (1.00 mmol) of lactone 167 in 100 mL of benzene, 18 mg (0.11 mmol) of AIBN was added, and the resulting solution was heated
to a gentle reflux under N$_2$ atmosphere. Tri-$n$-butylstannane (275 µL, 298 mg, 1.02 mmol) was added over 1 h and the resulting solution was stirred at reflux under N$_2$ for 1 h. TLC analysis (silica; EtOAc-hexanes, 1:1) showed no remaining starting lactone. The reaction mixture was cooled to room temperature and 3 mL of 17 M aqueous KF was added, resulting in formation of a fine white precipitate. Stirring was continued for 2 h. The resulting mixture was filtered, the aqueous phase was separated, and the organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo to yield 618 mg of a yellow oil. This oil was purified by flash chromatography over 32 g of silica gel (EtOAc-hexanes, 1:1), to yield 131 mg (78%) of a 5:1 (by NMR) mixture of 185 and 186 as a pale yellow oil. Spectral data for 185: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.27 (d, $J = 7.5$ Hz, 3H, CHCH$_3$), 1.58 (s, 3H, O-C-CH$_3$), 1.95 (m, 1H, cyclopentanone CH$_2$’s), 2.38 – 2.50 (m, 3H, cyclopentanone CH$_2$’s), 2.58 (d, $J = 10.4$ Hz, 1H, bridgehead CH), 3.09 (dq, $J = 10.4, 7.5$ Hz, 1H, CHCH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 11.0 (q), 24.3 (q), 33.3 (t), 37.7 (t), 38.0 (d), 55.4 (d), 88.5 (s), 177.1 (s), 214.3 (s). Spectral data for 186: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.46 (d, $J = 7.6$ Hz, 3H, CHCH$_3$), 1.66 (s, 3H, O-C-CH$_3$), 2.09 (m, 1H, cyclopentanone CH$_2$’s), 2.38 – 2.50 (m, 3H, cyclopentanone CH$_2$’s), 2.39 (d, $J = 10$ Hz, 1H, bridgehead CH), 2.80 (dq, $J = 7.7, 3.6$ Hz, 1H, CHCH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 17.7 (q), 26.6 (q), 33.8 (t), 36.7 (t), 40.5 (d), 59.6 (d), 89.0 (s), 177.6 (s), 215.7 (s); IR (neat, mixture): 2980, 2941, 1767, 1741 cm$^{-1}$; exact mass calcd. for C$_9$H$_{12}$O$_3$ + Na $m/z$ 191.0684, found (mixture) $m/z$ 191.0685.
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</table>
1,4,5-Trimethyl-2-oxabicyclo[3.3.0]octan-3,6-diones (187 and 188).

Nitrogen was bubbled through a solution of 252 mg (0.82 mmol) of lactone 168 in 85 mL of benzene, 13 mg (0.11 mmol) of AIBN was added, and the resulting solution was heated to a gentle reflux under N₂ atmosphere. Tri-ₙ-butylstannane (220 µL, 238 mg, 0.82 mmol) was added over 1 h and the resulting solution was stirred at reflux under N₂ for 5 h. TLC analysis (silica; EtOAc-hexanes, 1:3) showed only traces of the starting lactone. The reaction mixture was cooled to room temperature and 3 mL of 17 M aqueous KF was added, and stirring was continued for 2 h. The resulting mixture was filtered, the aqueous phase was separated, and the organic phase was dried (Na₂SO₄) and concentrated in vacuo. The residual yellow oil (500 mg) was purified by flash chromatography over 25 g of silica gel (EtOAc-hexanes, 1:3 → 1:1), to yield 111 mg (75%) of a 10:1 (by NMR) mixture of 187 and 188 as a yellow solid. Spectral data for 187: ¹H NMR (CDCl₃, 500 MHz) δ 1.14 (s, 3H, bridgehead CH₃), 1.20 (d, J = 7.4 Hz, 3H, CHCH₂), 1.47 (s, 3H, bridgehead CH₃), 1.88 (m, 1H, CH₂CH₂C=O), 2.41 (m, 3H, CH₂CH₂C=O + CH₂C=O), 2.59 (q, J = 7.4 Hz, 1H, CHCH₃); ¹³C NMR (CDCl₃, 125 MHz) δ 9.5 (q), 16.8 (q), 20.9 (q), 31.3 (t), 36.3 (t), 44.3 (d), 55.7 (s), 91.6 (s), 176.4 (s), 217.0 (s). Spectral data for 188: ¹H NMR (CDCl₃, 500 MHz) δ 1.04 (s, 3H, bridgehead CH₃), 1.28 (d, J = 7.8 Hz, 3H, CHCH₂), 1.50 (s, 3H, bridgehead CH₃), 2.01 (m, 1H,
\( \text{CH}_2\text{CH}_2\text{C}=\text{O} \), 2.45 (m, 3H, \text{CH}_2\text{CH}_2\text{C}=\text{O} + \text{CH}_2\text{C}=\text{O}), 2.76 (q, J = 7.8 \text{ Hz}, 1\text{H}, \text{CHCH}_3); \\
\text{\textsuperscript{13}C} \text{ NMR (CDCl}_3, 125 \text{ MHz}) \delta 12.3 \text{ (q), 12.5 \text{ (q), 22.7 \text{ (q), 31.7 \text{ (t), 34.7 \text{ (t), 42.3 \text{ (d), 56.7 \text{ (s), 92.1 \text{ (s), 177.5 \text{ (s), 219.2 \text{ (s); mp (mixture) 68-70}^\circ \text{C; IR (KBr, mixture) 2979, 2902, 1766, 1732, 1383, 1043, 940 cm}^{-1}; \text{exact mass calcd. for C}_{10}\text{H}_{14}\text{O}_3 + \text{Na m} / \text{z} 205.0841, \text{found (mixture) m} / \text{z} 205.0833.}

\text{Selected NOE difference experiments for lactone 187:}

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Selected NOE difference experiments for lactone 188:

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</table>
4-Methyl-5-phenyloxazolidin-2-one (264).\(^8\) To a stirred solution of 50.0 g (331 mmol) of (1S,2R)-(−)-norephedrine in 88 mL (86 g, 726 mmol) of diethyl carbonate was added 4.62 g (334 mmol) of solid potassium carbonate. The resulting mixture was heated to 135 °C under \( \text{N}_2 \) for 4 h as approximately 80 mL of ethanol was distilled from the reaction mixture. The reaction mixture was cooled to rt, diluted with 250 mL of \( \text{CH}_2\text{Cl}_2 \), washed with two 200-mL portions of \( \text{H}_2\text{O} \) and 200 mL of brine, dried (\( \text{Na}_2\text{SO}_4 \)), and concentrated to yield 52.9 g (90%) of oxazolidinone 264 as a light, pale yellow solid: mp 118-119°C (lit.\(^8\) 121°C); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 0.82 (d, \( J = 6.5 \) Hz, 3H, \( \text{CH}_3 \)), 4.22 (m, 1H, \( \text{CH}-\text{NH} \)), 5.72 (d, \( J = 8.0 \) Hz, \( \text{CH}-\text{Ph} \)), 6.19 (br, 1H, \( \text{NH} \)), 7.30 (m, 2H, ArH), 7.35 – 7.42 (m, 3H, ArH).

4-Methyl-3-pent-4-enoyl-5-phenyloxazolidin-2-one (265).\(^{84b}\) To a stirred solution of 25.2 g (252 mmol) of 4-pentenoic acid (263) in 450 mL of anhydrous THF, at \( -20 \) °C under \( \text{N}_2 \), was added 34 mL (33 g, 277 mmol) of pivaloyl chloride via syringe...
over 10 min, followed by 106 mL (76.5 g, 755 mmol) of triethylamine via syringe over 5 min. The resulting mixture was warmed to rt and stirring was continued for 2 h. Solid lithium chloride (16.0 g, 378 mmol) was added in one portion, followed by 44.6 g (252 mmol) of 4-methyl-5-phenyloxazolidin-2-one (265), added in four portions. An exothermic reaction occurred and the temperature rose to 40 ºC. The resulting mixture was stirred vigorously at rt for 14 h and was then diluted with 1500 mL of EtOAc. The solution was washed with 1000 mL of H2O and 1000 mL of brine, dried (Na2SO4), and concentrated to yield 64.2 g of an orange solid. The crude product was purified by flash chromatography over 1000 g of silica gel (EtOAc-hexanes, 10:90) to yield 56.3 g (86%) of amide 265 as a white solid: mp 70-71 ºC (lit.84b 69-70 ºC) 1H NMR (CDCl3, 500 MHz) δ 0.91 (d, J = 6.6 Hz, 3H, CH3), 2.46 (q, J = 7.1 Hz, 2H, CH2-CH=), 3.00 – 3.16 (m, 2H, CH2-C=O), 4.78 (p, J = 6.9 Hz, 1H, CH-N), 5.03 – 5.13 (m, 2H, =CH2), 5.68 (d, J = 7.3 Hz, 1H, CH-Ph), 5.90 (m, 1H, =CH), 7.31 (dd, J = 7.9, 1.6 Hz, 2H, Ar =CH), 7.38-7.45 (m, 3H, Ar =CH).

4-Methyl-5-phenyloxazolidin-2-one (267).84n To a stirred solution of 28.2 g (109 mmol) of imide 265
in 800 mL of anhydrous THF, at –78 ºC under N₂, was added 114 mL (114 mmol) of a
1.0 M solution of NaHMDS in THF via syringe over 20 min. The resulting solution was
stirred at –78 ºC for 1 h, followed by addition via syringe of a solution of 22.5 g (118
mmol) of bromide 277 in 30 mL of THF. The resulting solution was stirred at –78ºC for 2
h, and was then allowed to warm up to rt. Stirring was continued at rt for 14 h. The
reaction mixture was quenched by addition of 140 mL of saturated aqueous NH₄Cl and
the resulting layers were separated. The aqueous layer was extracted with three 500-mL
portions of EtOAc. The combined organic layers were washed with 700 mL of brine,
dried (Na₂SO₄), and concentrated in vacuo to yield 42.8 g of an orange oil. The crude
product was purified by flash chromatography over 1000 g of silica gel (EtOAc-hexanes,
10:90), to yield 25.3 g (63%) of alkylation product 267 as a pale yellow oil: ¹H NMR
(CDCl₃, 500 MHz) δ 0.11 (s, 9H, TMS), 0.90 (d, J = 6.6 Hz, 3H, CH₃), 2.38 (m, 1H,
HC=CH₂), 2.50  (m, 1H, HC=CH₂), 2.57 (dd, J = 6.9, 2.0 Hz, 2H, CH₂-C≡), 4.11 (p, J =
6.9 Hz, 1H, CH-C=O), 4.80 (p, J = 6.8 Hz, 1H, CH-CH₃), 5.10 (m, 2H, =CH₂), 5.65 (d, J
= 7.3 Hz, 1H, CH-Ph), 5.78 (m, 1H, =CH), 7.31 (dd, J = 7.8, 1.4 Hz, 2H, ArH), 7.38-7.44
(m, 3H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ -0.0 (q), 14.6 (q), 21.9 (t), 35.5 (t), 42.0
(d), 54.9 (d), 78.8 (d), 86.5 (s), 103.4 (s), 117.8 (t), 125.6 (d), 128.68 (d), 128.72 (d),
133.2 (s), 134.5 (d), 152.6 (s), 173.7 (s).
3-\{2-\{3-(\text{\textit{tert}}\text{-Butyldimethylsilyl})\text{prop-2-ynyl}\}\text{pent-4-enoyl}\}-4\text{-methyl-5-phenyl-oxazolidin-2-one} (268). To a stirred solution of 14.1 g (54.3 mmol) of imide 265 in 400 mL of anhydrous THF, at –78 ºC under N₂, was added 60.0 mL (60.0 mmol) of a 1.0 M solution of NaHMDS in THF via syringe over 20 min. The resulting solution was stirred at –78 ºC for 1 h, followed by addition via syringe of a solution of 15.2 g (65.2 mmol) of bromide 278 in 20 mL of THF. The resulting solution was stirred at –78 ºC for 2 h and was then allowed to warm to rt. Stirring was continued at rt for 14 h. The reaction mixture was quenched by addition of 70 mL of saturated aqueous NH₄Cl and the resulting layers were separated. The aqueous layer was extracted with three 250-mL portions of EtOAc. The combined organic layers were washed with 350 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 27.5 g of an orange oil. The crude product was purified by flash chromatography over 400 g of silica gel (EtOAc : hexanes 10:90), to yield 14.0 g (63%) of alkylation product 268 as a white solid: mp 74-74ºC; IR (film) 2954, 2928, 2856, 2176, 1783, 1703, 1343, 1195 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.04 (s, 3H, TBS CH₃), 0.05 (s, 3H, TBS CH₃), 0.90 (d, 3H, CH₃), 0.91 (s, 9H, TBS \text{\textit{t}}-\text{Bu}), 2.41 (m, 1H, =CH-CH₂), 2.50 (m, 1H, =CH-CH₂), 2.60 (t, J = 6.6 Hz, 2H, =C-CH₂), 4.09 (p, J = 6.7 Hz, 1H, CH-C=O), 4.79 (p, J = 6.8 Hz, 1H, CH-CH₃), 5.10 (m, 2H, =CH₂), 5.65 (d, J = 7.3 Hz, 1H, CH-Ph), 5.80 (m, 1H, =CH), 7.30 (d, J = 6.9 Hz, 2H,
ArH), 7.36-7.44 (m, 3H, ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.6 (q), 14.6 (q), 16.4 (s), 21.8 (t), 26.0 (q), 35.4 (t), 42.1 (d), 54.9 (d), 78.8 (d), 84.6 (s), 103.9 (s), 117.7 (t), 125.6 (d), 128.67 (d), 128.72 (d), 133.3 (s), 134.6 (d), 152.6 (s), 173.6 (s); exact mass calcd. for C$_{24}$H$_{33}$NO$_3$Si + Na $m/z$ 434.2122, found $m/z$ 434.2117; $[\alpha]_D = +41.8^\circ$ (CHCl$_3$, c = 5.5).

4-Methyl-5-phenyl-3-(2-prop-2-ynyl-pent-4-enoyl)-oxazolidin-2-one (269).

To a stirred solution of 1.08 g (4.18 mmol) of imide 265 in 30 mL of anhydrous THF, at –78 °C under N$_2$, was added 4.4 mL (4.4 mmol) of a 1.0 M solution of NaHMDS in THF via syringe over 20 min. The resulting solution was stirred at –78 °C for 1 h, followed by addition via syringe of a solution of 552 mg (4.64 mmol) of propargyl bromide (279) in 1 mL of THF. The resulting solution was allowed to warm to rt and stirring was continued at rt for 14 h. The reaction mixture was quenched by addition of 5 mL of saturated aqueous NH$_4$Cl and the resulting layers were separated. The aqueous layer was extracted with three 20-mL portions of EtOAc. The combined organic layers were washed with 25 mL of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to yield 1.31 g of an orange oil. The crude product was purified by flash chromatography over 65 g of silica gel (EtOAc-hexanes, 10:90), to yield 458 mg (37%) of alkylation product 269 as a pale yellow oil, as
well as 539 mg (46%) of a 1:1 mixture of 269 and starting material 265. Data on 269: IR (film) 3295, 3074, 2982, 2916, 1781, 1700, 1385, 1368, 1251, 1220, 1195 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 0.89 (d, \(J = 6.6\) Hz, 3 H, CH\(_3\)), 1.97 (t, \(J = 2.6\) Hz, 1H, =C-H), 2.39 (m, 1H, =CH-CH\(_2\)), 2.52 (m, 1H, =CH-CH\(_2\)), 2.54 (m, 2H, =C-CH\(_2\)), 4.09 (p, \(J = 6.8\) Hz, 1H, CH-C=O), 4.78 (p, \(J = 6.8\) Hz, 1H, CH-CH\(_3\)), 5.10 (m, 2H, =CH\(_2\)), 5.65 (d, \(J = 7.3\) Hz, 1H, CH-Ph), 5.79 (m, 1H, =CH), 7.30 (dd, \(J = 7.7, 1.2\) Hz, 2H, ArH), 7.34-7.42 (m, 3H, ArH); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 14.4 (q), 20.4 (t), 35.3 (t), 41.7 (d), 54.8 (d), 70.1 (s), 78.8 (d), 80.8 (d), 117.8 (t), 125.5 (d), 128.6 (d), 128.7 (d), 133.2 (s), 134.4 (d), 152.6 (s), 173.5 (s); exact mass calcd. for C\(_{18}\)H\(_{19}\)NO\(_3\) + Na \(m/z\) 320.1257, found \(m/z\) 320.1246; \([\alpha]_D\) = +11.2° (CH\(_2\)Cl\(_2\), c = 1.0).

2-Prop-2-ynylpent-4-enoic acid (266).\(^{84b}\) From 267: To a stirred solution of 21.8 g (59.1 mmol) of oxazolidinone 267 in 300 mL of THF-H\(_2\)O (4:1), at 0 °C, were sequentially added 4.99 g (119 mmol) of LiOH•H\(_2\)O and 25 mL of 30% aqueous H\(_2\)O\(_2\). The resulting solution was stirred at 0 °C for 4 h. A solution of 3.20 g of sodium sulfite in 30 mL of H\(_2\)O was added, and the resulting mixture was vigorously stirred at 0 °C for 15 min. The greater part of the THF was removed in vacuo and the residue was washed with
two 130-mL portions of CH$_2$Cl$_2$. The aqueous phase was carefully acidified to pH = 1 by addition of concentrated aqueous HCl in an ice bath. The resulting mixture was extracted with three 130-mL portions of CH$_2$Cl$_2$. The organic extracts were washed with 130 mL of brine, dried (Na$_2$SO$_4$), and concentrated to yield 7.55 g (92%) of acid 266 as a colorless liquid. This material was suitable for use in the next reaction.

**From 269:** To a stirred solution of 275 mg (0.92 mmol) of oxazolidinone 269 in 5 mL of THF-H$_2$O (4:1), at 0 ºC, were sequentially added 77.2 mg (1.84 mmol) of LiOH•H$_2$O and 0.4 mL of 30% aqueous H$_2$O$_2$. The resulting solution was stirred at 0 ºC for 4 h. A solution of 50 mg of sodium sulfite in 1 mL of H$_2$O was added, and the resulting mixture was vigorously stirred at 0 ºC for 15 min. The greater part of the THF was removed in vacuo, and the residue was washed with two 2-mL portions of CH$_2$Cl$_2$, carefully acidified to pH = 1 by addition of concentrated aqueous HCl in an ice bath. The mixture was extracted with three 2-mL portions of CH$_2$Cl$_2$. The dichloromethane extracts were washed with 2 mL of brine, dried (Na$_2$SO$_4$), and concentrated to yield 102 mg (81%) of acid 266 as a colorless liquid, suitable for use in subsequent reactions: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.04 (t, $J = 2.6$ Hz, 1H, -C-H), 2.43–2.56 (m, 4H, CH$_2$CH=CH$_2$C=), 2.71 (p, $J = 6.8$ Hz, 1H, CHCO$_2$H), 5.10 – 5.18 (m, 2H, =CH$_2$), 5.73 – 5.81 (m, 1H, =CH).
2-[3-(tert-Butyldimethylsilyl)prop-2-yny]pent-4-enoic acid (270). To a stirred solution of 13.8 g (33.5 mmol) of oxazolidinone 268 in 175 mL of THF-H_{2}O (4:1), at 0 °C, were sequentially added 2.81 g (66.9 mmol) of LiOH•H_{2}O and 14.5 mL of 30% aqueous H_{2}O_{2}. The resulting solution was stirred vigorously at 0 °C for 4 h. A solution of 1.85 g of sodium sulfite in 20 mL of H_{2}O was added, and the resulting mixture was vigorously stirred at 0 °C for 15 min. The greater part of the THF was removed in vacuo and the residue was extracted with two 75-mL portions of CH_{2}Cl_{2}. The combined organic extracts were washed with 75 mL of 1 N HCl, dried (Na_{2}SO_{4}), and concentrated in vacuo to yield 13.3 g of a pale yellow oil. The crude product was purified by flash chromatography over 400 g of silica gel (EtOAc : hexanes, 25:75), to yield 6.93 g (82%) of acid 270 as a colorless oil: IR (neat) 2954, 2930, 2858, 2179, 1712, 1251, 921, 826, 776 cm\(^{-1}\); \(^{1}\)H NMR (CDCl_{3}, 500 MHz) \(\delta\) 0.08 (s, 6H, TBS CH_{3}’s), 0.92 (s, 9H, TBS \(t\)-Bu), 2.46-2.59 (m, 4H, CH_{2}-CH= + CH_{2}-C≡), 2.68 (q, \(J = 6.8\) Hz, 1H, CH-CO_{2}H), 5.12 (m, 2H, =CH_{2}), 5.76 (m, 1H, =CH); \(^{13}\)C NMR (CDCl_{3}, 125 MHz) \(\delta\) -4.6 (q), 16.4 (s), 21.5 (t), 26.0 (q), 34.6 (t), 44.2 (d), 85.1 (s), 103.8 (s), 117.9 (t), 134.1 (d), 180.4 (s); exact mass calcd. for C_{14}H_{24}O_{2}Si + Na \(m/z\) 275.1438, found \(m/z\) 275.1416; \([\alpha]_D^0 = +46.3^\circ\) (CH_{2}Cl_{2}, c = 6.3).
(S)-N-(tert-butoxycarbonyl)hept-6-en-1-yn-4-ylamine (271). To a stirred solution of 8.45 g (61.1 mmol) of acid 266 in 140 mL of t-BuOH were sequentially added 13.3 mL (16.9 g, 61.5 mmol) of diphenylphosphoryl azide and 8.5 mL (6.2 g, 61 mmol) of triethylamine. The resulting solution was heated to a gentle reflux under N₂ for 24 h. The reaction mixture was cooled to rt and diluted with 500 mL of benzene. The resulting solution was washed sequentially with 130 mL of 5% aqueous citric acid, 60 mL of H₂O, 130 mL of saturated aqueous NaHCO₃ and 130 mL of brine. The solution was dried (Na₂SO₄), and concentrated in vacuo to yield 14.5 g of a tan paste. The crude product was purified by bulb-to-bulb distillation (bp 70–80 °C @ 0.1 mmHg) to yield 11.0 g (86%) of carbamate 271 as a pale yellow oil: \(^1\)H NMR (CDCl₃, 500 MHz) δ 1.44 (s, 9H, BOC), 2.02 (t, \(J = 2.7\) Hz, 1H, =C-H), 2.33 (m, 2H, =CH-CH₂), 2.42 (m, 2H, =C-CH₂), 3.79 (br, 1H, CH-NH), 4.67 (br, 1H, NH), 5.11 (m, 2H, =CH₂), 5.76 (m, 1H, =CH); \(^{13}\)C NMR (CDCl₃, 125 MHz) δ 24.2 (t), 28.8 (q), 38.3 (t), 48.7 (d), 71.3 (d), 79.8 (s), 80.7 (s), 118.6 (t), 134.4 (d), 155.6 (s).
From 271: To a stirred solution of 8.70 g (41.6 mmol) of alkyne 271 in 200 mL of anhydrous THF, at –78 ºC under N₂, was added dropwise 35 mL (87.5 mmol) of 2.5 M n-BuLi in hexanes over 30 min, followed by dropwise addition (over 30 min.) of a solution of 12.5 g (83.2 mmol) of tert-butyldimethylsilyl chloride in 20 mL of THF and 20 mL of DMPU. The resulting solution was stirred at –78 ºC for 1 h and then allowed to warm to rt. The reaction mixture was quenched by addition at 0 ºC of 120 mL of 0.6 N aqueous HCl and stirring was continued at 0 ºC for 30 min. The resulting layers were separated and the aqueous layer was extracted with two 120-mL portions of EtOAc. The combined organic layers were dried (Na₂SO₄) and concentrated to yield 27.8 g of a yellow oil. The crude product was purified by flash chromatography over 1000 g of silica gel (EtOAc-hexanes, 8:92), to yield 10.7 g (79%) of protected alkyne 272 as a pale yellow oil.

From 270: To a stirred solution of 6.93 g (27.4 mmol) of acid 270 in 65 mL of tert-BuOH were sequentially added 6.0 mL (7.66 g, 27.8 mmol) of diphenylphosphoryl azide and 3.9 mL (2.8 g, 28 mmol) of triethylamine. The resulting solution was heated to a gentle reflux under N₂ for 36 h. The reaction mixture was cooled to rt and diluted with 200 mL of benzene. The resulting solution was washed with 60 mL of 5% aqueous citric acid, 30 mL of H₂O, 60 mL of saturated aqueous NaHCO₃ and 60 mL of brine. The
organic phase was dried (Na$_2$SO$_4$), and concentrated in vacuo to yield 10.0 g of a dark yellow oil. The crude product was purified by flash chromatography over 400 g of silica gel (EtOAc-hexanes, 8:92), to yield 3.40 g (38%) of **272** as a colorless liquid: IR (film) 3338, 2954, 2857, 2175, 1719, 1500, 1366, 1250, 1172, 838, 825, 775 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.10 (s, 6H, TBS CH$_3$'s), 0.96 (s, 9H, TBS t-Bu), 1.45 (s, 9H, BOC), 2.36 (m, 2H, $=$CH-CH$_2$), 2.47 (d, $J$ = 5.1 Hz, 2H, $=$C-CH$_2$), 3.77 (br m, 1H, CH-NH), 4.64 (br, 1H, NH), 5.12 (m, 2H, $=$CH$_2$), 5.78 (m, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.5 (q), 16.5 (s), 25.0 (t), 26.1 (q), 28.4 (q), 38.1 (t), 48.4 (d), 79.3 (s), 85.7 (s), 103.3 (s), 118.1 (t), 134.1 (d), 155.2 (s); exact mass calcd. for C$_{18}$H$_{33}$NO$_2$Si + Na m/z 346.2173, found m/z 346.2149.

![3-Trimethylsilylprop-2-yn-1-ol (276)](image)

**3-Trimethylsilylprop-2-yn-1-ol (276)**. $^{89}$ To a stirred solution of 30 mL (19 g, 515 mmol) of propargyl alcohol (273) in 1300 mL of anhydrous THF at $-78$ °C under N$_2$ was added dropwise 460 mL (1150 mmol) of 2.5 M n-BuLi in hexanes over 1 h. A white slurry formed, which was stirred at $-78$ °C for 30 min, followed by dropwise addition of 200 mL (171 g, 157 mmol) of trimethylsilyl chloride over 30 min. The resulting mixture was stirred at $-78$ °C for 20 min and was then allowed to warm to rt. Aqueous 10% HCl (900 mL) was added and stirring was continued at rt for 16 h. The resulting layers were separated and the aqueous layer was extracted with three 1000-mL portions of Et$_2$O. The
combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to yield 98.9 g of an orange liquid. The crude product was purified by fractional distillation (bp 45-47 °C @ 3 mmHg, lit.⁸⁹ 95-96°C @ 22 mmHg) to yield 47.2 g (71%) of alcohol 276 as a yellow liquid: ¹H NMR (CDCl₃, 400 MHz) δ 0.18 (s, 9H, TMS), 1.66 (s, 1H, OH), 4.27 (s, 2H, CH₂).

![3-Bromoprop-1-ynyl)trimethylsilane (277)](image)

(3-Bromoprop-1-ynyl)trimethylsilane (277).⁸⁹ To a stirred solution of 46.4 g (362 mmol) of alcohol 276 and 770 µL (753 mg, 9.52 mmol) of pyridine in 190 mL of anhydrous Et₂O was added dropwise a solution of 17.1 mL (49.1 g, 181 mmol) of PBr₃ in 55 mL of Et₂O over 10 min. An exothermic reaction occurred and a white precipitate formed. The resulting mixture was heated to reflux for 3 h, over which time the precipitate redissolved. The reaction mixture was poured over 250 g of ice, the resulting layers were separated, and the aqueous layer was extracted with three 250-mL portions of Et₂O. The combined organic layers were sequentially washed with 250 mL of H₂O, 250 mL of saturated aqueous NaHCO₃, and 250 mL of saturated aqueous NH₄Cl, dried (Na₂SO₄), and concentrated in vacuo to yield 59.4 g of a dark yellow liquid. The crude product was purified by fractional distillation (bp 88-90 °C @ approximately 50 mmHg) to yield 51.8 g (75%) of alkyl bromide 277 as a colorless liquid: ¹H NMR (CDCl₃, 500 MHz) δ 0.19 (s, 9H, TMS), 3.92 (s, 2H, CH₂).
2-(Prop-2-ynyloxy)tetrahydropyran (274).\textsuperscript{135} To a stirred solution of 116 mg (0.5 mmol) of camphorsulfonic acid in 750 mL of anhydrous dichloromethane was added, via syringe at rt under N\textsubscript{2}, 29.4 mL (28.3 g, 505 mmol) of propargyl alcohol. The resulting mixture was cooled to 0 °C followed by dropwise addition of a solution of 50.2 mL (46.2 g, 549 mmol) of 3,4-dihydro-2H-pyran in 75 mL of dichloromethane, over 2 h. The resulting mixture was warmed to rt and stirring was continued for 2 h. The reaction mixture was washed with 100 mL of saturated aqueous NaHCO\textsubscript{3}, dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo to yield 74.0 g of a pale yellow liquid. The crude product was purified by fractional distillation (bp 110-115 °C @ approximately 45 mmHg, lit.\textsuperscript{136} 69-70 °C @ 13 mmHg) to yield 61.8 g (87\%) of protected alcohol 274 as a colorless liquid:

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 1.52–1.65 (m, 4H, THP CH\textsubscript{2}’s), 1.69–1.87 (m, 2H, THP CH\textsubscript{2}), 2.41 (d, \(J = 2.4\) Hz, 1H, \(=\text{C-H}\)), 3.53 (m, 1H, THP CH\textsubscript{2}-O), 3.83 (m, 1H, THP CH\textsubscript{2}-O), 4.20–4.31 (m, 2H, CH\textsubscript{2}-C\(=\)), 4.82 (t, \(J = 3.4\) Hz, 1H, O-CH-O); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 19.0 (t), 25.3 (t), 30.2 (t), 53.9 (t), 61.9 (t), 73.9 (d), 79.7 (s), 96.8 (d).
3-(tert-Butyldimethylsilyl)prop-2-yn-1-ol (275). To a stirred solution of 19.5 g (139 mmol) of alkyne 274 in 140 mL of anhydrous THF at \(-78 \, ^\circ\text{C}\) under N\(_2\), was added dropwise via syringe 14.0 mL (140 mmol) of 10 M n-BuLi in hexanes over 15 min. The resulting solution was stirred at \(-78 \, ^\circ\text{C}\) for 5 min., then warmed to 0 \, ^\circ\text{C} and stirred for a further 15 min. t-Butyldimethylsilyl chloride (22.0 g, 146 mmol) was added in one portion and the resulting mixture was allowed to warm to rt (a red coloration appeared). The reaction mixture was poured into 250 mL of 10% aqueous NaCl and 250 mL of hexanes. After vigorous mixing and separation of layers, the aqueous layer was extracted two 125-mL portions of hexanes and the combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to yield 38 g of a red oil. This material was dissolved in 500 mL of methanol and 532 mg (2.80 mmol) of \(p\)-toluenesulfonic acid was added. The resulting mixture was stirred at rt for 2 h and quenched with 100 mL of saturated aqueous NaHCO\(_3\). The resulting suspension was stirred vigorously for 10 min. and most of the methanol was removed in vacuo. To the residue was added 250 mL of 10% aqueous NaCl and the resulting mixture was extracted with three 200-mL portions of EtOAc : hexanes (1:1). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo, to yield 30.2 g of a red liquid. The crude product was purified by fractional distillation (bp 80-85 \, ^\circ\text{C} @ 3 mmHg, lit.\(^{136}\) 69-72 \, ^\circ\text{C} @ 1 mmHg) to yield 13.4 g (56%) of alcohol 275 as a colorless liquid: \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.11 (s, 6H, TBS CH\(_3\)’s), 0.93 (s, 9H, TBS t-Bu), 1.83 (s, 1H, OH), 4.27 (s, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) -4.7 (q), 16.4 (s), 26.0 (q), 51.6 (t), 88.8 (s), 104.5 (s).
(3-Bromo-1-propynyl)tert-butylidimethylsilane (278). To a stirred solution of 26.8 g (102 mmol) of triphenylphosphine and 6.95 g (102 mmol) of imidazole in 165 mL of anhydrous dichloromethane at 0 ºC under N₂ was added, via syringe, 5.3 mL (16.4 g, 103 mmol) of bromine over 15 min. The resulting suspension was stirred at 0 ºC for 15 min, followed by dropwise addition of 13.4 g (78.5 mmol) of alcohol 275 in 70 mL of CH₂Cl₂ over 30 min. The resulting suspension was stirred at 0 ºC for 15 min, followed by addition of 250 mL of pentane. The resulting suspension was filtered through a pad of 200 g of silica gel superposed with 200 g of Celite 545, and the filter cake was washed with pentane – Et₂O (1:1). The filtrate was concentrated in vacuo, to yield 23.9 g of a pale yellow liquid. The crude product was purified by fractional distillation (bp 118-120 ºC @ 40 mmHg, lit. 94 102-103 ºC @ 20 mmHg), to yield 15.2 g (83%) of alkyl bromide 278 as a pale yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 0.13 (s, 6H, TBS CH₃’s), 0.95 (s, 9H, TBS t-Bu), 3.93 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 100 MHz) δ -4.9 (q), 14.7 (t), 16.6 (s), 26.0 (q), 90.8 (s), 100.6 (s).
(3R)-N-(tert-butoxycarbonyl)-6-tert-butyldimethylsilyl-3-amino-5-hexynal (280).\textsuperscript{84c} To a stirred solution of 10.67 g (32.98 mmol) of alkene 272 in 175 mL of t-BuOH : H₂O (3:1) at 0 ºC was sequentially added 25 mL of 1% aqueous OsO₄ (250 mg OsO₄, 1 mmol) and 14.12 g (66.0 mmol) of NaIO₄. The resulting mixture was vigorously stirred at 0 ºC for 4 h and was then partitioned between 400 mL of H₂O and 400 mL of EtOAc. The aqueous layer was extracted with 450 mL of EtOAc and the combined organic layers were washed with 450 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 16.02 g of a black oil. The crude product was purified by flash chromatography over 400 g of silica gel (EtOAc-hexanes, 20:80) to yield 8.45 g (79%) of aldehyde 280 as a reddish oil: IR (film) 3352, 2954, 2930, 2857, 2175, 1722, 1505, 1366, 1251, 1171, 839, 826, 776 cm⁻¹, ¹H NMR (CDCl₃, 500 MHz) δ 0.10 (s, 6H, TBS CH₃’s), 0.93 (s, 9H, TBS t-Bu), 1.44 (s, 9H, BOC), 2.57 (m, 2H, =CHCH₂), 2.77 (d, \(J = 5.5\) Hz, 2H, =CCH₂), 4.21 (br m, 1H, CHN), 5.30 (br, 1H, NH), 9.78 (t, \(J = 1.4\) Hz, 1H, CHO); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), 16.5 (s), 25.7 (t), 26.1 (q), 28.3 (q), 44.8 (d), 47.4 (t), 79.9 (s), 86.6 (s), 102.5 (s) 154.9 (s), 200.3 (s); exact mass calcd. for C_{17}H_{31}NO_{3}Si + Na \(m/z\) 348.1965, found \(m/z\) 348.1962.
**Homoallylic alcohols 281 and 282.**

To a stirred suspension of 16.50 g of crushed activated 4 Å molecular sieves in 135 mL of anhydrous toluene under N₂ was added via syringe 116 mL (116 mmol) of a 1 M solution of the Roush (E)-crotylboronate in toluene. The resulting mixture was cooled to –78 ºC, followed by the dropwise addition, over 30 min, of a solution of 7.51 g (23.1 mmol) of aldehyde 280 in 135 mL of anhydrous toluene. The resulting mixture was stirred at –78 ºC under N₂ for 2 h followed by addition of 135 mL of 2 N aqueous NaOH. Stirring was then continued at 0 ºC for 20 min. The resulting mixture was filtered through Celite 545, and the filtrate was partitioned between 400 mL of Et₂O and 400 mL of H₂O. The aqueous layer was extracted with three 200-mL portions of Et₂O and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to yield 33.9 g of a yellow oil. The crude mixture was purified by flash chromatography over 1000 g of silica gel (EtOAc-hexanes, 12:88 → 50:50) to yield 6.10 g (69%) of alcohol 281 as a pale yellow oil and 1.49 g (17%) of diastereomeric alcohol 282 as a pale yellow oil. Data for 281: ¹H NMR (CDCl₃, 500 MHz) δ 0.07 (s, 6H, TBS CH₃’s), 0.92 (s, 9H, TBS t-Bu), 1.03 (d, J = 6.9 Hz, 3H, CH₃), 1.42 (s, 9H, BOC), 1.57 (ddd, J = 14.2, 9.6, 9.4 Hz, 1H, CH₂CHΟH), 1.84 (ddd, J = 14.2, 6.9, 3.0 Hz, 1H, CH₂CHOH), 2.23 (sextet, J = 6.7 Hz, 1H, CHCH₃, + br, 1H, OH), 2.50 (m, 2H, ≡CCH₂), 3.51 (m, 1H, CH-OH), 3.85 (br, 1H, CHNH), 4.94 (br, 1H, NH), 5.08
(m, 2H, =CH₂), 5.74 (m, 1H, =CH); \(^{13}\)C NMR (CDCl₃, 125 MHz) δ -4.6 (q), 15.9 (q), 16.4 (s), 25.6 (t), 26.0 (q), 28.3 (q), 38.0 (t), 44.4 (d), 47.6 (d), 72.6 (d), 79.4 (s), 85.6 (s), 103.4 (s), 116.3 (t), 139.8 (d), 155.4 (s). Data for 282: \(^1\)H NMR (CDCl₃, 500 MHz) δ 0.09 (s, 6H, TBS CH₃’s), 0.93 (s, 9H, TBS t-Bu), 1.04 (d, J = 6.9 Hz, 3H, CH₃), 1.45 (s, 9H, BOC), 1.56 (ddd, J = 14.0, 10.8, 3.1 Hz, 1H, CH₂CHOH), 1.68 (br m, 1H, CH₂CHOH), 2.23 (sextet, J = 6.8 Hz, 1H, CHCH₃), 2.49 (m, 2H, =CCH₂), 3.52 (dd, J = 9.0, 5.2 Hz, 1H, CHOH), 3.72 (br, 1H, OH), 3.98 (br m, CHNH), 4.96 (d, J = 8.6 Hz, 1H, NH), 5.06 (m, 2H, =CH₂), 5.81 (m, 1H, =CH); \(^{13}\)C NMR (CDCl₃, 125 MHz) δ -4.6 (q), 16.1 (q), 16.4 (s), 26.1 (q), 26.2 (t), 28.3 (q), 39.0 (t), 43.8 (d), 46.1 (d), 71.0 (d), 79.8 (s), 85.9 (s), 103.3 (s), 115.3 (t), 140.6 (d), 156.5 (s).

**Ester 283.** To a stirred solution of 84.8 mg (0.22 mmol) of alcohol 281 in 0.6 mL of anhydrous CH₂Cl₂ at rt under N₂, was added sequentially via syringe via syringe 81 µL (79 mg, 0.66 mmol) of pivaloyl chloride and 61 µL (44 mg, 0.44 mmol) of triethylamine. The resulting mixture was stirred at rt under N₂ for 16 h. The reaction mixture was diluted with 3 mL of CH₂Cl₂, washed with 3 mL of saturated aqueous NaHCO₃ and 3 mL of H₂O, dried (Na₂SO₄), and concentrated in vacuo to yield 115.0 mg of a yellow oil. The crude product was purified by flash chromatography over 6 g of
silica gel (Et$_2$O-hexanes, 15:85), to yield 36.7 mg (33%) of ester 283 as a yellow oil: IR (film) 3518, 2959, 2930, 2175, 1721, 1690, 1369, 1320, 1250, 1150 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.07 (s, 6H, TBS CH$_3$’s), 0.92 (s, 9H, TBS t-Bu), 1.05 (d, $J = 6.9$ Hz, 3H, CH$_3$), 1.32 (s, 9H, Piv), 1.53 (s, 9H, BOC), 1.81 (ddd, $J = 14.5, 9.4, 6.8$ Hz, 1H, CH$_2$CHOPiv), 1.95 (ddd, $J = 14.5, 6.6, 3.3$ Hz, 1H, CH$_2$CHOPiv), 2.0 (br, 1H, NH), 2.24 (sextet, 6.6 Hz, 1H, CHCH$_3$), 2.66 (m, 2H, $\equiv$CCH$_2$), 3.57 (m, 1H, CH-O), 4.28 (p, $J = 7.0$ Hz, 1H, CHNH), 5.07 (m, 2H, $\equiv$CH$_2$), 5.76 (m, 1H, $\equiv$CH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.5 (q), 16.1 (s), 16.5 (q), 22.6 (s), 25.0 (t), 26.1 (q), 28.1 (q), 28.4 (q), 38.4 (t), 44.0 (d), 56.3 (d), 72.9 (d), 83.0 (s), 84.5 (s), 104.9 (s), 116.1 (t), 139.8 (d), 153.7 (s), 188.6 (s); exact mass calcd. for C$_{26}$H$_{47}$NO$_4$Si + Na $m/z$ 488.3167, found $m/z$ 488.3253; $[\alpha]_D = +15.3^\circ$ (CHCl$_3$, c = 1.0).

Silyl Ether 284. To a stirred solution of 3.09 g (8.09 mmol) of alcohol 281 in 10 mL of DMF, at rt under N$_2$, were sequentially added 2.81 g (41.3 mmol) of imidazole in one portion and 10.5 mL (11.1 g, 40.4 mmol) of $t$-butyldiphenylsilyl chloride via syringe over 1 min. The resulting solution was stirred at rt under N$_2$ for 24 h. The reaction mixture was quenched by addition of 20 mL of saturated aqueous NaHCO$_3$ and diluted with 125 mL of EtOAc. The aqueous layer was separated and the organic layer
was washed with three 70-mL portions of H₂O and three 70-mL portions of brine, dried (Na₂SO₄), and concentrated in vacuo. The crude yellow oil (14.83 g) was purified by flash chromatography over 400 g of silica gel (Et₂O-hexanes, 10:90) to yield 4.47 g (89%) of silyl ether 284 as a colorless glassy oil: IR (film) 3426, 2956, 2930, 2857, 2174, 1717, 1498, 1249, 1171, 1111, 1040, 702 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.04 (s, 6 H, TBS CH₃’s), 0.90 (s, 9H, TBS t-Bu), 1.07 (s, 9H, TBDPS t-Bu), 1.09 (d, J = 7.1 Hz, 3H, CH₃), 1.39 (s, 9H, BOC with underlying m, 1H, CHCH₃), 1.83 (br m, 1H, CH₂CHO), 2.14 (br m, 2H, ≡CCH₂), 2.40 (br p, J = 6.7 Hz, 1H, CH₂CHO), 3.58 (br m, 1H, CH-O), 3.65 (br, 1H, NH), 3.85 (br d, J = 8.7 Hz, 1H, CHNH), 5.01 (m, 2H, ≡CH₂), 5.85 (m, 1H, ≡CH), 7.38-7.41 (m, 6H, ArH), 7.68-7.71 (m, 4H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ -4.5 (q), 16.4 (s), 19.5 (s), 26.1 (q), 26.3 (t), 27.1 (q), 28.3 (q), 38.4 (t), 42.1 (d), 46.2 (d), 74.7 (d), 78.9 (s), 85.0 (s), 103.3 (s), 115.4 (t), 127.6 (d), 129.7 (d), 129.8 (d), 134.0 (s), 134.3 (s), 135.9 (d), 136.0 (d), 139.7 (d), 154.9 (s); exact mass calcd. for C₃₇H₅₇NO₃Si₂ + Na m/z 642.3769, found m/z 642.3747 [α]D = -46.3º (CHCl₃, c = 1.9).

Silyl Ether 285. To a stirred solution of 5.38 g (14.1 mmol) of alcohol 282 in 19 mL of DMF, at rt under N₂, were sequentially added 4.91 g (72.1 mmol) of imidazole
in one portion, and 18.5 mL (19.8 g, 71.1 mmol) of \( t \)-butyldiphenylsilyl chloride via syringe over 1 min. The resulting solution was stirred at rt under \( \text{N}_2 \) for 24 h. The reaction mixture was quenched by addition of 36 mL of saturated aqueous NaHCO\(_3\) and diluted with 225 mL of EtOAc. The aqueous layer was separated and the organic layer was washed with three 125-mL portions of H\(_2\)O and three 125-mL portions of brine, dried (\( \text{Na}_2\text{SO}_4\)), and concentrated in vacuo. The crude yellow oil (26.0 g) was purified by flash chromatography over 1000 g of silica gel (Et\(_2\)O-hexanes, 10:90) to yield 7.15 g (82\%) of silyl ether 285 as a colorless glassy oil, which slowly crystallized into a soft white solid: mp 77-79 °C; IR (film) 3440, 2952, 2932, 2858, 2174, 1720, 1704, 1497, 1428, 1365, 1171, 1111, 824, 703 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 0.09 (s, 6H, TBS CH\(_3\)'s), 0.91 (s, 9H, TBS \( t \)-Bu), 1.01 (d, \( J = 6.8 \) Hz, 3H, CH\(_3\)), 1.10 (s, 9H, TBDPS \( t \)-Bu), 1.42 (s, 9H, BOC), 1.66 (br m, 1H, CH\(_2\)CHO), 1.76 (br m, 1H, CH\(_2\)CHO), 2.31-2.38 (m, 3H, CH\(_3\) + =CCH\(_2\)), 3.66 (br, 1H, CHNH), 3.81 (br, 1H, CHO), 4.42 (br, 1H, NH), 4.83-4.94 (m, 2H, =CH\(_2\)), 5.58 (m, 1H, =CH), 7.38-7.45 (m, 6H, ArH), 7.71 (m, 4H, ArH); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) -4.5 (q), 16.5 (s), 19.5 (s), 26.1 (q), 27.1 (q), 28.4 (q), 36.1 (t), 42.7 (d), 46.9 (d), 65.8 (t), 74.0 (d), 78.9 (s), 84.8 (s), 104.1 (s), 115.0 (t), 127.5 (d), 127.6 (d), 129.58 (d), 129.65 (d), 133.8 (s), 134.2 (s), 136.0 (d), 140.1 (d), 154.9 (s); exact mass calcd. for C\(_{37}\)H\(_{57}\)NO\(_3\)Si\(_2\) + Na \( m/z \) 642.3769, found \( m/z \) 642.3798.
**7-tert-Butoxycarbonylamino-10-(tert-butyldimethylsilyl)-5-(tert-butyldimethylsilyloxy)-4-methyldec-2-en-9-ynoic acid ethyl ester (295).** To a stirred solution of 420.8 mg (0.68 mmol) of alkene 284 in 12 mL of t-BuOH : H₂O (3:1) were sequentially added 0.70 mL of a 1% aqueous solution of osmium tetroxide (7.0 mg OsO₄, 0.028 mmol) and 302 mg (1.41 mmol) of sodium periodate. The resulting mixture was vigorously stirred at rt for 18 h. The reaction mixture was partitioned between 25 mL of EtOAc and 25 mL of H₂O. The layers were separated. The aqueous layer was extracted with 25 mL of EtOAc and the combined organic layers were washed with 25 mL of brine, dried (Na₂SO₄), and concentrated in vacuo, to yield 455.3 mg of intermediate amino aldehyde 292 as a dark red oil. To a stirred solution of 292 in 15 mL of anhydrous toluene was added 763 mg (2.19 mmol) of Ph₃P=CHCO₂Et and the resulting solution was heated to 80 °C under N₂ for 48 h. The reaction mixture was concentrated in vacuo to yield 1.45 g of a brown paste. The crude product was purified by flash chromatography over 75 g of silica gel (EtOAc-hexanes, 10:90), to yield 184.1 mg (36%) of α,β-unsaturated ester 295 as a yellow glassy oil: IR (film): 3418, 2957, 2931, 2857, 2174, 1718, 1366, 1250, 1172, 1112, 703 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.06 (s, 6H, TBS CH₃'s), 0.89 (s, 9H, TBS t-Bu), 1.07 (s, 9H, TBDPS t-Bu), 1.11 (d, J = 6.8 Hz, 3H, CHCH₃), 1.31 (t, J = 7.2 Hz, 3H, CH₂CH₃), 1.38 (s, 9H, BOC), 1.51 (m, 1H, CH₂CHO),
1.69 (m, 1H, CH$_2$CHO), 2.08-2.25 (m, 2H, CH$_2$C=), 2.60 (m, 1H, CHCH$_3$), 3.57 (br, 1H, CHNH), 3.69 (br m, 1H, CHO), 3.86 (br d, $J$ = 9.0 Hz, 1H, NH), 4.19 (m, 2H, CH$_2$CH$_3$), 5.80 (d, $J$ = 15.8 Hz, 1H, =CHCO$_2$Et), 7.08 (dd, $J$ = 15.7, 8.4 Hz, 1H, HCC=CHCO$_2$Et), 7.38-7.44 (m, 6H, ArH), 7.68 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.6 (q), 14.2 (q), 16.4 (s), 19.5 (s), 26.1 (q), 26.6 (q), 26.7 (t), 27.1 (q), 28.3 (q), 39.5 (t), 40.8 (d), 45.9 (d), 60.1 (t), 74.1 (d), 79.1 (s), 85.3 (s), 102.9 (s), 122.1 (d), 127.7 (d), 129.6 (d), 129.9 (d), 134.8 (s), 135.9 (d), 150.0 (d), 154.9 (s), 166.5 (s); exact mass calcd. for C$_{40}$H$_{61}$NO$_5$Si$_2$ + Na $m/z$ 714.3980, found $m/z$ 714.4007; [$\alpha$]$_D$ = -24.2º (CHCl$_3$, c = 0.5).

7-tert-Butoxycarbonylamino-10-(tert-butyldimethylsilyl)-5-(tert-butyldimethylsilyloxy)-4-methyldec-2-en-9-ynoic acid ethyl ester (296).$^{95,100a}$ To a stirred solution of 4.96 g (10.0 mmol) of alkene 290 in 160 mL of t-BuOH : H$_2$O (3:1) at 0 ºC were sequentially added 10.2 mL of a 1% aqueous solution of osmium tetroxide (102 mg OsO$_4$, 0.40 mmol) and 4.28 g (20.0 mmol) of sodium periodate. The resulting mixture was allowed to warm to rt and was vigorously stirred at rt for 20 h. The reaction mixture was partitioned between 350 mL of EtOAc and 350 mL of H$_2$O. The layers were separated. The aqueous layer was extracted with 350 mL of EtOAc and the combined
organic layers were washed with 350 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 4.95 g of amino aldehyde 293 as a dark red oil. To a stirred solution of 293 in 145 mL of anhydrous toluene was added 17.6 g (50 mmol) of Ph₃P=CHCO₂Et, and the resulting solution was heated to 80 ºC under N₂ for 48 h. The reaction mixture was concentrated in vacuo, to yield 41.3 g of a brown paste. The crude product was purified by flash chromatography over 1200 g of silica gel (EtOAc – hexanes 10:90), to yield 1.5518 g (36%) of α,β-unsaturated ester 296 as a yellow glassy oil: ¹H NMR (CDCl₃, 500 MHz) δ 0.07 (s, 3H, SiCH₃), 0.08 (s, 3H, SiCH₃), 0.089 (s, 3H, SiCH₃), 0.091 (s, 3H, SiCH₃), 0.91 (s, 9H, TBS t-Bu), 0.93 (s, 9H, TBS t-Bu), 1.09 (d, J = 6.8 Hz, 3H, CHCH₃), 1.29 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.45 (s, 9H, BOC), 1.68 (m, 2H, CH₂CHO), 2.36-2.58 (m, 2H, CH₂C≡), 2.61 (m, 1H, CHCH₃), 3.72 (m, 2H, CHNH + CHO), 4.19 (qd, J = 6.9, 0.7 Hz, 2H, CH₂CH₃), 4.72 (br d, J = 8.2 Hz, 1H, NH), 5.84 (d, J = 15.8 Hz, 1H, =CHCO₂Et), 6.95 (dd, J = 15.8, 8.2 Hz, 1H, HC=CHCO₂Et); ¹³C NMR (CDCl₃, 125 MHz) δ -4.55 (q), -4.50 (q), -4.3 (q), 14.2 (q), 16.0 (q), 16.5 (s), 18.0 (s), 25.9 (q), 26.1 (q), 26.4 (t), 28.4 (q), 39.2 (t), 41.4 (d), 46.1 (d), 60.2 (d), 73.0 (d), 79.3 (s), 86.0 (s), 103.2 (s), 121.9 (d), 150.3 (d), 155.2 (s), 166.5 (s).
Ethyl \{4-(tert-butyl dimethylsilyloxy)-6-[3-(tert-butyl dimethylsilyl)prop-2-ynyl]-3-methylpiperidin-2-yl\}acetate (297). To a stirred solution of 1.55 g (2.98 mmol) of carbamate 296 in 22 mL of anhydrous CH₂Cl₂, at rt under N₂, was added 2.2 mL of TFA. Stirring was then continued for 3 h. The resulting solution was diluted with 70 mL of CH₂Cl₂, washed with two 100-mL portions of saturated aqueous NaHCO₃ and 100 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 912 mg of a yellow oil. The crude product was purified by flash chromatography over 45 g of silica gel (EtOAc : hexanes 25:75), to yield 540.5 mg (39%) of piperidine 297 as a pale yellow oil:

^1^H NMR (CDCl₃, 500 MHz) δ 0.05 (s, 3H, TBS CH₃), 0.07 (s, 3H, TBS CH₃), 0.10 (s, 6H, TBS CH₃’s), 0.88 (d, J = 6.8 Hz, 3H, CHCH₂), 0.91 (s, 9H, TBS t-Bu), 0.93 (s, 9H, TBS t-Bu), 1.28 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.32 (m, 2H, CHCH₃ + CH₂CHO), 1.89 (br d, J = 13.2 Hz, 1H, CH₂CHO), 2.21-2.31 (m, 3H, CH₂C≡ + CH₂CO₂Et), 2.59 (d, J = 16.2 Hz, 1H, CH₂CO₂Et), 3.14 (br t, J = 9.7 Hz, 1H, CHCH₂CO₂Et), 3.21 (m, 1H, CHCH₂C≡), 3.87 (br s, 1H, CHO), 4.14 (q, J = 7.1 Hz, 2H, CH₂CH₃); ^1^C NMR (CDCl₃, 125 MHz) δ -4.9 (q), -4.5 (q), -4.2 (q), 14.2 (q), 15.2 (q), 16.5 (s), 18.2 (s), 25.9 (q), 26.1 (q), 27.8 (t), 38.4 (t), 40.1 (t), 40.7 (d), 49.2 (d), 52.7 (d), 60.3 (t), 70.8 (d), 84.7 (s), 104.4 (s), 172.7 (s).
Ethyl \{6-[3-(\text{tert}-\text{butyldimethylsilyl})prop-2-ynyl]-4-(\text{tert}-\text{butyldiphenylsilyloxy})-3-methylpiperidin-2-yl\}acetate (298). To a stirred solution of 2.61 g (3.77 mmol) of carbamate 295 in 38 mL of anhydrous CH$_2$Cl$_2$, at rt under N$_2$, was added dropwise 3.8 mL of TFA over 1 min. Stirring was then continued for 2 h. The reaction mixture was quenched by slow addition of 18.9 g of solid NaHCO$_3$, and stirring was continued for 15 min. The resulting mixture was filtered, and concentrated in vacuo to yield 3.41 g of a red oil. The crude product was purified by flash chromatography over 170 g of silica gel (EtOAc-hexanes, 20:80 → EtOAc) to yield 2.00 g (90%) of piperidine 298 as a pale yellow glassy oil: IR (film) 2173, 1732 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.11 (s, 3H, TBS CH$_3$), 0.12 (s, 3H, TBS CH$_3$), 0.79 (d, $J = 6.9$ Hz, 3H, CHCH$_3$), 0.95 (s, 9H, TBS t-Bu), 1.11 (s, 9H, TBDPS t-Bu), 1.18 (m, 1H, CH$_2$CHO), 1.27 (t, $J = 7.2$ Hz, 3H, CH$_2$CH$_3$), 1.31 (m, 1H, CHCH$_3$), 1.70 (dt, $J = 13.4$, 2.9 Hz, 1H, CH$_2$CHO), 2.17 (m, 2H, CH$_2$C≡), 2.24 (m, 1H, CH$_2$CO$_2$Et), 2.61 (dd, $J = 16.2$, 3.2 Hz, 1H, CH$_2$CO$_2$Et), 3.34 (m, 2H, 2 CHNH), 3.95 (br s, 1H, CH-O), 4.16 (q, $J = 7.1$ Hz, CH$_2$CH$_3$), 7.37-7.43 (m, 6H, ArH), 7.68-7.72 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.5 (q), 14.2 (q), 15.2 (q), 16.5 (s), 19.6 (s), 26.1 (q), 27.3 (q), 27.5 (t), 38.5 (t), 39.5 (t), 41.1 (d), 49.1 (d), 52.8 (d), 60.2 (t), 72.1 (d), 84.9 (s), 104.3 (s), 127.4 (d), 127.5 (d), 127.6 (d), 129.5 (d),
129.6 (d), 134.0 (s), 134.3 (s), 134.8 (d), 136.1 (d), 172.5 (s); exact mass calcd. for 
C_{35}H_{53}O_{3}Si_{2} + Na \text{ m/z } 614.3456, \text{ found m/z } 614.3444; [\alpha]_{D} = -106.7^\circ \text{ (CH}_2\text{Cl}_2, \text{ c } = 3.3).

\[
\begin{align*}
\text{TBSO} \quad &\text{H} \\
\text{CH}_3 &\text{H} \\
\text{TBSO} &\text{N} \\
&\text{H}_3\text{C} \\
\text{TBS} &\text{N} \\
\text{O} \\
\end{align*}
\]

7-\text{(tert-Butyldimethylsilyloxy)-5-[3-(tert-butyldimethylsilyl)prop-2-ynyl]-8-methylhexahydroimidazo[1,5-a]pyridin-3-one} (301). To a stirred solution of 227 mg (0.48 mmol) of ester 297 in 30 mL of MeOH : H\text{}_2\text{O (5:1) was added 44 mg (0.78 mmol) of KOH. The resulting solution was heated to reflux for 3 h. The reaction mixture was cooled to rt and the pH was adjusted to 4-5 by addition of 1 N aqueous HCl. The resulting solution was diluted with 70 mL of H\text{}_2\text{O and extracted with three 70-mL of Et}_2\text{O. The combined organic layers were dried (Na}_2\text{SO}_4) and concentrated in vacuo to yield 266 mg of crude amino acid 299 as a white solid. The crude amino acid was purified by flash chromatography over 13.4 g of silica gel (EtOAc-hexanes, 25:75), to yield 239 mg (100%) of amino acid 299 as a white solid. To a stirred solution 153 mg (0.35 mmol) of intermediate 299 in 1 mL of t-BuOH were sequentially added 75 \mu L (96 mg, 0.35 mmol) of diphenylphosphoryl azide and 50 \mu L (36 mg, 0.36 mmol) of triethylamine. The resulting solution was heated to 80 °C under N\textsubscript{2} for 24 h. The reaction mixture was diluted with 5 mL of benzene. The resulting solution was washed with 2 mL
of 5% aqueous citric acid, 2 mL of H₂O, 2 mL of saturated aqueous NaHCO₃, and 2 mL of brine. The organic phase was dried (Na₂SO₄), and concentrated in vacuo to yield 131 mg of a yellow paste. The crude product was purified by flash chromatography over 6.5 g of silica gel (EtOAc-hexanes, 25:75), to yield 61.7 mg (40% from 297) of urea 301 as a white paste: IR (film) 2174, 1698 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.07 (s, 9H, SiCH₃), 0.10 (s, 3H, SiCH₃), 0.87 (d, J = 6.7 Hz, CHCH₃), 0.91 (s, 9H, TBS t-Bu), 0.92 (s, 9H, TBS t-Bu), 1.55 (m, 2H, CHCH₃ + CH₂CHO), 2.16 (dt, J = 13.7, 3.1 Hz, 1H, CH₂CH-O), 2.84 (dd, J = 17.0, 10.0 Hz, 1H, CH₂C≡), 2.93 (t, J = 8.9 Hz, 1H, CH₂NH), 3.35 (t, J = 7.6 Hz, 1H, CH₂NH), 3.51 (m, 2H, 2 × CHN), 3.64 (dd, J = 16.9, 3.4 Hz, 1H, CH₂C≡), 3.90 (br s, 1H, CHO); ¹³C NMR (CDCl₃, 125 MHz) δ -5.0 (q), -4.5 (q), -4.2 (q), 13.6 (q), 16.5 (s), 18.1 (s), 23.7 (t), 25.9 (q), 26.1 (q), 39.7 (t), 40.0 (d), 43.4 (t), 48.9 (d), 57.7 (d), 69.5 (d), 84.3 (s), 105.0 (s), 162.7 (s).

5-[3-(tert-Butyldimethylsilyl)prop-2-ynyl]-7-(tert-butyldiphenylsilyloxy)-8-methylhexahydroimidazo[1,5-a]pyridin-3-one (302). To a stirred solution of 269 mg (0.45 mmol) of ester 298 in 30 mL of MeOH-H₂O (5:1) was added 47.0 mg (0.84 mmol) of KOH and the resulting solution was heated to reflux for 3 h. The reaction mixture was
cooled to rt and the pH was adjusted to 4-5 by slow addition of 1 N aqueous HCl. The resulting solution was diluted with 60 mL of H$_2$O, and extracted with three 60-mL portions of Et$_2$O. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to yield 303.2 mg (100%) of amino acid 300 as an off-white solid. To a stirred solution of 150.1 mg (0.27 mmol) of acid 300 in 0.8 mL of $t$-BuOH were sequentially added 60 µL (77 mg, 0.28 mmol) of diphenylphosphoryl azide and 40 µL (29 mg, 0.29 mmol) of triethylamine, and the resulting solution was heated to 80 °C under N$_2$ for 24 h. The reaction mixture was cooled to rt, diluted with 5 mL of benzene, and washed sequentially with 2 mL of 5% aqueous citric acid, 2 mL of H$_2$O, 2 mL of saturated aqueous NaHCO$_3$, and 2 mL of brine. The solution was dried (Na$_2$SO$_4$), and concentrated in vacuo to yield 128.3 mg of a pale brown oil. The crude product was purified by flash chromatography over 6.5 g of silica gel (EtOAc-hexanes, 40:60) to yield 79.1 mg (63% from 298) of urea 302 as a spongy white solid: mp 65-68°C; IR (KBr) 2173, 1701 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.04 (s, 3H, TBS CH$_3$), 0.06 (s, 3H, TBS CH$_3$), 0.73 (d, $J$ = 6.8 Hz, 3H, CHCH$_3$), 0.90 (s, 9H, TBS $t$-Bu), 1.10 (s, 9H, TBDPS $t$-Bu), 1.47 (m, 1H, CHCH$_3$), 1.57 (td, $J$ = 12.3, 1.9 Hz, 1H, CH$_2$CHO), 1.94 (dt, $J$ = 13.9, 3.2 Hz, 1H, CH$_2$CHO), 2.90 (t, $J$ = 9.2 Hz, 1H, CH$_2$NH), 3.13 (m, 2H, CH$_2$C≡), 3.37 (t, $J$ = 7.5 Hz, CH$_2$NH), 3.64 (m, 1H, CHCH$_2$C≡), 3.68 (m, 1H, CHCH$_2$NH), 4.00 (br s, 1H, CH-O), 7.37–7.45 (m, 6H, ArH), 7.68 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.5 (q), 13.6 (q), 16.5 (s), 19.6 (s), 23.7 (t), 26.1 (q), 27.3 (q), 39.0 (t), 40.3 (d), 43.7 (t), 48.3 (d), 57.6 (d), 70.7 (d), 84.4 (s), 104.7 (s), 127.5 (d), 127.6 (d), 129.6 (d), 129.8 (d), 133.68 (s),
{6-[3-(tert-Butyldimethylsilanyl)prop-2-ynyl]-4-hydroxy-3-methylpiperidin-2-yl}acetic acid ethyl ester (304). To a stirred solution of 51.0 mg (0.11 mmol) of carbamate 303 in 1.1 mL of CH$_2$Cl$_2$ was added 0.11 mL of TFA. The resulting solution was stirred at rt under N$_2$ for 4 h. The resulting mixture was concentrated in vacuo to yield 29.3 mg of an orange oil. The crude product was purified by flash chromatography over 1.5 g of silica gel to yield 19.4 mg (52%) of piperidine 304 as a dark yellow oil: IR (film) 3416, 2954, 2931, 2858, 2178, 1673, 1202, 1138; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.13 (s, 6H, SiCH$_3$), 0.94 (s, 9H, t-Bu), 1.04 (d, $J = 6.9$ Hz, 3H, CHCH$_3$), 1.29 (t, $J = 7.1$ Hz, 3H, CH$_2$CH$_3$), 2.02 (m, 3H, CHCH$_3$ + CH$_2$CHOH), 2.57–2.75 (m, 2H, CH$_2$CO$_2$Et), 2.84 (m, 2H, CH$_2$C≡), 3.57 (br, 1H, OH), 3.67 (br, 1H, CHCH$_2$C≡), 3.79 (br, 1H, CHCH$_2$CO$_2$Et), 4.03 (br s, 1H, CHOHOH), 4.19 (q, $J = 7.1$ Hz, 2H, CH$_2$CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.8 (q), 13.9 (q), 14.3 (q), 16.4 (s), 24.2 (t), 26.0 (q), 32.5 (t), 35.3 (t), 35.7 (d), 50.0 (d), 53.1 (d), 61.8 (t), 67.2 (d), 89.2 (s), 99.4 (s), 172.6 (s); exact mass calcd. for C$_{19}$H$_{35}$NO$_3$Si + H m/z 354.2466, found m/z 354.2470.
3-(4-Methoxybenzyl)-6-(1-methylallyl)-4-prop-2-ynyl-[1,3]-oxazinan-2-one (310). To a stirred solution of 310 mg (0.50 mmol) of carbamate 285 in 2 mL of DMF, at 0°C under N₂, was added 17.3 mg of a 60% dispersion of sodium hydride in mineral oil (10.4 mg NaH, 0.50 mmol). The resulting mixture was stirred at 0°C under N₂ for 30 min, followed by addition of a solution of 60 µL (69 mg, 0.50 mmol) of p-methoxybenzyl chloride in 1 mL of DMF. The resulting solution was warmed to rt, and stirring was continued for 3 h. The reaction mixture was poured into 7 mL of Et₂O, and the resulting solution was washed with 2 mL of water and 2 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 513 mg of a yellow oil. The crude product was purified by flash chromatography over 26 g of silica gel (Et₂O-hexanes, 10:90 → Et₂O), to yield 60.6 mg (39%) of cyclic carbamate 310 as a pale yellow oil: IR (neat) 3286, 2962, 2932, 1689, 1513, 1453, 1248 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.14 (d, J = 7.0 Hz, 3H, CHCH₃), 1.75 (td, J = 13.1, 5.7 Hz, 1H, CH₂CHO), 2.05 (t, J = 2.6 Hz, 1H, =CH), 2.07 (dt, J = 12.7, 1.9 Hz, CH₂CHO), 2.37 (ddd, J = 17.0, 10.0, 2.6 Hz, 1H, CH₂C≡), 2.46 (m, 1H, CHCH₃), 2.60 (dt, J = 17.0, 3.2 Hz, 1H, CH₂C≡), 3.47 (m, 1H, CHN), 3.80 (s, 3H, OCH₃), 4.14 (d, J = 15.1 Hz, 1H, PMB CH₂Ar), 4.36 (ddd, J = 12.2, 4.3, 2.5 Hz, 1H, CHO), 4.98 (d, J = 15.1 Hz, 1H, PMB CH₂Ar), 5.12 (m, 2H, =CH₂), 5.83 (m, 1H, =CH), 6.86 (d, J = 8.6 Hz, 2H, ArH), 7.23 (d, J = 8.6 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 125
MHz) δ 15.2 (q), 22.8 (t), 27.6 (t), 41.7 (d), 49.9 (t), 51.4 (d), 55.2 (q), 71.6 (s), 76.1 (d), 79.6 (s), 114.1 (d, 2C), 116.5 (t), 128.9 (s), 129.3 (d, 2C), 138.1 (d), 153.9 (s), 159.2 (s);

exact mass calcd. for C₁₉H₂₃NO₃ + Na m/z 336.1570, found m/z 336.1580.

1-[3-(tert-Butyldimethylsilyl)prop-2-ynyl]-3-(tert-butyldiphenylsilyloxy)-4-methylhex-5-enylamine (311). To a stirred solution of 119 mg (0.2 mmol) of carbamate 285 in 2 mL of CH₂Cl₂ was added 0.2 mL of trifluoroacetic acid. The resulting solution was stirred at rt for 24 h. TLC analysis (Et₂O–hexanes, 10:90, silica gel, PMA) showed no remaining starting material. The reaction mixture was neutralized by addition of 200 mg of solid NaHCO₃, filtered, and concentrated in vacuo to yield 114 mg of a pale yellow oil. The crude product was purified by flash chromatography over 5.5 g of silica gel (MeOH–CH₂Cl₂, 5:95) to yield 104 mg (100%) of amine 311 as a pale yellow oil: IR (film) 3071, 2953, 2931, 2858, 2178, 1684, 1202, 1111, 702 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.086 (s, 3H, SiCH₃), 0.088 (s, 3H, SiCH₃), 0.93 (s, 9H, TBS t-Bu), 1.08 (d, J = 6.9 Hz, 3H, CHCH₃), 1.10 (s, 9H, TBDPS t-Bu), 1.65 (ddd, J = 14.7, 9.2, 3.6 Hz, 1H, CH₂CHO), 1.96 (ddd, J = 14.7, 8.1, 3.9 Hz, 1H, CH₂CHO), 2.31–2.44, (m, 2H, CH₂C≡), 2.43 (m, 1H, CHCH₃), 3.19 (m, 1H, CHNH₂), 3.86 (m, 1H, CHO), 4.88–4.97 (m, 2H, =CH₂), 5.60 (m, 1H, =CH), 5.96 (br, 2H, NH₂), 7.39–7.46 (m, 6H, ArH), 7.69 (ddd, J =
$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.6 (q), 1.0 (q), 13.4 (q), 16.4 (s), 19.4 (s), 25.6 (t), 26.1 (q), 27.1 (q), 35.6 (t), 42.9 (d), 48.1 (d), 73.3 (d), 86.9 (s), 101.6 (s), 115.6 (t), 127.7 (d), 128.1 (d), 130.0 (d), 120.2 (d), 133.1 (s), 133.4 (s), 135.95 (d), 135.99 (d), 139.3 (d), some carbons were not observed due to magnetic equivalence; exact mass calcd. for C$_{32}$H$_{49}$NOSi$_2$ + H $m/z$ 520.3425, found $m/z$ 520.3422.

$N$-[1-[3-(tert-Butyldimethylsilyl)-prop-2-ynyl]-3-(tert-butylidiphenylsilyloxy)-4-methylhex-5-enyl]-2-hydroxybenzamide (313). To a stirred solution of 103 mg (0.2 mmol) of amine 311 in 6 mL of chloroform was added 62 mg (0.42 mmol) of solid phthalic anhydride in one portion. The resulting solution was heated to reflux under N$_2$ for 24 h. The reaction mixture was concentrated in vacuo to yield 262 mg of a yellow oil and the crude product was purified by flash chromatography over 13 g of silica gel (MeOH-CH$_2$Cl$_2$, 5:95) to yield 40.3 mg (31%) of amide 313 as a pale yellow oil: IR (film) 3404, 3256, 3073, 2958, 2932, 2857, 2174, 1703, 1428, 1111, 737, 703 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.08 (s, 6H, SiCH$_3$), 0.91 (s, 9H, TBS $t$-Bu), 1.07 (s, 9H, TBDPS $t$-Bu), 1.09 (d, $J = 6.8$ Hz, 3H, CHCH$_3$), 1.88 (m, 2H, CH$_2$CHO), 2.44 (m, 1H, CHCH$_3$), 2.52 (m, 2H, CH$_2$C≡), 3.81 (m, 1H, CHO), 4.04 (m, 1H, CHN), 4.87–4.96 (m,
2H, =CH2), 5.62 (m, 1H, =CH), 5.78 (br d, J = 7.9 Hz, 1H, NH), 7.20 (dd, J = 7.6, 1.0 Hz, 1H, ArH), 7.30–7.37 (m, 6H, ArH), 7.48 (td, J = 6.9, 1.3 Hz, ArH), 7.55 (td, J = 7.1, 1.1 Hz, ArH), 7.65–7.70 (m, 4H, ArH), 8.13 (d, J = 7.7 Hz, 1H, ArH); 13C NMR (CDCl3, 125 MHz) δ -4.5 (q), 13.5 (q), 16.4 (s), 19.4 (s), 25.2 (t), 26.1 (q), 27.1 (q), 35.9 (t), 42.8 (d), 47.3 (d), 74.0 (d), 85.6 (s), 103.5 (s), 115.4 (t), 127.5 (d, 2C), 127.68 (d, 2C), 127.75 (d), 129.7 (d), 129.8 (d), 130.0 (s), 130.7 (d), 132.1 (d), 132.7 (d), 133.5 (s), 133.9 (s), 135.89 (s), 135.93 (d, 2C), 136.0 (d, 2C), 140.1 (d), 168.1 (s), 170.2 (s); exact mass calcd. for C40H53NO4Si2 + Na m/z 690.3405, found m/z 690.3431.

![4-Bromo-2,6-dimethoxypyrimidine (325)](image)

4-Bromo-2,6-dimethoxypyrimidine (325). To a stirred solution of 225 g (785 mmol) of POBr3 in 350 mL of anhydrous toluene under N2 was added 24.96 g (195 mmol) of barbituric acid (323) in one portion, followed by 50.0 mL (47.8 g, 394 mmol) of N,N-dimethylaniline, and the resulting orange-brown suspension was heated to reflux for 5 h. The reaction mixture was cooled down to rt, diluted with 300 mL of toluene, washed with 500 mL of H2O and two 250-mL portions of saturated aqueous NaHCO3. The combined aqueous phases were extracted with two 250-mL portions of toluene, and the combined organic layers were dried (Na2SO4) and concentrated in vacuo, to yield 46.33 g (75%) of impure tribromopyrimidine 324 as a heterogeneous yellow solid. To a
stirred solution of 75 mL (59 g, 1.9 mol) of anhydrous methanol in 400 mL of anhydrous toluene, at 0 ºC under N₂, was added 13.18 g (330 mmol) of NaH (60% dispersion in mineral oil) in small portions. The resulting suspension was stirred at rt for 30 min, and was then added dropwise to a cooled, stirred solution of the tribromide 324 in 400 mL of anhydrous toluene under N₂, at a rate such that temperature did not exceed 0 ºC. The resulting mixture was then allowed to warm up to rt and stirring was continued for 18 h. The reaction mixture was filtered, and the filtrate was concentrated to yield 53.0 g of a yellow paste. The crude product was purified by flash chromatography in two batches over 1000 g of silica gel each (Et₂O : hexanes 10:90), to yield 15.02 g (55% from crude 324, 41% from 323) of bromopyrimidine 325 as a pale yellow solid: mp 88-90ºC; ¹H NMR (CDCl₃, 500 MHz) δ 3.97 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 6.60 (s, 1H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 54.4 (q), 55.4 (q), 105.0 (d), 152.0 (s), 164.5 (s), 171.7 (s).

7-(tert-Butyldiphenylsilyloxy)-8-methyl-5-prop-2-ynylhexahydroimidazo[1,5-a]pyridin-3-one (326) and 7-Hydroxy-8-methyl-5-prop-2-ynylhexahydroimidazo[1,5-a]pyridin-3-one (327). To a stirred solution of 231 mg (0.41 mmol) of
alkyne 302 in 4 mL of anhydrous THF was added under N₂ 0.43 mL (0.43 mmol) of 1 M TBAF in THF via syringe over 30 min. The resulting solution was stirred at rt for 4 h. The reaction mixture was diluted with 25 mL of H₂O and extracted with three 25-mL of EtOAc. The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to yield 366 mg of a yellow oil. The crude product was purified by flash chromatography over 20 g of silica gel (EtOAc-hexanes, 50:50 → EtOAc) to yield 115.2 mg (63%) of terminal alkyne 326 as a colorless glassy solid and 15.2 mg (18%) of alcohol 327 as a colorless glassy oil. Data on 326: mp 61-63°C; IR (film) 3303, 2962, 2858, 1698, 1428, 1110, 703 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.78 (d, J = 6.8 Hz, 3H, CH₃), 1.11 (s, 9H, TBDPS-t-Bu), 1.44 (td, J = 13.9, 3.2 Hz, 1H, CH₂CHO), 1.51 (m, 1H, CHCH₃), 1.93 (t, J = 2.6 Hz, 1H, CH), 1.94 (dt, J = 13.9, 3.2 Hz, 1H, CH₂CHO), 2.95 (m, 1H, CH₂NH), 2.97 (m, 1H, CH₂C≡), 3.22 (dt, J = 16.2, 3.3 Hz, 1H, CH₂C≡), 3.40 (t, J = 7.7 Hz, 1H, CH₂NH), 3.67 (m, 1H, CHCH₂C≡), 3.69 (m, 1H, CHCH₂NH), 4.00 (br s, 1H, CHO), 4.82 (br s, 1H, NH), 7.37–7.45 (m, 6H, ArH), 7.68 (td, J = 8.3, 1.2 Hz, 4H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 13.5 (q), 19.5 (s), 22.1 (t), 27.2 (q), 38.8 (t), 40.3 (d), 43.4 (t), 48.7 (d), 57.7 (d), 70.0 (d), 70.6 (d), 81.6 (s), 127.6 (d), 129.71 (d), 129.74 (d), 133.5 (s), 133.9 (s), 136.1 (d), 162.7 (s); exact mass calcd. for C₂₇H₃₄N₂O₂Si + Na m/z 469.2282, found m/z 469.2263; [α]D = -197.4° (CH₂Cl₂, c = 3.0). Data on 327: IR (film) 3378, 3281, 2880, 1680, 1441, 1338, 1241 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.96 (d, J = 6.9 Hz, 3H, CH₃), 1.65 (m, 1H, CHCH₃), 1.72 (ddd, J = 13.9, 11.8, 2.4 Hz, 1H, CH₂CHOH), 2.00 (t, J = 2.7 Hz, 1H, CH), 2.10 (dt, J = 14.0, 3.2 Hz, 1H, CH₂CHOH), 3.00 (dd, J = 9.0, 8.3 Hz, 1H, CH₂NH), 3.05 (ddd, J = 16.9, 8.5, 2.6 Hz, 1H, CH₂C≡),
3.30 (ddd, $J = 16.9, 4.0, 2.8$ Hz, 1H, CH$_2$C≡), 3.41 (t, $J = 7.8$ Hz, 1H, CH$_2$NH), 3.54 (m, 1H, CHCH$_2$NH), 3.57 (m, 1H, CHCH$_2$C≡), 3.98 (q, $J = 2.7$ Hz, 1H, CHOCH); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 13.0 (q), 22.2 (t), 39.1 (t), 39.1 (d), 43.3 (t), 48.5 (d), 57.4 (d), 68.7 (d), 70.2 (d), 81.7 (s), 162.4 (s); exact mass calcd. for C$_{11}$H$_{16}$N$_2$O$_2$ + Na m/z 231.1104, found m/z 231.1104; $[\alpha]_D = -38.2^\circ$ (CH$_2$Cl$_2$, c = 0.5).

7-(tert-Butyldiphenylsilyloxy)-5-[3-(2,6-dimethoxypyrimidin-4-yl)prop-2-ynyl]-8-methylhexahydroimidazo[1,5-a]pyridin-3-one (328) + Dimer (329). To a degassed, stirred solution of 144.8 mg (0.32 mmol) of alkyne 326 and 180.2 mg (0.96 mmol) of 4-bromo-2,6-dimethoxypyrimidine (325) in 1.6 mL of anhydrous diethylamine under N$_2$ were added 2.4 mg (3.4 µmol) of PdCl$_2$(PPh$_3$)$_2$ and 0.2 mg (1.1 µmol) of CuI. The resulting mixture was further degassed and stirred at rt under N$_2$ for 48 h. The solvent was evaporated under a stream of N$_2$ and 4 mL of H$_2$O was added. The resulting mixture was extracted with three 5-mL portions of benzene and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to yield 473 mg of a dark yellow oil. The crude product was purified by flash chromatography over 25 g of silica gel (EtOAc-hexanes, 25:75 → EtOAc) to yield 111.2 mg (59%) of coupling product 328 as a
yellow oil and 25.2 mg (17%) of dimer 329 as a yellow oil. Data for 328: IR (film) 3375, 2961, 2857, 2170, 1698, 1579, 1348, 1104, 1025 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 0.79 (d, \(J = 6.7 \text{ Hz}, 3\text{H}, \text{CHCH}_3\)), 1.10 (s, 9H, TBDPS \(t\)-Bu), 1.54 (m, 2H, CHCH\(_3\) + CH\(_2\)CHO), 1.96 (dt, \(J = 13.9, 3.1 \text{ Hz}, 1\text{H}, \text{CH}_2\)CHO), 2.98 (t, \(J = 8.9 \text{ Hz}, 1\text{H}, \text{CH}_2\)NH), 3.23 (dd, \(J = 17.1, 8.3 \text{ Hz}, 1\text{H}, \text{CH}_2C\equiv\)), 3.42 (t, \(J = 7.6 \text{ Hz}, 1\text{H}, \text{CH}_2\)NH), 3.45 (dd, \(J = 17.0, 3.6 \text{ Hz}, 1\text{H}, \text{CH}_2C\equiv\)), 3.73 (m, 2H, 2 \times \text{CHNH}), 3.98 (s, 3H, OCH\(_3\)), 4.00 (s, 3H, OCH\(_3\)), 4.01 (br s, 1H, CH-O), 6.35 (s, 1H, pyrimidine =CH), 7.33 (t, \(J = 7.1 \text{ Hz}, 2\text{H}, \text{ArH}\)), 7.38 (t, \(J = 7.6 \text{ Hz}, 3\text{H}, \text{ArH}\)), 7.44 (t, \(J = 7.3 \text{ Hz}, 1\text{H}, \text{ArH}\)), 7.67 (m, 4H, ArH); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 13.6 (q), 19.6 (s), 23.2 (t), 27.2 (q), 39.3 (t), 40.3 (d), 43.4 (t), 48.6 (d), 54.0 (q), 55.0 (q), 57.8 (d), 70.6 (d), 80.3 (s), 92.0 (s), 104.7 (d), 127.59 (d), 127.65 (d), 129.76 (d), 129.82 (d), 133.5 (s), 133.8 (s), 136.0 (d), 136.1 (d), 151.6 (s), 162.5 (s), 164.9 (s), 171.8 (s), all carbons not singly observed due to magnetic equivalency; exact mass calcd. for C\(_{33}\)H\(_{40}\)N\(_4\)O\(_4\)Si + Na \(m/z\) 607.2711, found \(m/z\) 607.2689; \([\alpha]_D = -45.9 \text{ (CH}_2\)Cl\(_2\), c = 0.9). Data for 329: IR (film) 3438, 2963, 1692 – 1643, 1427, 1344, 1255, 1110, 1034, 909 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 0.77 (d, \(J = 6.8 \text{ Hz}, 6\text{H}, \text{CHCH}_3\)), 1.10 (s, 18H, TBDPS \(t\)-Bu), 1.44 (m, 2H, CH\(_2\)CHO), 1.51 (m, 2H, CHCH\(_3\)), 1.89 (dt, \(J = 13.9, 3.1 \text{ Hz}, 2\text{H}, \text{CH}_2\)CHO), 2.96 (t, \(J = 9.0 \text{ Hz}, 2\text{H}, \text{CH}_2\)NH), 3.08–3.24 (m, 4H, CH\(_2\)C\equiv\)), 3.40 (t, \(J = 7.7 \text{ Hz}, 2\text{H}, \text{CH}_2\)NH), 3.63 (m, 2H, CHCH\(_2\)C\equiv\)), 3.68 (m, 2H, CHCH\(_2\)NH), 3.98 (br s, 2H, CHO), 7.38–7.45 (m, 12H, ArH), 7.64 – 7.68 (m, 8H, ArH); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 13.6 (q), 19.5 (s), 22.6 (t), 27.3 (q), 39.1 (t), 40.2 (d), 43.5 (t), 48.8 (d), 57.8 (d), 67.5 (s), 70.5 (d), 74.4 (s), 127.6 (d), 127.7 (d), 129.7 (d), 129.9 (d), 133.5 (s), 133.8 (s), 136.0 (d), 136.1 (d), 162.6 (s); exact mass calcd.
for C_{54}H_{66}N_{4}O_{4}Si_{2} + Na \ m/z \ 913.4515, \ found \ m/z \ 913.4563; [\alpha]_D = -119.7 (\text{CH}_2\text{Cl}_2, \ c = 1.7).

5-\{3-(2,6-Dimethoxypyrimidin-4-yl)-prop-2-ynyl\}-7-hydroxy-8-methylhexahydroimidazo[1,5-a]pyridin-3-one (331). To a degassed, stirred solution of 62.2 mg (0.30 mmol) of alkyne 330 and 169.0 mg (0.90 mmol) of 4-bromo-2,6-dimethoxypyrimidine (325) in 1.8 mL of anhydrous diethylamine under N\textsubscript{2} were added 2.1 mg (3.0 µmol) of PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} and 0.3 mg (1.6 µmol) of CuI. The resulting mixture was further degassed and stirred at rt under N\textsubscript{2} for 24 h. The solvent was evaporated under a stream of N\textsubscript{2} and 3 mL of H\textsubscript{2}O was added. The resulting mixture was extracted with three 3-mL portions of benzene, and the combined organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated in vacuo to yield 178 mg of a dark yellow oil. The crude product was purified by flash chromatography over 9 g of silica gel (EtOAc) to yield 13.8 mg (13%) of coupling product 331 as a white paste: IR (film) 3391, 2961, 2239, 1682, 1582, 1556, 1350, 1205, 1105, 1010, 732 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \delta 0.97 (d, J = 6.9 Hz, 3H, CH\textsubscript{3}), 1.65 (m, 1H, CH\textsubscript{2}CH\textsubscript{3}), 1.67 (m, 1H, CH\textsubscript{2}CHOH), 2.24 (dt, J = 13.9, 2.9 Hz, 1H, CH\textsubscript{2}CHOH), 2.39 (br, 1H, OH), 3.00 (t, J = 8.6 Hz, 1H, CH\textsubscript{2}NH), 3.18
(dd, \( J = 17.0 \), 9.0 Hz, 1H, \( \text{CH}_2\text{C} = \)), 3.41 (t, \( J = 7.7 \) Hz, 1H, \( \text{CH}_2\text{NH} \)), 3.56 (m, 1H, \( \text{CHCH}_2\text{NH} \)), 3.67 (m, 1H, \( \text{CHCH}_2\text{C} = \)), 3.71 (m, 1H, \( \text{CH}_2\text{C} = \)), 3.97 (s, 3H, OCH\(_3\)), 3.99 (br s, 1H, \( \text{CHOH} \)), 4.00 (s, 3H, OCH\(_3\)), 6.44 (s, 1H, ArH); \(^{13}\text{C}\) NMR (CDCl\(_3\), 125 MHz) \( \delta \) 13.0 (q), 23.2 (t), 39.0 (d), 39.4 (t), 43.3 (t), 48.5 (d), 54.0 (q), 55.0 (q), 57.5 (d), 68.6 (d), 80.2 (s), 92.6 (s), 104.4 (d), 151.3 (s), 162.5 (s), 165.0 (s), 171.8 (s); exact mass calcd. for \( \text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_4 + \text{Na} \) \( m/z \) 369.1533, found \( m/z \) 369.1537 \([\alpha]_D = -39.3 \) (CH\(_2\)Cl\(_2\), c = 0.7).

![Piperidin-2-ylacetic acid](image)

**Piperidin-2-ylacetic acid (340).**\(^{119}\) To a stirred solution of 47.7 g (369 mmol) of 2-pyrrolidineethanol (339) in 200 mL of H\(_2\)O at 0°C was added, dropwise over 30 min, a solution of 95.9 g (959 mmol) of chromium trioxide and 105 mL (193 g, 1970 mmol) of sulfuric acid in 1450 mL of H\(_2\)O. The resulting orange solution was warmed to rt and stirring was continued for 3 h. The reaction mixture was basified by addition of a suspension of approximately 1500 g of Ba(OH)\(_2\) in 1000 mL of H\(_2\)O, and CO\(_2\) was bubbled through the resulting green sludge until the pH was neutral. The resulting mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in 500 mL of MeOH, 3000 mL of Et\(_2\)O was added to cause precipitation of the product, and the resulting white solid collected to yield 37.7 g (71%).
of amino acid 340 as a white solid: mp 179-180 °C (lit.119 180-182 °C); 1H NMR (CDCl3, 500 MHz) δ 1.49 (m, 1H, CH2), 1.71-1.89 (m, 5H, CH2’s), 2.51 (m, 2H, CH2CO2H), 2.82 (m, 1H, CH2NH), 3.18 (m, 1H, CH2NH), 3.49 (br d, 1H, CHNH).

Hexahydroimidazo[1,5-a]pyridin-3-one (341). To a stirred suspension of 1.00 g (7.00 mmol) of piperidin-2-ylacetic acid (340) in 30 mL of t-BuOH under N2 was added 3.0 mL (3.8 g, 13.9 mmol) of diphenylphosphoryl azide and 2.0 mL (1.45 g, 14.3 mmol) of triethylamine. The resulting mixture was heated to 80 °C for 6 h. The reaction mixture was cooled to rt and partitioned between 100 mL of EtOAc and 40 mL of H2O. The organic layer was dried (Na2SO4) and concentrated in vacuo, to yield 5.40 g of an orange-brown oil. The crude product was purified by flash chromatography over 200 g of silica gel (acetone–hexanes, 50:50 → acetone) to yield 552 mg (56%) of urea 341 as a pale tan solid: mp 59-62°C; IR (film) 3232, 2938, 2856, 1700, 1488, 1446, 1275, 1107 cm\(^{-1}\), 1H NMR (CDCl3, 500 MHz) δ 1.39 (m, 3H, CH2’s), 1.62 (m, 1H, CH2CH2N), 1.74 (m, 1H, CH2CHN), 1.86 (m, 1H, CH2CH2CH2), 2.66 (m, 1H, CH2CH2N), 3.00 (m, 1H, CH2NH), 3.51 (m, 2H, CHN + CH2N), 3.86 (m, 1H, CH2CH2N), 4.91 (br, 1H, NH); 13C
NMR (CDCl$_3$, 125 MHz) $\delta$ 23.2 (t), 24.6 (t), 30.6 (t), 40.6 (t), 44.9 (t), 55.3 (d), 161.4 (s); exact mass calcd. for C$_7$H$_{12}$N$_2$O + Na $m/z$ 163.0842, found $m/z$ 163.0854.

3-Oxohexahydroimidazo[1,5-a]pyridine-2-carbaldehyde (343). To a stirred solution of 140 mg (1.0 mmol) of urea 341 in 2.5 mL of CH$_2$Cl$_2$, at rt under N$_2$, were sequentially added via syringe 500 µL (370 mg, 3.0 mmol) of ethyldiisopropylamine and 190 µL (200 mg, 2.5 mmol) of methoxymethyl chloride. The resulting solution was stirred at rt under N$_2$ for 24 h. The reaction mixture was diluted with 4 mL of CH$_2$Cl$_2$, washed with 2 mL of 10% aqueous HCl, 2 mL of saturated aqueous NaHCO$_3$, and 2 mL of brine. The organic phase was dried (Na$_2$SO$_4$), and concentrated in vacuo to yield 65 mg of a yellow oil. The crude product was purified by flash chromatography over 3.5 g of silica gel (Et$_2$O–hexanes, 10:90 → Et$_2$O), to yield 14.7 mg (10%) of 343 as a pale yellow oil: IR (film) 2939, 2858, 1731, 1448, 1344, 1262 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.30 (m, 1H, CH$_2$CHN), 1.50 (m, 2H, CH$_2$CH$_2$CH$_2$ + CH$_2$CH$_2$N), 1.74 (m, 1H, CH$_2$CH$_2$N), 1.94 (m, 2H, CH$_2$CH$_2$CH$_2$ + CH$_2$CHN), 2.81 (td, $J = 12.8$, 3.5 Hz, 1H, CH$_2$CH$_2$N), 3.34 (dd, $J = 11.3$, 5.8 Hz, 1H, CH$_2$NCHO), 3.61 (m, 1H, CHN), 3.93 (dd, $J = 11.3$, 8.8 Hz, 1H, CH$_2$NCHO), 4.03 (m, 1H, CH$_2$CH$_2$N), 8.95 (s, 1H, CHO); $^{13}$C NMR
(CDCl$_3$, 125 MHz) $\delta$ 23.0 (t), 24.3 (t), 31.8 (t), 40.5 (t), 43.8 (t), 52.4 (d), 153.3 (s), 160.2 (d); exact mass calcd. for C$_8$H$_{12}$N$_2$O$_2$ + Na $m/z$ 191.0791, found $m/z$ 191.0791.

2-Tritylhexahydroimidazo[1,5-a]pyridin-3-one (344). To a stirred solution of 142.1 mg (1.0 mmol) of urea 341 and 280 $\mu$L (203 mg, 2.0 mmol) of triethylamine in 1 mL of chloroform, at rt under N$_2$, was added via syringe a solution of 283 mg (1.0 mmol) of triphenylmethyl chloride in 0.5 mL of chloroform. The resulting solution was stirred at rt under N$_2$ for 48 h. The reaction mixture was diluted with 5 mL of CH$_2$Cl$_2$. The resulting solution was washed with 2 mL of 5% aqueous citric acid and 2 mL of H$_2$O, dried (Na$_2$SO$_4$), and concentrated in vacuo to yield 408 mg of an orange oil. The crude product was purified by flash chromatography over 20 g of silica gel (EtOAc–hexanes, 25:75 $\rightarrow$ EtOAc) to yield 200 mg (52%) of N-trityl urea 344 as a light white solid, and 43 mg (approximately 30%) of impure starting 341. Data on 344: mp 75-78°C; IR (film) 3054, 3031, 2937, 2857, 1698, 1447, 1415, 1246, 726, 699 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.25 (m, 1H, CH$_2$CHN), 1.36 (m, 2H, CH$_2$CH$_2$N + CH$_2$CH$_2$CH$_2$), 1.59 (m, 1H, CH$_2$CH$_2$N), 1.71 (m, 1H, CH$_2$CHN), 1.84 (m, 1H, CH$_2$CH$_2$CH$_2$), 2.61 (td, $J = 12.5$, 3.2 Hz, 1H, CH$_2$CH$_2$N), 2.93 (dd, $J = 8.9$, 6.6 Hz, 1H, CH$_2$NCPh$_3$), 3.36 (m, 1H, CHN), 3.50
(dd, $J = 8.8, 7.7$ Hz, 1H, CH$_2$NCPh$_3$), 3.81 (m, 1H, CH$_2$CH$_2$N), 7.21 (t, $J = 7.3$ Hz, 3H, p-ArH), 7.30 (t, $J = 7.8$ Hz, 6H, m-ArH), 7.46 (d, $J = 7.9$ Hz, 6H, o-ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 23.2 (t), 24.6 (t), 30.4 (t), 41.1 (t), 49.8 (t), 52.4 (d), 73.0 (s), 126.3 (d), 127.4 (d), 129.3 (d), 143.3 (s), 159.4 (s); exact mass calcd. for C$_{26}$H$_{26}$N$_2$O + Na $m/z$ 405.1937, found $m/z$ 405.1929.

![Diagram](346.png)

2-(4-Methoxybenzyl)hexahydroimidazo[1,5-a]pyridin-3-one (346). To a stirred solution of 419 mg (3.00 mmol) of urea 341 in 12 mL of DMF, at 0 ºC under N$_2$, was added 152 mg (3.80 mmol) of NaH (60% dispersion in mineral oil) in one portion. The resulting mixture was stirred for 30 min at 0 ºC, followed by addition of a solution of 637 mg (4.10 mmol) of 4-methoxybenzyl chloride in 3 mL of DMF over 30 sec. The resulting mixture was warmed to rt and stirring was continued for 3 h. The reaction mixture was poured into 60 mL of Et$_2$O and the resulting mixture was washed with 10 mL of H$_2$O (H$_2$ evolved). The aqueous layer was extracted with 20 mL of Et$_2$O and the combined organic layers were washed with 10 mL of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to yield 1.83 g of a yellow oil. The crude product was purified by flash chromatography over 90 g of silica gel (Et$_2$O–hexanes, 75:25 $\rightarrow$ Et$_2$O) to yield 565 mg (82%) of protected urea 346 as a pale yellow oil: IR (neat) 2934, 2856, 1694, 1513, 236
1444, 1246 cm⁻¹; \(^1\)H NMR (CDCl₃, 500 MHz) δ 1.27 (m, 1H, CH₂CHN), 1.40 (m, 2H, CH₂CH₂CH₂ + CH₂CH₂N), 1.61 (m, 1H, CH₂CH₂N), 1.67 (m, 1H, CH₂CHN), 1.85 (m, 1H, CH₂CH₂CH₂), 2.70 (td, \(J = 12.7, 3.3\) Hz, 1H, CH₂CH₂N), 2.74 (dd, \(J = 7.3, 6.1\) Hz, 1H, CH₂NPMB), 3.25 (t, \(J = 8.3\) Hz, 1H, CH₂NPMB), 3.35 (m, 1H, CHN), 3.79 (s, 3H, OCH₃), 3.94 (m, 1H, CH₂CH₂N), 4.24-4.36 (m, 2H, CH₂Ar), 6.85 (d, \(J = 8.7\) Hz, 2H, ArH), 7.18 (d, \(J = 8.7\) Hz, 2H, ArH); \(^13\)C NMR (CDCl₃, 125 MHz) δ 23.4 (t), 24.7 (t), 30.6 (t), 41.2 (t), 47.4 (t), 48.7 (t), 52.8 (d), 55.2 (q), 113.9 (d, 2C), 129.4 (d, 2C), 129.5 (s), 158.9 (s), 159.7 (s); exact mass calcd. for C₁₅H₂₀N₂O₂ + Na \(m/z\) 283.1417, found \(m/z\) 283.1423.

![Structure of 347](image.png)

**2-(4-Methoxybenzyl)hexahydroimidazo[1,5-a]pyridine-3-thione (347).** To a stirred solution of 629 mg (2.73 mmol) of urea 346 in 10 mL of anhydrous toluene under N₂ was added 1.162 g (2.87 mmol) of Lawesson’s reagent, and the resulting solution was heated to reflux for 24 h. The reaction mixture was cooled to rt and 10 mL of H₂O was added. The resulting mixture was extracted with three 10-mL portions of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to yield 1.63 g of a yellow oil. The crude product was purified by flash chromatography over 80 g of silica gel (CH₂Cl₂) to yield 610 mg (81%) of thiourea 347 as a pale yellow oil, which
slowly crystallized to a yellow solid: mp 77-79ºC; IR (neat) 2936, 2856, 1612, 1512, 1488, 1443, 1321, 1249, 1033 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.29 (qd, J = 12.1, 3.4 Hz, 1H, CH₂CH₂N), 1.44 (qt, J = 12.9, 2.9 Hz, 1H, CH₂CH₂CH₂), 1.49 (m, 1H, CH₂CH₂N), 1.70 (br m, 1H, CH₂CH₂N), 1.75 (m, 1H, CH₂CH₂N), 1.88 (br m, 1H, CH₂CH₂CH₂), 2.87 (td, J = 12.7, 3.1 Hz, 1H, CH₂CH₂N), 2.95 (dd, J = 9.5, 7.7 Hz, 1H, CH₂NPMB), 3.48 (t, J = 9.4 Hz, 1H, CH₂NPMB), 3.58 (m, 1H, CH₂N), 3.78 (s, 3H, OCH₃), 4.55 (m, 1H, CH₂CH₂N), 4.57-4.84 (m, 2H, NCH₂Ar), 6.85 (d, J = 8.6 Hz, 2H, ArH), 7.24 (d, J = 8.5 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 23.4 (t), 24.6 (t), 30.9 (t), 45.1 (t), 50.4 (t), 51.8 (t), 55.2 (q), 57.0 (d), 113.9 (d), 128.6 (s), 129.4 (d), 159.0 (s), 180.8 (s); exact mass calcd. for C₁₅H₂₀N₂OS + Na m/z 299.1189, found m/z 299.1208.

![3-Amino-2-(4-methoxybenzyl)-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyridin-2-ium trifluoromethanesulphonate (348)](image)

3-Amino-2-(4-methoxybenzyl)-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyridin-2-ium trifluoromethanesulphonate (348). To a stirred solution of 191.4 mg (0.69 mmol) of thiourea 347 in 10 mL of CH₂Cl₂, at rt under N₂, was added via syringe 70 µL (101 mg, 0.62 mmol) of methyl triflate. The resulting solution was stirred at rt under N₂ for 1 h, followed by addition via syringe in one portion of 7 mL of THF saturated with NH₃ by bubbling for 20 min. The resulting solution was heated to reflux
with stirring for 16 h under an ammonia atmosphere. The reaction mixture was concentrated in vacuo to yield 419 mg of a yellow oil. The crude product was purified by flash chromatography over 21 g of silica gel (MeOH–CH₂Cl₂, 10:90) to yield 239 mg (93%) of guanidinium triflate 348 as a pale yellow oil which crystallized slowly into a pale tan solid: mp = 99-101 °C; IR (film) 2258, 3176, 2941, 1677, 1572, 1275, 1252, 1162, 1028 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.32 (qd, J = 11.9, 2.5 Hz, 1H, CH₂CH₂CHN), 1.41 (qt, J = 12.9, 2.8 Hz, 1H, CH₂CH₂CH₂), 1.49 (qt, J = 12.8, 3.7 Hz, 1H, CH₂CH₂N), 1.75 (br d, J = 13.5 Hz, 1H, CH₂CH₂N), 1.82 (br dd, J = 12.9, 2.6 Hz, 1H, CH₂CH₂N), 1.87 (m, 1H, CH₂CH₂CH₂), 2.95 (td, J = 12.8, 3.0 Hz, 1H, CH₂CH₂N), 2.98 (t, J = 8.7 Hz, 1H, CH₂NPMB), 3.50 (t, J = 9.2 Hz, 1H, CH₂NPMB), 3.61 (m, 1H, CHN), 3.79 (s, 3H, OCH₃), 4.01 (dd, J = 13.8, 3.1 Hz, 1H, CH₂CH₂N), 4.46 (m, 2H, CH₂Ar), 6.87 (d, J = 8.6 Hz, 2H, ArH), 7.20 (d, J = 8.6 Hz, 2H, ArH), 7.35 (br, 2H, NH); ¹³C NMR (CDCl₃, 125 MHz) δ 22.4 (t), 24.0 (t), 30.1 (t), 42.7 (t), 48.6 (t), 51.5 (t), 55.3 (q), 56.7 (d), 114.3 (d, 2C), 120.4 (quartet, J = 120.4 Hz), 125.8 (s), 129.9 (d, 2C), 155.5 (s), 159.6 (s); exact mass calcd. for C₁₅H₂₂N₃O (for guanidinium ion) m/z 260.1757, found m/z 260.1757.
3-Amino-2,5,6,7,8,8a-hexahydro-1H-imidazo[1,5-a]pyridin-4-ylium trifluoroacetate (349). To 81.6 mg (0.3 mmol) of guanidinium triflate 348 was added 6 mL of trifluoroacetic acid at 0°C. The resulting solution was stirred at 0°C for 30 min, allowed to warm to rt, and stirring was continued for 4 h. TLC analysis (MeOH-CH₂Cl₂, 10:90, silica gel, PMA stain) showed no remaining starting material. The reaction mixture was concentrated in vacuo and the red residue was dissolved in 10 mL of CH₂Cl₂. The resulting solution was neutralized by addition of 300 mg of solid Na₂CO₃ followed by vigorous stirring for 10 min. The mixture was filtered and concentrated to yield 56.0 mg of a yellow solid. The crude product was purified by flash chromatography over 2.8 g of silica gel (MeOH-CH₂Cl₂, 10:90 → 70:30), to yield 28.9 mg (38%) of guanidinium trifluoroacetate 349 as a pale tan solid: mp 111-114 °C; IR (film) 3315, 3192, 2958, 2861, 1686, 1577, 1261, 1198, 1130, 1030 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.45 (m, 3H, CH₂’s), 1.76 (m, 1H, CH₂), 1.92 (m, 2H, CH₂), 2.94 (m, 1H, CH₂CH₂N), 3.23 (m, 1H, CHCH₂NH), 3.72 (m, 1H, CHNH), 3.75 (m, 1H, CHCH₂NH), 3.88 (dd, J = 13.7, 2.9 Hz, 1H, CH₂CH₂N), 7.68 (br s, 2H, NH₂), 8.43 (br s, 1H, NH); ¹³C NMR (CDCl₃, 125 MHz) δ 22.5 (t), 24.1 (t), 30.2 (t), 41.9 (t), 47.4 (t), 58.4 (d), 120.1 (quartet, J = 316.9 Hz), 157.6 (s); the trifluoroacetate carbonyl was not observed; exact mass calcd. for C₇H₁₄N₃ m/z 140.1182, found m/z 140.1179.
(2-Dimethylaminoethyl)-[2-(4-methoxybenzyl)hexahydroimidazo[1,5-a]-pyridin-3-ylidene]ammonium trifluoromethanesulfonate (350). To a stirred solution of 196 mg (0.71 mmol) of thiourea 347 in 10 mL of CH₂Cl₂, at rt under N₂, was added via syringe 78 µL (113 mg, 0.69 mmol) of methyl triflate. The resulting solution was stirred at rt under N₂ for 1 h, followed by addition via syringe in one portion of a solution of 120 µL (96 mg, 1.1 mmol) of N,N-dimethylethylenediamine in 2 mL of THF. The resulting solution was heated to reflux with stirring for 24 h under N₂, and was then concentrated in vacuo to yield 459 mg of a yellow oil. The crude product was purified by flash chromatography over 26 g of silica gel (MeOH–CH₂Cl₂, 10:90), to yield 271 mg (80%) of guanidinium triflate 350 as a pale yellow oil: IR (film) 3312, 2942, 2862, 1631, 1582, 1515, 1249, 1158, 1030, 637 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.41 (m, 2H, CH₂CH₂CH₂ + CH₂CHN), 1.54 (m, 1H, CH₂CH₂N), 1.77 (br d, J = 13.4 Hz, 1H, CH₂CH₂N), 1.88 (m, 2H, CH₂CH₂CH₂ + CH₂CHN), 2.35 (s, 6H, NMe₂), 2.77 (t, J = 6.1 Hz, 2H, CH₂NMe₂), 3.14 (td, J = 12.9, 3.3 Hz, 1H, CH₂CH₂N), 3.20 (t, J = 9.3 Hz, 1H, CH₂NPMB), 3.56 (m, 2H, CH₂CH₂NMe₂), 3.68 (t, J = 9.4 Hz, 1H, CH₂NPMB), 3.78 (s, 3H, OCH₃), 3.79 (m, 1H, CHN), 3.94 (dd, J = 13.2, 3.7 Hz, 1H, CH₂CH₂N), 4.47 (m, 2H, ArCH₂), 6.40 (br, 1H, NH), 6.88 (d, J = 8.7 Hz, 2H, ArH), 7.18 (d, J = 8.6 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 21.9 (t), 24.1 (t), 30.2 (t), 40.9 (t), 43.8 (t), 44.5 (q, 2C), 241
To a stirred solution of 200 mg (0.72 mmol) of thiourea 347 in 10 mL of CH₂Cl₂, at rt under N₂, was added via syringe 75 µL (109 mg, 0.66 mmol) of methyl triflate. The resulting solution was stirred at rt under N₂ for 1 h, followed by addition via syringe in one portion of a solution of 145 µL (111 mg, 1.1 mmol) of n-hexylamine in 2 mL of THF. The resulting solution was heated to reflux with stirring for 24 h under N₂, and was then concentrated in vacuo to yield 509 mg of a yellow oil. The crude product was purified by flash chromatography over 25 g of silica gel (MeOH–CH₂Cl₂, 10:90), to yield 307 mg (86%) of guanidinium triflate 351 as a pale yellow oil: IR (neat) 3300, 2938, 2861, 1633, 1580, 1515, 1248, 1158, 1031, 637 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.82 (t, J = 6.9 Hz, 3H, (CH₂)₅CH₃), 1.21 (m, 6H, CH₂CH₂(CH₂)₃CH₃), 1.32 (m, 1H, CH₂CHN), 1.43 (m, 2H, piperidine CH₂CH₂CH₂), 1.64 (p, J = 8.0 Hz, 2H, CH₂CH₂(CH₂)₃CH₃), 1.76 (br d, J = 11.1 Hz, 1H, piperidine
1.87 (m, 2H, piperidine CH₂CH₂CH₂ + CH₂CH₂N), 3.02 (td, J = 12.8, 3.1 Hz, 1H, piperidine CH₂CH₂N), 3.14 (dd, J = 9.3, 8.6 Hz, 1H, CH₂NPMB), 3.35 (m, 2H, NCH₂(CH₂)₄CH₃), 3.61 (t, J = 9.4 Hz, 1H, CH₂NPMB), 3.68 (m, 1H, CHN), 3.77 (s, 3H, OCH₃), 4.03 (m, 1H, piperidine CH₂CH₂N), 4.47 (m, 2H, ArCH₂), 6.88 (d, J = 8.6 Hz, 2H, ArH), 7.10 (t, J = 5.7 Hz, 1H, NH), 7.15 (d, J = 8.6 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 13.8 (q), 22.0 (t), 22.3 (t), 24.2 (t), 25.9 (t), 29.9 (t), 30.4 (t), 40.0 (t), 43.7 (t), 44.7 (t), 50.7 (t), 53.5 (t), 55.2 (q), 56.8 (d), 114.5 (d, 2C), 120.6 (quartet, JCF = 321 Hz), 125.9 (s), 128.7 (d, 2C), 156.5 (s), 159.6 (s); exact mass calcd. for C₂₁H₃₄N₃O m/z 344.2696, found m/z 344.2704.

2-(4-Methoxybenzyl)-3-methylsulfanyl-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyridin-2-ium trifluoromethanesulfonate (353). To a stirred solution of 50 mg (0.18 mmol) of thiourea 347 in 2 mL of CH₂Cl₂, at rt under N₂, was added via syringe 18 µL (26 mg, 0.16 mmol) of methyl triflate. The resulting solution was stirred at rt under N₂ for 1 h, and concentrated in vacuo to yield 105 mg of a yellow oil. The crude product was purified by flash chromatography over 5 g of silica gel (MeOH–CH₂Cl₂, 10:90), to yield 75.3 mg (95%) of methylated 353 as a pale yellow oil: IR (neat) 2942, 2862, 1575, 1515,
1260, 1153, 1031 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.55 (m, 3H, CH₂CH₂CH₂ + CH₂CH₂N + CH₂CHN), 1.89 (m, 2H, CH₂CH₂CH₂ + CH₂CH₂N), 1.98 (m, 1H, CH₂CHN), 2.68 (s, 3H, SCH₃), 3.37 (t, J = 10.6 Hz, 1H, CH₂NPMB), 3.42 (m, 1H, CH₂CH₂N), 3.79 (s, 3H, OCH₃), 4.03 (t, J = 11.3 Hz, 1H, CH₂NPMB), 4.13 (m, 1H, CH₂CH₂N), 4.33 (m, 1H, CH-N), 4.70–4.87 (m, 2H, ArCH₂), 6.90 (d, J = 8.7 Hz, 2H, ArH), 7.18 (d, J = 8.6 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 16.4 (q), 22.0 (t), 24.8 (t), 31.3 (t), 46.0 (t), 51.8 (t), 54.0 (t), 55.3 (q), 59.0 (d), 114.6 (d, 2C), 120.8 (quartet, J_CF = 321 Hz), 124.8 (s), 129.5 (d, 2C), 159.9 (s), 164.2 (s); exact mass calcd. for C₁₆H₂₃N₂OS m/z 291.1526, found m/z 291.1503.

10-(tert-Butyldimethylsilyl)-5-(tert-butyldiphenylsilyloxy)-7-(2,2-dimethylpro-pionylamino)-4-methyldec-2-en-9-ynoic acid ethyl ester (354). To a stirred solution of 2.50 g (4.0 mmol) of alkene 285 in 70 mL of 3:1 t-BuOH-H₂O were sequentially added 4.1 mL of a 1% solution of OsO₄ in H₂O (41 mg OsO₄, 0.16 mmol) and 1.72 g (8.0 mmol) of NaIO₄. The resulting mixture was vigorously stirred at rt for 18 h. TLC analysis (EtOAc – hexanes 25:75, silica gel, PMA) indicated no remaining starting olefin. The reaction mixture was partitioned between 150 mL of EtOAc and 150
mL of H₂O. The aqueous layer was extracted with 150 mL of EtOAc. The combined organic layers were washed with 150 mL of brine, dried (Na₂SO₄), and concentrated, to yield 2.89 g of crude intermediate aldehyde as a dark red oil. To a solution of this aldehyde in 150 mL of toluene was added 4.21 g of solid Ph₃P=CHCO₂Et and the resulting solution was heated to 80°C with stirring under N₂ for 48 h. The resulting mixture was concentrated in vacuo to yield 8.15 g of a brown paste. The crude product was purified by flash chromatography over 400 g of silica gel (EtOAc–hexanes, 10:90), to yield 1.21 g (48%) of α,β-unsaturated ester 354 as a yellow oil, contaminated with minor impurities: IR (film) 3426, 2932, 2857, 2174, 1718, 1502, 1472, 1428, 1367, 1250, 1172, 1112, 735, 703 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.07 (s, 6H, TBS CH₃’s), 0.92 (s, 9H, TBS t-Bu), 1.03 (d, J = 6.8 Hz, 3H, CHCH₃), 1.08 (s, 9H, TBDPS t-Bu), 1.27 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.42 (s, 9H, BOC t-Bu), 1.51 (m, 1H, CH₂CHO), 1.81 (br m, 1H, CH₂CHO), 2.32 (m, 2H, CH₂C≡), 2.45 (br m, 1H, CHCH₃), 3.65 (br, 1H, CHNH), 3.87 (m, 1H, CHO), 4.15 (q, J = 7.1 Hz, 2H, CH₂CH₃), 4.42 (br, 1H, NH), 5.66 (d, J = 15.7 Hz, 1H, =CHCO₂Et), 6.76 (dd, J = 15.6, 6.7 Hz, 1H, HC=CHCO₂Et), 7.38–7.41 (m, 6H, ArH), 7.68–7.72 (m, 4H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), 13.7 (q), 14.2 (q), 16.4 (s), 19.0 (s), 19.5 (s), 26.1 (q), 26.5 (t), 27.1 (q), 28.3 (q), 37.1 (t), 41.6 (d), 46.7 (d), 60.1 (t), 73.6 (d), 79.1 (s), 85.1 (s), 103.8 (s), 121.8 (d), 127.6 (d), 127.7 (d, 2C), 129.6 (d), 129.8 (d, 2C), 134.8 (d, 2C), 135.3 (s), 135.95 (s), 136.0 (d, 2C), 150.0 (d), 154.9 (s), 166.4 (s), not all carbons were observed due to magnetic equivalences; exact mass calcd. for C₄₀H₆₁NO₅Si₂ + Na m/z 714.3980, found m/z 714.3937.
5-[3-((tert-Butyldimethylsilyl)-prop-2-ynyl]-7-(tert-butyldiphenylsilyloxy)-8-methylhexahydroimidazo[1,5-a]pyridin-3-ones (357 and 358). To a solution of 1.103 g (1.59 mmol) of carbamate 354 in 16 mL of CH₂Cl₂ was added 1.5 mL of trifluoroacetic acid and the resulting solution was stirred at rt for 3 h. TLC analysis (EtOAc–hexanes, 10:90, silica gel, PMA) indicated that all starting material had been consumed. The reaction mixture was quenched by addition of 4.8 g of solid NaHCO₃, filtered, and concentrated in vacuo, to yield 878 mg of a dark yellow oil. The crude product was purified by flash chromatography over 44 g of silica gel (EtOAc–hexanes, 10:90 → EtOAc) to yield 517 mg (55%) of an inseparable mixture of isomeric amines 355 and 356 (1:2 respectively, by ¹H NMR) as a pale yellow glassy solid. To a stirred solution of 503 mg (0.85 mmol) of the 1:2 mixture of 355 and 366 in 54 mL of 5:1 MeOH-H₂O was added 99 mg (1.8 mmol) of solid KOH. The resulting solution was heated to reflux for 3 h. The solution was cooled to rt and the pH was adjusted to 4-5 by dropwise addition of 1 N aqueous HCl. The resulting solution was diluted by addition of 110 mL of H₂O and extracted with three 110-mL portions of Et₂O. The combined organic extracts were dried (Na₂SO₄) and concentrated to yield 461 mg of intermediate amino-acids as a pale brown solid. To a solution of this solid in 3 mL of t-BuOH were sequentially added via syringe 205 µL (262 mg, 0.95 mmol) of DPPA and 130 µL (94 mg, 0.93 mmol) of triethylamine.
The resulting solution was heated to 80ºC under N₂ for 24 h. The mixture was cooled to rt, diluted with 20 mL of benzene, and washed with 10 mL of 5% aqueous citric acid, 5 mL of H₂O, 10 mL of saturated aqueous NaHCO₃, and 10 mL of brine. The organic phase was dried (Na₂SO₄) and concentrated to yield 527 mg of a dark yellow oil. The crude product was purified by flash chromatography over 26 g of silica gel (EtOAc–hexanes, 20:80 → EtOAc), to yield 171.6 mg (36%) of urea 358 as a pale yellow oil, and 72.7 mg (15%) of epimeric urea 357 as a pale yellow oil. Data on 358: IR (film) 3250, 2930, 2856, 2175, 1701, 1428, 1251, 1114, 702 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.10 (s, 3H, SiCH₃), 0.11 (s, 3H, SiCH₃), 0.95 (s, 9H, TBS t-Bu), 1.07 (d, J = 6.8 Hz, 3H, CHCH₃), 1.10 (s, 9H, TBDPS t-Bu), 1.83–1.93 (m, 3H, CHCH₃ + CH₂CHO), 2.97 (m, 1H, CHCH₂C≡), 3.00 (m, 1H, CH₂C≡), 3.10 (m, 2H, CH₂NH), 3.26 (m, 1H, CHCH₂NH), 3.37 (d, J = 13.7 Hz, 1H, CH₂C≡), 3.81 (dt, J = 11.4, 4.6 Hz, 1H, CHO), 5.33 (d, J = 7.4 Hz, 1H, NH), 7.39 (m, 4H, ArH), 7.45 (m, 2H, ArH), 7.68 (m, 4H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ -4.5 (q), 6.2 (q), 16.4 (s), 19.2 (s), 23.9 (t), 26.1 (q), 26.8 (q), 34.5 (t), 35.8 (d), 40.3 (t), 52.0 (d), 60.0 (d), 72.1 (d), 84.5 (s), 104.6 (s), 127.6 (d), 129.7 (d), 133.8 (s), 134.0 (s), 135.5 (d), 135.6 (d), 163.1 (s); exact mass calcd. for C₃₃H₄₈N₂O₂Si₂ + Na m/z 583.3147, found m/z 583.3165. Data on 357: IR (film) 3246, 2931, 2857, 2174, 1698, 1428, 1256, 1112, 1024, 702 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.10 (s, 3H, SiCH₃), 0.11 (s, 3H, SiCH₃), 0.35 (d, J = 6.9 Hz, 3H, CHCH₃), 0.95 (s, 9H, TBS t-Bu), 1.13 (s, 9H, TBDPS t-Bu), 1.34 (m, 1H, CHCH₃), 1.69 (dd, J = 14.4, 6.7, 2.7 Hz, 1H, CH₂CHO), 2.38 (dd, J = 14.4, 2.4 Hz, 1H, CH₂CHO), 2.72 (dd, J = 16.2, 5.1 Hz, 1H, CH₂C≡), 2.97 (t, J = 7.8 Hz, 1H, CH₂NH), 3.04 (dd, J = 16.2, 10.2 Hz, 1H, CH₂C≡), 3.47
(t, J = 8.4 Hz, 1H, CH$_2$NH), 3.74 (m, 1H, CHCH$_2$NH), 4.13 (m, 2H, CHCH$_2$C≡ + CHO), 5.06 (br s, 1H, NH), 7.37–7.44 (m, 6H, ArH), 7.69–7.72 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ -4.4 (q), 13.4 (q), 16.5 (s), 19.6 (s), 24.8 (t), 26.1 (q), 27.4 (q), 32.9 (t), 40.5 (d), 43.3 (t), 46.5 (d), 51.5 (d), 71.0 (d), 84.7 (s), 105.4 (s), 127.6 (d), 129.6 (d), 129.9 (d), 133.1 (s), 134.0 (s), 136.0 (d), 136.5 (d), 160.8 (s); exact mass calcd. for C$_{33}$H$_{48}$N$_2$O$_2$Si$_2$ + Na m/z 583.3147, found m/z 583.3184.

Selected NOE difference experiments for urea 358:

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Selected NOE difference experiments for urea 357:

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</tbody>
</table>
5-[3-(\textit{tert\textendash}Butyldimethylsilyl)prop-2-yl\textendash]7-(\textit{tert\textendash}butyldiphenylsilyloxy)-8-methyl-3-oxo-hexahydroimidazo[1,5-a]pyridine-2-carbaldehyde (360). To a stirred solution of 153 mg (0.27 mmol) of urea 358 in 3 mL of DMF, at 0 °C under N₂, was added 11.2 mg of a 60% suspension of sodium hydride in mineral oil (6.7 mg of NaH, 0.28 mmol) in one portion. The resulting mixture was stirred at 0°C under N₂ for 1 h, followed by addition via syringe of 40 µL (46 mg, 0.30 mmol) of \textit{p}-methoxybenzyl chloride. The resulting mixture was allowed to warm to rt, and stirring was continued for 3 h. The reaction mixture was poured into 12 mL of Et₂O and washed with 3 mL of H₂O. The aqueous layer was extracted with 6 mL of Et₂O. The combined organic layers were washed with 3 mL of brine, dried (Na₂SO₄), and concentrated in vacuo to yield 245 mg of a yellow oil. The crude product was purified by flash chromatography over 12 g of silica gel (EtOAc-hexanes, 20:80 → EtOAc), to yield 42.1 mg (27%) of formylated 360 as a pale yellow oil and 92.9 mg (61%) of starting urea 358 as a pale yellow oil. Data on 360: IR (film) 3072, 2953, 2930, 2857, 2177, 1740, 1693, 1342, 1252, 1114, 824, 703 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.086 (s, 3H, TBS CH₃), 0.092 (s, 3H, TBS CH₃), 0.92 (s, 9H, TBDPS \textit{t}-Bu), 1.03 (d, J = 6.8 Hz, 3H, CHCH₂), 1.09 (s, 9H, TBDPS \textit{t}-Bu), 1.89 (m, 3H, \textit{CHCH₃} + \textit{CH₂CHO}), 3.08 (dd, J = 16.4, 3.4 Hz, 1H, CH₂C≡), 3.14 (m, 1H, \textit{CHCH₂C≡}), 3.22 (dd, J = 16.4, 7.7 Hz, 1H, \textit{CH₂NCHO}), 3.38 (m, 2H, \textit{CH₂NCHO} +
CHCH₂NCHO), 3.63 (dd, J = 9.6, 7.4 Hz, 1H, CH₂C≡), 3.82 (m, 1H, CH-O), 7.38–7.41 (m, 4H, ArH), 7.44–7.47 (m, 2H, ArH), 7.65–7.67 (m, 4H, ArH), 8.88 (s, 1H, CHO); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), 5.1 (q), 16.5 (s), 19.2 (s), 23.5 (t), 26.0 (q), 26.9 (q), 33.9 (t), 36.7 (d), 39.2 (t), 52.6 (d), 56.3 (d), 71.4 (d), 85.5 (s), 103.3 (s), 127.72 (d), 127.75 (d), 129.89 (d), 129.93 (d), 133.6 (s), 133.7 (s), 135.59 (d), 135.62 (d), 154.3 (s), 160.0 (d); exact mass calcd. for C₃₄H₄₈N₂O₃Si₂ + Na m/z 611.3103, found m/z 611.3330.

5-[3-(tert-Butyldimethylsilyl)prop-2-ynyl]-7-(tert-butyldiphenylsilyloxy)-2-(4-methoxybenzyl)-8-methylhexahydroimidazo[1,5-a]pyridin-3-one (363) and 7-(tert-butyldiphenylsilyloxy)-2-(4-methoxybenzyl)-8-methyl-5-prop-2-ynylhexahyridazo[1,5-a]pyridin-3-one (364). To a stirred solution of 773 mg (1.38 mmol) of urea 302 in 14 mL of DMF at 0 ºC under N₂ was added 112 mg of a 60% dispersion of NaH in mineral oil (67.4 mg NaH, 2.81 mmol). The resulting mixture was stirred at 0 ºC under N₂ for 1 h, followed by addition via syringe of 375 µL (433 mg, 2.77 mmol) of p-methoxybenzyl chloride. The resulting mixture was warmed to rt, and stirring was continued for 4 h. The reaction mixture was diluted with 80 mL of Et₂O, and washed with 25 mL of H₂O. The aqueous layer was extracted with 40 mL of Et₂O, and the combined
organic layers were washed with 25 mL of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to yield 2.44 g of a yellow oil. The crude product was purified by flash chromatography over 70 g of silica gel (EtOAc-hexanes, 18:82 → 25:75), to yield 636 mg (68%) of protected urea 363 as a colorless oil and 191 mg (24%) of terminal alkyne 364, as a colorless oil. Data for 363: IR (film) 2957, 2929, 2855, 1702, 1513, 1428, 1245, 1111, 1037, 703 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 0.04 (s, 3H, Si(CH$_3$)$_3$), 0.06 (s, 3H, Si(CH$_3$)$_3$), 0.69 (d, $J$ = 6.8 Hz, 3H, CHCH$_3$), 0.90 (s, 9H, TBS t-Bu), 1.09 (s, 9H, TBDPS t-Bu), 1.39 (m, 1H, CHCH$_3$), 1.56 (m, 1H, CH$_2$CHO), 1.87 (dt, $J$ = 13.9, 3.2 Hz, 1H, CH$_2$CHO), 2.62 (dd, $J$ = 10.5, 8.3 Hz, 1H, CH$_2$NPMB), 3.03 (dd, $J$ = 17.0, 3.4 Hz, 1H, CH$_2$C≡), 3.17 (t, $J$ = 7.6 Hz, 1H, CH$_2$NPMB), 3.28 (dd, $J$ = 17.0, 7.6 Hz, 1H, CH$_2$C≡), 3.52 (m, 1H, CHCH$_2$NPMB), 3.65 (m, 1H, CHCH$_2$C≡), 3.81 (s, 3H, OCH$_3$), 3.97 (br s, 1H, CHO), 4.12-4.45 (m, 2H, CH$_2$Ar), 6.87 (d, $J$ = 8.5 Hz, 2H, PMB ArH), 7.20 (d, $J$ = 8.5 Hz, 2H, PMB ArH), 7.38 (m, 4H, TBDPS ArH), 7.44 (m, 2H, TBDPS ArH), 7.66 (d, $J$ = 7.1 Hz, 4H, TBDPS ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ -4.5 (q), 13.7 (q), 16.6 (s), 19.6 (s), 23.7 (t), 26.1 (q), 27.3 (q), 39.0 (t), 40.2 (d), 47.3 (t), 47.5 (t), 48.6 (d), 54.9 (d), 55.2 (q), 70.7 (d), 84.2 (s), 104.9 (s), 113.9 (d, 2C), 127.5 (d, 2C), 127.6 (d, 2C), 129.5 (d, 2C), 129.58 (s), 129.65 (d), 129.9 (d), 133.7 (s), 133.8 (s), 136.0 (d, 2C), 136.1 (d, 2C), 158.9 (s), 161.1 (s); exact mass calcd. for C$_{41}$H$_{56}$N$_2$O$_3$Si$_2$ + Na m/z 703.3722, found m/z 703.3726; $[\alpha]_D$ = -41.7º (CHCl$_3$, c = 0.8). Data for 364: IR (film) 3307, 2958, 2930, 2859, 1696, 1243, 1106, 1035 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 0.73 (d, $J$ = 6.8 Hz, 3H, CHCH$_3$), 1.10 (s, 9H, TBDPS t-Bu), 1.43 (m, 2H, CHCH$_3$ + CH$_2$CHO), 1.93 (t, $J$ = 2.6 Hz, 1H, =CH), 1.98 (dt, $J$ = 13.9, 3.2 Hz, 1H, CH$_2$CHO), 2.67
(dd, J = 9.6, 8.4 Hz, 1H, CH₂N), 3.00 (ddd, J = 16.9, 8.6, 2.6 Hz, 1H, CH₂C≡), 3.19 (t, J = 7.8 Hz, 1H, CH₂N), 3.29 (ddd, J = 16.4, 3.7, 2.9 Hz, 1H, CH₂C≡), 3.52 (dt, J = 10.2, 7.7 Hz, 1H, CHCH₂N), 3.68 (m, 1H, CHCH₂C≡), 3.81 (s, 3H, PMB OCH₃), 3.98 (br s, 1H, CHO), 4.17–4.42 (m, 2H, ArCH₂), 6.87 (d, J = 8.6 Hz, 2H, ArH), 7.20 (d, J = 8.6 Hz, 2H, ArH), 7.38 (m, 4H, ArH), 7.43 (m, 2H, ArH), 7.67 (m, 4H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 1.0 (d), 13.6 (q), 19.6 (s), 22.2 (t), 27.3 (q), 39.0 (t), 40.2 (d), 47.1 (t), 47.3 (t), 49.1 (d), 55.1 (d), 55.2 (q), 70.0 (s), 70.6 (d), 81.8 (s), 113.9 (s), 127.6 (d), 128.6 (s), 129.5 (d), 129.7 (d), 129.8 (d), 133.6 (s), 134.0 (s), 136.1 (d), 158.9 (s), 161.0 (s); exact mass calcd. for C₃₅H₄₂N₂O₅Si + Na m/z 589.2857, found m/z 589.2850; [α]D = -39.9 (CH₂Cl₂, c = 0.9).
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APPENDIX A

$^1$H AND $^{13}$C NMR SPECTRA FOR SELECTED COMPOUNDS
COOH
SiMe₃

FH-1-166C (CDCl₃, 400 MHz)
FH-1-192B (CDCl₃, 400 MHz)
284

104

FH-1-218B1 (CDCl₃, 500 MHz)
106

FH1-227B2 (CDCl₃, 125 MHz)
Br

OAc

114

FH-1-153B2 (CDCl₃, 400 MHz)
FH-1-256C2 (CDCl₃, 400 MHz)

* = Impurity

Br⁻ 113
OPiv

ppm
FH-1-280D (CDCl₃, 500 MHz)
303

116

FH-1-280D (CDCl₃, 125 MHz)
119
FH-1-272B2 (CDCl₃, 500 MHz)
* = Impurity
126
FH-2-64B1 (C₆D₆, 500 MHz)
FH-2-64B1 (C₆D₆, 125 MHz)

* = Impurity

OMe

PSE 1
128
FH-1-297B2 (CDCl₃, 125 MHz)
FH-2-13B1 (CDCl₃, 125 MHz)
135
FH-1-288B5 (CDCl₃, 125 MHz)
323

138

FH-2-90B (CDCl₃, 125 MHz)
142
FH-3-68B1 (CDCl₃, 125 MHz)
143
FH-3-79B (CDCl₃, 500 MHz)
FH-3-79B (CDCl₃, 125 MHz)
164
FH-2-199B1 (CDCl₃, 500 MHz)
* = Impurity
164
FH-2-199B1 (CDCl₃, 125 MHz)
* = Impurity
FH-2,223A (CDCl₃, 100 MHz)
175
FH-2-219A (CDCl₃, 400 MHz)
* = Impurity
177
FH-3-20A (CDCl₃, 400 MHz)
178
FH-3-30A (CDCl₃, 400 MHz)
FH-3-39A (CDCl₃, 500 MHz)

* = Impurity
FH-3-43B (CDCl₃, 125 MHz)
FH-3-47B (CDCl₃, 500 MHz)
FH-3-54A (CDCl$_3$, 500 MHz)
183
FH-2-259B (CDCl₃, 125 MHz)
FH-2-263B (CDCl₃, 125 MHz)
FH-3-57B3 (CDCl₃, 500 MHz)

* = Impurity
FH-3-57B3 (CDCl$_3$, 125 MHz)
269
FH-5-89B1 (CDCl$_3$, 125 MHz)
271
FH-3-109B (CDCl₃, 500 MHz)
272
FH-3-148B (CDCl₃, 500 MHz)
OTHP

274

FH-5-4 (CDCl₃, 400 MHz)
TBS — Br

278

FH-5-11B (CDCl₃, 400 MHz)
280
FH-4-30B (CDCl₃, 500 MHz)
TBDPSO
\[
\text{HBOC} \quad \text{TBS}
\]

284
FH-4-90B (CDCl₃, 500 MHz)
FH-5-177B (CDCl₃, 500 MHz)

o = Et₂O
FH-3-225B (CDCl₃, 500 MHz)
TBDPSO

H
NH
CO₂Et
H₃C

298

FH-4-111B (CDCl₃, 125 MHz)

* = Impurity
311
FH-6-61B (CDCl₃, 500 MHz)
FH-6-61B (CDCl₃, 125 MHz)
Br
\begin{align*}
\text{OMe} \\
\text{N} & \text{N} \\
\text{OMe}
\end{align*}

325
FH-4-149 (CDCl$_3$, 125 MHz)
FH-4-162B2 (CDCl₃, 500 MHz)
FH-4-162B3 (CDCl₃, 500 MHz)

\( \n = \) Hexanes
346 PMB

FH-5-256B (CDCl₃, 500 MHz)
FH-6-15B (CDCl₃, 500 MHz)
FH-6-102B (CDCl₃, 500 MHz)
FH-6-102B (CDCl₃, 125 MHz)
FH-5-230B (CDCl₃, 125 MHz)

* = Impurity
FH-6-119B3 (CDCl$_3$, 500 MHz)
459

FH-6-119B2 (CDCl₃, 125 MHz)