Synthesis and Anticancer Evaluation of Agelastatin Alkaloid Derivatives and
Enantioselective Total Synthesis of Aspidosperma Alkaloids

by

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M.S., Chemistry
Stevens Institute of Technology, 2013

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DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

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Massachusetts Institute of Technology

June 2018

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Haslam and Dewey Professor of Chemistry
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Signature redacted

Professor Mohammad Movassaghi.................. Thesis Supervisor

Signature redacted

Professor Jeremiah A. Johnson..........
To my family
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Preface

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Synthesis and Anticancer Evaluation of Agelastatin Alkaloid Derivatives and Enantioselective Total Synthesis of Aspidosperma Alkaloids

by

Alyssa Hope Antropow

Submitted to the Department of Chemistry on May 25, 2018 in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Organic Chemistry

ABSTRACT

I. Synthesis and Evaluation of Agelastatin Derivatives as Potent Modulators for Cancer Invasion and Metastasis

The synthesis of new agelastatin alkaloid derivatives and their anticancer evaluation in the context of the breast cancer microenvironment is described. A variety of N1-alkyl and C5-ether agelastatin derivatives were accessed via application of our strategy for convergent imidazolone synthesis. We have discovered that agelastatin alkaloids are potent modulators for cancer invasion and metastasis at non-cytotoxic doses. We discuss the increased potency of (−)-agelastatin E as compared to (−)-agelastatin A in this capacity, in addition to identification of new agelastatin derivatives with activity that is statistically equivalent to (−)-agelastatin E.

II. Enantioselective Synthesis of (−)-Vallesine: Late-stage C17-Oxidation via Complex Indole Boronation

The first enantioselective total synthesis of (−)-vallesine via a strategy that features a late-stage regioselective C17-oxidation followed by a highly stereoselective transannular cyclization is described. The versatility of this approach is highlighted by divergent synthesis of the archetypal alkaloid of this family, (+)-aspidospermidine, and an A-ring oxygenated derivative (+)-deacetylaspidospermine, the precursor to (−)-vallesine, from a common intermediate.

III. Enantioselective Total Synthesis of (−)-Jerantinine A from (−)-Melodidine P via Bio-Inspired A-Ring Oxidation

The first enantioselective synthesis of (−)-melodidine P and its direct conversion to related alkaloid (−)-jerantinine A is described. A key para-aza-quinone methide pentacyclic intermediate enables A-ring to C-ring oxidation state transfer. Our synthesis is streamlined through the development of two multi-step single-pot procedures which proceed with high efficiency. We further demonstrate the utility of para-aza-quinone methide intermediates in our strategy for C16-methoxylation which provides entry to the (−)-jerantinine alkaloid family.

Thesis Supervisor: Mohammad Movassaghi
Title: Professor of Chemistry
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<thead>
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>[α]</td>
<td>specific rotation</td>
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<tr>
<td>app</td>
<td>apparent</td>
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<tr>
<td>aq</td>
<td>aqueous</td>
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<td>atm</td>
<td>atmosphere</td>
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<td>br</td>
<td>broad</td>
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<tr>
<td>Bu</td>
<td>butyl</td>
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<tr>
<td>°C</td>
<td>degree Celsius</td>
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<td>CAM</td>
<td>ceric ammonium molybdate</td>
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<td>cm⁻¹</td>
<td>wavenumber</td>
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<td>d</td>
<td>doublet</td>
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<tr>
<td>d</td>
<td>deuterium</td>
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<tr>
<td>δ</td>
<td>parts per million</td>
</tr>
<tr>
<td>DART</td>
<td>direct analysis in real time</td>
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<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>El</td>
<td>electron spray ionization</td>
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<td>Et</td>
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<tr>
<td>FT</td>
<td>fourier transform</td>
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<td>gCOSY</td>
<td>gradient-selected correlation spectroscopy</td>
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<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
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<td>high performance liquid chromatography</td>
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<td>Me</td>
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</tbody>
</table>
Mhz  megahertz
min  minute
mol  mole
M.p. melting point
MS  mass spectrometry
m/z mass to charge
N  normal
NMR nuclear magnetic resonance
nOe nuclear Overhauser effect
NOESY nuclear Overhauser effect spectroscopy
Nu nucleophile
o  ortho
p  para
Ph phenyl
piv pivaloyl
ppm parts per million
Pr propyl
q quartet
Rf retention factor
s sec
s singlet
s strong
str stretch
t tert
t triplet
TBS tert-butylidemethylsilyl
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
UV ultraviolet
Vis visible
w weak
Chapter I

Synthesis and Evaluation of Agelastatin Derivatives as Potent Modulators for Cancer Invasion and Metastasis
Introduction

The agelastatin alkaloids,\(^1\) a family of pyrrole-imidazole marine natural products, have been of interest to the scientific community for many years due to their intriguing molecular structure as well as potent biological activities.\(^2\) Agelastatin alkaloids have been isolated from marine sponges *Agelas dendromorpha*\(^{18,19}\) and *Cymbastela* sp.\(^{1e}\) and the scarcity of these alkaloids from natural sources has necessitated innovative synthetic strategies for effective access. Our group has reported a general strategy for the total synthesis of all known (-)-agelastatins (AgA–AgF, 1.1–1.6, Figure 1.1), thus enabling the comprehensive, comparative anticancer study of these naturally occurring alkaloids along with many synthetic derivatives.\(^3\) Our synthesis enables late-stage diversification of the agelastatin core and amplifies access to biologically interesting agelastatin alkaloid derivatives (1.7–1.8).

![Figure 1.1. Structures of (-)-agelastatins A–F (1.1–1.6) and designed agelastatin derivatives (1.7–1.8).](image)

Agelastatin A (1.1) has served as an archetypal synthetic target for this alkaloid family, and prior synthetic strategies offer diverse methodologies to access the agelastatin core.\(^4\) Distinct from prior approaches, our strategy, developed by Dr. Dustin S. Siegel and Dr. Sunkyu Han, employs late-stage C-ring formation with concomitant introduction of three stereocenters.\(^3\)
Inspired by linear clathrodin-like biosynthetic precursors, a largely unprecedented 5-exo-trig cyclization was envisioned to provide late-stage C-ring formation utilizing the pendant nucleophilic imidazolone D-ring (Scheme 1.1).

![Scheme 1.1](image)

**Scheme 1.1.** Retrosynthetic analysis of (−)-agelastatin A (1.1).

To support our ongoing interest in biological study of agelastatin alkaloids and development of derivatives, I prepared gram-scale quantities of (−)-agelastatin A (1.1) utilizing our synthetic strategy,\textsuperscript{3a} and my experience with this synthesis forms the basis of the studies discussed in this chapter (Scheme 1.2).\textsuperscript{5} Pyrrole (+)-1.13 is accessed from D-aspartic acid dimethyl ester and is selectively brominated at C13 using N-bromosuccinimide to afford bromopyrrole (+)-1.14 which is subject to treatment with chlorosulfonyl isocyanate to provide amide (+)-1.15. Upon dissolution in methanol, amide (+)-1.15 is cyclized to form the B-ring of the agelastatin alkaloids and immediate C8-reduction with sodium borohydride provides bicycle (+)-1.16 as a single diastereomer in 99% ee. Thioester (+)-1.17 was accessed readily from ester (+)-1.16 after treatment with trimethylaluminum and 4-methylbenzenethiol. Triazone 1.18 was efficiently coupled with thioester (+)-1.17 in the presence of stoichiometric copper(I)-thiophene-2-carboxylate to afford ketone (+)-1.19. Upon treatment with hydrogen chloride solution in methanol, triazone (+)-1.19 unravels the corresponding keto-urea compound which is subject to spontaneous condensative cyclization to afford pre-agelastatin A (+)-1.11. Heating an aqueous
solution of pre-agelastatin A (+)-1.11 with methanesulfonic acid, followed by introduction of methanol afforded (-)-agelastatin A (1.1, Scheme 1.2).

Scheme 1.2. Enantioselective synthesis of (-)-agelastatin A (1.1). Conditions: (a) 2,5-dimethoxytetrahydrofuran, ClCH₂CH₂Cl, H₂O, 80 °C, 82%. (b) NBS, DTBMP, THF, 85%. (c) ClSO₂NCO, CH₃CN, 0 °C; Na(Hg), NaH₂PO₄, 77%. (d) NaBH₄, MeOH, 0 °C, 1 h; pTsOH-H₂O, 23 °C, 67%. (e) HSC₆H₄-p-Me, AlMe₃, CH₂Cl₂, 0 °C, 88%. (f) CuTC, THF, 50 °C, 95%. (g) HCl (0.5 N), MeOH, 65 °C, 89%. (h) MeSO₃H, H₂O, 100 °C; MeOH, 41%. NBS = N-bromosuccinimide. DTBMP = 2,6-di-tert-butyl-4-methylpyridine. pTsOH = p-toluenesulfonic acid. CuTC = copper(I)-thiophene-2-carboxylate.

Critical to the success of our unified chemical synthesis of agelastatins was the development of a methodology for the introduction of the targeted imidazolone moiety. Our reported azaheterocycle synthesis involves the cross-coupling of thioesters with stannylurea derivatives which both streamlines our synthesis of agelastatin alkaloids (Scheme 1.3A) and provides the foundation for access to various derivatives (Scheme 1.3B). Notably, both alkyl and aryl thioesters could be efficiently coupled with a range of urea-, triazone-, or guanidine-based aminostannanes 1.23 to provide various azaheterocycles 1.25 (Scheme 1.3B). Through development of this methodology and completion of the first total synthesis of (-)-agelastatin D (1.4), we have demonstrated that diversifying the imidazolone D-ring is a viable strategy towards related, agelastatin-derived compounds and other oroidin-based natural products.⁷
A. Synthesis of Agelastatin Alkaloids

\[ \text{Br} + \text{C}_4\text{H}_4\text{-p-Me} + \text{CuTC} \rightarrow \text{THF} \rightarrow 50^\circ\text{C} \]

1.20

\[ \text{CuTC} \]

1.21

AgA (1.1)

R^1 = Me

AgD (1.4)

R^1 = H

B. Versatile Azaheterocycle Synthesis

\[ \text{R}^2\text{S}\text{-C}_4\text{H}_4\text{-p-Me} + \text{R}^1\text{N}\text{Sn}\text{H}(\text{c-C}_6\text{H},\text{1})_3 \rightarrow \text{CuTC} \rightarrow \text{THF} \rightarrow 50^\circ\text{C} \]

1.22

R^2 = alkyl, aryl

1.23

urea, triazole, or guanidine

1.24

X = 0, NR

Scheme 1.3. Copper-mediated thioester-aminostannane cross-coupling and versatile synthesis of azaheterocycles.

Comparative Biological Studies of Agelastatin Alkaloids. In collaboration with the Hergenrother group at the University of Illinois at Urbana-Champaign, we reported in 2013 the first side-by-side evaluation of all known (-)-agelastatin alkaloids (1.1–1.6) and key synthetic intermediates for treatment in nine human cancer cell lines. While previous studies had tested the potency of (-)-agelastatin A (AgA, 1.1) relative to other available derivatives in a single cell line, no comprehensive comparison of the class against multiple cell lines had been performed. Furthermore, the heterogeneity of previous studies of AgA (1.1) in a range of cancer types made a true assessment of selectivity for any one type of cancer impossible. In an assay for cell death against four human cancer cell lines and one immortalized normal human cell line, AgA (1.1) exhibited the highest potency in all cell lines with enhanced activity in U-937 and BT549 cells, while AgD (1.4) showed reasonable activity against the same cell lines (Table 1.1). AgB (1.2) and AgE (1.5) showed weak activity with the same overall pattern as alkaloids (-)-1.1 and (-)-1.4, while AgC (1.3) and AgF (1.6) showed no activity at the concentrations tested. Detailed studies of AgA (1.1) and AgD (1.4) revealed for the first time that both alkaloids induce apoptotic death of cancer cells without affecting tubulin dynamics within cells. Furthermore, the exquisite potency
of AgA (1.1) against blood cancer cell lines (20–190 nM) without affecting normal red blood cells (>333 μM) indicates significant potential for agelastatins as anticancer agents.3b,c

<table>
<thead>
<tr>
<th>Compound</th>
<th>U-937</th>
<th>HeLa</th>
<th>A549</th>
<th>BT549</th>
<th>IMR90</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgA (1.1)</td>
<td>0.067 ± 0.003</td>
<td>0.708 ± 0.090</td>
<td>1.05 ± 0.14</td>
<td>0.278 ± 0.076</td>
<td>1.11 ± 0.35</td>
</tr>
<tr>
<td>AgB (1.2)</td>
<td>1.06 ± 0.16</td>
<td>4.8 ± 1.2</td>
<td>&gt;10</td>
<td>4.8 ± 1.1</td>
<td>&gt;10</td>
</tr>
<tr>
<td>AgC (1.3)</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>AgD (1.4)</td>
<td>0.240 ± 0.033</td>
<td>1.00 ± 0.20</td>
<td>0.92 ± 0.16</td>
<td>0.631 ± 0.082</td>
<td>2.75 ± 0.60</td>
</tr>
<tr>
<td>AgE (1.5)</td>
<td>2.56 ± 0.13</td>
<td>8.60 ± 0.81</td>
<td>&gt;10</td>
<td>6.9 ± 2.5</td>
<td>&gt;10</td>
</tr>
<tr>
<td>AgF (1.6)</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Table 1.1. Anticancer activity (IC$_{50}$, μM) of AgA–AgF (1.1–1.6) against human cell lines after 48 h exposure. Cell lines: U-937, lymphoma; HeLa, cervical carcinoma; A549, non-small-cell lung carcinoma; BT549, breast carcinoma; IMR90, lung fibroblasts. Forty-eight hour IC$_{50}$ values (μM) as determined by MTS (U-937) and SRB (HeLa, A549, BT549, and IMR90). MTS = 3-(4,5-dimethylthiazol-2-yl)-5-(3-carbomethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium. SRB = sulforhodamine B.

**Agelastatin Alkaloids in Breast Cancer Microenvironments.** As part of our ongoing collaboration with the Buchsbaum group at Tufts Medical Center, our group has been interested in the effects of AgA (1.1) on the osteopontin pathway in breast cancer microenvironments. The tumor microenvironment is known to play a key role in tumor evolution, and there is increasing interest in elucidating the reciprocal signals that lead to more invasive and metastatic phenotypes.8 Buchsbaum and coworkers have developed a method of 3D co-culture which enables assessment of the effects of mammary fibroblasts on associated breast cancer cells.9 Through their studies of the Rac GTPase Tiam1,10 they have discovered a novel Tiam1-osteopontin pathway which modulates breast cancer invasion and metastasis through regulating epithelial-mesenchymal transition (EMT) and cancer stem cell populations in associated breast cancer cells. In this setting, osteopontin (OPN) transcription and secretion is induced by down-regulation of the Rac GTPase exchange factor Tiam1.11 Down-regulation of fibroblast Tiam1 and up-regulation of fibroblast OPN in the tumor microenvironment are associated with increased invasiveness in human breast cancers.12
AgA (1.1), a known inhibitor of OPN transcription and expression,\textsuperscript{2c} has been demonstrated in these studies to block OPN transcription and reverse all effects induced by Tiam1-deficient fibroblasts.\textsuperscript{12} The concentrations of AgA (1.1) in the aforementioned assays (75–100 nM) are far below cytotoxic range in cell culture. However, we found that direct dosing of mice with AgA (1.1) at the previously published in vivo dose used in one to four day studies\textsuperscript{1c,2b,d} (2.5mg/kg/day) led to toxicity in the animals within three to four weeks that precluded further dosing.\textsuperscript{13} We therefore sought to determine whether related compounds would have similar or enhanced potency compared with AgA (1.1).

In addition to the natural alkaloids of the family, we were particularly interested in accessing two types of derivatives arising from late-stage modifications to our strategy for synthesis of agelastatins.\textsuperscript{3} As illustrated in Figure 1.2, the AgE derivative series 1.7 includes C5-ether variants that were envisioned to be prepared by nucleophilic trapping of iminium ion 1.9, consistent with our reported preparative conditions for the conversion of AgA (1.1) to AgE (1.5).\textsuperscript{3a} Complementarily, the AgA derivative series 1.8 (Figure 1.2) includes N1-substituted analogs that

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Retrosynthetic analysis of agelastatin alkaloid derivatives.}
\end{figure}
were designed to be accessed from thioester (+)-1.17 and substituted urea 1.20 via application of our imidazolone D-ring synthesis methodology. We sought to introduce functional handles for diversification of agelastatin alkaloids while maintaining the newly discovered potency in breast cancer microenvironments.

**Review of Biological Studies of Agelastatin Alkaloids.** While recent work in the area of agelastatin alkaloids has offered new synthetic strategies, our bioinspired strategy provides the most efficient, robust, and scalable platform to access agelastatin alkaloids and remains of key importance to further studies. Diversifications of the agelastatin core have focused on the pyrrole A-ring, with a select few examples of modifications on the carbocyclic C-ring and imidazolone D-ring. In 2012, Romo proposed an alternative bioinspired approach towards agelastatin alkaloids which resulted in their synthesis of (±)-agelastatin A (1.1). The key cyclization step in this strategy relies on the nucleophilicity of the D-ring that we had previously demonstrated as a key element, and control of the absolute stereochemistry cannot be demonstrated. In follow-up reports regarding the synthesis of agelastatin derivatives and biological target identification studies, Romo and coworkers have utilized our synthetic strategy to access sufficient quantities of (−)-agelastatin A (1.1).

In 2014, Molinski and coworkers utilized isolated samples of AgA (1.1), AgC (1.3), and AgD (1.4) to synthesize an array of agelastatin derivatives for structure-activity relationship mapping and pharmacokinetic studies in chronic lymphocytic leukemia cells. Tun and Yoshimitsu have extensively studied agelastatin alkaloids in the central nervous system for treatment of brain tumors. In 2013, they reported that three chlorinated-pyrrole agelastatin analogs that maintained the desired cytotoxicity.
Modifications at the N1- and C5-positions of the agelastatin core have been the least thoroughly studied, and diversification at these two positions aligns with results of interest in our initial exploration of agelastatins in breast cancer microenvironments.\textsuperscript{12} We have developed the synthesis of two series of agelastatin derivatives (Figure 1.2) and evaluated their efficacy in blocking OPN transcription. Furthermore, we have demonstrated the increased potency of AgE (1.5) and distinct new derivatives as compared to AgA (1.1) as modulators for cancer invasion and metastasis.

**Results and Discussion**

Our studies of agelastatin alkaloid derivatives were conducted in collaboration with the Buchbaum group at Tufts Medical Center. My contribution to this study is the design and synthesis of agelastatin derivatives. Biological assays were performed by Dr. Kun Xu and were designed and analyzed in collaboration with Dr. Rachel J. Buchbaum. An outline of key agelastatin derivatives prepared for this study is illustrated in Table 1.2. Application of our methodology enables the synthesis of pre-agelastatin 1.27 that is subject to C-ring cyclization followed by C5-substitution. Under our optimal conditions (vide infra), C5-ionization of AgA (1.1) followed by nucleophilic trapping afforded the C5-substituted AgE derivative series 1.7 (Table 1.2, entries 1–11). Our versatile imidazolone synthesis methodology using the common thioester (+)-1.17 allowed for introduction of the N1-substituent in pre-agelastatin 1.27, which after cyclization afforded the desired N1-substituted AgA derivative series 1.8 (Table 1.2, entries 12–16). These new compounds offer diverse functional groups enabling additional derivatization with potential for future studies concerning agelastatin alkaloids. Importantly, our synthesis of agelastatin derivatives 1.7 and 1.8 was informed and guided by our concurrent biological studies of these
alkaloids. Specifically, our biological evaluation of AgA (1.1) and AgE (1.5) discussed herein has been critical to the design and synthesis of our agelastatin derivatives including those illustrated in Table 1.2.

Studies of AgE in Breast Cancer Microenvironments. In the aforementioned 3D assay system, AgA (1.1) at low concentrations abrogates the effects of up-regulated fibroblast OPN on cancer cell adhesion, invasion, and cancer stem cell populations. Cancer cells exposed in coculture to fibroblasts with up-regulated OPN demonstrated increased levels of lung metastasis in murine xenograft models, which were completely blocked by AgA (1.1) treatment of the cocultures.12 Given our interest in examining other agelastatins for their activity in blocking vitamin D-induced OPN transcription in fibroblasts, we first examined the other natural members of the
agelastatin alkaloid family, (-)-agelastatins B–F (1.2–1.6, Figure 1.1), prepared in our earlier synthetic studies. In our preliminary studies we only found AgA (1.1) and AgE (1.5) to have the desired activity, suggesting a possible negative influence of N1-dealkylation (AgD and AgF), C4-hydroxylation (AgC), or C14-bromination (AgB and AgF) of the agelastatin core. In initial experiments testing effects on cell proliferation, we confirmed that none of the natural agelastatin alkaloids induced cytotoxicity over a range of concentrations (25–250 nM). Given the duration of the 3D co-cultures and biologic assays, we specifically aim to use these compounds at non-cytotoxic concentrations. AgB–AgF (1.2–1.6) all have similar effects on cell viability, and even up to 250-nM concentration, none of these compounds suppress proliferation to a greater extent than AgA (1.1) at 100-nM concentration. In dose-response experiments in two-dimensional (2D) cultures, we have previously demonstrated that treatment with 100-nM AgA (1.1) results in maximal suppression of vitamin D-induced increase in OPN transcription. Interestingly our screening of the natural agelastatin alkaloids revealed that AgE (1.5) consistently blocked stimulated OPN transcription and demonstrated increased potency (Figure 1.3) in comparison to AgA (1.1), prompting future examination of new C5-substituted agelastatins in this context.

![Figure 1.3](image_url)  
**Figure 1.3.** AgE (1.5) blocks stimulated transcription of osteopontin in fibroblasts. VitD = vitamin D.
Furthermore, we tested the efficacy of AgE (1.5) in blocking the effects of up-regulated fibroblast OPN in 3D co-cultures with the breast cancer cell line SUM1315. Cancer cells were co-cultured in 3D media mixture with reduction mammary fibroblasts (RMF) with either wild-type retroviral hairpin control vector (C-RMF) or Tiam1 silencing hairpin vector (shTiam-RMF). While both control and Tiam1-deficient fibroblasts secrete OPN to some degree, fibroblasts with Tiam1 silencing have up-regulated OPN.\(^2\) Co-cultures were treated with dimethylsulfoxide (DMSO), AgA (1.1) at 75-nM concentration, or AgE (1.5) at 25-nM or 50-nM concentration. The reference concentration (75-nM) for AgA (1.1) in 3D co-culture assays was determined based on extensive prior biologic and in vivo testing over a range of concentrations, including demonstrated lack of toxicity against all cell lines used in the 3D co-cultures.\(^2\)

In the co-cultures, fibroblasts and breast cancer cells aggregate to form spheres, with the fibroblasts forming the interior core and the cancer cells on the exterior.\(^1\) SUM1315 is an aggressive breast cancer cell line, and under these conditions the cancer cells form multicellular projections extending out into the 3D matrix, with the number and/or length of the projections indicating degree of invasiveness. Co-culture with Tiam1-deficient fibroblasts promotes increased invasiveness, consistent with increased OPN secretion, seen as increased numbers of projections per sphere (Figure 1.4, column 5) as compared to control fibroblasts (Figure 1.4, column 1). Incorporation of AgA (1.1) at 75-nM concentration with Tiam1-deficient fibroblasts (Figure 1.7, column 6) decreased the number of projections to the baseline number seen with control fibroblast co-culture (Figure 1.4, column 1). Furthermore, including AgE (1.5) at 25-nM concentration (Figure 1.4, column 7) partially decreased the number of projections toward baseline, while AgE (1.5) at 50-nM concentration (Figure 1.4, column 8) reduced the number of projections to below
the baseline condition. Excitingly, these results suggest that AgE (1.5) is more potent than AgA (1.1) in decreasing the invasiveness induced by Tiam1-deficient fibroblasts.

![Bar graph showing the effect of AgA and AgE on breast cancer cell invasion](image)

**Figure 1.4.** Effect of AgA (1.1) and AgE (1.5) on breast cancer cell invasion in co-cultures with mammary fibroblasts. Number of projections per spheroid for SUM1315 breast cancer cells and indicated mammary fibroblasts in 3D mixed cell spheroid co-culture is shown as percent of total spheroids. shC = control silencing retroviral hairpin vector. shTiam = Tiam1 silencing hairpin vector.

For further assessment, we isolated the breast cancer cells from the 3D co-cultures to greater than 99% purity as described previously. Adhesion of these post-co-culture (PCC) cells was assessed through transwell migration assay (Figure 1.5). As with the invasion assay results, migration was notably increased in PCC cells exposed to Tiam1-deficient fibroblasts (Figure 1.5, column 5) compared with PCC cells exposed to control fibroblasts (Figure 1.5, column 1). This increased migration was blocked by incorporation of AgA (1.1) at 75-nM concentration in the co-cultures (Figure 1.5 column 6). Significantly, including AgE (1.5) at 25-nM and 50-nM concentrations (Figure 1.5, columns 7–8) also decreased the migration, with the 50-nM treatment decreasing the number of migrating cells below the baseline condition.
Figure 1.5. Effect of AgE (1.5) on migration potential of breast cancer cells isolated from co-culture with mammary fibroblasts.

Two assays for breast cancer stem cell populations include tumorsphere formation in low adherence culture conditions and flow cytometry for specific cell surface markers (CD44+/CD24-/ESA+). Results of both assays on the PCC cells showed analogous findings to the aforementioned invasion and migration assays. Incorporation of AgA (1.1) at 75-nM concentration completely blocked the increased numbers of tumorspheres (Figure 1.6, column 6) or cancer stem cells (Figure 1.7, column 6) induced by Tiam1-deficient fibroblasts, compared with control fibroblasts (Figures 1.6–1.7, column 1). Incorporation of AgE (1.5) at 25-nM concentration had a partial effect (Figures 1.6–1.7, column 7), while AgE (1.5) at 50-nM concentration decreased tumorsphere (Figure 1.6, column 8) and cancer stem cell (Figure 1.7, column 8) numbers below baseline. Significantly, these results consistently suggest that AgE (1.5) is more potent than AgA (1.1) in blocking the effects of fibroblast OPN on the invasiveness, migration potential, and cancer stem cell populations in associated breast cancer cells.
Figure 1.6. Effect of AgA (1.1) and AgE (1.5) on tumorsphere formation by breast cancer cells isolated from co-culture with mammary fibroblasts.

Figure 1.7. Effect of AgA (1.1) and AgE (1.5) on CD44+/CD24-/ESA+ populations in breast cancer cells isolated from co-culture with mammary fibroblasts.

With our increased understanding of the effects of the agelastatin alkaloids in breast cancer microenvironments, particularly the observation that AgE (1.5) showed increased potency as compared to AgA (1.1), we sought to prepare the two series of agelastatin derivatives illustrated in Table 1.2 and study their biological effects on breast cancer invasiveness.
Development of Agelastatin E Derivatives. We envisioned the preparation of AgE derivative series 1.7 would require similar conditions to those we developed for the direct conversion of the C5-hydroxy group of AgA (1.1) to the C5-methoxy group of AgE (1.5).\textsuperscript{3a} In the event, treatment of AgA (1.1) with methanesulfonic acid to promote the formation of C5-iminium ion 1.9 (Figure 1.2), followed by in situ trapping with a series of nucleophiles afforded the agelastatin derivatives 1.7a–1.7f (Table 1.3). Condensation of commercially available 3-butyn-1-ol and 3-buten-1-ol with AgA (1) provided the desired derivatives 1.7a and 1.7b, respectively (Table 1.3, entries 1–2). The use of 3-mercaptopropiophenone\textsuperscript{19} as the nucleophile afforded the C5-sulfide derivative 1.7c (Table 1.3, entry 3). The carbamate derivative 1.7d was prepared using the corresponding trimethylsilyl ethoxy carbamate-protected 4-aminobutan-1-ol as the nucleophile (Table 1.3, entry 4). Similarly, the condensation of 3-azidopropan-1-ol and 4-azidobutan-1-ol\textsuperscript{20} with AgA (1.1) resulted in formation of azide derivatives 1.7e and 1.7f, respectively (Table 1.3, entries 5–6). These derivatives provided functional groups amenable to further diversification for use in concurrent biological evaluation.

\begin{table}[h]
\centering
\begin{tabular}{c c c c}
entry & $R^1X$ & derivative & yield \\
\hline
1 & $\equiv C\equiv$ & 1.7a & 87% \\
2 & $\equiv C\equiv$ & 1.7b & 68% \\
3 & Ph & 1.7c & 93% \\
4 & Me$_3$Si & 1.7d & 63% \\
5$^*$ & $N_3$ & 1.7e, $n = 1$ & 74% \\
6$^*$ & $O$ & 1.7f, $n = 2$ & 76% \\
\hline
\end{tabular}
\caption{Synthesis of AgE derivatives 1.7a–1.7f from AgA (1.1). Conditions: (a) MeSO$_3$H, CH$_3$CN. *CH$_2$Cl$_2$ used as solvent.}
\end{table}
Azide derivatives 1.7e and 1.7f were reduced to the corresponding amines 1.7g and 1.7h, respectively, under Staudinger reaction conditions (Scheme 1.4). The primary amine 1.7g was converted to carbamate 1.7i upon treatment with 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate in the presence of triethylamine. Likewise, primary amine 1.7h was converted to acetamide 1.7j and benzamide 1.7k upon exposure to acetic anhydride and benzoyl chloride, respectively. This subset of AgE derivatives provided compounds with a range of linker length along with azide, amine, amide, and carbamate functional groups for our biological evaluation and comparison with AgA (1.1) and AgE (1.5) as modulators of breast cancer invasiveness (vide infra).

Scheme 1.4. Chemical diversification of AgE derivatives 1.7e–1.7h. Conditions: (a) PPh₃, THF-H₂O (9:1). (b) 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate, NEt₃, CH₂Cl₂. (c) Ac₂O, NEt₃, DMAP, THF. (d) BzCl, NEt₃, THF.

**Development of Agelastatin A Derivatives.** The application of our synthetic methodology³ for the introduction of substituents at the N1-position of agelastatins necessitated the preparation of urea-based organostannane reagent 1.20 (Table 1.4). The cyclohexyl substituent
of organostannane 1.20 was chosen to minimize undesired alkyl transfer during the cross-coupling step, which was previously observed utilizing n-butyl substituted stannanes. The use of substituted urea 1.20 in our convergent synthesis of substituted imidazolones enabled access to the corresponding N1-substituted pre-agelastatins en route to the desired AgA derivatives. Through the use of 1,1'-carbonyldiimidazole as a phosgene equivalent, we were able to access the versatile intermediate 1.30 that was converted to substituted ureas 1.20a–1.20c upon treatment with the desired primary amine (Table 1.4).3,22

![Chemical structure](image)

**Table 1.4.** Synthesis of substituted ureas 1.20a–1.20c. Conditions: (a) 1,1'-carbonyldiimidazole, DMAP, CH₂Cl₂, 85%. (b) DMAP, CH₂Cl₂, 40 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>R²-</th>
<th>derivative</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO</td>
<td>1.20a, n = 1</td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td>HO</td>
<td>1.20b, n = 3</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>HO</td>
<td>1.20c</td>
<td>84%</td>
</tr>
</tbody>
</table>

The copper-mediated coupling of substituted urea 1.20 with versatile thioester (+)-1.17 directly provided the N1-substituted imidazolone 1.27 that served as the substrate for our C-ring cyclization chemistry to afford the AgA derivative series 1.8 (Table 1.5).3 The use of N1-substituents with a primary alcohol functional group was envisioned to enable post-cyclization diversification of the agelastatin core in analogy with the C5-ether series. Pre-agelastatins 1.27b and 1.27c provided modest yield of the corresponding N1-substituted agelastatin derivatives 1.8b and 1.8c, respectively (Table 1.5, entries 2–3). Interestingly, the shorter 4-methylene spacer pre-agelastatin 1.27a provided the N1-substituted AgA derivative 1.8a (Table 1.5, entry 1) along with the pentacyclic agelastatin derivative 1.28 (Scheme 1.5). The inefficient formation of agelastatin derivative 1.8a is likely due to competitive intramolecular trapping of the C5-iminium ion 1.31 to
afford the pentacyclic derivative 1.28 (Scheme 1.5). Notably, ether 1.28 serves as a link between AgE and AgA derivatives, including both N1- and C5-modifications. An anticipated slower rate of intramolecular cyclization using the longer N1-substituents in pre-agelastatins 1.27b and 1.27c is consistent with the observed greater, albeit modest, yield of the corresponding derivatives 1.8b and 1.8c, respectively (Table 1.5).

Table 1.5. Synthesis of AgA derivatives 1.8a–1.8c using copper-mediated coupling. Conditions: (a) CuTC, THF, 50 ºC; HCl, MeOH, 50 ºC. (b) MeSO₃H, H₂O, 100 ºC. CuTC = copper (I) thiophene-2-carboxylate. *1.8a was isolated along with pentacyclic derivative 1.28 (11%).

<table>
<thead>
<tr>
<th>entry</th>
<th>R²</th>
<th>derivative</th>
<th>yield (1.27,1.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO</td>
<td>1.8a, n = 1</td>
<td>59%, 3ºa</td>
</tr>
<tr>
<td>2</td>
<td>HO</td>
<td>1.8b, n = 3</td>
<td>67%, 36%</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>1.8c</td>
<td>61%, 30%</td>
</tr>
</tbody>
</table>

Scheme 1.5. Observed double cyclization of tricycle 1.29a to pentacycle 1.28. Conditions: (a) MeSO₃H, H₂O, 100 ºC.

The primary alcohol of the N1-substituent of AgA derivatives 1.8a–1.8c presents an opportunity for introduction of an azide functional group that may be used in the future for further modifications similar to those accomplished in the AgE derivative series 1.7. Indeed, using the more readily accessible alcohols 1.8b and 1.8c, we prepared the corresponding azide derivatives.
in a single step (Scheme 1.6). The primary alcohol 1.8b was converted to the agelastatin azide 1.8d in 38% yield, along with 34% recovery of the starting material. When using more forcing conditions required for complete conversion of the more recalcitrant triethylene glycol derivative 1.8c to the corresponding azide, we observed the formation of bis-azide 1.8e consistent with an additional C5-azidation. Interestingly, mass spectrometric analysis of bis-azide 1.8e shows consistency with other AgA derivatives in formation of its corresponding C5-iminium ion as a major observed molecular ion. We were excited to explore bis-azide 1.8e in our biological screening conditions, as this is the first example of azide substitution at the C5-position of the agelastatin alkaloids. The covalent linkage of the alcohol and azide functional groups offered in the AgA derivatives 1.8a–1.8e was designed to be complementary to the ionizable linkage present in the AgE derivative series 1.7.

Scheme 1.6. Chemical diversification of AgA derivatives 1.8b and 1.8c to the corresponding azides. Conditions: PPh₃ (n equiv), diisopropylazodicarboxylate (n equiv), diphenyl phosphoryl azide (n equiv), THF. (a) n = 2, 1.8d isolated along with 34% recovered starting material. (b) n = 10.

Biological Study of Agelastatin Alkaloid Derivatives. As we accessed a variety of agelastatin derivatives as described, we systematically compared them to AgA (1.1) and AgE (1.5)
for efficacy in blocking vitamin D-induced OPN transcription. The results of these investigations with selected and most informative derivatives are summarized in Figure 1.8. Based on our prior work with AgA (1.1)\textsuperscript{12} the 100-nM concentration is our standard concentration used for screening large numbers of compounds, which is well within the non-cytotoxic range for all natural agelastatin alkaloids in the proliferation assays described above. Furthermore, upon treatment with agelastatin derivatives, all cells were observed to grow at equal rates and require equal handling during passage in culture, indicating similar effects on proliferation and viability.\textsuperscript{23} Of particular interest in our initial screens were the AgE derivative carbamate 1.7d and the AgA derivative azide 1.8d. In further studies of AgA derivatives, the triethylene glycol linked bis-azide 1.8e showed improved efficacy in our assays. Indeed, bis-azide 1.8e at 94-nM concentration demonstrates statistical equivalence to AgE (1.5) at 50-nM concentration in blocking vitamin D-induced OPN transcription. We designed AgE derivatives 1.7i–1.7k (Scheme 1.6) in an effort to better understand the promising potency of carbamate 1.7d in our preliminary assays. Our aim was to differentiate between the aspects of the linker that led to increased potency, such as the electronic properties, steric factors, and linker length. Interestingly, the 4-methylene linked carbamate 1.7d maintained slightly improved potency compared to the related 3-methylene linked carbamate 1.7i, consistent with the notion that the linker length is important to maintaining the desired inhibitory activity. While acetamide derivative 1.7j maintains the substituent chain length of carbamate 1.7d, its comparatively decreased activity suggests that the acetamide group is not as effective as the larger trimethylsilyl ethoxy substituent of carbamate 1.7d. Benzamide derivative 1.7k excitingly showed the desired potency comparable to carbamate 1.7d by preserving the substituent chain length of carbamate 1.7d while offering a larger amide group as compared to acetamide 1.7j. Notably, these results highlight the notion that both N1- and C5-substitution are not only tolerated
in agelastatins with potency in modulation of breast cancer invasiveness, but also have already offered ample opportunities to access compounds that begin to approach our newly discovered potency of AgE (1.5) in this context. We envision the chemistry described herein to enable access to a wide range of new synthetic AgA and AgE derivatives as potential modulators of breast cancer invasion and metastasis.

![Graph](image)

**Figure 1.8.** Varying effects of agelastatin derivatives in blocking stimulated fibroblast expression of osteopontin. All agelastatin derivatives were tested at 100-nM concentration unless noted otherwise. * indicates statistical equivalence with AgA (1.1) at 100-nM concentration; ** indicates equivalence with AgE (1.5) at 50-nM concentration, but not AgA (1.1) at 100-nM concentration by T-test (at 95% confidence interval; Dr. Buchsbaum, personal communication). No Tx = baseline control with values normalized to transcription of a housekeeping gene.

**Conclusion**

We demonstrate that AgE (1.5) is more potent than AgA (1.1) in blocking fibroblast-mediated effects on cancer cell invasion, migration, and cancer stem cell populations. Importantly, we have established non-cytotoxic doses for the delivery of agelastatin alkaloids to breast cancer microenvironments in order to study their activity in blocking induced OPN transcription in fibroblasts, which can modulate these cancer cell behaviors. Based on the exciting recognition of the potent activity of AgE (1.5) and AgA (1.1) in this context, we embarked on the synthesis of a variety of C5- and N1-substituted agelastatin derivatives, culminating in the AgE and AgA derivative series 1.7 and 1.8, respectively (Table 1.2). Highlights of our synthetic strategy include
efficient C5-derivatization of AgA (1.1) using a variety of nucleophiles based on our conversion of AgA (1.1) to AgE (1.5),\textsuperscript{3} selective N1-functionalization using our imidazolone synthesis methodology,\textsuperscript{3} and diversification of complex agelastatin derivatives and establishment of precedence for access to more complex synthetic derivatives. Furthermore, we demonstrate that our new derivatives $1.7d$ and $1.7k$ (100-nM concentration) as well as derivative $1.8e$ (94-nM concentration) are statistically equivalent to AgE (1.5) at 50-nM concentration. The chemistry described here provides a foundation for rapid access to agelastatin derivatives with high potency (50–100 nM) as modulators for cancer invasion and metastasis. Our findings highlight the outstanding potential for the development of potent agelastatin derivatives with functional handles for further chemical derivatization and biological applications.
Mice developed hunched posture, decreased mobility, fur ruffling, and lack of weight gain, leading to termination of experiment per established animal protocol guidelines.


(5) Yields in Scheme 1.2 represent results obtained by the author.


(9) Xu, K.; Buchsbaum, R. J. Vis. Exp. 2012, 62, e3760.


(13) Mice developed hunched posture, decreased mobility, fur ruffling, and lack of weight gain, leading to termination of experiment per established animal protocol guidelines.


(18) These studies were analogous with those detailed in reference 12 for (-)-agelasatin A.


(23) In prior assays of the natural agelasatin alkaloids, we have observed that differential activity against stimulated OPN transcription in 2D assays correlates exactly with differential potency in the more complex biologic assays.
EXPERIMENTAL SECTION

**General Procedures.** All reactions were performed in oven-dried or flame-dried round-bottom flasks. The flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of argon. Cannulae or gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Where necessary (so noted) solutions were deoxygenated by argon purging for a minimum of 10 min. Flash column chromatography was performed as described by Still et al. using granular silica gel (60-Å pore size, 40–63 µm, 4–6% H₂O content). Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to short wave ultraviolet light (254 nm) and irreversibly stained by treatment with an aqueous solution of ceric ammonium molybdate (CAM) or an aqueous solution of potassium permanganate (KMnO₄) or an alcoholic solution of ninhydrin, followed by heating (~1 min) on a hot plate (~250 °C). Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of ~2 Torr, then at ~0.5 Torr (vacuum pump) unless otherwise indicated. Proton (¹H) and carbon (¹³C) nuclear magnetic resonance spectra were recorded with 600 MHz, 500 MHz, and 400 MHz spectrometers. Proton nuclear magnetic resonance (¹H NMR) spectra are reported in parts per million on the δ scale and are referenced from the residual protium in the NMR solvent [CDCl₃: δ 7.26 (CHCl₃), CD₃OD: δ 3.31 (CD₂HOD), DMSO-d₆: δ 2.50 (DMSO-d₃)]. Data are reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constant(s) in Hertz, integration). Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra are recorded in parts per million on the δ scale and are referenced from the carbon signals of the solvent (CDCl₃: δ 77.16, CD₃OD: δ 49.15, DMSO-d₆: δ 39.52). Infrared data (IR) were obtained with a FTIR and are reported as follows: [frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad)]. High-resolution mass spectrometric data (HRMS) were recorded on a Fourier transform ion cyclotron resonance mass spectrometer (FTICR-MS) using electrospray ionization (ESI) source or direct analysis in real time (DART) ionization source.

**Positional Numbering System.** In assigning the ¹H and ¹³C data of all intermediates en route to our synthetic derivatives, we have employed a uniform numbering system consistent with that of the final targets.

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General Procedure for the Synthesis of AgE Derivatives 1.7a–1.7f

Methanesulfonic acid (10 equiv) was added slowly to a solution of (−)-agelastatin A (1 equiv) and nucleophile in acetonitrile or dichloromethane. Upon consumption of starting material as shown by thin layer chromatography, the reaction mixture was diluted with ethyl acetate or dichloromethane as indicated (10 mL). Reactions conducted over molecular sieves were filtered through a plug of cotton and further diluted with the indicated solvent (10 mL). The crude organic mixture was washed sequentially with saturated aqueous sodium bicarbonate solution (2 × 15 mL) and saturated aqueous sodium chloride solution (1 × 10 mL). The combined aqueous layers were extracted with organic solvent (2 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to afford AgE derivatives 1.7a–1.7f.

Alkyne Derivative 1.7a:

Alkyne derivative 1.7a was synthesized according to the general procedure for synthesis of AgE derivatives using 3-butyln-1-ol (0.5 mL) and acetonitrile (2.5 mL) over 4Å molecular sieves (30 mg). After 17.5 h, the crude residue after work-up using ethyl acetate was purified by flash column chromatography on silica gel (eluent: 10% acetone in dichloromethane, then 5% → 10% methanol in dichloromethane) to afford alkyne 1.7a (10.0 mg, 87.0%) as a white solid.

$^1$H NMR (500 MHz, CD$_3$OD, 23 °C):

$^13$C NMR (125 MHz, CD$_3$OD, 23 °C):

FTIR (thin film) cm$^{-1}$

HRMS (ESI) (m/z):

calc’d for C$_{16}$H$_{18}$BrN$_4$O$_3$, [M+H]$^+$: 393.0557, found: 393.0552.

TLC (10% methanol in dichloromethane), Rf: 0.69 (UV, CAM).
Alkene Derivative 1.7b:
Alkene derivative 1.7b was synthesized according to the general procedure for synthesis of AgE derivatives using 3-buten-1-ol (0.5 mL) and acetonitrile (2.5 mL) over 4Å molecular sieves (30 mg). After 18 h, the crude residue after work-up using ethyl acetate was purified by flash column chromatography on silica gel (eluent: 10% acetone in dichloromethane, then 5% → 10% methanol in dichloromethane) to afford alkene 1.7b (8.1 mg, 68%) as a white solid.

\(^1\)H NMR (500 MHz, CD\(_3\)OD, 23 °C):
δ 6.91 (d, \(J = 4.1\) Hz, 1H), 6.33 (d, \(J = 4.2\) Hz, 1H), 5.93–5.77 (m, 1H), 5.17–5.00 (m, 2H), 4.61 (dt, \(J = 12.2, 5.9\) Hz, 1H), 4.11 (d, \(J = 5.4\) Hz, 1H), 4.08 (s, 1H), 3.42 (q, \(J = 7.6\) Hz, 1H), 3.31–3.21 (m, 1H), 2.78 (s, 3H), 2.66 (dd, \(J = 13.4, 6.5\) Hz, 1H), 2.35 (q, \(J = 6.8\) Hz, 2H), 2.16 (t, \(J = 12.8\) Hz, 1H).

\(^13\)C NMR (125 MHz, CD\(_3\)OD, 23 °C):

FTIR (thin film) cm\(^{-1}\):
2926 (w), 1668 (s), 1551 (w), 1425 (m), 1091 (w), 747 (w).

HRMS (ESI) (m/z):
calc’d for C\(_{16}\)H\(_{20}\)BrNaO\(_3\), [M+H]\(^+\): 395.0713, found: 395.0692.

TLC (10% methanol in dichloromethane), \(R_f\): 0.43 (UV, CAM).
Sulfide Derivative 1.7c:

Sulfide derivative 1.7c was synthesized according to the general procedure for synthesis of AgE derivatives using 3-mercaptopropiophenone\(^2\) (99.7 mg, 6.00 \times 10^2 \mu\text{mol}, 20.5 \text{ equiv}) in acetonitrile (3.0 mL) over 4Å molecular sieves (20 mg). After 1 h, the crude residue after work-up using ethyl acetate was purified by flash column chromatography on silica gel (eluent: 0\% \rightarrow 10\% methanol in dichloromethane) to afford sulfide 1.7c (13.6 mg, 92.5\%) as a white solid.

\(^1\)H NMR (400 MHz, CD\(_3\)OD, 23 °C):

\[ \delta 8.04-7.94 \text{ (m, 2H)}, 7.65-7.58 \text{ (m, 1H)}, 7.54-7.47 \text{ (m, 2H)}, 6.91 \text{ (d, } J = 4.1 \text{ Hz, 1H)}, 6.32 \text{ (d, } J = 4.1 \text{ Hz, 1H)}, 4.78 \text{ (dt, } J = 11.8, 6.1 \text{ Hz, 1H)}, 4.47 \text{ (s, 1H)}, 4.19 \text{ (d, } J = 5.4 \text{ Hz, 1H)}, 3.35 \text{ (t, } J = 6.9 \text{ Hz, 2H)}, 2.91 \text{ (dd, } J = 12.5, 6.9 \text{ Hz, 1H)}, 2.87 \text{ (s, 3H)}, 2.81-2.67 \text{ (m, 2H)}, 1.95 \text{ (dd, } J = 13.5, 11.7 \text{ Hz, 1H}).\]

\(^1\)C NMR (100 MHz, CD\(_3\)OD, 23 °C):

\[ \delta 199.7, 161.6, 161.0, 138.0, 134.7, 130.0, 129.3, 124.3, 116.3, 114.1, 107.5, 77.9, 67.5, 63.4, 54.8, 41.0, 38.8, 25.2, 24.1.\]

FTIR (thin film) cm\(^{-1}\):

2920 (w), 2361 (w), 1667 (s), 1551 (w), 1423 (m), 1195 (w).

HRMS (ESI) (m/z):

calc’d for C\(_{21}\)H\(_{22}\)BrN\(_4\)O\(_3\)S, [M+H]\(^+\): 489.0591, found: 489.0595.

TLC (5\% methanol in dichloromethane), Rf:

0.46 (UV, CAM).

4-Methylene Carbamate Derivative 1.7d:
4-Methylene carbamate derivative 1.7d was synthesized according to the general procedure for synthesis of AgE derivatives using 2-(trimethylsilyl)ethyl (4-hydroxybutyl)carbamate\(^3\) (1.40 \times 10^2 \text{ mg}, 6.00 \times 10^2 \text{ mmol}, 20.5 \text{ equiv}) in acetonitrile (3.0 mL) over 4Å molecular sieves (25 mg). After 3 h, the crude residue after work-up using ethyl acetate was purified by flash column chromatography on silica gel (eluent: 20\% \rightarrow 30\% acetone in dichloromethane, then 5\% \rightarrow 10\% methanol in dichloromethane) to afford 4-methylene carbamate 1.7d (10.5 mg, 62.9\%) as a white solid.

\(^1\)H NMR (400 MHz, CD\(_3\)OD, 23 °C):
\[\delta 6.89 (d, J = 4.1 \text{ Hz}, 1\text{H}), 6.31 (d, J = 4.1 \text{ Hz}, 1\text{H}), 4.59 (dt, J = 12.1, 6.0 \text{ Hz}, 1\text{H}), 4.17–4.05 (m, 4\text{H}) 3.36 (dt, J = 9.0, 5.8 \text{ Hz}, 1\text{H}), 3.24 (dt, J = 9.1, 5.8 \text{ Hz}, 1\text{H}), 3.08 (td, J = 6.8, 4.3 \text{ Hz}, 2\text{H}), 2.76 (s, 3\text{H}), 2.68–2.60 (m, 1\text{H}), 2.20–2.10 (m, 1\text{H}), 1.65–1.49 (m, 4\text{H}), 0.99–0.92 (m, 2\text{H}), 0.02 (s, 9\text{H}).\]

\(^{13}\)C NMR (100 MHz, CD\(_3\)OD, 23 °C):
\[\delta 161.9, 161.1, 159.5, 124.2, 116.2, 114.0, 107.5, 99.9, 63.9, 63.7, 62.3, 61.7, 53.8, 41.4, 39.4, 27.9, 27.8, 24.9, 18.8, -1.3.\]

FTIR (thin film) cm\(^{-1}\):
2949 (w), 1669 (s), 1489 (w), 1423 (m), 1249 (m), 1106 (w), 835 (m), 747 (m).

HRMS (ESI) (m/z):
calc’d for C\(_{22}\)H\(_{35}\)BrN\(_3\)O\(_5\)Si, [M+H]\(^{+}\): 556.1585, found: 556.1567.

TLC (10\% methanol in dichloromethane), R\(_f\):
0.59 (UV, CAM).

---

3-Methylene Azide Derivative 1.7e:

3-Methylene azide derivative 1.7e was synthesized according to the general procedure for synthesis of AgE derivatives using 3-azidopropan-1-ol\(^4\) (415 mg, 4.10 mmol, 20.0 equiv) in dichloromethane (13 mL). The reaction mixture became homogeneous upon addition of methanesulfonic acid. After 14 h, the reaction mixture was diluted with dichloromethane and quenched with aqueous sodium hydroxide solution (0.5 N, 20 mL) before general work-up procedure using dichloromethane. The crude residue was purified by flash column chromatography on silica gel (eluent: 20% acetone in dichloromethane, then 5% → 10% methanol in dichloromethane) to afford 3-methylene azide 1.7e (64.4 mg, 74.0%) as a white solid.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\), 23 °C):
\[\delta 7.96 (s, 1H), 7.34 (d, J = 2.1 Hz, 1H), 6.74 (d, J = 4.0 Hz, 1H), 6.35 (d, J = 4.0 Hz, 1H), 4.41 (dt, J = 12.0, 5.9 Hz, 1H), 4.02 (d, J = 5.4 Hz, 1H), 3.97 (d, J = 1.8 Hz, 1H), 3.41 (td, J = 6.6, 2.6 Hz, 2H), 3.28 (dt, J = 9.3, 6.2 Hz, 1H), 3.24–3.17 (m, 1H), 2.65 (s, 3H), 2.56–2.51 (m, 1H), 1.99 (t, J = 12.6 Hz, 1H), 1.79 (p, J = 6.5 Hz, 2H).

\(^1\)3C NMR (125 MHz, DMSO-\(d_6\), 23 °C):
\[\delta 158.7, 157.6, 123.6, 113.5, 112.0, 104.7, 97.5, 60.1, 59.5, 59.3, 51.9, 47.8, 37.7, 28.3, 23.9.

FTIR (thin film) cm\(^{-1}\):
\[2928 \text{ (w)}, 2097 \text{ (w)}, 1666 \text{ (s)}, 1549 \text{ (w)}, 1423 \text{ (m)}, 1348 \text{ (w)}, 1107 \text{ (w)}, 746 \text{ (m)}.

HRMS (DART) (m/z):
calc'd for C\(_{15}\)H\(_9\)BrN\(_7\)O\(_3\), [M+H]\(^+\): 424.0727, found: 424.0717.

TLC (10% methanol in dichloromethane), R\(_f\):
\[0.53 \text{ (UV, CAM)}.

4-Methylene Azide Derivative 1.7f:

4-Methylene azide derivative 1.7f was synthesized according to the general procedure for synthesis of AgE derivatives using 4-azidobutan-1-ol\(^4\) (276 mg, 2.40 mmol, 20.0 equiv) in dichloromethane (8.0 mL). The reaction mixture became homogeneous upon addition of methanesulfonic acid. After 26 h, the reaction mixture was diluted with dichloromethane and quenched with aqueous sodium hydroxide solution (0.5 N, 20 mL) before general work-up procedure using dichloromethane. The crude residue was purified by flash column chromatography on silica gel (eluent: 20% acetone in dichloromethane, then 5% → 10% methanol in dichloromethane) to afford 4-methylene azide 1.7f (39.8 mg, 75.7%) as a white solid.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\), 23 °C):
δ 7.97 (s, 1H), 7.31 (d, \(J = 2.0\) Hz, 1H), 6.74 (d, \(J = 3.9\) Hz, 1H), 6.35 (d, \(J = 4.0\) Hz, 1H), 4.41 (dt, \(J = 11.9, 6.0\) Hz, 1H), 4.01 (d, \(J = 5.4\) Hz, 1H), 3.97 (d, \(J = 2.2\) Hz, 1H), 3.37–3.34 (m, 2H), 3.28–3.19 (m, 1H), 3.19–3.11 (m, 1H), 2.64 (s, 3H), 2.58–2.51 (m, 1H), 1.98 (t, \(J = 12.5\) Hz, 1H), 1.64–1.54 (m, 4H).

\(^13\)C NMR (125 MHz, DMSO-\(d_6\), 23 °C):
δ 158.7, 157.6, 123.6, 113.5, 112.0, 104.7, 97.5, 61.6, 60.1, 59.4, 51.9, 50.5, 37.8, 26.3, 25.4, 24.0.

FTIR (thin film) cm\(^{-1}\):
2925 (w), 2097 (w), 1668 (s), 1549 (w), 1424 (m), 1107 (w), 745 (w).

HRMS (DART) (\(m/z\)):
calc’d for C\(_{16}\)H\(_{21}\)BrN\(_7\)O\(_3\), [M+H]\(^{+}\): 438.0884, found: 438.0875.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R\(_f\): 0.43 (UV, CAM).
General Procedure for Staudinger Reduction of Azide Derivatives

Triphenylphosphine (2.40 equiv) was added to a suspension of azide derivative (1 equiv) in tetrahydrofuran–water (9:1, 0.1 M). Upon consumption of starting material as shown by thin layer chromatography, the reaction mixture was diluted with dichloromethane and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (eluent: 0 → 10% methanol in dichloromethane, then 18% methanol and 2% ammonium hydroxide in chloroform) to afford amines 1.7g–1.7h.

3-Methylene Amine Derivative 1.7g:

3-Methylene amine derivative 1.7g was synthesized according to the general procedure for Staudinger reduction of azide derivatives using 3-methylene azide 1.7e (26.5 mg, 62.5 µmol, 1 equiv). After 3.5 days, the crude residue was purified by flash column chromatography on silica gel to afford amine 1.7g (21.9 mg, 88.0%) as a white solid.

\[ \text{1H NMR (400 MHz, CD}_3\text{OD, 23 °C):} \]
\[ \delta 6.91 \text{ (d, } J = 4.1 \text{ Hz, } 1\text{H}) , \ 6.33 \text{ (d, } J = 4.1 \text{ Hz, } 1\text{H}) , \ 4.62 \text{ (dt, } J = 12.0, 6.0 \text{ Hz, } 1\text{H}) , \ 4.12 \text{ (d, } J = 5.5 \text{ Hz, } 1\text{H}) , \ 4.09 \text{ (s, } 1\text{H}) , \ 3.50–3.37 \text{ (m, } 1\text{H}) , \ 3.34–3.31 \text{ (m, } 1\text{H}) , \ 2.79 \text{ (s, } 3\text{H}) , \ 2.74 \text{ (t, } J = 7.0 \text{ Hz, } 2\text{H}) , \ 2.71–2.63 \text{ (m, } 1\text{H}) , \ 2.16 \text{ (t, } J = 12.7 \text{ Hz, } 1\text{H}) , \ 1.76 \text{ (p, } J = 6.5 \text{ Hz, } 2\text{H}). \]

\[ \text{13C NMR (100 MHz, CD}_3\text{OD, 23 °C):} \]
\[ \delta 161.9, \ 161.1, \ 124.2, \ 116.2, \ 114.0, \ 107.5, \ 99.9, \ 62.2 \text{ (2C), } 61.7, \ 53.8, \ 39.9, \ 39.4, \ 33.3, \ 24.9. \]

\[ \text{FTIR (thin film) cm}^{-1} \]
\[ 2925 \text{ (w), } 2359 \text{ (w), } 1695 \text{ (m), } 1652 \text{ (s), } 1550 \text{ (m), } 1424 \text{ (m), } 1096 \text{ (w), } 745 \text{ (w)}. \]

\[ \text{HRMS (DART) (m/z):} \]
\[ \text{calc'd for } \text{C}_{13}\text{H}_{21}\text{BrN}_3\text{O}_3, \ [M+H]^+: \ 398.0822, \text{ found: } 398.0823. \]

\[ \text{TLC (18% methanol, 2% ammonium hydroxide in chloroform), } R_f: \ 0.07 \text{ (UV, CAM, ninhydrin).} \]
4-Methylene Amine Derivative 1.7h:

4-Methylene amine derivative 1.7h was synthesized according to the general procedure for Staudinger reduction of azide derivatives using 4-methylene azide 1.7f (29.0 mg, 66.2 µmol, 1 equiv). After 3 days, the crude residue was purified by flash column chromatography on silica gel to afford 4-methylene amine 1.7h (26.6 mg, 97.4%) as a white solid.

\(^1\)H NMR (500 MHz, CD\(_3\)OD, 23 °C):

\[ \delta 6.91 (d, J = 4.1 \text{ Hz}, 1H), 6.33 (d, J = 3.9 \text{ Hz}, 1H), 4.61 (dt, J = 12.1, 6.0 \text{ Hz}, 1H), 4.12 (d, J = 5.4 \text{ Hz}, 1H), 4.08 (s, 1H), 3.38 (dt, J = 9.1, 5.9 \text{ Hz}, 1H), 3.26 (dt, J = 9.1, 6.1 \text{ Hz}, 1H), 2.78 (s, 3H), 2.71–2.63 (m, 3H), 2.15 (t, J = 12.7 \text{ Hz}, 1H), 1.69–1.50 (m, 4H). \]

\(^13\)C NMR (125 MHz, CD\(_3\)OD, 23 °C):

\[ \delta 161.8, 161.1, 124.2, 116.2, 114.0, 107.5, 99.8, 63.9, 62.2, 61.7, 53.8, 42.3, 39.4, 30.3, 28.1, 24.9. \]

FTIR (thin film) cm\(^{-1}\)

\[ 2926 (w), 2359 (w), 1652 (s), 1550 (m), 1423 (s), 1303 (w), 1096 (m), 745 (m). \]

HRMS (ESI) (m/z):

\[ \text{calc’d for } C_{16}H_{23}BrN_5O_3, [M+H]^+ : 412.0979, \text{ found: } 412.0994. \]

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R\(_f\): 0.08 (UV, CAM, ninhydrin).
3-Methylene Carbamate Derivative 1.7i:

A solution of 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate (5.8 mg, 21 µmol, 1.2 equiv) in dichloromethane (20 µL) was added to a solution of 3-methylene amine 1.7g (6.8 mg, 17 µmol, 1 equiv), triethylamine (3.6 µL, 26 µmol, 1.5 equiv), and 4-dimethylaminopyridine (0.4 mg, 3 µmol, 0.2 equiv) in dichloromethane (170 µL). After 26 h, the reaction mixture was diluted with dichloromethane (1 mL) and purified by flash column chromatography on silica gel (eluent: 20% acetone in dichloromethane, then 0 → 18 % methanol and 2% ammonium hydroxide in chloroform) to afford 3-methylene carbamate 1.7i (8.7 mg, 94%) as a white solid.

\[ \text{H NMR (500 MHz, CD}_3\text{OD, 23 }^\circ\text{C):} \]
\[ \delta 6.92 (d, J=4.2 \text{ Hz}, 1H), 6.34 (d, J=3.9 \text{ Hz, } 1H), 4.61 (dt, J=12.1, 6.0 \text{ Hz, } 1H), 4.15-4.10 (m, 3H), 4.08 (s, 1H), 3.43-3.34 (m, 1H), 3.30-3.11 (m, 3H), 2.78 (s, 3H), 2.71-2.63 (m, 1H), 2.17 (t, J=12.7 \text{ Hz, } 1H), 1.77 (p, J=6.3 \text{ Hz, } 2H), 1.03-0.93 (m, 2H), 0.05 (s, 9H). \]

\[ \text{C NMR (125 MHz, CD}_3\text{OD, 23 }^\circ\text{C):} \]
\[ \delta 161.8, 161.1, 159.5, 124.2, 116.2, 114.0, 107.5, 99.9, 64.0, 62.2, 61.6 (2C), 53.8, 39.4, 39.0, 31.0, 24.9, 18.8, -1.3. \]

FTIR (thin film) cm\(^{-1}\):
2950 (w), 1698 (s), 1661 (s), 1552 (w), 1424 (m), 1250 (w), 838 (w).

HRMS (DART) (m/z):
calc’d for C\(_{21}\)H\(_{33}\)BrN\(_3\)O\(_5\)Si, [M+H]\(^+\):
542.1429, found: 542.1429.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.63 (UV, CAM).

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**General Procedure for Acylation of Amines**

Acylating reagent (2.0 equiv) was added to a solution of amine derivative (1 equiv) and triethylamine (2.0 equiv) in tetrahydrofuran (400 µL). Upon complete conversion of starting material as shown by thin layer chromatography, the reaction mixture was diluted with dichloromethane (3 mL) and quenched with saturated aqueous sodium bicarbonate solution (3 mL). Layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (eluent: 0 → 7% methanol in dichloromethane, then 9% methanol and 1% ammonium hydroxide in chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford amides 1.7j–1.7k.

![Chemical structure](image)

**Acetamide Derivative 1.7j:**

Acetamide derivative 1.7j was synthesized according to the general procedure for acylation of amine derivatives using acetic anhydride and amine 1.7h (6.8 mg, 17 µmol, 1 equiv) with 4-dimethylaminopyridine (0.4 mg, 3 µmol, 0.2 equiv) additive. After 2.5 h, the crude residue after work-up was purified by flash column chromatography on silica gel to afford acetamide 1.7j (5.5 mg, 73%) as a white solid.

\[
\begin{align*}
\text{H NMR} (500 \text{ MHz, CD}_3\text{OD}, 23 ^\circ\text{C}): & \quad \delta 6.91 \text{ (d, } J= 4.1 \text{ Hz, 1H)}, 6.33 \text{ (d, } J= 4.0 \text{ Hz, 1H)}, 4.61 \text{ (dt, } J= 12.1, 6.1 \text{ Hz, 1H)}, 4.12 \text{ (d, } J= 5.5 \text{ Hz, 1H)}, 4.10 \text{ (s, 1H)}, 3.42–3.36 \text{ (m, 1H)}, 3.29–3.12 \text{ (m, 3H)}, 2.79 \text{ (s, 3H)}, 2.70–2.63 \text{ (m, 1H)}, 2.15 \text{ (t, } J= 12.7 \text{ Hz, 1H)}, 1.93 \text{ (s, 3H)}, 1.66–1.53 \text{ (m, 4H)}. \\
\text{C NMR} (125 \text{ MHz, CD}_3\text{OD}, 23 ^\circ\text{C}): & \quad \delta 173.4, 161.9, 161.1, 124.2, 116.2, 114.0, 107.5, 99.9, 63.7, 62.2, 61.7, 53.8, 40.2, 39.4, 27.9, 27.4, 24.9, 22.7. \\
\text{FTIR (thin film) cm}^{-1}: & \quad 2929 \text{ (w), 2359 \text{ (w), 1652 \text{ (s), 1550 \text{ (m), 1423 \text{ (m), 1373 \text{ (w), 1096 \text{ (w), 747 \text{ (w)}}.}}}} \\
\text{HRMS (ESI) (m/z):} & \quad \text{calc'd for } C_{18}H_{25}BrN_{2}O_{4}, [M+H]^+: 454.1084, \text{ found: } 454.1082. \\
\text{TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.34 (UV, CAM).}
\end{align*}
\]

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**Benzamide Derivative 1.7k:**

Benzamide derivative 1.7k was synthesized according to the general procedure for acylation of amine derivatives using benzoyl chloride and amine 1.7h (7.1 mg, 17 μmol, 1 equiv). After 3.5 h, the crude residue after work-up was purified by flash column chromatography on silica gel to afford benzamide 1.7k (7.7 mg, 87%) as a white solid.

\[
\text{Benzamide Derivative 1.7k:}
\]

\[\begin{align*}
\text{Benzamide derivative 1.7k was synthesized according to the general procedure for} & \\
\text{acylation of amine derivatives using benzoyl chloride and amine 1.7h (7.1 mg, 17 μmol, 1 equiv).} & \\
\text{After 3.5 h, the crude residue after work-up was purified by flash column chromatography on silica} & \\
\text{gel to afford benzamide 1.7k (7.7 mg, 87%) as a white solid.} & \\
\end{align*}\]

\[\begin{align*}
^1H \text{ NMR (500 MHz, CD}_3\text{OD, 23 °C):} & \quad \delta 7.85-7.78 \text{ (m, 2H), 7.56-7.49 \text{ (m, 1H), 7.48-} \\
& \quad 7.40 \text{ (m, 2H), 6.91 (d, } J = 4.1 \text{ Hz, 1H), 6.33 (d, } J = 3.9 \text{ Hz, 1H), 4.61 (dt, } J = 12.0, 6.0 \text{ Hz, 1H),} \\
& \quad 4.14 \text{ (s, 1H), 4.12 (d, } J = 5.4 \text{ Hz, 1H), 3.47-3.32 \text{ (m, 4H), 2.79 (s, 3H), 2.70-2.63 \text{ (m, 1H), 2.16 (t,} \\
& \quad J = 12.7 \text{ Hz, 1H), 1.77-1.65 \text{ (m, 4H).} & \\
\end{align*}\]

\[\begin{align*}
^13C \text{ NMR (125 MHz, CD}_3\text{OD, 23 °C):} & \quad \delta 170.5, 161.9, 161.1, 135.9, 132.7, 129.7, 128.4, \\
& \quad 124.2, 116.2, 114.0, 107.5, 99.9, 63.7, 62.3, 61.7, \\
& \quad 53.8, 40.8, 39.4, 28.0, 27.5, 24.9. & \\
\end{align*}\]

\[\begin{align*}
\text{FTIR (thin film) cm}^{-1} & \quad 2933 \text{ (w), 2359 \text{ (w), 1700 (s), 1652 \text{ (s), 1550 \text{ (m),} \\
& \quad 1424 \text{ (m), 1096 \text{ (w), 712 \text{ (w).} & \\
\end{align*}\]

\[\begin{align*}
\text{HRMS (ESI) (m/z):} & \quad \text{calc’d for C}_{23}\text{H}_{27}\text{BrN}_5\text{O}_4, [M+H]^+: 516.1241,} \\
& \quad \text{found: 516.1225.} & \\
\end{align*}\]

\[\begin{align*}
\text{TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.50 (UV, CAM).} & \\
\end{align*}\]
Urea Intermediate 1.30:

1,1'-Carbonyldiimidazole (362 mg, 2.23 mmol, 1.10 equiv) and 4-dimethylaminopyridine (37.3 mg, 305 µmol, 0.150 equiv) were added sequentially to a solution of 1-(tricyclohexylstannyl)-methanamine (1.29, 808 mg, 2.03 mmol, 1 equiv) in dichloromethane (34 mL). After 45 min, the reaction mixture was concentrated and the crude residue was purified by flash column chromatography on silica gel (eluent: 30 → 75% ethyl acetate in hexanes) to afford urea intermediate 1.30 (847 mg, 84.7% over two steps) as a white crystalline solid.

\(^{1}H\) NMR (600 MHz, CDCl₃, 23 °C):
δ 8.07 (s, 1H), 7.31 (s, 1H), 7.07 (s, 1H), 6.32 (t, \(J = 5.5\) Hz, 1H), 3.14–3.09 (m, 2H), 1.95–1.81 (m, 6H), 1.72–1.50 (m, 18H), 1.37–1.19 (m, 9H).

\(^{13}C\) NMR (100 MHz, CDCl₃, 23 °C):
δ 149.2, 135.7, 129.9, 116.3, 32.4, 29.3, 27.6, 27.2, 23.7.

FTIR (thin film) cm⁻¹:
3223 (w), 3036 (w), 2913 (s), 2843 (m), 1710 (s), 1288 (m), 1075 (m), 842 (m).

HRMS (ESI) (m/z):
calc'd for C\(_{23}\)H\(_{40}\)N\(_{3}\)OSn, [M+H]⁺: 494.2188, found: 494.2223.

TLC (50% ethyl acetate in hexanes), \(R_f\):
0.27 (UV, CAM).

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\(^{6}\) Synthesized from tricyclohexyltin chloride and diiodomethane according to our protocol: Movassaghi, M.; Siegel, D. S.; Han, S. Chem. Sci. 2010, 1, 561–566. Due to high sensitivity of 1-(tricyclohexylstannyl)-methanamine (1.32) to purification procedures, it is used crude immediately after work-up.
General Procedure for the Synthesis of Substituted Ureas

Amine (1.00 equiv) and 4-dimethylaminopyridine (0.150 equiv) were added to a solution of urea intermediate 1.30 (1 equiv) in dichloromethane (0.2 M). The reaction flask was sealed with a Teflon wrapped glass stopper and heated to 40 °C. Upon consumption of the starting material as shown by thin layer chromatography, the reaction mixture was cooled to 23 °C and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford substituted ureas 1.20a–1.20c.

4-Methylene Alcohol Urea 1.20a:

4-Methylene alcohol urea 1.20a was prepared according to the general procedure for synthesis of substituted ureas using 4-aminobutanol (156 µL, 1.69 mmol, 1.00 equiv). After 24 h, the crude residue was purified by flash column chromatography on silica gel (eluent: 30 → 100% ethyl acetate in hexanes) to afford 4-methylene alcohol urea 1.20a (790 mg, 91.1%) as a white solid.

\[ \text{H NMR (600 MHz, CDCl}_3, 23 ^\circ\text{C):} \]
\[ \delta 4.66 \text{ (s, 1H), 4.23 (t, } J = 4.8 \text{ Hz, 1H), 3.69 (q, } J = 5.6 \text{ Hz, 2H), 3.26 (q, } J = 6.3 \text{ Hz, 2H), 2.77–2.68 (m, 2H), 1.94–1.77 (m, 6H), 1.72–1.46 (m, 20H), 1.38–1.21 (m, 9H).} \]

\[ \text{C NMR (126 MHz, CDCl}_3, 23 ^\circ\text{C):} \]
\[ \delta 160.2, 61.9, 40.1, 32.2, 29.7, 29.2, 27.1, 27.0, 26.7, 21.9. \]

\[ \text{FTIR (thin film) cm}^{-1} \]
\[ 3307 \text{ (m), 2911 (s), 2841 (m), 1616 (m), 1569 (s), 1443 (m), 990 (m).} \]

\[ \text{HRMS (ESI) (m/z):} \]
\[ \text{calc'd for C}_{24}\text{H}_{46}\text{N}_{2}\text{NaO}_{2}\text{Sn [M+Na}^+\text{]: 537.2473, found: 537.2488.} \]

\[ \text{TLC (75% ethyl acetate in hexanes), Rf:} \]
\[ 0.28 \text{ (UV, CAM).} \]
6-Methylene Alcohol Urea 1.20b:

6-Methylene alcohol urea 1.20b was prepared according to the general procedure for synthesis of substituted ureas using 6-aminohexanol (357 mg, 3.05 mmol, 1.00 equiv). After 25 h, the crude residue was purified by flash column chromatography on silica gel (eluent: 40 → 80% ethyl acetate in hexanes) to afford 6-methylene alcohol urea 1.20b (1.56 g, 94.5%) as a white solid.

\[
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3, 23 ^\circ\text{C):} & \quad \delta 4.97 (t, J = 5.7 \text{ Hz}, 1H), 4.62 (s, 1H), 3.56 (q, J = 6.1 \text{ Hz}, 2H), 3.12 (q, J = 6.7 \text{ Hz}, 2H), 2.96 (d, J = 5.1 \text{ Hz}, 1H), 2.78–2.68 (m, 2H), 1.88–1.75 (m, 6H), 1.66–1.44 (m, 22H), 1.38–1.16 (m, 13H). \\
\text{13C NMR (125 MHz, CDCl}_3, 23 ^\circ\text{C):} & \quad \delta 160.0, 62.6, 40.5, 32.7, 32.4, 30.5, 29.3, 27.2, 26.9, 26.6, 25.4, 22.2. \\
\text{FTIR (thin film) cm}^{-1} & \quad 3336 (w), 2915 (s), 2845 (s), 1729 (w), 1585 (m), 1444 (m), 991 (m). \\
\text{HRMS (DART) (m/z):} & \quad \text{calc'd for } C_{28}H_{51}N_{2}O_{2}Sn, [M+H]^+: 543.2967, \text{ found: 543.2966.} \\
\text{TLC (75% ethyl acetate in hexanes), Rf:} & \quad 0.57 \text{ (UV, CAM).}
\end{align*}
\]
Triethylene Glycol Urea 1.20c:
Triethylene glycol urea 1.20c was prepared according to the general procedure for synthesis of substituted ureas using 2-(2-(2-aminoethoxy)ethoxy)ethan-1-ol\(^7\) (455 mg, 3.05 mmol, 1.00 equiv). After 24 h, the crude residue was purified by flash column chromatography on silica gel (eluent: 40 → 100% ethyl acetate in hexanes) to afford triethyleneglycol urea 1.20c (1.47 g, 84.0%) as a white solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\), 23 °C):
\[\delta 5.13 (t, J = 4.9 \text{ Hz}, 1\text{H}), 4.47 (s, 1\text{H}), 3.81-3.75 \text{ (m, 2H)}, 3.73-3.59 \text{ (m, 8H)}, 3.43 (q, J = 5.3 \text{ Hz}, 2\text{H}), 2.88-2.77 (m, 2\text{H}), 2.72 (t, J = 6.1 \text{ Hz}, 1\text{H}), 1.96-1.81 (m, 6\text{H}), 1.73-1.54 (m, 18\text{H}), 1.42-1.21 (m, 9\text{H}).\]

\(^13\)C NMR (125 MHz, CDCl\(_3\), 23 °C):
\[\delta 159.9, 72.6, 70.9, 70.5 \text{ (2C)}, 61.9, 40.5, 32.4, 29.3, 27.2, 26.9, 22.2.\]

FTIR (thin film) cm\(^{-1}\):
3339 (w), 2914 (s), 2845 (s), 1729 (w), 1553 (m), 1445 (m), 1070 (s), 991 (m).

HRMS (ESI) (m/z):
calc’d for C\(_{26}\)H\(_{50}\)N\(_2\)NaO\(_4\)Sn [M+Na]\(^+\): 597.2685, found: 597.2714.

TLC (75% ethyl acetate in hexanes), R\(_f\):
0.18 (UV, CAM).

4-Methylene Alcohol Preagelastatin 1.27a:

4-Methylene alcohol preagelastatin 1.27a was prepared according to our published procedure for synthesis of preagelastatins8 using urea 1.20a (659 mg, 1.28 mmol, 3.00 equiv). The crude residue adsorbed onto silica gel was purified by flash column chromatography on silica gel (eluent: 9% methanol and 1% ammonium hydroxide in chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford 4-methylene alcohol preagelastatin 1.27a (94.0 mg, 53.4% over two steps) as an off-white solid.

$^1$H NMR (600 MHz, CD$_3$OD, 23 °C):
\[
\delta 6.91 \text{ (d, } J = 4.0 \text{ Hz, } 1\text{H}), 6.28 \text{ (d, } J = 4.0 \text{ Hz, } 1\text{H}), 6.00 \text{ (s, } 1\text{H}), 4.78-4.75 \text{ (m, } 1\text{H}), 4.58-4.52 \text{ (m, } 1\text{H}), 3.68-3.60 \text{ (m, } 1\text{H}), 3.58-3.55 \text{ (m, } 2\text{H}), 3.52-3.46 \text{ (m, } 1\text{H}), 3.34 \text{ (s, } 3\text{H}), 2.93 \text{ (dd, } J = 15.5, 6.8 \text{ Hz, } 1\text{H}), 2.78 \text{ (dd, } J = 15.5, 7.9 \text{ Hz, } 1\text{H}), 1.71-1.64 \text{ (m, } 2\text{H}), 1.54-1.51 \text{ (m, } 2\text{H}).
\]

$^{13}$C NMR (125 MHz, CD$_3$OD, 23 °C):
\[
\delta 161.1, 155.9, 124.5, 119.7, 116.1, 113.5, 108.8, 108.7, 84.7, 62.5, 58.2, 55.2, 41.9, 30.8, 29.5, 27.5.
\]

FTIR (thin film) cm$^{-1}$

3207 (br-m), 2932 (w), 2871 (w), 1652 (s), 1550 (m), 1418 (m), 1076 (s).

HRMS (DART) (m/z):

calc'd for C$_{16}$H$_{22}$BrN$_4$O$_4$, [M+H]$^+$: 413.0819, found: 413.0816.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.31 (UV, CAM).

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8 Movassaghi, M.; Siegel, D. S.; Han, S. Chem. Sci. 2010, 1, 561–566.
6-Methylene Alcohol Preagelastatin Derivative 1.27b:

6-Methylene alcohol preagelastatin derivative 1.27b was prepared according to our published procedure for synthesis of preagelastatins8 using urea 1.20b (975 mg, 1.80 mmol, 3.00 equiv). The crude residue adsorbed onto silica gel was purified by flash column chromatography on silica gel (eluent: 6% methanol and 0.6% ammonium hydroxide in chloroform → 14% methanol and 1.6% ammonium hydroxide in chloroform) to afford 6-methylene alcohol preagelastatin 1.27b (178 mg, 67.2% over two steps) as an off-white solid.

1H NMR (500 MHz, CD3OD, 23 °C):
\[ \delta 6.91 \ (d, \ J = 4.1 \ Hz, \ 1H), 6.28 \ (d, \ J = 4.1 \ Hz, \ 1H), 6.02 \ (s, \ 1H), 4.76 \ (d, \ J = 1.4 \ Hz, \ 1H), 4.58-4.52 \ (m, \ 1H), 3.63-3.51 \ (m, \ 3H), 3.44-3.38 \ (m, \ 1H), 3.34 \ (s, \ 3H), 2.92 \ (dd, \ J = 15.4, 6.7 \ Hz, \ 1H), 2.77 \ (ddd, \ J = 15.4, 7.9, 0.9 \ Hz, \ 1H), 1.65-1.49 \ (m, \ 4H), 1.42-1.30 \ (m, \ 4H). \]

13C NMR (125 MHz, CD3OD, 23 °C):
\[ \delta 161.1, 155.9, 124.5, 119.8, 116.1, 113.6, 108.7 \ (2C), 84.7, 62.9, 58.3, 55.2, 42.0, 33.6, 30.9, 29.6, 27.7, 26.7. \]

FTIR (thin film) cm⁻¹:
3212 (br-m), 2931 (m), 2857 (w), 1658 (s), 1551 (w), 1419 (m), 1084 (m).

HRMS (DART) (m/z):
calc’d for C18H26BrN4O4, [M+H]+: 441.1132, found: 441.1132.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.56 (UV, CAM).
Triethylene Glycol Preagelastatin 1.27c:

Triethylene glycol preagelastatin 1.27c was prepared according to our published procedure for synthesis of preagelastatins\(^8\) using urea 1.20c (1.29 g, 2.25 mmol, 3.00 equiv). The crude residue adsorbed onto silica gel was purified by flash column chromatography on silica gel (eluent: 9% methanol and 1% ammonium hydroxide in chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford triethylene glycol preagelastatin 1.27c (218 mg, 61.4% over two steps) as an off-white solid.

\(^1\)H NMR (400 MHz, CD\(_3\)OD, 23 °C):
\[\delta\ 6.91\ (d, \ J = 4.1\ Hz,\ 1H),\ 6.27\ (d, \ J = 4.0\ Hz,\ 1H),\ 5.97\ (s,\ 1H),\ 4.76\ (d, \ J = 1.5\ Hz,\ 1H),\ 4.69\ (td, \ J = 7.4,\ 1.5\ Hz,\ 1H),\ 3.70-3.65\ (m,\ 2H),\ 3.65-3.61\ (m,\ 4H),\ 3.60-3.55\ (m,\ 4H),\ 3.54-3.47\ (m,\ 2H),\ 3.34\ (s,\ 3H),\ 2.99\ (dd, \ J = 15.5,\ 6.9\ Hz,\ 1H),\ 2.83\ (dd, \ J = 15.5,\ 7.8\ Hz,\ 1H).\]

\(^13\)C NMR (100 MHz, CD\(_3\)OD, 23 °C):
\[\delta\ 161.2,\ 155.9,\ 124.5,\ 120.9,\ 116.0,\ 113.4,\ 108.8,\ 108.2,\ 84.7,\ 73.8,\ 71.8,\ 71.5,\ 70.6,\ 62.3,\ 57.9,\ 55.2,\ 42.7,\ 29.7.\]

FTIR (thin film) cm\(^{-1}\): 3226 (br-m), 2921 (m), 2870 (m), 1652 (s), 1419 (m), 1086 (m).

HRMS (DART) (m/z): calc’d for C\(_{18}\)H\(_{26}\)BrN\(_4\)O\(_6\), [M+H]\(^+\): 473.1030, found: 473.1021.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R\(_f\): 0.47 (UV, CAM).
4-Methylene Alcohol Derivative 1.8a and Pentacyclic Derivative 1.28:

4-Methylene alcohol derivative 1.8a and pentacyclic derivative 1.28 were prepared according to our published procedure for synthesis of (−)-agelastatin A starting material 1.27a (26.0 mg, 63.0 μmol, 1 equiv). The crude residue adsorbed onto silica gel was purified by flash column chromatography on silica gel (chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford 4-methylene alcohol derivative 1.8a (0.8 mg, 3%) as an off-white solid along with the pentacyclic derivative 1.28 (2.6 mg, 11%) as an off-white solid.

**4-Methylene Alcohol Derivative 1.8a:**

\(^1\text{H NMR (600 MHz, CD}_3\text{OD, 23 °C):}\)

\[\delta \quad 6.91 \text{ (d, } J = 4.1 \text{ Hz, 1H)}, \quad 6.33 \text{ (d, } J = 4.1 \text{ Hz, 1H}), \quad 4.65 \text{ (dt, } J = 12.0, 5.9 \text{ Hz, 1H}), \quad 4.09 \text{ (d, } J = 5.5 \text{ Hz, 1H}), \quad 3.86 \text{ (s, 1H)}, \quad 3.61 \text{ (td, } J = 6.6, 2.8 \text{ Hz, 2H}), \quad 3.30–3.18 \text{ (m, 2H)}, \quad 2.65 \text{ (dd, } J = 13.1, 6.3 \text{ Hz, 1H}), \quad 2.17 \text{ (t, } J = 12.7 \text{ Hz, 1H}), \quad 1.84–1.75 \text{ (m, 2H)}, \quad 1.62 \text{ (p, } J = 6.8 \text{ Hz, 2H}).\]

\(^{13}\text{C NMR (100 MHz, CD}_3\text{OD, 23 °C):}\)

\[\delta \quad 161.9, \quad 161.2, \quad 124.3, \quad 116.2, \quad 113.9, \quad 107.4, \quad 96.1, \quad 67.7, \quad 62.8, \quad 62.4, \quad 54.5, \quad 41.3, \quad 40.3, \quad 31.4, \quad 28.0.\]

FTIR (thin film) cm\(^{-1}\)

3276 (br-s), 2933 (w), 1653 (s), 1552 (w), 1424 (m), 1375 (w).

HRMS (DART) (m/z):

calc’d for C\(_{18}\)H\(_{20}\)BrN\(_4\)O\(_4\), [M+H]\(^+\): 399.0662, found: 399.0655.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.19 (UV, CAM).

**Pentacyclic Derivative 1.31:**

\(^1\text{H NMR (500 MHz, CD}_3\text{OD, 23 °C):}\)

\[\delta \quad 6.91 \text{ (d, } J = 4.1 \text{ Hz, 1H)}, \quad 6.33 \text{ (d, } J = 4.1 \text{ Hz, 1H}), \quad 4.64 \text{ (dt, } J = 12.0, 6.0 \text{ Hz, 1H}), \quad 4.14 \text{ (d, } J = 5.3 \text{ Hz, 1H}), \quad 3.95 \text{ (s, 1H)}, \quad 3.87 \text{ (d, } J = 12.9 \text{ Hz, 1H}), \quad 3.79 \text{ (d, } J = 14.4 \text{ Hz, 1H}), \quad 3.41–3.32 \text{ (m, 2H), 2.97–2.89 (m, 1H), 2.50 (dd, } J = 13.1, 6.7 \text{ Hz, 1H}), \quad 2.14 \text{ (t, } J = 12.6 \text{ Hz, 1H}), \quad 1.77–1.59 \text{ (m, 4H).}\]
$^{13}$C NMR (100 MHz, CD$_3$OD, 23 °C): $\delta$ 161.9, 161.2, 124.3, 116.3, 114.0, 107.5, 100.7, 66.2, 64.8, 62.0, 54.2, 41.9, 41.2, 31.3, 27.4.

FTIR (thin film) cm$^{-1}$

3247 (br-m), 2940 (m), 1696 (s), 1659 (s), 1552 (m), 1422 (s), 1091 (m).

HRMS (DART) (m/z):

calc’d for C$_{15}$H$_{18}$BrN$_4$O$_3$, [M+H]$^+$: 381.0557, found: 381.0552.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R$_f$: 0.59 (UV, CAM).
6-Methylene Alcohol Derivative 1.8b:

6-Methylene alcohol derivative 1.8b was prepared according to our published procedure for synthesis of (−)-agelastatin A⁸ using 6-methylene alcohol preagelastatin 1.27b (1.00 × 10² mg, 227 µmol, 1 equiv). The crude residue adsorbed onto silica gel was purified by flash column chromatography on silica gel (6% methanol and 0.6% ammonium hydroxide in chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford 6-methylene alcohol derivative 1.8b (35.0 mg, 36.1%) as an off-white solid.

**¹H NMR (400 MHz, CD₃OD, 23 °C):**  δ 6.91 (d, J = 4.0 Hz, 1H), 6.33 (d, J = 4.1 Hz, 1H), 4.63 (dt, J = 12.0, 5.9 Hz, 1H), 4.09 (d, J = 5.5 Hz, 1H), 3.85 (s, 1H), 3.56 (t, J = 6.5 Hz, 2H), 3.28–3.15 (m, 2H), 2.63 (dd, J = 13.0, 6.3 Hz, 1H), 2.17 (t, J = 12.6 Hz, 1H), 1.84–1.67 (m, 2H), 1.62–1.52 (m, 2H), 1.47–1.39 (m, 4H).

**¹³C NMR (100 MHz, CD₃OD, 23 °C):**  δ 161.9, 161.2, 124.3, 116.2, 114.0, 107.3, 96.1, 67.7, 63.0, 62.4, 54.5, 41.4, 40.4, 33.8, 31.5, 28.3, 26.9.

**FTIR (thin film) cm⁻¹:** 3254 (br-s), 2929 (m), 2856 (m), 1652 (s), 1551 (m), 1422 (s), 1027 (w).

**HRMS (DART) (m/z):**  calc’d for C₁₁₇H₂₄BrN₄O₄, [M+H]⁺: 427.0975, found: 427.0970.

**TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.27 (UV, CAM).**
Triethyleneglycol Derivative 1.8c:

Triethyleneglycol derivative 1.8c was prepared according to our published procedure for synthesis of (−)-agelastatin A³ using triethyleneglycol preagelastatin 1.27c (1.80 × 10² mg, 3.80 × 10² μmol, 1 equiv). The crude residue adsorbed onto silica gel was purified by flash column chromatography on silica gel (6% methanol and 0.6% ammonium hydroxide in chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford triethyleneglycol derivative 1.8c (52.0 mg, 29.9%) as an off-white solid.

¹H NMR (600 MHz, CD₃OD, 23 °C):
δ 6.92 (d, J = 3.9 Hz, 1H), 6.33 (d, J = 3.9 Hz, 1H), 6.44 (dt, J = 12.1, 6.0 Hz, 1H), 4.09 (d, J = 5.7 Hz, 1H), 3.89 (s, 1H), 3.73–3.62 (m, 9H), 3.59–3.48 (m, 2H), 3.42–3.33 (m, 1H), 2.79 (dd, J = 12.9, 6.4 Hz, 1H), 2.13 (t, J = 12.6 Hz, 1H).

¹³C NMR (125 MHz, CD₃OD, 23 °C):
δ 161.7, 161.2, 124.3, 116.2, 113.9, 107.4, 95.9, 73.8, 71.6, 71.5, 70.6, 67.8, 62.3, 62.2, 54.6, 41.5, 40.1.

FTIR (thin film) cm⁻¹
3264 (br-s), 2921 (w), 1645 (s), 1551 (m), 1093 (m), 1024 (m).

HRMS (DART) (m/z):

TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.35 (UV, CAM).
General Procedure for the Synthesis of Azide Derivatives

Alcohol derivative (1 equiv) and triphenylphosphine were dissolved in tetrahydrofuran. After 5 min, diisopropylazodicarboxylate and diphenylphosphorylazide were added sequentially. After 21 h or upon consumption of starting material as shown by thin layer chromatography, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford azide derivatives 1.8d–1.8e.

6-Methylene Azide Derivative 1.8d:

6-Methylene azide derivative 1.8d was synthesized from 6-methylene alcohol derivative 1.8b according to the general procedure for the synthesis of azide derivatives using triphenylphosphine (12.6 mg, 48.0 μmol, 2.00 equiv), diisopropylazodicarboxylate (DIAD, 9.4 μL, 48 μmol, 2.0 equiv), and diphenylphosphorylazide (DPPA, 10.6 μL, 48.0 μmol, 2.00 equiv) in tetrahydrofuran (350 μL). After 21 h, the crude residue was purified by flash column chromatography on silica gel (chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford 6-methylene azide derivative 1.8d (4.2 mg, 38%) as a white solid along with recovered 6-methylene alcohol derivative 1.8b (3.5 mg, 34%).

\[ \text{1H NMR (600 MHz, CD3OD, 23 °C):} \]

\( \delta 6.91 \text{ (d, } J = 4.1 \text{ Hz, 1H), 6.34 \text{ (d, } J = 4.1 \text{ Hz, 1H), 4.64 \text{ (dt, } J = 12.1, 5.9 \text{ Hz, 1H), 4.09 \text{ (d, } J = 5.5 \text{ Hz, 1H), 3.86 \text{ (s, 1H), 3.31–3.16 (m, 2H), 2.63 (dd, } J = 13.1, 6.3 \text{ Hz, 1H), 2.17 (t, } J = 12.6 \text{ Hz, 1H), 1.83–1.67 (m, 2H), 1.66–1.37 (m, 6H), 1.32–1.22 (m, 2H).} \]

\[ \text{13C NMR (125 MHz, CD3OD, 23 °C):} \]

\( \delta 161.9, 161.2, 124.3, 116.2, 114.0, 107.2, 96.1, 67.7, 62.4, 54.5, 52.5, 41.4, 40.3, 31.4, 30.0, 27.9, 27.8. \]

\[ \text{FTIR (thin film) cm}^{-1} \]

3222 (br-m), 2930 (m), 2856 (s), 2095 (s), 1669 (s), 1118 (m).

\[ \text{HRMS (DART) (m/z):} \]

calc’d for \( \text{C}_{17}\text{H}_{23}\text{BrN}_{7}\text{O}_{3}, [\text{M+H}]^{+}: 452.1040, \) found: 452.1058.

\[ \text{TLC (9% methanol, 1% ammonium hydroxide in chloroform), Rf: 0.28 (UV, CAM).} \]
Triethyleneglycol Bis-Azide Derivative 1.8e:

Triethyleneglycol bis-azide derivative 1.8e was synthesized from triethyleneglycol derivative 1.8c according to the general procedure for the synthesis of azide derivatives using triphenylphosphine (36.0 mg, 137 µmol, 10.0 equiv), diisopropylazodicarboxylate (DIAD, 27.0 µL, 137 µmol, 10.0 equiv), and diphenylphosphorylazide (DPPA, 31.0 µL, 137 µmol, 10.0 equiv) in tetrahydrofuran (274 µL). After 6 h, the crude residue was purified by flash column chromatography on silica gel (chloroform → 18% methanol and 2% ammonium hydroxide in chloroform) to afford triethyleneglycol bis-azide derivative 1.8e (3.7 mg, 54%) as a white solid.

$^1$H NMR (500 MHz, CD$_3$OD, 23 °C):

δ 6.93 (d, $J = 4.1$ Hz, 1H), 6.35 (d, $J = 4.0$ Hz, 1H), 4.79 (dt, $J = 12.1$, 6.2 Hz, 1H), 4.23 (s, 1H), 4.18 (d, $J = 5.5$ Hz, 1H), 3.82–3.56 (m, 6H), 3.53 (t, $J = 5.7$ Hz, 2H), 3.35–3.32 (m, 2H), 2.98 (dd, $J = 13.5$, 6.5 Hz, 1H), 2.13–2.06 (m, 1H), 1.35–1.26 (m, 2H).

$^{13}$C NMR (125 MHz, CD$_3$OD, 23 °C):

δ 161.3, 161.0, 124.2, 116.4, 114.1, 107.7, 88.5, 71.7 (2C), 71.3, 70.4, 66.1, 62.1, 54.5, 51.9, 41.5, 39.9.

FTIR (thin film) cm$^{-1}$: 3255 (br-w), 2920 (m), 2852 (w), 2105 (s), 1700 (m), 1662 (s), 1424 (m), 1102 (br-m).

HRMS (ESI) (m/z): calc’d for C$_{17}$H$_{22}$BrN$_{10}$O$_4$, [M+H]$^+$: 509.1003, found: 509.0990.

TLC (18% methanol, 2% ammonium hydroxide in chloroform), Rf: 0.50 (UV, CAM).
Chapter II

Enantioselective Synthesis of (−)-Vallesine: Late-stage C17-Oxidation via Complex Indole Boronation
Introduction

The aspidosperma alkaloids, a family containing over 250 structurally diverse members, have been a subject of significant interest over several decades due to their structural complexity and diverse biological activity.\textsuperscript{1,2} The development of a unified strategy to access this diverse family of natural products is critical to enabling access to a multitude of these alkaloids for comprehensive chemical and biological studies. Our group has made significant contributions to the development of a unified strategy, which has enabled the synthesis of 13 aspidosperma alkaloids to date (Figure 2.1).\textsuperscript{3} Our strategy provides opportunities for diversification of common intermediates, enabling access to alkaloids with varying levels of oxidation of the pentacyclic core structure as well as complex dimeric aspidosperma alkaloids.

![Figure 2.1. Representative aspidosperma alkaloids previously synthesized by our group.](image)

In our synthesis of (-)-mehranine (2.2),\textsuperscript{3b} developed by Dr. Jonathan W. Medley and Dr. Marius Mewald, early installation of the C5-stereocenter was effected through two sequential alkylations of (+)-(1R,2R)-pseudoephedrine-based crotonamide (-)-2.7 (Scheme 2.1).\textsuperscript{4} After hydrolysis, carboxylic acid (+)-2.10 was afforded in quantitative yield with >99% enantiomeric excess. Friedel–Crafts type reductive C12-alkylation followed by hydrolysis provided amino acid (+)-2.11, which was then subjected to lactam formation induced by triphenylphosphine–iodine.
Lactam (+)-2.12 underwent efficient ring-closing metathesis upon exposure to 2nd generation Hoveyda–Grubbs catalyst to afford key intermediate lactam (+)-2.13. Electrophilic activation of lactam (+)-2.13 with trifluoromethanesulfonic acid led to efficient formation of the versatile pentacycle (+)-2.14 as a single diastereomer. With the archetypal aspidosperma pentacyclic core constructed, the first total synthesis of (-)-mehranine (2.2) was completed through exchange of the para-methoxybenzyl group for a formyl group which enabled a stereoselective epoxidation followed by formamide reduction using trifluoromethansulfonic acid and tri-n-butyltinhydride to afford the desired alkaloid (-)-2.2. Our versatile transannular cyclization strategy has served as the foundation for our unified synthesis of aspidosperma alkaloids.3c-f

Scheme 2.1. Enantioselective total synthesis of (-)-mehranine (2.2). Conditions: (a) lithium 2,2,6,6-tetramethylpiperidine, LiCl, THF, 0 °C; 2.8, THF, –40 → 23 °C, 54%. (b) lithium diisopropylamide, LiCl, THF, –78 → 0 °C; N,N'-dimethylpropylene urea, –40 °C; EtI –40 °C, 69%, >30:1 dr. (c) n-Bu4NOH, H2O, t-BuOH, 100 °C, 99%, >99% ee. (d) N-allyl-N-(2,2-dimethoxyethyl)-2,2,2-trifluoroacetamide, TFA, Et3SiH, CH2Cl2, 75%. (e) NaOH, H2O, MeOH, 100 °C, 99%. (f) PPh3, I2, i-Pr2NEt, CH2Cl2, –5 → 23 °C, 78%. (g) 2nd generation Hoveyda–Grubbs catalyst, CICH2CH2Cl, 80 °C, 87%. (h) Tf2O, n-Bu3SnH, MeCN; NaHB(OMe)3, THF, 89%, >20:1 dr. (i) thiophenol, TFA, 79%. (j) Ac2O, HCO2H, 91%. (k) m-CPBA, TFA, CH2Cl2, 77%. (l) n-Bu3SnH, Tf2O, CH2Cl2, –20 → 23 °C, 86%. m-CPBA = meta-chloroperbenzoic acid.

One intriguing subset of the aspidosperma alkaloids is those which contain C17-oxidation, including (-)-vallesine (2.15, Figure 2.2),5 (-)-aspidospermine (2.16),6 and (+)-deacetylaspidospermine (2.17).7 Related compounds include the C21-oxygenated variants (+)-
haplocidine (2.6),8 (+)-haplocine (2.18),8 and (–)-cylindrocarpidine (2.18).9 While arene-oxygenated aspidosperma alkaloids have been demonstrated to be some of the most potent biologically active compounds in this class,10 methods to selectively address oxygenation of the indoline core are lacking. Of particular interest to our synthetic campaign, (–)-vallesine (2.15) and (–)-aspidospermine (2.16) have been demonstrated as potent antiplasmodial agents with potential for the reversal of resistance to traditional treatments.11 Furthermore, aspidospermine (2.16) has been demonstrated to be a potent lipase inhibitor12 and anticancer agent.13 In studies of the cytotoxicity, genotoxicity, and mechanism of action of alkaloid 2.16 in treatment of HepG2 cells, chemical alteration to the molecule was recommended to achieve the optimal range of cytotoxicity/genotoxicity for therapeutic use.13 Of four natural product scaffolds tested as trypanothione reductase inhibitors for treatment of severe illnesses caused by parasites, aspidospermine (2.16) was the only one to show moderate activity and remains of interest due to the potential for chemical manipulation.14 Therefore, synthetic access to (–)-vallesine (2.15) via (+)-deacetylaspidospermine (2.17) could enable additional comprehensive biological studies of this intriguing alkaloid subclass.

Figure 2.2. Structures of representative C17-oxidized aspidosperma alkaloids (2.6, 2.15–2.20).
Recently, our group reported the first total synthesis of (+)-haplocidine (2.6) and (+)-haplocine (2.18) through a strategy developed by Dr. Kolby L. White which employs highly stereoselective cyclization events and regioselective late-stage A-ring functionalization (Scheme 2.2). This strategy relies on the in situ protection of the C9-amine via opening of the C19-hemiaminal to form the robust iminium ion 2.23 which is subject to directed, palladium-catalyzed ortho-C–H-acetoxylation of the aspidosperma indoline core. While this strategy provided direct access to oxidized members of the (+)-fendleridine (2.5) subfamily, it is not a viable approach for (-)-vallesine (2.15) and related alkaloids without C21-oxidation. We therefore sought a strategy towards these alkaloids as part of our interest in biogenetically inspired late-stage arene oxidation of aspidosperma alkaloids.

Scheme 2.2. Synthesis of (+)-haplocidine (2.6) and (+)-haplocine (2.18) via late-stage oxidation of (+)-fendleridine derivatives. Conditions: (a) Ac₂O, pyridine, CH₂Cl₂, 88%. (b) propionic anhydride, pyridine, CH₂Cl₂, 78%. (c) TFA, TFAA, 60 °C; Pd(OAc)₂ (20 mol %), Phl(OAc)₂ (4 equiv), 75 °C; MeOH, NEt₃. R = Me, 77%. R = Et, 74%.

While aspidospermine (2.16) has served as an archetypal target for C17-oxidized aspidosperma alkaloids, most current synthetic routes rely on a late-stage Fischer indole synthesis utilizing 2-methoxyphenylhydrazine (Figure 2.3A). This strategy towards (±)-aspidospermine (2.16) was initially introduced by Stork and Dolfini in 1963 and has since been improved upon.
by many others, including Ban in 1965, Kuehne in 1966, Pearson in 1981, and Coldham in 2007. Furthermore, this strategy has been applied to the synthesis of alkaloid (-)-2.16 by Shishido in 2003 and Jiang in 2017. In 2012, Boger reported the synthesis of (-)-aspidospermine (2.16) through an intramolecular cycloaddition cascade strategy (Figure 2.3B). In 2014, Peng and Shao utilized a palladium-catalyzed decarboxylative asymmetric allylation approach towards (+)-aspidospermine (2.16, Figure 2.3C). The reliance on introducing C17-oxidation from commercial materials including 2-methoxyphenylhydrazine (2.25), 7-benzyloxyindole (2.29), and 2-methoxyanisole (2.32) is a shared concept in all prior approaches to aspidospermine (2.16). We identified an opportunity to apply our strategy for regioselective indole boronation to offer a new opportunity for diversification of key intermediates en route to aspidosperma alkaloids.

Figure 2.3. Previous synthetic strategies towards aspidospermine (2.16)
Representative Strategies for Regioselective Indole Boronation. The prevalence of indole derivatives\textsuperscript{18} in natural products and pharmaceutical compounds has inspired numerous developments for their efficient and direct functionalization.\textsuperscript{19} The innate reactivity of the indole ring has enabled practical functionalization of the C2,\textsuperscript{20} C3,\textsuperscript{21} and C5\textsuperscript{22} positions, and to a lesser extent the C4\textsuperscript{23} and C6 positions,\textsuperscript{24} while C7 functionalization has been more challenging, particularly in the case of tryptamine and tryptophan derivatives.\textsuperscript{17,25} In 2014, our group disclosed an expedient methodology for C7-boronation of tryptophan and tryptamine derivatives\textsuperscript{17a} based on our interest in alkaloids containing this substructure, and a follow-up report in 2015 demonstrated the practicality and scalability of this procedure.\textsuperscript{17b} As described in the following pages, this work offered an efficient approach for late-stage arene functionalization of these important heterocycles and inspired my approach to C17-oxygenated aspidosperma alkaloids.

Metal catalyzed arene and heteroarene C–H boronations have led to significant advances towards C7-functionalization of indoles.\textsuperscript{26,27} In 2006, Smith demonstrated the first general approach to functionalizing unprotected indoles at C7 via iridium-catalyzed boronation and utilizing substituents to block the greater reactivity of the C2 position.\textsuperscript{28} The substrate scope of this study included C2-alkyl, aryl, ester and amide functionalities and additional functional group tolerance at the C3, C4, and C5 positions (Scheme 2.3). Notably, 2-trimethylsilyl indole was effectively used as a precursor to 7-boroindole, with selective boronation occurring in 76% yield followed by desilylation to afford the C2-unsubstituted mono-boronated indole. Furthermore, in the absence of a C2-substituent, C2/C7-diboronation was observed in high yields. Initial mechanistic investigations comparing the selectivity of boronation of indole and benzofuran indicated that hydrogen bonding to an acidic substrate proton is not strictly required for the observed regioselectivity.
In 2010, Hartwig reported the first truly C7-selective boronation\textsuperscript{29} utilizing a variant of their hydrosilyl-directed \textit{ortho}-boronation procedure.\textsuperscript{30} Borylation of 1-diethylsilylindole with bis(pinacolato)diboron in the presence of [Ir(cod)Cl]$_2$ and 4,4'-di-\textit{tert}-butylbipyridine occurs in good yield with complete selectivity for C7, with the hydrosilyl directing group completely overriding inherent site selectivity (Scheme 2.3). Mechanistically, it is likely that C7-boronation proceeds through an intermediate silyl complex with the iridium catalyst that forms a five-membered metallacycle through C–H bond cleavage at the C7 position. Substituents at the C3, C4, and C5 positions were well tolerated with functional groups including halogens, cyano groups, and alkoxy and benzyloxy groups. This methodology was additionally extended to the borylation of carbazole, phenothiazenes, and tetrahydroquinoline with excellent selectivity.

Baran reported a related advance in 2015 wherein regioselective C6-boronation of tryptophan and carbazole derivatives is effected through a combination of a large triisopropylsilyl blocking group and ligand choice that influence the regiochemical outcome (Scheme 2.3).\textsuperscript{31} While both C3-substituted and C2,C3-disubstituted indoles were efficiently boronated with high selectivity, sensitive functional groups, such as a primary alkyl bromide, were not tolerated.
Scheme 2.3. Previous advances in regioselective indole boronation.

Inspired by the early contributions of Hartwig and Smith, based upon our interest in guided complex fragment coupling for dimeric diketopiperazines, and following early observations in our group in 2010 by Dr. Dustin S. Siegel, our group has reported a direct and scalable method for the one-pot conversion of C3-alkylindoles, including tryptophans and tryptamines, to the corresponding C7-boronated compounds (Scheme 2.4). Central to this strategy is a diboronation/protodeboronation sequence that takes advantage of the increased nucleophilicity and basicity of the C2 position of the C3-substituted indoles. The utility of this strategy is highlighted by the gram-scale synthesis of C7-boronated N-Boc-L-tryptophan methyl ester and
rapid entry to various unnatural amino acid derivatives through halogenation, oxidation, or Suzuki–Miyaura cross coupling of C7-boronated C3-alkylindoles. Due to the demonstrated synthetic utility\textsuperscript{31,33} of iridium-catalyzed boronation of indoles, we endeavored to apply this method in the complex setting of aspidosperma alkaloid total synthesis.

Scheme 2.4. Regioselective indole boronation of C3-alkylindoles.

Results and Discussion

Our retrosynthetic analysis of the C17-oxidized aspidosperma alkaloids is illustrated in Scheme 2.5, wherein we envisioned \textred{(-)-vallesine (2.15)} to arise from N1-formylation of \textred{(+)-deacetylaspidospermine (2.17)}. Informed by our studies of transannular cyclization via amide activation\textsuperscript{3c,d} and key prior contributions,\textsuperscript{34} we envisioned \textred{(+)-deacetylaspidospermine (2.17)} to arise from lactam 2.45. The necessary oxidation state at C17 would be introduced via regioselective boronation of indole 2.47, a compound related to intermediates that we have employed in syntheses of other aspidosperma alkaloids without A-ring oxygenation.\textsuperscript{3c} In our planned boronation strategy to C17-oxygenated aspidosperma alkaloids the synthetic intermediate 2.47 contains a disubstituted indole,\textsuperscript{3c,e,f} possibly allowing a direct regioselective C17-boronation (Scheme 2.6).\textsuperscript{27m,28,29}
Scheme 2.5. Retrosynthetic analysis of C17-oxidized aspidosperma alkaloids.

Scheme 2.6. Indole boronation strategy.

We have previously demonstrated the synthesis of lactam (+)-2.13 in >99% ee via an asymmetric alkylation strategy (Scheme 2.1)\textsuperscript{3c} utilizing the synthetic (+)-(1R,2R)-pseudoephedrine chiral auxiliary, prepared in four steps from commercial materials.\textsuperscript{35} For the purposes of this study, we required lactam (−)-2.13, which we chose to synthesize through a parallel strategy utilizing the commercially available (+)-(1S,2S)-pseudoephedrine chiral auxiliary\textsuperscript{36} to provide lactam (−)-2.13 in 80% ee.\textsuperscript{36} In order to access the indole substrate for the planned boronation, we effected removal of the N1-para-methoxybenzyl group from lactam (−)-2.13 under Birch reductive conditions using sodium metal in liquid ammonia to afford lactam 2.48 in 91% yield (Scheme 2.7), followed by hydrogenation to afford indole 2.47 in 99% yield. Importantly, complete and regioselective boronation of indole 2.47 was accomplished using [Ir(cod)OMe]\textsubscript{2} and pinacolborane to provide boronic ester 2.46, which was then subjected to
oxidation using a solution of aqueous hydroxylamine to provide phenol 2.49 in 31% yield over two steps (Scheme 2.7).

![Scheme 2.7. Synthesis of C17-oxidized intermediate phenol 2.49.](image)

Next, we required optimal conditions for transannular cyclization to secure the pentacyclic aspidosperma core of (−)-vallesine (2.15). While we previously effected transannular cyclization of N1-protected lactam (+)-2.13 through an electrophilic amide activation strategy to access the corresponding C19-iminium ion for further derivatization, we envisioned a partial reduction strategy would be most effective for conversion of intermediate 2.49 to alkaloid (−)-2.15. Inspired by seminal reports using lithium aluminum hydride for the partial reduction of related lactams, we chose the milder diisobutylaluminum hydride to enable direct, efficient formation of imine 2.50 from lactam 2.47 as a model substrate for the projected cyclization en route to (−)-vallesine (1). The intermediate imine 2.50 was reduced using lithium aluminum hydride to afford (+)-aspidospermidine (2.1) in 77% yield over two steps from lactam 2.47 (Scheme 2.8).

![Scheme 2.8. Synthesis of (+)-aspidospermidine (2.1).](image)
With the optimized conditions for reductive transannular cyclization in hand, we evaluated their application to the requisite C17-oxygenated aspidosperma intermediate. Methylation of phenol 2.49 with iodomethane in the presence of cesium carbonate afforded C17-methyl ether 2.45 in 98% yield as the optimal substrate for transannular cyclization (Scheme 5). In the event, exposure of lactam 2.45 to diisobutylaluminum hydride effected transannular cyclization, and the resultant imine was reduced using lithium aluminum hydride to afford (+)-deacetylaspidospermine (2.17) in 55% yield over two steps. All spectroscopic data for (+)-deacetylaspidospermine (2.17) were consistent with the literature reports. The optical rotation data for alkaloid (+)-2.17 (observed $[\alpha]_D^{24} = +25$ (c = 0.83, CHCl$_3$); lit. $[\alpha]_D = +3$ (CHCl$_3$) and $[\alpha]_D = +8$ (MeOH)) indicated the correct sign with an increased magnitude as compared to the literature reports. Furthermore, completion of the first total synthesis of (-)-vallesine (2.15) was achieved via formylation of (+)-deacetylaspidospermine (2.17) using acetic anhydride in formic acid to afford alkaloid (-)-2.15 in 87% yield. All spectroscopic data as well as the optical rotation data for (-)-vallesine (2.15, observed $[\alpha]_D^{24} = -71$ (c = 0.71, CHCl$_3$); lit. $[\alpha]_D = -91$ (c = 1, CHCl$_3$)) were consistent with the literature reports.

Scheme 2.9. Synthesis of (+)-deacetylaspidospermine (2.17) and (-)-vallesine (2.15)

\[ (+)\text{-deacetylaspidospermine (2.17)} \]

\[ (--)\text{-vallesine (2.15)} \]
Conclusion

We have developed the first total synthesis of (-)-vallesine (2.15) based on a strategy involving late-stage regioselective complex indole boronation followed by transannular cyclization. This strategy uniquely offers access to both (+)-deacetylaspidospermine (2.17) and (+)-aspidospermidine (2.1), representing A-ring oxidized and non-oxidized aspidosperma alkaloids, respectively, from a common intermediate. This approach not only removes the need for reliance on starting material to introduce the C17-oxidation found in a subset of aspidosperma alkaloids, but it also serves as the first example of boronation chemistry to secure the C17-oxygenation in these alkaloids.


(36) Please see the Experimental Section for further details.

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EXPERIMENTAL SECTION

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks, modified Schlenk (Kjeldahl shape) flasks or glass pressure vessels. The flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of argon. Cannulae or gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al.\textsuperscript{1} using granular silica gel (60-Å pore size, 40–63 μm, 4–6% H₂O content, Zeochem). Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) or basic alumina impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to short wave ultraviolet light (254 nm) and irreversibly stained by treatment with an aqueous solution of ceric ammonium molybdate (CAM) or an alcoholic solution of vanillin followed by heating (~ 1 min) on a hot plate (~ 250 °C). Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of ~2 Torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, acetonitrile, tetrahydrofuran, toluene, and methanol were purchased from J. T. Baker (Cycletainer\textsuperscript{TM}) and were purified by the method of Grubbs et al. under positive argon pressure.\textsuperscript{2} Cesium carbonate was purchased from Alfa Aesar. All other solvents and chemicals were purchased from Sigma-Aldrich.

Instrumentation. Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded with a Varian inverse probe INOVA-500, Varian INOVA-500, Bruker Advance 400, or with a Bruker Advance III 400 spectrometer. Chemical shifts are recorded in parts per million on the δ scale and are referenced from the residual protium in the NMR solvent (CHCl₃: δ 7.26, CH₃CN: δ 1.94).\textsuperscript{3} Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance spectra were recorded with a Varian inverse probe INOVA-500, Varian INOVA-500, Bruker Advance 400, or with a Bruker Advance III 400 spectrometer and are recorded in parts per million on the δ scale and are referenced from the carbon resonances of the solvent (CDCl₃: δ 77.16, CD₃CN: δ 13.2).\textsuperscript{3} Data are reported as follows: chemical shift (assignment). Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. We thank Dr. Li Li at the Massachusetts Institute of Technology Department of Chemistry instrumentation facility for obtaining mass spectrophotometric data. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS using a direct analysis in real time (DART) ionization source.

**Positional Numbering System.** At least two numbering systems exist in the literature for the *aspidosperma* alkaloids.4,5 For direct comparison between structures, the numbering system shown below for (−)-vallesine (1) is optimal and is used throughout this report.

![Chemical structure of (−)-vallesine (2.15)](image)

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**Lactam 2.48:**

A solution of *N*-para-methoxybenzyl lactam (−)-2.13\(^6,7\) (300 mg, 0.724 mmol, 1 equiv) in THF (5 mL) was added to liquid ammonia (~100 mL) at −78 °C. After 5 min, sodium (200 mg, 8.70 mmol, 12.0 equiv) was added to the mixture as a solid in three portions, and the mixture was stirred at −78 °C. After 3 h, solid ammonium chloride (2 g) was added to the blue suspension. After 5 min, the ammonia was evaporated by slowly warming the colorless suspension to 23 °C. After evaporation of the solvent, water (100 mL) and dichloromethane (100 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL) and the combined organic layers were washed with brine (100 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 30% ethyl acetate in hexanes) to afford lactam 2.48 (194 mg, 91.0%) as a white solid. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments.

\(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C):

δ 7.87 (s, 1H, N\(_1\)H), 7.49–7.44 (m, 1H, C\(_{14}\)H), 7.17–7.11 (m, 1H, C\(_{17}\)H), 7.09–7.01 (m, 2H, C\(_{15}\)H, C\(_{16}\)H), 5.89 (app-dt, J = 3.0, 10.2 Hz, 1H, C\(_7\)H), 5.43 (app-dt, J = 2.0, 10.1 Hz, 1H, C\(_8\)H), 4.47 (ddd, J = 2.5, 11.4, 13.3 Hz, 1H, C\(_{10}\)H\(_a\)), 4.15 (d, J = 17.7 Hz, 1H, C\(_8\)H\(_b\)), 3.88 (d, J = 17.6 Hz, 1H, C\(_{11}\)H\(_b\)), 3.00 (app-dt, J = 3.2, 14.8 Hz, 1H, C\(_{11}\)H\(_a\)), 2.83 (ddd, J = 3.1, 11.3, 14.6 Hz, 1H, C\(_{11}\)H\(_b\)), 2.68 (app-dt, J = 3.7, 13.1 Hz, 1H, C\(_{10}\)H\(_b\)), 2.62 (dd, J = 8.1, 14.8 Hz, 1H, C\(_3\)H\(_a\)), 2.51 (dd, J = 10.3, 14.5 Hz, 1H, C\(_{12}\)H\(_b\)), 2.11 (ddd, J = 1.6, 10.5, 12.2 Hz, 1H, C\(_{14}\)H\(_a\)), 1.99 (qd, J = 7.4, 14.4 Hz, 1H, C\(_{20}\)H\(_b\)), 1.84 (ddd, J = 1.4, 8.4, 13.5 Hz, 1H, C\(_4\)H\(_b\)), 1.22 (qd, J = 7.4, 14.7 Hz, 1H, C\(_{20}\)H\(_a\)), 0.77 (t, J = 7.4 Hz, 3H, C\(_{21}\)H\(_3\)).

\(^13\)C NMR (100 MHz, CDCl\(_3\), 25 °C):

δ 172.3 (C\(_{19}\)), 136.1 (C\(_{13}\)), 135.6 (C\(_2\)), 131.3 (C\(_6\)), 128.3 (C\(_{18}\)), 121.3 (C\(_7\)), 121.2 (C\(_{15}\)), 118.9 (C\(_{16}\)), 117.6 (C\(_{14}\)), 110.6 (C\(_{17}\)), 109.5 (C\(_{12}\)), 49.1 (C\(_3\)), 46.8 (C\(_5\)), 46.1 (C\(_{10}\)), 45.7 (C\(_4\)), 31.2 (C\(_{20}\)), 21.9 (C\(_3\)), 21.8 (C\(_11\)), 9.8 (C\(_{21}\)).


\(^7\) *N*-para-methoxybenzyl lactam (−)-2.13 was prepared in 80% ee utilizing the commercially available (+)-(1S,2S)-pseudoephedrine chiral auxiliary. Enantiomeric excess was determined by chiral HPLC analysis of its corresponding C\(_6\),C\(_7\)-saturated compound, prepared by hydrogenation in the presence of platinum dioxide. Chiralcel OD-H, 25% i-PrOH / 75% hexanes, 1.0 mL/min, 230 nm, \(t_e\) (major) = 5.7 min, \(t_e\) (minor) = 6.7 min. For the preparation of lactam (+)-2.13 in >99% ee utilizing the synthetic (+)-(1R,2R)-pseudoephedrine chiral auxiliary, please see reference 6.
FTIR (thin film) cm\(^{-1}\): 3290 (s), 2920 (m), 1630 (s), 1457 (m), 1219 (w).

HRMS (DART) (m/z): calc’d for C\(_{19}\)H\(_{23}\)N\(_2\)O [M+H]\(^+\): 295.1805, found: 295.1800.

TLC (40% ethyl acetate in hexanes), R\(f\): 0.33 (UV, CAM, KMnO\(_4\)).
Indole 2.47:

Platinum dioxide (33.6 mg, 0.148 mmol, 20.0 mol%) was added as a solid to a solution of lactam 2.48 (218 mg, 0.740 mmol, 1 equiv) in a mixture of dichloromethane (2.5 mL) and ethyl acetate (25 mL) at 23 °C. The reaction mixture was purged with hydrogen gas for 30 min and then stirred under an atmosphere of hydrogen gas (balloon) at 23 °C. After 18 h, the reaction mixture was opened to air and filtered through silica gel (eluent: 20% ethyl acetate in hexanes) to afford indole 2.47 (218 mg, 99.5%) as a white solid. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments.

\(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C):

\(\delta\) 7.99 (br-s, 1H, \(\text{N}\_1\text{H}\)), 7.48 (d, \(J = 6.3\) Hz, 1H, \(\text{C}_{14}\text{H}\)), 7.21 (d, \(J = 6.5\) Hz, 1H, \(\text{C}_{17}\text{H}\)), 7.09 (td, \(J = 7.1, 1.5\) Hz, 1H, \(\text{C}_{10}\text{H}\)), 7.06 (td, \(J = 7.1, 1.4\) Hz, 1H, \(\text{C}_{13}\text{H}\)), 4.36 (ddd, \(J = 12.9, 6.7, 4.3\) Hz, 1H, \(\text{C}_{10}\text{H}_a\)), 3.27–3.15 (m, 1H, \(\text{C}_{11}\text{H}_a\)), 3.04 (br-s, 1H, \(\text{C}_8\text{H}_a\)), 2.95–2.78 (m, 3H, \(\text{C}_3\text{H}_a, \text{C}_{11}\text{H}_b, \text{C}_8\text{H}_b\)), 2.69–2.61 (m, 2H, \(\text{C}_{10}\text{H}_b, \text{C}_3\text{H}_b\)), 2.03 (ddd, \(J = 13.0, 7.4, 2.7\) Hz, 1H, \(\text{C}_9\text{H}_a\)), 1.90–1.76 (m, 3H, \(\text{C}_4\text{H}_b, \text{C}_6\text{H}_a, \text{C}_{20}\text{H}_a\)), 1.58–1.29 (m, 4H, \(\text{C}_6\text{H}_b, \text{C}_7\text{H}_2, \text{C}_{20}\text{H}_b\)), 0.87 (t, \(J = 7.4\) Hz, 3H, \(\text{C}_{21}\text{H}_3\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\), 25 °C):

\(\delta\) 175.8 (\(\text{C}_{19}\)), 136.4 (\(\text{C}_2\)), 135.6 (\(\text{C}_{18}\)), 128.5 (\(\text{C}_{13}\)), 121.2 (\(\text{C}_{16}\)), 119.1 (\(\text{C}_{15}\)), 117.6 (\(\text{C}_{14}\)), 110.6 (\(\text{C}_{17}\)), 109.6 (\(\text{C}_{12}\)), 50.7 (\(\text{C}_8\)), 48.3 (\(\text{C}_{10}\)), 45.8 (\(\text{C}_3\)), 43.7 (\(\text{C}_4\)), 32.7 (\(\text{C}_{20}\)), 31.9 (\(\text{C}_6\)), 22.5 (\(\text{C}_3\)), 21.6 (\(\text{C}_{11}\)), 21.2 (\(\text{C}_7\)), 9.2 (\(\text{C}_{21}\)).

FTIR (thin film) cm\(^{-1}\):

3266 (w), 2930 (m), 1610 (s), 1464 (s), 1443 (m), 1246 (m).

HRMS (ESI) (m/z):

calc’d for \(\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}[\text{M}+\text{H}]^+: 297.1961\), found: 297.1964.

TLC (30% ethyl acetate in hexanes), Rf:

0.15 (UV, CAM).
**(+)-Aspidospermidine (2.1):**

Diisobutylaluminum hydride (1.0 M in hexanes, 279 µL, 279 µmol, 4.00 equiv) was added slowly via syringe to a solution of indole 2.47 (20.7 mg, 69.8 µmol, 1 equiv) in THF (1.4 mL) at 0 °C, and the resulting solution was allowed to slowly warm to 23 °C. After 3 h, a saturated aqueous solution of sodium potassium tartrate (2 mL) was added and the solution was stirred vigorously. After 30 min, a saturated aqueous solution of sodium chloride (10 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford a clear light orange oil.

The resulting residue was dissolved in THF (1.4 mL) and the solution was cooled to 0 °C. Lithium aluminum hydride (13.2 mg, 349 µmol, 5.00 equiv) was added and the reaction solution was allowed to warm to 23 °C. After 16.5 h, the reaction mixture quenched by the sequential addition of water (13.2 µL), a 15% aqueous solution of sodium hydroxide (13.2 µL), and water (39.6 µL). The resulting suspension was diluted with ethyl acetate and filtered through cotton. The filtrate was concentrated and the resulting residue was purified by flash column chromatography on silica gel (eluent: 20% ethyl acetate in hexanes, then 20% to 30% ethyl acetate in hexanes with 2% triethylamine) to afford (+)-aspidospermidine (2.1, 15.1 mg, 76.6%) as a white solid. Spectroscopic data for (+)-2.1 were consistent with our previously reported data for (-)-2.1.6

\[\delta 7.08 (dd, J = 7.4, 1.2 Hz, 1H, C_{14}H), 7.01 (td, J = 7.6, 1.2 Hz, 1H, C_{10}H), 6.73 (td, J = 7.4, 1.0 Hz, 1H, C_{15}H), 6.64 (dd, J = 7.7 Hz, 1H, C_{17}H), 3.51 (dd, J = 11.1, 6.2 Hz, 1H, C_{21}H), 3.15–3.03 (m, 2H, C_{8}H_{2}, C_{10}H_{2}), 2.33–2.20 (m, 3H, C_{16}H_{3}, C_{11}H_{2}, C_{19}H), 1.99–1.90 (m, 2H, C_{4}H_{2}, C_{8}H_{2}), 1.79–1.60 (m, 3H, C_{3}H_{2}, C_{6}H_{2}), 1.55–1.34 (m, 4H, C_{3}H_{2}, C_{7}H_{2}, C_{11}H_{2}, C_{20}H_{2}), 1.14–1.02 (m, 2H, C_{4}H_{2}, C_{6}H_{2}), 0.86 (dq, J = 14.7, 7.6 Hz, 1H, C_{20}H_{2}), 0.63 (t, J = 7.5 Hz, 3H, C_{21}H_{3}).\]

\[\delta 149.6 (C_{18}), 135.9 (C_{13}), 127.2 (C_{16}), 123.0 (C_{14}), 119.1 (C_{15}), 110.5 (C_{17}), 71.4 (C_{19}), 65.8 (C_{2}), 54.0 (C_{6}), 53.5 (C_{12}), 53.2 (C_{10}), 39.0 (C_{11}), 35.8 (C_{5}), 34.6 (C_{4}), 30.1 (C_{20}), 28.3 (C_{3}), 23.2 (C_{4}), 21.9 (C_{7}), 7.0 (C_{21}).\]

\[[\alpha]_{D}^{24} +12 (c = 0.51, EtOH)^{8,9}\]

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8 The observed optical rotation value for alkaloid (+)-2.1 is consistent with the 80% ee value for starting material lactam (-)-2.13.
9 Literature value for alkaloid (-)-2.1: [\(\alpha\)]{D}^{24} = -15 (c = 0.27, MeOH), see reference 6.

82
C17-Alcohol 2.49:

Pinacolborane (537 µL, 3.72 mmol, 20.0 equiv) was added via syringe to a solution of indole 2.47 (55.1 mg, 0.186 mmol, 1 equiv), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (6.2 mg, 9.3 µmol, 5.0 mol%), and 4,4'-di-tert-butyl-2,2'-bipyridine (5.0 mg, 19 µmol, 10 mol%) in tetrahydrofuran (1.86 mL) in a glass pressure vessel at 23 °C. The vessel was sealed, and the reaction mixture was heated to 65 °C. After 36 h, the solution was allowed to cool to 23 °C. The reaction mixture was diluted with dichloromethane (10 mL), and a saturated aqueous solution of sodium bicarbonate (5 mL) was added slowly to the reaction mixture. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting brown residue was filtered through silica gel (eluent: 30% ethyl acetate in hexanes) to afford a pale yellow gel.

The yellow gel was dissolved in methanol (3.7 mL), and 50% aqueous hydroxylamine (342 µL, 5.58 mmol, 30.0 equiv) was added at 23 °C. After 48 h, a saturated aqueous solution of ammonium chloride (5 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 0 → 50% ethyl acetate in hexanes) to afford C17-alcohol 2.49 (18.0 mg, 30.9%) as an off-white solid. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments.

**1H NMR (400 MHz, CD3CN, 25 °C):**

δ 8.84 (s, 1H, N1H), 7.04 (s, 1H, C17OH), 6.97 (d, J = 7.8 Hz, 1H, C14H), 6.79 (t, J = 7.7 Hz, 1H, C15H), 6.45 (dd, J = 7.6, 0.9 Hz, 1H, C16H), 4.18 (dd, J = 12.9, 10.0, 2.9 Hz, 1H, C10Ha), 3.44 (br-s, 1H, C8Ha), 3.19 (d, J = 11.5 Hz, 1H, C6Hb), 2.92 (d, J = 15.0 Hz, 1H, C11Hb), 2.86–2.77 (m, 2H, C3Hb), 2.77–2.65 (m, 2H, C3Hb), 1.97–1.91 (m, 2H, C4H2), 1.90–1.71 (m, 3H, C6Hb, C7Hb), 1.68–1.52 (m, 2H, C6b, C7Hb), 1.35–1.17 (m, 1H, C20Hb), 0.81 (t, J = 7.4 Hz, 3H, C21H3).

**13C NMR (100 MHz, CD3CN, 25 °C):**

δ 176.4 (C19), 143.0 (C17), 137.5 (C2), 131.3 (C13), 126.2 (C18), 119.9 (C15), 111.0 (C12), 110.5 (C14), 106.4 (C16), 50.5 (C8), 49.1 (C10), 46.7 (C4), 46.5 (C3), 33.9 (C20), 32.5 (C6), 23.1 (C11), 22.7 (C7), 22.4 (C5), 9.7 (C21).

10 Extreme signal broadening was observed in the 'H NMR spectrum. The reported signal is corroborated by gHSQC data.
FTIR (thin film) cm\(^{-1}\): 3319 (w), 2935 (w), 1588 (m), 1434 (m), 1264 (m), 730 (s).

HRMS (ESI) (m/z): calc'd for C\(_{19}\)H\(_{25}\)N\(_2\)O\(_2\) [M+H]\(^+\): 313.1911, found: 313.1917.

TLC (50% ethyl acetate in hexanes), R\(_f\): 0.28 (UV, CAM, vanillin).
C17-Methyl Ether 2.45:

Iodomethane (67.1 μL, 1.08 mmol, 10.0 equiv) was added to a suspension of cesium carbonate (176 mg, 0.540 mmol, 5.00 equiv) and C17-alcohol 2.49 (33.8 mg, 0.108 mmol, 1 equiv) in acetone (2.2 mL) at 23 °C. After 4 h, a solution of saturated aqueous ammonium chloride (5 mL) and dichloromethane (10 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried with anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (eluent: 0 → 30% ethyl acetate in hexanes) to afford C17-methyl ether 2.45 (34.5 mg, 97.7%) as a white solid. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments.

$^1$H NMR (400 MHz, CDCl$_3$, 25 °C):

δ 7.98 (s, 1H, N$_1$H), 7.10 (d, $J = 7.9$ Hz, 1H, C$_{14}$H), 6.98 (dd, $J = 7.8$ Hz, 1H, C$_{15}$H), 6.58 (d, $J = 7.7$ Hz, 1H, C$_{16}$H), 4.40–4.29 (m, 1H, C$_{10}$H$_3$), 3.93 (s, 3H, OCH$_3$), 3.19 (br-s, 1H, C$_{11}$H$_3$), 3.09–2.87 (m, 3H, C$_8$H$_3$, C$_3$H$_3$), 2.85–2.76 (m, 1H, C$_{11}$H$_3$), 2.73–2.59 (m, 2H, C$_{10}$H$_2$, C$_3$H$_2$), 2.05 (ddd, $J = 13.4$, 7.4, 3.0 Hz, 1H, C$_{14}$H$_3$), 1.92–1.74 (m, 3H, C$_4$H$_2$, C$_6$H$_2$, C$_{20}$H$_2$), 1.57–1.29 (m, 4H, C$_5$H$_2$, C$_7$H$_2$, C$_{20}$H$_2$), 0.86 (t, $J = 7.5$ Hz, 3H, C$_{21}$H$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C):

δ 175.8 (C$_{19}$), 145.7 (C$_{17}$), 136.0 (C$_2$), 129.9 (C$_{13}$), 125.8 (C$_{18}$), 119.6 (C$_{15}$), 110.7 (C$_{14}$), 110.3 (C$_{12}$), 101.7 (C$_{16}$), 55.3 (OCH$_3$), 50.9 (C$_8$), 48.3 (C$_{10}$), 45.8 (C$_5$), 43.7 (C$_4$), 32.6 (C$_{20}$), 32.0 (C$_6$), 22.6 (C$_3$), 21.8 (C$_{11}$), 21.2 (C$_7$), 9.2 (C$_{21}$).

FTIR (thin film) cm$^{-1}$: 3282 (w), 2924 (m), 1612 (s), 1464 (m), 1256 (m), 1089 (m).

HRMS (ESI) (m/z): calc’d for C$_{20}$H$_{27}$N$_2$O$_2$ [M+H]$^+$: 327.2067, found: 327.2062.

TLC (30% ethyl acetate in hexanes), Rf: 0.16 (UV, CAM, vanillin).
Diisobutylaluminum hydride (1.0 M in hexanes, 636 µL, 636 µmol, 6.00 equiv) was added slowly via syringe to a solution of C17-methyl ether 2.45 (34.5 mg, 106 µmol, 1 equiv) in THF (2.1 mL) at −78 °C, and the resulting solution was stirred at −78 °C. After 7 h, a saturated aqueous solution of sodium potassium tartrate (5 mL) was added and the solution was stirred vigorously while warming to 23 °C. After 30 min, a saturated aqueous solution of sodium chloride (10 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford a clear colorless oil.

The resulting residue was dissolved in THF (2.1 mL) and the solution was cooled to 0 °C. Lithium aluminum hydride (24.1 mg, 636 gmol, 6.00 equiv) was added and the reaction solution was allowed to warm to 23 °C. After 14.5 h, the reaction mixture quenched by the sequential addition of water (24.1 µL), a 15% aqueous solution of sodium hydroxide (24.1 µL), and water (72.3 µL). The resulting suspension was diluted with ethyl acetate and filtered through cotton. The filtrate was concentrated and the resulting residue was purified by flash column chromatography on silica gel (eluent: 0 → 15% ethyl acetate in hexanes, then 20 → 25% ethyl acetate in hexanes with 2% triethylamine) to afford (+)-deacetylaspidospermine (2.17, 18.2 mg, 55.0%) as an off-white solid. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments.

**(+)-Deacetylaspidospermine (2.17):**

**1H NMR (500 MHz, CDCl₃, 25 °C):**

\[ \delta 6.77-6.68 \text{ (m, 2H, } C_{14}H, C_{15}H) \], 6.64 \text{ (d, } J = 7.5 \text{ Hz, 1H, } C_{16}H) \), 3.82 \text{ (s, 3H, OCH₃) }, 3.57 \text{ (dd, } J = 11.1, \text{ 1.6 Hz, 1H, } C_{2}H) \), 3.11 \text{ (td, } J = 8.8, \text{ 2.9 Hz, 1H, } C_{10}H) \), 3.05 \text{ (d, } J = 10.9 \text{ Hz, 1H, } C_{8}H) \), 2.36–2.28 \text{ (m, 1H, } C_{11}H) \), 2.26–2.21 \text{ (m, 1H, } C_{10}H) \), 2.19 \text{ (s, 1H, } C_{14}H) \), 1.97–1.90 \text{ (m, 2H, } C_{2}H) \), 1.79–1.59 \text{ (m, 3H, } C_{3}H, C_{6}H, C_{7}H) \), 1.55–1.45 \text{ (m, 2H, } C_{7}H, C_{20}H) \), 1.46 \text{ (d, } J = 7.6 \text{ Hz, 1H, } C_{11}H) \), 1.37 \text{ (q, } J = 14.1, \text{ 12.5 Hz, 1H, } C_{3}H) \), 1.11 \text{ (dd, } J = 13.5, \text{ 4.7 Hz, 1H, } C_{6}H) \), 1.08–1.02 \text{ (m, 1H, } C_{4}H) \), 0.86 \text{ (dq, } J = 14.7, \text{ 7.5 Hz, 1H, } C_{20}H) \), 0.63 \text{ (t, } J = 7.5 \text{ Hz, 3H, } C_{21}H) \).

**13C NMR (150 MHz, CDCl₃, 25 °C):**

\[ \delta 146.1 \text{ (C}_{17}\text{), 138.5 \text{ (C}_{18}\text{), 136.8 \text{ (C}_{13}\text{), 119.6 \text{ (C}_{15}\text{), 115.5 \text{ (C}_{14}\text{), 109.0 \text{ (C}_{16}\text{), 71.4 \text{ (C}_{19}\text{), 66.2 \text{ (C}_{2}\text{), 55.4 \text{ (OCH}_{3}\text{), 54.3 \text{ (C}_{12}\text{), 54.0 \text{ (C}_{8}\text{), 53.2 \text{ (C}_{10}\text{), 38.6 \text{ (C}_{11}\text{), 35.8 \text{ (C}_{5}\text{), 34.7 \text{ (C}_{6}\text{), 30.1 \text{ (C}_{20}\text{), 28.4 \text{ (C}_{3}\text{), 23.2 \text{ (C}_{4}\text{), 22.0 \text{ (C}_{7}\text{), 7.0 \text{ (C}_{21}\text{)}}).} \]
FTIR (thin film) cm$^{-1}$: 2916 (s), 2847 (m), 2777 (w), 1591 (m), 1488 (s), 1462 (s), 1332 (w), 1198 (m).

HRMS (ESI) (m/z): calc’d for C$_{20}$H$_{29}$N$_{2}$O [M+H]$^+$: 313.2274, found: 313.2254.

$[\alpha]_{D}^{24}$: +25 (c = 0.83, CHCl$_3$)$^{11,12}$

TLC (30% ethyl acetate in hexanes with 3% triethylamine), Rf: 0.62 (UV, CAM).

$^{11}$ $[\alpha]_{D}^{24}$ = +25 was consistently observed at c = 0.83 and c = 0.09.

Table S1. Comparison of our $^1$H NMR data for (+)-deacetylaspidospermine (2.17) with literature data (CDCl$_3$):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Jiang’s Report$^{1,3}$ (+)-deacetylaspidospermine (2.17) $^1$H NMR, 500 MHz, CDCl$_3$</th>
<th>This Work (+)-deacetylaspidospermine (2.17) $^1$H NMR, 500 MHz CDCl$_3$, 25 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>3.57 (dd, $J = 11.1, 6.2$ Hz, 1H)</td>
<td>3.57 (dd, $J = 11.1, 6.2$ Hz, 1H)</td>
</tr>
<tr>
<td>C2</td>
<td>1.75–1.63 (m, 3H)</td>
<td>1.79–1.59 (m, 3H)</td>
</tr>
<tr>
<td>C3</td>
<td>1.42–1.33 (m, 1H)</td>
<td>1.37 (q, $J = 14.1, 12.5$ Hz, 1H)</td>
</tr>
<tr>
<td>C4</td>
<td>1.97–1.91 (m, 2H)</td>
<td>1.97–1.90 (m, 2H)</td>
</tr>
<tr>
<td>C5</td>
<td>1.04 (dt, $J = 13.5, 3.0$ Hz, 1H)</td>
<td>1.08–1.02 (m, 1H)</td>
</tr>
<tr>
<td>C6</td>
<td>1.75–1.63 (m, 3H)</td>
<td>1.79–1.59 (m, 3H)</td>
</tr>
<tr>
<td>C7</td>
<td>1.09 (td, $J = 27.0, 13.5$ Hz, 1H)</td>
<td>1.11 (dd, $J = 13.5, 4.7$ Hz, 1H)</td>
</tr>
<tr>
<td>C8</td>
<td>3.05 (d, $J = 10.8$ Hz, 1H)</td>
<td>3.05 (d, $J = 10.9$ Hz, 1H)</td>
</tr>
<tr>
<td>C9</td>
<td>1.97–1.91 (m, 2H)</td>
<td>1.97–1.90 (m, 2H)</td>
</tr>
<tr>
<td>C10</td>
<td>3.11 (td, $J = 8.9, 2.8$ Hz, 1H)</td>
<td>3.11 (td, $J = 8.8, 2.9$ Hz, 1H)</td>
</tr>
<tr>
<td>C11</td>
<td>2.35–2.29 (m, 1H)</td>
<td>2.36–2.28 (m, 1H)</td>
</tr>
<tr>
<td>C12</td>
<td>1.46 (d, $J = 8.5$ Hz, 1H)</td>
<td>1.46 (d, $J = 7.6$ Hz, 1H)</td>
</tr>
<tr>
<td>C13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C14</td>
<td>6.74 (dd, $J = 7.4, 1.3$ Hz, 1H)</td>
<td>6.77–6.68 (m, 2H)</td>
</tr>
<tr>
<td>C15</td>
<td>6.71 (t, $J = 7.5$ Hz, 1H)</td>
<td>6.77–6.68 (m, 2H)</td>
</tr>
<tr>
<td>C16</td>
<td>6.64 (dd, $J = 7.7, 1.3$ Hz, 1H)</td>
<td>6.64 (d, $J = 7.5$ Hz, 1H)</td>
</tr>
<tr>
<td>C17</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C17-OCH$_3$</td>
<td>3.82 (s, 3H)</td>
<td>3.82 (s, 3H)</td>
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<tr>
<td>C18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C19</td>
<td>2.19 (s, 1H)</td>
<td>2.19 (s, 1H)</td>
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<tr>
<td>C20</td>
<td>1.53–1.47 (m, 2H)</td>
<td>1.55–1.45 (m, 2H)</td>
</tr>
<tr>
<td>C21</td>
<td>0.63 (t, $J = 7.5$ Hz, 3H)</td>
<td>0.63 (t, $J = 7.5$ Hz, 3H)</td>
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</tbody>
</table>

$^1$ The $^1$H and $^{13}$C NMR data was not assigned in reference 5; we have tabulated the published values for comparison and the values are in excellent agreement with our data and assignments.
Table S2. Comparison of our 13C NMR data for (+)-deacetylaspidospermine (2.17) with literature data (CDCl3):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Jiang's Report5,13 (+)-deacetylaspidospermine (2.17) 13C NMR, 125 MHz, CDCl3</th>
<th>This Work (+)-deacetylaspidospermine (2.17) 13C NMR, 150 MHz, CDCl3, 25 °C</th>
<th>Chemical Shift Difference Δδ = δ (this work)−δ (Jiang's Report)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>66.0</td>
<td>66.2</td>
<td>0.2</td>
</tr>
<tr>
<td>C3</td>
<td>28.2</td>
<td>28.4</td>
<td>0.2</td>
</tr>
<tr>
<td>C4</td>
<td>23.0</td>
<td>23.2</td>
<td>0.2</td>
</tr>
<tr>
<td>C5</td>
<td>35.6</td>
<td>35.8</td>
<td>0.2</td>
</tr>
<tr>
<td>C6</td>
<td>34.5</td>
<td>34.7</td>
<td>0.2</td>
</tr>
<tr>
<td>C7</td>
<td>21.8</td>
<td>22.0</td>
<td>0.2</td>
</tr>
<tr>
<td>C8</td>
<td>53.9</td>
<td>54.0</td>
<td>0.1</td>
</tr>
<tr>
<td>C10</td>
<td>53.0</td>
<td>53.2</td>
<td>0.2</td>
</tr>
<tr>
<td>C11</td>
<td>38.4</td>
<td>38.6</td>
<td>0.2</td>
</tr>
<tr>
<td>C12</td>
<td>54.0</td>
<td>54.3</td>
<td>0.3</td>
</tr>
<tr>
<td>C13</td>
<td>136.6</td>
<td>136.8</td>
<td>0.2</td>
</tr>
<tr>
<td>C14</td>
<td>115.3</td>
<td>115.5</td>
<td>0.2</td>
</tr>
<tr>
<td>C15</td>
<td>119.5</td>
<td>119.6</td>
<td>0.1</td>
</tr>
<tr>
<td>C16</td>
<td>108.8</td>
<td>109.0</td>
<td>0.2</td>
</tr>
<tr>
<td>C17</td>
<td>145.9</td>
<td>146.1</td>
<td>0.2</td>
</tr>
<tr>
<td>C17-OCH3</td>
<td>55.2</td>
<td>55.4</td>
<td>0.2</td>
</tr>
<tr>
<td>C18</td>
<td>138.2</td>
<td>138.5</td>
<td>0.3</td>
</tr>
<tr>
<td>C19</td>
<td>71.3</td>
<td>71.4</td>
<td>0.1</td>
</tr>
<tr>
<td>C20</td>
<td>29.9</td>
<td>30.1</td>
<td>0.2</td>
</tr>
<tr>
<td>C21</td>
<td>6.8</td>
<td>7.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

89
(−)-Vallesine (2.15):

Acetic anhydride (159 µL) was added to a solution of (+)-deacetylaspidospermine (2.17, 14.9 mg, 47.7 µmol, 1 equiv) in formic acid (1.2 mL) at 23 °C, and the reaction flask was sealed with a Teflon-wrapped glass stopper. After 2.25 h, the reaction mixture was cooled to 0 °C, and a saturated aqueous solution of sodium bicarbonate (15 mL) was added. The resulting mixture was extracted with dichloromethane (4 × 15 mL). The combined organic layers were dried with anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes, then 10–30% ethyl acetate in hexanes with 2% triethylamine) to afford (−)-vallesine (2.15, 14.1 mg, 87.0%) as a white solid. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments.

1H NMR (500 MHz, CDCl3, 25 °C):

\[ \delta 9.33 (s, 1H, C_{22}H), 7.00 (t, J = 7.8 Hz, 1H, C_{13}H), 6.85 (dd, J = 7.5, 0.9 Hz, 1H, C_{14}H), 6.80 (dd, J = 8.2, 0.9 Hz, 1H, C_{16}H), 4.53 (dd, J = 11.1, 6.4 Hz, 1H, C_{2}H), 3.88 (s, 3H, OCH₃), 3.10 (td, J = 9.0, 3.2 Hz, 1H, C_{10}H₉), 3.02 (ddt, J = 10.9, 3.8, 1.7 Hz, 1H, C_{8}H₉), 2.24 (s, 1H, C_{19}H), 2.23–2.18 (m, 1H, C_{10}H₉), 2.13 (ddt, J = 13.4, 6.6, 3.4 Hz, 1H, C_{3}H₉), 2.08–2.03 (m, 1H, C_{11}H₉), 1.94 (ddd, J = 12.4, 10.9, 2.9 Hz, 1H, C_{8}H₈), 1.80–1.68 (m, 1H, C_{7}H₉), 1.66–1.60 (m, 1H, C_{6}H₈), 1.52–1.43 (m, 2H, C_{10}H₉), 1.38 (dq, J = 14.9, 7.6 Hz, 1H, C_{20}H₉), 1.26 (td, J = 14.3, 11.2, 3.7 Hz, 1H, C_{3}H₉), 1.11–1.03 (m, 2H, C_{4}H₈, C_{6}H₈), 0.84 (dq, J = 14.6, 7.4 Hz, 1H, C_{20}H₉), 0.63 (t, J = 7.5 Hz, 3H, C_{21}H₃).

13C NMR (150 MHz, CDCl₃, 25 °C):

\[ \delta 161.6 (C_{22}), 148.5 (C_{17}), 141.5 (C_{13}), 127.5 (C_{18}), 124.7 (C_{15}), 116.0 (C_{14}), 110.5 (C_{16}), 71.0 (C_{19}), 64.3 (C_{2}), 55.6 (OCH₃), 53.8 (C₅), 52.7 (C₁₂), 52.6 (C₁₀), 40.0 (C₈), 35.7 (C₅), 34.5 (C₆), 30.2 (C₂₀), 24.6 (C₃), 22.9 (C₄), 21.8 (C₇), 6.9 (C_{21}).\]

FTIR (thin film) cm⁻¹:

2928 (m), 2856 (w), 1658 (s), 1490 (m), 1464 (m), 1366 (m).

HRMS (ESI) (m/z):

calc’d for C_{21}H_{29}N_{2}O_{2}[M+H]⁺: 341.2224, found: 341.2228.
TLC (30% ethyl acetate in hexanes with 3% triethylamine), Rf: 0.20 (UV, CAM).  

$[\alpha]_D^{24} = -71$ (c = 0.71, CHCl$_3$)$_{14}$

Table S3. Comparison of our $^1$H NMR data for (−)-vallesine (2.15) with literature data (CDCl3):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Zêches' Isolation Report$^{15}$ (−)-vallesine (2.15) $^1$H NMR, 300 MHz, CDCl3</th>
<th>This Work (−)-vallesine (2.15) $^1$H NMR, 500 MHz CDCl3, 25 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>4.53 (dd, $J = 11, 6.1$ Hz, 1H)</td>
<td>4.53 (dd, $J = 11.1, 6.4$ Hz, 1H)</td>
</tr>
<tr>
<td>C3</td>
<td>2.15 (m, 1H)</td>
<td>2.13 (ddt, $J = 13.4, 6.6, 3.4$ Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>1.27 (m, 1H)</td>
<td>1.26 (dd, $J = 14.3, 11.2, 3.7$ Hz, 1H)</td>
</tr>
<tr>
<td>C4</td>
<td>2.08 (m, 1H)</td>
<td>2.03–1.98 (m, 1H)</td>
</tr>
<tr>
<td></td>
<td>1.1 (dd, $J = 13.4, 4.4$ Hz, 1H)</td>
<td>1.11–1.03 (m, 2H)</td>
</tr>
<tr>
<td>C5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C6</td>
<td>1.63 (br-d, $J = 13$ Hz, 1H)</td>
<td>1.66–1.60 (m, 1H)</td>
</tr>
<tr>
<td></td>
<td>1.05 (dd, $J = 13, 4.3$ Hz, 1H)</td>
<td>1.11–1.03 (m, 2H)</td>
</tr>
<tr>
<td>C7</td>
<td>1.75 (qt, $J = 13, 4$ Hz, 1H)</td>
<td>1.80–1.68 (m, 1H)</td>
</tr>
<tr>
<td></td>
<td>1.45 (dd, $J = 13, 3$ Hz, 1H)</td>
<td>1.52–1.43 (m, 2H)</td>
</tr>
<tr>
<td>C8</td>
<td>3 (br-d, $J = 11$ Hz, 1H)</td>
<td>3.02 (dd, $J = 10.9, 3.8, 1.7$ Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>1.93 (dd, $J = 11, 2.8$ Hz, 1H)</td>
<td>1.94 (dd, $J = 12.4, 10.9, 2.9$ Hz, 1H)</td>
</tr>
<tr>
<td>C10</td>
<td>3.1 (td, $J = 9, 3.3$ Hz, 1H)</td>
<td>3.10 (td, $J = 9.0, 3.2$ Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>2.23 (m, 1H)</td>
<td>2.23–2.18 (m, 1H)</td>
</tr>
<tr>
<td>C11</td>
<td>2.03 (dd, $J = 12, 3.3$ Hz, 1H)</td>
<td>2.08–2.03 (m, 1H)</td>
</tr>
<tr>
<td></td>
<td>1.5 (dd, $J = 12, 3$ Hz, 1H)</td>
<td>1.52–1.43 (m, 2H)</td>
</tr>
<tr>
<td>C12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C14</td>
<td>6.85 (d, $J = 7.5$ Hz, 1H)</td>
<td>6.85 (dd, $J = 7.5, 0.9$ Hz, 1H)</td>
</tr>
<tr>
<td>C15</td>
<td>7.0 (t, $J = 7.5$ Hz, 1H)</td>
<td>7.00 (t, $J = 7.8$ Hz, 1H)</td>
</tr>
<tr>
<td>C16</td>
<td>6.8 (d, $J = 7.5$ Hz, 1H)</td>
<td>6.80 (dd, $J = 8.2, 0.9$ Hz, 1H)</td>
</tr>
<tr>
<td>C17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C17-OCH$_3$</td>
<td>3.87 (s, 3H)</td>
<td>3.88 (s, 3H)</td>
</tr>
<tr>
<td>C18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C19</td>
<td>2.21 (s, 1H)</td>
<td>2.24 (s, 1H)</td>
</tr>
<tr>
<td>C20</td>
<td>1.4 (dq, $J = 14, 7.3$ Hz, 1H)</td>
<td>1.38 (dq, $J = 14.9, 7.6$ Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>0.85 (dq, $J = 14, 7.3$ Hz, 1H)</td>
<td>0.84 (dq, $J = 14.6, 7.4$ Hz, 1H)</td>
</tr>
<tr>
<td>C21</td>
<td>0.63 (t, $J = 7.3$ Hz, 3H)</td>
<td>0.63 (t, $J = 7.5$ Hz, 3H)</td>
</tr>
<tr>
<td>C22</td>
<td>9.3 (s, 1H)</td>
<td>9.33 (s, 1H)</td>
</tr>
</tbody>
</table>

Table S4. Comparison of our $^{13}$C NMR data for (-)-vallesine (2.15) with literature data (CDCl$_3$):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Zèches' Isolation Report$^{15}$ ((-\text{-})\text{-vallesine (2.15)}) $^{13}$C NMR</th>
<th>This Work ((-\text{-})\text{-vallesine (2.15)}) $^{13}$C NMR, 150 MHz, CDCl$_3$, 25 °C</th>
<th>Chemical Shift Difference$^{16}$ $\Delta\delta = \delta \text{(this work)} - \delta \text{(Zèches' Report)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>63.9</td>
<td>64.3</td>
<td>0.4</td>
</tr>
<tr>
<td>C3</td>
<td>24.2</td>
<td>24.6</td>
<td>0.4</td>
</tr>
<tr>
<td>C4</td>
<td>22.5</td>
<td>22.9</td>
<td>0.4</td>
</tr>
<tr>
<td>C5</td>
<td>35.3</td>
<td>35.7</td>
<td>0.4</td>
</tr>
<tr>
<td>C6</td>
<td>34.1</td>
<td>34.5</td>
<td>0.4</td>
</tr>
<tr>
<td>C7</td>
<td>21.4</td>
<td>21.8</td>
<td>0.4</td>
</tr>
<tr>
<td>C8</td>
<td>53.5</td>
<td>53.8</td>
<td>0.3</td>
</tr>
<tr>
<td>C9</td>
<td>52.3</td>
<td>52.6</td>
<td>0.3</td>
</tr>
<tr>
<td>C10</td>
<td>39.6</td>
<td>40.0</td>
<td>0.4</td>
</tr>
<tr>
<td>C11</td>
<td>52.3</td>
<td>52.7</td>
<td>0.4</td>
</tr>
<tr>
<td>C12</td>
<td>127</td>
<td>141.5$^{17}$</td>
<td>14.5$^{17}$</td>
</tr>
<tr>
<td>C13</td>
<td>115.6</td>
<td>116.0</td>
<td>0.4</td>
</tr>
<tr>
<td>C14</td>
<td>124.4</td>
<td>124.7</td>
<td>0.3</td>
</tr>
<tr>
<td>C15</td>
<td>110.1</td>
<td>110.5</td>
<td>0.4</td>
</tr>
<tr>
<td>C16</td>
<td>148.1</td>
<td>148.5</td>
<td>0.4</td>
</tr>
<tr>
<td>C17</td>
<td>55.2</td>
<td>55.6</td>
<td>0.4</td>
</tr>
<tr>
<td>C17-OCH$_3$</td>
<td>140.8</td>
<td>127.5$^{17}$</td>
<td>-13.3$^{17}$</td>
</tr>
<tr>
<td>C18</td>
<td>70.7</td>
<td>71.0</td>
<td>0.3</td>
</tr>
<tr>
<td>C19</td>
<td>29.8</td>
<td>30.2</td>
<td>0.4</td>
</tr>
<tr>
<td>C20</td>
<td>6.6</td>
<td>6.9</td>
<td>0.3</td>
</tr>
<tr>
<td>C21</td>
<td>161.2</td>
<td>161.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

$^{16}$ The $^{13}$C NMR data are in excellent agreement with the isolation report. The solvent reference value was not provided in reference 15. The solvent reference value of $\delta$ 77.16 is used in this report.

$^{17}$ The $^1$H and $^{13}$C data are in excellent agreement with the isolation report. Analysis of key gHMBC correlations is most consistent with our revised assignment of C13 and C18 resonances.
Chapter III

Enantioselective Total Synthesis of (−)-Jerantinine A from (−)-Melodinine P
Introduction

While aspidosperma alkaloids have been identified in isolation reports as early as the late-1800s, new alkaloids in this family have continued to be identified as recently as this year. Innovative synthetic strategies continue to amplify access to these newly discovered aspidosperma alkaloids, enabling comprehensive chemical and biological studies of this class of natural products. Our unified synthesis of numerous aspidosperma alkaloids from common intermediates that enable rapid generation of molecular complexity is described in detail in Chapter II. Recent work focused on amplifying access to arene-oxidized aspidosperma alkaloids has culminated in the first total syntheses of (+)-haplocidine (3.6) and (-)-vallesine (3.9, Figure 3.1) through complementary methods for regioselective C17-oxidation. Development of additional site-selective oxidation strategies would enable access to the (-)-jerantinine alkaloids 3.1–3.5 and the first total synthesis of (-)-melodinine P (3.7, Figure 1). Based on the scarcity of these alkaloids in nature, with isolation yields ranging from 0.0004 to 0.184 g kg\(^{-1}\) of plant material, enantioselective total synthesis remains the most attractive and efficient technique to access these potent natural products for comprehensive studies.

\[ \text{Figure 3.1. Structures of representative arene-oxidized aspidosperma alkaloids (3.1–3.9).} \]
To date, two synthetic solutions to the jerantinine alkaloids have been reported with the first providing (±)-jerantinine E (3.5)\(^8\) and the second enabling access to (−)-jerantinines A (3.1), C (3.3), and E (3.5).\(^9\) An additional strategy towards (−)-jerantinine E (3.3) focuses on construction of the functionalized ABC-ring system.\(^10\) Importantly, all previous strategies towards this class of oxidized alkaloids have relied on commercial materials for the introduction of A-ring oxidation.

Scheme 3.1. Waser’s synthesis of (±)-jerantinine E (3.5). Conditions: (a) t-BuLi, LiCl, THF, \(-78 \rightarrow -20 \, ^\circ\text{C}, 72\%\). (b) Cu(OTf)\(_2\) (20 mol\%), CH\(_3\)CN, 85\%. (c) LiAlH\(_4\), THF, 96\%. (d) BF\(_3\)·OEt\(_2\), Me\(_3\)SiCN, CH\(_2\)Cl\(_2\); (e) HCl, MeOH, then H\(_2\)O; (f) Pd/C, H\(_2\), EtOH; (g) Na\(_2\)CO\(_3\), MeOH, BrCH\(_2\)CH\(_2\)OH, 78\% (4 steps). (h) MsCl, NEt\(_3\), CH\(_2\)Cl\(_2\); (i) t-BuOK, THF, 85\% (2 steps). (j) (NH\(_4\))\(_2\)Ce(NO\(_3\))\(_6\), H\(_2\)O, CH\(_3\)CN, then Na\(_2\)S\(_2\)O\(_4\), 79\%. Ms = methanesulfonyl.

Waser reported the first total synthesis of (±)-jerantinine E (3.5) in 2013, wherein alkaloid (±)-3.5 was accessed in 17 steps and 16\% overall yield from δ-valerolactam (3.10 Scheme 3.1).\(^8\) Coupling of Weinreb amide 3.11 with the oxygenated indole 3.12 provided access to aminocyclopropane 3.13, which undergoes a formal homo-Nazarov cyclization to provide tetracycle 3.14. This highly selective cyclization had previously been demonstrated on a non-arene oxygenated aminocyclopropane in their formal synthesis of (±)-aspidospermidine.\(^11\) After reduction of ketone 3.14, a four-step sequence was employed to install the C3-ester group and N9-alkyl substituent. Intermediate 3.15 underwent E-ring formation following Rawal’s procedure,\(^12\) and selective oxidative demethylation enabled access to (±)-jerantinine E (3.5). Separation of the
enantiomers by chiral chromatography and assay for cytotoxicity in human-derived breast- and lung- cancer cell lines revealed that only the naturally occurring (-)-jerantinine E (3.5) was significantly active.

Persistent interest in the jerantinine alkaloids has been demonstrated by the recent reports of Magauer in 2017\textsuperscript{10} and Jiang in 2018.\textsuperscript{9} Utilizing their protocol for one-pot \( \beta \)-C–H bromination of enones,\textsuperscript{13} Magauer demonstrated the synthesis of a highly functionalized potential ABC-ring precursor to (-)-jerantinine E (3.5, Scheme 3.2). While \( \beta \)-bromo enone 3.18 was quickly accessed from ketone 3.16, and efficient coupling with 3,4-dimethoxyaniline (3.19) provided entry to a versatile intermediate 3.20, the direct application of this strategy to the synthesis of jerantinine alkaloids remains unconfirmed. Strategies to install the C5-ethyl group, either directly or as a methyl ester that could be subsequently reduced, were met with reactivity and functional group compatibility issues. While \( \beta \)-keto ester 3.21 is highly functionalized and contains all carbon atoms of the pentacyclic aspidosperma core, application to the synthesis of (-)-jerantinine E (3.5) may not be straightforward, as initial attempts at palladium-catalyzed decarboxylative allylation\textsuperscript{14} were unsuccessful, and a methodology for homologation of the C3-ether to install the vinylogous carbamate moiety has not been provided.

Scheme 3.2. Magauer’s strategy towards (-)-jerantinine E (3.5). Conditions: (a) BocNHNH\textsubscript{2}, Na\textsubscript{2}SO\textsubscript{4}, CICH\textsubscript{2}CH\textsubscript{2}Cl, 85 \(^\circ\)C; NBS, then NE\textsubscript{t}\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, 0 \(\rightarrow\) 23 \(^\circ\)C; Amberlyst\textregistered\textsubscript{15}, H\textsubscript{2}O, acetone, 50 \(^\circ\)C, 57%. (b) SPhos (10 mol%), SPhos Pd GH (10 mol%), t-BuONa, PhMe, 80 \(^\circ\)C, 77%. (c) Pd(OAc)\textsubscript{2} (10 mol%), Cu(OAc)\textsubscript{2}, K\textsubscript{2}CO\textsubscript{3}, DMF, 140 \(^\circ\)C, 57%. (d) NaH, BnBr, DMF, 0 \(\rightarrow\) 23 \(^\circ\)C, 89%. (e) allyl cyanoformate, LHMDS, HMPA, THF, -78 \(\rightarrow\) 23 \(^\circ\)C; (f) tert-butyl (2-(benzyloxy)ethyl)(3-iodopropyl) carbamate,
LHMDS, THF, −78 → 23 °C, 33% (2 steps). Boc = tert-butyloxycarbonyl. NBS = N-bromosuccinimide.
LHMDS = lithium hexamethyldisilazide. HMPA = hexamethylphosphoramide.

In 2018, Jiang reported the asymmetric total synthesis of (−)-jerantinines A (3.1), C (3.3) and E (3.5),9 based upon their previously reported strategy15 for divergent aspidosperma alkaloid synthesis (Figure 2.3A, Chapter II). Inverse-electron-demand [4+2] cycloaddition was utilized to stereoselectively construct the CE-ring bicycle 3.24 (Scheme 3.3). Elaboration to enone 3.25 followed by Fischer indole synthesis16 provided entry to tetracycle 3.26 which was subject to D-ring construction and imine reduction and isomerization, followed by thiolactam formation to provide key intermediate pentacycle 3.27. Desulfurization of thiolactam 3.27 followed by oxidative C15-demethylation provided direct access to (−)-jerantine E (3.5), while oxidation to α,β-unsaturated thiolactam 3.28 provided entry to (−)-jerantinines A (3.1) and C (3.3).

Scheme 3.3. Jiang’s synthesis of (−)-jerantinines A (3.1), C (3.3) and E (3.5). Conditions: (a) PhMe, reflux, 60 h, 48% (72% brsm). (b) TFA, CH₂Cl₂, 99%. (c) Pd(OAc)₂, I₂, hv; (d) diisobutylaluminum hydride, PhMe; (e) Ph=P(CH₂O)₂, PhMe, 68% (3 steps). (f) Dess-Martin periodinane, CH₂Cl₂, 96%. (g) 3,4-dimethoxyphenylhydrazine hydrochloride, TFA, t-BuOH, 80 °C, 59%. (h) Pd(PPh₃)₄, CO, NaH₂, MeOH, DMF, 80 °C, 81%. (i) H₂, Pd/C, EtOH, 82%. (j) P₂S₅, THF, 82%. (k) H₂, Raney-Ni, THF, 81%. (l) (NH₄)₂Ce(NO₃)₆, H₂O, CH₃CN, then Na₂S₂O₄, 75% for (−)-3.1, 73% for (−)-3.3, 81% for (−)-3.5. (m) para-toluensulfinychloride, i-Pr₂NET, PhMe, reflux, 62%. (n) Me₃OBF₄, CH₂Cl₂; NaBH₄, MeOH, 62%. (o) meta-chloroperbenzoic acid, CH₂Cl₂, 34%.
**Biological Significance.** As described in Chapter II, methods to selectively address oxygenation of the aspidosperma indoline core are essential to further exploring the unique potency of this subclass of alkaloids. Upon their isolation in 2008, (−)-jerantinines A–E (3.1–3.5) were found to display significant cytotoxicity (IC₅₀ 0.3–0.8 μg/mL) towards drug-sensitive as well as vincristine-resistant KB cells, a subline of HeLa cervical cancer cells, a level of potency that is rare among aspidosperma alkaloids.⁶ In 2013, Waser demonstrated the potency of (−)-jerantinine E (3.5) in human-derived breast- and lung-cancer cell lines, with the highest cytotoxicity (IC₅₀ 1.0 μM) being demonstrated in A549 cells (lung carcinoma).⁸ In 2014 and 2016, respectively, (−)-jerantinines A (3.1) and B (3.2) were determined to cause profound G2/M cell cycle arrest and inhibit growth and colony formation of human-derived carcinoma cells.¹⁷ In 2017, Leong and coworkers reported that alkaloid (−)-3.1 induces tumor-specific cell death in breast cancer cell lines by causing abnormal splicing patterns and inhibiting microtubule polymerization and identified the jerantinine alkaloids as an attractive candidate for further development as an anticancer agent.¹⁸ Synthetic methodology to enable comparative studies of this alkaloid family could be key to elucidating biological mechanisms of action and identifying opportunities for development of clinical candidates.

**Results and Discussion**

Our retrosynthetic analysis of (−)-jerantinine A (3.1) was founded on the proposed utility of *para*-aza-quinone methide intermediate (+)-3.30 (Scheme 3.4). In a biosynthetic sense, (−)-jerantinine A (3.1) could arise directly from related natural product (−)-melodinine P (3.7) via final-stage site-selective C16-methoxylation. Alternatively, the highly oxidized indoline 3.29 could provide direct access to (−)-jerantinine A (3.1) through final-stage C-ring oxidation. Both (−)


(-)-melodinine P (3.7) and indoline 3.29 would be accessed through selective A-ring or C-ring functionalization, respectively, of para-aza-quinone methide (+)-3.30. The versatile C15-oxidized intermediate (+)-3.30 would be synthesized directly from pentacycle (-)-3.31, accessed previously from lactam (+)-3.32 in our synthesis of (-)-mehranine and related alkaloids.

Scheme 3.4. Retrosynthetic analysis of (-)-jerantinine A (3.1) and (-)-melodinine P (3.7)

Initial synthetic studies\textsuperscript{19} were enabled by material accessed in my previous studies (Chapter II) from lactam (-)-3.32, which affords pentacycle (+)-3.31 efficiently in two steps.\textsuperscript{3c,20} Based on literature precedent for C15-methoxylation of the indoline core of aspidosperma alkaloids,\textsuperscript{21} we utilized bisacetoxyiodosobenzene in acetic acid to afford para-aza-quinone methide (-)-3.30 from pentacycle (+)-3.31 (Scheme 3.5). We were interested in the utility of intermediate (-)-3.30 for either further A-ring oxidation or C-ring functionalization. Gratifyingly, exposure of para-aza-quinone methide (-)-3.30 to acid in methanol in the presence of bisacetoxyiodosobenzene resulted in selective C16-methoxylation to afford intermediate 3.33, albeit in a low 33% yield. Attempts to optimize this transformation by moving to basic
methoxylation conditions yielded quantitative tautomerization of para-aza-quinone methide (-)-3.30 via deprotonation of the C2-position to afford imine 3.34 in 93% yield. This transfer of oxidation state from the A-ring to the C-ring provided an exciting opportunity to complete the first total synthesis of (+)-melodinine P (3.7).

![Scheme 3.5](image)

Scheme 3.5. First generation synthesis of (+)-jerantinine A (3.1) and (+)-melodinine P (3.7). Conditions: (a) PhI(OAc)₂, AcOH, 87%. (b) p-TsOH·H₂O, PhI(OAc)₂, MeOH, 33%. (c) DBU, MeOH, 93%. (d) DBU, MeOH, 79%. (e) n-BuLi, THF, -78 °C; NCCO₂Me, -78 → 23 °C; NaOMe, MeOH, 41%. (f) n-BuLi, THF, -78 °C; NCCO₂Me, -78 → 23 °C, 19%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Exposure of imine 3.34 to n-butyllithium and trapping of the resulting metalloenamine with methylcyanformate followed by treatment with sodium methoxide in methanol affords (+)-melodinine P (3.7) in 41% yield (Scheme 3.5). While spectroscopic data was consistent with the literature, detailed characterization and assignment was conducted on the natural enantiomer accessed in our second generation synthesis and described herein. We were delighted to find that this methodology for C-ring functionalization could be extended to the C16-methoxylated para-aza-quinone methide 3.33 to enable our first generation synthesis of (+)-jerantinine A (3.1). Tautomerization of intermediate 3.33 was effected using 1,8-diazabicyclo[5.4.0]undec-7-ene in methanol to provide the highly oxidized imine 3.35 in 79% yield. Notably, in their synthesis of
(+)-jerantinine E (3.5), Waser and coworkers avoided the use of such highly electron-rich and reactive imines owing to decomposition upon isolation attempts.\(^8\) We were able to access a synthetically pure sample of imine 3.35 via flash column chromatography on alumina to utilize for C3-carbonylation. In the event, deprotonation of imine 3.35 with \(n\)-butyllithium and exposure to methylcyanoformate directly afforded (+)-jerantinine A (3.1) in 19% yield. While spectroscopic data for alkaloid (+)-3.1 was consistent with the literature, detailed characterization and assignment was conducted on the natural enantiomer.

While we were delighted to utilize our A-ring to C-ring oxidation state transfer to enable our first generation synthesis of (+)-melodinine P (3.7) and (+)-jerantinine A (3.1), we sought to optimize the efficiency of the C-ring functionalization. Based on the expected efficiency for C3-carbonylation in related systems,\(^3\) it was evident that the C15-phenol was having deleterious effects, and we hypothesized that silylation of that position could mitigate these effects.

**Scheme 3.6.** Second generation synthesis of (-)-melodinine P (3.7). (a) PhI(OAc)\(_2\), AcOH, 93%. (b) TBSOTf, \(\text{NEt}_3\), PhMe, 0 \(\rightarrow\) 23 °C; \(n\)-BuLi, THF, \(-78\) °C; NCCO\(_2\)Me, \(-78\) \(\rightarrow\) 23 °C, 54%. (c) \(\text{NEt}_3\cdot3\text{HF}\), CH\(_3\)CN, 60%. TBSOTf = tert-butyldimethylsilyl trifluoromethanesulfonate.
For our optimized, second generation synthetic strategy, pentacycle (-)-3.31 provides para-aza-quinone methide (+)-3.30 in 93% yield (Scheme 3).²⁴ Gratifyingly, we were able to access C15-O-silylated imine 3.37 in a single pot from para-aza-quinone-methide (+)-3.30 through a silylative-tautomerization process via intermediate 3.36. While imine 3.37 was stable and isolable by flash column chromatography, we optimized a single-pot procedure for maximal material throughput and scalability of the C-ring functionalization. In the event, silylative-tautomerization of para-aza-quinone methide (+)-3.30 occurs quantitatively in toluene, and dilution with tetrahydrofuran followed by deprotonation with n-butyllithium and exposure to methylcyanoformate affords vinylogous carbamate (-)-3.38 in a satisfying 54% yield (Scheme 3.6). tert-Butyldimethylsilyl ether (-)-3.38 is deprotected with triethylamine trihydrofluoride in acetonitrile to afford (-)-melodinine P (3.7) in 60% yield. All spectroscopic data as well as the optical rotation data [observed [α]D²⁴ = -289 (c = 0.13, MeOH); lit. [α]D²⁴ = -158.3 (c = 0.164, MeOH)] for (-)-melodinine P (3.7) were consistent with the literature.⁷

In addition to suffering the deleterious effects of the C15-phenol in the C-ring functionalization, our first generation synthesis of (-)-jerantinine A (3.1) was plagued by inefficient yields for C16-methoxylation. At this stage, we returned to our initial hypothesis that oxidative C16-methoxylation of (-)-melodinine P (3.7) would provide direct access to (-)-jerantinine A (3.1). In further attempts to streamline the use of the silyl protecting group, we utilized vinylogous carbamate (-)-3.38 as a surrogate for (-)-melodinine P (3.7) in our single-pot synthesis of (-)-jerantinine A (3.1, Scheme 3.7). Quantitative deprotection of tert-butyldimethylsilyl ether (-)-3.38 using triethylamine trihydrofluoride in methanol was followed by introduction of silver oxide to afford para-aza-quinone methide 3.39.²⁵ Ensuing C16-methoxylation occurs selectively to provide intermediate 3.40 which, after reductive workup using
sodium dithionite, directly affords \((-\)-jerantinine A (3.1)\) in 60% yield. All spectroscopic data as well as the optical rotation data \([\text{observed } [\alpha]_D^{24} = -300 (c = 0.305, \text{CHCl}_3); \text{lit. } [\alpha]_D = -294 (c = 0.65, \text{CHCl}_3)\) and \([\alpha]_D^{25} = -305.1 (c = 0.65, \text{CHCl}_3)\) for \((-\)-jerantinine A (3.1)\) were consistent with the literature.

\[\text{Scheme 3.7. Second generation synthesis of } (-\)-jerantinine A (3.7). Conditions: (a) \text{NEt}_3\cdot3\text{HF, MeOH; Ag}_2\text{O; Na}_2\text{S}_2\text{O}_4(1\text{M aq), 60%}.}\]

**Conclusion**

In summary, we have developed the efficient synthesis of \((-\)-melodinine P (3.7)\) which provides direct synthetic access to \((-\)-jerantinine A (3.1)\) via our biogenetically inspired A-ring oxidation. Alkaloids \((-\)-3.7 and \((-\)-3.1\) are synthesized in 3 steps each from the known aspidosperma pentacycle \((-\)-3.31\). This constitutes the first total synthesis of \((-\)-melodinine P (3.7)\) and the first strategy towards \((-\)-jerantinine A (3.1)\) which does not rely on commercial materials for the introduction of arene-oxidation. The successful synthesis of \text{para-aza-quinone methide } (+)-3.30\) and its silylative-tautomerization enabled rapid C3-functionalization via A-ring to C-ring oxidation state transfer. Utility of \text{tert-butyldimethylsilyl ether } (-)-3.38\) as a surrogate for \((-\)-melodinine P (3.7)\) ensures that no additional steps are introduced to make use of the additional
stability imparted by silylation in our synthesis of (-)-jerantinine A (3.1). Our unified strategy towards aspidosperma alkaloids continues to serve as an excellent platform for diversification of common intermediates to amplify our access to a diverse range of aspidosperma substructures.


(19) Please see the Experimental Section for further details.

(20) Lactam (−)-3.32 was synthesized in 80% ee (See Chapter II) via an asymmetric alkylation strategy\textsuperscript{3c} utilizing the readily commercially available (+)-(1S,2S)-pseudoephedrine chiral auxiliary.\textsuperscript{3a}


(24) Pentacycle (−)-3.31 was synthesized in >99% ee via an asymmetric alkylation strategy\textsuperscript{3c} utilizing the synthetic (+)-(1R,2R)-pseudoephedrine chiral auxiliary, prepared in four steps from commercial materials. Please see Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem. Int. Ed.* 2012, 51, 4568.

(25) Direct exposure of (−)-melodinine P (3.7) to silver oxide in methanol also efficiently provides imine 3.39 which proceeds to form (−)-jerantinine A (3.1) as described in Scheme 3.7.
EXPERIMENTAL SECTION

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks, modified Schlenk (Kjeldahl shape) flasks or glass pressure vessels. The flasks were fitted with rubber septa or Teflon-wrappped glass stoppers, and reactions were conducted under a positive pressure of argon. Cannulae or gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al.\(^1\) using granular silica gel (60-A pore size, 40–63 \(\mu\)m, 4–6% \(H_2O\) content, Zeochem) or non-activated alumina (80–325 mesh, chromatographic grade). Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) or basic alumina impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to short wave ultraviolet light (254 nm) and irreversibly stained by treatment with an aqueous solution of ceric ammonium molybdate (CAM) followed by heating (~ 1 min) on a hot plate (~ 250 °C). Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of ~2 torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, acetonitrile, tetrahydrofuran, toluene, and methanol were purchased from J. T. Baker (Cycletainer\textsuperscript{TM}) and were purified by the method of Grubbs et al. under positive argon pressure.\(^2\) The molarity of n-butyllithium solutions was determined by titration against diphenylacetic acid.\(^3\) tert-Butyldimethylsilyl trifluoromethanesulfonate was purchased from Chem-Impex International, Inc. Silver oxide was purchased from Strem Chemicals, Inc. Sodium dithionite was purchased from Mallinckrodt Pharmaceuticals. All other solvents and chemicals were purchased from Sigma-Aldrich.

Instrumentation. Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded with a Varian inverse probe INOVA-500, Varian INOVA-500, or Bruker AVANCE-600 spectrometer. Chemical shifts are recorded in parts per million on the \(\delta\) scale and are referenced from the residual protium in the NMR solvent [CDC\(_3\): \(\delta\) 7.26 (CHCl\(_3\), acetone-\(d_6\): \(\delta\) 2.05 (acetone-\(d_5\))]. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (\(^{13}\)C NMR) spectra were recorded with a Varian INOVA-500 or Bruker AVANCE-600 spectrometer. Chemical shifts are recorded in parts per million on the \(\delta\) scale and are referenced from the carbon resonances of the solvent (CDC\(_3\): \(\delta\) 77.16, acetone-\(d_6\): \(\delta\) 29.84). Data are reported as follows: chemical shift (assignment). Infrared data were obtained with a Perkin–Elmer 2000 FTIR and are reported as follows: frequency of absorption (\(cm^{-1}\)) [intensity of absorption (s = strong, m = medium, w = weak, br = broad)]. Optical rotations were measured on a Jasco-1010 polarimeter. We thank Dr. Li Li, Liam P. Kelly, and Dr. Mohanraja Kumar at the Massachusetts Institute of Technology Department of Chemistry instrumentation facility for obtaining mass spectroscopic data. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS using an electrospray ionization (ESI) source or a direct analysis in real time (DART) ionization source or on an Agilent 6510 Q-TOF-MS using an ESI source.

Positional Numbering System. At least two numbering systems exist in the literature for the aspidosperma alkaloids.\textsuperscript{4,5} For direct comparison between structures, the numbering system shown below for (−)-jerantinine A (3.1) is used throughout this report.

\begin{center}
\includegraphics[width=0.4\textwidth]{fig1}
\end{center}

(−)-jerantinine A (3.1)


Para-aza-quinone methide (+)-3.30:

Diacetoxyiodobenzene (224 mg, 0.695 mmol, 2.50 equiv) was added as a solid to a solution of pentacycle (-)-3.31\(^6\) (78.0 mg, 0.278 mmol, 1 equiv) in acetic acid (5.6 mL) at 23 °C. After 5 h, the reaction mixture was concentrated under reduced pressure to half volume. The resulting solution was diluted with ethyl acetate (10 mL) and a solution of saturated aqueous sodium bicarbonate (10 mL) was added slowly. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on alumina (eluent: 0 -- > 50% ethyl acetate in hexanes) to afford para-aza-quinone methide (+)-3.30 (75.7 mg, 92.5%) as a yellow crystalline solid. Structural assignments were made using additional information from gCOSY, deHSQC, and gHMBC experiments.

\(^1\)H NMR (500 MHz, CDCl\(_3\), 25 °C):

\[\begin{align*}
\delta & 7.44 (d, J = 9.8 \text{ Hz}, 1H, C_{17}H), 6.62 (dd, J = 9.9, 1.9 \text{ Hz}, 1H, C_{16}H), 6.29 (d, J = 1.8 \text{ Hz}, 1H, C_{14}H), 5.72 (dd, J = 10.0, 5.0, 1.7 \text{ Hz}, 1H, C_7H), 5.50 (dd, J = 10.0, 2.7, 1.5 \text{ Hz}, 1H, C_8H), 4.48 (dd, J = 9.6, 6.8 \text{ Hz}, 1H, C_3H), 3.44 (ddd, J = 15.9, 5.0, 1.5 \text{ Hz}, 1H, C_6H), 3.27 (td, J = 8.7, 2.4 \text{ Hz}, 1H, C_{10}H), 2.75 (dt, J = 16.1, 2.1 \text{ Hz}, 1H, C_9H), 2.42 (s, 1H, C_{19}H), 2.40--2.29 (m, 2H, C_{18}H, C_3H), 2.01 (dt, J = 13.0, 8.8 \text{ Hz}, 1H, C_{13}H), 1.89--1.76 (m, 2H, C_4H, C_{11}H), 1.34 (ddd, J = 13.8, 5.9, 3.1 \text{ Hz}, 1H, C_{12}H), 1.12 (qd, J = 7.4, 3.8 \text{ Hz}, 2H, C_{20}H), 1.01 (ddd, J = 13.9, 12.7, 9.6, 3.1 \text{ Hz}, 1H, C_5H), 0.74 (t, J = 7.4 \text{ Hz}, 3H, C_{21}H).
\end{align*}\]

\(^{13}\)C NMR (150 MHz, CDCl\(_3\), 25 °C):

\[\begin{align*}
\delta & 187.8 (C_{15}), 164.1 (C_{18}), 161.4 (C_{13}), 135.6 (C_{16}), 134.1 (C_{17}), 133.5 (C_6), 123.5 (C_7), 122.1 (C_{14}), 83.5 (C_2), 70.0 (C_{19}), 53.6 (C_{12}), 53.4 (C_{10}), 52.5 (C_8), 44.0 (C_4), 38.7 (C_5), 30.3 (C_{11}), 29.5 (C_{20}), 28.0 (C_3), 7.8 (C_{21}).
\end{align*}\]

FTIR (thin film) cm\(^{-1}\):

2933 (br-m), 2788 (br-w), 1644 (s), 1630 (s), 1456 (m), 1248 (w), 891 (m).

HRMS (ESI) (m/z):

calc’d for C\(_{19}\)H\(_{23}\)N\(_2\)O [M+H]\(^+\): 295.1805, found: 295.1814.

[α]D^24: +135 \( (c = 0.22, \text{CH}_2\text{Cl}_2) \).

M.p.: 108 °C, decomposition (hexanes).

TLC (Al₂O₃, 25% ethyl acetate in hexanes), Rf: 0.38 (UV, CAM).
Vinylogous carbamate (-)-3.38:

*tert*-Butyldimethylsilyl trifluoromethanesulfonate (60.4 µL, 0.263 mmol, 1.10 equiv) was added via syringe to a solution of para-aza-quinone methide (+)-3.30 (70.4 mg, 0.239 mmol, 1 equiv) and triethylamine (73.3 µL, 0.526 mmol, 2.20 equiv) in toluene (2.4 mL) at 0 °C, and the resulting mixture was allowed to warm to 23 °C. The solvent had been deoxygenated by purging with a stream of argon for 5 min. After 1.5 h, the reaction mixture was cooled to −78 °C and diluted with tetrahydrofuran (2.4 mL) which had been deoxygenated by purging with a stream of argon for 5 min. A solution of *n*-butyllithium (2.5 M in hexanes, 0.480 mL, 1.20 mmol, 5.00 equiv) was added via syringe. After 30 min, methyl cyanoformate (0.114 mL, 1.43 mmol, 6.00 equiv) was added via syringe. After 10 min, the reaction mixture was warmed to 0 °C. After 30 min, the reaction solution was warmed to 23 °C. After 10 min, a solution of saturated aqueous sodium bicarbonate (10 mL) was added. A solution of saturated aqueous sodium chloride (5 mL) and ethyl acetate (15 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 0 → 10% ethyl acetate in hexanes) to afford vinylogous carbamate (-)-3.38 (60.9 mg, 54.4%) as an off-white foam. An additional 9% of mass balance is accounted for as an inseparable 1:1.5 mixture of the desired product with the corresponding N-acylated product. Structural assignments were made using additional information from gCOSY, deHSQC, and gHMBC experiments.

**1H NMR (600 MHz, CDCl₃, 25 °C):**

δ 8.87 (s, 1H, N₁H), 6.73 (d, J = 2.2 Hz, 1H, C₁₄H), 6.65 (d, J = 8.3 Hz, 1H, C₁₇H), 6.61 (dd, J = 8.3, 2.3 Hz, 1H, C₁₃H), 5.79 (ddd, J = 10.0, 4.8, 1.5 Hz, 1H, C₇H), 5.70 (dt, J = 10.1, 1.9 Hz, 1H, C₈H), 3.75 (s, 3H, CO₂CH₃), 3.46 (ddd, J = 15.8, 4.8, 1.5 Hz, 1H, C₈H), 3.18 (dt, J = 15.9, 1.9 Hz, 1H, C₈H), 3.06–3.02 (m, 1H, C₁₀Η₃), 2.65 (ddd, J = 11.3, 8.5, 4.7 Hz, 1H, C₁₀H₆), 2.60 (s, 1H, C₁₉H), 2.53 (dd, J = 15.0, 1.8 Hz, 1H, C₄H₅), 2.43 (d, J = 15.0 Hz, 1H, C₄H₅), 2.07 (td, J = 11.4, 6.4 Hz, 1H, C₁₁H₆), 1.78 (dd, J = 11.9, 4.3 Hz, 1H, C₁₁H₆), 1.04–0.99 (m, 1H, C₂₀H₅), 0.98 (s, 9H, Si(CH₃)₂C(CH₃)₃), 0.94–0.83 (m, 1H, C₂₀H₅), 0.64 (t, J = 7.5 Hz, 3H, C₂₀H₃), 0.17 (d, J = 2.2 Hz, 6H, Si(CH₃)₂C(CH₃)₃).

**13C NMR (150 MHz, CDCl₃, 25 °C):**

δ 169.2 (CO₂CH₃), 167.6 (C₂), 150.0 (C₁₅), 139.5 (C₁₃), 137.5 (C₁₈), 133.4 (C₆), 125.0 (C₇), 118.5 (C₁₀), 114.5 (C₁₄), 109.6 (C₁₇), 91.7 (C₃), 70.1 (C₁₉), 55.5 (C₁₂), 51.1 (2C, C₁₁, CO₂CH₃), 50.8 (C₈), 44.7
FTIR (thin film) cm\(^{-1}\): 3365 (br-w), 2956 (m), 2929 (m), 2773 (br-w), 1675 (s), 1614 (s), 1473 (s), 1293 (m), 1164 (s), 1113 (m), 824 (w).

HRMS (ESI) (m/z): calc’d for C\(_{27}\)H\(_{39}\)N\(_2\)O\(_3\)Si [M+H]\(^+\): 467.2724, found: 467.2719.

\([\alpha]\)\(_{D}^{24}\): \(-270 (c = 0.73, \text{CH}_2\text{Cl}_2)\).

M.p.: 47 °C (hexanes).

TLC (10% ethyl acetate in hexanes), R\(_f\): 0.29 (UV, CAM).
(--)-Melodinine P (3.7):

Triethylamine trihydrofluoride (32.0 μL, 196 μmol, 4.00 equiv) was added via syringe to a solution of vinylogous carbamate (--)-3.38 (22.8 mg, 48.9 μmol, 1 equiv) in acetonitrile (0.98 mL). After 3.5 h, the reaction mixture was diluted with ethyl acetate (10 mL). A solution of saturated aqueous sodium bicarbonate (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 0 → 30% ethyl acetate in hexanes) to afford (--)-melodinine P (3.7) (10.3 mg, 59.9%) as a pale yellow solid. Structural assignments were made using additional information from gCOSY, deHSQC, and gHMBC experiments.

\(^1\)H NMR (500 MHz, acetone-\(d_6\), 25 °C): δ 9.15 (s, 1H, \(N_1\)), 7.87 (s, 1H, OH), 6.86 (d, \(J = 8.4\) Hz, 1H, \(C_1\)), 6.85 (d, \(J = 2.4\) Hz, 1H, \(C_{14}\)), 6.63 (dd, \(J = 8.3, 2.4\) Hz, 1H, \(C_{16}\)), 5.78 (ddd, \(J = 10.1, 4.8, 1.5\) Hz, 1H, \(C_7\)), 5.70 (dt, \(J = 9.9, 1.9\) Hz, 1H, \(C_6\)), 3.68 (s, 3H, \(CO_2CH_3\)), 3.43 (ddd, \(J = 15.9, 4.7, 1.5\) Hz, 1H, \(C_8\)), 3.18 (dt, \(J = 15.9, 1.9\) Hz, 1H, \(C_9\)), 3.01 (dd, \(J = 8.3, 6.5\) Hz, 1H, \(C_{10}\)), 2.71 (dd, \(J = 11.0, 8.4, 4.7\) Hz, 1H, \(C_{11}\)), 2.63 (s, 1H, \(C_{18}\)), 2.52 (dd, \(J = 14.8, 1.8\) Hz, 1H, \(C_9\)), 2.45 (d, \(J = 14.9\) Hz, 1H, \(C_8\)), 2.00 (td, \(J = 11.2, 6.5\) Hz, 1H, \(C_{11}\)), 1.74 (ddd, \(J = 11.5, 4.8, 1.1\) Hz, 1H, \(C_{11}\)), 0.99 (dq, \(J = 14.9, 7.5\) Hz, 1H, \(C_{20}\)), 0.84 (dq, \(J = 14.4, 7.4\) Hz, 1H, \(C_{20}\)), 0.64 (t, \(J = 7.5\) Hz, 3H, \(C_2\)).

\(^13\)C NMR (150 MHz, acetone-\(d_6\), 25 °C): δ 168.8 (CO_2CH_3), 168.0 (C_2), 152.8 (C_13), 140.3 (C_15), 137.2 (C_18), 133.5 (C_5), 126.0 (C_7), 114.4 (C_16), 110.9 (C_17), 110.5 (C_14), 91.2 (C_3), 70.8 (C_19), 56.5 (C_12), 51.4 (C_10), 51.0 (C_8), 50.8 (CO_2CH_3), 45.5 (C_11), 42.2 (C_3), 29.5 (C_4), 27.6 (C_20), 7.7 (C_21).

FTIR (thin film) cm\(^{-1}\): 3368 (br-m), 2961 (m), 2787 (br-w), 1655 (m), 1601 (s), 1465 (m), 1272 (m), 1186 (s), 1164 (s), 1113 (m), 1041 (w), 808 (m).

HRMS (DART) (m/z): calc’d for C_{21}H_{25}N_{2}O_{3} [M+H]\(^+\): 353.1860, found: 353.1869.
[α]_D^{24} = -289 (c = 0.13, MeOH)\(^7\)

M.p.: 118 °C, decomposition (hexanes).

TLC (25% ethyl acetate in hexanes), Rf: 0.20 (UV, CAM).

\(^7\) Literature value: [α]_D^{24} = -158.3 (c = 0.164, MeOH), see Liu, Y.-P.; Li, Y.; Cai, X.-H.; Li, X.-Y.; Kong, L.-M.; Cheng, G.-G.; Luo, X.-D. *J. Nat. Prod.* **2012**, *75*, 220.
Table S1. Comparison of our $^1$H NMR data for (−)-melodinine P (3.7) with literature data (acetone-$d_6$):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Luo’s Isolation Report$^2$</th>
<th>This Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>(−)-melodinine P (3.7) $^1$H NMR, 400 MHz, acetone-$d_6$</td>
<td>(−)-melodinine P (3.7) $^1$H NMR, 500 MHz acetone-$d_6$, 25 °C</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>9.16 (s, 1H)</td>
<td>9.15 (s, 1H)</td>
</tr>
<tr>
<td>C2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C3-CO$_2$CH$_3$</td>
<td>3.67 (s, 1H)</td>
<td>3.68 (s, 3H)</td>
</tr>
<tr>
<td>C4</td>
<td>2.44 (d, $J = 15$ Hz, 1H) 2.50 (d, $J = 15$ Hz, 1H)</td>
<td>2.45 (d, $J = 14.9$ Hz, 1H) 2.52 (dd, $J = 14.8$, 1.8 Hz, 1H)</td>
</tr>
<tr>
<td>C5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C6</td>
<td>5.70 (d, $J = 9.6$ Hz, 1H)</td>
<td>5.70 (dt, $J = 9.9$, 1.9 Hz, 1H)</td>
</tr>
<tr>
<td>C7</td>
<td>5.78 (ddd, $J = 9.6$, 4.8, 1.5 Hz, 1H)</td>
<td>5.78 (ddd, $J = 10.1$, 4.8, 1.5 Hz, 1H)</td>
</tr>
<tr>
<td>C8</td>
<td>3.42 (dd, $J = 10.2$, 4.8, 1.5 Hz, 1H) 3.17 (d, $J = 10.2$ Hz, 1H)</td>
<td>3.43 (ddd, $J = 15.9$, 4.7, 1.5 Hz, 1H) 3.18 (dt, $J = 15.9$, 1.9 Hz, 1H)</td>
</tr>
<tr>
<td>C10</td>
<td>3.00 (t, $J = 7.8$ Hz, 1H) 2.70 (m, 1H)</td>
<td>3.01 (dd, $J = 8.3$, 6.5 Hz, 1H) 2.71 (ddd, $J = 11.0$, 8.4, 4.7 Hz, 1H)</td>
</tr>
<tr>
<td>C11</td>
<td>2.97 (m, overlap, 1H)$^9$ 1.73 (dd, $J = 11.4$, 3.6 Hz, 1H)</td>
<td>2.00 (td, $J = 11.2$, 6.5 Hz, 1H) 1.74 (ddd, $J = 11.5$, 4.8, 1.1 Hz, 1H)</td>
</tr>
<tr>
<td>C12</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C14</td>
<td>6.74 (d, $J = 2.4$ Hz, 1H)$^{10}$</td>
<td>6.85 (d, $J = 2.5$ Hz, 1H)</td>
</tr>
<tr>
<td>C15</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C15-OH</td>
<td>–</td>
<td>7.87 (s, 1H)$^{11}$</td>
</tr>
<tr>
<td>C16</td>
<td>6.62 (d, $J = 7.8$, 2.4 Hz, 1H)</td>
<td>6.63 (dd, $J = 8.3$, 2.4 Hz, 1H)</td>
</tr>
<tr>
<td>C17</td>
<td>6.86 (d, $J = 7.8$ Hz, 1H)</td>
<td>6.86 (d, $J = 8.4$ Hz, 1H)</td>
</tr>
<tr>
<td>C18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C19</td>
<td>2.62 (s, 1H)</td>
<td>2.63 (s, 1H)</td>
</tr>
<tr>
<td>C20</td>
<td>0.84 (m, 1H) 0.98 (m, 1H)</td>
<td>0.84 (dq, $J = 14.4$, 7.4 Hz, 1H) 0.99 (dq, $J = 14.9$, 7.5 Hz, 1H)</td>
</tr>
<tr>
<td>C21</td>
<td>0.63 (t, $J = 7.8$ Hz, 3H)</td>
<td>0.64 (t, $J = 7.5$ Hz, 1H)</td>
</tr>
</tbody>
</table>


$^9$ This resonance is likely a typographical error, as the $^1$H NMR spectrum shows a peak at 1.97 ppm but no peaks at 2.97 ppm.

$^{10}$ This resonance is likely a typographical error, as the $^1$H NMR spectrum shows a peak at 6.84 ppm but no peaks at 6.74 ppm.

$^{11}$ An unreported peak is observed at 7.95 ppm in the $^1$H NMR spectrum of (−)-melodinine P (3.7) in reference 8, consistent with our observed data.
Table S2. Comparison of our $^{13}$C NMR data for (−)-melodinine P (3.7) with literature data (acetone-$d_6$):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Luo’s Isolation Report$^a$</th>
<th>This Work</th>
<th>Chemical Shift Difference</th>
<th>Δδ = δ (this work) − δ (Luo’s Report)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(−)-melodinine P (3.7) $^{13}$C NMR, 150 MHz acetone-$d_6$</td>
<td>(−)-melodinine P (3.7) $^{13}$C NMR, 125 MHz acetone-$d_6$, 25 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>168.0</td>
<td>168.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C3</td>
<td>91.0</td>
<td>91.2</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>C3-CO$_2$CH$_3$</td>
<td>168.8</td>
<td>168.8</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C3-CO$_2$CH$_3$</td>
<td>50.9</td>
<td>50.8</td>
<td></td>
<td>−0.1</td>
</tr>
<tr>
<td>C4</td>
<td>29.3</td>
<td>29.5</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>C5</td>
<td>42.2</td>
<td>42.2</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C6</td>
<td>133.5</td>
<td>133.5</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C7</td>
<td>126.0</td>
<td>126.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C8</td>
<td>51.0</td>
<td>51.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C10</td>
<td>51.4</td>
<td>51.4</td>
<td></td>
<td>0.0</td>
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<tr>
<td>C11</td>
<td>45.6</td>
<td>45.5</td>
<td></td>
<td>−0.1</td>
</tr>
<tr>
<td>C12</td>
<td>56.5</td>
<td>56.5</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C13</td>
<td>140.3</td>
<td>140.3</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C14</td>
<td>110.5</td>
<td>110.5</td>
<td></td>
<td>0.0</td>
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<tr>
<td>C15</td>
<td>152.8</td>
<td>152.8</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C16</td>
<td>114.3</td>
<td>114.4</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>C17</td>
<td>110.9</td>
<td>110.9</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C18</td>
<td>137.1</td>
<td>137.2</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>C19</td>
<td>70.8</td>
<td>70.8</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>C20</td>
<td>27.5</td>
<td>27.6</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>C21</td>
<td>7.7</td>
<td>7.7</td>
<td></td>
<td>0.0</td>
</tr>
</tbody>
</table>
(-)-Jerantinine A (3.1):
Triethylamine trihydrofluoride (30.0 μL, 18.4 μmol, 4.00 equiv) was added via syringe to a solution of vinylogous carbamate (-)-3.38 (21.5 mg, 4.61 μmol, 1 equiv) in methanol (1.3 mL). After 2 h, the lights in the fume hood were turned off and silver oxide (320 mg, 1.38 mmol, 30.0 equiv) was added. After full consumption of the resulting intermediate by thin layer chromatography, the reaction solution was diluted with ethyl acetate (5 mL) and hexanes (5 mL). The crude solution was filtered through a plug of Celite using ethyl acetate (20 mL). The bright yellow filtrate solution was stirred vigorously with a freshly prepared solution of aqueous sodium dithionite (1.0 M, 20 mL). After 10 min, the pale yellow reaction solution was diluted with a solution of saturated aqueous sodium chloride (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure to half volume. The resulting crude solution was washed with a 1:1:2 solution of saturated aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate, and water (3 × 15 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluens: 10 → 50% ethyl acetate in hexanes with 0 → 2% triethylamine) to afford (-)-jerantinine A (3.1) (10.6 mg, 60.2%) as a pale yellow solid. Structural assignments were made using additional information from gCOSY, deHSQC, and gHMBC experiments.

\(^1\)H NMR (500 MHz, CDCl\(_3\), 25 °C):
\[ \delta 8.86 (s, 1H, N\_H), 6.88 (s, 1H, C\textsubscript{14}H), 6.45 (s, 1H, C\textsubscript{17}H), 5.78 (ddd, \(J = 9.9, 4.8, 1.5\) Hz, 1H, C\textsubscript{7}H), 5.70 (dt, \(J = 9.9, 1.9\) Hz, 1H, C\textsubscript{6}H), 5.28 (s, 1H, C\textsubscript{15}OH), 3.87 (s, 3H, C\textsubscript{16}OCH\(_3\)), 3.76 (s, 3H, CO\textsubscript{2}CH\(_3\)), 3.44 (ddd, \(J = 15.8, 4.8, 1.5\) Hz, 1H, C\textsubscript{8}H\textsubscript{a}), 3.15 (dt, \(J = 15.9, 1.9\) Hz, 1H, C\textsubscript{9}H\textsubscript{a}), 3.02 (app-t, \(J = 7.5\) Hz, 1H, C\textsubscript{10}H\textsubscript{a}), 2.67 (ddd, \(J = 11.1, 8.4, 4.6\) Hz, 1H, C\textsubscript{10}H\textsubscript{b}), 2.59 (s, 1H, C\textsubscript{19}H), 2.53 (dd, \(J = 15.0, 1.9\) Hz, 1H, C\textsubscript{4}H\textsubscript{a}), 2.41 (d, \(J = 15.0\) Hz, 1H, C\textsubscript{4}H\textsubscript{b}), 2.05 (td, \(J = 11.3, 6.4\) Hz, 1H, C\textsubscript{11}H\textsubscript{a}), 1.76 (dd, \(J = 11.3, 4.7\) Hz, 1H, C\textsubscript{11}H\textsubscript{b}), 0.99 (dq, \(J = 14.9, 7.6\) Hz, 1H, C\textsubscript{20}H\textsubscript{b}), 0.85 (dq, \(J = 14.3, 7.4\) Hz, 1H, C\textsubscript{20}H\textsubscript{a}), 0.63 (t, \(J = 7.4\) Hz, 3H, C\textsubscript{21}H\textsubscript{3}).

\(^1\)C NMR (125 MHz, CDCl\(_3\), 25 °C):
\[ \delta 169.2 (CO\textsubscript{2}CH\(_3\)), 168.0 (C\textsubscript{2}), 146.0 (C\textsubscript{16}), 140.0 (C\textsubscript{15}), 136.2 (C\textsubscript{18}), 133.2 (C\textsubscript{6}), 130.2 (C\textsubscript{13}), 125.1 (C\textsubscript{7}), 108.9 (C\textsubscript{14}), 94.5 (C\textsubscript{17}), 91.9 (C\textsubscript{3}), 70.3 (C\textsubscript{19}), 117
FTIR (thin film) cm\(^{-1}\): 
3364 (br-m), 2921 (m), 2783 (w), 1669 (m), 1603 (s), 1492 (s), 1331 (w), 1264 (s), 1192 (s), 1042 (m).

HRMS (DART) (m/z): 

\([\alpha]\)\(_D\)^\(^{24}\): 
-300 (c = 0.305, CHCl\(_3\))^\(^{12,13}\)

TLC (50% ethyl acetate in hexanes with 3% triethylamine), Rf: 0.52 (UV, CAM).

---


\(^{13}\) The observed optical rotation for alkaloid (+)-3.1 prepared via our first generation route was \([\alpha]_D = +236\) (c = 0.02, CHCl\(_3\)). This value is consistent with the 80% ee value for starting material pentacycle (+)-3.31. For the preparation of pentacycle (+)-3.31 in 80% ee, see Chapter II.
Table S3. Comparison of our $^1$H NMR data for (−)-jerantinine A (3.1) with literature data (CDCl₃):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Kam’s Isolation Report $^{14}$ (−)-jerantinine A (3.1) $^1$H NMR, 400 MHz, CDCl₃</th>
<th>This Work (−)-jerantinine A (3.1) $^1$H NMR, 500 MHz CDCl₃, 25 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>8.87 (br-s, 1H)</td>
<td>8.86 (s, 1H)</td>
</tr>
<tr>
<td>C2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C3-CO₂CH₃</td>
<td>3.76 (s, 3H)</td>
<td>3.76 (s, 3H)</td>
</tr>
<tr>
<td>C4</td>
<td>2.53 (dd, $J = 15$, 1.5 Hz, 1H)</td>
<td>2.53 (dd, $J = 15.0$, 1.9 Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>2.42 (d, $J = 15$ Hz, 1H)</td>
<td>2.41 (d, $J = 15.0$ Hz, 1H)</td>
</tr>
<tr>
<td>C5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C6</td>
<td>5.70 (dt, $J = 10.0$, 1.3 Hz, 1H)</td>
<td>5.70 (dt, $J = 9.9$, 1.9 Hz, 1H)</td>
</tr>
<tr>
<td>C7</td>
<td>5.78 (ddd, $J = 10.0$, 4.6, 1.5 Hz, 1H)</td>
<td>5.78 (ddd, $J = 9.9$, 4.8, 1.5 Hz, 1H)</td>
</tr>
<tr>
<td>C8</td>
<td>3.45 (ddd, $J = 16$, 4.6, 1.3 Hz, 1H)</td>
<td>3.44 (ddd, $J = 15.8$, 4.8, 1.5 Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>3.16 (br-d, $J = 16$ Hz, 1H)</td>
<td>3.15 (dt, $J = 15.9$, 1.9 Hz, 1H)</td>
</tr>
<tr>
<td>C10</td>
<td>3.02 (t, $J = 7$ Hz, 1H)</td>
<td>3.02 (app-t, $J = 7.5$ Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>2.68 (ddd, $J = 11.5$, 7, 4.3 Hz, 1H)</td>
<td>2.67 (ddd, $J = 11.1$, 8.4, 4.6 Hz, 1H)</td>
</tr>
<tr>
<td>C11</td>
<td>2.06 (td, $J = 11.5$, 7 Hz, 1H)</td>
<td>2.05 (td, $J = 11.3$, 6.4 Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>1.76 (dd, $J = 11.5$, 4.3 Hz, 1H)</td>
<td>1.76 (dd, $J = 11.3$, 4.7 Hz, 1H)</td>
</tr>
<tr>
<td>C12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C14</td>
<td>6.89 (s, 1H)</td>
<td>6.88 (s, 1H)</td>
</tr>
<tr>
<td>C15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C15-OH</td>
<td>5.36 (br-s, 1H)</td>
<td>5.28 (s, 1H)</td>
</tr>
<tr>
<td>C16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C16-OCH₃</td>
<td>3.87 (s, 3H)</td>
<td>3.87 (s, 3H)</td>
</tr>
<tr>
<td>C17</td>
<td>6.45 (s, 1H)</td>
<td>6.45 (s, 1H)</td>
</tr>
<tr>
<td>C18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C19</td>
<td>2.60 (s, 1H)</td>
<td>2.59 (s, 1H)</td>
</tr>
<tr>
<td>C20</td>
<td>1.00 (dq, $J = 14$, 7.3 Hz, 1H)</td>
<td>0.99 (dq, $J = 14.9$, 7.6 Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>0.86 (dq, $J = 14$, 7.3 Hz, 1H)</td>
<td>0.85 (dq, $J = 14.3$, 7.4 Hz, 1H)</td>
</tr>
<tr>
<td>C21</td>
<td>0.64 (t, $J = 7.3$ Hz, 3H)</td>
<td>0.63 (t, $J = 7.4$ Hz, 3H)</td>
</tr>
</tbody>
</table>

Table S4. Comparison of our $^{13}$C NMR data for (-)-jerantinine A (3.1) with literature data (CDCl$_3$):

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Kam's Isolation Report$^{14}$ (-)-jerantinine A (3.1) $^{13}$C NMR, 100 MHz CDCl$_3$</th>
<th>This Work (-)-jerantinine A (3.1) $^{13}$C NMR, 125 MHz CDCl$_3$, 25 °C</th>
<th>Chemical Shift Difference $\Delta\delta = \delta$ (this work) - $\delta$ (Kam's Report)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>167.7</td>
<td>168.0</td>
<td>0.3</td>
</tr>
<tr>
<td>C3</td>
<td>91.6</td>
<td>91.9</td>
<td>0.3</td>
</tr>
<tr>
<td>C3-CO$_2$Me</td>
<td>169.2</td>
<td>169.2</td>
<td>0.0</td>
</tr>
<tr>
<td>C3-CO$_2$CH$_3$</td>
<td>50.9</td>
<td>51.1</td>
<td>0.2</td>
</tr>
<tr>
<td>C4</td>
<td>28.3</td>
<td>28.5</td>
<td>0.2</td>
</tr>
<tr>
<td>C5</td>
<td>41.4</td>
<td>41.6</td>
<td>0.2</td>
</tr>
<tr>
<td>C6</td>
<td>133.0</td>
<td>133.2</td>
<td>0.2</td>
</tr>
<tr>
<td>SC7</td>
<td>124.8</td>
<td>125.1</td>
<td>0.3</td>
</tr>
<tr>
<td>C8</td>
<td>50.6</td>
<td>50.8</td>
<td>0.2</td>
</tr>
<tr>
<td>C10</td>
<td>50.8</td>
<td>51.0</td>
<td>0.2</td>
</tr>
<tr>
<td>C11</td>
<td>44.3</td>
<td>44.5</td>
<td>0.2</td>
</tr>
<tr>
<td>C12</td>
<td>55.2</td>
<td>55.4</td>
<td>0.2</td>
</tr>
<tr>
<td>C13</td>
<td>130.1</td>
<td>130.2</td>
<td>0.1</td>
</tr>
<tr>
<td>C14</td>
<td>108.8</td>
<td>108.9</td>
<td>0.1</td>
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<tr>
<td>C15</td>
<td>139.9</td>
<td>140.0</td>
<td>0.1</td>
</tr>
<tr>
<td>C16</td>
<td>145.8</td>
<td>146.0</td>
<td>0.2</td>
</tr>
<tr>
<td>C16-OCH$_3$</td>
<td>56.3</td>
<td>56.5</td>
<td>0.2</td>
</tr>
<tr>
<td>C17</td>
<td>94.4</td>
<td>94.5</td>
<td>0.1</td>
</tr>
<tr>
<td>C18</td>
<td>135.9</td>
<td>136.2</td>
<td>0.3</td>
</tr>
<tr>
<td>C19</td>
<td>70.1</td>
<td>70.3</td>
<td>0.2</td>
</tr>
<tr>
<td>C20</td>
<td>26.8</td>
<td>27.0</td>
<td>0.2</td>
</tr>
<tr>
<td>C21</td>
<td>7.4</td>
<td>7.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Appendix A

Spectra for Chapter I
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C

1.7a
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

![NMR Spectrum](image)

1.7a
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C

1.7b
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

1.7b
$^1$H NMR, 400 MHz, CD$_3$OD, 23 °C

1.7c
$^{13}$C NMR, 100 MHz, CD$_3$OD, 23 °C
1.7c
\[ \text{H NMR, 400 MHz, CD}_3\text{OD, 23 °C} \]

\[ \text{Me}_3\text{Si} - \text{O} - \text{N} - \text{NH} - \text{Br} - \text{N} - \text{NH} - \text{O} - \text{Me} \]

1.7d
$^{13}$C NMR, 100 MHz, CD$_3$OD, 23 °C

1.7d
\[ ^1H \text{NMR, } 500 \text{ MHz, DMSO-}d_6, 23 \, ^\circ\text{C} \]

\[
\begin{align*}
\text{1.7e}
\end{align*}
\]
$^{13}$C NMR, 125 MHz, DMSO-$d_6$, 23 °C
$^{13}$C NMR, 125 MHz, DMSO-$d_6$, 23 °C
1.7f
\(^1\)H NMR, 400 MHz, CD\(_2\)OD, 23 °C

![NMR Spectrum of 1.7g](image-url)
$^{13}$C NMR, 100 MHz, CD$_3$OD, 23 °C
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

1.7h
$^1$H NMR, 400 MHz, CD$_3$OD, 23 °C
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

1.7j
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C
$^1\text{H NMR, } 600 \text{ MHz, CDCl}_3, 23 ^\circ\text{C}$

$$\text{N} \quad \text{Sn} \quad (\text{c-C}_6\text{H}_{11})_3$$

1.30
$^{13}$C NMR, 100 MHz, CDCl$_3$, 23 °C

1.30
$^1$H NMR, 600 MHz, CDCl$_3$, 23 °C

1.20a
$^{13}$C NMR, 125 MHz, CDCl$_3$, 23 °C

1.20a
$^1$H NMR, 400 MHz, CDCl$_3$, 23 °C

![NMR spectrum](image)

1.20b
$^{13}$C NMR, 100 MHz, CDCl$_3$, 23 °C

\[ \text{HO-} \text{NH} - \text{NH} \text{Sn}(c\text{-C}_6\text{H}_{11})_3 \]

1.20b
$^{13}$C NMR, 125 MHz, CDCl$_3$, 23°C

1.20c
$^1$H NMR, 600 MHz, CD$_3$OD, 23 °C

1.27a
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

1.27a
1.27a
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C

1.27b
$^{13}$C NMR, 100 MHz, CD$_3$OD, 23 °C
$^1$H NMR, 400 MHz, CD$_3$OD, 23 °C

1.27c
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

![Chemical structure](image)

1.27c
$^1$H NMR, 600 MHz, CD$_3$OD, 23 °C

1.8a
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

![Chemical Structure](image)
$^1\text{H NMR}$, 500 MHz, CD$_3$OD, 23 °C

1.28
$^{13}$C NMR, 100 MHz, CD$_3$OD, 23 °C

1.28
$^1$H NMR, 400 MHz, CD$_3$OD, 23 °C
$^{13}$C NMR, 100 MHz, CD$_3$OD, 23 $^\circ$C
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C

1.8c
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

1.8c
$^1$H NMR, 600 MHz, CD$_3$OD, 23 °C
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C
$^1$H NMR, 500 MHz, CD$_3$OD, 23 °C
$^{13}$C NMR, 125 MHz, CD$_3$OD, 23 °C

1.8e
Appendix B

Spectra for Chapter II
HPLC Conditions:
Chiralcel OD-H, column #ODH0CE-KF021
25% 2-propanol/75% Hexanes
1.0 mL/min
230 nM

enantioenriched-S1

HPLC Conditions:
Chiralcel OD-H, column #ODH0CE-KF021
25% 2-propanol/75% Hexanes
1.0 mL/min
230 nM
**$^1$H NMR, 400 MHz, CDCl$_3$, 25 °C**

![Chemical Structure](image)
$^{13}$C NMR, 125 MHz, CDCl$_3$, 25 °C
$^1$H NMR, 500 MHz, CDCl$_3$, 25 °C
$^{13}$C NMR, 125 MHz, CDCl$_3$, 25 °C

- 175.8
- 136.4
- 135.6
- 128.5
- 121.2
- 119.1
- 117.6
- 110.6
- 109.6
- 77.4
- 77.2
- 76.9
- 50.7
- 48.3
- 45.8
- 43.7
- 32.7
- 31.9
- 22.5
- 21.6
- 21.2
- 9.2
$^1$H NMR, 400 MHz, CDCl$_3$, 25 °C

(+)-2.1
$^{13}$C NMR, 150 MHz, CDCl$_3$, 25 °C

(+)2.1
$^1$H NMR, 400 MHz, CD$_3$CN, 25 °C
$^{13}$C NMR, 100 MHz, CD$_3$CN, 25 °C
$^1$H NMR, 400 MHz, CDCl$_3$, 25 °C
$^{13}$C NMR, 100 MHz, CDCl$_3$, 25 °C
1H NMR, 500 MHz, CDCl3, 25 °C

(+)-deacetylaspidospermine (2.17)
$^{13}$C NMR, 150 MHz, CDCl$_3$, 25 $^\circ$C

(+)-deacetylaspidospermine (2.17)
$^1$H NMR, 500 MHz, CDCl$_3$, 25 °C

(-)-vallesine (2.15)
$^{13}$C NMR, 150 MHz, CDCl$_3$, 25 °C

(-)-vallesine (2.15)
(-)-vallesine (2.15)
Appendix C

Spectra for Chapter III
$^1$H NMR, 500 MHz, CDCl$_3$, 25 °C

![NMR Spectrogram]
$^{13}$C NMR, 150 MHz, CDCl$_3$, 25 °C

(+)-3.30
$^1$H NMR, 500 MHz, CDCl$_3$, 25 °C

(-)-3.38
$^{13}$C NMR, 150 MHz, CDCl$_3$, 25 °C

169.2 167.6 139.5 137.5 125.0 118.5 114.5 109.6
-91.7 77.4 76.6 70.1 61.1 56.5 49.7 41.6
-28.8 -27.6 -18.4 -7.6 -4.3

(-)-3.38
\(^1\)H NMR, 500 MHz, acetone-\(d_6\), 25 °C

(-)-melodinine P (3.7)
$^{13}$C NMR, 150 MHz, acetone-$d_6$, 25 °C

(-)-melodinine P (3.7)
(-)-melodinine P (3.7)
\[ ^1H \text{NMR, 500 MHz, CDCl}_3, 25 ^\circ \text{C} \]

\[
\begin{align*}
&\text{HO} \\
&\text{MeO}
\end{align*}
\]
$^{13}\text{C NMR, 125 MHz, CDCl}_3, 25 \degree\text{C}$

$(-)$-jerantine A (3.1)
Alyssa Hope Antropow  antropow@mit.edu  (862)-377-3132

Current Location:  Boston, MA 02115

Permanent Location:  North Haledon, NJ 07508

EDUCATION

Massachusetts Institute of Technology  Cambridge, MA
Ph.D. Candidate in Organic Chemistry, June 2018  GPA: 4.7/5.0

Stevens Institute of Technology  Hoboken, NJ
Masters of Science in Chemistry, May 2013  GPA: 4.00/4.00
Bachelors of Science in Chemistry with High Honors, May 2013  GPA: 3.97/4.00

Academic Honors: ACS Division of Organic Chemistry Outstanding Senior Student Award; Stevens Priestly Prize for Distinguished Senior in Chemistry; Ann P. Neupauer Scholarship

RESEARCH EXPERIENCE

Movassaghi Group, Massachusetts Institute of Technology, Cambridge, MA  11/2013 – 05/2018
Graduate Student Researcher, Department of Chemistry  4 years 7 months
• Designed and synthesized over 20 functionalized derivatives of agelastatin alkaloids
• Advanced collaborative research studies of agelastatin derivatives in breast cancer microenvironments with Dr. Rachel J. Buchsbaum and coordinated targeted delivery studies with Professor Bradley L. Pentelute and Professor Angela Koehler
• Completed enantioselective total synthesis of seven aspidosperma alkaloids including first total synthesis of (−)-vallesine
• Pioneered strategies for biologically inspired late-stage oxidation of indole alkaloids

A. K. Ganguly Group, Stevens Institute of Technology, Hoboken, NJ  01/2011 – 05/2013
Undergraduate Researcher, Department of Chemistry and Chemical Biology  2 years 5 months
• Independently researched synthesis of novel cyclic sulfonamide based HIV-1 protease inhibitors
• Collaborated with scientists at Merck to enable structure optimization based on X-ray crystallographic analysis

Hoffmann-LaRoche, Inc., Nutley, NJ  05/2012 – 08/2012
Discovery Chemistry Intern, Advisors: Dr. Steven Berthel and Dr. John Brinkman  3 months
• Investigated synthesis of natural product analogs for treatment of hepatitis B

PUBLICATIONS


HONORS AND AWARDS

American Chemical Society: Women Chemists Committee and Eli Lilly Travel Grant  2018
• One of nine selected nationally to receive the WCC–Eli Lilly Travel Grant for the spring ACS National Meeting

Amgen Graduate Fellowship in Synthetic Chemistry, Cambridge, MA  2016–17
• One of two graduate students nationally to receive the Amgen Graduate Student Fellowship

Annual Student Leadership Awards, Stevens Institute of Technology  2013
• Woman of Distinction Award for well-rounded involvement and excellence in academics and research
• Distinguished Leader Award for continual exemplary leadership in numerous student life programs

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RESEARCH PRESENTATIONS


POSTER PRESENTATIONS


LEADERSHIP AND OUTREACH

Experiment Lead, Scientist for a Day Event
*MIT Women in Chemistry* Cambridge, MA 08/2016, 2017
- Developed polymer science demonstrations designed to engage small groups of middle school girls
- Organized discussions regarding relatable applications of chemistry and how scientists solve complex problems

Committee Chair, Student-Hosted Seminar Series
*MIT Organic Chemistry Seminar Program* Cambridge, MA 05/2014 – 12/2017
- Collaborated with student representatives to identify distinguished chemists to invite as seminar speakers
- Managed seminar planning and itinerary details for Professors Daisuke Uraguchi, M. Kevin Brown, and Noah Z. Burns

Graduate Student Volunteer
*MIT Chemistry Outreach Program* Cambridge, MA 05/2014 – 12/2017
- Presented six chemistry demonstrations to local high school classes and advised prospective students on possible scientific career pathways

Chemical Chaos Volunteer
*Cambridge Science Festival: NSF Center for C–H Functionalization booth* Cambridge, MA 04/2014, 2015
- Facilitated three hands-on demonstrations along with collaborators from Novartis for over 500 festival attendees

Biological Testing Coordinator
*Movassaghi Group* Cambridge, MA 09/2014 – 12/2017
- Created systematic processes for submitting samples from diverse project areas for biological testing
- Advanced collaborative research efforts and communicated with multidisciplinary teams regarding biochemical and cell-based assay results

Founding President
*American Chemical Society, Student Chapter* Hoboken, NJ 08/2012 – 05/2013
- Achieved reinstatement of student chapter by recruiting members, implementing bylaws, budgeting events, and consulting with faculty advisors
- Directed educational meetings and organized and publicized student events to promote interest in chemistry

Lead Orientation Coordinator
*Office of Student Life, Stevens Institute of Technology* Hoboken, NJ 05/2012 – 08/2012
- Orchestrated all aspects of orientation for over 700 students cooperatively with a student partner and institute employees
- Generated camaraderie and enthusiasm to drive productivity within orientation team of 50 student leaders

Chapter Officer, Alpha Phi Omega
- Planned community service events, increased member retention and participation in conferences, and contributed over 100 hours per year to local and national organizations
- Served chapter as Membership Vice President (2012), National Convention Voting Delegate (2012), Conference Chair (2011), and Regional Convention Voting Delegate (2011); Distinguished Service Key Recipient (2015)
TEACHING EXPERIENCE

Massachusetts Institute of Technology Cambridge, MA

Head Teaching Assistant, Organic Chemistry II 09/2015 – 12/2015

- Managed teaching team as liaison between professor and all teaching assistants
- Inspected teaching materials, problem sets, and exams to ensure content met learning objectives
- Continued Excellence in Teaching Award for sustained service and distinction in teaching

Teaching Assistant, Organic Chemistry I 09/2013 – 05/2014

- Conducted recitation sections, assessed student performance, and encouraged active participation
- Outstanding Teaching Award for excellence during the first year of teaching in the department

REFERENCES

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