TOTAL SYNTHESES OF THE MARINE NATURAL PRODUCTS
(−)-NAKADOMARIN A AND (±)-CORTISTATIN J VIA IMINIUM ION CYCLIZATIONS

A Dissertation in
Chemistry
by
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ABSTRACT

The total synthesis of the biologically active, marine alkaloid (−)-nakadomarin A is discussed in Part I. The key transformation in this synthesis is the stereoselective construction of the tetracyclic core via a novel, stereoselective enecarbamate conjugate addition/furan-\(N\)-acyliminium ion cyclization. A sequential ring-closing alkyne metathesis/semi-hydrogenation strategy was utilized to obtain the fifteen-membered macrocycle as a single configurational isomer. Moreover, the flexibility of this route was demonstrated by the preparation of several nakadomarin A structural analogs.

Part II discusses the total synthesis of the marine alkaloid (±)-cortistatin J, which is a potent and selective inhibitor of angiogenesis. The oxabicyclo[3.2.1]octane substructure was stereoselectively constructed using Funk group methodology, namely the intramolecular (4 + 3) cyclization of a furan onto a (\(Z\))-2-(trialkylsilyloxy)-2-enal, which was obtained via stereoselective retrocycloaddition of 5-(trialkylsilyloxy)-1,3-dioxin. The total synthesis was completed with the Overman-type (\(Z\))-vinylsilane/iminium ion cyclization to build the A-ring.
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Part I

Generation of N-Acyliminium Ions via Enecarbamate Conjugate Addition Reactions. Application to the Total Synthesis of (−)-Nakadomarin A
Chapter 1  
Total Synthesis of (−)-Nakadomarin A  

I. Introduction  

The manzamines are a class of architecturally fascinating, biologically active marine alkaloids (Figure 1).\(^1\) Perhaps the most structurally intriguing member is nakadomarin A (1), isolated by Kobayashi\(^{2a}\) from an Okinawan sponge *Amphimedon* sp. Its structure, consists of an unprecedented 6/5/5/5/8/15 hexacyclic ring system and is the only manzamine alkaloid that embodies a furan ring. A biosynthetic pathway from ircinal A (2) has been proposed by Kobayashi\(^{2b}\) (Scheme 1). Thus, it is postulated that ircinal A undergoes ring opening via a retro-vinylogous Mannich reaction followed by vinylogous Mannich closure of the resultant dienol that then undergoes cyclodehydration to the furan.  

Nakadomarin A exhibited cytotoxicity against murine lymphoma L1210 cells (IC\(_{50}\) 1.3 μg/mL), inhibitory activity against cyclin-dependent kinase 4 (IC\(_{50}\) 9.9 μg/mL), and anti-inflammatory activity against lipopolysaccharide-stimulated murine macrophage RAW 264.7 cells (IC\(_{50}\) 10 μg/mL).  

![Figure 1. Representative manzamine alkaloids](image-url)

![Scheme 1. Proposed biosynthesis of nakadomarin A (1) from ircinal A (2)](image-url)
μg/mL), and antimicrobial activity against a fungus (Trichophyton mentagrophytes, MIC 23 μg/mL) and a Gram-positive bacterium (Corynebacterium xerosis, MIC 11 μg/mL). It is conjectured that selective inhibitors for cyclin dependent kinase 4 might be useful for the treatment of cancer since 90% of all human tumors have the Cdk4/p16/Rb pathway up-regulated. However, further biological evaluation has been restricted due to its limited availability (6.0 mg from 1.0 kg sponge, 0.0018% isolated yield).

II. Previous synthetic approaches to nakadomarin A

This limited availability, coupled with an inspiring structure, have made nakadomarin A the target of a number of synthetic groups, resulting in numerous approaches, total and formal syntheses. Nishida and co-workers have reported pioneering, though lengthy, total syntheses of both ent-1 and 1 (36 and 38 steps, respectively). Young and Kerr completed the total synthesis of ent-1 in 29 steps from D-mannitol. The Dixon group reported three total syntheses of 1, one being the shortest synthesis of 1 to date, requiring only 16 total steps. The Zhai group has also reported a relatively concise total synthesis of 1 in 23 steps (longest linear sequence).

A. Sequential cyclization approaches

Several strategies have been employed to construct the compact, tetracyclic 6/5/5/5 core of nakadomarin A. Young and Kerr utilized their three-component nitrone/cyclopropane cycloaddition methodology. Thus, condensation of hydroxylamine 4 and aldehyde 5 afforded the corresponding nitrone, which underwent a Lewis acid-catalyzed cycloaddition with cyclopropane 6 to give the highly-substituted oxazine 7 (Scheme 2). Chemoselective DIBAL-H reduction of the more accessible ester followed by Horner-Emmons olefination and Heck cyclization provided unsaturated ester 8. The N-O bond was later cleaved with samarium diiodide, and the resulting alcohol was converted to the mesylate. Treatment of this mesylate with base effected closure to pyrrolidine 9. Following a series of reductions, bismesylate 10 underwent tandem S_N2 displacement with amine 11 to afford piperidine 12.
Nishida and co-workers synthesized the cores of 1 and ent-1 by conceptually different routes. The stereocenters of the core of 1 were installed by a stereoselective Diels-Alder cyclization of chiral dienophile 13 with Danishefsky’s diene (Scheme 3) to afford cycloadduct 14. Subsequent Luche reduction and S$_n$2’ cyclization of the corresponding allyl alcohol provided pyrrolidine 15. A series of transformations, including ozonolysis and aldol condensation, allowed elaboration to enal 16. Wittig olefination of aldehyde 16 gave the Z-alkene 17, which was converted to a mixture of endoperoxides 18. Treatment of peroxide 18 with potassium tert-butoxide followed by 6N HCl effected dehydration to the furan 19.
Scheme 3. Nishida’s construction of the core of 1

B. Polycyclization approaches

Zhai and co-workers were able to cyclize the A and B rings of the core of 1 in a single step via a Pt-catalyzed cascade sequence (Scheme 4). Reductive amination of aldehyde 20 with propargylamine hydrochloride, amine sulfonylation and Sonagashira coupling with iodo furan 21 provided the key cyclization substrate 22. Treatment of enyne 22 with catalytic PtCl₂ in toluene at 80 °C afforded tetracyclic core 24 in good yield, presumably through N-acyliminium ion 23. Efforts to introduce the remaining stereocenter at C-8 with standard hydrogenation procedures resulted only in reduction of the tetrasubstituted double bond in the furan moiety. Thus, a three step hydroboration/oxidation/Barton-McCombie deoxygenation sequence was used (24 → 26).
The Mukai group formed two rings of the tetracyclic core of nakadomarin A in a single step, in this case an intramolecular Pauson-Khand reaction (PKR), to form the A- and B-rings in their formal synthesis of ent-1. Reduction amination of aldehyde 28 with amine 29 followed by amine sulfonylation provided PKR substrate 30 (Scheme 5). Treatment of enyne 30 with Co$_2$(CO)$_8$ resulted in a cobalt complex which was refluxed in toluene in the presence of n-BuSMe to yield tricyclic enone 31. The furan was then installed after a PMB/Bz protecting group exchange by dihydroxylation of the isolated alkene functionality with OsO$_4$ followed by cyclization and dehydration with CSA in refluxing toluene to tetracycle 32. Efforts to introduce the stereocenter at C-8 by hydrogenation of substrate 32 yielded only a trace of the desired saturated product. However, protection of the free amine with the bulky Fmoc group significantly improved the reaction, producing the tetracyclic core 33 in 51% yield.
C. Iminium ion cyclization approaches

Several groups have followed Nature’s lead and have exploited iminium ion cyclizations for the construction of the central B-ring of the tetracyclic core. Thus, in their pioneering approach, Nishida and co-workers applied a novel N-acyliminium ion/furan cyclization strategy to assemble the tetracyclic core of ent-1.\textsuperscript{5a} Optically active 3-allylpiperidine 34 was elaborated to unsaturated ester 35, which underwent intramolecular Michael addition with the benzyl amide to provide the respective spiropyrrolidinone 36 (Scheme 6). Further transformations allowed the introduction of the furan through Suzuki coupling of triflate 37 with the appropriately substituted furan-3-boronic ester 38. Reduction of imide 41 and acylation of the corresponding hemiaminal afforded acetate 42. Upon treatment of acetate 42 with acid, N-acyliminium ion 43 was generated and it underwent stereoselective cyclization with the tethered furan to yield the tetracyclic core of ent-nakadomarin A 44.
Scheme 6. Nishida’s construction of the core of ent-1

In 2009, Dixon and co-workers reported the shortest total synthesis of nakadomarin A to date.5d Bicyclic lactam 46 (prepared in 6 steps from commercially available materials) underwent a stereoselective Michael addition with nitroalkene 47 in the presence of chiral Cinchona catalyst 48 to afford nitro ester 49 as a 10:1 mixture of diastereomers (Scheme 7). The A ring was constructed via a three component nitro-Mannich/lactamization cascade of ester 49, formaldehyde and hex-5-en-1-amine to provide lactam 50. The superfluous nitro group was reduced under radical conditions and the δ-lactam was chemoselectively reduced, leaving the γ-lactam 51. Partial reduction of γ-lactam 51 with DIBAL-H followed by treatment of the resultant hemiaminal 52 with dilute acid and heat effected an iminium ion/furan cyclization to the pentacyclic core 54.
D. Ring-closing metatheses to construct the macrocycle

1. Ring-closing alkene metathesis

A strategy common to most of the total syntheses is the utilization of ring-closing alkene metathesis\(^7\) to construct the fifteen-membered macrocycle. While attractive in its efficiency, this approach yielded a mixture of configurational isomers in each case, often favoring the undesired \(E\)-isomer (Scheme 8). Nishida and Kerr obtained a 1:1.8 and 1:1.7 ratio of \(Z:E\) isomers, respectively.\(^5\) Dixon and Zhai, however, obtained a favorable 1.7:1 and 2:1 \(Z:E\) ratio by including an excess of either enantiomer of camphorsulfonic acid in the metathesis reaction mixture.\(^5d,h\) It should be noted that each group employed Grubbs 1\(^{st}\) generation catalyst (60) and that the cyclization to the fifteen-membered macrocycle took place after the construction of the eight-membered azocine ring.
Scheme 8. Comparison of alkene metatheses to construct the 15-membered ring

\[
\begin{align*}
\text{Scheme 8. Comparison of alkene metatheses to construct the 15-membered ring.}
\end{align*}
\]

In a collaborative effort, Dixon, Schrock and Hoveyda employed a stereogenic-at-tungsten alkylidene catalyst to effect an impressive, highly Z-selective ring-closing metathesis to build nakadomarin A’s 15-membered macrocycle (Scheme 9).\(^8\) Traditional molybdenum or ruthenium alkylidene metathesis catalysts (63-65) cyclized diene 61 to macrocycle 62 with preference for formation of the E-configurational isomer in each case (Z/E ~37:63). However, tungsten alkylidene 66 provided the desired Z-isomer preferentially (Z/E: 97:3) in 90% yield. The stereochemical preference for the Z-isomer is thought to arise from the size differential between the large aryloxide and the smaller imido group in 66, with the metallocyclobutane intermediate (67) substituents oriented towards the latter. They further demonstrated the utility and efficiency of the catalyst with the metathesis of diene 54, which features two basic nitrogens, delivering nakadomarin A directly in 63% yield (Z/E 94:6).
Scheme 9. Highly Z-selective alkene metathesis with tungsten alkylidene 66

2. Ring-closing alkyne metathesis/semi-reduction strategies

The Dixon group also employed a ring-closing alkyne metathesis\textsuperscript{9}/semi-hydrogenation strategy to construct the Z-alkene macrocycle as a single configurational isomer in their 2\textsuperscript{nd} and 3\textsuperscript{rd} generation total syntheses.\textsuperscript{5f,g} Diaryne 68 underwent alkyne metathesis in the presence of the Schrock tungsten carbyne catalyst\textsuperscript{10} (69) in chlorobenzene at 80 °C to cycloalkyne 70 in 69% yield (Scheme 10). The stereo- and chemoselective reduction of the alkyne was achieved with nickel boride in the presence of excess ethylenediamine to yield cycloakene 71.
Difficulty was encountered in the attempted ring-closing alkene metathesis with diene substrate 71, so the lactam and amide functional groups were reduced with excess DIBAL-H. Subjection of diene 72, which possesses two basic nitrogens, to Grubbs 1st generation catalyst (60) in the presence of (+)-camphorsulfonic acid in refluxing dichloromethane furnished nakadomarin A (1) in 70% yield.

Scheme 10. Dixon’s 2nd generation endgame

A straightforward modification of Dixon’s 1st generation synthesis allowed for the preparation of diyne 73 (Scheme 11). However, subjection of diyne 73 to a variety of alkyne metathesis conditions resulted only in the recovery of starting material, as the basic amine functionalities most likely inhibited catalyst activity. Protonation of the amines with sulfonic acid did not result in a successful reaction. Thus, Dixon and co-workers altered the synthetic sequence so that the alkyne metathesis would precede the furan/iminium ion cyclization. Subjection of diyne 75 to Grela’s modified conditions11 of the Mortreux alkyne metathesis system12 [Mo(CO)6, 2-fluorophenol, chlorobenzene, reflux] provided cycloalkyne 76 in 36% yield. Subsequent Lindlar reduction provided Z-cycloalkene 77. The total synthesis was completed in two steps following their strategy for the cyclization of the tetracyclic core from their 1st generation synthesis (51 → 54, Scheme 7). It should be noted that
Dixon’s 2nd and 3rd generation total syntheses were reported after our own total synthesis of nakadomarin A, which features alkyne metathesis/semi-hydrogenation to introduce the Z-macrocyclic alkene.

Scheme 11. Dixon’s 3rd generation endgame

III. Our enecarbamate Michael addition/N-acyliminium ion cyclization strategy

Our retrosynthetic analysis for the total synthesis of nakadomarin A is outlined in Scheme 12. Ring-closing metathesis could provide the 15- and 8-membered azacycles of 1. We were intrigued by the possibility of generating an N-acyliminium ion by a Lewis acid-promoted intramolecular conjugate addition of the enecarbamate functionality of amide to the doubly activated Michael acceptor. Based upon the precedent set by Nishida (Scheme 6), the resulting N-acyliminium ion should undergo concomitant cyclization with the proximate furan
substituent to afford the tetracycle 80 that is suitably functionalized for completion of the total synthesis. In turn, amide 82 could be obtained by treatment of amine 84 with an appropriate acylating agent, such as acid 83. Of paramount concern was the stereochemical consequence of the proposed conjugate addition reaction. Although it seemed possible that the conjugated double bond would approach from the enecarbamate moiety from the face opposite to the vinyl substituent (or, if necessary, a more sterically encumbered vinyl equivalent), it was by no means certain that the iminium ion would prefer to emerge cis to the furan substituent on the six-membered lactam. It was anticipated that the stereochemistry would be dependent upon the conjugated double bond configuration, the stereoelectronic bias, if any, of the enecarbamate moiety (synclinal vs. anti) and steric factors. Inspection of molecular models suggested that the E-isomer might lead to a more favorable outcome (vide infra).

**Scheme 12. Retrosynthetic analysis of nakadomarin A**

![](image)

A. Functionalization of N-acyliminium ions generated from enecarbamates

*N*-Acyliminium ions have been utilized extensively for the construction of nitrogen-containing ring systems. Accordingly, a number of methods have been developed for the generation of these versatile electrophiles. A particularly attractive
protocol involves the treatment of an enecarbamate 85 (Scheme 13) with an
electrophile to afford the \( \text{N-acyliminium ion} \) 86 that is then trapped by a nucleophile
to afford carbamate 87, a product of tandem vicinal difunctionalization. Typically the
enecarbamates are activated by protonation, halogenation or oxidation, but
examples using the arguably more valuable carbon electrophiles are scarce.\(^{16}\)
Examples of enecarbamates using a carbon electrophile \textit{and} carbon nucleophile are
even more limited, most likely because of the incompatibility of these two reactive
species.\(^{17}\)

In fact, the three-component coupling method reported by Suga and Yoshida\(^{18}\) was accomplished by the sequential addition of an electrochemically
generated iminium ion 89 to the enecarbamate 88 to produce the \( \text{N-acyliminium ion} \) 90 followed by allyl silane addition to afford difunctionalized pyrrolidine 91 (Scheme 14).
Stevenson’s approach to the core of the martinelline alkaloids employed an
enecarbamate in a Lewis acid-catalyzed Povarov reaction.\(^{19,20}\) Although described as
a cycloaddition, this reaction most likely proceeds stepwise, with enecarbamate 93
attacking the iminium ion 92, generating \( \text{N-acyliminium ion} \) 95, which is then trapped
by the tethered aniline ring to form the hexahydropyrroloquinolines 96. An alternative
scenario for circumventing this hypothetical incompatibility problem is to design
enecarbamates capable of undergoing intramolecular activation and capture
processes wherein geometric constraints preclude the self-destruction of the
electrophilic and nucleophilic components. These factors are no doubt at play in the
Pt-catalyzed cycloisomerization of enecarbamate 97 and the subsequent closure of
the resultant \( \text{N-acyliminium ion} \) 98 with the modest methoxyphenyl nucleophile to
tetracycle 99 reported by Dake.\(^{21}\)
B. Stevens’ tandem vicinal difunctionalization of enamines

Modern enecarbamate chemistry undoubtedly benefited from the pioneering work of Stevens in expanding the chemistry of enamines, which were generated from treatment of cyclopropyl imines with acids or ammonium halides (Schemes 15 and 16). This methodology enabled the total syntheses of numerous natural products, as exemplified in the strategy employed for mesembrine shown in Scheme 17. Thus, enamine underwent an acid-promoted conjugate addition to methyl vinyl ketone, and the resultant iminium ion was trapped in a Mannich reaction to afford mesembrine. Moreover, this
transformation suggested that it might be possible to generate an *N*-acyliminium ion from a conjugate addition of an enecarbamate to a *doubly activated* Michael acceptor, especially in the intramolecular scenario for our planned synthesis of the nakadomarin A tetracyclic core.

**Scheme 15.** Stevens’ synthesis of enamines from cyclopropyl imines

![Scheme 15](image)

**Scheme 16.** Proposed mechanism of enamine formation

![Scheme 16](image)
C. Cossey and Funk’s Prins cyclizations of enecarbamates

It should be noted that the Funk group previously has found success in generating N-acyliminium ions from enecarbamates. It was discovered that enecarbamates participate in highly diastereoselective Prins cyclizations with oxocarbenium ions en route to all-cis-2,3,6-trisubstituted tetrahydropyran-4-ones\textsuperscript{16h} (Scheme 18). Thus, metalation of enecarbamate 115 followed by addition of propylene oxide and BF\(_3\)-OEt\(_2\) gave the desired reactant for a Prins cyclization, homoallylic alcohol 116. When alcohol 116 was subjected to InCl\(_3\) and benzaldehyde in methylene chloride, the all-cis-tetrahydropyran-4-one 118 was obtained in excellent yield. Presumably, this transformation proceeds by cyclization of the diequatorial, chairlike conformer of the oxocarbenium ion 117 to provide an N-acyliminium ion that is then hydrolyzed by the equivalent of water produced from the formation of the oxocarbenium ion.

Scheme 17. Stevens’ synthesis of mesembrine via enamine difunctionalization

Scheme 18. Cossey and Funk’s Prins cyclizations of enecarbamates
IV. Results and Discussion: Model system studies for the construction of the core of nakadomarin A

A. Determination of the appropriate Michael acceptor alkene geometry

We began this investigation by preparing the more accessible Z-unsaturated model amide that lacks the three alkenyl substituents present in amide 82 (Scheme 12). Thus, a ytterbium(III)-catalyzed Knoevenagel condensation of dimethyl malonate with 3-furaldehyde (119) gave the unsaturated diester 120 (Scheme 19). Chemoselective saponification of the less-hindered ester group of diester 120 gave the monoacid 121, a compound that was converted to the chromatographically stable mixed anhydride 122. Condensation of the mixed anhydride 122 with amine 125 (prepared by reductive amination of known aldehyde 124, Scheme 20) gave the desired amide 126 (Scheme 21) in moderate yield due, in part, to competitive attack of the amine on the other carbonyl group of the mixed anhydride 122 (15%). A variety of Lewis acids [Yb(OTf)_3, Mg(OTf)_2, Zn(OTf)_2, BF_3, ZnCl_2] were surveyed for effecting the key conjugate addition/N-acyliminium ion cyclization of the Z-unsaturated amide 126. The best results were observed when Sc(OTf)_3 was employed: a mixture of two hemiaminals 128α and 128β were obtained, presumably from conjugate addition and capture of the N-acyliminium ion by adventitious water, despite extensive efforts to maintain rigorously anhydrous conditions. Addition of
water (2 equiv.) to the reaction gave hemiaminals 128α,β in improved yield but required a longer reaction period (0 °C, 12 h, 54%). Each of the hemiaminals was independently converted to the same imide 129 by oxidation with PCC. Most importantly, the major isomer, hemiaminal 128β, afforded crystalline material suitable for X-ray crystallographic analysis (Figure 2). Thus, the N-acyliminium ion 127 was indeed generated by a conjugate addition reaction, but emerges trans to the furan substituent. Its closure to the relatively flat trans-5,6-ring system may be inhibited by angle strain in the corresponding Wheland intermediate. Moreover, subjection of the acetate derivative of hemiaminal 128β to the Nishida conditions (cat. TsOH, CH₂Cl₂, rt, 42 → 44, Scheme 6) only returned hemiaminal 128β.

**Scheme 21. Cyclization of (Z)-unsaturated amide 126 to hemiaminal 128**

We now directed our attention to the preparation of E-unsaturated amide 131, which was made easier by a serendipitous discovery. Thus, in an attempt to improve
the yield of $Z$-amide 126, we converted acid 121 to the acylimidazole derivative 130 (Scheme 22). The acylimidazole 130 underwent a slow but clean transformation

**Scheme 22.** Preparation of ($E$)-unsaturated amide 131 by alkene isomerization

Upon heating in methylene chloride in the presence of amine 125 to the $E$-unsaturated amide 131. In control experiments, we independently heated the $Z$-amide 126 and the $Z$-acylimidazole 130 in methylene chloride (40 °C, 48 h) but did not observe any isomerization (Scheme 23). However, treatment of $Z$-amide 126 with

1 equivalent of diethylamine under these conditions led to complete conversion to $E$-amide 131, presumably via an aza-Michael addition/retro-Michael addition pathway. This fortuitous thermodynamic control has been previously observed for related $\alpha$-alkylidene-$\beta$-carboxyamides$^{15a,25}$ (Scheme 24) and can be attributed to, in part, the
better overlap of the ester substituent with the adjacent double bond in

**Scheme 24.** Examples of thermodynamic isomerization of unsaturated amides

\[
\begin{align*}
\text{Brown:} & & \text{PhCHO, piperidine} & \quad & \text{EtO-} & \quad & \text{Ph} & \quad & \text{EtO-} & \quad & \text{Ph} \\
133 & \rightarrow & 134 & \rightarrow & 135 \\
\text{initial ratio:} & \quad & 4 & : & 1 & \quad & \text{upon prolonged standing:} & \quad & 1 & : & >20
\end{align*}
\]

\[
\begin{align*}
\text{Tietze:} & & \text{MeO} & + & \text{Me}_{3}\text{Si} & \quad & \text{EtO-} & \quad & \text{MeO} & \quad & \text{Me}_{3}\text{Si} \\
136 & + & 137 & \rightarrow & 138
\end{align*}
\]

\(E\)-amide 131, in comparison to the carbonyls of \(Z\)-amide 126, both of which are twisted out of conjugation. Our good fortune carried over to the next step where it was found that treatment of enecarbamate 131 with 10 mol % scandium triflate in methylene chloride (0 °C → rt, 0.5 h) gave tetracycle 139 (Scheme 25), whose relative stereochemistry was determined by X-ray crystallographic analysis (Figure 3) and shown to be that desired for the synthesis of nakadomarin A.

**Scheme 25.** Cyclization of \((E)\)-unsaturated amide 131 to tetracycle 139

\[
\begin{align*}
\text{Boc} & \quad & 131 & \rightarrow & 138 & \rightarrow & 139 \\
10 \text{ mol %} & & \text{Sc(OTf)}_3 & \quad & \text{CH}_2\text{Cl}_2 & \quad & 0 ^\circ \text{C} \rightarrow \text{rt}, 0.5 \text{ h}
\end{align*}
\]
Our working model for this favorable stereochemical outcome is diagrammed in Scheme 26. Thus, cyclization can take place through one of two boatlike transition states, *synclinal*-140 or *anti*-140. Two effects might conspire to destabilize *synclinal*-140; a steric interaction between the Boc and ester substituents as well as an electrostatic interaction between the developing positive charge on the enecarbamate nitrogen and the carbonyl carbon of the chelated ester. These interactions are not present in *anti*-140, and so cyclization leads directly to the boat conformer 141 of the *N*-acyliminium ion intermediate. Conformational adjustment by rotation to the alternative boat conformer 142 possessing a quasi-equatorial furan substituent (or even further to the corresponding half-chair conformer) before closure to the tetracycle 139 then rationalizes the observed diastereoselectivity.26

Scheme 26. Rationalization of observed diastereoselectivity of cyclization
There is little precedent to be found in the literature that would suggest whether an anti pathway is stereoelectronically preferred over the synclinal possibility. Two literature examples of enamine Michael additions which could proceed through synclinal or anti transition states, reported by d’Angelo\textsuperscript{27}, are shown in Scheme 27. In the first example, thermally-induced intramolecular cyclization of imine 143 (through the reactive enamine tautomer) and subsequent hydrolysis gave exclusively keto-ester 144. This cyclization presumably proceeds through transition state synclinal-143, as this arrangement between the ethylenic ester and the enamine allows for the concerted creation of the C-C bond and proton transfer from the enamine nitrogen to the α-carbon of the ester.\textsuperscript{27a} Further evidence for this aza-ene-like cyclic transition state was observed in the intermolecular reaction of deuterated imine im-145 and methyl acrylate to yield adduct 146, which contains a deuterium atom at the α-position to the ester group.\textsuperscript{27b} The complete control of the stereogenic center at C-2 position in adduct 146 supports the hypothesis that the deuteron bound to the nitrogen atom of the enamine (en-145) was transferred to the α-vinylic carbon of methyl acrylate concertedly with the formation of the C-C bond.
Scheme 27. Literature examples of synclinal and anti enamine Michael additions

Intramolecular cyclization through synclinal transition state$^{27c}$:

Conversely, subjection of imine 146 to similar conditions results in the isolation of keto-ester 147 (Scheme 27), which results from an anti approach of the enamine to the Michael acceptor.$^{27c}$ In this case, cyclization through acyclic transition state anti-148 is preferred over the energetically disfavored, boatlike transition state synclinal-148.
Thus, it can be seen from these examples that intramolecular conjugate additions are governed by stereoelectronic as well as steric factors.

B. Conjugate addition facial selectivity studies

Having demonstrated that an intramolecular Michael addition of an enecarbamate constitutes a new pathway to N-acyliminium ions and having successfully applied this protocol to the rapid construction of the tetracyclic core of nakadomarin A, we next turned to the installation of a substituent at C-14 that could control the facial selectivity of the enecarbamate conjugate addition and also be employed to elaborate the azocine by alkene metathesis. The preferred substituent was a C-14 vinyl group, as it was required for the alkene metathesis reaction. Thus, optically active ester 151, prepared via known procedures from D-pyroglutamic acid 149, underwent partial reduction to the aldehyde followed by Wittig olefination to afford the vinylpyrrrole 152 (Scheme 28). Vilsmeier-Haack formylation of the enecarbamate 152 gave the vinylogous imide 153, which was subjected to reductive amination with methylamine to furnish amine 154. The amine 154 was then acylated with methyl malonyl chloride to give amide 155. Knoevenagel condensation of amide 155 with furaldehyde 156, obtained by the Garst protocol for regioselective alkylation of 3-furaldehyde (Scheme 29), provided the desired unsaturated E-amide 157.
**Scheme 28. Preparation and cyclization of vinyl pyrroline 157**

![Chemical reactions and structures](image)

<table>
<thead>
<tr>
<th>conditions</th>
<th>result (158:159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mol % Sc(OTf)_3, CH_2Cl_2, 0 °C → rt, 5 h</td>
<td>1:1</td>
</tr>
<tr>
<td>10 mol % Sc(OTf)_3, PhMe, -15 °C → rt, 3 h</td>
<td>1:2</td>
</tr>
<tr>
<td>10 mol % Sc(OTf)_3, MeCN, -15 °C → rt, 5 h</td>
<td>1:2:1</td>
</tr>
<tr>
<td>10 mol % Yb(OTf)_3, PhMe, reflux, overnight</td>
<td>1:1</td>
</tr>
<tr>
<td>10 mol % BF_3·OEt_2, CH_2Cl_2, -78 °C → rt, 3 h</td>
<td>decomp.</td>
</tr>
<tr>
<td>10 mol % SnCl_4, CH_2Cl_2, -78 °C → rt, 3 h</td>
<td>decomp.</td>
</tr>
<tr>
<td>10 mol % Me_3AlCl, CH_2Cl_2, -78 °C → rt, 4 h</td>
<td>1:1</td>
</tr>
<tr>
<td>10 mol % Zn(OTf)_2, CH_2Cl_2, 0 °C → rt, overnight</td>
<td>no reaction</td>
</tr>
<tr>
<td>10 mol % Cu(OTf)_2, Et_2O, 0 °C → rt, overnight</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

**Scheme 29. Synthesis of 5-methyl-3-furaldehyde (156) by Garst**

![Chemical reactions and structures](image)

Treatment of amide 157 with catalytic scandium triflate provided a 1:1 mixture of separable stereoisomers 158 and 159. One of the products provided crystals suitable for X-ray crystallographic analysis. This product was determined to have the desired stereochemistry (Figure 4). The structure of the other product remains to be determined, but is likely the C-14 epimer of tetracycle 158 (159), suggesting that the
vinyl moiety's steric influence on the enecarbamate conjugate addition was insufficient. The putative structural of assignment of 159 is based on the observation that independent decarboxylation of tetracycles 158 and 159 delivered different lactams. Efforts directed toward increasing the ratio of the desired tetracycle 158 by varying the Lewis acid and solvent were unsuccessful.

**Figure 4.** X-ray crystal structure of vinyl substituted tetracycle 158

We next prepared several derivatives of pyrroline 152 that possessed a protected hydroxymethyl substituent in place of a vinyl group: a pivalate (165) and TBS (166) and TIPS ethers (167) (Scheme 30). These enecarbamates were elaborated to their respective E-unsaturated amides 177, 178, and 179 following the same synthetic route that was utilized for the preparation of vinyl congener 157.

**Scheme 30.** Preparation of protected hydroxymethyl cyclization substrates
When subjected to our standard cyclization conditions [10 mol % Sc(OTf)$_3$, CH$_2$Cl$_2$, 0 °C → rt], pivalate 177 cyclized to a favorable 3:1 mixture of stereoisomers (Table 1). The stereochemistry of the major product was confirmed by X-ray crystallography of the decarboxylated and deprotected tetracycle 185 (Scheme 31 and Figure 5). The bulkier TBS and TIPS ethers 178 and 179 provided the desired steric influence: their cyclizations each yielded a single diastereomer, which could be converted to the hydroxymethyl tetracycle 185 following deprotection and deprotection and decarboxylation of pivalate tetracycle 181.
Figure 5. X-ray crystal structure of hydroxymethyl tetracycle 185

The decarboxylation of the superfluous ester. However, the reaction conditions also caused partial cleavage of the silyl groups, resulting in isolation of a mixture of tetracyclic silyl ether and the corresponding alcohol. This minor setback could be avoided altogether for the TIPS ether 179 if InCl₃ was employed as the catalyst and the reaction was run at reflux, providing the tetracyclic silyl ether 184 as the sole product in good yield. Ultimately we decided on the TIPS ether, as it survived the Vilsmeier formylation while the TBS group was prone to deprotection and subsequent alcohol formylation (Scheme 32).

Scheme 32. Unexpected deprotection and formylation of TBS congener 166

V. Construction of the fifteen-membered macrocycle by metathesis

A. Ring-closing alkene metathesis approach

With the discovery of a suitable directing group for the conjugate addition, studies were directed towards the metathesis-driven completion of the total synthesis. In order to proceed, an appropriately substituted furaldehyde, namely 5-(but-3-en-1-yl)-3-furaldehyde (187), was required. Attempts to directly convert 3-furaldehyde 119 directly to substituted aldehyde 187 via the Garst protocol failed (Scheme 33).
Scheme 33. Inability to directly alkylate 3-furaldehyde with 1-iodo-3-butene

The preparation of furaldehyde 187 took advantage of Maldonado’s methodology for the synthesis of 2,4-disubstituted furans from γ,γ'-diacetoxyenones. Thus, dimetalation of β-ketophosphonate 188 followed by treatment with allyl iodide gave alkylated β-ketophosphonate 189 (Scheme 34). Horner-Wadsworth-Emmons reaction between phosphonate 189 and 1,3-diacetoxyacetone provided γ,γ'-diacetoxyenone 191. This enone underwent smooth, acid-catalyzed cyclization in methanol at 50 °C to furanmethanol 192. Finally, Swern oxidation of alcohol 192 furnished the desired aldehyde 187.

Scheme 34. Synthesis of 5-(but-3-en-1-yl)-3-furaldehyde 187

The β-carboxy amide 194 required for Knoevenagel condensation was prepared as shown above, except in this case reductive amination of aldehyde 187 took place with hex-5-en-1-amine (Scheme 35). Knoevenagel condensation of furaldehyde 187 with amide 194 in the presence of piperidine and benzoic acid provided E-unsaturated amide 195. Treatment of enecarbamate 195 with catalytic InCl₃ provided the cyclized tetracycle in 80% yield. Saponification of the ester functionality followed by thermally promoted decarboxylation gave the lactam 197, suitably functionalized for alkene metathesis.
Scheme 35. Preparation of tetracycle 197, fully substituted for alkene metathesis

It was hoped that the six-membered lactam present in diene 197 would offer some conformational preference for formation of the Z-configurational isomer during alkene metathesis. Nishida and Kerr both obtained an unfavorable mixture of Z:E isomers in their metathesis experiments (Scheme 8), but their systems possessed an exocyclic amide. Unfortunately, when diene 197 was subjected to Kerr’s conditions for ring-closing metathesis (20 mol % Grubbs 1, CH₂Cl₂, reflux), a 1:2 mixture of Z:E isomers 198 was obtained (Scheme 36). However, when Grubbs 2nd generation catalyst was employed, a reversal in selectivity was observed, (2.5:1 Z:E). Interestingly, when the 1:2 Z:E mixture was treated with Grubbs 2 in refluxing methylene chloride, the mixture was isomerized to the favorable mixture. Calculations (PC Model) found Z-198 to be favored over E-198 by 1.2 kcal/mol.
This type of thermodynamic control by the Grubbs 2nd generation catalyst has been previously observed; an example reported by Grubbs is given in Scheme 37. Unfortunately, the mixture of configurational isomers could not be separated by standard or silver-impregnated silica gel chromatography.

Scheme 37. Example of alkene metathesis under thermodynamic control

B. Ring-closing alkyne metathesis/semi-hydrogenation strategy

We next turned to a ring-closing alkyne metathesis (RCAM)/semi-hydrogenation strategy that would circumvent the E/Z selectivity problem and deliver the Z-cycloalkene as a single configurational isomer. The viability of this strategy was demonstrated by Fürstner and co-workers in their synthesis of the macrocyclic perimeter of nakadomarin A (Scheme 38). The alkynyl furaldehyde was prepared in similar fashion to the alkenyl furaldehyde. The lone difference was in the preparation of β-ketophosphonate, which in this case was obtained by
Scheme 38. Fürstner’s synthesis of the macrocyclic perimeter by alkyne metathesis

metalation of dimethyl methyl phosphonate followed by acylation with methyl 4-hexynonate (204 → 205, Scheme 39).

Scheme 39. Synthesis of 5-(pent-3-ynyl)-3-furaldehyde 208

The tetracyclic diyne 213 was prepared analogously as the tetracyclic diene 197, with the exception that hept-5-yn-1-amine was employed in the reductive amination of aldehyde 170 (Scheme 40).
Scheme 40. Preparation of tetracycle 213, fully substituted for alkyne metathesis

The diyne functionality of tetracycle 213 was subjected to several different alkyne metathesis systems with varying levels of success (Table 2). Grela’s optimized conditions\(^1\) of the Mortreux alkyne metathesis system\(^2\) \([\text{Mo(CO)}_6, 2\text{-fluorophenol, 3-hexyne, 1,2-diphenoxyethane in chlorobenzene at } 140 \, ^\circ\text{C, 3 h}]\) gave cycloalkyne 214 in 41% yield (54% brsm). The Schrock tungsten carbyne catalyst\(^3\) \((t\text{-BuO})_3\text{W≡C-t-Bu}\) in chlorobenzene (25 mol %, 80 °C, 3 h) proved more effective, allowing cyclization to 214 in 77% yield on a gram scale. It should be noted the air-stable molybdenum nitride complex \([\text{pyridine}(\text{Ph}_3\text{SiO})_3\text{Mo≡N}]\) recently developed by Fürstner\(^4\) gave comparable results with a slightly lower catalyst loading (20 mol %, toluene at 80 °C, 16 h, 80% yield). Deprotection of the TIPS group by TBAF provided an alcohol 215 that was analyzed by X-ray crystallography (Figure 6).
**Table 2. Alkyne metathesis experiments**

<table>
<thead>
<tr>
<th>conditions</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo(CO)$_3$, 2-fluorophenol, 3-hexyne, 1,2-diphenoxyethane</td>
<td>41% (54% brsm)</td>
</tr>
<tr>
<td>25 mol % (t-BuO)$_3$W≡C-t-Bu, PhCl, 80 °C, 3 h</td>
<td>77%</td>
</tr>
<tr>
<td>20 mol % [(pyridine)(Ph$_3$SiO)$_3$Mo≡N], PhMe, 80 °C 16 h</td>
<td>80%</td>
</tr>
</tbody>
</table>

**Figure 6. X-ray crystal structure of cycloalkyne 215**

**VI. Completion of the total synthesis of nakadomarin A**

Synthetic efforts were then directed to the construction of the azocine ring and the completion of the total synthesis. The cis double bond of the fifteen-membered ring was introduced by Lindlar reduction of cycloalkyne 214 and was unaccompanied by the E-olefin stereoisomer as verified by $^1$H NMR analysis (Scheme 41). Deprotection of the TIPS ether furnished alcohol 216. Oxidation of alcohol 216 with IBX in DMSO followed by Tebbe olefination (Wittig, Peterson and Nysted protocols were ineffective) proceeded uneventfully to yield vinyl pyrrolidine 217. Deprotection of the Boc carbamate with TFA and N-acylation with 5-hexenoyl
chloride gave alkene metathesis substrate 218. Ring-closing metathesis of diene 218 to azocine 219 proved problematic. Utilization of Grubbs 2nd generation catalyst did not provide any of the desired azocine and resulted in decomposition of the starting diene. The best yield was obtained when diene 218 was treated with an equimolar amount of Grubbs 1st generation catalyst in refluxing methylene chloride. It is possible that that the proximal double bond in the 15-membered ring could interact with the ruthenium catalyst, thus inhibiting catalytic activity. Reduction of the resultant bis-lactam 219 with alane provided (−)-nakadomarin A in 58% overall yield from diene 218. Spectral data was identical to that of natural 1. The optical rotation confirmed its absolute configuration ([α]D = −72.7 (c 0.12, MeOH), lit.5b [α]D = −73.0 (c 0.08, MeOH)).

**Scheme 41.** Completion of the total synthesis of nakadomarin A

A comparison of the nakadomarin A total syntheses by step count and key steps can be found in Table 3. Our total synthesis is relatively concise, and at the time was the first to feature the ring-closing alkyne metathesis/semi-hydrogenation strategy to construct the macrocycle as a single configurational isomer.
Table 3. Comparison of nakadomarin A total syntheses

<table>
<thead>
<tr>
<th>Year</th>
<th>Lead Author</th>
<th>Longest Linear Sequence</th>
<th>Key Steps</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Nishida</td>
<td>37 steps from methyl 4-oxopiperidino-3-carboxylate</td>
<td>furan/N-acyliminium ion cyclization, E-selective RCM macrocyclization</td>
<td>5a</td>
</tr>
<tr>
<td>2004</td>
<td>Nishida</td>
<td>36 steps from L-serine</td>
<td>Diels-Alder and $S_N$' cyclizations, E-selective RCM macrocyclization</td>
<td>5b</td>
</tr>
<tr>
<td>2007</td>
<td>Kerr</td>
<td>29 steps from D-mannitol</td>
<td>nitronine/cyclopropane cycloaddition, Heck cyclization, E-selective RCM macrocyclization</td>
<td>5c</td>
</tr>
<tr>
<td>2009</td>
<td>Dixon</td>
<td>13 steps from D-pyroglutaminol</td>
<td>nitro-Mannich/lactamization cascade, Z-selective RCM macrocyclization</td>
<td>5d</td>
</tr>
<tr>
<td>2010</td>
<td>Funk</td>
<td>21 steps from D-pyroglutamic acid</td>
<td>enecarbamate Michael addition/furan/ N-acyliminium ion cyclization, RCAM nitro-Mannich/lactamization cascade, RCAM/semi-hydrogenation</td>
<td>5e</td>
</tr>
<tr>
<td>2010</td>
<td>Dixon</td>
<td>19 steps from D-pyroglutaminol</td>
<td>RCAM nitro-Mannich/lactamization cascade, RCAM/semi-hydrogenation</td>
<td>5f</td>
</tr>
<tr>
<td>2010</td>
<td>Dixon</td>
<td>14 steps from D-pyroglutaminol</td>
<td>nitro-Mannich/lactamization cascade, RCAM/semi-hydrogenation</td>
<td>5g</td>
</tr>
<tr>
<td>2010</td>
<td>Zhai</td>
<td>23 steps from D-pyroglutamic acid</td>
<td>Cascade enecarbamate/alkyne furan/N-acyliminium ion cyclization</td>
<td>5h</td>
</tr>
</tbody>
</table>

VII. Future directions

A. Preparation of nakadomarin A structural analogs

The flexibility of the enecarbamate conjugate addition/N-acyliminium ion cyclization was demonstrated in the preparation of several tetracyclic nakadomarin A analogs (Scheme 42). Thus, the N-methylpyrrole analog 223 has been prepared, as well as the structurally intriguing dimethoxybenzene analog 228. The electron-poor phenyl substituent ($N < -4.2$, Mayr nucleophilicity scale\(^\text{34}\)) of enecarbamate 224, in comparison to the pyrrole moiety ($N = 5.85$) of 223 and the dimethoxybenzene ($N = 2.48$) of 227, was found to be insufficiently nucleophilic to capture the N-acyliminium ion, resulting in the isolation of hemiaminal 225. It should be noted that each of these cyclizations was slower than cyclization of the furan ($N = 1.36$) compound 131, which suggests that the rate-limiting step is the conjugate addition reaction which would be retarded by the electron-rich pyrrole and dimethoxyphenyl substituents.
Several nakadomarin A structural analogs were prepared for possible cytotoxicity and/or CDK-4 inhibition structure-activity relationship (SAR) studies (Scheme 43). The model system core 139 underwent a two-step decarboxylation process to furnish lactam 229. Boc deprotection and reduction amination afforded N-methylpyrrolidine 230. Finally, lactam reduction with alane delivered the bis-amine 231. Similarly, pentacycle 217 was converted to the N-methylpyrrolidine 232. Attempts to reduce the lactam functionality of 232 resulted in decomposition.
B. An approach to ircinal A and manzamine A

A natural evolution of this project would be to apply the key enecarbamate conjugate addition reaction to construct the tricyclic core of the parent manzamine alkaloid, ircinal A \( \text{(2)} \).\(^{35-37}\) A plausible retrosynthetic analysis of an ircinal A model system is presented in Scheme 44. Thus, the tricyclic core 233 could be assembled via a Lewis acid-catalyzed conjugate addition of the enecarbamate moiety of amide 236 to the doubly activated Michael acceptor. The resultant \( N \)-acyliminium ion 235 should undergo concomitant cyclization to form a six-membered ring vis-à-vis a five-membered ring obtained in our nakadomarin A synthesis. The resultant oxocarbenium ion 234 might then eject a \( t \)-butylcarbenium ion to afford the core of ircinal A. In turn, the amide 236 could be assembled via acylation of amine 125 with acid 237.
Scheme 44. Retrosynthetic analysis of the tricyclic core of ircinal A

Preliminary experiments towards this endeavor have been conducted. Thus, vinylogous formate 240 was prepared in two steps from 1,1,3,3-tetramethoxypropane 238 through intermediate bromomalonaldehyde 239 \(^\text{38}\) (Scheme 45). Stille coupling of tributyl(vinyl)tin with the vinyl bromide functionality of 240 provided the dienol ether 241. Knoevenagel condensation of aldehyde 241 with dimethyl malonate in the presence of TiCl\(_4\) was accompanied with isomerization and afforded unsaturated diester 242 as a 3:1 mixture of configurational isomers. Attempts to hydrolyze either ester of diester 242 resulted in the isolation of a mixture of mono- and diacids.

Scheme 45. Elaboration of vinylogous formate 239 to unsaturated diester 242
We also briefly examined the direct condensation of aldehyde 241 with β-carboxyamide 220 with our standard Knoevenagel conditions (piperidine and benzoic acid in benzene), but found that the piperidine was consumed in an conjugate addition/elimination reaction with vinylogous formate 241, resulting in the isolation of vinylogous formamide 243 (Scheme 46).

**Scheme 46. Attempted Knoevenagel condensation of aldehyde 241**

An alternative approach to manzamine A could take advantage of our knowledge gained in our nakadomarin A total synthesis as well as a report by Nishida and co-workers in their own manzamine A model studies, which is outlined in Scheme 47. Treatment of hemiaminal 244 with acetic acid resulted in the generation of N-acyliminium ion 245 which was trapped with the tethered furan. Interception of the resulting furonium ion 246 with water provided hemiacetal 247 which was oxidized with IBX to lactone 248. One possible adaptation of our enecarbamate conjugate addition/N-acyliminium ion cyclization strategy to this approach is depicted for a model system study in Scheme 48. Thus, DCC-mediated coupling of acid 250 with allylic alcohol 251 could deliver ester 252, which could

**Scheme 47. Nishida’s construction of the core of manzamine A**
undergo intramolecular Knoevenagel condensation to lactone 253. Treatment of substrate 253 with indium trichloride and water would hopefully effect a 1,4-conjugate addition of the enecarbamate to the unsaturated lactone. A comparison of the two possible pathways for the Michael addition suggests the synclinal one (255) might be preferred over the anti (254) due to steric factors: a less serious synpentane interaction between the planar N-acyliminium carbon with the acyloxy methylene carbon of the lactone and a less encumbered Boc substituent. Of course, an intrinsic stereoelectronic bias for anti-addition might override this perceived steric bias. Following Nishida’s precedent, trapping the N-acyliminium ion of Michael adduct 252 with the tethered furan followed by interception of the resulting furonium ion with water would deliver the core of manzamine A 256.

Scheme 48. Plausible core construction of manzamine A

C. Investigation into the scope and limitations of the methodology

Another future direction for this project would be a systematic investigation into the scope and limitations of the enecarbamate conjugate addition/N-acyliminium ion cyclization. Two examples that exemplify the range of possibilities are shown in Scheme 49. Thus, it seems likely that formation of the fused ring system 259 from enecarbamate 257 would be possible. On the other hand, enecarbamate 260 may represent a limiting example, since bridged bicyclic closure to 262 must take place with a less nucleophilic enecarbamate, less electrophilic Michael acceptor and an
inferior terminating group. To be sure, new targets for the application of this methodology are likely to emerge in the future.

**Scheme 49.** Possible studies of the scope and limits of the key cyclization reaction

VIII. Concluding remarks

In conclusion, we have completed a total synthesis of (−)-nakadomarin A in 21 steps from D–pyroglutamic acid. The tetracyclic core was constructed via a novel tandem enecarbamate conjugate addition/furan-\(N\)-acyliminium ion cyclization. Moreover, a sequential ring-closing alkyne metathesis/semi-hydrogenation strategy was utilized to obtain the fifteen-membered azacycle as a single configurational isomer. It remains to be seen whether other polycyclic systems can be constructed by the strategic placement of the enecarbamate, Michael acceptor, and various nucleophilic components for the interception of the \(N\)-acyliminium ion intermediate.
Part II

Retrocycloadditions of 5-(Trialkylsilyloxy)-1,3-dioxins and
(4 + 3) Cyclizations of (Z)-2-Trialkylsilyloxy-2-enals.
Application to the Synthesis of Cortistatins A and J
Chapter 2
Cortistatins A and J

I. Introduction

The cortistatins are a family of novel steroidal alkaloids isolated by Kobayashi and co-workers from the marine sponge *Corticium simplex* collected off Flores Island, Indonesia.\(^{40}\) The unprecedented reorganization of the steroidal framework in addition to the unusual amino and isoquinoline substituents contribute to the appeal of these natural products as targets for total synthesis. However, their biological properties are even more significant. Cortistatins A-D\(^{40a}\) and J-L\(^{40c}\) inhibited the proliferation of human umbilical vein endothelial cell (HUVECS) with high selectivity. Cortistatins A (263) and J (271) (Figure 7) are the most active and selective of the natural products, having shown cytostatic and anti-proliferative activity (IC\(_{50}\) = 1.8 and 8 nM for 263 and 271 respectively) against HUVECs with a selective index of 300-1100 for 1 and greater than 3000 for 263 in comparison with that of normal human dermal fibroblast or several tumor cell lines. The anti-angiogenic properties of 263 were also evaluated and it was found that the migration and tubular formation of HUVECs induced by VEGF or bFGF could be inhibited at 2 nM concentration. Thus, the cortistatins represent exciting new leads for anticancer drug discovery efforts based upon the inhibition of angiogenesis.\(^{41}\) Accordingly, these natural products have attracted significant attention from the synthetic community, resulting in numerous approaches\(^{42}\) and several total\(^{43}\) and formal\(^{44}\) syntheses.\(^{45}\)
II. Previous synthetic approaches towards the cortistatins

The rearranged steroidal ring system that is centered around the oxabicyclo[3.2.1]octane substructure has inspired a multitude of synthetic strategies, ranging from sequential ring construction to modifying the standard steroid skeleton. The following discussion of approaches has been organized according to method of assembly of the pentacyclic core.

A. Ring-expansion approaches

Baran and co-workers utilized a cyclopropane fragmentation to form the B ring in their semi-synthesis of cortistatin A from prednisone (274). The requisite
cyclopropane was installed by an innovative sequence. Thus, hydroxyl-directed, selective dibromination of the C-19 methyl group was achieved by treatment of hydroxy orthoamide 276 with AcOBr, generated in situ from Phl(OAc)$_2$ and Br$_2$. Alcohol protection gave dibromo TMS alcohol 277 (Scheme 50). Treatment of dibromide 277 with DBU effected intramolecular cyclization to the bromocyclopropane 278. The cyclopropane 278 was regioselectively fragmented to the seven-membered ring upon exposure to SmI$_2$, and the resulting samarium enolate was trapped with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) to give α-bromo ketone 279. Dehydrobromination of 279 with Li$_2$CO$_3$, alane reduction of the ketone and orthoamide moieties and acetylation of the secondary hydroxyl groups furnished triacetate 280. The ether bridge was installed by a magnesium-promoted, intramolecular displacement of the allylic acetate by the C-5 hydroxyl group of 280. Global deprotection afforded “cortistatinone” (281), which was converted to cortistatin A following vinyl iodide preparation, Stille coupling to install the isoquinoline, and chemo- and stereoselective alkene reduction.

**Scheme 50. Baran’s semi-synthesis of cortistatin A from prednisone**
The Shair group also employed a cyclopropane fragmentation in their total synthesis of cortistatin A.\textsuperscript{43c} Diene 284 underwent chemoselective cyclopropanation with dibromomethylene followed by fluoride-induced ring expansion of dibromocyclopropane 285 to afford trienyl vinyl bromide 286 (Scheme 51). Suzuki coupling of vinyl bromide 286 with boronic ester 287 gave tetraene 288. This product was elaborated to aldehyde 289 through a four-step sequence consisting of dihydroxylation, bisacylation, selective TES ether cleavage and alcohol oxidation. Upon exposure of aldehyde 289 to Me\textsubscript{2}NH and ZnBr\textsubscript{2}, an aza-Prins/transannular etherification took place with concomitant removal of the MEM ether to provide dimethylamino pentacycle 291. Cleavage of the TBS ether functionality of 291, oxidation of the resulting alcohol and acetate removal afforded the “cortistatinone” intermediate 281 from Baran’s semi-synthesis, and was converted to cortistatin A following their precented.

**Scheme 51.** Shair’s total synthesis of cortistatin A

Magnus and Littich took advantage of a cyclopropylcarbinyl rearrangement to access the BCD ring system of cortistatin A.\textsuperscript{42i} 2-Methylfuran (292) and 2-methylcyclopent-2-enone (293) were converted in six steps to aldehyde 294 (Scheme 52). Addition of lithiated cyclopropene 295 to aldehyde 294 led to formation
of lithium alkoxide 296, which, when allowed to warm to room temperature, underwent a furan-cyclopropene \([4 + 2]\) cycloaddition to cycloaduct 297. Hydrogenation of the alkene functionality of 297 yielded cyclopropane 298, which upon treatment with Tf\(_2\)O, underwent the desired cyclopropylcarbinyl rearrangement to the seven-membered diene 299 which possesses the BCDE core ring structure of cortistatin A.

**Scheme 52. Magnus and Littich’s approach to cortistatin A**

B. *Cascade sequence approaches*

Nicolaou and Chen reported the first total synthesis of cortistatins A and J, utilizing a oxa-Michael/aldol condensation cascade sequence to assemble the pentacyclic core.\(^{43b,d}\) Alkyne 301, prepared in 9 steps from Hajos-Parrish ketone derivative 300, underwent Sonagashira coupling with enol triflate 302 to give alkynyl enone 303 (Scheme 53). Removal of the dithiane moiety of 303 and chemoselective alkyne hydrogenation furnished keto aldehyde 304. Upon heating hydroxy enone 304 in dioxane in the presence of K\(_2\)CO\(_3\), the desired oxa-Michael/aldol condensation cascade cyclization sequence took place to afford pentacyclic dienone 306. A seven-step sequence converted dienone 306 to the isoquinoline 307. The A-ring ketone of 307 was oxidized to the corresponding enone 308 by IBX oxidation of the corresponding silyl enol ether. Nucleophilic epoxidation of this enone with TBHP/DBU to epoxide 309 followed by Luche reduction provided the alcohol 311, accompanied by an equal amount of the C-1 epimer 310. The total synthesis of cortistatin A (263) was completed by epoxide ring-opening with Me\(_2\)NH in the
presence of Ti(OiPr)_4, which delivered the natural product in 45% yield, along with 36% of the regioisomeric amino alcohol 312.

**Scheme 53.** Nicolaou and Chen’s total synthesis of cortistatin A

Nicolaou and Chen took advantage of the 1:1 regioselectivity that was obtained in the Luche reduction to prepare alcohol 311 and achieve the first total synthesis of cortistatin J (271). Thus, epoxide 310 (the C-1 epimer of alcohol 311) was opened with MeNH_2 and Ti(OiPr)_4 to provide amino diol 313, in this case as a single regioisomer (Scheme 54). Diol 313 was converted to the thiocarbonate 314.
which underwent Corey-Winter olefination with P(OEt)$_3$ at reflux to give cortistatin J (271) in 40% yield.

**Scheme 54.** Nicolaou and Chen’s total synthesis of cortistatin J

C. Oxidative dearomatization approaches

A common strategy employed for the construction of the oxo-bridge of the B ring of the cortistatins is oxidative dearomatization. Myers and co-workers successfully utilized this approach in their total synthesis of four members of the cortistatin natural products.$^{43e}$ Thus, Negishi coupling of dienol triflate 315 with benzylic zinc reagent 316 provided triene 317, which underwent ring-closing metathesis to elaborate the seven-membered diene 318 (Scheme 55). Stereo- and chemoselective epoxidation of the more substituted alkene functionality of diene 318 afforded epoxide 319. Alkene hydrogenation followed by eliminative epoxide opening with LiNEt$_2$ furnished allylic alcohol 320. The desired oxidative dearomatization was effected by cleavage of the TIPS ether of 320 with TBAF, and oxidative cyclization of the resulting phenol with [bis(trifluoroacetoxy)iodo]benzene to yield the cyclohexadienone 321. Hydrosilylation of diene 321 with Et$_5$SiH and Wilkinson’s catalyst provided an intermediate triethylsilyl enol ether that, upon treatment with pyridine and N-bromosuccinimide, afforded bromo ketone 322 as a single diastereomer. Bromide displacement with tetramethylguanidinium azide proceeded with clean inversion of stereochemistry and was followed by CBS-reduction of the
resulting azido ketone to azido alcohol 323, which was converted to cortistatins A, J, K and L (*vide infra*).

**Scheme 55. Myers’ preparation of the pentacyclic core of the cortistatins**

The route that Myers employed for the transformation of azido alcohol 323 to cortistatin A (263) is outlined in Scheme 56. A three-step sequence converted azido alcohol 323 to keto alcohol 324. Subjection of keto alcohol 324 to NBS in methanol led to stereoselective 1,4-bromoetherification of the conjugated diene, forming bromide 325, which was treated directly with superoxide to effect nucleophilic displacement to form the *trans*-diol methyl ether 326. When combined with TFA and catalytic Sc(OTf)$_3$, the allylic methyl ether 326 underwent 1,2-elimination of methanol to diene 327. Reductive dimethylation of the azido group of 327 followed by diol protection with TESCl furnishing *bis*-silyl ether 328. The isoquinoline moiety then was introduced stereoselectively in a three-step sequence. Addition of 7-lithioisoquinoline (329) to the ketone in 328 provided the corresponding tertiary alcohol 330. Activation of this alcohol as the corresponding trifluoroacetate, reductive deoxygenation, and finally TES ether deprotection delivered cortistatin A (263).
Myers’ key intermediate azido alcohol 323 also provided access to cortistatin J (271), although in a substantially more direct sequence (Scheme 57). Reductive methylation of the azido functionality of 323 gave dimethylamino alcohol 331. The requisite triene functionality was introduced by acid-promoted 1,6-elimination of water, which occurred with concomitant TBS deprotection to give allylic amine 332. Dess-Martin oxidation of the alcohol group of 332 afforded ketone 333, which was converted to cortistatin J (271) following the same isoquinoline installation sequence that was employed for cortistatin A (330 → 263, Scheme 56).
Sarpong and co-workers exploited a similar oxidative dearomatization strategy in their formal synthesis of cortistatin A.\textsuperscript{44a,c} The cycloheptadiene 338 was assembled by platinum-catalyzed cycloisomerization of enyne 337, which itself was prepared in four steps from indanone 335 and aldehyde 336 (Scheme 58). Diimide reduction of the disubstituted bond of diene 338, followed by protecting group exchange and \textit{m}CPBA epoxidation provided oxirane 339. Analogous to Myers’ approach, eliminative epoxide opening with concomitant silyl ether cleavage of 339 with butyllithium and oxidative dearomatization of the resultant phenol 340 with PhI(OAc)\textsubscript{2} furnished pentacyclic trienone 341. The trienone 341 was further elaborated to an intermediate (307, Scheme 53) that Nicolaou and co-workers converted into cortistatin A.
Scheme 58. Sarpong’s first-generation synthesis of the pentacyclic core

Li and Yang reported a model study of the pentacyclic core of the cortistatins that featured an intramolecular furan/alkyne cycloaddition to construct the AB rings, followed by oxidative dearomatization to install the B-ring oxo-bridge. Preparation of the Diels-Alder precursor 346 commenced with alkylation of ketone 342 with CH(OMe)3, followed by addition of furanyl lithium reagent 344 and acetal hydrolysis to give aldehyde 345 (Scheme 59). The alkyne dienophile component was introduced by addition of the lithium anion of ethyl propiolate to aldehyde 345 in the presence of AlMe3 to provide propargylic alcohol 346 as a single diastereomer. Dess-Martin oxidation of alcohol 346 effected spontaneous [4 + 2] cycloaddition to afford pentacycle 347 as a 3:1 mixture of diastereomers. Treatment of cycloadduct 347 with BF3 effected aromatization to phenol 348, which underwent oxidative dearomatization to pentacycle 349.

Scheme 59. Li and Yang’s [4 + 2] cycloaddition/oxidative dearomatization strategy
D. Electrocyclization approaches

Electrocyclization strategies have been successfully employed by several groups in order to build the oxabicyclo[3.2.1]octane B ring. Hirama and co-workers were the first to report their oxo-6π-electrocyclization approach to the pentacyclic framework of the cortistatins.\cite{42,43} Knoevenagel condensation of diene aldehyde 350 with cyclohexane-1,3-dione 351 gave the intermediate oxatriene 352, which underwent spontaneous 6π-electrocyclization to the tetracyclic 2H-pyran 353 as a 5:1 favorable mixture of diastereomers (Scheme 52). Deprotection of the TBS ether and iodination provided iodide 354. Completion of the pentacyclic core 307 was effected via intramolecular radical cyclization of iodide 354 in the presence of Et$_3$B and (TMS)$_3$SiH. The dienone 307 was transformed to ketone 356 in three steps. The isoquinoline was stereoselectively installed in a manner similar to Myers’ strategy. However, Hirama opted to use 1-chloro-7-lithioisoquinoline (357) for the cerium-mediated addition to ketone 356 to afford tertiary alcohol 358. It is of note that the yield for this addition (99%) was significantly higher than the yields Myers observed for analogous additions (52-62%). Activation of alcohol 358 as the thiocarbamate and subsequent stereoselective reduction of both thiocarbamate and isoquinoline chlorine groups gave isoquinoline 359. Acid hydrolysis of ketal 359 to the corresponding dienone and further oxidation to the trienone 308 with Mukaiyama reagent 360 constituted a formal synthesis\cite{43b} of cortistatins A and J, as Nicolaou had converted this intermediate to both natural products. However, Hirama carried this product forward, in hopes of achieving better regioselectivity than Nicolaou obtained in his total synthesis.
Hirama’s completion of the total synthesis of cortistatin A is outlined in Scheme 61. The steps closely mirror the endgame strategy that Nicolaou utilized (Scheme 53), although Hirama was able to achieve slightly better regioselectivity. Nucleophilic epoxidation of trienone 305 with TBHP and DBU provided epoxy ketone 306. Luche reduction of dienone 306 at -78 °C yielded a favorable 1.4:1 ratio of diastereomeric epoxy alcohols 307 and 308, as opposed to the 1:1 ratio observed by Nicolaou when the reaction was run at 0 °C. The total synthesis was completed with opening of the epoxide 308 with MeNH₂ in the presence of Yb(OTf)₃, which delivered cortistatin A (260) in a 2.2:1 ratio with its regioisomeric amino alcohol (309). It should be noted that Nicolaou obtained a 1.25:1 ratio in an analogous transformation when Ti(O₂Pr)₄ was employed.
Hirama’s completion of the total synthesis cortistatin J (271) is detailed in Scheme 62. Regio- and stereoselective conjugate addition of Me₂NH to triene 308 followed by LAH reduction of the ketone furnished the corresponding amino alcohol which underwent dehydration with MsCl and DBU to provide cortistatin J in 25% overall yield from 308.

Dai and Danishefsky reported two approaches toward the core of the cortistatins based on a 6π-electrocyclization/Masamune alkylative dearomatization strategy. In their first approach (Scheme 63), the 6π-electrocyclization substrate 365 was prepared as an intermediate via a Snieckus cascade (363→365),
and underwent spontaneous oxa-6π-electrocyclization under the reaction conditions to provide the tetracycle 366. The TBS ether 366 was converted in two steps to the corresponding mesylate, which underwent Masamune alkylation upon treatment with TBAF to give pentacycle 367.

**Scheme 63.** Danishefsky’s Snieckus/electrocyclization cascade approach

In a separate report, an alternate approach to the electrocyclization substrate was presented (Scheme 56). This strategy featured a 1,3-dipolar cycloaddition of nitrone 369 with the benzyne that resulted from treatment of bromophenyl triflate 368 with butyllithium to provide benzisoxazoline 370. Reductive cleavage of the N-O bond with Zn/AcOH was accompanied by 1,4-elimination of t-BuNH₂ to give the intermediate quinomethide, which underwent spontaneous 6π-electrocyclization to tricycle 371. Conversion of the PMB ether 371 to the corresponding alkyl bromide and subsequent Masamune alkylation afforded the tetracycle 372.
**Scheme 64.** Danishefsky’s 1,3-dipolar cycloaddition/electrocyclization approach

Several groups recognized that the oxabicyclo[3.2.1] substructure of the cortistatins could be directly constructed by \((4 + 3)\) cyclizations of substituted furans. Gung and co-workers utilized a transannular \((4 + 3)\) cyclization between a furan and an allene to construct the ABC core ring system in a cortistatin model system study.\(^{42a}\) The requisite 14-membered cycloallene 374 was prepared via ring-closing metathesis of bis-allene 373 (Scheme 65). After some experimentation, it was discovered that treating furanyl allene 374 with catalytic Pd(OAc)\(_2\) in the presence of LiBr effected the desired \((4 + 3)\) cyclization to tetracycle 375, which was further reduced to 376.

**Scheme 65.** Gung’s model system transannular \((4 + 3)\) cyclization

Zhai and co-workers reported a synthesis of the core of cortistatin A that featured an intermolecular furan-oxallyl \((4 + 3)\) cyclization and a double intramolecular aldol reaction.\(^{42l}\) Stereoselective, reductive \(\alpha\)-allylation of enone 377 and subsequent ketone protection provided ketal 378 (Scheme 66). Attempts to effect the intermolecular \((4 + 3)\) cyclization of disubstituted furan 378 with an oxallyl species resulted in a mixture of diastereomers 379 and 380, often favoring the
undesired species 379. The best result, a 1:1 mixture, was obtained when 378 was treated with 1,1,3-trichloroacetone and Et₃N, providing a 46% yield of desired cycloadduct 380 after reductive dehalogenation. Cycloadduct 380 was elaborated to keto dialdehyde 381 upon terminal alkene dihydroxylation, internal alkene hydrogenation, and vicinal diol cleavage. Subjection of keto dialdehyde 381 to K₂CO₃ resulted in double cyclization of both A- and C-rings to the pentacyclic hydroxy enone 382 in 82% yield.

**Scheme 66.** Zhai’s (4 + 3) cyclization/double aldol cyclization approach

Liu and Chiu utilized an intramolecular (4 + 3) cyclization between a disubstituted furan and an epoxy enol silane to form the B- and C-rings in their approach to cortistatin A.⁴² Reductive desymmetrization of cyclopentanedione 383 with CBS catalyst 384 and TBS protection of the resultant alcohol 385 provided optically active ketone 386 (Scheme 67). Addition of furanyl lithium reagent 387 to ketone 386 was followed by dehydration to cyclopentene 388. Cross-metathesis of the terminal alkene functionality with methyl vinyl ketone furnished enone 389. Chemoselective asymmetric epoxidation of the enone moiety in 389 with Deng’s *Cinchona* catalyst 390 afforded epoxy ketone 391 as a single diastereomer, with the desired stereochemistry to direct the (4 + 3) cyclization. Epoxy ketone 391 was converted to the requisite cyclization precursor, epoxy enol silane 392. The key (4 + 3) cyclization was effected with catalytic TESOTf to form the B- and C-rings and provide the desired cycloadduct 393 as a single diastereomer. Florisil–mediated dehydration of β-hydroxy tetracycle 393 was followed by global deprotection to diol 394. Chemo- and stereoselective alkene reduction of 394 with Crabtree’s catalyst occurred without enone reduction. *Bis*-oxidation of the diol with Dess-Martin
periodinane occurred with spontaneous intramolecular aldol cyclization to form the A-ring and the pentacyclic core 395.

**Scheme 67.** Liu and Chiu’s furan/epoxy enol silane (4 + 3) cyclization approach

III. Cortistatin analogs/SAR studies

The potent anti-angiogenic properties of the cortistatins inspired several research groups to investigate the structure/activity relationship of the natural products and several analogs to determine which structural features are necessary for biological activity. The estrone-derived analog 396 reported by Kiyota46 (Figure 8) possessed activity qualitatively analogous to the cortistatins, although it was more than three orders of magnitude less potent than those of the natural products. Corey
and co-workers also prepared a number of estrone-derived cortistatin analogs\textsuperscript{47} that further incorporated the dimethylamino moiety and differing aromatic substituents on the D-ring (\textbf{397}, \textbf{398} and \textbf{399}). The results of their studies suggest that a nitrogen heterocycle is necessary for inhibition in HUVEC growth, although the site of attachment to the steroidal core was not overly important for activity. Interestingly, one of their most active compounds (\textbf{399}) featured a D-ring pyridine substituent rather than an isoquinoline. The Baran group demonstrated that while analog \textbf{400} with an sp\textsuperscript{2} hybridized C17 center at the point of isoquinoline attachment suffered only a two-fold loss of activity, inversion of the C-17 center (analog \textbf{401}) completely abolished the anti-proliferative activity of cortistatin A.\textsuperscript{48} Finally, studies by Nicolaou and Chen confirmed previous observations that the isoquinoline is required for
inhibitory activity, but also found that the A-ring hydroxy and dimethylamino substituents are perhaps not necessary for activity.\textsuperscript{49} Thus, analogs 307 and 308, which are devoid of A-ring substituents, retained significant anti-proliferative properties. A summary of this preliminary SAR data is shown in Figure 9.

**Figure 9.** Preliminary cortistatin A SAR data

![Diagram](image)

In a collaborative effort, Cee, Chen and Nicolaou have discovered that cortistatin A is a ligand for a small group of kinases, with high affinity binding to cyclin- dependent kinase 8 (CDK8), CDK11, ROCK (Rho-associated coiled coil kinase) I and ROCK II.\textsuperscript{49} Protein crystal structures revealed CDK8, CDK11, ROCK I and ROCK II all contain extended C-termini, which apparently place an aromatic side chain proximal to cortistatin A, thereby encapsulating the ATP binding site. Furthermore, the cortistatin/kinase models put forward are supportive of the observed SAR. In particular, the significance of the isoquinoline moiety, which projects inside the kinase hinge while the steroidal skeleton blocks the ATP-binding cleft and the polar A-ring is exposed to solvent, is highlighted.

IV. Retrosynthesis and (4 + 3) cyclizations of (Z)-2-(trialkylsilyloxy)-2-enals

A. Retrosynthetic analysis

We recognized that the oxabicyclo[3.2.1]octane substructure of the cortistatins represented the ideal target to apply our methodology for the (4 + 3) cyclization\textsuperscript{50} of (Z)-2-(trialkylsilyloxy)-2-enals,\textsuperscript{51} which are readily prepared via retrocycloaddition of 5-(trialkylsilyloxy)-1,3-dioxins\textsuperscript{52} (\textit{vida infra}). A retrosynthetic analysis which features the application of this methodology in the total synthesis of cortistatin J is outlined in Scheme 68. Thus, the dimethylaminocyclohexene A ring
could be constructed stereoselectively by intramolecular addition of the (Z)-vinylsilane in 402 onto the equatorially oriented exo-iminium ion following the Overman protocol. This approach has the advantage over the previous syntheses of cortistatin J by Nicolaou, Myers and Hirama in that the A-ring would be constructed with all requisite functionality, as opposed to forming the carbocyclic skeleton and then subsequently adding the dimethylamino or alkene moieties. The (Z)-vinylsilane moiety of 402 could be installed by a Sonagashira coupling of triflate 403 with (trimethylsilyl)acetylene followed by semi-reduction with DIBAL-H. Oxidation of the alcohol functionality would provide the aldehyde precursor to the iminium ion. Dienol triflate 403 could be obtained via triflation of the dienolate derived from enone 404. In turn, enone 404 would be provided by oxidation of α-hydroxy ketone 405 to an α-hydroxy enone and reductive removal of the superfluous hydroxyl functionality. Stille coupling with of the enol triflate moiety of 405 with 7-(trimethylstannyl)isoquinoline would install the isoquinoline functionality. In the key step, it was hoped that the tetracyclic core 405 could be constructed by a diastereoselective, endo (4 + 3) cyclization between the disubstituted furan and the (Z)-2-(triethylsilyloxy)-2-enal moiety in 406, which could be obtained by stereoselective retrocycloaddition of 5-(triethylsilyloxy)-1,3-dioxin 407.

Scheme 68. Retrosynthetic analysis of cortistatin J (271)
B. Representative (4 + 3) cyclizations

The direct construction of seven-membered rings via (4 + 3) cyclization reactions is an attractive strategy for preparing this frequently observed natural product substructure. Accordingly, a considerable amount of effort has been directed toward the discovery of three-atom component reactants that will participate in this type of reaction. Several examples of this reaction are shown in Scheme 69.

**Scheme 69. Literature examples of (4 + 3) cyclization reactions**

*From monohaloketones*\(^{54}\)

\[
\begin{array}{c}
\text{MeO} \\
\text{OMe}
\end{array}
\text{408} + \begin{array}{c}
\text{Cl} \\
\text{409}
\end{array} \xrightarrow{\text{NaH, Et}_2\text{O, rt}} \begin{array}{c}
\text{OCH}_3 \\
\text{H}_3\text{CO}
\end{array}
\text{410}
\]

*From α,α'-dibromoketones*\(^{55}\)

\[
\begin{array}{c}
\text{Br} \\
\text{Br}
\end{array}
\text{411} \xrightarrow{\text{Fe}_2(\text{CO})_9, \text{benzene, 80 °C, 3 h}} \begin{array}{c}
\text{412}
\end{array}
\]

*From allylic alcohols*\(^{56}\)

\[
\begin{array}{c}
\text{413}
\end{array}
+ \begin{array}{c}
\text{414}
\end{array} \xrightarrow{1. (\text{CF}_3\text{CO})_2\text{O, 0 °C} \rightarrow \text{rt}} \begin{array}{c}
\text{415} \\
10 : 1 : 2.3
\end{array}
\]

*From allene oxides*\(^{57}\)

\[
\text{418} \xrightarrow{66\%} \text{413} \xrightarrow{\text{419}}
\]

C. (4 + 3) Cyclizations of (Z)-2-(trialkylsilyloxy)-2-enals

The Funk group was particularly attracted to the report by Sasaki\(^{51a}\) that the treatment of 2-(trimethylsilyloxy)acrolein (421) with a Lewis acid in the presence of a diene afforded, after acidic workup, a 2-hydroxycyclohept-4-enone (422, Scheme 70) instead of the anticipated Diels-Alder adduct. However, attempts to expand the scope of this reaction by employing β-substituted enal analogs of propenal 421 in

67
both inter- and intramolecular (4 + 3) cyclization reactions were not reported,\textsuperscript{58} perhaps due to the inaccessibility of the requisite \((Z)-2-(\text{trialkylsilyloxy})-2\)-enals.

**Scheme 70.** Sasaki’s (4 + 3) cyclization reactions

\[
\begin{align*}
\text{O} & \quad \text{Me}_3\text{SiCl, Et}_2\text{N} \quad \text{OSiMe}_3 \quad \text{SnCl}_4 \quad \text{CH}_2\text{Cl}_2 \quad \text{H}_2\text{O}^+ \\
\text{420} & \quad \text{421} & \quad \text{422} \\
\text{OSiMe}_3 & \quad \text{SnCl}_4 \quad \text{CH}_2\text{Cl}_2 \quad \text{H}_2\text{O}^+ \\
\text{421} & \quad \text{423}
\end{align*}
\]

Aungst and Funk reported the convenient, stereoselective preparation of \((Z)-2-(\text{trialkylsilyloxy})-2\)-alkenals by application of the Funk group’s 1,3-dioxin-based methodology.\textsuperscript{52} Thus, based on this previous work, it was anticipated that 4-alkyl-5-(trialkylsilyloxy)-4\textit{H}-1,3-dioxins \textit{424} would be available by regioselective silylation of the corresponding 4-alkyl-1,3-dioxin-5-ones and would undergo facile retrocycloadditions in refluxing toluene to provide the \((Z)\)-enals \textit{425} (Scheme 71). A stereoselective preparation of these enals was considered to be critical for investigating the regio- and stereoselectivity of the subsequent (4 + 3) cyclization reactions.

**Scheme 71.** Proposed use of dioxin retrocycloaddition for the Sasaki reaction

\[
\begin{align*}
\text{R}_1\text{OSiR}_3 & \quad \text{R}_1\text{OSiR}_3 \quad \text{R}_1\text{OSiR}_3 \quad \text{R}_2 \quad \text{R}_2 \\
\text{424} & \quad \text{425} & \quad \text{426}
\end{align*}
\]

While the work of Aungst and Funk was underway, Harmata reported that, not surprisingly, 2-(triethylsilyloxy) and 2-(triisopropylsilyloxy)acroleins, \textit{428a} and \textit{428b}, respectively, also participate in (4 + 3) cyclization reactions and could be prepared from the 2-methoxy-1,3-dioxanone \textit{427} via the more labile 2-methoxy-1,3-
dioxin intermediates (Scheme 72),\textsuperscript{51b} that were generated in situ and underwent concomitant retrocycloadditions.

**Scheme 72.** Harmata’s (4 + 3) cyclization reactions

\[
\text{R}_2\text{SiOTf, Et}_3\text{N} \quad \text{benzene} \quad \text{OSiR}_3 \quad \text{furan} \quad \text{Sc(O Tf)}_3
\]

The synthesis of the 5-(silyloxy-1,3-dioxins) \textit{432} was easily accomplished.\textsuperscript{52} The aza-enolate derivative of the imine \textit{430} (the enolate of the parent dioxanone undergoes homo-aldol reactions) underwent efficient alkylation and upon hydrolytic workup afforded the desired butylated dioxanone \textit{431} (Scheme 73). Kinetic deprotonation of ketone \textit{431} with NaHMDS afforded the less-substituted enolate that could be \textit{O}-silylated with several trialkylsilyl halides. As expected, each

**Scheme 73.** Synthesis of (Z)-2-(trialkylsilyloxy)-2-enals \textit{433} by Aungst

The resulting (trialkylsilyloxy)dioxins \textit{432} was smoothly converted to only the (Z)-stereoisomer of the (silyloxy)enals \textit{433} in nearly quantitative yields in refluxing toluene. The stereoselectivity is presumably a consequence of preferential retrocycloaddition through the boat-like conformer \textit{eq-434} rather than boat-like conformer \textit{ax-434} that is destabilized by a flagpole-flagpole interaction between the butyl group and the axial lone pair. Thermodynamically-controlled isomerization to
(Z)-enals 433 was ruled out by heating a mixture of 433c and its (E)-isomer (83:17), obtained by photoisomerization of 433c (Hanovia 500 W, toluene), and observing no change in the ratio of isomers. Finally, the (Z)-2-(tert-butyldimethylsilyloxy)-2-enals 435 and 436 were also prepared by straightforward application of this protocol (Figure 10).

Figure 10. Additional examples of (Z)-2-(trialkylsilyloxy)-2-enals (Aungst)

Aungst and Funk were pleased to discover that (Z)-2-(trialkylsilyloxy)alkenals smoothly participated in Lewis acid-catalyzed (4 + 3) cyclization reactions with a variety of dienes (Table 4). Several observations merit comment. In all cases, the silyl group was transferred cleanly to what was the aldehyde oxygen. Moreover, all of the cycloadducts possess a cis-stereochemical relationship (as determined by NOESY studies) between the β-alkyl substituent of the enal and the newly formed silyloxy substituent. In addition, endo adducts are uniformly preferred over their exo counterparts with the cyclic dienes furan and cyclopentadiene. Moreover, the stereoselectivity is better for smaller silyl substituents (compare entries a vs. b and c vs. d). The endo/exo ratio can also be improved significantly by the choice of the Lewis acid catalyst (entry c). Not surprisingly, acyclic dienes are not as reactive as the cyclic dienes, but acceptable yields were obtained with butadiene, isoprene, and trans-piperylene. It is of interest to note that the regioselectivity of the cyclization with isoprene is also sensitive to the substituents on the silyl group (entries g and h) and that the acyclic diene piperylene favors the exo-adduct in a highly regio- and stereoselective cyclization (entry i).
Table 4. (4 + 3) Cyclization reactions of (Z)-2-(trialkylsilyloxy)-2-enals by Aungst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>433c +</td>
<td>1 equiv. Me₂AlCl₂</td>
<td>H₂O Bu₂ CH₂Cl₂ &lt;br&gt; -78 °C, 12 h &lt;br&gt; R = TBS 76% &lt;br&gt; L.A. = SnCl₂ 76%</td>
</tr>
<tr>
<td>b</td>
<td>433b</td>
<td>R = TES 78%</td>
<td>92 : 8</td>
</tr>
<tr>
<td>c</td>
<td>433c +</td>
<td>1 equiv. L.A. &lt;br&gt; CH₂Cl₂ &lt;br&gt; -78 °C, 12 h &lt;br&gt; R = TBS &lt;br&gt; L.A. = SnCl₂ 76% &lt;br&gt; L.A. = Me₂AlCl 100%</td>
<td>endo : exo</td>
</tr>
<tr>
<td>d</td>
<td>433b</td>
<td>R = TES &lt;br&gt; L.A. = SnCl₂ 70%</td>
<td>90 : 10</td>
</tr>
<tr>
<td>e</td>
<td>436 +</td>
<td>1 equiv. Me₂AlCl₂</td>
<td>H₂O Ph OTBS &lt;br&gt; CH₂Cl₂ &lt;br&gt; -78 °C, 12 h 63%</td>
</tr>
<tr>
<td>f</td>
<td>436 +</td>
<td>1 equiv. EtAlCl₂</td>
<td>TBSO Ph OPh &lt;br&gt; CH₂Cl₂ &lt;br&gt; -78 °C, 12 h 65%</td>
</tr>
<tr>
<td>g</td>
<td>435c +</td>
<td>1 equiv. TiCl₄</td>
<td>RO Bu₂ &lt;br&gt; CH₂Cl₂ &lt;br&gt; -78 °C, 12 h &lt;br&gt; R = TBS 54%</td>
</tr>
<tr>
<td>h</td>
<td>435b</td>
<td>R = TES 40%</td>
<td>50 : 50</td>
</tr>
<tr>
<td>i</td>
<td>435c +</td>
<td>1 equiv. EtAlCl₂</td>
<td>H₂O Bu₂ endo : exo &lt;br&gt; CH₂Cl₂ &lt;br&gt; -78 °C, 12 h 50%</td>
</tr>
</tbody>
</table>

Their methodology was not limited, however, to the intermolecular version of the (4 + 3) cyclization reaction. The retrocycloaddition of the appropriately substituted 5-(trialkylsilyloxy)-1,3-dioxins 437 can be catalyzed by a Lewis acid with concomitant (4 + 3) cyclization of the resulting 2-(trialkylsilyloxy)-2-enal 438 to afford
fused bicyclic adducts 440 of potential value in natural product synthesis (Scheme 74). The Lewis acid-catalyzed retrocycloaddition was necessary in this case since thermolysis of the dioxin 437a in refluxing toluene gave rise to product 439 (relative stereochemistry unknown) derived from an intramolecular Diels-Alder reaction of the intermediate 2-(tert-butyldimethylsilyloxy)-2-enal 438.

Scheme 74. Intramolecular (4 + 3) cyclization reactions by Aungst

In an attempt to better understand the mechanism and reactive species of this reaction, a crossover experiment was investigated that suggests the silyl group is transferred both intra- and intermolecularly. Thus, when the cyclization shown in Table 4, entry b was performed in the presence of equivalent amounts of enals 433c and 436, the endo adduct 441a (as in entry b) was obtained accompanied by the endo adduct 441b (as in entry a) in a ratio of 86:14, respectively (Scheme 75). Similarly, the endo cyclization product 442b derived from enal 436 (TBS ether) was accompanied by the corresponding endo adduct 442a in a similar ratio of 86:14, respectively.

Scheme 75. Investigation of the silyl transfer step by Aungst
Several mechanistic possibilities have been advanced for this type of (4 + 3) cyclization. The Davies group provided evidence that the related (4 + 3) cyclizations with cyclic or acyclic enals proceed via an initial [4 + 2] cycloaddition at low temperature (-78 °C) followed by subsequent α-ketol rearrangement in the presence of stoichiometric Lewis acid at 0 °C (Scheme 76).\(^5\) They were able to isolate [4 + 2] cycloadducts 443 by quenching the reaction at -78 °C, and upon treatment with a stoichiometric amount of aluminum chloride at 0 °C, the α-ketol rearrangement occurred to provide the penultimate seven-membered ring 444. However, attempts to isolate a [4 + 2] adduct using the Harmata enal 428b/429b (Scheme 73) were unsuccessful and they were only able to isolate the seven-membered ring product 429b. They did discover when the reaction was run under microwave conditions (instead of Lewis acid catalysis), that they were able to obtain the Diels-Alder adduct 445. This product was then subjected to Harmata’s conditions [Sc(OTf)\(_3\), 0 °C → rt] and a facile ring expansion to the (4 + 3) product 429b was observed. Thus, this observation opens the possibility that this reaction may occur via a sequential Diels-Alder/α-ketol rearrangement pathway.

An additional study by Domingo and co-workers investigated the mechanism of the Sasaki-type (4 + 3) cyclization via density functional theory (DFT) analysis of the endo and exo cyclization pathways.\(^6\) This work provides evidence that this reaction proceeds in a stepwise fashion via intermediate zwitterions 447 or 451 as a result of 1,4-nucleophilic attack of furan onto the activated acrolein moiety 446.
Domingo's DFT analysis of the (4 + 3) cyclization reaction pathways (Scheme 77). The \textit{endo} attack pathway is favored over the \textit{exo} pathway by 2.6 kcal/mol (\textit{endo}TS1 vs. \textit{exo}TS1). Cyclization by nucleophilic attack of the silyl enol ether of zwitterionic intermediates 447 and 451 onto the pendant furonium ion is the second step of the process. As before, the \textit{endo} pathway was calculated to have a lower energy barrier (\textit{endo}TS2 vs. \textit{exo}TS2, 5.7 kcal/mol). The intermediate \textit{endo} and \textit{exo} cycloadducts 448 and 452 then undergo transfer of the trimethylsilyl group from the oxonium ion to the oxygen on the $\alpha$-carbon to intermediates 449 and 453, respectively. This process was calculated to be the rate-limiting step, with the \textit{endo} pathway being 4 kcal/mol lower in energy than the \textit{exo} pathway (\textit{endo}TS3 vs. \textit{exo}TS3). Finally, the (4 + 3) cycloadducts formed after silyl transfer, 449 and 453, quickly equilibrate with the thermodynamically more stable cycloadducts 450 and 454 by migration of the Lewis acid to the more basic carbonyl oxygen. This
computational analysis seems to fit the observations that were realized in our studies as well, since larger silyl groups and Lewis acids tended to slow the reaction sequence significantly. In addition, smaller silyl groups and Lewis acids tend to enhance the preference for the more sterically encumbered endo transition state.

V. Overman-type (Z)-vinylsilane/iminium ion cyclizations

In the early 1980s, the Overman group reported a number of examples of vinylsilane/iminium ion cyclizations. A particularly relevant example of a cyclization that is exocyclic with respect to the iminium ion is shown in Scheme 78. Cyclization of (Z)-vinylsilane imine 457 in refluxing acetonitrile proceeded cleanly in the presence of one equivalent of CF₃CO₂H to provide cis-hexahydroindole 458 in 90% yield. Conversely, attempted cyclization of the corresponding (E)-vinylsilane imine 459 under identical conditions afforded no trace of cyclization product 458 after 48 h. The marked difference in the reactivity of the configurational vinylsilane isomers provides a striking demonstration of the importance of σ-π (hyperconjugative or vertical) stabilization of the transition state. As shown in Scheme 79, only the (Z)-alkene substituent can initially participate in σ-π stabilization of the developing β-silyl cation. This situation is unchanged if the cyclization were to occur in the alternate boat conformer. Indeed, if our strategy for the late stage formation of the A ring by
vinylsilane/iminium ion cyclization was to succeed, we would need access to configurationally pure (Z)-vinylsilane.

**Scheme 79.** $\sigma$-$\pi$ stabilization of the $\beta$-silyl cation by the (Z)-vinylsilane

VI. Cortistatin model system studies

A model system that lacked the isoquinoline moiety and appropriate functionality to elaborate the A-ring was initially investigated by Funk and Roach to determine the viability of this approach. To that end, 1,2-addition of 5-lithio-2-methylfuran to vinylogous ester 466 gave an enone upon acidic workup that was converted to the thermodynamically-favored silyl enol ether 467 via Birch reduction and trapping of the resultant enolate with TMSCl (Scheme 80). Alkylation of the regenerated enolate with methyl iodoacetate gave the separable keto ester 468 as the major isomer that was converted to vinyl benzene 469 via Stille coupling of the corresponding triflate. The ester group of 469 was reduced and converted to the iodide 470 that then was used to alkylate the azaenolate of the cyclohexyl imine of 2,2-dimethyl-1,3-dioxan-5-one 471. After hydrolytic workup, the resulting 1,3-dioxin-5-one 472 then was converted regioselectively to the 5-silyloxy-1,3-dioxin 473 via the kinetic enolate. While it has been previously shown that dioxins similar to 473 can be used directly in the (4 + 3) cyclizations, this study used the corresponding retrocycloaddition products 474 since they are not prone to concomitant Diels-Alder cycloadditions with the poorly reactive furan diene.
The initial result was not encouraging. Treatment of the (t-butyldimethylsilyloxy)enal 474a with Me₂AlCl (CH₂Cl₂, -78 °C, 12 h) gave a single compound (50% conversion) that was shown by nOe experiments to be the corresponding undesired “exo” adduct possessing an endo TBS ether 475a (Scheme 81.) This assignment also was confirmed by X-ray crystallographic analysis of the alcohol derivative. It had been previously observed that a smaller silyl substituent and Lewis acid favored the endo adduct. Accordingly, the (triethylsilyloxy)enal 474b was subjected to BF₃ (toluene, -78°C, 12 h) and a mixture of silyl ethers and alcohols was obtained. The diastereomeric ratio could be determined easily since the dihydrofuran olefinic resonances for both the silyl ether 476b and alcohol 476c are downfield of the analogous resonances for silyl ether 475b and alcohol 475c. Although the diastereomeric silyl ethers were inseparable, the “endo” alcohol 476c could be isolated by chromatography (63%); its structure was secured by X-ray crystallographic analysis. The ratio could be improved further to 13:1 favoring the endo adduct by running the reaction in acetonitrile at -20 °C for 1 hour. It should be noted that under these conditions, the alcohols 475c and 476c were obtained uncontaminated by the corresponding silyl ethers, thereby obviating a subsequent deprotection step. The X-ray crystal structures of alcohols 475c and 476c are shown in Figures 11 and 12, respectively.
Scheme 81. Model system (4 + 3) cyclizations by Roach

![Scheme Diagram]

<table>
<thead>
<tr>
<th>substrate</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>474a R = TBS</td>
<td>1 equiv. Me₂AlCl, CH₂Cl₂, -78 °C, 12 h</td>
<td>20 (475a) (75%) : 1 (476a) (3.8%)</td>
</tr>
<tr>
<td>474b R = TES</td>
<td>1 equiv. Me₂AlCl, PhMe, -78 °C, 12 h</td>
<td>1 (475b) (9.5%) : 6.6 (476b) (63%)</td>
</tr>
<tr>
<td>474a R = TBS</td>
<td>1 equiv. BF₃·OEt₂, MeCN, -20 °C, 1 h</td>
<td>1 (475c) (17%) : 3.6 (476c) (61%)</td>
</tr>
<tr>
<td>474b R = TES</td>
<td>1 equiv. BF₃·OEt₂, MeCN, -20 °C, 1 h</td>
<td>1 (475c) (6%) : 13 (476c) (80%)</td>
</tr>
</tbody>
</table>

Figure 11. X-ray crystal structure of exo adduct 475c

![Figure 11 Diagram]

Figure 12. X-ray crystal structure of endo adduct 476c

![Figure 12 Diagram]
The model \((4 + 3)\) cycloadduct \(476c\) was carried further to explore the feasibility of transformations that would be encountered in the total synthesis (Scheme 82). Thus, global alkene reduction to tetrahydrofuran \(477\) was achieved via hydrogenation in the presence of \(\text{Pd(OH)}_2\). The \(\alpha\)-hydroxy ketone functionality of adduct \(477\) underwent Swern oxidation to \(\alpha\)-hydroxy enone \(478\). Finally, the superfluous alcohol moiety was removed in a two-step sequence: activation as the triflate and \(\text{Pd}\)-mediated reduction with triethylsilane to enone \(479\).

**Scheme 82. Late-stage model system transformations by Roach**

**VII. Results and Discussion: total synthesis of cortistatin J**

With a successful model study, synthetic efforts were directed towards the preparation of a system that was suitably functionalized for the total syntheses of both cortistatins A and J. To that end, TIPS-protected 2-furylethanol \(^{62}\) \(480\) was metalated with \(n\)-butyllithium and then converted to the lithium trimethylaluminate, which underwent trimethylsilyl triflate-promoted conjugate addition \(^{63}\) to 2-methylcyclopenten-1-one to afford the TMS enol ether \(481\) (Scheme 83).\(^{43h}\) The
enolate derivative of 481, generated upon treatment with methyllithium, was diastereoselectively alkylated with methyl iodoacetate to provide ketone 482. A simple two-step sequence (preparation of the enol triflate 483 and ester reduction) yielded alcohol 484. The isoquinoline group was introduced at this point via Stille coupling of the enol triflate functionality of 484 with 7-(trimethylstannyl)isoquinoline (282), which was prepared in a three step sequence by known procedures (Scheme 84). The alcohol group of 485 was converted to an iodide 486. When this

Scheme 83. Preparation and attempted alkylation of iodide 486

Scheme 84. Preparation of 7-(trimethylstannyl)isoquinoline (282)
iodide was subjected to the alkylation conditions Roach used for the model system (azaenolate 471, THF, -20 °C → rt), only starting material 486 was recovered. Addition of HMPA to the reaction mixture did not have an effect. It was determined that a less-hindered and/or more nucleophilic azaenolate was most likely required for the alkylation. Thus, several imines and hydrazones of the 1,3-dioxan-5-one were prepared (Figure 13) and the reactivity of their corresponding azaenolates toward iodide 486 was investigated. The only successful result was obtained with the metalated dimethylhydrazone 492 in the presence of five equivalents of HMPA, delivering the corresponding alkylated dioxanone 487 after hydrolytic workup with aqueous acetic acid in 75% yield (Scheme 85). Conversion of dioxanone 487 to the (triethylsilyloxy)dioxin 493 was followed by thermally-promoted, stereoselective retrocycloaddition and provided the (Z)-2-(triethylsilyloxy)-2-enal 494, setting the stage for the key (4 + 3) cyclization.
When enal 494 was subjected to Roach’s conditions for the model system (4 + 3) cyclization (1 equiv. BF₃·OEt₂, MeCN, -20 → 0 °C), no reaction was detected. Even heating the reaction mixture to 50 °C resulted in the isolation of unchanged starting material. We suspected that the isoquinoline nitrogen may be complexing with the Lewis acid, and that more than one equivalent might be required. Indeed, when an additional equivalent of BF₃·OEt₂ was added, the starting material was completely consumed after ten minutes at 0 °C. However, analysis of the ¹H NMR spectrum, in particular the C-9 proton shifts, of the crude reaction mixture suggested that a mixture of endo and exo (4 + 3) cycloadducts was formed. After chromatographic separation, it was determined that the desired endo stereoisomer 496 was formed in preference to the exo adduct 495 in a 3:1 ratio (Scheme 86). The high Lewis acidity of the reaction mixture cleaved both TIPS and TES groups from the endo adduct, but interestingly only the TIPS was cleaved in the exo adduct. These tentative assignments were based on comparisons of the C-9 proton chemical shifts in the ¹H NMR spectra of the endo and exo cycloadducts with those that Roach obtained during the model system study (Figure 14). Thus, the endo adducts 496
and 476c possessed C-9 proton shifts at 2.78 and 2.72 ppm, respectively. The corresponding shifts in the $^1$H spectra for the exo adducts 495 and 475c were significantly more upfield, at 2.39 and 2.45 ppm, respectively. This trend was also observed in the adducts obtained by Aungst, with the endo adduct 498 having a shift at 2.65 ppm, while exo adduct 497 displayed a shift at 2.24 ppm. This observation can be rationalized by deshielding of the C-9 proton by the proximate furan oxygen, which in the endo adducts have a cis relationship.

Figure 14. Observed chemical shifts in endo and exo cycloadducts

Despite the slightly disappointing stereoselectivity of the initial (4 + 3) cyclization (Roach obtained a 13:1 endo/exo ratio), we were hopeful that a more
favorable result could be obtained if a triflate moiety was substituted for the Lewis basic isoquinoline substituent. This investigation\textsuperscript{43h} began with the iodination of alcohol 484 (Scheme 87). When this iodide (499) was subjected to the conditions for the alkylation of hydrazone 492 (addition of the iodide 499 to the azaenolate/HMPA solution in THF at -78 °C followed by hydrolytic workup), the desired alkylated dioxanone 500 was isolated in 67% yield, accompanied by 10% of the corresponding diketone that resulted from cleavage of the triflate S-O bond. This side reaction could be avoided by performing an inverse addition of the azaenolate/HMPA solution to the iodide 499, resulting in a 75% yield of the dioxanone with no byproduct formation. This dioxanone was converted to the corresponding 5-(triethylsilyloxy)-1,3-dioxinone and enal 406 following the usual pathway.

\textbf{Scheme 87. Preparation of enal 406}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_87.png}
\end{center}

Enal 406 was subjected to a variety of conditions for the attempted (4 + 3) cyclization (Table 5). Several interesting observations were made during this investigation. Most of the Lewis acids effected the desired (4 + 3) cyclization, and the undesired exo stereoisomer was never observed as a product. The majority of the cyclizations took place with concomitant cleavage of the TES group, which was favorable as it obviated the need for a subsequent deprotection step. However, many of the reaction conditions also caused cleavage of the TIPS ether, which was
undesired as it would necessitate a re-protection step. The challenge became to find conditions that would effect the (4 + 3) cyclization, not cleave the TIPS ether yet possibly cleave the TES ether. The best result was actually achieved with a Brönsted acid, namely triflic acid (50 mol %, CH₂Cl₂, -78 °C 1 h; PPTS, MeOH, 79%), which delivered the desired endo cycloadduct 405a as a single diastereomer after TES cleavage during workup. The structural assignment was based on extensive nOe experiments; the key nOes are displayed in Figure 15.

**Table 5. Conditions attempted for the (4 + 3) cyclization of enal 406**

<table>
<thead>
<tr>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mol % Sc(OTf)₃, CH₂Cl₂, 0 °C → rt, overnight</td>
<td>mostly b, some decomp.</td>
</tr>
<tr>
<td>10 mol % TESOTf, CH₂Cl₂, -78 °C, 1 h</td>
<td>mixture of a, b and c</td>
</tr>
<tr>
<td>1 equiv. BF₃ OEt₂, CH₃CN, 0 °C, 10 min</td>
<td>mostly b, some decomp.</td>
</tr>
<tr>
<td>20 mol % InCl₃, CH₂Cl₂, 0 °C rt, overnight</td>
<td>a and b (2:1)</td>
</tr>
<tr>
<td>10 mol % PPh₃AuCl/AgOTf, PhMe, 0 °C → rt, overnight</td>
<td>messy reaction</td>
</tr>
<tr>
<td>10 mol % AgNTf₂, PhMe, 0 °C → rt, overnight</td>
<td>messy reaction</td>
</tr>
<tr>
<td>10 mol % Tf₂NH, CH₂Cl₂, -78 °C, 1 h</td>
<td>mostly b, decomp.</td>
</tr>
<tr>
<td>10 mol % TiPSOTf, PhMe, 0 °C → rt, 6 h</td>
<td>mostly a, decomp.</td>
</tr>
<tr>
<td>1 equiv. Et₂AlCl, CH₂Cl₂, -78 °C, 1 h</td>
<td>mostly a, but irreproducible</td>
</tr>
<tr>
<td>1 equiv. Me₂AlCl, CH₂Cl₂, -78 °C 1 h</td>
<td>mostly b, decomp.</td>
</tr>
<tr>
<td>1 equiv. dry HCl, CH₂Cl₂, -78 °C → rt</td>
<td>mostly b, decomp.</td>
</tr>
<tr>
<td><strong>50 mol % TfOH, CH₂Cl₂, -78 °C, 1 h</strong></td>
<td>a, 79%</td>
</tr>
<tr>
<td>20 mol % TfOH, PhMe, -78 °C, 3 h</td>
<td>mostly a, decomp.</td>
</tr>
<tr>
<td>20 mol % TfOH, CH₃CN, 0 °C, 10 min</td>
<td>decomp.</td>
</tr>
<tr>
<td>10 mol % ZnCl₂, CH₂Cl₂, -78 °C rt, overnight</td>
<td>no reaction</td>
</tr>
<tr>
<td>10 mol % camphorsulfonic acid, CH₂Cl₂, -78 °C → rt, overnight</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

**Figure 15. Key nOes observed in cycloadduct 405a**
With gram quantities of the tetracyclic core 405a in hand, we turned our attention to installation of the isoquinoline functionality at this point in the synthesis since its presence was not expected to complicate subsequent steps. (Scheme 88). Thus, Stille coupling of the enol triflate moiety of 405a with 7-(trimethylstannyl)isoquinoline 282 proceeded uneventfully to give isoquinoline 501.

Scheme 88. Stille coupling to install the isoquinoline moiety

The reduction of both alkene moieties proved to be challenging. It was believed that the reduction of the trisubstituted double bond would proceed stereoselectively, opposite to from the axial methyl group. When we subjected diene 501 to the conditions that Roach employed in the model system [cat Pd(OH)$_2$, 1 atm H$_2$, EtOAc], no reaction took place and starting material was recovered. Indeed, most conventional heterogeneous and homogeneous hydrogenations resulted in no reaction, or under forcing conditions, reduction of the isoquinoline and/or decomposition (Table 6). It was again suspected that the isoquinoline could be interfering with catalyst activity and that a reduction that did not employ a transition metal catalyst would be required. The first attempt of reduction with diimide, generated by addition of acetic acid to potassium azodicarboxylate in 2:1 THF/DMSO, was encouraging. Both alkenes underwent reduction, although some isoquinoline reduction byproduct was observed. Simply changing the solvent to the less polar dichloromethane resulted in a cleaner reaction, providing the desired tetrahydrofuran 502 in 97% yield.
Table 6. Attempted conditions for the global alkene reduction

<table>
<thead>
<tr>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mol % Pd(OH)₂, 1 atm H₂, EtOAc, rt, overnight</td>
<td>no reaction</td>
</tr>
<tr>
<td>10% Pd/C, 1 atm H₂, MeOH/EtOAc (3:1), rt, overnight</td>
<td>decomp.</td>
</tr>
<tr>
<td>10% Pd/C, 1 atm H₂, EtOAc, rt, overnight</td>
<td>only styrene reduction</td>
</tr>
<tr>
<td>10% Pd/C, 50 psi H₂, EtOAc, rt, overnight</td>
<td>decomp.</td>
</tr>
<tr>
<td>5% Rh/Al₂O₃, 1 atm H₂, EtOAc, rt, overnight</td>
<td>no reaction</td>
</tr>
<tr>
<td>20 mol % PtO₂, 1 atm H₂, EtOAc, rt, overnight</td>
<td>no reaction</td>
</tr>
<tr>
<td>5% Rh/C, 1 atm H₂, EtOAc, rt, overnight</td>
<td>no reaction</td>
</tr>
<tr>
<td>5% Pt/C, 1 atm H₂, EtOAc, rt, overnight</td>
<td>no reaction</td>
</tr>
<tr>
<td>30 mol % RhCl(PPH₃)₃, 1 atm H₂, EtOAc, rt, overnight</td>
<td>isoquinoline reduction</td>
</tr>
<tr>
<td>KO₂CN=NCO₂K, AcOH, THF/DMSO (1:1), rt, overnight</td>
<td>isoquinoline reduction</td>
</tr>
<tr>
<td>KO₂CN=NCO₂K, AcOH, CH₂Cl₂, 0 °C, 5 h</td>
<td>97%</td>
</tr>
</tbody>
</table>

The next goal of the synthetic strategy was to transform the α-hydroxy ketone functionality of 502 to the enone moiety embodied in 404 (Scheme 69). To that end, Swern oxidation of α-hydroxy ketone 502 provided a 1,2-diketone that tautomerized to the α-hydroxy enone in accord with the model system study (Scheme 89). This reaction was found to proceed much more cleanly if oxalyl chloride was used instead of TFAA. Standard conditions for the triflation of the hydroxyl group (Tf₂O, Et₃N or pyridine) afforded the desired triflate 503, albeit in only 53% yield and accompanied by byproducts. Following a protocol reported by Williams,⁶³ treatment of the α-hydroxy enone with NaH followed by PhNTf₂ resulted in a much more efficient reaction, affording the desired triflate 503 in 83% yield. Pd-catalyzed reduction of the triflate with Bu₃SnH yielded enone 404. The 9(11),10(19)-diene unit was introduced as a dienol triflate via generation of the dienolate of enone 404 with LiHMDS and sulfonylation with PhNTf₂. Removal of the TIPS protecting group with aqueous HCl yielded alcohol 403.
The stage was now set for the second key cyclization to form the A ring and complete the total synthesis. All that remained was to install the (Z)-vinylsilane functionality, oxidize the alcohol to the corresponding aldehyde, and find conditions that effect the desired iminium ion/vinylsilane cyclization. A simple model system study determined that this strategy was indeed viable (Scheme 90). Enol triflate 504 underwent Sonagashira coupling with (trimethylsilyl)acetylene to provide enyne 505. Reduction of the alkyne functionality to the requisite (Z)-vinylsilane 506 was achieved with DIBAL-H. Dess-Martin oxidation of the alcohol of 506 gave the key cyclization substrate, aldehyde 507. To our delight, heating this aldehyde overnight in acetonitrile at 60 °C with an excess of dimethylamine furnished the desired dimethylaminocyclohexene 508 as a single diastereomer.
We next turned our attention to application of this chemistry to the full system. Sonagashira coupling of (trimethylsilyl)acetylene with dienol triflate proceeded uneventfully (Scheme 91). However, attempts to reduce the alkyne 509 (DIBAL-H, Lindlar, LAH) resulted in the recovery of starting material or, worse, reduction of the isoquinoline. It became clear that the (Z)-vinylsilane moiety would have to be introduced by other means.

**Scheme 91. Failed attempts to reduce the (trimethylsilyl)alkyne 509**

<table>
<thead>
<tr>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIBAL-H, Et₂O</td>
<td>isoquinoline reduction</td>
</tr>
<tr>
<td>Lindlar's catalyst, 1 atm H₂, EtOAc</td>
<td>no reaction</td>
</tr>
<tr>
<td>DIBAL-H, TFA, Et₂O</td>
<td>isoquinoline reduction</td>
</tr>
<tr>
<td>Cy₂BH, 1-hexene, AcOH, Et₂O</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

In light of the inability to access the requisite (Z)-vinylsilane 510 from the silylalkyne 509, we became interested in the possibility of introducing the (Z)-vinylsilane directly via a Suzuki or Stille reaction of dienol triflate 403 with a
suitably functionalized, stereochemically-defined vinyl boronate or stannane. Such a reagent had been reported by Molander and co-workers, potassium trifluoroborate\textsuperscript{514}, which was prepared by hydroboration/proto-deborylation of alkynyl pinacol borane \textsuperscript{511} followed by conversion to the potassium trifluoroborate (Scheme 92). It should be noted that the use of this reagent in a Suzuki coupling had not been reported. Nevertheless, Suzuki coupling of trifluoroborate \textsuperscript{514} with dienol triflate \textsuperscript{403} under conditions reported by Molander\textsuperscript{67} proceeded cleanly to provide the desired (Z)-vinylsilane \textsuperscript{510} in 84% yield (Scheme 93). Oxidation of the alcohol to aldehyde \textsuperscript{515} was achieved under Parikh-Doering conditions (Py·SO\textsubscript{3}, Et\textsubscript{3}N, DMSO). Dess-Martin periodinane also successfully oxidized the alcohol but partially isomerized the vinylsilane to a mixture of \textit{Z} and \textit{E} isomers.

With key aldehyde \textsuperscript{515} in hand, the stage was set to attempt the final step of the totally synthesis: formation of the A ring by vinylsilane/iminium ion cyclization. When subjected to conditions that proved successful for the model system (excess
Me$_2$NH, acetonitrile, 60 °C), only starting material was recovered. However, when the hydrochloride salt of dimethylamine was used, conditions more amenable to iminium ion formation, the desired cyclization took place to provide cortistatin J (271) as a single diastereomer (Scheme 94) whose spectral data (NMR, IR, MS) was identical to that of natural cortistatin J. The cyclization presumably takes place through conformer 518 with the dimethyliminium ion adopting a pseudo-equatorial position to avoid an incipient 1,3-diaxial interaction with the ethylene bridge of the tetrahydrofuran (shown in conformer 517) as well as a significant syn-pentane interaction between the trimethylsilyl substituent and the ethylene bridge (shown in conformer 516).

**Scheme 94.** Rationale for stereoselectivity in vinylsilane/iminium ion cyclization

A comparison of the total syntheses of cortistatin J by step count and key steps can be found in Table 7. Our total synthesis is the shortest (longest linear sequence) to date and was the first synthesis of a cortistatin alkaloid to feature a (4 + 3) cyclization.
Table 7. Comparison of cortistatin J total syntheses.

<table>
<thead>
<tr>
<th>Year</th>
<th>Lead Author</th>
<th>Longest Linear Sequence</th>
<th>Key Steps</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Nicolaou</td>
<td>32 steps from Hajos-Parrish ketone</td>
<td>oxa-Michael addition/aldol condensation, 43d</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Myers</td>
<td>22 steps from Hajos-Parrish ketone</td>
<td>ring-closing alkene metathesis, oxidative dearomatization</td>
<td>43e</td>
</tr>
<tr>
<td>2011</td>
<td>Hirama</td>
<td>26 steps from Hajos-Parrish ketone</td>
<td>oxatriene 6π-electrocycliation, radical/eneone conjugate addition</td>
<td>43f</td>
</tr>
<tr>
<td>2011</td>
<td>Funk</td>
<td>20 steps from furan</td>
<td>furan/2-silyloxy-2-enal (4 + 3) cyclization, Z-vinylsilane/iminium ion cyclization</td>
<td></td>
</tr>
</tbody>
</table>

VIII. Approaches to the total synthesis of cortistatin A

A. Enecarbamate/iminium ion cyclization approach

We hoped that the completion of the total synthesis of cortistatin J (271) would serve as the opening act for the total synthesis of the more biologically active and structurally complex cortistatin A (263). In particular, we were intrigued by the possibility of effecting an intramolecular enecarbamate/iminium ion cyclization, analogous to the strategy utilized for cortistatin J, to build the A-ring with enecarbamate 523 (Scheme 95). Thus, cortistatin A could be obtained by hydroxyl-directed reduction [Me₄NBH(OAc)₃] of enone 520. In turn, α-hydroxy enone 520 could be constructed stereoselectively by intramolecular addition of the enecarbamate of 522 onto the equatorially oriented exo-iminium ion following the precedent set during the cortistatin J synthesis. The resultant N-acyliminium ion could then undergo hydrolysis to yield α-hydroxy enone 520. Finally enecarbamate 523 could arise from Stille coupling of dienol triflate 403 with known stannane 524.
A model system study was initially investigated. Stannane 524, previously prepared by Huntley,\textsuperscript{66} underwent Stille coupling with enol triflate 504 to yield diene 525 (Scheme 96). Ley oxidation of the alcohol functionality in 525 provided an unstable aldehyde 526. Unfortunately, all attempts to effect a cyclization to either desired products 527 or 528 through formation of the corresponding dimethyliminium ion or methyl imine of 526 caused complete decomposition of the starting material.
Despite the lack of success in the model system, we attempted the same strategy on the fully substituted system (Scheme 97). The Stille coupling in this case
did not proceed as expected, as tetrahydrofuran 529 was formed as a major byproduct regardless of the reaction concentration or how many equivalents of stannane 524 were included. Such cyclizations are well known but typically require much more basic conditions (Scheme 98).68 Even more disappointing was the inability to oxidize the alcohol of the coupled product 530 without complete decomposition of the starting material, most likely due to the high reactivity of the enecarbamate.

**Scheme 98.** Examples of intramolecular alcohol/triflate cyclizations

Scheme 98. Examples of intramolecular alcohol/triflate cyclizations

**Shibasaki,**69a

**Williams,**69b

B. *Dioxin/iminium ion cyclization approach*

The failure of our enecarbamate/iminium ion cyclization approach led us to consider other options for the construction of the A-ring of cortistatin A with all the requisite functionality in place. One possibility involves an intramolecular dioxin (or benzodioxin)/iminium ion cyclization (536 → 535, Scheme 99). Thus, cortistatin A could be obtained by hydroxyl-directed reduction [Me₄NBH(OAc)₃] of enone 520. In turn, α-hydroxy enone 520 could be constructed stereoselectively by intramolecular addition of the dioxin of 536 onto the equatorially oriented exo-iminium ion following the precedent set during the cortistatin J synthesis. The resultant oxonium ion could then undergo hydrolysis to yield α-hydroxy enone 520. Finally, dioxin 537 could arise from Stille coupling of dienol triflate 403 with known stannane 538.
The dioxin and benzodioxin stannanes were prepared via known procedures (Scheme 100). As before, model systems were initially investigated.

Stille coupling of enol triflate 504 with dioxin stannane 540 proceeded uneventfully (Scheme 101). Parikh-Doering oxidation of alcohol 545 provided an aldehyde which, when treated with dimethylamine hydrochloride in acetonitrile at room temperature, cyclized to give a 1:1 mixture of inseparable diastereomers 549 and 550. This lack of diastereoselectivity stood in contrast with the model system cyclization investigated
for cortistatin J (507 → 508, Scheme 90) which delivered a single diastereomer. This result led us to believe that the steric influence of the trimethylsilyl substituent present in that model system, as well as the full system which cyclized directly to cortistatin J (515 → 271, Scheme 94), accounted for much of the stereoselectivity of those cyclizations. Nevertheless, we attempted to carry the cyclization mixture forward. However, all attempts to hydrolyze the dioxin functionality resulted in elimination of the dimethylamino substituent to either benzodioxane 552 or α-alkoxyenone 553. The desired hydrolysis product 551 was never observed.

This strategy was also attempted on the fully-substituted system (Scheme 102). As before, the Stille coupling of 403 was problematic and provided a mixture of tetrahydrofuran 529 and the desired coupled dioxin 554. Attempts to prepare aldehyde 555 via oxidation of alcohol 554 resulted in decomposition of the starting material, most likely due to the high reactivity of the dioxin moiety.
Similar observations were made during the model study of the benzodioxin system (Scheme 103). The analogous cyclization to a 1:1 diastereomeric mixture of dimethylamines 558 went smoothly. However, attempts to hydrolyze the benzodioxin mixture 558 to catechol derivative 559 failed.

The application of the benzodioxin cyclization strategy on the full system was marginally more successful than application of the dioxin cyclization strategy (Scheme 104). In this case, Ley oxidation of alcohol 560 provided aldehyde 561, which cyclized in the presence of dimethylamine hydrochloride to give a 1:1 mixture
of dimethylamines 562. Similarly, we were unable to hydrolyze the benzodioxin functionality of 562.

**Scheme 104. Cyclization of benzodioxin 561**

![Scheme 104](image)

C. *Oxygenated vinylsilane/iminium ion cyclization approach*

The results from the dioxin/benzodioxin cyclization studies led us to re-evaluate our synthetic strategy for the cyclization of the A-ring and completion of the total synthesis. In particular, it became apparent that the trimethylsilyl substituent served not only as an activating group for the iminium ion cyclization but also as a stereocontrol element by enforcing a single, chair-like conformer for ring closure. Our 3rd generation retrosynthesis is outlined in Scheme 105. Thus, cortistatin A (263) could be obtained by hydroxyl-directed reduction [Me₄NBH(OAc)₃] of α-hydroxy ketone 564. The hydroxyl ketone 564 could be generated via Rubottom oxidation of trienol ether 565. In turn, trienol ether 565 could be delivered via cyclization of the (Z)-vinylsilane moiety of 566 onto the iminium ion, itself derived from aldehyde 568. Finally, aldehyde 568 could be produced via Stille coupling of triflate 403 with stannane 569.
Scheme 105. 3\textsuperscript{rd} generation approach to A-ring of cortistatin A

The requisite stannanes were prepared via the known palladium-catalyzed addition of silylstannanes to ethoxyacetylene in the presence of an isocyanide ligand (Scheme 106).\textsuperscript{71} It should be noted that TMS-SnBu\textsubscript{3} provided a 3:1 inseparable mixture of regioisomers, the desired stannane 571\textsubscript{a} and undesired 572\textsubscript{a}, while TBS-SnMe\textsubscript{3} delivered exclusively 571\textsubscript{b}.

Scheme 106. Preparation of silylstannanes 571 and 572

\[ \text{EtO}_2C\text{CH}_2\text{SnR}_3 + \text{EtO}_2C\text{C}_2\text{H}_5 \rightarrow \text{R}_3\text{Sn} + \text{EtO}_2C\text{R}_3\text{Sn} \]
The cyclization of the TBS congener was investigated first (Scheme 107). Stille coupling of dienol triflate 573 with TBS-vinylstannane 571b furnished trienol ether 574. Removal of the TIPS group of 574 with TBAF followed by Ley oxidation provided the key aldehyde 575. However, treatment of aldehyde 575 with either free dimethylamine or the hydrochloride resulted in decomposition of the starting material.

Scheme 107. Attempted cyclization of ethoxyvinylsilane 575

The investigation of the TMS congener was slightly more challenging. In this case, the removal of the TIPS group from the TMS-enol ether analogous to 574 was complicated by attack on the vinylsilane. Thus, acetate 576 was prepared and underwent Stille coupling with the 3:1 mixture of regioisomeric stannanes 571a and 572a to give a 5:1 mixture of 577 and its regioisomer (Scheme 108). This mixture was carried through the acetate transesterification and subsequent Ley oxidation to aldehyde 578. However, as before, attempts to effect cyclization to trienol ether 565 with either dimethylamine or its hydrochloride resulted in decomposition of the starting material.
The reactivity of the corresponding methyl imine of aldehyde 578 was also briefly examined (Scheme 109). Treatment of imine 579 with 10 mol % TMSOTf in the presence of proton sponge in dichloromethane led to complete decomposition of the starting material. Even simply heating the imine in $d_5$-acetonitrile resulted in partial decomposition.

### Scheme 109. Attempted cyclizations of imine 579

<table>
<thead>
<tr>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>cat. TMSOTf, proton sponge,</td>
<td>decomp.</td>
</tr>
<tr>
<td>$\text{CH}_2\text{Cl}_2$, rt, overnight</td>
<td></td>
</tr>
<tr>
<td>$d_5$-acetonitrile, 60 °C, overnight</td>
<td>partial decomp.</td>
</tr>
</tbody>
</table>

### D. Formal synthesis of cortistatin A

A fallback synthesis of cortistatin A that involves the preparation of the Nicolaou intermediate trienone 308 is outlined in Scheme 110. Stille coupling of dienol triflate 573 with ethoxy vinylstannane 581 delivered trienol ether 582. TBAF
removal of the TIPS group with silica gel work up also hydrolyzed the enol ether to yield dienone 583. Parikh-Doering oxidation of the alcohol of 583 provided ketoaldehyde 584. Attempts to effect a direct aldol condensation to trienone 308 utilizing conventional methods (NaOEt, K₂CO₃ or DBU) resulted in decomposition. For this reason, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 585) was utilized, following a protocol by Baati,⁷² to deliver the corresponding β-hydroxyketone, which underwent elimination to enone 308 in the same pot upon treatment with mesyl chloride and triethylamine. This enone had been converted to cortistatin A independently by Nicolaou (three steps, 13%) and Hirama (three steps, 18%).

**Scheme 110. Preparation of triene 308/formal synthesis of cortistatin A**

![Scheme 110. Preparation of triene 308/formal synthesis of cortistatin A](image)

**IX. Future directions**

**A. Completion of the total synthesis of cortistatin A**

The introduction of the all-equatorial amino diol functionality has been more challenging than expected in many of the previous cortistatin A total syntheses and has suffered from poor regio- and/or stereoselectivity. A possible endgame that addresses these issues is outlined in Scheme 111. We believe that the enol ether
functionality of 588 is optimal for a swift A-ring endgame. This intermediate could be accessed from the key dienol triflate 403. Oxidation of the alcohol moiety of 403 to the corresponding aldehyde would be followed by addition of a Grignard reagent such as THPOCH₂MgBr and oxidation of the corresponding alcohol to α-alkoxy ketone 586. Palladium-catalyzed carbonylation of the triflate group could be utilized to deliver dienal 587, which, upon aldol condensation with the ketone, would furnish α-alkoxy enone 588. At this point, 1,2-reduction of the enone with a bulky reducing agent such as L-selectride should yield selectively the corresponding axial alcohol, which upon Mitsunobu reaction with diphenylphosphoryl azide would provide azide 589 with the requisite equatorial stereochemistry. Hydroboration/oxidation of the enol ether of 589, followed by acidic workup to hydrolyze the THP ether, could be employed to introduce stereoselectively the diol functionality. Finally, reductive dimethylation of the azido group would complete the total synthesis.

Scheme 111. Proposed endgame for cortistatin A
### B. Possible preparation of cortistatin analogs

The preparation of a cortistatin analog, compound 595 \((R^1, R^2 = \text{Me}, R^3 = \text{H})\), that possesses what is considered to be the minimum pharmacophore, namely the dimethylamino substituent and isoquinoline substituents separated by an orienting rigid, planar tricyclic core, is also a worthy endeavor. The molecular model of this analog nicely superimposes with a molecular model of cortistatin A, but has an additional degree of rotational freedom that could prove to be energetically costly to freeze out. Nonetheless, preliminary scouting experiments have shown that we can prepare the triflate 592 from diacyl bromide 590 proceeding through diketone 591, albeit by an inefficient route in its present form. If analog 595 has significant biological activity, then we will attempt to optimize the preparation of 592 and prepare a series of cortistatin analogs.

#### Scheme 112. Proposed synthesis of cortistatin analogs

![Scheme 112](image)

### X. Concluding remarks

In conclusion, we have completed a total synthesis of \((\pm)-\text{cortistatin J}\) in 20 steps from furan. The tetracyclic core was assembled by an intramolecular, diastereoselective \((4+3)\) cyclization of a disubstituted furan and a \((Z)-2-\)
(triethylsilyloxy)-2-enal, obtained by retrocycloaddition of a 5-(triethylsilyloxy)-1,3-dioxin, and represents the first application of our methodology. The total synthesis was completed with the Overman-type (Z)-vinylsilane/iminium ion cyclization to construct the A-ring. The preparation of other cortistatin congeners, in particular, cortistatins A and K via the pivotal dienol triflate 403, were not successful and will require further investigation.
EXPERIMENTAL

General Procedures

Unless otherwise noted, all reactions were carried out under an argon or nitrogen atmosphere using flame-dried glassware. All moisture sensitive reagents were added via a dry syringe or cannula where possible. Anhydrous acetonitrile (CH$_3$CN), tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), dimethylformamide (DMF), benzene, toluene, and triethylamine (Et$_3$N) were from obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources and used without further purification. $^1$H and $^{13}$C NMR spectra were obtained on Bruker 300, 400 or 600 MHz spectrometers. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR. Chromatographic purification was performed using Silicycle SiliaFlash® P60 (230-400 mesh) silica gel. Optical rotations were recorded in a cell of 50 mm path length on a Rudolph Research Analytical Autopol® II automatic polarimeter.

Diester 120. To a solution of 3-furaldehyde (119) (6.96 mL, 83.3 mmol) in MeCN (83 mL) at 40 °C was added dimethyl malonate (10.0 mL, 87.5 mmol) and ytterbium trifluoromethanesulfonate hydrate (1.29 g, 2.08 mmol). The solution was stirred for 48 h then quenched with sat. NaHCO$_3$ (aq) and extracted with ether. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated to give diester 120 as a yellow oil (15.8 g, 90%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 3.83 (s, 3H), 3.90 (s, 3H), 6.46 (s, 1H), 7.44 (s, 1H), 7.63 (s, 1H), 7.75 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 52.5, 52.6, 108.6, 120.0, 123.5, 133.3, 144.5, 146.8, 164.5, 166.9; IR (neat) 3135, 3003, 2954, 1732, 1634, 1509, 1437 cm$^{-1}$; HRMS (M$^+$) calcd for C$_{10}$H$_{10}$O$_5$ 210.0528, found 210.0525.
**Acid 121.** To a solution of diester 120 (5.00 g, 23.8 mmol) in THF (119 mL) at rt was added 1 M NaOH (aq) (96 mL, 96 mmol). The biphasic solution was stirred vigorously for 6 h, cooled to 0 °C, acidified by dropwise addition of 2 M HCl (aq) and extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude acid was recrystallized from ether to give acid 121 as colorless crystals (mp 121-123°C, 4.18 g, 89%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.93 (s, 3H), 6.55 (s, 1H), 7.47 (s, 1H), 7.84 (s, 1H), 7.86 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 52.7, 109.0, 120.2, 121.7, 136.7, 144.7, 148.2, 166.9, 169.0; IR (neat) 3133 (br), 2956, 2927, 1732, 1697, 1633, 1440 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_9$H$_9$O$_5$ 197.0450, found 197.0452.

**Mixed anhydride 122.** To a solution of acid 121 (1.62 g, 8.26 mmol) in THF (83 mL) at rt was added 4-methylmorpholine (1.00 mL, 9.09 mmol) and isobutyl chloroformate (1.18 mL, 9.09 mmol). The solution was stirred for 3 h, quenched with sat. NH$_4$Cl (aq) and extracted with Et$_2$O. The combined organic layers were washed with sat. NaHCO$_3$ (aq), dried over Na$_2$SO$_4$ and concentrated to give mixed anhydride 122 as a brown oil (2.42 g, 99%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.97 (d, $J$ = 6.7 Hz, 6H), 2.05 (septet, $J$ = 6.7, 1H), 3.91 (s, 1H), 4.06 (d, $J$ = 6.7 Hz, 2H), 6.52 (s, 1H), 7.46 (s, 1H), 7.74 (s, 1H), 7.85 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 18.6, 27.5, 52.8, 75.8, 108.8, 120.0, 121.2, 137.3, 144.9, 148.4, 148.6, 158.7, 165.4; IR (neat) 3138, 2964, 2877, 1805, 1731, 1628, 1510, 1470, 1438, 1372 cm$^{-1}$; HRMS (M+Na$^+$) Calcd for C$_{14}$H$_{16}$O$_7$Na 319.0794, found 319.0800.
Amine 125. To a solution of 4-formyl-2,3-dihydropyrrrole-1-carboxylic acid tert-butyl ester\(^1\) (124) (5.20 g, 28.3 mmol) in MeOH (282 mL) at rt was added methylamine hydrochloride (7.63 g, 113 mmol) and triethylamine (4.33 mL, 31.2 mmol). The solution was stirred for 3 h at rt. The solution was then cooled to 0 °C and sodium borohydride (1.18 g, 31.1 mmol) was added. The solution was stirred for 15 min, quenched with sat. NaHCO\(_3\) (aq) and extracted with ether. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated. The crude material was purified by silica gel column chromatography (Et\(_3\)N-EtOAc, 5:95) to give amine 125 as a yellow oil (4.87 g, 81\%). \(^1\)H NMR (CDCl\(_3\), 400 MHz, amide rotamers) \(\delta\) 1.43 (s, 9H), 2.39 (br s, 3H), 2.55 (br t, \(J = 8.9\) Hz, 2H), 3.21 (br s, 2H), 3.33 (br m, 1H), 3.71 (br t, 2H), 6.32 and 6.46 (br s, 1H, rotamers); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz, rotamers) \(\delta\) 28.4, 29.9 (major) and 30.8 (minor), 35.1 (br), 45.1 (major) and 45.7 (minor), 49.3 (br), 78.9 (minor) and 79.9 (major), 120.1 (br), 126.0 (major) and 126.4 (minor), 151.4 (major) and 152.0 (minor); IR (neat) 3323 (br), 2974, 2931, 2788, 1689, 1478, 1416 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{11}\)H\(_{21}\)N\(_2\)O\(_2\) 213.1603, found 213.1587.

Z-Amide 126. To a solution of mixed anyhydride 122 (500 mg, 1.69 mmol) in CH\(_2\)Cl\(_2\) (17 mL) at 0°C was added amine 125 (395 mg, 1.86 mmol) in CH\(_2\)Cl\(_2\) (1.86 mL). The resultant solution was stirred for 2 h at 0 °C then quenched with sat. NH\(_4\)Cl (aq). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated. The crude material was purified by silica gel column chromatography (Et\(_2\)O-CH\(_2\)Cl\(_2\), 15:85) to give Z-amide 126 as a white foam (334 mg, 50%) and byproduct carbamate (75 mg, 15%). \(^1\)H
NMR (\textit{d}$_6$-acetone, 400 MHz, amide rotamers) $\delta$ 1.44 (s, 9H), 2.47-2.64 (br app t, 2H), 2.91 (s, 3H), 3.64-3.77 (br t, $J = 8.8$ Hz, 2H), 3.79 (s, 3H), 6.42-6.56 (br s, 1H, rotamers), 6.93 (br s, 2H), 7.60 (t, $J = 1.5$ Hz, 1H), 8.17 (br s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz, major rotamer) $\delta$ 28.8, 30.0, 36.0, 45.8, 49.7, 52.5, 80.7, 112.1, 117.2, 120.7, 126.4, 127.8, 133.6, 143.7, 148.1, 151.7, 164.9, 168.6; IR (neat) 3120, 2975, 2931, 1697, 1637, 1479, 1420, 1401, 1365 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{27}$N$_2$O$_6$ 391.1869, found 391.1893.

Hemiaminals 128$\alpha$ and 128$\beta$. To a solution of Z-amide 126 (182 mg, 0.466 mmol) in CH$_2$Cl$_2$ (9 mL) at 0 °C was added scandium trifluoromethanesulfonate (23 mg, 0.046 mmol). The solution was stirred at 0 °C for 3 h and quenched with sat. NH$_4$Cl (aq). The organic layer was dried over Na$_2$SO$_4$ and concentrated. The crude material was purified by silica gel column chromatography (MeOH-Et$_2$O, 3:97) to afford epimeric hemiaminals 128$\alpha$ and 128$\beta$ as white foams (128$\alpha$: 34 mg, 18%; 128$\beta$: 68 mg, 36%) and recovered 126 (18 mg, 10%). Hemiaminal 128$\beta$ was recrystallized from EtOAc/Et$_2$O, mp 168-170 °C. Hemiaminal 128$\alpha$: HRMS (MH$^+$) calcd for C$_{20}$H$_{29}$N$_2$O$_7$ 409.1975, found 409.1980. Hemiaminal 128$\beta$: $^1$H NMR (CDCl$_3$, 300 MHz, amide rotamers) 1.25-1.5 (br s, 9H), 1.85-1.98 (br s, 1H), 2.13 (ddd, $J = 13.0$, 8.60, 4.33 Hz, 1H), 2.89-3.01 (br s, 3H), 3.05-3.19 (br app t, 1H), 3.21-3.42 (br m, 3H), 3.45-3.56 (br s, 3H), 3.58-3.70 (br m, 1H), 3.72-3.82 (d, $J = 11.4$ Hz, 2H), 4.85-4.98 (br s, 1H), 5.15-5.33 (br s, 1H), 6.52 (br s, 1H), 7.47 (br s, 1H), 7.49 (br s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 26.3, 28.3, 35.4, 38.5, 43.6, 46.9, 52.5, 52.8, 53.0, 80.6, 84.7, 110.2, 120.7, 140.6, 143.3, 155.0, 164.8, 169.9; IR (neat) 3368 (br), 3130, 2976, 1742, 1687, 1644, 1501, 1478, 1432, 1392 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{29}$N$_2$O$_7$ 409.1975, found 409.1943.
Imide 129. To a solution of hemiaminal 128α (12 mg, 0.029 mmol) in CH₂Cl₂ (1 mL) at rt was added pyridinium chlorochromate (9.5 mg, 0.441 mmol). The solution was allowed to stir overnight at rt. The reaction mixture was then filtered through silica gel, washed thoroughly with EtOAc, and concentrated. The crude material was purified by silica gel column chromatography (MeOH-Et₂O, 3:97) to give imide 129 as a white solid (7 mg, 59%). ¹H NMR (CDCl₃, 400 MHz) δ 1.49 (s, 9H), 1.90 (ddd, J = 13.3, 8.8, 4.7 Hz, 1H), 2.08 (ddd, J = 13.3, 9.0, 6.6 Hz, 1H), 3.00 (s, 3H), 3.12 (d, J = 12.4 Hz, 1H), 3.29 (ddd, J = 11.0, 9.3, 4.8 Hz, 1H), 3.55 (ddd, J = 11.0, 8.8, 6.6 Hz, 1H), 3.61 (d, J = 12.8 Hz, 1H), 3.67 (s, 3H), 3.86 (d, J = 12.4 Hz, 1H), 3.96 (d, J = 12.8 Hz, 1H), 6.33 (s, 1H), 7.34 (s, 1H), 7.36 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 22.7, 27.9, 35.2, 38.5, 43.1, 50.3, 51.0, 52.7, 56.1, 83.5, 110.0, 120.6, 140.8, 143.4, 149.4, 164.4, 169.3, 173.3; IR (neat) 3130, 2980, 2933, 1778, 1744, 1651, 1503, 1455, 1435, 1370, 1298 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₂₇N₂O₇ 407.1818, found 407.1803.

Imide 129. To a solution of hemiaminal 128β (12 mg, 0.029 mmol) in CH₂Cl₂ (1 mL) at rt was added pyridinium chlorochromate (9.5 mg, 0.441 mmol). The solution was allowed to stir overnight at rt. The reaction mixture was then filtered through silica gel, washed thoroughly with EtOAc, and concentrated. The crude material was purified by silica gel column chromatography (MeOH-Et₂O, 3:97) to give imide 129 as a white solid (5 mg, 42%).
**Imidazolide 130.** To a solution of acid 121 (1.00 g, 5.10 mmol) in THF (20.4 mL) at rt was added 1,1'-carbonyldiimidazole (992 mg, 6.12 mmol). The solution was stirred for 15 min, quenched with 1 N H₂SO₄ (aq) and extracted with ether. The combined organic layers were washed with NaHCO₃ (aq), dried over Na₂SO₄ and concentrated to give imidazolide 130 as a tan solid (1.09 g, 86%). ¹H NMR (CDCl₃, 400 MHz) δ 3.80 (s, 3H), 6.18 (s, 1H), 7.12 (s, 1H), 7.35 (s, 1H), 7.50 (s, 1H), 7.77 (s, 1H), 7.92 (s, 1H), 8.01 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 53.0, 107.9, 116.1, 119.5, 122.5, 131.8, 136.1, 145.4, 148.0, 163.4, 163.7; IR (neat) 3128, 2954, 1727, 1630, 1471, 1436 cm⁻¹; HRMS (MH⁺) calcd for C₁₂H₁₁N₂O₄ 247.0719, found 247.0736.

**E-Amide 131.** To a solution of imidazolide 130 (600 mg, 2.44 mmol) in CH₂Cl₂ (25 mL) at rt was added amine 125 (544 mg, 2.56 mmol) in CH₂Cl₂ (2.5 mL). The resulting solution was heated to 40 °C with stirring for 72 h. The reaction was quenched with 1 N H₂SO₄ (aq). The organic phase was dried over Na₂SO₄ and concentrated. Purification by silica gel column chromatography (Et₂O-CH₂Cl₂, 15:85) to afford E-amide 131 as a white foam (715 mg, 75%). ¹H NMR (CDCl₃, 400 MHz, amide rotamers) δ 1.45 and 1.46 (s, 9H), 2.30 and 2.53-2.71 (br t, J = 9.2 Hz, 2H), 2.81, 2.82, 3.01 and 3.04 (br s, 3H), 3.57-3.97 (br m, 4H), 3.79 (s, 3H), 6.29 and 6.58 (br s, 1H), 6.46 and 6.51 (br s, 1H), 7.40 (br s, 1H), 7.56 and 7.58 (br s, 1H), 7.70 and 7.72 (br s, 1H); ¹³C NMR (CDCl₃, 75 MHz, major rotamer) δ 28.3, 30.2, 34.7, 44.4, 48.7, 52.4, 80.3, 108.9, 116.5, 120.3, 126.0, 127.9, 131.2, 131.6, 144.6, 146.1, 164.9, 167.1; IR (neat) 3124, 2975, 2931, 1698, 1636, 1478, 1420, 1366 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₂₇N₂O₆ 391.1869, found 391.1847.
Tetracycle 139. To a solution of amide 131 (100 mg, 0.256 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C was added scandium trifluoromethanesulfonate (12.6 mg, 0.0256 mmol). The solution was stirred at 0 °C for 1.5 h, allowed to warm to rt over 30 minutes and quenched with sat. NH$_4$Cl (aq). The organic layer was dried over Na$_2$SO$_4$ and concentrated. The crude material was purified by silica gel column chromatography (MeOH-Et$_2$O, 3:97) and recrystallized from EtOAc to afford tetracycle 139 as colorless crystals (mp 180-182 °C, 80 mg, 80%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 1.50 (br s, 9H) 1.89 (ddd, $J = 12.8, 7.5, 7.5$ Hz 1H), 2.08 (ddd, $J = 12.8, 6.1, 6.1$ Hz, 1H), 3.02 (s, 3H), 3.26-3.55 (m, 4H), 3.56-3.76 (m, 2H), 3.81 (s, 3H), 4.63 and 4.77 (br s, 1H, rotamers), 6.10 (d, $J = 1.91$ Hz, 1H), 7.53 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 28.3, 35.6, 36.5, 43.8, 44.3, 52.7, 54.1, 55.7, 61.7, 62.7, 80.2, 106.7, 127.6, 148.2, 154.0, 155.6, 167.3, 169.5; IR (neat) 2975, 1742, 1670, 1487, 1436, 1399, 1365 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{27}$N$_2$O$_5$ 391.1869, found 391.1850.

Silyl ether S1. To a solution of D-pyroglutaminol$^{73}$ (33.8 g, 294 mmol) and imidazole (40 g, 588 mmol) in a 2:1 mixture of CH$_2$Cl$_2$/DMF (600 mL) at rt was added dropwise TIPSCl (75.5 mL, 353 mmol). The solution was stirred overnight at rt. The reaction mixture was poured into H$_2$O and extracted with Et$_2$O. The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica gel chromatography (EtOAc) gave silyl ether S1 as a clear oil (70.2 g, 88%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.05 (s, 21H), 1.74 (dddd, $J = 13.1, 9.4, 5.5, 3.9$ Hz, 1H), 2.17 (ddd, $J = 7.7, 13.0, 15.4$ Hz, 1H), 2.34 (dd, $J = 6.5, 5.3$ Hz, 1H), 2.36 (7.5, 5.3 Hz, 1H), 3.52 (dd, $J = 9.8, 8.0$ Hz, 1H), 3.72 (dd, $J = 9.8, 3.9$ Hz, 1H), 3.75-3.82 (m, 1H), 5.78 (br s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 11.7, 17.8, 22.6, 29.7, 55.9, 67.0, 178.1;
IR (neat) 3223 (br), 2942, 2865, 1697, 1462, 1383, 1258, 1121 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{14}\)H\(_{30}\)NO\(_2\)Si 272.2046, found 272.2039; [\(\alpha\)]\(_D\) = -36.6 (c = 0.328, CHCl\(_3\)).

**Imide 164.** To a solution of lactam S\(_1\) (41.91 g, 154 mmol) in MeCN (260 mL) at rt was added and DMAP (1.88 g, 15.4 mmol) and di-\(\text{-}t\text{-}\text{ert}\)-butyl dicarbonate (38.84 g, 185 mmol). The solution was stirred at rt for 3 h then concentrated. Purification by silica gel chromatography (EtOAc-hexanes 20:80) gave imide 164 as a clear oil (51.24 g, 90%). \(^1\)H NMR (CDCl\(_3\), 400.13 MHz, amide rotamers) \(\delta\) 1.05 (s, 21 H), 1.52 and 1.56 (s, 9H), 2.01-2.16 (m, 1H), 2.36 (ddd, \(J = 12.0, 8.9, 3.0\) Hz, 1H), 2.74 (dt, \(J = 17.5, 10.5\) Hz, 1H), 3.78 (dd, \(J = 12.4, 10.1\) Hz, 1H), 4.01 (dd, \(J = 10.1, 4.1\) Hz, 1H), 4.14-4.24 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 11.7, 17.8, 20.9, 27.9, 32.2, 58.9, 64.5, 82.5, 149.9, 174.8; IR (neat) 2943, 2866, 1790, 1753, 1711, 1462, 1366, 1312, 1257, 1161 cm\(^{-1}\); HRMS (M+Na\(^+\)) calcd for C\(_{19}\)H\(_{37}\)NO\(_4\)SiNa 394.2390, found 394.2379; [\(\alpha\)]\(_D\) = +62.5 (c = 0.32, CHCl\(_3\)).

**Enecarbamate 167.** To a solution of imide 164 (51.14 g, 138 mmol) in toluene (275 mL) at -78 °C was added dropwise Super Hydride (146 mL of a 1.0 M solution in THF, 146 mmol). The solution was stirred at -78 °C for 0.5 h, then diisopropylethylamine (137 mL, 787 mmol), DMAP (337 mg, 2.76 mmol) and trifluoroacetic anhydride (23.4 mL, 166 mmol) were added. The solution was allowed to warm to rt and stirred for 3 h. The reaction mixture was then washed with water, brine, dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-\(\text{Et}_2\)N, 2.5:95:2.5) to give enecarbamate 167 as a yellow oil (43.38 g, 88%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.05 (s, 21 H), 1.47 (s, 9H), 2.62-2.84 (br m, 2H), 3.76-3.93 (br m, 2H), 4.13 and 4.21 (br s, 1H), 4.88 and 4.97 (br s, 1H), 6.39 and 6.53 (br s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz, amide rotamers) \(\delta\) 11.8, 17.8, 28.3, 31.8.
Aldehyde 170. To a solution of DMF (45.7 mL, 590 mmol) in CH₂Cl₂ (590 mL) at 0 °C was added oxalyl chloride (12.4 mL, 142 mmol). The solution was stirred at 0 °C for 10 min. To the resultant white suspension was then added enecarbamate 167 (41.98 g, 118 mmol) in CH₂Cl₂ (118 mL). After 15 minutes, the solution was poured into saturated aqueous Na₂CO₃ (480 mL) and the mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 20:80) gave aldehyde 170 as a yellow oil (39.2 g, 87%). ¹H NMR (CDCl₃, 400 MHz, amide rotamers) δ 1.05 (s, 21H), 1.51 (s, 9H), 2.93 (br m, 2H), 3.64-3.97 and 4.04-4.20 (br m, 2H), 4.23-4.47 (br m, 1H), 7.37 and 7.51 (br s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 11.7, 17.7, 27.4, 28.2, 60.8, 63.1 (broad), 82.3, 124.1, 147.6, 150.2 (broad), 185.6; IR (neat) 2943, 2866, 1719, 1662, 1613, 1462, 1412, 1314, 1154 cm⁻¹; HRMS (MH⁺) calcd for C₁₉H₃₆NO₃Si 356.2621, found 356.2631; [α]₀ = +56.8 (c = 0.352, CHCl₃).

β-ketophosphonate 205. To a solution of dimethyl methyl phosphonate (20.3 mL, 190 mmol) in THF (475 mL) at -78 °C was added dropwise n-BuLi (76 mL of a 2.5 M solution in hexanes, 190 mmol). The reaction mixture was stirred for 0.5 h at -78 °C, then a solution of methyl 4-hexynoate⁷⁴ (204) (20.0 g, 159 mmol) in THF (160 mL) was added dropwise. The solution was stirred for 1 h at -78 °C, then allowed to warm
to rt and stirred for 1 h. The reaction was quenched with saturated aqueous NH₄Cl, extracted with EtOAc, dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (EtOAc) gave β-ketophosphonate 205 as a yellow oil (22.5 g, 54%, 94% based on recovered methyl 4-hexynoate). ¹H NMR (CDCl₃, 300 MHz) δ 1.74 (t, 2.5 Hz, 3H), 2.40 (tq, 7.4, 2.5 Hz, 2H), 2.80 (t, 7.4 Hz, 2H), 3.11 (d, J = 22.7 Hz, 2H), 3.77 (d, 11.2 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 3.1, 12.9, 41.5 (d, J = 6 Hz), 43.0, 52.8 (d, J = 6 Hz), 76.0, 77.0, 199.9 (d, J = 6 Hz); IR (neat) cm⁻¹; HRMS (MH⁺) calcd for C₉H₁₆O₄P 219.0786, found 219.0804.

**Enone 206.** To a solution of NaH (60% wt in mineral oil, 4.52 g, 113 mmol) in THF (225 mL) at 0 °C was added dropwise β-ketophosphonate 205 (22.5 g, 103 mmol) in THF (65 mL). The solution was allowed to warm to rt and stirred for 1 h. A solution of 1,3-diacetoxy-2-propanone (190) (18.8 g, 108 mmol) in THF (85 mL) was added dropwise, and the solution was stirred for 1 h. The reaction mixture was poured into water, the layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 25:75) gave enone 206 as a yellow oil (22.5 g, 82%). ¹H NMR (CDCl₃, 400 MHz) δ 1.74 (t, J = 2.5Hz, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 2.41 (tq, J = 7.4, 2.5 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 4.72 (s, 2H), 5.19 (s, 2H), 6.32 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 3.1, 13.0, 20.3, 20.4, 43.0, 61.7, 63.2, 75.8, 77.2, 123.9, 147.3, 169.8, 170.0, 198.2; IR (neat) 2922, 1744, 1692, 1629, 1578, 1430, 1371, 1221 cm⁻¹; HRMS (MH⁺) calcd for C₁₄H₁₉O₅ 267.1232, found 267.1224.

**Furan 207.** To a solution of enone 206 (22.5 g, 84.2 mmol) in MeOH (840 mL) at rt was added conc. HCl (1.4 mL, 16.8 mmol). The solution was heated at 50 °C
overnight. The reaction mixture was concentrated to about one-quarter of its original volume, then poured into saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 30:70) gave furan 207 as an orange oil (11.3 g, 82%). ¹H NMR (CDCl₃, 300 MHz) δ 1.53 (br s, 1H), 1.77 (t, J = 2.4 Hz, 3H), 2.44 (tq, J = 7.5, 2.4 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 4.5 (s, 2H), 6.12 (s, 1H), 7.28 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 3.2, 17.6, 27.8, 56.3, 76.1, 77.8, 105.5, 125.6, 138.1, 155.4; IR (neat) 3241 (br), 2920, 1759, 1638, 1442 cm⁻¹; HRMS (M⁺) calcd for C₁₀H₁₃O₂ 165.2090, found 165.2120.

Furaldehyde 208. To a solution of oxalyl chloride (12.0 mL, 138 mmol) in CH₂Cl₂ (275 mL) at -78 °C was added DMSO (19.5 mL, 275 mmol). The solution was stirred for 15 minutes, then furan 207 (11.3 g, 68.8 mmol) in CH₂Cl₂ (46 mL) was added, followed by Et₃N (57.6 mL, 413 mmol). The solution was allowed to warm to rt and stirred for 30 minutes before being poured into water. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 10:90) gave furaldehyde 208 as a yellow oil (8.39 g, 75%). ¹H NMR (CDCl₃, 360 MHz) δ 1.75 (t, J = 2.5 Hz, 3H), 2.47 (tq, J = 7.5, 2.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 6.48 (s, 1H), 7.94 (s, 1H), 9.86 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 3.2, 17.3, 27.5, 76.6, 77.0, 102.5, 129.3, 150.4, 157.5, 184.3; IR (neat) 3123, 2919, 2844, 2735, 1544, 1442, 1408, 1134 cm⁻¹; HRMS (MH⁺) calcd for C₁₀H₁₁O₂ 163.1961, found 163.1931.
Amide 210. To a solution of aldehyde 170 (20.0 g, 52.1 mmol) in MeOH (260 mL) at rt was added 5-heptynyl amine\textsuperscript{4a} (6.95 g, 62.5 mmol). The solution was stirred at rt for 3 h, cooled to 0 °C and NaBH\textsubscript{4} (2.96 g, 78.2 mmol) was added in one portion. The solution was allowed to warm to rt and stirred for 5 h. The reaction mixture was poured into saturated aqueous NaHCO\textsubscript{3} and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated to give amine 209 (24.6 g) as a yellow oil which was used without further purification. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz, amide rotamers) \(\delta\) 1.05 (s, 21H), 1.46 (s, 9H), 1.47-1.67 (br m, 4H), 1.77 (t, J = 2.5 Hz, 3H), 2.08-2.20 (br m, 2H), 2.52-2.87 (br m, 4H), 3.75-3.94 (br m, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz, amide rotamers, major rotamer resonances reported) \(\delta\) 3.0, 11.5, 17.6, 18.2, 26.5, 28.0, 28.8, 30.9, 47.3, 48.6, 58.3, 62.8, 75.0, 78.9, 79.2, 119.5, 125.2, 151.0; IR (neat) 3323 (br), 2941, 2865, 1698, 1462, 1413, 1366, 1247, 1165, 1120 cm\textsuperscript{-1}; HRMS (MH\textsuperscript{+}) calcd for C\textsubscript{27}H\textsubscript{51}N\textsubscript{2}O\textsubscript{3}Si 479.3669, found 479.3659.

To a solution of amine 209 (24.6 g, 51.4 mmol) and Et\textsubscript{3}N (14.4 mL, 103 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (510 mL) at 0 °C was added dropwise methyl malonyl chloride (6.60 mL, 61.7 mmol). The solution was stirred at 0 °C for 1 h and then quenched with saturated aqueous NaHCO\textsubscript{3}. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2}, the combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-Et\textsubscript{3}N, 27.5:70:2.5) gave amide 210 as a yellow oil (19.56 g, 66%, two steps).\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz, multiple amide rotamers) \(\delta\) 1.04 (s, 21H), 1.39-1.52 (br m, 2H), 1.46 (s, 9H), 1.57-1.72 (br m, 2H), 1.72-1.82 (br m, 3H), 2.08-2.24 (br m, 2H), 2.49-2.81 (br m, 2H), 3.13-3.50 (br m, 2H), 3.44, 3.46 and 3.47 (s, 2H), 3.60-4.33 (br m, 5H), 3.73 and 3.74 (s, 3H), 6.28, 6.36 and 6.47 (br s, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz, amide rotamers, major rotamer resonance reported) \(\delta\) 2.7, 11.4, 17.4, 17.9, 25.1, 26.7, 27.8, 33.7, 40.2, 44.6, 46.0, 51.6, 58.4,
62.7, 75.0, 78.1, 79.3, 115.3, 126.8, 151.1, 165.1, 167.5 ; IR (neat) 2942, 2865, 1746, 1698, 1651, 1414, 1366, 1330, 1251, 1162 cm⁻¹; HRMS (MH⁺) calcd for C₃₁H₅₅N₂O₆Si 579.3829, found 579.3835; [α]₀ = +56.1 (c = 0.57, CHCl₃).

**Enoate 211.** To a solution of amide 210 (11.58 g, 20.0 mmol) and furaldehyde 208 (6.49 g, 40.0 mmol) in benzene (200 mL) at rt was added benzoic acid (1.06 g, 8.80 mmol) and piperidine (1.30 mL, 13.2 mmol). The flask was equipped with a Dean-Stark trap and a condenser, and the solution was heated at reflux overnight. The solution was allowed to cool to room temperature, and then poured into saturated aqueous NaHCO₃. The aqueous layer was extracted with EtOAc. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-Et₃N, 17.5:80:2.5) gave 211 as an orange oil (12.68 g, 87%).¹H NMR (CDCl₃, 400 MHz, multiple amide rotamers) δ 1.03 (s, 21 H), 1.18-1.32 (br m, 2H), 1.45 (s, 9H), 1.48-1.60 (br m, 2H), 1.65-1.87 (br m, 6H), 1.90-2.06 (br m, 2H), 2.12-2.27 (br m, 2H), 2.27-2.57 (br m, 2H), 2.60-2.92 (br m, 2H), 3.00-3.27 (br m, 2H), 3.27-4.34 (br m, 8H), 6.16-6.50 (br m, 1H), 6.21 (br s, 1H), 7.50 (br s, 1H), 7.58 (br s, 1H); ¹³C NMR (CDCl₃, 75 MHz, amide rotamers, major rotamer resonance reported) δ 2.9, 3.0, 11.5, 17.2, 17.5, 18.1, 25.5, 25.9, 27.4, 27.9, 33.6, 41.1, 46.2, 51.7, 58.5, 63.0, 75.5, 76.0, 77.7, 78.2, 79.6, 104.5, 114.9, 121.0, 125.1, 128.3, 131.4, 144.9, 151.2, 156.5, 164.6, 166.6; IR (neat) 2943, 2865, 1698, 1634, 1414, 1366, 1239, 1163 cm⁻¹; HRMS (MH⁺) calcd for C₄₁H₆₃N₂O₇Si 723.4405, found 723.4410; [α]₀ = +34.8 (c = 0.689, CHCl₃).
Tetracycle 212. To a solution of 211 (12.18 g, 16.8 mmol) in CH₂Cl₂ (336 mL) at rt was added InCl₃ (372 mg, 1.68 mmol) in one portion. The solution was heated at reflux overnight, cooled to rt and poured over saturate aqueous NH₄Cl. The aqueous layer was extracted with CH₂Cl₂, the combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 20:80) gave 212 as an orange gum (9.62 g, 79%). ¹H NMR (CDCl₃, 400 MHz) δ 1.08 (s, 21 H), 1.37-1.48 (br m, 2H), 1.51 (br s, 9H), 1.55-1.67 (br m, 2H), 1.76 (br t, J = 2.5 Hz, 6H), 2.08-2.18 (br m, 2H), 2.19-2.28 (br m, 2H), 2.37-2.47 (br m, 2H), 2.75 (br t, J = 7.4 Hz, 2H), 3.24-3.33 (br m, 1H), 3.31 (d, 6.7 Hz), 3.41 (d, 6.7 Hz), 3.45-3.57 (br m, 2H), 3.59-3.75 (br m, 2H), 3.76-3.86 (br m, 1H), 3.81 (s, 3H), 3.97-4.06 (br m, 1H), 4.13-4.23 (br m, 1H), 4.71 (br m, 1H) 5.81 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 3.2, 3.2, 11.8, 17.6, 17.7, 18.2, 25.9, 27.1, 27.9, 28.1, 28.6, 39.8, 45.9, 47.3, 52.3, 53.6, 54.2, 58.8, 59.1, 62.9, 64.9, 75.5, 76.2, 77.4, 78.3, 79.7, 102.6, 127.2, 153.6, 154.5, 167.4, 169.5; IR (neat) 2942, 2865, 1745, 1695, 1674, 1435, 1383, 1257, 1173, 1108, 1062 cm⁻¹; HRMS (MH⁺) calcd for C₄₁H₆₆N₂O₇Si 723.4405, found 723.4419; [α]₀ = +43.8 (c = 0.32, CHCl₃).
Lactam 213. To a solution of ester 212 (9.21 g, 12.99 mmol) in MeOH (260 mL) at rt was added KOH (43.3 mL of a 3 M aqueous solution, 130 mmol). The solution was heated at reflux overnight, cooled to 0 °C, and acidified with 1M HCl until a pH of about 4 was obtained. The reaction mixture was extracted with EtOAc, dried and concentrated to give a mixture of the carboxylic acid and the decarboxylated lactam 213. This mixture was dissolved in toluene (260 mL) and the solution was heated at reflux overnight. The solution was then concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 30:70) gave lactam 213 as an orange gum (6.94 g, 80%, two steps). $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.08 (s, 21H), 1.34-1.45 (br m, 2H), 1.51 (s, 9H), 1.52-1.63 (br m, 2H), 1.75 (br t, $J$ = 2.5 Hz, 3H), 1.76 (br t, $J$ = 2.5 Hz, 3H), 2.07-2.23 (br m, 4H), 2.33 (dd, $J$ = 14.9, 5.0, 1H), 2.38-2.47 (br m, 2H), 2.67 (dd, $J$ = 14.9, 7.0, 1H), 2.76 (br t, $J$ = 7.5 Hz, 2H), 2.97-3.05 (br m, 1H), 3.11-3.23 (br m, 1H), 3.45-3.61 (br m, 1H), 3.50 (br d, $J$ = 13.3 Hz, 1H), 3.56 (br d, $J$ = 13.3 Hz, 1H), 3.71 (br d, $J$ = 9.5 Hz, 1H), 3.93-4.05 (br m, 1H), 4.15 (br d, $J$ = 9.5 Hz, 1H), 4.68 (s, 1H), 5.87 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 3.3, 11.9, 17.7, 17.8, 18.4, 26.0, 27.3, 28.2, 28.7, 37.3, 39.4, 43.3, 46.9, 54.1, 58.8, 59.5, 63.1, 64.9, 75.5, 76.2, 77.6, 78.4, 79.7, 102.5, 128.7, 153.7, 154.3, 160.1, 171.2; IR (neat) 2941, 2865, 1694, 1656, 1446, 1384, 1257, 1176, 1141, 1103 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{39}$H$_{61}$N$_2$O$_5$Si 665.4350, found 665.4348; [α]$_D$ = +49.1 (c = 0.448, CHCl$_3$).
**Cycloalkyne 214. Method A:** To a solution of diyne 213 (1.00 g, 1.50 mmol) in PhCl (240 mL) at 80 °C was added a solution of Schrock carbyne catalyst\(^{73}\) (178 mg, 0.376 mmol) in PhCl (1 mL). The solution was heated at 80 °C for 3 h, then allowed to cool to rt and concentrated. Purification by silica gel chromatography (EtOAc-hexanes 70:30) gave cycloalkyne 214 as a foam (705 mg, 77%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.07 (s, 21H), 1.07-1.18 (br m, 1H), 1.18-1.37 (br m, 3H), 1.50 (s, 9H), 1.85-2.04 (br m, 2H), 2.07-2.23 (br m, 2H), 2.32-2.55 (br m, 3H), 2.57 (dd, \(J = 14.9\), 4.6 Hz, 1H), 2.64 (dd, \(J = 14.9\), 2.5 Hz, 1H), 2.68-2.85 (br m, 2H), 3.25 (d, \(J = 14.0\) Hz, 1H), 3.27 (br s, 1H), 3.63 (d, \(J = 14.0\) Hz, 1H), 3.87-4.02 (br m, 1H), 4.12-4.26 (br m, 1H), 4.65 (s, 1H), 5.92 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 11.8, 17.8, 18.2, 18.8, 25.9, 27.5, 28.0, 34.6, 37.5, 42.2, 46.5, 57.4, 58.7, 59.4, 62.7, 67.8, 79.3, 79.5, 102.7, 129.9, 153.7, 155.0, 159.4, 170.2; IR (neat) 2939, 2864, 1696, 1669, 1458, 1426, 1390, 1364, 1255, 1146, 1104 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for \(\text{C}_{35}\text{H}_{55}\text{N}_{2}\text{O}_{5}\text{Si}\) 611.3880, found 611.3906; [\(\alpha\)]\(_D\) = +37.5 (c = 0.16, CHCl\(_3\)).

**Method B:** To a solution of diyne 213 (48 mg, 0.072 mmol) in toluene (3.6 mL) was added [[(pyridine)(Ph\(_3\)SiO\(_3\))Mo≡N]\(^{32a}\) (16 mg, 0.014 mmol). The solution was heated at 80 °C overnight, then allowed to cool to rt and concentrated. Purification by silica gel column chromatography (EtOAc-hexanes 70:30) gave cycloalkyne 214 as a foam (35 mg, 80%).
Alcohol 216. A solution of cycloalkyne 214 (1.00 g, 1.64 mmol), quinoline (1.0 mL), and Lindlar catalyst (500 mg) in MeOH (82 mL) at rt was placed under an atmosphere of \( \text{H}_2 \) and stirred for 4 h. The reaction mixture was filtered through Celite and concentrated. The crude cycloalkane could not be separated from quinoline by silica gel chromatography and was thus used without further purification. To a solution of the silyl ether (1.00 g, 1.64 mmol) in THF (82 mL) at 0 °C was added dropwise TBAF (4.92 mL of a 1.0 M solution in THF, 4.92 mmol). The solution was allowed to rt and stirred 1 h. The reaction was quenched with saturated aqueous \( \text{NH}_4\text{Cl} \). The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 20:80) gave alcohol 216 as a colorless solid (600 mg, 80%, two steps). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 0.90-1.19 (m, 2H), 1.39 (app t, \( J = 12.3 \) Hz, 2H), 1.56 (s, 9H), 1.85 (ddd, \( J = 16.5, 11.3, 5.1 \) Hz, 1H), 1.95 (dd, \( J = 12.6, 5.0, 1H \)), 2.06-2.16 (m, 1H), 2.35-2.46 (m, 1H), 2.47-2.58 (m, 2H), 2.63 (d, \( J = 15.4, 2.4 \) Hz, 1H), 2.67-2.87 (m, 1H), 2.80 (dd, \( J = 14.5, 5.8 \) Hz, 1H), 3.16 (d, \( J = 13.8 \) Hz, 1H), 3.21-3.26 (m, 1H), 3.61 (d, \( J = 13.8 \) Hz, 1H), 3.65-3.80 (m, 2H), 3.82-3.90 (m, 1H), 4.0 (ddd, \( J = 14.0, 11.2, 2.8 \) Hz, 1H), 4.74 (s, 1H), 5.25 (ddd, 10.4, 10.4, 6.2 Hz, 1H), 5.34 (ddd, 11.0, 11.0, 4.5), 5.44 (br d, \( J = 9.6 \) Hz, 1H), 5.94 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 25.0, 27.5, 28.0, 28.4, 28.6, 30.3, 34.3, 38.1, 41.4, 46.7, 57.1, 57.5, 60.7, 64.7, 67.6, 80.7, 103.4, 126.0, 129.6, 132.1, 154.5, 155.2, 160.2, 170.4; IR (neat) 3392 (br), 2929, 1665, 1554, 1477, 1455, 1427, 1404, 1365, 1255, 1152, 1089, 912 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{26}\)H\(_{37}\)N\(_2\)O\(_4\) 457.2702, found 457.2686; [\( \alpha \)]\(_D\) = +33.3 (c = 0.12, CHCl\(_3\)).
Vinylpyrrolidine 217. To a solution of alcohol 216 (486 mg, 1.06 mmol) in DMSO (53 mL) at rt was added IBX (1.52 g, 5.30 mmol). The solution was stirred overnight at rt. The reaction mixture was poured into saturated aqueous NaHCO₃, and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na₂SO₄) and concentrated. The crude aldehyde was found to be unstable to silica gel chromatography and was used without further purification. To a solution of the aldehyde (481 mg, 1.06 mmol) in THF (53 mL) at 0 °C was added dropwise Tebbe reagent (2.54 mL of a 0.5 M solution in PhMe, 1.27 mmol). The solution was stirred for 10 minutes, then poured into saturated aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 5:95) gave olefin 217 as a yellow foam (324 mg, 68%, two steps). 

**1H NMR** (CDCl₃, 300 MHz) δ 0.77-1.67 (m, 7H), 1.53 (s, 9H), 1.87 (ddd, J = 12.1, 11.0, 5.0 Hz, 1H), 2.03 (dd, J = 13.8, 5.5 Hz, 1H), 2.04-2.16 (m, 1H), 2.32-2.45 (m, 1H), 2.46-2.57 (m, 2H), 2.64 (dd, J = 15.3, 2.5 Hz, 1H), 2.68-2.85 (m, 2H), 3.20 (d, J = 13.9 Hz, 1H), 3.23-3.29 (m, 1H), 3.64 (d, J = 13.9 Hz, 1H), 4.04 (ddd, J = 15.3, 8.0, 3.0 Hz, 1H), 4.23 (ddd, J = 12.1, 6.5, 5.5 Hz, 1H), 4.75 (s, 1H), 5.05-5.30 (m, 3H), 5.35 (dd, J = 10.8, 10.8, 4.3 Hz, 1H), 5.77-5.93 (m, 1H), 5.81 (s, 1H); 

**13C NMR** (CDCl₃, 100 MHz) δ 24.9, 27.4, 28.0, 28.3, 28.5, 30.1, 34.2, 41.3, 42.3, 46.6, 57.2, 58.4, 59.7, 66.7, 79.7, 103.2, 114.0, 125.9, 129.2, 132.0, 138.5, 153.7, 154.7, 159.9, 170.4; IR (neat) 2927, 2359, 1698, 1664, 1553, 1477, 1425, 1388, 1364, 1299, 1170, 1146 cm⁻¹; HRMS (MH⁺) calcd for C₂₇H₃₇N₂O₄ 453.2753, found 453.2760; [α]D = +28.6 (c = 0.14, CHCl₃).
Amide 218. To a solution of carbamate 217 (324 mg, 0.716 mmol) in CH$_2$Cl$_2$ (27 mL) at rt was added TFA (9 mL). The solution was stirred for 1 h at rt, then cooled to 0 °C and quenched with saturated aqueous Na$_2$CO$_3$. The layers were separated and the aqueous phase extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. The crude pyrrolidine was used without further purification. To a solution of the pyrrolidine (252 mg, 0.716 mmol) in benzene (36 mL) at rt was added Et$_3$N (300 µL, 2.15 mmol) and 5-hexenoyl chloride (122 µL, 0.931 mmol). The solution was stirred for 10 min, then quenched with saturated aqueous NaHCO$_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 5:95) gave amide 218 as a yellow foam (238 mg, 74%, two steps). $^1$H NMR (CDCl$_3$, 400 MHz amide rotamers) δ 0.78-1.18 (br m, 3H), 1.20-1.47 (br m, 2H), 1.48-1.90 (br m, 6H), 1.91-2.27 (br m, 5H), 2.28-2.42 (br m, 1H), 2.43-2.57 (br m, 3H), 2.44-2.92 (br m, 4H), 3.13-3.30 (br m, 2H), 3.55-3.74 (br m, 1H), 3.91-4.11 (br m, 1H), 4.27-4.47 (br m, 1H), 4.73-5.40 (br m, 7H), 5.61-5.92 (br m, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz, amide rotamers) δ 23.8 and 23.9, 24.9 and 25.2, 27.3 and 27.5, 28.3, 28.5, 29.7 and 30.3, 32.8 and 33.1, 33.9, 34.1, 41.3 and 41.7, 43.3, 47.0, 57.4, 60.0, 60.4 and 60.6, 66.9 and 67.4, 103.0 and 103.6, 113.1, 114.7 and 115.8, 126.1 and 126.5, 129.1 and 130.1, 131.9, 138.1, 138.6 and 139.0, 153.6 and 155.4, 160.5 and 160.7, 170.3, 172.6 and 172.9; IR (neat) 2923, 1654, 1553, 1479, 1424, 1406, 1349, 1274, 1169, 1104, 995 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{28}$H$_{37}$N$_2$O$_3$ 449.2804, found 449.2822; [α]$_D$ = +30.8 (c = 0.13, CHCl$_3$).
(--)-Nakadomarin A (1). To a solution of diene 218 (50 mg, 0.111 mmol) in CH₂Cl₂ (111 mL) at reflux was added Grubbs 1st generation catalyst (91 mg, 0.111 mmol) in CH₂Cl₂ (3 mL) by syringe over 5 h. The solution was stirred at reflux overnight. The reaction mixture was concentrated and subjected to silica gel column chromatography (MeOH-EtOAc, 5:95) to afford bis-lactam 219 contaminated with triphenylphosphine (38 mg total). To a suspension of AlCl₃ (63 mg, 0.469 mmol) in THF (11 mL) at 0 °C was added LiAlH₄ (1.42 mL of a 1.0 M solution in THF, 1.42mmol). The resulting mixture was allowed to warm to rt and stir for 1 h. The solution was then cooled to 0 °C, and a solution of bis-lactam 219 (38 mg of the above mixture) in THF (3.4 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred 2 h. The solution was cooled to 0 °C and quenched by dropwise addition of H₂O (1 mL) to precipitate aluminum salts. After the mixture had been stirred for 15 min, 3 M aqueous KOH (1 mL) was added to coagulate the precipitate. The reaction mixture was filtered through Celite and the solid residue was extracted with EtOAc. The organic extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 67:33) gave (--) nakadomarin A 1 as a foam (25 mg, 57%, two steps). ¹H NMR (CD₃OD, 600 MHz) δ 0.82-0.93 (m, 1H), 1.01-1.10 (m, 2H), 1.28-1.36 (m, 2H), 1.36-1.43 (m, 1H), 1.49 (dd, J = 12.4, 10.0 Hz, 1H), 1.56-1.75 (m, 4H), 1.82 (ddd, J = 14.0, 7.1, 2.8 Hz, 1H), 1.88-1.95 (m, 1H), 1.91 (dd, J = 12.4, 4.8 Hz, 1H), 1.96-2.02 (m, 1H), 2.04-2.10 (m, 1H), 2.10-2.19 (m, 2H), 2.29-2.38 (m, 2H), 2.30 (d, J = 12.2 Hz, 1H), 2.40 (ddd, J = 11.8, 3.7, 3.7 Hz, 1H), 2.44-2.53 (m, 1H), 2.57-2.65 (m, 2H), 2.71 (ddd, J = 14.3, 7.3, 2.2 Hz, 1H), 2.75-2.82 (m, 1H), 2.84 (br s, 1H), 2.97-3.07 (m, 1H), 3.04 (d, J = 12.2 Hz, 1H), 3.71-3.76 (m, 1H), 3.94 (s, 1H), 5.22-5.29 (m, 1H), 5.40-5.47 (m, 1H), 5.50 (dd, J = 9.6, 8.9 Hz, 1H), 5.81 (br q, J = 17.1, 9.4 Hz, 1H), 5.87 (s, 1H); ¹³C NMR (CD₃OD, 75 MHz) δ 23.0, 25.8, 25.9, 27.1, 27.2, 28.8, 29.1, 29.2, 29.5, 43.1, 43.4, 46.1, 50.9, 58.3, 59.3, 60.6, 63.6, 74.7, 104.7, 129.3, 131.4, 132.2, 134.7,
135.3, 156.4, 162.5; IR (neat) 3003, 2923, 2855, 2791, 1443, 1132, 1081, 952 cm\(^{-1}\); HRMS (M\(^+\)) calcd for C\(_{26}\)H\(_{37}\)N\(_2\)O 393.2906, found 393.2918, found; \([\alpha]_D = -72.7\) (c = 0.12, MeOH), [lit.\(^{5b}\) \([\alpha]_D = -73.0\) (c = 0.08, MeOH)].

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**Pyrrole tetracycle 223.** To a solution of amide 220 (100 mg, 0.32 mmol) and pyrrole aldehyde 221 (70 mg, 0.64 mmol) in benzene (3.2 mL) at rt was added benzoic acid (17 mg, 0.141 mmol) and piperidine (21 μL, 0.211 mmol). The flask was equipped with a Dean-Stark trap and a condenser, and the solution was heated at reflux overnight. The solution was allowed to cool to room temperature, and then poured into saturated aqueous NaHCO$_3$. The aqueous layer was extracted with EtOAc. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-Et$_3$N, 67.5:30:2.5) gave 222 as an orange oil (94 mg, 73%).
To a solution of amide 222 (40 mg, 0.099 mmol) in CH$_2$Cl$_2$ (2 mL) at 0 °C was added scandium trifluoromethanesulfonate (4.8 mg, 0.010 mmol). The solution was stirred at 0 °C for 1.5 h, allowed to warm to rt over 30 minutes, stirred overnight at rt before being quenched with sat. NH$_4$Cl (aq). The organic layer was dried over Na$_2$SO$_4$ and concentrated. The crude material was purified by silica gel column chromatography (EtOAc-hexanes, 65:35) to afford tetracycle 223 as an orange foam (17 mg, 43%).

$^1$H NMR (CDCl$_3$, 400 MHz) δ 1.47 (br s, 9H) 1.77 (ddd, $J = 12.8, 7.5, 7.5$ Hz 1H), 2.09 (ddd, $J = 12.8, 6.1, 6.1$ Hz, 1H), 3.02 (s, 3H), 3.15-3.26 (br m, 1H), 3.35-3.40 (br m, 1H) 3.39 (d, $J = 7.2$ Hz, 1H), 3.46-3.54 (br m, 1H), 3.60 (dd, $J = 7.2, 1.0$ Hz, 1H), 3.64 (br s, 3H), 3.73-3.83 (br m, 1H), 3.82 (s, 3H), 4.92 (br s, 1H), 5.71 (d, $J = 2.7$ Hz, 1H), 6.54 (d, $J = 2.7$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 28.4, 35.1, 35.5, 38.1, 44.8, 45.7, 52.5, 55.2, 56.4, 61.6, 62.8, 79.7, 101.5, 128.0, 128.1, 134.6, 154.0, 167.9, 170.0; IR (neat) 2928, 1744, 1669, 1405, 1365, 1165, cm$^{-1}$; LRMS (MH$^+$) calcd for C$_{21}$H$_{30}$N$_3$O$_5$ 404.5, found 404.5.

**Dimethoxybenzene tetracycle 228.** To a solution of amide 220 (100 mg, 0.32 mmol) and 3,5-dimethoxybenzaldehyde (226) (106 mg, 0.64 mmol) in benzene (3.2 mL) at rt was added benzoic acid (17 mg, 0.141 mmol) and piperidine (21 µL, 0.211 mmol). The flask was equipped with a Dean-Stark trap and a condenser, and the solution was heated at reflux overnight. The solution was allowed to cool to room temperature, and then poured into saturated aqueous NaHCO$_3$. The aqueous layer was extracted with EtOAc. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-Et$_3$N, 57.5:40:2.5) gave 227 as an orange oil (94 mg, 90%).

To a solution of amide 227 (60 mg, 0.130 mmol) in CH$_2$Cl$_2$ (2.6 mL) at 0 °C was added scandium trifluoromethanesulfonate (6.4 mg, 0.013 mmol). The solution was stirred at 0 °C for 1.5 h, allowed to warm to rt over 30 minutes, stirred overnight.
before being quenched with sat. NH₄Cl (aq). The organic layer was dried over Na₂SO₄ and concentrated. The crude material was purified by silica gel column chromatography (EtOAc-hexanes, 50:50) to afford tetracycle 228 as an orange foam (45 mg, 75%). ¹H NMR (CDCl₃, 400 MHz) δ 1.49 (br s, 9H) 1.73 (ddd, J = 12.7, 6.4, 2.4 Hz 1H), 1.95 (ddd, J = 12.7, 6.4, 2.4 Hz, 1H), 2.93-3.03 (m, 1H), 3.00 (s, 3H), 3.48 (d, J = 13.5 Hz, 1H), 3.54 (d, J = 4.5 Hz, 1H), 3.72-3.78 (m, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 3.86 (d, J = 4.4 Hz, 1H) 5.31 (br s, 1H), 6.17 (d, J = 1.9 Hz, 1H), 6.27 (d, J = 1.9 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 28.4, 35.6, 51.5, 52.8, 53.4, 55.0, 55.1, 55.2, 55.3, 55.6, 68.0, 79.3, 98.5, 98.9, 145.6, 157.8, 162.5, 166.8, 170.1; IR (neat) 2952, 1737, 1672, 1600, 1492, 1455, 1428, 1402, 1322, 1245, 1204, 1167 cm⁻¹; LRMS (MH⁺) calcd for C₂₄H₃₃N₂O₄ 461.5, found 461.4.

**Lactam 229.** To a solution of ester 139 (884 mg, 2.26 mmol) in MeOH (45 mL) at rt was added KOH (5.27 mL of a 3M aqueous solution, 15.8 mmol). The solution was heated at reflux overnight, cooled to 0 °C, and acidified with 1M HCl until a pH of about 4 was obtained. The reaction mixture was extracted with EtOAc, dried and concentrated to give a mixture of the carboxylic acid and the decarboxylated lactam 229. This mixture was dissolved in toluene (46 mL) and the solution was heated at reflux overnight. The solution was then concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 30:70) gave lactam 229 as an orange foam (608 mg, 81%, two steps). ¹H NMR (CDCl₃, 400 MHz) δ 1.51 (s, 9H), 1.75-1.90 (br m, 1H), 1.90-2.10 (br m, 1H), 2.39 (dd, J = 14.9, 5.3 Hz, 1H), 2.72 (dd, J = 14.9, 6.6 Hz), 2.99 (br s, 3H), 3.11 (br s, 1H), 3.33 (br s, 1H), 3.37 (d, J = 13.6 Hz, 1H), 3.45 (d, J = 13.3 Hz, 1H), 3.64 (br s, 1H), 4.64 and 4.78 (br s, 1H), 6.18 (br s, 1H), 7.35 (br s, 1H).
Pyrrolidine S2. To a solution of carbamate 229 (700 mg, 2.11 mmol) in CH₂Cl₂ (32 mL) at rt was added TFA (10 mL). The solution was stirred for 1 h at rt, then cooled to 0 °C and quenched with saturated aqueous Na₂CO₃. The layers were separated and the aqueous phase extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. The crude pyrrolidine S2 was used without further purification. ¹H NMR (CDCl₃, 360 MHz) δ 1.52-1.72 (br m, 1H), 1.81-2.00 (br m, 1H), 2.20 (br s, 1H), 2.40 (dd, J = 14.8, 4.8 Hz, 1H), 2.73 (dd, J = 14.8, 6.7 Hz, 1H), 2.82 (br s, 1H), 2.98 (s, 3H), 2.99-3.14 (br m, 2H), 3.29 (d, J = 13.3 Hz, 1H), 3.50 (d, J = 13.3 Hz, 1H), 4.22 (br s, 1H), 6.17 (s, 1H), 7.35 (s, 1H).

N-methylpyrrolidine 230. To a solution of pyrrolidine S2 (100 mg, 0.43 mmol) in a 25:1 mixture of CH₂Cl₂/aq. CH₂O (10 mL) at rt was added NaBH(OAc)₃ (142 mg, 0.671 mmol). The solution was stirred vigorously overnight, then quenched with 1M NaOH. The aqueous phase was extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated to give N-methylpyrrolidine 230 as a yellow foam (86 mg, 81%). ¹H NMR (CDCl₃, 360 MHz) δ 1.80-1.98 (m, 2H), 2.34 (dd, J = 14.8, 5.8 Hz, 1H), 2.67 (s, 3H), 2.60-2.78 (m, 3H), 2.99 (s, 3H), 3.10 (dd, J = 7.2, 1.6 Hz, 1H), 3.32 (d, J = 13.0 Hz, 1H), 3.41 (d, J = 13.3 Hz), 3.72 (br s, 1H), 6.20 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H).
**Bis-amine 231.** To a solution of lactam 230 (40 mg, 0.162 mmol) in THF (8.1 mL) at rt was added a solution of alane-dimethyllethylamine complex (0.5M in PhMe, 97 μL, 0.486 mmol). After 10 min, the solution was quenched with a 1:1 THF/water solution. Five drops of Et₃N were added and the reaction mixture was poured into brine. The aqueous layer was extracted with EtOAc. The combined extracts were dried (Na₂SO₄) and concentrated to provide bis-amine 231 (27 mg, 73%) as a yellow foam that did not require further purification. ¹H NMR (CDCl₃, 360 MHz) δ 1.42-1.53 (m, 1H), 1.74-1.92 (m, 2H), 1.98-2.09 (m, 1H), 2.11-2.21 (m, 1H), 2.14 (d, J = 12.2 Hz, 1H), 2.26 (s, 3H), 2.37-2.62 (m, 2H), 2.57 (s, 3H), 2.64-2.78 (m, 2H), 2.70 (d, J = 13.7 Hz, 1H), 3.79 (s, 1H), 6.21 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H).

**N-methylpyrrolidine 232.** To a solution of carbamate 217 (72 mg, 0.159 mmol) in CH₂Cl₂ (6 mL) at rt was added TFA (2 mL). The solution was stirred for 1 h at rt, then cooled to 0 °C and quenched with saturated aqueous Na₂CO₃. The layers were separated and the aqueous phase extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. The crude pyrrolidine was used without further purification.

To a solution of the pyrrolidine (30 mg, 0.085 mmol) in a 25:1 mixture of CH₂Cl₂/aq. CH₂O (4.25 mL) at rt was added NaBH(OAc)₃ (28 mg, 0.133 mmol). The solution was stirred vigorously overnight, then quenched with 1M NaOH. The aqueous phase was extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and
concentrated to give \( N \)-methylpyrrolidine \( \text{229} \) as a yellow foam (20 mg, 63%). \( ^1 \)H NMR (CDCl\(_3\), 360 MHz) \( \delta \) 1.12-1.22 (m, 1H), 1.32-1.45 (m, 1H), 1.46-1.64 (m, 3H), 1.78-1.89 (m, 1H), 1.91 (dd, \( J = 11.9, 4.3 \) Hz, 1H), 2.02-2.12 (m, 1H), 2.35 (s, 3H), 2.51 (dt, \( J = 18.7, 8.6 \) Hz, 1H), 2.58 (d, \( J = 9.0 \) Hz, 1H), 2.59 (d, \( J = 6.5 \) Hz, 1H), 2.68-2.90 (m, 2H), 3.02-3.13 (m, 1H), 3.13-3.17 (m, 1H), 3.22 (d, \( J = 13.3 \) Hz, 1H), 3.66 (d, \( J = 13.7 \) Hz, 1H), 4.04 (ddd, \( J = 14.0, 11.2, 2.9 \) Hz, 1H), 4.28 (br s, 1H), 5.13-5.29 (m, 3H), 5.35 (ddd, \( J = 11.2, 11.2, 4.7 \) Hz, 1H), 5.58-5.72 (m, 1H), 5.85 (s, 1H).

**Vinylogous formate 240.** To a suspension of vinylogous acid \( \text{239} \) (7.00 g, 46.4 mmol) in benzene (100 mL) at rt was added \( t \)-butanol (17.8 mL, 186 mmol) and \( p \)-TsOH·H\(_2\)O (132 mg, 0.696 mmol). The solution was refluxed for 3 h under Dean-Stark conditions then quenched with sat. NaHCO\(_3\) (aq.). The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated to give vinygous formate \( \text{240} \) (9.60 g, quant.) as a white solid. The crude solid could be recrystallized from chloroform. \( ^1 \)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 1.48 (s, 9H), 7.77 (s, 1H), 9.14 (s, 1H).

**Dienol ether 241.** A mixture of vinylogous formate \( \text{240} \) (477 mg, 2.30 mmol), Pd(PPh\(_3\))\(_4\) (266 mg, 0.230 mmol), and LiCl (585 mg, 13.8 mmol) in a round bottom flask equipped with a condenser was evacuated under hi-vac and flushed with N\(_2\). Toluene (23 mL) was added, followed by tributyl(vinyl)tin (807 μL, 2.76 mmol). The reaction flask was placed in a preheated oil bath at 100 °C and stirred overnight. The reaction mixture was allowed to cool to rt and poured into brine. The layers were separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic
layers were dried (Na$_2$SO$_4$) and concentrated to give dienol ether **241** (274 mg, 77%) as a yellow oil. $^1$H NMR (CDCl$_3$, 300 MHz) δ 1.47 (s, 9H), 5.33 (dd, $J = 11.9$, 2.3 Hz, 1H), 6.06 (dd, $J = 18.0$, 2.4 Hz, 1H), 6.50 (dd, $J = 18.0$, 11.9 Hz, 1H), 7.18 (s, 1H), 9.23 (s, 1H).

**Alkylidene malonate 242.** To THF (5 mL) at 0 °C was added a solution of TiCl$_4$ in CH$_2$Cl$_2$ (1.0 M, 2.10 mL, 2.10 mmol) dropwise to give a yellow suspension of TiCl$_4$(thf)$_2$. Dimethyl malonate (126 μL, 1.10 mmol) was added dropwise to the suspension of TiCl$_4$(thf)$_2$ at 0 °C. After 40 min at 0 °C, pyridine (321 μL, 4.00 mmol) was added dropwise to the reaction mixture at 0 °C. After 40 min at 0 °C, a solution of dienol ether 241 (154 mg, 1.00 mmol) in THF (5 mL) was added dropwise via cannula to the reaction mixture. After 5 min, the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. Silica gel chromatography (15% EtOAc in hexanes) gave a 3:1 $E$:Z mixture of alkylidene malonates 242 (196 mg, 73%) as a yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz, major isomer) δ 1.36 (s, 9H), 3.77 (s, 3H), 3.78 (s, 3H), 5.17 (d, $J = 11.3$ Hz, 1H), 5.35 (d, $J = 17.8$ Hz, 1H), 6.43 (dd, $J = 17.8$, 11.3 Hz, 1H), 6.96 (s, 1H), 7.39 (s, 1H).

**Furan 480.** To a solution of furan (31.4 mL, 432 mmol) in THF (440 mL) at -20 °C was added $n$-BuLi in hexanes (2.5M, 115 mL, 288 mmol) dropwise. The solution was then allowed to warm to 0 °C. After 1 h, a solution of (2-iodoethoxy)triisopropylsilane$^{77}$ (47.3 g, 144 mmol) in THF (55 mL) was added dropwise via cannula to the 2-lithiofuran solution. The solution was then allowed to warm to rt and stirred overnight. The reaction was quenched with sat. aqueous
NH₄Cl. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (2.5% EtOAc in hexanes) to give furan 480 (31.5 g, 81%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.30 (dd, J = 1.7, 0.7 Hz, 1H), 6.28 (dd, J = 3.0, 1.9 Hz, 1H), 6.06 (3.1, 0.7 Hz, 1H), 3.92 (t, J = 7.0 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H), 1.06 (br s, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 153.3, 140.9, 110.1, 106.0, 62.0, 32.0, 17.9, 11.9; IR (neat) 2943, 2866, 1463, 1109 cm⁻¹; HRMS [MH⁺] calcd for C₁₃H₂₉O₂Si 269.1915, found 269.1940.

Cyclopentanone 482. To a solution of furan 481 (21.0 g, 80.1 mmol) in THF (355 mL) at 0 °C was added n-BuLi in hexanes (2.5 M, 32.0 mL, 80.1 mmol) dropwise. After 1 h, the solution was cooled to -78 °C and a solution of AlMe₃ in PhMe (2.0 M, 40.0 mL, 80.1 mmol) was added dropwise. After 1 h, the solution of the resultant lithioaluminate was added dropwise via cannula to a solution of 2-methylcyclopent-2-enone (6.0 mL, 61.5 mmol) and TMSOTf (12.8 mL, 70.7 mmol) in THF (410 mL) at -78 °C. The reaction mixture was then allowed to warm to rt and stirred overnight. The reaction was quenched with sat. aqueous NaHCO₃ and the layers were separated. The aqueous layer was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated. The TMS enol ether 481 could not be separated from the excess furan 480, and thus the mixture was used without purification.

To a solution of crude TMS enol ether 481 in THF (615 mL) at rt was added MeLi in Et₂O (1.6 M, 45.8 mL, 73.2 mmol). After 1 h, the solution of the resultant enolate was added dropwise via cannula to a solution of methyl 2-iodoacetate (61.6 g, 308 mmol) and HMPTA (42.8 mL, 246 mmol) in THF (308 mL) at -20 °C. The solution was then allowed to warm to rt and stirred overnight. The reaction was quenched with sat. aqueous NH₄Cl and the layers were separated. The aqueous layer was extracted with Et₂O. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc in hexanes) to give cyclopentanone 482 (20.2 g, 75%, two steps) as a yellow oil. ¹H NMR (400
MHz, CDCl$_3$ $\delta$ 5.98 (s, 2H), 3.90 (t, $J$ = 6.9 Hz, 2H), 3.66 (s, 3H), 3.63 (t, $J$ = 6.5 Hz, 1H), 2.84 (t, $J$ = 6.9 Hz, 2H), 2.79 (d, $J$ = 17.5 Hz, 1H), 2.69 (d, $J$ = 17.5 Hz, 1H), 2.37-2.64 (m, 2H), 2.17-2.34 (m, 1H), 2.10 (ddd, $J$ = 14.6, 10.8, 2.2 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.9, 152.9, 152.3, 106.9, 106.3, 61.9, 51.4, 49.7, 42.0, 40.1, 36.5, 32.0, 22.4, 18.5, 17.8, 11.8; IR (neat) 2944, 2866, 1745, 1463, 1352, 1173, 1106 cm$^{-1}$; HRMS [M+NH$_4^+$] calcd for C$_{24}$H$_{44}$NO$_5$Si 454.2989, found 454.2985.

**Enol triflate 483.** To a solution of cyclopentanone 482 (20.2 g, 46.1 mmol) in THF (170 mL) at -78 °C was added a solution of NaHMDS in THF (1.0 M, 50.7 mL, 50.7 mmol) dropwise. After 30 min, a solution of PhNTf$_2$ (19.8 g, 55.3 mmol) in THF (92 mL) was added dropwise via cannula to the enolate solution. The reaction mixture was then allowed to warm to rt and stirred overnight. The reaction was quenched with sat. aqueous NH$_4$Cl and the layers were separated. The aqueous layer was extracted with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Silica gel chromatography (4% EtOAc in hexanes) gave enol triflate 483 (26.2 g) as a yellow oil, which was contaminated with PhNTf$_2$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.02 (d, $J$ = 3.0 Hz, 1H), 5.98 (d, $J$ = 3.0 Hz, 1H), 5.65 (t, $J$ = 2.5 Hz, 1H), 3.90 (t, $J$ = 6.8 Hz, 2H), 3.69 (s, 3H), 3.66 (t, $J$ = 8.7 Hz, 1H), 2.83 (t, $J$ = 6.8 Hz, 2H), 2.58-2.74 (m, 2H), 2.59 (d, $J$ = 15.1 Hz, 1H), 2.53 (d, $J$ = 15.1 Hz, 1H), 1.07 (br s, 21H), 0.875 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.7, 152.8, 152.0, 151.9, 131.9, 130.9, 129.8, 120.6, 116.3, 111.3, 108.0, 106.5, 61.8, 51.2, 48.7, 42.7, 40.9, 32.1, 29.5, 20.0, 18.4, 17.7, 11.9; IR (neat) 2945, 2867, 1742, 1444, 1423, 1214, 1143 cm$^{-1}$; HRMS [M+NH$_4^+$] calcd for C$_{25}$H$_{43}$NO$_7$F$_3$SiS 586.2482, found 586.2496.
Alcohol 484. To a solution of ester 483 (26.2 g, 46.1 mmol) in CH₂Cl₂ (461 mL) at -78 °C was added DIBAl-H in PhMe (1.5 M, 69.2 mL, 103.8 mmol) dropwise. The solution was then allowed to warm to 0 °C. After 1 h, the reaction was quenched with sat. aqueous Rochelle’s salt and stirred vigorously overnight. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. Siilica gel chromatography (30% EtOAc in hexanes) gave alcohol 484 (20.4 g, 82%, two steps) as a yellow oil.

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta 6.02 (d, J = 3.0 \text{ Hz}, 1H), 5.99 (d, J = 3.0 \text{ Hz}, 1H), 5.66 (t, J = 2.5 \text{ Hz}, 1H), 3.90 (t, J = 6.9 \text{ Hz}, 2H), 3.81 (dd, J = 11.3, 6.7 \text{ Hz}, 1H), 3.55 (t, J = 8.7 \text{ Hz}, 1H), 2.83 (t, J = 6.8 \text{ Hz}, 1H), 2.64 (ddd, J = 8.6, 4.4, 2.4 \text{ Hz}, 2H), 1.95 - 1.78 (m, 2H), 1.04 (br s, 21H), 0.834 (s, 3H); \]

\[ ^13C \text{NMR (75 MHz, CDCl}_3 \] \( \delta 153.0, 152.6, 152.5, 116.3, 111.9, 107.8, 106.6, 61.9, 58.9, 48.8, 42.9, 39.9, 32.0, 29.9, 19.9, 17.7, 11.8; IR (neat) 3353 (br), 2943, 2866, 1423, 1213, 1142, 1106 cm\(^{-1}\); HRMS [M+NH\(_4\)\(^+\)] calcd for C\(_{24}\)H\(_{43}\)NO\(_6\)F\(_3\)SiS 558.2532, found 558.2535.

(4 + 3) Cycloadducts 495 and 496. To a solution of enal 494 (138 mg, 0.200 mmol) in CH₃CN (4 mL) at 0 °C was added BF₃·OEt\(_2\) (50 μL, 0.400 mmol) dropwise. After 10 min, Et\(_3\)N (84 μL, 0.600 mmol) was added. The reaction mixture was poured into sat. aqueous NaHCO\(_3\). The layers were separated and the aqueous layer was extracted with ErOAc. The combined organic layers were dried (Na₂SO₄) and concentrated. Siilica gel chromatography (80% EtOAc in hex → 5% MeOH in EtOAc) gave exo adduct 495 (19 mg, 18%) and endo adduct 496 (45 mg, 54%) as yellow foams. exo adduct 495: \[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta 9.1 (s, 1H), 8.47 (s, 1H), 7.67-7.77 (m, 2H), 7.52-7.65 (m, 2H), 6.13 (d, J = 2.6 \text{ Hz}, 1H), 6.10 (d, J = 2.9 \text{ Hz}, 1H), 5.69 (d, J = 9.0 \text{ Hz}, 1H), 3.98-4.09 (m, 1H), 3.94 (t, J = 6.3 \text{ Hz}, 2H), 3.18 (d, J = 7.5 \text{ Hz}, 1H), 2.97 (t, J = 6.3 \text{ Hz}, 2H), 2.47-2.67 (m, 2H), 2.39 (dd, J = 12.7, 6.7 \text{ Hz}, 1H),
1.85-2.07 (m, 2H), 0.79 (s, 3H), 0.63 (t, J = 7.9 Hz, 9 H), 0.30-0.55 (m, 6H). *endo* adduct 496: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.24 (s, 1H), 8.51 (d, J = 4.7 Hz, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 8.6, 1.4 Hz, 1H), 7.63 (d, J = 5.7 Hz, 1H), 6.44 (d, J = 6.2 Hz, 1H), 6.9 (d, J = 6.1 Hz, 1H), 6.14 (br s, 1H), 4.22 (s, 1H), 3.87 (t, J = 4.1 Hz, 2H), 3.50-3.80 (br s, 1H), 2.78 (dd, J = 12.2, 3.9 Hz, 1H), 2.11-2.57 (m, 5H), 1.98-2.08 (m, 1H), 1.63-1.81 (m, 3H), 1.19 (s, 3H).

Iodide 499. To a solution of alcohol 484 (23.7 g, 43.8 mmol), imidazole (3.87 g, 56.9 mmol) and PPh\(_3\) (24.9 g, 56.9 mmol) in CH\(_2\)Cl\(_2\) (440 mL) was added a solution of iodine (13.3 g, 52.6 mmol) in CH\(_2\)Cl\(_2\) (105 mL) dropwise via cannula. After 3 h at rt, the solution was quenched with a 1:1 mixture of sat. aqueous NaHCO\(_3\)/sat. aqueous Na\(_2\)S\(_2\)O\(_3\). The layers were separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated. Silica gel chromatography (10 % EtOAc in hexanes) to give iodide 499 (24.0 g, 84%) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.02 (d, J = 3.0 Hz, 1H), 5.99 (d, J = 3.0 Hz, 1H), 5.70 (t, J = 2.3 Hz, 1H), 3.39 (t, J = 8.6 Hz, 1H), 3.26 – 3.12 (m, 2H), 2.84 (t, J = 8.6 Hz, 2H), 2.64 (dd, J = 8.6 Hz, 2.5 Hz, 2H), 2.15-2.31 (m, 2H), 1.05 (br s, 21H), 0.815 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 152.9, 152.0, 151.9, 112.8, 108.0, 106.6, 61.9, 52.2, 43.1, 42.6, 32.1, 30.1, 19.0, 17.9, 11.9 ; IR (neat) 2942, 2866, 1424, 1215, 1141, 1103 cm\(^{-1}\); HRMS [M+NH\(_4^+\)] calcd for C\(_{24}\)H\(_{36}\)NO\(_5\)F\(_3\)SiS\(_2\) 668.1550, found 668.1536.

Hydrazone 492. To a solution of 2,2-dimethyl-1,3-dioxan-5-one\(^{78}\) (9.60 g, 73.6 mmol) in benzene (368 mL) at rt was added 1,1-dimethylhydrazine (7.30 mL, 95.7 mmol). The solution was then heated to reflux under Dean-Stark conditions. After 6
h, the solution was cooled to rt and concentrated to give hydrazone 492 (12.7 g, quant.) as a yellow oil, which was used without further purification. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.52 (s, 2H), 4.27 (s, 2H), 2.43 (s, 6H), 1.41 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.7, 99.6, 61.8, 58.8, 46.9, 23.3; IR (neat) 2987, 2858, 1652, 1372, 1221, 1089 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_8$H$_{17}$N$_2$O$_2$ 173.1290, found 173.1272.

**Dioxanone 500.** To a solution of hydrazone 492 (9.51 g, 55.2 mmol) in THF (262 mL) at -78 °C was added n-BuLi in hexanes (2.5 M, 19.1 mL, 47.8 mmol). After 10-15 min, the solution became an unstirrable tan slurry. After 1 h, HMPA (28.9 mL, 166 mmol) was added dropwise. After 10 min, the aza-enolate/HMPA solution was added dropwise via cannula to a solution of iodide 499 (24.0 g, 36.8 mmol) in THF (147 mL) at -78 °C. After 1 h, the reaction mixture was poured into a solution of NaOAc (22.6 g, 276 mmol) in 1:2.5 H$_2$O/AcOH 356 mL). This solution was stirred vigorously overnight, then cooled to 0 °C and carefully neutralized with solid NaHCO$_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Silica gel chromatography (10% EtOAc in hexanes) gave dioxanone 500 (18.0 g, 75%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.05 – 5.95 (m, 2H), 5.71 – 5.64 (m, 1H), 4.27 (ddd, J = 17.0, 4.6, 1.3 Hz, 1H), 4.20 (dd, J = 8.2, 3.8 Hz, 1H), 3.89 (t, J = 6.9 Hz, 2H), 3.40 (dd, J = 16.7, 8.4 Hz, 1H), 2.83 (t, J = 6.9 Hz, 2H), 2.74 – 2.55 (m, 2H), 2.07 – 1.82 (m, 1H), 1.75 – 1.61 (m, 2H), 1.51 – 1.42 (m, 6H), 1.04 (br s, 21 H), 0.82 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 209.6, 209.4, 153.4, 153.1, 153.1, 153.0, 152.9, 112.7, 112.5, 108.2, 108.1, 106.9, 101.2, 101.1, 75.0, 74.9, 67.0, 66.9, 62.3, 50.3, 50.2, 42.7, 42.6, 33.0, 32.9, 32.5, 30.5, 24.2, 24.1, 24.0, 23.9, 23.8, 20.3, 18.3, 12.3; IR (neat) 2927, 1746, 1374, 1222, 1101 cm$^{-1}$; HRMS [M+NH$_4^+$] calcd for C$_{30}$H$_{51}$NO$_8$F$_3$SiS 670.3057, found 670.3061.
Silyloxy dioxin 407. To a solution of NaHMDS (1.0 M, 36.4 mL, 36.4 mmol) in THF (150 mL) at -78 °C was added a solution of dioxanone 500 (18.0 g, 27.6 mmol) in THF (200 mL) dropwise via cannula. After 1 h, TESCl (6.2 mL, 36.7 mmol) was added dropwise. The solution was allowed to rt and stirred overnight. The reaction was quenched with sat. aqueous NaHCO₃. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (5% EtOAc in hexanes + 1% Et₃N) gave silyloxy dioxin 407 (19.9 g, 94%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.18 – 6.16 (m, 1H), 6.02 – 5.94 (m, 2H), 5.67 – 5.61 (m, 1H), 4.20 – 4.08 (m, 1H), 3.89 (t, J = 7.0 Hz, 2H), 3.41 (ddd, J = 8.4, 8.4, 3.8 Hz, 1H), 3.41 (t, J = 7.0 Hz, 2H), 2.76 – 2.52 (m, 2H), 1.93 – 1.50 (m, 4H), 1.46 (s, 3H), 1.44 (s, 3H), 1.05 (br s, 21H), 0.98 (t, J = 7.8 Hz, 9H), 0.80 (s, 3H), 0.67 (q, J = 7.8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 153.3, 153.1, 153.0, 152.9, 152.4, 152.3, 134.1, 126.4, 126.3, 112.0, 111.7, 107.7, 107.6, 106.4, 98.4, 98.3, 69.9, 69.8, 61.9, 50.0, 49.9, 42.3, 42.0, 32.2, 31.9, 31.7, 30.3, 30.1, 27.7, 27.6, 25.8, 25.8, 20.9, 20.8, 20.3, 19.8, 17.9, 11.9, 6.7, 4.9; IR (neat) 2956, 1563, 1457, 1368, 1204 cm⁻¹; HRMS [M+NH₄⁺] calcd for C₃₆H₆₅NO₈F₃Si₂S 784.3922, found 784.3937.

Enal 406. A solution of silyloxy dioxin 407 (19.9 g, 25.9 mmol) in PhMe (518 mL) was heated to reflux. After 3 h, the solution was cooled to rt and concentrated to give enal 406 (18.4 g, quant.) as a yellow oil, which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 9.16 (s, 1H), 6.00 (d, J = 3.1 Hz, 1H), 5.99 (d, J = 3.1
Hz, 1H), 5.75 – 5.65 (m, 2H), 3.89 (t, J = 6.9 Hz, 2H), 3.43 (t, J = 8.6 Hz, 1H), 2.83 (t, J = 6.9 Hz, 2H), 2.66 (ddd, J = 8.6, 8.6, 2.3 Hz, 2H), 2.55 – 2.28 (m, 2H), 1.68 (ddd, J = 10.5, 10.5, 5.7 Hz, 2H), 1.04 (br s, 21 H), 0.96 (t, J = 7.8 Hz, 9H), 0.91 (s, 3H), 0.72 (q, J = 7.8 Hz, 6H); 13C NMR (75 MHz, CDCl3) 188.9, 152.7, 152.5, 151.6, 134.6, 112.5, 107.8, 106.5, 61.9, 50.0, 42.4, 35.9, 32.1, 30.2, 21.1, 19.8, 17.9, 11.9, 6.7, 5.7; IR (neat) 2957, 2359, 1691, 1369 cm⁻¹; HRMS [M+NH₄⁺] calcd for C₃₃H₆₉NO₇F₃Si₂S 726.3503, found 726.3517.

(4 + 3) Cycloadduct 405a. To a solution of enal 406 (18.4 g, 25.9 mmol) in CH₂Cl₂ (518 mL) at -78 °C was added TfOH (1.2 mL, 13.0 mmol). After 1 h, the solution was quenched with pyridine (1.05 mL, 13.0 mmol). MeOH (1 L) was added, and the solution was allowed to warm to rt and stir overnight. The reaction mixture was concentrated, and the residue was taken up in CH₂Cl₂ (250 mL) and transferred to a separatory funnel. The organic layer was washed with sat. aqueous NaHCO₃ and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc in hexanes) gave (4 + 3) cycloadduct 405a (15.4 g, 79%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.29 (d, J = 6.1 Hz, 1H), 6.15 (d, J = 6.1 Hz, 1H), 5.70 – 5.64 (m, 1H), 4.13 (d, J = 3.3 Hz, 1H), 3.93 – 3.76 (m, 2H), 3.55 (d, J = 3.3 Hz, 1H), 2.67 (dd, J = 12.2, 4.0 Hz, 1H), 2.45 – 2.30 (m, 3H), 2.18 -2.04 (m, 2H), 2.01 – 1.93 (m, 1H), 1.86 – 1.77 (m, 1H), 1.67 – 1.49 (m, 3H), 1.10 (s, 3H), 1.06 (br s, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 206.3, 157.2, 138.9, 130.8, 114.8, 88.9, 87.9, 80.9, 59.2, 58.5, 52.9, 46.5, 36.1, 31.1, 26.3, 19.9, 17.8, 17.0, 11.8; IR (neat) 3484 (br), 2944, 2866, 2716, 1767, 1424, 1215, 1142, 1108 cm⁻¹; HRMS [M+NH₄⁺] calcd for C₂₃H₄₅NO₇F₃Si₂S 612.2638, found 612.2626.
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7-Hydroxyisoquinoline 489. Prepared according to a procedure reported by Kucznerz and co-workers. To a solution of 3-benzoylbenzaldehyde (488) (63.7 g, 300 mmol) in PhMe (667 mL) was added aminoacetaldehyde dimethyl acetal (488).
mL, 450 mmol). The solution was heated to reflux overnight under Dean-Stark conditions. The Dean-Stark trap and condenser were removed and the reaction mixture was sparged with N₂ for 10 min. The reaction was cooled to 0 °C and TFAA (127 mL, 900 mmol) and BF₃·OEt₂ (114 mL, 900 mmol) were added and the solution was stirred for 5 days. The precipitated material was collected by filtration and washed with Et₂O and then dissolved in water. The pH was adjusted to 9 with addition of concentrated aqueous ammonia and the precipitate collected by filtration. The solid was washed with ether and dried in vacuo to give 7-hydroxyisoquinoline 488 (27.9 g, 64%) as a off-white solid whose spectral and physical data matched those reported.⁶³ᵃ

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\begin{align*}
    \text{HO} & \quad \rightarrow \\
    489 & \quad \text{TF} \quad 489
\end{align*}
\]

**Isoquinolin-7-yl trifluoromethanesulfonate.** Prepared according to a procedure reported by Denni-Dischert and co-workers.⁶⁴ᵇ To a suspension of 7-hydroxyisoquinoline (489) (24.2 g, 167 mmol) in EtOAc (326 mL) at 0 °C was added pyridine (67.3 mL, 835 mmol) and Tf₂O (31.0 mL, 184 mmol) dropwise. The reaction was allowed to warm to rt and stirred overnight. The reaction was then quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (40% EtOAc in hexanes) gave isoquinolin-7-yl trifluoromethanesulfonate (31.5 g, 68%) as a yellow oil whose spectral data matched those reported.⁶³ᵇ

\[
\begin{align*}
    \text{TF} & \quad \rightarrow \\
    282 & \quad \text{Me₃Sn}
\end{align*}
\]

**7-(Trimethylstannyl)isoquinoline 279.** Prepared according to a procedure reported by Shenvi and co-workers.⁴³ᵃ To a solution of isoquinolin-7-yl trifluoromethanesulfonate (30.5 g, 110 mmol), LiCl (28.0 g, 660 mmol), and Pd(PPh₃)₄ (12.7 g, 11.0 mmol) in benzene (220 mL) was added Me₃Sn₂ (25.1 mL, 121 mmol). The solution was heated to reflux and stirred overnight. The reaction
mixture was allowed to cool to rt and filtered through Celite. The filtrate was then washed with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (40% EtOAc in hexanes) gave stannane 282 (23.5 g, 73%) as an orange solid whose spectral data matched those reported.⁴²a

![Chemical Structure](image)

**Isoquinoline 404a.** To a round bottom flask containing enol triflate 404a (11.7 g, 19.6 mmol) stannane 282 (11.4 g, 39.2 mmol), LiCl (8.3 g, 196 mmol), CuCl (19.4 g, 196 mmol) and Pd(PPh₃)$_4$ (2.3 g, 1.96 mmol) was added DMSO (200 mL). The solution was sparged with Ar while sonicated for 10 min, then heated to 60 °C for 1 h. The reaction mixture was poured into a 1:1 mix of 5% aqueous ammonia/brine and extracted with EtOAc. The combined organic layers were washed with a 2:1 mix of 5% aqueous ammonia/brine, then dried over Na₂SO₄ and concentrated. Silica gel chromatography (50% EtOAc in hexanes) gave isoquinoline 501 (7.9 g, 70%) as a white foam. $^1$H NMR (400 MHz, CDCl₃) δ 9.91 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 7.92 (s, 1H), 7.77 (d, $J = 8.6$ Hz, 1H), 7.73 (d, $J = 8.6$ Hz, 1H), 7.61 (d, $J = 5.6$ Hz, 1H), 6.29 (s, 2H), 6.14 (s, 1H), 4.16 (s, 1H), 3.97 – 3.81 (m, 2H), 3.66 (br s, 1H), 2.72 (dd, $J = 11.9, 3.9$ Hz, 1H), 2.55 – 2.35 (m, 3H), 2.29 – 2.06 (m, 2H), 2.05 – 1.95 (m, 1H), 1.78 – 1.65 (m, 2H), 1.17 (s, 3H), 1.07 (br s, 21 H); $^{13}$C NMR (75 MHz, CDCl₃) δ 206.9, 152.8, 152.4, 142.7, 138.3, 135.1, 134.7, 131.6, 130.2, 128.9, 128.6, 126.3, 124.4, 120.0, 89.7, 87.7, 81.0, 59.0, 58.6, 56.0, 49.5, 36.2, 33.8, 29.1, 20.0, 18.0, 17.9, 11.8; IR (neat) 3474 (br), 3052, 2942, 2865, 1715, 1594, 1463, 1360, 1109 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_{35}$H$_{48}$NO$_4$Si 574.3353, found 574.3353.
Tetrahydrofuran 502. To a solution of diene 501 (6.65 g, 11.6 mmol) and potassium azodicarboxylate (281 g, 1.45 mol) in CH$_2$Cl$_2$ (230 mL) at 0 °C was added a solution of AcOH (166 mL, 2.90 mol) in CH$_2$Cl$_2$ (166 mL) over 5 h. The reaction was then carefully basified with sat. aqueous NaHCO$_3$. The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Silica gel chromatography (40% EtOAc in hexanes) gave tetrahydrofuran 502 (6.52 g, 97 %) as a white solid (mp 73-74 °C). $^1$H NMR (300 MHz, CDCl$_3$) δ 9.21 (s, 1H), 8.48 (d, $J = 5.6$ Hz, 1H), 7.75 (s, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.61 (d, $J = 5.6$ Hz, 1H), 7.54 (d, $J = 8.6$ Hz, 1H), 4.15 (s, 1H), 3.95 (t, $J = 6.4$ Hz, 2H), 3.88 (s, 1H), 3.03 (t, $J = 9.6$ Hz, 1H), 2.59 (d, $J = 11.6$ Hz, 1H), 2.41-2.26 (m, 2H), 2.22-1.33 (m, 12H), 1.08 (br s, 21H), 0.45 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 208.1, 152.3, 142.5, 139.4, 134.6, 132.1, 128.5, 127.1, 126.3, 125.7, 119.9, 87.1, 86.0, 79.3, 59.7, 59.2, 57.4, 45.8, 39.0, 36.2, 30.1, 26.2, 25.6, 20.3, 19.3, 17.9, 13.5, 11.8; IR (neat) 3478 (br), 2942, 2865, 1714, 1593, 1462, 1366, 1108 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_{35}$H$_{52}$NO$_4$Si 578.3666, found 578.3665.

α-Hydroxy enone S3. To a solution of DMSO (7.7 mL, 109 mmol) in CH$_2$Cl$_2$ (218 mL) at -78 °C was added oxalyl chloride (4.70 mL, 54.5 mmol) dropwise. After 30 min, a solution of α–hydroxy ketone 502 (6.30 g, 10.9 mmol) in CH$_2$Cl$_2$ (110 mL) was added dropwise via cannula to the solution of dimethylchlorosulfonylum chloride at -78 °C. After 40 min, Et$_3$N (27.3 mL, 196 mmol) was added dropwise to the reaction mixture. The reaction was allowed to warm to rt, then quenched with sat. aqueous NaHCO$_3$. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated.
Silica gel chromatography (50% EtOAc in hexanes) gave α-hydroxy enone S3 (5.11 g, 81%) as a yellow foam. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.22 (s, 1H), 8.50 (d, $J = 5.5$ Hz, 1H), 7.80 (s, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.63 (d, $J = 5.5$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 1H), 5.90 (s, 1H), 3.94 – 3.76 (m, 2H), 3.10 – 2.96 (m, 2H), 2.42 – 2.27 (m, 4H), 2.24 – 2.03 (m, 4H), 2.01 – 1.88 (m, 1H), 1.87 – 1.69 (m, 3H), 1.68 – 1.55 (m, 2H), 1.07 (br s, 21H), 0.62 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.2, 152.3, 142.5, 140.6, 139.5, 135.7, 134.7, 132.2, 128.5, 126.4, 125.8, 120.1, 83.8, 83.1, 58.9, 57.5, 53.6, 44.7, 35.9, 32.3, 28.7, 25.7, 20.9, 20.2, 17.9, 12.8, 11.8; IR (neat) 3060 (br), 2941, 2863, 1669, 1579, 1462, 1374 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_{35}$H$_{50}$NO$_4$Si 576.3509, found 576.3523.

**Enol triflate 503.** To a solution of α-hydroxy enone S3 (2.00 g, 3.47 mmol) in THF (70 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 153 mg, 3.82 mmol). After 30 min, PhNTf$_2$ (1.49 g, 4.16 mmol) was added in one portion. The reaction mixture was stirred for 1 h at 0 °C, then quenched with sat. aqueous NaHCO$_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Silica gel chromatography (40% EtOAc in hexanes) gave enol triflate 503 (2.03 g, 83%) as a yellow foam. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.24 (s, 1H), 8.51 (d, $J = 5.5$ Hz, 1H), 7.79 (s, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 1H), 7.56 (dd, $J = 8.5$, 1.3 Hz, 1H), 3.94-3.75 (m, 2H), 3.08 (t, $J = 9.7$ Hz, 1H), 2.97 (dd, $J = 17.8$, 2.9 Hz, 1H), 2.53-1.58 (m, 14H), 1.06 (br s, 21H), 0.64 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 189.5, 156.5, 152.2, 142.6, 138.8, 138.5, 134.8, 131.9, 129.4, 128.5, 126.4, 126.0, 120.0, 84.7, 84.6, 58.6, 57.1, 53.1, 44.3, 35.5, 35.4, 31.9, 29.0, 25.6, 22.7, 20.0, 17.8, 12., 11.8; IR (neat) 2943, 2865, 1709, 1422, 1209, 1140 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_{96}$H$_{69}$NO$_6$F$_3$SiS 708.3002, found 708.3013.
Enone 404. To a solution of enol triflate 503 (2.03 g, 2.87 mmol), LiCl (365 mg, 8.60 mmol) and Pd(PPh₃)₄ (165 mg, 0.143 mmol) in THF was added Bu₃SnH (1.85 mL, 6.88 mmol). The solution was heated to reflux for 1 h, then allowed to cool to rt. The reaction mixture was transferred to a separatory funnel and washed with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (50% EtOAc in hexanes) gave enone 404 (1.13 g, 70%) as a yellow foam. ¹H NMR (300 MHz, CDCl₃) δ 9.23 (s, 1H), 8.49 (d, J = 5.6 Hz, 1H), 7.79 (s, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 7.56 (dd, J = 8.5, 1.4 Hz, 1H), 5.76 (s, 1H), 3.96-3.74 (m, 2H), 3.05 (t, J = 9.8 Hz, 1H), 2.54-2.41 (m, H), 2.40-1.55 (m, 12H), 1.06 (br s, 21H), 0.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 198.6, 167.8, 152.2, 142.5, 139.3, 134.6, 132.0, 128.5, 126.3, 125.8, 121.4, 120.0, 83.9, 83.8, 59.0, 57.2, 53.0, 44.8, 36.4, 35.7, 28.7, 28.5, 25.8, 20.0, 17.8, 12.7, 11.8; IR (neat) 2941, 2864, 1681, 1462, 1381, 1095 cm⁻¹; HRMS [MH⁺] calcd for C₃₅H₅₀NO₃Si 560.3560, found 560.3571.

Dienol triflate 573. To a solution of LiHMDS (1.0 M in THF, 4.0 mL, 4.00 mmol) in THF (40 mL) at rt was added a solution of enone 404 (1.12 g, 2.00 mmol) in THF (20 mL) dropwise via cannula. After 1 h, HMPA (1.74 mL, 10.0 mmol) was added dropwise. After 1 h, a solution of PhNTf₂ (857 mg, 2.40 mmol) in THF (24 mL) was added dropwise via cannula. After 1 h, the reaction was quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (30% EtOAc in hexanes) gave dienol triflate 573 (1.04 g,
75%) as a yellow foam. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.24 (s, 1H), 8.50 (s, 1H), 7.79 (s, 1H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.64 (d, $J = 5.4$ Hz, 1H), 7.58 (dd, $J = 8.5$, 1.5 Hz, 1H), 6.06 (s, 1H), 5.51 (dd, $J = 5.1$, 2.3 Hz, 1H), 4.00-3.70 (m, 2H), 3.16 (t, $J = 9.6$ Hz, 1H), 2.50 (dd, $J = 11.4$, 8.4 Hz, 1H), 2.44-2.12 (m, 6H), 2.07-1.73 (m, 6H), 1.06 (br s, 21H), 0.55 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.1, 150.8, 142.2, 139.8, 137.9, 134.7, 131.9, 129.4, 126.3, 125.9, 124.8, 120.2, 116.2, 83.1, 80.3, 58.9, 56.8, 51.2, 44.6, 40.0, 38.0, 35.6, 29.6, 26.2, 20.4, 17.9, 15.2, 11.8; IR (neat) 2944, 2866, 1419, 1214, 1140 1092 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_{36}$H$_{49}$NO$_5$F$_3$SiS 692.3053, found 692.3058.

Alcohol 403. To a solution of TIPS ether 573 (700 mg, 1.01 mmol) in THF (40 mL) at rt was added 6M HCl (1.20 mL, 7.07 mmol) dropwise. The solution was then stirred overnight at rt. The reaction was quenched with sat. aqueous NaHCO$_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Silica gel chromatography (80% EtOAc in hexanes) gave alcohol 403 (439 mg, 81%) as a white foam. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.23 (s, 1H), 8.49 (s, 1H), 7.79 (s, 1H), 7.77 (d, $J = 8.5$ Hz, 1H), 7.63 (d, $J = 5.5$ Hz, 1H), 7.57 (dd, $J = 8.5$, 1.6 Hz, 1H), 6.11 (s, 1H), 5.56 (dd, $J = 5.3$, 2.4 Hz, 1H), 3.80 (t, $J = 5.5$ Hz, 2H), 3.16 (t, $J = 9.2$ Hz, 1H), 2.62-2.46 (br s, 1H), 2.51 (dd, $J = 11.5$, 8.4 Hz, 1H), 2.45-2.13 (m, 6H), 2.08-1.85 (m, 6H), 0.55 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.1, 149.8, 142.4, 139.4, 137.3, 134.7, 131.8, 128.5, 126.3, 125.9, 125.6, 120.0, 116.9, 83.8, 82.5, 59.0, 56.7, 51.1, 44.5, 39.9, 37.9, 34.3, 29.2, 26.2, 20.2, 15.2; IR (neat) 3368 (br) 2962, 2880, 1419, 1214, 1139, 1050 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_{27}$H$_{29}$NO$_5$F$_3$S 536.1719, found 536.1758.
(Z)-Vinylsilane 510. A mixture of dienol triflate 403 (55 mg, 0.103 mmol), potassium trifluoroborate 514 (64 mg, 0.309 mmol), Cs₂CO₃ (101 mg, 0.309 mmol), and Pd(PPh₃)₄ (12 mg, 0.010 mmol) in a round bottom flask equipped with a reflux condenser was evacuated under hi-vac and flushed with N₂ three times. THF (1.8 mL) and water (0.2 mL) were added to the mixture via syringe through the condenser. The solution was then heated to 70 °C overnight. The reaction mixture was then allowed to cool to rt and quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (60% EtOAc in hexanes) gave (Z)-vinylsilane 510 (42 mg, 84%) as a white foam. 

¹H NMR (360 MHz, CDCl₃) δ 9.23 (s, 1H), 8.49 (s, 1H), 7.78 (s, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 5.0 Hz, 1H), 7.58 (dd, J = 8.5, 1.5 Hz, 1H), 6.70 (d, J = 14.7 Hz, 1H), 5.99 (s, 1H), 5.62 (d, J = 14.7 Hz, 1H), 5.39 (dd, J = 5.1, 2.5 Hz, 1H), 3.79 (s, 2H), 3.26-3.06 (br s, 1H), 3.15 (t, J = 9.2 Hz, 2H), 2.53 (dd, J = 11.5, 8.4 Hz, 1H), 2.45-2.27 (m, 2H), 2.26-2.11 (m, 3H), 2.07-1.79 (m, 6H), 1.78-1.65 (m, 1H), 0.54 (s, 3H), 0.13 (s, 9H); ¹³C NMR (90 MHz, CDCl₃) δ 152.3, 143.2, 142.5, 142.2, 140.2, 139.9, 134.6, 133.0, 131.9, 128.7, 126.3, 125.8, 124.4, 121.6, 120.1, 83.4, 83.2, 59.7, 56.0, 51.5, 44.6, 40.1, 37.8, 36.2, 29.9, 26.4, 20.4, 15.4, 0.21; IR (neat) 3441 (br), 2955, 1376, 1245, 1048, 996 cm⁻¹; HRMS [MH⁺] calcd for C₃₁H₄₀NO₂Si 486.2828, found 486.2828.

Aldehyde 515. To a solution of alcohol 510 (20 mg, 0.041 mmol) and Et₃N (34 µL, 0.246 mmol) in CH₂Cl₂ (1 mL) at rt was added sulfur trioxide pyridine complex (33 mg, 0.295 mmol). After 1 h, the reaction mixture quenched with sat. aqueous...
NaHCO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (50% EtOAc in hexanes) gave aldehyde 515 (15 mg, 75%) as a white foam. ¹H NMR (300 MHz, CDCl₃) δ 9.80 (t, J = 2.7 Hz, 1H), 9.25 (s, 1H), 8.50 (s, 1H), 7.79 (s, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.64 (d, 4.35 Hz, 1H), 7.59 (dd, J = 8.5, 1.6 Hz, 1H), 6.67 (d, J = 14.7 Hz, 1H), 6.01 (s, 1H), 5.66 (d, J = 14.7 Hz, 1H), 5.44 (dd, J = 5.2, 2.5 Hz, 1H), 3.16 (t, J = 9.2 Hz, 1H), 2.90 (dd, J = 15.9, 2.5 Hz, 1H), 2.62 (dd, J = 15.9, 3.0 Hz, 1H), 2.56 (dd, J = 11.5, 8.3 Hz, 1H), 2.47-2.11 (m, 1H), 2.08-1.94 (m, 2H), 1.93-1.67 (m, 4H), 0.56 (s, 3H), 0.12 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 202.4, 152.7, 142.9, 142.8, 142.0, 140.5, 140.3, 135.1, 134.5, 132.4, 129.0, 126.7, 126.3, 124.9, 122.7, 120.6, 83.5, 80.5, 57.4, 51.8, 48.3, 45.0, 40.6, 39.0, 30.6, 26.8, 20.9, 15.8, 0.61; IR (neat) 2957, 2883, 1722, 1631, 1591, 1377, 1246, 1089, 995 cm⁻¹; HRMS [MH⁺] calcd for C₃₁H₃₈NO₂Si 484.2672, found 484.2673.

(±)-Cortistatin J (271). To a solution of aldehyde 515 (12 mg, 0.025 mmol) in MeCN (2.5 mL) in a round bottom flask was added dimethylamine hydrochloride (82 mg, 0.375 mmol). The flask was then sealed with a ground glass stopper and heated to 60 °C overnight. The reaction mixture was allowed to cool to rt and quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (EtOAc + 1% 1:1 MeOH/sat. NH₃ (aq) → 2:1 MeOH/EtOAc gave (±)-cortistatin J (10 mg, 90%) as a white foam. ¹H NMR (600 MHz, CDCl₃) δ 9.22 (br s, 1H), 8.49 (br d, J = 4.3 Hz, 1H), 7.79 (s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 7.59 (dd, J = 8.5, 1.6 Hz, 1H), 6.09 (dd, J = 9.8, 2.6 Hz, 1H), 5.83 (s, 1H), 5.80 (d, J = 9.8 Hz), 5.41 (dd, J = 5.3, 2.6 Hz, 1H), 3.46 (br d, J = 10.7 Hz, 1H), 3.16 (dd, J = 10.7, 9.1 Hz, 1H), 2.56 (dd, J = 11.6, 8.5 Hz, 1H), 2.40 (d, J = 17.5 Hz, 1H), 2.31 (s, 6H), 2.26-2.38 (m, 2H), 2.14-2.22 (m, 1H), 1.95-2.11 (m, 4H), 1.83-1.93 (m, 2H), 1.65-1.80 (m, 2H), 0.57 (s, 3H); ¹³C NMR (75 MHz, CDCl₃)
$\text{CDCl}_3$ $\delta$ 152.3, 142.5, 141.1, 140.0, 139.8, 134.6, 132.2, 131.9, 128.6, 127.3, 126.3, 125.8, 121.7, 121.0, 120.0, 82.2, 78.9, 60.4, 56.9, 51.7, 44.8, 40.5, 40.2, 37.9, 30.9, 30.4, 26.4, 20.6, 15.4; IR (neat) 3377 (br), 2960, 2931, 1593, 1503, 1455, 1376, 1303, 1275, 1145, 1022 cm$^{-1}$; HRMS [MH$^+$] calcd for C$_{30}$H$_{35}$N$_2$O 439.2749, found 439.2767.
**Dienone 583.** A round-bottom flask containing a mixture of dienol triflate 573 (43 mg, 0.062 mmol), Pd(PPh₃)₄ (7 mg, 0.006 mmol), LiCl (8 mg, 0.186 mmol), CuCl (18 mg, 18 mmol) and stannane 581 (42 μL, 0.124 mmol) was evacuated under hi-vac and backfilled with N₂ (g) three times. DMF (1 mL) was added, and the solution was stirred at rt overnight. The reaction mixture was poured into a 1:1 mix of 5% aqueous ammonia/brine and extracted with EtOAc. The combined organic layers were washed with a 2:1 mix of 5% aqueous ammonia/brine, then dried over Na₂SO₄ and concentrated. Silica gel chromatography (20% EtOAc + 3% Et₃N in hexanes) gave trienol ether 582 as a yellow foam (33 mg, 87%).

To a solution of trienol ether 582 (33 mg, 0.054 mmol) in THF (2 mL) at rt was added dropwise a solution of TBAF in THF (1M, 65 μL, 0.065 mmol). The solution was stirred overnight at rt and silica gel (28 mg) was added stirred for 3 h. The reaction was quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (80% EtOAc in hexanes) gave keto alcohol 583 (20 mg, 85%) as a yellow foam. ¹H NMR (400 MHz, CDCl₃) δ 9.26 (br s, 1H), 8.52 (br s, 1H), 7.79 (s, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.65 (br s, 1H), 7.58 (dd, J = 8.6, 1.6 Hz, 1H), 6.90 (s, 1H), 5.78 (dd, J = 5.3, 2.6 Hz, 1H), 3.75-3.67 (m, 1H), 3.59-3.53 (m, 1H), 3.16 (t, J = 9.1 Hz, 1H), 2.63 (dd, J = 14.8, 9.0, 3.0 Hz, 1H), 2.50 (dd, J = 11.6, 8.5 Hz, 1H), 2.40 (br s, 1H), 2.38-2.31 (m, 1H), 2.32 (s, 3H), 2.28-2.15 (m, 4H), 2.11-1.96 (m, 4H), 1.95-1.80 (m, 2H), 1.67-1.58 (m, 1H), 0.55 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 198.8, 152.6, 143.4, 143.3, 142.9, 140.5, 140.1, 136.7, 135.2, 132.3, 129.4, 126.8, 126.4, 84.2, 83.0, 64.6, 60.8, 57.2, 52.0, 45.1, 41.1, 39.8, 36.6, 32.0, 30.1, 26.8, 26.7; 20.8, 15.9; IR (neat) 3416 (br), 2962, 2926, 2878, 1660, 1632, 1593, 1377, 1234 cm⁻¹; LRMS [MH⁺] calcd for C₂₈H₃₂NO₃ 430.6, found 430.5.
Trienone 308. To a solution of keto alcohol 583 (20 mg, 0.047 mmol) and Et₃N (33 μL, 0.235 mmol) in 4:1 mix of CH₂Cl₂/DMSO (1 mL) at rt was added sulfur trioxide pyridine complex (30 mg, 0.188 mmol). After 1 h, the reaction mixture quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (50% EtOAc in hexanes) gave aldehyde 584 (20 mg as a yellow foam which was used without further purification.

To a solution of aldehyde 584 (20 mg, 0.047 mmol) in THF (1 mL) at rt was added TBD 585 (6.5 mg, 0.047 mmol). The solution was stirred for 1 h before Et₃N (48 μL, 0.470 mmol) and MsCl (18 μL, 0.235 mmol) was added. The reaction was quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (60% EtOAc in hexanes) to give trienone 308 (13 mg, 70%) as a yellow foam. 

1H NMR (400 MHz, CDCl₃) δ 9.24 (br s, 1H), 8.52 (br s, 1H), 7.80 (s, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.62 (br s, 1H), 7.59 (dd, J = 8.6, 1.6 Hz, 1H), 7.09 (s, 1H), 6.96 (ddd, J = 10.2, 8.4, 1.8 Hz, 1H), 6.20 (dd, J = 4.2, 1.8 Hz, 1H), 5.86 (dd, J = 5.7, 2.7 Hz, 1H), 3.18 (dd, J = 10.8, 8.9 Hz, 1H), 2.97 (ddd, J = 18.9, 2.7, 2.7 Hz, 1H), 2.60 (dd, J = 18.9, 6.2 Hz, 1H), 2.55 (dd, J = 11.4, 8.2 Hz, 1H), 2.49–2.16 (m, 5H), 2.14 – 2.02 (m, 2H), 1.89 (ddd, J = 24.6, 11.9, 5.3, 1H), 1.83-1.67 (m, 2H) 0.57 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 185.8, 145.7, 140.5, 139.6, 131.9, 131.5, 130.7, 130.2, 126.4, 126.0, 82.1, 80.3, 60.6, 56.8, 51.5, 44.7, 41.6, 34.5, 30.5, 29.7, 27.0, 20.6, 15.5; IR (neat) 2959, 2924, 1657, 1582, 1387, 1286m 1251, 1139 cm⁻¹; LRMS [MH⁺] calcd for C₂₈H₂₈NO₄ 410.5, found 410.3.
Trienol ether 574. A mixture of dienol triflate 573 (14 mg, 0.02 mmol), silylstannane 571b (14 mg, 0.04 mmol), LiCl (2.5 mg, 0.06 mmol), CuCl (6 mg, 0.06 mmol) and Pd(PPh₃)₄ (2.3 mg, 0.002 mmol) in a round bottom flask was evacuated under hi-vac and flushed with N₂ three times. DMF (1.0 mL) was added to the mixture via syringe. The solution was then stirred at rt overnight. The reaction mixture was poured into a 1:1 mix of 5% aqueous ammonia/brine and extracted with EtOAc. The combined organic layers were washed with a 2:1 mix of 5% aqueous ammonia/brine, then dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc in hexanes + 5%Et₃N) gave trienol ether 574 (13 mg, 93%) as a yellow foam. ¹H NMR (300 MHz, CDCl₃) δ 9.22 (br s, 1H), 8.48 (br s, 1H), 7.78 (s, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.52-7.71 (m, 2H), 5.84 (s, 1H), 5.81 (s, 1H), 5.24 (dd, J = 4.9, 2.2 Hz, 1H), 3.60-3.98 (m, 4H), 3.13 (t, J = 9.1 Hz, 1H), 2.49-2.61 (m, 1H), 2.23-2.48 (m, 3H), 2.02-2.22 (m, 4H), 1.54-2.05 (m, 8H), 1.28 (t, J = 6.9 Hz, 3H), 1.07 (s, 9H), 0.53 (s, 3H), 0.09 (s, 6H).

Alcohol S4. To a solution of trienol ether 574 (7 mg, 0.010 mmol) in THF (1.0 mL) at 0 °C was added a solution of TBAF in THF (1.0 M, 12 μL, 0.012 mmol) dropwise. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was then quenched with sat. aqueous NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Silica gel chromatography (30% EtOAc in hexanes + 5% Et₃N) gave alcohol S4 (5 mg, 88%) as a yellow foam. ¹H NMR (360 MHz, CDCl₃) δ 9.22 (s, 1H), 8.48 (d, J = 5.7 Hz, 1H), 7.78 (s, 1H), 7.76 (d, J = 3.8 Hz, 1H), 7.62 (d, J = 5.7 Hz, 1H), 7.57 (dd, J = 8.5, 1.2 Hz, 1H), 5.84 (s, 1H), 5.72 (s, 1H), 5.28 (dd, J = 5.0, 2.4 Hz, 1H), 3.70-3.90 (m, 2H), 3.68 (dd, J = 13.8, 6.9 Hz, 1H), 3.66 (s, 3H), 3.61 (q, 3H), 3.06 (t, J = 8.7 Hz, 1H), 2.48-2.61 (m, 1H), 2.23-2.48 (m, 3H), 2.02-2.22 (m, 4H), 1.54-2.05 (m, 8H), 1.28 (t, J = 6.9 Hz, 3H), 1.07 (s, 9H), 0.53 (s, 3H), 0.09 (s, 6H).
3.22-3.39 (br s, 1H), 3.14 (t, J = 9.7 Hz, 1H), 2.52 (dd, J = 11.6, 8.5 Hz, 1H), 2.10-2.45 (m, 6H), 1.55-2.05 (m, 8H), 1.28 (t, J = 6.8 Hz, 3H), 1.05 (s, 9H), 0.54 (s, 3H), 0.09 (s, 6H).

**Aldehyde 575.** To a solution of alcohol S4 (2.0 mg, 0.004 mmol) in CH$_2$Cl$_2$ (0.5 mL) at rt was added 4Å molecular sieves (2.0 mg), NMO (0.5 mg, 0.042 mmol) and TPAP (0.14 mg, 0.0004 mmol). After 2.5 h, the reaction was quenched with sat. aqueous NaHCO$_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The aldehyde was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.83 (s, 1H), 9.23 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 7.79 (s, 1H), 7.77 (d, J = 3.8 Hz, 1H), 7.63 (d, J = 5.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 5.86 (s, 1H), 5.66 (s, 1H), 5.33 (br s, 1H), 3.55-3.82 (m, 3H), 3.16 (t, J = 9.7 Hz, 1H), 2.80-2.94 (m, 1H), 1.56-2.79 (m, 11 H), 1.27 (t, J = 6.8 Hz, 3H), 0.95 (s, 9H), 0.56 (s, 3H), 0.09 (s, 6H).

**Dione 591.** To a suspension of 1,3-phenylenediacetic acid (1.94 g, 10.0 mmol) in CH$_2$Cl$_2$ (29 mL) at rt was added DMF (4 drops) and a solution of oxalyl bromide in CH$_2$Cl$_2$ (2.0 M, 11.0 mL, 22.0 mmol) dropwise. The solution was then heated to reflux overnight. The reaction mixture was allowed to cool to rt, then concentrated to give diacyl bromide 590 (3.20 g, quant.) as a red oil that was used without further purification.

To a suspension of AlBr$_3$ (3.33 g, 12.5 mmol) in CH$_2$Cl$_2$ (25 mL) at -78 °C was added a solution of diacyl bromide 591 (1.00 g, 3.13 mmol) in CH$_2$Cl$_2$ (3.1 mL) dropwise via cannula. Ethylene was then bubbled through the solution vigorously for 10 min. The reaction flask was then stoppered and the cooling bath was removed. The reaction
mixture was allowed to warm to rt and stirred overnight. The reaction mixture was 
then cooled to 0 °C and cold water (15 mL) was carefully added to quench the 
reaction. The layers were separated and the aqueous layer was extracted with 
CH₂Cl₂. The combined organic layers were washed with 5% aq. HCl, sat. aq. 
NaHCO₃, brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography 
(50% EtOAc in hexanes) gave dione 591 (165 mg, 25%) white powder. If necessary, 
the product was recrystallized from isopropanol. ¹H NMR (CDCl₃, 400 MHz) δ 2.55 (t, 
J = 6.7 Hz, 4H), 3.05 (t, J = 6.7 Hz, 4H), 3.55 (s, 4H), 6.90 (s, 1H), 7.12 (s, 1H).

Enol triflate 592. To a solution of NaHMDS in THF (1.0 M, 5.50 mL, 5.50 mmol) in 
THF (6 mL) at -78 °C was added a solution of dione 591 (1.07 g, 5.00 mmol) in THF 
(33 mL) dropwise via cannula. The solution was stirred for 1 h at -78 °C, then a 
solution of Comins’ reagent (2.16 g, 5.50 mmol) in THF (11 mL) was added dropwise 
via cannula. The solution was allowed to warm to rt and then quenched with sat. aq. 
NH₄Cl. The layers were separated and the aqueous layer was extracted with Et₂O. 
The combined organic layers were dried (Na₂SO₄) and concentrated. Silica gel 
chromatography (15-25% EtOAc in hexanes) gave enol triflate 592 (930 mg, 41%) 
as a yellow oil and the corresponding dienol triflate S5 (890 mg, 29%) as a white 
solid. Enol triflate 592: ¹H NMR (CDCl₃, 300 MHz) δ 2.54 (t, J = 2.54 Hz, 6.9 Hz, 2H), 
2.69 (t, J = 8.0 Hz, 2H), 2.97-3.12 (m, 4H), 3.54 (s, 2H), 6.45 (s, 1H), 6.86 (s, 1H), 
7.03 (s, 1H). Dienol triflate S5: ¹H NMR (CDCl₃, 300 MHz) δ 2.68 (t, J = 8.1 Hz, 4H), 
3.02 (t, J = 8.5 Hz, 4H), 6.43 (s, 2H), 6.81 (s, 1H), 6.94 (s, 1H).
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VITA

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