DEVELOPMENT OF VERSATILE METHODOLOGY FOR HETERO-AND CARBOCYCLE CONSTRUCTION: APPLICATION IN COMPLEX NATURAL PRODUCT SYNTHESIS

A Thesis in
Chemistry
by
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ABSTRACT

The total synthesis of the cytotoxin lepadiformine is discussed in Part I. The key transformation in this synthesis involves methodology previously developed in the Funk group, namely, a regio- and endo-selective cycloaddition of a 2-amidoacrolein with the dimethyl acetal of 4,6-heptadienal. This Diels-Alder reaction not only established the C(5)-C(10) relative stereochemistry of lepadiformine, but was also strategically functionalized for elaboration to the tricyclic ring system. These steps included a diastereoselective addition of an organoytterbium reagent to an aldehyde, cyclization to the trans-perhydroquinoline substructure via a Mitsonobu reaction, and an iodine-promoted amine cyclization with an alkene to introduce the pyrrolidine ring.

Part II discusses the development of 6-haloalkyl-4H-1,3-dioxins and their utility as haloalkyl vinyl ketone equivalents for the construction of hetero- and carbocyclic ring systems. In particular, 6-bromomethyl-4H-1,3-dioxin has proven to be useful for the preparation of complex bicyclo[4.3.1]decane-3,10-diones. In addition, a novel method for the construction of both aromatic rings of indoles from readily available α-haloenones and α-(trialkylstannylenecarbamates using a 5-step sequence that features facile electrocyclic ring closures of trienecarbamates is described. This method has proven to be most useful for the preparation of indoles possessing complex or difficult substitution patterns. Finally, these two methods have been successfully employed in a stereoselective synthesis of a fully functionalized welwistatin ring system. The key transformation in this synthesis is a sterically encumbered 7-end intramolecular conjugate addition reaction of a β-ketonitrile to deliver the strained bicyclo[4.3.1]decanone ring system present in welwistatin.
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Part I

Cycloaddition Reactions of 2-Amidoacroleins. Application to the Total Synthesis of (±)-Lepadiformine
CHAPTER 1
Total Synthesis of (±)-Lepadiformine via an Amidoacrolein Cycloaddition

I. Introduction

In the mid-1990s, several structurally intriguing and biologically active tricyclic alkaloids were discovered from various marine invertebrates. One of these natural products, lepadiformine, was isolated from the acidic extracts of the marine tunicate Clavelina lepadiformis by Biard and coworkers.\(^1\) The structure was proposed as the rather unusual zwitterionic amino alcohol 1 (Figure 1), based primarily on extensive NMR experiments involving \(^1\)H, \(^{13}\)C, HMQC, HMBC, NOESY, COSY, and \(^{13}\)C INADEQUATE techniques. The absolute stereochemistry of lepadiformine had not been determined by Biard.

Figure 1. The postulated structure of lepadiformine

\[ \text{Figure 1. The postulated structure of lepadiformine} \]

It was shown that lepadiformine exhibits moderate \textit{in vitro} activity against KB (IC\(_{50} = 9.20 \ \mu\text{g/mL}\)), HT29 (IC\(_{50} = 0.75 \ \mu\text{g/mL}\)), P388 (IC\(_{50} = 3.10 \ \mu\text{g/mL}\)), and NSCLC-N6 (IC\(_{50} = 6.10 \ \mu\text{g/mL}\)) cells.\(^1\) A more recent study\(^2\) has found that lepadiformine significantly lengthened the repolarizing phase of action potential (AP) in rat papillary muscle and frog atrium. Moreover, the lengthening of the AP in frog atrium induced by lepadiformine still developed after the delayed outward \(K^+\) current (\(I_k\)) was blocked by tetraethylammonium (10 mM). These
observations led to the conclusion that lepadiformine-induced lengthening of AP duration was not due to decreases of I\textsubscript{K} (outward K\textsuperscript{+} current), but could be attributed to a reduction of the inward rectifying K\textsuperscript{+} current (I\textsubscript{KI}). This suggests that lepadiformine is also very active in the cardiovascular system \textit{in vivo} and indicates that it may have antiarrhythmic properties.\textsuperscript{3}

The putative structure 1 of lepadiformine closely resembles another class of \textit{cis}-perhydroquinoline alkaloid natural products known as the cylindricines\textsuperscript{4,5} (Figure 2). The cylindricines were isolated by Blackman and co-workers\textsuperscript{4} from the marine ascidian \textit{Clavelina cylindrica} around the time that lepadiformine was discovered. The structures of cylindricines A-F were established by a combination of spectroscopic methods as well as X-ray crystallography of their picrate salts. It is also interesting to note that cylindricines A (2) and B (4) exist as a 3:2 equilibrium mixture, likely interconverting through aziridinium ion 3.

\textbf{Figure 2.} Cylindricines A-F

\begin{center}
\begin{tikzpicture}
\node at (0,0) {cylindricine A (2)};
\node at (2,0) {3};
\node at (4,0) {cylindricine B (4)};
\node at (1,-2) {Cl=OH cylindricine C};
\node at (1,-3) {Cl=OMe cylindricine D};
\node at (1,-4) {Cl=OAc cylindricine E};
\node at (1,-5) {Cl=SCN cylindricine F};
\end{tikzpicture}
\end{center}

Through X-ray analysis, it is known that the cylindricines favor the \textit{cis}-perhydroquinoline conformations shown in Figure 2, at least in the solid state. When lepadiformine was isolated Biard and co-workers assigned the conformation as \textit{cis}-perhydroquinoline 5 (Figure 3) based on results observed through extensive NMR analysis. Molecular mechanics calculations (PC Model)
performed by the Weinreb group however, have indicated that conformer 1 (axial hexyl group) is 2.6 kcal/mol lower in energy than the alternate chair 5 (equatorial hexyl group) proposed by Biard.⁶

**Figure 3.** Alternate chair conformers of proposed lepadiformine structure

![Alternate chair conformers of proposed lepadiformine structure](image)

Shortly after the discovery of lepadiformine and the cylindricines, fasicularin (6) was isolated from a marine invertebrate, the ascidian *Nephtes fasicularis* (Figure 4).⁷⁻⁹ The structure was established primarily by NMR spectroscopy and is quite similar to cylindricine B (4) but is epimeric at C(10) making it a *trans-* rather than *cis-*perhydroquinoline. Fasicularin was shown to be cytotoxic to Vero cells (IC₅₀ = 14 µg/mL).⁷ It has also demonstrated selective activity in the yeast strain in which the RAD 52 gene had been deleted, thus rendering the organism incapable of recombination and repair of DNA double

**Figure 4.** Fasicularin

![Fasicularin](image)
strand breaks. More recently, fasicularin was discovered to have DNA-alkylation properties. Gates, Kibayashi, and co-workers found that 5′-32P-labeled DNA duplex undergoes alkylation at the guanine residues in the presence of fasicularin (100 - 800 µM in pH 7 buffer). They proposed that alkylation occurs at N(7) of the guanine residues by means of the aziridinium ion 7 (Scheme 1), which is generated through intramolecular displacement of the thiocyanate with the basic nitrogen present in 6. Direct evidence for the formation of the fasicularin-DNA adduct was found through LC-ESI/MS, which showed a single compound whose mass corresponded to the fasicularin-N(7) guanine adduct 10 (MH⁺ calcd 427.3, found 427.2). Moreover, further MS/MS analysis revealed that

Scheme 1. DNA damage by fasicularin

![Scheme 1](image-url)
collision-induced dissociation of the parent ion produced the neutral loss of guanine ($m/z$ 427 $\rightarrow$ 276) and the fasicularin fragment ($m/z$ 427 $\rightarrow$ 152), similar to the fragmentations seen previously for other N(7)-alkylguanine adducts.$^{9,10}$

II. Structure Elucidation of Lepadiformine by Total Synthesis

The combination of information that had compiled over several years with regards to lepadiformine, the cylindricines, and fasicularin had cast some doubts as to whether the structure assigned by Biard was correct. Several groups became involved in total synthesis endeavors that culminated in reassignment of the structure of lepadiformine.$^{12}$

A. Disproof of the Biard Lepadiformine Structure via Synthesis

Synthetic approaches to the putative structure of lepadiformine 1 will be classified by the order in which the individual rings were introduced leading to the ABC ring system (Figure 5).

Figure 5. The proposed lepadiformine ring system
1. C→CA→CAB approach

In 1996, the Weinreb group became involved in a program directed towards the total synthesis of the proposed structure for lepadiformine 1.\(^{6,13c}\) Initially they had concerns over the validity of the structural assignment, but believed that they could develop methodology that would be general enough for construction of the cylindricines as well. Treatment of hydroxylamine ketal 12 with 3 N HCl produced nitrone intermediate 13 (Scheme 2). Subjection of nitrone 13 to thermolysis (190 °C, DMSO) effected an intramolecular cycloaddition from the face opposite the phenoxy methyl group to afford spirocycle 14 as a single stereoisomer. Cleavage of the N-O bond afforded an intermediate alcohol that,

**Scheme 2. Weinreb's synthesis of 1**
when oxidized, underwent an intramolecular conjugate addition reaction to produce tricyclic 15. Subsequent functional group manipulations finally gave rise to the proposed structure of lepadiformine 1. However, after direct comparison of the $^1$H and $^{13}$C NMR spectra of this material and its hydrochloride salt with the spectra of Biard, it became clear that the two compounds were different. Weinreb also obtained an X-ray structure of the intermediate prior to removal of the phenyl protecting group and found that their stereochemical assignment was indeed correct and corresponded to that proposed by Biard. Moreover, it was established that 1 preferred to adopt the confirmation proposed by Weinreb$^6$, and not that of Biard (see compound 5, Figure 3).

2. A$\rightarrow$AC$\rightarrow$ACB approach

Shortly after Weinreb’s work was published, Kibayashi and coworkers confirmed the structural misassignment with their own synthesis of 1 (Scheme 3)$^{13d}$. They utilized an intramolecular acylnitroso Diels-Alder reaction of intermediate 17 to set the stereochemistry for the desired cis-perhydroquinoline. The bromine presumably acts as a stereocontrol element that favors a reactive conformer possessing an axial tether rather than an equatorial arrangement, which encounters A$^{1,3}$ strain. Conversion of cycloadduct 18 to compound 1 was accomplished in 13 steps.
At the same time that the Weinreb and Kibayashi research was ongoing, Pearson and coworkers published work related to lepadiformine. Their strategy involved construction of the spirocyclic ring system by an intermolecular [3+2] cycloaddition of the 2-azapentadienyl anion 25 with phenyl vinyl sulfide to afford cycloadduct 26 (Scheme 4). While the cycloaddition reaction proceeded with the predicted facial selectivity, opposite the ketal sidechain, it was found to have the incorrect C(10)-C(13) relative stereochemistry. Spirocycle 26 proved useful however, as it was further converted to the remaining three of the four diastereomers that Kibayashi did not synthesize (Scheme 4). None of these compounds had spectral data matching that of the natural alkaloid.
B. Discovery and synthesis of the unequivocal structure of lepadiformine

The synthetic efforts previously described led to speculation that lepadiformine was epimeric at C(10) and possessed a trans-perhydroquinoline substructure like fasicularin (6). This conjecture was first confirmed by Kibayashi and coworkers,\textsuperscript{8a} who reported the total synthesis of the revised structure shown in Figure 6 and discovered that the corresponding hydrochloride salt was identical to the natural product isolated by Biard. This structure was unambiguously determined by X-ray crystallographic analysis, which also showed that the trans-perhydroquinoline substructure prefers to adopt a chair-boat conformation. Molecular mechanics calculations (MMX, PCMODEL) performed in our laboratory place the chair-chair conformer, which possesses an unfavorable 1,3-diaxial interaction at C(2) and C(10), 4.7 kcal/mol higher in energy than the chair-boat conformer shown in Figure 6. More recently, lepadiformine B and lepadiformine C were isolated from \textit{Clavelina moluccensis}.\textsuperscript{10}

Synthetic approaches to the unambiguous structure of lepadiformine 35 will be classified by the order in which the individual rings were introduced leading to the ABC ring system (Figure 6).

\textbf{Figure 6.} The lepadiformine ring system
1. A→AC→ACB approach

Kibayashi and coworkers\textsuperscript{8a} used an approach for the synthesis of lepadiformine (35) that was similar to that described for their synthesis of the misassigned structure 1. Thus, upon generation of acynitroso derivative 38, an intramolecular cycloaddition ensued to afford cycloadduct 39 in preference to the corresponding cis-azadecalin isomer (4.8 : 1 ratio, Scheme 5). This result was rationalized by the endo transition state depicted in structure 38. The alternative endo transition suffers from unfavorable steric interactions with the cyclohexane A ring. Cycloadduct 39 was then transformed to amino alcohol 40 in 8 steps. Finally, Mitsonobu-type cyclization of amino alcohol 40 and removal of the MOM protecting group provided lepadiformine 35. Spectral data of the hydrochloride salt 41 was identical to that of Biard’s natural sample.

Scheme 5. Kibayashi’s total synthesis of lepadiformine
2. C→CA→CAB approach

By far the most common approach to the lepadiformine ring system is; 1) preparation of an appropriate pyrrolidine ring; 2) generation of the spirocyclic C-A ring system; and 3) final elaboration to the trans-perhydroquinoline. Five approaches of this type have been described, and three of them feature N-acyliminium ion intermediates.

Weinreb and coworkers\textsuperscript{14a,b} were able to trap N-acyliminium ion 42 with a tethered allyl silane to give rise to spirocycle 43 as a single diastereomer (Scheme 6). The trans-perhydroquinoline was prepared by acid catalyzed cyclization of amino acetal 46 to afford the unstable tricyclic enamide 47, which was immediately treated with HCl/KCN to furnish amino nitrile 48. Treatment of nitrile 48 with hexylmagnesium bromide in the presence of BF\textsubscript{3}·Et\textsubscript{2}O at -20 °C and subsequent removal of the benzyl group with Na/NH\textsubscript{3} afforded lepadiformine (35) along with a small amount of its C(2) epimer. Weinreb has more recently published the first enantioselective synthesis of (-)-lepadiformine and established the absolute configuration of the natural alkaloid as 2\textit{R}, 5\textit{S}, 10\textit{S}, 13\textit{S}. 
Scheme 6. Weinreb's approach to lepadiformine

\[ \text{Scheme 6. Weinreb's approach to lepadiformine} \]

\[ \text{42} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{57\%} \xrightarrow{\text{57\%}} \text{43} \xrightarrow{\text{1. NaBH}_4, \text{Cu(acac)}_2, \text{95\%}} \text{44} \]

\[ \text{42} \xrightarrow{\text{44}} \text{43} \xrightarrow{\text{2. NaNO}_2, \text{CuCl}, \text{HCl, MeOH, 0 °C - rt, 81\%}} \text{44} \]

\[ \text{47} \xrightarrow{\text{p-TsOH, acetone}} \text{46} \xrightarrow{\text{5 steps}} \text{45} \]

\[ \text{47} \xrightarrow{\text{HCl, MeOH, KCN}} \text{48} \]

\[ \text{48} \xrightarrow{\text{1. HexMgBr, BF}_3\cdot\text{Et}_2\text{O, THF, -20 °C - rt, 67\% 3 steps}} \text{35} \]

\[ \text{48} \xrightarrow{\text{2. Na, NH}_3, \text{THF, -78 °C, 100\%}} \text{35} \]
Kim and coworkers\textsuperscript{14h} have recently published a formal total synthesis of \((\rightarrow)-\)lepadiformine that intersects with the Weinreb intermediate nitrile 48 (Scheme 7). The key transformation in this approach is a stereoselective Claisen rearrangement of cyclic amino acid ester-enolate 50 to afford acid 51. The Claisen rearrangement, like Weinreb’s \(\text{N}^{-}\)-acyliminium ion closure, sets the relative stereochemistry at C(5) and C(10) for eventual construction of the trans-perhydroquinoline. Following an olefin metathesis to close the A-ring, aldehyde 52 was transformed to the Weinreb intermediate 48 via an amine/aldehyde condensation to cyclic enamine 47, followed by treatment with HCl/KCN.

**Scheme 7.** Kim’s formal synthesis of \((\rightarrow)-\)lepadiformine

In addition to their racemic synthesis, Kibayashi and coworkers\textsuperscript{14c,e,f,g} have also recently completed an enantioselective synthesis of \((\rightarrow)-\)lepadiformine. This route employs an aza-Prins cyclization of the iminium ion generated from amidoketone 53 followed by trapping of the resultant carbocation with formic acid to provide spirocycle 55 (Scheme 8). A single stereoisomer was obtained in this
reaction and can be rationalized by attack of the iminium ion through chair-like transition state 54 on the face opposite the benzoyloxymethyl substituent. Spirocycle 55 was then transformed to amino alcohol 56 in 5 steps. Finally, Mitsonobu-type cyclization of amino alcohol 56 and removal of the benzyl protecting group provided lepadiformine 35.

**Scheme 8.** Kibayashi's enantioselective approach to (-)-lepadiformine

Hsung$^{59}$ has utilized an almost identical aza-Prins approach to spirocycle 59 that Kibayashi and coworkers used in their synthesis (Scheme 9). Interestingly, they were able to convert epoxide 60 to allylic alcohol 61 through the seldom used Wharton rearrangement.$^{15}$ Oxidation with MnO$_2$, followed by removal of the BOC with TFA resulted in cyclization to tricyclic compound 62. This compound was not only converted to (-)-lepadiformine, but also could be epimerized to the cis-perhydroquinoline for the preparation of (+)-cylidricines C-E.
Finally, Hunter has disclosed an olefin metathesis approach to generate the spirocyclic lactam 64 (Scheme 10). Addition of 3-(benzyl oxy)propyl magnesium bromide to ketone 64, followed by dehydration, afforded cyclohexene 64. Hydrogenation of the olefin and concomitant removal of the benzyl group provided an alcohol that was cyclized to the lepadiformine ring system 66 through the mesylate. No further progress on conversion of 66 to lepadiformine 35 has been reported.

Scheme 10. Hunter’s approach to lepadiformine
Although several synthetic strategies have been reported for the total synthesis of lepadiformine, all of them proceed via the aza-spirocyclic (AC) ring system, and subsequently elaborate the B ring to complete the ring system. Moreover, several of the approaches have steps yielding undesirable diastereomeric mixtures of products. Therefore, a unique approach to this tricyclic marine alkaloid, such as initial preparation of the trans-perhydroquinoline AB ring system, followed by the pyrrolidine ring is worthy of investigation and may afford better stereochemical control.

III. Total synthesis of (±)-lepadiformine: A→AB→ABC approach

The simplest common substructure embodied in lepadiformine, fasicularin, and the cylindricines is the 1-alkyl-1-aminocyclohexane (Figure 7). The Funk group has recently developed methodology for the general preparation of 1-alkyl-1-aminocyclohexanes via Diels-Alder cycloaddition reactions of 2-amidoacroleins

Figure 7. 1-Alkyl-1-aminocyclohexane substructure in natural products
with dienes. Moreover, this methodology was used to prepare the trans-perhydroquinoline substructure of fasicularin.\textsuperscript{8b} Thus, upon learning that lepadiformine embodied a trans- rather than a cis-perhydroquinoline subunit, it became immediately clear, based upon our fasicularin total synthesis, that a synthetic route to lepadiformine should also be possible.

**A. Cycloaddition reactions of 2-amidoacroleins**

The major transformation in the proposed synthetic route, vida infra, is an intermolecular cycloaddition of a 2-amidoacrolein with a diene. Although several amidoacroleins have been previously synthesized\textsuperscript{16}, their chemistry has remained largely unexplored. Two specific examples are illustrated in Schemes 11 and 12. Hon was able to prepare amidoacrolein \textsuperscript{72} through ozonolysis of \textit{N}-allylbenzylamide \textsuperscript{70} followed by treatment of the resultant ozonide \textsuperscript{71} with diethylamine and dibromomethane (Scheme 11).

![Scheme 11. Hon's synthesis of amidoacroleins](image)

In another example (Scheme 12), Kato\textsuperscript{16b} has shown that Swern oxidation of one alcohol in 2-amidopropanediol \textsuperscript{73}, followed by \textit{in situ} elimination of the remaining alcohol gives rise to amidoacrolein \textsuperscript{74}. The amidoacrolein can then be transformed to the 1,4-diazepine \textsuperscript{75} by treatment with \textit{N},\textit{N}-dimethylethylenediamine and NaBH\textsubscript{4}. 
Scheme 12. Kato’s synthesis of amidoacroleins

\[
\begin{align*}
73 & \xrightarrow{(\text{COCl})_2, \text{DMSO}, \text{Et}_3\text{N} \ 65\%} 74 \xrightarrow{\text{NaBH}_4 \ 58\%} 75
\end{align*}
\]

The Funk group has recently developed a general method for the preparation of 2-amidoacroleins 77 via the thermal or Lewis acid catalyzed retrocycloaddition reactions of 5-amido-1,3-dioxins 76 (Scheme 13). Further studies have shown that 2-amidoacroleins are useful substrates in cycloaddition and electrophilic aromatic substitution reactions. With respect to the former,

Scheme 13. Retrocycloaddition of an amidodioxin

\[
\begin{align*}
76 & \xrightarrow{\Delta \text{ or Lewis acid}} 77
\end{align*}
\]

thermal retrocycloaddition reactions of amidodioxins 78 and 81 smoothly afforded amidoacroleins 79 and 82 (Scheme 14). While amidoacrolein 79 was trapped in situ with 2-trimethylsilyloxy-1,3-butadiene to afford formamide 80, we have also shown that amidoacrolein cycloadditions occur under the influence of high pressure giving products such as sulfonamide 83.
Scheme 14. 2-Amidoacroleins as dienophiles in Diels-Alder reactions

This methodology was exploited in the total synthesis of two natural products, namely, fasicularin\textsuperscript{8b} and FR901483.\textsuperscript{18} The cycloaddition reaction performed by Funk and Maeng\textsuperscript{8b} in the total synthesis of fasicularin is perhaps the most important precedent for our synthetic route to lepadiformine (Scheme 15). They found that subjection of amidoacrolein \textsuperscript{85} and diene \textsuperscript{84} to 12 kbar of pressure resulted in a regio- and endo-selective cycloaddition to give rise to a single stereoisomer of the 1-alkyl-1-aminocyclohexane \textsuperscript{86}. The endo selectivity can be rationalized by putative secondary orbital overlap of the aldehyde moiety of amidoacrolein \textsuperscript{85} with diene \textsuperscript{84}. One can see that cycloadduct \textsuperscript{86} possesses the necessary stereochemistry at C(5) and C(10) for subsequent transformation to the trans-perhydroquinoline ring system. This was accomplished by reduction of the aldehyde moiety with LiAlH\textsubscript{4} and concomitant removal of the trifluoromethanesulfonyl group, followed by simultaneous reduction of the cyclohexene double bond and hydrogenolysis of the \textit{N}-benzyl substituent to afford amino alcohol \textsuperscript{87}. Subjection of amino alcohol \textsuperscript{87} to hydrolysis conditions
afforded the intermediate oxazolidine 88, which was stereoselectively reduced with NaBH₄ to furnish the trans-perhydroquinoline 89. Compound 89 was subsequently transformed to fasicularin in 9 steps. This result gave us a good deal of confidence that our proposed cycloaddition (vida infra) to generate the 1-alkyl-1-aminocyclohexane embodied in lepadiformine would be successful.

Scheme 15. Total synthesis of fasicularin via an amidoacrolein cycloaddition
With respect to FR901483, it was found that amidodioxin 92 undergoes a retrocycloaddition reaction in warm benzonitrile, generating the amidoacrolein, which was trapped in situ by silyloxydiene 93 to give the desired 1-alkyl-1-aminocyclohexane 94 (Scheme 16). It should be noted that the intermolecular cycloaddition not only installed the central 1-alkyl-1-aminocyclohexane substructure of FR901483 but also both of the electrophilic and nucleophilic components, appropriately tuned, for the subsequent sequential aldol cyclizations to afford tricycle 96.

**Scheme 16.** Total synthesis of FR901483 via an amidoacrolein cycloaddition
B. Retrosynthetic analysis of lepadiformine

Our retrosynthetic plan for the total synthesis of lepadiformine is outlined in Scheme 17. We envisaged the pyrrolidine ring of lepadiformine 35 to arise from a stereoselective electrophile-promoted cyclization\(^{19}\) of the amine 98 with the angular butenyl substituent. Iodine is a common electrophile used in cyclizations of this type.\(^{19}\) Guo-qiang and coworkers\(^{19e}\) have used iodine and NaHCO\(_3\) to effect stereoselective cyclization of the secondary benzylamine with

**Scheme 17. Retrosynthetic analysis of lepadiformine**
the proximal vinyl substituent to give iodide 108 (Scheme 18). Interestingly, treatment of iodide 108 with 4 M NaOH and catalytic tetrabutylammonium iodide delivered alcohol 110 along with a small amount of the hydroxypiperidine 111. This reaction presumably proceeds through attack of hydroxide ion on the corresponding aziridinium intermediate 109. The regioselectivity shown in this example served as a precedent for a similar outcome for the construction of the pyrrolidine ring of lepadiformine.

Scheme 18. Iodine-promoted electrophilic cyclization of an amine

We believed that the hexyl substituent of sulfonamide 99 could be introduced by a stereoelectronically controlled addition of an organometallic reagent to the N-tosyliminium ion 100 (Scheme 17). This type of transformation is well preceded in the literature. Stevens has published a stereochemical rationale for addition of nucleophiles to tetrahydropyridinium salts (Scheme 19). In this example, there are two possible iminium ion conformers, 112 and 113, which can undergo nucleophilic addition. Thus, there are four possible transition
states wherein maximum orbital overlap is maintained between the approaching nucleophile and the developing lone pair on the nitrogen, resulting in products where the newly formed sp\(^3\) orbitals are anti-periplanar. Two of these, 114, and 117, initially result in products bearing a boat conformation and are kinetically disfavored. The remaining two possibilities form the more stable chair adducts 115 and 116, however 116 suffers from an unfavorable 1,3-diaxial interaction of the approaching nucleophile with the R group on the piperidine ring. Therefore the observed product is piperidine 115.

Scheme 19. Nucleophilic addition to tetrahydropyridinium salts

Stevens used this stereoelectronic principle in an elegant synthesis of coccinelline 124 (Scheme 20).\(^{21a}\) Amino dialdehyde dimethyl acetal 118 reacted with acetonedicarboxylic acid methyl ester 120 under acidic conditions to afford tricycle 123 as a single diastereomer. This unique transformation involves two
separate nucleophilic additions to iminium ions, both following the principles outlined above.

Scheme 20. Stevens’ approach to coccinelline

Next, in our retrosynthetic analysis, we believed that allylmagnesium bromide would be a sufficient nucleophile for the ring opening of activated aziridine 102 and allow for introduction of the required butenyl sidechain (Scheme 17). Aziridine 102 could, in turn, be available by Mitsonobu ring closure of the debenzylated derivative of tosylamide 103. Finally, the key transformation in this synthesis involves methodology previously developed in the Funk group, namely, a regio- and endo-selective cycloaddition of the amidoacrolein 105 with the diene 106. This Diels-Alder reaction will not only establish the C(5)-C(10) relative stereochemistry, but also will be appropriately functionalized for eventual closure to the trans-perhydroquinoline. In principle, an asymmetric Diels-Alder reaction using a chiral Lewis acid could provide the 1-alkyl-1-aminocyclohexane as a
single enantiomer. This product could then be transformed to the natural enantiomer of lepadiformine.

C. Total synthesis of (±)-lepadiformine

The total synthesis of lepadiformine began with preparation of diene 106 and 2-amidoacrolein 105, the substrates for the requisite cycloaddition reaction. To that end, deprotonation of ethyl sorbate (125) with LDA at -78 °C, followed by a kinetic quench with acetic acid afforded the deconjugated ester 126 in good yield (Scheme 21). The ester was then transformed to nitrile 128 through reduction with LiAlH₄, conversion of the resultant alcohol 127 to the iodide (PPh₃, I₂, imidazole), and subsequent displacement with NaCN. Finally, treatment of nitrile 128 with DIBALH provided the intermediate aldehyde 129, which was then protected as its dimethyl acetal using trimethyl orthoformate and Amberlyst-15 ion-exchange resin giving the desired diene 106.

Scheme 21. Preparation of diene 106

\[
\begin{align*}
\text{125} &\xrightarrow{\text{LDA, HMPA, THF, -78 °C, HOAc, 84%}} \text{126} \\
\text{126} &\xrightarrow{\text{LiAlH}_4, \text{ether, 0 °C, 95%}} \text{127} \\
\text{127} &\xrightarrow{\text{1. I}_2, \text{PPh}_3, \text{Imidazole, 70%}} \text{128} \\
\text{128} &\xrightarrow{\text{2. NaCN, DMSO, 82%}} \text{129} \\
\text{129} &\xrightarrow{\text{DIBALH, CH}_2\text{Cl}_2, -78 °C, 88%}} \text{106}
\end{align*}
\]
The preparation of amidoacrolein 105 is outlined in Scheme 22. Thus, condensation of 2,2-dimethyl-1,3-dioxin-5-one (130) with benzylamine, followed by sulfonylation of the resulting imine with tosyl chloride furnished the desired 5-amido-1,3-dioxin 131. Retrocycloaddition of dioxin 131 in refluxing toluene gave amidoacrolein 105 in nearly quantitative yield.

**Scheme 22. Preparation of amidoacrolein 105**

We were pleased to find that subjection of amidoacrolein 105 to diene 106 under the influence of high pressure conditions (12 kbar) gave exclusively the endo cycloadduct 104 (Scheme 23). Like the cycloaddition performed by Funk in the total synthesis of fasicularin, putative secondary orbital overlap of the aldehyde functionality in amidoacrolein 105 with the diene 106 could be an explanation for the observed endo selectivity. In addition, the exo transition state would be destabilized by steric interactions of the N-benzyl functionality with the diene. In contrast to other examples of 2-amidoacrolein Diels-Alder cycloadditions performed in our laboratories (Schemes 14 and 16), the cycloaddition of 2-tosylamidoacrolein 105 could not be accomplished under thermal conditions as a result of competing polymerization of the dienophile. In addition, the acid sensitivity of the acetal functionality of diene 106 precluded the use of Lewis acid catalysts.
Scheme 23. Intermolecular amidoacrolein cycloaddition

Reduction of the aldehyde functionality in cycloadduct 104 with NaBH₄, and subsequent hydrogenation of both the N-benzyl and alkene moieties (Pearlman’s catalyst, H₂) afforded alcohol 132 (Scheme 24). By taking advantage of the acidity of the tosylamide functionality, alcohol 132 was found to undergo a Mitsonobu type ring closure to aziridine 102 upon treatment with

Scheme 24. Introduction of the butenyl sidechain
PPh₃/Liylimidazole. Aziridine 102 proved to be a useful intermediate for the introduction of the allyl side chain, the crucial segment needed for the eventual closure to the pyrroloquinoline. Accordingly, addition of allylmagnesium bromide to aziridine 102 effected nucleophilic ring opening without problem to afford acetal 101.

Our initial strategy for introducing the hexyl substituent required Lewis acid-promoted generation of N-tosyliminium ion 100 from acetal 101 (Scheme 25), followed by stereoselective interception with a hexyl derived nucleophile (HexLi, HexMgBr, Hex₂CuLi). Unfortunately, all attempts to generate and trap the iminium ion were unsuccessful and in most cases led to the formation of the cyclic enamide 133 (Scheme 25).

**Scheme 25.** Reaction of acetal 101 with a Lewis acid and organometallic reagent

<table>
<thead>
<tr>
<th>Attempted Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BF₃·OEt₂, HexLi, ether, -78 °C</td>
</tr>
<tr>
<td>2. BF₃·OEt₂, HexLi, THF, -78 °C</td>
</tr>
<tr>
<td>3. BF₃·OEt₂, HexMgBr, ether, -78 °C</td>
</tr>
<tr>
<td>4. BF₃·OEt₂, HexMgBr, THF, -78 °C</td>
</tr>
<tr>
<td>5. BF₃·OEt₂, HexMgBr, ether, -50 °C</td>
</tr>
<tr>
<td>6. BF₃·OEt₂, HexCu₂Li, THF, -50 °C</td>
</tr>
<tr>
<td>7. BF₃·OEt₂, HexCu₂Li, ether, -50 °C</td>
</tr>
<tr>
<td>8. Me₂AlCl, HexLi, ether, -78 °C</td>
</tr>
<tr>
<td>9. Me₂AlCl, HexLi, THF, -78 °C</td>
</tr>
<tr>
<td>10. Me₂AlCl, HexMgBr, ether, -78 °C</td>
</tr>
<tr>
<td>11. Me₂AlCl, HexMgBr, THF, -78 °C</td>
</tr>
<tr>
<td>12. ZnCl₂, HexMgBr, THF, 0 °C - rt</td>
</tr>
</tbody>
</table>
We then attempted to introduce the hexyl substituent by subjecting α-methoxytosylamide 134 to a Lewis acid in the presence of a hexyl Grignard or cuprate reagent (Scheme 26). However, all attempts to prepare α-methoxytosylamide 134 using a variety of acid catalysts were unsuccessful, and once again most conditions yielded cyclic enamide 133. For example, treatment of acetal 101 with one equivalent of BF$_3$·OEt$_2$ in ether at 0 °C provided the enamide in high yield.

**Scheme 26.** Conditions attempted for closure to 134

<table>
<thead>
<tr>
<th>Attempted Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. cat. BF$_3$·OEt$_2$, CH$_3$CN, 0 °C</td>
</tr>
<tr>
<td>2. cat. Yb(OTf)$_3$, CH$_3$CN, rt</td>
</tr>
<tr>
<td>3. cat. CSA, mol. sieves, toluene, 50 °C</td>
</tr>
<tr>
<td>4. cat. p-TsOH, toluene, rt</td>
</tr>
<tr>
<td>5. ZnCl$_2$, CH$_2$Cl$_2$, 0 °C</td>
</tr>
<tr>
<td>6. TFA, CH$_2$Cl$_2$, -78 °C</td>
</tr>
<tr>
<td>7. BF$_3$·OEt$_2$, MeOH, 0 °C</td>
</tr>
<tr>
<td>8. PPTS, MeOH, 0 °C</td>
</tr>
</tbody>
</table>
We were also able to hydrolyze the acetal 101 and obtained aldehyde 135 (Scheme 27). It should be noted that aldehyde 135 showed no tendency to exist as the corresponding cyclic \( \alpha \)-hydroxytosylamide in a variety of solvents.

**Scheme 27. Preparation of aldehyde 135**

\[ \begin{align*}
101 & \xrightarrow{1 \text{ M HCl}} 135 \\
& \quad \text{THF, 2 h, 98%}
\end{align*} \]

\( ^1 \text{H NMR} \)

We next turned our attention to generating the desired \( N \)-tosyliminium ion 100 by protonation of enamide 133 and intercepting it with an allyl silane.\(^{25-27}\) Indeed, we were pleased to find that treatment of enamide 133 with 4 equiv of trifluoroacetic acid and 6 equiv of allyltrimethylsilane in methylene chloride at \(-20^\circ\text{C}\) gave a single product which we tentatively assigned as tosylamide 139 on the basis of the aforementioned stereoelectronic considerations (Scheme 29).\(^{21}\) With

\[ \begin{align*}
136 & \xrightarrow{\text{DIBAL, CH}_2\text{Cl}_2, -78^\circ\text{C}} 137 \\
& \quad \text{87%}
\end{align*} \]

\[ \begin{align*}
137 & \xrightarrow{\text{PPTS, HC(O\text{Me})}_3, \text{MeOH}} 138 \\
& \quad \text{98%}
\end{align*} \]
this result in hand, we next attempted to employ (3-hexenyl)trimethylsilane (140)\textsuperscript{28} in this transformation. Unfortunately, all attempts using a variety of proton sources (TFA, HOAc, HCO\textsubscript{2}H), gave only recovered enamide 133.

**Scheme 29.** Interception of tosyliminium ion 100 with allyl silanes

We suspected that allylsilane 140 was undergoing competitive protodesilylation that may have been faster than that of allyltrimethylsilane. A \textsuperscript{1}H NMR experiment using 1 equiv of allyltrimethylsilane, 1 equiv of 140, and 1 equiv of TFA supported this conjecture. TFA was added to a mixture of the two allylsilanes in CDCl\textsubscript{3} at room temperature and the progress of protodesilylation was followed by \textsuperscript{1}H NMR. After 17 minutes virtually all of silane 140 disappeared by NMR and resonances for the resulting 2-hexene were observed.

We then examined an alternative approach to the *trans*-perhydroquinoline ring system that involved stereoselective introduction of the hexyl group prior to ring closure (135→142). We surveyed a variety of conditions for the stereoselective nucleophilic addition of an organometallic reagent to aldehyde 135 (Scheme 30).\textsuperscript{29} Initial experiments were not encouraging. For example,
Scheme 30. Nucleophilic addition to aldehyde 135

<table>
<thead>
<tr>
<th>conditions</th>
<th>ratio of 142 : 143</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 equiv. HexMgBr, ether, -78 °C</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>5 equiv. HexMgBr, THF, -78 °C</td>
<td>1.1 : 1</td>
</tr>
<tr>
<td>5 equiv. HexLi, THF, -78 °C</td>
<td>1 : 1</td>
</tr>
<tr>
<td>5 equiv. HexMgBr, toluene, -78 °C</td>
<td>1 : 1</td>
</tr>
<tr>
<td>5 equiv. Hex₂CuLi, ether, -78 °C</td>
<td>1 : 2.7</td>
</tr>
<tr>
<td>5 equiv. HexMgBr, 10 equiv THF, ether, -78 °C</td>
<td>4.1 : 1</td>
</tr>
<tr>
<td>3 equiv. HexLi, 3 equiv Yb(OTf)₃, THF, -78 °C</td>
<td>3.4 : 1</td>
</tr>
<tr>
<td>3 equiv. HexMgBr, 3 equiv Yb(OTf)₃, THF, -78 °C</td>
<td>10.9 : 1</td>
</tr>
</tbody>
</table>

treatment of aldehyde 135 with hexylmagnesium bromide (5 equiv, -78 °C) in THF gave alcohols 142 and 143 as an inseparable 1.1 : 1 mixture. Changing the solvent to ether resulted in an increase in selectivity to 2.5 : 1, favoring what we believed to be alcohol 142 (vide infra). Interestingly, addition of 10 equiv of THF to the ether reaction effected an even better ratio at 4.1 : 1. At this point we had no data to unequivocally assign the stereochemistry to either isomer, however, we did believe that chelation between the aldehyde, a metal, and the deprotonated N-tosylamide was possible (Scheme 31). If a bidentate metal were to orient itself in a manner depicted in structure 144, this could allow for
Scheme 31. Chelation controlled addition to aldehyde 135

nucleophilic attack on the aldehyde from the desired face, thus producing alcohol 142. This rationale could help explain why we have seen lower ratios when using lithium nucleophiles in place of magnesium. With this in mind, it was finally determined that the Molander protocol\textsuperscript{39} using an organoytterbium reagent (3 equiv HexMgBr, 3 equiv Yb(OTf)\textsubscript{3}) gave the best selectivity (10.9 : 1). An inferior ratio of 3.4 : 1 was obtained if hexyllithium was used to prepare the organoytterbium reagent. The superiority of the organoytterbium reagent may be a consequence of its greater steric bulk as well as attenuated reactivity with a magnesium chelated aldehyde (see structure 144). Indeed, the starting aldehyde 135 was observed to slowly disappear (TLC) using the Molander reagent, whereas it instantaneously disappeared with the Grignard reagent alone.

The tentative stereochemical assignment for alcohol 142 was confirmed by transforming it in a short three step sequence to lepadiformine. Thus, cyclization of the diastereomeric mixture of tosylamides 142 and 143 (Scheme 32) was effected under Mitsunobu conditions (PPh\textsubscript{3}, DEAD) to afford the trans-perhydroquinoline 99 (and its separable C(2) epimer in 78% and 5% isolated yields, respectively). The tosyl group could easily be removed under standard conditions (Na/NH\textsubscript{3}) to provide amine 98.
Finally, upon treatment with iodine in ether\textsuperscript{19f} (-40 °C – rt, 1 h), amine 98 underwent an iodocyclization reaction to give (iodomethyl)pyrrolidinium salt 145 (Scheme 33) that was immediately subjected to a solution of THF and aqueous NaOH\textsuperscript{19e} to furnish racemic lepadiformine (35) in good yield. This transformation presumably proceeds through regioselective attack of hydroxide on aziridinium ion intermediate 146.\textsuperscript{19e} We could not detect any product derived from ring opening at the more substituted site (cf. cylindricines A and B). The stereochemistry observed is likely a result of iodonium ion formation of the vinyl group oriented as depicted in structure 98. The alternative conformation 147 results in an unfavorable steric interaction between the vinyl group and the \textit{trans}-perhydroquinoline ring system. The spectral properties of the free amine 35 were identical to those reported by Kibayashi\textsuperscript{8a} and the spectra of the hydrochloride salt 41 were indistinguishable from those of Biard’s authentic material.\textsuperscript{1}
**Scheme 33.** Completion of (±)-lepadiformine

In conclusion, we have completed a total synthesis of the cytotoxin (±)-lepadiformine in 16 steps and 13% overall yield from ethyl sorbate. Moreover, we have further demonstrated that 2-amidoacroleins are useful substrates in Diels-Alder cycloaddition reactions, and can provide easy access to the 1-alkyl-1-aminocyclohexane substructure embodied in a number of tricyclic alkaloid natural products.
Part II

Development of Versatile Methodology for Hetero- and Carbocycle Construction:
Application Towards the Total Synthesis of Welwistatin
CHAPTER 2
Welwistatin

I. Introduction

Marine organisms, particularly cyanobacteria, have become abundant sources of biologically active natural products possessing complex and diverse ring systems. In 1994, Moore and coworkers isolated an intriguing tetracyclic indole alkaloid, welwitindolinone C isothiocyanate (welwistatin), from the lipophilic extracts of the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricate* (Figure 8). The most notable of its structural features is the strained and densely functionalized bicyclo[4.3.1]decanone, that includes vicinal quaternary centers, a gem-dimethyl substituent, and the sensitive bridgehead isothiocyanate and vinyl chloride functionalities.

![Welwistatin Structure](Figure 8)

*welwistatin*

*(welwitindolinone C isothiocyanate)*

In addition to welwistatin (149), a number of other structurally related alkaloids were also isolated (Figure 9), including welwistatin’s *N*-methyl congener 150, *N*-methylwelwitindolinone C isonitrile (151), and isothiocyanates 152 and 153 which possess a C(13) alkyl chloride rather than the vinyl chloride
substituent present in welwistatin. This family of alkaloids became known as the welwitindolinones. More recently, the C(3) oxidized welwitindolinones 154 – 156 were also isolated from the cyanobacteria *Fischerella muscicola.* Importantly, the structural assignment of this family of compounds was confirmed by X-ray crystallographic analysis of the most abundant alkaloid isolated, *N*-methylwelwitindolinone C isothiocyanate (150).

**Figure 9.** Additional naturally occurring welwitindolinones

In addition to the aforementioned welwitindolinones, a number of other structurally related natural products were isolated from the same extracts. The most intriguing of these alkaloids include welwitindolinone A, fischerindole G, and hapalindole E (Figure 10). The structural similarities of these compounds

**Figure 10.** Additional natural products related to welwistatin
in relation to the bridged bicyclic welwitindolinones has led Moore and coworkers to propose that they are all, in some way, biogenetically related. The proposed biosynthetic pathway of welwistatin is outlined in Scheme 34.\textsuperscript{33a} It is believed that isonitrile 160, derived from L-tryptophan,\textsuperscript{36} and polyene 161, derived from geranyl pyrophosphate, undergo a chloronium ion-induced condensation reaction to afford hapalindole E (159), a common precursor to the fischerindoles as well.\textsuperscript{34}

**Scheme 34.** Moore's proposed biosynthesis of welwistatin

Oxidation of indole 159 would give indolinone intermediate 162 (not isolated), and a subsequent acid-catalyzed cyclization might afford welwitindolinone A (157). The bridged bicyclic welwitindolinones, including welwistatin, could then arise from welwitindolinone A (157) through stereoselective epoxidation of the hindered tetrasubstituted double bond, followed by cyclization at C(4). The origin of the isothiocyanate is less clear, but possibly could arise directly from inorganic
thiocyanate or indirectly by introduction of sulfur into an intermediate organic isonitrile.

Arguing that the unusual cationic cyclization of 162 to welwitindolinone A (157), hypothesized by Moore, seems unlikely due to thermodynamic considerations, Baran\textsuperscript{37} has recently proposed a more likely alternative biosynthetic route to the welwitindolinones proceeding through fischerindole G and fischerindole I (Scheme 35). Thus, acid catalyzed cyclization of hapalindole E (159) would afford fischerindole G (158), which could get easily get oxidized to fischerindole I (164). Welwitindolinone A (157) could then arise through an oxidative ring contraction of fischerindole I.

\textbf{Scheme 35.} Baran's proposed biosynthesis of welwistatin
The welwitindolinones have been found to possess potent biological activity. It was originally believed that welwistatin reversed P-glycoprotein mediated multiple drug-resistance (MDR). A study found that welwistatin attenuated the resistance of MCF-7/AdR cells to anticancer drugs, vinblastine, taxol, and colchicine (Figure 11). These three compounds are well known anti-microtubule agents that inhibit the dynamic equilibrium of microtubule assembly and disassembly in cells. Since microtubules play such a vital role in the dynamic process of mitotic spindle formation and chromosome motion during cell division, these compounds can arrest the cell cycle in the mitotic phase, thus rendering it inoperable. Unfortunately, most anti-microtubule agents, including vinblastine, taxol, and colchicine, are excellent substrates for the drug-efflux pump P-glycoprotein, which is thought to be a significant factor in both intrinsic

---

**Figure 11.** Selected anti-microtubule agents

- **taxol** (165)
- **colchicine** (166)
- **epothilone A** (167, R = H)
- **epothilone B** (168, R = Me)
- **vinblastine** (169)
and acquired drug resistance for cancer cells. One approach to overcome the problem of drug resistance is to combine P-glycoprotein antagonists with the anti-microtubule agent in an effort to inhibit its function. Welwistatin was originally believed to act as this sort of antagonist.

An alternative approach to overcoming P-glycoprotein mediated MDR is to find an anti-microtubule drug that not only potently induces microtubule depolymerization, but is also equally toxic to P-glycoprotein-overexpressing cells. The epothilones A and B (Figure 11), have been found to be competitive inhibitors of the taxol binding site, with similar IC$_{50}$ values, and have also been shown to retain much greater toxicity against P-glycoprotein-overexpressing cells. These intrinsic properties have lead to the design of several epothilone analogues, which are currently in phase I and phase II clinical trials as antitumor agents. A recent study by Smith and coworkers has found that welwistatin may also possess these same characteristics. Smith has shown that welwistatin is, in fact, a cytotoxin and inhibits the proliferation of SK-OV-3 human ovarian carcinoma cells (IC$_{50}$ = 72 nM) and A-10 vascular smooth muscle cells (IC$_{50}$ = 900 nM) and, more importantly, is equally cytotoxic toward P-glycoprotein-overexpressing MCF-7/AdR cells (IC$_{50}$ = 130 nM) in the G2 mitotic phase. Moreover, immunofluorescence studies of tubulin organization revealed that welwistatin causes dose-dependent disruption of microtubules in intact cells. Additional experimentation found that the taxol and colchicine microtubule domains were not affected in welwistatin-treated cells, suggesting that it does not bind to either the taxol or colchicine sites. These results are in contrast to the original findings that welwistatin could be used in conjunction with anti-microtubule agents, such as taxol, vinblastine, and colchicine to fight P-glycoprotein mediated MDR, and further suggest that welwistatin is actually a new anti-microtubule agent itself that may be useful for the treatment of drug resistant tumors.
II. Previous synthetic approaches to the welwitindolinones

Due to its inherent biological activity, as well as its unprecedented ring system, welwistatin has become an attractive target for synthetic chemists. There are currently several approaches to the total synthesis of welwistatin published in the literature, but no successful syntheses have been reported to date. The synthetic approaches described below are classified by the order of ring formation in the proposed route. The numbering and lettering of the carbons and rings of welwistatin shown in Figure 12 will be used throughout the following discussion.

Figure 12. Labeling of the welwistatin ring system

A. AB→ABD→ABDC approach

Baran recently published the first biosynthetically-patterned approach to welwistatin that culminated in the first total synthesis of (+)-welwitindolinone A, the proposed biosynthetic precursor to welwistatin (Scheme 36). As previously discussed, Baran speculated that welwitindolinone A actually arises biogenetically from fischerindole I (164), and not intermediate 162 (Scheme 34) proposed by Moore. Thus, using an indole coupling protocol recently developed in their lab, the lithium enolate of chloroketone 170 (prepared from S-carvone
oxide) was coupled at the 3-position of indole using copper(II) 2-ethylhexanoate giving rise to ketone 171 as a single diasteromer. It should be noted that compound 171 is very similar in structure to that of hapalindole E, a compound in the proposed biosynthesis of welwistatin. Thermolysis of indole 171 in the presence of Montmorillonite K-10 acidic clay effected Friedel-Crafts cyclization to the desired tetracycle, which further underwent stereoselective reductive amination and formylation to give formamide 172. It was fortuitously found that treatment of indole 172 with t-BuOCl, followed by stirring with silica gel in Et₃N and then addition of Burgess reagent provided(-)-fischerindole I (164). The presumed pathway of this multistep reaction is through chlorinated indolenine intermediate 173, which then eliminates HCl and undergoes tautomerization to

Scheme 36. Baran's biosynthetic approach
regenerate the indole. Addition of the Burgess reagent then effects dehydration of the formamide to the isonitrile. Finally, stereoselective chlorination at the 3-position of indole 164 with t-BuOCl at -30 °C followed by addition of TFA effected the key oxidative ring contraction to afford welwitindolinone A (157). No further progress has been reported on epoxidation of the tetrasubstituted double bond of oxindole 157 in order to complete the biomimetic approach to the welwistatin ring system.

Rawal has reported the construction of a model welwitindolinone ring system (Scheme 37).44h The key step involves a palladium catalyzed intramolecular enolate arylation reaction of 4-bromoindole 174 to close the C(4)-C(11) bond of the ring system affording tetracyclic indole 175. Rawal has further shown that the bridgehead nitrogen present in welwistatin can be installed through a Curtius rearrangement to provide isocyanate 176.

**Scheme 37.** Rawal’s palladium catalyzed enolate arylation approach
In another approach, Simpkins\textsuperscript{44i} used a Pd-catalyzed enolate arylation similar to that of Rawal's to introduce the ABD ring system, for example, the coupling of the enolate of cyclohexanone with bromide 177 (Scheme 38). Following a Vilsmeier-Hack formylation, aldehyde 179 was treated with $p$-TsOH in THF to effect an aldol-type ring closure giving rise to a mix of bridged bicyclic indoles 181 and 182. This reaction constitutes the first C(15)-C(16) bond closure enroute to the welwitindolinone ring system.

**Scheme 38.** Simpkins' approach

\[
\begin{align*}
\text{Br} & \quad + \quad \begin{array}{c}
\text{CHO} \\
\text{N} \\
\text{O}
\end{array} & \quad \text{Pd(OAc)}_2 & \quad \text{biphenyl-PCy}_2 & \quad \text{K}_3\text{PO}_4 \\
\text{177} & \quad \text{178} & \quad \text{179} & \quad \text{POCl}_3, \text{DMF}; \quad \text{KOH} & \quad 75\% \\
& & & & \\
\text{OH} & \quad \text{H} & \quad \text{H} & \quad \text{O} & \quad 60\% \\
\text{182} & \quad \text{181} & \quad \text{180} & \quad 1:1 & \\
& & & & \\
\text{p-TsOH} & \quad \text{THF} & \quad \text{50 }^\circ\text{C, 24 h}
\end{align*}
\]
Konopelski\textsuperscript{44a,d} had previously reported a conceptually similar approach to that of Simpkins, although he has apparently not been able to execute the C(15)-C(16) bond closure step with a more functionalized ketone. Thus, a stereoselective aryllead(IV) insertion reaction of indole 183 with β-ketoester 184 gave rise to tricycle 185 in 98% yield (Scheme 39). However, all attempts to formylate the indole for eventual closure via the C(15)-C(16) bond were unsuccessful, and instead gave the vinyl chloride 186.

**Scheme 39.** Konopelski's aryllead(IV) insertion approach

\[ \begin{align*}
\text{Pb(OAc)}_3 & \quad \text{TBDMSO} \\
\text{Indole} & \quad \text{MeO}_2\text{C} \\
\text{BoC} & \quad \text{MeO}_2\text{C} \\
\text{Pyridine, CHCl}_3 & \quad 40^\circ\text{C} \\
\text{40\%} & \quad 98\% \\
\text{POCl}_3 & \quad \text{DMF} \\
\text{78\%} & \quad \text{CHO} \\
\text{183} & \quad \text{184} \\
\text{185} & \quad \text{186}
\end{align*} \]

**B. AB→ABC→ABCD approach**

Wood and coworkers\textsuperscript{44b} were the first to prepare the complete carbon skeleton of welwistatin using an aryl C-H insertion reaction to prepare the ABC ring system followed by an olefin metathesis to close the D ring (Scheme 40). Treatment of diazoketone 187 with Rh\textsubscript{2}(TFA)\textsubscript{4} effected C-H insertion at the 4-position of the indole to afford cyclopropylketone 188. Further oxidation to the diketone and regioselective diazotization gave 189, which underwent a rhodium carbenoid cyclopropane ring expansion in the presence of allyl alcohol to furnish enone 190. The ring system was completed by an olefin metathesis reaction of diene 191 that afforded tetracycle 192 in 15 total steps.
Scheme 40. Wood's aryl C-H insertion approach

Jung has also attempted a rhodium catalyzed insertion reaction, albeit more direct than Woods approach, to close the ABC ring at the C(4)-C(11) bond (Scheme 41). However treatment of \( \alpha \)-diazo-\( \beta \)-ketoester 193 with \( \text{Rh}_2(\text{OAc})_4 \) afforded a mixture of products, consisting mostly of the C(2) insertion adduct 194.

Scheme 41. Jung's rhodium insertion approach
C. AD→ADB→ADBC approach

In addition to their rhodium insertion approach (Scheme 40), Wood and coworkers have recently reported a total synthesis of welwitindolinone A\textsuperscript{44g,45}, and will likely attempt a biomimetic-type closure to form welwistatin. They found that treatment of alkene 195 with NaOCl and CeCl\textsubscript{3} effected a stereoselective semi-pinacol rearrangement to give chloroketone 196 as a single diastereomer (Scheme 42). It is believed that the stereochemical control is a result of chloronium ion formation from the seemingly more hindered concave face directed by the bulky silyloxy substituent, followed by methyl migration \textit{anti} to the chloronium ion. After a number of functional group transformations, it was found that cyclobutene 197 could undergo a base induced intramolecular cyclization

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme42.png}
\end{scheme}

\textbf{Scheme 42.} Wood’s approach to welwistatin/welwitindolinone A
onto the aryl isocyanate to afford welwitindolinone A. This constitutes a unique, albeit lengthy (25 steps), approach to the synthesis of the welwitindolinones.

Although several synthetic strategies have been reported for the construction of the welwitindolinone ring system, all of them have in common the elaboration of the complete ring system from an appropriately substituted indole or oxindole (AB rings). In addition, many utilize similar transformations for the construction of key bonds. Therefore, it may prove to be advantageous to envisage alternative syntheses that involve conceptually distinct ring construction strategies.

D. A novel approach to the welwistatin ring system: D→DC→DCA→DCAB

A retrosynthetic plan for the total synthesis of welwistatin that begins with the six-membered D ring is outlined in Scheme 43. Our conceptually distinct strategy addresses the construction of the strained bridged bicyclic substructure at an early stage through formation of the C(4)-C(11) bond (D → DC), and subsequently elaborates the indole/oxindole ring system through successive C(4)-C(5) and C(2)-C(3) bond formations (DC → DCA → DCAB).
Scheme 43. Retrosynthetic analysis of welwistatin

welwistatin 149

198

199

202

201

200

203

204

205

208

207

206
Thus, it seems likely that the natural product could be obtained from indole 198 through introduction of the vinyl chloride, bridgehead isothiocyanate, and oxindole functionalities from the respective vinyl triflate,47 bridgehead ester, and indole44d,e moieties (Scheme 43). Indole 198 in turn could be prepared from acetic acid derivative 199 by taking advantage of a reaction noted by Răileanu and coworkers,48 in which they converted the analogous benzaldehyde derivative 209 to \(N\)-acetylindole 210 by treatment with sodium acetate in refluxing acetic anhydride (Scheme 44). The C(13) silyloxy substituent would also need to be transformed to the vinyl triflate, through the corresponding ketone.

**Scheme 44.** Răileanu's indole closure

![Scheme 44. Răileanu's indole closure](image)

Amine 199 could arise through an unprecedented electrocyclic ring closure of trienecarbamate 200, followed by oxidation of the resulting cyclohexadiene to the aromatic ring and introduction of the acetic acid side chain. The triene 200 was envisaged to come from a coupling reaction of the \(\alpha\)-stannylenecarbamate 201 with \(\alpha\)-iodoenone 202, in turn available from enone 203 by gem-dimethylation. It seemed likely that the bicyclo[4.3.1]decanone 204 could be regio- and chemoselectively enolized based upon a precedent by Danishefsky.49 Thus, bicyclo[4.3.1]decanone 211 was treated with LiHMDS to afford the corresponding enolate regioselectively, which was trapped \textit{in situ} with TMSCl to afford silyl enol ether 212 (Scheme 45). Without purification, silyl enol ether 212 then underwent a Saegusa reaction to furnish enone 213 in good yield.
Thus, our synthesis was reduced to the preparation of bicyclo[4.3.1]decanone 204, which we thought to be accessible through an intramolecular 7-endo conjugate addition reaction of enone 205. We believed that enone 205 could arise by a straightforward retrocycloaddition of dioxin 206, chemistry that had been extensively investigated in the Funk group. It was hoped that a kinetically controlled stereoselective axial alkylation of the Weiler dianion derivative of the known β-ketoester 208 with bromomethyl dioxin 207 would be possible and thereby set in place the critical C(12)-C(15) relative stereochemistry. Although, precedent for a Weiler dianion-type alkylation reaction could not be found in the literature, the desired stereochemical outcome was substantiated by several examples of highly diastereoselective C(6)-alkylations of related 3,3,4-trisubstituted cyclohexene-1-ones. For example, Bohlmann has found that alkylation of the regioselective enolate derived from ketone 214 with methyl bromoacetate at -78 °C afforded ketoester 215 almost exclusively, with only traces of the C(6)-epimer detected (Scheme 46). This is presumably a result of preferential axial alkylation from the α-face of the half-chair conformer 216 in which the vinyl and isopropenyl substituents are oriented equatorially. Axial alkylation from the β-face of the alternate chair conformer 217 suffers from a developing 1,3-diaxial interaction with the isopropenyl substituent. Alkylation from the β-face through boat conformer 218 is destabilized by a developing flagpole-flagpole interaction with the methyl substituent and is
unlikely. Similarly, alkylation from the \( \alpha \)-face of 219 is also destabilized by a flagpole-flagpole interaction, even though it would lead to the desired product.

**Scheme 46.** Stereoselective alkylation of 3,3,4-cyclohexane-1-ones

possible enolate conformers

**216** favored
Additional examples of stereoselective alkylations of 3,3,4-cyclohexane-1-ones are illustrated in Scheme 47. Thus, alkylation of the enolate derivative of \textit{trans}-decalin \textbf{220} with methyl bromoacetate afforded \(\gamma\)-ketoester \textbf{221} as a single diastereomer.\textsuperscript{52b} In addition, Natsume\textsuperscript{52d} has shown that stereoselective Lewis acid catalyzed addition of silyl enol ether \textbf{222} to indole \textbf{223} gave rise to the ketone \textbf{224}.

\textbf{Scheme 47.} Additional stereoselective alkylations of 3,3,4-cyclohexane-1-ones

Clearly, this hypothetical approach to the total synthesis of the anti-microtubule agent welwistatin is distinct from the previously described strategies. We hoped that addressing the construction of the strained bridged bicyclic substructure at an early stage would alleviate some problems others have encountered in attempting to form the C(4)-C(11) or C(11)-C(12) bonds using more advanced intermediates. Moreover, the opportunity to introduce the C(12) quaternary carbon by preparing the appropriately substituted cyclohexanone and then controlling the C(12)-C(15) relative stereochemistry using well established enolate chemistry was particularly enticing, especially since all of the previous approaches have ignored this challenging problem. However, our approach
necessitated the development of new methodology for several of the key steps, specifically; 1) preparation of 6-bromomethyl-4H-1,3-dioxin (207) and its application in the described retrocycloaddition/Michael addition sequence; and 2) a new indole annelation method that involves the preparation and electrocyclic ring closures of trienecarbamates.
CHAPTER 3
6-Haloalkyl-4H-1,3-dioxins: Versatile bromoalkyl vinyl ketone equivalents for hetero- and carbocycle construction

I. Introduction

The discovery of more convenient and efficient strategies for hetero- and carbocycle ring construction is an ongoing endeavor. For years, sequential reactions of doubly nucleophilic compounds with bis electrophiles have been a cornerstone method in achieving this goal. There are numerous examples of bis electrophiles that have been employed in ring annulation sequences, a few of which are illustrated in Figure 13. One that caught our attention as a potentially valuable and versatile building block for the general construction of natural

Figure 13. Examples of bis electrophiles used in ring annulations

![Examples of bis electrophiles used in ring annulations](image)

product ring systems is a halomethyl vinyl ketone 225. However, only a few examples of this type of cyclization have been reported in the literature. This is most likely due to lack of selectivity between the β and α’ sites towards nucleophilic addition, as well as the instability of these compounds under basic reaction conditions. To circumvent these inherent problems, we proposed
halomethyl dioxin 227 to represent a halomethyl vinyl ketone equivalent, which permits its unambiguous initial alkylation (including the use of highly basic nucleophiles) on the halocarbon electrophilic site vis-à-vis the β-enone carbon (Scheme 48). Following the alkylation reaction, the second electrophilic site can be readily unveiled through retrocycloaddition of the 1,3-dioxin17 to afford the enone represented in structure 228. Finally, upon activation of the remaining nucleophilic site, conjugate addition62 into the newly derived enone could ensue to furnish the desired cyclic compounds 229. Simple variation of the bis nucleophile could potentially generate a wide variety of both hetero- and carbocyclic compounds.

Scheme 48. Strategy for employing a halomethyl vinyl ketone equivalent

A. Preparation of halomethyl vinyl ketones

Preparation of chloromethyl vinyl ketone (231) was first reported by Catch and coworkers54 (Scheme 49). Friedel-Crafts acylation of ethylene with 2-chloroacetyl chloride afforded 1,4-dichlorobutanone 230, which was then subjected to diethylaniline at room temperature to give rise to chloromethyl vinyl ketone (231) in 50% yield. It should be noted however that chloromethyl vinyl ketone was found to undergo rapid polymerization at room temperature in the absence of a stabilizer such as hydroquinone. This observation speaks to the difficulties encountered in handling halomethyl vinyl ketones, and could be a significant reason why they have remained largely unexplored.
**Scheme 49.** Preparation of chloromethyl vinyl ketone

More recently, Carlson and coworkers\(^\text{55}\) have reported the preparation of bromomethyl vinyl ketone (235) using a four step sequence beginning with 2-butanone (Scheme 50). Ketal formation with 1,2-bis-trimethylsilyloxyethane, followed by bromination of the resultant ketal afforded dibromide 233. Elimination of the secondary bromide with t-BuOK in THF gave 234 that was subsequently deprotected with H\(_3\)PO\(_4\) to give rise to bromomethyl vinyl ketone (235) in low yield. Carlson also noted the instability of this compound to polymerization, and suggested that it be freshly prepared prior to each use.

**Scheme 50.** Preparation of bromomethyl vinyl ketone
B. Previous reactions with halomethyl vinyl ketones

The earliest reactions of halomethyl vinyl ketones were reported by Arbuzov\textsuperscript{56} and Rosnati,\textsuperscript{57} who obtained conflicting results upon treatment of chloromethyl vinyl ketone with potassium acetate in refluxing acetic acid (Scheme 51). Arbuzov claimed that acetate undergoes S\textsubscript{N}2 displacement of chloromethyl vinyl ketone affording enone 236. Rosnati on the other hand, has demonstrated that potassium acetate actually initially adds in a 1,4 fashion giving compound 238 after only 15 min. It was also noted that after 1 h, displacement of the chloride also occurred providing 1,4-diacetate 237, a compound that Arbuzov never saw. Other nucleophiles such as thiophenol\textsuperscript{58} and ethyl nitroacetate\textsuperscript{59} were found to undergo 1,4-addition to chloromethyl vinyl ketone.

Scheme 51. Reaction of potassium acetate with chloromethyl vinyl ketone

**Arbuzov**

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{CH}_2 & \quad \text{CH} & \quad \text{CH}_2 \\
\text{Cl} & \quad 231 & \quad \text{KOAc} & \quad \text{HOAc} & \text{reflux} & \text{1 h} & \text{46\%} & \text{AcO} & \text{O} \\
& & & & & \text{AcO} & \text{O} & \text{Ac} & \text{236} & \text{237}
\end{align*}
\]

**Rosnati**

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{CH}_2 & \quad \text{CH} & \quad \text{CH}_2 \\
\text{Cl} & \quad 231 & \quad \text{KOAc} & \quad \text{HOAc} & \text{reflux} & \text{15 min} & \text{75\%} & \text{Cl} & \text{O} \\
& & & & & \text{Cl} & \text{OAc} & \text{238} & \text{237}
\end{align*}
\]

In addition to reactions with a single nucleophile, there have been several reported examples of halomethyl vinyl ketones being used as bis electrophiles in reactions with doubly nucleophilic compounds to prepare hetero- and carbocyclic...
rings. For example, Michael and coworkers\textsuperscript{60} reported that the reaction of thiolactam \textsuperscript{239} with chloromethyl vinyl ketone \textsuperscript{231} in refluxing nitromethane, followed by addition of Hünigs base furnished indolizidine \textsuperscript{241} in good yield (Scheme 52). The proposed pathway of this reaction is by initial displacement of chloride ion with the thiolactam, followed by loss of sulfur, and subsequent conjugate addition of the resulting enamine \textsuperscript{240}.

**Scheme 52.** Chloromethyl vinyl ketone used to prepare an indolizidine

\[
\begin{array}{c}
\text{Ar} \\
\text{N} \\
\text{S} \\
\text{239} \\
\text{Cl} \\
\text{O} \\
\text{231} \\
\text{CH}_3\text{NO}_2 \\
\text{reflux, 24 h;} \\
\text{Ar} \\
\text{N} \\
\text{240} \\
\text{Cl} \\
\text{O} \\
\text{241} \\
\end{array}
\]

Carlson has reported\textsuperscript{55b} the preparation of 3-pyrrolidinones from bromomethyl vinyl ketone involving initial displacement of bromide ion by a primary amine, followed by a conjugate addition reaction of the resulting secondary amine (Scheme 53). In this case, they were able to obtain \(N\)-benzyl pyrrolidinone \textsuperscript{243} in 39% yield.

**Scheme 53.** Carlson’s 3-pyrrolidinone method

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{235} \\
\text{BnNH}_2 \\
\text{K}_2\text{CO}_3 \\
\text{Et}_2\text{O} \\
\text{BnN} \\
\text{O} \\
\text{242} \\
\text{39\%} \\
\text{Bn} \\
\text{N} \\
\text{243} \\
\end{array}
\]

The previous two examples detailed annulation sequences that involve initial displacement of the halide ion, followed by an intramolecular conjugate addition reaction. There have also been a few examples complementary to that approach. Smith and coworkers\textsuperscript{61} utilized a chloromethyl cyclohexenyl ketone in
a conjugate addition/$S_N2$ displacement strategy (Scheme 54). Treatment of enone 244 with thiolacetic acid in toluene effected a 1,4-addition reaction to give the intermediate thiolacetate 245, which was subjected to sodium methoxide in methanol thus affording the tetrahydrothiophen-3-one 246 as a single diastereomer. Smith also mentioned that use of the analogous bromoenone in this reaction was abandoned due to competing displacement of bromide ion with thiolacetic acid prior to conjugate addition.

**Scheme 54.** Smith's conjugate addition/$S_N2$ displacement sequence

Danishefsky's work with halomethyl vinyl ketones likely represents the most in depth study of annulation reactions reported to date.\(^49\) This sequence, which is referred to as an $\alpha,\alpha'$-annulation, involves sequential reactions of enamines with iodomethyl vinyl ketone, and has been used to prepare a variety of bridged bicyclic diones (Scheme 55). For example, treatment of enamine 247 with iodomethyl vinyl ketone (248) in THF effects a conjugate addition producing iminium ion 249, which immediately tautomerizes to the regioisomeric

**Scheme 55.** Danishefsky's $\alpha,\alpha'$-annulation sequence
enamine 250. When heated, enamine 250 undergoes displacement of iodine ion and subsequent hydrolysis on workup to afford the bicyclo[4.3.1]decanone 211. This methodology was developed in an effort to access the bridged bicyclic ring system of CP225,917 and CP263,114.

II. 6-Bromomethyl-4H-1,3-dioxin: Scope and utility

The previous examples suggest that halomethyl vinyl ketones can be useful substrates in reactions with doubly nucleophilic compounds, and could be of broader utility if the relative reactivity of the two electrophilic sites could be better controlled. Accordingly, we set out to prepare and test the scope and limitations of our proposed halodioxin for the construction of a variety of hetero- and carbocyclic ring systems (Figure 14).

**Figure 14.** 6-Bromomethyl-4H-1,3-dioxin

![6-Bromomethyl-4H-1,3-dioxin](image)

A. Preparation of 6-bromomethyl-4H-1,3-dioxin

Our synthesis of bromide 207 commenced with a Prins cyclization\(^\text{63}\) of allyl iodide with formaldehyde in the presence of sulfuric acid (Scheme 56) to provide 4-iodomethyl-1,3-dioxane (251). This protocol was originally reported by Price\(^\text{64}\) for preparation of the analogous chloride. The iodide 251 was then heated with solid KOH under reduced pressure (55 °C, 160 mmHg) to afford 4-methylene-1,3-dioxane (252) which was distilled directly from the reaction mixture. It should be
noted that the iodide-leaving group is critical for the success of this reaction. Treatment of chloride 253 with KOH (Scheme 57) required higher temperatures (>150 °C) for elimination to occur, and thus enol ether 252 was accompanied by comparable amounts of the endocyclic double bond isomer, 6-methyl-4H-1,3-dioxin (254). It was later found that iodide 251 could also be distilled from KOH at atmospheric pressure (116 °C) with no endocyclic isomer 254 observed. Bromination of the enol ether 252 at -78 °C in the presence of Hünigs base proceeded smoothly to provide the bromomethyl vinyl ketone equivalent 207. The synthesis can be easily scaled to provide multigram quantities of the stable bromide 207 and, in fact, is accomplished in fewer steps than those required for the preparation of the aforementioned bromomethyl vinyl ketone itself (Scheme 50).

Scheme 56. Preparation of 6-Bromomethyl-4H-1,3-dioxin

Scheme 57. Elimination of 4-chloromethyl-1,3-dioxane
B. Uses of bromodioxin 207 as a halomethyl vinyl ketone equivalent

1. Preparation of carbocyclic ring systems

We first examined the alkylation reactions of bromomethyl dioxin 207 with β-ketoester Weiler dianions\textsuperscript{65,66} (Scheme 58). We were pleased to find that several β-ketoesters 255, 259, and 263 could be cleanly alkylated to afford the desired dioxins (256, 260, and 264). Retrocycloaddition reactions of these dioxins were found to occur at temperatures as low as 110 °C (toluene, 12 h) to give the corresponding enones. However, products requiring no chromatographic purification were obtained by performing the reactions at higher temperatures for shorter periods of time (toluene, sealed tube, 180 °C, 15 min). This may be the

\textbf{Scheme 58.} 7-\textit{endo} Michael additions leading to cyclohepta-1,4-diones
result of removing the reactive by product, formaldehyde, from the reaction mixture, as the top of the sealed tube is often coated with a white film of paraformaldehyde. The enones (257, 261, and 265) resulting from the retrocycloaddition reactions were all found to undergo facile 7-endo conjugate addition reactions when subjected to catalytic amounts of Cs$_2$CO$_3$ in CH$_3$CN providing the corresponding cyclohepta-1,4-diones (258, 262, and 266). These conditions were originally reported by Deslongchamps and coworkers for related 7-endo ring closures using exocyclic enolates of cyclic β-ketoesters. For example, β-ketoester 267 was cyclized to hydroazulene 268 in 4 hours at room temperature (Scheme 59). They have also reported these conditions to be successful for conjugate addition reactions of β-ketoesters to ynones.

**Scheme 59.** Deslongchamps’ conditions for 7-endo ring closures of exocyclic enolates

To the best of our knowledge, these cyclizations are the first examples of endo-Michael additions of endocyclic enolates leading to seven-membered rings. Christoffers, like Deslongchamps, has also reported conditions for endo-cyclizations of exocyclic enolates. He found that treatment of cyclic β-ketoester 269 with catalytic FeCl$_3$ effected a 7-endo ring closure to give the trans-fused
Scheme 60. Christoffers' conditions for 7-endo ring closures of exocyclic enolates

\[
\begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me} \\
\text{O} \\
\text{O} \\
\text{CO}_2\text{Me} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{5\% FeCl}_3\cdot 6\text{H}_2\text{O} \\
\text{CH}_2\text{Cl}_2 \\
\text{rt, 12 h} \\
80\%
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me} \\
\text{O} \\
\text{O} \\
\text{H}
\end{array}
\]

\text{269} \quad \Rightarrow \quad \text{270}

Dione 270 (Scheme 60). These conditions were also found useful for intermolecular Michael addition reactions of \(\beta\)-ketoesters with enones. In another related example, Pollini and coworkers\textsuperscript{69} utilized a 7-exo-Michael addition of an endo enolate to access the isoclovene ring system (Scheme 61). \(\beta\)-Ketoester 271 was found to undergo an intramolecular conjugate addition reaction upon treatment with potassium carbonate in methanol affording tricycle 272 in 80\% yield, which was subsequently transformed to isoclovene in 6 steps.

Scheme 61. 7-exo ring closure of an endo enolate

\[
\begin{array}{c}
\text{O} \\
\text{CO}_2\text{Et} \\
\text{H} \\
\text{O} \\
\text{CO}_2\text{Et} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{K}_2\text{CO}_3 \\
\text{MeOH} \\
\text{rt, 3 h} \\
80\%
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Et} \\
\text{H} \\
\text{O} \\
\text{CO}_2\text{Et} \\
\text{H}
\end{array} \quad \text{6 steps}
\]

\text{271} \quad \Rightarrow \quad \text{272} \quad \Rightarrow \quad \text{isoclovene}

We next turned our attention to annulation reactions using bromide 207 that would substantiate the viability of this methodology in our projected welwistatin total synthesis. Reaction of the Weiler dianion of \(\beta\)-ketoester 273 with bromide 207 smoothly afforded the corresponding alkylation product 274 (Scheme 62). This compound was then subjected to the aforementioned retrocycloaddition/conjugate addition reaction sequence to furnish bicyclo[4.3.1]decanone 275. We also found that \(\beta\)-ketoester 276 could similarly
be converted to the corresponding bridged bicyclic ketone 278. This was a
noteworthy result, since vicinal quaternary centers were created in the cyclization
step. A similar transformation would be necessary in our proposed welwistatin
synthesis.

**Scheme 62.** Cyclizations forming bicyclo[4.3.1]decanones

In addition to β-ketoesters, we also found that β-ketosulfides participated
in the conjugate addition step (Scheme 62). Alkylation of cyclohexanone with
bromide 207 followed by sulfenylation of the regioselective enolate provided
ketosulfide 279. Using our standard protocol, sulfide 279 was smoothly
transformed to the bicyclic dione 280. Interestingly, the rate of these cyclizations
appears to correlate with the pKₐ's of the enolate precursors. The β-ketoester
(pKₐ = 11) ring closures all occurred at a faster rate (under 3 h) than the β-ketosulfide (pKₐ = 16), which needed 12 hours to fully cyclize. Moreover, all attempts to cyclize ketone 282 (pKₐ = 20) to bicyclo[4.3.1]decanone 211 (Scheme 63) with Cs₂CO₃ failed, with most reactions resulting in recovery of starting material. Other bases, including NaHMDS, t-BuOK, and NaH led to rapid decomposition.

**Scheme 63. Attempted cyclization with a ketone enolate**

However, we were able to demonstrate that a dienolate anion is capable of undergoing a conjugate addition reaction and in the course of preparing this substructure we were able to demonstrate the stability of the dioxin functionality to a variety of reaction conditions. Thus, we found that the dioxin could tolerate the nucleophilic and acidic conditions of the Stork-Danheiser enone synthesis⁷¹ (Scheme 64). Upon treatment of vinylogous ester 284 with MeMgBr, followed by an acidic workup (1 M HCl, 10 min) we were able to obtain the cyclohexenone 285 in good yield. Subsequent retrocycloaddition of the dioxin gave rise to enone
Scheme 64. Bicyclo[4.3.1]decanone prepared from a vinylogous ester

286, that underwent intramolecular Michael addition at the \( \alpha \)-position of the
dienolate 287 to furnish the bicyclo[4.3.1]decanone 288. The conditions required
to effect conjugate addition (2 equiv Cs\(_2\)CO\(_3\), CH\(_3\)CN, 80 °C, 16 h) of the
extended ketone enolate 287 are consistent with our previous observation that
rate of cyclization is correlated to the pK\(_a\) of the enolate precursor.

Fused-bicyclic products are also accessible using this annulation strategy.
Addition of the enolate of \( \tau \)-butyl acetate\(^{72}\) to vinylogous ester 290, followed by an
acidic workup gave rise to Stork-Danheiser product 291 (Scheme 65). In contrast
to enone 285, the \( \gamma \)-methyl carbon of the retrocycloaddition product of enone 291
is activated by an ester substituent and, consequently, furnishes a diastereomeric
mixture of the fused bicyclic diketo esters 292 upon completion of the annulation
sequence.
Scheme 65. Conjugate addition of a vinylogous β-ketoester

Scheme 66. Intramolecular Heck reaction

We have also found retrocycloadducts to be useful substrates for reactions other than Michael additions. Scheme 66 details a sequence in which a ring is annulated via an intramolecular Heck reaction. Stereoselective alkylation of cis-3,5-dimethylcyclohexanone (293) with bromide 207, followed by regioselective triflate formation afforded dioxin 294. Upon retrocycloaddition, the resultant enone was subjected to Heck reaction conditions employed by Fu

providing the fused bicyclic dienone 295 as a single diastereomer. Our stereochemical assignment was confirmed through nOe experiments as well as coupling constants in the 1H NMR (Figure 15). The nOe’s between all three axial protons on the bottom face of the ring system and lack of a diagnostic nOe between the ring fusion proton and either of the other two methine protons unequivocally verified our assignment.
2. Preparation of heterocyclic ring systems

In addition to the aforementioned preparation of carbocyclic ring systems, we have also been able to prepare a variety of heterocyclic, specifically, nitrogen-containing ring systems via this general method. To that end, the alkylation of the carbanion derivatives of nitrile 296 and ester 300 with bromide 207 proceeded uneventfully and furnished the expected dioxin-containing products 297 and 301, respectively, in excellent yield (Scheme 67). As before, the dioxin moieties survived subsequent manipulation of the nitrile 297 and ester 301 alkylation products to arrive at the desired cyclization precursors 298 and 302, respectively. In the case of nitrile 297, LAH reduction of the nitrile, followed by protection of the resultant amine with trifluoroacetic anhydride produced acetamide 298. Dioxin 301 underwent LAH reduction to the corresponding alcohol, subsequent reduction of the aryl nitro group\textsuperscript{76} with Cu(acac)\textsubscript{2} and NaBH\textsubscript{4}, and protection to afford the BOC aniline 302. The retrocycloaddition of these compounds could be accomplished in good yields at temperatures lower than those previously utilized, although the subsequent Michael additions could be
effected using the same conditions employed for the carbon nucleophiles (Schemes 58, 62, 64, 65, and 66). Both Michael adducts, azepine 299 and benzazocine 303, were obtained in good yield. It should be noted that benzazocines related to 303 have been the object of considerable synthetic activity since they have been prepared en route to the antitumor compound FR900482.\textsuperscript{77-79} This sequence suggests that it may be possible to prepare intermediates of FR900482 in a more rapid fashion than those previously reported.\textsuperscript{77}

3. Total synthesis of (2S,4R)-4-hydroxypipecolic acid

We have also found that this general strategy can be applied to the total synthesis of natural products. (2S,4R)-4-Hydroxypipecolic acid (304) is a biologically active natural amino acid isolated from the leaves of \textit{Calliandra pittieri} and \textit{Strophantus scandeus} (Figure 16).\textsuperscript{80} It is also a substructure of some cyclodepsipeptide antibiotics such as virginiamicin S2,\textsuperscript{81} and has also been
Figure 16. (2S,4R)-4-Hydroxyproline acid

(2S,4R)-4-hydroxyproline acid

employed as a precursor in the preparation of selective NMDA receptor antagonists. More recently this amino acid has been used as a building block in the synthesis of Palinavir, a potent peptidomimetic-based HIV protease inhibitor (Figure 17). For these reasons, several racemic and enantioselective syntheses of 4-hydroxyproline acid (304) have been reported, the most common of which is through stereoselective ring closure of an acyclic β-amino alcohol onto an electrophilic carbonyl species.

Figure 17. HIV protease inhibitor Palinavir

Our synthesis began with alkylation of the enolate of the Williams lactone 305 with bromide 207 to afford the desired dioxin 306 as a single diastereomer (Scheme 68). As with previous alkylations of lactone 305, the
electrophile approaches from the face opposite the bulky phenyl substituents. Retrocycloaddition of dioxin 306 proceeded smoothly (150 °C, 3 h) to afford N-BOC protected enone 307. The 1H NMR of this compound, along with its dioxin precursor, was difficult to decipher due to the carbamate rotamers. However, an acceptable spectrum of enone 307 (d8-toluene) was obtained at 90 °C.

Subjection of enone 307 to conditions introduced by Ohfune87 for removal of the BOC group led to concomitant conjugate addition88 of the secondary amine generated during methanolysis of the intermediate trimethylsilyl carbamate. The carbonyl of the resulting piperdin-4-one 308 was then reduced stereoselectively (BH3, -78 °C) to provide only the equatorial alcohol 309. Kadouri-Puchot and coworkers84o also performed a similar axial borane reduction89 in their pipecolic acid synthesis. Finally, removal of the Williams auxiliary by the standard hydrogenation protocol85 afforded the naturally occurring (2S,4R)-4-hydroxypipeolic acid in excellent yield. This relatively concise synthesis is one of the few84a,b involving an intramolecular Michael addition to prepare a piperdin-
4-one intermediate. Moreover, this synthesis once again demonstrated the versatility of bromodioxin 207, and in this case, in natural product synthesis.

4. Cycloaddition reactions of alkylation substrates

This methodology has also been extended to include alkylation adducts as precursors in cycloaddition reactions (Scheme 69). Alkylation of sorbyl alcohol (310) with the bromide 207 (NaH, THF, rt) gave rise to dioxin 311, which, when subjected to thermolysis (150 °C, 45 min) conditions, underwent an intramolecular Diels-Alder reaction to furnish exclusively the endo cycloadduct

Scheme 69. Cycloaddition reactions employing bromodioxin 207

312. This stereochemical assignment was confirmed by the diagnostic nOe’s and proton NMR couplings depicted in Figure 18. In addition, we have examined retrocycloaddition/cycloaddition reactions with nitrones. Alkylation of the anion
derived from $t$-butyl imine 313 with bromide 207 followed by acid hydrolysis afforded an intermediate aldehyde, that was subjected to $N$-benzylhydroxylamine and MgSO$_4$ to furnish the desired nitrone 314. When nitrone 314 was heated to 160 °C in a sealed tube, retrocycloaddition of the dioxin took place producing an enone, which was immediately trapped by the tethered nitrone giving rise to the cis-fused adduct 315. It should be noted that the endo adduct is the only stereoisomer produced in this cycloaddition, which is highly favored over the exo adduct that would embody a strained trans-fused 5,5-bicyclic ring system.
III. 6-(2-Iodoethyl)-2,2-dimethyl-4H-1,3-dioxin: Scope and utility

In view of the variety of ring systems that could be readily prepared using 6-bromomethyl-4H-1,3-dioxin (207), we considered it worthy to investigate the scope and utility of the homologous reagent, 6-(2-iodoethyl)-2,2-dimethyl-4H-1,3-dioxin (Figure 19).

**Figure 19.** 6-(2-Iodoethyl)-2,2-dimethyl-4H-1,3-dioxin

A. Preparation of 6-(2-Iodoethyl)-2,2-dimethyl-4H-1,3-dioxin

Preparation of iododioxin 316 was straightforward (Scheme 70). The known β-ketoester 317 was prepared in a two step sequence involving initial alkylation of the dianion of ethyl acetoacetate with benzyloxymethyl chloride, followed by hydrogenation of the benzyl group with Pd(OH)$_2$. This compound is also available by direct reaction of the Weiler dianion of ethyl acetoacetate with gaseous formaldehyde. However, a much lower yield and the difficulty in generating gaseous formaldehyde warranted us to follow the easier two step sequence. Keto-alcohol 317 was then smoothly converted to acetonide 318 upon treatment with 2-methoxypropene and pyridinium tosylate in THF. The acetonide is formed relatively quickly in this reaction (1-2 h), however a large amount of the exocyclic conjugated ester is initially produced. Allowing the reaction to stir for an extended period of time produces almost exclusively the
desired endocyclic isomer 318. Finally, reduction of the ester moiety with LiAlH₄, followed by Mitsonobu reaction (PPh₃, I₂, imidazole) successfully produced iodoethyl dioxin 316. It should be noted that this compound is not nearly as stable as bromodioxin 207, and it was found to readily polymerize if left on the benchtop for an extended period of time. It can, however, be stored in the freezer (-50 °C) for several months with no noticeable decomposition. The analogous bromide 319 was also prepared from ester 318 in an attempt to obtain a more stable alkylating agent. However, the bromide seemed to decompose just as readily as the iodide.

B. Uses of iododioxin 316 as a haloethyl vinyl ketone equivalent

Haloethyl dioxins 316 and 319 were found to be excellent substrates for ring annulations. Our first test case, as with bromide 207, was Weiler dianion chemistry with a β-ketoester. Indeed, we were pleased to find iodide 316 alkylated smoothly with the dianion of ethyl acetoacetate to afford dioxin 320 (Scheme 71). Subjection to the standard retrocycloaddition/conjugate addition reaction sequence effected an unprecedented 8-endo ring closure of an endocyclic enolate to give the cyclooctane-1,5-dione 321.
In addition to the Heck reaction illustrated in Scheme 66, we have also found the retrocycloaddition products to be useful substrates in olefin metathesis reactions (Scheme 72). To that end, iodide 316 was alkylated with the dianion prepared from β-ketoester 322. Alkylation product 323, which preferred to exist in its enol form, was easily sulfonylated with Tf₂O and Hünigs base to provide

Scheme 71. Eight membered ring synthesis

Scheme 72. Ring closure via olefin metathesis
enol triflate 324. Stille coupling with tributylvinyltin followed by thermolysis of the resultant dienoate 325 effected a facile retrocycloaddition (110 °C, 1 h) to give rise to the desired enone 326. Finally, enone 326 underwent an olefin metathesis reaction to give the bicyclic dienone 327 in good yield using Grubbs’s second generation catalyst.93

In a similar application, we have also been able to prepare the tetrahydroazulenone 331 through olefin metathesis of its enone precursor 330 (Scheme 73). In this sequence, rather than a Weiler dianion, iodide 316 was successfully alkylated with the less reactive mono-enolate of methyl cyclopentanone-2-carboxylate (328). In addition, we also found that retrocycloadducts could be obtained through treatment of the requisite dioxin with a Lewis acid. In this case, a competing thermally induced intramolecular cycloaddition reaction of enone 330 warranted the use of ZnCl₂ as a mild alternative in the retrocycloaddition reaction.

Scheme 73. Tetrahydroazulenone prepared via olefin metathesis

In addition to using the haloethyl dioxins 316 and 319 as electrophiles in nucleophilic displacement reactions, we also examined their utility as nucleophiles in conjugate addition reactions (Scheme 74). We were pleased to find that the 2-thienylcyanocuprate reagent94 of bromodioxin 319 could be prepared and used in a conjugate addition with the α,β-unsaturated ketoester
**Scheme 74.** Use of bromoethyl dioxin 319 as a cuprate reagent

332. The retrocycloaddition product derived from dioxin 333 was found to be unstable and could not be isolated. However, upon heating dioxin 333 in the presence of Cs₂CO₃, the β-ketoester anion effectively trapped the enone intermediate, thus producing hydroazulene 334 in good yield. The cis-stereochemistry was assigned based on the previously described Michael addition reactions reported by Deslongchamps⁶⁷, in which similar β-ketoesters were transformed to cis-hydroazulenes.

**IV. Conclusion**

In conclusion, we have prepared 6-haloalkyl-4H-1,3-dioxins and used them as haloalkyl vinyl ketone equivalents for the construction of a variety of hetero- and carbocyclic ring systems.⁹⁵ The allylic and homoallylic halide moieties of dioxins 207 and 316 are sufficiently reactive to allow for facile substitution by a variety of nucleophiles. The 1,3-dioxin ring is quite robust and permits, if necessary, further multistep transformations of the alkylation products. The potentially sensitive enone moiety can then be released under mild, thermal or Lewis acid mediated conditions, and smoothly participates in a variety of ring closure reactions forming hetero- and carbocyclic ring systems.
I. Introduction

Indoles constitute an important substructure embodied in many of nature’s most potent bioactive alkaloids (Figure 20), which has stimulated the development of new methodology for their construction. These methods have not only been useful for the preparation of biologically active natural products, but have also had considerable impact in medicinal drug discovery.

Figure 20. Bioactive indole alkaloids

lysergic acid

dragmacidin E

vinblastine

reserpine

penitrem C
The basic strategies for the synthesis of indoles can be broadly categorized based on the order in which the individual aromatic substructures are introduced (Figure 21). By far the most common approach involves beginning the synthesis with a substituted benzene ring and then fashion the pyrrole ring. One such possibility is depicted in A and involves sequentially forming the indicated C(3)-C(3a) and N-C(2) bonds. A classic example of this strategy is the venerable Fischer indole synthesis,\(^{100}\) in which an aryl hydrazine and a ketone (or aldehyde) condense in the presence of acid to produce 2,3-disubstituted indoles.

**Figure 21.** General strategies of the synthesis of indoles

The Fischer indole synthesis has been used extensively in the total synthesis of indole-containing natural products. One recent example was reported by Aubé in the total synthesis of (+)-aspidospermidine.\(^{101}\) Treatment of ketone 335 with phenylhydrazine in refluxing acetic acid was found to undergo clean conversion to the indolinene intermediate 336 as a single regioisomer (Scheme 75). A subsequent stereoselective reduction of the indolinene provided (+)-aspidospermidine (337).

**Scheme 75.** Application of Fischer indole synthesis
A second, and less common approach, to substituted indoles is through the annelation of the benzene ring onto a pyrrole. Many of these examples involve the cycloaddition of 2- or 3-vinyl pyrroles with dieneophiles as shown in B (Figure 21).\textsuperscript{102} For example, Jones and coworkers\textsuperscript{102c} have performed cycloadditions of 2- and 3-vinyl pyrroles (339 and 342) with dimethyl acetylenedicarboxylate (338) to give 3,4,5- and 2,6,7-trisubstituted dihydroindoles (340 and 343), respectively (Scheme 76). The dihydroindoles were conveniently aromatized to the corresponding indoles (341 and 344) upon subjection to DDQ in refluxing benzene. It should be noted that the electron-withdrawing group on the pyrrole ring was critical to the success of these reactions, as it shut down competing Michael additions with dimethyl acetylenedicarboxylate. In addition, van Leusen\textsuperscript{102a,b} has shown that indoles can be prepared through electrocyclic ring closures of 2,3-divinylpyrroles. For example, triene 345 was found to

\textbf{Scheme 76.} Synthesis of indoles from vinylpyrroles

\begin{center}
\begin{tikzpicture}
\node[anchor=center] at (0,0) {338}; \node[anchor=center] at (0.75,-1) {339}; \node[anchor=center] at (2.5,-2) {66 °C \text{ 48 h \ CHCl}_3 \ 50\% \ 340}; \node[anchor=center] at (4.5,-2) {DDQ \ benzene \ reflux \ 41\% \ 341}; \node[anchor=center] at (0,0.5) {338}; \node[anchor=center] at (0.75,0.5) {342}; \node[anchor=center] at (2.5,1.5) {120 °C \text{ 24 h \ CHCl}_3 \ 69\% \ 343}; \node[anchor=center] at (4.5,1.5) {DDQ \ benzene \ reflux \ 50\% \ 344}; \node[anchor=center] at (0,-3) {338}; \node[anchor=center] at (0.75,-3) {345}; \node[anchor=center] at (2.5,-4.5) {triglyme \ 216 °C \ 1 h \ 346}; \node[anchor=center] at (4.5,-4.5) {DDQ \ 91\% \ 347};
\end{tikzpicture}
\end{center}
undergo a thermally induced electrocyclic ring closure to the tricycle 346, which was subsequently oxidized to furnish indole 347 in good yield.

The third and least explored strategy for the construction of indoles is one in which both aromatic rings of the indole are constructed in consecutive bond forming processes from acyclic precursors. Of the many hypothetical disconnections possible, the ones shown in C, D, and E (Figure 21) are the most common and is frequently accomplished by the implied intramolecular/intermolecular cycloaddition reactions as the key step in the construction of the substituted benzene rings.103-107

An example of the C approach was reported by Kanematsu,103 who utilized an intramolecular Diels-Alder reaction of an allenic trisubstituted dianeamide to prepare both rings of an indole in a single step enroute to the total synthesis of cis-trikentren B (Scheme 77). Thermolysis of allene 350 effected cyclization to the tetrahydroindole 351, which was immediately oxidized with DDQ to the desired 5,6,7-trisubstituted indole 352. Conversion of indole 352 to cis-trikentren B (353) was accomplished in 9 subsequent steps.

**Scheme 77.** Kanematsu’s indole synthesis
Indoles with rings spanning the C(3) and C(4) positions are common substructures in a number of alkaloid natural products. Padwa has recently developed a method for the rapid construction of the core tricyclic ring system of the ergot alkaloids (see lysergic acid, Figure 20). Sequential cycloaddition reactions are used in the indole forming process (Scheme 78). For example, cycloaddition reaction of Rawal’s diene \(354\) with \(\alpha,\beta\)-unsaturated ester \(355\) in refluxing \(\text{CH}_3\text{CN}\) cleanly produced silyl enol ether \(356\). After treatment with HF to unmask the enone, \(357\) underwent a thermally driven intramolecular Diels-Alder reaction, ring opening, and dehydration cascade to give rise to the tricyclic indoline \(359\). Oxidative decarboxylation at C(3) was effected through a Kochi reaction of the corresponding des-BOC acid to give the desired indole \(360\), also known as Uhlé’s ketone\(^{108}\), a key intermediate in many Ergot alkaloid syntheses.

**Scheme 78.** Padwa’s indole synthesis

\[
\text{Scheme 78. Padwa's indole synthesis}
\]
Boger has developed a much more general approach to the preparation of substituted indoles using the D strategy (Figure 21), which employs two sequential heteroaromatic azadiene Diels-Alder reactions.\textsuperscript{105} This method has been applied in an efficient 5 step synthesis of cis-trikentrin A from enamine 361 (Scheme 79).\textsuperscript{105b} Treatment of 3,6-bis(methylthio)-1,2,4,5-tetrazine with pyrrolidine enamine 361 effected an intermolecular cycloaddition with concomitant loss of nitrogen to provide the 4,5-dihydro-1,2-diazine 362 as a single diastereomer. Following acid-catalyzed elimination of pyrrolidine, bis-sulfide 363 was oxidized to the bis-sulfone. Selective displacement of a single sulfone by 1-aminohexa-2,3-diene under high pressure conditions (13 kbar, 4 d) produced the key indole precursor 364. This was found to cyclize to N-acetyl-cis-trikentrin A through an intramolecular allene 1,2-diazine Diels-Alder reaction in Scheme 79. Boger’s indole synthesis

\begin{align*}
\begin{array}{c}
\text{Boger's indole synthesis} \\
\end{array}
\end{align*}
refluxing $\text{Ac}_2\text{O}$, following loss of nitrogen and methyl sulfinate. Removal of the acetyl group furnished the natural product 366 in a concise sequence.

Danheiser has recently developed a method$^{106}$ for the synthesis of substituted indolines and indoles along the lines shown in D, which features intramolecular cycloaddition reactions of ynamides and conjugated enynes. In a typical reaction (Scheme 80), heating ynamide 368 to 210 °C promotes a [4+2] cycloaddition to generate a highly strained isoaromatic cyclic allene 369, that rearranges via a proton or hydrogen atom transfer pathway to afford the desired indoline 370. Danheiser has also shown that the indoline cycloadducts, such as 372, can be easily oxidized to the corresponding indole 373 by treatment with chloranil.

**Scheme 80.** Danheiser's indole synthesis

\[ \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \rightarrow \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \]

1. $\text{Cul}$, $\text{PdCl}_2(\text{PPh}_3)_2$, THF-piperidine 80%
2. $\text{KHMDS}$, $\text{Cul}$, pyridine $\text{Br} \rightarrow \text{Si} 59$

\[ \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \rightarrow \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \]

210 °C, toluene 1.5 h 56%

\[ \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \rightarrow \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \]

56%

\[ \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \rightarrow \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \]

2. chloranil, benzene 88%

\[ \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \rightarrow \text{HN} \underset{\text{Ts}}{\text{N}} \text{Me}_3\text{Si} \]

91%
Wasserman has developed a method using the E strategy (Figure 21) for the synthesis of substituted indoles via sequential reactions of acetylenic vicinal tricarbonyls (Scheme 81).\(^\text{107}\) In the first step, ynone 375 undergoes a cycloaddition reaction with diene 374 to produce cyclohexadiene 376. Subsequent condensation of butylamine with the central carbonyl, followed by an intramolecular Michael addition and loss of water produced the dihydroindole 378. Oxidation to the corresponding 2,3,4-trisubstituted indole 379 was then accomplished by treatment with DDQ.

**Scheme 81.** Wasserman's indole synthesis
II. A novel strategy for the synthesis of indoles via method C

We have recently developed a new indole annelation method in which both aromatic rings are constructed in consecutive bond forming reactions according to the C strategy (Figure 21). The general strategy of this annelation is outlined in Scheme 82. We envisaged formation of the C(3a)-C(7a) bond of the indole 385 to arise from a Stille coupling of α-stannylenecarbamate 380 with α-haloenone 381. Electrocyclic ring closure of the resulting trienecarbamate 382 could effect connection of C(4) and C(5) to produce aniline 383. Transformation of aniline 383 to the corresponding acid 384 would permit condensation of a C(2) enolate upon the C(3) carbonyl in order to complete the indole construction.

Scheme 82. General strategy for the synthesis of highly substituted indoles
A. Preparation and Stille coupling of α-(trialkylstannyl)enecarbamates

Although a few α-(trialkylstannyl)enecarbamates have been previously synthesized and used in coupling reactions, their chemistry has remained largely unexplored. The reported procedures for the preparation of α-stannylenecarbamates are illustrated below. For example, Hegedus and coworkers\textsuperscript{109a} have shown that metallation of enecarbamate 386 with lithium tetramethylpiperidine followed by treatment with Me\textsubscript{3}SnCl provided α-stannylenamide 387 in good yield (Scheme 83).\textsuperscript{110} Subsequent coupling of stannane 387 with propionyl chloride afforded α-amidoenone 388.

**Scheme 83.** Hegedus’ preparation of α-stannylenamides

Another preparation of α-(trialkylstannyl)enamides by Cintrat\textsuperscript{109b-d} involves the hydrostannylation of ynamides (Scheme 84). Subjection of tosyl ynamide 389 to Bu\textsubscript{3}SnH in the presence of Pd(PPh\textsubscript{3})\textsubscript{4} afforded the α-isomer 390 in 67% yield (10% β-isomer). Coupling of 390 with iodobenzene proceeded uneventfully to afford α-phenylenamide 391.

**Scheme 84.** Cintrat’s preparation of α-stannylenamides
In order to prepare stannane 380, we believed that the metallation protocol employed by Hegedus would be the most convenient and flexible for preparing dienes with varying substitution patterns. Thus, preparation of the parent \( \alpha \)-(tributylstannyl)dienecarbamate 393 began with the BOC derivative of the Overman diene 392\(^{111} \) (Scheme 85). Initially, we investigated formation of the dianion of enecarbamate 392 and stannylation with \( \text{Bu}_3\text{SnCl} \) to produce stannane 393 in one step. Unfortunately, all attempts to generate and trap the dianion using a variety of alkyllithiums, solvents, and temperatures proved unsuccessful, most resulting in recovery of starting material. Consequently, we turned to a nitrogen protecting group in order to avoid forming a dianion. After several protecting groups (benzyl, PMB, and TBS) produced undesired results

**Scheme 85.** Preparation of \( \alpha \)-(tributylstannyl)dienecarbamate 393
Scheme 86. Attempted enecarbamate metallations

(Scheme 86), we found that the trimethylsilylethoxymethyl (SEM)\textsuperscript{112} group was robust enough to handle the metallation step and could be easily removed under mild conditions (Scheme 85). Thus, the SEM protected Overman diene 394 was found to undergo clean metallation (BuLi, TMEDA, THF, -60 °C) and stannylation with Bu\textsubscript{3}SnCl to produce diene 395. Removal of the SEM group proceeded uneventfully by treatment of 395 with HF-acetone to produce the isolable hydroxy methyl intermediate, which was then subjected to NH\textsubscript{4}OH in MeOH to furnish the desired α-(tributylstannyl)-ene carbamate 393 in good yield.

Several other α-stannyl enecarbamates have also been prepared via similar methods (Scheme 87). We were delighted to find that our sequence also works well with enecarbamates which possess C(4) and C(2) substituents. Metallation of enecarbamates 398 and 402, proceeded without problem and were subsequently transformed to stannanes 400 and 403, respectively. Interestingly however, metallation of enecarbamate 405 was unsuccessful, with all reaction conditions returning only starting material. The C(3) alkyl group is the likely
source of the problem and suggests that the metallation of the dienes 394, 396, 398, and 402 proceeds through the s-trans conformation. The s-trans conformer of 405 would position the methyl substituent nearby the enecarbamate hydrogen atom.

Scheme 87. Other α-(tributylstannyl)enecarbamates prepared

B. 6π-Electrocyclic ring closures of trienecarbamates

With a general method for the preparation of α-(trialkylstannyl)-enecarbamates in hand we next looked at their utility in the proposed Stille coupling reactions and subsequent electrocyclic ring closures. Indeed, we were pleased to find that Stille coupling\(^{113}\) of α-(tributylstannyl)enecarbamate 393 with
2-iodo-cyclohexenone\textsuperscript{114} proceeded smoothly to afford amidotriene 408 (Scheme 88). More importantly triene 408 was found to undergo an especially facile electrocyclic ring closure\textsuperscript{115,116} (110 °C, 1 h) to furnish cyclohexadiene 409. Electrocyclization occurred at a much faster rate than that of typical 1,3,5-hexatrienes,\textsuperscript{116a} which generally require temperatures near 150 °C and prolonged reaction times. We believe that this closure is most likely facilitated by a push/pull type mechanism of the hydrogen bonded enecarbamate functionality with the proximal carbonyl enroute to the resonance stabilized vinylogous imide product. In support of this hypothesis, it is of interest to note that the resonance for the N-H proton in the amidotriene 408 is observed at δ 6.2 ppm, whereas the analogous N-H proton in the resulting product moves downfield to δ 12.4 ppm, indicating a more acidic proton, and hence a stronger hydrogen bond with the proximal carbonyl.

**Scheme 88.** 6π-Electroyclic ring closure of trienecarbamate 408

To the best of our knowledge, this is the first reported 6π-electroyclic ring closure of a 3-amidotriene. In fact, there are very few examples of 6π-electroyclic ring closures that have demonstrated such a pronounced acceleration due to a C(3) donating substituent on the hexatriene. Magomedov and coworkers\textsuperscript{117} have recently reported that 3-oxido-hexatrienes bearing a C(2) electron withdrawing group also undergo remarkably facile electrocyclizations to produce substituted cyclohexenones (Scheme 89). Addition of the vinyl sulfone anion 411 to cyclobutenone 410 produced an alkoxide intermediate 412 that
immediately underwent a 4π-electrocyclic ring opening to produce the desired 3-oxido-hexatriene 413. Upon warming to room temperature, triene 413 cyclized to the more stable enolate 414, which protonates on workup to afford the trisubstituted-cyclohexenone 415. This cyclization can also be formally classified as an intramolecular Michael addition of an extended enolate to an electron-deficient alkene. Nonetheless, this example is consistent with our observation that C(2) withdrawing groups and C(3) donating groups significantly lower the activation energy of 6π-electrocyclizations in 1,3,5-hexatrienes.

In order to gain some insight on the relative effects of the C(2) carbonyl and hydrogen bond on the rate of electrocyclization in our 3-amidotriene system, we prepared the N-methyl triene 416 as well as its des-oxo derivative 419 (Scheme 90). Both were available through Stille coupling reactions of stannane 397 with the appropriate vinyl iodide or triflate, respectively. Electrocyclization rates of both amidotrienes (416 and 419) were indeed retarded when compared to the des-methyl derivative 408 previously described. While cyclization of amidotriene 416 still proceeded at the same temperature (110 °C, toluene) as the parent 408, the reaction took 3 hours to reach completion (versus 1 h for 408). More significantly, the des-oxo derivative 419 required both higher temperatures
and prolonged reaction times (120 °C, 12 h) to produce cyclohexadiene 420. These results indicate that both the C(2) carbonyl and a hydrogen bond provided by the C(3) enecarbamate may play a significant role in lowering the activation energy of the electrocyclic ring closure.

**Scheme 90.** Additional 6π-Electrocyclic ring closures

While the electrocyclic ring closures of the amidotrienes described above as well as those reported by Magomedov\textsuperscript{117} offer qualitative evidence of substituent influence on the rate of cyclization of 1,3,5-hexatrienes, a systematic kinetic analysis is lacking in the literature. Lewis and Steiner\textsuperscript{118} reported the first gas-phase kinetic study of the thermal cyclization of cis-1,3,5-hexatriene (Scheme 91), and determined the activation energy for this process to be

**Scheme 91.** Electrocyclization of cis-1,3,5-hexatriene
Moreover, they found that the electrocyclization to form 1,3-cyclohexadiene is exothermic by 15.2 kcal/mol.

A few years later, Spangler\(^{119}\) disclosed a study on the kinetics of thermal electrocyclic ring closures of 3-alkyl-1,3,5-hexatrienes (Scheme 92). The trienes 423 \((R = H, \text{Me}, \text{Et}, \text{and} \ t-\text{Bu})\) were subjected to thermolysis conditions \((100 – 150 ^\circ\text{C})\) and the rates of closure were determined. The results of this study are illustrated in Table 1. It was found that an increase in electron-donating character of the C(3) substituent in triene 423, correlated with an increase in rate of cyclization \((t-\text{Bu} > \text{Et} > \text{Me} > H)\). Activation energies \((E_a)\) for the 3-alkyl-hexatrienes \((\sim 26 \text{ kcal/mol})\) were also found to be over 3 kcal/mol lower than that of the parent 1,3,5-hexatriene. Spangler gave two possible explanations for the observed results; (1) a more electron-donating substituent at the C(3) position of the triene causes an increase in the \(\pi\)-electron density within the polyene

**Scheme 92. Electrocyclization of 3-alkyl-1,3,5-hexatrienes**

\[
\begin{array}{c}
\text{423} \\
\text{T} = 100 - 150 ^\circ\text{C} \\
\text{424}
\end{array}
\]

\(R = H, \text{Me}, \text{Et}, \text{t-Bu}\)

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Temperature</th>
<th>Rate (k \times 10^5 \text{s}^{-1})</th>
<th>(E_a) kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H)</td>
<td>150</td>
<td>24.1</td>
<td>29.1</td>
</tr>
<tr>
<td>(\text{Me})</td>
<td>150</td>
<td>88.8</td>
<td>26.1</td>
</tr>
<tr>
<td>(\text{Et})</td>
<td>150</td>
<td>92.8</td>
<td>26.0</td>
</tr>
<tr>
<td>(t-\text{Bu})</td>
<td>125</td>
<td>84.6</td>
<td>26.7</td>
</tr>
</tbody>
</table>
system, thereby increasing the rate of cyclization; or (2) varying the size of the substituent at C(3) of the triene alters the relative amounts of the s-cis and s-trans conformer about the C(2)-C(3) bond, resulting in an increase in cyclization as the percentage of the s-cis conformer increases. A larger R-group at C(3) results in a higher percentage of the s-cis conformer.

Another interesting study by Spangler\textsuperscript{120} found that the electrocyclization of 3-vinyl-1,3,5-hexatriene (425) proceeds at a rate over 30 times faster than that of its saturated ethyl counterpart (Scheme 93). Temperatures as low as 84 °C were found to effect closure to cyclohexadiene 427. The enthalpy of activation was found to be only 22 kcal/mol. This unforeseen acceleration was attributed to anchimeric participation of the vinyl group depicted in the electrocyclization transition state 426.

Scheme 93. Electrocyclization of 3-vinyl-1,3,5-hexatriene

\[ \text{425} \xrightarrow{84 \text{ } ^\circ\text{C}} \text{426} \rightarrow \text{427} \]

In addition to rate acceleration studies done on 3-alkyl-1,3,5-hexatrienes, Houk and coworkers\textsuperscript{121} have studied substituent effects at C(1) of the hexatriene. Using ab initio molecular orbital calculations, the transition state structures for the disrotatory electrocyclizations of various 1-substituted-1,3,5-hexatrienes were calculated and relative energies were determined using Moller-Plesset theory.\textsuperscript{122} The transition state energies for several of the calculations performed are illustrated in Table 2. In general, transition state energies were found to increase as the electron-withdrawing character of the substituent increased. Houk claims that electron-withdrawing groups at C(1) tend to stabilize the triene through conjugation with the \( \pi \)-system. In the case of the \emph{cis}-substituents, however, this
rise in energy can also be somewhat attributed to steric interactions that destabilize the boat-like transition state.

Table 2. Relative energies calculated for electrocyclization of 1-substituted-1,3,5-hexatrienes using AM1

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Transition State E (kcal/mol)</th>
<th>Substituent</th>
<th>Transition State E (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = H</td>
<td>29.9</td>
<td>R = trans-Me</td>
<td>31.5</td>
</tr>
<tr>
<td>cis-Me</td>
<td>36.4</td>
<td>trans-CN</td>
<td>30.2</td>
</tr>
<tr>
<td>cis-CN</td>
<td>35.8</td>
<td>trans-CHO</td>
<td>30.2</td>
</tr>
<tr>
<td>cis-CHO</td>
<td>34.6</td>
<td>trans-NO</td>
<td>29.0</td>
</tr>
<tr>
<td>cis-NO</td>
<td>29.0</td>
<td>trans-NO</td>
<td>29.0</td>
</tr>
</tbody>
</table>

Marvel and coworkers\(^{123}\) have found that electron-withdrawing groups at C(2) and C(5) of the hexatriene can have a remarkable affect on the rate of electrocyclization (Scheme 94). The relative rate of ring closures increased significantly when ester groups were introduced at the C(2) and C(5) positions. Calculations of the transition state geometry 428 of cis-1,3,5-hexatriene showed that p-orbitals at C(2) and C(5) were partially twisted out of conjugation thus imposing a destabilizing effect on the transition state. It is suggested that an electron-withdrawing group at either of these two positions has a stabilizing effect on the twisted p-orbitals in the transition state thus resulting in a rate enhancement. A similar stabilizing effect by the C(2) ketone carbonyl might be operative in our electrocyclic closures.
C. Delineation of a novel indole annelation method

We were delighted to find that the preparation of \( \alpha \)- (trialkylstannyl)ene car bamates, their Stille coupling to form 3-amidotrienes, and subsequent electrocyclic ring closures to provide the desired substituted cyclohexadienes was a straightforward process. We next turned our attention to completing the proposed indole annelation. Thus, cyclohexadiene 409 was easily oxidized to the BOC protected aniline 429 by treatment with DDQ (Scheme 95). We found that this aromatization can be conveniently accomplished in the same pot as the electrocyclization, once complete conversion to the cyclohexadiene is observed by TLC. Removal of the BOC group with TFA was uneventful and a reductive amination of the resultant aniline with glyoxylic acid provided acid 431. It was hoped that this compound would cyclize to an indole upon subjection to the aforementioned conditions (Ac\(_2\)O, NaOAc, 130 °C) that were reported by Râileanu and coworkers\(^{48}\) (Chapter 2, Scheme 44) for cyclization of the analogously substituted \textit{ortho}-aminobenzaldehyde to \textit{N}-acetylindole. Indeed, this underutilized transformation proceeded smoothly to deliver the desired \textit{N}-acetylindole 432.
Scheme 95. Completion of the indole synthesis

In addition to the single example reported by Răileanu, ring closures to pyrroles have been demonstrated by Heron and coworkers\textsuperscript{124} (Scheme 96). For example, subjection of enamino acid 433 to a solution of refluxing Ac\textsubscript{2}O and Et\textsubscript{3}N (3 : 1) effected a decarboxylative cyclization to afford the 3,4-disubstituted pyrrole 434 in moderate yield. Interestingly, we found that Heron’s conditions for cyclization to indole 432 were even more efficient than those reported by Răileanu (62% v.s. 77% yield from aniline 430).

Scheme 96. Synthesis of pyrroles via the Răileanu closure
We propose two possible mechanisms by which this indole ring closure likely takes place. One involves a Perkin-type reaction of the mixed anhydride intermediate derived from acid 431 (Scheme 97). Cyclization of the enolate of mixed anhydride 435 would give an alkoxide 436 that would undergo intramolecular acylation to afford ester 437. Subsequent decarboxylative elimination would then produce N-acetylindole 432. The more likely mechanism, however, is through the münchnone intermediate 439 generated from the bisacylated derivative 438 (Scheme 98). Addition of the münchnone enolate to the aryl ketone would produce the highly reactive cyclic iminium ion 440 that could undergo a transacylation reaction to afford the strained β-lactone 441. Finally, loss of CO₂ would produce N-acetylindole 432.
Scheme 98. Possible mechanism for closure via a Münchnone intermediate

Münchnones generated from α-amino acids under these conditions are not uncommon. Padwa has extensively studied the generation of münchnones and their utility in 1,3-dipolar cycloadditions. An example closely related to our proposed münchnone intermediate is illustrated in Scheme 99. Treatment of N-(α-allylphenyl)alanine (442) with acetic anhydride at a temperature lower than what we have employed (55 °C) generated the münchnone intermediate 444 which was trapped in situ by the allyl group to produce tetracycle 445.

Scheme 99. Münchnone generated by Padwa
We next turned our attention to delineating the scope and generality of this new indole annelation. Our proof-of-principle example suggested that this method would be especially useful for constructing indoles that are bridged at the C(3) and C(4) positions, a substructure that complicates the synthesis of many indole natural products. We began our investigation by subjecting cyclic α-haloenones of varying ring size to the annelation sequence. Thus, we were also able to incorporate seven and eight membered rings into the indole substructure.

For example, 2-bromocyclooctenone\textsuperscript{126} was coupled with stannane \textsuperscript{393} by the standard protocol to afford trienecarbamate \textsuperscript{447} (Scheme 100). After an uneventful electrocyclic ring closure and oxidation, BOC protected aniline \textsuperscript{448} was subjected to the previously described reaction sequence to afford the unprecedented indole \textsuperscript{450}, with a cyclooctane ring connecting the indole at C(3) and C(4).

**Scheme 100.** Indole prepared with a cyclooctane ring embedded at the C(3) and C(4) positions
With regard to the seven-membered ring, the $\alpha$-iodoenone 452 derived from benzosuberone$^{127}$ proved to be a useful precursor in the annelation sequence, giving rise to another heretofore unknown indole-containing ring system 456 (Scheme 101). We attempted to oxidize indole 456 to the corresponding fully aromatic compound with hopes that it might be a new DNA intercalator.$^{128}$ Unfortunately, subjection of indole 456 and its deacylated counterpart to a variety of oxidants (DDQ, chloranil, MnO$_2$, and Pd/C) were unsuccessful, providing, what appeared to be largely polymeric material.

**Scheme 101.** Indole substituted at the C(3) and C(4) positions

We then attempted to annelate the indole with the aromatic 7-membered ring already in place (Scheme 102). Thus, the iodide 458 derived from benzo-cycloheptenone (457)$^{127}$ was coupled and successfully converted to acid 461 following the same sequence used to prepare acid 455. Surprisingly, however,
subsequent closure to the desired indole 462 was unsuccessful, once again leading to polymeric products.

Scheme 102. Preparation of a possible DNA intercalator

In addition to substituents at the C(3) and C(4) positions of the indole, we were able to successfully incorporate alkyl groups at C(5) by employing the 4-methyl-α-stannylene carbamate 400 in the annelation sequence (Scheme 103). The coupling of stannane 400 with iodide 407 proceeded uneventfully, and electrocyclic ring closure of the resultant triene 463 did not appear to be slowed significantly by the trans-methyl substituent at C(6). Subjection of protected aniline 464 to the remainder of the annelation sequence produced the 3,4,5-trisubstituted indole 465.
It was also of interest to determine whether the Răileanu closure would tolerate the incorporation of a substituent on nitrogen of the indole product. To our knowledge, this type of closure had not yet been reported. Thus, thermolysis of the previously described trienecarbamate 416, followed by in situ oxidation of the resultant cyclohexadiene, smoothly afforded the N-methyl aniline 466 (Scheme 104). Following removal of the BOC group with TFA, the resulting secondary aniline was alkylated with methyl iodoacetate giving rise to ester 467. It should be noted that all attempts to reductively aminate the secondary aniline with glyoxylic acid resulted in complete recovery of starting material. Moreover, alkylation of the secondary aniline with methyl iodoacetate required excessively harsh conditions (3 equiv. K₂CO₃, 100 °C, 12 h). Ester 467 was subsequently hydrolyzed with 4 M NaOH, and following an acidic workup (2 M HCl), we were surprised to obtain clean conversion to the N-methyl indole 468. It appears that strongly acidic conditions (HCl) are essential to effect this...
condensation/decarboxylation sequence, since workup of the hydrolysis with saturated \( \text{KH}_2\text{PO}_4 \) resulted in isolation of the acid intermediate. This intermediate could then be further cyclized to the indole 468 using our standard conditions (\( \text{Ac}_2\text{O}, \text{Et}_3\text{N}, 130 \, ^\circ\text{C} \)), which in this case cannot proceed through the münchnone intermediate and, thus, the Perkin pathway is most likely operating.

This methodology has also proven useful for incorporation of substituents at C(2) of the indole product (Scheme 105). This was accomplished through alkylation of the previously prepared aniline 430 (Scheme 95) with methyl \( \alpha \)-bromophenylacetate (469) under forcing conditions (\( \text{K}_2\text{CO}_3, \text{DMF}, 110 \, ^\circ\text{C} \)) to afford ester 470. Saponification of the ester, followed by subjection of the resultant acid to the Răileanu conditions afforded the desired 2-phenyl indole 471, albeit lacking the acetyl moiety.

**Scheme 105.** Closure to form a C(2) substituted indole

\[ \begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{K}_2\text{CO}_3, \text{DMF} \\
110 \, ^\circ\text{C}
\end{array} \quad \begin{array}{c}
\text{NaOH} \\
1. \\
1. \\
\text{Ac}_2\text{O}, 130 \, ^\circ\text{C}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{N}
\end{array} \]

In addition to cyclic \( \alpha \)-haloenones, we have also employed acyclic \( \alpha \)-haloenones as the starting materials in the annelation sequence. For example, the cis-phenyl ring of \( \alpha \)-bromo-enone 472\textsuperscript{130} did not diminish the yield (90%) of the Stille coupling reaction leading to trienecarbamate 473 (Scheme 106). However, the electrocyclization of trienecarbamate 473 required higher temperatures (150 °C), perhaps due to a more out of plane carbonyl in comparison to the
conformationally locked cyclic trienecarbamates heretofore discussed. The previously discussed transition state calculations performed by Houk on electrocyclic ring closures of cis-1-substituted-1,3,5-hexatrienes (Table 2) may also provide insight as to the retarded rate of cyclization of triene 473. Following oxidation to the protected aniline 474, subsequent transformation to the desired N-acetyl indole 475 was uneventful.

Stille coupling of β,β-disubstituted-α-iodoenone 476 proceeded smoothly to afford amidotriene 477 (Scheme 107). Upon subjection to thermolysis conditions (150 ºC, 6 h), amidotriene 477 underwent a [1,7]-sigmatropic rearrangement to triene intermediate 478, which then cyclized via 6π-ring closure to the cyclohexadiene 479. This result was not entirely unexpected.
since it is well known that [1,7]-sigmatropic rearrangements are often competitive with 6π-electrocyclic ring closures.\textsuperscript{116b} Our standard protocol then furnished the 3,4,6-trisubstituted indole 481.

We also found that β,β-disubstituted cyclic enones can be used in our annelation sequence to form 3,4,5-trisubstituted indoles. For example, electrocyclic ring closure of trienecarbamate 483, prepared from Stille coupling of iodide 482 with stannane 393, afforded the vinylogous imide 484 (Scheme 108). Interestingly, none of the corresponding [1,7]-sigmatropic rearrangement product was seen in this reaction. The \textsuperscript{1}H NMR spectrum (CDCl\textsubscript{3}) of the thermolysis product showed a sharp singlet at δ 1.07 confirming that cyclization to 484 was indeed favored in this case. Subsequent oxidation of cyclohexadiene 484 cleanly afforded the anticipated carbocation rearrangement product 464, which had previously been prepared from 2-iodocyclohexenone and stannane 400 (Scheme 103).

\textbf{Scheme 108.} Carbocation rearrangement during DDQ oxidation

\begin{center}
\begin{tikzpicture}
\node (A) [circle, draw] at (0,0) {482};
\node (B) [circle, draw] at (2,0) {483};
\node (C) [circle, draw] at (4,0) {484};
\node (D) [circle, draw] at (6,0) {464};
\node (E) [above of=A, yshift=-0.5cm] {393 Pd(PPh\textsubscript{3})\textsubscript{4}};
\node (F) [above of=B, yshift=-0.5cm] {150 °C, 6 h DDQ, 110 °C 3 h DDQ, 110 °C 3 h}
\node (G) [below of=A, yshift=-0.5cm] {Cul, THF 50 °C 84%}
\node (H) [below of=B, yshift=-0.5cm] {BOC}
\node (I) [below of=C, yshift=-0.5cm] {BOC}
\node (J) [below of=D, yshift=-0.5cm] {BOC}
\node (K) [below of=E, yshift=-0.5cm] {Pd(PPh\textsubscript{3})\textsubscript{4}};
\node (L) [below of=F, yshift=-0.5cm] {\textsuperscript{1}H NMR spectrum (CDCl\textsubscript{3}) of the thermolysis product showed a sharp singlet at δ 1.07 confirming that cyclization to 484 was indeed favored in this case. Subsequent oxidation of cyclohexadiene 484 cleanly afforded the anticipated carbocation rearrangement product 464, which had previously been prepared from 2-iodocyclohexenone and stannane 400 (Scheme 103).
Intrigued by the potentially complex indole ring systems that could arise from [1,7]-sigmatropic and carbocation rearrangements, we prepared the highly substituted trienecarbamates 485 and 486 (Scheme 109) from their respective α-iodoenones. Unfortunately, all attempts to thermalize trienes 485 and 486 in hopes of obtaining potential rearrangement products resulted in complex mixtures largely consisting of polymerized material.

Scheme 109. Other attempted [1,7]-sigmatropic rearrangements

We have also found that additional heterocyclic rings can be incorporated into the product indole by initiating the annelation sequence with heterocyclic α-iodoenones or α-stannylencarbamates. With respect to the former, iodoenone 487\textsuperscript{131} underwent clean coupling with stannane 400 to afford amidotriene 488 (Scheme 110). Subsequent electrocyclization of amidotriene 488 proceeded smoothly with a negligible electronic/steric impact of the additional carbamate substituent to afford a cyclohexadiene that was oxidized (DDQ) \textit{in situ} to the desired protected aniline 489. Completion of the annelation afforded indole 490, a substructure embodied in several biologically active natural products, e.g., prianosins D.\textsuperscript{132}
Finally, the versatility of this indole annelation method is showcased in the preparation of the unusual tetracyclic indole 495 (Scheme 111). Employing the heterocyclic α-stannylene carbamate 403 in the reaction sequence allows for introduction of an N-C(7) ring in the product indole, a substructure that may not be accessible using other established indole annelation methods. It should be noted that the acid derived from hydrolysis of ester 494 showed no tendency to cyclize to the indole 495, as with the N-methyl derivative (467 → 468, Scheme 104), regardless of the acidity employed during workup. In addition, closure to the indole under Răileanu conditions (Ac₂O, Et₃N) in this case cannot proceed through the proposed münchnone intermediate (Scheme 98) previously described since the aniline nitrogen is fully substituted and cannot be acylated by acetic anhydride. Therefore, the likely pathway is through a Perkin-type reaction as discussed in Scheme 97.
In conclusion, we have shown that both of the aromatic rings of indoles can be constructed from readily available α-haloenones and α-(trialkylstannyl)enecarbamates using a 5-step sequence that features facile electrocyclic ring closures of trienecarbamates. Simple variation of the stannane or enone employed in the reaction sequence can lead to a variety of substituted indoles that may not be easily accessible via established annelation methods. Application of this method towards the total synthesis of welwistatin will be discussed in the following chapter.
In Chapter 3 we demonstrated the ability to effect intramolecular 7-endo conjugate addition reactions of β-ketoesters to afford bicyclo[4.3.1]decan-3,10-diones. Thus, we were confident that dioxin 206 would be a suitable precursor to the desired bicyclo[4.3.1]decanone 204 in our proposed welwistatin synthesis (Scheme 112). Once transformed to α-iodoenone 202, we believed that application of our newly developed indole annelation sequence (Chapter 4) could lead to construction of a fully functionalized welwistatin ring system. This chapter discusses efforts directed towards the total synthesis of welwistatin through application of these two new methods.

Scheme 112. Proposed synthetic route to welwistatin

welwistatin
II. Model systems for the synthesis of welwistatin

In order to explore the viability of the proposed synthetic route, a model system lacking the C(13) silyloxy and C(12) methyl and vinyl substituents was first undertaken. Thus, bridged bicyclic β-ketoester 499 (Scheme 113) was prepared in a similar manner to the analogous ethyl ester 275 (Scheme 62) using our standard alkylation/retrocycloaddition/conjugate addition reaction sequence. For scale up purposes, we found that the conjugate addition reaction leading to bicyclic dione 499 worked comparably well using K$_2$CO$_3$ in ethanol as opposed to the standard Deslongchamps conditions (Cs$_2$CO$_3$, CH$_3$CN).$^{67a}$ Regioselective deprotonation at the more accessible α-carbon of ketone 499, followed by trapping of the resultant enolate with TMSCl gave a silyl enol ether, which was further oxidized using the Larock protocol$^{134}$ to afford enone 500 in 72% over two steps. Geminal dimethylation of the saturated α-carbon of enone 500 was accomplished by treatment with NaH and excess methyl iodide to give ketone

Scheme 113. Preparation of a model system α-bromoenone
Finally, bromination of enone 501 followed by elimination of the resultant vicinal dibromide afforded the desired α-bromoeneone 502 in good yield. It should be noted that the gem-dimethyl group is essential to the success of this reaction sequence, as competing α-bromination occurs upon treatment of enone 500 with bromine, giving rise to a mixture of products. In addition, all attempts to prepare the analogous iodide 503 via the Johnson protocol were unsuccessful.

**Scheme 114. Attempts to iodinate enone 501**

(Scheme 114). Molecular modeling of the possible chair and boat cycloheptenone conformers of 501 (Figure 22) indicate a sterically congested enone that is twisted out of conjugation with the carbonyl, thereby preventing the initial Michael addition of pyridine (or pyridine derivative). While starting material was typically recovered in reactions run at room temperature, heating resulted in decomposition of enone 501 to a number of unidentifiable products.

**Figure 22. Chair and boat cycloheptenone conformers of enone 501**

- 501a: boat cycloheptenone  
  MMXE = 16.5
- 501b: chair cycloheptenone  
  MMXE = 15.3
We were pleased to discover that the α-bromoenone 502 was a suitable precursor for our indole annelation sequence. Stille coupling of bromoenone 502 with α-stannylene carbamate 393 smoothly afforded the desired amidotriene 504 (Scheme 115). When subjected to thermolysis (110 °C, 3 h), triene 504 underwent a facile electrocyclic ring closure to afford a cyclohexadiene, which was oxidized in situ with DDQ to furnish BOC protected aniline 505. Further removal of the BOC group with TFA and a reductive amination of the resultant aniline 506 with glyoxylic acid provided acid 507. Closure to the indole under standard Răileanu conditions (Ac₂O, Et₃N, 130 °C) proved to be uneventful, giving rise to N-acetylindole 508 in excellent yield.

At this point, we believed that it would be useful to know if the planned introduction of the bridgehead nitrogen and oxidation of the indole to the indolinone were feasible transformations. To that end, the labile N-acyl group
was removed (K$_2$CO$_3$, MeOH) and replaced with a methyl group (NaH, MeI) to afford N-methyl indole 510 (Scheme 116). Subsequent hydrolysis of the ester 510 with 4 M NaOH under forcing conditions smoothly provided the bridgehead acid 511. After surveying a variety of conditions employed for the Curtius rearrangements$^{135}$ of acids that are fully substituted $\alpha$ to a carbonyl, we found

**Scheme 116. Introduction of bridgehead carbamate**

![Diagram of the reaction scheme]

that the isopropyl mixed anhydride derived from acid 511 could be converted to the corresponding acyl azide with NaN$_3$ in acetone. Subsequent thermolysis of the acyl azide effected a Curtius rearrangement to produce intermediate isocyanate 512, that was immediately trapped *in situ* with MeOH to furnish the desired bridgehead carbamate 513.

Although we were pleased to find that the bridgehead nitrogen could be introduced at the indole stage of the synthesis, hydrolysis of the hindered bridgehead ester 510 required elevated temperatures (70 °C) and prolonged reaction times (8 h), and would likely be even more problematic when the C(12)
vinyl and methyl substituents are present. In anticipation of possible problems associated with the bridgehead ester in the fully substituted welwistatin ring system, we realized that it may be advantageous to install the bridgehead nitrogen prior to indole annelation. This turned out to be quite straightforward.

Hydrolysis of bridgehead ester 501 proceeded at a much lower temperature (0 °C) than that needed for the more hindered indole derivative 510 (Scheme 117). Subsequent Curtius rearrangement of the resultant acid and trapping of the isocyanate with MeOH smoothly provided bridgehead carbamate 514. This compound once again failed to iodinate to the corresponding α-iodoenone. However, the previously described bromination/elimination sequence worked quite well giving rise to bromoenone 515. Subjection of bromoenone 515 to our standard annelation protocol then furnished the N-acyl indole 518.

Scheme 117. Introduction of bridgehead carbamate prior to indole closure
We next set out to test the viability of the proposed indole oxidation and determine the stereochemistry resulting at the C(3) position of the oxindole. Thus, N-acyl indole 518 was deprotected and methylated as previously described to afford N-methyl indole 513 (Scheme 118). Subjection of indole 513 to warm HCl (70 °C) in DMSO\textsuperscript{14e} effected oxidation to the mixture of oxindoles 521 and 522 (1.7 : 1, respectively). Interestingly, the vinyl chloride 520 is the product from the reaction if it is performed at room temperature. Subjection of indole 520 to the original conditions affords the same mixture of oxindoles 521 and 522. It is known\textsuperscript{136} that chlorodimethylsulfonium ion is generated from DMSO in concentrated HCl and this is the likely chlorinating agent that leads to 520. After separation by silica gel chromatography, the stereochemical assignment of each isomer was confirmed through NMR studies. Key nOe correlations of isomer 521

Scheme 118. Oxidation to indolinone
were observed between the C(3) oxindole proton and the C(16) equatorial methyl substituent, and the C(14) equatorial proton and the C(16) axial methyl substituent (Figure 23). Furthermore, isomer 522 showed a diagnostic nOe between the C(3) oxindole proton and the C(13) axial proton.

**Figure 23.** Confirmation of oxindole stereochemistry

![Figure 23](image)

The undesirable stereoselectivity was not entirely unexpected. Molecular modeling calculations (PC Model) suggest that oxindole 521 is thermodynamically favored over 522 by 0.7 kcal. It is likely that these isomers are in thermodynamic equilibrium with one another under these conditions. Indeed, oxindole 521 was recycled by subjecting it to the same reaction conditions to afford the same mixture of diastereomers (Scheme 119). In contrast, molecular modeling calculations (PC Model) also suggest that

**Scheme 119.** Thermodynamic equilibration of oxindole 521

![Scheme 119](image)
welwitatin (149) is thermodynamically favored by 1.5 kcal over its C(3) epimer counterpart. In addition, welwitindolinone B isothiocyanate (152) was isolated as a 12 : 1 mixture along with its C(3) epimer 523 (Figure 24), suggesting that there may be a thermodynamic equilibrium achieved when nature is synthesizing these compounds. Calculations (PC Model) also found welwitindolinone B 152 (boat cyclohexane ring) to be favored by 1.3 kcal over its epimer 523 (chair cyclohexane ring).

**Figure 24.** Isolation of welwitindolinone B isothiocyanate and its C(3) epimer

III. Synthetic studies towards a β-ketoester Michael addition

Based on the success of our model system, we were now encouraged to explore our proposed route to the anti-microtule agent welwistatin. Our synthesis commenced with preparation of the known β-ketoester 208,50,137 the substrate required for our key alkylation/retrocycloaddition/Michael addition reaction sequence (Scheme 120). To that end, Birch reduction of 3-methylanisole with Li/NH₃ in t-BuOH, followed by hydrolysis of the resultant enol ether afforded 3-methylcyclohex-3-enone (524) in good yield. Treatment of 524 with peracetic acid afforded an intermediate epoxide that underwent base induced ring opening to the hydroxy enone 525. Protection of the alcohol, followed by stereoselective conjugate addition of vinyl magnesium bromide in the presence of TMSCl
produced silyl enol ether 527 as a single diastereomer. Finally, regeneration of the enolate regioselectively with MeLi, followed by treatment with Mander's reagent\(^\text{38}\) cleanly furnished the desired \(\beta\)-ketoester 208.

**Scheme 120.** Synthesis of \(\beta\)-ketoester 208

With \(\beta\)-ketoester 208 in hand we began to focus our attention on the stereoselective Weiler dianion alkylation reaction with bromodioxin 207 (Scheme 121). Initial experiments were not encouraging. Attempts to form the dianion under standard conditions using NaH and BuLi in THF resulted in formation of a number of products, one of which appeared to be butyl addition to ketone 208. This led us to believe that NaH was not deprotonating the hindered \(\beta\)-ketoester proton. However, all attempts to form the dianion with two equivalents of LDA using a variety of solvents and temperatures resulted in a similar mixture of unknown byproducts. After extensive investigation, a combination of LiH/catalytic HMDS, followed by BuLi at -78 °C cleanly produced a dianion of 208 that was subsequently treated with bromide 207 to afford the desired dioxin 528 as a 1 : 1 mixture of diastereomers. Based on the aforementioned literature
precedent\textsuperscript{52} of stereoselective alkylation of 3,3,4-cyclohexane-1-ones (Schemes 46 and 47), we hoped that the mixture was the result of non-stereoselective protonation at the \( \beta \)-ketoester carbon. However, separation of the two isomers by silica gel chromatography and silylation of each under mildly basic conditions (TMSCl, Et\(_3\)N, CH\(_2\)Cl\(_2\)) resulted in formation of two different silyl enol ether products 530 and 531. Thus, it seemed likely that the dianion alkylation of \( \beta \)-ketoester 208 gave a 1 : 1 mixture of dioxins 529 and 206.

We then began searching for an alternative route to form the desired ketone 206 as a single diastereomer. We first examined the prospect of introducing the dioxin sidechain prior to formation of the \( \beta \)-ketoester. Thus, ketone 532 was easily prepared through hydrolysis of silyl enol ether 527 with aqueous acetic acid (Scheme 122). We were pleased to find that alkylation of the enolate of ketone 532 with bromide 207 proceeded with greater than 10 : 1
diastereoselectivity favoring alkylation adduct 533. The assignment of 533 was based on the \(^1\)H NMR (CDCl\(_3\)) integration of the two observed silyloxy methine proton resonances. We were much more confident with this stereochemical assignment based on the similarity of this example with the previously discussed alkylations\(^{52}\) of similar ketones. All attempts, however, to C-acylate ketone 533 to form 534 were unsuccessful, with the majority resulting in formation of the undesired O-acylation\(^{139}\) product 535 (Scheme 122). Interestingly, the \(^1\)H NMR spectrum (CDCl\(_3\)) of ketone 533 shows a broad triplet (8.0 Hz) for the proton next to the silyloxy substituent. This indicates that the silyloxy group is oriented in an axial position, which could lead to an unfavorable 1,3-diaxial interaction with the approaching electrophile at C(2) in a chair-like transition state, as well as a steric interaction with the adjacent methyl substituent, thus favoring O-acylation (Scheme 123). Similarly, C-acylation though the alternate chair conformer would be inhibited by the axial dioxin substituent and the adjacent vinyl substituent.
Scheme 123. Steric interactions encountered with C-acylation of ketone 533

In view of these difficulties, we examined the alkylation the of α,β-unsaturated ketoester 538, which already incorporates the ester substituent (Scheme 124). This compound was easily prepared in three steps from cyclohexenone 525, through iodination of the enone, protection of the alcohol with TBSCI, and a subsequent palladium catalyzed ethoxy carbonylation reaction.

Scheme 124. Alternate route to β-ketoester 206
of iodide 537. Our hope was that deprotonation at the α-position to the ketone would be kinetically favored over the more acidic vinylogous β-ketoester protons. Unfortunately all attempts to alkylate ketoester 538 at the desired α-position resulted in complete recovery of starting material. Moreover, attempts to form the dianion with two equivalents of LDA resulted in formation of a complex mixture of unidentifiable products.

In addition to acyclic β-ketoesters, we also explored the possibility of accessing 206 through the bicyclic keto-lactone 540137 (Scheme 125). Thus, alkylation of keto-lactone 540 with bromide 207 afforded a single diastereomer that we tentatively assigned as compound 541. We had hoped that ring opening of the lactone 541 with basic ethanol would result in formation of β-ketoester 542. However, complete conversion to carbonate 543 was observed.

**Scheme 125.** Synthetic studies towards β-ketoester 206
Unable to easily access the desired $\beta$-ketoester 206 in high diastereomeric excess, we turned our attention to the preparation of the acetonide 547 (Scheme 126) in hopes that a more rigid ring conformation would lead to a more favorable stereoselectivity in the Weiler dianion alkylation. The acetonide 547 was prepared in a four-step sequence from $\beta$-ketoester 208. Ozonolysis of the vinyl group, followed by deprotection of the TBS ether with TBAF afforded the $\beta$-hydroxyaldehyde 545. Following reduction of the aldehyde moiety, the resulting diol 546 was cyclized with 2,2-dimethoxypropane and catalytic $p$-TsOH to cleanly provide acetonide 547 in good yield. We were disappointed, however, to find that

Scheme 126. Weiler dianion alkylation with rigid $\beta$-ketoester 547

alkylation of the Weiler dianion of 547 with bromide 207 once again produced a 1 : 1 mixture of alkylation adducts 548. Similarities in the $^1$H NMR spectrum of $\beta$-ketoester 548 with that of 528 (Scheme 121) confirmed that the mixture was indeed at the C(6) stereocenter and not the $\beta$-ketoester carbon as we had hoped.
In addition, ketone 551, prepared in a similar fashion to that of 547, was found to undergo clean alkylation with bromide 207 (Scheme 127). However, attempts to acylate the resulting ketone 552 with Mander’s reagent once again resulted in exclusive O-acylation to afford enol carbonate 553.

**Scheme 127. Preparation of protected ketone 552**

In another attempt to add rigidity to the molecule, cyclic β-ketoester 555 was prepared in four steps from ethyl acetoacetate and allyl bromide 554.\(^{140}\) (Scheme 128). Unfortunately, dianion alkylation with bromide 207 produced a mixture of alkylation adducts 556 as well.
At this point, it became clear that construction of the desired β-ketoester through Weiler dianion chemistry was problematic. Since we were confident of the stereochemical assignment of ketone 533, we moved on to explore introduction of the vinyl chloride substituent in hopes that flattening the cyclohexanone ring would result in C-acylation to form β-ketoester 561 (Scheme 129). Thus, ketone 533 was transformed to enol carbonate 557 through O-acylation of the ketone enolate, followed by removal of the silyl protecting group and oxidation of the resulting alcohol with TPAP/NMO. Following formation of the enol triflate and palladium catalyzed coupling with hexamethylditin, stannane 558 was smoothly converted to vinyl chloride 559 by treatment with excess CuCl₂ and Et₃N. Finally, removal of the enol carbonate with 3 equivalents of MeLi furnished the desired ketone 560. However, all attempts to reform the enolate of ketone 560 regioselectively were unsuccessful, resulting in a complex mixture of byproducts. Moreover, generation of the enolate by treatment of enol carbonate 559 with MeLi, followed by in situ addition of Mander’s reagent resulted in
recovery of enol carbonate 559, indicating that the vinyl chloride substituent has no affect on acylation of the C(2) enolate.

**Scheme 129.** Preparation of vinyl chloride 560

Knowing that we likely had a mixture of diastereomers at C(6) in the dianion products 528, 548, and 556 (Scheme 130), we thought that it might be possible to equilibrate that stereocenter during the Michael addition reaction to afford the desired bicyclo[4.3.1]decanones 204, 564, and 566, respectively. Unfortunately, all attempts to effect 7-endo cyclizations of the corresponding enones 562, 563, and 565 were unsuccessful, usually resulting in decomposition of starting material. At this point, we were unsure as to whether our problems with the Michael addition had to do with the C(6) relative stereochemistry or the reactivity of the hindered β-ketoester carbon. Considering the success of the Michael addition producing bicyclo[4.3.1]decanone 278 (Scheme 62) which bears
a C(2) *gem*-dimethyl substituent, the C(6) stereochemistry seemed the likely culprit.

**Scheme 130.** Substrates and conditions for Michael addition reactions

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cs₂CO₃, CH₃CN</td>
<td></td>
</tr>
<tr>
<td>2. Cs₂CO₃, DMF</td>
<td></td>
</tr>
<tr>
<td>3. KOEt, THF</td>
<td></td>
</tr>
<tr>
<td>4. t-BuOK, THF</td>
<td></td>
</tr>
<tr>
<td>5. K₂CO₃, EtOH</td>
<td></td>
</tr>
<tr>
<td>6. t-BuOK, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>7. FeCl₃, CH₂Cl₂</td>
<td></td>
</tr>
<tr>
<td>8. DBU, CH₂Cl₂</td>
<td></td>
</tr>
<tr>
<td>9. Et₃N</td>
<td></td>
</tr>
<tr>
<td>10. Mg(OEt)₂, EtOH</td>
<td></td>
</tr>
</tbody>
</table>

In addition to the conjugate addition reaction approach to prepare the desired bicyclo[4.3.1]decanone ring system embodied in welwistatin, we also briefly examined the related palladium-catalyzed enolate arylation cyclizations,¹⁴⁸,¹⁴¹ since the substrates were easily available. To test the feasibility of this approach, we prepared the allyl bromide 569 in a three step sequence from methyl 2-iodophenylacetate (Scheme 131). Alkylation of bromide
Scheme 131. Preparation of allyl bromide 569

569 with the dianions of β-ketoesters 208, 547, and 555 afforded aryl iodides 570, 572, and 574, albeit as 1:1 mixtures of diastereomers once again (Scheme 132). Attempts to effect the desired palladium-catalyzed enolate arylation reaction of these three substrates, however, did not result in isolation of any of the desired products. A variety of catalysts, bases, and temperatures were employed, but most reactions returned large amounts of starting material.

Scheme 132. Substrates and conditions for palladium-catalyzed enolate arylation

Reaction Conditions
1. Cs₂CO₃, CuI, THF, 100 °C
2. Cs₂CO₃, CuI, phenol, THF 100 °C
3. Pd₂(db₃)a, Pt-Bu₃, Cs₂CO₃, DMF
4. Pd₂(db₃)a, Pt-Bu₃, Cs₂CO₃, CH₃CN
5. tBuOK, Pd(PPh₃)₄, THF, 70 °C
6. K₃PO₄, Pd₂(db₃)a, Pt-Bu₃, toluene
7. Cs₂CO₃, Pd₂(db₃)a, CH₃CN, 80 °C

1. Cs₂CO₃, CuI, phenol, THF 100 °C
2. Pd₂(db₃)a, Pt-Bu₃, Cs₂CO₃, DMF
3. tBuOK, Pd(PPh₃)₄, THF, 70 °C
4. K₃PO₄, Pd₂(db₃)a, Pt-Bu₃, toluene
5. Cs₂CO₃, Pd(PPh₃)₄, CH₃CN, 80 °C

1. Cs₂CO₃, CuI, phenol, THF 100 °C
2. Pd₂(db₃)a, Pt-Bu₃, Cs₂CO₃, DMF
3. K₃PO₄, Pd₂(db₃)a, Pt-Bu₃, toluene
IV. Synthetic studies involving a bridgehead β-ketonitrile

The disappointing results associated with the β-ketoester dianion alkylation as well as its failure in the subsequent Michael addition led us to consider a possible functional group alternative to the ester moiety. A nitrile group was the first that came to mind. We believed that a smaller, flatter, and more electron-withdrawing substituent, such as a nitrile, could be the key to forming the strained bicyclo[4.3.1]decanone ring system present in welwistatin. Moreover, β-ketonitriles are readily available through treatment of ketone enolates with TsCN,\textsuperscript{142} and hopefully would prefer to cyanate on carbon vis-à-vis oxygen thereby allowing us to exploit our stereoselective synthesis of ketone 533. We were pleased to discover that regioselective enolate formation of ketone 533, followed by addition of TsCN smoothly afforded the desired β-ketonitrile 576 as a single diastereomer (Scheme 133). The tentatively assigned

\textbf{Scheme 133.} Synthesis of bicyclo[4.3.1]decanone via β-ketonitrile 577
stereochemistry of β-ketonitrile 576 was confirmed through NOE experiments as well as $^1$H NMR analysis. The $^1$H NMR spectrum (CDCl$_3$) shows a broad triplet for the C(4) proton (7.1 Hz), indicating an axial silyloxy substituent. In addition, a key diagnostic nOe was observed between the C(2) and C(6) protons, thereby confirming their axial orientation as depicted in structure 576.

With the correct relative stereochemistry required for welwistatin now in place, we turned to completion of the bridged bicyclic structure. Thus, thermolysis of dioxin 576 effected a retrocycloaddition to cleanly afford enone 577. To our delight, treatment of enone 577 with Et$_3$N in THF/MeOH effected a smooth 7-endo intramolecular conjugate addition$^{143}$ reaction to deliver the desired bicyclo[4.3.1]decanone 578 with no indication of competing epimerization at C(15).

With the fully substituted bridged bicyclic ring system in hand, we directed our attention toward the preparation of the α-haloenone required for the indole annelation sequence. Thus, treatment of ketone 578 with TMSOTf and Et$_3$N, followed by oxidation of the resultant silyl enol ether with IBX$^{144}$ afforded enone 579 in good yield (Scheme 134). Our initial plan was to introduce the gem-dimethyl group through bis-alkylation of enone 579 as we had in the model system (500 $\rightarrow$ 501, Scheme 113). Unfortunately enone 579 turned out to be extremely labile to basic reaction conditions, and therefore could not be methylated. Addition of bases such as NaH, KH, t-BuOK, LiHMDS, and LDA to enone 579 all lead to rapid decomposition. Attempts to prepare α-haloenone 581 from 579 were also unsuccessful. Iodination following the Johnson protocol$^{114}$ resulted in recovery of starting material, while treatment with bromine lead to a variety of products, including α-bromination and bromination of the vinyl group.
We then turned our attention to developing an alternative route to the required α-bromo-enone. To that end, silyl enol ether 582 could be easily brominated with NBS to afford α-bromoketone 583 (Scheme 135). Regeneration of the silyl enol ether with TMSI, followed by treatment with PhSeCl gave rise to the α-bromo-α-phenylselenyl ketone 584 in good yield. Oxidation to the selenoxide was best accomplished with m-CPBA at -20 °C, which was then found to undergo smooth syn elimination, in the presence of ethyl vinyl ether as an acid scavenger, to afford the desired α-bromo-enone 585. Attempts to install the gem-dimethyl group at this point once again failed. Since it may be less problematic to install the gem-dimethyl group once the aromatic ring is in place, we decided to subject α-bromo-enone 585 to our indole annelation sequence. The coupling of bromoenone 585 with α-stannylene carbamate 393 proceeded as expected to afford the amidotriene 586. While subjection of triene 586 to thermolysis conditions did effect the desired electrocyclic ring closure, unfortunately,
cyclohexadiene 587 was thermally unstable, and underwent a concomitant vinlylogous retro-Mannich reaction\textsuperscript{145} to afford the protected aniline 589. Attempts to suppress the vinlylogous retro-Mannich using a variety of solvents, or accelerate the electrocyclic rearrangement using basic, microwave, or high pressure reaction conditions were unsuccessful (Scheme 135).

Scheme 135. Electrocyclization resulting in a vinlylogous retro-Mannich reaction

<table>
<thead>
<tr>
<th>Conditions attempted</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Et\textsubscript{3}N, toluene, 100\textdegree C</td>
<td>589 starting material decomposition</td>
</tr>
<tr>
<td>2. Et\textsubscript{3}N, 100\textdegree C</td>
<td>589 decomposition</td>
</tr>
<tr>
<td>3. octane, 115 \textdegree C</td>
<td>589 decomposition</td>
</tr>
<tr>
<td>4. NaH, THF, 0 \textdegree C</td>
<td>589 decomposition</td>
</tr>
<tr>
<td>5. BuLi, THF, -78 \textdegree C</td>
<td>589 decomposition</td>
</tr>
<tr>
<td>6. microwave, octane, 5 min, 110 \textdegree C</td>
<td>589 decomposition</td>
</tr>
<tr>
<td>7. 12 kbar, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>589 decomposition</td>
</tr>
</tbody>
</table>
We attributed this unwanted secondary reaction during the electrocyclic ring closure of triene 586, in comparison to the successful closures observed for the model system trienes 504 and 516 (Scheme 136), to the strain associated with the vicinal quaternary carbons as well as a smaller electron-withdrawing nitrile substituent, which can better overlap with a developing carbanion. We

considered two possible solutions to suppress the undesired vinylogous retro-Mannich reaction: (1) Convert the bridgehead nitrile to a protected amine with the hope that a less electron-withdrawing substituent will shut down the competing side reaction; (2) Reduce and protect the bridgehead ketone which would even more so destabilize the developing carbanion in the vinylogous retro-Mannich reaction. The former solution initially seemed the most appealing, since it would not cost us additional steps in our synthetic route, and we had already successfully performed an electrocyclic ring closure with a bridgehead carbamate substituent (516 → 591, Scheme 136).
To that end, we began surveying conditions for hydrolysis of the
bridgehead nitrile 578 to the corresponding amide or acid. Initial experiments did
not look promising. Subjection of nitrile 578 to basic conditions, such as aqueous
NaOH or K₂CO₃/H₂O₂ resulted in immediate decomposition, while acidic
conditions such as HCl and H₂SO₄ did little other than remove the TBS group.
However, a literature search of nitrile hydrolysis methods uncovered an
underappreciated, highly reactive platinum catalyst 593 (Scheme 137) reported
by Parkins¹⁴⁶ for the hydrolysis of hindered nitriles to amides under mild and
essentially neutral conditions. Indeed, Myers has recently utilized this catalyst in
his stephacidin B synthesis¹⁴⁷ to hydrolyze the sensitive quaternary nitrile 592 to
amide 594 in good yield (Scheme 137). In our case, we were delighted to find
that the Parkins catalyst 593 (5 mol%) successfully converted bridgehead nitrile
578 to the desired bridgehead amide 595 in 90% yield (Scheme 138).

**Scheme 137.** Platinum catalyzed hydrolysis of a nitrile to an amide

![Scheme 137](image)

**Scheme 138.** Hydrolysis of bridgehead nitrile 578

![Scheme 138](image)
The proposed catalytic cycle of hydrolysis is outlined in Figure 25. Upon loss of a hydride and addition of solvent, the nitrile then coordinates to the platinum catalyst as depicted by cationic intermediate 597. The proximal hydroxyl group attached to the phosphorus then undergoes an extremely facile intramolecular nucleophilic attack on the coordinated nitrile to give the five-membered ring intermediate 598. Addition of water to the imidate produces intermediate 599, which can then ring open to a nitrogen coordinated amide, which dissociates to afford the desired amide and regenerate the catalyst 596. This remarkable catalyst was found to have a turnover number of 5700 mol/mol of catalyst (0.017 mol%) in the hydrolysis of acetonitrile to acetamide.\textsuperscript{146b}

**Figure 25.** Proposed catalytic cycle for nitrile hydrolysis with Parkins catalyst
With amide 595 in hand, we directed our attention toward introduction of the bridgehead nitrogen present in welwistatin. It was pleasing to discover that the Baumgarten variant\textsuperscript{148} of the Hofmann rearrangement was successful for transformation of amide 595 to isocyanate 600 (Scheme 139). Subjection of isocyanate 600 to methanolysis, however, did not afford the desired carbamate 601, but instead gave what we believed to be the cyclic diketal 602. In addition, treatment of isocyanate 600 with benzyl alcohol produced the bis-ketal 603. This structural assignment was confirmed by X-ray crystallographic analysis of the $N$-benzylated derivative 604 (Figure 26). This transformation presumably proceeds through initial carbamate formation, followed by addition of the alcohol to the

\textbf{Scheme 139. Hofmann rearrangement of bridgehead amide 595}
C(3) ketone, which then cyclizes to the bis-ketal (Scheme 140). In the case of benzyl alcohol, up to 25% of the carbamate can be isolated if the reaction is stopped after one hour, but resubjection of the mixture to the reaction conditions effects complete conversion to the bis-ketal 603 (Scheme 140). Attempts to prepare the corresponding BOC carbamate by treatment of isocyanate 600 with t-BuOH or t-BuOK resulted in complete recovery of the starting material.

**Scheme 140. Formation of cyclic carbamate 602**
Unable to access the bridgehead carbamate directly from isocyanate 600, we next examined protection of the corresponding bridgehead amine (Scheme 141). Thus, treatment of isocyanate 600 with 1 M NaOH at 0 °C effected formation of the intermediate carbamic acid, which underwent smooth decarboxylation to furnish amine 608 in good yield. Unfortunately, the hindered amine 608 proved to be inert to a variety of reagents, including, chloroformates, sulfonyle halides, and alkyl halides. Attempts to protect amine 608 through reductive amination with various benzaldehyde derivatives resulted in full recovery of starting material. After extensive investigation, we found that anhydrides and acid chlorides were the only electrophiles reactive enough to provide a viable protecting group for the bridgehead amine. We first examined the feasibility of a trifluoroacetamide group in the subsequent indole annelation sequence. Thus, treatment of amine 608 with trifluoroacetic anhydride and Et$_3$N afforded trifluoroacetamide 609 in excellent yield (Scheme 141). Trifluoroacetamide 609 was conveniently transformed to the desired α-bromoenone 612 via the same sequence used to prepare bromoenone 585 (Scheme 135). Stille coupling of α-bromoenone 612 proceeded as expected to provide amidotriene 613. Much to our dismay however, thermolysis of triene 613 did not result in formation of the desired cyclohexadiene, but instead produced a complex mixture of products, one of which appeared to be N-Boc protected aniline 614, resulting from the undesired vinylogous retro-Mannich reaction.
Scheme 141. Attempted electrocyclization with bridgehead trifluoroacetamide

\[
\begin{align*}
\text{OTBS} & \quad \text{OCN} \\
\text{600} & \quad \xrightarrow{1 \text{ M NaOH}} \text{THF} \quad 80\% \\
\text{OTBS} & \quad \text{N} \\
\text{608} & \quad \xrightarrow{(\text{CF}_3\text{CO})_2\text{O}} \text{THF, 0 \text{oC}} \quad 95\% \\
\text{OTBS} & \quad \text{F}_3\text{C} \\
\text{609} & \quad \xrightarrow{1. \text{TMSOTf}} \text{Et}_3\text{N} \\
\text{70\%} & \quad 2. \text{NBS} \\
\text{CH}_2\text{Cl}_2 & \quad 0 \text{oC} \\
\text{OTBS} & \quad \text{F}_3\text{C} \\
\text{610} & \quad \xrightarrow{m\text{-CPBA}} \text{CH}_2\text{Cl}_2 \\
\text{612} & \quad \xrightarrow{45\%} \\
\text{OTBS} & \quad \text{N} \\
\text{611} & \quad \xrightarrow{1. \text{TMSCl, Nal}} \text{Et}_3\text{N, CH}_3\text{CN} \\
\text{OTBS} & \quad \text{F}_3\text{C} \\
\text{610} & \quad \xrightarrow{2. \text{PhSeCl}} \text{THF} \\
\text{82\% 2 steps} & \\
\text{OTBS} & \quad \text{F}_3\text{C} \\
\text{612} & \quad \xrightarrow{89\%} \text{Pd(PPh}_3)_4 \text{CuI} \\
\text{THF, 65 \text{oC}} & \text{393} \\
\text{TBSO} & \quad \text{N} \\
\text{613} & \quad \xrightarrow{\text{toluene}} 110 \text{oC} \\
\text{F}_3\text{C} & \quad \text{H} \\
\text{614} & \quad 1 \text{h} \\
\text{BOC} & \quad \text{N-H} \\
\text{~ 15\%} & \quad \text{polymerization}
\end{align*}
\]
We wondered if the steric encumbrance of substitution at the bridgehead position could be used to our advantage. Therefore, we decided to introduce the bridgehead isothiocyanate at an early stage in hopes that it could withstand the conditions of our indole annelation sequence. To that end, treatment of amine 608 with thiophosgene afforded the desired isothiocyanate 615 (Scheme 142). Following silylation of 615 with TMSOTf, the resulting enol ether was selenylated with PhSeCl to produce ketone 616 as a single diastereomer. NOE experiments as well as coupling constants in the $^1$H NMR proved this stereochemical assignment. In an attempt to convert ketone 616 to the corresponding

$$\text{Scheme 142. Studies with a bridghead isothiocyanate}$$

$$\alpha$$-phenylselenyl $\alpha$-bromoketone$^{449}$ by treatment with excess NBS, we were surprised to obtain clean conversion to the $\alpha$-bromoeneone 617. This fortuitous transformation likely proceeds through the $\alpha$-phenylselenyl $\alpha$-bromoketone as detailed by the proposed mechanism in Scheme 143. Unfortunately, all attempts
to effect Stille coupling of $\alpha$-bromoenone 617 with stannane 393 to produce the desired triene 618 were unsuccessful (Scheme 142), possibly due to coordination of the isothiocyanate moiety to the palladium catalyst.

**Scheme 143.** Proposed mechanism for formation of $\alpha$-bromoenone 617

In addition to the trifluoroacetamide, a significant synthetic effort was made with the corresponding bridgehead formamide in attempts to achieve a clean electrocyclization reaction. Thus, formamide 623 was found to undergo smooth conversion to the enone 624 (Scheme 144) through the previously described silyl enol ether/IBX oxidation protocol ($578 \rightarrow 579$, Scheme 134). In this case, however, bromination and regioselective elimination of the resultant vicinal dibromide worked quite well to afford $\alpha$-bromoenone 625 in 85% yield, with no noticeable bromination of the vinyl substituent. We were also pleased to find that bromoenone 625 was a suitable precursor for introduction of the gem-dimethyl substituent (NaH, MeI) to provide enone 628. Unfortunately, once again,
Scheme 144. Bridgehead formamide studies

608

623

1. TMSOTf
   Et$_3$N
   THF, 0 °C
   93%
2. IBX
   MPO
   DMSO
   79% 2 steps

624

85%
1. Br$_2$, CCl$_4$
2. Cs$_2$CO$_3$
CH$_3$CN

627

626

Pd(PPh$_3$)$_4$
CuI
THF, 65 °C
80%

625

628

393

66%
NaH
Mel
THF, 0 °C

632

631

99%

Tf$_2$O
/Pr$_2$NEt
CH$_2$Cl$_2$, -78 °C

629

78%
Pd(PPh$_3$)$_4$
CuI
THF, 65 °C

Additional electrocyclic conditions
1. Et$_3$N, toluene, 110 °C
2. Et$_3$N, 110 °C
3. octane, 115 °C
4. pyridine, 115 °C
5. DMF, 115 °C
6. microwave, octane
   110 °C, 5 min

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following the Stille coupling of bromoenones 625 and 628, thermolysis of the resulting trienes 626 and 629 failed to produce either of the desired cyclohexadiene products. While the crude $^1$H NMR spectra for these two reactions were difficult to interpret, both appeared to have small amounts of the corresponding vinylogous retro-Mannich products 627 and 630, based on observed aromatic resonances similar to retro-Mannich product 589 (Scheme 135). In addition, the corresponding isonitrile 631, prepared via dehydration of formamide 626 ($\text{Tf}_2\text{O}, \text{Hünigs}$), was found to undergo clean conversion to the undesired protected aniline 632, upon heating in toluene.

V. A viable route to the welwistatin ring system

After this exhaustive investigation involving various substituents at the bridgehead position, it became clear that we needed to explore an alternate approach to effect a clean electrocyclic ring closure to the desired cyclohexadiene. Since it appeared that the competing vinylogous retro-Mannich reaction had been the major cause of our synthetic difficulties, we decided to pursue our second option of reduction of the bridgehead ketone. Accordingly, the bridgehead ketone of silyl enol ether 582 was stereoselectively reduced (9 : 1) with LiAlH(O-tBu)$_3$ and the resulting alcohol 633 was protected with TBSOTf to afford the more robust bicyclic compound 634 (Scheme 145).

Scheme 145. Reduction and protection of the bridgehead ketone
Drawing on the fortuitous result obtained for conversion of \(\alpha\)-phenylselenyl ketone 616 to bromoenone 617 (Scheme 142) through treatment with excess NBS, we decided to attempt the analogous transformation in the case at hand. Thus, treatment of silyl enol ether 634 with PhSeCl at -78 °C produced selenide 635 as a 4 : 1 mixture of diastereomers (Scheme 146). We immediately treated the selenides 635 with 3.5 equivalents of NBS and obtained a mixture of the desired \(\alpha\)-bromoenone 636 (~60%) along with its des-bromo derivative 637 (~20%). The ratio of enone products correlated with the ratio of diastereomeric

\[
\begin{align*}
\text{Scheme 146. Preparation of } \alpha\text{-bromoenone 636} \\
\end{align*}
\]

selenides, which led us to believe that each selenide gave rise to an independent product. Accordingly, the selenides were separated by silica gel chromatography and each subjected individually to 3.5 equivalents of NBS (Scheme 147). Indeed, the major selenide 635a proceeded to exclusively afford \(\alpha\)-bromoenone 636, while the minor selenide 635b cleanly produced the des-bromo enone 637. The major selenide was assigned the stereochemistry depicted in 635a based on similarities in the \(^1\)H NMR spectrum with that of selenide 616 (Scheme 142), whose structure had been confirmed based upon NOE experiments. Moreover, the minor diastereomer 635b is conformationally well suited to undergo a facile anti elimination via selenium ion 639 to produce enone 637 (Scheme 147). Molecular modeling calculations (PC Model) of the two selenides showed 635a to be thermodynamically favored by 2.7 kcal over 635b, thus affording the
opportunity for equilibration of the undesired isomer 635b. To our delight, we found that this equilibration to form 635a exclusively could be accomplished all in one pot from silyl enol ether 634 by initial treatment with PhSeCl, followed by a brief thermodynamic equilibration with Cs$_2$CO$_3$ (Scheme 148). Once 635a was obtained, treatment with NBS successfully produced the desired α-bromoenoone 636 in good overall yield.

**Scheme 148. Equilibration to selenide 635a**

$\text{R} = \text{TBS}$

634

$\text{PhSeCl}$

-78 °C;

$\text{Cs}_2\text{CO}_3$

$\text{CH}_2\text{Cl}_2$

$\text{rt}$

67%

635a

$\text{NBS}$

CCl$_4$

-15 °C - rt

3 h

79%

636
At this point, we found that $\alpha$-bromoenone 636 was sufficiently stable to withstand the basic reaction conditions required for introduction of the gem-dimethyl group, a transformation that failed with the bridgehead ketone in place (see 579 → 580, Scheme 134). Thus, sequential enolate methylations with LiHMDS and MeI gave the desired $\alpha$-bromoenone 641 in good yield (Scheme 149).

### Scheme 149. Dimethylation of $\alpha$-bromoenone 636

With the fully functionalized $\alpha$-bromoenone 641 in hand, we turned to its Stille coupling with $\alpha$-stannylene-carbamate 393 in order to prepare the key electrocyclization precursor, amidotriene 642 (Scheme 150). We were gratified to discover that upon heating in toluene (110 °C, 3 h), triene 642 now underwent an uneventful electrocyclic ring closure to afford a stable cyclohexadiene, that was oxidized in situ with DDQ to furnish the protected aniline 643.

### Scheme 150. Preparation of protected aniline 643
We were now in a position to direct our attention to completion of the welwistatin ring system. The BOC protecting group of carbamate 643 was conveniently removed with TFA to afford aniline 644 (Scheme 151). Subsequent reductive amination of the aniline 644 with glyoxylic acid and NaCNBH₃ smoothly provided the indole closure substrate, acid 645. We were pleased to discover that subjection of acid 645 to our standard reaction conditions (Ac₂O, Et₃N, 130 °C) effected a clean cyclization to the desired N-acetylimidole 646, thereby completing the construction of the most advanced welwistatin ring system reported to date. We had anticipated that the vicinal quaternary carbons of welwistatin presented a major synthetic challenge, especially since none of the previous approaches had solved this problem.

Scheme 151. Completion of the welwistatin ring system
Although the eventual plan is to introduce the bridgehead nitrogen at a later stage in the projected total synthesis, we thought it would be prudent to document the feasibility of this Hofmann-rearrangement-based transformation in such a congested environment. To that end, we found that hydrolysis of the encumbered nitrile 646 with Parkins catalyst 593 (Scheme 152) proceeded equally as well, albeit a longer reaction time (60 h), as that of the previously described nitrile 578 (Scheme 138). It was also pleasing to discover that the Baumgarten variant\textsuperscript{148} of the Hofmann rearrangement was successful in transforming amide 647 to the desired isocyanate 648, upon treatment with Pb(OAc)$_4$ in DMF at 90 °C. NMR studies support the structural assignment for this compound, in particular, the stereochemistry of the newly introduced silyloxy

**Scheme 152. Preparation of bridgehead isocyanate 648**

<table>
<thead>
<tr>
<th>R = TBS</th>
<th>EtOH : H$_2$O 4 : 1 100 °C 60 h</th>
<th>TBSO</th>
<th>Pb(OAc)$_4$ 90 °C DMF 15 min 78%</th>
</tr>
</thead>
<tbody>
<tr>
<td>646</td>
<td>TBSO</td>
<td>593</td>
<td>TBSO</td>
</tr>
<tr>
<td>647</td>
<td></td>
<td>648</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 27. Confirmation of stereochemistry of indole 648**
stereogenic carbon. Key nOe correlations were observed between the bridgehead methine proton and the C(16) axial methyl substituent and the C(14) equatorial proton and the C(16) equatorial methyl substituent (Figure 27).

It is hoped that indole 646 is suitably functionalized for the intensive functional group manipulation phase of the total synthesis endeavor. A possible strategy for completion of N-methyl welwistatin (150) from indole 646 is outlined in Scheme 153. Replacement of the N-acyl group with a methyl substituent, followed by deprotection of the TBS groups and oxidation of the resultant alcohols would provide dione 650. The vinyl chloride substituent could then be introduced by following the previously described procedure (557 → 559, Scheme 129) via treatment of stannane 651 with excess CuCl₂ and Et₃N. Indole 652 would then likely be transformed to the corresponding oxindole 653 by subjection to HCl in DMSO as we had done for the oxidation of our model system indole 513 (Scheme 118). The bridgehead nitrile 653 could then be converted to the bridgehead amine 655 through hydrolysis of the nitrile to the amide 654 with Parkins catalyst, followed by a Hofmann rearrangement and subsequent hydrolysis of the resulting isocyanate. Finally, treatment of the bridgehead amine 655 with thiophosgene (see 608 → 615, Scheme 142) would provide N-methylwelwitindolinone C isothiocyanate (N-methyl welwistatin 150).
Scheme 153. Proposed completion of N-methyl welwistatin

\[
\begin{align*}
\text{646} & \quad R = \text{TBS} \\
& \quad \xrightarrow{1. K_2CO_3, \ MeOH} \quad \xrightarrow{2. \text{NaH, MeI}} \\
& \quad 1. \ TBAF \quad 2. \ TPAP, \ NMO \\
& \quad \text{649} \\
& \quad \text{650} \\
& \quad \xrightarrow{1. \text{LDA, T} \text{f}_2\text{NPh}} \\
& \quad \xrightarrow{2. \text{Pd(PPh}_3)_4, (\text{Me}_3\text{Sn})_2} \\
& \quad \text{651} \\
& \quad \xrightarrow{\text{HCl, DMSO}} \\
& \quad \text{652} \\
& \quad \xrightarrow{\text{CuCl}_2, \ Et_3\text{N}} \\
& \quad \text{653} \\
& \quad \xrightarrow{\text{EtOH : H}_2\text{O}} \\
& \quad \text{593} \\
& \quad \xrightarrow{\text{1. Pb(OAc)}_4, \ 2. \ H_2\text{O}} \\
& \quad \xrightarrow{\text{NaHCO}_3} \\
\end{align*}
\]

\[
\begin{align*}
\text{654} & \quad \xrightarrow{1. \text{Pb(OAc)}_4} \quad \xrightarrow{2. \ H_2\text{O}} \\
& \quad \text{655} \\
& \quad \quad \text{N-methyl welwistatin} \\
\end{align*}
\]

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VI. Concluding remarks

In conclusion, we have developed 6-haloalkyl-4H-1,3-dioxins and used them as haloalkyl vinyl ketone equivalents for the construction of a variety of hetero- and carbocyclic ring systems. In particular, this methodology has proven to be useful for the construction of complex bicyclo[4.3.1]decane-3,10-diones.

In addition, we have also shown that both aromatic rings of indoles can be constructed from readily available α-haloenones and α-(trialkylstanny1)-enecarbamates using a 5-step sequence that features facile electrocyclic ring closures of trienecarbamates. This method has proven to be most useful for the preparation of indoles with rings connected at C(3) and C(4) positions.

We have successfully applied these two novel methods to an efficient synthesis (21 linear steps) of a welwistatin analog possessing a bridgehead carbamate and lacking the C(12) and C(13) functionalities. In addition, a stereoselective synthesis of the fully functionalized welwistatin ring system\textsuperscript{150} was also completed in 24 linear steps (Scheme 154). The key transformation in this synthesis is a sterically encumbered 7-\textit{endo} intramolecular conjugate addition reaction of a β-ketonitrile to deliver the strained bicyclo[4.3.1]decanone ring system present in welwistatin. Significant effort was also directed towards suppressing an undesired vinylogous retro-Mannich reaction during the key 6π-electrocyclic ring closure reaction.
Scheme 154. An approach to the total synthesis of welwistatin

1. Li/NH₃
   t-BuOH
   90% 2 steps
2. (CO₂H)₂
3. CH₃CO₂H;
   Et₃N, 75%
4. TBSCI, ImH
   92%
5. MgBr
   CuBr-DMSC
   TMSCl, 100%
6. HOAc, H₂O
   THF, rt
   99%
7. LHMDS
   75%
8. LDA;
   TsCN, THF
   81%
9. 160 °C
   45 min.
10. THF : MeOH
    (1 : 1)
    Et₃N, rt, 16 h
    79%
11. TMSOTf, Et₃N
    0 °C, 1.5 h
12. LiAlH(O-βu)₃
    THF, -78 °C - 0 °C
13. TBSOTf, Et₃N
    rt, 3 h
14. PhSeCl, -78 °C;
    Cs₂CO₃, CH₂Cl₂, rt
15. 3.5 equiv. NBS
    CCl₄
    -15 °C - rt, 3 h
16. LiHMDS; MeI
17. LiHMDS; MeI
    83% 2 steps
18. Pd(PPh₃)₄
    SnBu₂
19. 110 °C,
    3 h;
    DDQ
    95 °C, 20 h
20. TFA
    98%
21. NaCNBH₃
    OHC-CO₂H
22. Ac₂O, NEt₃
    130 °C
    0.5 h
23. EtOH : H₂O
    100 °C, 60 h
24. Pb(OAc)₄
    90 °C, 15 min
    78%
593, 73%
EXPERIMENTAL SECTION

7,7-Dimethoxyhepta-1,3-diene (106). To a solution of 4,6-heptadienal 129 (5.73 g, 52.0 mmol) in trimethyl orthoformate (34 mL, 311.9 mmol) was added amberlyst-15 resin (3.76 g). The solution was stirred overnight at rt. The mixture was filtered, washed with ether, and concentrated to provide acetal 106 as an oil (7.95 g, 98%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.68 (dt, $J$ = 5.7, 7.5 Hz, 2 H), 2.13 (br q, $J$ = 7.5 Hz, 2 H), 3.31 (s, 6 H), 4.36 (t, $J$ = 5.7 Hz, 1 H), 4.96 (br d, $J$ = 10.2 Hz, 1 H), 5.09 (br d, $J$ = 16.9 Hz, 1 H), 5.69 (dt, $J$ = 7.5, 15.2 Hz, 1 H), 6.16 (br dd, $J$ = 10.2, 15.2 Hz, 1 H), 6.29 (dt, $J$ = 10.2, 16.9 Hz, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 27.5, 31.9, 52.6, 103.9, 115.0, 131.4, 134.0, 137.0; IR (neat) 1652, 1603 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_9$H$_{17}$O$_2$ 157.1229, found 157.1226.

N-Benzyl-N-(2,2-dimethyl-4H-[1,3]dioxin-5-yl)-4-methylbenzenesulfonamide (131). To a solution of 2,2-dimethyl-1,3-dioxane-5-one (130) (5.0 g, 38.4 mmol) in toluene (35 mL) were added molecular sieves (4Å, 7.5 g) and benzylamine (3.8 mL, 34.9 mmol). The solution was stirred at rt overnight and then diluted with dry toluene (80 mL). To the resulting solution at 0 °C was added Et$_3$N (9.7 mL, 69.8 mmol) and TsCl (7.3 g, 38.4 mmol). The solution was stirred at rt for 3 h. The mixture was quenched with brine and
extracted with CH$_2$Cl$_2$. The combined extracts were washed with H$_2$O, dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 6) gave a white solid: mp 131 – 132 °C (10.0 g, 77%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.28 (s, 6 H), 2.45 (s, 3 H), 3.88 (d, $J$ = 1.5 Hz, 2 H), 4.48 (s, 2 H), 5.99 (t, $J$ = 1.5 Hz, 1 H), 7.31 (m, 5 H), 7.33 (d, $J$ = 8.2 Hz, 2 H), 7.76 (d, $J$ = 8.2 Hz, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 21.4, 23.7, 54.6, 60.9, 99.3, 113.2, 127.4, 127.9, 128.4, 128.6, 128.8, 129.5, 135.7, 136.0, 143.5, 143.8; IR (neat) 3000, 1666, 1599 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{24}$NO$_4$S 374.1426, found 374.1442.

$N$-Benzyl-$N$-(1-formylvinyl)-4-methyl-benzenesulfonamide (105). A solution of dioxin 131 (9.2 g, 24.6 mmol) in toluene (245 mL) was stirred at 110 °C for 3 h. The solution was concentrated and purified by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) to provide a white solid: mp 99 – 101 °C (7.7 g, 99%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.42 (s, 3 H), 4.62 (s, 2 H), 5.98 (s, 1 H), 6.08 (s, 1 H), 7.23 (m, 5 H), 7.31 (d, $J$ = 8.0 Hz, 2 H), 7.71 (d, $J$ = 8.0 Hz, 2 H), 9.23 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 21.4, 51.2, 127.5, 127.6, 127.7, 128.3, 128.4, 129.5, 131.8, 135.0, 135.2, 142.9, 144.0, 188.7; IR (neat) 1701, 1597 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{17}$H$_{18}$NO$_3$S 316.1007, found 316.1007.

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$N$-Benzyl-$N$-[2-(3,3-dimethoxypropyl)-1-formylcyclohex-3-enyl]-4-methylbenzenesulfonamide (104). To a solution of diene 106 (818 mg, 5.23 mmol) in CH$_2$Cl$_2$ (8 mL) was added amidoacrolein 105 (1.50 g, 4.76 mmol) and propylene oxide (333 mL, 4.76 mmol). The solution was reacted at 12 kbar for 16 h. The resulting mixture was concentrated and purified by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) to provide a colorless oil (1.67 g, 74%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.02 (m, 1 H), 1.19 (br q, $J$ = 10.4 Hz, 1 H), 1.14 – 1.68 (m, 3 H), 1.97 – 2.20 (m, 3 H), 2.25 (br d, $J$ = 9.0 Hz, 1 H), 2.42 (s, 3 H), 3.19 (s, 3 H), 3.21 (s, 3 H), 4.05 (t, $J$ = 5.4 Hz, 1 H), 4.47 (d, $J$ = 17.2 Hz, 1 H), 4.82 (d, $J$ = 17.2 Hz, 1 H), 5.57 (br d, $J$ = 10.3 Hz, 1 H), 5.69 (br d, $J$ = 10.3 Hz, 1 H), 5.77 (d, $J$ = 7.8 Hz, 2 H), 7.28 (m, 5 H), 7.40 (d, $J$ = 7.8 Hz, 2 H), 7.75 (d, $J$ = 7.8 Hz, 2 H), 9.77 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 21.4, 22.4, 24.7, 26.7, 30.0, 37.8, 49.4, 52.8, 53.0, 71.7, 104.2, 126.8, 127.3, 127.4, 127.6, 128.2, 128.6, 129.6, 138.1, 138.8, 143.6, 198.2; IR (neat) 1733, 1599 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{26}$H$_{34}$NO$_5$S 472.2157, found 472.2125.

$N$-Benzyl-$N$-[2-(3,3-dimethoxypropyl)-1-hydroxymethylcyclohex-3-enyl]-4-methylbenzenesulfonamide (103). To a suspension of NaBH$_4$ (306 mg, 8.09 mmol) in MeOH (80 mL) at 0 °C was added aldehyde 104 (3.82 g, 8.09 mmol). The solution was stirred at 0 °C for 1 h. The mixture was quenched with
saturated aqueous NH₄Cl and extracted with Et₂O. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) gave a colorless oil (3.80 g, 99%); ¹H NMR (400 MHz, CDCl₃) δ 0.65 (m, 1 H), 0.83 (br q, J = 11.5 Hz, 1 H), 1.42 (m, 2 H), 1.81 (m, 1 H), 1.98 (m, 2 H), 2.13 (m, 1 H), 2.42 (s, 3 H), 2.57 (br d, J = 11.2 Hz, 1 H), 3.20 (s, 3 H), 3.25 (s, 3 H), 3.70 (br dd, J = 6.5, 13.0 Hz, 1 H), 3.96 (br d, J = 13.0 Hz, 1 H), 4.00 (t, J = 5.4 Hz, 1 H), 4.58 (d, J = 17.2 Hz, 1 H), 4.75 (d, J = 17.2 Hz, 1 H), 5.27 (br d, J = 10.0 Hz, 1 H), 5.57 (br d, J = 10.0 Hz, 1 H), 7.29 (m, 5 H), 7.47 (d, J = 7.8 Hz, 2 H), 7.78 (d, J = 7.8 Hz, 2 H); ¹³C NMR (50 MHz, CDCl₃) δ 21.4, 23.8, 24.0, 27.3, 29.9, 41.0, 50.4, 52.4, 52.9, 62.3, 71.1, 104.4, 126.3, 127.2, 127.3, 127.4, 128.3, 129.5, 139.2, 139.6, 143.2; IR (neat) 3531, 1599 cm⁻¹; HRMS (MH⁺) calcd for C₂₆H₃₆NO₅S 474.2314, found 474.2297.

**N-[2-(3,3-Dimethoxypropyl)-1-hydroxymethylcyclohexyl]-4-methylbenzenesulfonamide (132).** To a solution of alcohol 103 (1.04 g, 2.20 mmol) in ethyl acetate (22 mL) was added 5% Pd(OH)₂ (208 mg). The mixture was stirred under a hydrogen atmosphere (30 psi) for 3 d. The solution was filtered through celite, washed with ethyl acetate, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 1) gave a colorless oil (794 mg, 94%); ¹H NMR (400 MHz, CDCl₃) δ 0.99 (br q, J = 8.9 Hz, 1 H), 1.05 – 1.47 (m, 6 H), 1.54 (br dd, J = 3.3, 9.3 Hz, 1 H), 1.59 – 1.72 (m, 4 H), 1.80 (br dd, J = 6.1, 9.3 Hz, 1 H), 2.42 (s, 3 H), 2.70 (br s, 1 H), 3.29 (s, 3 H), 3.31 (s, 3 H), 3.65 (dd, J = 5.5, 12.2 Hz, 1 H), 3.72 (dd, J = 7.3, 12.2 Hz, 1 H), 4.28 (t, J = 5.3 Hz, 1 H), 5.23
(br s, 1 H), 7.28 (d, $J = 8.3$ Hz, 2 H), 7.79 (d, $J = 8.3$ Hz, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 21.3, 22.0, 23.4, 23.9, 27.0, 30.6, 31.9, 42.7, 52.4, 52.8, 62.5, 64.3, 104.5, 126.6, 129.4, 140.3, 142.8; IR (neat) 3483, 3282, 1598 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{19}$H$_{32}$NO$_5$S 386.2001, found 386.2000.

4-(3,3-Dimethoxypropyl)-1-(toluene-4-sulfonyl)-1-azaspiro[2.5]octane (102). To a solution of the debenzylated N-tosylamide 132 (672 mg, 1.74 mmol) in benzene (17 mL) at 5 °C were added imidazole (261 mg, 3.83 mmol), PPh$_3$ (503 mg, 1.92 mmol), and iodine (531 mg, 2.09 mmol). The solution was warmed to rt and stirred for 30 min. The mixture was quenched with 10% aqueous Na$_2$S$_2$O$_3$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 3) gave a colorless oil (552 mg, 86%); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.12 (m, 1 H), 1.34 (m, 1 H), 1.40 – 1.76 (m, 7 H), 1.82 – 1.98 (m, 3 H), 2.11 (m, 1 H), 2.30 (s, 1 H), 2.43 (s, 3 H), 2.47 (s, 1 H), 3.28 (s, 3 H), 3.29 (s, 3 H), 4.30 (t, $J = 5.5$ Hz, 1 H), 7.30 (d, $J = 8.3$ Hz, 2 H), 7.82 (br d, $J = 8.3$ Hz, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 21.4, 22.3, 23.9, 25.4, 29.4, 29.7, 30.4, 38.3, 40.8, 52.5, 56.9, 104.3, 127.1, 129.3, 138.1, 143.4; IR (neat) 2934, 1598 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{19}$H$_{30}$NO$_4$S 368.1895, found 368.1899.
N-[1-But-3-enyl-2-(3,3-dimethoxypropyl)-cyclohexyl]-4-methylbenzenesulfonamide (101). To a solution of aziridine 102 (439 mg, 1.19 mmol) in THF (12 mL) at 0 °C was added dropwise allylmagnesium bromide (1.0 M in ether, 4.78 mL, 4.78 mmol). The solution was warmed to rt and stirred for 18 h. The mixture was poured onto saturated aqueous NH₄Cl and extracted with ether. The combined extracts were washed with brine, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) gave a colorless oil (478 mg, 98%); ¹H NMR (400 MHz, CDCl₃) δ 0.97 (br q, J = 11.0 Hz, 1 H), 1.03 – 1.34 (m, 5 H), 1.45 – 1.83 (m, 9 H), 1.95 (m, 2 H), 2.41 (s, 3 H), 3.30 (s, 3 H), 3.31 (s, 3 H), 4.30 (t, J = 5.4 Hz, 1 H), 4.64 (br s, 1 H), 4.94 (d, J = 10.2 Hz, 1 H), 4.97 (d, J = 17.0 Hz, 1 H), 5.70 (ddt, J = 6.6, 10.2, 17.0 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 2 H), 7.77 (d, J = 8.2 Hz, 2 H); ¹³C NMR (50 MHz, CDCl₃), δ 21.3, 22.1, 23.2, 24.1, 26.7, 27.0, 30.5, 31.4, 31.9, 44.1, 52.4, 52.6, 63.2, 104.4, 114.7, 126.7, 129.3, 138.1, 141.0, 142.5; IR (neat) 3284, 1640, 1598 cm⁻¹; HRMS (MH⁺Na⁺) calcd for C₂₂H₃₆NO₄SNa 433.2263, found 433.2227.
8a-But-3-enyl-1-(toluene-4-sulfonyl)-1,4,4a,5,6,7,8,8a-octahydro-quinoline (133). To a solution of acetal 101 (241 mg, 0.59 mmol) in ether (6 mL) at 0 °C was added BF$_3$OEt$_2$ (74 µL, 0.59 mmol). The solution was stirred at 0 °C for 20 min. The mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:19) afforded 133 as a colorless oil (199 mg, 98%); $^1$H NMR (300 MHz, CDCl$_3$) δ 0.89 – 1.44 (m, 5 H), 1.48 – 1.60 (m, 5 H), 1.65 (dt, $J = 2.2, 11.4$ Hz, 1 H), 1.89 (ddt, $J = 1.5, 8.8, 18.2$ Hz, 1 H), 2.17 (m, 1 H), 2.31 (m, 1 H), 2.42 (s, 3 H), 2.82 (br d, $J = 12.9$ Hz, 1 H), 4.94 (dd, $J = 1.8, 10.1$ Hz, 1 H), 5.02 (dd, $J = 1.8, 17.0$ Hz, 1 H), 5.03 (m, 1 H), 5.83 (ddt, $J = 6.6, 10.1, 17.0$ Hz, 1 H), 6.92 (dt, $J = 1.9, 8.4$ Hz, 1 H), 7.27 (d, $J = 8.4$ Hz, 2 H), 7.68 (d, $J = 8.4$ Hz, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 21.5, 22.7, 25.1, 26.2, 27.1, 27.3, 30.2, 31.4, 40.6, 65.6, 107.7, 114.3, 126.3, 126.9, 129.5, 139.1, 140.9, 142.7; IR (neat) 2926, 1654 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{27}$NO$_2$S 346.1841, found 346.1841.

2-Allyl-8a-but-3-enyl-1-(toluene-4-sulfonyl)-decahydroquinoline (139). To a solution of enamide 133 (28.1 mg, 0.081 mmol) in CH$_2$Cl$_2$ (800 µL) at −20 °C was added allyltrimethylsilane (78 µL, 0.49 mmol) followed by trifluoroacetic acid
After 2 h at –20 °C, another portion of allyltrimethylsilane (39 µL, 0.25 mmol) and trifluoroacetic acid (13 µL, 0.17 mmol) were added. The solution was then stirred for 2 h at –20 °C. The reaction mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (CH₂Cl₂-hexane, 55 : 45) provided a colorless oil (22.1 mg, 70%); ¹H NMR (400 MHz, CDCl₃) δ 1.08 - 1.83 (m, 14 H), 2.21 (m, 1 H), 2.41 (s, 3 H), 2.46 (m, 1 H), 2.57 (m, 1 H), 2.68 (m, 1 H), 2.95 (br d, J = 13.1 Hz, 1 H), 4.27 (m, 1 H), 4.96 (d, J = 1.8, 10.2 Hz, 1 H), 5.04 (m, 2 H), 5.07 (d, J = 1.8, 17.1 Hz, 1 H), 5.80 (m, 1 H), 5.88 (ddt, J = 6.6, 10.2, 17.1 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 2 H); ¹³C NMR (50 MHz, CDCl₃) δ 21.4, 22.7, 22.9, 25.4, 26.7, 27.8, 28.6, 30.4, 33.3, 41.3, 47.4, 56.4, 66.9, 114.3, 117.1, 126.0, 129.4, 136.6, 139.0, 142.0, 142.6; IR (neat) 2928, 1640 cm⁻¹; HRMS (MH⁺) calcd for C₂₃H₃₄NO₂S 388.2310, found 388.2302.

**N-[1-But-3-enyl-2-(3-oxopropyl)-cyclohexyl]-4-methylbenzenesulfonamide (135).** To a solution of acetal 101 (372 mg, 0.91 mmol) in THF (18 mL) was added 1 M HCl (3.2 mL). The solution was stirred at rt for 2 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (isopropanol-hexane, 1 : 19) provided a colorless oil (323 mg, 98%); ¹H NMR (300 MHz, CDCl₃) δ 0.99 – 1.33 (m, 5 H), 1.43-1.67 (m, 4 H), 1.71 (m, 6 H), 2.20 (dddd, J = 1.3, 6.0, 9.5, 15.8 Hz, 1 H), 170
2.41 (s, 3 H), 2.42 (dddd, J = 1.3, 5.3, 10.0, 16.0 Hz, 1 H), 4.83 (s, 1 H), 4.94 (br dd, J = 1.7, 10.2 Hz, 1 H), 4.99 (br dd, J = 1.7, 16.8 Hz, 1 H), 5.71 (ddt, J = 6.6, 10.2, 16.8 Hz, 1 H), 7.27 (br d, J = 8.1 Hz, 2 H), 7.77 (br d, J = 8.1 Hz, 2 H), 9.73 (t, J = 1.4 Hz, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 21.1, 21.4, 22.2, 24.5, 26.7, 27.4, 31.0, 32.3, 42.4, 44.2, 63.3, 115.2, 126.8, 129.5, 137.9, 140.9, 142.8, 202.6; IR (neat) 3273, 2931, 1720 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{30}$NO$_3$S 364.1946, found 364.1957.

\(N\)-[1-But-3-ethyl-2-(3-hydroxynonyl)-cyclohexyl]-4-methylbenzenesulfonamide (142). To a solution of Yb(OTf)$_3$ (163 mg, 0.26 mmol) in THF (4 mL) at −78 °C was added hexylmagnesium bromide (2.0 M in ether, 131 µL, 0.26 mmol). The mixture was stirred at −78 °C for 1 h. To the resulting solution at −78 °C was added aldehyde 135 dropwise in THF (200 µL). The solution was stirred at −78 °C for 30 min. The mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) afforded alcohols 142 and 143 as a mixture of diastereomers, 10.9 : 1 (33.4 mg, 85%); $^1$H NMR (400 MHz, d$^6$-benzene) δ 0.69 – 1.12 (m, 7 H), 1.20 – 1.78 (m, 20 H), 1.88 (m, 2 H), 1.90 (s, minor, 3 H), 1.94 (s, major, 3 H), 2.20 (m, 2 H), 3.50 (m, major, 1 H), 3.86 (m, minor, 1 H), 4.92 (d, major, J = 10.1 Hz, 1 H), 4.94 (d, minor, J = 10.1 Hz, 1 H), 5.02 (d, major, J = 17.1 Hz, 1 H), 5.04 (d, minor, J = 17.1 Hz, 1 H), 5.72 (ddt, J = 6.6, 10.1, 17.1 Hz, 1 H), 5.80 (br s, minor, 1 H), 5.89 (br s, major, 1 H), 6.83 (d, minor, J = 8.1 Hz, 2
H), 6.95 (d, major, \( J = 8.1 \) Hz, 2 H), 7.97 (d, minor, \( J = 8.1 \) Hz, 2 H), 8.03 (d, major, \( J = 8.1 \) Hz, 2 H); \(^{13}\)C NMR (75 MHz, d\(^6\)-benzene) \( \delta \) 14.4, 21.1, 22.6, 23.1, 25.4, 25.9, 26.4 (major), 26.5 (minor), 27.5, 28.2, 30.0, 31.2, 32.3, 32.4, 36.9, 38.7, 46.0, 63.6 (major), 63.8 (minor), 72.7, 114.8, 127.1 (minor), 127.4 (major), 129.6 (minor), 129.8 (major), 138.9, 142.3, 142.4; IR (neat) 3464, 3283, 1634, 1596 cm\(^{-1}\); HRMS (MH\(^{+}\)) calcd for C\(_{26}\)H\(_{44}\)NO\(_3\)S 450.3041, found 450.3042.

8a-But-3-enyl-2-hexyl-1-(toluene-4-sulfonyl)-decahydroquinoline (99).

To a solution of alcohols \( \text{142} \) and \( \text{143} \) (33.4 mg, 0.074 mmol) in THF (1.5 mL) was added PPh\(_3\) (27.3 mg, 0.10 mmol) and DEAD (15.2 mL, 0.097 mmol). The solution was stirred overnight at rt. Removal of the solvent and purification by silica-gel chromatography (CH\(_2\)Cl\(_2\)-hexane, 1.5 : 1) provided a mixture of diastereomers (26.7 mg, 83%). Major diastereomer 99 (24.9 mg, 78%): \( R_i \) = 0.61; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.88 (t, \( J = 6.8 \) Hz, 3 H), 1.09 – 1.42 (m, 15 H), 1.50 – 1.87 (m, 9 H), 2.20 (m, 1 H), 2.41 (s, 3 H), 2.48 (m, 1 H), 2.91 (br d, \( J = 13.1 \) Hz, 1 H), 4.97 (dd, \( J = 1.8, 10.2 \) Hz, 1 H), 5.08 (dd, \( J = 1.8, 17.0 \) Hz, 1 H), 5.87 (ddt, \( J = 6.7, 10.2, 17.0 \) Hz, 1 H), 7.25 (br d, \( J = 8.2 \) Hz, 2 H), 7.69 (br d, \( J = 8.2 \) Hz, 2 H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \( \delta \) 14.1, 21.4, 22.6, 22.7, 23.1, 25.4, 27.7, 27.8, 28.5, 29.2, 30.4, 31.8, 33.3, 37.0, 47.3, 57.4, 66.7, 114.2, 125.9, 129.4, 139.0, 141.8, 142.8; IR (neat) 2927, 1640, 1591 cm\(^{-1}\); HRMS (MH\(^{+}\)) calcd for C\(_{26}\)H\(_{42}\)NO\(_2\)S 432.2936, found 432.2936. Minor diastereomer (1.8 mg, 5%): \( R_i \) = 0.54; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.85 (t, \( J = 7.3 \) Hz, 3 H), 0.99 – 2.09 (m, 25
H), 2.36 (m, 1 H), 2.41 (s, 3 H), 2.91 (br d, J = 10.9 Hz, 1 H), 3.59 (m, 1 H), 4.96 (dd, J = 1.8, 10.1 Hz, 1 H), 5.06 (dd, J = 1.8, 17.0 Hz, 1 H), 5.85 (ddt, J = 6.7, 10.1, 17.0 Hz, 1 H), 7.25 (br d, J = 8.2 Hz, 2 H), 7.76 (br d, J = 8.2 Hz, 2 H); \(^1\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\) 14.0, 21.4, 22.5, 22.7, 23.3, 23.6, 25.7, 28.6, 29.1, 29.9, 31.6, 32.0, 37.2, 39.2, 41.2, 55.9, 57.4, 66.3, 114.1, 127.6, 129.2, 139.5, 140.5, 142.4; IR (neat) 2926, 1635, 1593 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{26}\)H\(_{42}\)NO\(_2\)S 432.2936, found 432.2923.

\[\text{8a-But-3-enyl-2-hexyl-decahydroquinoline (98).}\]

To a solution of tosylamide 99 (119 mg, 0.28 mmol) in THF (500 mL) and NH\(_3\) (15 mL) at –78 °C was added sodium (159 mg, 6.90 mmol). The solution was warmed to –40 °C and stirred for 1 hr. The mixture was quenched with CH\(_2\)Cl\(_2\) (1 mL) and warmed to rt. Brine was added and the mixture was extracted with CH\(_2\)Cl\(_2\). The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane-NH\(_4\)OH, 30 : 70 : 1) provided a colorless oil (68 mg, 89%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.87 (t, J = 6.8 Hz, 3 H), 0.94 (dt, J = 3.2, 12.8 Hz, 1 H), 1.20 – 1.38 (m, 14 H), 1.40 – 1.56 (m, 7 H), 1.62 – 1.73 (m, 4 H), 1.92 (m, 1 H), 2.17 (m, 1 H), 2.95 (p, J = 6.0 Hz, 1 H), 4.94 (dd, J = 2.0, 10.1 Hz, 1 H), 5.03 (dd, J = 2.0, 17.0 Hz, 1 H), 5.85 (ddt, J = 6.6, 10.1, 17.0 Hz, 1 H); \(^1\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\) 14.1, 22.2, 22.6, 23.3, 26.4, 27.0, 27.8, 28.9, 29.4, 29.5, 29.6, 31.9, 37.9, 38.2, 45.7, 51.6, 53.8, 113.8, 139.8; IR
(neat) 3340, 1639 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{19}H_{36}N\) 278.2848, found 278.2859.

(5-Hexyldecahydropyrrolo[2,1-j]quinolin-3-yl)-methanol

\([\pm\)-lepadiformine\] (35). To a solution of amine 98 (33 mg, 0.12 mmol) in ether (1.2 mL) at \(-40^\circ\)C was added dropwise a solution of I\(_2\) (30 mg, 0.12 mmol) in CH\(_2\)Cl\(_2\) (100 mL). The solution was warmed to rt over 1h. The mixture was concentrated to provide the crude hydroiodide salt 145; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 0.87 (br t, \(J = 6.8\) Hz, 3 H), 1.00 – 2.77 (m, 27 H), 3.58 (t, \(J = 14.0\) Hz, 1 H), 3.75 – 4.05 (m, 3 H), 7.65 (br s, 1 H). The hydroiodide salt 145 was brought up in THF (5 mL). 4 M NaOH (5 mL) and tetrabutylammonium iodide (22 mg, 0.060 mmol) were added. The mixture was stirred overnight at rt. The reaction mixture quenched with brine and extracted with ethyl acetate. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (CHCl\(_3\)-MeOH-NH\(_4\)OH, 97 : 2 : 1) yielded 35 as a colorless oil (27 mg, 77%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.87 (t, \(J = 6.8\) Hz, 3 H), 1.02 (dq, \(J = 3.1, 12.4\) Hz, 1 H), 1.13 – 1.82 (m, 26 H), 3.14 (m, 1 H), 3.22 (d, \(J = 7.9\) Hz, 1 H), 3.30 – 3.39 (m, 2 H), 3.75 (br s, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 14.1, 22.5, 22.6, 23.2, 24.3, 26.3, 27.5, 27.6, 28.2, 29.6, 30.5, 31.8, 34.1, 38.2, 40.1, 53.3, 58.4, 62.3, 67.4; IR (neat) 3401, 2926 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{19}H_{36}NO\) 294.2797, found 294.2815.
The free base 35 was dissolved in MeOH-1 M aqueous HCl (95 : 5). The solution was evaporated to dryness in vacuo to afford the hydrochloride salt of (+)-lepadiformine 41 as a white solid: mp 111 – 114 °C; 1H NMR (500 MHz, CDCl₃) δ 0.87 (t, J = 6.8 Hz, 3 H), 1.03 (q, J = 10.5 Hz, 1 H), 1.15 – 1.85 (m, 18 H), 1.94 (br t, J = 11.9 Hz, 2 H), 2.05 (dd, J = 7.2, 12.7 Hz, 2 H), 2.18 (m, 2 H), 2.40 (m, 1 H), 2.51 (m, 1 H), 3.61 (m, 2 H), 3.67 (t, J = 11.4 Hz, 1 H), 4.19 (dd, J = 6.0, 12.9 Hz, 1 H), 5.22 (dd, J = 6.0, 8.9 Hz, 1 H), 10.23 (br s, 1 H); 1H NMR (500 MHz, CDCl₃, homodecoupling at proton at δ 5.22) δ 0.87 (t, J = 6.8 Hz, 3 H), 1.03 (q, J = 10.5 Hz, 1 H), 1.15 – 1.85 (m, 18 H), 1.94 (br t, J = 11.9 Hz, 2 H), 2.05 (dd, J = 7.2, 12.7 Hz, 2 H), 2.18 (m, 2 H), 2.40 (m, 1 H), 2.51 (m, 1 H), 3.59 (d, J = 12.9 Hz, 1 H), 3.60 (m, 1 H), 3.67 (t, J = 11.4 Hz, 1 H), 4.19 (d, J = 12.9 Hz, 1 H), 10.23 (br s, 1 H); 13C NMR (75 MHz, CDCl₃) δ 14.0, 19.1, 22.4, 22.5, 23.2, 24.3, 24.8, 26.3, 26.4, 29.0, 29.8, 30.7, 31.6, 33.7, 36.1, 58.7, 59.9, 63.5, 77.2; IR (neat) 3286, 2926 cm⁻¹; HRMS (M⁺) calcd for C₁₉H₃₆NO 294.2797, found 294.2797.

NMR data of Biard's natural sample; 1H NMR (500 MHz, CDCl₃, homodecoupling at proton at δ 5.22) δ 0.82 (t, J = 6.5 Hz, 3 H), 1.00 – 2.40 (m, 27 H), 3.56 (d, J = 13.4 Hz, 1 H), 3.61 (m, 2 H), 4.10 (d, J = 13.4 Hz, 1 H), 10.0 (br s, 1 H); 13C NMR (125 MHz, CDCl₃) δ 13.8, 19.2, 22.3, 22.5, 23.2, 24.3, 24.9, 26.3, 26.4, 28.9, 29.8, 30.7, 31.5, 33.8, 36.2, 58.7, 60.0, 63.5, 76.6.
\textbf{\textsuperscript{1}H NMR Spectrum of Synthetic Lepadiformine}
$^{13}$C NMR Spectrum of Synthetic Lepadiformine
'H NMR Spectrum of Synthetic Lepadiformine HCl
$^{13}$C NMR Spectrum of Synthetic Lepadiformine HCl
Comparison of \(^1\)H NMR Spectra of Synthetic Lepadifomine HCl and Biard's Natural Sample
4-Iodomethyl-1,3-dioxane (251). To a suspension of paraformaldehyde (9.20 g, 304 mmol) in CH$_2$Cl$_2$ (36 mL) at 0 °C was added concentrated H$_2$SO$_4$ (6 mL). The mixture was stirred at 0 °C for 10 min. To the resulting solution at 0 °C was added allyl iodide (16.3 mL, 179 mmol) dropwise over 10 min. The reaction mixture was then stirred at rt overnight. The mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were washed with saturated aqueous NaHCO$_3$, dried (Na$_2$SO$_4$), and concentrated. Distillation of the crude product at 71 °C under reduced pressure (2 mm Hg) provided iodide 251 as a colorless oil (26.2 g, 76%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.69 (m, 2 H), 3.15 (d, $J$ = 6.0 Hz, 2 H), 3.61 (m, 2 H), 4.05 (dt, $J$ = 3.3, 11.1 Hz, 1 H), 4.64 (d, $J$ = 6.4 Hz, 1 H), 5.01 (d, $J$ = 6.4 Hz, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 8.1, 31.6, 65.8, 75.4, 93.5; IR (neat) 2853 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_5$H$_{10}$O$_2$I 228.9725, found 228.9720.

4-Methylene-1,3-dioxane (252). To iodide 251 (26.2 g, 115 mmol) at rt was added KOH (25.8 g, 460 mmol). The mixture was distilled under reduced pressure (160 mm Hg) at 54 °C to afford enol ether 252 as a colorless liquid (10.2 g, 89%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 2.42 (t, $J$ = 5.9 Hz, 2 H), 3.92 (t, $J$ = 5.9 Hz, 2 H), 4.20 (s, 1 H), 4.48 (s, 1 H), 4.95 (s, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 29.5, 66.5, 93.1, 93.8, 155.9; IR (neat) 2908, 1737 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_5$H$_9$O$_2$ 101.0602, found 101.0607.
6-Bromomethyl-4H-1,3-dioxin (207). To a solution of enol ether 252 (9.89 g, 90.9 mmol) in CH₂Cl₂ (360 mL) at –78 °C was added N,N-diisopropylethylamine (24.6 mL, 141 mmol) followed by bromine (6.2 mL, 120 mmol). The solution was slowly warmed to 0 °C over 1 h. The mixture was quenched with 10% aqueous Na₂S₂O₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded bromide 207 as a yellow solid: mp 45 - 46 °C (13.7 g, 84%); ¹H NMR (200 MHz, CDCl₃) δ 3.82 (s, 2 H), 4.22 (d, J = 2.7 Hz, 2 H), 5.07 (s, 2 H), 5.09 (t, J = 2.7 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 30.0, 63.6, 90.9, 101.7, 149.5; IR (neat) 2874, 1671 cm⁻¹; HRMS (MH⁺) calcd for C₅H₈O₂Br 179.9708, found 179.9690.

5-(6H-1,3-Dioxin-4-y1)-3-oxopentanoic acid ethyl ester (256). To a solution of diisopropylamine (859 µL, 6.13 mmol) in THF (13 mL) at –20 °C was added n-BuLi (2.5 M in hexane, 2.35 mL, 5.86 mmol). The solution was stirred at –20 °C for 20 min. The mixture was then warmed to –10 °C and ethyl acetoacetate (340 µL, 2.67 mmol) in THF (1 mL) was added dropwise. The solution was stirred at –10 °C for 20 min. To the resulting solution was added bromide 207 (501 mg, 2.80 mmol) in THF (1 mL). The solution was warmed to rt
and stirred 1.5 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:4) provided 256 as a colorless oil (519 mg, 85%); ¹H NMR (200 MHz, CDCl₃) δ 1.28 (t, J = 7.2 Hz, 3 H), 2.37 (t, J = 7.5 Hz, 2 H), 2.74 (t, J = 7.5 Hz, 2 H), 3.45 (s, 2 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.21 (m, 2 H), 4.70 (t, J = 3.0 Hz, 1 H), 5.02 (s, 2 H); ¹³C NMR (50 MHz, CDCl₃) δ 14.0, 27.4, 39.6, 49.2, 61.3, 63.7, 90.4, 97.4, 152.4, 167.0, 201.6; IR (neat) 1741, 1716, 1682, 1646 cm⁻¹; HRMS (MH⁺) calcd for C₁₁H₁₇O₅ 229.1076, found 229.1057.

2,5-Dioxocycloheptanecarboxylic acid ethyl ester (258). A solution of dioxin 256 (161 mg, 0.71 mmol) in toluene (15 mL) was heated at 180 °C in a sealed tube for 20 min. The resulting solution was concentrated to afford the crude enone 257 which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ 1.30 (t, J = 7.2 Hz, 3 H), 2.88 (m, 4 H), 3.52 (s, 2 H), 4.19 (q, J = 7.2 Hz, 2 H), 5.87 (dd, J = 1.5, 10.5 Hz, 1 H), 6.25 (dd, J = 1.5, 17.8 Hz, 1 H), 6.40 (dd, J = 10.5, 17.8 Hz, 1 H). The crude enone was then dissolved in CH₃CN (70 mL) and Cs₂CO₃ (46 mg, 0.14 mmol) was added. The resulting mixture was stirred at rt for 1.5 h. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:4) afforded cycloheptadione 258 as a mixture with its enol (120 mg, 86%); ¹H NMR (200 MHz, CDCl₃) δ 1.25 (t, J = 7.2 Hz, 3 H), 2.20 (m, 2 H), 2.49 – 2.88 (m,
6 H), 3.67 (dd, J = 5.0, 8.5 Hz, 1 H), 4.22 (q, J = 7.2 Hz, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 13.9, 14.1, 20.0, 22.8, 29.6, 37.1, 37.5, 39.7, 40.8, 43.0, 58.4, 60.8, 61.5, 100.2, 169.1, 172.4, 175.1, 205.2, 209.3, 210.7; IR (neat) 2981, 1740, 1707, 1642 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{10}$H$_{15}$O$_4$ 199.0970, found 199.0955.

5-(6H-1,3-Dioxin-4-yl)-2-methyl-3-oxopentanoic acid ethyl ester (260).

To a solution of diisopropylamine (327 µL, 2.34 mmol) in THF (6 mL) at −20 °C was added $n$-BuLi (2.5 M in hexane, 894 µL, 2.23 mmol). The solution was stirred at −20 °C for 20 min. The mixture was then warmed to −10 °C and ethyl 2-methylacetoacetate (144 µL, 1.02 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred at −10 °C for 20 min. To the resulting solution was added bromide 207 (200 mg, 1.12 mmol) in THF (0.5 mL). The solution was warmed to rt and stirred 1.5 h. The mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided 260 as a colorless oil (190 mg, 77%); $^1$H NMR (200 MHz, CDCl$_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.33 (d, J = 7.1 Hz, 3 H), 2.35 (t, J = 7.0 Hz, 2 H), 2.74 (q, J = 7.0 Hz, 2 H), 3.55 (q, J = 7.1 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.21 (m, 2 H), 4.70 (t, J = 3.0 Hz, 1 H), 5.01 (s, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 12.6, 14.0, 27.6, 38.1, 52.8, 61.3, 63.8, 90.4, 97.3, 152.6, 170.4, 204.7; IR (neat) 1742, 1716, 1683 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{12}$H$_{19}$O$_5$ 243.1232, found 243.1222.
1-Methyl-2,5-dioxocycloheptanecarboxylic acid ethyl ester (262). A solution of dioxin 260 (52 mg, 0.21 mmol) in toluene (4.3 mL) was heated at 180 °C in a sealed tube for 20 min. The resulting solution was concentrated to afford the crude enone 261 which was used without further purification; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta \) 1.24 (t, \(J = 7.2\) Hz, 3 H), 1.35 (d, \(J = 7.1\) Hz, 3 H), 2.89 (m, 4 H), 3.55 (q, \(J = 7.1\) Hz, 1 H), 4.19 (q, \(J = 7.2\) Hz, 2 H), 5.86 (dd, \(J = 1.4, 10.6\) Hz, 1 H), 6.22 (dd, \(J = 1.4, 17.5\) Hz, 1 H), 6.38 (dd, \(J = 10.6, 17.5\) Hz, 1 H). The crude enone was then dissolved in CH\(_3\)CN (22 mL) and Cs\(_2\)CO\(_3\) (14 mg, 0.043 mmol) was added. The resulting mixture was stirred at rt for 2 h. The reaction mixture was quenched with saturated aqueous NH\(_4\)Cl and extracted with ether. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) afforded cycloheptadione 262 as a colorless oil (36 mg, 80%); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta \) 1.26 (t, \(J = 7.0\) Hz, 3 H), 1.37 (s, 3 H), 1.65 (m, 1 H), 2.48 – 2.68 (m, 5 H), 2.89 (m, 2 H), 4.22 (q, \(J = 7.0\) Hz, 2 H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta \) 14.0, 21.4, 31.1, 36.1, 38.1, 39.9, 59.3, 61.7, 172.4, 206.5, 209.8; IR (neat) 1740, 1709 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{11}\)H\(_{17}\)O\(_4\) 213.1127, found 213.1131.
5-(6H-1,3-Dioxin-4-yl)-4,4-dimethyl-3-oxopentanoic acid ethyl ester (264). To a suspension of NaH (66 mg, 1.64 mmol) in THF (7.5 mL) at 0 °C was added ethyl isobutyrylacetate (241 μL, 1.50 mmol) dropwise in THF (0.5 mL). The mixture was stirred at 0 °C for 10 min. To the resulting solution at 0 °C was added n-BuLi (2.5 M in hexane, 628 μL, 1.57 mmol). The mixture was stirred at 0 °C for 10 min and then cooled to –50 °C. Bromide 207 (294 mg, 1.64 mmol) in THF (1 mL) was then added dropwise, and the solution was warmed to –20 °C over 20 min. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided 264 as a colorless oil (234 mg, 61%); ¹H NMR (200 MHz, CDCl₃) δ 1.15 (s, 6 H), 1.25 (t, J = 7.2 Hz, 3 H), 2.30 (s, 2 H), 3.57 (s, 2 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.19 (m, 2 H), 4.69 (t, J = 2.7 Hz, 1 H), 4.94 (s, 2 H); ¹³C NMR (50 MHz, CDCl₃) δ 14.1, 24.3, 44.0, 44.6, 47.2, 61.0, 63.7, 90.2, 100.1, 150.9, 167.8, 206.9; IR (neat) 1744, 1708, 1677, 1620 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₂₁O₅ 257.1389, found 257.1408.
3,3-Dimethyl-2,5-dioxocycloheptanecarboxylic acid ethyl ester (266).

A solution of dioxin 264 (66 mg, 0.26 mmol) in toluene (5 mL) was heated at 180 °C in a sealed tube for 20 min. The resulting solution was concentrated to afford the crude enone 265 which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ 1.26 (s, 6 H), 1.29 (t, J = 7.2 Hz, 3 H), 2.95 (s, 2 H), 3.57 (s, 2 H), 4.18 (q, J = 7.2 Hz, 2 H), 5.83 (dd, J = 1.5, 10.5 Hz, 1 H), 6.18 (dd, J = 1.5, 17.6 Hz, 1 H), 6.35 (dd, J = 10.5, 17.6 Hz, 1 H). The crude enone was then dissolved in CH₃CN (26 mL) and Cs₂CO₃ (17 mg, 0.051 mmol) was added. The resulting mixture was stirred at rt for 2 h. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) afforded cycloheptadione 266 as a colorless oil (47 mg, 80%); ¹H NMR (200 MHz, CDCl₃) δ 1.13 (s, 3 H), 1.25 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 2.20 (m, 2 H), 2.52 (d, J = 13.4 Hz, 1 H), 2.55 (dt, J = 2.5, 6.3 Hz, 2 H), 2.75 (d, J = 13.4 Hz, 1 H), 4.07 (dd, J = 5.3, 9.6 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H); ¹³C NMR (50 MHz, CDCl₃) δ 14.0, 23.2, 24.0, 26.9, 41.8, 46.2, 51.7, 53.9, 61.4, 169.6, 208.7, 209.3; IR (neat) 1744, 1705 cm⁻¹; HRMS (MH⁺) calcd for C₁₂H₁₉O₄ 227.1283, found 227.1280.
3-(6H-1,3-Dioxin-4-ylmethyl)-2-oxocyclohexanecarboxylic acid ethyl ester (274). To a solution of diisopropylamine (587 µL, 4.19 mmol) in THF (8 mL) at −20 °C was added n-BuLi (2.5 M in hexane, 1.61 mL, 4.02 mmol). The solution was stirred at −20 °C for 20 min. The mixture was then warmed to −10 °C and ethyl cyclohexanone-2-carboxylate (327 µL, 2.01 mmol) in THF (1 mL) was added dropwise. The solution was stirred at −10 °C for 20 min. To the resulting dianion was added bromide 207 (300 mg, 1.68 mmol) in THF (0.5 mL). The solution was warmed to rt and stirred 3 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane-NH₄OH, 10 : 89 : 1) provided 274 as a mixture with its enol (298 mg, 66%); ¹H NMR (200 MHz, CDCl₃) δ 1.21 (m, 3 H), 1.30 – 2.85 (m, 9 H), 3.37 (m, 1 H), 4.05 – 4.28 (m, 4 H), 4.66 (m, 1 H), 4.91 – 5.05 (m, 2 H), 12.35 (s, enol, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 14.0, 14.1, 19.5, 21.5, 22.6, 23.8, 26.5, 30.1, 30.6, 33.0, 33.1, 33.4, 33.5, 35.8, 36.0, 46.3, 47.6, 56.0, 57.6, 60.1, 60.7, 61.1, 63.7, 90.4, 97.9, 98.4, 98.6, 151.6, 151.8, 152.1, 169.7, 172.7, 173.4, 206.5, 207.0; IR (neat) 1742, 1713, 1682, 1650, 1612 cm⁻¹; HRMS (MH⁺) calcd for C₁₄H₂₁O₅ 269.1389, found 269.1393.
4,10-Dioxobicyclo[4.3.1]decane-1-carboxylic acid ethyl ester (275). A solution of β-ketoester 274 (106 mg, 0.40 mmol) in toluene (6 mL) was heated at 180 °C in a sealed tube for 1 h. The resulting solution was concentrated to afford the crude enone which was used without further purification; 1H NMR (200 MHz, CDCl₃) δ 1.21 (m, 3 H), 1.30 – 1.70 (m, 7 H), 2.95 – 3.51 (m, 3 H), 4.19 (m, 2 H), 5.83 (dd, J = 1.5, 10.6 Hz, 1 H), 6.25 (dd, J = 1.5, 17.5 Hz, 1 H), 6.37 (dd, J = 10.6, 17.5 Hz, 1 H). The crude enone was then dissolved in CH₃CN (40 mL) and Cs₂CO₃ (25.8 mg, 0.079 mmol) was added. The mixture was stirred at rt for 3 h. The resulting solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 1) afforded 275 as a colorless oil (79.1 mg, 84%); 1H NMR (200 MHz, CDCl₃) δ 1.27 (t, J = 7.1 Hz, 3 H), 1.59 – 2.12 (m, 5 H), 2.26 (m, 1 H), 2.38 – 2.66 (m, 5 H), 2.81 (m, 1 H), 2.90 (dd, J = 6.7, 12.2 Hz, 1 H), 4.22 (q, J = 7.1 Hz, 2 H); 13C NMR (50 MHz, CDCl₃) δ 13.9, 16.2, 27.3, 32.3, 35.0, 40.6, 43.7, 44.8, 60.8, 61.3, 172.3, 209.7, 210.4; IR (neat) 2933, 1732, 1710 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₉O₄ 239.1283, found 239.1294.
5-(6H-[1,3]Dioxin-4-ylmethyl)-2,2-dimethyl-6-oxo-cyclohexane-carboxylic acid ethyl ester (277). To a suspension of NaH (102 mg, 2.54 mmol) in THF (23 mL) at 0 °C was added β-ketoester 276 (458 mg, 2.31 mmol) dropwise in THF (2 mL). The mixture was stirred at 0 °C for 10 min. To the resulting solution at 0 °C was added n-BuLi (2.5 M in hexane, 1.02 mL, 2.54 mmol). The mixture was stirred at 0 °C for 30 min and then cooled to –10 °C. Bromide 207 (414 mg, 2.31 mmol) in THF (2 mL) was then added dropwise, and the solution was warmed to rt and stirred 16 h. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:9) provided 277 as a colorless oil (491 mg, 72%); ¹H NMR (200 MHz, CDCl₃) δ 1.08 (s, 3 H), 1.09 (s, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.45 – 1.95 (m, 4 H), 2.04 (m, 1 H), 2.50 – 2.68 (m, 2 H), 3.30 (s, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 4.20 (m, 2 H), 4.68 (t, J = 2.9 Hz, 1 H), 4.99 (s, 2 H).
9,9-Dimethyl-4,10-dioxobicyclo[4.3.1]decane-1-carboxylic acid ethyl ester (278). A solution of \(\beta\)-ketoester 277 (56 mg, 0.19 mmol) in toluene (3 mL) was heated at 160 °C in a sealed tube for 1 h. The resulting solution was concentrated to afford the crude enone, which was used without further purification. The crude enone was then dissolved in CH\(_3\)CN (19 mL) and Cs\(_2\)CO\(_3\) (15 mg, 0.047 mmol) was added. The mixture was stirred at 50 °C for 3 h. The resulting solution was quenched with saturated aqueous NH\(_4\)Cl and extracted with ether. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) afforded 278 as a colorless oil (38.2 mg, 76%); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.08 (s, 3 H), 1.25 (s, 3 H), 1.27 (t, \(J = 7.1\) Hz, 3 H), 1.73 (m, 1 H), 2.13 – 2.69 (m, 8 H), 2.81 (m, 1 H), 2.90 (dd, \(J = 6.7, 12.2\) Hz, 1 H), 4.22 (q, \(J = 7.1\) Hz, 2 H).

2-(6\(H\)-1,3-Dioxin-4-ylmethyl)cyclohexanone (281). To a solution of diisopropylamine (235 \(\mu\)L, 1.68 mmol) in THF (7 mL) at –20 °C was added \(n\)-BuLi (2.5 M in hexane, 614 \(\mu\)L, 1.54 mmol). The solution was stirred at –20 °C for 20 min. The mixture was then cooled to –78 °C and cyclohexanone (159 \(\mu\)L, 1.54 mmol) in THF (1 mL) was added dropwise. The solution was stirred at –78 °C for 1 h. To the resulting solution was added bromide 207 (250 mg, 1.40 mmol) in
THF (1 mL). The mixture was warmed to 0 °C over 2 h and then quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded a colorless oil (219 mg, 80%); ¹H NMR (200 MHz, CDCl₃) δ 1.23 (m, 1 H), 1.48 – 2.69 (m, 10 H), 4.15 (m, 2 H), 4.63 (t, J = 2.5 Hz, 1 H), 4.94 (d, J = 5.4 Hz, 1 H), 4.98 (d, J = 5.4 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 24.9, 27.8, 33.3, 33.4, 41.9, 47.4, 63.8, 90.4, 98.3, 152.2, 212.0; IR (neat) 2937, 1709, 1682 cm⁻¹; HRMS (MH⁺) calcd for C₁₁H₁₇O₃ 197.1178, found 197.1175.

![Chemical structure](image)

2-(6H-1,3-Dioxin-4-ylmethyl)-6-phenylsulfanylcyclohexanone  (279).

To a solution of diisopropylamine (177 µL, 1.26 mmol) in THF (10 mL) at −20 °C was added n-BuLi (2.5 M in hexane, 467 µL, 1.17 mmol). The solution was stirred at −20 °C for 20 min. The mixture was then cooled to −78 °C and the alkylated cyclohexenone 281 (191 mg, 0.97 mmol) in THF (1 mL) was added dropwise. The solution was stirred at −78 °C for 1 h. To the resulting solution was added PhSSO₂Ph (316 mg, 1.26 mmol) dropwise in THF (1 mL). The mixture was stirred at −78 °C for 4 h and then warmed to −20 °C. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ether-hexane, 1 : 9) provided 279 as a colorless oil (238 mg, 81%); ¹H NMR (200 MHz, CDCl₃) δ 1.33 (m, 1 H), 1.70 – 2.37 (m, 6 H), 2.58 (dd, J = 5.7, 14.9 Hz, 1 H), 3.46 (m, 1 H), 3.86 (t, J = 3.4 Hz, 1 H), 4.15 (m, 2 H), 4.61 (t, J = 2.5 Hz, 1 H), 4.94 (d, J = 5.4 Hz, 1 H), 4.98 (d, J = 5.4 Hz, 1 H),
7.19 – 7.40 (m, 5 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 21.1, 33.3, 33.6, 33.9, 42.4, 55.3, 63.9, 90.4, 98.4, 127.3, 129.0, 131.1, 132.5, 152.1, 209.3; IR (neat) 1706, 1683 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{17}$H$_{21}$O$_3$S 305.1211, found 305.1205.

![PhS]$_2$O

6-phenylsulfanyl-bicyclo[4.3.1]decane-3,10-dione (280). A solution of dioxin 279 (49.5 mg, 0.16 mmol) in toluene (3.2 mL) was heated at 150 °C in a sealed tube for 1 h. The resulting solution was concentrated to afford the crude enone which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) δ 1.45 (m, 1 H), 1.72 (m, 1 H), 2.02 – 2.28 (m, 3 H), 2.31 (m, 1 H), 2.36 (dd, $J = 7.2$, 17.0 Hz, 1 H), 3.13 (dd, $J = 6.2$, 17.0 Hz, 1 H), 3.76 (m, 1 H), 3.90 (m, 1 H), 5.82 (dd, $J = 1.5$, 10.5 Hz, 1 H), 6.22 (dd, $J = 1.5$, 17.5 Hz, 1 H), 6.35 (dd, $J = 10.5$, 17.5 Hz, 1 H), 7.17 – 7.48 (m, 5 H). The crude enone was dissolved in CH$_3$CN (16 mL) and Cs$_2$CO$_3$ (11.0 mg, 0.032 mmol) was added. The solution was stirred at rt overnight. The mixture was then quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided 280 as a white solid: mp 104 – 106 °C (38.7 mg, 88%); $^1$H NMR (200 MHz, CDCl$_3$) δ 1.67 (m, 1 H), 1.85 – 2.13 (m, 6 H), 2.26 – 2.53 (m, 3 H), 2.58 (d, $J = 11.9$ Hz, 1 H), 2.92 (br d, $J = 7.4$ Hz, 1 H), 2.98 (br d, $J = 7.4$ Hz, 1 H), 7.22 – 7.39 (m, 3 H), 7.51 (dd, $J = 1.6$, 7.5 Hz, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 17.8, 30.0, 32.1, 38.8, 40.9, 43.3, 45.9, 64.4, 128.7, 129.2, 130.7, 137.9, 209.3, 210.3; IR (neat) 2932, 1710 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{16}$H$_{19}$O$_2$S 275.1106, found 275.1101.
6-(6\textit{H}-1,3-Dioxin-4-ylmethyl)-3-ethoxy-5,5-dimethylcyclohex-2-enone (284). To a solution of diisopropylamine (509 \( \mu \)L, 3.63 mmol) in THF (14 mL) at –20 °C was added \( n \)-BuLi (2.5 M in hexane, 1.34 mL, 3.35 mmol). The solution was stirred at –20 °C for 20 min. The mixture was then cooled to –78 °C and ketone 283 (564 mg, 3.32 mmol) in THF (1 mL) was added dropwise. The solution was stirred at –78 °C for 1 h. To the resulting solution at –78 °C was added bromide 207 (500 mg, 2.79 mmol) in THF (1 mL). The solution was warmed to rt over 2 h and then stirred overnight. The mixture was quenched with saturated aqueous \( \text{NH}_4\text{Cl} \) and extracted with ether. The combined extracts were dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated. Purification by silica-gel chromatography (ether-benzene, 1 : 3) provided a colorless oil (650 mg, 87%); \( ^1 \text{H} \) NMR (200 MHz, CDCl\(_3\)) \( \delta \) 0.97 (s, 3 H), 1.11 (s, 3 H), 1.35 (t, \( J = 7.0 \) Hz, 3 H), 2.21 (m, 1 H), 2.28 (s, 2 H), 2.30 – 2.52 (m, 2 H), 3.88 (q, \( J = 7.0 \) Hz, 2 H), 4.22 (br s, 2 H), 4.71 (t, \( J = 2.5 \) Hz, 1 H), 5.01 (d, \( J = 5.2 \) Hz, 1 H), 5.08 (d, \( J = 5.2 \) Hz, 1 H), 5.28 (s, 1 H); \( ^{13} \text{C} \) NMR (50 MHz, CDCl\(_3\)) \( \delta \) 13.9, 23.4, 28.5, 30.0, 35.1, 42.2, 53.5, 63.8, 63.9, 90.4, 97.8, 100.6, 152.9, 174.0, 200.5; IR (neat) 2961, 1741, 1654, 1612 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{15}\)H\(_{23}\)O\(_4\) 267.1596, found 267.1587.
4-(6\textit{H}-1,3-Dioxin-4-ylmethyl)-3,5,5-trimethylcyclohex-2-enone  (285).

To a solution of the ketone 284 (147 mg, 0.55 mmol) in THF (5.5 mL) at 0 °C was added methylmagnesium bromide (3.0 M in ether, 550 \(\mu\)L, 1.65 mmol). The resulting solution was stirred at 0 °C for 2 h. The mixture was quenched with 1 M aqueous HCl and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO\(_3\), dried (Na\(_2\)SO\(_4\)), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) provided 285 as a colorless oil (103 mg, 79%); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.01 (s, 3 H), 1.05 (s, 3 H), 1.99 (d, \(J = 1.3\) Hz, 3 H), 2.01 (m, 1 H), 2.05 (d, \(J = 17.3\) Hz, 1 H), 2.24 (dd, \(J = 5.1, 8.2\) Hz, 1 H), 2.45 (d, \(J = 17.3\) Hz, 1 H), 2.53 (m, 1 H), 4.19 (br s, 2 H), 4.68 (t, \(J = 2.6\) Hz, 1 H), 5.04 (s, 2 H), 5.58 (s, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 24.9, 27.1, 28.3, 34.8, 36.2, 46.7, 47.8, 63.9, 90.6, 98.5, 125.2, 153.0, 165.9, 199.1; IR (neat) 2956, 1664 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{14}\)H\(_{21}\)O\(_3\) 237.1491, found 237.1478.

9,9-Dimethyl-10-methylene-bicyclo[4.3.1]decane-3,7-dione  (288). A solution of dioxin 285 (148 mg, 0.63 mmol) in toluene (6.3 mL) was heated at 180 °C in a sealed tube for 1 h. The resulting solution was concentrated to afford the crude enone 286 which was used without further purification; \(^1\)H NMR (200 MHz,
CDCl\textsubscript{3} δ 0.88 (s, 3 H), 1.06 (s, 3 H), 1.90 (s, 3 H), 2.09 (d, J = 17.3 Hz, 1 H), 2.32 (d, J = 17.3 Hz, 1 H), 2.43 (m, 1 H), 2.97 (m, 2 H), 5.83 (s, 1 H), 5.86 (dd, J = 1.5, 10.5 Hz, 1 H), 6.27 (dd, J = 1.5, 17.5 Hz, 1 H), 6.45 (dd, J = 10.5, 17.5 Hz, 1 H).

The crude enone was then dissolved in CH\textsubscript{3}CN (63 mL) and Cs\textsubscript{2}CO\textsubscript{3} (408 mg, 1.25 mmol) was added. The resulting mixture was heated at reflux for 16 h. The reaction mixture was quenched with saturated aqueous NH\textsubscript{4}Cl and extracted with ether. The combined extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. Purification by silica-gel chromatography (ether-CH\textsubscript{2}Cl\textsubscript{2}, 1 : 9) afforded 288 as a colorless oil (92.8 mg, 72%); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 0.85 (s, 3 H), 1.30 (s, 3 H), 1.60 – 2.19 (m, 6 H), 2.22 (br s, 1 H), 2.43 (dt, J = 1.2, 5.4 Hz, 1 H), 2.53 (br s, 1 H), 2.92 (br d, J = 7.8 Hz, 1 H), 4.70 (br s, 2 H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 23.8, 26.2, 28.0, 34.1, 42.7, 52.7, 54.9, 71.9, 83.1, 109.7, 152.5, 212.8, 212.9; IR (neat) 1719, 1715, 1641 cm\textsuperscript{-1}; HRMS (MH\textsuperscript{+}) calcd for C\textsubscript{13}H\textsubscript{19}O\textsubscript{2} 207.1385, found 207.1380.

\[\text{6-(6H-1,3-Dioxin-4-ylmethyl)-3-ethoxycyclohex-2-enone (290).}\]

To a solution of diisopropylamine (342 µL, 2.44 mmol) in THF (10 mL) at −20 °C was added n-BuLi (2.5 M in hexane, 894 µL, 2.23 mmol). The solution was stirred at −20 °C for 20 min. The mixture was then cooled to −78 °C and 3-ethoxy-2-cyclohexen-1-one (296 µL, 2.03 mmol) in THF (1 mL) was added dropwise. The solution was stirred at −78 °C for 1 h. To the resulting solution at −78 °C was added bromide 207 (400 mg, 2.23 mmol) in THF (1 mL). The mixture was warmed slowly to rt and stirred 2 h. The mixture was quenched with saturated
aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:1) afforded a white solid: mp 66 – 67 °C (424 mg, 88%); ¹H NMR (200 MHz, CDCl₃) δ 1.35 (t, J = 7.0 Hz, 3 H), 1.68 (m, 1 H), 1.95 (dd, J = 9.8, 14.5 Hz, 1 H), 2.13 (m, 1 H), 2.38 – 2.56 (m, 3 H), 2.81 (br d, J = 14.5 Hz, 1 H), 3.88 (q, J = 7.0 Hz, 2 H), 4.21 (br s, 2 H), 4.71 (br s, 1 H), 5.01 (d, J = 5.3 Hz, 1 H), 5.05 (d, J = 5.3 Hz, 1 H), 5.32 (s, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 13.7, 25.7, 28.0, 33.4, 42.3, 63.5, 63.8, 90.1, 98.3, 101.7, 152.0, 176.6, 199.6; IR (neat) 2943, 1650, 1606 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₉O₄ 239.1283, found 239.1270.

[6-(6H-1,3-Dioxin-4-ylmethyl)-3-oxocyclohex-1-enyl]acetic acid tert-butyl ester (291). To a solution of diisopropylamine (248 µL, 1.77 mmol) in THF (6 mL) at −20 °C was added n-BuLi (2.5 M in hexane, 662 µL, 1.66 mmol). The solution was stirred at −20 °C for 20 min. The mixture was then cooled to −78 °C and tert-butyl acetate (238 µL, 1.77 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred at −78 °C for 30 min. To the resulting solution at −78 °C was added the alkylated ketone 290 (263 mg, 1.10 mmol) in THF (0.5 mL). The mixture was stirred at −78 °C for 2 h. The resulting solution was quenched with 1 M aqueous HCl at −78 °C and the mixture was allowed to warm to rt and then stirred for 10 min. The aqueous layer was extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1
1) afforded 291 as a colorless oil (301 mg, 88 %); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.44 (s, 9 H), 1.83 – 2.21 (m, 3 H), 2.28 – 2.57 (m, 3 H), 2.73 (m, 1 H), 3.10 (d, $J$ = 15.7 Hz, 1 H), 3.26 (d, $J$ = 15.7 Hz, 1 H), 4.23 (br s, 2 H), 4.75 (br s, 1 H), 5.03 (d, $J$ = 5.4 Hz, 1 H), 5.08 (d, $J$ = 5.4 Hz, 1 H), 5.90 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 26.2, 27.7, 33.2, 35.1, 35.2, 42.6, 63.5, 81.4, 90.4, 99.0, 128.4, 151.3, 160.3, 168.4, 198.6; IR (neat) 2944, 1728, 1676 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{17}$H$_{25}$O$_5$ 309.1702, found 309.1726.

![Chemical Structure](image)

3,8-Dioxo-2,3,5,6,7,8,9,9a-octahydro-1H-benzocycloheptene-5-carboxylic acid tert-butyl ester (292). A solution of dioxin 291 (127 mg, 0.41 mmol) in toluene (8 mL) was heated at 180 °C in a sealed tube for 40 min. The resulting solution was concentrated to afford the crude enone which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.44 (s, 9 H), 1.85 (m, 1 H), 2.09 (m, 1 H), 2.36 (m, 2 H), 2.80 (m, 2 H), 3.05 (d, $J$ = 15.7 Hz, 1 H), 3.10 (m, 1 H), 3.19 (d, $J$ = 15.7 Hz, 1 H), 5.85 (dd, $J$ = 1.5, 10.5 Hz, 1 H), 5.90 (s, 1 H), 6.23 (dd, $J$ = 1.5, 17.8 Hz, 1 H), 6.37 (dd, $J$ = 10.5, 17.8 Hz, 1 H). The crude enone was then dissolved in CH$_3$CN (41 mL) and Cs$_2$CO$_3$ (26.9 mg, 0.083 mmol) was added. The mixture was stirred at rt for 2 h. The resulting solution was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 1) afforded 292 as a mixture of diastereomers, 2.9 : 1 (107.7 mg, 94%). Major diastereomer (79.4 mg, 69%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.43 (s, 9 H), 1.91 (m, 2 H), 2.19 (m, 1 H), 2.35 – 2.54
(m, 4 H), 2.60 (dd, J = 10.6, 15.5 Hz, 1 H), 2.69 (dd, J = 4.9, 15.5 Hz, 1 H), 2.78 (m, 1 H), 3.02 (m, 1 H), 3.46 (t, J = 6.4 Hz, 1 H), 5.91 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 24.9, 27.7, 29.5, 31.3, 33.1, 39.7, 46.4, 53.0, 82.0, 129.3, 162.8, 170.1, 198.0, 209.8; IR (neat) 1719, 1701, 1672 cm$^{-1}$; HRMS (M+H$^+$) calcd for C$_{18}$H$_{25}$O$_4$ 279.1596, found 279.1596. Minor diastereomer (28.3 mg, 25%): $^1$H NMR (300 MHz, CDCl$_3$) δ 1.45 (s, 9 H), 1.84 – 2.07 (m, 2 H), 2.13 – 2.27 (m, 2 H), 2.32 – 2.55 (m, 2 H), 2.59 (m, 2 H), 2.68 (m, 2 H), 2.78 (m, 1 H), 3.36 (dd, J = 4.2, 9.9 Hz, 1 H), 5.90 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 26.3, 27.9, 29.7, 34.4, 35.4, 41.2, 46.2, 52.3, 82.1, 126.2, 163.1, 170.5, 198.0, 209.8; IR (neat) 1719, 1701, 1672 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{18}$H$_{25}$O$_4$ 279.1596, found 279.1581.

2-($6H$-1,3-Dioxin-4-ylmethyl)-3,5-dimethylcyclohexanone. To a solution of diisopropylamine (509 µL, 3.63 mmol) in THF (14 mL) at −20 °C was added n-BuLi (2.5 M in hexane, 1.34 mL, 3.35 mmol). The solution was stirred at −20 °C for 20 min. The mixture was then cooled to −78 °C and cis-3,5-dimethylcyclohexanone$^{73}$ (423 mg, 3.35 mmol) in THF (1 mL) was added dropwise. The solution was stirred at −78 °C for 1 h. To the resulting solution at −78 °C was added bromide 207 (500 mg, 2.79 mmol) in THF (1 mL). The mixture was warmed to 0 °C over 2 h and then quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided a colorless oil (559 mg, 89%); $^1$H NMR (200 MHz, CDCl$_3$) δ 1.00 (d, J = 6.1 Hz, 3 H), 1.09 (d, J = 6.4 Hz, 3 H), 1.23 (m, 1 H), 1.57 (m, 1 H), 1.70 – 1.90 (m, 2 H), 2.03 (t, J = 12.5 Hz, 1 H), 2.11 – 2.28 (m, 2 H), 2.37 (dt, J = 2.6,
12.0 Hz, 1 H), 2.56 (dd, J = 8.2, 15.5 Hz, 1 H), 4.20 (br s, 2 H), 4.71 (br s, 1 H), 4.97 (d, J = 5.3 Hz, 1 H), 5.02 (d, J = 5.3 Hz, 1 H); 13C NMR (50 MHz, CDCl₃) δ 20.7, 22.3, 29.9, 33.6, 43.6, 50.0, 53.2, 63.9, 90.4, 97.7, 153.1, 210.9; IR (neat) 2953, 1708, 1640 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₂₁O₃ 225.1491, found 225.1478.

Trifluoromethanesulfonic acid 6-(6H-1,3-dioxin-4-ylmethyl)-3,5-dimethylcyclohex-1-enyl ester (294). To a solution of NaHMDS (1.0 M in THF, 1.74 mL, 1.74 mmol) in THF (7 mL) at −78 °C was added a solution of the alkylated ketone (326 mg, 1.45 mmol) and N-phenyltrifluoromethanesulfonylimide (623 mg, 1.74 mmol) in THF (7 mL) dropwise over 30 min. The solution was allowed to warm to rt over 1 h. The reaction mixture was quenched with 3 M aqueous Na₂CO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded triflate 294 as a colorless oil (438 mg, 85%); 1H NMR (200 MHz, CDCl₃) δ 1.00 (m, 1 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.06 (d, J = 5.7 Hz, 3 H), 1.67 – 1.88 (m, 2 H), 2.25 – 2.49 (m, 4 H), 4.22 (br s, 2 H), 4.74 (br s, 1 H), 5.01 (s, 2 H), 5.62 (s, 1 H); 13C NMR (50 MHz, CDCl₃) δ 19.9, 21.0, 29.8, 33.2, 33.9, 39.3, 43.0, 63.7, 90.3, 99.4, 118.5 (q, J = 318.3 Hz), 125.0, 151.0, 151.3; IR (neat) 2929, 1680 cm⁻¹; HRMS (MH⁺) calcd for C₁₄H₂₀SO₅F₃ 357.0983, found 357.0998.
6,8-Dimethyl-6,7,8,8a-tetrahydro-1H-napthalen-2-one (295). A solution of dioxin 294 (258 mg, 0.72 mmol) in toluene (7.2 mL) was heated at 180 °C in a sealed tube for 1 h. The resulting solution was concentrated to afford the crude enone which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ 0.87 (m, 1 H), 0.96 (d, J = 6.1 Hz, 3 H), 1.02 (d, J = 6.4 Hz, 3 H), 1.73 (m, 2 H), 2.43 (m, 1 H), 2.60 – 2.97 (m, 3 H), 5.62 (s, 1 H), 5.85 (dd, J = 1.5, 10.5 Hz, 1 H), 6.21 (dd, J = 1.5, 17.6 Hz, 1 H), 6.38 (dd, J = 10.5, 17.6 Hz, 1 H). The crude enone was dissolved in THF (72 mL) and cooled to 0 °C. To the resulting solution at 0 °C was added Cs₂CO₃ (259 mg, 0.80 mmol), P(t-Bu)₃ (10.8 µL, 0.043 mmol), and Pd₂(dba)₂·CHCl₃ (11.2 mg, 0.011 mmol). The mixture was warmed slowly to rt and stirred for 3 h. The reaction mixture was filtered through celite, washed with ether, and concentrated. Purification by silica-gel chromatography (hexane-CH₂Cl₂, 1 : 3) afforded 295 as a colorless oil (79.4 mg, 62%); ¹H NMR (400 MHz, CDCl₃) δ 0.89 (m, 1 H), 0.98 (d, J = 6.5 Hz, 3 H), 1.04 (d, J = 7.1 Hz, 3 H), 1.52 (m, 1 H), 1.78 (m, 1 H), 2.04 (br t, J = 15.3 Hz, 1 H), 2.18 (m, 1 H), 2.40 (m, 1 H), 2.73 (dd, J = 4.8, 15.3 Hz, 1 H), 5.86 (d, J = 9.7 Hz, 1 H), 5.93 (s, 1 H), 6.98 (d, J = 9.7 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 19.2, 20.9, 31.9, 35.2, 39.4, 40.8, 41.9, 125.9, 134.1, 141.2, 148.2, 199.7; IR (neat) 2925, 1676, 1630 cm⁻¹; HRMS (MH⁺) calcd for C₁₂H₁₇O 177.1279, found 177.1269.
**3-(6H-1,3-Dioxin-4-yl)-2-phenylpropionitrile (297).** To a solution of diisopropylamine (509 µL, 3.63 mmol) in THF (14 mL) at −20 °C was added n-BuLi (2.5 M in hexane, 1.34 mL, 3.35 mmol). The solution was stirred at −20 °C for 20 min. The mixture was then cooled to −78 °C and phenylacetonitrile (322 µL, 2.79 mmol) in THF (1 mL) was added dropwise. The solution was stirred at −78 °C for 1 h. To the resulting solution at −78 °C was added bromide 207 (600 mg, 3.35 mmol) in THF (1 mL). The solution was warmed to rt over 2 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided a colorless oil (547 mg, 91%); ^1^H NMR (200 MHz, CDCl₃) δ 2.62 (m, 2 H), 4.11 (dd, J = 7.0, 8.7 Hz, 1 H), 4.22 (br d, J = 9.5 Hz, 2 H), 4.81 (t, J = 2.6 Hz, 1 H), 5.08 (s, 2 H), 7.27 – 7.47 (m, 5 H); ^1^C NMR (50 MHz, CDCl₃) δ 35.0, 40.2, 63.6, 90.7, 100.8, 120.1, 127.2, 128.2, 129.1, 135.0, 148.9; IR (neat) 2866, 2242, 1683, 1600 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₄NO₂ 216.1024, found 216.1020.
3-(6H-1,3-Dioxin-4-yl)-2-phenylpropylamine. To a solution of the alkylated nitrile 297 (450 mg, 2.09 mmol) in ether (20 mL) at 0 °C was added LiAlH₄ (238 mg, 6.27 mmol). The mixture was stirred overnight at rt. The solution was quenched successively with H₂O (238 µL), 10% aqueous NaOH (357 µL), and H₂O (714 µL). The resulting solution was filtered, washed with ether, and concentrated. Purification by silica-gel chromatography (NH₄OH-ethyl acetate, 1 : 99) provided a colorless oil (347 mg, 76%); ¹H NMR (200 MHz, CDCl₃) δ 1.25 (br s, 2 H), 2.39 (m, 2 H), 2.85 – 3.10 (m, 3 H), 4.13 (br s, 2 H), 4.55 (t, J = 2.5 Hz, 1 H), 4.95 (d, J = 5.3 Hz, 1 H), 5.03 (d, J = 5.3 Hz, 1 H), 7.15 – 7.45 (m, 5 H); ¹³C NMR (50 MHz, CDCl₃) δ 38.2, 46.3, 47.0, 63.7, 90.3, 98.4, 126.4, 127.7, 128.4, 142.6, 152.1; IR (neat) 3368, 2941, 1681, 1583 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₈NO₂ 220.1338, found 220.1335.

N-[3-(6H-1,3-Dioxin-4-yl)-2-phenylpropyl]-2,2,2-trifluoroacetamide (298). To a solution of the amino dioxin (327 mg, 1.49 mmol) in CH₂Cl₂ (15 mL) at 0 °C was added Et₃N (624 µL, 4.48 mmol) and trifluoroacetic anhydride (843 µL, 5.97 mmol). The solution was stirred at 0 °C for 2 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The
combined extracts were washed with brine, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided 298 as a colorless oil (447 mg, 95%); ¹H NMR (200 MHz, CDCl₃) δ 2.40 (d, J = 7.3 Hz, 2 H), 3.18 (p, J = 7.3 Hz, 1 H), 3.45 (dd, J = 5.7, 8.3 Hz, 1 H), 3.71 (m, 1 H), 4.12 (br s, 2 H), 4.64 (t, J = 2.5 Hz, 1 H), 4.95 (d, J = 5.3 Hz, 1 H), 5.01 (d, J = 5.3 Hz, 1 H), 6.62 (br s, 1 H), 7.10 – 7.39 (m, 5 H); ¹³C NMR (50 MHz, CDCl₃) δ 38.2, 42.0, 44.3, 63.6, 90.4, 99.3, 115.5 (q, J = 286.3 Hz), 127.2, 127.3, 128.8, 140.8, 151.1, 157.0 (q, J = 36.8 Hz); IR (neat) 3312, 1711 cm⁻¹; HRMS (MH⁺) calcd for C₁₅H₁₇NO₃F₃ 316.1160, found 316.1141.

6-Phenyl-1-(2,2,2-trifluoroacetyl)azepan-4-one (299). A solution of trifluoroacetamide 298 (120 mg, 0.38 mmol) in toluene (19 mL) was heated at reflux for 24 h. The resulting solution was concentrated to afford the crude enone which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ 3.03 (m, 1 H), 3.33 – 3.77 (m, 4 H), 5.86 (dd, J = 1.3, 10.4 Hz, 1 H), 6.21 (dd, J = 1.3, 17.5 Hz, 1 H), 6.36 (dd, J = 10.4, 17.5 Hz, 1 H), 6.65 (br s, 1 H), 7.10 – 7.41 (m, 5 H). The crude enone was diluted with CH₃CN (38 mL) and Cs₂CO₃ (147 mg, 0.45 mmol) was added. The resulting mixture was stirred at rt overnight. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) provided 299 as a colorless oil (91 mg, 84%); ¹H NMR (200 MHz, CDCl₃, amide rotamers) δ 2.70 (dt, J = 3.1, 17.9 Hz, 1 H), 2.74 – 3.18 (m, 3 H), 3.25 – 3.79 (m, 3 H), 4.16 (br d,
major, $J = 14.0$ Hz, 1 H), 4.21 (m, minor, 1 H), 4.54 (br d, major, $J = 14.0$ Hz, 1 H), 4.63 (m, minor, 1 H), 7.10 – 7.41 (m, 5 H); $^{13}$C NMR (50 MHz, CDCl$_3$, amide rotamers) δ 41.0 (minor), 41.8 (major), 44.2, 44.6, 49.0 (major), 49.4 (minor), 56.4 (minor), 57.4 (major), 116.2 (q, $J = 286.2$ Hz), 126.6, 127.5, 127.8, 129.1, 140.3 (major), 140.9 (minor), 207.7 (minor), 208.2 (major); IR (neat) 2927, 1691 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{14}$H$_{15}$NO$_2$F$_3$ 286.1055, found 286.1039.

![Chemical structure](image)

**3-(6H-1,3-Dioxin-4-yl)-2-(2-nitrophenyl)propionic acid methyl ester (301).** To a solution of bromide 207 (329 mg, 1.84 mmol) and 2-nitrophenylacetic acid methyl ester (359 mg, 1.84 mmol) in THF (27 mL) at $-78^\circ$C was added potassium tert-butoxide (1.0 M in THF, 2.02 mL, 2.02 mmol) dropwise. The solution was slowly warmed to rt over 1 h and then stirred an additional 2 h at rt. The reaction mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were washed with H$_2$O and brine, dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided a colorless oil (409 mg, 76%); $^1$H NMR (200 MHz, CDCl$_3$) δ 2.57 (dd, $J = 8.4$, 14.6 Hz, 1 H), 2.98 (dd, $J = 6.6$, 14.6 Hz, 1 H), 3.68 (s, 3 H), 4.05 (m, 2 H), 4.47 (dd, $J = 6.6$, 8.4 Hz, 1 H), 4.56 (t, $J = 2.5$ Hz, 1 H), 4.81 (d, $J = 5.3$ Hz, 1 H), 4.96 (d, $J = 5.3$ Hz, 1 H), 7.30 – 7.44 (m, 3 H), 7.90 (dd, $J = 1.2$, 8.1 Hz, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 36.7, 44.3, 52.3, 63.6, 90.5, 99.4, 124.7, 128.2, 130.8, 132.7, 132.9, 150.5, 172.2; IR (neat) 1737, 1680 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{14}$H$_{16}$NO$_6$ 294.0977, found 294.0980.
3-(6H-1,3-Dioxin-4-yl)-2-(2-nitrophenyl)propan-1-ol. To a suspension of LiAlH₄ (95.1 mg, 2.50 mmol) in ether (23 mL) at −78 °C was added the alkylated ester 301 (334 mg, 1.14 mmol) dropwise in ether (1 mL). The solution was warmed slowly to −20 °C over 1 h. The mixture was quenched successively with H₂O (95 µL), 10% aqueous NaOH (143 µL), and H₂O (285 µL). The mixture was then filtered, washed with ether, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 1) afforded a colorless oil (284 mg, 94%); ¹H NMR (200 MHz, CDCl₃) δ 1.93 (br s, 1 H), 2.40 (dd, J = 7.9, 14.4 Hz, 1 H), 2.57 (dd, J = 7.1, 14.4 Hz, 1 H), 3.65 (p, J = 7.0 Hz, 1 H), 3.89 (m, 2 H), 4.10 (m, 2 H), 4.60 (t, J = 2.5 Hz, 1 H), 4.82 (d, J = 5.4 Hz, 1 H), 4.97 (d, J = 5.4 Hz, 1 H), 7.40 (m, 1 H) 7.47 – 7.61 (m, 2 H), 7.73 (d, J = 8.0 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 36.1, 39.5, 63.7, 65.7, 90.5, 99.1, 123.9, 127.3, 128.9, 132.3, 136.1, 151.4; IR (neat) 3420, 1682 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₆NO₅ 266.1028, found 266.1040.

2-(2-Aminophenyl)-3-(6H-1,3-dioxin-4-yl)propan-1-ol. To a solution of Cu(acac)₂ (48.3 mg, 0.18 mmol) in ethanol (19 mL) was added NaBH₄ (34.9 mg, 0.92 mmol). The mixture was stirred 5 min at rt. To the resulting mixture was added the nitrophenyl alcohol (245 mg, 0.92 mmol) in ethanol (1 mL), followed by
NaBH₄ (69.9 mg, 1.84 mmol). The solution was stirred at rt for 2 h. The reaction mixture was then quenched with water and filtered to remove the solid. The aqueous layer was extracted with CH₂Cl₂. The combined extracts were washed with brine, dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 1) provided a colorless oil (214 mg, 98%); 'H NMR (200 MHz, CDCl₃) δ 2.34 (dd, J = 6.5, 14.4 Hz, 1 H), 2.46 (dd, J = 7.9, 14.4 Hz, 1 H), 3.25 (p, J = 7.1 Hz, 1 H), 3.78 (dd, J = 7.4, 10.8 Hz, 1 H), 3.91 (dd, J = 5.4, 10.8 Hz, 1 H), 4.15 (m, 2 H), 4.66 (t, J = 2.5 Hz, 1 H), 5.01 (d, J = 5.4 Hz, 1 H), 5.02 (d, J = 5.4 Hz, 1 H), 6.65 – 6.85 (m, 2 H), 6.99 – 7.12 (m, 2 H); ^{13}C NMR (50 MHz, CDCl₃) δ 36.0, 38.5, 63.9, 66.0, 90.6, 98.8, 116.5, 119.2, 126.6, 127.4, 145.0, 152.2; IR (neat) 3381, 1683, 1636 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₈NO₃ 236.1287, found 236.1270.

{2-[1-(6H-1,3-Dioxin-4-ylmethyl)-2-hydroxyethyl]phenyl}-carbamic acid tert-butyl ester (302). To a solution of the primary aniline (28.9 mg, 0.12 mmol) in dioxane (250 µL) and H₂O (125 µL) at 0 °C was added saturated aqueous NaHCO₃ (125 µL) and (BOC)₂O (31 µL, 0.14 mmol). The mixture was warmed to rt and stirred overnight. The reaction mixture was quenched with H₂O and extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 1) provided 302 as a colorless oil (37.7 mg, 92%); 'H NMR (200 MHz, CDCl₃) δ 1.50 (s, 9 H), 2.25 (dd, J = 6.9, 14.2 Hz, 1 H), 2.49 (dd, J = 6.9, 14.2 Hz, 1 H), 3.34 (m, 1 H), 3.67 (m, 1 H), 3.85 (m, 1 H), 4.10 (br s, 2
H), 4.57 (t, $J = 2.5$ Hz, 1 H), 4.92 (d, $J = 5.4$ Hz, 1 H), 5.01 (d, $J = 5.4$ Hz, 1 H), 7.05 – 7.30 (m, 3 H), 7.63 (d, $J = 7.8$ Hz, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 28.3, 36.3, 38.9, 63.7, 66.6, 80.1, 90.5, 98.9, 124.0, 124.8, 126.5, 127.0, 133.9, 136.7, 151.6, 153.9; IR (neat) 3368, 1722, 1687 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{18}$H$_{26}$NO$_5$ 336.1811, found 336.1793.

6-Hydroxymethyl-4-oxo-3,4,5,6-tetrahydro-2$H$-benzo[\textit{b}]azocine-1-carboxylic acid tert-butyl ester (303). A solution of dioxin 302 (37 mg, 0.11 mmol) in toluene (2.3 mL) was heated at reflux for 16 h. The resulting solution was concentrated to afford the crude enone which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.51 (s, 9 H), 2.20 (br s, 1 H), 2.93 (dd, $J = 8.0$, 19.0 Hz, 1 H), 3.15 (dd, $J = 6.5$, 19.0 Hz, 1 H), 3.55 – 3.86 (m, 3 H), 5.83 (dd, $J = 1.6$, 10.6 Hz, 1 H), 6.20 (dd, $J = 1.6$, 17.7 Hz, 1 H), 6.33 (dd, $J = 10.6$, 17.7 Hz, 1 H), 7.05 – 7.27 (m, 3 H), 7.61 (d, $J = 7.8$ Hz, 1 H), 7.75 (br s, 1 H). The crude enone was dissolved in CH$_3$CN (11 mL) and Cs$_2$CO$_3$ (7.2 mg, 0.022 mmol) was added. The mixture was stirred at rt for 2 h. The solution was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 1) provided benzazocene 303 as a colorless oil (28 mg, 83%); $^1$H NMR (200 MHz, CDCl$_3$, amide rotamers) $\delta$ 1.30 (s, major, 9 H), 1.53 (s, minor, 9 H), 2.24 (br t, $J = 13.0$ Hz, 2 H), 2.82 – 3.11 (m, 2 H), 3.19 (dt, $J = 3.1$, 11.8 Hz, 1 H), 3.69 (m, 1 H), 3.80 – 4.11 (m, 2 H), 4.38 (m, minor, 1 H), 4.52 (dt, major, $J = 3.1$, 13.6 Hz, 1 H), 7.05 – 7.39 (m, 4 H); $^{13}$C NMR
(75 MHz, CDCl₃) δ 28.3, 37.0, 41.7, 47.7, 52.2, 64.1, 80.4, 124.9, 128.5, 128.8, 129.1, 138.3, 141.5, 154.4, 210.9; IR (neat) 3454, 1697 cm⁻¹; HRMS (MH⁺) calcd for C₁₇H₂₄NO₄ 306.1705, found 306.1713.

3-(6H-1,3-Dioxin-4-ylmethyl)-2-oxo-5,6-diphenylmorpholine-4-carboxylic acid tert-butyl ester (306). To a solution of bromide 207 (836 mg, 4.67 mmol) and lactone 305⁸⁵ (1.50 g, 4.24 mmol) in THF (85 mL) and HMPA (8.1 mL) at −78 °C was added NaHMDS (1.0 M in THF, 6.37 mL, 6.37 mmol). The solution was stirred at −78 °C for 2 h. The mixture was quenched with brine and extracted with ethyl acetate. The combined extracts were washed with brine and H₂O, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided 306 as a yellow solid: mp 149 – 150 °C (1.65 g, 86%); [α]D²⁰ = −11.5 (c 1, CHCl₃); ¹H NMR (200 MHz, CDCl₃, amide rotamers) δ 1.07 (s, major, 9 H), 1.46 (s, minor, 9 H), 2.78 (m, minor, 2 H), 2.91 (br d, major, J = 6.0 Hz, 2 H), 4.11 (br s, 2 H), 4.75 – 5.27 (m, 5 H), 6.02 (d, major, J = 2.9 Hz, 1 H), 6.16 (d, minor, J = 3.5 Hz, 1 H), 6.53 – 6.63 (m, 2 H), 6.90 – 7.43 (m, 8 H); ¹³C NMR (50 MHz, CDCl₃, amide rotamers) δ 27.8 (major), 28.3 (minor), 37.9 (major), 38.9 (minor), 55.3 (major), 56.2 (minor), 60.1 (minor), 61.2 (major), 63.7 (minor), 63.9 (major), 78.8 (major), 79.3 (minor), 81.1 (major), 81.7 (minor), 90.9, 101.2 (major), 101.3 (minor), 126.5, 126.6, 127.5, 127.6, 128.0, 128.5, 134.5 (major), 135.1 (minor), 135.5 (minor), 136.7 (major), 149.2 (minor), 149.4 (major), 152.9 (minor), 153.6 (major), 169.0 (minor), 169.2 (major); IR (neat) 2976, 1755, 1699 cm⁻¹; HRMS (MH⁺) calcd for C₂₆H₃₀NO₆ 452.2073, found 452.2115.
2-Oxo-3-(2-oxo-but-3-enyl)-5,6-diphenylmorpholine-4-carboxylic acid tert-butyl ester (307). A solution of dioxin 306 (307 mg, 0.68 mmol) in toluene (14 mL) was heated at 150 °C in a sealed tube for 3 h. Concentration of the mixture followed by purification by silica-gel chromatography (ethyl ether–CH$_2$Cl$_2$, 1 : 50) afforded a white solid: mp 135 – 137 °C (272 mg, 95%); [α]$_D^{20}$ = +5.2 (c 1, CHCl$_3$); $^1$H NMR (300 MHz, δ$^8$-toluene, 363 K) δ 1.09 (s, 9 H), 3.18 (dd, J = 4.8, 16.2 Hz, 1 H), 3.57 (br d, J = 16.2 Hz, 1 H), 5.03 (br d, J = 2.6 Hz, 1 H), 5.29 (t, J = 5.0 Hz, 1 H), 5.37 (dd, J = 1.2, 10.5 Hz, 1 H), 6.02 (dd, J = 1.2, 17.7 Hz, 1 H), 6.18 (dd, J = 10.5, 17.7 Hz, 1 H), 6.25 (br d, J = 2.6 Hz, 1 H), 6.63 (br d, J = 7.6 Hz, 2 H), 6.80 – 6.98 (m, 8 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 27.6, 43.3, 52.6, 61.2, 79.2, 81.4, 126.4, 127.5, 127.6, 128.2, 128.5, 129.9, 134.8, 135.9, 136.8, 154.5, 169.7, 197.3; IR (neat) 1749, 1701 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{25}$H$_{26}$NO$_5$ 422.1967, found 422.1958.

3,4-Diphenylhexahydropyrido[2,1-c]-1,4-oxazine-1,8-dione (308). To a solution of the retrocycloadduct 307 (310 mg, 0.73 mmol) in CH$_2$Cl$_2$ (7 mL) was added 2,6-lutidine (342 µL, 2.94 mmol) followed by TMSOTf (406 µL, 2.20 mmol). The solution was stirred at rt for 30 min. The mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. The crude mixture was then diluted with
methanol (74 mL) and stirred at rt for 3 h. Concentration of the mixture followed by purification by silica-gel chromatography (ether-CH₂Cl₂, 1 : 50) afforded 308 as a white solid: mp 63 – 65 °C (138 mg, 59%); [α]²⁰ D = -40.3 (c 1, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 2.25 (dt, J = 2.9, 9.1 Hz, 1 H), 2.39 (m, 1 H), 2.61 (m, 1 H), 2.69 (dd, J = 12.2, 14.8 Hz, 1 H), 3.07 (dt, J = 2.0, 15.0 Hz, 1 H), 3.22 (ddd, J = 2.0, 6.7, 11.3 Hz, 1 H), 3.49 (dd, J = 3.6, 12.2 Hz, 1 H), 4.40 (d, J = 3.8 Hz, 1 H), 6.20 (d, J = 3.8 Hz, 1 H), 7.00 – 7.35 (m, 10 H); ¹³C NMR (50 MHz, CDCl₃) δ 41.0, 43.5, 50.3, 56.6, 65.9, 83.2, 125.5, 127.8, 128.2, 128.4, 129.8, 130.6, 135.5, 168.6, 205.2; IR (neat) 1742, 1715 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₂₀NO₃ 322.1443, found 322.1446.

8-Hydroxy-3,4-diphenylhexahydropyrido[2,1-c]-1,4-oxazin-1-one (309). To a solution of ketone 308 (105 mg, 0.33 mmol) in THF (3.3 mL) at -78 °C was added borane (1.0 M in THF, 652 µL, 0.65 mmol). The solution was stirred at -78 °C for 20 min. The mixture was quenched with saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 2) provided alcohol 309 as a white solid: mp 162 – 163 °C (88 mg, 83%); [α]²⁰ D = -25.8 (c 1, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 1.65 (m, 2 H), 1.96 (m, 2 H), 2.68 (br d, J = 10.0 Hz, 1 H), 2.95 (dt, J = 2.9, 10.0 Hz, 1 H), 3.13 (dd, J = 2.6, 11.6 Hz, 1 H), 3.50 (hextet, J = 4.7 Hz, 1 H), 4.25 (d, J = 3.8 Hz, 1 H), 6.12 (d, J = 3.8 Hz, 1 H), 7.00 – 7.33 (m, 10 H); ¹³C NMR (50 MHz, CDCl₃) δ 34.1, 37.5, 49.9, 56.0, 65.9, 68.8, 83.1, 125.5, 127.6, 128.0, 128.1, 128.2, 129.9,
131.0, 135.9, 169.7; IR (neat) 3389, 1738 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{20}\)H\(_{22}\)NO\(_3\) 324.1600, found 324.1603.

\[ \text{cis-4-Hydroxypiperidine-2-carboxylic acid [}(2S,4R)-4-hydroxy-pipecolic acid\text{]} (304). \] To a solution of alcohol 309 (63 mg, 0.20 mmol) in ethyl acetate (4 mL) was added 5% Pd(OH)\(_2\) (13 mg). The mixture was stirred under a hydrogen atmosphere at 50 psi for 12 h. The mixture was concentrated and then dissolved in methanol (4 mL). The resulting solution was then filtered through celite, concentrated, and triturated with ether. Recrystallization from hot methanol afforded (2S,4R)-4-hydroxypipecolic acid (304) as a white solid: mp 271 – 273 °C (27.6 mg, 97%); [\(\alpha\)]\(_{D}^{20}\) = -19.6 (c 0.3, H\(_2\)O); \(^1\)H NMR (300 MHz, D\(_2\)O) \(\delta\) 1.44 (m, 2 H); 1.99 (br d, \(J = 13.5\) Hz, 1 H), 2.36 (br d, \(J = 13.5\) Hz, 1 H), 2.87 (dt, \(J = 3.2, 13.2\) Hz, 1 H), 3.34 (ddd, \(J = 2.7, 4.4, 13.2\) Hz, 1 H), 3.49 (dd, \(J = 3.2, 12.9\) Hz, 1 H), 3.79 (tt, \(J = 4.3, 11.0\) Hz, 1 H); \(^{13}\)C NMR (75 MHz, D\(_2\)O) \(\delta\) 30.6, 35.4, 42.1, 58.5, 66.2, 174.1; IR (neat) 3390, 1624 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_6\)H\(_{12}\)NO\(_3\) 146.0817 found 146.0817.

\[ \text{6-Hexa-2,4-dienyloxymethyl-4H-1,3-dioxin (311). To a solution of alcohol 310 (263 mg, 2.68 mmol) in THF (11 mL) at 0 °C was added NaH (60\% dispersion in mineral oil, 107 mg, 2.68 mmol). The mixture was stirred at 0 °C for} \]
30 min and then bromide 207 (400 mg, 2.23 mmol) in THF (1 mL) was added. The solution was warmed to rt and stirred overnight. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded 311 as a colorless oil (403 mg, 92%); ¹H NMR (200 MHz, CDCl₃) δ 1.76 (d, J = 6.7 Hz, 3 H), 3.88 (s, 2 H), 4.04 (d, J = 6.5 Hz, 2 H), 4.28 (m, 1 H), 5.09 (s, 2 H), 5.67 (m, 2 H), 6.05 (m, 1 H), 6.20 (dd, J = 10.2, 14.8 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 17.9, 63.5, 68.6, 70.6, 90.4, 99.9, 126.0, 129.9, 130.6, 133.4, 150.6; IR (neat) 2853, 1681 cm⁻¹; HRMS (MH⁺) calcd for C₁₁H₁₇O₃ 197.1178, found 197.1181.

6-Methyl-4a,5,6,8a-tetrahydro-1H-isochromen-4-one (312). A solution of dioxin 311 (98.6 mg, 0.50 mmol) in toluene (10 mL) was heated at 160 °C in a sealed tube for 45 min. The resulting mixture was concentrated and purified by silica-gel chromatography (ether-hexane, 3 : 17) to afford cycloadduct 312 as a single diastereomer (80.4 mg, 96%); ¹H NMR (400 MHz, CDCl₃) δ 1.00 (d, J = 7.1 Hz, 3 H), 1.44 (ddd, J = 10.5, 12.8, 23.3 Hz, 1 H), 1.77 (dt, J = 4.4, 12.8 Hz, 1 H), 2.29 (m, 1 H), 2.68 (dt, J = 3.6, 13.2 Hz, 1 H), 2.82 (m, 1 H), 3.46 (dd, J = 11.0, 11.1 Hz, 1 H), 3.88 (dd, J = 4.6, 11.0 Hz, 1 H), 3.98 (dd, J = 0.9, 16.6 Hz, 1 H), 4.06 (d, J = 16.6 Hz, 1 H), 5.49 (ddd, J = 2.6, 4.4, 10.0 Hz, 1 H), 5.69 (dd, J = 1.4, 10.0 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 21.2, 30.6, 31.1, 36.0, 46.5, 67.7, 72.8, 123.1, 136.4, 210.3; IR (neat) 2926, 1718 cm⁻¹; LRMS (MH⁺) calcd for C₁₅H₁₅O₂ 167.1, found 167.1.
3-(6H-1,3-Dioxin-4-yl)-2,2-dimethylpropionaldehyde. To a solution of diisopropylamine (376 µL, 2.68 mmol) in THF (5 mL) at –20 °C was added n-BuLi (2.5 M in hexane, 983 µL, 2.46 mmol). The solution was stirred at –20 °C for 20 min. To the resulting mixture at –20 °C was added imine 313 (313 mg, 2.46 mmol) dropwise in THF (0.5 mL). The solution was stirred at 0 °C for 2 h. To the resulting anion at 0 °C was added HMPA (777 µL, 4.47 mmol) followed by bromide 207 (400 mg, 2.23 mmol) in THF (0.5 mL). The solution was warmed to rt and stirred 2 h. The mixture was quenched with saturated aqueous NaCl and extracted with ether. The combined extracts were washed with H₂O, dried (Na₂SO₄), and concentrated to afford the crude alkylated imine. The imine was then dissolved in CH₂Cl₂ (11 mL) and oxalic acid (282 mg, 2.23 mmol) in H₂O (7 mL) was added. The resulting mixture was heated at reflux for 1 h. The aqueous layer was separated and then extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided the resultant aldehyde as a colorless oil (267 mg, 70%); ¹H NMR (200 MHz, CDCl₃) δ 1.07 (s, 6 H), 2.25 (s, 2 H), 4.20 (br s, 2 H), 4.70 (t, J = 2.6 Hz, 1 H), 4.95 (s, 2 H), 9.50 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 21.5, 42.1, 45.2, 63.7, 90.3, 99.9, 150.9, 205.1; IR (neat) 2866, 1726, 1681 cm⁻¹; HRMS (MH⁺) calcd for C₉H₁₅O₃ 171.1021, found 171.1023.
**1-Benzyl-6,6-dimethylhexahydrocyclopenta[c]isoxazol-4-one (315).**

To a solution of the alkylated aldehyde (59.1 mg, 0.35 mmol) in ethanol (1.7 mL) was added MgSO₄ (41.8 mg, 0.35 mmol) and benzylhydroxylamine (42.8 mg, 0.35 mmol). The mixture was stirred at rt overnight. The resulting solution was filtered through a pad of celite and concentrated to afford the crude nitrone 314 which was used without further purification; H NMR (200 MHz, CDCl₃) δ 1.27 (s, 6 H), 2.46 (s, 2 H), 4.08 (br s, 2 H), 4.52 (t, J = 2.5 Hz, 1 H), 4.82 (s, 2 H), 4.86 (s, 2 H), 6.56 (s, 1 H), 7.30 – 7.50 (m, 5 H). The crude nitrone was then dissolved in toluene (7 mL) and heated at 150 °C in a sealed tube for 2 h. The resulting mixture was concentrated and purified by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) to afford cycloadduct 315 as a colorless oil (57.1 mg, 67%); H NMR (400 MHz, CDCl₃) δ 0.97 (s, 3 H), 1.16 (s, 3 H), 2.02 (dt, J = 1.5, 17.1 Hz, 1 H), 2.47 (d, J = 17.1 Hz, 1 H), 3.26 – 3.36 (m, 2 H), 3.92 (d, J = 13.3 Hz, 1 H), 3.99 (dd, J = 2.2, 8.9 Hz, 1 H), 4.04 (d, J = 13.3 Hz, 1 H), 4.16 (dd, J = 7.0, 8.9 Hz, 1 H), 7.27 – 7.42 (m, 5 H); C NMR (50 MHz, CDCl₃) δ 24.1, 28.9, 29.6, 38.4, 51.2, 57.2, 62.3, 68.7, 127.5, 128.4, 129.1, 137.1, 217.8; IR (neat) 2956, 1744 cm⁻¹; HRMS (MH⁺) calcd for C₁₅H₂₀NO₂ 246.1494, found 246.1486.
(2,2-Dimethyl-6H-[1,3]dioxin-4-yl)acetic acid ethyl ester (318). To a solution of alcohol 317 (5.16 g, 32.2 mmol) in THF (105 mL) at 0 °C was added 2-methoxypropene (9.26 mL, 96.7 mmol) followed by pyridinium p-toluenesulfonate (2.43 g, 9.67 mmol). The resulting mixture was warmed to rt and stirred for 16 h. To the resulting solution was added solid Na$_2$CO$_3$ (10 g). The mixture was stirred at rt for 1 h, filtered, and concentrated. Purification by silica gel chromatography (ethyl acetate – hexanes, 1 : 4) provided dioxin 318 as a colorless oil (5.48 g, 85%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.25 (t, $J = 7.5$ Hz, 3 H), 1.47 (s, 6 H), 3.03 (s, 2 H), 4.17 (q, $J = 7.5$ Hz, 2 H), 4.20 (m, 2 H), 4.78 (m, 1 H).

2-(2,2-Dimethyl-6H-[1,3]dioxin-4-yl)ethanol. To a solution of LiAlH$_4$ (1.06 g, 28.0 mmol) in ether (215 mL) at 0 °C was added ester 318 (4.32 g, 21.6 mmol) in ether (15 mL) dropwise over 10 min. The mixture was stirred at 0 °C for 20 min. The resulting solution was quenched successively with H$_2$O (1.1 mL), 10% NaOH (1.7 mL), and H$_2$O (3.3 mL). The resulting mixture was filtered, washed with ether, and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 2 : 3) provided the alcohol as a colorless oil (3.40 g, 99%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.43 (s, 6 H), 2.28 (t, $J = 6.2$ Hz, 2 H), 3.75 (m, 2 H), 4.19 (m, 2 H), 4.71 (t, $J = 2.7$ Hz, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 24.0, 37.1, 58.9, 59.6, 95.4, 98.6, 148.4.
6-(2-Iodoethyl)-2,2-dimethyl-4H-1,3-dioxin (316). To a solution of the 6-(2-hydroxyethyl)-2,2-dimethyl-4H-1,3-dioxin (611 mg, 3.86 mmol) in THF (38 mL) at 0 °C was added imidazole (605 mg, 8.89 mmol), PPh$_3$ (1.11 g, 4.25 mmol), and iodine (1.08 g, 4.25 mmol). The resulting solution was stirred at 0 °C for 1 h. The mixture was quenched with 10% aqueous Na$_2$S$_2$O$_3$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 19) afforded iodide 316 as a colorless oil (734 mg, 71%); $^1$H NMR (300 MHz, CDCl$_3$) δ 1.43 (s, 6 H), 2.53 (t, $J = 7.1$ Hz, 2 H), 3.22 (t, $J = 7.1$ Hz, 2 H), 4.13 (m, 2 H), 4.66 (t, $J = 2.6$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 2.3, 24.3, 38.1, 58.9, 95.9, 98.8, 148.8.

6-(2,2-Dimethyl-6H-[1,3]dioxin-4-yl)-3-oxo-hexanoic acid ethyl ester (320). To a solution of diisopropylamine (146 µL, 1.04 mmol) in THF (2 mL) at –20 °C was added n-BuLi (2.5 M in hexane, 403 µL, 1.01 mmol). The solution was stirred at –20 °C for 20 min. The mixture was then warmed to –10 °C and ethyl acetoacetate (62 µL, 0.49 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred at –10 °C for 20 min. To the resulting solution was added iodide 316 (100 mg, 0.37 mmol) in THF (0.5 mL). The solution was warmed to rt and stirred 1.5 h. The mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and
concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:4) provided 320 as a colorless oil (89 mg, 68%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.25 (t, $J = 7.2$ Hz, 3 H), 1.42 (s, 6 H), 1.78 (p, $J = 7.5$ Hz, 2 H), 2.05 (t, $J = 7.5$ Hz, 2 H), 2.57 (t, $J = 7.5$ Hz, 2 H), 3.44 (s, 2 H), 4.16 (m, 2 H), 4.17 (q, $J = 7.2$ Hz, 2 H), 4.59 (m, 1 H).

2,6-Dioxocyclooctanecarboxylic acid ethyl ester (321). A solution of dioxin 320 (16 mg, 0.058 mmol) in toluene (5 mL) was heated to 110 °C for 2 h. The resulting solution was concentrated to afford the crude enone which was used without further purification. The crude enone was then dissolved in CH$_3$CN (6 mL) and Cs$_2$CO$_3$ (4 mg, 0.012 mmol) was added. The resulting mixture was stirred at rt for 16 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:4) afforded cyclooctadione 321 as a mixture with its enol (9.1 mg, 74%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.25 (t, $J = 7.2$ Hz, 3 H), 1.65 – 2.05 (m, 4 H), 2.30 – 2.70 (m, 6 H), 3.52 (m, 1 H), 4.22 (q, $J = 7.2$ Hz, 2 H), 12.61 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.0, 14.2, 20.7, 22.7, 29.4, 29.7, 30.2, 31.9, 33.0, 40.5, 41.2, 41.7, 47.4, 57.8, 60.7, 61.6, 99.5, 172.2, 175.3, 207.4, 212.1, 213.7.
3-[2-(2,2-Dimethyl-6H[1,3]dioxin-4-yl)ethyl]-3-methyl-2-oxocyclohexanecarboxylic acid methyl ester (323). To a solution of diisopropylamine (725 µL, 5.17 mmol) in THF (8 mL) at –20 °C was added n-BuLi (2.5 M in hexane, 1.97 mL, 4.93 mmol). The solution was stirred at –20 °C for 20 min. The mixture was then warmed to –10 °C and β-ketoester 322 (400 mg, 2.35 mmol) in THF (1 mL) was added dropwise. The solution was stirred at 40 °C for 3 h. The resulting dianion was cooled to -20 °C and DMPU (284 µL, 2.35 mmol) followed by iodide 316 (693 mg, 2.59 mmol) in THF (1 mL) were added. The solution was warmed to rt and stirred 12 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane-NH₄OH, 10 : 89 : 1) provided 323 as a colorless oil (430 mg, 59%); ¹H NMR (200 MHz, CDCl₃) δ 1.17 (s, 3 H), 1.42 (s, 6 H), 1.52 – 2.35 (m, 10 H), 3.75 (s, 3 H), 4.18 (m, 2 H), 4.58 (m, 1 H), 12.4 (s, 1 H).

3-[2-(2,2-Dimethyl-6H[1,3]dioxin-4-yl)ethyl]-3-methyl-2-trifluoromethanesulfonyloxy-cyclohex-1-enecarboxylic acid methyl ester (324). To a solution of β-ketoester 323 (459 mg, 1.48 mmol) in ether (15 mL) at 0 °C was added NaH (76.8 mg, 1.92 mmol). The mixture was warmed to rt and stirred for
20 min. The resulting solution was cooled to -78 °C and \( \text{i-Pr}_2\text{NET} \) (386 \( \mu \)L, 2.22 mmol) and \( \text{Tf}_2\text{O} \) (274 \( \mu \)L, 1.68 mmol) were added. The solution was stirred at -78 °C for 15 min. The resulting mixture was quenched with saturated aqueous NaHCO\(_3\) and extracted with ether. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 9) afforded triflate 324 as a colorless oil (589 mg, 90%); \(^1\text{H NMR} \ (200 \text{ MHz, } \text{CDCl}_3) \ \delta \ 1.20 \ (s, 3 \text{ H}), \ 1.48 \ (s, 6 \text{ H}), \ 1.50 – 1.85 \ (m, 6 \text{ H}), \ 1.99 \ (m, 2 \text{ H}), \ 2.35 \ (m, 1 \text{ H}), \ 2.60 \ (m, 1 \text{ H}), \ 3.77 \ (s, 3 \text{ H}), \ 4.17 \ (m, 2 \text{ H}), \ 4.58 \ (t, \text{ } J = 2.7 \text{ Hz, 1 H}).$

![Chemical Structure](image)

3-[(2,2-Dimethyl-6\text{H}[1,3]\text{dioxin-4-yl})\text{ethyl}]3-methyl-2-vinylcyclohex-1-enecarboxylic acid methyl ester (325). To a solution of triflate 324 (114 mg, 0.26 mmol) in N-methylpyrrolidinone (2.6 mL) was added LiCl (32.9 mg, 0.78 mmol), Pd\(_2\)(dba)\(_2\)-CHCl\(_3\) (8.0 mg, 0.0078 mmol), and tributylvinyltin (91 \( \mu \)L, 0.31 mmol). The mixture was stirred at rt for 2 h. The resulting solution was quenched with brine and extracted with hexanes. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 9) afforded 325 as a colorless oil (60.8 mg, 73%); \(^1\text{H NMR} \ (200 \text{ MHz, } \text{CDCl}_3) \ \delta \ 1.05 \ (s, 3 \text{ H}), \ 1.41 \ (s, 6 \text{ H}), \ 1.50 – 1.75 \ (m, 6 \text{ H}), \ 1.93 \ (m, 2 \text{ H}), \ 2.21 \ (m, 2 \text{ H}), \ 3.63 \ (s, 3 \text{ H}), \ 4.18 \ (m, 2 \text{ H}), \ 4.58 \ (t, \text{ } J = 2.7 \text{ Hz, 1 H}), \ 5.08 \ (dd, \text{ } J = 2.1, 17.3 \text{ Hz, 1 H}), \ 5.13 \ (dd, \text{ } J = 2.1, 10.0 \text{ Hz, 1 H}), \ 6.32 \ (dd, \text{ } J = 10.0, 17.3 \text{ Hz, 1 H}).}$
4a-Methyl-7-oxo-3,4,4a,5,6,7-hexahydro-2H-benzocycloheptene-1-carboxylic acid methyl ester (327). A solution of dioxin 325 (103 mg, 0.32 mmol) in toluene (5 mL) was heated to 110 °C for 1 h. The resulting solution was concentrated to afford the crude enone 326, which was used without further purification. To a solution of the enone 326 in CH₂Cl₂ (16 mL) was added Grubbs #2 catalyst (13.7 mg, 0.016 mmol). The mixture was heated to reflux for 16 h. The resulting solution was concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 4) afforded dieneone 327 as a colorless oil (45.5 mg, 61%); ¹H NMR (200 MHz, CDCl₃) δ 1.13 (s, 3 H), 1.48 – 1.85 (m, 6 H), 2.25 – 2.60 (m, 4 H), 3.72 (s, 3 H), 5.96 (d, J = 14.0 Hz, 1 H), 7.28 (d, J = 14.0 Hz, 1 H).

1-[2-(2,2-Dimethyl-6H[1,3]dioxin-4-yl)ethyl]-2-oxo-cyclopentane-carboxylic acid methyl ester. To a solution of β-ketoester 328 (111 µL, 0.90 mmol) in DMF (4 mL) was added NaH (60% dispersion in oil, 37 mg, 0.93 mmol). The mixture was stirred at rt for 20 min. To the resulting solution was added iodide 316 (200 mg, 0.75 mmol) in DMF (0.5 mL). The mixture was stirred at rt for 4 h. The resulting solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were washed with brine, dried
(Na₂SO₄), and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 4) afforded a colorless oil (170 mg, 81%); ¹H NMR (200 MHz, CDCl₃) δ 1.38 (s, 3 H), 1.60 – 2.15 (m, 6 H), 2.28 – 2.67 (m, 4 H), 3.70 (m, 3 H), 4.19 (m, 2 H), 4.60 (t, J = 2.9 Hz, 1 H).

1-[2-(2,2-Dimethyl-6H[1,3]dioxin-4-yl)ethyl]-2-trifluoromethanesulfonyloxy-cyclo-pent-2-enecarboxylic acid methyl ester (329). To a solution of NaHMDS (1.0 M in THF, 880 µL, 0.88 mmol) in THF (4 mL) at -78 °C was added a solution of the β-ketoester (207 mg, 0.73 mmol) and N-phenyltrifluoromethanesulfonimide (314 mg, 0.88 mmol) in THF (4 mL) dropwise over 30 min. The mixture was warmed to rt over 1 h. The resulting solution was quenched with saturated aqueous Na₂CO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 9) afforded triflate 329 as a colorless oil (262 mg, 86%); ¹H NMR (200 MHz, CDCl₃) δ 1.40 (s, 6 H), 1.72 – 2.20 (m, 4 H), 2.30 – 2.62 (m, 4 H), 3.68 (s, 3 H), 4.13 (m, 2 H), 4.60 (t, J = 2.7 Hz, 1 H), 5.78 (t, J = 3.0 Hz, 1 H).
1-[2-(2,2-Dimethyl-6H[1,3]dioxin-4-yl)ethyl]-2-vinylcyclopent-2-ene-carboxylic acid methyl ester. To a solution of triflate 329 (100 mg, 0.24 mmol) in N-methylpyrrolidinone (2.5 mL) was added LiCl (31 mg, 0.72 mmol), Pd$_2$(dba)$_2$-CHCl$_3$ (7.5 mg, 0.0072 mmol), and tributylvinyltin (85 µL, 0.29 mmol). The mixture was stirred at rt for 16 h. The resulting solution was quenched with brine and extracted with hexanes. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 9) afforded a colorless oil (57.8 mg, 82%); $^1$H NMR (200 MHz, CDCl$_3$) δ 1.42 (s, 6 H), 1.72 – 2.16 (m, 4 H), 2.33 – 2.52 (m, 4 H), 3.67 (s, 3 H), 4.16 (m, 2 H), 4.59 (t, $J$ = 2.7 Hz, 1 H), 5.02 (d, $J$ = 13.1 Hz, 1 H), 5.20 (d, $J$ = 18.3 Hz, 1 H), 5.91 (m, 1 H), 6.30 (dd, $J$ = 13.1, 18.3 Hz, 1 H).

6-Oxo-2,4,5,6-tetrahydro-3H-azulene-3a-carboxylic acid methyl ester (331). To a solution of the dioxin (95 mg, 0.32 mmol) in CH$_2$Cl$_2$ (4 mL) at 0 °C was added ZnCl$_2$ (44 mg, 0.32 mmol). The mixture was stirred at 0 °C for 3 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude enone 330, which was used without further
purification. To a solution of the crude enone 330 in CH₂Cl₂ (16 mL) was added Grubbs #2 catalyst 93 (14 mg, 0.016 mmol). The mixture was heated to reflux for 16 h. The resulting solution was concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 3 : 7) afforded dieneone 331 as a colorless oil (48.2 mg, 72%); ¹H NMR (200 MHz, CDCl₃) δ 1.85 – 2.05 (m, 2 H), 2.20 – 2.75 (m, 6 H), 3.65 (s, 3 H), 5.80 (d, J = 12.5 Hz, 1 H), 6.29 (m, 1 H), 6.82 (d, J = 12.5 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 30.1, 30.6, 40.0, 40.4, 52.1, 59.5, 127.4, 136.4, 143.2, 143.6, 175.2, 201.3.

2-[2-(2,2-Dimethyl-6H[1,3]dioxin-4-yl)ethyl]-2-methyl-5-oxo-cyclopentanecarboxylic acid allyl ester (333). To a solution of t-BuLi (1.7 M in pentane, 830 µL, 1.41 mmol) in ether (15 mL) at -78 °C was added bromide 319 (152 mg, 0.69 mmol) in ether (1 mL) dropwise. The mixture was stirred at -78 °C for 10 min. To the resulting solution was added lithium 2-thienyl-cyanocuprate (0.25 M in ether, 3.0 mL, 0.76 mmol) dropwise over 5 min. The solution was stirred at -78 °C for 30 min. To the resulting mixture was added enone 332 (136 mg, 0.76 mmol) in ether (1 mL). The mixture was stirred at -78 °C for 2 h. The resulting solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 4) afforded dioxin 333 as a colorless oil; ¹H NMR (200 MHz, CDCl₃) δ 1.42 (s, 6 H), 1.48 – 1.60 (m, 2 H), 2.40 – 2.65 (m, 6 H), 4.20 (m, 2 H), 4.55 – 4.75 (m, 3 H), 5.28 (d, J = 10.5 Hz, 1 H), 5.33 (d, J = 18.2 Hz, 1 H), 5.95 (ddt, J = 9.5, 10.5, 18.2 Hz, 1 H).
8a-Methyl-3,6-dioxooctahydroazulene-3a-carboxylic acid allyl ester (334). To a solution of dioxin 333 (120 mg, 0.37 mmol) in CH$_3$CN (8 mL) was added Cs$_2$CO$_3$ (133 mg, 0.40 mmol). The mixture was heated to 110 °C in a sealed tube for 1.5 h. The resulting solution was filtered and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 4) afforded hydroazulene 334 as a colorless oil (72 mg, 74%); $^1$H NMR (200 MHz, CDCl$_3$) δ 1.20 (s, 3 H), 1.40 – 2.32 (m, 10 H), 2.39 – 2.66 (m, 2 H), 4.65 (d, 9.5 Hz, 2 H), 5.27 (d, $J$ = 10.5 Hz, 1 H), 5.36 (d, $J$ = 18.2 Hz, 1 H), 5.91 (ddt, $J$ = 9.5, 10.5, 18.2 Hz, 1 H).

Buta-1,3-dienyl-[2-(trimethylsilyl)ethoxymethyl]carbamic acid tert-butyl ester (394). To a suspension of sodium hydride (426 mg, 10.7 mmol) in THF (48 mL) at 0 °C was added buta-1,3-dienylcarbamic acid tert-butyl ester (392)$^{111}$ (1.64 g, 9.69 mmol) in THF (5 mL) dropwise over 5 min. The mixture was stirred at 0 °C for 20 min. To the resulting solution was added SEMCl (1.80 mL, 10.2 mmol). The solution was warmed to rt and stirred 2 h. The mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 20) provided the carbamate 394 as a colorless oil (2.70 g, 93%); $^1$H NMR (200 MHz, CDCl$_3$) δ 0.02 (s, 9 H), 0.94
(ddd, $J = 2.7, 7.2, 8.2$ Hz, 2 H), 1.51 (s, 9 H), 3.56 (ddd, $J = 2.7, 7.2, 8.2$ Hz, 2 H), 4.93 (dd, $J = 1.7, 10.2$ Hz, 1 H), 5.03 (s, 2 H), 5.09 (dd, $J = 1.7, 16.9$ Hz, 1 H), 5.91 (dd, $J = 10.6, 14.3$ Hz, 1 H), 6.31 (dt, $J = 10.4, 16.9$ Hz, 1 H), 7.02 (m, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ -1.5, 17.8, 28.1, 65.3, 74.2, 81.7, 112.3, 113.3, 130.4, 135.4, 152.6; IR (neat) 2954, 1715, 1645 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{15}$H$_{30}$NO$_3$Si 300.1990, found 300.2002.

1-(Tributylstannyl)buta-1,3-dienyl-[2-(trimethylsilyl)ethoxymethyl]-carbamic acid tert-butyl ester (395). To a solution of the enecarbamate 394 (2.70 g, 9.01 mmol) in THF (90 mL) at $-78$ °C was added TMEDA (1.36 mL, 9.01 mmol) followed by $n$-BuLi (2.5 M in hexane, 4.33 mL, 10.8 mmol) dropwise over 10 min. The mixture was warmed to $-60$ °C and stirred for 1 h. To the resulting solution was added Bu$_3$SnCl (3.06 mL, 11.3 mmol). The solution was warmed to 0 °C over 2 h. The mixture was quenched with brine and extracted with hexanes. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 97) afforded the stannane 395 (mixture of amide rotamers) as a colorless oil (3.98 g, 75%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.02 (s, 9 H), 0.88 (t, $J = 7.3$ Hz, 9 H), 0.94 (m, 8 H), 1.25 – 1.71 (m, 12 H), 1.47 (s, 9 H), 3.58 (br t, $J = 8.3$ Hz, 2 H), 4.88 (s, 2 H), 5.03 – 5.27 (m, 2 H), 6.37 (m, 1 H), 6.83 (br d, $J = 10.7$ Hz, 1 H), $^{13}$C NMR (50 MHz, CDCl$_3$, amide rotamers) $\delta$ -1.4, 12.4, 13.5 (minor), 13.6 (major), 17.4 (major), 18.2 (minor), 26.1 (minor), 26.8 (major), 27.3 (minor), 27.9 (major), 29.1, 65.5, 78.8, 80.6, 116.6, 133.1, 136.1, 153.1, 154.2; IR (neat) 2955, 1689, 1619 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{27}$H$_{56}$NO$_3$SiSn 590.3046, found 590.3068.
1-(Tributylstannyl)buta-1,3-dienylcarbamic acid tert-butyl ester (393).

To a solution of the stannane 395 (3.00 g, 5.10 mmol) in acetone (50 mL) at 0 °C was added 48% aqueous HF (5 mL) dropwise. The resulting solution was stirred at 0 °C for 45 min. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude N-hydroxymethyl amide. The N-hydroxymethyl amide was then dissolved in MeOH (50 mL) and concentrated aqueous NH₄OH (15 mL) was added. The mixture was stirred at rt for 30 min. The solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 97) afforded carbamate 393 as a colorless oil (1.61 g, 69%); ¹H NMR (200 MHz, CDCl₃) δ 0.89 (t, J = 7.1 Hz, 9 H), 1.01 (br t, J = 8.1 Hz, 6 H), 1.32 (hextet, J = 7.1 Hz, 6 H), 1.45 (s, 9 H), 1.40 – 1.60 (m, 6 H), 4.91 (d, J = 9.5 Hz, 1 H), 5.02 (d, J = 16.9 Hz, 1 H), 6.25 – 6.50 (m, 2 H), 6.33 (s, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 13.1, 13.7, 27.3, 28.2, 29.0, 80.0, 114.0, 126.1, 135.9, 145.4, 153.9; IR (neat) 3304, 2956, 1712, 1617 cm⁻¹; HRMS (MH⁺) calcd for C₂₁H₄₂NO₂Sn 460.2232, found 460.2228.
1-(6-Oxocyclohex-1-enyl)buta-1,3-dienylcarbamic acid tert-butyl ester (408). To a solution of 2-iodocyclohex-2-enone (407) (346 mg, 1.56 mmol) and stannane 393 (650 mg, 1.42 mmol) in THF (14 mL) was added Cul (67.5 mg, 0.35 mmol) and Pd(PPh₃)₄ (49.2 mg, 0.043 mmol). The mixture was stirred at 50 °C for 3 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ether-CH₂Cl₂, 3 : 97) provided triene 408 as a colorless oil (301 mg, 81%); ¹H NMR (300 MHz, CDCl₃) δ 1.42 (s, 9 H), 2.07 (p, J = 6.3 Hz, 2 H), 2.45 – 2.56 (m, 4 H), 4.91 (dd, J = 1.6, 10.1 Hz, 1 H), 5.15 (dd, J = 1.6, 16.7 Hz, 1 H), 6.22 (s, 1 H), 6.25 (ddd, J = 10.1, 11.0, 16.7 Hz, 1 H), 6.46 (d, J = 11.0 Hz, 1 H), 6.98 (t, J = 4.2 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 22.5, 26.1, 28.2, 38.4, 80.2, 115.4, 117.0, 132.7, 133.4, 135.0, 151.6, 152.4, 197.8; IR (neat) 3325, 2977, 1732, 1710 cm⁻¹; HRMS (MH⁺) calcd for C₁₅H₂₂NO₃ 264.1594, found 264.1586.

8-Oxo-5,6,7,8-tetrahydronapthalen-1-ylcarbamic acid tert-butyl ester (429). A solution of triene 408 (301 mg, 1.14 mmol) in toluene (23 mL) was heated at reflux for 1 h. The resulting solution was cooled to rt and DDQ (311 mg, 1.37 mmol) was added. The mixture was stirred at 50 °C for 6 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃,
dried (Na$_2$SO$_4$), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided the protected aniline 429 as a white solid: mp 84 – 86 °C (271 mg, 91%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.52 (s, 9 H), 2.06 (p, $J = 6.3$ Hz, 2 H), 2.67 (t, $J = 6.3$ Hz, 2 H), 2.95 (t, $J = 6.3$ Hz, 2 H), 6.83 (dd, $J = 1.0$, 7.6 Hz, 1 H), 7.40 (dd, $J = 7.6$, 8.4 Hz, 1 H), 8.31 (dd, $J = 1.0$, 8.4 Hz, 1 H), 11.40 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 22.7, 28.3, 31.0, 40.7, 80.3, 116.6, 118.0, 121.5, 134.8, 142.8, 145.9, 153.2, 202.7; IR (neat) 3213, 2976, 1727, 1650 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{15}$H$_{20}$NO$_3$ 262.1438, found 262.1453.

8-Amino-3,4-dihydro-2H-napthalen-1-one (430). To a solution of carbamate 429 (250 mg, 0.96 mmol) in CH$_2$Cl$_2$ (9.6 mL) at –50 °C was added TFA (147 µL, 1.91 mmol). The solution was warmed to rt over 30 min and stirred for 3 h. The mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided a white solid: mp 77 – 79 °C (145 mg, 94%); $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 2.02 (p, $J = 6.3$ Hz, 2 H), 2.61 (t, $J = 6.3$ Hz, 2 H), 2.86 (t, $J = 6.3$ Hz, 2 H), 6.44 (d, $J = 7.3$ Hz, 1 H), 6.45 (br s, 2 H), 6.47 (d, $J = 8.3$ Hz, 1 H), 7.14 (dd, $J = 7.3$, 8.3 Hz, 1 H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 22.9, 30.9, 40.3, 114.5, 115.4, 115.8, 134.2, 145.9, 151.1, 201.2; IR (neat) 3436, 3326, 2940, 1638, 1606 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{10}$H$_{12}$NO 162.0913, found 162.0903.
1-(4,5-Dihydro-3H-benzo[cd]indol-1-yl)ethanone (432). To a solution of the aniline 430 (56.7 mg, 0.35 mmol) in MeOH (4 mL) at 0 °C was added NaOAc (57.7 mg, 0.70 mmol), glacial acetic acid (80.5 µL, 1.41 mmol), glyoxylic acid monohydrate (48.6 mg, 0.53 mmol), and NaCNBH₃ (24.3 mg, 0.39 mmol). The solution was warmed slowly to rt over 1 h. The mixture was then filtered through a plug of silica gel and washed with 1% glacial acetic acid in ethyl acetate. The solution was then washed with brine, dried (Na₂SO₄), and concentrated to afford the crude carboxylic acid 431, which was used without further purification. ¹H NMR (300 MHz, d⁶-Acetone) δ 1.99 (p, J = 6.2 Hz, 2 H), 2.57 (t, J = 6.2 Hz, 2 H), 2.87 (t, J = 6.2 Hz, 2 H), 4.07 (d, J = 5.1 Hz, 2 H), 6.47 (d, J = 7.4 Hz, 1 H), 6.49 (d, J = 8.4 Hz, 1 H), 7.26 (dd, J = 7.4, 8.4 Hz, 1 H), 9.56 (br s, 1 H). To the crude carboxylic acid 5 was added a solution of acetic anhydride (3.5 mL) and Et₃N (490 µL, 3.52 mmol). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded the N-acetylindole 432 (mixture of amide rotamers) as a colorless oil (54.2 mg, 77%); ¹H NMR (400 MHz, CDCl₃) δ 2.04 (pentet, J = 6.1 Hz, 2 H), 2.60 (s, 3 H), 2.80 (t, J = 6.1 Hz, 2 H), 2.90 (t, J = 6.1, 2 H), 7.02 (d, J = 7.3 Hz, 1 H), 7.06 (br s, 1 H), 7.26 (t, J = 7.3 Hz, 1 H), 8.06 (br s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 21.7, 23.8, 24.0, 27.0, 114.0, 118.0, 120.2, 120.8, 125.6, 129.5, 132.3, 133.9, 168.5; IR (neat) 2930, 1697, 1642 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₄NO 200.1069, found 200.1064. The N-acetyl group was then removed to obtain cleaner spectra without broadening due to amide rotamers. Treatment of the N-acetylindole 432 with K₂CO₃ (75.2 mg, 0.54) in MeOH (3 mL) at rt for 1 h, upon workup, afforded the corresponding deprotected
indole in quantitative yield as a white solid: mp 46 – 48 °C (42.7 mg, quantitative); 

\(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 2.07 (p, \(J = 6.2\) Hz, 2 H), 2.87 (t, \(J = 6.2\) Hz, 2 H), 2.95 (t, \(J = 6.2\) Hz, 2 H), 6.84 (d, \(J = 6.8\) Hz, 1 H), 6.85 (s, 1 H), 7.11 (dd, \(J = 6.8, 8.1\) Hz, 1 H), 7.16 (d, \(J = 8.1\) Hz, 1 H), 7.79 (br s, 1 H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 21.9, 24.6, 27.5, 108.0, 113.9, 115.8, 117.1, 122.6, 127.2, 132.3, 133.9; IR (neat) 3410, 2924 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{11}\)H\(_{12}\)N 158.0964, found 158.0949.

\[
\begin{align*}
\text{H} & \quad \text{SnBu}_3 \quad \text{BOC} \quad \text{+} \quad \text{Cyclooct-1-enyl} \\
\text{N} & \quad \text{Br} \quad \text{CO} \quad \text{O} \\
& \text{BOC} \quad \text{H} \\
\end{align*}
\]

1-(8-Oxocyclooct-1-enyl)buta-1,3-dienylcarbamic acid tert-butyl ester (447). To a solution of 2-bromocyclooct-2-enone (446) (160 mg, 0.79 mmol) and stannane 393 (300 mg, 0.65 mmol) in THF (7 mL) was added Cul (31.2 mg, 0.16 mmol) and Pd(PPh\(_3\))\(_4\) (37.8 mg, 0.033 mmol). The mixture was stirred at reflux for 3 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ether-CH\(_2\)Cl\(_2\), 1 : 99) provided triene 447 as a colorless oil (166 mg, 87%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.44 (s, 9 H), 1.66 (br pentet, \(J = 2.9\) Hz, 4 H), 1.98 (m, 2 H), 2.38 (m, 2 H), 2.55 (m, 2 H), 4.94 (dd, \(J = 1.9, 10.1\) Hz, 1 H), 5.18 (dd, \(J = 1.9, 16.8\) Hz, 1 H), 6.15 (t, \(J = 5.1\) Hz, 1 H), 6.53 (ddd, \(J = 10.1, 11.0, 16.8\) Hz, 1 H), 6.55 (s, 1 H), 6.75 (d, \(J = 11.0\) Hz, 1 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.9, 22.2, 28.0, 28.6, 29.8, 43.7, 80.3, 115.1, 115.3, 133.2, 133.3, 134.8, 140.4, 152.5, 210.3; IR (neat) 3354, 2931, 1721 cm\(^{-1}\).
10-Oxo-5,6,7,8,9,10-hexahydrobenzocycloocten-1-yl)carbamic acid tert-butyl ester (448). A solution of triene 447 (109 mg, 0.37 mmol) in toluene (7.4 mL) was heated at reflux for 2 h. The resulting solution was cooled to rt and DDQ (101 mg, 0.45 mmol) was added. The mixture was stirred at 70 °C for 3 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided the protected aniline 448 as a colorless oil (93.9 mg, 87%); ¹H NMR (200 MHz, CDCl₃) δ 1.48 (s, 9 H), 1.61 (m, 2 H), 1.78 (m, 4 H), 2.79 (m, 4 H), 6.88 (d, J = 7.7 Hz, 1 H), 7.29 (t, J = 8.0 Hz, 1 H), 7.62 (s, 1 H), 7.86 (d, J = 8.2 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 23.5, 27.3, 28.3, 28.5, 33.6, 46.7, 80.5, 119.4, 125.0, 130.0, 130.7, 134.8, 140.3, 153.1, 212.2; IR (neat) 3307, 2931, 1730, 1690 cm⁻¹; HRMS (MH⁺) calcd for C₁₇H₂₄NO₃ 290.1751, found 290.1773.

4-Amino-7,8,9,10-tetrahydro-6H-benzocycloocten-5-one. To a solution of carbamate 448 (64.6 mg, 0.22 mmol) in CH₂Cl₂ (4 mL) at −50 °C was added TFA (86 µL, 1.12 mmol). The solution was warmed to rt over 30 min and stirred for 3 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and
concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided a colorless oil (40.8 mg, 97%); 1H NMR (200 MHz, CDCl3) δ 1.48 – 1.61 (m, 2 H), 1.69 – 1.90 (m, 4 H), 2.92 (t, J = 6.8 Hz, 2 H), 2.95 (t, J = 6.1 Hz, 2 H), 5.20 (br s, 2 H), 6.51 (d, J = 7.5 Hz, 1 H), 6.55 (d, J = 7.5 Hz, 1 H), 7.10 (t, J = 7.5 Hz, 1 H); 13C NMR (50 MHz, CDCl3) δ 24.2, 25.4, 28.4, 35.0, 45.3, 115.3, 120.1, 123.7, 131.8, 142.3, 147.2, 209.7; IR (neat) 3448, 3342, 2926, 1678, 1604 cm⁻¹; HRMS (MH⁺) calcd for C₁₂H₁₆NO 190.1226, found 190.1217.

1-(7,8,9,10-Tetrahydro-6H-2-aza-cycloocta[cd]inden-2-yl)-ethanone (450). To a solution of the aniline (21.2 mg, 0.11 mmol) in MeOH (2 mL) at 0 °C was added NaOAc (18.4 mg, 0.22 mmol), glacial acetic acid (26 µL, 0.45 mmol), glyoxylic acid monohydrate (25.8 mg, 0.28 mmol), and NaCNBH₃ (7.7 mg, 0.12 mmol). The solution was warmed slowly to rt over 1 h. The mixture was then filtered through a plug of silica gel and washed with 1% glacial acetic acid in ethyl acetate. The solution was then washed with brine, dried (Na₂SO₄), and concentrated to afford the crude carboxylic acid 449, which was used without further purification. To the crude carboxylic acid was added a solution of acetic anhydride (1.1 mL) and Et₃N (156 µL, 1.12 mmol). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 17) afforded the N-acetylindole 450 (mixture of amide rotamers) as a colorless oil (19.2 mg, 75%); 1H NMR (300 MHz, CDCl₃) δ 1.36 – 1.46 (m, 2 H), 1.77 – 1.88 (m, 4 H), 2.60 (s, 3 H), 3.00 (t, J = 7.1 Hz, 2 H), 3.14 (t, J = 6.9 Hz, 2 H), 6.97 (d, J = 7.3 Hz, 1 H), 7.11 (s, 1 H), 7.24 (dd, J = 7.3, 8.3 Hz, 1 H), 8.30 (d, J = 8.3 Hz, 1 H); 13C NMR
(75 MHz, CDCl$_3$) $\delta$ 22.6, 24.1, 25.4, 29.1, 29.5, 32.3, 114.6, 121.7, 123.3, 124.4, 125.4, 131.6, 134.5, 135.6, 168.3; IR (neat) 2929, 1704 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{15}$H$_{16}$NO 228.1388, found 228.1391.

\[
\begin{array}{c}
\text{SnBu}_3 \text{N-BOC} + \text{O} \\
\rightarrow \text{O} \\
\end{array}
\]

1-(5-Oxo-8,9-dihydro-5H-benzocyclohepten-6-yl)buta-1,3-dienyl-carbamic acid tert-butyl ester (453). To a solution of iodide 452 (186 mg, 0.65 mmol) and stannane 393 (300 mg, 0.65 mmol) in DMF (8 mL) was added CuI (31.2 mg, 0.16 mmol) and Pd(PPh$_3$)$_4$ (37.8 mg, 0.033 mmol). The mixture was stirred at rt for 30 min. The solution was quenched with water and extracted with ether. The combined extracts were washed with water, dried (Na$_2$SO$_4$), and concentrated. Purification by silica-gel chromatography (ether-CH$_2$Cl$_2$, 1 : 99) provided triene 453 as a colorless oil (185 mg, 87%); $^1$H NMR 400 MHz, CDCl$_3$) $\delta$ 1.41 (s, 9 H), 2.69 (m, 2 H), 3.04 (br t, $J = 6.0$ Hz, 2 H), 4.89 (dd, $J = 1.8, 9.9$ Hz, 1 H), 5.13 (dd, $J = 1.8, 16.4$ Hz, 1 H), 6.30 (dt, $J = 10.4, 16.4$ Hz, 1 H), 6.33 (s, 1 H), 6.39 (d, $J = 11.0$ Hz, 1 H), 6.78 (t, $J = 5.0$ Hz, 1 H), 7.16 (d, $J = 7.5$ Hz, 1 H), 7.27 (dt, $J = 1.2, 7.7$ Hz, 1 H), 7.38 (dt, $J = 1.2, 7.5$ Hz, 1 H), 7.59 (dd, $J = 1.2, 7.7$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 28.1, 30.2, 33.4, 80.0, 115.0, 116.4, 126.5, 126.7, 128.1, 129.4, 131.8, 132.9, 136.8, 138.6, 140.9, 148.3, 152.3, 194.8; IR (neat) 3328, 2976, 1722, 1643 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{24}$NO$_3$ 326.1751, found 326.1768.
5-Oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-4-ylcarbamic acid tert-butyl ester (454). A solution of triene 453 (164 mg, 0.50 mmol) in toluene (10 mL) was heated at reflux for 2 h. The resulting solution was cooled to rt and DDQ (137 mg, 0.60 mmol) was added. The mixture was stirred at 70 °C for 3 h. The solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO$_3$, dried (Na$_2$SO$_4$), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided the protected aniline 454 as a colorless oil (151 mg, 93%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.51 (s, 9 H), 3.08 (m, 2 H), 3.23 (m, 2 H), 6.89 (d, $J = 7.5$ Hz, 1 H), 7.20 (d, $J = 7.5$ Hz, 1 H), 7.29 – 7.38 (m, 2 H), 7.44 (dt, $J = 1.5$, 7.5 Hz, 1 H), 8.05 (d, $J = 8.4$ Hz, 1 H), 8.09 (dd, $J = 1.5$, 7.9 Hz, 1 H), 8.63 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 28.2, 34.0, 35.2, 80.4, 119.1, 122.2, 126.3, 128.9, 130.3, 131.2, 131.9, 132.7, 137.5, 138.0, 140.5, 142.3, 153.0, 198.5; IR (neat) 3381, 2978, 1729, 1638 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{22}$NO$_3$ 324.1594, found 324.1619.
**4-Amino-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one.** To a solution of carbamate 454 (119 mg, 0.37 mmol) in CH₂Cl₂ (8 mL) at –50 °C was added TFA (141 µL, 1.84 mmol). The solution was warmed to rt over 30 min and stirred for 3 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3:20) provided a colorless oil (77.9 mg, 95%); ¹H NMR (400 MHz, CDCl₃) δ 3.09 (m, 2 H), 3.19 (m, 2 H), 5.51 (s, 2 H), 6.52 (d, J = 7.3 Hz, 1 H), 6.57 (d, J = 8.2 Hz, 1 H), 7.12 (dd, J = 7.3, 8.2 Hz, 1 H), 7.18 (d, J = 7.6 Hz, 1 H), 7.31 (dt, J = 1.2, 7.6 Hz, 1 H), 7.40 (dt, J = 1.5, 7.6 Hz, 1 H), 8.05 (dd, J = 1.5, 7.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 35.0, 35.3, 115.4, 117.5, 122.6, 126.2, 129.2, 131.0, 131.9, 132.4, 139.4, 141.7, 142.7, 148.9, 197.5; IR (neat) 3472, 3366, 2931, 1607 cm⁻¹; HRMS (MH⁺) calcd for C₁₅H₁₄NO 224.1070, found 224.1076.

**1-(6,7-Dihydro-2-aza-dibenzo[cd,h]azulen-2-yl)ethanone (456).** To a solution of the aniline (50.5 mg, 0.23 mmol) in MeOH (4 mL) at 0 °C was added NaOAc (37.1 mg, 0.45 mmol), glacial acetic acid (51.8 µL, 0.90 mmol), glyoxylic acid monohydrate (52.0 mg, 0.57 mmol), and NaCNBH₃ (15.6 mg, 0.25 mmol). The solution was warmed slowly to rt over 1 h. The mixture was then filtered
through a plug of silica gel and washed with 1% glacial acetic acid in ethyl acetate. The solution was then washed with brine, dried (Na₂SO₄), and concentrated to afford the crude carboxylic acid 455, which was used without further purification. To the crude carboxylic acid was added a solution of acetic anhydride (2.3 mL) and Et₃N (315 µL, 2.26 mmol). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded the N-acetylindole 456 (mixture of amide rotamers) as a white solid: mp 144 – 147 °C (49.6 mg, 84%); ¹H NMR (400 MHz, CDCl₃) δ 2.72 (s, 3 H), 3.16 (m, 2 H), 3.22 (m, 2 H), 7.08 (d, J = 7.4 Hz, 1 H), 7.22 – 7.32 (m, 4 H), 7.69 (d, J = 7.7 Hz, 1 H), 7.70 (s, 1 H), 8.35 (d, J = 8.2 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 24.2, 34.1, 36.4, 114.3, 120.8, 123.2, 123.5, 125.0, 126.6, 126.9, 127.3, 127.4, 130.4, 132.5, 136.3, 137.0, 141.2, 168.5; IR (neat) 2928, 1703 cm⁻¹; HRMS (MH⁺) calcd for C₃₈H₅₆NO 626.1226, found 262.1225.

Penta-1,3-dienylcarbamic acid tert-butyl ester. To a solution of sorbic acid (10.0 g, 89.2 mmol) in acetone (45 mL) was added i-Pr₂NEt (19.4 mL, 111 mmol). The solution was cooled to 0 °C and ethyl chloroformate (8.70 mL, 91.0 mmol) in acetone (25 mL) was added over 5 min. The mixture was stirred at 0 °C for 30 min. To the resulting solution at 0 °C was added NaN₃ (11.6 g, 178 mmol) in H₂O (25 mL) dropwise over 5 min. The solution was stirred at 0 °C for 30 min. The resulting mixture was quenched with H₂O and extracted with toluene. The combined extracts were dried (Na₂SO₄) and concentrated to approximately 80 mL of toluene containing the acyl azide. To a solution of t-BuOH (25.6 mL, 268 mmol) and BHT (79 mg, 0.36 mmol) in toluene (45 mL) at 110 °C was added the
crude acyl azide solution dropwise over 20 min. The resulting solution was refluxed for 3 h, cooled to rt, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded a yellow solid: mp 57 – 59 °C (12.3 g, 75%); \(^1^H\) NMR (200 MHz, CDCl\(_3\)) \(\delta 1.46\) (s, 9 H), 1.72 (dd, \(J = 1.3, 6.7\) Hz, 3 H), 5.35 – 5.65 (m, 2 H), 5.95 (ddd, \(J = 1.3, 10.5, 15.1\) Hz, 1 H), 6.21 (m, 1 H), 6.58 (br t, \(J = 12.8\) Hz, 1 H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta 18.0, 28.1, 80.3, 110.7, 124.7, 125.4, 128.8, 152.7;\) IR (neat) 3351, 2975, 1691, 1662, 1638 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{10}\)H\(_{18}\)NO\(_2\) 184.1332, found 184.1347.

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\text{Penta-1,3-dienyl-[2-(trimethylsilyl)ethoxymethyl]carbamic acid tert-butyl ester (398).} \quad \begin{array}{c}
\text{N} \\
\text{BOC} \\
\text{H} \\
\text{N} \\
\text{BOC} \\
\text{SEM}
\end{array}
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To a suspension of sodium hydride (720 mg, 18.0 mmol) in THF (82 mL) at 0 °C was added penta-1,3-dienylcarbamic acid tert-butyl ester (3.00 g, 16.4 mmol) in THF (10 mL) dropwise over 5 min. The mixture was stirred at 0 °C for 20 min. To the resulting solution was added SEMCl (3.19 mL, 18.0 mmol). The solution was warmed to rt and stirred 2 h. The mixture was quenched with saturated aqueous NH\(_4\)Cl and extracted with ether. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 20) provided carbamate 398 as a colorless oil (4.79 g, 93%); \(^1^H\) NMR (200 MHz, CDCl\(_3\)) \(\delta 0.00\) (s, 9 H), 0.93 (t, \(J = 8.3\) Hz, 2 H), 1.50 (s, 9 H), 1.74 (d, \(J = 6.6\) Hz, 3 H), 3.54 (t, \(J = 8.3\) Hz, 2 H), 5.01 (s, 2 H), 5.56 (m, 1 H), 5.80 – 6.08 (m, 2 H), 6.91 (m, 1 H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta -1.5, 17.8, 18.0, 28.0, 65.1, 74.2, 81.3, 112.0, 125.4, 127.7, 129.5, 152.7;\) IR (neat) 2954, 1713, 1657, 1626 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{16}\)H\(_{32}\)NO\(_3\)Si 314.2146, found 314.2160.
1-(Tributylstannyl)penta-1,3-di-enyl-[2-(trimethylsilyl)ethoxymethyl]-carbamic acid tert-butyl ester (399). To a solution of enecarbamate 398 (3.20 g, 10.2 mmol) in THF (100 mL) at –78 °C was added TMEDA (1.54 mL, 10.2 mmol) followed by n-BuLi (2.5 M in hexane, 5.72 mL, 14.3 mmol) dropwise over 10 min. The mixture was warmed to –60 °C and stirred for 1 h. To the resulting solution was added Bu₃SnCl (4.15 mL, 15.3 mmol). The solution was warmed to 0 °C over 2 h. The mixture was quenched with brine and extracted with hexanes. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 97) afforded stannane 399 (mixture of amide rotamers) as a colorless oil (4.69 g, 76%); ¹H NMR (200 MHz, CDCl₃) δ 0.01 (s, 9 H), 0.90 (t, J = 7.3 Hz, 9 H), 0.91 – 1.00 (m, 8 H), 1.31 (hextet, J = 7.3 Hz, 6 H), 1.48 (s, 9 H), 1.52 (m, 6 H), 1.77 (d, J = 6.1 Hz, 3 H), 3.57 (t, J = 8.5 Hz, 2 H), 4.85 (br s, 2 H), 5.65 (m, 1 H), 6.03 (m, 1 H), 6.79 (br, d, J = 11.1 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃, amide rotamers) δ -1.4, 12.2 (minor), 13.6 (major), 18.2 (minor), 18.3 (major), 27.3, 28.3, 28.9, 32.0, 35.5, 65.4 (major), 67.1 (minor), 78.9, 80.3, 128.9, 130.5, 133.4, 149.4, 154.2; IR (neat) 2955, 1688 cm⁻¹; HRMS (MH⁺) calcd for C₂₈H₅₈NO₃SiSn 604.3203, found 604.3180.
1-[(Tributylstanny1)penta-1,3-dienylcarbamic acid tert-butyl ester (400). To a solution of stannane 399 (6.00 g, 9.96 mmol) in acetone (200 mL) at 0 °C was added 48% aqueous HF (19.9 mL) dropwise. The resulting solution was stirred at 0 °C for 1 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude N-hydroxymethyl amide. The N-hydroxymethyl amide was then dissolved in MeOH (100 mL) and concentrated aqueous NH₄OH (25 mL) was added. The mixture was stirred at rt for 30 min. The solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 97) afforded stannane 400 as a colorless oil (3.28 g, 70%); ¹H NMR (200 MHz, CDCl₃) δ 0.89 (t, J = 7.2 Hz, 9 H), 0.96 (m, 6 H), 1.32 (hextet, J = 7.2 Hz, 6 H), 1.46 (s, 9 H), 1.49 – 1.54 (m, 6 H), 1.75 (dd, J = 1.4, 6.7 Hz, 3 H), 5.51 (dq, J = 6.7, 14.5 Hz, 1 H), 6.08 (dd, J = 10.8, 14.5 Hz, 1 H), 6.25 (s, 1 H), 6.30 (d, J = 10.8 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ 13.0, 13.7, 18.3, 27.4, 28.3, 29.0, 79.8, 126.0, 126.5, 130.2, 141.6, 154.0; IR (neat) 3294, 2956, 1760, 1704 cm⁻¹.
1-(6-Oxocyclohex-1-enyl)penta-1,3-dienylcarbamic acid tert-butyl ester (463). To a solution of 2-iodocyclohex-2-enone (169 mg, 0.76 mmol) and stannane 400 (300 mg, 0.63 mmol) in THF (7.5 mL) was added Cul (30.2 mg, 0.16 mmol) and Pd(PPh₃)₄ (36.7 mg, 0.032 mmol). The mixture was stirred at 50 °C for 3 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ether-CH₂Cl₂, 3:97) provided triene 463 as a colorless oil (180 mg, 85%); ^1H NMR (300 MHz, CDCl₃) δ 1.39 (s, 9 H), 1.68 (dd, J = 1.5, 6.7 Hz, 3 H), 2.04 (m, 2 H), 2.47 (m, 4 H), 5.61 (dq, J = 6.7, 15.0 Hz, 1 H), 5.90 (ddq, J = 1.5, 10.8, 15.0 Hz, 1 H), 6.18 (s, 1 H), 6.33 (d, J = 10.8 Hz, 1 H), 6.94 (t, J = 4.1 Hz, 1 H); ^13C NMR (75 MHz, CDCl₃) δ 18.5, 22.6, 26.1, 28.2, 38.4, 79.9, 124.9, 125.0, 127.0, 128.3, 130.3, 135.3, 151.2, 198.0; IR (neat) 3319, 2978, 1721, 1678, 1612 cm⁻¹; HRMS (MH⁺) calcd for C₁₆H₂₄NO₃ 278.1751, found 278.1749.

4-Methyl-8-oxo-5,6,7,8-tetrahydronaphthalen-1-ylcarbamic acid tert-butyl ester (464). A solution of triene 463 (120 mg, 0.43 mmol) in toluene (8.5 mL) was heated at reflux for 2 h. The resulting solution was cooled to rt and DDQ (144 mg, 0.52 mmol) was added. The mixture was stirred at 50 °C for 4 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃,
dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided the protected aniline 464 as a colorless oil (107 mg, 90%); ¹H NMR (300 MHz, CDCl₃) δ 1.51 (s, 9 H), 2.07 (pentet,  J = 6.3 Hz, 2 H), 2.22 (s, 3 H), 2.65 (t,  J = 6.3 Hz, 2 H), 2.83 (t,  J = 6.3 Hz, 2 H), 7.29 (d,  J = 8.7 Hz, 1 H), 8.21 (d,  J = 8.7 Hz, 1 H), 11.34 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 19.4, 22.0, 27.5, 28.3, 40.4, 80.1, 116.2, 118.3, 128.5, 136.5, 140.8, 143.5, 153.3, 203.2; IR (neat) 3217, 2931, 1726, 1650 cm⁻¹; HRMS (MH⁺) calcd for C₁₆H₂₂NO₃ 276.1594, found 276.1576.

8-Amino-5-methyl-3,4-dihydro-2H-naphthalen-1-one. To a solution of carbamate 464 (95.0 mg, 0.34 mmol) in CH₂Cl₂ (7 mL) at −50 °C was added TFA (266 µL, 3.45 mmol). The solution was warmed to rt over 30 min and stirred for 3 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided a white solid: mp 84 – 85 °C (58.9 mg, 98%); ¹H NMR (300 MHz, CDCl₃) δ 2.05 (pentet,  J = 6.1 Hz, 2 H), 2.15 (s, 3 H), 2.61 (t,  J = 6.1 Hz, 2 H), 2.78 (t,  J = 6.1 Hz, 2 H), 6.32 (s, 2 H), 6.44 (d,  J = 8.4 Hz, 1 H), 7.06 (d,  J = 8.4 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 19.0, 22.2, 27.5, 40.1, 114.2, 115.7, 122.5, 136.4, 143.1, 149.5, 201.6; IR (neat) 3422, 3330, 2944, 1630, 1609 cm⁻¹; HRMS (MH⁺) calcd for C₁₁H₁₄NO 176.1070, found 176.1055.
1-(6-Methyl-4,5-dihydro-3H-benzo[cd]indol-1-yl)ethanone (465). To a
solution of the aniline (20.0 mg, 0.11 mmol) in MeOH (2 mL) at 0 °C was added
NaOAc (18.7 mg, 0.23 mmol), glacial acetic acid (26 µL, 0.46 mmol), glyoxylic
acid monohydrate (26.3 mg, 0.29 mmol), and NaCNBH₃ (7.9 mg, 0.13 mmol). The
solution was warmed slowly to rt over 1 h. The mixture was then filtered
through a plug of silica gel and washed with 1% glacial acetic acid in ethyl
acetate. The solution was then washed with brine, dried (Na₂SO₄), and
concentrated to afford the crude carboxylic acid, which was used without further
purification. To the crude carboxylic acid was added a solution of acetic
anhydride (1.1 mL) and Et₃N (159 µL, 1.14 mmol). The mixture was heated to
reflux for 30 min. The resulting solution was concentrated in vacuo. Purification
by silica-gel chromatography (ethyl acetate-hexane, 3 : 20) afforded the N-acetylindole 465 (mixture of amide rotamers) as a colorless oil (17.2 mg, 71%);
¹H NMR (300 MHz, CDCl₃, amide rotamers) δ 2.04 (pentet, J = 6.0 Hz, 2 H), 2.33
(s, 3 H), 2.59 (s, 3 H), 2.76 (m, 2 H), 2.81 (t, J = 6.0 Hz, 2 H), 7.03 (br m, 1 H),
7.11 (d, J = 8.4 Hz, 1 H), 7.76 (br, m, 1 H); HRMS (MH⁺) calcd for C₁₄H₁₆NO
214.1226, found 214.1242. The N-acetyl group was then removed to obtain
cleaner spectra without broadening due to amide rotamers. Treatment of the N-acetylindole 465 with K₂CO₃ (22.3 mg, 0.16) in MeOH (3 mL) at rt for 1 h, upon
workup, afforded the corresponding deprotected indole in quantitative yield as a
colorless oil (13.8 mg, quantitative); ¹H NMR (300 MHz, CDCl₃) δ 2.07 (pentet, J
= 6.1 Hz, 2 H), 2.34 (s, 3 H), 2.80 – 2.88 (m, 4 H), 6.82 (s, 1 H), 6.97 (d, J = 8.1
Hz, 1 H), 7.07 (d, J = 8.1 Hz, 1 H), 7.69 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ
17.3, 21.6, 24.4, 25.0, 107.6, 113.6, 117.2, 123.6, 124.8, 127.3, 129.5, 132.6; IR
(neat) 3401, 2928 cm⁻¹.
Buta-1,3-dienylmethylcarbamic acid tert-butyl ester (396). To a suspension of sodium hydride (624 mg, 15.6 mmol) in THF (130 mL) at 0 °C was added buta-1,3-dienylcarbamic acid tert-butyl ester 392 (2.20 g, 13.0 mmol) in THF (5 mL) dropwise over 5 min. The mixture was stirred at 0 °C for 20 min. To the resulting solution was added MeI (1.21 mL, 19.5 mmol). The solution was warmed to rt and stirred 2 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:20) provided carbamate 396 as a colorless oil (2.19 g, 92%); ¹H NMR (360 MHz, CDCl₃) δ 1.46 (s, 9 H), 2.99 (s, 3 H), 4.83 (d, J = 10.2 Hz, 1 H), 5.00 (d, J = 16.6 Hz, 1 H), 5.47 (dd, J = 10.2, 14.1 Hz, 1 H), 6.27 (dt, J = 10.2, 16.6 Hz, 1 H), 7.23 (m, 1 H); ¹³C NMR (90 MHz, CDCl₃) δ 28.1, 30.3, 81.2, 109.7, 112.3, 132.1, 135.4, 152.6; IR (neat) 2954, 1714, 1643 cm⁻¹; HRMS (MH⁺) calcd for C₁₀H₁₈NO₂ 184.1332, found 184.1339.

Methyl-1-(tributylstannyl)buta-1,3-dienylcarbamic acid tert-butyl ester (397). To a solution of dienamide 396 (2.00 g, 10.9 mmol) in THF (110 mL) at −78 °C was added TMEDA (1.65 mL, 10.9 mmol) followed by n-BuLi (2.5 M in hexane, 5.24 mL, 13.1 mmol) dropwise over 10 min. The mixture was warmed to −60 °C and stirred for 1 h. To the resulting solution was added Bu₃SnCl (3.55 mL, 13.1 mmol). The solution was warmed to 0 °C over 2 h. The mixture was quenched with brine and extracted with hexanes. The combined
extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 99) afforded stannane 397 (mixture of amide rotamers) as a colorless oil (3.97 g, 77%); ¹H NMR (360 MHz, CDCl₃) δ 0.89 (t, J = 7.3 Hz, 9 H), 0.95 (m, 6 H), 1.33 (hept, J = 7.3 Hz, 6 H), 1.47 (s, 9 H), 1.50 (m, 6 H), 3.10 (s, 3 H), 4.95-5.18 (m, 2 H), 6.32-6.55 (m, 2 H); 13C NMR (50 MHz, CDCl₃, amide rotamers) δ 13.2 (minor), 13.7 (major), 26.8 (minor), 27.4 (major), 28.0 (minor), 28.4 (major), 28.8, 29.0 (minor), 29.2 (major), 35.1, 80.3, 115.1, 129.2, 136.4, 154.5, 154.7; IR (neat) 2929, 1682, 1616 cm⁻¹; HRMS (MH⁺) calcd for C₂₂H₄₄NO₂Sn 474.2389, found 474.2385.

Methyl-1-(6-oxocyclohex-1-enyl)buta-1,3-dienylcarbamic acid tert-butyl ester (416). To a solution of 2-iodocyclohex-2-enone (181 mg, 0.82 mmol) and stannane 397 (350 mg, 0.74 mmol) in DMF (8 mL) was added CuI (35.3 mg, 0.19 mmol) and Pd(PPh₃)₄ (25.7 mg, 0.022 mmol). The mixture was stirred at rt for 8 h. The solution was quenched with saturated aqueous NaCl and extracted with ether. The combined extracts were washed with water, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ether-CH₂Cl₂, 3 : 97) provided triene 416 (mixture of amide rotamers) as a colorless oil (189 mg, 92%); ¹H NMR (300 MHz, CDCl₃) δ 1.38 (s, 9 H), 2.06 (pentet, J = 6.1 Hz, 2 H), 2.48 (m, 4 H), 3.16 (s, 3 H), 5.05 (dd, J = 1.7, 9.8 Hz, 1 H), 5.22 (dd, J = 1.7, 16.7, 1 H), 6.06 (d, J = 11.0 Hz, 1 H), 6.25 (m, 1 H), 6.91 (t, J = 4.3 Hz, 1 H); 13C NMR (50 MHz, CDCl₃) δ 22.7, 26.1, 28.3, 37.8, 38.6, 79.9, 117.4, 125.9, 132.8, 136.6, 139.9, 150.3, 154.2, 197.0; IR (neat) 2975, 1699, 1624 cm⁻¹; HRMS (MH⁺) calcd for C₁₆H₂₄NO₃ 278.1751, found 278.1753.
Methyl-(8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamic acid tert-butyl ester (466). A solution of triene 416 (121 mg, 0.43 mmol) in toluene (8.7 mL) was heated at reflux for 3 h. The resulting solution was concentrated to afford the crude cyclohexadiene. The residue was diluted with dioxane (8.7 mL) and DDQ (128 mg, 0.57 mmol) was added. The mixture was stirred at rt for 16 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided the protected aniline 466 (mixture of amide rotamers) as a colorless oil (106 mg, 88%); ¹H NMR (300 MHz, CDCl₃, amide rotamers) δ 1.27 (s, major, 9 H), 1.50 (s, minor, 9 H), 2.10 (m, 2 H), 2.62 (m, 2 H), 2.94 (m, 2 H), 3.14 (s, minor, 3 H), 3.16 (s, major, 3 H), 7.04 (d, major, J = 7.7 Hz, 1 H), 7.10 (d, minor, J = 7.7 Hz, 1 H), 7.16 (d, J = 7.7 Hz, 1 H), 7.40 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃, amide rotamers) δ 22.8 (minor), 22.9 (major), 28.2 (major), 28.4 (minor), 30.4 (minor), 30.5 (major), 37.1 (major), 37.7 (minor), 40.2 (minor), 40.4 (major), 79.3 (major), 80.1 (minor), 127.4 (major), 127.5 (minor), 127.8 (major), 127.9 (minor), 129.0 (major), 129.4 (minor), 132.9 (major), 133.2 (minor), 143.4 (minor), 143.6 (major), 145.6 (major), 146.1 (minor), 154.4 (major), 155.4 (minor), 197.2 (major), 197.6 (minor); IR (neat) 2966, 1702, 1590 cm⁻¹; HRMS (MH⁺) calcd for C₁₆H₁₂NO₃ 276.1594, found 276.1576.
8-Methylamino-3,4-dihydro-2H-naphthalen-1-one. To a solution of carbamate 466 (80.4 mg, 0.29 mmol) in CH$_2$Cl$_2$ (6 mL) at –50 °C was added TFA (113 µL, 1.46 mmol). The solution was warmed to rt over 30 min and stirred for 2 h. The mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 20) provided a colorless oil (47.7 mg, 93%); $^1$H NMR (300 MHz, CDCl$_3$) δ 2.02 (pentet, $J = 6.3$ Hz, 2 H), 2.62 (t, $J = 6.3$ Hz, 2 H), 2.87 (t, $J = 6.3$ Hz, 2 H), 2.90 (d, $J = 5.1$ Hz, 3 H), 6.41 (d, $J = 7.3$ Hz, 1 H), 6.52 (d, $J = 8.5$ Hz, 1 H), 7.26 (t, $J = 7.8$ Hz, 1 H), 9.13 (br s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 23.0, 29.4, 31.2, 40.4, 108.7, 114.3, 114.7, 134.9, 146.5, 152.8, 201.2; IR (neat) 3292, 2934, 1629, 1579 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{11}$H$_{14}$NO 176.1070, found 176.1063.

1-Methyl-1,3,4,5-tetrahydrobenzo[cd]indole (468). To a solution of the aniline (40.0 mg, 0.23 mmol) in DMF (2 mL) at rt was added methyl iodoacetate (137 mg, 0.68 mmol) and K$_2$CO$_3$ (95.0 mg, 0.68 mmol). The mixture was heated at 100 °C for 12 h. The solution was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated. Purification by silica-gel chromatography (ether-CH$_2$Cl$_2$, 3 : 97) provided ester 467 as a colorless oil (40.1 mg, 71%); $^1$H NMR
(200 MHz, CDCl₃) δ 2.01 (pentet, J = 6.1 Hz, 2 H), 2.61 (t, J = 6.1 Hz, 2 H), 2.89 (t, J = 6.1 Hz, 2 H), 3.00 (s, 3 H), 3.75 (s, 3 H), 3.86 (s, 2 H), 6.72 (d, J = 7.5 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H), 7.29 (t, J = 7.9 Hz, 1 H).

To a solution of ester 467 (25.0 mg, 0.10 mmol) in MeOH (1 mL) was added 4 M aqueous NaOH (500 µL). The mixture was stirred at rt for 2 h. The resulting solution was acidified with 2 M HCl and extracted with ethyl acetate. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 19) afforded indole 468 as a colorless oil (16.1 mg, 93%); ¹H NMR (300 MHz, CDCl₃) δ 2.06 (pentet, J = 6.2 Hz, 2 H), 2.85 (t, J = 6.2 Hz, 2 H), 2.94 (t, J = 6.2 Hz, 2 H), 3.75 (s, 3 H), 6.70 (s, 1 H), 6.81 (dd, J = 1.0, 6.7 Hz, 1 H), 7.08 (d, J = 8.2 Hz, 1 H), 7.14 (dd, J = 6.7, 8.2 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 21.8, 24.7, 27.5, 32.6, 106.2, 112.6, 115.1, 122.0, 122.2, 127.5, 132.4, 134.9; IR (neat) 2924, 1610 cm⁻¹; HRMS (MH⁺) calcd for C₁₂H₁₄N 172.1121, found 172.1110.

8-Oxo-5,6,7,8-tetrahydronaphthalen-1-ylaminophenylacetic acid methyl ester (470). To a solution of aniline 430 (34.8 mg, 0.22 mmol) in DMF (2 mL) at rt was added methyl α-bromophenylacetate (203 µL, 1.30 mmol) and K₂CO₃ (89.5 mg, 0.65 mmol). The mixture was heated at 110 °C for 8 h. The solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were washed with brine, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (CH₂Cl₂) provided ester 470 as a colorless oil (38.5 mg, 59%); ¹H NMR (300 MHz, CDCl₃) δ 2.05 (pentet,
$J = 6.4 \text{ Hz}, 2 \text{ H}$), 2.68 (t, $J = 6.4 \text{ Hz}, 2 \text{ H}$), 2.88 (t, $J = 6.4 \text{ Hz}, 2 \text{ H}$), 3.74 (s, 3 H), 5.17 (d, $J = 6.1 \text{ Hz}, 1 \text{ H}$), 6.27 (d, $J = 8.6 \text{ Hz}, 1 \text{ H}$), 6.45 (d, $J = 7.5 \text{ Hz}, 1 \text{ H}$), 7.14 (br t, $J = 7.8 \text{ Hz}, 1 \text{ H}$), 7.30 – 7.41 (m, 3 H), 7.50 (m, 2 H), 10.31 (d, $J = 6.1 \text{ Hz}, 1 \text{ H}$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 22.9, 31.2, 40.4, 52.8, 60.5, 109.8, 115.7, 127.2, 127.7, 128.4, 128.9, 134.8, 137.1, 146.7, 149.5, 171.4, 201.5; IR (neat) 3260, 2951, 1745, 1635 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{19}$H$_{20}$NO$_3$ 310.1438, found 310.1418.

2-Phenyl-1,3,4,5-tetrahydrobenzo[cd]indole (471). To a solution of ester 470 (28.1 mg, 0.091 mmol) in MeOH (2 mL) was added 4 M aqueous NaOH (1 mL). The mixture was stirred at rt for 2 h. The resulting solution was acidified with 2 M HCl and extracted with ethyl acetate. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude carboxylic acid, which was used immediately without further purification. To the crude carboxylic acid was added a solution of acetic anhydride (1 mL) and Et$_3$N (127 µL, 0.91 mmol). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (CH$_2$Cl$_2$-hexane, 1 : 1) afforded the indole 471 as a colorless oil (16.5 mg, 78%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.11 (pentet, $J = 6.1 \text{ Hz}, 2 \text{ H}$), 2.97 (t, $J = 6.1 \text{ Hz}, 2 \text{ H}$), 3.07 (t, $J = 6.1 \text{ Hz}, 2 \text{ H}$), 6.85 (dd, $J = 1.0, 6.8 \text{ Hz}, 1 \text{ H}$), 7.12 (dd, $J = 6.8, 8.1 \text{ Hz}, 1 \text{ H}$), 7.18 (d, $J = 8.1 \text{ Hz}, 1 \text{ H}$), 7.28 (m, 1 H), 7.46 (t, $J = 7.5 \text{ Hz}, 2 \text{ H}$), 7.59 (m, 2 H), 8.03 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 23.2, 24.6, 27.5, 107.8, 111.6, 116.3, 249
123.0, 126.1, 126.7, 128.8, 128.9, 130.3, 132.6, 133.3, 134.2; IR (neat) 3417, 2925, 1602 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{17}\)H\(_{16}\)N 234.1283, found 234.1289.

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\text{SnBu}_3\text{H}^+ + \text{PhBr} \rightarrow \text{Ph}^+\text{N}^+\text{BOC}
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1-(1-Acetyl-2-phenylvinyl)buta-1,3-dienylcarbamic acid tert-butyl ester (473). To a solution of bromide 472 (177 mg, 0.79 mmol) and stannane 393 (300 mg, 0.65 mmol) in THF (6.5 mL) was added CuI (31.2 mg, 0.16 mmol) and Pd(PPh\(_3\))\(_4\) (37.8 mg, 0.033 mmol). The mixture was stirred at 65 °C for 4 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ether-CH\(_2\)Cl\(_2\), 3 : 97) provided triene 473 as a colorless oil (185 mg, 90%); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.41 (s, 9 H), 2.36 (s, 3 H), 4.88 (dd, \(J = 1.9, 10.3\) Hz, 1 H), 5.13 (dd, \(J = 1.9, 16.3\) Hz, 1 H), 6.10 (ddd, \(J = 10.3, 11.2, 16.3\) Hz, 1 H), 6.14 (s, 1 H), 6.64 (d, \(J = 11.2\) Hz, 1 H), 7.28 - 7.37 (m, 3 H), 7.55 - 7.66 (m, 3 H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 26.9, 28.0, 80.8, 116.3, 116.4, 128.6, 130.2, 130.6, 131.9, 132.2, 133.6, 133.9, 140.7, 152.6, 197.9; IR (neat) 3325, 2978, 1718 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{19}\)H\(_{24}\)NO\(_3\) 314.1751, found 314.1773.
2-Acetylbiphenyl-3-ylcarbamic acid tert-butyl ester (474). A solution of triene 473 (173 mg, 0.55 mmol) in toluene (5.5 mL) was heated at 150 °C in a sealed tube for 2 h. The resulting solution was cooled to rt, transferred to a flask, and DDQ (150 mg, 0.66 mmol) was then added. The mixture was stirred at 70 °C for 16 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided the protected aniline 474 as a white solid: mp 113 - 115 °C (152 mg, 89%); ¹H NMR (300 MHz, CDCl₃) δ 1.51 (s, 9 H), 1.83 (s, 3 H), 7.07 (dd, J = 1.1, 7.6 Hz, 1 H), 7.30 - 7.36 (m, 2 H), 7.39 - 7.47 (m, 4 H), 8.16 (dd, J = 1.1, 8.4 Hz, 1 H), 8.41 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 28.2, 32.3, 80.6, 119.6, 124.4, 128.1, 128.8, 128.9, 131.0, 132.2, 136.2, 141.0, 141.5, 153.0, 206.9; IR (neat) 3378, 2978, 1732, 1668 cm⁻¹; HRMS (MH⁺) calcd for C₁₉H₂₂NO₃ 312.1594, found 312.1614

1-(3-Aminobiphenyl-2-yl)ethanone. To a solution of carbamate 474 (110 mg, 0.35 mmol) in CH₂Cl₂ (7 mL) at −50 °C was added TFA (272 µL, 3.53 mmol). The solution was warmed to rt over 30 min and stirred for 2 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-
gel chromatography (ethyl acetate-hexane, 1 : 4) provided a colorless oil (72.0 mg, 96%); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta 1.79\) (s, 3 H), 5.03 (s, 2 H), 6.69 (dd, \(J = 1.1, 8.1\) Hz, 1 H), 6.71 (dd, \(J = 1.1, 7.5\) Hz, 1 H), 7.22 (dd, \(J = 7.5, 8.1\) Hz, 1 H), 7.33 - 7.45 (m, 5 H); \(^13\)C NMR (50 MHz, CDCl\(_3\)) \(\delta 32.0, 115.8, 119.6, 123.7, 127.8, 128.6, 128.9, 131.3, 142.0, 143.0, 146.2, 206.1\); IR (neat) 3476, 3370, 2923, 1660, 1602 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{14}\)H\(_{14}\)NO 212.1070, found 212.1054.

![Chemical structure](image)

1-(3-Methyl-4-phenylindol-1-yl)ethanone (475). To a solution of the aniline (43.8 mg, 0.21 mmol) in MeOH (4 mL) at 0 \(^\circ\)C was added NaOAc (34.0 mg, 0.41 mmol), glacial acetic acid (47 \(\mu\)L, 0.83 mmol), glyoxylic acid monohydrate (47.7 mg, 0.52 mmol), and NaCNBH\(_3\) (14.3 mg, 0.23 mmol). The solution was warmed slowly to rt over 1 h. The mixture was then filtered through a plug of silica gel and washed with 1% glacial acetic acid in ethyl acetate. The solution was then washed with brine, dried (Na\(_2\)SO\(_4\)), and concentrated to afford the crude carboxylic acid, which was used without further purification. To the crude carboxylic acid was added a solution of acetic anhydride (2.1 mL) and Et\(_3\)N (289 \(\mu\)L, 2.07 mmol). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded the \(N\)-acetylindole 475 as a white solid: mp 114 – 116 \(^\circ\)C (46.6 mg, 90%); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 1.76\) (d, \(J = 1.6\) Hz, 3 H), 2.61 (s, 3 H), 7.15 (d, \(J = 7.4\) Hz, 1 H), 7.17 (s, 1 H), 7.37 - 7.45 (m, 6 H), 8.52 (d, \(J = 8.3\) Hz, 1 H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 12.9, 24.1, 115.6, 118.8, 123.4, 124.7, 125.2, 127.1, 127.5, 128.3, 129.7, 136.0, 136.4, 140.6, 168.2; IR
(neat) 2924, 1705, 1604 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{17}\)H\(_{18}\)NO 250.1226, found 250.1251.

\[
\text{SnBu}_3 \quad + \quad \text{HOC}
\]

1-(1-Acetyl-2-methylpropenyl)buta-1,3-dienylcarbamic acid tert-butyl ester (477). To a solution of iodide 476 (176 mg, 0.79 mmol) and stannane 393 (300 mg, 0.65 mmol) in THF (8 mL) was added CuI (31.2 mg, 0.16 mmol) and Pd(PPh\(_3\))\(_4\) (37.8 mg, 0.033 mmol). The mixture was stirred at 50 °C for 3 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ether-CH\(_2\)Cl\(_2\), 1 : 99) provided triene 477 as a colorless oil (154 mg, 88%); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.45 (s, 9 H), 1.81 (s, 3 H), 2.06 (s, 3 H), 2.20 (s, 3 H), 4.96 (dd, \(J = 1.6, 10.3\) Hz, 1 H), 5.19 (dd, \(J = 1.6, 16.8\) Hz, 1 H), 5.82 (s, 1 H), 6.15 (ddd, \(J = 10.3, 11.1, 16.8\) Hz, 1 H), 6.77 (d, \(J = 11.1\) Hz, 1 H); \(^13\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\) 22.2, 23.8, 28.2, 29.6, 80.7, 115.7, 116.1, 132.4, 133.0, 133.6, 150.2, 152.0, 200.6; IR (neat) 3320, 2978, 1718, 1684, 1653 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{15}\)H\(_{24}\)NO\(_3\) 266.1751, found 266.1734.
2-Acetyl-3,5-dimethylphenylcarbamic acid tert-butyl ester (480). A solution of triene 477 (145 mg, 0.55 mmol) in toluene (5.5 mL) was heated at 150 °C in a sealed tube for 6 h. The resulting solution was cooled to rt, transferred to a flask, and DDQ (161 mg, 0.71 mmol) was then added. The mixture was stirred at 60 °C for 2 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:4) provided the protected aniline 480 as a colorless oil (95 mg, 66%); ¹H NMR (300 MHz, CDCl₃) δ 1.49 (s, 9 H), 2.32 (s, 3 H), 2.36 (s, 3 H), 2.50 (s, 3 H), 6.72 (s, 1 H), 7.70 (s, 1 H), 7.93 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 21.3, 21.5, 28.3, 32.5, 80.4, 119.4, 126.7, 128.3, 135.1, 135.7, 141.3, 153.1, 206.4; IR (neat) 3322, 2977, 1729, 1613 cm⁻¹; HRMS (MH⁺) calcd for C₁₅H₂₂NO₃ 264.1594, found 264.1586.

1-(2-Amino-4,6-dimethylphenyl)ethanone. To a solution of carbamate 480 (96.1 mg, 0.36 mmol) in CH₂Cl₂ (7 mL) at −50 °C was added TFA (141 µL, 1.82 mmol). The solution was warmed to rt over 30 min and stirred for 3 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:4) provided a colorless oil (56.8 mg, 95%); ¹H NMR (200 MHz, CDCl₃) δ 2.21 (s, 3 H), 2.38 (s, 3
H), 2.51 (s, 3 H), 4.87 (br s, 2 H), 6.35 (s, 1 H), 6.38 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 21.2, 22.3, 32.7, 115.1, 121.8, 122.6, 136.9, 141.8, 146.6, 205.2; IR (neat) 3460, 3365, 2920, 1613 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{10}$H$_{14}$NO 164.1070, found 164.1063.

To a solution of the aniline (28.5 mg, 0.17 mmol) in MeOH (2 mL) at 0 °C was added NaOAc (28.6 mg, 0.35 mmol), glacial acetic acid (40.0 $\mu$L, 0.70 mmol), glyoxylic acid monohydrate (40.2 mg, 0.44 mmol), and NaCNBH$_3$ (12.1 mg, 0.19 mmol). The solution was warmed slowly to rt over 1 h. The mixture was then filtered through a plug of silica gel and washed with 1% glacial acetic acid in ethyl acetate. The solution was then washed with brine, dried (Na$_2$SO$_4$), and concentrated to afford the crude carboxylic acid, which was used without further purification. To the crude carboxylic acid was added a solution of acetic anhydride (1.7 mL) and Et$_3$N (243 $\mu$L, 1.75 mmol). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded the $N$-acetylindole 481 as a colorless oil (30.4 mg, 87%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.42 (s, 3 H), 2.43 (s, 3 H), 2.56 (s, 3 H), 2.62 (s, 3 H), 6.85 (s, 1 H), 7.05 (s, 1 H), 8.15 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 13.4, 19.7, 21.7, 24.1, 114.7, 119.2, 122.0, 126.7, 127.1, 130.6, 135.2, 136.9, 168.2; IR (neat) 2919, 1693, 1608 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{13}$H$_{16}$NO 202.1226, found 202.1217.

1-(3,4,6-Trimethylindol-1-yl)ethanone (481). 1H NMR (300 MHz, CDCl$_3$) $\delta$ 2.42 (s, 3 H), 2.43 (s, 3 H), 2.56 (s, 3 H), 2.62 (s, 3 H), 6.85 (s, 1 H), 7.05 (s, 1 H), 8.15 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 13.4, 19.7, 21.7, 24.1, 114.7, 119.2, 122.0, 126.7, 127.1, 130.6, 135.2, 136.9, 168.2; IR (neat) 2919, 1693, 1608 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{13}$H$_{16}$NO 202.1226, found 202.1217.
1-(2-Methyl-6-oxocyclohex-1-enyl)buta-1,3-dienylcarbamic acid tert-butyl ester (483). To a solution of iodide 482 (185 mg, 0.79 mmol) and stannane 393 (300 mg, 0.65 mmol) in THF (8 mL) was added Cul (31.2 mg, 0.16 mmol) and Pd(PPh$_3$)$_4$ (37.8 mg, 0.033 mmol). The mixture was stirred at 50 °C for 3 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1:4) provided triene 483 as a white solid: mp 136 – 138 °C (184 mg, 84%); $^1$H NMR (300 MHz, CDCl$_3$) δ 1.42 (s, 9 H), 1.93 (s, 3 H), 2.01 (m, 2 H), 2.40 – 2.47 (m, 4 H), 4.89 (dd, $J$ = 1.9, 10.2 Hz, 1 H), 5.12 (dd, $J$ = 1.9, 16.9 Hz, 1 H), 5.89 (s, 1 H), 5.95 (ddd, $J$ = 10.2, 11.0, 16.9 Hz, 1 H), 6.58 (d, $J$ = 11.0 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 21.9, 22.5, 28.2, 32.2, 37.6, 80.1, 115.2, 116.3, 131.4, 132.1, 132.8, 152.3, 161.3, 197.1; IR (neat) 3306, 2928, 1723, 1660, 1623 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{16}$H$_{24}$NO$_3$ 278.1751, found 278.1754.

4-Methyl-8-oxo-5,6,7,8-tetrahydronaphthalen-1-ylcarbamic acid tert-butyl ester (464). A solution of triene 483 (94.2 mg, 0.34 mmol) in toluene (6.8 mL) was heated at 150 °C in a sealed tube for 6 h. The resulting solution was cooled to rt, transferred to a flask, and DDQ (116 mg, 0.51 mmol) was then added. The mixture was stirred at 110 °C for 3 h. The solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined
extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided the protected aniline 464 as a colorless oil (82.9 mg, 89%).

\[
\text{SnBu}_3^+\text{NBOC} + \text{PhO}_2\text{C} \rightarrow \text{PhO}_2\text{C}
\]

5-(1-tert-Butoxycarbonylamino)penta-1,3-dienyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (488). To a solution of iodide 487₁³¹ (170 mg, 0.50 mmol) and stannane 400 (234 mg, 0.50 mmol) in THF (5 mL) was added Cul (23.6 mg, 0.12 mmol) and Pd(PPh₃)_₄ (28.7 mg, 0.025 mmol). The mixture was stirred at 50 °C for 3 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) provided triene 488 (mixture of amide rotamers) as a colorless oil (154 mg, 78%); ^1H NMR (300 MHz, CDCl₃) $\delta$ 1.42 (s, 9 H), 1.73 (d, $J = 6.6$ Hz, 3 H), 2.75 (t, $J = 7.2$ Hz, 2 H), 4.22 (m, 2 H), 5.69 (dq, $J = 6.6$, 14.9 Hz, 1 H), 6.02 (br dd, $J = 10.9$, 14.9 Hz, 1 H), 6.25 (s, 1 H), 6.38 (d, $J = 10.9$ Hz, 1 H), 7.17 (d, $J = 9.1$ Hz, 2 H), 7.29 (t, $J = 9.1$ Hz, 1 H), 7.41 (t, $J = 9.1$ Hz, 2 H), 8.03 (s, 1 H); ^1³C NMR (75 MHz, CDCl₃) $\delta$ 13.5, 18.5, 28.1, 35.6, 80.0, 118.7, 121.2, 121.6, 126.4, 126.6, 127.8, 128.9, 129.6, 143.3, 150.3, 151.1, 152.8, 191.5; IR (neat) 3331, 2974. 1737, 1720, 1678, 1609 cm⁻¹; HRMS (MH⁺) C₂₂H₂₇N₂O₅ 399.1915, found 399.1944.
5-**tert**-Butoxycarbonylamino-8-methyl-4-oxo-3,4-dihydro-2*H*-quinoline-1-carboxylic acid phenyl ester (489). A solution of triene 488 (109 mg, 0.27 mmol) in toluene (6 mL) was heated at reflux for 2 h. The resulting solution was cooled to rt and DDQ (74 mg, 0.33 mmol) was added. The mixture was stirred at 50 °C for 4 h. The solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO$_3$, dried (Na$_2$SO$_4$), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 20) provided the protected aniline 489 (mixture of amide rotamers) as a colorless oil (93.1 mg, 87%); $^1$H NMR (300 MHz, CDCl$_3$, amide rotamers) $\delta$ 1.53 (s, 9 H), 2.32 (s, 3 H), 2.73 and 3.10 (m, 2 H), 3.63 and 4.71 (m, 2 H), 7.19 (m, 2 H), 7.23 (d, $J = 8.7$ Hz, 1 H), 7.38 (m, 3 H), 8.30 (d, $J = 8.7$ Hz, 1 H), 11.00 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 17.9, 28.3, 40.4, 45.3, 80.7, 114.2, 117.3, 121.3, 125.8, 126.9, 129.4, 138.0, 140.6, 141.8, 150.9, 153.0, 154.4, 198.9; IR (neat) 3260, 2977, 1725, 1654 cm$^{-1}$; HRMS (MNH$_4^+$) calcd for C$_{22}$H$_{28}$N$_3$O$_5$ 414.2024, found 414.1995.

5-Amino-8-methyl-4-oxo-3,4-dihydro-2*H*-quinoline-1-carboxylic acid phenyl ester. To a solution of carbamate 489 (75.5 mg, 0.19 mmol) in CH$_2$Cl$_2$ (4 mL) at −50 °C was added TFA (73.4 µL, 0.95 mmol). The solution was warmed to rt over 30 min and stirred for 3 h. The mixture was quenched with saturated
aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided the aniline (mixture of amide rotamers) as a colorless oil (54.0 mg, 96%); $^1$H NMR (200 MHz, CDCl$_3$, amide rotamers) $\delta$ 2.23 (s, 3 H), 2.66 and 3.04 (m, 2 H), 3.57 and 4.70 (m, 2 H), 6.38 (s, 2 H), 6.51 (d, $J$ = 8.6 Hz, 1 H), 7.03 – 7.25 (m, 3 H), 7.14 (d, $J$ = 8.6 Hz, 1 H), 7.37 (br t, $J$ = 7.4 Hz, 2 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 17.6, 39.8, 45.4, 111.0, 115.3, 120.8, 121.4, 125.6, 129.3, 137.7, 141.1, 149.3, 151.1, 197.5; IR (neat) 3448, 3330, 2931, 1645 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{17}$H$_{17}$N$_2$O$_3$ 297.1234, found 297.1239.

1-Acetyl-6-methyl-3,4-dihydro-1H-pyrrolo[4,3,2-de]quinoline-5-carboxylic acid phenyl ester (490). To a solution of the aniline (29.2 mg, 0.099 mmol) in MeOH (2 mL) at 0 $^\circ$C was added NaOAc (16 mg, 0.20 mmol), glacial acetic acid (23 $\mu$L, 0.39 mmol), glyoxylic acid monohydrate (23 mg, 0.29 mmol), and NaCNBH$_3$ (6.8 mg, 0.11 mmol). The solution was warmed slowly to rt over 1 h. The mixture was then filtered through a plug of silica gel and washed with 1% glacial acetic acid in ethyl acetate. The solution was then washed with brine, dried (Na$_2$SO$_4$), and concentrated to afford the crude carboxylic acid, which was used without further purification. To the crude carboxylic acid was added a solution of acetic anhydride (1 mL) and Et$_3$N (137 $\mu$L, 0.99 mmol). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) afforded the N-acetylindole 490 (mixture of amide rotamers) as a colorless oil.
(25.4 mg, 77%); 'H NMR (400 MHz, CDCl₃) δ 2.41 (s, 3 H), 2.62 (s, 3 H), 3.01 (br m, 2 H), 3.48 – 4.95 (br m, 2 H), 7.08 – 7.25 (m, 5 H), 7.37 (t, J = 7.9 Hz, 2 H), 7.97 (br s, 1 H). The N-acetyl group was then removed to obtain cleaner spectra without broadening due to amide rotamers. Treatment of the N-acetylindole 490 with K₂CO₃ (21 mg, 0.15) in MeOH (3 mL) at rt for 1 h, upon workup, afforded the corresponding deprotected indole (mixture of amide rotamers) in quantitative yield as a colorless oil (22.2 mg, quantitative); 'H NMR (300 MHz, CDCl₃, amide rotamers) δ 2.41 (s, 3 H), 3.06 (br m, 2 H), 3.70 – 5.17 (br m, 2 H), 6.89 (d, J = 1.6 Hz, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 7.13 – 7.24 (m, 3 H), 7.36 (t, J = 7.8 Hz, 2 H), 7.91 (br s, 1 H); 13C NMR (75 MHz, CDCl₃) δ 18.2, 23.2, 47.5, 108.2, 110.3, 118.2, 121.6, 121.7, 122.4, 125.3, 126.3, 129.0, 129.3, 130.6, 132.8, 151.4; IR (neat) 3355, 2923, 1708, 1602 cm⁻¹; HRMS (MH⁺) calcd for C₁₈H₁₇N₂O₂ 293.1285, found 293.1292.

4-Formyl-2,3-dihydropyrrole-1-carboxylic acid tert-butyl ester (401). To a solution of DMF (9.07 mL, 117 mmol) in CH₂Cl₂ (27 mL) at 0 °C was added oxalyl chloride (949 µL, 10.9 mmol) dropwise. The solution was stirred at 0 °C for 10 min. To the resultant white suspension was added 2,3-dihydropyrrole-1-carboxylic acid tert-butyl ester (1.54 g, 9.07 mmol) in CH₂Cl₂ (9 mL). The solution was warmed to rt and stirred for 1 h. The mixture was quenched with saturated aqueous Na₂CO₃ (40 mL) and stirred vigorously for 1 h. The resultant solution was extracted with CH₂Cl₂, dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 10) provided aldehyde 401 (mixture of amide rotamers) as a white solid: mp 62 – 63 °C (1.71 g, 95%); 'H NMR (400 MHz, CDCl₃) δ 1.49 (s, 9 H), 2.81 (t, J = 9.3 Hz, 2 H), 3.88 (t, J = 9.3
Hz, 2 H), 7.47 (m, 1 H), 9.54 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 24.7, 28.0, 47.1, 82.5, 124.7, 147.5, 151.8, 185.6; IR (neat) 2977, 1718, 1659, 1609 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{10}$H$_{16}$NO$_3$ 198.1125, found 198.1125.

4-Vinyl-2,3-dihydropyrrole-1-carboxylic acid tert-butyl ester (402). To a solution of aldehyde 401 (1.88 g, 9.53 mmol) in ether (38 mL) at 0 °C was added (trimethylsilyl)methylmagnesium chloride (1.0 M in THF, 14.3 ml, 14.3 mmol) dropwise. The solution was stirred at 0 °C for 1.5 h. The resultant solution was cooled to −78 °C and acetic acid (2.76 mL, 47.7 mmol) was added dropwise. The solution was warmed to −40 °C over 30 min. The mixture was quenched with saturated NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 40) gave diene 402 (mixture of amide rotamers) as a colorless oil (1.47 g, 79%); $^1$H NMR (300 MHz, d$_6$-acetone) δ 1.45 (s, 9 H), 2.69 (m, 2 H), 3.73 (m, 2 H), 4.89 (m, 2 H), 6.62 (m, 2 H); $^{13}$C NMR (75 MHz, d$_6$-acetone, amide rotamers) δ 27.7, 28.4, 46.1 (major), 46.5 (minor), 80.4, 111.2 (minor), 111.4 (major), 122.6, 129.6, 131.7, 151.6 (major), 152.2 (minor); IR (neat) 2976, 1704, 1634 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{11}$H$_{18}$NO$_2$ 196.1332, found 196.1337.
5-(Trimethylstannyl)-4-vinyl-2,3-dihydropyrrole-1-carboxylic acid tert-butyl ester (403). To a solution of diene 402 (1.19 g, 6.09 mmol) in THF (27 mL) at -30 °C was added n-BuLi (2.5 M in hexane, 2.68 ml, 6.70 mmol) dropwise over 5 min. The solution was stirred at -30 °C for 20 min. To the resulting solution was added trimethyltin chloride (1.0 M in THF, 6.70 mL, 6.70 mmol) dropwise over 5 min. The solution was warmed to rt over 30 min. The mixture was quenched with saturated NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated to afford stannane 403 (mixture of amide rotamers) as a yellow oil (1.84 g, 84%); ¹H NMR (400 MHz, CDCl₃) δ 0.25 (s, 9 H), 1.46 (s, 9 H), 2.76 (t, J = 9.3 Hz, 2 H), 3.71 (t, J = 9.3 Hz, 2 H), 4.86 (d, J = 17.1 Hz, 1 H), 4.93 (d, J = 10.6 Hz, 1 H), 6.74 (dd, J = 10.6, 17.1 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ -4.7, 28.3, 30.1, 46.1, 80.0, 110.8, 132.8, 133.0, 145.4, 153.4; IR (neat) 2977, 1683, 1614 cm⁻¹; HRMS (MH⁺) calcd for C₁₄H₂₆NO₂Sn 360.0980, found 360.0974.

5-(3,3-Dimethyl-6-oxocyclohex-1-enyl)-4-vinyl-2,3-dihydropyrrole-1-carboxylic acid tert-butyl ester (492). To a solution of 2-iodo-4,4-dimethylcyclohexeneone 491 (183 mg, 0.73 mmol) and stannane 403 (219 mg, 0.61 mmol) in THF (6 mL) was added CuI (29.1 mg, 0.15 mmol) and Pd(PPh₃)₄ (35.3 mg, 0.031 mmol). The mixture was stirred at 50 °C for 3 h. The solution was filtered through a plug of silica-gel, washed with ether, and concentrated.
Purification by silica-gel chromatography (ether-CH\(_2\)Cl\(_2\), 3 : 97) provided triene 492 (mixture of amide rotamers) as a colorless oil (158 mg, 82%); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.23 (s, 6 H), 1.40 (s, 9 H), 1.93 (t, \(J = 6.8\) Hz, 2 H), 2.57 (m, 2 H), 2.67 (t, \(J = 9.3\) Hz, 2 H), 3.84 (t, \(J = 9.3\) Hz, 2 H), 4.87 (dd, \(J = 1.4, 7.8\) Hz, 1 H), 4.95 (s, 1 H), 6.35 (m, 1 H), 6.39 (s, 1 H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\) 27.4, 27.8, 28.3, 33.1, 34.4, 35.7, 46.6, 80.0, 111.3, 121.6, 130.1, 130.4, 136.7, 151.4, 156.1, 196.8; IR (neat) 2961, 1690 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{19}\)H\(_{28}\)NO\(_3\) 318.2064, found 318.2085.

\[
\begin{align*}
\text{N-BOC} & \quad \rightarrow \\
\text{N-BOC}
\end{align*}
\]

6,6-Dimethyl-9-oxo-2,3,6,7,8,9-hexahydrobenzo[g]indole-1-carboxylic acid tert-butyl ester (493). A solution of triene 492 (113 mg, 0.35 mmol) in toluene (7 mL) was heated at reflux for 12 h. The resulting solution was cooled to rt and DDQ (81 mg, 0.35 mmol) was added. The mixture was stirred at rt for 6 h. The solution was quenched with saturated aqueous NaHCO\(_3\) and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO\(_3\), dried (Na\(_2\)SO\(_4\)), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided the protected aniline 493 as a colorless oil (96 mg, 86%); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.32 (s, 6 H), 1.48 (s, 9 H), 1.98 (t, \(J = 6.6\) Hz, 2 H), 2.72 (t, \(J = 6.6\) Hz, 2 H), 2.97 (t, \(J = 8.1\) Hz, 2 H), 4.14 (t, \(J = 8.1\) Hz, 2 H), 7.02 (d, \(J = 7.8\) Hz, 1 H), 7.25 (d, \(J = 7.8\) Hz, 1 H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\) 27.9, 28.3, 29.7, 34.3, 35.7, 36.7, 50.3, 80.8, 120.4, 122.9, 128.1, 132.6, 141.5, 150.9, 153.0, 197.8; IR (neat) 2961, 1686 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{19}\)H\(_{26}\)NO\(_3\) 316.1907, found 316.1919.
6,6-Dimethyl-1,2,3,6,7,8-hexahydrobenzo[g]indol-9-one. To a solution of carbamate 493 (90.0 mg, 0.29 mmol) in CH$_2$Cl$_2$ (6 mL) at −50 °C was added TFA (110 µL, 1.43 mmol). The solution was warmed to rt over 30 min and stirred for 3 h. The mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided a colorless oil (58.1 mg, 94%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.32 (s, 6 H), 1.91 (t, $J = 6.7$ Hz, 2 H), 2.65 (t, $J = 6.7$ Hz, 2 H), 2.99 (t, $J = 8.5$ Hz, 2 H), 3.75 (t, $J = 8.5$ Hz, 2 H), 6.50 (d, $J = 7.4$ Hz, 1 H), 7.11 (d, $J = 7.4$ Hz, 1 H), 7.30 (br s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 27.5, 29.8, 33.7, 35.2, 37.2, 46.9, 111.7, 111.9, 128.8, 128.9, 150.5, 154.6, 199.7; IR (neat) 3390, 2918, 1641 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{14}$H$_{18}$NO 216.1383, found 216.1365.

6,6-Dimethyl-1,4,5,6-tetrahydro-2H-2a-azacyclopenta-[bc]naphthylene (495). To a solution of the aniline (42 mg, 0.20 mmol) in DMF (2 mL) at rt was added methyl iodoacetate (117 mg, 0.59 mmol) and K$_2$CO$_3$ (81 mg, 0.59 mmol). The mixture was heated at 100 °C for 16 h. The solution was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated. The residue was filtered through a plug of silica-gel, washed with ether-CH$_2$Cl$_2$ (3 : 97), and concentrated.
to afford the crude methyl ester 494, which was used without further purification; 

\[ ^1 \text{H NMR (200 MHz, CDCl}_3\text{)} \delta ] \ 1.29 \ (s, \ 6 \text{ H}), 1.90 \ (t, \ J = 6.9 \text{ Hz, 2 H}), 2.61 \ (t, \ J = 6.9 \text{ Hz, 2 H}), 3.04 \ (t, \ J = 8.8 \text{ Hz, 2 H}), 3.73 \ (t, \ J = 8.8 \text{ Hz, 2 H}), 3.76 \ (s, \ 3 \text{ H}), 3.99 \ (s, \ 2 \text{ H}), 6.69 \ (d, \ J = 7.6 \text{ Hz, 1 H}), 7.13 \ (d, \ J = 7.6 \text{ Hz, 1 H}). \] 

The crude methyl ester was dissolved in MeOH (2 mL) and 4 M aqueous NaOH (1 mL) was added. The solution was stirred at rt for 2 h. The resulting mixture was acidified with 2 M aqueous HCl and extracted with ethyl acetate. The combined extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated to afford the crude carboxylic acid, which was used immediately without further purification.

To the crude carboxylic acid was added a solution of acetic anhydride (2 mL) and Et\textsubscript{3}N (272 \text{ µL, 1.95 mmol}). The mixture was heated to reflux for 30 min. The resulting solution was concentrated in vacuo. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 19) afforded the indole 495 as a white solid: mp 130 – 132 °C (28 mg, 67% 3 steps); 

\[ ^1 \text{H NMR (300 MHz, CDCl}_3\text{)} \delta ] \ 1.36 \ (s, \ 6 \text{ H}), 1.85 \ (t, \ J = 6.0 \text{ Hz, 2 H}), 2.90 \ (t, \ J = 6.0 \text{ Hz, 2 H}), 3.73 \ (t, \ J = 6.7 \text{ Hz, 2 H}), 4.39 \ (t, \ J = 6.7 \text{ Hz, 2 H}), 6.73 \ (d, \ J = 6.8 \text{ Hz, 1 H}), 6.76 \ (s, \ 1 \text{ H}), 6.85 \ (d, \ J = 6.8 \text{ Hz, 1 H}); \] 

\[ ^13 \text{C NMR (75 MHz, CDCl}_3\text{)} \delta ] \ 20.6, 28.4, 34.6, 35.3, 41.9, 52.3, 113.1, 116.5, 119.3, 119.9, 121.1, 121.8, 139.7, 149.7; \] 

IR (neat) 2916, 1614 \text{ cm}^{-1}; \] 

HRMS (MH\textsuperscript{+}) calcd for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2} 212.1434, found 212.1430.
3-(6H-[1,3]Dioxin-4-ylmethyl)-2-oxocyclohexanecarboxylic acid methyl ester (498). To a solution of diisopropylamine (13.7 mL, 97.6 mmol) in THF (233 mL) at –60 °C was added n-BuLi (2.5 M in hexane, 38.2 mL, 95.5 mmol) dropwise over 15 min. The solution was warmed to –30 °C and stirred for 20 min. To the resulting mixture at –30 °C was added methyl cyclohexanone-2-carboxylate (497) (7.30 g, 46.7 mmol) dropwise over 15 min. The solution was warmed to –10 °C and stirred for 20 min. To the resulting dianion was added bromide 207 (7.60 g, 42.5 mmol) in THF (10 mL). The solution was warmed to rt and stirred 3 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane-NH₄OH, 14 : 85 : 1) provided β-ketoester 498 as a mixture with its enol (8.49 g, 79%); ¹H NMR (360 MHz, CDCl₃) δ 1.44 – 1.88 (m, 4 H), 1.95 (dd, J = 10.2, 14.1 Hz, 1 H), 2.16 (m, 2 H), 2.55 (m, 1 H), 2.68 (m, 1 H), 3.37 (m, 1 H), 3.70 (s, 3 H), 4.18 (m, 2 H), 4.67 (m, 1 H), 4.98 (d, J = 4.2 Hz, 1 H), 5.02 (d, J = 4.2 Hz, 1 H), 12.29 (s, enol, 1 H); ¹³C NMR (90 MHz, CDCl₃) δ 19.6, 21.8, 22.7, 23.9, 26.6, 30.1, 30.7, 31.9, 32.8, 33.2, 33.5, 33.6, 35.9, 36.0, 46.4, 47.7, 51.3, 51.8, 52.2, 55.9, 57.6, 63.7, 63.8, 90.4, 97.7, 98.6, 98.7, 151.6, 151.8, 152.2, 170.2, 173.1, 173.6, 206.3, 206.8; IR (neat) 2954, 1747, 1714, 1682, 1654, 1614 cm⁻¹; HRMS (MH⁺) calcd for C₁₃H₁₉O₅ 255.1227, found 255.1242.
4,10-Dioxobicyclo[4.3.1]decane-1-carboxylic acid methyl ester (499).

A solution of β-ketoester 498 (3.00 g, 11.8 mmol) in toluene (90 mL) was heated in a sealed tube at 175 °C for 25 min. The resulting solution was concentrated to afford the crude enone (as a mixture with its enol), which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) δ 1.30 – 1.70 (m, 5 H), 2.20 (m, 2 H), 2.61 (dd, $J = 8.7$, 16.5 Hz, 1 H), 2.95 – 3.25 (m, 2 H), 3.72 (s, 3 H), 5.84 (d, $J = 9.8$ Hz, 1 H), 6.22 (d, $J = 17.8$ Hz, 1 H), 6.40 (dd, $J = 9.8$, 17.8 Hz, 1 H), 12.34 (s, enol, 1 H). The crude enone was then dissolved in EtOH (470 mL) and K$_2$CO$_3$ (407 mg, 2.95 mmol) was added. The mixture was stirred at rt for 3 h. The resulting solution was filtered through a plug of silica-gel and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) afforded 499 as a white solid: mp 107 – 109 °C (1.99 g, 75%); $^1$H NMR (300 MHz, CDCl$_3$) δ 1.69 (m, 1 H), 1.83 – 2.04 (m, 4 H), 2.20 (m, 1 H), 2.35 (t, $J = 4.2$ Hz, 1 H), 2.41 (m, 1 H), 2.46 – 2.58 (m, 3 H), 2.72 (m, 1 H), 2.87 (dd, $J = 7.0$, 12.9 Hz, 1 H), 3.68 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 16.1, 27.2, 32.2, 34.9, 40.4, 43.5, 44.7, 52.3, 61.0, 172.8, 209.5, 210.4; IR (neat) 2950, 1736, 1709 cm$^{-1}$; HRMS (MNH$_4^+$) calcd for C$_{12}$H$_{20}$NO$_4$ 242.1387, found 242.1379.
4,10-Dioxobicyclo[4.3.1]dec-2-ene-1-carboxylic acid methyl ester (500). To a solution of LiHMDS (1.0 M in THF, 5.99 mL, 5.99 mmol) in THF (30 mL) at –78 °C was added Et₃N (2.28 mL, 16.3 mmol) followed by a solution of ketone 499 (1.22 g, 5.44 mmol) and TMSCl (1.04 mL, 8.16 mmol) in THF (20 mL) dropwise over 20 min. The mixture was warmed to –40 °C over 1 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude silyl enol ether, which was used without further purification. The crude silyl enol ether was then dissolved in dry DMSO (27 mL) and Pd(OAc)₂ (183 mg, 0.82 mmol) was added. The mixture was stirred at rt for 16 h under an O₂ atmosphere. The solution was quenched with H₂O and extracted with ether. The combined extracts were washed with brine, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided enone 500 as a white solid: mp 104 – 107 °C (875 mg, 72%); ¹H NMR (300 MHz, CDCl₃) δ 1.48 – 1.75 (m, 2 H), 1.87 – 2.00 (m, 2 H), 2.05 (dt, J = 5.4, 13.4 Hz, 1 H), 2.50 (ddd, J = 4.0, 13.5, 17.5 Hz, 1 H), 2.63 (d, J = 4.7 Hz, 2 H), 2.94 (br q, J = 4.9 Hz, 1 H), 3.81 (s, 3 H), 6.23 (d, J = 12.7 Hz, 1 H), 6.55 (d, J = 12.7 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 16.5, 31.5, 34.2, 45.0, 46.0, 52.9, 65.8, 132.6, 137.9, 171.0, 200.8, 204.9; IR (neat) 2951, 1742, 1713, 1665 cm⁻¹; HRMS (MH⁺) calcd for C₁₂H₁₆O₄ 223.0965, found 223.0946.
5,5-Dimethyl-4,10-dioxobicyclo[4.3.1]dec-2-ene-1-carboxylic acid methyl ester (501). To a solution of enone 500 (929 mg, 4.18 mmol) in THF (40 mL) at −50 °C was added NaH (60% dispersion in mineral oil, 418 mg, 10.5 mmol) and MeI (1.56 mL, 25.1 mmol). The mixture was warmed to rt and stirred for 8 h. The solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ether-CH₂Cl₂, 1 : 99) afforded the α-dimethyl ketone 501 as a white solid: mp 80 – 82 °C (718 mg, 69%); ¹H NMR (360 MHz, CDCl₃) δ 1.08 (s, 3 H), 1.18 (s, 3 H), 1.42 – 1.60 (m, 2 H), 1.77 – 1.95 (m, 2 H), 2.15 (br d, J = 16.2 Hz, 1 H), 2.48 (ddd, J = 4.3, 12.9, 17.2 Hz, 1 H), 2.57 (d, J = 5.7 Hz, 1 H), 3.80 (s, 3 H), 6.17 (d, J = 13.1 Hz, 1 H), 6.38 (d, J = 13.1 Hz, 1 H); ¹³C NMR (90 MHz, CDCl₃) δ 16.6, 23.3, 26.9, 27.6, 35.7, 45.8, 52.8, 59.5, 65.4, 131.4, 134.2, 171.3, 204.8, 204.9; IR (neat) 2953, 1742, 1708, 1670 cm⁻¹; HRMS (MH⁺) calcd for C₁₄H₁₉O₄ 251.1278, found 251.1287.

3-Bromo-5,5-dimethyl-4,10-dioxobicyclo[4.3.1]dec-2-ene-1-carboxylic acid methyl ester (502). To a solution of enone 501 (498 mg, 1.99 mmol) in CCl₄ (10 mL) was added Br₂ (123 µL, 2.39 mmol). The mixture was stirred at rt for 12 h. The solution was quenched with 10% aqueous Na₂S₂O₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude vicinal dibromide, which was used without further purification; ¹H
NMR (200 MHz, CDCl₃) δ 1.20 (s, 3 H), 1.35 (s, 3 H), 1.50 – 1.60 (m, 2 H), 1.82 –
2.08 (m, 3 H), 2.41 – 2.53 (m, 2 H), 3.80 (s, 3 H), 5.04 (d, J = 9.8 Hz, 1 H), 5.15
(d, J = 9.8 Hz, 1 H). The vicinal dibromide was dissolved in CH₃CN (38 mL) and
Cs₂CO₃ (938 mg, 2.88 mmol) was added. The mixture was stirred at rt for 4 h.
The solution was filtered through a plug of silica-gel, washed with ether, and
concentrated. Purification by silica-gel chromatography (CH₂Cl₂) provided the α-
bromoenone 502 as a colorless oil (554 mg, 88%); ¹H NMR (360 MHz, CDCl₃) δ
1.15 (s, 3 H), 1.27 (s, 3 H), 1.48 (m, 1 H), 1.62 (m, 1 H), 1.88 (m, 1 H), 2.02 (dq, J
= 3.8, 15.1 Hz, 1 H), 2.18 (br d, J = 16.2 Hz, 1 H), 2.49 (ddd, J = 4.3, 13.2, 17.5
Hz, 1 H), 2.61 (d, J = 5.8 Hz, 1 H), 3.85 (s, 3 H), 7.11 (s, 1 H); ¹³C NMR (90 MHz,
CDCl₃) δ 16.9, 24.2, 26.0, 27.5, 35.8, 46.9, 53.1, 59.5, 66.2, 124.6, 134.4, 170.5,
199.5, 203.4; IR (neat) 2952, 1743, 1713, 1689 cm⁻¹; HRMS (MH⁺) calcd for
C₁₄H₁₈O₄Br 329.0383, found 329.0373.

3-(1-tert-Butoxycarbonylaminobuta-1,3-dienyl)-5,5-dimethyl-4,10-
dioxobicyclo[4.3.1]dec-2-ene-1-carboxylic acid methyl ester (504). To a
solution of bromide 502 (420 mg, 1.28 mmol) and stannane 393 (643 mg, 1.40
mmol) in THF (13 mL) was added Cul (60.8 mg, 0.32 mmol) and Pd(PPh₃)₄ (73.7
mg, 0.064 mmol). The mixture was heated to reflux for 5 h. Upon cooling to rt,
the solution was filtered through a plug of silica-gel, washed with ether, and
concentrated. Purification by silica-gel chromatography (ether-CH₂Cl₂, 3 : 97)
provided triene 504 as a yellow solid: mp 57 – 60 °C (439 mg, 82%); ¹H NMR
(300 MHz, CDCl₃) δ 1.16 (s, 3 H), 1.19 (s, 3 H), 1.43 (s, 9 H), 1.52 – 1.65 (m, 2
H), 1.86 (m, 1 H), 2.02 (br dq, J = 2.9, 13.6 Hz, 1 H), 2.18 (br d, J = 14.6 Hz, 1

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6-tert-Butoxycarbonylamino-9,9-dimethyl-8,14-dioxotricyclo-
[8.3.1.0^2,7]tetradeca-2(7),3,5-triene-1-carboxylic acid methyl ester (505). A solution of triene 504 (350 mg, 0.84 mmol) in toluene (17 mL) was heated to reflux for 3 h. The resulting solution was cooled to rt and DDQ (228 mg, 1.01 mmol) was added. The mixture was stirred at 70 °C for 12 h. The solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3:20) provided the protected aniline 505 as a white solid: mp 64 – 67 °C (270 mg, 78%); ¹H NMR (360 MHz, CDCl₃) δ 1.21 (s, 3 H), 1.28 (s, 3 H), 1.48 (s, 9 H), 1.51 – 1.58 (m, 2 H), 1.91 (hextet, J = 7.2 Hz, 1 H), 2.14 (dq, J = 4.1, 14.1 Hz, 1 H), 2.48 (dt, J = 5.0, 14.1 Hz, 1 H), 2.58 (m, 1 H), 2.68 (dd, J = 4.1, 7.2 Hz, 1 H), 3.69 (s, 3 H), 6.79 (d, J = 8.0 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 1 H), 7.61 (s, 1 H), 7.95 (d, J = 8.0 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 18.3, 22.7, 26.4, 27.6, 28.2, 38.8, 48.8, 52.7, 57.4, 69.0, 80.8, 122.0, 122.6, 131.0, 131.3,
136.6, 136.8, 153.1, 171.9, 207.9, 209.6; IR (neat) 3378, 2951, 1736, 1702, 1678 cm\(^{-1}\); HRMS (MNH\(_4^+\)) calcd for C\(_{23}H_{33}N_2O_6\) 433.2333, found 433.2358.

6-Amino-9,9-dimethyl-8,14-dioxotricyclo[8.3.1.0\(^2,7\)]tetradeca-2(7),3,5-triene-1-carboxylic acid methyl ester (506). To a solution of amide 505 (223 mg, 0.54 mmol) in CH\(_2\)Cl\(_2\) (11 mL) at –50 °C was added TFA (83 µL, 1.08 mmol). The solution was warmed to rt over 30 min and stirred for 4 h. The mixture was quenched with saturated aqueous NaHCO\(_3\) and extracted with CH\(_2\)Cl\(_2\). The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 4) provided aniline 506 as a colorless oil (114 mg, 67%); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.23 (s, 3 H), 1.25 (s, 3 H), 1.45 – 1.70 (m, 2 H), 1.90 (m, 1 H), 2.18 (br d, \(J = 13.6\) Hz, 1 H), 2.38 (ddt, \(J = 2.0, 4.6, 13.6\) Hz, 1 H), 2.52 (ddd, \(J = 5.5, 11.1, 14.0\) Hz, 1 H), 2.66 (dd, \(J = 3.4, 7.1\) Hz, 1 H), 3.73 (s, 3 H), 4.63 (s, 2 H), 6.37 (d, \(J = 8.0\) Hz, 1 H), 6.64 (d, \(J = 8.0\) Hz, 1 H), 7.14 (t, \(J = 8.0\) Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 18.2, 23.4, 26.3, 28.0, 39.6, 48.1, 52.5, 57.9, 69.6, 116.3, 117.4, 124.8, 131.5, 137.5, 147.2, 172.5, 208.7, 209.4; IR (neat) 3478, 3384, 2949, 1739, 1704, 1666, 1611 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{18}H_{22}NO_4\) 316.1543, found 316.1558.
6-(Carboxymethylamino)-9,9-dimethyl-8,14-dioxotricyclo[8.3.1.0^{2,7}]-tetradeca-2(7),3,5-triene-1-carboxylic acid methyl ester (507). To a solution of aniline 506 (106 mg, 0.33 mmol) in MeOH (3.3 mL) was added NaOAc (54.9 mg, 0.67 mmol), glacial acetic acid (77 µL, 1.34 mmol), and glyoxylic acid monohydrate (77 mg, 0.84 mmol). The mixture was cooled to –20 °C and NaCNBH$_3$ (23.1 mg, 0.37 mmol) was added in one portion. The solution was stirred at –20 °C for 25 min. The mixture was filtered through a plug of silica-gel and washed with ethyl acetate. The solution was then washed with brine, dried (Na$_2$SO$_4$), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane-AcOH, 39 : 60 : 1) provided carboxylic acid 507 as a colorless oil (105 mg, 84%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.24 (s, 3 H), 1.25 (s, 3 H), 1.48 – 1.73 (m, 2 H), 1.92 (m, 1 H), 2.17 (br d, $J$ = 12.0 Hz, 1 H), 2.42 (m, 1 H), 2.53 (ddd, $J$ = 5.5, 11.0, 14.1 Hz, 1 H), 2.67 (dd, $J$ = 3.2, 7.0 Hz, 1 H), 3.72 (s, 3 H), 3.93 (s, 2 H), 6.42 (d, $J$ = 8.1 Hz, 1 H), 6.45 (br s, 1 H), 6.52 (d, $J$ = 8.1 Hz, 1 H), 7.26 (t, $J$ = 8.1 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 18.3, 23.3, 26.5, 28.0, 39.4, 45.4, 48.5, 52.6, 57.8, 69.6, 110.8, 117.1, 125.2, 132.0, 137.6, 146.3, 172.4, 175.1, 208.5, 209.8; IR (neat) 3000-3400, 3295, 2926, 1738, 1708, 1672 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{20}$H$_{24}$NO$_6$ 374.1598, found 374.1591.
**Indole 509.** A solution of carboxylic acid 507 (81.1 mg, 0.22 mmol) and NaOAc (178 mg, 2.17 mmol) in acetic anhydride (4.3 mL) was heated to reflux for 30 min. The mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, filtered through a plug of silica-gel, and washed with ethyl acetate. The organic solvent was concentrated to afford the crude N-acetylindole 508 which was used without further purification; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.22 (s, 3 H), 1.31 – 1.40 (m, 2 H), 1.56 (s, 3 H), 1.95 (m, 1 H), 2.08 – 2.25 (m, 2 H), 2.63 (ddd, $J$ = 4.4, 13.1, 17.7 Hz, 1 H), 2.66 (s, 3 H), 2.76 (dd, $J$ = 2.2, 8.0 Hz, 1 H), 3.83 (s, 3 H), 6.84 (d, $J$ = 8.0 Hz, 1 H), 7.31 (s, 1 H), 7.36 (t, $J$ = 8.0 Hz, 1 H), 8.48 (d, $J$ = 8.0 Hz, 1 H). The crude N-acetylindole 508 was dissolved in MeOH (4.3 mL) and K$_2$CO$_3$ (60.0 mg, 0.43 mmol) was added. The mixture was stirred at rt for 1 h. The solution was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ether-CH$_2$Cl$_2$, 1 : 99) provided indole 509 as a colorless oil (58.6 mg, 87%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.21 (s, 3 H), 1.27 – 1.38 (m, 2 H), 1.53 (s, 3 H), 1.96 (m, 1 H), 2.07 – 2.25 (m, 2 H), 2.67 (ddd, $J$ = 4.4, 11.7, 13.2 Hz, 1 H), 2.75 (dd, $J$ = 2.5, 8.0 Hz, 1 H), 3.83 (s, 3 H), 6.67 (dd, $J$ = 1.0, 7.4 Hz, 1 H), 7.13 (d, $J$ = 2.5 Hz, 1 H), 7.19 (dd, $J$ = 7.4, 8.0 Hz, 1 H), 7.30 (dd, $J$ = 1.0, 8.0 Hz, 1 H), 8.14 (br s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 18.7, 28.0, 28.3, 34.8, 35.2, 42.6, 52.4, 61.9, 69.9, 109.9, 118.5, 121.5, 122.7, 123.2, 124.9, 131.1, 138.3, 173.9, 210.8; IR (neat) 3389, 2923, 1733, 1696 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{19}$H$_{22}$NO$_3$ 312.1594, found 312.1613.
**N-Methylindole 510.** To a solution of indole 509 (44.1 mg, 0.14 mmol) at rt was added NaH (60% dispersion in mineral oil, 6.8 mg, 0.17 mmol) and MeI (44 µL, 0.71 mmol). The mixture was warmed to 50 °C for 15 min. Upon cooling to rt, the solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ether-CH₂Cl₂, 1 : 99) provided N-methylindole 510 as a colorless oil (42.6 mg, 92%); ¹H NMR (300 MHz, CDCl₃) δ 1.21 (s, 3 H), 1.27 – 1.37 (m, 2 H), 1.51 (s, 3 H), 1.95 (m, 1 H), 2.07 – 2.25 (m, 2 H), 2.67 (ddd, J = 4.8, 11.6, 13.3 Hz, 1 H), 2.74 (dd, J = 2.8, 8.1 Hz, 1 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 6.66 (m, 1 H), 6.98 (s, 1 H), 7.21 (m, 1 H), 7.23 (d, J = 1.2 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 18.8, 28.0, 28.4, 32.9, 34.8, 35.5, 42.5, 52.4, 62.0, 69.9, 107.9, 118.0, 121.5, 122.1, 125.2, 126.5, 131.3, 136.9, 173.9, 210.8; IR (neat) 2922, 1735, 1695 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₂₄NO₃ 326.1750, found 326.1742.
**Carboxylic acid 511.** To a solution of ester 510 (35.3 mg, 0.11 mmol) in MeOH (2 mL) was added 4 M aqueous NaOH (1 mL). The mixture was heated to 70 °C for 8 h. Upon cooling to 0 °C, the solution was acidified with phosphate buffer (pH 5.0) and extracted with ethyl acetate. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane-AcOH, 30 : 69 : 1) provided carboxylic acid 511 as a colorless oil (25.0 mg, 74%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.24 (s, 3 H), 1.35 (m, 2 H), 1.54 (s, 3 H), 1.93 (m, 1 H), 2.17 – 2.38 (m, 2 H), 2.59 (ddd, $J = 4.8, 11.6, 13.3$ Hz, 1 H), 2.78 (dd, $J = 2.8, 8.1$ Hz, 1 H), 3.77 (s, 3 H), 6.93 (m, 1 H), 6.98 (s, 1 H), 7.21 – 7.28 (m, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 18.6, 27.7, 28.7, 29.7, 32.9, 35.1, 35.9, 41.9, 61.2, 108.5, 117.8, 121.6, 122.3, 125.0, 126.6, 130.2, 136.9, 174.9, 212.1.; IR (neat) 3365, 2922, 1711 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{19}$H$_{22}$NO$_3$ 312.1594, found 312.1621.

![Diagram](image1)

**5,5-Dimethyl-4,10-dioxobicyclo[4.3.1]dec-2-en-1-yl-carbamic acid methyl ester (514).** To a solution of methyl ester 501 (778 mg, 3.11 mmol) in MeOH (31 mL) at 0 °C was added 4 M aqueous NaOH (15.5 mL). The resulting mixture was warmed to rt and stirred 2 h. The solution was slowly acidified with 1 M aqueous HCl and extracted with ethyl acetate. The combined extracts were dried Na$_2$SO$_4$ and concentrated to afford the crude acid which was used without
further purification. To a solution of the crude acid in acetone (15 mL) at 0 °C was added diisopropylethylamine (1.08 mL, 6.22 mmol) and isopropyl chlorofomate (1.0 M in toluene, 3.73 mL, 3.73 mmol). The resulting solution was stirred at 0 °C for 20 min. To the resulting solution at 0 °C was added NaN₃ (1.01 g, 15.5 mmol). The mixture was warmed to rt and stirred 3 h. The solid was then filtered off and washed with acetone. The resulting solution was concentrated to afford the crude acyl azide, which was used without further purification. A solution of the crude acyl azide in toluene (30 mL) was heated to 110 °C for 1 h. The resulting solution was then cooled to rt and MeOH (7.5 mL) was added. The mixture was heated at 75 °C for 4 h and then concentrated. Purification by silica-gel chromatography (ether–CH₂Cl₂, 3 : 97) afforded the bridghead carbamate 514 as a white solid: mp 177 – 179 °C (696 mg, 84%); ¹H NMR (300 MHz, CDCl₃) δ 1.10 (s, 3 H), 1.20 (s, 3 H), 1.51 – 1.85 (m, 4 H), 2.15 (br d, J = 12.4 Hz, 1 H), 2.74 (d, J = 5.7 Hz, 1 H), 2.77 (m, 1 H), 3.67 (s, 3 H), 6.09 (d, J = 13.1 Hz, 1 H), 6.20 (br s, 1 H), 6.48 (d, J = 13.1 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 17.9, 23.4, 27.1, 28.1, 39.2, 45.9, 52.0, 59.4, 67.3, 129.5, 137.2, 155.4, 204.7, 204.9; IR (neat) 3354, 2953, 1734, 1715, 1655 cm⁻¹; HRMS (MH⁺) calcd for C₁₄H₂₀NO₄ 266.1387, found 266.1400.

3-Bromo-5,5-dimethyl-4,10-dioxobicyclo[4.3.1]dec-2-en-1-yl-carbamic acid methyl ester (515). To a solution of enone 514 (412 mg, 1.55 mmol) in CCl₄ (10 mL) was added Br₂ (96 µL, 1.86 mmol). The mixture was stirred at rt for 1 h. The solution was quenched with 10% aqueous Na₂S₂O₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated to afford
the crude vicinal dibromide, which was used immediately without further purification. The vicinal dibromide was dissolved in CH$_2$CN (30 mL) and Cs$_2$CO$_3$ (1.01 g, 3.11 mmol) was added. The mixture was stirred at rt for 3 h. The solution was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ether-CH$_2$Cl$_2$, 1 : 99) provided the α-bromoenone 515 as a yellow solid: mp 185 – 187 ºC (399 mg, 75%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.16 (s, 3 H), 1.26 (s, 3 H), 1.43 – 1.88 (m, 4 H), 2.17 (br d, $J$ = 14.7 Hz, 1 H), 2.76 (d, $J$ = 6.1 Hz, 1 H), 2.91 (br d, $J$ = 11.4 Hz, 1 H), 3.69 (s, 3 H), 6.29 (s, 1 H), 7.12 (s, 1 H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 18.0, 24.3, 26.1, 28.0, 39.3, 46.9, 52.2, 59.1, 67.9, 122.7, 137.3, 155.2, 199.3, 203.3; IR (neat) 3406, 2931, 1711, 1690, 1637 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{14}$H$_{19}$NO$_4$Br 344.0492, found 344.0483.

3-(1-tert-Butoxycarbonylaminobuta-1,3-dienyl)-5,5-dimethyl-4,10-dioxobicyclo[4.3.1]dec-2-en-1-ylcarbamic acid methyl ester (516). To a solution of bromide 515 (399 mg, 1.16 mmol) and stannane 393 (638 mg, 1.39 mmol) in THF (12 mL) was added CuI (55.2 mg, 0.29 mmol) and Pd(PPh$_3$)$_4$ (67.0 mg, 0.058 mmol). The mixture was heated to reflux for 3 h. Upon cooling to rt, the solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) provided triene 516 as a yellow solid: mp 57 – 59 ºC (432 mg, 86%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.20 (s, 3 H), 1.21 (s, 3 H), 1.44 (s, 9 H), 1.57 – 1.88 (m, 4 H), 2.20 (br d, $J$ = 11.2 Hz, 1 H), 2.75 (d, $J$ = 5.1 Hz, 1 H), 2.90 (br d, $J$ = 12.2 Hz, 1 H), 3.67 (s, 3 H), 5.02 (dd, $J$ = 1.6, 10.0 Hz, 1 H), 5.22 (dd, $J$ = 1.6, 16.6 Hz, 1
H), 6.19 (s, 1 H), 6.42 (m, 2 H), 6.56 (s, 1 H), 6.64 (d, J = 11.0 Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 18.1, 23.8, 26.3, 28.1, 28.2, 39.6, 47.2, 52.1, 59.4, 67.0, 80.4, 117.2, 119.9, 132.2, 134.8, 134.9, 139.8, 152.7, 155.4, 204.2, 205.7; IR (neat) 3404, 2977, 1705, 1668 cm\(^{-1}\); HRMS (MH\(^{+}\)) calcd for C\(_{23}\)H\(_{33}\)N\(_2\)O\(_6\) 433.2333, found 433.2295.

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\text{1-Methoxycarbonylamino-9,9-dimethyl-8,14-dioxotricyclo[8.3.1.0\(_{0,0}\)\]-tetradeca-2,4,6-trien-6-ylcarbamic acid tert-butyl ester.} \quad \text{A solution of triene 516 (432 mg, 1.00 mmol) in toluene (20 mL) was heated to reflux for 3 h. The resulting solution was cooled to rt and DDQ (272 mg, 1.20 mmol) was added. The mixture was stirred at 70 °C for 5 h. The solution was quenched with saturated aqueous NaHCO\(_3\) and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO\(_3\), dried (Na\(_2\)SO\(_4\)), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) provided a white solid: mp 174 – 176 °C (389 mg, 90%); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.91 (s, 3 H), 1.27 (s, 3 H), 1.46 (s, 9 H), 1.58 – 1.77 (m, 2 H), 1.96 – 2.21 (m, 2 H), 2.38 (m, 1 H), 2.74 (dd, J = 3.2, 8.5 Hz, 1 H), 2.78 (m, 1 H), 3.68 (s, 3 H), 6.31 (s, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 1 H), 7.70 (s, 1 H), 7.95 (d, J = 8.0 Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 18.7, 23.5, 25.4, 26.9, 28.2, 39.0, 50.8, 52.1, 57.7, 69.2, 80.7, 121.1, 122.2, 128.2, 131.1, 136.2, 136.9, 152.9, 155.3, 206.5, 211.0; IR (neat) 3397, 2976, 1730, 1708, 1678 cm\(^{-1}\); HRMS (MH\(^{+}\)) calcd for C\(_{23}\)H\(_{31}\)N\(_2\)O\(_6\) 431.2176, found 431.2217.
6-Amino-9,9-dimethyl-8,14-dioxotricyclo[8.3.1.0199]tetradeca-2,4,6-trien-1-yl-carbamic acid methyl ester (517). To a solution of the carbamate (252 mg, 0.59 mmol) in CH₂Cl₂ (12 mL) at −50 °C was added TFA (225 µL, 2.93 mmol). The solution was warmed to rt over 30 min and stirred for 1.5 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) provided aniline 517 as a white solid: mp 104 – 106 °C (189 mg, 97%); ¹H NMR (300 MHz, CDCl₃) δ 0.93 (s, 3 H), 1.28 (s, 3 H), 1.42 (m, 1 H), 1.75 (m, 1 H), 2.01 (m, 1 H), 2.16 (m, 1 H), 2.47 (m, 1 H), 2.65 (m, 1 H), 2.73 (dd, J = 2.9, 8.1 Hz, 1 H), 3.69 (s, 3 H), 4.59 (s, 2 H), 6.38 (s, 1 H), 6.63 (dd, J = 1.0, 8.0 Hz, 1 H), 6.75 (dd, J = 1.0, 8.0 Hz, 1 H), 7.14 (t, J = 8.0 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 18.7, 23.9, 25.4, 27.2, 39.5, 50.3, 52.0, 58.1, 69.3, 115.7, 117.2, 121.8, 131.5, 137.6, 146.3, 155.3, 207.1, 210.6; IR (neat) 3477, 3376, 2926, 1730, 1706, 1670 cm⁻¹; HRMS (MH⁺) calcd for C₁₈H₂₃N₂O₄ 331.1652, found 331.1628.
**N-Acetylindole 518.** To a solution of aniline 517 (147 mg, 0.44 mmol) in MeOH (9 mL) was added NaOAc (73.0 mg, 0.89 mmol), glacial acetic acid (102 µL, 1.78 mmol), and glyoxylic acid monohydrate (102 mg, 1.11 mmol). The mixture was cooled to −10 °C and NaCNBH₃ (30.8 mg, 0.49 mmol) was added in one portion. The solution was stirred at −10 °C for 20 min. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude acid, which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ 0.91 (s, 3 H), 1.28 (s, 3 H), 1.40 (m, 1 H), 1.75 (m, 1 H), 2.12 (m, 2 H), 2.48 (m, 1 H), 2.69 (m, 1 H), 2.74 (dd, J = 2.7, 7.8 Hz, 1 H), 3.69 (s, 3 H), 3.92 (s, 2 H), 6.43 (s, 1 H), 6.53 (d, J = 8.0 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 7.26 (t, J = 8.0 Hz, 1 H). A solution of the crude acid in acetic anhydride (5 mL) and triethylamine (620 µL, 4.45 mmol) was heated to reflux for 20 min. The resulting solution was concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) afforded the N-acetylindole 518 as a white solid: mp 83 – 85 °C (121 mg, 74%); ¹H NMR (300 MHz, CDCl₃) δ 1.20 (s, 3 H), 1.29 – 1.41 (m, 2 H), 1.56 (s, 3 H), 1.84 – 2.20 (m, 4 H), 2.65 (s, 3 H), 2.86 (d, J = 7.2 Hz, 1 H), 3.69 (s, 3 H), 5.51 (s, 1 H), 7.31 (s, 1 H), 7.40 (t, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 8.47 (d, J = 8.0 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 19.1, 24.2, 27.7, 27.8, 34.4, 34.6, 44.5, 52.1, 60.2, 70.8, 115.8, 120.5, 122.0, 126.3, 126.8, 129.6, 133.3, 135.9, 156.5, 168.3, 207.9; IR (neat) 3332, 2955, 1731, 1703 cm⁻¹; HRMS (MH⁺) calcd for C₂₁H₂₅N₂O₄ 369.1809, found 369.1791.
**N-Methylindole 513.** To a solution of *N*-acetylindole 518 (80.0 mg, 0.22 mmol) in MeOH (5.2 mL) was added K₂CO₃ (60.0 mg, 0.43 mmol). The mixture was stirred at rt for 2 h. The solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude indole 519, which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ 1.20 (s, 3 H), 1.35 (m, 2 H), 1.52 (s, 3 H), 1.93 (m, 1 H), 2.18 (m, 2 H), 2.55 (m, 1 H), 2.84 (dd, J = 1.9, 7.5 Hz, 1 H), 3.71 (s, 3 H), 5.58 (s, 1 H), 7.08 (d, J = 2.5 Hz, 1 H), 7.21 (t, J = 8.0 Hz, 1 H), 7.28 (dd, J = 1.6, 8.0 Hz, 1 H), 7.35 (dd, J = 1.6, 8.0 Hz, 1 H), 8.32 (s, 1 H). To a solution of the crude indole in acetone (4.2 mL) was added KOH (42.6 mg, 0.76 mmol) and MeI (108 µL, 1.74 mmol). The resulting solution was stirred at rt for 15 min. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) provided the *N*-methylindole 513 as a white solid: mp 116 – 118 °C (60.1 mg, 81%); ¹H NMR (300 MHz, CDCl₃) δ 1.21 (s, 3 H), 1.37 (m, 2 H), 1.53 (s, 3 H), 1.95 (m, 1 H), 2.12 – 2.28 (m, 2 H), 2.58 (m, 1 H), 2.83 (d, J = 7.8 Hz, 1 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 5.59 (s, 1 H), 6.97 (s, 1 H), 7.22 (dd, J = 1.6, 8.0 Hz, 1 H), 7.26 (t, J = 8.0 Hz, 1 H), 7.35 (dd, J = 1.6, 8.0 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 19.7, 27.7, 28.4, 32.9, 34.7, 35.9, 44.1, 52.0, 60.2, 70.9, 108.5, 115.4, 122.1, 122.3, 124.0, 126.4, 133.6, 136.8, 156.7, 209.0; IR (neat) 3331, 2923, 1725, 1696 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₂₅N₂O₃ 341.1860, found 341.1858.
Oxindoles 521 and 522. To a solution of N-methylindole 513 (31.1 mg, 0.091 mmol) in DMSO (1 mL) was added concentrated HCl (2 mL). The solution was heated to 70 °C for 40 min. The mixture was quenched slowly with saturated aqueous NaHCO₃ and extracted with ethyl acetate. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 2 : 3) afforded the oxindole as a mixture of diastereomers (26.1 mg, 80%); Minor diastereomer 522: Rf = 0.27 (9.5 mg, 29%); ¹H NMR (400 MHz, CDCl₃) δ 0.62 (s, 3 H), 1.50 (m, 1 H), 1.53 (s, 3 H), 1.84 (m, 1 H), 2.20 (m, 1 H), 2.35 (m, 1 H), 2.49 (br t, J = 11.7 Hz, 1 H), 2.68 (dd, J = 3.5, 9.7 Hz, 1 H), 3.01 (m, 1 H), 3.19 (s, 3 H), 3.74 (s, 3 H), 3.94 (s, 1 H), 6.36 (br s, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 7.02 (m, 1 H), 7.29 (t, J = 8.0 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 20.0, 22.4, 25.2, 26.3, 27.1, 29.7, 35.9, 50.9, 52.1, 60.8, 68.5, 107.5, 119.6, 123.5, 129.0, 135.9, 144.6, 155.7, 175.0, 206.9; IR (neat) 3366, 2924, 1731, 1703 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₂₅N₂O₄ 357.1809, found 357.1794. Major diastereomer 521: Rf = 0.23 (16.6 mg, 51%); ¹H NMR (400 MHz, CDCl₃) δ 0.83 (s, 3 H), 1.47 (m, 2 H), 1.64 (s, 3 H), 1.68 (m, 1 H), 1.85 (m, 1 H), 2.06 (dt, J = 7.0, 13.7 Hz, 1 H), 2.79 (t, J = 7.3 Hz, 1 H), 2.97 (m, 1 H), 3.17 (s, 3 H), 3.38 (s, 1 H), 3.57 (s, 3 H), 5.40 (s, 1 H), 6.74 (dd, J = 1.8, 6.7 Hz, 1 H), 7.35 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 19.4, 19.5, 26.1, 26.8, 29.7, 30.4, 39.3, 52.0, 52.3, 59.8, 67.1, 106.9, 120.2, 125.6, 129.1, 137.9, 143.7, 155.7, 175.1, 209.9; IR (neat) 3326, 2924, 1716, 1698 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₂₅N₂O₄ 357.1809, found 357.1815.
5-((tert-Butyldimethylsilyloxy)-3-(6H-[1,3]dioxin-4-ylmethyl)-6-methyl-2-(trimethylsilyloxy)-6-vinylcyclohex-1-enecarboxylic acid ethyl ester (530).

To a solution of β-ketoester 529 (25 mg, 0.57 mmol) in CH₂Cl₂ (1 mL) at rt was added Et₃N (16 µL, 0.11 mmol) and TMSCl (11 µL, 0.85 mmol). The mixture was stirred at reflux for 2 h. The resulting solution was cooled to rt, quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude silyl enol ether 530 as a colorless oil (22 mg, 76%); ¹H NMR (200 MHz, CDCl₃) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.20 (s, 9 H), 0.87 (s, 9 H), 1.22 (t, J = 7.5 Hz, 3 H), 1.28 (s, 3 H), 1.62 – 1.90 (5 H), 2.48 (m, 1 H), 2.71 (m, 1 H), 3.58 (dd, J = 4.8, 11.5 Hz, 1 H), 4.09 (q, J = 7.5 Hz, 2 H), 4.20 (m, 2 H), 4.69 (m, 1 H), 4.90 – 5.10 (m, 4 H), 5.63 (dd, J = 10.9, 17.9 Hz, 1 H).

5-((tert-Butyldimethylsilyloxy)-3-(6H-[1,3]dioxin-4-ylmethyl)-6-methyl-2-(trimethylsilyloxy)-6-vinylcyclohex-1-enecarboxylic acid ethyl ester (531).

To a solution of β-ketoester 206 (25 mg, 0.57 mmol) in CH₂Cl₂ (1 mL) at rt was added Et₃N (16 µL, 0.11 mmol) and TMSCl (11 µL, 0.85 mmol). The mixture was stirred at reflux for 2 h. The resulting solution was cooled to rt, quenched with
saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude silyl enol ether 531 as a colorless oil (25 mg, 86%); ¹H NMR (200 MHz, CDCl₃) δ 0.02 (s, 3 H), 0.20 (s, 9 H), 0.22 (s, 3 H), 0.94 (s, 9 H), 1.20 (t, J = 7.5 Hz, 3 H), 1.25 (s, 3 H), 1.55 – 1.96 (6 H), 2.88 (m, 1 H), 3.56 (m, 1 H), 4.13 (q, J = 7.5 Hz, 2 H), 4.21 (m, 2 H), 4.71 (m, 1 H), 4.93 – 5.11 (m, 4 H), 5.72 (dd, J = 10.9, 17.9 Hz, 1 H).

4-(tert-Butyldimethylsilyloxy)-2-(6H-[1,3]dioxin-4-ylmethyl)-5-methyl-5-vinylcyclohexanone (533). To a solution of 4-(tert-butyldimethylsilyloxy)-3-methyl-3-vinylcyclohexanone (532) (8.21 g, 30.6 mmol) and bromide 207 (6.57 g, 36.7 mmol) in THF (150 mL) at -78 °C was added LiHMDS (1.0 M in THF, 45.8 mL, 45.8 mmol) dropwise over 10 min. The solution was warmed to rt over 1 h and stirred for 12 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (CH₂Cl₂–hexane, 2 : 1) provided dioxin 533 as a yellow oil (8.42 g, 75%); ¹H NMR (400 MHz, CDCl₃) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.94 (s, 9 H), 1.06 (s, 3 H), 1.63 (dt, J = 1.9, 13.5 Hz, 1 H), 1.78 (dd, J = 9.8, 14.7 Hz, 1 H), 2.01 (ddd, J = 3.6, 5.9, 13.5 Hz, 1 H), 2.32 (d, J = 13.8 Hz, 1 H), 2.68 (d, J = 13.8 Hz, 1 H), 2.73 (br d, J = 14.7 Hz, 1 H), 2.92 (m, 1 H), 3.67 (m, 1 H), 4.19 (br t, J = 2.2 Hz, 1 H), 4.64 (br t, J = 2.2 Hz, 2 H), 4.96 (d, J = 5.3 Hz, 1 H), 5.02 (d, J = 5.3 Hz, 1 H), 5.03 (d, J = 10.9 Hz, 1 H), 5.04 (d, J = 17.8 Hz, 1 H), 5.62 (dd, J = 10.9, 17.8 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ -5.0, -4.6, 18.1, 25.7, 25.8, 32.5, 35.6, 40.7, 46.2, 47.6, 63.9, 72.9, 90.4,
98.2, 114.6, 143.4, 152.2, 211.1; IR (neat) 2929, 1711, 1682 cm\(^{-1}\); HRMS (MH\(^{+}\)) calcd for \(\text{C}_{20}\text{H}_{35}\text{O}_{4}\text{Si}\) 367.2305, found 367.2306.

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3-(6\(H\)[1,3]Dioxin-4-ylmethyl)-8-methyl-8-vinyl-6-oxabicyclo[3.2.1]-octane-2,7-dione (541). To a solution of diisopropylamine (76 \(\mu\)L, 0.54 mmol) in THF (3.5 mL) at \(-20^\circ\)C was added \(n\)-BuLi (2.5 M in hexane, 199 \(\mu\)L, 0.50 mmol) dropwise. The solution was warmed to 0 \(^\circ\)C and stirred for 20 min. To the resulting mixture at \(-78^\circ\)C was added lactone 540 (82 mg, 0.45 mmol) in THF (0.5 mL) dropwise. The solution was stirred at \(-78^\circ\)C and stirred for 1 h. To the resulting solution was added bromide 207 (89 mg, 0.50 mmol) in THF (0.5 mL). The mixture was warmed to rt and stirred 16 h. The resulting solution was quenched with saturated aqueous NH\(_4\)Cl and extracted with ether. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica gel chromatography afforded dioxin 541 as a colorless oil (106 mg, 84%); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 0.75 (s, 3 H), 1.38 (ddd, \(J = 1.2, 9.9, 14.5\) Hz, 1 H), 1.77 (dd, \(J = 9.1, 14.5\) Hz, 1 H), 2.11 (dd, \(J = 4.0, 9.1, 14.5\) Hz, 1 H), 2.65 (ddd, \(J = 4.0, 9.1, 18.6\) Hz, 1 H), 2.74 (m, 1 H), 3.19 (s, 1 H), 3.76 (m, 1 H), 3.82 (m, 2 H), 4.18 (t, \(J = 2.5\) Hz, 1 H), 4.63 (d, \(J = 5.4\) Hz, 1 H), 4.65 (d, \(J = 5.4\) Hz, 1 H), 4.73 (d, \(J = 17.5\) Hz, 1 H), 4.79 (d, \(J = 11.1\) Hz, 1 H), 5.08 (dd, \(J = 11.1, 17.5\) Hz, 1 H).
8-(tert-Butyldimethylsilyloxy)-7-methyl-3-oxo-oct-6-enoic acid ethyl ester. To a suspension of NaH (290 mg, 7.25 mmol) in THF (25 mL) at 0 °C was added ethyl acetoacetate (890 µL, 6.98 mmol) dropwise in THF (1 mL). The mixture was stirred at 0 °C for 10 min. To the resulting solution at 0 °C was added n-BuLi (2.5 M in hexane, 2.90 mL, 7.25 mmol) dropwise. The mixture was stirred at 0 °C for 10 min and then cooled to −50 °C. Bromide 554140 (1.50 g, 5.37 mmol) in THF (1 mL) was then added dropwise, and the solution was warmed to rt over 45 min. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate - hexane, 1 : 9) provided a colorless oil (1.61 g, 91%); ¹H NMR (200 MHz, CDCl₃) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.61 (s, 3 H), 2.32 (p, J = 8.0 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.41 (s, 2 H), 3.98 (s, 2 H), 4.18 (q, J = 7.2 Hz, 2 H), 5.35 (t, J = 8.0 Hz, 1 H).

2-(tert-Butyldimethylsilyloxymethyl)-2-methyl-6-oxo-3-phenylselenyl-cyclohexanecarboxylic acid ethyl ester. To a solution of the β-ketoester (1.61 g, 4.90 mmol) in CH₂Cl₂ (25 mL) at 0 °C was added AlCl₃ (653 mg, 4.90 mmol) and PhSeCl (938 mg, 4.90 mmol). The mixture was stirred at 0 °C for 5 min. The resulting solution was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were washed with 10 % aqueous
Rochelle’s salt, dried (Na₂SO₄), and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 9) afforded the selenide as a colorless oil (1.20 g, 51%); ¹H NMR (200 MHz, CDCl₃) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 1.10 (s, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 2.10 – 2.51 (m, 4 H), 3.48 (d, J = 11.5 Hz, 1 H), 3.75 (dd, J = 3.5, 12.0 Hz, 1 H), 3.83 (s, 1 H), 3.95 (d, J = 11.5 Hz, 1 H), 4.15 (m, 2 H), 7.20 – 7.30 (m, 3 H), 7.50 – 7.60 (m, 2 H).

3a-Methyl-4-phenylselenyltetrahydroisobenzofuran-1,7-dione. A solution of the selenide (288 mg, 0.59 mmol) and p-TsOH·H₂O (142 mg, 0.74 mmol) in toluene (6 mL) was heated to reflux for 30 min. The resulting mixture was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 4) afforded the lactone as a colorless oil (140 mg, 73%); ¹H NMR (200 MHz, CDCl₃) δ 1.33 (s, 3 H), 2.15 – 2.50 (m, 4 H), 3.26 (s, 1 H), 3.47 (dd, J = 3.4, 11.9 Hz, 1 H), 3.90 (d, J = 9.4 Hz, 1 H), 4.78 (d, J = 9.4 Hz, 1 H), 7.26 – 7.40 (m, 3 H), 7.55 – 7.65 (m, 2 H).
3a-Methyltetrahydro-isobenzofuran-1,7-dione (555). To a solution of the selenide (610 mg, 1.89 mmol) in toluene (19 mL) was added Bu$_3$SnH (1.02 mL, 3.77 mmol) and AIBN (31 mg, 0.19 mmol). The mixture was heated to reflux for 2 h. The resulting solution was cooled to rt and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 2 : 3) afforded lactone 555 as a colorless oil (243 mg, 77%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.22 (s, 3 H), 1.63 – 2.10 (m, 4 H), 2.25 – 2.45 (m, 2 H), 3.09 (s, 1 H), 3.88 (d, $J$ = 9.4 Hz, 1 H), 4.07 (d, $J$ = 9.4 Hz, 1 H).

Carbonic acid 6-(6H-[1,3]dioxin-4-ylmethyl)-3-methyl-4-oxo-3-vinyl-cyclohex-1-enyl ester ethyl ester (557). To a solution of diisopropylamine (836 $\mu$L, 5.97 mmol) in THF (35 mL) at $-60$ °C was added $n$-BuLi (2.5 M in hexane, 2.29 mL, 5.73 mmol) dropwise over 10 min. The solution was warmed to $-30$ °C and stirred for 20 min. The resulting mixture was cooled to $-78$ °C and ketone 533 (1.75 g, 4.77 mmol) in THF (5 mL) was added dropwise over 5 min. The solution was warmed slowly to $-10$ °C and stirred for 1 h. The resulting enolate was cooled to $-78$ °C and ethyl chloroformate (913 $\mu$L, 9.54 mmol) was added in one portion. The solution was warmed to 0 °C over 1.5 h. The resulting mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The
combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude enol carbonate, which was used without further purification. To a solution of the crude enol carbonate in THF (45 mL) at 0 °C was added TBAF (1.0 M in THF, 12.0 mL, 12.0 mmol). The mixture was warmed to rt and stirred 5 h. The resulting solution was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude alcohol, which was used without further purification. To a solution of the crude alcohol in CH$_2$Cl$_2$ (45 mL) was added 4 Å molecular sieves (1.5 g), N-methylmorpholine-N-oxide (838 mg, 7.16 mmol), and TPAP (50.3 mg, 0.14 mmol). The mixture was stirred at rt for 3 h. The resulting mixture was filtered through a plug of celite, washed with CH$_2$Cl$_2$, and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 4) afforded ketone 557 as a colorless oil (1.37 g, 90% 3 steps); $^1$H NMR (200 MHz, CDCl$_3$) δ 1.25 (s, 3 H), 1.34 (t, $J$ = 7.5 Hz, 3 H), 2.00 (m, 1 H), 2.25 – 2.50 (m, 3 H), 3.09 (m, 1 H), 4.18 (m, 2 H), 4.20 (q, $J$ = 7.5 Hz, 2 H), 4.70 (m, 1 H), 4.98 (d, $J$ = 5.0 Hz, 1 H), 5.00 (d, $J$ = 5.0 Hz, 1 H), 5.19 (d, $J$ = 11.1 Hz, 1 H), 5.25 (d, $J$ = 17.8 Hz, 1 H), 5.40 (s, 1 H), 5.91 (dd, $J$ = 11.1, 17.8 Hz, 1 H).

Carbonic acid 6-(6H-[1,3]dioxin-4-ylmethyl)-3-methyl-4-(trimethylstannyl)-3-vinylcyclohexa-1,4-dienyl ester ethyl ester (558). To a solution of diisopropylamine (516 µL, 3.68 mmol) in THF (25 mL) at –60 °C was added n-BuLi (2.5 M in hexane, 1.41 mL, 3.54 mmol) dropwise over 10 min. The solution was warmed to –30 °C and stirred for 20 min. The resulting mixture was cooled
to −78 °C and ketone 557 (950 mg, 2.95 mmol) in THF (2 mL) was added dropwise over 5 min. The solution was stirred at −78 °C for 15 min. To the resulting mixture was added PhNTf$_2$ (1.32 g, 3.68 mmol) in THF (3 mL). The mixture was warmed to 0 °C over 1 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude enol triflate (1.22 g, 91%), which was used without further purification. To a solution of the crude enol triflate (300 mg, 0.66 mmol) in THF (7 mL) was added hexamethylditin (137 µL, 0.66 mmol), LiCl (84 mg, 1.98 mmol), and Pd(PPh$_3$)$_4$ (38 mg, 0.033 mmol). The mixture was heated to reflux for 2 h. The resulting solution was filtered through a plug of silica gel, washed with ether, and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 9) afforded stannane 558 as a colorless oil (234 mg, 76%); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.12 (s, 9 H), 1.22 (s, 3 H), 1.33 (t, $J$ = 7.5 Hz, 3 H), 2.08 (dd, $J$ = 10.0, 16.8 Hz, 1 H), 2.37 (dd, $J$ = 7.2, 16.8 Hz, 1 H), 3.21 (m, 1 H), 4.20 (m, 2 H), 4.21 (q, $J$ = 7.5 Hz, 2 H), 4.69 (t, $J$ = 2.7 Hz, 1 H), 4.98 (d, $J$ = 11.0 Hz, 1 H), 5.00 (d, $J$ = 17.9 Hz, 1 H), 5.01 (m, 2 H), 5.39 (s, 1 H), 5.73 (d, $J$ = 6.2 Hz, 1 H), 5.75 (dd, $J$ = 11.0, 17.9 Hz, 1 H).

![Chemical structure](image)

**Carbonic acid 4-chloro-6-(6H-[1,3]dioxin-4-ylmethyl)-3-methyl-3-vinyl-cyclohexa-1,4-dienyl ethyl ester (559).** To a solution of stannane 558 (125 mg, 0.27 mmol) in THF (3 mL) was added Et$_3$N (297 µL, 2.13 mmol) and CuCl$_2$ (143 mg, 1.07 mmol). The mixture was stirred at rt for 12 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The
combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica
gel chromatography (CH$_2$Cl$_2$ – hexane, 3 : 2) afforded vinyl chloride 559 as a
colorless oil (72 mg, 80%); $^1$H NMR (200 MHz, CDCl$_3$) δ 1.33 (t, $J$ = 7.5 Hz, 3 H),
1.39 (s, 3 H), 2.10 (dd, $J$ = 10.0, 16.8 Hz, 1 H), 2.45 (dd, $J$ = 7.2, 16.8 Hz, 1 H),
3.40 (m, 1 H), 4.21 (m, 2 H), 4.22 (q, $J$ = 7.5 Hz, 2 H), 4.72 (t, $J$ = 2.7 Hz, 1 H),
5.00 (d, $J$ = 5.0 Hz, 1 H), 5.03 (d, $J$ = 5.0 Hz, 1 H), 5.12 (d, $J$ = 11.0 Hz, 1 H),
5.15 (d, $J$ = 17.9 Hz, 1 H), 5.39 (s, 1 H), 5.75 (d, $J$ = 6.2 Hz, 1 H), 5.91 (dd, $J$ =
11.0, 17.9 Hz, 1 H).

3-(tert-Butyldimethylsilyloxy)-5-(6H-[1,3]dioxin-4-ylmethyl)-2-methyl-
6-oxo-2-vinyl-cyclohexanecarbonitrile (576). To a solution of diisopropylamine
(3.28 mL, 23.4 mmol) in THF (100 mL) at −60 °C was added n-BuLi (2.5 M in
hexane, 8.94 mL, 22.4 mmol) dropwise over 10 min. The solution was warmed
to −30 °C and stirred for 20 min. The resulting mixture was cooled to −78 °C and
ketone 533 (8.20 g, 22.4 mmol) in THF (10 mL) was added dropwise over 15
min. The solution was warmed slowly to −10 °C and stirred for 1 h. The resulting
enolate was cooled to −78 °C and p-toluenesulfonyl cyanide (3.68 g, 20.3 mmol)
in THF (15 mL) was added in one portion. The solution was warmed to 0 °C over
1.5 h, and then concentrated aqueous NH$_4$OH was added. After stirring to rt, the
mixture was diluted with saturated aqueous NH$_4$Cl and extracted with ether. The
combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-
gel chromatography (ethyl acetate-hexane, 1 : 9) provided β-ketonitrile 576 as a
yellow oil (6.41 g, 81%); $^1$H NMR (400 MHz, CDCl$_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H),
0.87 (s, 9 H), 1.27 (s, 3 H), 1.68 (dt, J = 1.9, 14.0 Hz, 1 H), 1.81 (dd, J = 9.7, 14.7 Hz, 1 H), 2.00 (ddd, J = 3.5, 6.1, 14.0 Hz, 1 H), 2.64 (br d, J = 14.7 Hz, 1 H), 2.93 (m, 1 H), 3.70 (m, 1 H), 3.93 (s, 1 H), 4.10 (br t, J = 2.1 Hz, 2 H), 4.63 (br t, J = 2.1 Hz, 1 H), 4.87 (d, J = 5.3 Hz, 1 H), 4.92 (d, J = 5.3 Hz, 1 H), 5.17 (d, J = 11.2 Hz, 1 H), 5.19 (d, J = 17.6 Hz, 1 H), 5.53 (dd, J = 11.2, 17.6 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ -5.2, -4.9, 17.8, 23.3, 25.5, 32.2, 35.0, 40.5, 48.8, 51.1, 63.5, 72.3, 90.2, 98.8, 115.2, 117.7, 137.9, 150.7, 200.7; IR (neat) 2930, 2200, 1726, 1682 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{21}$H$_{33}$NO$_4$SiNa 414.2077, found 414.2064.

8-(tert-Butyldimethylsilyloxy)-9-methyl-4,10-dioxo-9-vinylbicyclo[4.3.1]decane-1-carbonitrile (578). A solution of β-ketonitrile 576 (4.66 g, 11.9 mmol) in toluene (160 mL) was heated in a sealed tube at 165 °C for 45 min. The resulting solution was concentrated to afford the crude enone 577, which was used immediately without further purification; $^1$H NMR (200 MHz, CDCl$_3$) δ 0.16 (s, 3 H), 0.18 (s, 3 H), 0.97 (s, 9 H), 1.37 (s, 3 H), 1.89 (dt, J = 2.0, 13.8 Hz, 1 H), 2.02 (ddd, J = 3.2, 6.4, 13.8 Hz, 1 H), 2.41 (dd, J = 6.1, 17.9 Hz, 1 H), 3.19 (dd, J = 6.1, 17.9 Hz, 1 H), 3.38 (hextet, J = 6.1 Hz, 1 H), 3.75 (br t, J = 2.5 Hz, 1 H), 4.08 (s, 1 H), 5.28 (d, J = 10.8 Hz, 1 H), 5.29 (d, J = 17.9 Hz, 1 H), 5.64 (dd, J = 10.8, 17.9 Hz, 1 H), 5.88 (dd, J = 2.0, 9.5 Hz, 1 H), 6.24 (dd, J = 2.0, 17.7 Hz, 1 H), 6.38 (dd, J = 9.5, 17.7 Hz, 1 H). To the crude enone 577 was added a 1 : 1 solution of THF-MeOH (1.30 L) followed by Et$_3$N (8.30 mL, 59.5 mmol). The mixture was stirred at rt for 16 h. The resulting solution was concentrated. Purification by silica-gel chromatography (ethyl acetate-hexanes, 1 : 3) afforded
bicyclic ketone 578 as a white solid: mp 160 – 162 °C (3.39 g, 79%); ^1H NMR (400 MHz, CDCl3) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.82 (s, 9 H), 1.18 (s, 3 H), 1.94 – 2.08 (m, 2 H), 2.23 (ddd, J = 2.7, 5.5, 15.6 Hz, 1 H), 2.39 (ddd, J = 2.7, 13.2, 19.0 Hz, 1 H), 2.57 (ddd, J = 2.5, 5.5, 19.0 Hz, 1 H), 2.69 (dd, J = 7.8, 11.0 Hz, 1 H), 2.79 (dt, J = 2.5, 18.1 Hz, 1 H), 2.86 – 2.98 (m, 2 H), 4.49 (dd, J = 5.5, 11.0 Hz, 1 H), 5.34 (d, J = 17.3 Hz, 1 H), 5.36 (d, J = 10.9 Hz, 1 H), 5.87 (dd, J = 10.9, 17.3 Hz, 1 H); ^13C NMR (100 MHz, CDCl3) δ -4.7, -4.1, 14.5, 17.8, 25.5, 27.6, 35.5, 38.6, 42.8, 44.6, 50.0, 62.1, 66.9, 117.8, 118.9, 137.7, 203.5, 206.5; IR (neat) 2930, 2238, 1723 cm⁻¹; HRMS (MNa^+) calcd for C_{20}H_{31}NO_{3}SiNa 384.1971, found 384.1978.

3-Bromo-8-(tert-butyldimethylsilyloxy)-9-methyl-4,10-dioxo-9-vinylbicyclo[4.3.1]dec-2-ene-1-carbonitrile (585). To a solution of selenide 584 (93 mg, 0.16 mmol) in CH₂Cl₂ (2 mL) at -20 °C as added m-CPBA (44 mg, 0.19 mmol). The mixture was stirred at -20 °C for 1.5 h. To the resulting solution was added ethyl vinyl ether (89 µL, 0.93 mmol). The solution was warmed to rt and stirred 20 min. The resulting mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (CH₂Cl₂ – hexane, 3 : 2) afforded bromide 585 as a colorless oil (44 mg, 65%); ^1H NMR (200 MHz, CDCl₃) δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.80 (s, 9 H), 1.25 (s, 3 H), 1.90 – 2.20 (m, 2 H), 2.81 (dd, J = 4.9, 14.9 Hz, 1 H), 2.93 (dd, J = 5.5, 14.9 Hz, 1 H), 3.13 (m, 1
H), 3.95 (dd, J = 4.8, 11.5 Hz, 1 H), 5.39 (d, J = 17.3 Hz, 1 H), 5.44 (d, J = 10.9 Hz, 1 H), 5.65 (dd, J = 10.9, 17.3 Hz, 1 H), 6.85 (s, 1 H).

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\text{1-[8-(\text{tert-Butyldimethylsilyloxy})-1-cyano-9-methyl-4,10-dioxo-9-vinylbicyclo[4.3.1]dec-2-en-3-yl]-buta-1,3-dienyl}-\text{carbamic acid tert-butyl ester (586).} \]

To a solution of bromide 585 (31.1 mg, 0.071 mmol) and stannane 393 (42.2 mg, 0.092 mmol) in THF (1 mL) was added Cul (3.4 mg, 0.018 mmol) and Pd(PPh\textsubscript{3})\textsubscript{4} (4.1 mg, 0.0035 mmol). The mixture was heated to reflux for 1 h. Upon cooling to rt, the solution was filtered through a plug of silica-gel, washed with ether, and concentrated. Purification by silica-gel chromatography (ether-CH\textsubscript{2}Cl\textsubscript{2}, 2 : 98) provided triene 586 as a colorless oil (33.1 mg, 89%); \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \(\delta\) 0.02 (s, 3 H), 0.04 (s, 3 H), 0.73 (s, 9 H), 1.27 (s, 3 H), 1.39 (s, 9 H), 1.90 – 2.28 (m, 2 H), 2.90 (m, 1 H), 3.10 – 3.22 (m, 2 H), 4.38 (dd, J = 4.5, 11.2 Hz, 1 H), 5.06 (d, J = 10.1 Hz, 1 H), 5.19 (d, J = 16.7 Hz, 1 H), 5.38 (d, J = 10.9 Hz, 1 H), 5.41 (d, J = 17.3 Hz, 1 H), 5.87 (dd, J = 10.9, 17.3 Hz, 1 H), 5.88 (d, J = 10.1 Hz, 1 H), 6.12 (s, 1 H), 6.21 (s, 1 H), 6.22 (m, 1 H).
(2-[(5-(tert-Butyldimethylsilyloxy)-3-cyano-4-methyl-2-oxo-4-vinyl-cyclohexyl]acetyl]phenyl)carbamic acid tert-butyl ester (589). A solution of triene 586 (14.1 mg, 0.027 mmol) in toluene (1 mL) was heated to 110 °C for 1 h. The resulting solution was cooled to rt and concentrated to afford protected aniline 589 as a colorless oil (14 mg, 98%); ¹H NMR (200 MHz, CDCl₃) δ 0.18 (s, 6 H), 0.95 (s, 9 H), 1.39 (s, 3 H), 1.52 (s, 9 H), 1.70 – 2.05 (m, 2 H), 2.78 (m, 1 H), 3.50 – 3.70 (m, 2 H), 3.75 (m, 1 H), 4.11 (s, 1 H), 5.28 (d, J = 17.3 Hz, 1 H), 5.29 (d, J = 10.9 Hz, 1 H), 5.67 (dd, J = 10.9, 17.3 Hz, 1 H), 7.03 (t, J = 8.5 Hz, 1 H), 7.51 (t, J = 8.5 Hz, 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 8.46 (d, J = 8.5 Hz, 1 H).

8-(tert-Butyldimethylsilyloxy)-9-methyl-4,10-dioxo-9-vinylbicyclo-[4.3.1]decane-1-carboxylic acid amide (595). A solution of nitrile 578 (950 mg, 2.63 mmol) and Parkins catalyst¹⁴⁶ 593 (34 mg, 0.079 mmol) in 80% ethanol (15 mL) was heated to 90 °C for 36 h. The resulting mixture was cooled to rt, filtered through a plug of silica gel, washed with ether and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 1) afforded amide 595 as a colorless oil (897 mg, 90%); ¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.81 (s, 9 H), 1.04 (s, 3 H), 2.00 – 2.10 (m, 3 H), 2.44 (ddd, J = 1.8, 5.9, 19.0
Hz, 1 H), 2.58 (m, 1 H), 2.67 (dd, J = 9.7, 13.2 Hz, 1 H), 2.83 – 3.03 (m, 3 H), 4.43 (t, J = 7.3 Hz, 1 H), 4.96 (d, J = 17.3 Hz, 1 H), 5.15 (d, J = 10.9 Hz, 1 H), 6.01 (dd, J = 10.9, 17.3 Hz, 1 H), 6.05 (s, 1 H), 8.03 (s, 1 H); 13C NMR (100 MHz, CDCl₃) δ -4.6, -4.3, 15.5, 17.9, 25.5, 25.6, 36.1, 39.0, 44.7, 45.0, 51.7, 65.3, 67.7, 115.2, 139.2, 171.5, 208.3, 214.4; IR (neat) 3442, 2929, 1711, 1673 cm⁻¹; HRMS (MNa⁺) calcd for C₂₀H₃₃NO₄SiNa 402.2077, found 402.2070.

8-(tert-Butyldimethylsilyloxy)-6-isocyanato-7-methyl-7-vinylbicyclo-[4.3.1]decane-3,10-dione (600). A solution of amide 595 (453 mg, 1.19 mmol) and Pb(OAc)₄ (589 mg, 1.31 mmol) in DMF (12 mL) was heated to 90 °C for 30 min. The resulting mixture was cooled to rt, diluted with ether, and washed with saturated aqueous NaHCO₃. The ethereal layer was dried (Na₂SO₄) and concentrated to afford isocyanate 600 as a colorless oil (396 mg, 88%); ¹H NMR (200 MHz, CDCl₃) δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.00 (s, 3 H), 1.20 (m, 1 H), 1.89 – 2.10 (m, 2 H), 2.27 (m, 1 H), 2.44 (m, 1 H), 2.60 – 2.75 (m, 2 H), 2.90 – 3.05 (m, 2 H), 4.50 (dd, J = 7.1, 9.4 Hz, 1 H), 5.20 (d, J = 17.3 Hz, 1 H), 5.29 (d, J = 10.9 Hz, 1 H), 5.85 (dd, J = 10.9, 17.3 Hz, 1 H); IR (neat) 2930, 2234, 1719 cm⁻¹.
Cyclic carbamate 604. A solution of isocyanate 600 (21 mg, 0.056 mmol) and benzyl alcohol (27 µL, 0.26 mmol) in toluene (1 mL) was heated to reflux for 6 h. The resulting solution was concentrated to afford the crude diketal 603. The crude diketal 603 was cooled to 0 °C in DMF (1 mL) and NaH (60% dispersion in oil, 2.5 mg, 0.062 mmol) was added. The mixture was stirred at 0 °C for 10 min. To the resulting solution was added benzyl bromide (13 µL, 0.11 mmol). The mixture was warmed to rt and stirred 30 min. The resulting solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Recrystallization from isobutanol/hexane afforded 604 as a white solid: mp 136 – 139 °C (33 mg, 95%); ¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.83 (s, 9 H), 1.22 (s, 3 H), 1.51 – 1.90 (m, 5 H), 1.98 (ddd, J = 5.4, 11.6, 14.3 Hz, 1 H), 2.13 (m, 1 H), 2.46 (t, J = 13.2 Hz, 1 H), 2.91 (m, 1 H), 4.00 (dd, J = 4.7, 11.6 Hz, 1 H), 4.31 (d, J = 16.5 Hz, 1 H), 4.62 (d, J = 11.7 Hz, 1 H), 4.68 (d, J = 11.7 Hz, 1 H), 4.87 (d, J = 16.5 Hz, 1 H), 5.30 (d, J = 17.3 Hz, 1 H), 5.37 (d, J = 10.9 Hz, 1 H), 5.97 (dd, J = 10.9, 17.3 Hz, 1 H), 7.21 – 7.38 (m, 10 H).
6-Amino-8-(tert-butyldimethylsilyloxy)-7-methyl-7-vinylbicyclo-[4.3.1]decane-3,10-dione (608). To a solution of isocyanate 600 (681 mg, 1.80 mmol) in THF (24 mL) at 0 °C was added aqueous 1 M NaOH (12 mL). The mixture was warmed to rt and stirred 30 min. The resulting solution was quenched with brine and extracted with ethyl acetate. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 1) afforded amine 608 as a white solid: mp 129 – 131 °C (507 mg, 80%); $^1$H NMR (400 MHz, CDCl$_3$) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.83 (s, 9 H), 1.18 (s, 3 H), 1.54 (ddd, $J$ = 2.6, 5.5, 15.0 Hz, 1 H), 1.82 (br s, 2 H), 1.93 – 2.08 (m, 2 H), 2.30 – 2.48 (m, 2 H), 2.62 – 2.75 (m, 2 H), 2.85 (m, 1 H), 3.03 (dd, $J$ = 7.9, 13.2 Hz, 1 H), 4.58 (dd, $J$ = 5.5, 11.0 Hz, 1 H), 5.15 (d, $J$ = 17.3 Hz, 1 H), 5.31 (d, $J$ = 10.9 Hz, 1 H), 5.91 (dd, $J$ = 10.9, 17.3 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ -4.5, -4.1, 10.9, 18.0, 25.7, 31.4, 36.7, 38.0, 42.9, 44.4, 54.3, 67.9, 69.3, 117.7, 139.5, 209.0, 211.8; IR (neat) 3400, 2929, 1714 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{19}$H$_{34}$NO$_3$Si 352.2308, found 352.2302.
8-({\textit{tert}-Butyldimethylsilyloxy})-6-isothiocyanato-7-methyl-4-phenylselenyl-7-vinylbicyclo[4.3.1]decane-3,10-dione (616). To a solution of isothiocyanate 615 (110 mg, 0.28 mmol) in CH$_2$Cl$_2$ (3 mL) at 0 °C was added Et$_3$N (117 µL, 0.83 mmol) and TMSOTf (101 µL, 0.56 mmol). The mixture was stirred at 0 °C for 1 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude silyl enol ether, which was used without further purification. To the crude silyl enol ether in CH$_2$Cl$_2$ (3 mL) at 0 °C was added PhSeCl (59 mg, 0.31 mmol). The mixture was stirred at 0 °C for 20 min and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 9) afforded selenide 616 as a colorless oil (97 mg, 63% 2 steps); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.81 (s, 9 H), 1.00 (s, 3 H), 1.85 (ddd, $J$ = 1.6, 5.5, 14.1 Hz, 1 H), 1.94 (ddd, $J$ = 5.7, 11.0, 14.1 Hz, 1 H), 2.33 (dd, $J$ = 3.5, 15.6 Hz, 1 H), 2.42 – 2.58 (m, 2 H), 2.70 (dd, $J$ = 13.6, 15.6 Hz, 1 H), 2.92 (m, 1 H), 3.64 (dd, $J$ = 3.5, 13.6 Hz, 1 H), 4.20 (dd, $J$ = 5.5, 11.1 Hz, 1 H), 5.23 (d, $J$ = 17.3 Hz, 1 H), 5.35 (d, $J$ = 10.9 Hz, 1 H), 5.72 (dd, $J$ = 10.9, 17.3 Hz, 1 H), 7.33 – 7.47 (m, 3 H), 7.59 – 7.62 (m, 2 H); IR (neat) 2929, 2042, 1716 cm$^{-1}$. 
4-Bromo-8-(tert-butylidimethylsilyloxy)-6-isothiocyanato-7-methyl-7-vinylbicyclo[4.3.1]dec-4-ene-3,10-dione (617). To a solution of selenide 616 (60 mg, 0.11 mmol) in CCl₄ (2 mL) at -15 °C was added NBS (58 mg, 0.33 mmol). The mixture was warmed to rt and stirred for 6 h. The resulting solution was quenched with 10% aqueous Na₂S₂O₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (CH₂Cl₂) afforded α-bromoenone 617 as a colorless oil (47.5 mg, 93%); ¹H NMR (200 MHz, CDCl₃) δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.80 (s, 9 H), 1.10 (s, 3 H), 1.85 – 2.20 (m, 2 H), 2.81 (dd, J = 4.9, 14.9 Hz, 1 H), 2.93 (dd, J = 5.5, 14.9 Hz, 1 H), 3.19 (m, 1 H), 3.93 (dd, J = 4.9, 11.5 Hz, 1 H), 5.28 (d, J = 17.3 Hz, 1 H), 5.35 (d, J = 10.9 Hz, 1 H), 5.62 (dd, J = 10.9, 17.3 Hz, 1 H), 6.75 (s, 1 H).

N-[8-(tert-Butyldimethylsilyloxy)-9-methyl-4,10-dioxo-9-vinylbicyclo-[4.3.1]dec-1-yl]formamide (623). To a solution of amine 608 (725 mg, 2.06 mmol) in THF (20 mL) at 0 °C was added Et₃N (862 µL, 6.18 mmol) and formic acetic anhydride (810 µL, 10.3 mmol). The mixture was stirred at 0 °C for 1 h. The resulting solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were dried (Na₂SO₄) and
concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 1) afforded formamide 623 as a mixture of rotamers (727 mg, 93%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.03 (s, 3 H), 0.04 (s, 3 H), 0.80 (s, 9 H), 0.81 (s, 9 H), 0.89 (s, 3 H), 0.92 (s, 3 H), 1.98 – 2.12 (m, 2 H), 2.20 (m, 1 H), 2.40 (m, 1 H), 2.48 (m, 1 H), 2.69 (m, 1 H), 2.86 (m, 1 H), 2.95 (m, 1 H), 3.06 (m, 1 H), 3.40 (m, 1 H), 4.41 (dd, $J$ = 5.0, 8.7 Hz, 1 H), 4.54 (m, 1 H), 5.02 (d, $J$ = 17.3 Hz, 1 H), 5.18 (d, $J$ = 17.3 Hz, 1 H), 5.19 (d, $J$ = 17.3 Hz, 1 H), 5.40 (d, $J$ = 17.3 Hz, 1 H), 5.98 (dd, $J$ = 10.9, 17.3 Hz, 1 H), 6.26 (dd, $J$ = 10.9, 17.3 Hz, 1 H), 6.62 (s, 1 H), 6.84 (d, $J$ = 12.3 Hz, 1 H), 8.15 (d, $J$ = 12.3 Hz, 1 H), 8.26 (d, $J$ = 12.3 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -4.7, -4.6, -4.3, 11.3, 14.6, 17.8, 17.9, 24.6, 25.5, 25.6, 28.9, 36.0, 37.3, 38.2, 40.9, 41.9, 44.1, 44.8, 54.0, 54.8, 68.1, 68.7, 70.8, 115.4, 120.2, 137.9, 140.0, 160.1, 161.9, 206.7, 206.8, 208.3, 209.2; IR (neat) 3359, 2929, 1719, 1677 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{20}$H$_{33}$NO$_4$SiNa 402.2077, found 402.2083.

**$N$-[8-(tert-Butyldimethylsilyloxy)-9-methyl-4,10-dioxo-9-vinylbicyclo-[4.3.1]dec-2-en-1-yl]formamide (624).** To a solution of formamide 623 (300 mg, 0.79 mmol) in CH$_2$Cl$_2$ (8 mL) at 0 °C was added Et$_3$N (330 µL, 2.37 mmol) and TMSOTf (301 µL, 2.37 mmol). The mixture was stirred at 0 °C for 1 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude silyl enol ether, which was used without further purification. To a suspension of IBX (664 mg, 2.37 mmol) in DMSO (3 mL) was added MPO (297
mg, 2.37 mmol). The mixture was stirred for 15 min until all solids were dissolved. To the resultant solution was added the crude silyl enol ether in CH₂Cl₂ (0.5 mL). The solution was stirred at rt for 3 h. The resultant mixture was diluted with ether and washed with saturated aqueous NaHCO₃. The ethereal layer was dried (Na₂SO₄) and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 1 : 1) afforded enone 624 (mixture of amide rotamers) as a white solid: mp 78 – 80 °C (235 mg, 79% 2 steps); ¹H NMR (400 MHz, CDCl₃) δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.79 (s, 9 H), 1.00 (s, 3 H), 1.89 – 2.17 (m, 2 H), 2.62 – 2.80 (m, 2 H), 3.12 (m, 1 H), 4.10 (m, 1 H), 5.12 (d, J = 17.3 Hz, 1 H), 5.19 (d, J = 17.3 Hz, 1 H), 5.28 (d, J = 10.9 Hz, 1 H), 5.34 (d, J = 10.9 Hz, 1 H), 5.71 (dd, J = 10.9, 17.3 Hz, 1 H), 6.80 (dd, J = 10.9, 17.3 Hz, 1 H), 6.09 (m, 1 H), 6.25 (m, 1 H), 6.48 (d, J = 13.3 Hz, 1 H), 8.15 (d, J = 12.0 Hz, 1 H), 8.26 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ -4.8, -4.4, -4.3, 11.2, 11.4, 17.8, 25.5, 25.6, 25.7, 25.9, 34.9, 35.0, 43.6, 43.7, 44.9, 46.2, 52.0, 52.3, 68.4, 72.0, 72.7, 117.9, 119.6, 130.4, 132.9, 137.7, 138.5, 140.5, 141.7, 161.0, 164.4, 199.2, 200.1, 201.0, 202.8; IR (neat) 3350, 2929, 1731, 1668 cm⁻¹; HRMS (MNa⁺) calcd for C₂₀H₃₁NO₄SiNa 400.1920, found 400.1912.

\[ \text{N-[3-Bromo-8-(tert-butyldimethylsilyloxy)-9-methyl-4,10-dioxo-9-vinylbicyclo[4.3.1]dec-2-en-1-yl]formamide (625).} \]

To a solution of enone 624 (170 mg, 0.45 mmol) in CH₂Cl₂ (5 mL) at -78 °C was added Et₃N (188 µL, 1.35 mmol) and Br₂ (46 µL, 0.90 mmol). The mixture was warmed to rt over 20 min and stirred for 1 h. The resulting solution was quenched with saturated aqueous
Na$_2$S$_2$O$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude dibromide, which was used without further purification. To a solution of the crude dibromide in CH$_3$CN (5 mL) was added Cs$_2$CO$_3$ (293 mg, 0.90 mmol). The mixture was stirred at rt for 1 h. The resulting mixture was filtered through a plug of silica gel, washed with ether, and concentrated. Purification by silica gel chromatography (ethyl acetate – hexane, 2 : 3) afforded bromoenone 625 (mixture of amide rotamers) as a yellow solid: mp 71 – 73 ºC (175 mg, 85%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ -0.08 (s, 3 H), -0.05 (s, 3 H), 0.77 (s, 9 H), 0.98 (s, 3 H), 1.93 – 2.10 (m, 2 H), 2.77 – 2.95 (m, 2 H), 3.10 (m, 1 H), 4.03 (dd, $J$ = 5.7, 11.1 Hz, 1 H), 5.17 (d, $J$ = 17.3 Hz, 1 H), 5.22 (d, $J$ = 17.3 Hz, 1 H), 5.31 (d, $J$ = 10.9 Hz, 1 H), 5.39 (d, $J$ = 10.9 Hz, 1 H), 5.69 (dd, $J$ = 10.9, 17.3 Hz, 1 H), 6.73 (dd, $J$ = 10.9, 17.3 Hz, 1 H), 6.25 (s, 1 H), 6.80 (s, 1 H), 7.10 (s, 1 H), 8.18 (d, $J$ = 12.0 Hz, 1 H), 8.25 (s, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -4.9, -4.4, -4.0, 11.1, 11.2, 17.8, 25.5, 25.6, 34.5, 34.6, 43.7, 43.8, 44.3, 45.8, 52.7, 53.2, 68.2, 72.1, 72.6, 118.5, 120.0, 123.6, 126.4, 128.1, 128.9, 137.5, 138.1, 141.1, 143.3, 161.2, 164.1, 193.2, 193.6, 199.4, 201.5; IR (neat) 3332, 2929, 1734, 1683 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{20}$H$_{30}$NO$_4$SiBrNa 478.1025, found 478.1029.
8,10-Bis-(tert-butylidimethylsilyloxy)-9-methyl-4-(trimethylsilyloxy)-9-vinylbicyclo[4.3.1]dec-3-ene-1-carbonitrile (634). To a solution of ketone 578 (1.32 g, 3.65 mmol) in CH$_2$Cl$_2$ (36 mL) at 0 °C was added Et$_3$N (1.53 mL, 10.9 mmol) followed by TMSOTf (1.32 mL, 7.30 mmol). The mixture was stirred at 0 °C for 90 min. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude silyl enol ether 582, which was used without further purification; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.20 (s, 9 H), 0.83 (s, 9 H), 1.23 (s, 3 H), 1.93 – 2.07 (m 2 H), 2.35 – 2.49 (m, 3 H), 2.82 (dd, $J$ = 8.3, 15.8 Hz, 1 H), 2.92 (m, 1 H), 4.84 (dd, $J$ = 6.2, 10.9 Hz, 1 H), 4.95 (dd, $J$ = 5.6, 8.3 Hz, 1 H), 5.33 (d, $J$ = 17.3 Hz, 1 H), 5.35 (d, $J$ = 10.9 Hz, 1 H), 5.82 (dd, $J$ = 10.9, 17.3 Hz, 1 H). To the crude silyl enol ether 582 in THF (25 mL) at -78 °C was added LiAlH(O-tBu)$_3$ (1.0 M in THF, 5.47 mL, 5.47 mmol) dropwise over 5 min. The resulting mixture was warmed to 0 °C over 1 h and stirred at 0 °C an additional 1 h. The solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude alcohol 633 as a 9 : 1 mixture of diastereomers, which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) major diastereomer δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.18 (s, 9 H), 0.82 (s, 9 H) 1.48 (s, 3 H), 1.59 (m, 1 H), 2.05 – 2.65 (m, 6 H), 3.89 (br s, 1 H), 4.64 (dd, $J$ = 5.5, 11.6 Hz, 1 H), 4.78 (m, 1 H), 5.27 (d, $J$ = 17.5 Hz, 1 H), 5.29 (d, $J$ = 10.7 Hz, 1 H), 5.77 (dd, $J$ = 10.7, 17.5 Hz, 1 H). To a solution of the crude alcohol 633 in CH$_2$Cl$_2$ (5 mL) was added Et$_3$N (1.53 mL, 10.9 mmol) followed by TBSOTf (1.68 mL, 7.30 mmol). The mixture was stirred at rt for 3 h. The resulting
solution was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexanes, 3 : 97) afforded 634 as a colorless oil (1.48 g, 74% 3 steps); ¹H NMR (300 MHz, CDCl₃) δ -0.03 (s, 3 H), 0.02 (s, 3 H), 0.10 (s, 3 H) 0.19 (s, 9 H), 0.20 (s, 3 H), 0.83 (s, 9 H), 0.95 (s, 9 H), 1.46 (s, 3 H), 1.53 (m, 1 H), 2.03 – 2.18 (m, 3 H), 2.33 (dt, J = 2.8, 16.2 Hz, 1 H), 2.52 (m, 1 H), 2.54 (dd, J = 9.5, 16.2 Hz, 1 H), 3.82 (br s, 1 H), 4.64 (dd, J = 5.5, 11.7 Hz, 1 H), 4.78 (m, 1 H), 5.23 (dd, J = 0.9, 10.8 Hz, 1 H), 5.26 (dd, J = 0.9, 17.4 Hz, 1 H), 5.75 (dd, J = 10.8, 17.4 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ -5.0, -4.7, -4.6, -4.0, 0.3, 17.0, 17.9, 18.0, 25.8, 25.9, 31.3, 33.3, 37.6, 39.1, 46.7, 52.4, 69.9, 79.0, 102.8, 116.5, 122.4, 143.6, 156.6; IR (neat) 2929, 2238, 1664 cm⁻¹; HRMS (MNa⁺) calcd for C₂₉H₅₅NO₅Si₃Na 572.3388, found 572.3394.

8,10-Bis-(tert-butyldimethylsilyloxy)-9-methyl-4-oxo-3-phenylselenyl-9-vinylbicyclo[4.3.1]decane-1-carbonitrile (635a). To a solution of silyl enol ether 634 (1.48 g, 2.69 mmol) in CH₂Cl₂ (27 mL) at -78 °C was added phenylselenyl chloride (567 mg, 2.96 mmol) in CH₂Cl₂ (5 mL) dropwise over 2 min. The mixture was warmed to rt over 30 min. The resulting solution was concentrated to afford the crude α-selenyl ketone as a mixture of diastereomers (4 : 1). The mixture of α-selenyl ketones was dissolved in CH₂Cl₂ (40 mL) and Cs₂CO₃ (2.63 g, 8.08 mmol) was added. The mixture was stirred at rt for 3 h. The resulting solution was filtered and concentrated. Purification by silica-gel...
chromatography (CH$_2$Cl$_2$-hexane, 2 : 1) afforded the desired $\alpha$-selenyl ketone 635a as a white solid: mp 53 – 55 °C (1.14 g, 67%); $^1$H NMR (300 MHz, CDCl$_3$) δ -0.02 (s, 3 H), -0.01 (s, 3 H), 0.01 (s, 3 H), 0.12 (s, 3 H), 0.82 (s, 9 H), 0.89 (s, 9 H), 1.42 (s, 3 H), 1.45 (m, 1 H), 1.95 – 2.40 (m, 5 H), 2.47 (dd, $J = 3.9$, 16.0 Hz, 1 H), 3.67 (dd, $J = 3.9$, 13.6 Hz, 1 H), 3.82 (br s, 1 H), 3.89 (dd, $J = 4.7$, 11.6 Hz, 1 H), 5.27 (d, $J = 17.3$ Hz, 1 H), 5.30 (d, 11.0 Hz, 1 H), 5.72 (dd, $J = 11.0$, 17.3 Hz, 1 H), 7.33 – 7.48 (m, 3 H), 7.57 – 7.64 (m, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ -5.1, -5.0, -4.7, -3.8, 17.7, 17.9, 18.0, 25.6, 25.7, 29.6, 35.6, 36.9, 40.1, 44.7, 46.6, 49.8, 68.3, 71.7, 117.8, 121.9, 124.7, 129.4, 129.8, 137.5, 141.8, 205.7; IR (neat) 2929, 2238, 1707 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{32}$H$_{51}$NO$_3$Si$_2$SeNa 656.2470, found 656.2473.

3-Bromo-8,10-bis-(tert-butyldimethylsilyloxy)-9-methyl-4-oxo-9-vinylbicyclo[4.3.1]dec-2-ene-1-carbonitrile (636). To a solution of selenide 635a (633 mg, 1.00 mmol) in CCl$_4$ (20 mL) at -15 °C was added NBS (623 mg, 3.50 mmol). The mixture was warmed to rt and stirred for 2.5 h. The resulting solution was quenched with 10% aqueous Na$_2$S$_2$O$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (CH$_2$Cl$_2$-hexane, 1 : 1) afforded $\alpha$-bromoenone 636 as a white solid: mp 122 – 124 °C (439 mg, 79%); $^1$H NMR (400 MHz, CDCl$_3$) δ -0.07 (s, 3 H), -0.01 (s, 3 H), 0.12 (s, 3 H), 0.22 (s, 3 H), 0.81 (s, 9 H), 0.96 (s, 9 H), 1.50 (s, 3 H), 1.57 (m, 1 H), 2.21 (dt, $J = 5.6$, 13.1 Hz, 1 H), 2.39 (m, 1 H), 2.76 (dd, $J = 5.3$, 14.9 Hz, 1 H), 2.81 (dd, $J = 4.9$, 14.9 Hz, 1 H), 3.55 (dd, $J = 4.3$, 3.55 Hz, 1 H).
12.2 Hz, 1 H), 4.22 (br s, 1 H), 5.32 (d, J = 10.7 Hz, 1 H), 5.36 (d, J = 17.3 Hz, 1 H), 5.55 (dd, J = 10.7, 17.3 Hz, 1 H), 6.90 (s, 1 H); 13C NMR (100 MHz, CDCl₃) δ -5.1, -4.9, -4.7, -4.1, 15.5, 17.9, 18.0, 25.6, 25.7, 30.5, 38.0, 46.7, 47.6, 57.5, 68.6, 72.7, 118.7, 119.4, 126.1, 139.3, 141.6, 194.6; IR (neat) 2929, 2238, 1688 cm⁻¹; HRMS (MNa⁺) calcd for C₂₆H₄₄NO₅Si₂BrNa 576.1941, found 576.1933.

3-Bromo-8,10-bis-(tert-butylidimethylsilyloxy)-5,5,9-trimethyl-4-oxo-9-vinylbicyclo[4.3.1]dec-2-ene-1-carbonitrile (641). To a solution of enone 636 (300 mg, 0.54 mmol) in THF (5.5 mL) at -78 °C was added LiHMDS (1.0 M in THF, 650 µL, 0.65 mmol) dropwise. The mixture was stirred at -78 °C for 1 h. To the resulting enolate was added MeI (337 µL, 5.41 mmol). The mixture was warmed to rt over 20 min and stirred an additional 1 h at rt. The resulting solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude monomethylated enone 640 which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ -0.02 (s, 3 H), 0.01 (s, 3 H), 0.08 (s, 3 H), 0.18 (s, 3 H), 0.83 (s, 9 H), 0.94 (s, 9 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.50 (s, 3 H), 1.52 (m, 1 H), 2.02 (m, 1 H), 2.25 (dt, J = 5.6, 13.1 Hz, 1 H), 2.76 (m, 1 H), 3.70 (dd, J = 4.0, 11.9 Hz, 1 H), 4.17 (br s, 1 H), 5.33 (d, J = 10.7 Hz, 1 H), 5.36 (d, J = 17.1 Hz, 1 H), 5.64 (dd, J = 10.7, 17.1 Hz, 1 H), 6.76 (s, 1 H). To the crude monomethyl ketone 640 in THF (5.5 mL) at -78 °C was added LiHMDS (1.0 M in THF, 650 µL, 0.65 mmol) dropwise. The mixture was warmed to -20 °C stirred for 2 h. The resulting enolate was cooled to -78 °C and MeI (337 µL, 5.41 mmol) was added. The
mixture was warmed to rt over 20 min and stirred an additional 1 h at rt. The resulting solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (CH₂Cl₂-hexane, 1 : 1) afforded the dimethylated enone 641 as a white solid: mp 57 – 59 °C (262 mg, 83%); ¹H NMR (400 MHz, CDCl₃) δ -0.08 (s, 3 H), 0.00 (s, 3 H), 0.15 (s, 3 H), 0.25 (s, 3 H), 0.81 (s, 9 H), 0.96 (s, 9 H), 1.30 (s, 3 H), 1.34 (s, 3 H), 1.48 (s, 3 H), 1.74 (m, 1 H), 2.00 (m, 1 H), 2.09 (ddd, J = 5.6, 12.5, 14.2 Hz, 1 H), 3.39 (dd, J = 4.0, 12.5 Hz, 1 H), 4.54 (br s, 1 H), 5.29 (d, J = 10.7 Hz, 1 H), 5.32 (d, J = 17.3 Hz, 1 H), 5.54 (dd, J = 10.7, 17.3 Hz, 1 H), 6.75 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ -5.0, -4.8, -4.4, -4.1, 15.7, 17.8, 17.9, 25.2, 25.6, 25.7, 26.0, 26.4, 48.0, 48.4, 51.2, 56.8, 68.3, 69.2, 118.5, 120.2, 125.0, 135.7, 141.5, 199.9; IR (neat) 2895, 2233, 1694 cm⁻¹; HRMS (MNa⁺) calcd for C₂₈H₄₈NO₃Si₂BrNa 604.2254, found 604.2249.

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\{1-[8,10-Bis-(\text{tert-butyldimethylsilyloxy})-1-cyano-5,5,9-trimethyl-4-oxo-9-vinylbicyclo[4.3.1]dec-2-en-3-yl]-buta-1,3-dienyl}carbamic acid tert-butyl ester (642). To a solution of bromoenone 641 (262 mg, 0.45 mmol) and stannane 393 (247 mg, 0.54 mmol) in DMSO (4 mL) and THF (1 mL) at rt was added LiCl (95 mg, 2.25 mmol), CuCl (178 mg, 1.80 mmol), and Pd(PPh₃)₄ (52 mg, 0.045 mmol). The mixture was stirred at rt for 4 h. The resulting solution was quenched with saturated aqueous NaHCO₃ and ether. The mixture was filtered through a plug of celite and washed with ether. The organic layer was washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated.
Purification by silica-gel chromatography (CH$_2$Cl$_2$) afforded enecarbamate 642 as a colorless oil (227 mg, 75%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ -0.04 (s, 3 H), 0.03 (s, 3 H), 0.17 (s, 3 H), 0.27 (s, 3 H), 0.83 (s, 9 H), 0.96 (s, 9 H), 1.26 (s, 3 H), 1.34 (s, 3 H), 1.47 (s, 9 H), 1.51 (s, 3 H), 1.77 (m, 1 H), 2.01 (m, 1 H), 2.11 (m, 1 H), 3.53 (dd, $J$ = 4.1, 12.4 Hz, 1 H), 4.61 (br s, 1 H), 5.07 (d, $J$ = 10.1 Hz, 1 H), 5.23 (d, $J$ = 10.7 Hz, 1 H), 5.24 (d, $J$ = 16.7 Hz, 1 H), 5.32 (d, $J$ = 17.3 Hz, 1 H), 5.64 (dd, $J$ = 10.7, 17.3 Hz, 1 H), 6.20 (s, 1 H), 6.37 (dt, $J$ = 10.1, 16.7 Hz, 1 H), 6.63 (s, 1 H), 6.65 (d, $J$ = 10.1 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -4.8, -4.7, -4.4, -4.0, 15.8, 17.9, 18.0, 24.6, 25.7, 25.8, 26.2, 26.5, 28.3, 48.2, 48.9, 51.2, 56.0, 68.5, 69.8, 80.5, 117.6, 118.2, 120.5, 131.7, 134.6, 135.1, 137.2, 137.6, 142.1, 152.6, 206.4; IR (neat) 3389, 2955, 2238, 1713 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{37}$H$_{62}$N$_2$O$_5$Si$_2$Na 693.4095, found 693.4072.

[12,14-Bis-(tert-butyldimethylsilyloxy)-1-cyano-9,9,13-trimethyl-8-oxo-13-vinyltricyclo[8.3.1.0]tetradeca-2,4,6-trien-6-yl]carbamic acid tert-butyl ester (643). A solution of enecarbamate 642 (225 mg, 0.34 mmol) in toluene (14 mL) was heated to 110 °C for 3 h. The resulting solution was concentrated to afford the crude cyclohexadiene, which was used without further purification. To the crude cyclohexadiene in dioxane (10 mL) was added DDQ (380 mg, 1.68 mmol). The mixture was heated at 95 °C for 20 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO$_3$, dried
(Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 19) afforded the Boc protected aniline 643 as a colorless oil (188 mg, 84%); ¹H NMR (300 MHz, CDCl₃) δ -0.16 (s, 3 H), 0.03 (s, 3 H), 0.12 (s, 3 H), 0.23 (s, 3 H), 0.80 (s, 9 H), 0.99 (s, 9 H), 1.16 (s, 3 H), 1.38 (s, 3 H), 1.48 (s, 9 H), 1.62 (s, 3 H), 1.82 (m, 1 H), 2.07 (m, 1 H), 2.20 (ddd, J = 5.1, 12.4, 14.0 Hz, 1 H), 3.69 (dd, J = 4.1, 12.4 Hz, 1 H), 4.58 (br s, 1 H), 4.74 (dd, J = 10.8, 17.2 Hz, 1 H), 4.97 (dd, J = 1.0, 10.8 Hz, 1 H), 5.15 (dd, J = 1.0, 17.2 Hz, 1 H), 7.40 (t, J = 8.2 Hz, 1 H), 7.69 (dd, J = 1.0, 8.2 Hz, 1 H), 7.84 (s, 1 H), 8.00 (dd, J = 1.0, 8.2 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ -4.8, -4.7, -4.3, -4.1, 16.3, 17.8, 18.0, 25.2, 25.5, 25.6, 25.7, 25.9, 28.3, 47.6, 49.9, 51.2, 63.0, 68.1, 70.1, 80.7, 116.7, 120.2, 123.8, 127.3, 130.3, 130.9, 131.7, 137.6, 142.7, 153.1, 212.1; IR (neat) 3425, 2931, 2238, 1735, 1664 cm⁻¹; HRMS (MNa⁺) calcd for C₃₇H₆₀N₂O₅Si₂Na 691.3939, found 691.3916.

6-Amino-12,14-bis-(tert-butyldimethylsilyloxy)-9,9,13-trimethyl-8-oxo-13-vinyltricyclo[8.3.1.0]tetradeca-2,4,6-triene-1-carbonitrile (644). To a solution of BOC protected aniline 643 (125 mg, 0.19 mmol) in CH₂Cl₂ (5 mL) at -50 °C was added TFA (500 µL). The mixture was warmed to rt over 20 min and stirred for 1.5 h. The resulting solution was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 20) afforded aniline 644 as a colorless oil (104 mg, 98%); ¹H NMR
(300 MHz, CDCl$_3$) $\delta$ -0.15 (s, 3 H), 0.03 (s, 3 H), 0.13 (s, 3 H), 0.24 (s, 3 H), 0.80 (s, 9 H), 0.99 (s, 9 H), 1.17 (s, 3 H), 1.35 (s, 3 H), 1.61 (s, 3 H), 1.82 (m, 1 H), 2.03 (m, 1 H), 2.18 (dd, $J = 5.2, 12.4, 14.0$ Hz, 1 H), 3.80 (dd, $J = 4.1, 12.4$ Hz, 1 H), 4.60 (br s, 1 H), 4.71 (br s, 2 H), 4.80 (dd, $J = 10.8, 17.0$ Hz, 1 H), 4.94 (dd, $J = 1.4, 10.8$ Hz, 1 H), 5.12 (dd, $J = 1.4, 17.0$ Hz, 1 H), 6.69 (dd, $J = 1.1, 8.0$ Hz, 1 H), 7.15 (t, $J = 8.0$ Hz, 1 H), 7.34 (dd, $J = 1.1, 8.0$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -4.7, -4.6, -4.3, -4.1, 16.3, 17.8, 18.0, 25.5, 25.6, 25.8, 25.9, 26.0, 47.6, 49.8, 51.0, 63.1, 68.3, 70.2, 116.3, 117.9, 120.5, 121.6, 123.0, 131.3, 132.5, 142.8, 147.7, 211.2; IR (neat) 3486, 3383, 2930, 2238, 1776, 1720, 1661 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{32}$H$_{53}$N$_2$O$_3$Si$_2$ 569.3595, found 569.3541.

$N$-Acetylindole 646. To a solution of aniline 644 (50.4 mg, 0.089 mmol) in MeOH (2 mL) at rt was added NaOAc (36 mg, 0.44 mmol), HOAc (51 $\mu$L, 0.89 mmol), and glyoxylic acid monohydrate (20 mg, 0.22 mmol). The mixture was cooled to -10 °C and NaCNBH$_3$ (11 mg, 0.18 mmol) was added. The reaction mixture was warmed to 0 °C over 1 h. The resulting solution was quenched with saturated aqueous KH$_2$PO$_4$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude acid 645 which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ -0.15 (s, 3 H), 0.03 (s, 3 H), 0.12 (s, 3 H), 0.24 (s, 3 H), 0.80 (s, 9 H), 0.99 (s, 9 H), 1.16 (s, 3 H), 1.38 (s, 3 H), 1.62 (s, 3 H), 1.83 (m, 1 H), 2.05 (m, 1 H), 2.18 (dt, $J = 5.3, 12.2$ Hz, 1 H), 3.81 (dd, $J = 3.8, 12.2$ Hz, 1 H), 3.96 (br s, 2 H), 4.61 (br s, 1 H), 4.79
(dd, \( J = 10.7, 16.8 \text{ Hz}, 1 \text{ H} \)), 4.95 (d, \( J = 10.7 \text{ Hz}, 1 \text{ H} \)), 5.14 (d, \( J = 16.8 \text{ Hz}, 1 \text{ H} \)), 6.61 (d, \( J = 8.2 \text{ Hz}, 1 \text{ H} \)), 7.27 (t, \( J = 8.2 \text{ Hz}, 1 \text{ H} \)), 7.40 (d, \( J = 8.2 \text{ Hz}, 1 \text{ H} \)), 11.8 (br s, 1 H). To the crude acid was added Et\(_3\)N (1 mL) followed by Ac\(_2\)O (1 mL) at rt. The mixture was heated to 130 °C for 30 min. The resulting solution was cooled to rt and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded \( N \)-acetylindole \( \text{646} \) as a white solid: mp 140 – 143 °C (36.5 mg, 68% 2 steps); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) -0.42 (s, 3 H), -0.19 (s, 3 H), 0.15 (s, 3 H), 0.25 (s, 3 H), 0.72 (s, 9 H), 1.02 (s, 9 H), 1.36 (s, 3 H), 1.62 (s, 3 H), 1.63 (s, 3 H), 1.89 (br dd, \( J = 4.0, 14.2 \text{ Hz}, 1 \text{ H} \)), 2.14 (br d, \( J = 6.3 \text{ Hz}, 1 \text{ H} \)), 2.25 (ddd, \( J = 6.3, 12.6, 14.2 \text{ Hz}, 1 \text{ H} \)), 2.66 (s, 3 H), 3.46 (dd, \( J = 4.0, 12.6 \text{ Hz}, 1 \text{ H} \)), 4.19 (dd, \( J = 10.8, 17.3 \text{ Hz}, 1 \text{ H} \)), 4.80 (br s, 1 H), 4.95 (dd, \( J = 0.9, 10.8 \text{ Hz}, 1 \text{ H} \)), 5.16 (dd, \( J = 0.9, 17.3 \text{ Hz}, 1 \text{ H} \)), 7.32 (s, 1 H), 7.33 (t, \( J = 8.0 \text{ Hz}, 1 \text{ H} \)), 7.64 (dd, \( J = 0.9, 8.0 \text{ Hz}, 1 \text{ H} \)), 8.52 (d, \( J = 8.0 \text{ Hz}, 1 \text{ H} \)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) -4.9, -4.7, -4.1, -3.9, 15.2, 17.8, 18.1, 24.3, 25.6, 26.0, 26.9, 29.3, 35.5, 37.0, 49.1, 53.1, 61.0, 68.5, 70.7, 116.0, 116.5, 120.8, 121.9, 124.4, 126.8, 127.1, 127.9, 131.0, 136.3, 144.0, 168.2; IR (neat) 2929, 2226, 1711 cm\(^{-1}\); HRMS (MNH\(_4^+\)) calcd for C\(_{35}\)H\(_{58}\)N\(_3\)O\(_3\)Si\(_2\) 624.4017, found 624.3968.
**Amide 647.** To a solution of nitrile 646 (16 mg, 0.026 mmol) in EtOH-H$_2$O (4 : 1) (265 µL) was added [PtH(PMe$_2$OH)(PMe$_2$O)$_2$H] 593 (4.5 mg, 0.011 mmol). The mixture was heated in a sealed tube at 100 °C for 60 h. The resulting solution was diluted with ether, filtered through a plug of silica-gel, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) afforded amide 647 as a mixture of N-acetyl rotamers (12.0 mg, 73%); $^1$H NMR (300 MHz, CDCl$_3$) δ -0.52 (s, 3 H), -0.27 (s, 3 H), 0.13 (s, 3 H), 0.15 (s, 3 H), 0.71 (s, 9 H), 0.93 (s, 9 H), 1.43 (s, 3 H), 1.60 (s, 3 H), 1.73 (s, 3 H), 1.88 (m, 1 H), 2.11 – 2.28 (m, 2 H), 2.64 (s, 3 H), 3.37 (br d, $J$ = 12.6 Hz, 1 H), 4.95 (br dd, $J$ = 11.0, 17.4 Hz, 1 H), 5.10 (br d, $J$ = 11.0 Hz, 1 H), 5.22 (br d, $J$ = 17.4 Hz, 1 H), 5.37 (br s, 1 H), 5.96 (br s, 1 H), 6.89 (br s, 1 H), 7.17 – 7.40 (m, 3 H), 8.47 (br d, $J$ = 8.8 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ -5.0, -4.9, -4.8, -4.4, 14.1, 17.8, 18.3, 24.3, 25.7, 26.1, 27.4, 29.7, 35.8, 36.4, 48.3, 52.4, 67.4, 69.3, 72.3, 115.5, 115.6, 121.7, 124.2, 126.7, 128.9, 131.6, 131.9, 136.5, 147.0, 168.2, 176.7; IR (neat) 3461, 3166, 2927, 1709, 1684 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{35}$H$_{56}$N$_2$O$_4$Si$_2$Na 647.3676, found 647.3661.
Isocyanate 648. To a solution of amide 647 (8.5 mg, 0.014 mmol) in DMF (0.5 mL) was added Pb(OAc)$_4$ (9.1 mg, 0.020 mmol). The mixture was heated at 90 °C for 15 min. The resulting solution was cooled to rt, diluted with ether, and washed with H$_2$O. The ethereal layer was dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded isocyanate 648 as a colorless oil (6.6 mg, 78%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ -0.46 (s, 3 H), -0.21 (s, 3 H), 0.14 (s, 3 H), 0.21 (s, 3 H), 0.71 (s, 9 H), 1.01 (s, 9 H), 1.34 (s, 3 H), 1.50 (s, 3 H), 1.62 (s, 3 H), 1.89 (dd, $J$ = 3.9, 14.0 Hz, 1 H), 2.15 (br d, $J$ = 6.8 Hz, 1 H), 2.23 (ddd, $J$ = 6.8, 12.4, 14.0 Hz, 1 H), 2.65 (s, 3 H), 3.43 (dd, $J$ = 3.9, 12.4 Hz, 1 H), 4.20 (dd, $J$ = 10.9, 17.4 Hz, 1 H), 4.55 (s, 1 H), 4.95 (d, $J$ = 10.9 Hz, 1 H), 5.06 (d, $J$ = 17.4 Hz, 1 H), 7.29 (s, 1 H), 7.33 (t, $J$ = 8.0 Hz, 1 H), 7.51 (d, $J$ = 8.0 Hz, 1 H), 8.50 (d, $J$ = 8.0 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -4.9, -4.7, -4.2, -4.0, 13.2, 17.8, 18.1, 24.3, 25.7, 26.0, 27.0, 29.6, 35.5, 36.8, 52.1, 53.9, 69.5, 73.2, 74.0, 115.8, 116.2, 121.5, 122.9, 124.2, 125.9, 126.6, 131.5, 131.8, 136.2, 144.0, 168.2; IR (neat) 2927, 2276, 1713 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{35}$H$_{55}$N$_2$O$_4$Si$_2$ 623.370, found 623.370.
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