Published in final edited form as:

Tetrahedron. 2013 July 8; 69(27-28): 5588–5603. doi:10.1016/j.tet.2013.03.010.

Studies toward welwitindolinones: formal syntheses of *N*-methylwelwitindolinone C isothiocyanate and related natural products

Tsung-hao Fu, William T. McElroy, Mariam Shamszad, Richard W. Heidebrecht Jr., Brian Gulledge, and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station A5300, Austin, TX 78712-0165, USA

Abstract

The formal syntheses of *N*-methylwelwitindolinone C isothiocyanate (**4**) and several other welwitindolinones **5–8** were achieved by the independent synthesis of **79**. The synthesis featured a Lewis acid-mediated coupling between a heteroaryl carbinol and bis-TMS enol ether, an intramolecular enolate arylation, and an unprecedented intramolecular allylic alkylation of a γ -acyloxyenone.

Keywords

Alkaloids; Allylic alkylation; Lewis acid-mediated coupling; Welwitindolinones; Enolate arylation

1. Introduction

In 1994 Moore and co-workers isolated alkaloids **1–5** (Fig. 1), which were collectively named welwitindolinones, from the Micronesian blue-green algae *Hapalosiphon welwitschii*.¹ These novel alkaloids possess a unique bicyclo[4.3.1]decane skeleton that is densely functionalized with a bridgehead isothiocyanate or isonitrile, a vinyl or alkyl chloride, a vinyl group, and an oxindole. The core structure of these alkaloids also contained two contiguous fully substituted carbon atoms, which poses a significant challenge for organic synthesis. In 1999 Moore isolated the three additional structurally-related welwitindolinones **6–8** from cyanophytes *Fischerella muscicola* and *Fischerella major*.²

The welwitindolinones exhibit various useful biological activities, which include reversal of P-glycoprotein-mediated multiple drug resistance in human cancer cell lines, induction of microtubule depolymerization, and insecticidal activity.^{3,4} Of the members of the welwitindolinone family, *N*-methylwelwitindolinone C isothiocyanate (**4**) was found to be the most effective in reversing P-glycoprotein-mediated multiple drug resistance. Because of the combination of its novel structural and biological properties, **4** has attracted the attention of numerous laboratories in the synthetic community, and these efforts have collectively resulted in a myriad of publications.⁵ However, the challenges associated with preparing these compounds are reflected by the fact that the total syntheses of **4–8** were only recently reported.⁶

We began our investigations toward the syntheses of the welwitindolinone alkaloids with goals of developing an efficient entry to these compounds that could be adapted for analog synthesis and of discovering new and generally useful C–C bond constructions. In particular, we were interested in extending the scope of transition metal-catalyzed allylic alkylations to include complex ketoesters and ketones. During the course of this endeavor, we also discovered a useful means of preparing β -heteroaryl carbonyl compounds. We now wish to report the details of these studies that ultimately led to formal syntheses of several natural welwitindolinones.⁷

2. Results and discussion

2.1. First generation approach

Our first approach to welwitindolinones **3–8** is outlined in retrosynthetic format in Scheme 1. The objective was to design a strategy that would enable access to a variety of welwitindolinones through a common intermediate, such as **9**, which might be derived from alkene **10** via oxidative cleavage of the exocyclic methylene group followed by regioselective enolate alkylations. We envisioned that **10** could be prepared from **11** by two sequential allylic alkylations. The tricycle **11** would then be formed by the intramolecular enolate arylation of the ketoester **12**, which would be assembled by a Michael addition involving the enolate of *N*-methyl-4-bromooxindole (**13**).

Having thus formulated our plan, the first task required the preparation of the ketoester **12**. Toward this objective, readily available 4-bromooxindole (**14**)⁸ was *N*-methylated using the Bordwell protocol⁹ to give **13** in 66% yield (Scheme 2). Reaction of **13** with methyl 3-methylcrotonate (**15**) in methanolic sodium methoxide gave ester **16** in 74% yield. We found that it was essential to rigorously deoxygenate the sodium methoxide solution prior to the reaction in order to avoid forming the isatin derivative of **13**. The Claisen condensation of **16** with the anion generated from *tert*-butyl acetate provided ketoester **17** in good yield. We discovered that the *tert*-butyl ester moiety was not sufficiently stable for our needs as it underwent relatively facile decarboxylation under the somewhat forcing conditions of the subsequent enolate arylation. Accordingly, it was converted into the methyl ester **12** in 95% yield in a two-step procedure that furnished **12** in higher overall yield than the base-promoted Claisen condensation of **16** with methyl acetate.

In order to advance the synthesis, the intramolecular enolate arylation of ketoester **12** was then examined (Scheme 3). In initial experiments, we found that the use of Pd(OAc)₂ and bis-*tert*-butyl-2-biphenylphosphine¹⁰ provided tricycle **11** in 58% yield, but significant quantities (25–30%) of **12** were also recovered, and we were unable to effect complete conversion of **12** into **11**. After screening various catalysts and reaction conditions, we discovered that a modified procedure, in which a combination of tri-*tert*-butylphosphine palladium dimer¹¹ and bis-dibenzylideneacetone were employed in accord with a report by Fu,¹² gave the tricycle **11** in 88% yield; the structure of **11** was confirmed with X-ray analysis. In each of these reactions it was necessary to exclude oxygen using a freeze–pump–thaw protocol in order to obtain optimal yields. In an attempt to form the final ring of the welwitindolinone skeleton, tricycle **11** was treated with the bis-allylic carbonate **18** in the presence of Pd(Ph₃P)₄ and DBU. However, neither epimer of the requisite tetracycle **21** was detected in the reaction mixture, and **20** was obtained in 59% yield. The undesired product **20** presumably formed because the proton α to the amide moiety in intermediate **19**, which could be isolated as a mixture (4:1) of two diastereomers, was more acidic than those α to the keto group. A revised plan was thus pursued.

2.2. Second generation approach

We reasoned that the aforementioned deleterious cyclization could be avoided simply by removing the offending acidic proton on the indole moiety. Accordingly, we decided to target the alternative tetracycle **22** (Scheme 4). Moreover, because we anticipated that an allylic alkylation of a β -ketoester would be easier to achieve than an allylic alkylation of a ketone, we decided to explore a different sequence of carbon–carbon bond forming steps in which the C11–C12 bond of **22** would be formed after the C14–C15 bond. In order to test this idea, we needed to prepare the enol **23**, and one viable precursor would be the ketoester **24**. Because preliminary efforts to prepare **24** via alkylation of precursor β -ketoester dianions using an appropriate alkyl halide failed (Scheme 4, Path A), alternative pathways were explored. One of these involved a Lewis acid-mediated coupling between the tertiary alcohol **25** and the silyl ketene acetal **26** (Scheme 4, Path B), a bond construction that benefited from little literature precedent at the time we initiated the study,¹³ although a related reaction was reported by Rawal subsequent to our early experiments in the area.^{5j}

At this juncture, it was necessary to set the stage to examine the key Lewis acid-mediated coupling of **25** and **26**, the silyl ketene acetal **26** was first prepared by alkylation of the dianion generated from *tert*-butylacetoacetate (**27**) with the allylic halide **28** to give ketoester **29** in 70% yield (Scheme 5). Transformation of **29** into **26** was then achieved by acid-catalyzed acetonide formation to give the dioxinone **30**, subsequent treatment of which with NaHMDS and TMSCl gave silyl ketene acetal **26**, which was used without purification in the next step of the sequence.

The synthesis of the requisite tertiary alcohol **25** commenced with the N-methylation of 4-bromoindole (**31**) followed by subsequent Friedel–Crafts acetylation to provide ketone **32** (Scheme 6). Treatment of **32** with methylmagnesium bromide furnished the alcohol **25**, which was somewhat unstable and hence used directly without purification. After screening several Lewis acids, we found that TMSOTf facilitated the coupling of **25** and **26** to give **33** in 35% yield over two steps. To our knowledge, this reaction represents the first Lewis acid-mediated coupling between a heterocyclic carbinol and a vinyl silyl ketene acetal. The ability to generate a stabilized carbocation from a hydroxyl group is beneficial from a synthetic perspective because alcohols are often more readily available than their corresponding halides or acetates. It is also noteworthy that this experiment served as the basis for developing a general method for preparing β -heteroaryl carbonyl compounds by trapping carbocations with different π -nucleophiles.^{14,15}

Dioxinone **33** was then converted into the β -ketoester **34** by heating in the presence of MeOH to trap the acylketene intermediate (Scheme 7). Cyclization of **34** by a palladium-catalyzed enolate arylation followed by cleavage of the TBDPS protecting group gave **35** in 51% yield. In initial attempts to acetylate the primary alcohol in **35**, we observed that competitive acetylation of the enol moiety also occurred. However, after some experimentation, we found that the combination of collidine and AcCl at -78°C selectively provided an intermediate allylic acetate that underwent cyclization in the presence of NaH and Pd₂dba₃ to deliver **22** in 43% overall yield from **35**. Oxidative cleavage of the exocyclic olefin in **22** then gave tetracycle **36** in 66% yield.

At this point the tetracyclic core of the welwitindolinones was in place, and the next objective was to create the quaternary carbon center at C(12) via enolate alkylation. However, prior to embarking on this effort, studies were conducted to determine if selective deprotonation at C(12) was possible (Scheme 8). When the lithium enolate of **36** was generated under kinetic conditions and then quenched with CD₃OD, a mixture (ca. 3:4) of **37** and **38** was obtained. Interestingly, deuterium incorporation occurred with complete

facial selectivity, as one diastereomer of **37** and one diastereomer of **38** were obtained. The tentative assignments shown are based upon steric considerations. When the deprotonation of **36** and enolate quenching was repeated under equilibrating conditions, **37** was favored by a factor of about 3.5:1 over **38**, but equal amounts of two diastereomers of **37** were formed. These studies suggested that selective alkylation of C(12) of **36** might be problematic. Confirming this hypothesis, we found that methylation of the lithium enolate of ketone **36** under equilibrating and non-equilibrating conditions was not selective.

2.3. Third generation approach

Given our inability to selectively alkylate ketone **36**, it was apparent that a new plan to access welwitindolinones **3–8** needed to be formulated that provided a solution to the problem of generating the quaternary center at C(12) in an intermediate such as **39** (Scheme 9). For example, the vinyl moiety in **40** would favor dienolate formation at C(12), thereby allowing selective methylation. We envisioned that the tetracycle **40** might be formed via a novel intramolecular allylic alkylation of the γ -acyloxyenone **41**. Although intramolecular allylic alkylations have been extensively utilized in syntheses,¹⁶ alkylations of γ -acyloxyenone moieties, such as that present in **41** have not been reported. The preparation of tricycle **41** via a palladium-catalyzed enolate arylation of **42** follows directly from the precedent established for the syntheses of **11** and **35**. Because we had exploited furans as latent 1,4-enediacarbonyl compounds several times in the past,¹⁷ it occurred to us that the furan ring in **42** might serve as a precursor to the requisite γ -acyloxyenone moiety needed for the key allylic alkylation. The assembly of **42** would then be accomplished by the Lewis acid-mediated coupling of **25** with π -nucleophile **43**.

2.3.1. Lewis acid-mediated coupling—Following the precedent set forth in Scheme 6, we initially choose **49** as the π -nucleophile for the key Lewis acid-mediated coupling step (Scheme 10). Deprotonation of commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**44**) with LDA, followed by a directed aldol reaction of the intermediate enolate with furfural (**45**) gave alcohol **46** in 84% yield. Because several attempts to reduce **46** directly to **48** in one step (e.g., with TFA and Et₃SiH) were unsuccessful, a two step sequence was developed. In the event, treatment of alcohol **46** with MsCl and NEt₃ afforded diene **47**, which was selectively reduced with nickel boride to give **48** in 34% yield. The corresponding palladium-catalyzed hydrogenation of **47** was problematic because variable amounts of reduction of the furan ring were observed. Deprotonation of **48** with NaHMDS and O-silylation gave the vinyl silyl ketene acetal **49**, which was used directly in the coupling with **25** to give **51** in 36% overall yield. During the course of optimizing this key conversion, we discovered that the vinyl silyl ketene acetal **50**, which was prepared analogously as **49**, underwent reaction with **25** in the presence of TMSOTf to give **51** in an improved 48% yield. When **51** was heated to 110 °C in toluene, the dioxinone moiety underwent retro [4+2] cycloaddition to give an intermediate acylketene, which was trapped by MeOH to give ketoester **42** in 73% yield.

Although the sequence depicted in Scheme 10 provided a reasonable route to **42**, we queried whether we might be able to develop a more concise route. Toward this goal, we targeted the π -nucleophile **55** as a potential reaction partner for use in the pivotal Lewis acid-mediated coupling step (Scheme 11). Accordingly, when the dianion of methyl acetoacetate (**52**) was allowed to react with furfuryl chloride (**53**), highly selective γ -alkylation occurred to furnish the ketoester **54** in 68% yield. Treatment of **54** with 2 equiv of NaHMDS and TMSCl in cyclopentyl methyl ether (CPME) gave **55** as a single isomer.¹⁸ Owing to its lability, **55** was coupled directly without purification with **25** in the presence of TMSOTf to deliver the requisite ketoester **42** in 60% over two steps. This outcome was significant for two reasons. Not only was the yield of the Lewis acid-mediated coupling step higher, but the

overall synthetic sequence was shortened by three steps. This new and more efficient route to **42** significantly facilitated our synthetic efforts.

2.3.2. Synthesis and elaboration of tricyclic core—Having developed an effective route to **42**, the next objective was to construct the seven-membered ring via an enolate arylation. Drawing from our previous work, we first examined the use of $\text{Pd}(P\text{-}t\text{-Bu}_3)_2$, but we discovered that it was necessary to use microwave heating to get significant conversion, and even then **56** was obtained in only 30% yield. After examining several other catalysts, we found that PEP-PSI-IPr¹⁹ catalyzed the transformation, providing **56** in 89% yield under the simple thermal conditions of refluxing toluene. This protocol allowed the facile preparation of **56** in multigram quantities (Scheme 12).

The next step of the synthesis required the oxidative cleavage of the furan ring of **56** to reveal an enedione or derived functional array. This conversion proved to be surprisingly difficult. For example, treating **56** with standard oxidants,²⁰ such as Br_2 , *N*-bromosuccinimide (NBS), or *m*-chloroperbenzoic acid (*m*-CPBA) gave complex mixtures of products. When **56** was treated with pyridinium chlorochromate (PCC),²¹ lactone **58** was obtained as the sole product. We reasoned that this product was formed by cyclization of the intermediate *Z*-enonal array generated from the furan ring onto the enol moiety of the β -ketoester, followed by oxidation with PCC. Several preliminary attempts to refunctionalize **58** by selective reduction were unavailing, so we decided to protect the enol moiety of **56** as its *tert*-butylsilyl enol ether **57**. However, selective oxidative cleavage of furan **57** once again proved highly problematic owing to competing halogenation of the indole ring. Reaction of **57** with Br_2 and dibromohydantoin in aqueous solvents gave low yields of **59** along with significant quantities of over brominated products in which one or more bromine atoms had been introduced onto the indole ring. Utilization of *N*-chlorosuccinimide (NCS) in aqueous solvents led to chlorination of the furan and indole rings, and no aldehydic products were detected in the reaction mixtures. Similarly, exposure of **57** to MeReO_3 /urea hydrogen peroxide,²² dimethyldioxirane (DMDO),²³ and magnesium monoperoxyphthalate (MMPP)²⁴ did not provide significant quantities of **59**, whereas reaction of singlet oxygen²⁵ with **57** furnished 20% of the *Z*-isomer of **59**. Eventually, we discovered that treating **57** with NBS in aqueous DMF gave **59** in 34% yield, along with 7% of brominated **59** and 6% of brominated **57**. Despite extensive experimentation, we were unable to improve the yield of this step.

At this juncture, it was necessary to elaborate the enonal moiety of **59** into the allylic acetate **62** via the selective reduction of the aldehyde moiety in **59**. Although preliminary experiments using NaBH_4 gave mixtures of 1,2- and 1,4-addition products, we found that reduction of **59** under Luche's conditions²⁶ gave diol **60** in 36% yield (Scheme 13). Selective mono-acetylation of the primary alcohol in **60**, followed by oxidation of the secondary alcohol with 2-iodoxybenzoic acid (IBX) gave acetate **62**.

Although this approach to **62** could be used to provide sufficient quantities of material for further study, a more concise route involving the selective reduction of the aldehyde moiety of **59** was desired. When **59** was treated with L-Selectride at low temperatures, the desired product **63** was obtained, but significant amounts of diol **60** were also formed. We eventually discovered that *t*- BuNH_2BH_3 ²⁷ reduced **59** cleanly to give the alcohol **63** in 82% yield (Scheme 14). Acetylation of the alcohol proceeded smoothly to give **62** in 89% yield, shortening the overall synthetic sequence by one step compared to the route presented in Scheme 13. We would later find that the benzoate **64**, which was prepared from **63** in 98% yield, would be a better substrate for the eventual intramolecular allylic alkylation (vide infra).

In order to set the stage for forming the tetracyclic core of the welwitindolinones via an intramolecular allylic alkylation, the silyl protecting group was removed from **62** using TBAF to give **65** (Scheme 15). Enol **65** was treated with a variety of transition metal catalysts known to induce allylic alkylations, such as Pd₂dba₃, Mo(CO)₆,²⁸ and W(CO)₃(MeCN)₃,²⁹ but none of these delivered any detectable quantity of cyclized product. After some experimentation, we discovered that reaction of **65** with Pd₂dba₃, trifurylphosphine, and Bu₃SnOMe furnished a mixture (5.8:1:3.5) of the isomeric olefins **67**, **68**, and **40** in 60% yield from **62**. The presence of Bu₃SnOMe, which presumably generated the tin enolate of **65** in situ and has been reported to enhance allylic alkylations,³⁰ was critical to the success of this transformation. When the benzoate **64** was used in identical sequence, the mixture of **67**, **68**, and **40** was obtained in 84% yield.

The creation of the quaternary carbon at C(12) by methylation of the derived dienolate proceeded according to plan, but it was necessary to treat the mixture of **67**, **68**, and **40** with freshly prepared NaHMDS as the base to obtain optimal results. The desired product **39**, with the structure confirmed by X-ray crystallography, was thus obtained as a single diastereomer in 80% yield. At this point all of the carbon atoms in the welwitindolinone skeleton had been installed, and only a few functional group manipulations remained to complete the synthesis. We were not prepared, however, for the travails that lurked.

The seemingly straightforward task of converting a ketone into a vinyl chloride was next on the agenda, and we explored a number of methods that were known to effect this transformation. Unfortunately, we would soon realize that this would not be an easy task. We initiated our efforts by examining known methods for directly converting ketones into vinyl chlorides. For example, when **39** was treated with 1 equiv of PCl₅,³¹ chloroindole **69** was obtained in 60% yield (Scheme 16). Use of excess PCl₅ produced only poly-chlorinated products having the general structure **70** while leaving the ketone moiety untouched. Treatment of **39** with other electrophilic chlorine reagents known to effect conversion of ketones into vinyl chlorides, such as PPh₃/CCl₄³² and P(OPh)₃/Cl₂,³³ also failed to deliver the desired vinyl chloride, and dichlorination of the indole ring was again observed. When the more oxophilic reagent WCl₆ was employed,³⁴ a complex mixture was obtained.

Because the indole ring of **39** thus appeared to be more reactive toward electrophilic chlorinating reagents than the ketone moiety, we reasoned that deactivating the indole ring by conversion to its oxindole counterpart, the oxidation state present in the natural product, might lead to preferential reaction of the ketone. Recognizing that 2-haloindoles can be hydrolyzed to oxindoles,^{5r,35} chloroindole **69** was treated with concentrated HCl in dioxane to give a mixture (1:1.2) of epimeric oxindoles **71** and **72** in 36% yield. The isolation of epimers was somewhat surprising because Garg has reported that the hydrolysis of a related 2-bromoindole gave a single diastereomer.^{5r} We also found that **39** could be converted directly into a mixture of **71** and **72** in 34% yield with MeReO₃/urea hydrogen peroxide.³⁶ The stereochemical configuration of **71** and **72** was assigned based upon a 2-D NOESY experiment. In particular, the proton at C(3) (δ =3.57 ppm) of **71** exhibited an NOE interaction with the proton at C(14) (δ =2.93 ppm), whereas the C(3) proton of **72** did not. Unfortunately, exposure of the mixture of **71** and **72** to the action of various electrophilic chlorine reagents did not provide detectable amounts of the desired vinyl chloride **73**.

Having exhausted possible one-step procedures for converting ketones to vinyl chlorides, we turned to examining several two-step protocols. Mori and Tsuneda had previously shown that ketone-derived hydrazones can be converted into vinyl chlorides with NCS.³⁷ When we treated ketone **39** with hydrazine hydrate, reduction of the vinyl group gave **74** as the sole product, albeit in only 26% yield (Scheme 17). Presumably **74** was formed by reduction of **39** with diimide that was generated during the course of the reaction by the presence of

oxygen or trace metals. Unfortunately, even when oxygen and trace metals were rigorously excluded, none of the desired hydrazone was formed, even under forcing conditions. This result is also somewhat confounding because Rawal employed such a procedure to prepare a vinyl chloride that was structurally similar to **73** in his recent synthesis of **4**.^{6c}

We also explored several known methods for transforming ketones into vinyl chlorides via intermediate vinyl triflates. For example, vinyl triflates may be converted into vinyl stannanes and then to vinyl chlorides.^{38,39} Hayashi and co-workers reported a ruthenium catalyzed procedure of converting vinyl triflates to vinyl chlorides,⁴⁰ and Buchwald recently described a similar process that was catalyzed by palladium.⁴¹ Although the vinyl triflate **75** was readily prepared in 80% yield by sequential reaction of **39** with LiHMDS and then Comins' reagent,⁴² we were unable to identify any conditions that enabled conversion of **75** into **76**. Inasmuch as Garg recently converted a closely related ketone into a vinyl halide using such a two-step method in his synthesis of **3**,^{6b} this failure again highlights the diabolical vagaries inherent in the chemistry of the compact welwitindolinone skeleton.

Contemporaneous with our efforts to convert **39** into a naturally-occurring welwitindolinone, both Rawal and Garg reported elegant syntheses of several welwitindolinones from compounds closely related to **39**.⁶ We thus opted to examine the feasibility of completing a formal synthesis of these alkaloids using **39** as an intermediate. Although we were aware that conversion of the bridgehead ester in **39** into its carboxylic acid might be problematic,^{5j} we still examined several saponification and nucleophilic dealkylation tactics to prepare **77**; however, even forcing conditions failed to yield detectable amounts of **77** (Scheme 18). We eventually discovered that **39** could be reduced with LiAlH₄ to deliver an inseparable mixture of the diastereomeric triols **78** that were in turn globally oxidized with Dess–Martin periodinane to give **79** in 89% yield over two steps. The spectroscopic data (²H and ¹³C NMR spectroscopy) for the synthetic **79** thus obtained were consistent with those reported by Rawal,^{6a} who used this compound as a pivotal intermediate in his syntheses of **4–8**.^{6c} Our preparation of **79** thus constitutes a formal synthesis of **4–8**.

3. Conclusions

In summary, formal syntheses of a number of natural welwitindolinones were completed by the synthesis of aldehyde **79**, the pivotal intermediate in Rawal's elegant syntheses of the welwitindolinone alkaloids, via a sequence of reactions that requires 14 steps in the longest linear sequence. The synthesis showcases several interesting steps and discoveries. One of these is the Lewis acid-mediated coupling of alcohol **25** with a number of vinyl silyl ketene acetals to generate γ -heteroaryl ketoesters. This novel process involves a variant of a vinylogous Mannich reaction in which a benzylic-type carbocation is trapped by a π -nucleophile, and this discovery was subsequently extended to a more general entry to the synthesis of β -heteroaryl carbonyl compounds.¹⁴ We also extended the scope of cyclizations via allylic alkylations to include γ -acyloxyenones, and we developed an improved method for enolate arylations of carbonyl compounds.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.⁴³ Acetonitrile (MeCN), and dimethylformamide (DMF) were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. These solvents

were determined to have less than 50 ppm H₂O by Karl Fischer coulometric moisture analysis. Methylene chloride (CH₂Cl₂), pyridine, chlorotrimethylsilane (TMSCl), trimethylsilyl trifluoromethanesulfonate (TMSOTf), benzoyl chloride (BzCl), and collidine were distilled from calcium hydride immediately prior to use. Thionyl chloride was distilled before use. Furfuryl alcohol was distilled from sodium carbonate before use. Methyl acetoacetate was distilled from calcium chloride before use. *N*-Bromosuccinimide (NBS) was recrystallized from water. Methyl iodide (MeI) was distilled from phosphorus pentoxide. Sodium *tert*-butoxide (NaO*t*-Bu) was sublimed before use. Trifurylphosphine⁴⁴ and Dess–Martin periodinane⁴⁵ were synthesized according to literature procedures. All reagents were reagent grade and used without purification unless otherwise noted, and air or moisture sensitive reagents were weighed in a glovebox. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame or oven dried. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator at 25–30 °C (bath temperature). Thin layer chromatography was run on pre-coated plates of silica gel with a 0.25 mm thickness containing 60F-254 indicator (EMD Millipore). Chromatography was performed using forced flow (flash chromatography) and the indicated solvent system on 230–400 mesh silica gel (Silicycle flash F60) according to the method of Still,⁴⁶ unless otherwise noted. Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated and reported as wave-numbers (cm⁻¹). Proton nuclear magnetic resonance (²H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were obtained at the indicated field as solutions in CDCl₃ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent (e.g., for CDCl₃, δ =7.24 ppm and 77.0 ppm for ²H and ¹³C NMR, respectively) and are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ =0.00 ppm). Coupling constants (*J*) are reported in hertz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons; br, broad; app, apparent.

4.2. Experimental procedures

4.2.1. 4-Bromo-1-methyl-1,3-dihydro-2-oxindole (13)—A suspension of sodium hydride (331 mg, 8.63 mmol, 60% in oil) and xylenes (17.3 mL) was heated to reflux, and 4-bromo-1,3-dihydro-2-oxindole (**14**) (1.83 g, 8.63 mmol) was added in ~10 equal portions over 5 min. The resulting light orange suspension was heated under reflux for 1 h, whereupon dimethylsulfate (1.09 g, 818 μ L, 8.63 mmol) was added slowly dropwise at reflux. After heating at reflux for an additional 1 h, the reaction was cooled and diluted with EtOAc (30 mL). The organic layer was washed with water (3 $\times$ 15 mL), brine (15 mL), dried (MgSO₄) and concentrated to provide a yellow solid that was purified by flash column chromatography eluting with a solvent gradient (CH₂Cl₂ to 10% Et₂O in CH₂Cl₂) to give 1.29 g (66%) of **13** as a fluffy light yellow solid: mp 138–139 °C; ²H NMR (500 MHz) δ 7.15–7.10 (comp, 2H), 6.73–6.69 (m, 1H), 3.43 (s, 2H), 3.17 (s, 3H); ¹³C NMR (126 MHz) δ 173.7, 146.0, 129.4, 125.4, 125.3, 119.0, 106.8, 37.0, 26.5; IR 3054, 2939, 1717, 1611, 1458, 1340, 1296, 1106, 925, 770, 708 cm⁻¹; HRMS (CI) *m/z* calcd for C₉H₉⁷⁹BrNO⁺ (*M* + 1), 225.9868; found, 225.9875.

4.2.2. Methyl-3-(4-bromo-1-methyl-2,3-dihydro-2-oxindol-3-yl)-3-methylbutyrate (16)—A suspension of **13** (264 mg, 1.17 mmol), MeOH (780 μ L), and methyl 3-methylcrotonate (667 mg, 765 μ L, 5.85 mmol) was treated with sodium methoxide (63.2 mg, 1.17 mmol), and the mixture was heated for 40 h. The reaction was cooled, and 1 M aqueous HCl (~2 mL) and water (15 mL) were added. The mixture was stirred for 5 min and extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were dried (MgSO₄)

and concentrated to provide an orange oil that was purified by flash column chromatography eluting with 10% EtOAc in benzene (mixed fractions rechromatographed twice) to give 236 mg (62%) of **16** as a light yellow solid; mp 75–77 °C; ^2H NMR (400 MHz) δ 7.13 (dd, $J=7.9, 1.0$ Hz, 1H), 7.08 (td, $J=7.9, 1.0$ Hz, 1H), 6.68 (dd, $J=7.9, 1.0$ Hz, 1H), 3.82 (s, 1H), 3.66 (s, 3H), 3.09 (s, 3H), 2.92 (A of AB, $J_{AB}=15.1$ Hz, 1H), 2.49 (B of AB, $J_{AB}=15.1$ Hz, 1H), 1.31 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (101 MHz) δ 176.4, 172.4, 147.2, 129.4, 127.9, 126.6, 120.9, 106.4, 54.0, 51.2, 43.3, 39.6, 27.6, 25.9, 24.2; IR (neat) 2950, 2882, 1713 (br), 1603, 1454, 1330, 1172, 1100, 932, 767 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{15}\text{H}_{19}^{79}\text{BrNO}_3^+$ (M+1), 340.0548; found, 340.0554.

4.2.3. tert-Butyl 5-(4-bromo-1-methyl-2,3-dihydro-2-oxindol-3-yl)-5-methyl-3-oxohexanoate (17)—*n*-BuLi (0.28 mL, 2.5 M in hexanes, 0.69 mmol) was added to a solution of *i*-Pr₂NH (70 mg, 97 μL , 0.69 mmol) in THF (4.4 mL) at –78 °C, and the resulting solution was stirred at 0 °C for 30 min. The solution was cooled to –50 °C, and a solution of *t*-BuOAc (81 mg, 94 μL , 0.69 mmol) in THF (0.44 mL) was added dropwise. The reaction was stirred for 1 h between –45 °C and –30 °C, whereupon a solution of **16** (39 mg, 0.12 mmol) in THF (0.20 mL) was added dropwise. The reaction was stirred for 1 h between –45 °C and –30 °C and then slowly warmed to room temperature over the next 1 h. Saturated aqueous NH₄Cl (5 mL) and water (20 mL) were added, and the mixture was extracted with Et₂O (3 $\times$ 20 mL). The combined organic layers were dried (MgSO₄) and concentrated to provide a yellow oil. The residue was purified by flash column chromatography eluting with a solvent gradient (10% Et₂O in hexanes to 40% Et₂O in hexanes) to give 35 mg (72%) of **17** as a light yellow oil; ^2H NMR (300 MHz) δ 7.20–7.08 (comp, 2H), 6.71 (d, $J=7.3$ Hz, 1H), 3.94 (s, 1H), 3.44 (A of AB, $J_{AB}=15.3$ Hz, 1H), 3.39 (B of AB, $J_{AB}=15.3$ Hz, 1H), 3.17 (A of AB, $J_{AB}=17.8$ Hz, 1H), 3.11 (s, 3H), 2.70 (B of AB, $J_{AB}=17.8$ Hz, 1H), 1.47 (s, 9H), 1.40 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (75 MHz) δ 202.2, 176.6, 166.5, 147.1, 129.4, 128.1, 126.7, 120.7, 106.4, 81.7, 53.1, 52.0, 51.3, 39.5, 28.4, 28.0, 25.9, 23.9; IR (neat) 2973, 1713 (br), 1603, 1455, 1368, 1327, 1251, 1158, 1101, 932, 768 cm^{-1} ; HRMS (CI) m/z $\text{C}_{20}\text{H}_{27}^{79}\text{BrNO}_4^+$ (M+1), 424.1124; found, 424.1109.

4.2.4. Methyl 5-(4-bromo-1-methyl-2,3-dihydro-2-oxindol-3-yl)-5-methyl-3-oxohexanoate (12)—A solution of **17** (142 mg, 0.335 mmol) in trifluoroacetic acid (669 μL) was stirred at 0 °C for 1 h, whereupon the reaction was concentrated under reduced pressure, and the residue was dissolved in Et₂O (0.669 mL). The solution was cooled to 0 °C, and an ethereal solution of diazomethane (~0.3 M) was added until the yellow color persisted. The reaction was quenched with 1 M aqueous HCl (5 mL), stirred 5 min, and extracted with Et₂O (3 $\times$ 5 mL). The combined organic layers were dried (MgSO₄) and concentrated to provide a clear light yellow oil. The residue was purified by flash column chromatography eluting with a solvent gradient (20% EtOAc in hexanes to 40% EtOAc in hexanes) to give 121 mg (95%) of **12** as a clear light yellow oil; ^2H NMR (300 MHz) δ 7.20–7.08 (comp, 2H), 6.71 (dd, $J=7.3, 1.0$ Hz, 1H), 3.95 (s, 3H), 3.75 (s, 3H), 3.55 (s, 2H), 3.23 (A of AB, $J_{AB}=17.9$ Hz, 1H), 3.10 (s, 3H), 2.63 (B of AB, $J_{AB}=17.9$ Hz, 1H), 1.43 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz) δ 201.8, 176.6, 167.7, 147.1, 129.4, 128.1, 126.7, 120.7, 106.5, 52.8, 52.3, 51.4, 50.5, 39.5, 28.8, 26.9, 23.9; IR (neat) 2963, 2881, 1747, 1714 (br), 1603, 1454, 1329, 1102, 932, 768 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{17}\text{H}_{21}^{79}\text{BrNO}_4^+$ (M+1), 382.0654; found, 382.0654.

4.2.5. Methyl 7-hydroxy-2,9,9-trimethyl-1-oxo-2,8,9,9a-tetrahydro-2-azabenz[cd]azulene-6-carboxylate (11)—Aryl bromide **12** (28 mg, 74 μmol), bis-(tri-*tert*-butylphosphine)palladium (0) (8.0 mg, 14 μmol), bis-dibenzylidenepalladium (0) (4.0 mg, 7.5 μmol), and sodium *tert*-butoxide (7.9 mg, 82 μmol) were added to a dry Kjeldahl-shaped Schlenk flask. The flask was evacuated and back-filled with argon three

times, and DMF (0.52 mL) was added. The brown suspension was deoxygenated via a freeze–pump–thaw protocol (3 cycles, 20 min each) and then heated at 75 °C (oil bath temperature). After 3 h, the reaction was cooled, 1 M aqueous HCl (5 mL) was added, and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by flash column chromatography eluting with a solvent gradient (10% EtOAc in hexanes to 30% EtOAc in hexanes) to give 20 mg (88%) of **11** as a white solid, mp 114–117 °C; ²H NMR (500 MHz) δ 13.1 (d, *J*=1.0 Hz, 1H), 7.25 (td, *J*=7.8, 0.7 Hz, 1H), 7.11 (dd, *J*=7.8, 0.7 Hz, 1H), 6.66 (d, *J*=7.8 Hz, 1H), 3.79 (s, 3H), 3.16 (s, 3H), 2.98 (s, 1H), 2.20 (d, *J*=12.6 Hz, 1H), 2.06 (d, *J*=12.6 Hz, 1H), 1.51 (s, 3H), 0.88 (s, 3H); ¹³C NMR (126 MHz) δ 177.5, 176.1, 171.7, 143.6, 131.3, 127.5, 126.8, 123.4, 105.5, 101.3, 52.5, 51.8, 48.3, 48.2, 28.6, 26.0, 24.8; IR (neat) 3016, 2928, 2855, 1703, 1644, 1604, 1444, 1370, 1334, 1296, 1236, 770 cm⁻¹; HRMS (CI) *m/z* calcd for C₁₇H₂₀NO₄⁺ (*M*+1), 302.1392; found, 302.1382.

4.2.6. Oxindole-bridged[2.2.3]bicycle (20)—To a solution of **11** (14 mg, 47 μmol) and THF (0.24 mL) was added DBU (8.0 mg, 8.0 μL, 51 μmol). To this orange solution was added carbonate **18** (10 mg, 9.0 μL, 51 μmol) and this mixture was added to a solution of tetrakis(triphenylphosphine) palladium (5.4 mg, 47 μmol) and THF (0.24 mL) over 10 min. After 2 h, the reaction was concentrated under reduced vacuum, and the residue was purified by flash chromatography eluting with a solvent gradient (10% EtOAc in hexanes to 20% EtOAc in hexanes) to afford 9.8 mg (59%) of **21** as an amorphous white solid; ²H NMR (500 MHz) δ 7.29 (t, *J*=7.8 Hz, 1H), 6.82 (dd, *J*=7.8, 0.8 Hz, 1H), 6.56 (dd, *J*=7.8, 0.8 Hz, 1H), 4.91 (br s, 1H), 4.86 (br s, 1H), 3.83 (s, 3H), 3.31 (d, *J*=13.8 Hz, 1H), 3.22 (s, 3H), 2.92 (d, *J*=14.9 Hz, 1H), 2.65 (d, *J*=12.1 Hz, 1H), 2.53 (d, *J*=13.8 Hz, 1H), 2.15 (d, *J*=12.1 Hz, 1H), 2.13 (d, *J*=14.9 Hz, 1H), 1.44 (s, 3H), 0.78 (s, 3H); ¹³C (126 MHz) δ 208.0, 178.6, 171.1, 143.2, 141.7, 137.3, 129.2, 129.0, 119.9, 118.8, 107.3, 67.2, 56.9, 54.4, 52.6, 45.1, 41.6, 38.7, 28.3, 26.1, 22.9; IR (neat) 3018, 2955, 1746, 1707, 1607, 1470, 1246 cm⁻¹; HRMS (CI) *m/z* calcd for C₂₁H₂₄NO₄⁺ (*M*+1), 354.1705; found, 354.1701.

4.2.7. 2-(tert-Butyl-diphenylsilanyloxymethyl)prop-2-en-1-yl bromide (28)—Triphenylphosphine (526 mg, 2.01 mmol) and carbon tetra-bromide (664 mg, 2.00 mmol) were added to a stirred solution of 2-((tert-butyldiphenylsilyloxy)methyl)prop-2-en-1-ol⁴⁷ (662 mg, 2.03 mmol) in CH₂Cl₂ (8.0 mL) at 0 °C. The reaction mixture was stirred for 40 min and then concentrated in vacuo. The crude product was purified via flash chromatography eluting with 10% EtOAc in hexanes to afford 864 mg (99%) of **28** as a colorless oil; ²H NMR (500 MHz) δ 7.67 (dd, *J*=8.0, 1.4 Hz, 4H), 7.44–7.36 (comp, 6H), 5.29 (dd, *J*=3.0, 1.6 Hz, 1H), 5.27–5.26 (m, 1H), 4.29 (t, *J*=1.3 Hz, 2H), 4.01 (s, 2H), 1.06 (s, 9H); ¹³C NMR (125 MHz) δ 144.4, 135.5, 133.3, 129.7, 127.7, 114.9, 64.2, 32.7, 26.8, 19.3; IR 3070, 2958, 2930, 2857, 1112 cm⁻¹; HRMS (CI) *m/z* calcd for C₂₀H₂₆⁷⁹BrOSi⁺ (*M*+1), 389.0936; found, 389.0921.

4.2.8. tert-Butyl 7-tert-butyldiphenylsilanyloxy-6-methylidene-hept-3-one-ate (29)—*n*-BuLi (1.0 mL, 2.1 M in hexanes, 2.2 mmol) was added to a stirred solution of *i*-Pr₂NH (0.23 g, 0.32 mL, 2.3 mmol) in THF (7.0 mL) at –78 °C. The solution was warmed to 0 °C (replaced the dry ice/isopropanol bath with ice), stirred for 40 min, and then *tert*-butylacetoacetate (**27**) (0.17 g, 0.18 mL, 1.1 mmol) was added dropwise over 5 min and stirring continued for 45 min. The solution was cooled to –78 °C, and the allylic bromide **28** (0.24 mg, 0.92 mmol) in THF (3.0 mL) was added over 10 min. The reaction mixture was stirred for 1.25 h, warmed to room temperature (by removing the dry ice/isopropanol bath) and stirred for 2.5 h. The solution was poured into saturated aqueous NH₄Cl (40 mL), and the resultant mixture was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (40 mL), dried (MgSO₄), and concentrated in vacuo. The residue

was purified by flash chromatography eluting with 10% EtOAc in hexanes, afforded 0.30 g (70%) of the product **29** as a colorless oil; ^2H NMR (400 MHz) δ 7.69–7.66 (comp, 4H), 7.46–7.36 (comp, 6H), 5.18–5.17 (m, 1H), 4.85 (dd, $J=2.7, 1.3$ Hz, 1H), 4.10 (s, 2H), 3.32 (s, 2H), 2.65 (t, $J=7.6$ Hz, 2H), 2.30 (t, $J=7.5$ Hz, 2H), 1.46 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz) δ 202.5, 166.4, 146.5, 135.5, 133.5, 129.7, 127.7, 109.3, 81.9, 66.4, 50.6, 41.1, 27.9, 26.8, 26.2, 19.2; IR (thin film) 3071, 2931, 1739, 1716 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{28}\text{H}_{39}\text{O}_4\text{Si}^+$ ($M+1$), 467.2618; found, 467.2615.

4.2.9. 6-(4-tert-Butyldiphenylsilyloxy-2-methylidenebutyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (30)—The β -ketoester **29** (177 mg, 0.378 mmol) was dissolved in acetone (110 mg, 140 μL , 1.90 mmol), trifluoroacetic acid (421 mg, 290 μL , 3.70 mmol), and acetic anhydride (1.90 g, 1.80 mL, 19.0 mmol). After standing for 22 h, saturated aqueous NaHCO_3 (60 mL) was added. The solution was then extracted with CH_2Cl_2 (4 $\times$ 15 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography eluting with 30% EtOAc in hexanes to give 114 mg (67%) of **30** as a pale yellow oil; ^2H NMR (500 MHz) δ 7.66–7.64 (comp, 4H), 7.44–7.36 (comp, 6H), 5.17 (s, 1H), 5.15 (d, $J=1.4$ Hz, 1H), 4.86 (d, $J=1.2$ Hz, 1H), 4.09 (s, 2H), 2.35–2.32 (comp, 2H), 2.31–2.24 (comp, 2H), 1.63 (s, 6H), 1.05 (s, 9H); ^{13}C NMR (125 MHz) δ 171.2, 161.2, 145.9, 135.5, 133.3, 129.8, 127.7, 110.3, 106.3, 93.4, 66.3, 31.8, 28.7, 26.8, 25.0, 19.2; HRMS (CI) m/z calcd for $\text{C}_{27}\text{H}_{35}\text{O}_4\text{Si}^+$ ($M+1$), 451.2305; found, 451.2320.

4.2.10. 4-Bromo-3-acetyl-1-methyl-1H-indole (32)—A suspension of **31** (8.8 g, 45 mmol), potassium carbonate (4.5 g, 32 mmol), and dimethyl carbonate (12 g, 0.13 mol) in DMF (56 mL) was gradually heated to 140 $^\circ\text{C}$ over 30 min and stirred for 3.5 h. After cooling to room temperature, the insoluble solids were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was distilled under reduced pressure (0.2 mmHg, 155–180 $^\circ\text{C}$) to give 8.5 g (91%) of 4-bromo-1-methylindole as a yellow liquid. Its ^2H NMR spectroscopic data were consistent with those reported in the literature.⁴⁸

Me_2AlCl (1.0 M in hexanes, 81 mL, 81 mmol) was added drop-wise over 30 min to a solution of 4-bromo-1-methylindole (8.5 g, 40 mmol) in CH_2Cl_2 (100 mL) at -20 $^\circ\text{C}$. The reaction mixture was stirred for 45 min, and a solution of acetyl chloride (4.7 g, 60 mmol) in CH_2Cl_2 (40 mL) was added over 15 min. The resulting suspension was stirred at room temperature for 5.5 h, whereupon pH 7 phosphate buffer (100 mL) was slowly added at 0 $^\circ\text{C}$. The organic solvents were removed under reduced pressure, and the resulting mixture was extracted with CH_2Cl_2 (3 $\times$ 80 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallized (CH_2Cl_2 /hexanes) to give 8.5 g (84%) of **32** as a light tan solid: mp=124–125 $^\circ\text{C}$; ^2H NMR (500 MHz) δ 7.59 (s, 1H), 7.44 (dd, $J=8.0, 1.0$ Hz, 1H), 7.22 (dd, $J=8.0, 1.0$ Hz, 1H), 7.08 (t, $J=8.0$ Hz, 1H), 3.76 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (125 MHz) δ 192.1, 139.0, 136.1, 127.5, 125.2, 124.0, 118.2, 114.9, 108.9, 33.6, 29.9; IR 3106, 1660, 1106 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{11}\text{H}_{11}^{79}\text{BrNO}^+$ ($M+1$), 252.0024; found, 252.0032.

4.2.11. O-(tert-Butyldiphenylsilyl)-2-methylene-4-(2,2-dimethyl-4H-1,3-dioxin-4-one)-5-(4-bromo-1-methylindol-3-yl)-5-methyl-hexan-1-ol (33)—A solution of NaHMDS (9.21 mL, 1.27 M in THF, 11.7 mmol) was added to a stirred solution of the dioxinone **30** (1.78 g, 3.95 mmol) in THF (40 mL) at -78 $^\circ\text{C}$. After stirring for 45 min, TMSCl (2.14 g, 2.50 mL, 19.7 mmol) was added, and the solution was stirred for 50 min. The mixture was warmed to room temperature and concentrated in vacuo to give crude silyl ketene acetal **26** that was then dissolved in PhMe (10 mL). In a separate flask, MeMgBr (2.37 M, 5.10 mL, 12.1 mmol) was added dropwise to a solution of ketone **32** (1.01 g, 4.03

mmol) in THF (20 mL) at 0 °C. The reaction was stirred at room temperature for 4 h, whereupon 50% saturated aqueous NaHCO₃ (ca. 32 mL) was added dropwise at 0 °C. The insoluble salts were removed by filtration, and the filtrate was extracted with EtOAc (3×30 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give crude **25** (1.08 g, 4.03 mmol), which was dissolved in PhMe (40 mL). The solution was cooled to −78 °C, and TMSOTf (0.428 g, 350 μL, 1.93 mmol) was added with stirring. After 2 min, the above solution of **26** was added, and the mixture was stirred for 2.5 h. The reaction mixture was warmed to room temperature and stirred for 17 h, whereupon the mixture was poured into saturated aqueous NaHCO₃ (70 mL). The phases were separated, and the aqueous portion was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na₂SO₄), and concentrated in vacuo. The product was purified via flash chromatography eluting with 20→35% EtOAc in hexanes to afford 960 mg (35% from **32**) of **33** as a colorless oil; ²H NMR (500 MHz) δ 7.59–7.51 (comp, 4H), 7.40–7.31 (comp, 7H), 7.20 (dd, *J*=8.2, 1.0 Hz, 1H), 6.98 (t, *J*=7.9 Hz, 1H), 6.89 (s, 1H), 5.24 (br s, 1H), 5.09 (s, 1H), 4.82 (s, 1H), 4.17 (d, *J*=12.1 Hz, 1H), 3.97 (br s, 1H), 3.67 (s, 3H), 2.25 (t, *J*=13.3 Hz, 1H), 1.68–1.36 (comp, 14H), 0.94 (s, 9H); ¹³C NMR (125 MHz) δ 172.6, 161.2, 145.4, 139.9, 135.5, 135.4, 133.54, 133.48, 129.62, 129.58, 127.6, 125.9, 122.4, 122.3, 113.7, 110.3, 109.0, 105.9, 66.0, 48.9, 38.0, 34.1, 33.0, 30.3, 26.7, 25.5, 24.9, 22.3, 19.2, 14.0; IR 2958, 2856, 1724, 1620, 1112 cm^{−1}; HRMS (CI) *m/z* calcd for C₃₉H₄₇⁷⁹BrO₄Si⁺ (M+1), 700.2458; found, 700.2462.

4.2.12. (Z)-Methyl 8,9-dihydro-7-hydroxy-8-(2-(tert-butylidiphenylsilyloxymethyl)allyl)-2,9,9-trimethyl-2H-cyclohepta[cd]indole-6-carboxylate (**34**)

—The dioxinone **33** (960 mg, 1.37 mmol) was heated under reflux in a mixture of MeOH (5.5 mL) and PhMe (110 mL) for 21 h. The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was purified by flash chromatography eluting with 25% EtOAc in hexanes to afford 871 mg (94%) of **34** as an oil; ²H NMR (400 MHz) δ 7.64–7.52 (comp, 4H), 7.42–7.32 (comp, 7H), 7.26 (d, *J*=7.9 Hz, 1H), 7.04 (t, *J*=7.9 Hz, 1H), 6.92 (s, 1H), 5.15 (s, 1H), 4.84 (s, 1H), 4.51 (dd, *J*=11.8, 1.9 Hz, 1H), 4.04 (br s, 2H), 3.71 (s, 3H), 3.58 (s, 3H), 3.05 (br s, 2H), 2.52–2.38 (comp, 2H), 1.70–1.46 (comp, 7H), 1.00 (s, 9H); ¹³C NMR (100 MHz) δ 207.0, 167.5, 146.3, 140.2, 135.7, 133.8, 129.8, 129.3, 127.9, 126.1, 123.0, 122.5, 122.0, 113.7, 110.6, 109.4, 66.1, 57.5, 52.0, 39.0, 38.1, 33.4, 27.0, 19.5; IR 2955, 2856, 1749, 1708, 1112, 1075 cm^{−1}; HRMS (CI) *m/z* calcd for C₃₇H₄₄⁷⁹BrO₄Si⁺ (M⁺), 673.2223; found, 673.2220.

4.2.13. Methyl-8,9-dihydro-7-hydroxy-8-(2-(hydroxymethyl)allyl)-2,9,9-trimethyl-2H-cyclohepta[cd]indole-6-carboxylate (**35**)—NaO*t*-Bu (252 mg, 2.62 mmol) was added to a solution of the ketoester **34** (890 mg, 1.32 mmol) in PhMe (20 mL).

The solution was then degassed (freeze–pump–thaw×2 cycles), and Pd(OAc)₂ (30.0 mg, 0.134 mmol) and tri-*tert*-butylphosphine (0.400 mL, 1 M in PhMe, 0.400 mmol) were added. The solution was partitioned into four microwave vials (previously purged with argon twice). Each vial was heated to 150 °C in the microwave for 5 min (80 W, 20 psi) and cooled to room temperature. The reaction mixtures were combined and added to 0.5 M aqueous HCl (30 mL). The mixture was extracted with EtOAc (3×30 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), and concentrated in vacuo. The crude product was purified by column chromatography, eluting with 25% EtOAc in hexanes to afford 602 mg (77%) of the intermediate tricycle as a colorless oil. Triethylamine trihydrofluoride (1.60 mL, 9.80 mmol) was added to a stirred solution of the tricycle (0.600 g, 1.00 mmol) and Et₃N (2.10 mL, 15.0 mmol) in MeCN (10 mL). The reaction was stirred for 20 h, and saturated NaHCO₃ (15 mL) and H₂O (15 mL) were added. The aqueous portion was extracted with CH₂Cl₂ (3×25 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), and concentrated in vacuo. The

residue was purified by flash chromatography eluting with 40% EtOAc in hexanes to give 0.24 g (67%) of **35** as an oil; ^2H NMR (400 MHz) δ 13.64 (s, 1H), 7.25 (dd, $J=7.4$, 1.1 Hz, 1H), 7.20 (t, $J=7.7$ Hz, 1H), 7.15 (dd, $J=7.4$, 1.1 Hz, 1H), 6.84 (s, 1H), 4.94 (s, 1H), 4.66 (s, 1H), 4.02 (br s, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.73 (dd, $J=7.8$, 2.4 Hz, 1H), 1.98 (dd, $J=9.8$, 2.4 Hz, 1H), 1.65 (dd, $J=9.8$, 7.8 Hz, 1H), 1.48 (s, 3H), 1.49 (br s, 1H), 1.38 (s, 3H); ^{13}C NMR (100 MHz) δ 178.6, 174.6, 147.2, 137.1, 125.0, 124.9, 123.9, 121.70, 121.66, 121.1, 112.4, 107.3, 102.3, 66.2, 58.5, 52.2, 36.7, 33.0, 32.1, 31.4, 28.5; IR 3416, 2952, 1741, 1633, 1588, 1298, 1224 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_4^+$ (M), 355.1784; found, 355.1786.

4.2.14. 3,3-Dimethyl-4,8-methano-6-methylene-12-oxo-cyclonon[cd]-N-methyl-indole-8-carboxylate methyl ester (22)—To a solution of alcohol **35** (0.13 g, 0.35 mmol) and collidine (46 mg, 50 μL , 0.38 mmol) in CH_2Cl_2 was added AcCl (28 mg, 25 μL , 0.36 mmol) dropwise at -78°C . The solution was stirred for 3.5 h, whereupon 1 N aqueous HCl (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with column chromatography, eluting with 35% EtOAc in hexanes to give 0.11 g (78%) of the intermediate acetate. Sodium hydride (9.0 mg, 0.23 mmol, 60% dispersion in oil) was added to a solution of a portion of the intermediate acetate (82 mg, 0.21 mmol) in THF (6.0 mL). The solution was degassed (freeze–pump–thaw $\times 2$ cycles) and purged with argon. $\text{Pd}_2(\text{dba})_3$ (8.7 mg, 9.5 μmol) was added, and the solution was heated with stirring at 50°C for 17 h. After cooling to room temperature, 1 N aqueous HCl (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography eluting with 25% EtOAc in hexanes to furnish 50 mg (55%) of **22** as an oil; ^2H NMR (500 MHz) δ 7.21–7.15 (comp, 2H), 6.92 (s, 1H), 6.66 (dd, $J=6.8$, 1.6 Hz, 1H), 4.42 (s, 1H), 4.29 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.44 (d, $J=14.0$ Hz, 1H), 2.88 (d, $J=14.0$ Hz, 1H), 2.75 (dd, $J=9.0$, 4.5 Hz, 1H), 2.69 (dd, $J=15.0$, 4.5 Hz, 1H), 2.62 (dd, $J=15.0$, 9.0 Hz, 1H), 1.48 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz) δ 209.5, 173.1, 140.0, 136.9, 130.9, 126.5, 124.8, 122.1, 120.8, 117.7, 112.9, 108.0, 69.3, 61.3, 52.3, 48.8, 35.6, 34.3, 32.9, 28.8, 14.0; HRMS (CI) m/z calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_3^+$ (M+1), 338.1756; found, 338.1745.

4.2.15. 3,3-Dimethyl-4,8-methano-6,12-oxo-cyclonon[cd]-N-methyl-indole-8-carboxylate methyl ester (36)— OsO_4 (2.0 mg, 7.9 μmol) and NaIO_4 (97 mg, 0.45 mmol) were added to a solution of the olefin **22** (16 mg, 47 μmol) in THF (2.0 mL) and H_2O (0.5 mL). After stirring for 22 h, the solution was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash chromatography eluting with 40% EtOAc in hexanes to give 11 mg (66%) of **36** as an oil; ^2H NMR (500 MHz) δ 7.23–7.21 (comp, 2H), 7.00 (s, 1H), 6.73 (dd, $J=5.8$, 2.6 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.51 (dd, $J=17.9$, 0.7 Hz, 1H), 3.24 (d, $J=17.9$ Hz, 1H), 2.97 (dd, $J=9.5$, 6.6 Hz, 1H), 2.82–2.78 (comp, 2H), 1.43 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz) δ 206.9, 205.6, 171.6, 137.4, 127.9, 127.8, 123.7, 122.6, 119.4, 118.9, 109.1, 66.7, 57.4, 53.9, 52.9, 43.2, 37.0, 32.7, 29.3, 13.9; IR 2923, 1737, 1732, 1713, 1454, 1246 cm^{-1} .

4.2.16. 6-(2-(Furan-2-yl)-2-hydroxyethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (46)— $n\text{-BuLi}$ (2.00 M in hexanes, 41.0 mL, 82.7 mmol) was added dropwise to a solution of $i\text{-Pr}_2\text{NH}$ (9.09 g, 90.2 mmol) in THF (62 mL) at 0°C . The mixture was stirred for 20 min and cooled to -78°C , and dioxinone **44** (10.7 g, 75.2 mmol) was added drop-wise. The solution was stirred at -78°C for 1 h, and furfural (**45**) (7.89 g, 82.7 mmol) was added dropwise. The mixture was stirred for 10 min at -78°C , whereupon saturated aqueous NH_4Cl (ca. 50

mL) was added slowly, and the mixture was warmed to room temperature. The mixture was extracted with EtOAc (3×80 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:3→1:1) to give 15.1 g (84%) of **46** as a yellow oil; ²H NMR (500 MHz) δ 7.38 (dd, *J*=2.0, 1.0 Hz, 1H), 6.33 (dd, *J*=3.0, 2.0 Hz, 1H), 6.27 (dt, *J*=3.0, 1.0 Hz, 1H), 5.30 (s, 1H), 5.01–4.97 (m, 1H), 2.83–2.72 (comp, 2H), 2.12–2.04 (m, 1H), 1.66 (s, 3H), 1.62 (s, 3H); ¹³C NMR (126 MHz) δ 167.7, 161.1, 154.7, 142.7, 110.6, 107.0, 106.9, 95.8, 64.9, 40.0, 25.4, 25.0; IR 3417, 1722, 1634 cm⁻¹. HRMS (CI) *m/z* calcd for C₁₂H₁₅O₅⁺ (M+1), 239.0919; found, 239.0921.

4.2.17. (E)-6-(2-(Furan-2-yl)vinyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (47)—MsCl (93.0 g, 0.820 mol) was added dropwise to a solution of alcohol **46** (122 g, 0.510 mol) and NEt₃ (165 g, 1.64 mol) in CH₂Cl₂ (511 mL) at 0 °C. The solution was stirred for 30 min, whereupon aqueous HCl (1 M, 450 mL) was added in portions. The mixture was extracted with CH₂Cl₂ (3×450 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with hexanes/EtOAc (1:5→1:1) to give 85.0 g (75%) of **47** as a pale yellow oil that crystallized upon standing in the freezer, mp 84–85 °C; ²H NMR (500 MHz) δ 7.46 (d, *J*=2.0 Hz, 1H), 7.03 (d, *J*=15.5 Hz, 1H), 6.54 (d, *J*=2.0 Hz, 1H), 6.46 (app t, *J*=2.0 Hz, 1H), 6.42 (d, *J*=15.5 Hz, 1H), 5.38 (s, 1H), 1.73 (s, 6H); ¹³C NMR (125 MHz) δ 163.1, 161.8, 151.4, 144.6, 124.3, 117.6, 114.0, 112.4, 106.4, 94.9, 25.1; IR 1720, 1629, 1607 cm⁻¹; HRMS (CI) *m/z* calcd for C₁₂H₁₃O₄⁺ (M+1), 221.0814; found, 221.0818.

4.2.18. 6-(2-(Furan-2-yl)ethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (48)—NaBH₄ (24.7 g, 654 mmol) was added in one portion to a mechanically stirred suspension of CoCl₂·6H₂O (23.3 g, 98.0 mmol) in DMF (540 mL) at –5 °C. Additional DMF (50 mL) was added to the resulting paste to facilitate stirring. A solution of diene **47** (72.1 g, 327 mmol) in DMF (110 mL) was added dropwise via an addition funnel, and the mixture was stirred for 3 h. Et₂O (ca. 300 mL) and water (ca. 300 mL) were added at 0 °C, and the suspension was filtered. The filtrate was divided into two portions, and each portion was extracted with Et₂O (4×400 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/hexanes (1:5→1:1) to give 24.5 g (34%) of **48** as a yellow liquid; ²H NMR (500 MHz) δ 7.29 (dd, *J*=2.0, 1.0 Hz, 1H), 6.26 (dd, *J*=3.0, 2.0 Hz, 1H), 6.01 (dd, *J*=3.0, 1.0 Hz, 1H), 5.21 (s, 1H), 2.87 (t, *J*=7.5 Hz, 2H), 2.56 (t, *J*=7.5 Hz, 2H), 1.64 (s, 6H); ¹³C NMR (125 MHz) δ 170.2, 161.1, 153.1, 141.4, 110.2, 106.5, 105.8, 93.9, 32.1, 25.0, 24.3; IR 2923, 1729, 1635 cm⁻¹; HRMS (CI) *m/z* calcd for C₁₂H₁₅O₄⁺ (M+1), 223.0970; found, 223.0972.

4.2.19. 6-(3-(4-Bromo-1-methyl-1H-indol-3-yl)-1-(furan-2-yl)-3-methylbutan-2-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one (51)—*n*-BuLi (2.00 M in hexanes, 0.600 mL, 1.20 mmol) was added dropwise to a solution of *i*-Pr₂NH₂ (131 mg, 1.30 mmol) in THF (1 mL) at 0 °C. The solution was stirred for 20 min and cooled to –78 °C. A solution of furan **48** (244 mg, 1.11 mmol) in THF (0.3 mL) was added dropwise and stirring continued for 1 h. A solution of TBSCl (203 mg, 1.30 mmol) in THF (0.5 mL) was added dropwise, and the mixture was gradually warmed up to room temperature over 16 h and stirred for an additional 5 h. The solvent was concentrated under reduced pressure, and the residue was partitioned between pentane (5 mL) and water (5 mL). The aqueous layer was extracted with pentane (2×5 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give crude **50** (373 mg, 1.11 mmol). The crude **50** thus obtained and crude **25** (268 mg, 1.00 mmol), which had been freshly prepared from **32** (252 mg, 1.00 mmol) according to the same procedure used for the synthesis of **33**, were dissolved in THF (9 mL) at –78 °C, and TMSOTf (222 mg, 180 μL, 1.00 mmol) was added dropwise. The

resulting solution was stirred for 40 min, where-upon NEt₃ (6 mL) was added dropwise. After warming to room temperature, water (10 mL) was added. The mixture was extracted with Et₂O (3×50 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with EtOAc/hexanes (1:5→1:2) to give 230 mg (48% over two steps) of **51** as a white solid: mp=145–146 (decomp.); ²H NMR (500 MHz) δ 7.42 (dd, *J*=8.0, 1.0 Hz, 1H), 7.24 (dd, *J*=8.0, 1.0 Hz, 1H), 7.16 (s, 1H), 7.02 (app t, *J*=8.0 Hz, 1H), 6.95 (s, 1H), 6.15 (s, 1H), 5.91 (s, 1H), 5.28 (br s, 1H), 4.48 (dd, *J*=13.0, 3.0 Hz, 1H), 3.71 (s, 3H), 2.90 (t, *J*=13.0 Hz, 2H), 1.66 (s, 3H), 1.55 (s, 6H), 1.36 (s, 3H); ¹³C NMR (125 MHz) δ 172.1, 161.3, 153.7, 140.8, 140.0, 128.9, 125.9, 125.2, 122.3, 122.1, 113.7, 110.2, 109.1, 106.2, 105.8, 96.4, 50.0, 37.8, 33.1, 26.9, 25.9, 23.9; IR 2920, 1723 cm⁻¹; HRMS (CI) *m/z* calcd for C₂₄H₂₇⁷⁹BrNO₄⁺ (M+1), 472.1123; found, 472.1128.

4.2.20. Methyl 5-(4-bromo-1-methyl-1H-indol-3-yl)-4-(furan-2-ylmethyl)-5-methyl-3-oxohexanoate (**42**)

4.2.20.1. Method A: A solution of **51** (900 mg, 1.91 mmol) in MeOH (3 mL) and toluene (30 mL) was heated under reflux for 14 h. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography eluting with EtOAc/hexanes (3:7) to give 620 mg (73%) of **42** as a white solid: mp 111–113 °C. The product existed as a mixture (4:1) of keto and enol tautomers in CDCl₃. Keto isomer: ²H NMR (500 MHz), δ 7.44 (dd, *J*=8.0, 1.0 Hz, 1H), 7.26 (dd, *J*=8.0, 1.0 Hz, 1H), 7.20 (s, 1H), 7.04 (t, *J*=8.0 Hz, 1H), 6.94 (s, 1H), 6.18 (br s, 1H), 5.89 (s, 1H), 4.77 (dd, *J*=12.0, 3.0 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 2H), 3.52 (s, 3H), 3.12–3.07 (comp, 2H), 1.67–1.56 (comp, 6H); ¹³C NMR (125 MHz) δ 206.6, 167.2, 153.9, 141.1, 140.0, 129.0, 125.9, 125.3, 122.4, 121.6, 113.6, 110.2, 109.2, 105.8, 57.7, 51.9, 51.2, 51.0, 37.7, 33.1, 26.8, 26.3. Enol isomer: ²H NMR (500 MHz), δ 12.10 (br s, 1H), 7.40 (dd, *J*=8.0, 1.0 Hz, 1H), 7.23 (dd, *J*=8.0 Hz, 1H), 7.13 (app s, 1H), 7.01 (t, *J*=8.0 Hz, 1H), 6.98 (s, 1H), 6.12 (dd, *J*=3.0, 2.0 Hz, 1H), 5.89 (s, 1H), 5.10 (br s, 1H), 4.26 (dd, *J*=12.0, 3.0 Hz, 1H), 3.71 (s, 3H), 3.52 (s, 3H), 3.06–3.00 (comp, 2H), 1.67–1.56 (comp, 6H); ¹³C NMR (125 MHz) δ 179.1, 172.9, 154.5, 140.6, 140.0, 129.0, 125.7, 125.3, 122.6, 122.1, 113.9, 110.0, 108.9, 105.3, 57.7, 51.9, 51.2, 37.7, 37.2, 33.1, 26.8, 26.3; IR 2952, 1747, 1709 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₂H₂₅⁷⁹BrNO₄⁺ (M+1), 446.0959; found, 446.0961.

4.2.20.2. Method B: A solution of ketoester **54** (1.60 g, 8.16 mmol) in CPME (1 mL) was added dropwise to a solution of NaHMDS (1.80 M, 10.0 mL, 17.9 mmol) in CPME (12 mL) at 0 °C. The solution was stirred for 35 min, and TMSCl (2.12 g, 2.48 mL, 19.6 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C and then for 2.5 h at room temperature. Hexanes (ca. 200 mL) were added, and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to give crude **55** (2.40 g, 7.04 mmol). The crude **55** thus obtained and crude **25** (1.02 g, 3.80 mmol), which had been freshly prepared from **32** (1.03 g, 4.08 mmol) according to the same procedure used for the synthesis of **33**, were dissolved in THF (14 mL) at –78 °C, and TMSOTf (906 mg, 730 μL, 4.08 mmol) was added dropwise. The resulting solution was stirred for 35 min, whereupon *n*-Bu₃N (1.4 mL) was added dropwise. The solvent was removed in vacuo, and the residue was dissolved in Et₂O (ca. 50 mL). The solution was washed with aqueous citric acid (1 M, 3×8 mL), and the organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with hexanes/EtOAc (1:9→1:1) to give 1.12 g (60%) of **42** that had a mp and spectroscopic properties identical to those obtained by *Method A*.

4.2.21. Furfuryl chloride (53**)**—A solution of benzotriazole (30 g, 0.25 mol) and thionyl chloride (30 g, 19 mL, 0.25 mol) in CH₂Cl₂ (33 mL) was added dropwise to a solution of

freshly distilled furfuryl alcohol (20 g, 18 mL, 0.20 mol) in CH_2Cl_2 (136 mL) at 0 °C. The reaction was stirred for 30 min, and the solids were removed by filtration. The filtrate was washed with water (400 mL), 2% aqueous NaOH (400 mL), and brine (200 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was distilled under reduced pressure (1 mmHg, 25–40 °C) to give 12 g (52%) of **53** as a pale yellow liquid; ^2H NMR (400 MHz, C_6D_6) δ 7.33 (dd, $J=2.0, 1.0$ Hz, 1H), 6.28–6.24 (comp, 2H), 4.50 (s, 2H). The ^2H NMR spectroscopic data of **53** were consistent with those reported in the literature.⁴⁹

4.2.22. Methyl 5-(furan-2-yl)-3-oxopentanoate (54)—Methyl ace-toacetate (**52**) (5.98 g, 51.5 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 2.27 g, 56.8 mmol) in THF (70 mL) at 0 °C. The reaction was stirred for 10 min, and *n*-BuLi (2.5 M in hexanes, 22.0 mL, 54.1 mmol) was added dropwise. The resulting clear orange mixture was stirred for an additional 10 min, and a solution of furfuryl chloride (**53**) (7.20 g, 61.8 mmol) in THF (16 mL) was added dropwise. The reaction was stirred for 45 min at room temperature, whereupon saturated NH_4Cl (ca. 50 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3×50 mL), and the combined organic layers were washed with saturated NaHCO_3 (ca. 50 mL). The aqueous layer was back-extracted with Et_2O (2×10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude orange oil was purified by distillation (150 °C, 1–2 Torr) to give 6.90 g (68%) of **54** as a yellow oil; ^2H NMR (400 MHz), δ 7.27 (dd, $J=2.0, 1.0$ Hz, 1H), 6.25 (dd, $J=3.0, 2.0$ Hz, 1H), 5.98 (dd, $J=3.0, 1.0$ Hz, 1H), 3.71 (s, 3H), 3.44 (s, 2H), 2.95–2.86 (comp, 4H); ^{13}C NMR (100 MHz) δ 201.2, 167.4, 153.9, 141.1, 110.2, 105.3, 52.3, 48.8, 41.0, 21.8; IR 3119, 2955, 1743, 1720, 1656 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{13}\text{O}_4^+$ ($M+1$), 197.0808; found, 197.0807.

4.2.23. Methyl-5-(tert-butyldimethylsilyloxy)-4-(furan-2-ylmethyl)-1,3,3-trimethyl-3,4-dihydro-1H-cyclohepta[cd]indole-6-carboxylate (57)— $\text{NaO}t\text{-Bu}$ (2.50 g, 26.3 mmol) was added to a mixture of bromoindole **42** (5.86 g, 13.1 mmol) and PEPPSI-IPr (356 mg, 0.520 mmol) in a glovebox, and toluene (109 mL) was added. The suspension was gradually heated to reflux and stirred for 25 min. The solution was cooled to room temperature, whereupon saturated aqueous NH_4Cl (ca. 120 mL) was added. The mixture was extracted with Et_2O (3×100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give crude **56** (4.27 g) that was used without further purification. NaH (60% dispersion in mineral oil, 1.05 g, 26.3 mmol) was added to a solution of crude **56** (4.27 g) and TBSCl (4.11 g, 26.3 mmol) in THF (130 mL). The suspension was stirred at room temperature for 41 h, whereupon the mixture was cooled to 0 °C, and saturated aqueous NH_4Cl (ca. 120 mL) was added. The mixture was extracted with Et_2O (3×100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with hexanes/ EtOAc (1:9→1:5) to give 5.61 g (89% over two steps) of **57** as an orange oil; ^2H NMR (500 MHz) δ 7.23 (dd, $J=2.0, 1.0$ Hz, 1H), 7.16 (app t, $J=7.5$ Hz, 1H), 7.11 (dd, $J=7.5, 1.0$ Hz, 1H), 6.84 (s, 1H), 6.78 (dd, $J=7.5, 1.0$ Hz, 1H), 6.18 (dd, $J=3.0, 2.0$ Hz, 1H), 5.90 (dd, $J=3.0, 1.0$ Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.71 (dd, $J=9.5, 4.5$ Hz, 1H), 2.52 (dd, $J=15.0, 4.5$ Hz, 1H), 2.37 (dd, $J=15.0, 9.5$ Hz, 1H), 1.46 (s, 3H), 1.34 (s, 3H), 0.84 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz) δ 170.0, 155.6, 154.3, 140.6, 137.2, 125.8, 124.4, 122.7, 121.8, 117.2, 116.8, 110.5, 107.2, 106.7 (two overlapping peaks), 56.7, 51.7, 36.3, 32.8, 32.5, 28.6, 27.9, 25.5 (three overlapping peaks), 18.1, –3.6, –3.7; IR 2929, 1729 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{28}\text{H}_{38}\text{NO}_4\text{Si}^+$ ($M+1$), 480.2570; found, 480.2571.

4.2.24. (Z)-Methyl 2,13,13-trimethyl-8,11-dioxo-2,8,11,12,12a,13-hexahydrooxocino[2',3':5,6]cyclohepta[1,2,3-cd]indole-6-carboxylate (58)—

PCC (54 mg, 0.25 mmol) was added to a solution of furan **56** (39 mg, 0.11 mmol) in CH₂Cl₂ (3 mL) at 0 °C. The suspension was stirred for 2 h, whereupon water (ca. 10 mL) was added. The mixture was extracted with CH₂Cl₂ (3×10 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/hexanes (1:5→2:1) to give 18 mg (45%) of **58** as a yellow oil; ²H NMR (500 MHz) δ 7.51 (d, *J*=5.5 Hz, 1H), 7.29 (d, *J*=8.0 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 7.01 (s, 1H), 6.81 (d, *J*=8.0 Hz, 1H), 6.13 (d, *J*=5.5 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.70 (app t, *J*=8.5 Hz, 1H), 2.58 (dd, *J*=13.5, 8.5 Hz, 1H), 2.15 (dd, *J*=13.5, 8.5 Hz, 1H), 1.50 (s, 3H), 1.36 (s, 3H); ¹³C NMR (125 MHz) δ 205.2, 171.8, 168.5, 157.3, 136.7, 127.8, 124.2, 122.6, 121.8, 121.5, 119.5, 118.8, 109.8, 90.8, 73.6, 57.1, 52.6, 37.1, 34.6, 33.1, 31.8, 31.4; IR 2924, 1756, 1731 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₂H₂₁NNaO₅⁺ (*M*+23), 402.1311; found, 402.1313.

4.2.25. (E)-Methyl-5-(tert-butyldimethylsilyloxy)-4-(2,5-dioxopent-3-enyl)-1,3,3-trimethyl-3,4-dihydro-1H-cyclohepta[cd]indole-6-carboxylate (59)—A solution of NBS (845 mg, 4.75 mmol) in DMF (5 mL) was added dropwise using an addition funnel to a solution of furan **57** (2.28 g, 4.75 mmol) and pyridine (1.50 g, 1.46 mL, 19.0 mmol) in DMF/H₂O (85:15, 50 mL) at 0 °C. The resulting orange-brown solution was stirred for 2 h, whereupon furan (966 mg, 1.00 mL, 14.2 mmol) was added to quench any unreacted NBS. Brine (40 mL) was added, and the reaction mixture was extracted with Et₂O (3×60 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure, and the residue was purified on florisil eluting with EtOAc/hexanes (1:9→1:3) to give 814 mg (34%) of **59** as a yellow solid: mp=127–128 °C; ²H NMR (500 MHz) δ 9.64 (d, *J*=7.5 Hz, 1H), 7.20–7.14 (comp, 2H), 6.84 (s, 1H), 6.75 (dd, *J*=7.0, 1.0 Hz, 1H), 6.74 (d, *J*=16.0 Hz, 1H), 6.44 (dd, *J*=16.0, 7.5 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.97 (dd, *J*=8.0, 4.5 Hz, 1H), 2.58 (dd, *J*=15.5, 8.0 Hz, 1H), 2.46 (dd, *J*=15.5, 4.5 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H); ¹³C NMR (125 Hz) δ 199.6, 193.5, 169.5, 154.4, 145.2, 137.4, 137.3, 125.1, 124.7, 122.4, 122.1, 121.5, 117.9, 117.5, 107.8, 53.0, 51.8, 42.7, 36.7, 32.9, 32.0, 28.1, 25.6 (three overlapping peaks), 18.1, -3.2, -3.5; IR 2929, 2857, 1729, 1693, 1619 cm⁻¹; HRMS (CI) *m/z* calcd for C₂₈H₃₇NO₅Si⁺ (*M*⁺), 495.2441; found, 495.2442.

4.2.26. (E)-Methyl-5-(tert-butyldimethylsilyloxy)-4-(5-hydroxy-2-oxopent-3-enyl)-1,3,3-trimethyl-3,4-dihydro-1H-cyclohepta[cd]indole-6-carboxylate (63)—A solution of *t*-BuNH₂BH₃ (37 mg, 0.42 mmol) in THF (0.5 mL) was added dropwise to a solution of aldehyde **59** (0.59 g, 1.2 mmol) in THF (6.0 mL) at -78 °C. The solution was stirred for 3.5 h, whereupon acetone (2 mL) was added. The solvent was removed under reduced pressure, and the residue was purified on florisil eluting with EtOAc/hexanes (1:3/1:1) to give 0.48 g (82%) of **63** as a white foam; ²H NMR (600 MHz) δ 7.19–7.14 (comp, 2H), 6.83 (s, 1H), 6.74 (dd, *J*=7.0, 1.0 Hz, 1H), 6.60 (ddd, *J*=16.0, 4.5, 3.5 Hz, 1H), 6.21 (dt, *J*=16.0, 2.0 Hz, 1H), 4.28–4.24 (m, 1H), 4.22–4.17 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.99 (dd, *J*=8.5, 4.5 Hz, 1H), 2.78 (dd, *J*=10.0, 4.5 Hz, 1H), 2.48 (dd, *J*=13.0, 10.0 Hz, 1H), 2.21 (dd, *J*=13.0, 4.5 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 0.87 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H); ¹³C NMR (150 Hz) δ 200.2, 171.1, 154.1, 146.3, 137.3, 128.8, 124.9, 124.5, 122.4, 122.0, 121.7, 117.6, 117.0, 107.6, 62.2, 54.5, 52.1, 41.0, 36.4, 32.8, 32.2, 27.9, 25.5 (three overlapping peaks), 18.0, -2.9, -3.6; IR 3466, 2927, 2855, 1725, 1618 cm⁻¹; HRMS (CI) *m/z* calcd for C₂₈H₃₉NO₅Si⁺ (*M*⁺), 497.2598; found, 497.2590.

4.2.27. (E)-Methyl 4-(5-acetoxy-2-oxopent-3-en-1-yl)-5-((tert-butyldimethylsilyl)oxy)-1,3,3-trimethyl-3,4-dihydro-1H-cyclo-hepta[cd]indole-6-

carboxylate (62)—AcCl (52 mg, 45 μ L, 0.66 mmol) was added dropwise to a solution of allylic alcohol **63** (0.29 g, 0.58 mmol) and collidine (70 mg, 0.19 mL, 0.58 mmol) in MeCN (2.9 mL) at -20°C . The solution was stirred for 1.2 h, whereupon aqueous citric acid (0.2 M, ca. 12 mL) was added. The solution was saturated with solid NaCl and extracted with CH_2Cl_2 (4 $\times$ 10 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with EtOAc/hexanes (1:5 $\rightarrow$ 1:2) to give 0.68 g (89%) of **62** as a yellow oil; ^2H NMR (500 MHz) δ 7.18–7.12 (comp, 2H), 6.84 (s, 1H), 6.75 (dd, $J=7.0, 1.0$ Hz, 1H), 6.49 (dt, $J=16.0, 4.5$ Hz, 1H), 6.09 (dt, $J=16.0, 2.0$ Hz, 1H), 4.64 (dd, $J=4.5, 2.0$ Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.03 (dd, $J=7.0, 5.0$ Hz, 1H), 2.51 (dd, $J=16.5, 7.0$ Hz, 1H), 2.32 (dd, $J=16.5, 5.0$ Hz, 1H), 2.05 (s, 3H), 1.36 (s, 6H), 0.90 (s, 9H), 0.27 (s, 3H), 0.25 (s, 3H); ^{13}C NMR (125 MHz) δ 198.7, 170.3, 169.8, 155.8, 139.7, 137.3, 129.9, 125.6, 124.8, 122.5, 121.9, 121.8, 117.2, 117.1, 107.4, 62.6, 52.1, 51.8, 42.1, 36.7, 32.8, 32.0, 28.1, 25.6, 20.7, 18.1, $-3.4, -3.5$; IR 2929, 1728, 1620 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{30}\text{H}_{42}\text{NO}_6\text{Si}^+$ ($M+1$), 540.2781; found, 540.2779.

4.2.28. (E)-Methyl-4-[5-(benzoyloxy)-2-oxopent-3-en-1-yl]-5-[(tert-butyldimethylsilyl)oxy]-1,3,3-trimethyl-3,4-dihydro-1H-cyclo-hepta[cd]indole-6-carboxylate (64)—BzCl (236 mg, 285 μ L, 1.68 mmol) was added dropwise to a solution of alcohol **63** (380 mg, 0.760 mmol) and collidine (277 mg, 254 μ L, 2.29 mmol) in MeCN (3 mL) at 0°C . The cloudy yellow solution was stirred for 2 h at 0°C . The mixture was diluted with CH_2Cl_2 (10 mL) and washed with aqueous citric acid (0.2 M, 5 mL). The aqueous layer was saturated with solid NaCl and extracted with CH_2Cl_2 (4 $\times$ 5 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/hexanes (1:9 $\rightarrow$ 1:3) to give 452 mg (98%) of **64** as a pale yellow oil; ^2H NMR (400 MHz), δ 8.05–8.02 (comp, 2H), 7.58–7.53 (m, 1H), 7.47–7.41 (comp, 2H), 7.19–7.13 (comp, 2H), 6.86 (s, 1H), 6.76 (dd, $J=1.5, 6.5$ Hz, 1H), 6.63 (dt, $J=4.0, 16.0$ Hz, 1H), 6.22 (dt, $J=2.0, 16.0$ Hz, 1H), 4.92–4.90 (comp, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.06 (dd, $J=4.5, 7.0$ Hz, 1H), 2.56 (dd, $J=7.0, 16.0$ Hz, 1H), 2.36 (dd, $J=4.5, 16.0$ Hz, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 0.92 (s, 9H), 0.29 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (100 MHz), δ 198.8, 169.7, 165.8, 155.6, 140.0, 137.2, 133.2, 129.8, 129.7, 129.5 (two overlapping peaks), 128.4 (two overlapping peaks), 125.5, 124.8, 122.4, 121.9, 121.7, 117.2, 117.1, 107.4, 63.0, 52.2, 51.8, 41.9, 36.7, 32.8, 32.0, 28.0, 25.6 (three overlapping peaks), 18.1, $-3.39, -3.47$; IR 2952, 2859, 1728, 1621 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{35}\text{H}_{43}\text{NO}_6\text{Si}^+$ (M^+), 601.2860; found, 601.2855.

4.2.29. Methyl-(3Z)-3-ethylidene-7,7,10-trimethyl-4,16-dioxo-10-azatetracyclo[6.6.1.1 2,6 .0 11,15]hexadeca-1(15),8,11,13-tetraene-2-carboxylate (67), methyl (3E)-3-ethylidene-7,7,10-trimethyl-4,16-dioxo-10-azatetracyclo[6.6.1.1 2,6 .0 11,15]hexadeca-1(15),8,11,13-tetraene-2-carboxylate (68), methyl 3-ethenyl-7,7,10-trimethyl-4,16-dioxo-10-azatetracyclo[6.6.1.1 2,6 .0 11,15]hexadeca-1(15), 8,11,13-tetraene-2-carboxylate (40)—A solution of TBAF $\cdot$ 3H $_2$ O (882 mg, 2.80 mmol) in THF (5 mL) was added dropwise to a solution of benzoate **64** (1.40 g, 2.33 mmol) in THF (120 mL) at 0°C . The resulting yellow solution was stirred for 10 min, whereupon saturated NH_4Cl (ca. 100 mL) was added. The mixture was extracted with Et $_2$ O (3 $\times$ 200 mL), and the combined organic layers were dried (MgSO_4) and concentrated under reduced pressure. The residue was dissolved in toluene (25 mL), and a suspension of Pd_2dba_3 (430 mg, 0.470 mmol) and trifurylphosphine (860 mg, 3.73 mmol) in toluene (95 mL) was added at room temperature. Bu_3SnOMe (899 mg, 1.00 mL, 2.80 mmol) was added, and the mixture was heated at 100°C for 4 h. After

cooling to room temperature, saturated aqueous NaHCO_3 (ca. 75 mL) was added, and the mixture was extracted with EtOAc (75 mL) and CH_2Cl_2 (3×75 mL). The combined organic layers were passed through a short plug of florisil, and the eluent was concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/hexanes (1:3→1:1) to give 710 mg (84% over two steps) of a mixture (5.8:1:3.5) of **67**, **68**, and **40** as a yellow oil; ^2H NMR (600 MHz) δ 7.22–7.21 (comp, 2H), 7.20–7.19 (comp, 2H), 7.16 (q, $J=7.5$ Hz, 1H), 7.04 (q, $J=8.0$ Hz, 1H), 7.00 (s, 1H), 6.97 (s, 1H), 6.87–6.83 (m, 1H), 6.81–6.78 (m, 1H), 5.99 (ddd, $J=17.5, 10.5, 5.5$ Hz, 1H), 5.27 (ddd, $J=10.5, 2.0, 0.5$ Hz, 1H), 5.16 (ddd, $J=17.5, 2.0, 0.5$ Hz, 1H), 4.06 (dd, $J=5.5, 2.0$ Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 2.98–2.94 (m, 1H), 2.91–2.87 (comp, 2H), 2.86–2.80 (m, 1H), 2.73–2.68 (m, 1H), 2.51 (ddd, $J=19.0, 3.5, 1.5$ Hz, 1H), 2.13 (d, $J=7.5$ Hz, 3H), 2.05 (d, $J=8.0$ Hz, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (151 MHz) δ 205.6, 204.6, 204.4, 198.0, 170.9, 170.8, 142.2, 137.2, 131.5, 129.0, 127.9, 127.4, 123.6, 122.8, 122.0, 120.2, 119.71, 119.4, 119.3, 118.4, 109.4, 108.6, 73.4, 69.4, 66.6, 57.4, 56.8, 52.6, 42.4, 39.7, 37.4, 37.0, 33.0, 32.9, 32.6, 32.4, 29.8, 29.6, 29.0, 16.9; IR 2292, 2852, 1741, 1711, 1607, 1451, 1418, 1232 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_4^+$ ($M+1$), 366.1699; found, 366.1698.

4.2.30. Methyl-3-ethenyl-3,7,7,10-tetramethyl-4,16-dioxo-10-azatetracyclo[6.6.1.1^{2,6}.0^{11,15}]hexadeca-1(15),8,11,13-tetraene-2-carboxylate (39**)**—

Freshly prepared NaHMDS (0.72 M in toluene, 0.46 mL, 0.33 mmol) was added dropwise to a solution of **67**, **68**, and **40** (0.15 g, 0.41 mmol) in DMF (8 mL) at -40°C . The solution was stirred for 20 min and then for 30 min at room temperature. The solution was recooled to -40°C , and MeI (26 μL , 0.41 mmol) was added dropwise. The solution was gradually warmed up to room temperature over 5 h and then stirred for an additional 15 h, whereupon saturated aqueous NH_4Cl (ca. 8 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/hexanes (1:3→1:1) to give 0.10 g (80%) of **39** as a yellow solid: mp $210\text{--}211^\circ\text{C}$ (decomp.); ^2H NMR (500 MHz) δ 7.23 (dd, $J=7.5, 1.0$ Hz, 1H), 7.15 (t, $J=7.5$ Hz, 1H), 6.95 (s, 1H), 6.66 (dd, $J=7.5, 1.0$ Hz, 1H), 5.98 (dd, $J=18.0, 11.0$ Hz, 1H), 5.45–5.41 (comp, 2H), 3.73 (s, 3H), 3.66 (s, 3H), 3.09 (dd, $J=10.5, 3.0$ Hz, 1H), 2.95 (dd, $J=19.0, 10.5$ Hz, 1H), 2.64 (dd, $J=19.0, 3.0$ Hz, 1H), 1.69 (s, 3H), 1.47 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz) δ 207.7, 206.0, 170.3, 137.7, 135.9, 127.2, 124.0, 123.4, 122.8, 120.7, 119.6, 118.2, 109.4, 73.6, 58.9, 57.7, 52.0, 39.3, 37.2, 33.0, 32.9, 28.4, 19.3; IR 2921, 2847, 1744, 1705 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{23}\text{H}_{26}\text{NO}_4^+$ ($M+1$), 380.1862; found, 380.1860.

4.2.31. Methyl-9-chloro-3-ethenyl-3,7,7,10-tetramethyl-4,16-dioxo-10-azatetracyclo[6.6.1.1^{2,6}.0^{11,15}]hexadeca-1(15),8,11,13-tetraene-2-carboxylate (69**)**—

PCl_5 (35 mg, 0.17 mmol) was added to a solution of ketone **39** (66 mg, 0.17 mmol) in CH_2Cl_2 (2.8 mL) at room temperature. The suspension was stirred for 1 h, whereupon saturated aqueous NaHCO_3 (ca. 4 mL) was added slowly. The mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with hexanes/EtOAc (1:9→1:1) to provide 42 mg (60%) of **69** as a yellow solid: mp $240\text{--}241^\circ\text{C}$; ^2H NMR (600 MHz) δ 7.21 (dd, $J=8.0, 1.0$ Hz, 1H), 7.14 (t, $J=8.0$ Hz, 1H), 6.77 (dd, $J=8.0, 1.0$ Hz, 1H), 6.19–6.15 (m, 1H), 5.51–5.46 (comp, 2H), 3.71 (s, 3H), 3.58 (s, 3H), 3.01–2.95 (m, 2H), 2.81–2.75 (m, 1H), 1.72 (s, 3H), 1.65 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 Hz) δ 207.8, 205.1, 170.1, 136.1, 136.0, 125.5, 124.4, 123.8, 123.3, 120.8, 118.8, 113.9, 109.3, 72.8, 58.7, 58.6, 52.1, 39.7, 38.9, 30.0, 28.9, 28.5, 19.5; IR 2948, 1747, 1707 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{25}\text{NNaO}_4^+$ ($M+23$), 436.1286; found, 436.1284.

4.2.32. N-Methyl-3-ethenyl-3,7,7,10-tetramethyl-4,9,16-trioxo-10-azatetracyclo[6.6.1.1^{2,6}.0^{11,15}]hexadeca-1(15),11,13-triene-2-carboxylate (71, 72)

4.2.32.1. Method A: Urea–hydrogen peroxide adduct (20 mg, 0.21 mmol) was added to a stirred suspension of MeReO₃ (1.0 mg, 4.0 μmol) in CH₂Cl₂ (0.2 mL) at room temperature. The resulting yellow suspension was stirred for 10 min, and a solution of indole **39** (6.0 mg, 10 μmol) in CH₂Cl₂ (0.2 mL) was added dropwise. The mixture was stirred for 6 h and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography eluting with EtOAc/hexanes (1:3→1:1) to give 2.0 mg (34%) of a mixture (1:1.5) of **71** and **72** as a yellow oil. For **71**: ²H NMR (600 MHz) δ 7.19–7.16 (m, 1H), 6.73 (d, *J*=8.0 Hz, 1H), 6.39 (d, *J*=8.0, 1.0 Hz, 1H), 5.75 (dd, *J*=17.5, 11.0 Hz, 1H), 5.40 (dd, *J*=17.5, 1.0 Hz, 1H), 5.34 (dd, *J*=11.0, 1.0 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 1H), 3.30 (dd, *J*=16.5, 10.0 Hz, 1H), 3.16 (s, 3H), 3.08 (d, *J*=10.0 Hz, 1H), 2.93 (d, *J*=16.5 Hz, 1H), 1.72 (s, 3H), 1.60 (s, 3H), 0.85 (s, 3H); ¹³C NMR (151 MHz) δ 208.3, 203.8, 173.8, 169.6, 144.0, 134.3, 129.5, 127.0, 126.5, 124.1, 117.9, 107.3, 75.3, 63.1, 58.9, 51.9, 51.0, 39.2, 38.2, 26.3, 25.6, 22.7, 19.3. For **72**: ²H NMR (600 MHz) δ 7.27 (dd, *J*=8.0, 1.0 Hz, 1H), 7.22 (dt, *J*=8.0, 1.0 Hz, 1H), 6.79 (dd, *J*=8.0, 1.0 Hz, 1H), 6.54 (dd, *J*=18.0, 11.0 Hz, 1H), 5.55 (dd, *J*=18.0, 1.0 Hz, 1H), 5.51 (dd, *J*=11.0, 1.0 Hz, 1H), 3.60 (s, 3H), 3.40 (s, 1H), 3.17 (s, 3H), 2.74 (t, *J*=9.0 Hz, 1H), 2.62–2.58 (comp, 2H), 1.70 (s, 3H), 1.55 (s, 3H), 0.89 (s, 3H); ¹³C NMR (151 MHz) δ 207.3, 205.7, 174.1, 168.2, 144.7, 137.4, 133.6, 128.8, 125.4, 122.5, 119.6, 108.3, 70.9, 58.3, 54.4, 52.6, 51.8, 41.2, 40.3, 28.4, 26.2, 22.8, 20.5; IR 2926, 1746, 1711, 1609, 1590, 1462 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₃H₂₆NO₅⁺ (*M*+1), 396.1805; found, 396.1804.

4.2.32.2. Method B: Concentrated HCl (0.5 mL) was added to a solution of chloroindole **69** (12 mg, 0.028 mmol) in dioxane (0.5 mL) at room temperature. The resulting suspension was stirred vigorously at 100 °C for 8 h. After cooling to room temperature, saturated aqueous NaHCO₃ was added until gas evolution ceased. The mixture was extracted with CH₂Cl₂ (3×10 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/hexanes (1:3→1:1) to give 4.0 mg (36%) of a mixture (1:1.2) of **71** and **72** as a yellow oil.

4.2.33. (6S,7S,10R)-Methyl-7-ethyl-2,7,11,11-tetramethyl-8,12-dioxo-6,7,8,9,10,11-hexahydro-2H-6,10-methanocyclonona[cd]indole-6-carboxylate (74).—NEt₃ (9.0 mg, 90 μmol) and N₂H₄·H₂O (64%, 11 mg, 0.23 mmol) were added to a suspension of ketone **39** (4.0 mg, 10 μmol) in EtOH (0.2 mL) at room temperature. The mixture was heated at 70 °C for 6 h. The solution was diluted with CH₂Cl₂ (ca. 2 mL) and washed with water (ca. 1 mL). The aqueous layer was extracted with CH₂Cl₂ (2×3 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with hexanes/EtOAc (1:5→1:2) to give 1.0 mg (26%) of **74** as a yellow oil; ²H NMR (600 MHz) δ 7.20 (dd, *J*=8.0, 1.0 Hz, 1H), 7.14 (t, *J*=8.0 Hz, 1H), 6.91 (s, 1H), 6.62 (dd, *J*=8.0, 1.0 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.08 (dd, *J*=11.0, 2.0 Hz, 1H), 2.92 (dd, *J*=17.5, 11.0 Hz, 1H), 2.48 (dd, *J*=17.5, 2.0 Hz, 1H), 1.82–1.72 (comp, 2H), 1.51 (s, 3H), 1.47 (s, 3H), 1.17 (s, 3H), 0.83 (t, *J*=7.5 Hz, 3H); ¹³C NMR (150 MHz) δ 208.2, 207.1, 171.0, 137.6, 126.9, 124.5, 123.5, 122.4, 120.5, 119.6, 109.2, 75.7, 58.8, 57.1, 52.1, 39.1, 36.7, 33.4, 33.0, 28.1, 24.4, 18.5, 10.1; IR 2918, 2849, 1737, 1702, 1611 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₃H₂₇NNaO₄⁺ (*M*+23), 404.1832; found, 404.1835.

4.2.34. Methyl-2,7,11,11-tetramethyl-12-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-7-vinyl-6, 7,10,11-tetrahydro-2H-6,10-

methanocyclonona[cd]indole-6-carboxylate (75)—LiHMDS (0.850 M, 3.00 mL, 2.58 mmol) was added dropwise to a solution of ketone **39** (109 mg, 0.290 mmol) in THF (3 mL) at -40°C . The reaction mixture was stirred for 45 min, and a solution of Comins' reagent (1.01 g, 2.58 mmol) in THF (1 mL) was added dropwise. After stirring for 1 h, the mixture was quenched with saturated aqueous NaHCO_3 (ca. 5 mL) and extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were washed with brine (ca. 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:9 $\rightarrow$ 1:3) to give 118 mg (80%) of **75** as a yellow oil; ^2H NMR (400 MHz), δ 7.29 (dd, $J=8.0, 1.0$ Hz, 1H), 7.18 (t, $J=8.0$ Hz, 1H), 6.96 (s, 1H), 6.69 (dd, $J=8.0, 1.0$ Hz, 1H), 5.80 (d, $J=3.0$ Hz, 1H), 5.69 (dd, $J=11.0, 17.5$ Hz, 1H), 5.50–5.43 (comp, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.28 (d, $J=3.0$ Hz, 1H), 1.75 (s, 3H), 1.62 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz), δ 204.0, 170.4, 152.0, 137.5, 134.8, 126.1, 125.0, 124.2, 123.0, 120.4, 120.3, 118.9, 116.3, 109.2, 74.1, 60.3, 52.1, 52.0, 36.2, 33.2, 33.0, 28.5, 21.1; IR 2952, 1746, 1714, 1418 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{24}\text{H}_{24}\text{F}_3\text{NO}_6\text{S}^+$ (M^+), 511.1276; found, 511.1275.

4.2.35. 3-Ethenyl-3,7,7,10-tetramethyl-4,16-dioxo-10-azatetra-tnqh_0009;cyclo[6.6.1.1^{2,6}.0^{11,15}]-hexadeca-1(14),8,11(15),12-tetraene-2-carbaldehyde (79)—A suspension of LiAlH_4 (64 mg, 1.7 mmol) in Et_2O (2 mL) was sonicated for 1 min and filtered through a nylon syringe filter (pore size: 0.45 μm) into a dry 2 DRAM glass vial. An aliquot (0.3 mL) of this solution was added dropwise to a suspension of **39** (11 mg, 0.029 mmol) in Et_2O (0.8 mL) at 0°C . The mixture was stirred for 30 min and then for 3.5 h at room temperature. The mixture was cooled to 0°C , and water was added dropwise until gas evolution ceased. Aqueous HCl (1 N, 1 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 $\times$ 4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a mixture of diastereomeric triols **78**. Dess–Martin periodinane (61 mg, 0.14 mmol) was added to a mixture of crude triols and NaHCO_3 (33 mg, 0.39 mmol) in a glovebox, and CH_2Cl_2 (1 mL) was added. The mixture was stirred at room temperature for 2.5 h, whereupon saturated aqueous NaHCO_3 (ca. 1 mL) was added. The mixture was extracted with CH_2Cl_2 (4 $\times$ 4 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (EtOAc/hexanes=1:1) to give 9.0 mg (89% over two steps) of **79** as a light yellow solid; ^2H NMR (600 MHz) δ 9.61 (s, 1H), 7.29 (dd, $J=8.1, 0.5$ Hz, 1H), 7.21 (app t, $J=7.5$ Hz, 1H), 7.00 (s, 1H), 6.60 (dd, $J=7.5, 0.5$ Hz, 1H), 5.81 (dd, $J=17.6, 11.0$ Hz, 1H), 5.40 (dd, $J=11.0, 0.8$ Hz, 2H), 5.36 (dd, $J=17.6, 0.8$ Hz, 1H), 3.76 (s, 3H), 3.01–2.95 (comp, 2H), 2.79–2.74 (m, 1H), 1.65 (s, 3H), 1.49 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (150 MHz) δ 209.2, 207.7, 194.7, 138.0, 135.9, 127.6, 124.5, 122.8, 121.3, 120.3, 119.7, 117.9, 110.3, 72.4, 58.0, 57.5, 39.6, 37.6, 33.1, 33.0, 28.6, 19.1; IR 2968, 2924, 2853, 1736, 1713, 1692, 1454, 1417, 1333, 1214, 1147 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_3^+$ ($M+1$), 350.1750; found, 350.1751.

Acknowledgments

We thank the National Institutes of Health (GM 25439) the Robert A. Welch Foundation (F-0652) for their generous support of this research. We are also grateful to Vince Lynch (The University of Texas) for X-ray crystallography and Steve Sorey (The University of Texas) for NMR spectroscopy.

References and notes

- Stratmann K, Moore RE, Bonjouklian R, Deeter JB, Patterson GML, Shaffer S, Smith CD, Smitka TA. *J Am Chem Soc.* 1994; 116:9935–9942.
- Jimenez JJ, Huber U, Moore RE, Patterson GML. *J Nat Prod.* 1999; 62:569–572. [PubMed: 10217710]

3. Smith CD, Zilfou JT, Stratmann K, Patterson GML, Moore RE. *Mol Pharmacol*. 1995; 47:241–247. [PubMed: 7870031]
4. Zhang XQ, Smith CD. *Mol Pharmacol*. 1996; 49:288–294. [PubMed: 8632761]
5. For reviews, see: Avendaño C, Menéndez JC. *Curr Org Synth*. 2004; 1:65–82. Brown LE, Konopelski JP. *Org Prep Proced Int*. 2008; 40:411–445. Hutters AD, Styduhar ED, Garg NK. *Angew Chem, Int Ed*. 2012; 51:3758–3765. Wood JL. *Nature Chem*. 2012; 4:341–343. [PubMed: 22522248] See also: Konopelski JP, Deng H, Schiemann K, Keane JM, Olmstead MM. *Synlett*. 1998:1105–1107. Wood JL, Holubec AA, Stoltz BM, Weiss MM, Dixon JA, Doan BD, Shamji MF, Chen JM, Heffron TP. *J Am Chem Soc*. 1999; 121:6326–6327. Deng H, Konopelski JP. *Org Lett*. 2001; 3:3001–3004. [PubMed: 11554828] Jung ME, Slowinski F. *Tetrahedron Lett*. 2001; 42:6835–6838. López-Alvarado P, García-Granda S, Álvarez-Rúa C, Avendaño C. *Eur J Org Chem*. 2002; 2002:1702–1707. MacKay JA, Bishop RL, Rawal VH. *Org Lett*. 2005; 7:3421–3424. [PubMed: 16048307] Baudoux J, Blake AJ, Simpkins NS. *Org Lett*. 2005; 7:4087–4089. [PubMed: 16146358] Greshock TJ, Funk RL. *Org Lett*. 2006; 8:2643–2645. [PubMed: 16737334] Lauchli R, Shea KJ. *Org Lett*. 2006; 8:5287–5289. [PubMed: 17078699] Xia J, Brown LE, Konopelski JP. *J Org Chem*. 2007; 72:6885–6890. [PubMed: 17685656] Richter JM, Ishihara Y, Masuda T, Whitefield BW, Llamas T, Pohjakallio A, Baran PS. *J Am Chem Soc*. 2008; 130:17938–17954. [PubMed: 19035635] Boissel V, Simpkins NS, Bhalay G, Blake AJ, Lewis W. *Chem Commun*. 2009:1398–1400. Boissel V, Simpkins NS, Bhalay G. *Tetrahedron Lett*. 2009; 50:3283–3286. Tian X, Hutters AD, Douglas CJ, Garg NK. *Org Lett*. 2009; 11:2349–2351. [PubMed: 19432408] Trost BM, McDougall PJ. *Org Lett*. 2009; 11:3782–3785. [PubMed: 19606876] Brailsford JA, Lauchli R, Shea KJ. *Org Lett*. 2009; 11:5330–5333. [PubMed: 19860385] Freeman DB, Holubec AA, Weiss MW, Dixon JA, Kakefuda A, Ohtsuka M, Inoue M, Vaswani RG, Ohki H, Doan BD, Reisman SE, Stoltz BM, Day JJ, Tao RN, Dieterich NA, Wood JL. *Tetrahedron*. 2010; 66:6647–6655. [PubMed: 20733933] Heidebrecht RW, Gullede B, Martin SF. *Org Lett*. 2010; 12:2492–2495. [PubMed: 20446675] Ruiz M, Lopez-Alvarado P, Menendez JC. *Org Biomol Chem*. 2010; 8:4521–4523. [PubMed: 20717611] Bhat V, Rawal VH. *Chem Commun*. 2011:9705–9707. Bhat V, MacKay JA, Rawal VH. *Org Lett*. 2011; 13:3214–3217. [PubMed: 21615098] Bhat V, MacKay JA, Rawal VH. *Tetrahedron*. 2011; 67:10097–10104. Zhang M, Tang WP. *Org Lett*. 2012; 14:3756–3759.
6. (a) Bhat V, Allan KM, Rawal VH. *J Am Chem Soc*. 2011; 133:5798–5801. [PubMed: 21446729] (b) Hutters AD, Quasdorf KW, Styduhar ED, Garg NK. *J Am Chem Soc*. 2011; 133:15797–15799. [PubMed: 21819133] (c) Allan KM, Kobayashi K, Rawal VH. *J Am Chem Soc*. 2012; 134:1392–1395. [PubMed: 22235963] (d) Quasdorf KW, Hutters AD, Lodewyk MW, Tantillo DJ, Garg NK. *J Am Chem Soc*. 2012; 134:1396–1399. [PubMed: 22235964]
7. Fu TH, McElroy WT, Shamszad M, Heidebrecht RW Jr, Gullede B, Martin SF. *Org Lett*. 2012; 14:3834–3837. [PubMed: 22830424]
8. Kosuge T, Ishida H, Inaba A, Nukaya H. *Chem Pharm Bull*. 1985; 33:1414–1418.
9. Bordwell FG, Fried HE. *J Org Chem*. 1991; 56:4218–4223.
10. Fox JM, Huang S, Chieffi A, Buchwald SL. *J Am Chem Soc*. 2000; 122:1360–1370.
11. Kawatsura M, Hartwig JF. *J Am Chem Soc*. 1999; 121:1473–1478.
12. Littke AF, Schwarz L, Fu GC. *J Am Chem Soc*. 2002; 124:6343–6348. [PubMed: 12033863]
13. (a) Comins DL, Stroud ED. *Tetrahedron Lett*. 1986; 27:1869–1872. (b) Muratake H, Natsume M. *Tetrahedron*. 1990; 46:6331–6342. (c) Grieco PA, Handy ST. *Tetrahedron Lett*. 1997; 38:2645–2648.
14. Fu TH, Bonaparte A, Martin SF. *Tetrahedron Lett*. 2009; 50:3253–3256. [PubMed: 20161309]
15. For other recent related processes, see: Mendoza O, Rossey G, Ghosez L. *Tetrahedron Lett*. 2011; 52:2235–2239. Zhong X, Li Y, Han FS. *Chem — Eur J*. 2012; 18:9784–9788. [PubMed: 22744831]
16. (a) Trost BM, Van Vranken DL. *Chem Rev*. 1996; 96:395–422. [PubMed: 11848758] (b) Lu Z, Ma S. *Angew Chem, Int Ed*. 2008; 47:258–297.
17. For some examples, see: Martin SF, Gluchowski C, Campbell CL, Chapman RC. *J Org Chem*. 1984; 49:2512–2513. Martin SF, Guinn DE. *J Org Chem*. 1987; 52:5588–5593. Martin SF, Gluchowski C, Campbell CL, Chapman RC. *Tetrahedron*. 1988; 44:3171–3180. Martin SF, Zinke PA. *J Org Chem*. 1991; 56:6600–6606. Martin SF, Hida T, Kym PR, Loft M, Hodgson A. *J Am Chem Soc*. 1997; 119:3193–3194. Martin SF, Limberakis C, Burgess LE, Hartmann M. *Tetrahedron*. 1999; 55:3561–3572. Hergenrother PJ, Hodgson A, Judd AS, Lee WC, Martin SF.

- Angew Chem, Int Ed. 2003; 42:3278–3281. Breton P, Hergenrother PJ, Hida T, Hodgson A, Judd AS, Kraynack E, Kym PR, Lee WC, Loft MS, Yamashita M, Martin SF. Tetrahedron. 2007; 63:5709–5729.
18. Okabayashi T, Iida A, Takai K, Nawate Y, Misaki T, Tanabe Y. J Org Chem. 2007; 72:8142–8145. [PubMed: 17877405]
19. O'Brien CJ, Kantchev EAB, Valente C, Hadei N, Chass GA, Lough A, Hopkinson AC, Organ MG. Chem—Eur J. 2006; 12:4743–4748. [PubMed: 16568494]
20. (a) Jurczak J, Pikul S. Tetrahedron Lett. 1985; 26:3039–3040. (b) Kobayashi Y, Nakano M, Kumar GB, Kishihara K. J Org Chem. 1998; 63:7505–7515. [PubMed: 11672404] (c) Williams PD, LeGoff E. J Org Chem. 1981; 46:4143–4147.
21. Piancatelli G, Scettri A, D'Auria M. Tetrahedron. 1980; 36:661–663.
22. Finlay J, McKervey MA, Nimal Gunaratne HQ. Tetrahedron Lett. 1998; 39:5651–5654.
23. Adger B, Barrett C, Brennan J, McKervey MA, Murray RW. J Chem Soc, Chem Commun. 1991:1553–1554.
24. Dominguez C, Csaky AG, Plumet J. Tetrahedron Lett. 1990; 31:7669–7670.
25. Cermola F, Iesce MR, Buonerba G. J Org Chem. 2005; 70:6503–6505. [PubMed: 16050717]
26. Luche JL. J Am Chem Soc. 1978; 100:2226–2227.
27. Andrews GC. Tetrahedron Lett. 1980; 21:697–700.
28. Trost BM, Lautens M. J Am Chem Soc. 1982; 104:5543–5545.
29. Trost BM, Hung MH. J Am Chem Soc. 1983; 105:7757–7759.
30. (a) Trost BM, Keinan E. Tetrahedron Lett. 1980; 21:2591–2594. (b) Tsuji J, Minami I, Shimizu I. Tetrahedron Lett. 1983; 24:4713–4714. (c) Johns DM, Mori M, Williams RM. Org Lett. 2006; 8:4051–4054. [PubMed: 16928071]
31. (a) Braude EA, Bruun T, Weedon BCL, Woods RJ. J Chem Soc. 1952:1419–1425. (b) Fleming I, Pearce A. J Chem Soc, Perkin Trans 1. 1980:2485–2489. (c) Hudrlik PF, Kulkarni AK. Tetrahedron. 1985; 41:1179–1182.
32. Isaacs NS, Kirkpatrick D. J Chem Soc, Chem Commun. 1972:443–444.
33. Spaggiari A, Vaccari D, Davoli P, Torre G, Prati F. J Org Chem. 2007; 72:2216–2219. [PubMed: 17295542]
34. Jung ME, Wasserman JI. Tetrahedron Lett. 2003; 44:7273–7275.
35. (a) Lawson WB, Patchornik A, Witkop B. J Am Chem Soc. 1960; 82:5918–5923. (b) Phillips RS, Cohen LA. J Am Chem Soc. 1986; 108:2023–2030. (c) Chen JJ, Wei Y, Drach JC, Townsend LB. J Med Chem. 2000; 43:2449–2456. [PubMed: 10882372]
36. Lazzaro F, Crucianelli M, De Angelis F, Neri V, Saladino R. Tetrahedron Lett. 2004; 45:9237–9240.
37. Mori H, Tsuneda K. Chem Pharm Bull. 1963; 11:1413–1417. [PubMed: 14090590]
38. (a) Wulff WD, Peterson GA, Bauta WE, Chan KS, Faron KL, Gilbertson SR, Kaesler RW, Yang DC, Murray CK. J Org Chem. 1986; 51:277–279. (b) Knight SD, Overman LE, Piraudeau G. J Am Chem Soc. 1995; 117:5776–5788. (c) Smith BJ, Sulikowski GA. Angew Chem, Int Ed. 2010; 49:1599–1602.
39. (a) Kumamoto H, Shindoh S, Tanaka H, Itoh Y, Haraguchi K, Gen E, Kittaka A, Miyasaka T, Kondo M, Nakamura KT. Tetrahedron. 2000; 56:5363–5371. (b) Simpkins SME, Kariuki BM, Aricó CS, Cox LR. Org Lett. 2003; 5:3971–3974. [PubMed: 14535756]
40. Shirakawa E, Imazaki Y, Hayashi T. Chem Commun. 2009:5088–5090.
41. Shen X, Hyde AM, Buchwald SL. J Am Chem Soc. 2010; 132:14076–14078. [PubMed: 20857936]
42. Comins DL, Dehghani A. Tetrahedron Lett. 1992; 33:6299–6302.
43. Pangborn AB, Giardello MA, Grubbs RH, Rosen RK, Timmers FJ. Organometallics. 1996; 15:1518–1520.
44. Allen DW, Hutley BG, Mellor MTJ. J Chem Soc, Perkin Trans 2. 1972:63–67.
45. Boeckman RK, Shao P, Mullins JJ. Org Synth. 2000; 77:141–146.
46. Still WC, Kahn M, Mitra A. J Org Chem. 1978; 43:2923–2925.

47. Marce P, Diaz Y, Matheu MI, Castillon S. *Org Lett.* 2008; 10:4735–4738. [PubMed: 18816138]
48. Stadlwieser JF, Dambaur ME. *Helv Chim Acta.* 2006; 89:936–946.
49. Altamura M, Perrotta E. *J Org Chem.* 1993; 58:272–274.

Fig. 1.
Selected welwitindolinone natural products.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

Scheme 12.

Scheme 13.

Scheme 14.

Scheme 15.

Scheme 16.

Scheme 17.

Scheme 18.