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Pentacyclic Furanosteroids: The Synthesis of Potential Kinase Inhibitors Related to Viridin and Wortmannolone

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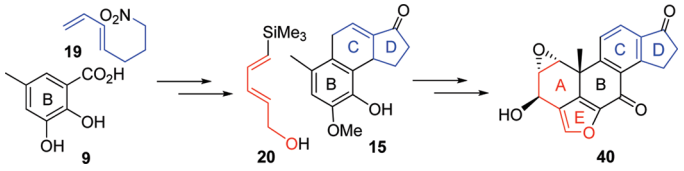

A regiocontrolled intermolecular Diels−Alder reaction of an *o*-benzoquinone followed by an intramolecular nitrile oxide cyclization is employed to prepare the BCD fragment of viridin. The AE segment is attached to it by means of an intramolecular Diels−Alder reaction of an *o*-benzoquinone monoketal generated in situ from tricycle **15** and 5-trimethylsilyl-2*E*,4*E*-pentadienol **20**. The silyl substituent at C-1 of the pentacyclic product directs the dihydroxylation of the C_2-C_3 double bond to its β-face. Various transformations of the 1α-trimethylsilyl-2β,3β-dihydroxy pentacycle into several others with oxygen substituents in ring A are described. One of these products **40** possesses the same structure and relative stereochemistry in rings A, B, and E as that of the natural product wortmannolone **3**.

Introduction

Viridin **1** and wortmannin **2** are the best known examples of a small group of pentacyclic furanosteroidal natural products (Figure 1)[1] with interesting and important biological activity. All members of the group feature a furan ring (E) fused at C-3a, C-11c, and C-5a (CA Ring Index numbering) to the A and B rings of the pentacycle, thus imposing significant strain on this portion of the molecule. An X-ray structure[2] of viridin showed the ring A buckled, and ring B to be a slightly flattened boat. The presence of carbonyl groups at C-3 and C-6 activates the $C_{3a}-C_4$ double bond toward attack by uncharged nitrogen, sulfur, and oxygen nucleophiles resulting in facile cleavage of the furan ring and release of the strain. The much studied[3] biological activity of these compounds, attributed to inhibition of many cellular kinases, in particular phosphatidylinositol-3-kinase (PI-3K), is a consequence of the same chemistry. Indeed, a crystal structure of wortmannin with its furan ring cleaved and covalently bound at C-4 to the amine group of a lysine residue of the enzyme has been published.[4] Since PI-3K regulates one step in the signal transduction sequence responsible for cell growth and differentiation, its inhibition represents an opportunity for the development of clinically useful remedies based on the viridin/wortmannin platform for the alleviation of proliferative diseases.[5] However, this prospect has been hampered by the toxicity and instability of these compounds and most of the biological assays

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(1) Hanson, J. R. *Nat. Prod. Rep.* **1995**, *12*, 381–384. Some earlier authors have favored steroid numbering for carbon atoms of these pentacycles as shown in structure **1** of viridin. In this paper we use the Ring Systems Handbook (CAS, 1993) numbering as in structure **4** (Figure 1). Accordingly, the pentacyclic ring system is named cyclopenta[7,8]phenanthro[10,1-*bc*] furan as specified in entry RF 67468.

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(5) (a) Wipf, P.; Halter, R. J. *Org. Biomol. Chem.* **2005**, *3*, 2053–2061. (b) Wipf, P.; Minion, D. J.; Halter, R. J.; Berggren, M. I.; Ho, C. B.; Chiang, G. G.; Kirkpatrick, L.; Abraham, R.; Powis, G. *Org. Biomol. Chem.* **2004**, *2*, 1911–1920.

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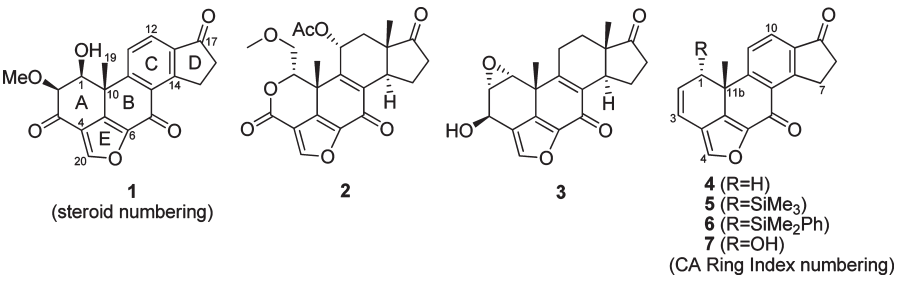
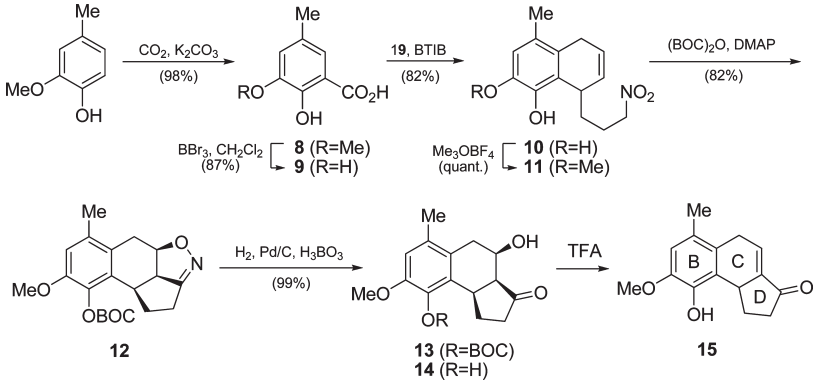


FIGURE 1. Some natural and synthetic pentacyclic furanosteroids.

SCHEME 1



undertaken to date have been conducted with analogues of wortmannin generated by cleavage of the furan ring with nitrogen nucleophiles.[5b,6] An acknowledged problem[5a] with the evaluation of viridin or any of its close relatives as candidates for clinical use has been the lack of practical synthetic routes to ring A functionalized pentacyclic platforms in sufficient quantity and variety. Although it was first isolated in 1945, only one synthesis of viridin in 26 steps and 5% overall yield has been published.[7] This singular achievement speaks to the magnitude of the problems associated with the synthesis of this molecule. Other prospective routes to the pentacycle have been explored[8,9] but not completed as yet.

Some years ago, we completed[10] a rapid nine-step synthesis of the pentacycle **4** in 12% overall yield. Although the product contained a C_2-C_3 double bond we were unable to use this feature to introduce the needed ring A oxygen substituents with any degree of regio- or stereocontrol. After many attempts, and as many failures, it became evident that the strong proclivity of the pentacyclic platform to react at its α-face could not be overcome in our simple synthetic product. We therefore concluded that it was necessary to incorporate a blocking group on ring A, on its α-face, to counteract the steric influence of the β-methyl group carried at C-11b. This led us to define a slightly modified synthetic target, (±)**5**, which we set out to prepare by a similar but operationally improved route.

Results and Discussion

Starting again from 4-methylguaiacol, Kolbe–Schmidt carboxylation was followed by boron tribromide demethylation to provide 2,3-dihydroxy-5-methylbenzoic acid **9**, in excellent yield. Reaction of **9** with a 4-fold excess of nitrodiene **19** in the presence of bis(trifluoroacetoxy)iodobenzene (BTIB) produced the dihydronaphthalene **10** after a sequence of four reactions in one pot in 86% yield and unreacted **19** was recovered by Kugelrohr distillation. The regioselectivity of the *o*-quinone–nitrodiene cycloaddition and spontaneous decarboxylation of the β-ketoacid cycloadduct made the overall conversion of **9** to **10** the equivalent of a regiocontrolled intermolecular Diels–Alder addition of a dihydroxy benzyne to a diene[11] (Scheme 1).

The nitrodiene **19**, previously synthesized by a known[12] but cumbersome process that started with the expensive 1,4-pentadien-3-ol and required a large-scale LAH reduction, was improved to eliminate both deficiencies. Thus, beginning with the much cheaper 2,3-dihydrofuran, the synthesis was completed in five steps and ca. 42% yield (Scheme 2). The hydrolysis of dihydrofuran, the first step, is highly exothermic and can become uncontrollable if conducted on a large scale without efficient stirring (and cooling as necessary). The protected hydroxy aldehyde **16** was accompanied by a small amount of the ether **17**, which was separated by chromatography and recycled. Olefination of **16** with diethyl allyl phosphonate[13] afforded the protected dienol **18** (70%, 22:1 *E*/*Z*). Hydrolysis with ethanolic hydrochloric

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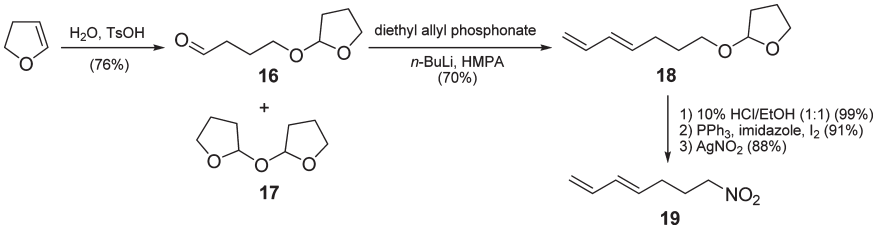
SCHEME 2



acid and reaction of the resulting alcohol with triphenylphosphine−iodine−imidazole gave the iodide (91%), which was converted to the desired nitrodiene **19** with silver nitrite.

Selective methylation of the more exposed hydroxyl group of **10** as before set the stage for the second cycloaddition, the intramolecular nitrile oxide [3 + 2] cyclization (INOC) process that can be accomplished with a variety of reagents. In our earlier studies[10] we used phenyl isocyanate for this purpose, but the free phenolic hydroxyl group of **11** had to be protected as an acetate and deprotected in a subsequent step. We have now turned to employing di-*tert*-butyl dicarbonate (BOC_2O)/DMAP[14] with the phenol **11** as the substrate. This combination of reagents not only promotes the INOC reaction, but also protects the phenol as a BOC ester and affords a purer product **12** in high yield. The isoxazline **12** was cleaved as before by catalytic hydrogenolysis and the resulting benzindanone **13** isolated in quantitative yield. This BOC-protected precursor of the BCD fragment of viridin was produced in six steps and 60% overall yield from 4-methylguaiacol. The next improvement implemented in the current synthesis arose from the decision to use the hydroxy enone **15** as the BCD synthon rather than the previously employed[10] dihydroxy benzindanone **14** for reasons that will be discussed later.

To realize our first objective (**5**), a TMS group had to be incorporated into the dienol employed for the final AE + BCD annulation. Placing the silyl substituent at the terminal carbon of the dienol mitigated its adverse steric effect on the contemplated intramolecular Diels−Alder (IMDA) reactions because the long carbon−silicon bond would take the bulky TMS group away from the site of the cycloaddition. Furthermore, it was necessary that both double bonds of the prospective dienol be in the *E* configuration if the annulation reaction was to have any chance of succeeding. These considerations led us to synthesize 5-trimethylsilyl-2*E*,4*E*-pentadienol **20** representing the AE segment of the pentacycle. This was accomplished in three steps and 63% yield from trimethylsilylacetylene (Scheme 3). The *anti*-Markovnikov addition of gaseous hydrogen bromide[15] to the acetylene must be monitored carefully by ^{1}H NMR spectroscopy to prevent over addition; all three possible addition products are easily detectable in the spectra. Sonogashira coupling of the *trans*-1-bromo-2-(trimethylsilyl)ethylene with propargyl alcohol was followed by LAH reduction to afford the desired 2*E*,4*E* silyl dienol **20**.

The synthesis had reached its first critical test. The question of whether the presence of the bulky silyl group would permit any cycloaddition to occur in synthetically useful yields had to be answered. Our earlier work with transient *o*-benzoquinone monoketals[16] had shown that two reaction modes (I and II in Figure 2) could operate in these intramolecular cycloadditions and that *endo* adducts were generally preferred.

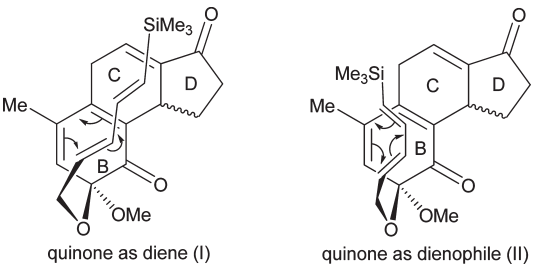


FIGURE 2. Two possible modes for the IMDA reactions of *o*-benzoquinone monoketals.

The diene moiety in I but not in II is already constrained in the *s-cis* conformation required for the Diels−Alder reaction and furthermore this reaction mode (but not II) takes the bulky silyl substituent away from the reaction site and away from the steric interactions with the methyl substituent carried on ring B, and the methylene and methine protons of ring C. A bridged adduct is therefore expected to predominate and its formation will also be favored by using the enone **15**, rather than the dihydroxy ketone **14**,[10] as the BCD precursor. Steric interactions between the ring C protons of **14** and the trimethylsilyl group that may have existed in I would be reduced by the use of **15** instead. However, enone **15** is prone to facile aromatization of ring C and conversion thereby to a naphthol bearing a 4-methyl substituent. Such compounds have been shown[16] to be unsuitable as substrates in the planned oxidative cyclization process. For this reason **15** was not stored, but was prepared just before use by dehydration and deprotection of **13** with TFA under an atmosphere of argon. The solvents were removed in vacuo and the residue committed to the next step immediately after confirming its identity by ^{1}H NMR spectroscopy. After much study of the experimental parameters of the reaction, the optimum conditions were identified (Scheme 4). The crude phenolic enone **15** in THF was oxidized with 1.2 equiv of BTIB in the presence of 12.5 equiv of silyl dienol **20** and a crystal of butylated hydroxy toluene (BHT). The mixture was degassed with argon to minimize aromatization of **15**, then stirred at 0 °C for 1 h and at room temperature for an additional 2 h. The reaction was also protected from light because on one occasion a significant amount of a hydroperoxide **25** was isolated and its structure and stereochemistry determined by X-ray crystallography (see the SI, p S33). We believe that this compound was the product of a self-sensitized

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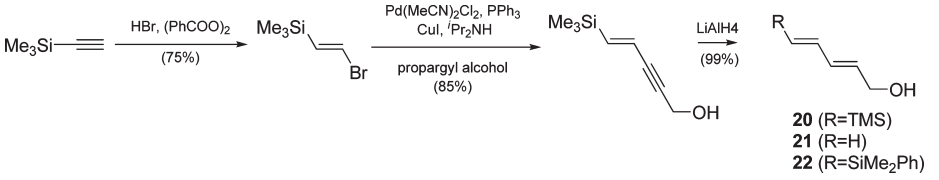
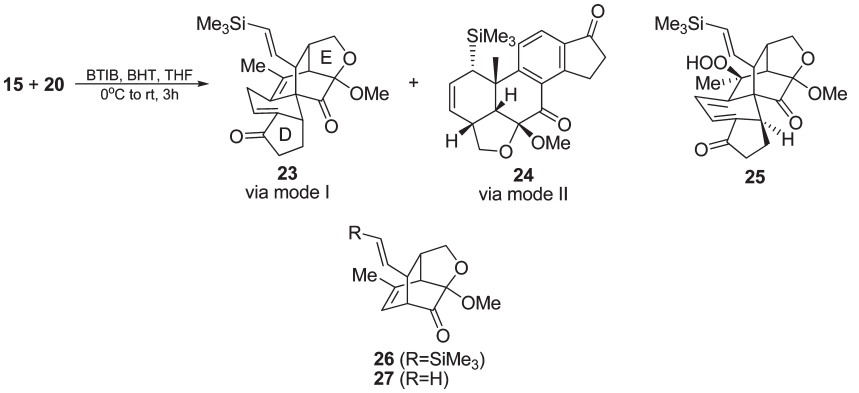
SCHEME 3



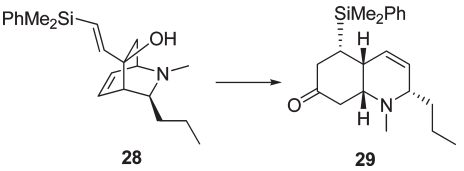
SCHEME 4



photochemical ene reaction between the bridged IMDA adduct **23** and singlet oxygen. Under these anaerobic conditions, **23** formed from conformation I was isolated in 43% yield together with the pentacycle **24** (from II) in much smaller amounts (ca. 5%) in accordance with our expectations discussed above. The structure and stereochemistry of the pentacycle was established by X-ray crystallography (see the SI, p S32). It is noteworthy that the *E*,*E* stereochemistry of the silyl dienol transforms into the desired *anti* stereochemistry of the methyl and silyl groups in ring A and that in keeping with our previous results, **24** is an *endo* adduct. Spontaneous aromatization of ring C has also occurred during the reaction, and this may have aided its formation. When the same oxidative cyclization was performed with 4-methylguaiacol and silyl dienol **20**, only the bridged adduct **26** could be isolated, unlike our earlier results[16] with 2*E*,4*E*-pentadienol **21**.

In view of the almost exclusive formation of bridged adduct **23** it was imperative that the next step, the Cope rearrangement, succeed in order that the pentacyclic product (**5**) be obtained in a similar fashion to the earlier work.[10] Although we had some concerns that the bulky silyl group would impede the rearrangement, we were encouraged by a report that a [2,2,2]bicyclo vinylsilane **28** underwent an anionic oxy-Cope rearrangement to the bicyclic product **29** (Scheme 5), with the expected *anti*-relationship between the silyl substituent and neighboring hydrogen.[17] However, in our projected rearrangement (of **23**) the silyl and methyl substituents would eclipse each other in the obligatory boat-like transition state (Scheme 6). We were delighted to find that the rearrangement of **23** conducted in tetrachloroethane as before, at 120 °C for two days in the absence of light, did produce the desired pentacycle **5** in acceptable yield with the *anti*-relationship between the silyl and methyl substituents on ring A. On occasion, especially at temperatures lower than 120 °C, the reaction produced significant amounts of pentacycle **31**. We

SCHEME 5



therefore interpret the progression of steps (**23** → **5**) as shown in Scheme 6. The reversible 3,3-sigmatropic shift is followed by aromatization of ring C, which renders the conversion of **23** to **24** irreversible. Subsequently, the elimination of methanol produces **31**, a pentacycle isolable at lower temperatures, because aromatization of ring E introduces bond angle strain as noted earlier. The bridged adduct **26** could not be rearranged, in spite of many attempts under similar conditions, but **27** lacking the silyl substituent and several others like it were rearranged[16] easily. It thus seems evident that the crucial event in the conversion of **23** to **5** is the aromatization of ring C, which successfully counters the adverse steric effect of the trimethylsilyl substituent in the boat transition state. The three steps that lead from **30** → **5** (Scheme 6) are similar to our previous results.[10] The first, the aromatization of ring C, did not require heating in a chlorinated solvent. The dihydroaromatic intermediate **30**, is presumably dehydrogenated by exposure to air at 120 °C. The elimination of methanol (**24** → **31**) in our experience,[10,16,23] requires strongly acidic

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(20) The progress of the epoxidation was conveniently monitored by conducting the reaction in $CDCl_3$ and observing the diminution of signals due to alkene protons H-1 and H-2.

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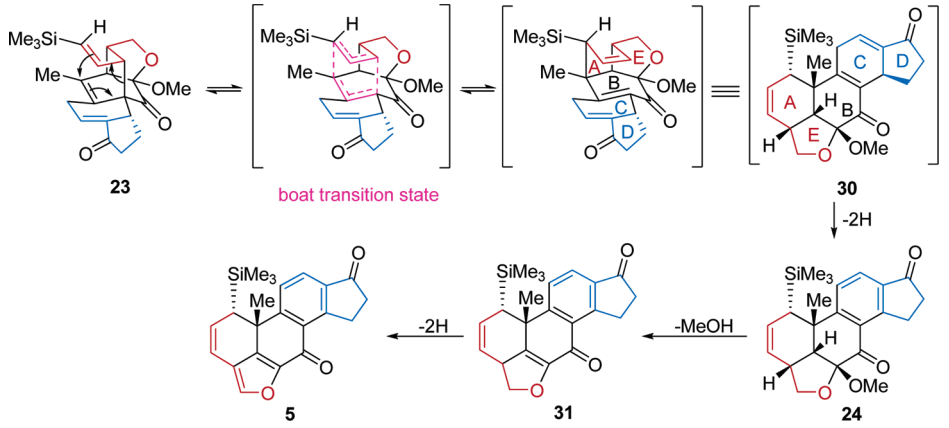
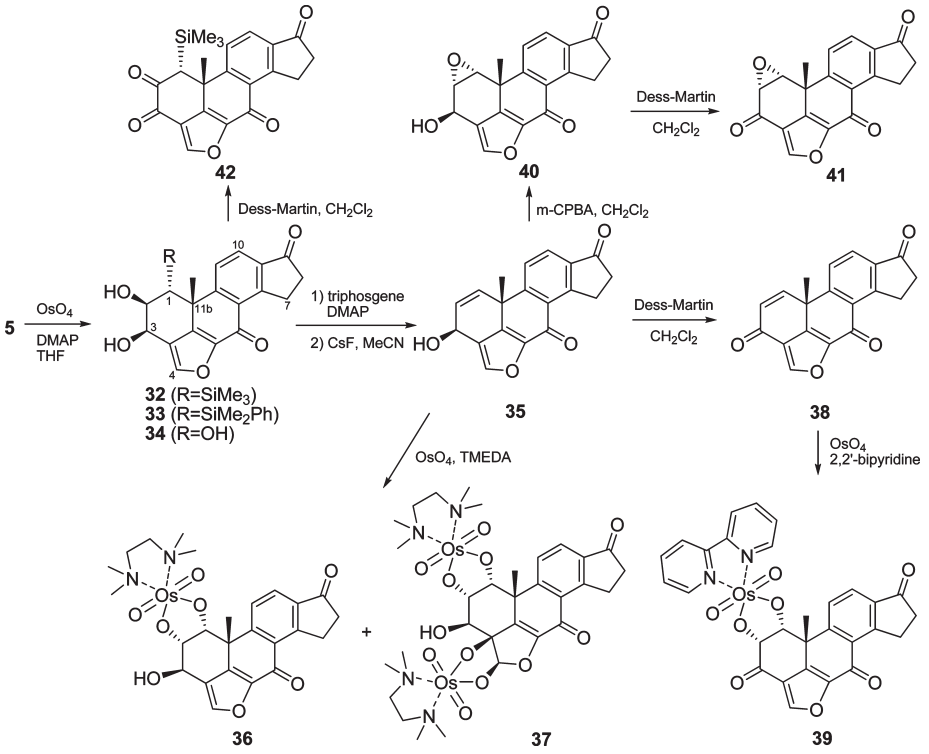
SCHEME 6



SCHEME 7



conditions which can only be met in this case by the generation of HCl from the solvent in some way. The final step, however (**31** → **5**), is more difficult to accomplish and usually requires dehydrogenation with *p*-chloranil in a boiling hydrocarbon solvent. Here, it appears that hydrogen abstraction at the doubly allylic center (C-3a) followed by a chlorination−dehydrochlorination sequence is a likely pathway for this transformation. The formation of mixtures in the Diels−Alder and Cope reactions made it more efficient to not routinely isolate and purify the individual products **23**, **34**, and **31**; after recovery of the excess silyl dienol in vacuo, the oily brown residue was subjected to the rearrangement and the final product **5** was purified by column chromatography and crystallization. The BCD tricycle **13** was thus converted to the pentacycle **5** in 24% overall yield after a multistep sequence of eight chemical reactions and our initial objective (**5**) was reached in 14.4% overall yield from 4-methylguaiacol. The ^{1}H NMR spectrum of **5** was similar to that of **4** and the existence of the 1,11b-*anti* diaxial stereochemistry, the expected result, was indicated by the upfield shift of the TMS signal to δ −0.47 (9H, s). The X-ray crystallographic structure (see the SI, p S31) confirmed these conclusions.

Having reached the initial objective, thereby establishing the tolerance of the synthesis to the presence of the silyl group, it was now time to verify the original hypothesis that this bulky C-1α substituent would overcome the noted[18] preference of the system for α-attack. Osmylation of **5** (stoichiometric OsO_4, DMAP, THF) at room temperature was slow and traces of starting material still remained after 4−5 days. The osmate was decomposed with aqueous sodium bisulfite and the diol **32** was isolated after column chromatography and crystallization (Scheme 7). The X-ray structure (see the SI, p S34) confirmed that dihydroxylation

had indeed occurred at the β-face of the C_2-C_3 double bond as we had hoped. This was a gratifying result, because only one other example of β-attack on a similar pentacycle has been recorded.[7] Epoxidation of **5** (*m*-CPBA) was unsuccessful, however; after several days, most of the starting material remained.

The silyl diol **32** was converted to the cyclic carbonate with triphosgene and subjected to desilylative elimination with anhydrous CsF in dry acetonitrile to provide the allyl alcohol **35**, a key compound we hoped to transform into many ring A derivatives of viridin. Our first attempt was the Donohoe hydroxyl directed osmylation[19] (OsO_4, TMEDA) undertaken in the hope that the C-3 β-hydroxyl group would direct the osmylation of the C_1-C_2 double bond to the β-face of ring A. Two osmates were formed and they were separated by column chromatography on silica (CH_2Cl_2/MeOH 85:15), then each one was crystallized (CH_2Cl_2/pentane) and subjected to X-ray crystallographic analysis. The major product **36** (2.5:1), faster on TLC, showed that osmylation had occurred at the α-face, *anti* to the angular methyl group and the C-3 hydroxyl group (see the SI, p S35). The minor product **37** (see the SI, p S36) was an unusual bis-osmate, its formation another manifestation of the enhanced reactivity of the $C_{3a}-C_4$ double bond of the furanoid ring in these compounds. These TMEDA coordinated osmates are very stable and provide good ^{1}H NMR and ESI mass spectra consistent with their structures. The X-ray data of **36** show the methyl and C-3 hydroxyl group of ring A in a "bow-stern" relationship, with the latter quite distant from the glycolate oxygen atom of the cyclic osmate.[19] The C-3 hydroxyl group does not control the stereochemistry of the osmylation and may in this case hinder β-attack on the C_1-C_2 double bond.

The alcohol **35** was oxidized by the Dess−Martin reagent to the enone **38** in excellent yield. This compound previously obtained from natural 2-demethoxy viridin had a ^{1}H NMR spectrum identical with one published[18] earlier. In addition, ^{13}C NMR and mass spectra also supported the structure of **38**. Conjugate addition of nucleophiles (e.g., H_2O, MeOH) to the enone and catalytic hydrogenation/deuteration were reported to occur at its α-face. In the course of this work, the authors noted that the NMR chemical shift of H-11 was diagnostic of the configuration of the oxygen substituent at C-1. They also found that the 1,2-dideuterio product was incorporated into 2-demethoxy viridin when it was incubated with the fungus *Nodulisporium hinnuleum*[18] (Scheme 7).

We attempted osmylation of **38** with the less space demanding bidentate ligand 2,2′-bipyridyl in the hope that the flatter ring A and lack of the C-3 hydroxyl group would make the β-face of the C_1-C_2 double bond more accessible. Osmylation was complete after 2 days in THF at room temperature and the crude product crystallized from CH_2Cl_2/pentane provided excellent ^{1}H NMR and ESI MS data, but the X-ray structure of **39** (see the SI, p S37) was disappointing because it again showed that it was a bipyridyl coordinated α-osmate. Not being successful in achieving the desired stereochemistry of the osmylations, we turned our attention to epoxidation of the C_1-C_2 double bond of **35**, again hoping that the C-3 hydroxyl group would direct the reagent to the β-face of the molecule. The reaction (*m*-CPBA/$CDCl_3$[20] or CH_2Cl_2/room temperature) was slow, and after 4 days, a small amount of starting material could still be detected by ^{1}H NMR spectroscopy. The product **40** was not easily separated from the residual reactants but its ^{1}H NMR spectrum displayed signals for H-1 (δ 4.02, d, J = 3.7 Hz), H-2 (δ 3.63, t), and H-3 (δ 5.45, d, J = 2.8 Hz) while its mass spectrum supported the expected composition ($C_{19}H_{14}O_5$). The configuration of the epoxide was uncertain at this stage but oxidation with the Dess−Martin reagent smoothly produced the epoxy ketone purified by chromatography, whose ^{1}H NMR spectrum showed loss of the signal due to H-3 and a substantial downfield shift of H-4 singlet to 8.20 ppm. However, the doublets due to H-11 and H-10 were at δ 7.82 and 8.05 (J = 8 Hz), which implied that the oxygen atom at C-1 was not equatorially oriented.[8,18] The configurational question was settled by an X-ray structure (see the SI, p S38), which showed the epoxide **41** to be α and *anti* to the angular methyl group. This also establishes the configuration of its precursor epoxy alcohol **40** as *anti* to the C-3 hydroxyl group and identical with the structure and relative stereochemistry of rings A, B, and E of the natural product wortmannolone **3**, isolated from *Penicillium wortmannii*[21] (Scheme 7).

A final attempt was made to take advantage of the successful β-dihydroxylation of **5**. Oxidation of the silyl diol **32** was investigated with the hope that it would be selective for the C-3 hydroxyl group and lead eventually to 1-deoxy viridin. We were not able to achieve selectivity in the oxidation with either the Dess−Martin[22] or IBX reagents and all attempts at isolation of a product were plagued by decomposition, which occurred with the appearance of orange colored compounds, probably diosphenolic,[5a] resulting from cleavage of the furan ring. However, it was possible to isolate a 2,3-diketone by oxidation of **32** with two molar proportions of the Dess−Martin reagent. The product **42**, though not very stable, could be characterized by low- and high-resolution mass spectrometry and high-field ^{1}H and ^{13}C NMR spectroscopy. The diketone was prevented from enolization by the inability of the molecule to accommodate the TMS group at C-1 in a planar configuration. Our attempts to remove the silyl group resulted in extensive decomposition with the formation of orange solutions once again.

As has been appropriately noted,[5a,10,23] postponement of the aromatization of the furan ring in similar pentacycles may confer improved stability on these intermediates and permit easier chemical manipulation. We therefore investigated the reactivity of the C_2-C_3 double bond of the dihydrofuranoid pentacycle **31**. Stoichiometric osmylation with osmium tetraoxide and bipyridyl in THF was unsuccessful. After 117 h at room temperature most of the starting material was recovered. Epoxidation with *m*-CPBA in methylene chloride for 45 h at room temperature afforded a low yield of a product with a ^{1}H NMR spectrum very similar to that of the starting material. The C_2-C_3 double bond had remained intact, and the only significant difference was in the signal of H-4β, coupled geminally to H-4α and vicinally to H-3aβ. This signal, a triplet at 4.92 ppm (J = 7.3 Hz) in **31**, was shifted upfield to 4.50 ppm (J = 9 Hz) in the product. Its low resolution mass spectrum showed a molecular ion at m/z 380 indicating the incorporation of one oxygen atom. We therefore suggest that the epoxidation has occurred at the $C_{11c}-C_{5a}$ double bond. Access to the C_2-C_3 double bond of **31** is difficult from either face. The

α-face is crowded by the C-1α silyl group and the β-face by the methyl group at C-11b. In addition, since this pentacycle is an *endo* adduct the hydrogen atom at C-3a is β-oriented and pseudoaxial.

Conclusions

The synthetic route described above has succeeded in reaching a variety of ring A functionalized pentacycles which are relatively stable and should be useful for evaluation as kinase inhibitors. However, it has not succeeded, as yet, in achieving the desired 1β,2β configuration of oxygen substituents as found in viridin. There remains a distinct possibility that the experience gained here can lead to a reasonable solution of this problem. The dienol **22** can be prepared from dimethylphenylsilylacetylene[24] by using the route employed for **20** (Scheme 3). Likewise, the pentacycles **6** and **33** should be accessible in the same manner as before, provided that the slight change in the silyl substituent does not interfere with the sequence of Diels−Alder and Cope reactions. Many different procedures have been developed to transform the dimethylphenylsilyl group to a hydroxyl group[25] so that **7** and/or a suitably protected variant of **34** may be available to us. Two methods[7,8] are known for inverting the stereochemistry of the C-1α hydroxyl group in such compounds as **7** and **34**, and if successful, a second synthesis of (±) viridin owing much to the previous reasearch[7,8,10] may result.

Experimental Section

(Tetrahydrofuranyl-2′-oxo)butanal (16).[26] **16** was prepared by the published procedure from 2,3-dihydrofuran, *p*-toluene sulfonic acid, and water in the same yield. **Caution**: The reaction can easily become uncontrollable when done on a large scale (> 50 g). Efficient and vigorous stirring is essential and cooling in ice may be necessary. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6−2.0 (m, 1H), 2.40 (m, 2H), 3.1−3.9 (m, 4H), 5.0 (dd, 1H), 9.7 (t, 1H, J = 1.0 Hz).

Hepta-4(*E*)-6-dienol.[27] To a solution of diethyl allylphosphonate[13] (1.12 g, 6.3 mmol) in dry THF (50 mL) at −78 °C was added *n*-BuLi (3.9 mL, 1.6 M, 6.3 mmol) dropwise. After the mixture was stirred for 15 min a solution of the aldehyde **16** (1 g, 6.3 mmol) and HMPA (1.09 mL, 6.3 mmol) was added dropwise through a cannula. The mixture was then stirred at −78 °C for 2 h, warmed to rt, and allowed to stand overnight. The solution was quenched with saturated aq ammonium chloride and the layers were separated. The aq phase was extracted with ether (3×30 mL) and the organic layers were combined. The solvents were removed in vacuo and the residue was hydrolyzed with 10% aq HCl and ethanol (1:1) at 40 °C for 4 h. The mixture was neutralized with 10% aq sodium bicarbonate and extracted with ethyl acetate (4×25 mL). The extract was dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was chromatographed on silica (EtOAc/hexane 1:1) and the dienol obtained as a colorless liquid (0.49 g, 68% yield). The *trans*/*cis* ratio was determined as 22:1 by 300 MHz ^{1}H NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 2H), 2.16 (m, 2H), 2.93 (br, s, 1H), 3.6 (t, 2H, J = 7 Hz), 4.96 (d, 1H, J = 10.3 Hz), 5.13 (d, 1H, J = 16.5 Hz), 5.7 (m, 1H), 6.07 (dd, 1H, J = 15.1, 10.3 Hz), 6.30 (m, 1H).

1-Iodo-4(*E*),6-heptadiene.[28] 1-Iodo-4(*E*),6-heptadien was prepared by the published method from hepta-4(*E*),6-dienol in similar yield. The ^{1}H NMR spectrum was identical with one already recorded.

1-Nitro-4(*E*),6-heptadiene (19).[12] **19** was prepared from 1-iodo-4(*E*),6-heptadiene dissolved in ether by treatment with a 1.3 M proportion of solid silver nitrite and stirring in the dark for 3 days. After separation of the silver salts by filtration, the solvent was removed in vacuo and the residual red oil was chromatographed on silica (hexane) to provide the titled compound as a slightly yellow liquid. The ^{1}H NMR spectrum was identical with one already published. ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 28.9, 74.7, 116.3, 131.4, 133.0, 136.5. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.41; H, 7.77; N, 9.89.

2-Hydroxy-3-methoxy-5-methylbenzoic Acid (8).[29] 4-Methylguaiacol (10.0 g, 72.5 mmol) and solid oven-dried K_2CO_3 (30.0 g, 217 mmol) were mixed and placed in a high-pressure vessel under a CO_2 atmosphere (800 psi). The reaction vessel was kept at 200 °C for 4.5 h and subsequently allowed to cool to room temperature. The pressure was released, the contents of the reaction vessel were dissolved in water (400 mL), and the resulting solution was extracted once with ether, boiled with activated carbon, filtered, and acidified to pH 1 with HCl. The precipitated acid (13.0 g, 98% yield) was collected by filtration, dried in a vacuum desiccator over P_2O_5, and used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.91 (s, 3H), 6.93 (d, 1H, J = 1.7 Hz), 7.31 (d, 1H, J = 1.7 Hz), 10.35 (br, s, 1H).

2,3-Dihydroxy-5-methylbenzoic Acid (9). To a cooled (−78 °C) solution of **8** (13.0 g, 71.4 mmol) in CH_2Cl_2 (500 mL) was added neat BBr_3 (53.8 g, 215 mmol) dropwise. After warming to room temperature, the solution was stirred overnight and then quenched with MeOH. The solvent was removed under reduced pressure and the solids were redissolved in MeOH and rotoevaporated dry three times. Sublimation of the crude product (120 °C, high vacuum) gave **9** as a white solid (10.5 g, 87% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.11 (s, 3H), 6.87 (d, 1H, J = 1.7 Hz), 7.05 (d, 1H, J = 1.7 Hz), 10.49 (br, s, 1H).[30]

4-Methyl-8-(3-nitropropyl)-5,8-dihydronaphthalene-1,2-diol (10). To a cooled (0 °C) solution of **9** (828 mg, 4.93 mmol), **19** (3.5 g, 24.8 mmol), and BHT (one crystal, ca. 3 mg) in THF (40 mL) was added solid BTIB (2.50 g, 5.81 mmol) portionwise over a period of 2 min. After 30 min, the reaction was removed from the ice bath and stirred for another 3.5 h at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with ether, and washed with a saturated solution of $NaHCO_3$. The aqueous layers were extracted with ether (3 × 25 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Kugelrohr distillation of the excess **19** and iodobenzene gave a red viscous oil, which was purified by column chromatography (20% EtOAc/hexane) to provide **7** as a light yellow oil (1.12 g, 86% yield). IR 3496, 2919, 1620, 1550, 1382, 1295, 1194, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63−2.09 (m, 4H), 2.12 (s, 3H), 3.13 (m, 2H), 3.76 (m, 1H), 4.29 (t, 2H, J = 6.9 Hz), 5.20 (br, s, 2H), 5.85−5.91 (m, 1H), 5.99−6.05 (m, 1H), 6.57 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 23.7, 27.5, 31.7, 33.5, 75.9, 115.0, 124.9, 125.6, 126.5,

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127.0, 127.8, 139.4, 140.2. HRMS (EI) m/z required for $C_{14}H_{17}NO_4$ 263.1157, found 263.1142.

2-Methoxy-4-methyl-8-(3-nitropropyl)-5,8-dihydronaphthalene-1-ol (11). To a solution of **10** (200 mg, 0.76 mmol) in CH_2Cl_2 (20 mL) was added oven-dried K_2CO_3 (1.07 g, 7.74 mmol) and the resulting suspension was stirred for 30 min. The reaction mixture was cooled (0 °C), Me_3OBF_4 (230 mg, 1.55 mmol) was added, and the flask was purged with N_2. The reaction was allowed to warm to room temperature, and stirring was continued for 20 h. After quenching with dilute HCl (0.1 M), the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatopgraphy (20% EtOAc/hexane) gave **11** as a light yellow oil (215 mg, 100% yield). IR 3504, 2939, 1618, 1551, 1489, 1381, 1301 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.62−2.15 (m, 4H), 2.18 (s, 3H), 3.13 (m, 2H), 3.78 (m, 1H), 3.85 (s, 3H), 4.27 (t, 2H, J = 7.0 Hz), 5.60 (s, 1H), 5.85−5.91 (m, 1H), 5.97−6.03 (m, 1H), 6.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.7, 27.4, 31.7, 33.5, 56.0, 75.9, 110.6, 123.8, 125.4, 126.1, 126.2, 128.0, 140.5, 143.9. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.12; H, 6.81; N, 4.96.

8-Methoxy-6-methyl-1,2,4a,5,9b,9c-hexahydrobenzo[4,5]indeno[1,7-*cd*]isoxazol-9-yl-*tert*-butylcarbonate (12). To a solution of phenol **11** (3.08 g, 11.1 mmol) in toluene (50 mL) was added the solution of $(BOC)_2O$ (9.7 g, 44.5 mmol) in toluene (50 mL) in a 500 mL flask, followed by DMAP (0.2 g, 1.7 mmol). (NOTE: Due to the vigorous bubbling during the reaction, a large flask was required.) The reaction mixture was stirred at 90 °C for 18 h, after which the solvent was removed under reduced pressure. Ether (20 mL) was added in portions to the brown residue to give isoxazoline **12** (3.256 g, 81.6% yield) as a light brown solid, recrystallization of which from ether/pentane provided white crystals. Mp 174−6 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (m, 10H), 2.22 (m, 1H), 2.27 (s, 3H), 2.47−2.73 (m, 3H), 3.10 (dd, 1H, J = 6.2, 14.5 Hz), 3.74 (m, 1H), 3.79 (s, 3H), 3.93 (m, 1H), 4.65 (m, 1H), 6.67 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 26.7, 27.6, 30.7, 38.2, 53.3, 56.0, 81.1, 83.4, 112.6, 124.1, 132.1, 134.3, 135.8, 148.9, 151.6, 170.6. HRMS (EI) m/z required for $C_{20}H_{25}NO_5$ 359.1733, found 359.1737. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01. Found: C, 66.86; H, 7.14.

8-Methoxy-4-hydroxy-6-methyl-9-O-*tert*-butyloxycarbonyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]inden-3-one (13). To a solution of isoxazoline **12** (3.8 g, 10.6 mmol) in THF (80 mL), MeOH (208 mL), and water (76 mL) were added H_3BO_3 (2.94 g, 48 mmol) and Pd/C (10%, 291 mg). The reaction flask was evacuated and refilled with H_2 five times, and stirring was continued at room temperature overnight. The reaction mixture was filtered through a pad of Celite, the organic solvents were removed under vacuum, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ then filtered and the solvent was removed under vacuum to give hydroxyketone **13** as a white solid (3.79 g, 99% yield), recrystallization of which from ether/pentane provided white crystals. Mp 152−3 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (m, 10H), 2.16−2.43 (m, 3H), 2.21, (s, 3H), 2.55 (dd, 1H, J = 8.3, 16.3 Hz), 2.68 (dd, 1H, J = 4.8, 8.9 Hz), 2.85 (dd, 1H, J = 4.1, 16.2 Hz), 3.08 (d, 1H, J = 8.6 Hz), 3.76 (m, 1H), 3.79 (s, 3H), 4.24 (m, 1H), 6.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 27.6, 29.0, 33.6, 36.3, 38.5, 50.5, 56.0, 67.3, 83.2, 113.0, 124.6, 130.3, 134.7, 136.8, 149.2, 151.4, 223.5. HRMS (EI) m/z required for $C_{20}H_{26}O_6$ 362.1729, found 362.1734. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.64; H, 7.10.

8-Methoxy-4-hydroxy-6-methyl-9-hydroxy-1,2,5,9b-hexahydro-1*H*-benz[*e*]inden-3-one (15). To a solution of **13** (720 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added TFA (3 mL). The resulting solution was degassed with argon and stirred for 2 days in the dark at room temperature. Solvent was evaporated to give crude product **15** as a black solid, which was used in the next step without purification. ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (m, 2H), 2.20 (s, 3H), 2.40 (m, 2H), 3.24 (m, 2H), 3.33 (dd, 1H, J = 8.8, 2.2 Hz), 3.52 (dt, 1H, J = 5.5, 18.8 Hz), 3.81 (m, 1H), 3.87 (s, 3H), 6.64 (s, 1H), 6.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 28.81, 28.82, 38.0, 38.6, 56.1, 111.1, 122.9, 124.0, 126.4, 127.4, 139.4, 142.3, 144.5, 205.9. HRMS (EI) m/z required for $C_{15}H_{16}O_3$ 244.1099, found 244.1096.

(*E*)-(2-bromovinyl)trimethylsilane. To a mixture of trimethylsilylacetylene (20 g, 0.2 mol) and benzoyl peroxide (145 mg, 0.6 mmol, 0.3 mol %) cooled in an ice bath was bubbled HBr gas for 15 min (the progress of the reaction was monitored by ^1H NMR). The reaction mixture was diluted with ether (50 mL) and carefully washed with saturated $NaHCO_3$ (30 mL) and then with saturated NaCl (30 mL). The ether layer was dried over $MgSO_4$. Filtration and evaporation gave a crude product mixture mainly containing (*E*)-(2-bromovinyl)trimethylsilane (27.4 g, 75% yield) as a colorless liquid. This mixture is used without purification in the next step. ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 9H), 6.46 (d, 1H, J = 15.3 Hz), 6.54 (d, 1H, J = 15.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5, 116.8, 138.8.

(*E*)-5-(trimethylsilyl)pent-4-en-2-yn-1-ol. To a mixture of the crude (*E*)-(2-bromovinyl)trimethylsilane (3.58 g, 20 mmol) dessolved in diisopropylamine (45 mL) at room temperature was added $Pd(MeCN)_2Cl_2$ (43 mg, 0.166 mmol), Ph_3P (86.9 mg, 0.331 mmol), and CuI (44.8 mg, 0.236 mmol). The mixture was degassed in a stream of argon for 5 min. Propargyl alcohol (2.89 mL, 49.7 mmol) was added and the reaction was stirred at room temperature. After 1 h, the reaction was diluted with ether (100 mL), washed with water (4 × 40 mL) and saturated NaCl (40 mL), and dried over $MgSO_4$. Following filtration and evaporation, the residue was purified by flash chromatograpgy (EtOAc/hexane, 1:12) to give (*E*)-5-(trimethylsilyl)pent-4-en-2-yn-1-ol (2.62 g, 85.1% yield) as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 4.37 (s, 2H), 5.93 (d, 1H, J = 19.2 Hz), 6.43 (d, 1H, J = 19.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8, 51.1, 85.5, 87.7, 122.7, 145.9.

(2*E*,4*E*)-5-(Trimethylsilyl)penta-2,4-dien-1-ol (20). To a suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in ether (100 mL) was added dropwise a solution of (*E*)-5-(trimethylsilyl)pent-4-en-2-yn-1-ol (2.3 g, 15 mmol) in ether (50 mL) over 20 min with the reaction cooled by cold water. The resulting mixture was refluxed for 2.5 h and cooled in ice quenched with water and 1 M H_2SO_4 with the system cooled by ice. The mixture was separated and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by Kugelrohr distillation (0.01 Torr, 37 °C) to give the silyl dienol **20** (2.3 g, 99% yield) as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 9H), 4.18 (dd, 2H, J = 5.7, 1.2 Hz), 5.84 (dd, 1H, J = 5.7, 15.3 Hz), 5.86 (d, 1H, J = 18.3 Hz), 6.24 (dd, 1H, J = 9.9, 15.3 Hz), 6.50 (dd, 1H, J = 9.9, 18.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.4, 62.7, 132.7, 133.7, 134.3, 143.3. HRMS (EI) m/z required for $C_8H_{16}OSi$ 156.0970, found 156.0968. Anal. Calcd for $C_8H_{16}OSi$: C, 61.48; H, 10.32. Found: C, 61.67; H, 10.51.

The Bridged Adduct (23). To a solution of the crude enone **15** (488 mg, 2 mmol), dienol **20** (7.8 g, 25 mmol), and a crystal of BHT in THF (5 mL) was added BTIB (1.032 g, 2.4 mmol) in four portions over 20 min in the dark. The resulting mixture was degassed with argon and stirred at 0 °C for 1 h followed by 2 h at rt. Solvent was evaporated and the excess dienol was removed under high vacuum (0.01 Torr, 37 °C) by Kugelrohr to give the crude IMDA reaction product mixture as a dark brown oil, which was used in the next step without purification. ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 1.88 (s, 3H), 2.04 (m, 2H), 2.35

(m, 1H), 2.36 (m, 1H), 2.42 (m, 1H), 2.60 (d, 1H, J = 8.8 Hz), 2.72 (m, 1H), 2.86 (m, 1H), 3.04 (d, 1H, J = 4.4 Hz), 3.40 (dd, 1H, J = 18.1, 7.0 Hz), 3.44 (s, 3H), 3.86 (d, 1H, J = 8.2 Hz), 4.16 (dd, 1H, J = 8.2, 3.2 Hz), 5.61 (dd, 1H, J = 18.4, 8.8 Hz), 5.74 (d, 1H, J = 18.4 Hz), 6.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.2, 18.4, 19.3, 27.8, 38.4, 37.2, 43.6, 47.4, 51.6, 52.5, 60.6, 74.2, 100.6, 126.0, 127.9, 130.5, 133.9, 142.6, 145.3, 197.2, 205.9. HRMS (EI) m/z required for $C_{22}H_{27}O_4Si$ (M − CH_3) 383.1679, found 383.1686. Two byproducts, 1α-trimethylsilyl-5aβ-methoxy-11bβ-methyl-1,3aβ,4,5a,6,7,8,9,11b,11c-decahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (**24**) (19 mg, 5% yield) and the hydroperoxide-bridged adduct (**25**) (72 mg, 8.3% yield), were isolated in this reaction. Both of them were recrystallized from EtOAc/pentane. NMR data for **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.41 (s, 9H), 1.69 (s, 3H), 2.67−2.74 (m, 3H), 3.10 (m, 3H), 3.25 (s, 3H), 3.7−3.8 (m. 1H), 3.83−3.87 (dd, 1H, J = 8.0, 1.5 Hz), 4.13 (t, 1H, J = 7.4, 8.0 Hz), 5.65 (m, 1H), 5.85 (m, 1H), 7.56 (d, 1H, J = 8 Hz), 7.90 (d, 1H, J = 8 Hz). HRMS (EI) m/z required for $C_{23}H_{28}O_4Si$ 396.1757, found 396.1752. See the SI for X-ray crystal structure data. NMR data for **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.08 (s, 9H), 1.49 (s, 3H), 1.87 (m, 1H), 2.04 (m, 1H), 2.38 (m, 3H), 2.57 (m, 1H), 3.14 (d, 1H, J = 3.9 Hz), 3.54 (s, 3H), 3.73 (d, 1H, J = 7.8 Hz), 3.91 (m, 1H), 4.09 (dd, 1H, J = 7.8, 2.5 Hz), 5.64 (d, 1H, J = 18.4 Hz), 5.93 (dd, 1H, J = 18.4, 9.5 Hz), 6.47 (d, 1H, J = 5.9 Hz), 6.53 (m, 1H), 7.78 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5, 19.9, 21.1, 36.3, 41.6, 44.8, 38.4, 49.8, 50.6, 56.5, 74.0, 81.7, 103.4, 121.2, 123.9, 133.4, 138.4, 141.0, 144.5, 200.8, 205.2. See the SI for X-ray crystal structure data.

1α-Trimethylsilyl-11bβ-methyl-1,6,7,8,9,11b-hexahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (5). The crude material from the previous IMDA reaction was dissolved in $Cl_2CHCHCl_2$ (10 mL) in a test tube and stirred at 120 °C for 2 days in the dark. The solvent was removed under high vacuum (0.01 Torr, 40 °C), and the residue was flashed by column chromatography (EtOAc/hexane, 3:7) to give allyl silane **5** (172 mg, 23.8% yield from **13**) as a yellow solid, recrystallization of which from benzene/pentane provided colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.47 (s, 9H), 1.56 (s, 3H), 2.67 (d, 1H, J = 6.48 Hz), 2.75 (m, 2H), 3.80 (m, 2H), 6.11 (dd, 1H, J = 9.62, 6.48 Hz), 6.51 (d, 1H, J = 9.62 Hz), 7.51 (s, 1H), 7.57 (d, 1H, J = 8 Hz), 7.91 (d, 1H, J = 8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.8, 28.5, 32.8, 36.4, 38.9, 39.1, 114.1, 126.2, 127.9, 133.2, 121.5, 130.8, 137.1, 143.6, 143.7, 156.2, 158.5, 141.0, 173.2, 206.7. HRMS (EI) m/z required for $C_{21}H_{19}O_3Si$ (M − CH_3) 347.1103, found 347.1096. See the SI for X-ray crystallographic data. On some occasions, the formation of 1α-trimethylsilyl-11bβ-methyl-1,3aβ,4,6,7,8,9,11b-octahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (**31**) was observed (124 mg, 17% yield from **13**). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.50 (s, 9H), 1.59 (s, 3H), 2.46 (d, 1H, J = 5.1 Hz), 2.72 (m, 2H), 3.65 (dt, 1H, J = 5.7, 19.5 Hz), 3.79 (dt, 1H, J = 5.7, 19.5 Hz), 4.18 (m, 2H), 4.92 (t, 1H, J = 7.3 Hz), 5.69 (d, 1H, J = 8.1 Hz), 5.87 (dd, 1H, J = 9.8, 5.1 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.89 (d, 1H, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.2, 27.1, 28.3, 36.5, 40.5, 41.4, 45.0, 76.5, 121.6, 126.1, 127.8, 130.0, 130.3, 137.0, 139.5, 147.5, 156.4, 157.9, 176.7, 206.7. HRMS (EI) m/z required for $C_{22}H_{24}O_3Si$ 364.1495, found 364.1481.

1α-Trimethylsilyl-11bβ-methyl-5a,11c-epoxy-1,3a,4,5a,6,7,8,9,11b,11c-decahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione. The dihydrofuran **31** (20 mg, 0.055 mmol) and *m*-CPBA (12.99 mg, 0.08 mmol) were dissolved in CH_2Cl_2 (2 mL). The resulting solution was stirred at room temperature for 45 h and then washed with saturated $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was flashed by column chromatography (EtOAc/hexane, 1:1) to give the epoxide (5 mg, 24% yield) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.49 (s, 9H), 1.77 (s, 3H), 2.16 (d, 1H, J = 5.3 Hz), 2.72 (m, 2H), 3.29 (m, 1H), 3.77 (m, 1H),4.11 (m, 1H), 4.26 (m, 1H), 4.50 (t, 1H, J = 9 Hz), 5.61 (dd, 1H, J = 10.2, 3.45 Hz), 5.81 (m, 1H), 7.50 (d, 1H, J = 8.1 Hz), 7.92 (d, 1H, J = 8.1 Hz).

(3,8-*trans*)-7a-Methoxy-4-methyl-8-(2′-trimethylsilyl)-(*E*)-ethenyl-2,3,3a,6,7,7a- hexahydro-3,6-methanobenzofuran-7-one (26). To a solution of 4-methylguaiacol (0.414 g, 3 mmol) and silyl dienol **20** (2.1 g, 12 mmol) in THF was added BHT (3 crystals), $NaHCO_3$ (2.4 g, 28.6 mmol), and BTIB (1.3 g, 3 mmol) as a solid in portions at 0 °C. The mixture was stirred for 0.5 h followed by addition of $NaHCO_3$ (2.4 g, 28.6 mmol). The resulting mixture was allowed to warm to room temperature and was stirred overnight. Solvent was evaporated and the residue was diluted with ether and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated. The excess dienol **20** was removed by Kugelrohr distillation (0.01 Torr, 37 °C). The residue was purified by column chromatography to give **26** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 1.91 (s, 3H), 2.33 (m, 1H), 2.68 (d, 1H, J = 7.3 Hz), 3.06 (dd, 1H, J = 3.0, 6.7 Hz), 3.12 (dd, 1H, J = 4.1, 2.1 Hz), 3.50 (s, 3H), 3.82 (d, 1H, J = 8.1 Hz), 4.12 (dd, 1H, J = 8.1, 3.3 Hz), 5.70 (m, 3H). HRMS (EI) m/z required for $C_{15}H_{21}O_3Si$ (M − CH_3) 277.1260, found 277.1267.

1α-Trimethylsilyl-2β,3β-dihydroxy-11bβ-methyl-1,2,3,6,7,8,9,11b-octahydrocyclopenta[7,8] phenanthro[10,1-*bc*]furan-6,9-dione (32). To a solution of **5** (72 mg, 0.2 mmol) and DMAP (27 mg, 0.22 mmol) in THF/CH_2Cl_2(10 mL) was added solid OsO_4 (58 mg, 0.23 mmol). The resulting mixture was stirred at room temperature for 4 days followed by addition of 10% aq $NaHSO_3$ (10 mL). After 4 h of stirring, the layers were separated and the aqueous layer was extracted with EtOAc (3×2 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EtOAc/hexane, 7:3) to give diol **32** (52 mg, 66% yield) as a white solid, recrystallization of which from EtOAc/pentane provided colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.46 (s, 9H), 1.82 (s, 3H), 2.48 (d, 1H, J = 2.11 Hz), 2.74 (t, 2H, J = 5.8 Hz), 3.78 (dt, 2H, J = 4.75, 5.37 Hz), 4.61 (br d, 1H, J = 5.5 Hz), 4.97 (m, 1H), 7.57 (d, 1H, J = 8 Hz), 7.85 (s, 1H), 7.92 (d, 1H, J = 8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0, 28.5, 36.4, 39.2, 39.9, 40.9, 62.0, 70.9, 123.3, 129.7, 136.8, 126.5, 127.5, 144.3, 145.5, 147.6, 158.2, 158.7, 173.4, 206.9. HRMS (EI) m/z required for $C_{22}H_{24}O_5Si$ 396.1393, found 396.1398. See the SI for X-ray crystallographic data.

1α-Trimethylsilyl-2β,3β-dioxolonyl-11bβ-methyl-1,2,3,6,7,8,9,11b-octahydrocyclopenta[7, 8]phenanthro[10,1-*bc*]furan-6,9-dione. A solution of triphosgene (134 mg, 0.45 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a mixture of DMAP (329 mg, 2.7 mmol) and the diol **32** (180 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction was stirred for 15 min and then was allowed to warm to room temperature. The resulting solution was quenched with saturated NH_4Cl and the aqueous layer was separated and extracted with CH_2Cl_2. The organic extract was washed with water, dried (over $MgSO_4$), filtered, and evaporated under vacuum to give the carbonate (138 mg, 72% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.51 (s, 9H), 1.67 (s, 3H), 2.67 (s, 1H), 2.76 (t, 2H, J = 5.5 Hz), 3.78 (t, 2H, J = 5.5 Hz), 5.49 (d, 1H, J = 8.8 Hz), 5.88 (d, 1H, J = 8.8 Hz), 7.60 (d, 1H, J = 8.0 Hz), 7.98 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.59, 28.4, 29.6, 36.3, 36.5, 38.2, 67.3, 78.9, 117.3, 126.9, 127.2, 129.6, 137.4, 142.4, 144.6, 148.4, 153.4, 156.3, 158.7, 172.8, 206.1. HRMS (EI) m/z required for $C_{23}H_{22}O_6Si$ 422.1186, found 422.1185.

3β-Hydroxy-11bβ-methyl-3,6,7,8,9,11b-hexahydro[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (35). Cesium fluoride (70 mg, 0.46 mmol) was vacuum dried at 100 °C (0.5 Torr) for 4 h. The

carbonate (21 mg, 0.05 mmol) dissolved in dry acetonitrile (10 mL) was added and the mixture was stirred, protected from moisture, at 80 °C for 2 h and at rt for a further 48 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water, and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was chromatographed on silica (EtOAc/hexane, 3:1) to produce **35**, which resisted crystallization. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 3H), 2.74 (qt, 2H, J = 19, 6 Hz), 5.34 (d, 1H, J = 4 Hz), 6.26 (dd, 1H, J = 9.6, 4 Hz), 6.88 (d, 1H, J = 9.6 Hz), 7.78 (d, 1H, J = 7.6 Hz), 7.81 (s, 1H), 7.98 (d, 1H, J = 7.6 Hz). HRMS (EI) m/z required for $C_{19}H_{14}O_4$ 306.0892, found 306.0886.

Acetylation of 35. The 3β-acetate of **35** was prepared by standard methods (Ac_2O, pyridine, DMAP) to obtain a clean NMR spectrum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, 3H), 2.11 (s, 3H), 2.74 (t, 2H, J = 5.8 Hz), 3.76 (qt, 2H, J = 19.8, 5.7 Hz), 6.12 (d, 1H, J = 5.3 Hz), 6.2 (dd, 1H, J = 9.6, 5.3 Hz), 7.0 (d, 1H, J = 9.5 Hz), 7.78 (d, 1H, J = 8 Hz), 7.87 (s, 1H), 7.98 (d, 1H, J = 8 Hz).

Osmylation of 35. A mixture of TMEDA (0.015 mL, 0.1 mmol) and **35** (25 mg, 0.08 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and cooled to −78 °C. Solid OsO_4 (25.5 mg, 0.1 mmol) was added and the solution was removed under reduced pressure. The residue was chromatographed on silica (CH_2Cl_2/MeOH, 85:15). Two osmates were eluted from the column in turn and crystallized from CH_2Cl_2/pentane. (1) First eluted was osmate **36** (35 mg, 65% yield). $R_f \approx 0.3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 3H), 2.46 (s, 3H), 2.64 (s, 3H), 2.78 (m, 2H), 2.76−3.07 (m, 10H), 3.82 (m, 2H), 4.66 (t, 1H, J = 3.9 Hz), 5.09 (d, 1H, J = 3 Hz), 5.44 (d, 1H, J = 4.1 Hz), 7.11 (d, 1H, J = 8 Hz), 7.76 (d, 1H, J = 0.8 Hz), 7.92 (d, 1H, J = 8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 34.2, 36.7, 42.5, 51.6, 51.8, 52.2, 52.4, 64.6, 64.7, 67.4, 93.0, 97.1, 124.8, 125.9, 126.2, 131.7, 136.7, 144.7, 145.8, 146.2, 157.0, 158.5, 174.1, 207.2. ESI MS: the monoprotonated molecular ion $(M + H)^+$ displayed an isotopic peak pattern identical with that calculated for its expected composition. See the SI for comparison of the experimental and theoretical traces. and for X-ray crystallographic data. (2) Second eluted was osmate **37** (14 mg, 17% yield). $R_f \approx$ 0.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77 (s, 3H), 2.41 (s, 3H), 2.43 (s, 3H), 2.71 (m, 2H), 2.84 (s, 3H), 2.85 (s, 3H), 2.85−3.2 (m, 20H), 3.70 (m, 2H), 4.45 (dd, 1H, J = 9.3, 8 Hz), 4.59 (m, 1H), 5.10 (d, 1H, J = 3.8 Hz), 6.14 (s, 1H), 7.58 (d, 1H, J = 8.2 Hz), 7.82 (d, 1H, J = 8.2 Hz). ESI MS: the monoprotonated molecular ion $(M + H)^+$ displayed an isotopic peak pattern identical with that calculated for its expected composition. See the SI for comparison of the experimental and theoretical traces and for X-ray crystallographic data.

11bβ-Methyl-3,6,7,8,9,11b-hexahydro[7,8]phenanthro[10,1-*bc*]furan-3,6,9-trione (38). A mixture of **35** (10 mg, 0.033 mmol) and the Dess−Martin periodinane (27.7 mg, 0.066 mmol) dissolved in dry CH_2Cl_2 (20 mL) was stirred at rt for 2 h. The progress of the reaction was monitored by TLC (EtOAc/hexane, 4:1). After the starting material was consumed, the solution was diluted with ether (30 mL) and the precipitated iodobenzoate residues were filtered and washed with more ether (2 × 10 mL). The filtrate was evaporated under vacuum and the residue was chromatographed on silica (EtOAc/hexane, 4:1) to obtain **38** (9 mg, 90% yield) whose ^{1}H NMR spectrum was identical with 360 MHz spectral data published earlier.[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 3H), 2.76 (t, 2H, J = 6 Hz), 3.72 (dt, 1H, J = 20.1, 6 Hz), 3.81 (dt, 1H, J = 20.1, 6 Hz), 6.39 (d, 1H, J = 10.1, 4 Hz), 7.68 (d, 1H, J = 10.1 Hz), 7.80 (d, 1H, J = 8.0 Hz), 8.02 (d, 1H, J = 8.0 Hz), 8.26 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4, 36.4, 40.7, 41.1, 121.6, 124.2, 127.6, 130.7, 131.3, 137.7, 145.4, 145.8, 147.9, 148.2, 151.9, 159.1, 172.9, 179.3, 205.9. HRMS (EI) m/z required for $C_{19}H_{12}O_4$ 304.0736, found 304.0733.

Osmylation of 38 (Synthesis of 39). The enone **38** (7 mg, 0.023 mmol) and 2,2′-bipyridine (4.5 mg, 0.029 mmol) dissolved in dry THF (20 mL) was treated with solid OsO_4 (6.6 mg, 0.026 mmol) and the solution was stirred at rt for 2 days. The solvent was removed under reduced pressure and the residue chromatographed on silica (CH_2Cl_2/MeOH, 5:1). The product **39** was crystallized from CH_2Cl_2/pentane (12 mg, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$ and one drop of acetone-d_6) δ 1.81 (s, 3H), 2.72 (t, 2H, J = 5.7 Hz), 3.75 (qt, 1H, J = 19.6, 5.7 Hz), 5.11 (d, 1H, J = 3.5 Hz), 5.87 (d, 1H, J = 3.5 Hz), 7.47 (t, 1H, J = 6.5 Hz), 7.73 (t, 1H, J = 6.5 Hz), 7.81 (d, 1H, J = 8 Hz), 7.95 (d, 1H, J = 8 Hz), 8.10 (t, 1H, J = 7.9 Hz), 8.12 (s, 1H), 8.21 (t, 1H, J = 7.9 Hz), 8.30 (d, 1H, J = 8.2 Hz), 8.33 (d, 1H, J = 8.2 Hz), 8.62 (d, 1H, J = 4.9 Hz), 9.44 (d, 1H, J = 4.9 Hz). ESI MS: the monoprotonated molecular ion $(M + H)^+$ displayed an isotopic peak pattern identical with that calculated for its expected composition. See the SI for comparison of the experimental and theoretical traces and for X-ray crystallographic data.

1α,2α-Epoxy-3β-hydroxy-11bβ-methyl-1,2,3,6,7,8,9,11b-octahydro[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (40). To the solution of **35** (11.2 mg, 0.037 mmol) in CH_2Cl_2 (25 mL) was added *m*-CPBA (8 mg, 0.05 mmol). After the mixture was stirred at rt for 16 h, more *m*-CPBA was added periodically and stirring was continued until almost all the starting material was consumed (55 mg *m*-CPBA over 4 days). The reaction mixture was washed successively with 20 mL portions of aq sodium bisulfite, sodium bicarbonate, and water. The organic layer was separated and evaporated under reduced pressure. The residue was chromatographed on silica (EtOAc/hexane, 3:1). This removed most, but not all the remaining chlorobenzoic acid. ^{1}H NMR (300 MHz, $CDCl_3$ and one drop of acetone-d_6) δ 1.70 (s, 3H), 2.72 (t, 2H, J = 5.8 Hz), 3.63 (t, 1H, J = 3.3 Hz), 3.75 (qt, 2H, J = 19.4, 6 Hz), 4.02 (d, 1H, J = 3.7 Hz), 5.45 (d, 1H, J = 2.8 Hz), 7.73 (s, 1H), 7.79 (d, 1H, J = 8 Hz), 7.96 (d, 1H, J = 8 Hz). HRMS (EI) m/z required for $C_{19}H_{14}O_5$ 322.0842, found 322.0849.

1α,2α-Epoxy-11bβ-methyl-1,2,3,6,7,8,9,11b-octahydro[7,8]-phenanthro[10,1-*bc*]furan-3,6,9-trione (41). The solution of **40** (16 mg, 0.05 mmol) and the Dess−Martin periodinane (50 mg, 0.12 mmol) in dry CH_2Cl_2 (20 mL) was stirred at rt for 48 h. Most of the solvent was removed under reduced pressure and ether (30 mL) was added. The precipitated solids were filtered and washed with ether (2×15 mL) and the organic extracts were combined. The solvents were evaporated under reduced pressure and the residue chromatographed on silica (EtOAc/hexane, 3:1). The product **41** (12 mg) was crystallized from CH_2Cl_2/hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.72 (t, 2H, J = 5.9 Hz), 3.65 (d, 1H, J = 3.7 Hz), overlapping with 3.70 (m, 1H), 3.88 (dt, 1H, J = 19.7, 5.9 Hz), 4.35 (d, 1H, J = 3.7 Hz), 7.82 (d, 1H, J = 8 Hz), 8.05 (d, 1H, J = 8 Hz), 8.20 (s, 1H). HRMS (EI) m/z required for $C_{19}H_{12}O_5$ 320.0685, found 320.0688. See the SI for X-ray crystallographic data.

1α-Trimethylsilyl-11bβ-methyl-1,2,3,6,7,8,9,11b-octahydro-[7,8]phenanthro[10,1-*bc*]furan-2,3,6,9-tetraone (42). The solution of **32** (27 mg, 0.068 mmol) and the Dess−Martin periodinane (57.8 mg, 0.136 mmol) in dry CH_2Cl_2 (20 mL) was stirred at rt for 1 h. The reaction mixture was quenched with 10% aq sodium thiosulfate (20 mL), washed with saturated sodium bicarbonate (2×20 mL), and dried (Na_2SO_4). The solvents were removed under reduced pressure (0−1 Torr). Attempts to further purify this product by chromatography resulted in decomposition with the formation of orange products trailing on the column. The data below were obtained on the crude reaction product. ^{1}H NMR (300 MHz, $CDCl_3$ and one drop of acetone-d_6) δ −0.39 (s, 9H), 1.74 (s, 3H), 2.79 (t, 2H, J = 5.8 Hz), 3.80 (s, 1H), overlapping with 3.80 (m, 2H), 7.56 (d, 1H, J = 8 Hz), 8.03 (d, 1H, J = 8 Hz), 8.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.73, 28.4, 36.3, 40.2, 40.5, 58.9, 122.7, 126.7, 130.3, 138.0, 144.1, 145.5, 158.8, 172.4, 194.2, 205.8.

HRMS (EI) m/z required for $C_{22}H_{20}O_5Si$ 392.1080, found 392.1088.

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Supporting Information Available: NMR spectra of compounds **5**, **10**, **15**, **23**, **24**, **25**, **26**, **31**, **32**, carbonate of **32**, **35**, acetate of **35**, **36**, **37**, **38**, **39**, **40**, **41**, and **42**; X-ray crystallographic data (thermal ellipsoid plots and cif) of compounds **5**, **24**, **25**, **32**, **36**, **37**, **39**, **41**; ESI MS traces for the isotopic peaks of the protonated molecular ions of **36**, **37**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.