Total Synthesis of Natural and *ent*-Fredericamycin A

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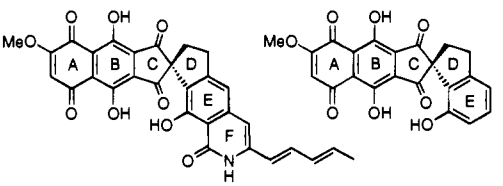
Abstract: A total synthesis of both enantiomers of the potent antitumor-antibiotic fredericamycin A (**1**) is detailed based on a room temperature inverse electron demand Diels–Alder reaction of a *N*-sulfonyl-1-aza-1,3-butadiene for assemblage of a pyridone F ring precursor, a single-step Michael addition-intramolecular acylation for annulation of the DE ring system onto this pyridone F ring precursor, implementation of a regiospecific chromium carbene benzannulation reaction for AB ring construction, and a simple aldol closure for introduction of the spiro CD ring system. Resolution of the penultimate precursor **41** followed by deprotection provided natural and *ent*-fredericamycin A. The indistinguishable cytotoxic potency of the two enantiomers (L1210 IC_{50}, 0.03 and 0.04 μg/mL, respectively) is disclosed along with that of the key partial structures **2** (IC_{50} = 2 μg/mL) and **21** (IC_{50} = 7 μg/mL) constituting the fully functionalized ABCDE and DEF ring systems of the natural product.

Fredericamycin A (**1**), a structurally unique and potent antitumor antibiotic isolated from *Streptomyces griseus*,[1,2] has been the subject of extensive investigation since its unambiguous structure determination by single-crystal X-ray analysis[3] after extensive spectroscopic studies failed to resolve tautomeric structures.[4] Fredericamycin A exhibits potent in vitro cytotoxic activity and has been shown to possess efficacious antitumor activity in two mouse tumor models, P388 T/C = 200 at 0.5 mg/kg and 93% reduction of CD8F mammary tumor weight at 1.25 mg/kg.[5] Studies have shown that procaryotic RNA and protein synthesis are inhibited earlier and to a greater extent than DNA synthesis and that the inhibition of protein synthesis was more pronounced than RNA synthesis under conditions where DNA synthesis was unaffected.[5] Although studies on the single electron oxidation of fredericamycin A and its role in generating oxygen free radicals have been detailed in support of such a nondiscriminant mode of action,[6] more recent investigations[7] have disputed the results of the original studies. In addition, recent studies have demonstrated that fredericamycin A inhibits both topoisomerase I and II at biologically relevant concentrations and additional DNA processing enzymes at higher concentrations.[8] This latter observation is in spite of the report that the agent may not interact directly or detectably with DNA[5] suggesting direct enzyme inhibition or selective stabilization of a tertiary complex of DNA, topoisomerase, and **1**. Since the disclosure of **1**, little work has been described with derivative analogs[10,11] or key partial structures[12] of the natural product that might shed light on its site of action or the structural features responsible for the biological activity. In fact, only one such study with the key partial structure **2** lacking the functionalized F ring has been disclosed and suggests that the nondiscriminant redox properties of **1** cannot account for its biological potency.[12] We have pursued such studies in parallel with the development of a convergent total synthesis of **1** in efforts to provide the natural product and key agents necessary to address the origin of its biological properties. These studies[12–15] and the resulting synthetic approach are complementary to the initial[16] and recently described[17–20] total syntheses of racemic **1** and the extensive preliminary efforts on the development of methodology for the construction of the unusual spiro[4.4]nonene (CD ring system)[21] or DEF ring system.[22]



1, Fredericamycin A 2, Fredericamycin A ABCDE ring system

Herein we detail the first total synthesis of natural and *ent*-fredericamycin A and the preliminary comparative biological

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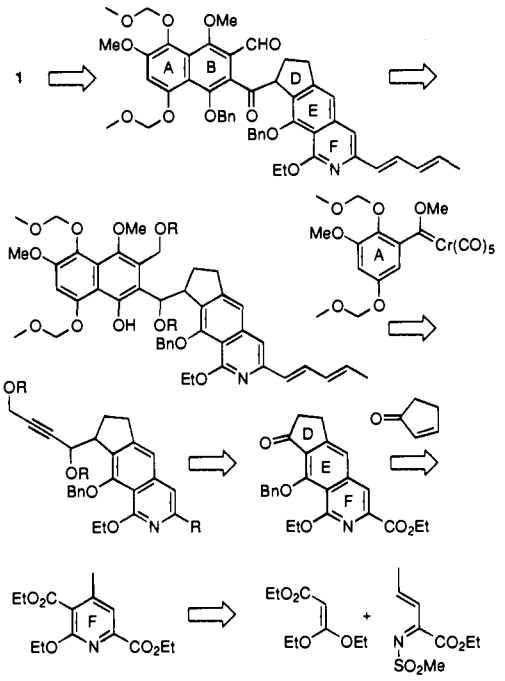
properties of the two enantiomers as well as that of a set of key partial structures. The key steps of our convergent approach extends our prior efforts and rest on the implementation of a regiospecific intermolecular chromium carbene benzannulation reaction[23-28] for AB ring construction,[12-14] a simple aldol closure for introduction of the spiro[4.4]nonene CD ring system,[12-14] a room temperature inverse electron demand Diels–Alder reaction[29] of a *N*-sulfonyl-1-aza-1,3-butadiene[30] for assemblage of a pyridone F ring precursor,[15] and a single-step Michael addition-Claisen condensation for annulation of the DE ring system on this pyridone F ring precursor[15] (Scheme 1). The early introduction of the pentadienyl side chain increased the convergency of the synthesis and provided the opportunity to prepare the fully functionalized DEF ring system and the incorporation of readily removed protecting groups at the unactivated phenol sites assured a high yielding deprotection of the resolved penultimate intermediate **41**.

Scheme 1



Construction of the DEF Ring System of Fredericamycin A. Our approach is based on a concise, four step synthesis of **11** employing a key $LUMO_{diene}$-controlled Diels–Alder reaction of the *N*-sulfonyl-1-aza-1,3-butadiene **4** followed by a single-step Michael addition-Claisen condensation for annulation of the DE ring system and the further elaboration of **11** to the fully functionalized DEF ring system. The development of the approach to **11** has been described[15] and in the conduct of the work detailed herein has benefitted from one significant improvement. In the preceding studies, the [4 + 2] cycloaddition of **4** with **5** to provide the cycloadduct **6** was conducted under pressure-promoted Diels–Alder conditions (13 kbar, CH_2Cl_2, 25 °C, 48 h, 82%). We have found that this reaction may be conducted at 25 °C and room pressure (0.5 equiv **5**, CH_2Cl_2, 25 °C, 20 h, 95% based on **5**, 47% based on **3**) to provide the adduct **6** as a 1:1 mixture of C3-diastereomers in superb conversions (Scheme 2). The noncomplementary addition of the strong electron-withdrawing C2-ethoxycarbonyl[30] group further lowers the inherent low lying LUMO of the *N*-sulfonyl-1-aza-1,3-butadiene to the extent that even the modestly reactive dienophile **5** participates in a room temperature [4 + 2] cycloaddition reaction. This unusually facile reaction at 25 °C precludes the need for conventional thermal reaction conditions and the competitive tautomerization of **4**[31] that occurs at elevated temperatures, *i.e.*, 100 °C.[30] The crude diene **4** prepared from oxime **3**[32] by low temperature, homolytic rearrangement of the in situ generated *O*-sulfinate[30] (1.1 equiv CH_3SOCl, 1.0 equiv

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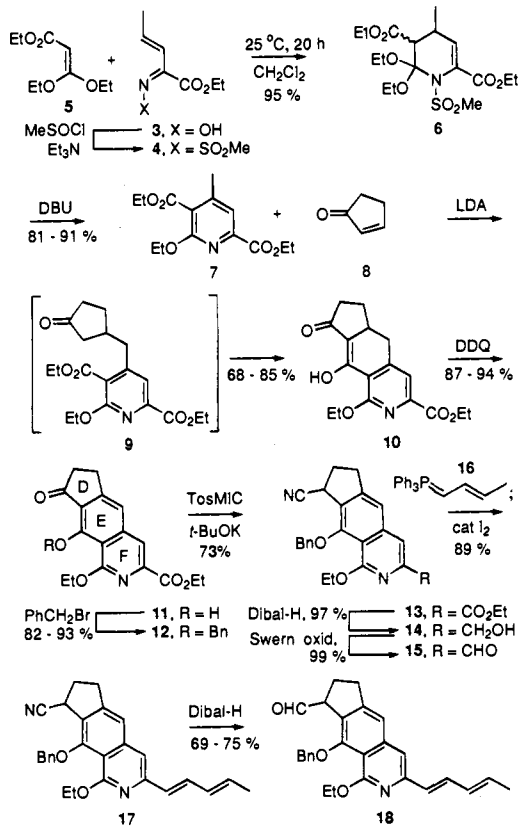
(31) For the diene tautomer: 7.25 (1H, d, J = 8 Hz), 6.95 (1H, ddd, J = 17, 10, 8 Hz), 6.10 (1H, br s), 5.70 (1H, d, J = 17 Hz), 5.60 (1H, d, J = 10 Hz), 4.25 (2H, q, J = 7 Hz), 2.99 (3H, s), 1.36 (3H, t, J = 7 Hz).

Scheme 2



Et_3N, CCl_4, 0 °C, 10 min) was used directly in the reaction with **5** and was obtained as a 7:3 mixture of trans and cis isomers of which only the trans isomer productively reacts at 25 °C. The use low reaction temperatures (0 versus 25 °C), short reaction times (10 min versus 2−12 h), and 1.0 equiv versus 1.2 equiv Et_3N[15] in its generation avoid inadvertent tautomerization of the *N*-sulfonyl-1−aza-1,3-butadiene during the reaction or upon conventional aqueous workup and isolation. It is notable that this diene, while sensitive, is stable to imine hydrolysis during a rapid aqueous workup and could be occasionally purified by flash chromatography (SiO_2) indicating that hydrolysis or tautomerization is much less facile than the diene structure might suggest.

The sensitive [4 + 2] cycloadduct **6** was converted directly to pyridine **7** by treatment with DBU (4.5 equiv, THF, 70 °C, 80−91%). Treatment of **7** with LDA (4−9.6 equiv, −78 °C, 30−50 s) followed by cyclopentenone (5−11 equiv, −78 °C, 20−30 s) and finally EtOH (−78 to 25 °C, 50−85%) under carefully defined reaction conditions provided **10** derived from a single-step Michael addition−Dieckmann condensation. The exceptionally short deprotonation period conducted with excess LDA (4.0−9.6 equiv, 30−50 s) was not only sufficient but was also required to prevent self-Claisen condensation.[15] The intermediate Michael adduct **9**[15] could be isolated and characterized (96%, HOAc quench after 30 s) and subsequently converted to **10** (NaH, THF, catalytic EtOH, 25 °C) but was more conveniently obtained simply by extending the Michael addition reaction time from 30 s (−78 °C) to 3 h (25 °C). The addition of EtOH shortly following the addition of cyclopentenone (20−30 s) served to significantly improve the conversion of **7** to **10**.

Overall yields of **10** as high as 85% were obtained on small scales (200−300 mg)[15] but diminished as the scale of the reaction was increased due to the rapid reaction times of the competitive reactions and the technical time limitations encountered in the addition of the requisite reagents. Typically, 0.5−1.5 g scale reactions provided **10** in 50−68% overall conversions.

DDQ oxidation of **10** to the naphthol **11** (87−94%) followed by protection of the free phenol as its benzyl ether provided **12** (82−93%) and completed the preparation of the carbon skeleton of an appropriately functionalized DEF ring system. MnO_2 oxidation (3 equiv, CH_2Cl_2 or C_6H_6, 24−48 h, 85−96%) of **10** also provided **11** in excellent conversions but proved less reproducible from batch to batch of commercial oxidant. Therefore, the former procedure was generally employed to prepare **11**. Similarly, efforts to invert the two-step sequence for conversion of **10** to **12** by first forming the benzyl ether of **10**[33] (10 equiv K_2CO_3, 0.2 equiv Bu_4NI, 3 equiv $PhCH_2Br$, DMF, 25 °C, 2 h, 86%) followed by MnO_2 or DDQ oxidation did not lead to aromatization and provided only recovered starting material.

In our approach, we elected to introduce the pentadienyl side chain prior to the alkyne and its subsequent use in the key benzannulation reaction. Not only was this anticipated to provide more advanced intermediates and simplify the final stages of the synthesis but, by design, would also allow the preparation of the fully functionalized DEF subunit of fredericamycin A. This preparation of key partial structures of the natural product for biological assessment was instrumental in our decision to install the pentadienyl side chain at this juncture of the synthesis. Treatment of **12** with TosMIC (1.2 equiv, 1.4 equiv *t*-BuOK, 1.2 equiv EtOH, CH_2Cl_2, −67 to 25 °C, 7 h, 73%) provided the homologated nitrile **13** in excellent conversions. This convenient one carbon homologation to a nitrile served to introduce a suitable aldehyde precursor and permitted the elaboration of the pentadienyl side chain without deliberate protection. However, initial attempts to conduct this TosMIC homologation under prescribed reaction conditions[34] failed to provide **13**. Only when the reaction was conducted at low temperature (<0 °C) was the desired product observed. In the optimization of this reaction, the temperature (−67 to 25 °C, 7 h) and use of a suitable inert solvent (CH_2Cl_2 > DME > THF > DMSO) that solubilizes the substrate effectively were found to be most important to its successful implementation. Further improvements were obtained by running the reaction for at least 2 h at 25 °C prior to workup, at modest concentrations (0.1 M) with only a slight excess of reagent (1.2 equiv TosMIC), anhydrous base (1.4 equiv *t*-BuOK),[35] and added EtOH (1.2 equiv) while the prescribed conditions recommend much larger excesses.[34] Under the modified conditions, **13** was obtained in excellent conversions (70−73%) and only a trace amount (0−12%) of the corresponding carboxylic acid derived from in situ hydrolysis of **13** was observed as a competitive reaction

(32) The diene **3** was prepared in six steps (typically 80%, 63−86% overall) from ethyl bromopyruvate as described[30] with the exception that EtOH was substituted for CH_3OH in the initial step of oxime formation which avoided an occasional generation of a trace amount of the corresponding methyl ester, and the final THP deprotection step was conducted with Amberlyst-15 (EtOH, 50 °C, 19 h, 100%).

(33) For 1-ethoxy-3-(ethoxycarbonyl)-5,5a,7,8-tetrahydro-9-benzyloxy-6*H*-cyclopent[*g*]isoquinolin-8-one: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (1H, s, C4-H), 7.19−7.15 (3H, m), 7.12−7.05 (2H, m), 4.52 (2H, m, OCH_2CH_3), 4.38 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.27 (1H, d, J = 13.7 Hz, CHHPh), 3.19 (1H, d, J = 13.7 Hz, CHHPh), 2.87 (1H, dd, J = 17.6, 5.6 Hz, C5-H), 2.73 (1H, dd, J = 17.6, 3.2 Hz, C5-H), 2.63 (1H, m, C8-H), 2.34 (1H, ddd, J = 18.9, 8.9, 2.3 Hz, C6-H), 2.10 (1H, m, C6-H), 1.97 (1H, m, C7-H), 1.58 (1H, m, C7-H), 1.44 (3H, t, J = 7.8 Hz, OCH_2CH_3), 1.38 (3H, t, J = 6.9 Hz, $CO_2CH_2CH_3$).

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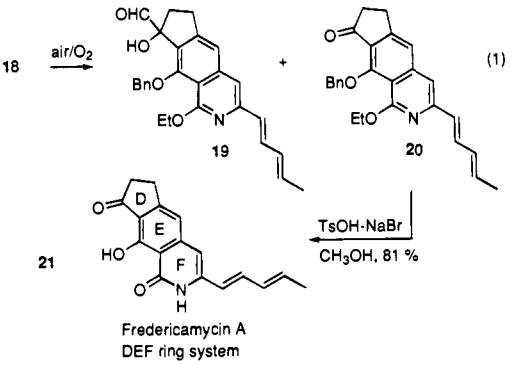
(35) Use of larger excesses of *t*-BuOK (2.7 equiv) provided larger amounts of the corresponding carboxylic acid (30−60%) depending on the reaction conditions. This carboxylic acid could be converted to **13** (1.1 equiv of Et_3N, 1 equiv of $ClCO_2Et$, 0.5 equiv of DMAP, 68%).

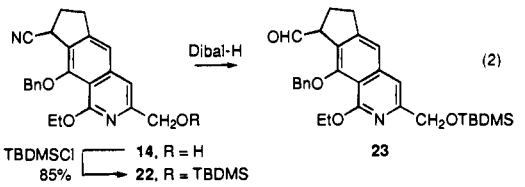
byproduct. Although this was not routinely effected, conversion of the byproduct carboxylic acid to the ethyl ester provided additional **13** and resulted in combined overall conversions in yields as high as 85−90%.[35]

Selective ester reduction of **13** achieved by treatment with Dibal-H (3 equiv, CH_2Cl_2 or toluene, −78 °C, 97%) followed by Swern oxidation[36] of **14** (oxalyl chloride-DMSO, 99%) provided the aldehyde **15**. Reduction of **13** with $LiBH_4$ (1 equiv, THF, 25 °C, 7 h, 63%) and MnO_2 oxidation (5 equiv, CH_2Cl_2, −45 to 25 °C, 2 h, 61%) of **14** also provided **15** as a single clean product but in lower yields. The subsequent introduction of the pentadienyl side chain was best accomplished with the Wittig reagent **16**[37] (1.2 equiv, THF, −78 to 25 °C, 12 h, 89%) which provided a 8:40:12:40 ratio of cis−cis, cis−trans, trans−cis, and trans−trans isomers, respectively. Exposure of this mixture to I_2 (0.05 equiv) in CH_2Cl_2 or $CHCl_3$ led to isomerization[16] to a clean 85:15 mixture of the desired *trans,trans*-**17** and *cis,trans*-**17** (95−100% recovery). Careful chromatography could be employed to provide a further enrichment of the desired *trans,trans*-**17** (22:1) but proved unnecessary. Further enrichment of the mixture was routinely accomplished in the subsequent purifications. The use of 5 equiv HMPA in the Wittig reaction provided only three isomers (Z,E; E,Z; and E,E) in a better ratio of 17:21:62 but in a lower 63% yield, and the use of 10 equiv HMPA gave even lower conversions (56%). A final improvement was ultimately accomplished using KHMDS as the base and provided three isomers (Z,E; E,Z; and E,E) in a ratio of 18:18:64 in 82% yield. In all cases, the isomerization using I_2 in CH_2Cl_2 yielded a 15:85 ratio of E,Z and the desired E,E isomers. In handling **17** and related intermediates, we noted that both prolonged exposure to light and slow or careful chromatography on SiO_2 led to consumption of agent. Although this was not unambiguously established, cursory studies revealed that light or acid-catalyzed electrocyclization of the trans,cis isomer may be responsible for this consumption but could be minimized or avoided by protecting the agents from exposure to light and minimizing their contact time with chromatographic supports.

This set the stage for introduction of the alkyne side chain for use in the chromium carbene benzannulation reaction. For this purpose, Dibal-H reduction of the nitrile **17** (2.0 equiv Dibal-H, 0.02 M toluene, −30 °C, 1 h, 69−75%) provided cleanly the aldehyde **18** but only when the reaction was conducted in the noncoordinating solvent toluene. Initial modest conversions were improved substantially by the choice of workup conditions necessary to promote hydrolysis of the resulting imine (pH 4 phosphate buffer, 25 °C, 20 min) and, importantly, with the rigorous exclusion of air (O_2) not only during the reduction reaction but also throughout the hydrolysis, workup, and chromatographic purification. The aldehyde **18** proved to be remarkably prone to benzylic oxidation and simply subjecting it to chromatographic purification without the precaution of rigorously excluding air (O_2) resulted in rapid conversion to the α-hydroxyaldehyde **19** and the oxidative decarbonylation product **20** (eq 1). The nitrile **17** exhibited similar behavior but was sufficiently stable such that special precautionary efforts were not required for its handling or purification. Thus, although the aldehyde **18** could be isolated, purified, and characterized, it could also be isolated crude from the reduction reaction in an exceptionally clean form (>95%) in good yields (≥70%) and used directly in the subsequent alkyne addition reaction with improvements in the overall conversions. With **20** in hand, deprotection of the benzyl ether and pyridone ethyl ether was examined (TsOH, NaBr, CH_3OH, reflux, 6.5 h, 81%) and found to cleanly provide **21**. In addition to providing the fully functionalized DEF ring system, this insured that the pyridone ethyl ether could be readily deprotected at the final stages of the synthesis.



Suspecting that the sensitivity of aldehyde **18** might be enhanced by the C3 electron-withdrawing group on the isoquinoline, we explored the use of the alternative substrate **22** (eq 2). This less attractive approach would require the late stage introduction of the pentadienyl side chain, but if the resulting intermediates proved easier to handle, this alternative might prove more productive. Protection of the primary alcohol **14** as its TBDMS ether **22**[38] (1.5 equiv of TBDMSCl, 2 equiv of imidazole, DMF, 25 °C, 45 min, 85%) followed by Dibal-H reduction of the nitrile (2 equiv of Dibal-H, toluene, −30 °C, 1 h) cleanly provided the aldehyde **23**[38] which proved to be as sensitive to adventitous air (O_2) oxidation as **18**. Thus, it would seem that the approaches to fredericamycin A that proceed through such intermediates must contend with their unusual air sensitivity. Those disclosed to date[17] do detail similar difficulties in working with the agents but have not discussed the extent of this behavior or defined its origin.

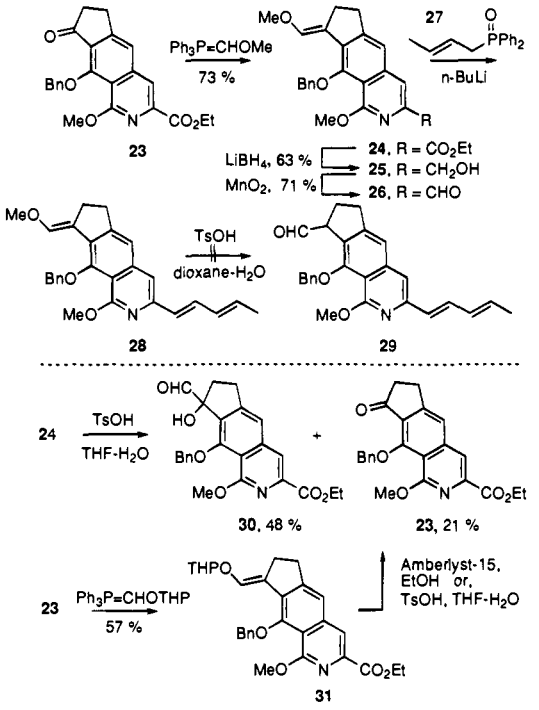


Before the extent of the sensitivity of aldehyde **18** toward air (O_2) was fully appreciated, we had examined an alternative approach[12−14] which relied on an acid-catalyzed liberation of the aldehyde from an enol ether obtained by Wittig reaction of the C8 ketone (Scheme 3). Thus, reaction of **23**[15] with $Ph_3P{=}CHOMe$ (10 equiv, THF−HMPA, −78 to 25 °C, 25 h,

(36) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(37) Bohlmann, F.; Mannhardt, H.-J. *Chem. Ber.* **1956**, *89*, 1307. Hug, R.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1828.

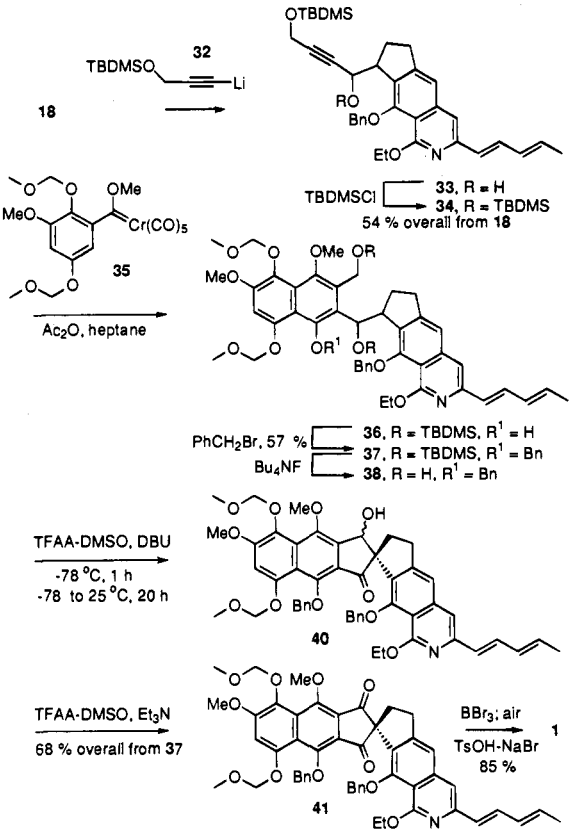
(38) For 9-(benzyloxy)-8-cyano-1-ethoxy-3-((*tert*-butyldimethylsilyloxy)-methyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline (**22**): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49−7.46 (2H, m), 7.40−7.32 (4H, m), 5.24 (1H, d, J = 11.2 Hz, C*H*HPh), 5.11 (1H, d, J = 11.2 Hz, CH*H*Ph), 4.77 (1H, s, C*H*HOSi), 4.76 (1H, s, CH*H*OSi), 4.52 (2H, m, OCH_2CH_3), 3.82 (1H, dd, J = 4.1, 8.4 Hz, C8-H), 3.25 (1H, m, C6-H), 3.02 (1H, m, C6-H), 2.44−2.24 (2H, m, C7-H), 1.34 (3H, t, J = 7.1 Hz, OCH_2CH_3), 0.98 (9H, s, $SiC(CH_3)_3$), 0.15 (6H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 152.5, 152.4, 146.7, 143.1, 137.4, 129.5, 128.4 (two CH), 128.0 (two CH), 120.8, 110.4, 109.8, 76.9, 65.7, 62.1, 31.70, 31.67, 31.4, 26.0, 14.5, −5.2. For 9-(benzyloxy)-1-ethoxy-3((*tert*-butyldimethylsilyloxy)methyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline-8-carboxaldehyde (**23**): ^1H NMR ($CDCl_3$, 400 MHz) δ 9.70 (1H, s, CHO), 7.5−7.3 (7H, m), 5.14 (1H, d, J = 11.4 Hz, C*H*HPh), 4.96 (1H, d, J = 11.4 Hz, CH*H*Ph), 4.77 (1H, s, C*H*HOSi), 4.76 (1H, s, CH*H*OSi), 4.56 (1H, dq, J = 10.8, 7.1 Hz, CH*H*CH_3), 4.46 (1H, dq, J = 10.8, 7.1 Hz, OC*H*HCH_3), 3.79 (1H, ddd, J = 8.2, 5.3, 2.7 Hz, C8-H), 3.01 (2H, m, C6-H), 2.37 (1H, m, C7-H), 2.10 (1H, m, C7-H), 1.32 (3H, t, J = 7.1 Hz, OCH_2CH_3), 0.98 (9H, s, $SiC(CH_3)_3$), 0.14 (6H, s, $SiCH_3$).

Scheme 3



73%) cleanly provided **24**[39] as a 4:1 mixture of isomers but only under conditions where *t*-BuOK (10 equiv)[12-14] serves as the base to generate the ylid and the reaction failed under more conventional conditions. Ester reduction (1 equiv of $LiBH_4$, THF, 25 °C, 7 h, 63%) and oxidation of the alcohol **25**[40] (10 equiv MnO_2, CH_2Cl_2, 25 °C, 20 h, 71%) provided the aldehyde **26**.[41] Without optimization, introduction of the pentadienyl side chain to provide **28**[42] was achieved with the phosphine oxide **27**[43] (THF–HMPA, −78 to −25 °C, 10 h, 32%) which, in our hands, has proven less satisfactory than the Wittig reagent **16**. Attempted acid-catalyzed deprotection of **28** with hydrolysis of the enol ether (TsOH, dioxane–H_2O) failed to provide **29** in acceptable conversions. Similarly, acid-catalyzed deprotection of **24** (1 equiv of TsOH, 3:1 THF–H_2O, 25 °C, 36 h) failed to provide the corresponding aldehyde but provided a mixture of **30**[44] (48%) and **23** (21%) derived from its benzylic oxidation. Finally, reasoning that a more acid labile enol ether that may be deprotected without protonation of the vinyl ether might successfully provide the aldehyde, we prepared **31**. However, attempts to deprotect **31** provided the same mixture of **30** and **23**.

Scheme 4



Introduction of the ABC Ring System of Fredericamycin A and Completion of the Total Synthesis. In preceding studies,[12-14] we described a highly convergent approach to the ABC ring system based on a regiospecific chromium carbene benzannulation reaction for assemblage of the AB ring system followed by a simple aldol closure for construction of the spiro-[4.4]nonene with introduction of ring C. The successful use of this approach in the preparation of the key partial structure **2**[12] suggested all elements of this sequence might be fully adaptable to the natural product, and we were guardedly optimistic that the presence of the F ring and its pentadienyl side chain would not compromise its implementation. The extension of these studies to fredericamycin A proved straightforward.

Treatment of the sensitive aldehyde **18** with the lithium acetylide **32**[45] and subsequent protection of the resulting alcohol **33** provided the alkyne **34** (54%) and a key component for the benzannulation reaction (Scheme 4). Due to the extraordinary sensitivity of the aldehyde **18** and the chromatographic losses often encountered in careful purifications of substrates containing the diene side chain, the three-step conversion of **17** to **34** was generally accomplished without the intermediate purification

(39) Compound **24** (73 mg, 73%) was isolated as a mixture of two isomers (4:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 and 7.97 (1H, s, C4-H), 7.59 and 7.50 (2H, d, J = 7.2 Hz), 7.45 and 7.42 (1H, s, C5-H), 7.44 and 7.37 (2H, t, J = 7.1 Hz), 7.29 and 7.27 (1H, t, J = 7.1 Hz), 7.32 and 6.26 (1H, s, C=C*H*OCH$_3$), 4.98 and 4.96 (2H, s, PhCH$_2$), 4.45 and 4.44 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_2$), 4.22 and 4.09 (3H, s, OCH$_3$), 3.58 and 3.49 (3H, s, CH$_3$OCH=C), 3.13 and 3.00 (2H, t, J = 7.4 Hz, C*H*$_2$CH$_2$), 2.82 and 2.72 (2H, t, J = 7.4 Hz, CH$_2$C*H*$_2$), 1.45 and 1.44 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); FABHRMS (NBA-CsI) *m/e* 552.0787 (M + Cs$^+$ requires 552.0787).

(40) Compound **25** was obtained as a mixture of two isomers (5:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 and 7.53 (2H, d, J = 7.2 Hz), 7.45 and 7.38 (2H, t, J = 7.2 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.28 (1H, s, C5-H), 7.23 and 6.21 (1H, s, CH$_3$OC*H*=C), 7.03 and 6.98 (1H, s, C4-H), 4.96 and 4.99 (2H, s, PhCH$_2$), 4.72 and 4.70 (2H, s, C*H*$_2$OH), 4.13 and 4.00 (3H, s, OCH$_3$), 3.59 and 3.48 (3H, s, C=CHOC*H*$_3$), 3.09 and 2.97 (2H, m, C*H*$_2$CH$_2$), 2.81 and 2.69 (2H, m, CH$_2$C*H*$_2$).

(41) For the major isomer of **26**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.02 (1H, s, CHO), 7.82 (1H, s, C4-H), 7.59 (2H, d, J = 6.8 Hz), 7.50 (1H, s, C5-H), 7.45 (2H, t, J = 6.8 Hz), 7.39 (1H, t, J = 6.8 Hz), 7.34 (1H, t, J = 2.5 Hz, C=C*H*OCH$_3$), 4.98 (2H, s, PhCH$_2$), 4.21 (3H, s, OCH$_3$), 3.58 (3H, s, C=CHOC*H*$_3$), 3.14 (2H, m, C*H*$_2$CH$_2$), 2.85 (2H, m, CH$_2$C*H*$_2$).

(42) For the major isomer of **28**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (2H, d, J = 8.3 Hz), 7.45 (2H, t, J = 8.3 Hz), 7.38 (1H, t, J = 8.3 Hz), 7.24 (2H, m, CH=C*H*-CH=CHCH$_3$ and C5-H), 6.94 (1H, s, C4-H), 6.47 (1H, d, J = 14.9 Hz, C*H*=CH-CH=CHCH$_3$), 6.27 (1H, t, J = 14.9 Hz, C*H*=CHCH$_3$), 5.95 (1H, m, CH=C*H*CH$_3$), 4.96 (2H, s, PhCH$_2$), 4.16 (3H, s, OCH$_3$), 3.57 (3H, s, CHOC*H*$_3$), 3.08 (2H, m, C*H*$_2$CH$_2$), 2.81 (2H, m, CH$_2$C*H*$_2$), 1.87 (3H, d, J = 6.9 Hz, CH=CHC*H*$_3$).

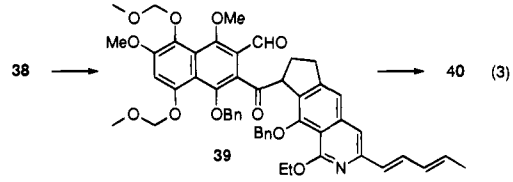
(43) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2386.

(44) For **30**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.69 (1H, s, CHO), 8.09 (1H, s, C4-H), 7.61 (1H, s, C5-H), 7.46 (5H, m), 5.04 (1H, d, J = 10.1 Hz, PhC*H*H), 4.97 (1H, d, J = 10.1 Hz, PhCH*H*), 4.46 (2H, q, J = 7.2 Hz, C*H*$_2$CH$_3$), 4.13 (3H, s, OCH$_3$), 4.04 (1H, s, OH), 3.52 (1H, m, C*H*HCH$_2$), 3.19 (1H, m, CH*H*CH$_2$), 2.52 (1H, dt, J = 13.7, 8.8 Hz, CH$_2$C*H*H), 2.14 (1H, ddd, J = 13.7, 7.9, 2.8 Hz, CH$_2$CH*H*), 1.45 (3H, t, J = 7.2 Hz, CH$_2$C*H*$_3$); FABMS (NBA-CsI) *m/e* 442 (M + H$^+$) and 554 (M + Cs$^+$).

(45) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

of **18** or **33** and provided **34** in better overall yield. The challenging step in this conversion proved to be the addition of the acetylide **32** to the sensitive aldehyde **18** which required the rigorous exclusion of air. The corresponding cerium reagent[46] derived from **32** was also examined and dependably provided **33/34**. In agreement with our preceding studies, the benzannulation reaction of **34** with the functionalized chromium carbene complex **35**[12] proceeded best in heptane (0.16 M in alkyne) in the presence of Ac_2O[27] (1−2 equiv) under conditions (50 °C, 48 h) that do not acetylate the product phenol and provided **36** as a single regioisomer and as a 3:1 mixture of diastereomers. Notably, this reaction failed to provide **36** in the absence of Ac_2O which, in preceding studies, was shown to accelerate the benzannulation reaction[12-14] and may affect the reaction course. Consistent with past observations, the regioselectivity of this reaction may be attributed to the modest steric differences in the alkyne α substituents that dictate the regioselectivity of the initial [2 + 2] chromium metallocyclobutene adduct preferentially placing the large substituent ortho to the product phenol. More subtle is the overall effect of the alkyne structure on the success of the benzannulation reaction of the chromium carbene complex **35** which incorporates an alkoxy substituent ortho to the carbene. As defined in the independent observations of Semmelhack,[28] the facility and reaction course with which such complexes participate in the benzannulation reactions with propargylic substrates is substantially diminished although the use of bulky alcohol protecting groups favors naphthol formation over competitive reactions. This subtle but important contribution to the success of the reaction of **35** through employment of the bulky bis-TBDMS ether **34** together with the modified reaction conditions[12] proved necessary for significant generation of **36**.

Subsequent protection of the free phenol **36** as the benzyl ether **37** was accomplished under mild conditions (25 equiv of $PhCH_2Br$, 2 equiv of Bu_4NI, 15 equiv of K_2CO_3, acetone, 25 °C, 44−54 h, 57%) notably without competitive elimination of *t*-$BuMe_2SiOH$ via orthoquinomethide generation. The use of higher reaction temperatures (55 °C, refluxing acetone) provided a mixture of uncharacterized products. Deprotection of the benzylic alcohols was effectively accomplished through treatment with Bu_4NF (5.2 equiv, THF, 10.5 h),[47] provided the diol **38**, and set the stage for introduction of the spiro CD ring system. Following our prescribed conditions,[12] Swern oxidation[36] of the diol **38** to the keto aldehyde **39** under carefully designed conditions precedes in situ base-catalyzed aldol closure to **40**. The success of the Swern oxidation (TFAA−DMSO) proved dependent on the reaction conditions where activation of both alcohols through formation of the bisalkoxysulfonium salt (60 min, −78 °C) preceded introduction of DBU and base-catalyzed elimination of dimethyl sulfide with formal oxidation of the primary and secondary alcohols. If the base was added prior to complete activation of both alcohols, competitive displacement reactions effectively compete with the desired oxidations. In addition, when this Swern oxidation was carried out with a stronger base (DBU versus Et_3N) and the reaction time and temperature extended (30 h, −78 to 25 °C), clean base-catalyzed aldol closure to **40** was observed under the reaction conditions (eq 3). Subsequent Swern oxidation of **40** (TFAA−DMSO, Et_3N, CH_2Cl_2, −78 °C, 60 min, 25 °C, 30 min) provided our penultimate intermediate **41**. Each of the steps in the transformation of **37** to **41** were so clean that it was accomplished without the purification of intermediates and provided **41** in superb conversions (57−68% overall from **37**) with an average yield of approximately 93−94% for each of the six reactions.



Two-step deprotection of **41** (BBr_3, CH_2Cl_2, −78 °C, 1 h; TsOH, NaBr, CH_3OH, 70 °C, 12 h) with air oxidation (3 h) following the BBr_3 treatment served admirably to provide **1** (85%) and completed the synthesis of fredericamycin A. Analogous to our earlier observations,[12] the BBr_3 treatment cleanly removed the two MOM ethers, the two benzyl ethers, and the activated C4 methyl ether leaving intact the required C6 methyl ether. Partial deprotection of the pyridone *O*-ethyl ether was observed under the conditions of the BBr_3 treatment, and this was cleanly and completely removed upon air oxidation and subsequent treatment with TsOH−NaBr.[16] This provided **1** identical in all respects with a sample of authentic material (^1H NMR, IR, UV, MS, TLC:$CHCl_3$−CH_3OH−HOAc (87:3:3), CH_2Cl_2−EtOAc−HOAc (10:10:1), and 5% CH_3OH−$CHCl_3$). The deliberate use of labile protecting groups introduced throughout the synthesis permitted a dependably clean final deprotection sequence that leaves the C6 methyl ether unaffected and distinguishes the final stages of this synthesis from some of the prior efforts.[17-19]

Resolution and Preparation of Natural and *ent*-Fredericamycin A. As a consequence of the potent activity of the natural product and the uncertainty surrounding its mechanism of action, we were especially interested in the evaluation of both enantiomers of fredericamycin A. The examination of the unnatural enantiomer, like key partial structures, is anticipated to provide seminal observations that may distinguish both the site of action and the structural features contributing to the biological effects of the natural product.[48] To this end, the resolution of the penultimate precursor **41** was examined on a series of HPLC chiral phases (ChiralPac OD, OB-H, AD, OT). The best resolution was observed on a ChiralPac OD column. Racemic **41** could be resolved on a HPLC analytical column (0.46 × 25 cm, 10% *i*-PrOH−hexane, 0.9 mL/min flow rate, α = 1.38) and preparatively separated on a semipreparative HPLC column (2 × 25 cm, 20% *i*-PrOH−hexane, 2−6 mL/min, α = 1.14) to afford the two enantiomers (>99% ee). Independent deprotection of the two enantiomers as detailed above provided natural and *ent*-fredericamycin A (>99% ee). The circular dichroism spectra of the two enantiomers of the synthetic and natural fredericamycin A permitted the unambiguous assignments of the natural and unnatural enantiomers of synthetic **1** as well as **41** (Figures 1−3). Like the CD for natural fredericamycin A recorded at a pH of 8.0 ($[\Theta]^{25}_{396}$ +2.5 × 10^4 deg·cm^2·$dmol^{-1}$, 20% DMF−CH_3OH/blue form), synthetic *ent*-**1** exhibited the same but opposite CD ($[\Theta]^{25}_{396}$ −2.4 × 10^4 deg·cm^2·$dmol^{-1}$, 20% DMF−CH_3OH).[49] At acidic pH with the red, protonated form of fredericamycin A, the long wavelength CD band becomes considerably less intense, reverses sign, and more closely resembles the CD spectrum of the corresponding enantiomers of **41** (Figure 3).

(46) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747.
(47) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(48) For representative examples, see: Boger, D. L.; Johnson, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3642.
(49) The agent exhibits a pH dependent CD and the addition of TFA (acid) led to a decrease in the $[\Theta]^{25}_{396}$. This accounts for the small discrepancy in the molar ellipticities for the two enantiomers as shown in Figure 2. Both enantiomers were >99% ee (HPLC analysis on ChiralCel OD column).

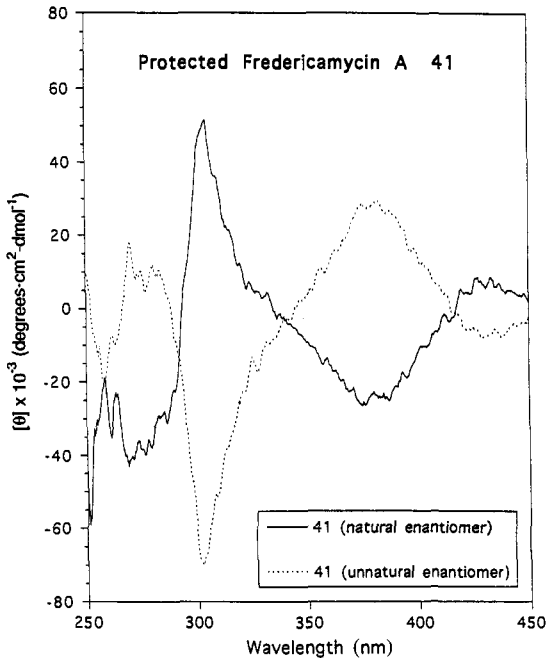


Figure 1. CD spectrum of **41** in *i*-PrOH.

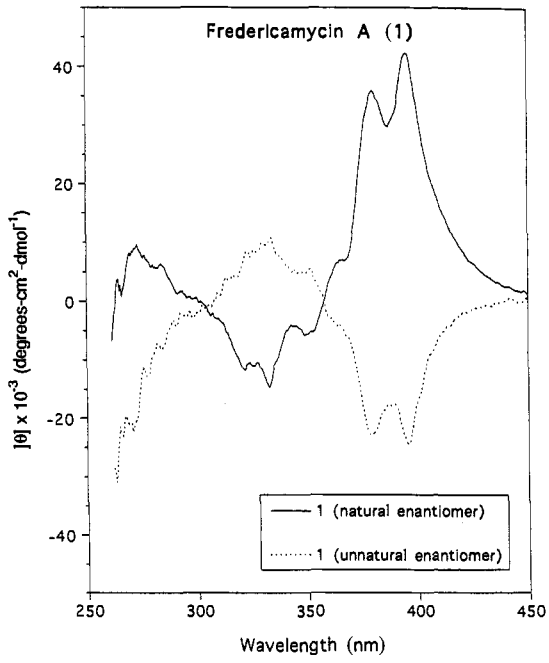


Figure 2. CD spectrum of **1** in 20% DMF−CH_3OH/Et_3N (blue form).

In Vitro Cytotoxic Activity. Summarized in Table 1 is the L1210 cytotoxic activity of natural and *ent*-fredericamycin A, the key partial structure **2** constituting the fully functionalized ABCDE ring system of fredericamycin A and **21** constituting the fully functionalized DEF ring system. Both natural and *ent*-**1** exhibited potent and essentially indistinguishable cytotoxic activity (IC_{50} = 0.03 and 0.04 μg/mL, respectively). Both **2** and **20** were considerably less potent than **1** (*ca.* 100×) and comparable in cytotoxic potency with each other. While it is perhaps surprising that **21** exhibits any activity, the considerably diminished activity of **2** illustrates that the functionalized F ring of fredericamycin contributes significantly to its properties. The surprising but informative comparable cytotoxic potency of the two enantiomers of **1** should permit their use in distinguishing the site and potential mechanism of action of fredericamycin A and such studies are in progress.

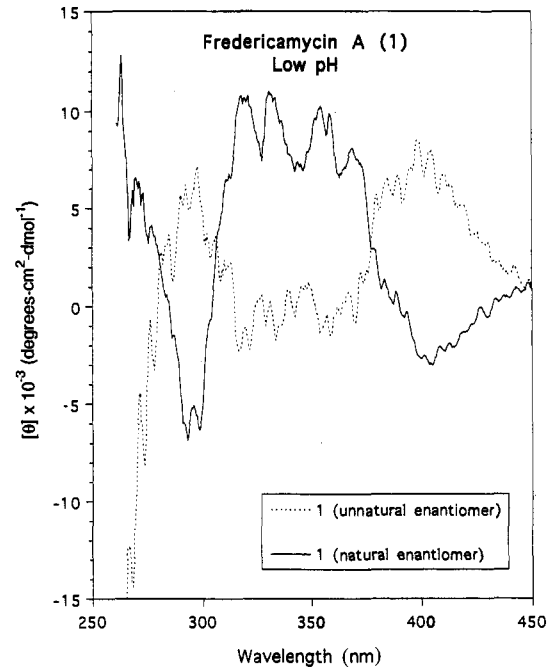


Figure 3. CD spectrum of **1** in 20% DMF−CH_3OH/TFA (red form).

Table 1. In Vitro Cytotoxic Activity

agent	IC_{50} (μg/mL, L1210)
fredericamycin A	0.03
ent-fredericamycin A	0.04
2	2
21	7

Experimental Section

3,6-Bis(ethoxycarbonyl)-2,2-diethoxy-4-methyl-1-(methylsulfonyl)-1,2,3,4-tetrahydropyridine (6). A solution of ethyl (*E*)-2-(hydroxyimino)-3-pentenoate **3**[15,30] (8.17 g, 52 mmol) in CCl_4 (350 mL) was treated sequentially with Et_3N (13 mL, 52 mmol, 1.0 equiv) and methylsulfinyl chloride (3.8 mL, 57.2 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 10 min during which time the formation of a white precipitate was observed. The mixture was poured into a separatory funnel containing 200 mL of cold water. CCl_4 (100 mL) was used to wash the reaction flask and was added to the contents of the separatory funnel. After decantation, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude diene **4** which was used without further purification.

The crude diene **4** was dissolved in CH_2Cl_2 (10 mL) and treated with ethyl 3,3-diethoxyacrylate (**5**, 4.9 mL, 26 mmol, 0.5 equiv), and the mixture was stirred at 25 °C for 20 h. The mixture was evaporated under reduced pressure and purified by chromatography (SiO_2, 7 × 30 cm, 30% EtOAc−hexane) to afford **6** (10.04 g, 95% based on **5**; 47% based on **3**) as a 1:1 mixture of endo and exo isomers identical in all respects with authentic material.[15]

3,6-Bis(ethoxycarbonyl)-2-ethoxy-4-methylpyridine (7). A solution of **6** (13.11 g, 32.2 mmol) in THF (300 mL) at 25 °C was treated with DBU (22 mL, 145 mmol, 4.5 equiv). The mixture was stirred at 70 °C for 40 h under N_2 before it was concentrated under vacuum. Chromatography (SiO_2, 7 × 25 cm, 20% EtOAc−hexane) afforded **7** (7.52 g, 9.05 g theoretical, 83%; typically 81−91%) identical in all respects with authentic material.[15]

1-Ethoxy-3-(ethoxycarbonyl)-5,5a,7,8-tetrahydro-9-hydroxy-6*H*-cyclopent[*g*]isoquinolin-8-one (10). 1.0 mmol: Freshly distilled THF (90 mL) was introduced into a flame-dried 250 mL flask under Ar through a syringe. Anhydrous *i*-Pr_2NH (0.67 mL, 4.8 mmol, 4.8 equiv) and *n*-BuLi (1.60 mL of 2.5 M in hexane, 4.0 mmol, 4.0 equiv) were added at −20 °C with stirring. The solution was cooled to −78 °C and stirred for 10 min before 10 mL of a 0.10 M solution of **7** in THF (1.0 mmol, 1 equiv) was introduced by syringe over 5 s. The reaction mixture was stirred at −78 °C for an additional 25 s before cyclopen-

tenone (**8**, 0.40 mL, 5.0 mmol, 5.0 equiv) was introduced. Immediately following the addition, the reaction mixture turned from blood-red to bright yellow. After 20 s, EtOH (1.0 mL) was added, the cold bath was removed, and the mixture was stirred at 25 °C (3 h) under Ar. The mixture was acidified with the addition of HOAc (1.0 mL), diluted with saturated aqueous NH_4Cl (150 mL), extracted with CH_2Cl_2 (100 mL, 2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (SiO_2, 1.5 × 20 cm, 25–40% EtOAc–hexane gradient elution) afforded **10** (271 mg, 317 mg theoretical, 85%) as a bright yellow solid identical in all respects with authentic material: mp 125–126 °C (EtOAc–hexane, yellow flakes), lit.[15] mp 125–126 °C.

2.0 mmol: Freshly distilled THF (190 mL) was introduced into an oven-dried, flame-dried 500 mL flask equipped with a three-way joint under Ar through a syringe. Freshly distilled *i*-Pr_2NH (2.8 mL, 20 mmol, 10.4 equiv) was added followed by dropwise addition of *n*-BuLi (7.4 mL, 18.5 mmol, 9.6 equiv, 2.5 M in hexane) at −36 °C with stirring. The solution was cooled to −80 °C and stirred for 20 min before 10 mL of a 0.192 M solution of **7** (540 mg, 1.92 mmol) was introduced by syringe over 5 s. The reaction mixture was stirred at −80 °C for an additional 45 s before cyclopentenone (**8**, 1.8 mL, 21.8 mmol, 11 equiv) was introduced over 3 s. After 27 s, EtOH (2.5 mL) stored over 4 Å MS was added, the cold bath was removed, and the mixture was stirred at 25 °C under Ar for 2 h. The mixture was treated with HOAc (2.5 mL) and concentrated under reduced pressure without heating. The residue was dissolved in CH_2Cl_2 (70 mL) and extracted with half-saturated aqueous NH_4Cl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Two such reactions were combined. Flash chromatography (SiO_2, 3.5 × 26 cm, 36% EtOAc–hexane) afforded **10** (774 mg, 1.218 g theoretical, 64%) as a yellow solid identical in all respects with authentic material.[15]

5.0 mmol: Freshly distilled THF (450 mL) was introduced into a flame-dried 1 L flask under Ar. Anhydrous *i*-Pr_2NH (2.8 mL, 20 mmol, 4 equiv) was added followed by dropwise addition of *n*-BuLi (8.0 mL, 20 mmol, 4 equiv, 2.5 M in hexane) at −20 °C with stirring. The solution was cooled to −78 °C before 50 mL of a 0.1 M solution of **7** (1.41 g, 5.0 mmol) was introduced over 5 s. The reaction mixture was stirred at −78 °C for 30 s before cyclopentenone (1.86 mL, 22.5 mmol, 4.5 equiv) was introduced. After 20 s, EtOH (5.0 mL) was added, the cold bath was removed, and the mixture stirred at 25 °C for 6 h. The mixture was treated with HOAc (5.0 mL) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with saturated aqueous NH_4Cl (2 × 125 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (SiO_2, 3.5 × 26 cm, 35% EtOAc–hexane) afforded **10** (1.09 g, 1.58 g theoretical, 69%) as a yellow solid identical in all respects with authentic material.[15]

1-Ethoxy-3-(ethoxycarbonyl)-7,8-dihydro-9-hydroxy-6*H*-cyclopent-[*g*]isoquinolin-8-one (11). Method A: A solution of **10** (2 g, 6.3 mmol) in CH_2Cl_2 (50 mL) was treated with DDQ (1.5 g, 6.62 mmol, 1.05 equiv). The reaction mixture was stirred at 25 °C for 10 min, filtered over Celite and the solid washed with CH_2Cl_2 (150 mL). The organic phase was successively washed with saturated aqueous NH_4Cl (70 mL), saturated aqueous $NaHCO_3$ (50 mL), and distilled H_2O (50 mL). The solution was dried (Na_2SO_4) and concentrated under reduced pressure to afford pure **11** (1.72 g, 1.99 g theoretical, 87%) identical in all respects with authentic material and sufficiently pure for use in the following step: mp 188–189 °C (CH_2Cl_2–EtOAc), lit.[15] mp 188–189 °C.

Method B: A suspension of MnO_2 (495 mg, 5.64 mmol, 3.6 equiv) in CH_2Cl_2 (30 mL) was treated at 25 °C with a solution of **10** in CH_2Cl_2 (30 mL). The mixture was stirred at 25 °C over 44 h and filtered over Celite. The Celite was washed with CH_2Cl_2 (250 mL), and the combined solutions were concentrated under reduced pressure to afford **11** (457 mg, 492 mg theoretical, 93%) identical in all respects with authentic material.[15]

9-(Benzyloxy)-1-ethoxy-3-(ethoxycarbonyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-8-one (12). Method A: A solution of **11** (2.65 g, 7.85 mmol) in DMF (100 mL) was treated sequentially with K_2CO_3 (5.5 g, 39.8 mmol, 5.07 equiv), Bu_4NI (540 mg, 1.46 mmol, 0.18 equiv), and $PhCH_2Br$ (2.5 mL, 21 mmol, 2.7 equiv). The reaction mixture was stirred at 25 °C (6 h) before it was diluted with H_2O (500 mL), extracted with CH_2Cl_2 (3 × 300 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc–hexane) afforded **12** (2.96 g, 3.18 g theoretical, 93%) identical in all respects with authentic material.[15]

Method B: A suspension of **11** (500 mg, 1.6 mmol) in DMF (12 mL) was treated sequentially with benzyl bromide (0.6 mL, 4.76 mmol, 3 equiv) and Ag_2O (514 mg, 2.22 mmol, 1.4 equiv). The mixture was stirred at 25 °C for 2 h, filtered over Celite, and diluted with Et_2O (100 mL). The solution was washed with H_2O (30 mL) and decanted, and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated, and chromatographed (SiO_2, 3 × 15 cm, 25% EtOAc–hexane) to afford **12** (530 mg, 643 mg theoretical, 82%) identical in all respects with authentic material: mp 159–160 °C (CH_2Cl_2–EtOAc), lit.[15] mp 159–160 °C.

9-(Benzyloxy)-8-cyano-1-ethoxy-3-(ethoxycarbonyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline (13). A solution of **12** (800 mg, 1.97 mmol) in CH_2Cl_2 (20 mL) was treated with TosMIC (468 mg, 2.40 mmol, 1.21 equiv) and cooled to −67 °C. EtOH (116 μL, 1.97 mmol, 1.21 equiv) and *t*-BuOK (337 mg, 2.76 mmol, 1.4 equiv) were added sequentially and stirring was continued for 5 h while the cold bath was allowed to warm to 10 °C gradually. The cold bath was removed and the mixture was stirred at 25 °C (2 h) before it was diluted with CH_2Cl_2 (50 mL) and acidified with the addition of aqueous HCl (0.06 M, 50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 3.5 × 25 cm, 20% EtOAc–hexane) afforded **13** (598 mg, 820 mg theoretical, 73%) as a white solid: mp 123–124 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (1H, s, C4-H), 7.48 (1H, s, C5-H), 7.47–7.32 (5H, m), 5.26 (1H, d, J = 11.2 Hz, PhC*H*H), 5.09 (1H, d, J = 11.2 Hz, PhCH*H*), 4.69 (1H, dq, J = 17.2, 7.1 Hz, C1–OC*H*HCH$_3$), 4.66 (1H, dq, J = 17.2, 7.1 Hz, C1-OCH*H*CH$_3$), 4.43 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.82 (1H, dd, J = 8.4, 4.4 Hz, CHCN), 3.25 (1H, m, C7–*H*H), 3.04 (1H, m, C7-H*H*), 2.36 (2H, m, C6-H_2), 1.43 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.37 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6 (e, CO_2Et), 159.7 (e), 152.5 (e), 147.7 (e), 141.8 (e), 139.4 (e), 137.1 (e), 132.9 (e), 128.5 (o, two CH), 128.1 (o), 128.0 (o, two CH), 120.3 (e), 119.8 (o), 118.3 (o), 115.3 (e), 77.3 (e, $PhCH_2$), 62.8 (e, CH_2CH_3), 61.5 (e, CH_2CH_3), 31.8 (o, CHCN), 31.7 (e, CH_2CH_2), 31.3 (e, CH_2CH_2), 14.4 (o, two CH_2CH_3); IR (KBr) ν_{max} 2983, 2930, 2879, 2228, 1700, 1566, 1483, 1421, 1339, 1241, 1091, 1029, 889, 750, 693 cm^{-1}; FABHRMS (NBA) *m/e* 417.1825 (M + H$^+$, $C_{25}H_{24}N_2O_4$ requires 417.1814). Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 71.73; H, 5.44; N, 6.67.

The corresponding carboxylic acid was also isolated on occasion in variable amounts (0–12%). For 9-(benzyloxy)-8-cyano-1-ethoxy-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline-3-carboxylic acid: mp 156–157 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.05 (1H, br s, CO_2H), 8.01 (1H, s, C4-H), 7.49 (1H, s, C5-H), 7.44–7.30 (5H, m), 5.25 (1H, d, J = 11.3 Hz, PhC*H*H), 5.03 (1H, d, J = 11.3 Hz, PhCH*H*), 4.54 (2H, m, CH_2CH_3), 3.80 (1H, dd, J = 8.2, 5.0 Hz, CHCN), 3.28 (1H, m, C7-*H*H), 3.07 (1H, m, C7-H*H*), 2.38 (2H, m, C6-H_2), 1.36 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0 (e, CO_2H), 159.4 (e), 152.8 (e), 148.9 (e), 141.9 (e), 136.8 (e), 136.7 (e), 133.7 (e), 128.5 (o, two CH), 128.3 (o), 127.8 (o, two CH), 120.4 (o), 120.2 (e), 117.3 (o), 115.5 (e), 77.3 (e, $PhCH_2$), 63.5 (e, CH_2CH_3), 31.8 (o, CHCN), 31.7 (e, CH_2CH_2), 31.1 (e, CH_2CH_2), 14.2 (o, CH_2CH_3); IR (KBr) ν_{max} 2995, 2892, 2626 (br), 2236, 1697, 1564, 1451, 1323, 1277, 1103, 954, 882, 728, 692 cm^{-1}; FABHRMS (NBA) *m/e* 389.1510 (M + H$^+$, $C_{23}H_{20}N_2O_4$ requires 389.1501). Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.04; H, 5.01; N, 7.07.

9-(Benzyloxy)-8-cyano-1-ethoxy-3-(hydroxymethyl)-7,8-dihydro-6*H*-cyclo-pent[*g*]isoquinoline (14). A solution of **13** (723 mg, 1.74 mmol) in anhydrous THF (25 mL) at −78 °C under Ar was treated with 1.0 M solution of Dibal-H in toluene (5.8 mL, 3.3 equiv). The resulting reaction mixture was allowed to stir at −78 °C for 3 h before it was quenched with the addition of CH_3OH (2.0 mL) at −78 °C. The mixture was allowed to warm to 25 °C, diluted with saturated aqueous NH_4Cl (50 mL), and stirred at 25 °C for 1 h. The reaction mixture was further diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The organic phase was dried (Na_2SO_4) and concentrated under

reduced pressure. Chromatography (SiO_2, 3 × 20 cm, 30% EtOAc–hexane) afforded **14** (599 mg, 92%, typically 92–97%) as a white solid and **15** (40 mg, 5%). The combined yield of the desired products **14** and **15** was 97%. For **14**: mp 100–101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.33 (5H, m), 7.27 (1H, s, C5-H), 7.07 (1H, s, C4-H), 5.24 (1H, d, J = 11.2 Hz, PhC*H*H), 5.07 (1H, d, J = 11.2 Hz, PhCH*H*), 4.69 (2H, s, CH_2OH), 4.56 (2H, two dq, J = 13.8, 6.8 Hz, OCH_2CH_3), 3.80 (1H, dd, J = 8.4, 4.3 Hz, CHCN), 3.35 (1H, br s, OH), 3.22 (1H, dt, J = 16.5, 8.2 Hz, C7–*H*H), 3.00 (1H, ddd, J = 16.4, 8.0, 4.3 Hz, C7-H*H*), 2.35 (2H, m, C6-H_2), 1.35 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4 (e), 152.3 (e), 150.3 (e), 147.1 (e), 142.8 (e), 137.1 (e), 129.8 (e), 128.3 (o, two CH), 127.9 (o), 127.8 (o, two CH), 120.5 (e), 118.1 (o), 112.6 (e), 110.2 (o), 76.8 (e, $PhCH_2$), 64.3 (e, CH_2OH), 62.3 (e, CH_2CH_3), 31.5 (e, CH_2CH_2), 31.4 (o, *C*HCN), 31.2 (e, CH_2CH_2), 14.3 (o, CH_2CH_3); IR (KBr) ν_{max} 3308 (br), 3220 (br), 3065, 3032, 2993, 2976, 2952, 2896, 2236, 1630, 1570, 1478, 1458, 1415, 1376, 1360, 1325, 1140, 1103, 1077, 1061, 978, 958, 873, 730, 694 cm^{-1}; FABHRMS (NBA) *m/e* 375.1718 (M + H$^+$, $C_{23}H_{22}N_2O_3$ requires 375.1709). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.44; H, 5.95; N, 7.25.

9-(Benzyloxy)-8-cyano-1-ethoxy-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline-3-carboxaldehyde (15). A solution of oxalyl chloride (1.0 M in CH_2Cl_2, 2.5 mL, 2.5 mmol) in CH_2Cl_2 (5 mL) at −70 °C under Ar was treated with anhydrous DMSO (0.38 mL). After stirring at −70 °C for 5 min, the resulting solution was treated with a solution of **14** (310 mg, 0.83 mmol) in CH_2Cl_2 (3 mL) and stirred at −70 °C for 15 min before Et_3N (1.4 mL) was introduced. The cold bath was removed, and the reaction mixture was allowed to warm to 25 °C over 20 min before it was diluted with H_2O (50 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 2 × 20 cm, 20% EtOAc–hexane) afforded **15** (304 mg, 308 mg theoretical, 99%) as a white solid: mp 89–90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.04 (1H, s, CHO), 7.87 (1H, s, C4-H), 7.59 (1H, s, C5-H), 7.50–7.35 (5H, m), 5.32 (1H, d, J = 11.2 Hz, PhC*H*H), 5.14 (1H, d, J = 11.2 Hz, PhCH*H*), 4.70 (2H, two dq, J = 14.8, 7.1 Hz, OCH_2CH_3), 3.84 (1H, dd, J = 8.5, 4.4 Hz, CHCN), 3.33 (1H, dt, J = 16.7, 8.4 Hz, C7–*H*H), 3.11 (1H, ddd, J = 16.5, 8.4, 4.7 Hz, C7-H*H*), 2.42 (2H, m, C6-H_2), 1.43 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.9 (o, CHO), 160.4 (e), 152.7 (e), 148.0 (e), 144.5 (e), 141.5 (e), 137.0 (e), 133.7 (e), 128.5 (o, two CH), 128.2 (o), 128.0 (o, two CH), 120.6 (o, C4), 120.2 (e), 117.0 (o, C5), 116.1 (e), 77.4 (e, $PhCH_2$), 63.0 (e, CH_2CH_3), 31.9 (o, C8), 31.7 (e, CH_2CH_2), 31.3 (e, CH_2CH_2), 14.4 (o, CH_2CH_3); IR (KBr) ν_{max} 3064, 3032, 2981, 2934, 2897, 2813, 2715, 2244, 1704, 1619, 1594, 1567, 1485, 1474, 1456, 1417, 1359, 1338, 1220, 1170, 1158, 1143, 1102, 1054, 1028, 1003, 969, 899, 735, 695, 669 cm^{-1}; FABHRMS (NBA) *m/e* 373.1565 (M + H$^+$, $C_{23}H_{20}N_2O_3$ requires 373.1552). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.27; H, 5.46; N, 7.59.

9-(Benzyloxy)-8-cyano-1-ethoxy-3-(1′,3′-pentadienyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline (17). A white suspension of *trans*-2-butenyltriphenylphosphonium bromide[37] (470 mg, 1.2 equiv) in anhydrous THF (5 mL) under Ar at −78 °C was treated with a solution of *n*-BuLi (1.6 M in hexane, 0.73 mL, 1.2 equiv). The cold bath was removed, and the resulting red suspension was allowed to stir at 25 °C for 40 min to effect a blood-red solution. The reaction mixture was cooled to −78 °C before a solution of **15** (366 mg, 0.98 mmol) in anhydrous THF (5 mL) was introduced through a syringe dropwise. The resulting orange-red suspension was allowed to stir overnight (12 h) during which time the cold bath temperature warmed from −78 to 25 °C gradually. The reaction mixture was diluted with H_2O (200 mL), acidified with the addition of dilute aqueous HCl (3.0 M, 2 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 1.5 × 30 cm, 10% EtOAc–hexane) afforded **17** (361 mg, 403 mg theoretical, 89%) as a mixture of four olefin isomers (*cis*–*cis*:*cis*–*trans*:*trans*–*cis*:*trans*–*trans* = 1:5.5:1.6:5.4), which were isomerized to a *trans*–*trans*:*cis*–*trans* mixture of isomers (85:15) by treatment of a solution of the isomeric mixture in CH_2Cl_2 or $CHCl_3$ (0.1 M) with I_2 (0.05 equiv) at 25 °C for 4–5 days. The isomerization reaction mixture was diluted with CH_2Cl_2 (120 mL) and washed with aqueous 0.25 M $Na_2S_2O_3$ (80 mL) and H_2O (80 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, azeotropically dried with toluene (2 × 5 mL), and carried directly into the following reaction. For **17**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50–7.35 (6H, m, Ph and CH_3CH=CH-C*H*=CH), 7.30 (1H, s, C5-H), 6.96 (1H, s, C4-H), 6.45 (1H, d, J = 15.0 Hz, CH=C*H*Ar), 6.29 (1H, t, J = 11.6 Hz, CH_3CH=C*H*), 5.97 (1H, dq, J = 15.0, 6.8 Hz, CH_3CH=CH), 5.25 (1H, d, J = 11.1 Hz, PhC*H*H), 5.12 (1H, d, J = 11.1 Hz, PhCH*H*), 4.64 (2H, dq, J = 14.1, 7.0 Hz, OCH_2CH_3), 3.81 (1H, dd, J = 8.4, 4.0 Hz, CHCN), 3.24 (1H, m, C7-*H*H), 3.02 (1H, m, C7-H*H*), 2.36 (2H, m, C6-H_2), 1.85 (3H, d, J = 6.8 Hz, CH_3CH=CH), 1.40 (3H, t, J = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9 (e), 152.5 (e), 147.3 (e), 146.9 (e), 143.1 (e), 137.4 (e), 132.6 (o, CH), 132.3 (o, CH), 131.6 (o, CH), 129.1 (e), 128.8 (o, CH), 128.4 (o, two CH), 128.0 (o, three CH), 120.8 (e), 118.3 (o), 113.2 (o), 76.9 (e, $PhCH_2$), 62.1 (e, CH_2CH_3), 31.7 (e, CH_2CH_2), 31.6 (o, *C*HCN), 31.3 (e, CH_2CH_2), 18.6 (o, $CHCH_3$), 14.5 (o, CH_2CH_3); IR (KBr) ν_{max} 2972, 2930, 2238, 1618, 1571, 1328, 1096, 987, 879, 734, 693 cm^{-1}; FABHRMS (NBA) *m/e* 411.2059 (M + H$^+$, $C_{27}H_{26}N_2O_2$ requires 411.2073).

9-(Benzyloxy)-1-ethoxy-3-(1′,3′-pentadienyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline-8-carboxaldehyde (18). A solution of **17** (230 mg, 0.56 mmol) in toluene (20 mL) at −30 °C under Ar was treated with a solution of Dibal-H (1.0 M, 1.10 mL, 2.0 equiv). The resulting solution was allowed to stir at −30 °C for 1 h before 40 mL of aqueous 1.0 M phosphate buffer (pH = 4.0) was introduced, and the cold bath was removed. The mixture was stirred at 25 °C for 20 min under Ar, diluted with H_2O (300 mL), extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure under an atmosphere of Ar. This crude material was sufficiently pure to use directly and generally was azeotropically dried with C_6H_6 (2 × 2 mL) under Ar and carried into the subsequent reaction. Chromatography under Ar (SiO_2, 1.5 × 40 cm, 5–10% EtOAc–hexane) of the product from the above reaction afforded **18** (160 mg, 232 mg theoretical, 69%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (1H, s, CHO), 7.38–7.32 (6H, m), 7.30 (1H, s, C5-H), 6.96 (1H, s, C4-H), 6.45 (1H, d, J = 15.1 Hz, CH=C*H*Ar), 6.29 (1H, t, J = 14.0 Hz, CH_3CH=C*H*), 5.96 (1H, dq, J = 15.0, 7.0 Hz, CH_3CH=CH), 5.15 (1H, d, J = 11.3 Hz, PhC*H*H), 4.97 (1H, d, J = 11.3 Hz, PhCH*H*), 4.68 (1H, m, CH_3CHH), 4.58 (1H, m, CH_3CHH), 3.78 (1H, m, CHCN), 3.03 (2H, m, CH_2CH_2), 2.36 (1H, m, CH_2CHH), 2.10 (1H, m, CH_2CHH), 1.85 (3H, d, J = 5.7 Hz, CH_3CH=CH), 1.38 (3H, t, J = 7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.7 (o, CHO), 152.5 (e), 148.9 (e), 148.1 (e), 146.8 (e), 142.8 (e), 137.3 (e), 132.3 (o), 132.0 (o), 131.6 (o), 131.5 (e), 128.4 (o, two CH), 127.9 (o, two CH), 125.1 (o), 118.5 (o), 115.7 (o), 113.4 (o). 76.7 (e, $PhCH_2$), 62.0 (e, CH_2CH_3), 55.7 (o, *C*HCHO), 32.0 (e, CH_2CH_2), 25.9 (e, CH_2CH_2), 18.6 (o, $CHCH_3$), 14.5 (o, CH_2CH_3); IR (film) ν_{max} 2933, 2715, 1723, 1618, 1567, 1453, 1414, 1359, 1329, 1149, 1097, 990, 881, 733, 697 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 414.2050 (M + H$^+$, $C_{27}H_{27}NO_3$ requires 414.2069).

9-(Benzyloxy)-1-ethoxy-3-(1′,3′-pentadienyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-8-one (20). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (2H, d, J = 7.2 Hz), 7.40–7.25 (5H, m), 6.89 (1H, s, C4-H), 6.42 (1H, d, J = 15.0 Hz, CH_3CH=CH-CH=C*H*), 6.29 (1H, t, J = 11.1 Hz, CH_3CH=C*H*), 6.00 (1H, dq, J = 14.6, 6.9 Hz, CH_3CH=CH), 5.23 (2H, s, $PhCH_2$), 4.59 (2H, q, J = 7.1 Hz, CH_2CH_3), 3.17 (2H, m, CH_2CH_2), 2.73 (2H, m, CH_2CH_2), 1.86 (3H, d, J = 6.3 Hz, CH_3CH=CH), 1.32 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.3 (e, C=O), 161.4 (e), 157.3 (e), 154.7 (e), 149.3 (e), 145.8 (e), 137.4 (e), 133.9 (o), 133.2 (o), 131.5 (o), 128.7 (o), 128.4 (o, two CH), 128.2 (o, two CH), 127.8 (o), 118.8 (o), 112.6 (o), 77.4 (e, $PhCH_2$), 62.2 (e, CH_2CH_3), 37.3 (e, CH_2CH_2), 25.1 (e, CH_2CH_2), 18.6 (o, CH_3CH=CH), 14.4 (o, CH_2CH_3); IR (film) ν_{max} 3030, 2927, 1708, 1609, 1560, 1497, 1481, 1376, 1358, 1331, 1108, 1065, 990, 698 cm^{-1}; FABHRMS (NBA) *m/e* 400.1901 (M + H$^+$, $C_{26}H_{25}NO_3$ requires 400.1913).

9-Hydroxy-3-(1′,3′-pentadienyl)-2,6,7,8-tetrahydro-1*H*-cyclopent[*g*]isoquinolin-1,8-dione (21). A solution of **20** (8.6 mg) in CH_3OH (4 mL) was treated with NaBr (135 mg) and TsOH (61 mg) at 25 °C. The resulting reaction mixture was allowed to stir at reflux under Ar for 6.5 h before it was cooled to 25 °C, diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chro-

matography (SiO_2, 0.5 × 5 cm, CH_2Cl_2–EtOAc–HOAc = 10:10:1) afforded **21** (5.0 mg, 6.2 mg theoretical, 81%) as a light yellow solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 13.55 (1H, s, OH), 10.15 (1H, s, NH), 6.88 (1H, m, C6-H) 6.85 (1H, dd, J = 16.2, 11.3 Hz, CH_3CH=CH-C*H*=CH), 6.42 (1H, s, C4-H), 6.26–6.16 (1H, m, CH_3CH=C*H*), 6.12 (1H, d, J = 15 Hz, CH=C*H*Ar), 6.15–6.04 (1H, m, CH_3CH=CH), 3.15–3.06 (2H, m, CH_2CH_2), 2.74–2.64 (2H, m, CH_2CH_2), 1.86 (3H, d, J = 7.2 Hz, CH_3CH=CH); FABHRMS (NBA-CsI) *m/e* 414.0106 (M + Cs^+, $C_{17}H_{15}NO_3$ requires 414.0106).

1,4-Bis[[(1,1-dimethylethyl)dimethylsilyl]methyl]-1-[1′-ethoxy-3′-(1″,3″-pentadienyl)-9′-(phenylmethoxy)-6′,7′-dihydro-8′*H*-cyclopent[*g*]isoquinolinyl]-2-butyne (34). A solution of 3-((*tert*-butyldimethyl)silyl)oxypropyne[45] (55 mg, 1.6 equiv) in THF (1 mL) under Ar was treated with *n*-BuLi (1.6 M, 0.20 mL, 0.32 mmol) at −78 °C. The reaction mixture was stirred at 0 °C for 30 min and recooled to −78 °C, and **18** (85 mg, 0.21 mmol) in THF (1 mL) was added. Stirring was continued for 2 h during which time the cold bath temperature gradually warmed from −78 to 0 °C. The reaction mixture was diluted with H_2O (30 mL), neutralized with the addition of dilute aqueous HCl, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give crude **33**.

A solution of **33** in DMF (2.0 mL) was treated with imidazole (53 mg, 3.8 equiv) and TBDMSCl (120 mg, 3.9 equiv). The reaction mixture was stirred at 25 °C for 22 h, diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1.5 × 30 cm, 5% EtOAc–hexane) afforded **34** (78 mg, 147 mg theoretical, 54%) as a light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.26 (6H, m), 7.20 (1H, s, C5-H), 6.93 (1H, s, C4-H), 6.45 (1H, d, J = 15.0 Hz, CH=C*H*Ar), 6.28 (1H, t, J = 14.0 Hz, CH_3CH=C*H*), 5.93 (1H, dq, J = 15.0, 6.8 Hz, CH_3C*H*=CH), 5.21 (1H, d, J = 11.4 Hz, PhC*H*H), 5.03 (1H, m, CHOTBDMS), 4.87 (1H, d, J = 11.4 Hz, PhC*H*H), 4.60 (2H, m, OCH_2CH_3), 4.34 (2H, s, CH_2OTBDMS), 3.38 (1H, m, C8-H), 3.16 (1H, C*H*HCH$_2$), 2.86 (1H, m, CH*H*CH$_2$), 2.46 (1H, m, CH_2CH*H*), 2.07 (1H, m, CH_2CH*H*), 1.84 (3H, d, J = 6.6 Hz, CH_3CH=CH), 1.34 (3H, t, J = 7.2 Hz, OCH_2CH_3), 0.90 (9H, s, SiC(CH$_3$)$_3$), 0.58 (9H. s, SiC(CH$_3$)$_3$), 0.12 (6H, s, Si(CH$_3$)$_2$), −0.12 (3H, s, SiCH$_3$), −0.43 (3H, s, SiCH$_3$); IR (film) ν_{max} 2954, 2928, 2856, 1735, 1620. 1567, 1471, 1462, 1360, 1329, 1253. 1126, 1094, 990, 836, 777 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 698.4050 (M + H^+, $C_{42}H_{59}NO_4Si_2$ requires 698.4061).

Intermediate **33** was isolated in a separate experiment by chromatography (SiO_2, 10% EtOAc–hexane) as a light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.25 (6H, m), 6.95 (1H, s, C4-H), 6.45 (1H, d, J = 14.9 Hz, CH=C*H*Ar), 6.29 (1H, t, J = 11.4 Hz, CH_3-CH=C*H*), 5.96 (1H, dq, J = 14.6, 6.8 Hz, CH_3C*H*=CH), 5.27 (1H, d, J = 11.3 Hz, PhC*H*H), 4.88 (1H, d, J = 11.3 Hz, PhCH*H*), 4.84 (1H, m, C*H*OH), 4.66 (1H, m, C*H*HCH$_3$), 4.56 (1H. m, CH*H*CH$_3$), 4.18 (2H, s, CH_2OTBDMS), 3.42 (2H, m, C*H*CHO*H*), 3.22 (1H, m, C*H*HCH$_2$), 2.88 (1H, m, CH*H*CH$_2$), 2.16 (2H, m, CH_2CH_2), 1.85 (3H, d, J = 6.4 Hz, CH_3CH=CH), 1.37 (3H, t, J = 7.1 Hz, CH_2CH_3), 0.82 (9H, s, SiC(CH$_3$)$_3$), −0.01 (3H, s, SiCH$_3$), −0.02 (3H, s, SiCH$_3$); IR (film) ν_{max} 3441, 2928, 2856, 1700, 1621, 1568, 1497, 1472, 1456, 1416, 1361, 1328, 1257, 1123, 1094, 990, 836, 778, 732, 697 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 584.3180 (M + H^+, $C_{36}H_{45}NO_4Si$ requires 584.3196).

5,8-Bis(methoxymethoxy)-1,7-dimethoxy-2-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-[1-[1′-ethoxy-3′-(1″,3″-pentadienyl)-9′-(phenylmethoxy)-6′,7′-dihydro-8′*H*-cyclopent[*g*]isoquinolinyl]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-napthalenol (36). A solution of **34** (37 mg, 53 μmol), **35**[12] (70 mg, 0.15 mmol, 2.9 equiv), and Ac_2O (8.0 μL, 1.5 equiv) in heptane (0.3 mL) was warmed at 50 °C for 47 h. The cooled reaction mixture was diluted with Et_2O (20 mL) and filtered through Florisil (60–100 mesh), and the filtrate was concentrated in vacuo. Chromatography (SiO_2, 30 × 1.0 cm, 10–20% EtOAc–hexane gradient elution) afforded **36** (yellow oil, 18 mg, 52 mg theoretical, 35%) as a 3:1 mixture of two diasteromers: ^1H NMR ($CDCl_3$, 400 MHz) δ 9.87 and 9.13 (1H, s, OH), 7.40–6.85 (9H, m), 6.47 (1H, d, J = 15.0 Hz, CH=C*H*Ar), 6.29 (1H, t, J = 11.5 Hz, CH_3-CH=C*H*), 5.93 (1H, dq, J = 14.4, 6.9 Hz, CH_3C*H*=CH), 5.44 (1H, d, J = 5.3 Hz, PhC*H*H), 5.09 (1H, d, J = 5.3 Hz, PhCH*H*), 5.08–4.96 (4H, m, two OCH_2OCH_3), 4.78 (1H, d, J = 11.9 Hz, C*H*HOTBDMS), 4.60 (1H, d, J = 11.9 Hz, CH*H*OTBDMS), 4.48 (2H, dq, J = 13.4, 7.1 Hz, CH_2CH_3), 3.97 and 3.95 (3H, s, OCH_3), 3.67 and 3.62 (3H, s, OCH_3), 3.57 and 3.52 (3H, s, OCH_3), 3.53 and 3.36 (3H, s, OCH_3), 3.40–3.22 (2H, m, C*H*OTBDMS and C8′-H), 2.87 (2H, m, CH_2CH_2), 2.51 (2H, m, CH_2CH_2), 1.85 (3H, d, J = 5.6 Hz, CH_3CH=CH), 1.25 (3H, t, J = 7.1 Hz, CH_2CH_3), 0.84 and 0.91 (9H, s, SiC(CH$_3$)$_3$), 0.72 and 0.64 (9H, s, SiC(CH$_3$)$_3$), 0.12 and 0.18 (3H, s, SiCH$_3$), 0.01 and 0.14 (3H, s, SiCH$_3$), −0.27 and −0.28 (3H, s, SiCH$_3$), −0.34 and −0.49 (3H, s, SiCH$_3$); IR (film) ν_{max} 3385, 3249, 2929, 2854, 1612, 1566, 1462, 1329, 1253, 1154, 1060, 1004, 837, 778 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 996.5110 (M + H^+, $C_{56}H_{77}NO_{11}Si_2$ requires 996.5113).

5,8-Bis(methoxymethoxy)-1,7-dimethoxy-2-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-(phenylmethoxy)-3-[1-[1′-ethoxy-3′-(1″,3″-pentadienyl)-9′-(phenylmethoxy)-6′,7′-dihydro-8′*H*-cyclopent[*g*]isoquinolinyl]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]naphthalene (37). A solution of **36** (23 mg) in acetone (0.3 mL) at 25 °C was treated with a finely powdered K_2CO_3 (50 mg), Bu_4NI (15 mg), and benzyl bromide (80 μL) sequentially. The resulting reaction mixture was allowed to stir at 25 °C for 53 h before it was concentrated. Chromatography (SiO_2, 1 × 17 cm, 15% EtOAc–hexane) afforded **37** (13 mg, 25 mg theoretical, 52%; typically 50–57%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.25 (4H, m), 7.09–6.85 (6H, m), 6.80–6.72 (2H, m), 6.16–6.52 (1H, m), 6.45–6.36 (2H, m), 6.28 (1H, m, CH_3CH=C*H*-CH), 5.89 (1H, dq, J = 14.9, 6.8 Hz, CH_3C*H*=CH), 5.59 (1H, d, J = 10.0 Hz), 5.37 (1H, d, J = 9.4 Hz), 5.17 (2H, s), 5.02 (1H, d, J = 9.8 Hz), 4.96 (1H, d, J = 6.7 Hz), 4.93 (1H, d, J = 12 Hz), 4.84 (1H, d, J = 6.7 Hz), 4.64 (1H, d, J = 19 Hz), 4.57 (1H, d, J = 19 Hz), 4.49–4.37 (1H, m), 4.36–4.23 (1H, m, CH_3CH*H*O), 4.00–3.89 (1H, m, CH_3CH*H*O), 4.01 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.04 (3H, s, OCH_3), 3.09–2.93 (1H, m, CH_2CH_2CH*H*), 2.87 (2H, m, CH_2CH_2), 2.04 (2H, m, CH_2CH_2), 1.83 (3H, d, J = 6.8 Hz, CH_3CH=CH), 0.86 (9H, s, SiC(CH$_3$)$_3$), 0.82 (9H, s, SiC(CH$_3$)$_3$), 0.68 (3H, t, J = 7.2 Hz, CH_3-CH_2O), 0.14 (3H, s, SiCH$_3$), 0.02 (3H, s, SiCH$_3$), −0.15 (3H, s, SiCH$_3$), −0.51 (3H, s, SiCH$_3$); IR (film) ν_{max} 2929, 2855, 1751, 1605, 1586, 1566, 1497, 1454, 1359, 1329, 1306, 1256, 1155, 1062, 1012, 974, 835, 775, 731, 696 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 1086.5590 (M + H^+, $C_{63}H_{83}NO_{11}Si_2$ requires 1086.5583.

5,8-Bis(methoxymethoxy)-1,7-dimethoxy-2-(1-hydroxymethyl)-4-(phenylmethoxy)-3-[1-[1′-ethoxy-3′-(1″,3″-pentadienyl)-9′-(phenylmethoxy)-6′,7′-dihydro-8′*H*-cyclopent[*g*]isoquinolinyl]-1-(hydroxymethyl)naphthalene (38). A solution of **37** (8.5 mg, 7.8 μmol) in THF (0.85 mL) at 25 °C under Ar was treated with 1.0 M Bu_4NF (40 μL, 5.1 equiv) in THF. The resulting solution was allowed to stir at 50 °C for 10.5 h before it was concentrated under a stream of N_2. Et_2O (2 mL) and saturated aqueous NH_4Cl (0.8 mL) were added, and the aqueous layer was extracted with Et_2O (7 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was kept in vacuo for 4 h to afford crude **38** (8.9 mg, 6.7 mg theoretical) as an orange colored syrup which was sufficiently pure to be used directly for the next step after it was azeotropically dried with benzene (2 × 0.2 mL). In another experiment, the residue was transferred directly onto a chromatography column (SiO_2, 1 × 12 cm, 60% EtOAc–hexane) without aqueous workup to provide pure **38** as a colorless syrup: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–6.90 (14H, m), 6.42 (1H, d, J = 14.8 Hz, CH=C*H*Ar), 6.26 (1H, m, CH_3CH=C*H*), 5.90 (1H, dq, J = 15.0, 6.5 Hz, CH_3C*H*=CH), 5.33 (1H, br d, J = 7.3 Hz), 5.05 (1H, d, J = 5.8 Hz), 5.00 (1H, d, J = 5.8 Hz), 4.92 (1H, d, J = 11.5 Hz), 4.70–4.45 (6H, m), 4.44–4.20 (5H, m), 3.95 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.72–3.62 (1H, m, CH_2CH_2CH*H*), 3.07 (3H, s, OCH_3), 2.95–2.70 (2H, m, CH_2CH_2), 2.45 (1H, m, CH_2CH*H*), 1.95 (1H, m, CH_2CH*H*), 1.82 (3H, d, J = 6.5 Hz, CH_3CH=CH), 1.00 (3H, t, J = 7.1 Hz, CH_3CH_2O); IR (film) ν_{max} 3372, 2919, 2849, 1606, 1567, 1453, 1329, 1153, 1069, 1016, 974, 734, 698 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 858.3875 (M + H^+, $C_{51}H_{55}NO_{11}$ requires 858.3853).

5,8-Bis(methoxymethoxy)-9,9′-bis(phenylmethoxy)-6′,7′-dihydro-4,6-dimethoxy-1′-ethoxy-3-hydroxy-3′-(1″,3″-pentadienyl)spiro[2*H*-benz[*f*]indene-2,8′-8′*H*-cyclopent[*g*]isoquinolin]-1(3*H*)-one (40). A 1 M solution of DMSO in CH_2Cl_2 (312 μL, 40 equiv) was treated at −78 °C under Ar with 0.5 M solution of TFAA in CH_2Cl_2 (312 μL, 20 equiv) and stirred for 10 min at −78 °C. A solution of the crude

diol **38** (8.9 mg, ≤7.8 μmol) in CH_2Cl_2 (0.8 mL) was added, and the mixture was stirred at −78 °C for 1 h. A 1 M solution of DBU in CH_2Cl_2 (390 μL, 50 equiv) was added, and the mixture was stirred for 20 h during which time the cooling bath was warmed gradually to 25 °C. The mixture was concentrated and saturated aqueous NH_4Cl (1.0 mL) was added. The mixture was extracted with Et_2O (6 × 2 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in Et_2O and transferred onto a small plug of SiO_2 (0.5 × 4 cm) and eluted (20−50% EtOAc−hexane) to afford the crude **40** (7.3 mg, 6.6 mg theoretical) as a yellow syrup which was sufficiently pure to be used directly for the next step after it was azeotropically dried with benzene (2 × 0.5 mL). In a separate experiment, column chromatography (SiO_2, 0.5 × 5 cm, 0−20% EtOAc-hexane) provided pure **40** as a colorless syrup: ^{1}H NMR of the major isomer ($CDCl_3$, 400 MHz) δ 7.58−6.75 (14H, m), 6.44 (1H, d, *J* = 15.4 Hz, CH=C*H*Ar), 6.32−6.20 (1H, m, CH_3-CH=C*H*), 5.91 (1H, dq, *J* = 14.0, 6.3 Hz, CH_3-C*H*=CH), 5.35 (1H, d, *J* = 10 Hz, PhC*H*H), 5.21 (1H, d, *J* = 10 Hz, PhCH*H*), 5.08−5.02 (2H, m, OCH_2O), 4.99−4.92 (2H, m, OCH_2O), 4.95 (1H, s, C*H*OH), 4.81 (1H, d, *J* = 10 Hz, PhC*H*H), 4.54 (1H, d, *J* = 10 Hz, PhC*H*H), 4.52−4.43 (2H, m, CH_3CH_2O), 4.00 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.65−3.55 (1H, br s, OH), 3.36 (3H, s, OCH_3), 3.27−3.22 (2H, m, CH_2CH_2), 2.60−2.51 (1H, m, CH_2CH*H*), 2.18−2.09 (1H, m, CH_2CH*H*), 1.83 (3H, d, *J* = 6.3 Hz, CH_3-CH=CH), 1.08 (3H, t, *J* = 7.1 Hz, CH_3CH_2O); IR (film) ν_{max} 3454, 2916, 2848, 1710, 1600, 1567, 1463, 1330, 1262, 1153, 1099, 1017, 984, 731 cm^{-1}; FABHRMS (NBA-CsI) *m/e* 986.2516 (M + Cs$^+$, $C_{51}H_{51}NO_{11}$ requires 986.2516).

5,8-Bis(methoxymethoxy)-9,9′-bis(phenylmethoxy)-6′,7′-dihydro-4,6-dimethoxy-1′-ethoxy-3′-(1″,3″-pentadienyl)spiro[2*H*-benz[*f*]indene-2,8′-8′*H*-cyclopent[*g*]isoquinolin]-1,3-one (41). A 1 M solution of DMSO in CH_2Cl_2 (234 μL, 30 equiv) was treated at −78 °C under Ar with a 0.5 M solution of TFAA in CH_2Cl_2 (234 μL, 15 equiv) and stirred for 10 min at −78 °C. A solution of crude **40** (7.3 mg, ≤7.8 μmol) in CH_2Cl_2 (0.9 mL) was added, and the mixture was stirred at −78 °C for 1 h. A 1 M solution of Et_3N in CH_2Cl_2 (312 μL, 40 equiv) was added. After 10 min, the cooling bath was removed, and the mixture was stirred for 30 min at 25 °C before being concentrated in a N_2 stream. Saturated aqueous NH_4Cl (1.0 mL) was added, and the mixture was extracted with Et_2O (5 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography (SiO_2, 0.5 × 4 cm, 20−50% EtOAc−hexane) afforded **41** (4.5 mg, 6.6 mg theoretical, 68% from **37**, typically 57−68% overall) as a green-yellow syrup: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64−7.61 (2H, m), 7.40−7.24 (5H, m), 7.18 (1H, s), 6.96 (1H, s), 6.89−6.68 (5H, m), 6.43 (1H, d, *J* = 14.8 Hz, CH=C*H*Ar), 6.24 (1H, m, CH_3CH=C*H*), 5.90 (1H, dq, *J* = 14.9, 6.8 Hz, CH_3CH=CH), 5.04−4.97 (5H, m), 4.82 (1H, d, *J* = 9.7 Hz, PhC*H*H), 4.74 (2H, br s, $PhCH_2$), 4.44 (2H, q, *J* = 7.1 Hz, CH_3CH_2O), 4.02 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 3.43−3.37 (2H, m, CH_2CH_2), 2.53 (2H, t, *J* = 7.4 Hz, CH_2CH_2), 1.82 (3H, d, *J* = 6.8 Hz, CH_3CH=CH), 1.06 (3H, t, *J* = 7.1 Hz, CH_3CH_2O); IR (film) ν_{max} 2935, 1732, 1703, 1598, 1568, 1455, 1358, 1328, 1263, 1153, 1099, 1019, 971, 736, 699 cm^{-1}; UV (*i*-PrOH) λ_{max} 370 (14 400), 354 (16 700), 327 (25 300), 315 (26 200), 292 (43 950) nm; CD (Figure 1); FABHRMS (NBA-CsI) *m/e* 984.2318 (M + Cs$^+$, $C_{51}H_{49}NO_{11}$ requires 984.2360).

Preparative Resolution of 41. A solution of racemic **41** in *i*-PrOH-hexane (2:1) was subjected to chromatography on a semipreparative HPLC CHIRACEL OD column (2 cm × 25 cm, 20% *i*-PrOH−hexane, 2 mL/min, (10 min), 5 mL/min (10 min), 6 mL/min (40 min) flow rate). The effluent was monitored at 280 nm, and the enantiomers eluted with retention time of 41.8 min (natural **41**) and 47.6 min (*ent*-**41**), respectively (α = 1.14). The fractions were assayed by injection onto an analytical CHIRACEL OD HPLC column (0.46 cm × 25 cm, 10% *i*-PrOH−hexane, 0.9 mL/min flow rate, α = 1.38). The retention times on the analytical column were 11.2 min (natural **41**) and 15.1 min (*ent*-**41**), respectively. Appropriate fractions were combined and concentrated to afford each enantiomer (>99% ee). The circular dichroism spectra of the enantiomers **41** show the highest molar ellipticity at 303 nm with a [Θ] value of +7.1 × 10^4 deg·cm^2·dmol^{-1} for the natural enantiomer **41** (t_R = 11.2 min, analytical column) and at 303 nm with a [Θ] value of −7.1 × 10^4 deg·cm^2·dmol^{-1} for the unnatural enantiomer (t_R = 15.1 min, analytical column).

Natural and *ent*-Fredericamycin A (1). A solution of **41** (0.6 mg, 0.7 μmol) in CH_2Cl_2 (0.2 mL) was treated at −78 °C under Ar with a 1.0 M solution of BBr_3 in CH_2Cl_2 (40 μL, 57 equiv) which resulted in a deep red colored solution. The mixture was stirred for 1 h at −78 °C before it was treated with aqueous 1.5 M HCl (0.6 mL) and stirred for additional 3 h at 25 °C open to air. The solution was extracted with Et_2O-CH_2Cl_2 (10:1, 4 × 2 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 and transferred onto a small plug of SiO_2 (0.5 × 5 cm) and eluted with $CHCl_3$−CH_3OH−HOAc (87:3:3) to afford a mixture of **1** and **1**-OEt (0.5 mg). The residue (0.5 mg) was dissolved in CH_3OH (0.2 mL) under Ar, and NaBr (7.0 mg, 68 μmol) and TsOH (3.0 mg, 16 μmol) were introduced. The mixture was stirred at 70 °C for 12 h before being treated with aqueous 1.5 M HCl (0.6 mL) and extracted with Et_2O−CH_2Cl_2 (10:1, 4 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography (SiO_2, 0.5 × 5 cm, CH_2Cl_2−EtOAc−HOAc 10:10:1) afforded **1** (0.34 mg, 0.4 mg theoretical, 85%) which was identical with a sample of the authentic natural product: (TLC: $CHCl_3$−CH_3OH−HOAc 87:3:3; CH_2Cl_2−EtOAc−HOAc 10:10:1). During evaporation to dryness, the chromatographed material turned blue. Before the NMR was measured the substance was dissolved in CH_2Cl_2, treated with 1.5 M HCl, extracted with EtO_2:CH_2Cl_2 (10:1, 4 × 2 mL), dried (Na_2SO_4), and concentrated to afford the red form which was more soluble in $CDCl_3$ than the blue form: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.19 (1H, s, OH), 12.55 (1H, s, OH), 12.24 (1H, s, OH), 8.20 (1H, s, NH), 6.88 (1H, s), 6.46 (1H, dd, *J* = 15.8, 10.3 Hz, C*H*=CHAr), 6.34 (1H, s), 6.28 (1H, s), 6.23−6.12 (1H, m, CH_3-CH=C*H*), 6.08 (1H, d, *J* = 15.8 Hz, CH=C*H*Ar), 5.95 (1H, dq, *J* = 15.0, 6.0 Hz, CH_3-C*H*=CH), 3.93 (3H, s, OCH_3), 3.31 (2H, d, *J* = 7.2 Hz, CH_2CH_2), 2.54 (2H, t, *J* = 7.2 Hz, CH_2CH_2), 1.83 (3H, d, *J* = 6.0 Hz, CH_3-CH=CH); IR (film) ν_{max} 2913, 2851, 1713, 1605, 1415, 1292, 1261, 1195, 1175, 1138, 1108, 1060, 1012, 884, 848, 816 cm^{-1}; UV (20% DMF−CH_3OH + trace Et_3N) λ_{max} 635 (7930), 393 (24 200), 374 (29 500), 359 (23 800), 332 (23 400), 318 (24 900), 306 (23 000), 260 (42 900) nm; CD (Figure 2); FABHRMS (NBA-CsI) *m/e* 542.1441 (M$^+$ + H, hydroquinone), negative ion FABMS (NBA) *m/e* 538 (M$^-$ − H).

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