Synthesis of (±)-Fredericamycin A

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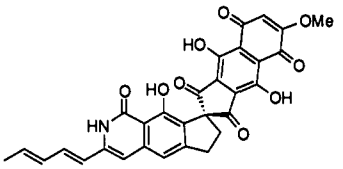
Abstract: The synthesis of (±)-fredericamycin A (**1**) is reported with full experimental detail. Preparations of building blocks for the upper (**2**) and lower (**3**) units of **1** are described. The union of **2** and **3** by a two-step 1,4-dipolar cycloaddition and the elaboration of the resulting product (**19**) into **1** are presented. The spiro 1,3-dione center in **1** was introduced utilizing a mild mercury-mediated pinacol rearrangement involving a 1,2-carbonyl migration. The reaction of benzylic cuprate anions ortho to aromatic esters has been shown to produce isochromarins in good yield. These isochromarins afford the biologically relevant isoquinolones upon treatment with ammonia.

Introduction

Fredericamycin A (**1**), a unique quinone antitumor antibiotic, was isolated from a new strain of *Streptomyces griseus* at the Frederick Cancer Research Center in Frederick, MD, in 1981.[1] The structure of this hexacycle, which contains a single (spiro) center of asymmetry, was elucidated by a single-crystal X-ray analysis[2] after spectroscopic studies could not resolve its tautomeric forms.[3]



fredericamycin A (1)

Fredericamycin A is the most active of several classes of antibiotics isolated from this soil bacterium including the tetracyclines and streptomycin. It has been suggested that its biological properties derive from inhibition of RNA and protein synthesis.[4,5] The first total synthesis that appeared in the literature was reported by Kelly and co-workers.[6] During the course of our own efforts in this area,[7] two additional syntheses have appeared in preliminary form,[8a,9a] and a fourth total synthesis has been communicated since the completion of our synthesis.[10a] The number of model studies aimed at the synthesis of **1** is a testimonial to the difficulty in introducing the unprecedented spiro[4.4]nonane structural moiety that it contains.[5-21]

Our interest in this rather unusual molecule stems from a previous study of the mechanism of 1,2-carbonyl migration reactions.[22] We established the 1,2-rearrangement of a series of carbonyl groups (ketones and esters) adjacent to a developing positive center to be a stereospecific concerted process that proceeds with inversion of configuration at the migration terminus

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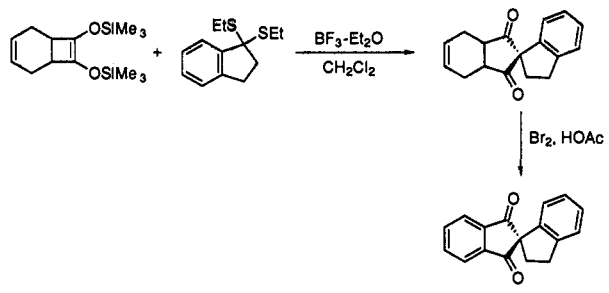
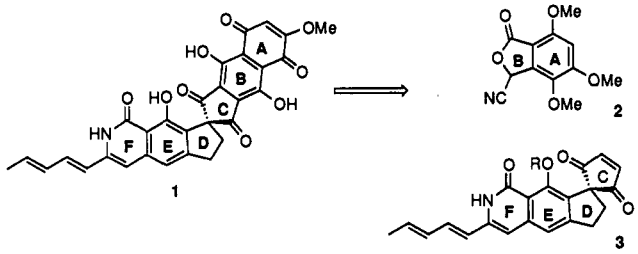
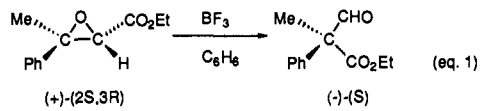
Scheme 1



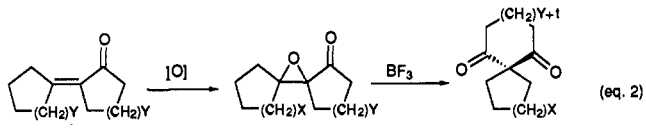
Scheme 2



to afford 1,3-dicarbonyl compounds (eq 1). An extension of this



work leads to an efficient synthesis of a variety of spiro 1,3-dione compounds (eq 2).[7a] When the isolation of fredericamycin A



was reported, we initiated our first foray into the area of total synthesis since **1** appeared to be a natural target for our spiro 1,3-diketone methodology. Since the unique spiro 1,3-dione functionality in **1** posed the most challanging problem, we developed a protocol for its introduction (Scheme 1).

In an earlier report we suggest a retrosynthetic strategy for **1** via a coupling reaction that would combine the lower CDEF ring fragment of **1** (**3**) with the upper AB ring fragment (**2**) (Scheme 2).[7f] We examined the feasibility of constructing rings ABCDE of fredericamycin A as shown in **6** by employing a Diels–Alder strategy involving enedione **4** and a highly reactive isobenzofuran **5** that was generated *in situ* from **2** (Scheme 3). This cycloaddition protocol introduced all the requisite oxygen functionality in the upper half of **1**.

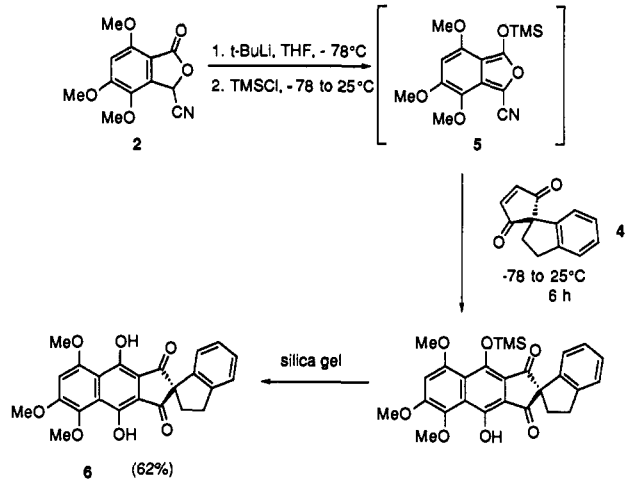
The synthesis of **2** was highlighted in our earlier paper[7f] as airising from commercially available 2,4,5-trimethoxybenzoic acid (**7**) (Scheme 4). The sequence in Scheme 4 routinely affords **2** in multigram quantities in an overall 42% yield.

Results and Discussion

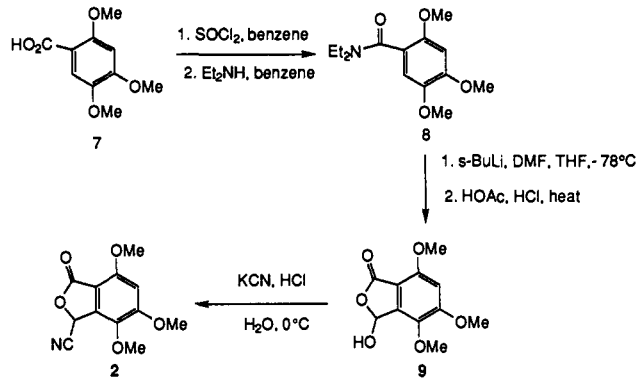
Construction of Fragment 3. Two problematic features of **3** are the spiro center and the pentadienyl side chain. Our initial route for the synthesis of compound **3** involved the construction of the DEF rings complete with the diene moiety followed by introduction of the C ring spiro enedione functionality. However, the electrophilic nature of the reagents essential for the projected spinoannulation procedure portended difficulties. We therefore elected to introduced the spiro dione moiety much earlier in our synthetic reaction sequence (Scheme 5).

The spiro center of **3** was assembled utilizing a modification of the mercury-mediated 1,2-carbonyl migration chemistry

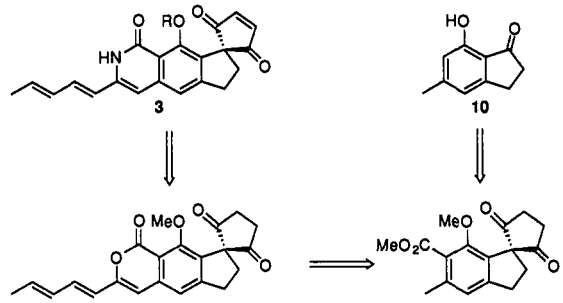
Scheme 3



Scheme 4



Scheme 5

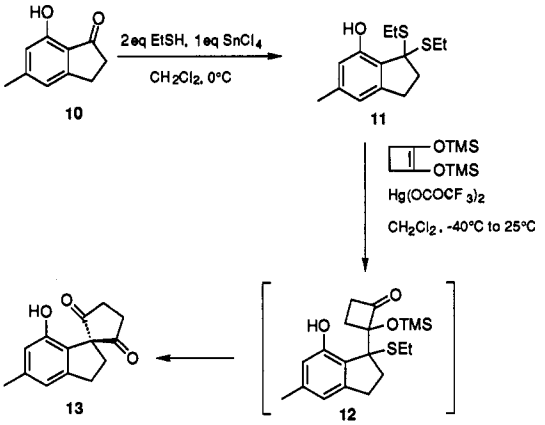


developed in our laboratory to synthesize dieneophile **4**, which contained the CDE rings and the enedione, but not the requisite hydroxyl functionality or the F ring with its pendant pentadienyl side chain.[7d,f] Therefore, 7-hydroxy-5-methylindan-1-one (**10**) was chosen as an appropriate starting material since it contains the necessary hydroxyl moiety along with a methyl group in the 5-position of **10** which provides an activated carbon for the subsequent introduction of the F ring.

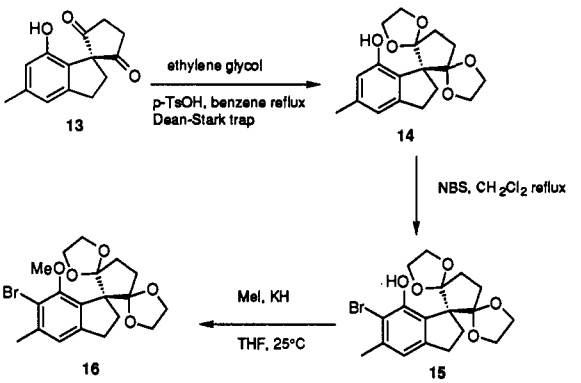
Indanone **10** was synthesized from *m*-cresol by an adaptation of a literature procedure.[23] Dithioacetal **11** was synthesized and subsequently treated with mercuric trifluoroacetate in the presence of 1,2-bis((trimethylsilyl)oxy)cyclobut-1-ene in methylene chloride at −40 °C. Upon warming to 25 °C the acyl migration afforded spiro diketone **13**, the complete CDE ring system, in a one-pot reaction (54% from **10**, Scheme 6). This spiroexpansion protocol involving a cyclobutanone intermediate was developed earlier by Kuwajima and his co-workers[24] and most recently improved upon by Burnell and co-workers.[25]

(23) Buryan, P.; Macak, J.; Walter, K. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2174.

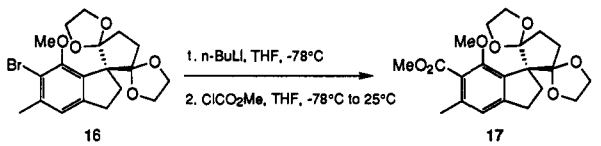
Scheme 6



Scheme 7



Scheme 8



In order to introduce the F ring, it was necessary to activate the position ortho to both the hydroxyl and the methyl substituent on the E ring. Protection of the diketone moieties was also required to carry out the ensuing reactions that would furnish the F ring. Diketone **13** was bisacetalated under Dean–Stark trap conditions to afford **14** in quantitative yield. The diacetal (**14**) was brominated (99%) regioselectively ortho to the phenol with NBS to afford **15**.[26] The phenol was then protected (94%) as its methyl ether **16** (Scheme 7). The carbonyl group (1′ carbon atom) of the isoquinolone F ring was introduced as a methyl ester via a metalation reaction involving bromide **16** and *n*-BuLi followed by subsequent trapping with methyl chloroformate to afford methyl ester **17** in 94% yield (Scheme 8).

Since the methodology for the conversion of an isochromarin to an isoquinolone is well established, we chose to introduce the pentadienyl side chain via an acylation with sorboyl chloride of a putative benzylic anion derived from the methyl substituent on **17**. We anticipated that an *in situ* base-catalyzed lactonization would afford the desired isochromarin, complete with pentadienyl tail, in one step. In choosing sorboyl chloride, we started with a molecule which had the necessary (*E*,*E*)-pentadienyl fragment in place and therefore avoided the need to undergo an *E*/*Z* isomerization that troubled Kelly,[6] Cliver,[8a] and Rao.[9a] The initial plan was to add the benzylic anion directly to sorboyl chloride; however, the anion appeared to be quenched by deprotonation of

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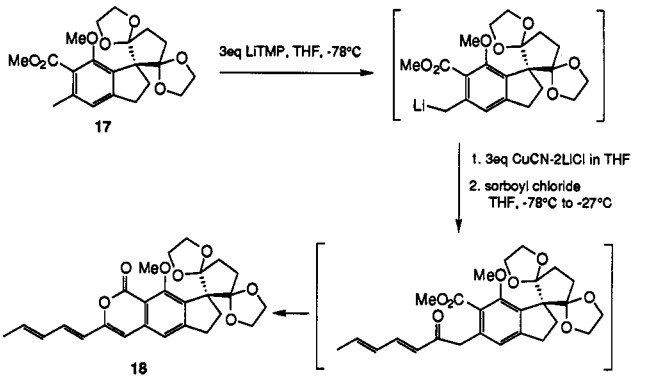
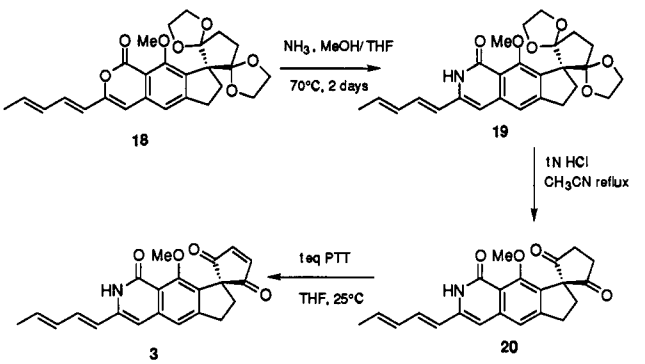
Scheme 9



Scheme 10



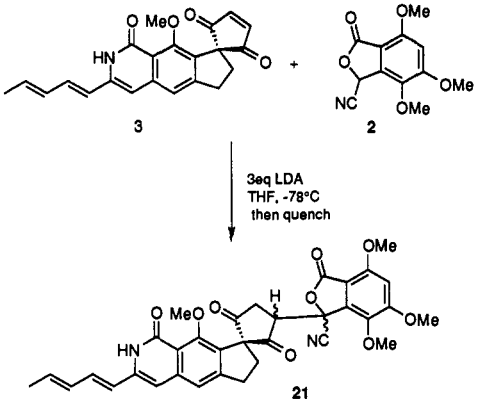
the terminal methyl group on the sorboyl chloride. It therefore became necessary to develop a route that circumvented this problem. Conversion of the benzylic anion to its less basic cuprate allowed the acylation to proceed smoothly without deprotonation of sorboyl chloride. In a typical reaction, treatment of **17** with 3 equiv of lithium tetramethylpiperidide followed by 3 equiv of a THF solution of CuCN·2LiCl[27] generated the corresponding cuprate. This benzylic organocuprate was acylated with an excess of sorboyl chloride to furnish isochromarin **18** upon the loss of methanol in a 63% yield on a multigram scale (Scheme 9).

Aminolysis of isochromarin **18** with an excess of ammonia in THF/MeOH afforded **19** (80%) after heating at 70 °C in a sealed vessel for 2 days. Attempts to introduce the nitrogen atom in the absence of the acetal protecting groups met with failure. Apparently the spiro[4.4]nonane 1,3-dione is sufficiently strained that attack of ammonia on the carbonyl group led to carbon–carbon bond cleavage and destruction of the spiro center. It now remained to remove the acetal protecting groups from **19** and to introduce the unsaturation in the cyclopentanedione C ring. The acetal protecting groups were removed with 1 N HCl in refluxing CH_3CN (83%) to afford the CDEF ring assembly of fredericamycin A **20**. Although many procedures are available to oxidize a ketone to an enone, we felt that a base-catalyzed introduction of the double bond would prove difficult due to the acidity of the amide hydrogen in **20**. Preliminary experiments designed to introduce the carbon–carbon double bond in **20** and with related model compounds under neutral or acidic conditions proved problematic with reagents such as DDQ, Br_2, SeO_2, $PdCl_2$, and NBS. The dehydrogenation of adduct **20** was best carried out via a halogenation/dehydrohalogenation route. Syringe pump addition of a solution of phenyltrimethylammonium tribromide (PTT) over 1 h to a dilute THF solution of **20** afforded the CDEF ring fragment **3** (59%) (Scheme 10).[28]

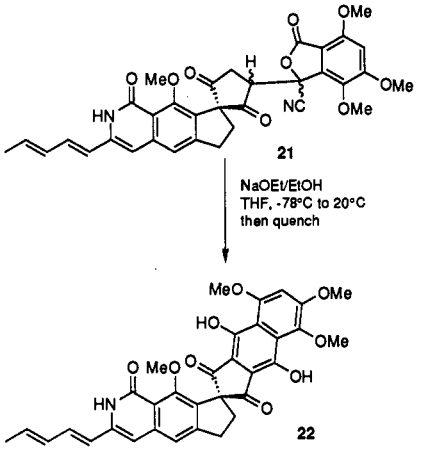
Coupling of the AB and CDEF Fragments. Completion of the Synthesis of Fredericamycin A. The Diels–Alder strategy

(27) Knochel, P.; Yeh, M. C. P.; Chen, H. G. *Org. Synth.* **1991**, *72*, 195.
(28) Johnson, W. S.; Bass, J. D.; Williamson, K. L. *Tetrahedron* **1963**, *19*, 861.

Scheme 11



Scheme 12

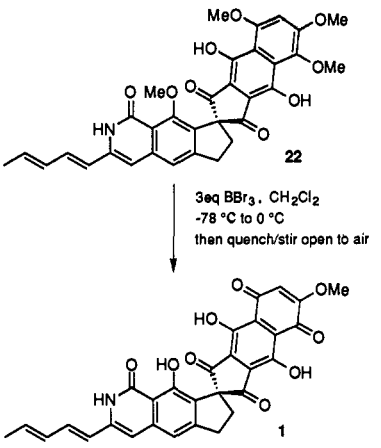


described (Scheme 3) for the construction of the model compound **6** comprising the upper half of **1** presents an obvious method for the crucial coupling of ring fragments **2** and **3**. However, the additional functionality in **3** presented difficulties in the timing of the sequence of the reactions essential to the preparation of the isobenzofuran **5**. Initial efforts to carry out the 1,4-dipolar cycloaddition of the anion of **2** with model enediones as described by Kraus[29] afforded relatively low yields of expected product. During the course of this work, we inadvertently isolated the initial Michael adduct **21** and subsequently found that its ring closure to **22** could be achieved in high yield by simple treatment with a relatively weak base. The lithio anion of **2** was generated in a THF solution by the action of 3 equiv of LDA at −78 °C. Enedione **3** was added dropwise and the reaction mixture was stirred for 30 min at −78 °C. Quenching at −78 °C with 1 N HCl afforded adduct **21** as a mixture of diastereomers (Scheme 11). The crude diastereomeric mixture was cyclized readily to (±)-**22** with NaOEt/EtOH in THF between −78 and 20 °C to complete an overall two-step yield of 78% (Scheme 12). The milder base (NaOEt), unlike LDA, apparently does not destroy the product **22** at the higher temperatures (≥0 °C) needed for the second step of this cyclization to occur. The two-step sequence routinely afforded ~100-mg quantities of the fredericamycin A precursor.

The final step in the synthesis of **1** utilizes the demethylation/air oxidation protocol as described by Boger[5] and Clive.[8a] Compound **22** was treated with 3 equiv of boron tribromide in CH_2Cl_2 at −78 °C and warmed to 0 °C followed by quenching and stirring open to the air for 2 days to afford (±)-fredericamycin A (**1**) (80%) as a violet solid after purification (Scheme 13). The structure of synthetic **1** was confirmed by comparison of the

(29) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *26*, 2263.

Scheme 13



spectroscopic and physical properties of **1** with those of an authentic sample of fredericamycin A kindly provided by R. Pandey.

In conclusion, a convergent synthesis of (±)-fredericamycin A has been accomplished in 12 steps from compounds **2** and **10** in an overall yield of 6%. This relatively straightforward synthetic route should be readily adaptable to the preparation of a variety of derivatives of **1**.

Experimental Section

General Procedures. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. For reactions conducted under an inert atmosphere, flasks were flame dried and purged with dry Ar until cool. Tetrahydrofuran (THF) was distilled from potassium metal. Methylene chloride (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled from CaH_2. Diisopropylamine was distilled from BaO. Acetone was distilled from $CaCl_2$. Potassium hydride was washed with hexanes from a mineral oil dispersion prior to use. Sorboyl chloride was prepared following the procedure described by Washburne and MacMillan,[30] and 1,2-bis((trimethylsilyl)oxy)cyclobut-1-ene was prepared following the procedure described by Bloomfield and Nelke.[31]

Flash column chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvent mixture. All chromatographic separations were monitored by TLC analyses, performed on Merck DC Alufolien Kieselgel 60F-254. Melting points are uncorrected. Infrared spectra were recorded with a Nicolet 20-DX FT-IR spectrometer with the use of either NaCl plates or KBr pellets and are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance spectra were recorded at either 300 MHz (^1H NMR) or 76.46 MHz (^{13}C NMR) on the following spectrometers: Nicolet GN-300 and Nicolet QE-300. The Unity Q-500 spectrometer recorded spectra at 500 MHz (^1H NMR) and 76.48 MHz (^{13}C NMR). Chemical shifts are reported in parts per million (ppm, δ) using either tetramethylsilane (TMS) (δ = 0.00 ppm) or the respective NMR deuterated solvent as the internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; and br, broad. Coupling constants are given in hertz (Hz). All NMR samples were dissolved in the respective deuterated solvent indicated. All deuterated solvents were obtained from Cambridge Isotope Laboratories. All high-resolution CI and EI mass spectral analyses were performed by the Central Instrumentation Facility at Wayne State University. All high-resolution FAB mass spectral analyses were performed by Tony Pavia at Miles, Inc., New Haven, CT. Elemental analyses were performed by either Midwest Microlabs, Inc., Indianapolis, IN, or Galbraith Laboratories, Inc., Knoxville, TN.

2′,3′-Dihydro-7-hydroxy-5-methylinden-1-one (10). *m*-Cresol (89.0 mL, 850 mmol) was dissolved in benzene (100 mL), and 2-chloropropionyl chloride (127 mL, 870 mmol) was added. The reaction mixture was heated to reflux for 12 h, then cooled, and concentrated to a yellow oil. Purification by distillation (101–103 °C/0.1 Torr) afforded 160 g (95%) of 3-methylphenyl β-chloropropionate as a colorless oil, bp 101–103 °C (0.1 Torr): IR (NaCl) 3034, 2972, 2923, 2866, 1762 (s), 1615, 1588,

(30) Washburne, S. S.; MacMillan, J. H. *J. Org. Chem.* **1973**, *38*, 2982.
(31) Bloomfield, J. J.; Nelke, J. N. *Org. Synth.* **1977**, *57*, 1.

1488, 1371, 1361, 1309, 1244, 1228, 1187, 1149, 1130, 1003, 966, 934, 910, 875, 781, 745, 691, 678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (t, 1H, J = 7.5 Hz), 7.04 (d, 1H, J = 3.5 Hz), 6.91 (s, 1H), 6.89 (d, 2H, J = 3.75 Hz), 3.83 (t, 2H, J = 6.6 Hz), 2.99 (t, 2H, J = 6.6 Hz), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.9, 150.3, 139.6, 129.1, 126.8, 121.9, 118.3, 38.8, 37.5, 21.1; HRMS calcd for $C_{10}H_{11}O_2Cl$ (CI) 198.0447, found 198.0451.

3-Methylphenyl β-chloropropionate (59.5 g, 500 mmol) and aluminum chloride (200 g, 1.50 mol) were combined, and the resulting mixture was heated without stirring at 80 °C for 1 h. The temperature was increased to 160 °C over 2 h and maintained at that temperature for an additional 1 h. The temperature was then increased to 180 °C for 1 h, followed by cooling to 25 °C. Concentrated hydrochloric acid (100 mL) and water (100 mL) were added to this black oil. Steam distillation of the resulting mixture afforded a white, wet solid. The solid was dissolved in CH_2Cl_2, dried (anhydrous $MgSO_4$), filtered through Celite, and concentrated to afford 26.7 g (55%) of **10** as a white solid of suitable purity for the next step, mp 112–114 °C (lit.[23] mp 98 °C) (hexane): IR (KBr) 3379 (s), 2966, 2933, 2917, 1680 (vs), 1623, 1598, 1486, 1470, 1437, 1325, 1308, 1286, 1169, 985, 843, 718, 654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.96 (s, 1H), 6.76 (s, 1H), 6.58 (s, 1H), 3.06 (t, 2H, J = 5.4 Hz), 2.69 (t, 2H, J = 5.4 Hz), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.0, 157.1, 155.3, 149.4, 120.6, 118.2, 113.9, 36.0, 25.6, 22.3; HRMS calcd for $C_{10}H_{10}O_2$ (CI) 162.0681, found 162.0684.

2′,3′-Dihydro-7′-hydroxyl-5′-methylspiro[cyclopentane-1,1′-indene]-2,5-dione (13). A solution of **10** (13.25 g, 81.74 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C, and ethanethiol (13.0 mL, 172 mmol) was added all at once via syringe. Tin(IV) tetrachloride (10.5 mL, 90.2 mmol) was added dropwise over 15 min to this solution. This mixture was stirred for 8 h at 0 °C before being cooled to −27 °C for 24 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (100 mL) and stirred vigorously at 25 °C for 1 h. The organic layer was then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 125 mL). The organic layers were combined, dried (anhydrous $MgSO_4$), and concentrated to afford a yellow oil. Flash chromatography (19:1 hexanes/EtOAc) yielded a crude mixture in which the major product was **11**. This clear viscous oil, which was immediately dissolved in 150 mL of CH_2Cl_2, was cooled to −40 °C, and 1,2-bis((trimethylsilyl)oxy)cyclobut-1-ene[30] (16.0 mL, 60.0 mmol) was added to this mixture all at once. Mercuric(II) trifluoroacetate (25.6 g, 60.0 mmol) was added all at once with vigorous stirring. This reaction mixture was stirred at −40 °C for 6 h before being warmed slowly to 25 °C over 1 h and stirred at 25 °C for an additional 3 h. The mixture was carefully added to a 1 N HCl solution (100 mL). The organic layer was separated, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a black oil. Flash chromatography (4:1 hexanes/EtOAc) afforded 10.24 g (54%) of **13** as a tan solid, mp 206–207 °C (heptane): IR (KBr) 3265 (br), 2920, 2860, 1708 (s), 1598, 1450, 1433, 1412, 1333, 1172, 1114, 1043, 999, 961, 918, 845, 696 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.53 (s, 1H), 6.56 (s, 1H), 6.40 (s, 1H), 3.01–2.92 (m, 4H), 2.87–2.72 (m, 2H), 2.23 (t, 2H, J = 7.5 Hz), 2.16 (s, 3H); ^{13}C NMR (acetone-d_6) δ 205.4, 151.7, 147.6, 139.5, 116.7, 113.3, 102.3, 65.3, 36.2, 34.8, 31.9, 20.4; HRMS calcd for $C_{14}H_{14}O_3$ (CI) 230.0943, found 230.0945. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.99; H, 6.10.

2′,3′-Dihydro-7′-hydroxyl-5′-methylspiro[cyclopentane-1,1′-indene]-2,5-dione Bis(ethylene acetal) (14). A solution of **13** (1.00 g, 4.35 mmol) in benzene (50 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid (~0.050 g). Ethylene glycol (0.50 mL, 8.9 mmol) was added, and the mixture was refluxed under Dean–Stark trap conditions until water ceased to evolve (~48 h). The mixture was then cooled and quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a tan solid. Flash chromatography (1:1 hexanes/EtOAc) afforded 1.38 g (100%) of **14** as a white solid, mp 131–132 °C (heptane): IR (KBr) 3394, 2959, 2893, 1624, 1576, 1469, 1340, 1318, 1199, 1154, 1044, 951, 849 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (s, 1H), 6.44 (s, 1H), 6.41 (s, 1H), 3.86–3.76 (m, 6H), 3.40 (q, 2H, J = 6.9 Hz), 2.84 (t, 2H, J = 7.2 Hz), 2.24 (t, 2H, J = 7.5 Hz), 2.17 (s, 3H), 2.11–1.98 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.9, 149.6, 139.8, 120.6, 118.9, 116.4, 115.1, 67.4, 65.3, 65.0, 33.1, 32.9, 31.1, 21.0; HRMS calcd for $C_{18}H_{22}O_5$ (CI) 318.1467, found 318.1470. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 68.20; H, 7.11.

6′-Bromo-2′,3′-dihydro-7′-hydroxyl-5′-methylspiro[cyclopentane-1,1′-indene]-2,5-dione Bis(ethylene acetal) (15). A solution of **14** (6.02 g, 18.9 mmol) in CH_2Cl_2 (100 mL) was treated with *N*-bromosuccimide (3.37 g, 18.9 mmol), and the mixture was refluxed for 3 h. The solution was cooled and washed with water. The organic layer was separated, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a yellow solid. Flash chromatography (1:1 hexanes/EtOAc) afforded 7.46 g (99%) of **15** as a white solid, mp 161–162 °C (heptane): IR (KBr) 3373 (s, br), 2985, 2844, 2885, 1615, 1566, 1463, 1351, 1313, 1284, 1197, 1149, 1043, 954, 866 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.18 (s, 1H), 6.60 (s, 1H), 3.92–3.85 (m, 6H), 3.53–3.49 (m, 2H), 2.96 (t, 2H, J = 7.5 Hz), 2.38–2.30 (m, 5H), 2.15–2.08 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.1, 149.2, 139.1, 122.6, 118.8, 117.3, 111.5, 68.8, 65.3, 65.1, 33.8, 32.9, 32.2, 22.4; HRMS calcd for $C_{18}H_{21}O_5Br$ (CI) 396.0573, found 396.0576. Anal. Calcd for $C_{18}H_{21}O_5Br$: C, 54.42; H, 5.33. Found: C, 54.81; H, 5.52.

6′-Bromo-2′,3′-dihydro-7′-methoxy-5′-methylspiro[cyclopentane-1,1′-indene]-2,5-dione Bis(ethylene acetal) (16). A solution of **15** (10.0 g, 25.1 mmol) in THF (100 mL) at 25 °C was treated with solid KH (1.20 g, 30 mmol), and the reaction mixture was stirred until hydrogen gas ceased to evolve. Methyl iodide (3.11 mL, 50.0 mmol) was added, and the solution was stirred for 6 h. The mixture was filtered through Celite and concentrated to afford a tan solid. Flash chromatography (2:1 hexanes/EtOAc) afforded 9.74 g (94%) of **16** as a white solid, mp 180 °C (heptane): IR (KBr) 2946, 2882, 1564, 1468 (s), 1333 (s), 1308, 1231, 1200, 1146, 1057 (s), 1013, 957 (s), 895, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.68 (s, 1H), 3.99–3.94 (m, 4H), 3.86–3.72 (m, 4H), 3.81 (s, 3H), 2.78–2.75 (t, 2H, J = 7.5 Hz), 2.36 (s, 3H), 2.32–2.28 (m, 2H), 2.20–2.18 (t, 2H, J = 7.5 Hz), 2.00–1.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 155.1, 148.1, 137.9, 129.6, 117.2, 113.7, 113.4, 68.2, 65.1, 64.6, 56.0, 34.8, 33.2, 28.8, 22.9; HRMS calcd for $C_{19}H_{23}O_5Br$ (EI) 410.0729, found 410.0734. Anal. Calcd for $C_{19}H_{23}O_5Br$: C, 55.48; H, 5.64. Found: C, 55.62; H, 5.81.

2′,3′-Dihydro-7′-methoxy-6′-(methoxycrbonyl)-5′-methylspiro[cyclopentane-1,1′-indene]-2,5-dione Bis(ethylene acetal) (17). A solution of **16** (8.00 g, 19.5 mmol) in THF (100 mL) at −78 °C was treated with a solution of *n*-BuLi in hexanes (8.00 mL, 2.5 M, 20.0 mmol) over a 10-min period. The mixture was stirred at −78 °C for 10 min before 2.32 mL (30.0 mmol) of methyl chloroformate was added dropwise. The dry ice/acetone bath was removed, and the solution was allowed to warm to 25 °C, where it was stirred for 24 h. The mixture was quenched with water (100 mL), and EtOAc (100 mL) was added. The organic layer was separated, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a tan solid. Flash chromatography (1:1 hexanes/EtOAc) afforded 7.13 g (94%) of **17** as a white solid, mp 144–145 °C (heptane): IR (KBr) 2996, 2951, 2881, 1712 (s), 1591, 1577, 1447, 1318, 1280, 1221, 1143, 1112, 1049, 953, 923, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (s, 1H), 3.97–3.93 (m, 4H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82–3.77 (m, 2H), 3.73–3.66 (m, 2H), 2.89 (t, 2H, J = 7.5 Hz), 2.45 (s, 3H), 2.34–2.28 (m, 2H), 2.17 (t, 2H, J = 7.5 Hz), 2.01–1.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 169.0, 157.8, 149.4, 139.7, 128.9, 120.8, 117.2, 113.2, 66.6, 65.0, 64.6, 55.5, 51.1, 34.9, 31.6, 29.7, 21.4; HRMS calcd for $C_{21}H_{26}O_7$ (CI) 390.1678, found 390.1683. Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.61; H, 6.67. Found: C, 64.40; H, 6.66.

(*E,E*)-6′,7′-Dihydro-9′-methoxy-3′-(1,3-pentadienyl)spiro[cyclopentane-1,8′-cyclopent[*g*]isochromarin]-2,6-dione Bis(ethylene acetal) (18). Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was prepared by the addition of *n*-BuLi in hexanes (3.08 mL, 2.5 M, 7.70 mmol) to a cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidide (1.30 mL, 7.70 mmol) in THF (20 mL). The reaction mixture was stirred for 10 min before being cooled to −78 °C. A solution of **17** (1.00 g, 2.56 mmol) in THF (10 mL) was added dropwise over 5 min to the solution of LiTMP in THF at −78 °C. The dark blood-red solution was stirred at −78 °C for 1 h. A THF solution of CuCN·2LiCl (7.70 mL, 1.0 M, 7.70 mmol) was added dropwise at −78 °C. This yellow solution was stirred at −78 °C for 20 min. Sorboyl chloride[31] (1.31 g, 10.0 mmol, 1.23 mL) dissolved in 5 mL of THF was added at −78 °C over 5 min, and the reaction mixture was stirred for 1 h before being warmed to −27 °C for 18 h. The yellow solution was quenched at −27 °C with aqueous $NaHCO_3$ (10 mL) and was extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a yellow solid. Flash chromatography (1:1 hexanes/EtOAc) afforded 0.740 g (63.5%) of **18** as a light yellow solid, mp 161–162 °C (hexanes/EtOAc): IR (KBr) 3009, 2949, 2876, 1711 (s), 1632, 1605, 1585, 1558, 1479, 1445, 1372, 1319, 1239, 1213, 1146, 1113, 1053 (s), 947, 873 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (dd, 1H, J = 10.8, 15.0 Hz), 6.59 (s, 1H), 6.18 (s, 1H), 6.16–6.07 (m, 1H), 5.95–5.87 (m, 2H), 3.91–3.84 (m, 4H), 3.77–3.70 (m, 2H), 3.63–3.56 (m, 2H), 3.25 (t, 2H, J = 7.2 Hz), 2.28–2.20 (m, 4H), 1.98–1.91 (m, 2H), 1.77 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 161.1 (2 C), 152.7, 152.5, 140.1, 134.1, 132.9, 132.4, 130.6,

120.5, 117.0, 110.1, 105.5, 105.0, 67.0, 64.9, 64.5, 55.3, 35.0, 32.0, 29.8, 18.4; HRMS calcd for $C_{26}H_{28}O_7$ (EI) 452.1835, found 452.1839.

(*E,E*)-6′,7′-Dihydro-9′-methoxy-3′-(1,3-pentadienyl)spiro[cyclopentane-1,8′-cyclopent[*g*]isoquinoline]-2,5-(2′*H*)-dione Bis(ethylene acetal) (19). Compound **18** (1.184 g, 2.620 mmol) was dissolved in a mixture of 1 mL of MeOH and 2 mL of THF and placed in a Parr bomb. Ammonia gas was condensed to a liquid (approximately 3 mL) and was added to the bomb at −78 °C. The bomb was quickly closed, and the vessel was heated at 70 °C for 2 days. The reaction vessel was then recooled to −78 °C and carefully opened. The mixture was poured into a flask, and the solid residue was rinsed out with 50 mL of CH_2Cl_2. The solution was carefully concentrated to afford a yellow solid. Flash chromatography (1:1 CH_2Cl_2/EtOAc) afforded 0.980 g (83.2%) of **19** as a light yellow solid, mp 228–230 °C dec: IR (KBr) 3157, 3057, 2950, 2877, 1635 (s), 1601, 1581, 1448, 1415, 1354, 1328, 1274, 1228, 1208, 1121, 1054, 994, 947, 847 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.14 (s, 1H), 6.96 (dd, 1H, J = 10.0, 16.0 Hz), 6.73 (s, 1H), 6.31 (s, 1H), 6.23–5.97 (m, 3H), 3.96–3.93 (m, 4H), 3.91 (s, 3H), 3.83–3.78 (m, 2H), 3.68–3.64 (m, 2H), 3.49 (t, 2H, J = 7.5 Hz), 2.35–2.27 (m, 4H), 2.03–1.99 (m, 2H), 1.87 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 164.0, 160.0, 150.9, 141.1, 137.1, 133.1, 131.7, 131.2, 130.5, 122.9, 117.5, 115.8, 106.9, 105.9, 67.1, 65.2, 64.7, 55.5, 35.2, 32.6, 30.3, 18.6; FABHRMS (glycerol, M + H), m/e calcd for $C_{26}H_{29}O_6N_1$ 350.1392, found 350.1393.

(*E,E*)-6′,7′-Dihydro-9′-methoxy-3′-(1,3-pentadienyl)spiro[cyclopentane-1,8′-cyclopent[*g*]isoquinoline]-2,5(2′*H*)-dione (20). A solution of **19** (0.984 g, 2.18 mmol) in CH_3CN (20 mL) was treated with a 10% HCl (aqueous) solution (10 mL), and the mixture was refluxed for 24 h before being quenched with aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a yellow solid. Flash chromatography (1:1 EtOAc/CH_2Cl_2) afforded 0.630 g (80%) of **20** as a light yellow solid, mp >250 °C dec: IR (KBr) 3161, 3076, 2978, 2942, 2872, 1724 (s), 1633 (s), 1604 (s), 1456, 1365, 1259, 1224, 1196, 1118, 992, 886, 872 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.98 (s, 1H), 7.16 (dd, 1H, J = 10.5, 15.6 Hz), 6.87 (s, 1H), 6.51 (s, 1H), 6.29–6.16 (m, 2H), 5.97–5.85 (m, 1H), 3.77 (s, 3H), 3.52 (t, 2H, J = 7.2 Hz), 2.89 (s, 4H), 2.28 (t, 2H, J = 7.2 Hz), 1.80 (d, 3H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 215.8, 162.3, 156.7, 149.3, 141.8, 138.5, 133.2, 132.2, 131.5, 130.8, 122.7, 115.8, 105.0, 104.7, 65.3, 55.8, 36.3, 35.8, 33.9, 18.4; FABHRMS (glycerol, M + H), m/e calcd for $C_{22}H_{21}O_4N_1$ 364.1549, found 364.1549.

(*E,E*)-6′,7′-Dihydro-9′-methoxy-3′-(1,3-pentadienyl)spiro[3-cyclopentene-1,8′-cyclopent[*g*]isoquinoline]-2,5(2′*H*)-dione (20). Phenyltrimethylammonium tribromide (PTT) (0.117 g, 0.310 mmol) in THF (25 mL) at 25 °C was added via syringe pump over 1 h to a solution of **19** (0.113 g, 0.311 mmol) in THF (50 mL). The mixture was stirred for 10 min before being quenched with aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford 66.0 mg (59%) of **20** as an orange solid after flash chromatography (4:1 CH_2Cl_2/EtOAc), mp >250 °C dec: IR (KBr) 3161, 3061, 2961, 2928, 2868, 1723 (s), 1637 (s), 1590 (s), 1457, 1410, 1377, 1357, 1271, 1217, 1117, 991, 838 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.97 (s, 1H), 7.64 (s, 2H), 7.16 (dd, 1H, J = 10.2, 15.9 Hz), 6.86 (s, 1H), 6.51 (s, 1H), 6.27–6.17 (m, 2H), 5.97–5.87 (m, 1H), 3.66 (s, 3H), 3.55 (t, 2H, J = 7.2 Hz), 2.25 (t, 2H, J = 7.2 Hz), 1.80 (d, 3H, J = 6.9 Hz); ^{13}C NM R (DMSO-d_6) δ 205.8, 162.3, 157.5, 149.9, 148.8, 142.0, 138.6, 133.2, 132.2, 131.4, 127.8, 122.6, 115.8, 105.0, 104.6, 60.5, 55.8, 34.0, 33.6, 18.3; FABHRMS (glycerol, M + H), m/e calcd for $C_{22}H_{19}O_4N_1$ 362.1392, found 362.1382.

(±)-(*E,E*)-6′,7′-Dihydro-4,9-dihydroxy-5,6,8,9′-tetramethoxy-3′-(1,3-pentadienyl)spiro[2*H*-benz[*f*]indene-2,8′-cyclopent[*g*]isoquinoline]-1′,1,3-(2′*H*)-trione (22). Lithium diisopropylamide (LDA) was prepared by the addition of *n*-BuLi in hexanes (0.332 mL, 2.5 M, 0.831 mmol) to a cooled (0 °C) solution of diisopropylamine (0.120 mL, 0.831 mmol) in THF (10 mL). This reaction mixture was stirred for 10 min before being cooled to −78 °C. A solution of 3-cyano-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone[7f] (**2**) (69.0 mg, 0.277 mmol) in THF (5 mL) was added slowly over 5 min. This yellow mixture was stirred for 30 min at −78 °C before addition of a solution of **20** (0.100 g, 0.277 mmol) in THF (10 mL) dropwise over 15 min. This greenish-yellow reaction mixture was stirred for 1 h before being quenched with 1 N HCl (5 mL) at −78 °C. The resulting solution was extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a tan solid. This mixture of diastereomers was dissolved in THF (20 mL) and was cooled to −78 °C. An excess of freshly prepared NaOEt [~0.01 g of sodium metal in EtOH (5 mL)] in EtOH was added, and the resulting dark yellow mixture was stirred for 15 min at −78 °C before being slowly warmed. The dark yellow solution changed to a dark red solution at about 0 °C, and the reaction was quenched with a 1 N HCl solution (10 mL) at 20 °C. The mixture was extracted with EtOAc (3 × 25 mL), and the organic layers were combined. The organic solution was washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a yellow solid. Flash chromatography (15:1 CH_2Cl_2/methanol) afforded 0.125 g (78% overall) of **22** as a yellow solid, mp >350 °C dec: IR (KBr) 3321 (br), 2962, 2929, 2849, 1718, 1698, 1638, 1618, 1598 (s), 1459, 1386, 1312, 1259, 1219, 1153, 1126, 1080, 1060, 1020, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.84 (s, 1H), 10.67 (s, 1H), 10.45 (s, 1H), 7.02 (dd, 1H, J = 10.2, 15.9 Hz), 6.85 (s, 1H), 6.53 (s, 1H), 6.28 (s, 1H), 6.22–6.07 (m, 1H), 6.04–5.93 (m, 1H), 4.09 (s, 3H), 4.05 (2, 3H), 4.01 (s, 3H), 3.94–3.89 (m, 2H), 3.55 (s, 3H), 2.59–2.55 (m, 2H), 1.84 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 202.5, 202.4, 163.9, 158.0, 157.0, 152.3, 151.3, 149.4, 146.6, 142.6, 140.3, 137.9, 133.4, 131.5, 131.3, 129.9, 125.3, 122.7, 117.1, 115.1, 115.0, 107.0, 104.7, 104.5, 98.6, 66.7, 62.6, 57.1, 56.8, 55.5, 36.2, 34.5, 18.5; FABHRMS (glycerol, M + H), m/e calcd for $C_{33}H_{30}O_9N$ 584.19207, found 584.19206.

(±)-Fredericamycin A (1). A solution of **22** (0.093 g, 0.160 mmol) in CH_2Cl_2 (25 mL) at −78 °C was treated by dropwise addition of boron tribromide in CH_2Cl_2 (0.560 mL, 1.0 M, 0.558 mmol). The solution immediately changed from yellow to a deep red color. The mixture was stirred at −78 °C for 1 h before being warmed to 0 °C for 20 min and then quenched with water. The mixture was diluted with THF (100 mL), and the reaction was stirred open to the air for 24 h before being extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine, dried (anhydrous $MgSO_4$), and concentrated to afford a red solid. Purification by flash chromatography (1:1:trace CH_2Cl_2/EtOAc/acetic acid) afforded 67.0 mg (80%) of fredericamycin A (**1**) as a violet solid, mp >350 °C dec: IR (KBr) 3328 (br), 3195, 3015, 2942, 2849, 1751, 1718 (s), 1652, 1612 (s), 1432, 1419, 1359, 1266 (s), 1199, 1173, 1139, 1060, 986, 953, 933, 867, 813, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, 1 drop of CF_3CO_2H) δ 13.15 (s, 1H), 12.20 (s, 1H), 11.60 (s, 1H), 7.17 (dd, 1H, J = 10.3, 15.9 Hz), 7.03 (s, 1H), 6.71 (s, 1H), 6.58 (s, 1H), 6.26–6.21 (m, 2H), 5.95–5.90 (m, 2 H), 1.83 (d, 3H, J = 7.1 Hz). TLC: the assigned structure was also supported by a direct comparison with authentic fredericamycin A in three different solvent mixtures (95:5 $CHCl_3$/methanol, 1:1:trace EtOAc/CH_2Cl_2/HOAc, 87:3:3 $CHCl_3$/methanol/HOAc).

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