C_{19} Quassinoids: Total Synthesis of *dl*-Samaderin B

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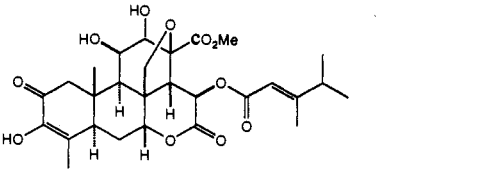
Abstract: The total synthesis of the novel C_{19} quassinoid *dl*-samaderin B (**2**) is described. The synthesis commences with the known racemic pentacyclic ketone **6**, which permits introduction of the C(11), C(12) trans diaxial arrangement of the hydroxyl groups in ring C. The synthesis features a copper(II)-mediated ring contraction of a δ-lactone (**28**) to a γ-lactone (**29**). Subsequent elaboration of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit, cleavage of the C(7), C(11) methoxymethyl ethers, selective oxidation at C(7), and deprotection of the C(1) hydroxyl affords samaderin B (**2**).

Quassinoids are a diverse group of highly oxygenated polycyclic lactones.[2] The vast majority of the known quassinoids possess a C_{20} picrasane-like carbon framework bearing a δ-lactone [cf. bruceantin (**1**)[3]]. Hundreds of C_{20} quassinoids have been isolated and characterized during the past half-century. During this period, a relatively small number (less than 10) of C_{19} quassinoids bearing a γ-lactone, of which samaderin B (**2**) is representative, have been isolated and characterized. Samaderin B, isolated from



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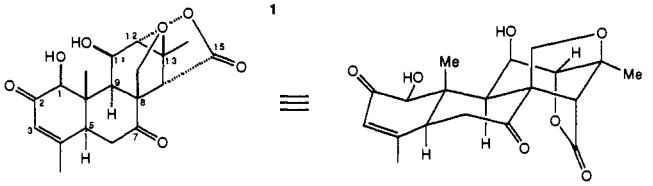

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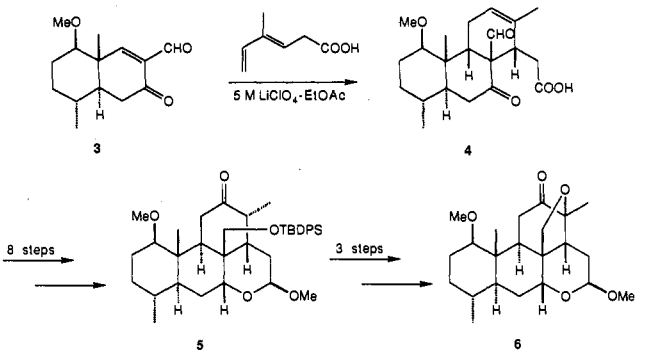
Samadera indica (Simaroubaceae) by Polonsky[4] in the early 1960s, was the first C_{19} quassinoid characterized. Whereas the C_{20} quassinoids possess a wide spectrum of pharmacological properties,[5] the biological activity, if any, associated with samaderin B and related C_{19} quassinoids has not been examined, in part due to their scarcity. We detail below the first total synthesis of *dl*-samaderin B.

A rational starting point for the synthesis of **2** was pentacyclic ketone **6**, which has served as a key intermediate in our synthesis of simalikalactone D.[6] Pentacyclic ketone **6** is readily available in 12 steps from dienophile **3** *via* a lithium perchlorate–ethyl acetate mediated intermolecular Diels–Alder[7] reaction followed by straightforward transformation of **4** into **5** and subsequent construction of the C(8), C(13) epoxymethano bridge. Our



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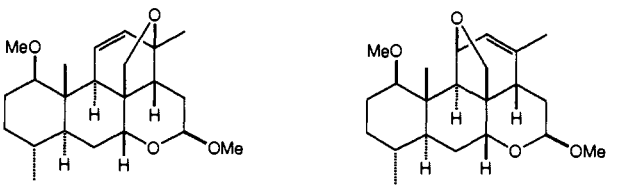
strategy for the conversion of **6** into samaderin B involved initial elaboration of the C(11), C(12) trans diaxial arrangement of the hydroxyls in ring C followed by installation of the γ-lactone *via* a copper(II)-mediated ring contraction reaction[8] and subsequent introduction of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit.

It was anticipated that incorporation of the C(11), C(12) vicinal diol unit into ring C would be a straightforward operation requiring osmylation from the least hindered face of the $\Delta^{11,12}$ olefin derived from ketone **6**, followed by inversion of configuration at C(11) *via* a selective oxidation–reduction sequence. Toward this end, pentacyclic ketone **6** was converted into the corresponding tosylhydrazone and treated with excess methyllithium, giving rise to olefin **7**, mp 149–150 °C, in 70% overall yield. Olefin **7** proved to be exceedingly sensitive to traces of acid, rapidly isomerizing to the rearranged olefin **8**. Similar observations have been made by Ganem and Fuchs on very similar systems.[9]



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(1) Recipient of a GAANN Fellowship from the Department of Education, 1993–1994.

(2) (a) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 227; (b) **1973**, *30*, 101.

(3) For the isolation and characterization of bruceantin, see: (a) Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; Ziegler, M. F.; Sigel, C. W. *J. Org. Chem.* **1975**, *40*, 648. For the total synthesis of bruceantin, see: (b) Grieco, P. A.; VanderRoest, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 5841. (c) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528.

(4) (a) Zylber, J.; Polonsky, J. *Bull. Soc. Chim. Fr.* **1962**, 1715. (b) Zylber, J. Etude des Constituants de l'Ecorce de Samadera Indica; Structures des Samaderins B, C et D. Doctoral Thesis, Universite de Paris, Orsay, 1967.

(5) (a) Polonsky, J. Chemistry and Biological Activity of the Quassinoids. In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grandon, M. F., Eds.; Academic Press: New York, 1983; p 247. (b) Lidert, Z.; Wing, K.; Polonsky, J.; Imakura, Y.; Okano, M.; Tani, S.; Lin, Y.-M.; Kiyokawa, H.; Lee, K.-H. *J. Nat. Prod.* **1987**, *50*, 442. (c) Wall, M. E.; Wani, M. International Symposium on the Chemistry of Natural Products, Riga, USSR, IUPAC 7th, 1970; Abstracts E 138, 614.

(6) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764.

(7) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.

(8) Inanaga, J.; Sasaki, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 4800.

(9) (a) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. (b) Chiu, C. K.-F.; Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311.

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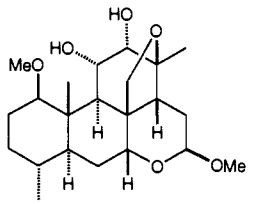
Exposure of **7** to osmium tetraoxide in pyridine followed by workup with sodium bisulfite afforded in 98% yield the cis vicinal diol **9**, mp 229–231 °C, derived from approach of the bulky reagent from the least hindered α-face of the molecule. The structural



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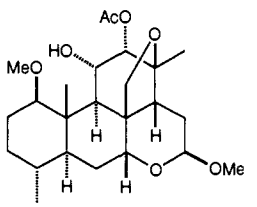

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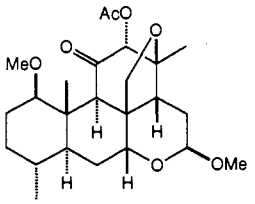
assignment follows directly from the ^{1}H NMR spectrum, which revealed the C(9) proton as a doublet at δ 1.89 with a coupling constant of 10.4 Hz. It was anticipated that inversion of configuration at C(11) could be realized *via* selective oxidation at C(11) utilizing the Fuchs protocol.[10] Unfortunately, when **9** was oxidized utilizing Swern conditions in the absence of triethylamine, diol **9** was recovered unchanged. Since we had shown previously that vicinal diols similar to **9** can be selectively protected at C(12)[11] and subsequently oxidized at C(11), **9** was acetylated, giving rise to **10**, mp 217–219 °C. Best results were obtained when the acetylation was carried out to 50% completion. Unfortunately, Collins oxidation of **10** afforded only recovered starting alcohol. Apparently the presence of the C(1) methyl ether further exacerbates the situation about an already highly encumbered C(11) α hydroxyl group. This problem was overcome by using the Dess–Martin reagent,[12] which is capable of oxidizing highly hindered alcohols. Thus, exposure of **10** to 2.0 equiv of the Dess–Martin periodinane reagent in methylene chloride furnished keto acetate **11** as a crystalline compound, mp 232–233 °C, in essentially quantitative yield. Reduction of **11** with lithium aluminum hydride effected cleavage of the acetate and reduction of the C(11) ketone from the α face, providing **12**, mp 239–241 °C, possessing the desired arrangement of the C(11), C(12) vicinal hydroxyl groups.



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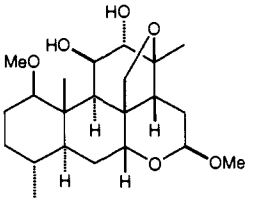

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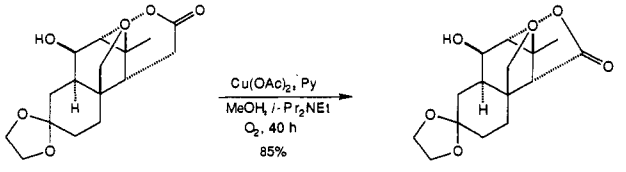
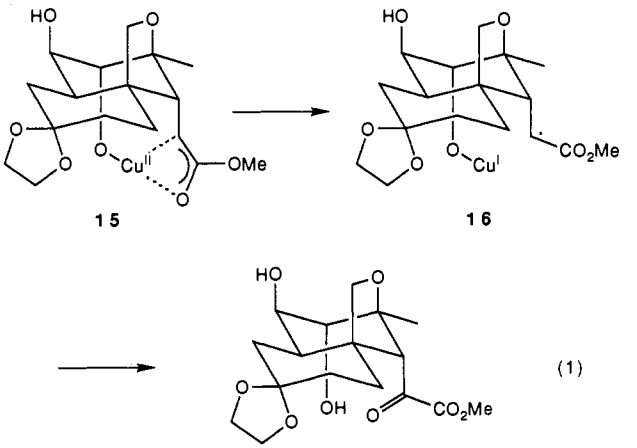
Our strategy for elaboration of the γ-lactone ring of samaderin B was based upon a novel copper(II)-mediated ring contraction reaction[8] which we discovered some years ago in connection with model studies directed toward the total synthesis of quassimarin.[13] We had observed that bubbling oxygen into a 0.02 M solution of δ-lactone **13** in methanol containing copper(II) acetate monohydrate, pyridine, and Hunig's base gave rise to γ-lactone **14**. The ring contraction observed in the transformation of **13**



13 **14**

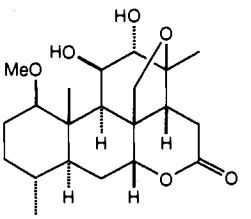
into **14** can be rationalized by initial methanolysis followed by base-catalyzed copper(II) enolate formation and subsequent electron transfer (eq 1) leading to **16**, which gives rise to α-oxo ester **17** in the presence of oxygen.



15 **16**

17 (1)

It was our hope that subjection of δ-lactone **18**, which was prepared in straightforward fashion from **12** *via* hydrolysis (10% HCl–THF, 1:1) of the protected lactol followed by mild oxidation (MnO_2, $CHCl_3$), to the conditions described above for the transformation of **13** into **14** would give rise to a mixture of the desired γ-lactone **19** and the isomeric γ-lactone **20**. Unfortunately, all attempts to induce **18** to undergo the ring contraction reaction failed. Only recovered δ-lactone was observed.



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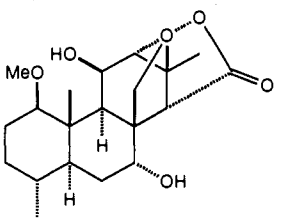

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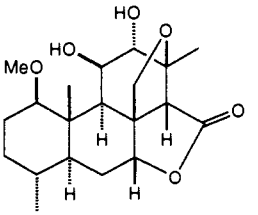

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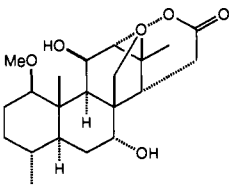
Unsuccessful in our attempts to transform **18** into **19**, we set out to convert **18** into the isomeric pentacyclic δ-lactone **21**. It was anticipated that under equilibrating conditions **18** would give rise to an equilibrium mixture of the two δ-lactones **18** and **21**. All our efforts to convert **18** into **21** *via* equilibration failed.



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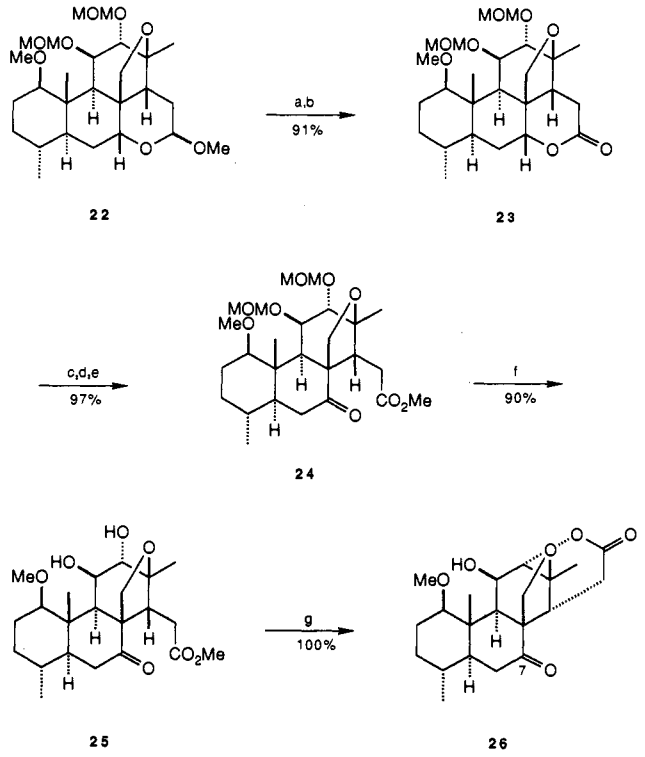
In order to circumvent the difficulties encountered above, we attempted to transform **12** into pentacyclic δ-lactone **26** (Scheme 1). The C(11), C(12) vicinal hydroxyl groups in **12** were protected

(10) Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216.

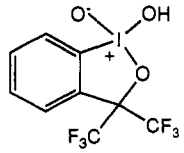
(11) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.

Scheme 1[a]



[a] (a) 5% HCl/THF (1:1), 0 °C → room temperature; (b) PCC, NaOAc, CH_2Cl_2; (c) NaOH, MeOH/THF (1:1); (d) **27**, CH_2Cl_2/THF (1:1), py; (e) CH_2N_2 (excess), 0 °C; (f) $AlCl_3$/NaI, CH_3CN/CH_2Cl_2 (2:1), 0 °C → room temperature; (g) *p*-TsOH·H_2O, benzene, reflux.

as their methoxymethyl ethers, giving rise to **22**, mp 138–139 °C, in 84% yield. Acid-catalyzed hydrolysis of the protected lactol in **22** was carried out to *ca* 50% completion. After recovered **22** was recycled, a >95% yield of the corresponding lactols could be realized. Subsequent oxidation afforded lactone **23**, mp 177–179 °C, in 91% overall yield. Transformation of lactone **23** into lactone **26** necessitated eventual oxidation at C(7). Toward this end, **23** was saponified with 1.0 equiv of sodium hydroxide in methanol. The resulting sodium carboxylate possessing the C(7) α hydroxyl was directly treated with the Dess–Martin periodinane reagent buffered with pyridine. Workup with etheral diazomethane provided a 60% yield of keto ester **24** along with *ca.* 40% of lactone **23** which re-formed during the oxidation. It was reasoned that replacement of the Dess–Martin periodinane with the little used hydroxyiodinane oxide[3b,11,12b] **27** would alleviate the problems associated with relactonization during the oxidation of the C(7) hydroxyl since **27** generates water instead of acetic acid during the course of the oxidation reaction. Indeed, treatment



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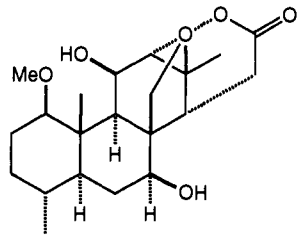
of a solution [methylene chloride–tetrahydrofuran (1:1)] of the corresponding hydroxy sodium carboxylate derived from **23** with a solution of hydroxyiodinane **27** in methylene chloride–tetrahydrofuran (1:1) containing pyridine followed by treatment with diazomethane gave rise to a 97% yield of keto ester **24**, mp 138–139 °C. Deprotection of the methoxymethyl ethers in **24**, which was efficiently carried out utilizing a procedure developed by Fujita,[14] afforded **25**, mp 214–217 °C, in 90% yield. Treatment of **25** with acid in benzene at reflux provided the desired δ-lactone **26**, mp 205–207 °C, which set the stage for the critical ring contraction reaction. Unfortunately, when **26** was subjected to the ring contraction reaction, none of the desired γ-lactone was present among the numerous products isolated.

Since the ketone at C(7) in **26** appeared to complicate the ring contraction reaction, **26** was reduced with sodium borohydride, giving rise (95%) to pentacyclic alcohol **28**, mp 257–259 °C, as the sole product. Thus, **28** was dissolved in methanol containing



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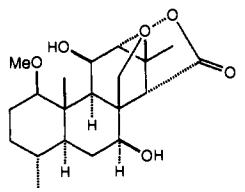
pyridine and Hunig's base and treated with copper(II) acetate monohydrate. After 48 h at ambient temperature, TLC revealed that all the starting material had been completely consumed. Workup gave rise (98%) to the ring-contracted γ-lactone **29**, mp 242–244 °C, and hemiketal **30**, mp 183–185 °C, in a ratio of *ca.* 1:1. None of ring-opened hydroxy ester **31** was isolated. The



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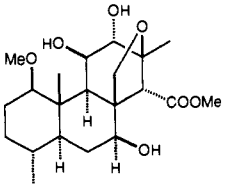

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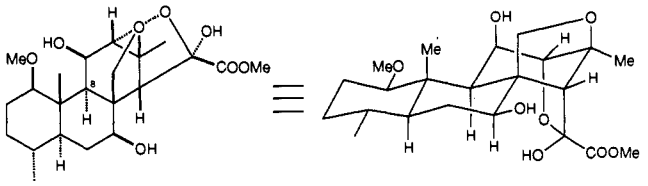

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structures for **29** and **30** were unequivocally established by single-crystal X-ray analysis. Interestingly, treatment of **30** with *p*-toluenesulfonic acid in benzene at reflux gave rise to a 33% yield of **32**. When **30** was resubmitted to the conditions of the ring contraction reaction, it gave rise after 48 h to a 50% yield of γ-lactone **29**. However, when **30** was treated with peracetic acid in tetrahydrofuran at 60 °C, **30** was transformed into γ-lactone **29** in 90% yield *via* the corresponding anhydride.[15]

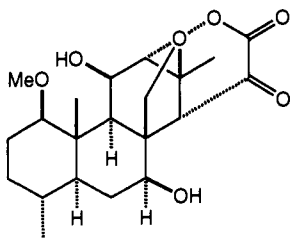
At this point in the synthesis, we focused our attention on the installation of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality into substrate **29**. Prior to liberating the C(1) hydroxyl group, the C(7) hydroxyl was selectively protected as its acetate over the more sterically encumbered C(11) β hydroxyl, giving rise to **33**, mp 235–237 °C, in 98% yield. Subsequent attempts to cleave the C(1) methyl ether in **33** proved to be especially challenging. No reaction was observed when **33** was treated with aluminum chloride/sodium iodide in acetonitrile–methylene chloride. When boron tribromide was employed, the yield of **34**

(12) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; (b) *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(13) For the total synthesis of quassimarin, see: Moher, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3789.

(14) Node, M.; Ohta, K.; Kajimoto, T.; Nishide, K.; Fujita, E.; Fuji, K. *Chem. Pharm. Bull.* **1983**, *31*, 4178.

(15) Cf.: Hassall, C. H. *Org. React. (N.Y.)* **1957**, *9*, 73.



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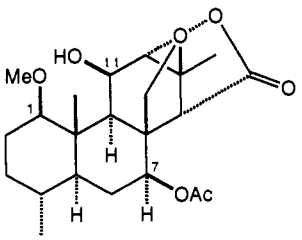

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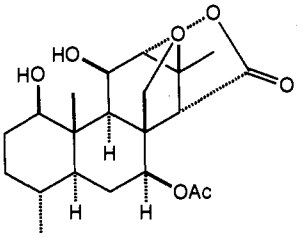

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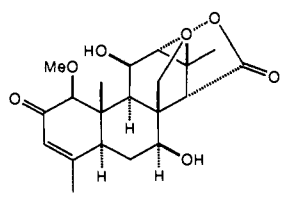
was very poor. Fortunately, use of Olah's conditions[16] for cleaving methyl ethers solved our problem. Thus, treatment of **33** with methyltrichlorosilane/sodium iodide in acetonitrile–methylene chloride (1:1) afforded **34**, mp 269–270 °C, in 90% yield.

Introduction of the ring A functionality is outlined in Scheme 2. Selective oxidation employing Swern conditions of the C(1) hydroxyl in **34** was realized in 82% yield, giving rise to **35**, mp 278–279 °C. The presence of the C(7) acetate proved to be incompatible with the conditions required to introduce the ring A functionality. Therefore, the C(7) acetate in **35** was cleaved, and the resulting C(7) hydroxyl and the C(11) hydroxyl were both converted to their methoxymethyl ethers. The transformation of **36** into **40** was achieved *via* a five-step sequence which we had developed previously in conjunction with the total synthesis of glaucarubolone.[11] Thus, the enolate of **36** was trapped with dimethyl sulfate, and the resulting enol ether was subjected to hydroboration, giving rise to **37**, mp 138–141 °C. Oxidation with pyridinium chlorochromate provided ketone **38**, mp 159–161 °C, which was brominated at C(3) *via* the $\Delta^{2,3}$ silyl enol ether and subsequently dehydrobrominated with 2.2 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran [0 °C (20 min) → room temperature (1.5 h)], giving rise to **40**, mp 191–193 °C.

At this point, completion of the total synthesis of samaderin B requires deprotection of the C(7) and C(11) hydroxyl groups, selective oxidation at C(7), and cleavage of the C(1) methyl ether. Brief treatment (35 min, 0 °C) of **40** with aluminum chloride–sodium iodide (1:1) in acetonitrile–methylene chloride (2:1) provided in 87% yield pentacyclic diol **41**, mp 248–250 °C, which upon oxidation (Swern) gave (83%) ketone **42**. Treatment of **42** with excess boron tribromide at –45 °C in methylene chloride provided crystalline racemic samaderin B (**2**), whose spectral properties (IR, ^{1}H NMR, ^{13}C NMR) were identical in all respects with those published in the literature.[4,17]



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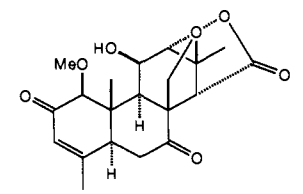

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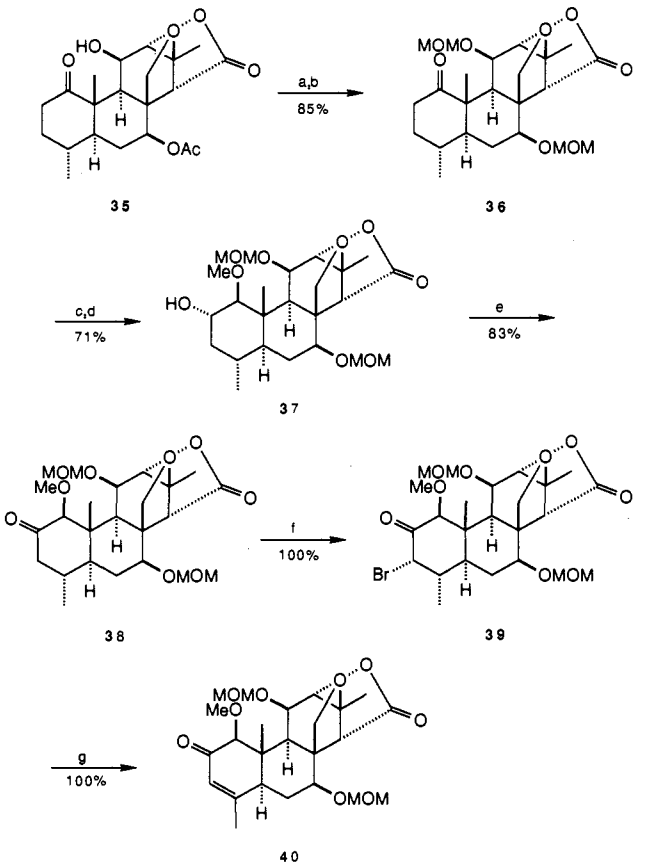
(16) Olah, G. A.; Husain, A.; Balaram Gupta, B. G.; Narang, S. C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 690.
(17) Polonsky, J.; Baskevitch, Z.; Gottlieb, H. E.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1975**, *40*, 2499.

Scheme 2[a]



[a] (a) NaOH, THF/MeOH (1:1), 0 °C → room temperature; (b) MOMCl, *i*-Pr_2NEt, $ClCH_2CH_2Cl$, 0 °C → 48 °C; (c) LDA, HMPA, THF; SO_4Me_2; (d) B_2H_6, THF; NaOH, H_2O_2; (e) PCC, NaOAc, CH_2Cl_2; (f) LiHMDS, THF; TMSCl; NBS; (g) TBAF, THF, 0 °C → room temperature.

Experimental Section

Proton and carbon nuclear magnetic resonance (^{1}H, ^{13}C NMR) spectra were recorded on a Varian VXR-400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken on a Perkin-Elmer Model 298 spectrophotometer or on a Mattson Galaxy 4020 series FTIR spectrometer, either as a solution in chloroform or as a KBr pellet, as indicated. Absorption intensities are indicated as strong (s), medium (m), or weak (w). High-resolution and low-resolution mass spectra were obtained on a Kratos MS 80/RFAQ spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or by Robertson Microlit Laboratories, Inc., Madison, NJ. Melting points were obtained on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) using E. Merck precoated silica gel 60 F-254 (0.25-mm thickness) plates. The plates were visualized by immersion in a *p*-anisaldehyde solution and warming on a hot plate. E. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. All solvents are reagent grade unless otherwise stated. Anhydrous solvents were dried immediately before use. Dichloromethane, 1,2-dichloroethane, acetonitrile, hexamethyldisilazane, pyridine, triethylamine, *N,N*-diisopropylethylamine, diisopropylamine, hexamethylphosphoramide, chloromethyl methyl ether, chlorotrimethylsilane, dimethyl sulfate, and oxalyl chloride were distilled from calcium hydride. Ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl. Methanol was distilled from methoxymagnesium iodide and stored over molecular sieves. Sodium iodide was oven dried at 110 °C and cooled in a desiccator prior to use.

(1β,13β,16β)-13,20-Epoxy-1,16-dimethoxypicras-11-ene (7). A solution of ketone **6** (1.02 g, 2.69 mmol) in tetrahydrofuran (58.6 mL, 0.046 M) was treated with anhydrous magnesium sulfate (3.24 g, 26.92 mmol), *p*-toluenesulfonic acid monohydrate (138 mg, 0.73 mmol), and *p*-toluenesulfonohydrazide (1.51 g, 8.11 mmol). After being stirred at room temperature for 16 h, the heterogeneous reaction mixture was filtered through a pad of flash silica gel and washed with ethyl acetate. The

filtrate and washings were concentrated *in vacuo* to a yellow solid, which was chromatographed on silica gel. Elution with diethyl ether–hexanes (1:1) provided 1.59 g of crude tosylhydrazone as a white solid, which was taken on to the next step without further purification. An analytical sample was prepared via crystallization from ethyl acetate–hexanes: mp 206–208 °C; R_f 0.28 (diethyl ether–hexanes, 2:1); IR ($CHCl_3$) 3300 (w), 3040 (w), 3000 (m), 2950 (m), 2840 (w), 1600 (w), 1450 (w), 1380 (m), 1340 (w), 1320 (w), 1190 (w), 1170 (s), 1140 (m), 1120 (s), 1090 (s), 1040 (s), 1000 (m), 980 (m), 920 (m), 890 (w), 870 (w), 860 (w), 840 (w), 810 (w), 700 (w), 660 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.2 Hz), 6.97 (s, 1H), 4.82–4.78 (m, 1H), 4.28 (d, 1H, J = 8.0 Hz), 3.69 (br s, 1H), 3.41 (dd, 1H, J = 8.0, 0.8 Hz), 3.35 (s, 3H), 3.33 (s, 3H), 2.97 (dd, 1H, J = 15.4, 5.4 Hz), 2.93 (dd, 1H, J = 11.0, 5.0 Hz), 2.14–1.93 (m, 4H), 1.77 (dd, 1H, J = 11.2, 3.6 Hz), 1.73–1.65 (m, 2H), 1.58–1.52 (m, 2H), 1.48–1.16 (m, 3H), 1.26 (s, 3H), 1.06–0.92 (m, 1H), 0.93 (s, 3H), 0.80 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.38, 144.04, 134.93, 129.32 (2C), 128.22 (2C), 97.08, 89.37, 82.99, 72.61, 70.42, 55.68, 54.55, 49.06, 44.57, 43.72, 42.81, 40.65, 33.78, 29.63, 28.20, 25.57, 25.28, 23.91, 21.57, 19.99, 18.82, 9.71; high-resolution MS (CI) calcd for $C_{29}H_{43}O_6N_2S$ (M + 1) m/e 547.2844, found 547.2829. Anal. Calcd for $C_{29}H_{42}O_6N_2S$: C, 63.71; H, 7.74. Found: C, 63.80; H, 7.92.

A solution of the above tosylhydrazone (1.59 g) in tetrahydrofuran (104 mL) under argon cooled to 0 °C was treated dropwise with 31.2 mL (43.63 mmol) of a 1.4 M solution of methyllithium in diethyl ether. The mixture was stirred at 0 °C for 1.5 h and at room temperature for 6 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous ammonium chloride solution. The mixture was diluted with water–diethyl ether and extracted with diethyl ether. The combined ethereal layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a yellow oil, which was chromatographed on flash silica gel. Elution with diethyl ether–hexanes (3:1) followed by diethyl ether afforded 680 mg (70% from ketone **6**) of alkene **7** as a white foam: R_f 0.70 (diethyl ether–hexanes, 3:1); IR ($CHCl_3$) 3010 (s), 2990 (s), 2970 (s), 2950 (s), 2840 (s), 1640 (w), 1460 (m), 1400 (w), 1380 (m), 1360 (w), 1320 (w), 1280 (w), 1190 (w), 1170 (w), 1150 (m), 1140 (m), 1120 (s), 1080 (s), 1050 (s), 1040 (s), 990 (s), 970 (s), 940 (m), 890 (s), 870 (m), 850 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (dd, 1H, J = 10.0, 2.0 Hz), 5.50 (ddd, 1H, J = 10.2, 3.2, 1.4 Hz), 4.92–4.88 (m, 1H), 4.36 (d, 1H, J = 8.8 Hz), 3.72–3.68 (m, 1H), 3.39 (dd, 1H, J = 8.8, 2.4 Hz), 3.37 (s, 3H), 3.29 (s, 3H), 3.01 (dd, 1H, J = 11.0, 5.0 Hz), 2.74 (br d, 1H, J = 2.4 Hz), 2.01–1.93 (m, 1H), 1.89 (br dd, 1H, J = 11.4, 5.8 Hz), 1.78–1.64 (m, 4H), 1.56–1.42 (m, 1H), 1.36–1.14 (m, 3H), 1.24 (s, 3H), 1.80–0.94 (m, 1H), 0.96 (s, 3H), 0.80 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.27, 130.36, 97.59, 89.89, 77.68, 72.51, 71.02, 55.76, 54.61, 46.21, 46.05, 45.48, 44.43, 42.36, 34.10, 29.59, 27.89, 26.57, 25.84, 21.48, 19.82, 12.40; high-resolution MS (EI) calcd for $C_{22}H_{34}O_4$ (M) m/e 362.2458, found 362.2449. An analytically pure sample was prepared *via* crystallization from diethyl ether–hexanes, mp 149–150 °C. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.15; H, 9.70.

(1β,11α,12α,13β,16β)-13,20-Epoxy-1,16-dimethoxypicrasane-11,12-diol (9). A solution of alkene **7** (680 mg, 1.88 mmol) in pyridine (18.8 mL, 0.1 M) under argon was treated with osmium tetraoxide (668 mg, 2.63 mmol) in one portion. After 22.5 h, sodium bisulfite (1.95 g, 18.76 mmol) was added as a solution in water–pyridine (11 mL, 2 mL). The mixture was stirred for 12 h, filtered through a plug of flash silica gel, and washed with ethyl acetate. Filtrate and washings were combined and concentrated *in vacuo* to a solid, which was chromatographed on flash silica gel. Elution with ethyl acetate–hexanes (1:3) followed by ethyl acetate provided 720 mg (97%) of cis diol **9** as a white foam: R_f 0.28 (diethyl ether–hexanes, 3:1); IR ($CHCl_3$) 3520 (w), 3400–3050 (m), 3000 (s), 2940 (s), 2840 (m), 1450 (m), 1380 (m), 1360 (w), 1340 (w), 1300 (w), 1200 (w), 1140 (m), 1120 (s), 1070 (s), 1040 (s), 1010 (w), 990 (w), 970 (m), 950 (w), 910 (w), 890 (w), 880 (w), 860 (w), 830 (w), 720 (s), 660 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 4.80 (d, 1H, J = 3.6 Hz), 4.06 (d, 1H, J = 8.2 Hz), 3.96 (ddd, 1H, J = 10.2, 4.8, 1.4 Hz), 3.68, (dd, 1H, J = 4.6, 1.4 Hz), 3.60 (br t, 1H, J = 3.0 Hz), 3.35 (s, 3H), 3.33 (s, 3H), 3.24 (dd, 1H, J = 8.4, 1.2 Hz), 3.20 (dd, 1H, J = 10.8, 4.8 Hz), 3.06 (s, 1H), 2.39 (td, 1H, J = 14.5, 4.3 Hz), 2.16–2.08 (m, 1H), 1.89 (d, 1H, J = 10.4 Hz), 1.82–1.68 (m, 4H), 1.60–1.30 (m, 3H), 1.36 (s, 3H), 1.24–1.18 (m, 1H), 1.06–0.80 (m, 1H), 1.03 (s, 3H), 0.84 (d, 3H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.71, 87.22, 81.03, 76.66, 72.27, 70.99, 66.07, 55.06, 54.45, 46.04, 44.75, 44.44, 44.37, 43.40, 33.45, 30.00, 28.19, 27.18, 25.27, 21.41, 20.46, 10.16; high-resolution MS (CI) calcd for $C_{22}H_{37}O_6$ (M + 1) m/e 397.2591, found 397.2572. An analytically pure sample was prepared *via* crystallization from ethyl acetate, mp 229–231 °C. Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.63; H, 9.23.

(1β,11α,12α,13β,16β)-12-(Acetyloxy)-13,20-epoxy-1,16-dimethoxypicrasan-11-ol (10). A solution of cis diol **9** (3.24 g, 8.17 mmol) in methylene chloride (102 mL, 0.08 M) under argon was treated sequentially with 4-(dimethylamino)pyridine (998 mg, 8.17 mmol), triethylamine (5.7 mL, 40.86 mmol), and acetic anhydride (3.5 mL, 36.77 mmol). After 13 h, the reaction was quenched by addition of saturated aqueous sodium bicarbonate. The water layer was extracted with methylene chloride, and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a yellow oil, which was chromatographed on flash silica gel. Elution with ethyl acetate–hexanes (1:1) followed by ethyl acetate yielded 1.61 g (45%) of monoacetate **10** as a white solid [R_f 0.43 (diethyl ether); IR ($CHCl_3$) 3600–3100 (m), 2980 (s), 2940 (s), 2900 (s), 2840 (m), 1740 (s), 1450 (m), 1380 (m), 1240–1200 (s), 1140 (m), 1120 (s), 1070 (s), 1040 (s), 1010 (m), 1000 (m), 980 (m), 950 (m), 910 (m), 890 (w), 870 (m), 860 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, 1H, J = 2.4 Hz), 5.18 (dd, 1H, J = 5.2, 1.6 Hz), 4.84 (d, 1H, J = 3.2 Hz), 4.15–4.10 (m, 1H), 4.12 (d, 1H, J = 8.4 Hz), 3.62 (br t, 1H, J = 2.7 Hz), 3.34 (s, 3H), 3.30 (s, 3H), 3.31–3.23 (m, 2H), 2.34 (td, 1H, J = 13.7, 3.7 Hz), 2.15–2.06 (m, 1H), 2.07 (s, 3H), 1.91 (d, 1H, J = 10.4 Hz), 1.84–1.66 (m, 4H), 1.56–1.18 (m, 4H), 1.20 (s, 3H), 1.10–0.94 (m, 1H), 1.01 (s, 3H), 0.84 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.15, 97.51, 86.23, 80.10, 76.18, 72.43, 70.93, 65.13, 54.91, 54.49, 46.40, 45.78, 44.59, 44.48, 43.62, 33.40, 30.10, 28.37, 26.90, 25.34, 21.19, 20.77, 20.46, 10.38; high-resolution MS (CI) calcd for $C_{24}H_{39}O_7$ (M + 1) m/e 439.2697, found 439.2705. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 217–219 °C. Anal. Calcd for $C_{24}H_{38}O_7$: C, 65.73; H, 8.73. Found: C, 65.73; H, 8.93] and 1.62 g (50%) of recovered cis diol **9**.

(1β,12α,13β,16β)-12-(Acetyloxy)-13,20-epoxy-1,16-dimethoxypicrasan-11-one (11). A solution of acetate **10** (1.77 g, 4.04 mmol) in methylene chloride (135 mL, 0.03 M) was treated with the Dess–Martin periodinane reagent (3.50 g, 8.25 mmol) in three portions over 45 min. The cloudy suspension was stirred under the same conditions for 2 h. The reaction was quenched with 41 mL of an aqueous solution of sodium thiosulfate and sodium bicarbonate (prepared with 25 g of sodium thiosulfate/100 mL of saturated sodium bicarbonate aqueous solution). After the mixture was stirred for 90 min, more saturated sodium bicarbonate solution was added and the organic layer was separated and washed again with water. The combined aqueous layers were extracted with methylene chloride. The combined organic extracts were dried over magnesium sulfate and filtered, and the filtrates were concentrated *in vacuo* to a yellow-white solid, which was purified by chromatography on flash silica gel. Elution with ethyl acetate–hexanes (1:1) afforded 1.76 g (100%) of keto acetate **11** as a white solid: R_f 0.72 (diethyl ether); IR ($CHCl_3$) 3000 (s), 2940 (s), 2900 (s), 2860 (m), 2820 (m), 1760 (s), 1520 (w), 1450 (m), 1390 (m), 1380 (m), 1340 (w), 1300 (w), 1270 (w), 1240 (s), 1130 (s), 1100 (m), 1090 (m), 1040 (s), 1000 (w), 980 (m), 960 (m), 950 (m), 930 (w), 920 (w), 850 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (br d, 1H, J = 3.6 Hz), 4.68 (d, 1H, J = 1.6 Hz), 4.00 (d, 1H, J = 8.4 Hz), 3.84–3.81 (m, 1H), 3.39 (dd, 1H, J = 8.4, 1.4 Hz), 3.37 (s, 3H), 3.13 (s, 3H), 2.92 (br s, 1H), 2.75 (dd, 1H, J = 11.6, 1.6 Hz), 2.45 (td, 1H, J = 13.7, 3.7 Hz), 2.10 (ddd, 1H, J = 14.4, 3.6, 1.6 Hz), 2.07 (s, 3H), 1.89 (ddd, 1H, J = 13.4, 3.8, 0.8 Hz), 1.85–1.68 (m, 3H), 1.58–1.44 (m, 2H), 1.38–1.28 (m, 1H), 1.35 (s, 3H), 1.29 (s, 3H), 1.24–1.15 (m, 1H), 1.06–0.93 (m, 1H), 0.81 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.55, 167.99, 97.16, 91.63, 83.54, 83.18, 73.81, 70.01, 57.03, 54.69, 49.40, 47.29, 46.75, 43.65, 41.58, 33.95, 28.61, 27.43, 27.06, 24.54, 20.74, 20.64, 19.94, 9.64; high-resolution MS (CI) calcd for $C_{24}H_{37}O_7$ (M + 1) m/e 437.2540, found 437.2527. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 232–233 °C. Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 65.76; H, 8.24.

(1β,11β,12α,13β,16β)-13,20-Epoxy-1,16-dimethoxypicrasane-11,12-diol (12). A solution of keto acetate **11** (1.72 g, 3.94 mmol) in tetrahydrofuran (65 mL, 0.06 M) was treated dropwise at 0 °C with a 1.0 M solution of lithium aluminum hydride in diethyl ether (16.3 mL, 16.27 mmol). After being stirred at 0 °C for 10 min, the mixture was warmed to room temperature and stirred for an additional 45 min. The reaction was quenched at 0 °C with 1.2 mL of water, followed by 1.2 mL of a 15% sodium hydroxide aqueous solution and an additional 1.2 mL of water. The cloudy white suspension was stirred for 1 h, filtered through a pad of silica gel, and washed well with ethyl acetate. The filtrate was concentrated *in vacuo*, and the resulting white solid was purified *via* chromatography on silica gel. After elution with diethyl ether followed by ethyl acetate, 1.45 g (93%) of trans diol **12** was obtained as a white

solid: R_f 0.20 (diethyl ether); IR ($CHCl_3$) 3620 (w), 3600–3400 (m), 3000 (s), 2940 (s), 2900 (s), 2840 (m), 1450 (m), 1380 (m), 1360 (m), 1350 (m), 1300 (m), 1200 (m), 1150 (m), 1120 (s), 1090 (s), 1050 (s), 1030 (s), 1000 (w), 980 (w), 960 (m), 940 (m), 920 (w), 900 (m), 870 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (br d, 1H, J = 3.2 Hz), 4.47 (d, 1H, J = 7.6 Hz), 3.96 (br t, 1H, J = 5.2 Hz), 3.89 (d, 1H, J = 5.2 Hz), 3.69–3.66 (m, 1H), 3.63 (br d, 1H, J = 4.4 Hz), 3.38 (s, 3H), 3.32 (s, 3H), 3.33–3.29 (m, 1H), 3.10 (dd, 1H, J = 11.0, 5.0 Hz), 2.17 (td, 1H, J = 13.9, 3.7 Hz), 2.07–1.99 (m, 1H), 1.92–1.84 (m, 2H), 1.80 (d, 1H, J = 4.4 Hz), 1.76–1.62 (m, 3H), 1.52–1.30 (m, 4H), 1.34 (s, 3H), 1.23 (s, 3H), 1.05–0.93 (m, 1H), 0.82 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.30, 88.35, 80.06, 79.66, 75.20, 72.56, 71.20, 55.62, 54.39, 46.18, 45.19, 43.91, 43.61, 42.14, 33.47, 29.23, 28.96, 26.89, 25.09, 21.84, 19.90, 12.23; high-resolution MS (CI) calcd for $C_{22}H_{37}O_6$ (M + 1) m/e 397.2591, found 397.2586. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 239–241 °C. Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.30; H, 9.10.

(1β,11β,12α,13β,16β)-13,20-Epoxy-11,12-bis(methoxymethoxy)-1,-16-dimethoxypicrasane (22). A solution of trans diol **12** (1.57 g, 3.96 mmol) in 1,2-dichloroethane (39.6 mL, 0.1 M) at 0 °C under argon was treated sequentially with *N,N*-diisopropylethylamine (31 mL, 178.18 mmol) and chloromethyl methyl ether (9 mL, 118.79 mmol). The reaction mixture was warmed to 48–50 °C and stirred for 40 h. The dark orange solution was transferred *via* cannula to a mixture of 60 mL of diethyl ether and 60 mL of saturated sodium bicarbonate aqueous solution with stirring at 0 °C. After dilution with water and diethyl ether, the organic layer was separated and washed with saturated sodium chloride aqueous solution. The combined aqueous layers were extracted with diethyl ether, and the combined ethereal extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a dark orange oil, which was purified *via* chromatography on silica gel (diethyl ether–hexanes, 2:1) followed by crystallization from diethyl ether followed by chromatography of the mother liquor. Repetition of this process afforded 1.62 g (84%) of pure diprotected diol **22** as a white foam: R_f 0.47 (diethyl ether–hexanes, 2:1); IR ($CHCl_3$) 3000 (s), 2940 (s), 2900 (s), 2840 (m), 1470 (m), 1450 (m), 1380 (m), 1360 (m), 1300 (w), 1200 (s), 1150 (s), 1120 (s), 1110 (s), 1090 (s), 1040 (s), 1000 (m), 990 (m), 980 (m), 950 (m), 920 (w), 900 (m), 880 (w), 810 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (br d, 1H, J = 3.2 Hz), 4.68 (AB q, 2H, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 17.95 Hz), 4.63 (AB q, 2H, J_{AB} = 6.4 Hz, $\Delta\nu_{AB}$ = 32.98 Hz), 4.53 (d, 1H, J = 6.8 Hz), 4.17 (dd, 1H, J = 4.6, 1.4 Hz), 3.68–3.64 (m, 2H), 3.39 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 3.31 (dd, 1H, J = 7.2, 1.6 Hz), 3.29 (s, 3H), 2.96 (dd, 1H, J = 11.2, 4.8 Hz), 2.15 (td, 1H, J = 14.0, 3.6 Hz), 1.98–1.90 (m, 1H), 1.90–1.81 (m, 2H), 1.74–1.60 (m, 3H), 1.47–1.28 (m, 4H), 1.29 (s, 3H), 1.18 (s, 3H), 1.05–0.93 (m, 1H), 0.82 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.51, 97.41, 97.34, 89.81, 84.27, 82.05, 79.34, 73.41, 71.86, 55.92, 55.40, 55.18, 54.39, 46.16, 45.25, 43.84, 43.73, 41.44, 33.89, 29.21, 28.28, 27.03, 25.42, 21.97, 20.23, 11.06; high-resolution MS (CI) calcd for $C_{26}H_{45}O_8$ (M + 1) m/e 485.3116, found 485.3106. An analytically pure sample was prepared *via* crystallization from diethyl ether–hexanes, mp 138–139 °C. Anal. Calcd for $C_{26}H_{44}O_8$: C, 64.44; H, 9.15. Found: C, 64.29; H, 9.44.

(1β,11β,12α,13β)-13,20-Epoxy-11,12-bis(methoxymethoxy)-1-methoxypicrasan-16-one (23). A solution of the protected lactol **22** (2.12 g, 4.37 mmol) in tetrahydrofuran (162 mL, 0.027 M) at 0 °C was treated dropwise over a period of 25 min with 5% hydrochloric acid (162 mL) *via* an addition funnel. After addition was completed, the mixture was warmed to room temperature and stirred for 50 min before quenching with solid sodium bicarbonate. After dilution with water and diethyl ether, the organic layer was separated and washed once more with a saturated sodium chloride aqueous solution. The combined aqueous layers were extracted with diethyl ether, and the combined ethereal extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a foam, which was purified *via* chromatography on silica gel. After elution with diethyl ether–hexanes (3:1), 784 mg (38%) of the corresponding lactol (white foam) and 1.35 g (62%) of recovered **22** were obtained. The mixture of lactols (784 mg, 1.67 mmol), determined to be roughly 1:1 (α:β) by ^{1}H NMR, was dissolved in methylene chloride (29 mL, 0.057 M) containing Celite (3.07 g), and treated with solid sodium acetate (307 mg, 3.75 mmol) and pyridinium chlorochromate (1.08 g, 5.00 mmol). The dark brown mixture was stirred for 7.5 h, subsequently filtered through a pad of silica gel, and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to a yellow solid, which was chromatographed on silica gel (diethyl ether–hexanes, 3:1), providing 700 mg (90%) of lactone **23** as a white solid: R_f 0.64 (diethyl ether); IR ($CHCl_3$) 3000 (s), 2940 (s), 2900 (s), 2840 (m), 1720 (s), 1470 (m), 1450 (m), 1380 (m), 1340 (w), 1300 (w), 1280 (w), 1270 (w), 1230 (m), 1210 (m), 1190 (m), 1150 (s), 1100 (s), 1050 (s), 1040 (s), 1020 (s), 980 (m), 960 (m), 920 (m), 860 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, 1H, J = 7.6 Hz), 4.67 (AB q, 2H, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 56.39 Hz), 4.68 (AB q, 2H, J_{AB} = 6.4 Hz, $\Delta\nu_{AB}$ = 10.15 Hz), 4.46 (br t, 1H, J = 2.8 Hz), 4.26 (dd, 1H, J = 4.6, 1.4 Hz), 3.75 (t, 1H, J = 1.6 Hz), 3.41 (dd, 1H, J = 7.4, 1.4 Hz), 3.39 (s, 3H), 3.37 (s, 3H), 3.29 (s, 3H), 3.24 (dd, 1H, J = 19.0, 14.2 Hz), 2.89 (dd, 1H, J = 11.4, 4.6 Hz), 2.57 (dd, 1H, J = 18.8, 5.6 Hz), 2.02–1.91 (m, 3H), 1.75–1.67 (m, 2H), 1.50–1.32 (m, 3H), 1.33 (s, 3H), 1.17 (s, 3H), 1.08–0.92 (m, 2H), 0.83 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.62, 98.57, 97.41, 89.38, 85.15, 84.40, 81.48, 79.21, 73.58, 56.19, 55.36, 55.34, 50.50, 45.28, 43.15, 42.61, 42.26, 33.47, 29.28, 28.40, 27.96, 25.15, 21.72, 19.98, 11.03; high-resolution MS (CI) calcd for $C_{25}H_{41}O_8$ (M + 1) m/e 469.2802, found 469.2800. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 177–179 °C. Anal. Calcd for $C_{25}H_{40}O_8$: C, 64.08; H, 8.60. Found: C, 64.00; H, 8.53.

Methyl (1α,3α,4β,4aα,4bβ,5β,8α,8aα,10aβ)-3,4-Bis(methoxymethoxy)-2β,10a-(epoxymethano)-5-methoxy-10-oxo-1,2,3,4,4a,4b,5,6,7,8,-8a,9,10,10a-tetradecahydro-2α,4b,8-trimethylphenanthrene-1-acetate (24). A solution of lactone **23** (1.30 g, 2.77 mmol) in methanol-tetrahydrofuran (23 mL, 23 mL) was treated with a 1 N sodium hydroxide aqueous solution (2.77 mL) and stirred at room temperature for 14 h. The solvent was removed *in vacuo*, and the obtained solid was dried under vacuum for 1 h. After the solid was redissolved in methylene chloride–tetrahydrofuran (35 mL, 35 mL), hydroxyiodinane oxide **27** (2.79 g, 6.94 mmol) was added as a solution in pyridine–methylene chloride–tetrahydrofuran (7.2 mL, 8.5 mL, 8.5 mL). The heterogeneous mixture was stirred in the dark under argon at room temperature. After 3 h, the reaction mixture was concentrated and chromatographed directly on silica gel. Elution with diethyl ether–hexanes (2:1), followed by straight ethyl acetate, followed by ethyl acetate–acetic acid (100:1) afforded the corresponding carboxylic acid as a white solid. After eliminating the acetic acid via azeotrope formation with hexanes, the solid was redissolved in ethyl acetate and treated with diazomethane. Removal of the solvent *in vacuo* furnished 1.34 g (97%) of desired keto ester **24**, which was taken directly into the next step: R_f 0.41 (diethyl ether–hexanes, 2:1); IR ($CHCl_3$) 3040 (w), 3000 (m), 2960 (s), 2900 (m), 2860 (m), 2840 (m), 1740 (s), 1700 (s), 1470 (m), 1440 (m), 1380 (m), 1260 (m), 1220 (s), 1150 (s), 1100 (s), 1040 (s), 990 (m), 920 (m), 850 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73–4.58 (m, 5H), 4.13 (dd, 1H, J = 4.0, 1.2 Hz), 3.70 (br s, 1H), 3.64 (dd, 1H, J = 6.8, 0.8 Hz), 3.59 (s, 3H), 3.38 (br s, 6H), 3.33 (s, 3H), 3.02 (dd, 1H, J = 11.2, 4.4 Hz), 2.86 (ddd, X of ABX, 1H, J_{AX} = 10.0 Hz, J_{BX} = 5.2 Hz, J = 1.2 Hz), 2.57 (AB of ABX, 2H, J_{AB} = 14.4 Hz, $\Delta\nu_{AB}$ = 27.88 Hz), 2.51 (dd, 1H, J = 18.4, 4.0 Hz), 2.12 (d, 1H, J = 4.0 Hz), 2.10–1.98 (m, 2H), 1.78–1.70 (m, 1H), 1.47–1.22 (m, 3H), 1.34 (s, 3H), 1.16 (s, 3H), 1.12–0.99 (m, 1H), 0.84 (d, 3H, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.59, 172.80, 98.57, 97.47, 87.70, 84.26, 82.33, 81.79, 75.62, 57.89, 56.15, 55.36 (2C), 52.11, 51.44, 48.33, 46.06, 42.26, 40.63, 33.00, 31.17, 30.83, 25.15, 21.81, 19.68, 10.15; high-resolution MS (CI) calcd for $C_{26}H_{43}O_9$ (M + 1) m/e 499.2908, found 499.2899. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 138–139 °C. Anal. Calcd for $C_{26}H_{42}O_9$: C, 62.63; H, 8.49. Found: C, 62.33; H, 8.29.

Methyl (1α,3α,4β,4aα,4bβ,5β,8α,8aα,10aβ)-3,4-Dihydroxy-2β,10a-(epoxymethano)-5-methoxy-10-oxo-1,2,3,4,4a,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-2α,4b,8-trimethylphenanthrene-1-acetate (25). A solution of aluminum trichloride (5.09 g, 38.51 mmol) in acetonitrile (128 mL) cooled to 0 °C was treated with solid sodium iodide (5.73 g, 38.51 mmol) in four portions. The faint yellow solution was stirred at 0 °C in the dark for several minutes before turning cloudy. At this point, protected diol **24** (1.20 g, 2.41 mmol) was added as a solution in methylene chloride (64 mL, 0.04 M) *via* cannula. The orange mixture was stirred at room temperature in the dark for 45 min before quenching at 0 °C with 100 mL of water. After the mixture was stirred at room temperature for 15 min, diethyl ether and brine were added. The organic layer was separated and washed again with brine. The combined aqueous layers were extracted with diethyl ether; and the combined ethereal extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to an orange solid, which was purified *via* chromatography on silica gel. Elution with diethyl ether, followed by ethyl acetate, afforded 892 mg (90%) of pure diol **25** as a white crystalline solid: R_f 0.25 (diethyl ether); IR ($CHCl_3$) 3640 (w), 3600–3300 (m), 3010 (m), 2990 (m), 2960 (m), 2940 (m), 2910 (m), 2860 (w), 2840 (w), 1730 (s), 1700 (s), 1450 (m), 1410 (w), 1380 (m), 1360 (w), 1300–1150 (m), 1130 (m), 1080 (s), 1040 (m), 1020 (s), 980 (m), 920 (w), 890 (w), 850 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, 1H, J = 6.8 Hz), 4.11 (d, 1H, J = 4.4 Hz), 3.96 (br t, 1H, J = 4.4

Hz), 3.76 (dd, 1H, J = 7.0, 1.0 Hz), 3.66 (br d, 1H, J = 4.4 Hz), 3.60 (s, 3H), 3.44 (s, 3H), 3.24 (dd, 1H, J = 11.2, 4.4 Hz), 2.78 (ddd, X of ABX, 1H, J_{AX} = 10.2 Hz, J_{BX} = 5.1 Hz, J = 1.3 Hz), 2.62 (AB of ABX, 2H, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 44.15 Hz), 2.57 (dd, 1H, J = 19.8, 6.2 Hz), 2.18 (br dd, 1H, J = 4.4, 0.4 Hz), 2.18–2.10 (m, 1H), 2.02 (dd, 1H, J = 19.6, 12.0 Hz), 1.86 (d, 1H, J = 4.8 Hz), 1.80–1.72 (m, 1H), 1.60–1.20 (m, 3H), 1.39 (s, 3H), 1.13–1.01 (m, 1H), 1.08 (s, 3H), 0.84 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.01, 172.85, 85.96, 82.11, 79.56, 75.36, 75.03, 57.85, 55.61, 52.21, 51.60, 49.19, 45.82, 41.64, 41.27, 32.55, 31.61, 30.73, 24.83, 21.59, 19.14, 10.99; high-resolution MS (CI) calcd for $C_{22}H_{35}O_7$ (M + 1) m/e 411.2384, found 411.2395. An analytically pure sample was prepared *via* crystallization from diethyl ether–hexanes–ethyl acetate, mp 214–217 °C. Anal. Calcd for $C_{22}H_{34}O_7$: C, 64.37; H, 8.35. Found: C, 64.24; H, 8.51.

(1β,2β,6β,6aβ,8aα,9α,12β,12aβ,12bα,15α)-1-Hydroxy-12-methoxy-1,8a,9,10,11,12,12a,12b-octahydro-9,12a,15-trimethyl-2*H*-6a,2,6-(methanoxymetheno)naphth[1,2-*d*]oxocin-4,7(5*H*,8*H*)-dione (26). A suspension of hydroxy ester **25** (852 mg, 2.08 mmol) and *p*-toluenesulfonic acid monohydrate (39 mg, 0.21 mmol) in benzene (52 mL, 0.04 M) was placed in an oil bath equilibrated at 80 °C. The solution turned homogeneous after several minutes. After 5 h, diethyl ether and a saturated sodium bicarbonate aqueous solution were added. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with diethyl ether, and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a white-yellow solid. Purification *via* chromatography on silica gel eluting with diethyl ether–hexanes (3:1) furnished 786 mg (100%) of pure δ-lactone **26** as a white crystalline solid: R_f 0.54 (diethyl ether); IR ($CHCl_3$) 3600–3300 (m), 2960 (m), 2940 (m), 2880 (m), 1730 (s), 1700 (s), 1460 (w), 1410 (w), 1380 (w), 1360 (m), 1240 (m), 1190 (m), 1170 (m), 1080 (s), 1050 (s), 1030 (s), 990 (m), 980 (m), 950 (m), 900 (w), 860 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (d, 1H, J = 7.2 Hz), 4.24 (t, 1H, J = 2.0 Hz), 4.19–4.14 (m, 1H), 4.05 (d, 1H, J = 5.2 Hz), 3.74 (dd, 1H, J = 7.2, 1.2 Hz), 3.42 (s, 3H), 3.12 (dd, 1H, J = 11.2, 4.4 Hz), 2.92 (dd, 1H, J = 7.8, 2.2 Hz), 2.76 (dd, 1H, J = 19.8, 7.8 Hz), 2.63 (dd, 1H, J = 19.2, 5.6 Hz), 2.44 (d, 1H, J = 20.0 Hz), 2.16 (dd, 1H, J = 19.2, 12.8 Hz), 2.17–2.08 (m, 1H), 1.82–1.74 (m, 1H), 1.65 (br d, 1H, J = 4.0 Hz), 1.54–1.32 (m, 2H), 1.49 (s, 3H), 1.26–1.16 (m, 1H), 1.20 (s, 3H), 1.09–0.96 (m, 1H), 0.82 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.92, 168.47, 85.90, 83.69, 75.97, 74.44, 71.92, 59.42, 55.60, 50.54, 47.16, 46.51, 41.76, 40.78, 32.46, 31.17, 28.41, 24.56, 21.12, 19.05, 11.11; high-resolution MS(CI) calcd for $C_{21}H_{31}O_6$ (M + 1) m/e 379.2121, found 379.2135. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 205–207 °C. Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.41; H, 7.95.

(1β,2β,6β,6aβ,7β,8aα,9α,12β,12aβ,12bα,15α)-1,7,8,8a,9,10,11,12,-12a,12b-Decahydro-1,7-dihydroxy-12-methoxy-9,12a,15-trimethyl-2*H*-6a,2,6-(methanoxymetheno)naphth[1,2-*d*]oxocin-4(5*H*)-one (28). Keto lactone **26** (745 mg, 1.97 mmol) was dissolved in a 1:1 mixture of methanol and tetrahydrofuran (39 mL). After the solution was cooled to −78 °C, sodium borohydride (223 mg, 5.91 mmol) was added in two portions. The mixture was warmed to 0 °C and stirred for 10 min, before quenching with acetone. Diethyl ether and a saturated sodium bicarbonate aqueous solution were added, and the organic layer was separated and washed with brine. After extraction of the combined aqueous layers with diethyl ether, the ethereal extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting yellow oil was purified *via* chromatography on silica gel, eluting with diethyl ether followed by ethyl acetate. Concentration provided 713 mg (95%) of hydroxy lactone **28** as a white solid: R_f 0.23 (diethyl ether); IR ($CHCl_3$) 3620 (w), 3600–3300 (m), 3020 (m), 2980 (m), 2960 (m), 2890 (m), 2860 (m), 1720 (s), 1460 (m), 1420 (m), 1390 (m), 1370 (s), 1240 (m), 1200 (m), 1170 (m), 1100 (s), 1040 (s), 1000 (m), 980 (m), 960 (m), 880 (m), 840 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (d, 1H, J = 8.0 Hz), 4.20–4.14 (m, 2H), 4.03 (dd, 1H, J = 8.0, 1.6 Hz), 3.76 (d, 1H, J = 6.0 Hz), 3.50–3.42 (m, 1H), 3.35 (s, 3H), 2.94 (dd, 1H, J = 11.2, 4.8 Hz), 2.74 (dd, 1H, J = 20.0, 8.4 Hz), 2.57 (d, 1H, J = 20.0 Hz), 2.42 (dd, 1H, J = 8.2, 2.2 Hz), 2.06–1.99 (m, 1H), 1.94 (ddd, 1H, J = 12.7, 5.5, 2.3 Hz), 1.78–1.68 (m, 2H), 1.46 (s, 3H), 1.50–1.28 (m, 3H), 1.24 (s, 3H), 1.04 (br, d, 1H, J = 3.6 Hz), 1.00–0.84 (m, 1H), 0.84 (d, 3H, J = 6.4 Hz), 0.75–0.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.02, 87.80, 84.47, 74.38, 72.14, 69.42, 67.85, 55.62, 51.09, 50.75, 47.01, 43.14, (2C), 32.98, 31.74, 29.26, 27.12, 24.73, 21.66, 19.98, 12.05; high-resolution MS (CI) calcd for $C_{21}H_{33}O_6$ (M + 1) m/e 381.2278, found 381.2271. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 257–259 °C. Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.39; H, 8.51.

(1β,2β,5β,5aβ,6β,7aα,8aα,11β,11aβ,11bα,14α)-1,6-Dihydroxy-1,6,7,-7a,8,9,10,11,11a,11b-decahydro-11-methoxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4(5*H*)-one (29). A solution of δ-lactone **28** (962 mg, 2.53 mmol) in methanol (84 mL, 0.03 M) was treated with copper(II) acetate monohydrate (505 mg, 2.53 mmol), pyridine (49 mL, 605.84 mmol), and *N*,*N*-diisopropylethylamine (16.3 mL, 93.57 mmol). Oxygen was bubbled through the green solution for 48 h, with stirring at room temperature. The mixture was diluted with diethyl ether–ethyl acetate and washed with 3% phosphoric acid. The combined aqueous layers were subsequently extracted with diethyl ether–ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a yellowish foam. Chromatography on silica gel, eluting with ethyl acetate–hexanes (2:1) followed by ethyl acetate, provided 410 mg (44%) of γ-lactone **29** as a white solid [R_f 0.55 (ethyl acetate–hexanes 4:1) IR ($CHCl_3$) 3620 (w), 3600–3300 (m), 3010 (m), 2960 (s), 2940 (s), 2880 (m), 2860 (m), 2840 (m), 1770 (s), 1460 (m), 1390 (w), 1350 (m), 1320 (m), 1260 (m), 1180 (m), 1170 (m), 1140 (m), 1090 (s), 1070 (s), 1000 (s), 990 (w), 970 (w), 920 (w), 900 (m), 860 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (d, 1H, J = 8.4 Hz), 4.28–4.23 (m, 2H), 4.19 (dd, 1H, J = 8.8, 1.6 Hz), 3.79 (d, 1H, J = 5.6 Hz), 3.73 (dt, 1H, J = 12.0, 5.0 Hz), 3.35 (s, 3H), 3.05 (s, 1H), 2.98 (dd, 1H, J = 11.2, 4.8 Hz), 2.30–2.20 (m, 1H), 2.08–2.00 (m, 1H), 1.90 (ddd, 1H, J = 12.8, 5.2, 2.4 Hz), 1.75–1.67 (m, 1H), 1.53–1.32 (m, 2H), 1.50 (s, 3H), 1.34 (dd, 1H, J = 4.4, 1.6 Hz), 1.28 (q, 1H, J = 12.5 Hz), 1.27 (s, 3H), 1.00–0.86 (m, 1H), 0.81 (d, 3H, J = 6.4 Hz), 0.84–0.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.09, 87.86, 85.91, 85.00, 70.47, 70.07, 69.60, 55.60, 55.57, 54.68, 51.08, 50.37, 43.20, 33.16, 31.64, 28.97, 24.67, 21.00, 19.84, 12.10; high-resolution MS (CI) calcd for $C_{20}H_{31}O_6$ (M + 1) m/e 367.2121, found 367.2121. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 242–244 °C. Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.29; H, 8.43] and 580 mg (54%) of hemiketal **30**, also as a white solid [R_f 0.19 (ethyl acetate–hexanes, 4:1); FTIR ($CHCl_3$) 3619 (w), 3488 (m), 3437 (m), 3009 (m), 2949 (s), 2847 (w), 1751 (s), 1454 (m), 1404 (w), 1379 (w), 1339 (w), 1260 (s), 1244 (s), 1221 (m), 1194 (m), 1161 (s), 1086 (s), 1055 (s), 1018 (s), 891 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (d, 1H, J = 8.4 Hz), 4.22–4.17 (m, 1H), 4.16–4.09 (m, 1H), 4.08 (dd, 1H, J = 8.4, 1.6 Hz), 3.93 (s, 1H), 3.85–3.82 (m, 2H), 3.82 (s, 3H), 3.35 (s, 3H), 3.15 (s, 1H), 3.02 (dd, 1H, J = 11.2, 5.2 Hz); 2.62 (br dd, 1H, J = 5.2, 0.8 Hz), 2.07–1.99 (m, 1H), 1.90 (d, 1H, J = 5.6 Hz), 1.87 (ddd, 1H, J = 12.4, 4.8, 2.4 Hz), 1.74–1.67 (m, 1H), 1.56–1.43 (m, 1H), 1.41–1.27 (m, 1H), 1.35 (s, 3H), 1.29 (s, 3H), 1.20 (q, 1H, J = 12.4 Hz), 1.01–0.89 (m, 1H), 0.89–0.80 (m, 1H), 0.81 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.84, 101.54, 89.04, 86.58, 85.84, 72.76, 69.88, 69.21, 55.64, 54.20, 52.82, 51.28, 51.08, 47.60, 43.34, 33.45, 31.93, 28.94, 24.89, 22.51, 19.99, 12.40; high-resolution MS (CI) calcd for $C_{22}H_{35}O_8$ (M + 1) m/e 427.2333, found 427.2313. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 183–185 °C. Anal. Calcd for $C_{22}H_{34}O_8$: C, 61.95; H, 8.04. Found: C, 61.96; H, 8.23].

(1β,2β,6β,6aβ,7β,8aα,9α,12β,12aβ,12bα,15α)-1,7,8,8a,9,10,11,12,-12a,12b-Decahydro-1,7-dihydroxy-12-methoxy-9,12a,15-trimethyl-2*H*-6a,2,6-(methanoxymetheno)naphth[1,2-*d*]oxocin-4,5-dione (32). A suspension of hemiketal **30** (20 mg, 0.047 mmol) in benzene (1.2 mL, 0.04 M) was treated with *p*-toluenesulfonic acid monohydrate (0.9 mg, 0.005 mmol) and was stirred at reflux. After 20 h, the mixture was diluted with diethyl ether and washed with saturated aqueous sodium bicarbonate and brine. The combined aqueous layers were extracted with diethyl ether, and the combined ethereal extracts were concentrated *in vacuo* to a crude oil which was purified *via* chromatography on silica gel. Elution with diethyl ether provided 6 mg (33%) of α-keto lactone **32** as a white solid: R_f 0.81 (ethyl acetate–hexanes, 4:1); FTIR (KBr) 3518 (s), 2972 (m), 2928 (m), 2835 (m), 1759 (s), 1730 (s), 1464 (m), 1381 (m), 1346 (m), 1275 (w), 1240 (m), 1217 (m), 1145 (w), 1111 (m), 1088 (s), 1022 (s), 986 (w), 960 (w), 878 (w), 829 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55–4.54 (m, 1H), 4.53 (d, 1H, J = 8.4 Hz), 4.32–4.27 (m, 1H), 4.15 (dd, 1H, J = 8.0, 1.6 Hz), 3.95 (d, 1H, J = 5.6 Hz), 3.79 (dd, 1H, J = 12.0, 5.6 Hz), 3.36 (s, 3H), 3.24 (d, 1H, J = 2.8 Hz), 2.87 (dd, 1H, J = 10.8, 4.8 Hz), 2.06–1.98 (m, 1H), 1.92 (ddd, 1H, J = 13.2, 5.6, 2.4 Hz), 1.90–1.83 (m, 1H), 1.75–1.67 (m, 1H), 1.54 (s, 3H), 1.46–1.30 (m, 1H), 1.33 (q, 1H, J = 12.4 Hz), 1.30–1.15 (m, 1H), 1.24 (s, 3H), 1.10 (dd, 1H, J = 4.8, 1.6 Hz), 0.96–0.78 (m, 1H), 0.82 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.51, 154.10, 87.43, 85.86, 71.58, 68.46, 68.10, 59.44, 57.46, 55.65, 50.66, 49.56, 43.70, 32.79, 31.24, 29.70, 29.21, 24.61, 22.11, 19.86, 12.16; high-resolution MS (CI) calcd for $C_{21}H_{31}O_7$ (M + 1) m/e 395.2070, found 395.2083.

(1β,2β,5β,5aβ,6β,7aα,8α,11β,11aβ,11bα,14α)-6-(Acetyloxy)-1,6,7,-7a,8,9,10,11,11a,11b-decahydro-1-hydroxy-11-methoxy-8,11a,14-trimethyl-2*H*,5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4(5*H*)-one (33). A solution of diol **29** (338 mg, 0.92 mmol) in methylene chloride (11.5 mL, 0.08 M), cooled to 0 °C under argon, was treated sequentially with *N,N*-diisopropylethylamine (321 μL, 1.84 mmol), acetic anhydride (130.5 μL, 1.38 mmol), and 4-(dimethylamino)pyridine (22.5 mg, 0.18 mmol). After being stirred at 0 °C for 1.5 h, the reaction mixture was washed with 10% hydrochloric acid (3×). The combined aqueous layers were extracted with diethyl ether–ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a white solid, which was purified *via* chromatography on silica gel. Elution with ethyl acetate–hexanes (3:2), followed by ethyl acetate, afforded 370 mg (98%) of pure monoacetate **33** as a white solid: R_f 0.51 (ethyl acetate–hexanes, 3:2): IR ($CHCl_3$) 3600–3400 (m), 2940 (m), 2860 (m), 1780 (s), 1740 (s), 1450 (m), 1380 (m), 1350 (m), 1310 (m), 1230 (s), 1170 (m), 1160 (m), 1130 (m), 1090 (m), 1050 (m), 1000 (s), 950 (w), 920 (w), 900 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (dd, 1H, J = 12.0, 5.2 Hz), 4.63 (d, 1H, J = 8.8 Hz), 4.80–4.75 (m, 1H), 4.30–4.25 (m, 2H), 4.15 (dd, 1H, J = 8.6, 1.8 Hz), 3.36 (s, 3H), 3.01 (dd, 1H, J = 10.8, 4.8 Hz), 2.62 (s, 1H), 2.09 (s, 3H), 2.11–2.02 (m, 2H), 1.75–1.68 (m, 1H), 1.52–1.28 (m, 3H), 1.49 (s, 3H), 1.29 (s, 3H), 1.20 (q, 1H, J = 12.5 Hz), 1.02–0.82 (m, 2H), 0.80 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.64, 169.81, 87.67, 85.80, 84.76, 71.47, 70.79, 70.35, 55.63, 55.59, 52.99, 50.74, 50.47, 43.11, 33.06, 29.07, 27.59, 24.66, 21.10, 20.96, 19.66, 12.13; high-resolution MS (EI) calcd for $C_{22}H_{32}O_7$ (M) m/e 408.2149, found 408.2155. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 235–237 °C. Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.69; H, 7.90. Found: C, 64.48; H, 7.94.

(1β,2β,5β,5aβ,6β,7aα,8α,11β,11aβ,11bα,14α)-6-(Acetyloxy)-1,6,7,-7a,8,9,10,11,11a,11b-decahydro-1,11-dihydroxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4(5*H*)-one (34). A suspension of sodium iodide (762 mg, 5.08 mmol) in acetonitrile (4.25 mL), cooled to 0 °C under argon in the dark, was treated dropwise with trichloromethylsilane (598 μL, 5.08 mmol). Methyl ether **33** (346 mg, 0.85 mmol) was added dropwise as a solution in methylene chloride (4.25 mL, 0.2 M) *via* cannulation. The yellow mixture was stirred in the dark at room temperature. After 6.5 h, the reaction was quenched at 0 °C with saturated aqueous sodium bicarbonate and diluted with diethyl ether–ethyl acetate. The organic layer was separated and washed with saturated aqueous sodium thiosulfate and brine. The combined aqueous layers were extracted with diethyl ether–ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a solid, which was purified *via* chromatography on silica gel. Elution with diethyl ether, followed by ethyl acetate, furnished 302 mg (90%) of diol **34** as a white solid: R_f 0.34 (diethyl ether); IR ($CHCl_3$) 3620 (w), 3600–3300 (m), 2980 (m), 2940 (m), 2880 (m), 1780 (s), 1740 (s), 1450 (m), 1380 (m), 1310 (m), 1220 (s), 1150 (m), 1130 (m), 1090 (m), 1050 (s), 1020 (s), 950 (w), 900 (m), 880 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, 1H, J = 11.6, 5.2 Hz), 4.63 (dd, 1H, J = 5.2, 3.6 Hz), 4.61 (d, 1H, J = 8.8 Hz), 4.26 (dd, 1H, J = 3.6, 1.2 Hz), 4.15 (dd, 1H, J = 8.8, 1.6 Hz), 3.52 (dd, 1H, J = 10.6, 5.4 Hz), 2.66 (d, 1H, J = 1.2 Hz), 2.14–2.06 (m, 1H), 2.10 (s, 3H), 1.84–1.76 (m, 1H), 1.72–1.58 (m, 2H), 1.51 (s, 3H), 1.48 (dd, 1H, J = 4.8, 1.6 Hz), 1.40–1.26 (m, 1H), 1.33 (s, 3H), 1.22 (q, 1H, J = 12.4 Hz), 1.10–0.96 (m, 1H), 0.94–0.85 (m, 1H), 0.80 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.13, 169.73, 86.54, 83.78, 78.06, 71.31, 71.25, 70.59, 55.55, 52.94, 50.49, 50.07, 43.33, 33.37, 31.04, 28.98, 27.78, 21.09, 21.00, 19.65, 11.37; high-resolution MS (EI) calcd for $C_{21}H_{31}O_7$ (M + 1) m/e 395.2070, found 395.2051. An analytically pure sample was prepared *via* crystallization from diethyl ether–ethyl acetate, mp 269–270 °C. Anal. Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: C, 63.69; H, 7.64.

(1β,2β,5β,5aβ,6β,7aα,8α,11aβ,11bα,14α)-6-(Acetyloxy)-1-hydroxy-1,6,7,7a,8,9,11a,11b-octahydro-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,11(5*H*,10*H*)-dione (35). Dimethyl sulfoxide (516 μL, 7.28 mmol) was added dropwise to a solution of oxalyl chloride (317 μL, 3.64 mmol) in methylene chloride (10.4 mL), cooled to −78 °C under argon. After 45 min, a solution of diol **34** (287 mg, 0.73 mmol) in methylene chloride (10.4 mL) was added dropwise *via* cannula. The reaction mixture was stirred at −78 °C. After 1.5 h, triethylamine (1.0 mL, 7.28 mmol) was added dropwise and the reaction mixture was warmed to room temperature. After 1.5 h, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether–ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a yellow solid. Chromatography on silica gel, eluting with diethyl ether–hexanes (3:1) followed by diethyl ether, provided 235 mg (82%) of ketone **35** as a white solid: R_f 0.43 (diethyl ether); IR ($CHCl_3$) 3500 (m), 2980 (m), 2960 (m), 1780 (s), 1740 (s), 1710 (s), 1430 (m), 1380 (m), 1360 (m), 1310 (m), 1230 (s), 1170 (m), 1150 (m), 1120 (m), 1110 (m), 1050 (s), 1010 (s), 990 (m), 940 (m), 900 (m), 860 (w), 830 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (dt, 1H, J = 11.6, 4.0 Hz), 4.84–4.78 (m, 1H), 4.53 (d, 1H, J = 8.8 Hz), 4.24–4.19 (m, 2H), 3.67 (d, 1H, J = 12.0 Hz), 2.95 (td, 1H, J = 13.7, 6.9 Hz), 2.72 (br s, 1H), 2.20 (ddd, 1H, J = 13.4, 5.4, 2.0 Hz), 2.14–2.00 (m, 3H), 2.11 (s, 3H), 2.00–1.89 (m, 1H), 1.76 (s, 3H), 1.51 (s, 3H), 1.47–1.32 (m, 1H), 1.32–1.22 (m, 2H), 0.89 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.59, 171.51, 169.54, 88.09, 82.45, 71.71, 71.02, 69.91, 55.19, 52.96, 52.34, 51.36, 42.49, 37.08, 36.35, 29.04, 28.02, 21.16, 21.08, 19.04., 15.39; high-resolution MS (CI) calcd for $C_{21}H_{29}O_7$ (M + 1) m/e 393.1914, found 393.1898. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 278–279 °C. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.04; H, 6.97.

(1β,2β,5β,5aβ,6β,7aα,8α,11aβ,11bα,14α)-1,6-Bis(methoxymethoxy)-1,6,7,7a,8,9,11a,11b-octahydro-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,11(5*H*,10*H*)-dione (36). A solution of acetate **35** (58 mg, 0.148 mmol) in methanol–tetrahydrofuran (2.2 mL, 2.2 mL) was treated at 0 °C with a 2.0 N sodium hydroxide solution (1.1 mL). After being stirred for 3 h at room temperature, the reaction mixture was quenched with 10% hydrochloric acid. The aqueous layers were extracted with diethyl ether. The combined organic layers were concentrated to a few milliliters, cooled to 0 °C, and treated with excess of an ethereal solution of diazomethane. Removal of the solvent *in vacuo* and chromatography of the crude product on silica gel, eluting with diethyl ether–hexanes (1:1), afforded 49 mg (95%) of the corresponding diol as a pure white solid: R_f 0.43 (diethyl ether); IR ($CHCl_3$) 3600–3450 (m), 2980 (m), 2960 (m), 1780 (s), 1710 (s), 1450 (m), 1380 (m), 1360 (m), 1320 (m), 1280 (m), 1250 (m), 1160 (s), 1120 (s), 1060 (s), 1010 (s), 980 (m), 900 (m), 860 (w), 840 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03–4.96 (m, 1H), 4.22 (d, 1H, J = 9.2 Hz), 4.29 (dd, 1H, J = 8.8, 1.6 Hz), 4.21 (dd, 1H, J = 3.6, 1.2 Hz), 3.80–3.74 (m, 1H), 3.72 (dd, 1H, J = 12.0, 4.4 Hz), 3.12 (d, 1H, J = 1.2 Hz), 2.96 (td, 1H, J = 13.7, 7.1 Hz), 2.18 (ddd, 1H, J = 13.2, 5.4, 2.2 Hz), 2.09–1.88 (m, 5H), 1.75 (s, 3H), 1.51 (s, 3H), 1.47–1.30 (m, 1H), 1.38 (q, 1H, J = 12.4 Hz), 1.26–1.15 (m, 1H), 0.90 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.19, 172.99, 88.11, 82.71, 71.05, 69.99, 69.03, 55.19, 54.03, 53.39, 51.50, 42.26, 37.14, 36.50, 32.02, 28.96, 21.18, 19.18, 15.42; high-resolution MS (EI) calcd for $C_{19}H_{26}O_6$ (M) m/e 350.1730, found 350.1713. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 239–240 °C. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.93; H, 7.41.

The above diol (171 mg, 0.49 mmol) was dissolved in 1,2-dichloroethane (4.9 mL, 0.1 M) and was treated at 0 °C with *N,N*-diisopropylethylamine (5 mL, 29.27 mmol), followed by chloromethyl methyl ether (1.5 mL, 19.51 mmol). The solution was warmed to 48 °C. After 13 h, the reaction was quenched at 0 °C with saturated aqueous sodium bicarbonate and diluted with diethyl ether. The organic layer was separated and washed with brine, and the combined aqueous layers were extracted with diethyl ether–ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to an orange oil. Purification *via* chromatography on silica gel (eluting with diethyl ether–hexanes, 3:1) provided a yellow solid, which, after recrystallization from diethyl ether–hexanes, afforded 190 mg (89%) of bisprotected diol **36** as a white crystalline solid: R_f 0.78 (diethyl ether); IR ($CHCl_3$) 2940 (m), 2900 (m), 1780 (s), 1710 (s), 1450 (m), 1380 (m), 1320 (m), 1280 (w), 1250 (w), 1150 (s), 1100 (s), 1030 (s), 990 (s), 970 (m), 920 (m), 900 (m), 860 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (dd, 1H, J = 5.2, 3.6 Hz), 4.74 (AB q, 2H, J_{AB} = 6.6 Hz, $\Delta\nu_{AB}$ = 33.56 Hz), 4.59 (s, 2H), 4.48 (d, 1H, J = 8.4 Hz), 4.43 (dd, 1H, J = 3.6, 1.2 Hz), 4.17 (dd, 1H, J = 8.2, 1.8 Hz), 3.50 (dd, 1H, J = 11.4, 4.6 Hz), 3.41 (s, 3H), 3.36 (s, 3H), 2.92 (d, 1H, J = 1.6 Hz), 2.89 (td, 1H, J = 13.8, 6.8 Hz), 2.17 (ddd, 1H, J = 13.6, 5.2, 2.4 Hz), 2.10 (ddd, 1H, J = 13.0, 5.0, 2.4 Hz), 2.08 (dd, 1H, J = 5.0, 1.8 Hz), 2.06–1.98 (m, 1H), 1.97–1.84 (m, 1H), 1.62 (s, 3H), 1.46 (s, 3H), 1.43–1.29 (m, 1H), 1.26 (q, 1H, J = 12.3 Hz), 1.21–1.12 (m, 1H), 0.90 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214. 55, 173.42, 98.11, 96.50, 85.89, 83.81, 78.12, 75.76, 70.60, 55.82, 55.40, 55.34, 53.52, 53.04, 51.38, 43.04, 37.31, 36.16, 29.12, 28.76, 21.28, 19.23, 15.64; high-resolution MS (EI) calcd for $C_{23}H_{34}O_8$ (M) m/e 438.2254, found 438.2270. An analytically pure sample was prepared *via* crystallization from diethyl ether–hexanes, mp 122–124 °C. Anal. Calcd for $C_{23}H_{34}O_8$: C, 63.00; H, 7.81. Found: C, 62.93; H, 7.88.

(1β,2β,5β,5aβ,6β,7aα,8α,10α,11β,11aβ,11bα,14α)-1,6,7,7a,8,9,10,-11,11a,11b-Decahydro-1,6-bis(methoxymethoxy)-10-hydroxy-11-meth-

oxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]-oxepin-4(5*H*)-one (37). All reagents in this experiment with the exception of *n*-butyllithium were deoxygenated prior to distillation, utilizing the freeze–pump–thaw method. A solution of ketone **36** (136 mg, 0.31 mmol) in tetrahydrofuran (4.4 mL, 0.07 M) containing hexamethylphosphoramide (740 μL, 4.34 mmol) cooled to –78 °C was treated dropwise with lithium diisopropylamide (1.5 mL of a freshly prepared 1.0 M solution in tetrahydrofuran). After 1 h, dimethyl sulfate (176 μL, 1.86 mmol) was added, and the solution was stirred at –78 °C for 2 h and at 0 °C for 10 min. Direct chromatography of the mixture on silica gel, eluting with diethyl ether–hexanes (2:1), provided 188 mg (>100%) of the crude methyl enol ether, which was dissolved in tetrahydrofuran (5.0 mL, 0.06 M) and cooled to 0 °C. The above solution was treated with borane–tetrahydrofuran (930 μL, 0.93 mmol) and stirred for 1 h 25 min before oxidative workup with 3 N sodium hydroxide (1.4 mL) and 30% hydrogen peroxide (1.4 mL). After being stirred at room temperature for 1 h, the mixture was diluted with diethyl ether and brine, and the organic layer was separated. The aqueous layer was diluted with aqueous potassium phosphate monobasic sodium hydroxide buffer solution (pH = 7) and extracted (10×) with diethyl ether–ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a yellow oil, which was chromatographed on silica gel (eluting with ethyl acetate–hexanes, 1:2, then ethyl acetate) providing 104 mg (71% over two steps) of alcohol **37** as a white foam: R_f 0.52 (diethyl ether): IR ($CHCl_3$) 3600 (w), 3580–3400 (w), 2980 (s), 2940 (s), 2860 (m), 1770 (s), 1450 (m), 1380 (m), 1360 (m), 1310 (m), 1270 (m), 1250–1200 (m), 1140 (s), 1100 (s), 1030 (s), 1000 (s), 970 (s), 910 (m), 890 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (AB q, 2H, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 38.77 Hz), 4.71 (AB q, 2H, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 33.88 Hz), 4.54 (d, 1H, J = 8.0 Hz), 4.46 (dd, 1H, J = 4.0, 1.2 Hz), 4.25 (dd, 1H, J = 4.2, 4.2 Hz), 4.19 (dd, 1H, J = 8.0, 1.6 Hz), 3.88 (ddd, 1H, J = 12.0, 8.8, 5.2 Hz), 3.62 (s, 3H), 3.48 (dd, 1H, J = 11.8, 4.6 Hz), 3.42 (s, 3H), 3.41 (s, 3H), 2.92 (d, 1H, J = 1.6 Hz), 2.66 (d, 1H, J = 8.4 Hz), 2.06–1.99 (m, 1H), 1.93 (ddd, 1H, J = 12.6, 5.2, 4.0 Hz), 1.65–1.50 (m, 1H), 1.54 (dd, 1H, J = 4.4, 1.6 Hz), 1.47 (s 3H), 1.21 (s, 3H), 1.11–0.95 (m, 2H), 0.88 (d, 3H, J = 6.4 Hz), 0.83–0.70 (m 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.97, 98.13, 96.31, 94.69, 86.04, 83.85, 79.45, 76.68, 72.30, 70.55, 61.41, 55.82, 55.28, 54.17, 50.60, 49.73, 45.01, 43.00, 28.25, 27.81, 21.21, 19.96, 12.04; high-resolution MS (CI) calcd for $C_{22}H_{33}O_8$ (M – C_2H_5O) m/e 425.2176, found 425.2156. An analytically pure sample was prepared *via* crystallization from diethyl ether–hexanes, mp 138–141 °C.

(1β,2β,5β,5aβ,6β,7aα,8α,11β,11aβ,11bα,14α)-1,6-Bis-(methoxymethoxy)-1,6,7,7a,8,9,11a,11b-octahydro-11-methoxy-8,11a,-14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,10-(5*H*,11*H*)-dione (38). A solution of alcohol **37** (147 mg, 0.31 mmol) in methylene chloride (7.8 mL, 0.04 M), containing 640 mg of Celite, was treated at room temperature with sodium acetate (64 mg, 0.78 mmol) and pyridinium chlorochromate (202 mg, 0.94 mmol). After 3.5 h, the reaction mixture was filtered through a plug of silica gel and washed well with ethyl acetate. The combined filtrate and washings were concentrated *in vacuo*, and the crude residue was purified on silica gel. Elution with ethyl acetate–hexanes (1:1) followed by ethyl acetate furnished 121 mg (83%) of ketone **38** as a white crystalline solid: R_f 0.27 (diethyl ether–hexanes, 2:1); IR ($CHCl_3$) 2960 (s), 2840 (m), 1770 (s), 1725 (s), 1470 (m), 1450 (m), 1390 (m), 1370 (m), 1310 (m), 1270 (m), 1250 (m), 1240 (m), 1150 (s), 1120 (s), 1100 (s), 1030 (s), 990 (s), 900 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (AB q, 2H, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 34.54 Hz), 4.68 (AB q, 2H, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 13.84 Hz), 4.49 (dd, 1H, J = 4.0, 1.2 Hz), 4.44 (d, 1H, J = 8.0 Hz), 4.26 (dd, 1H, J = 4.8, 4.0 Hz), 4.17 (dd, 1H, J = 8.0, 2.0 Hz), 3.58 (dd, 1H, J = 12.2, 4.6 Hz), 3.54 (s, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 2.94 (d, 1H, J = 1.2 Hz), 2.45 (dd, 1H, J = 13.4, 4.2 Hz), 2.15 (ddd, 1H, J = 13.0, 4.4, 2.2 Hz), 2.05 (br t, 1H, J = 13.0 Hz), 1.88–1.76 (m, 1H), 1.78 (dd, 1H, J = 4.4, 1.6 Hz), 1.47 (s, 3H), 1.38–1.29 (m, 1H), 1.23–1.10 (m, 1H), 1.17 (s, 3H), 1.00 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.13, 173.83, 98.79, 96.50, 94.24, 85.83, 83.97, 80.02, 76.07, 70.07, 58.59, 55.87, 55.62, 55.21, 54.05, 50.25, 49.36, 48.80, 47.85, 31.78, 28.09, 21.20, 20.21, 11.82; high-resolution MS (CI) calcd for $C_{24}H_{37}O_9$ (M + 1) m/e 469.2438, found 469.2458. An analytically pure sample was prepared *via* crystallization from ethyl acetate–diethyl ether–hexanes, mp 159–161 °C. Anal. Cacld for $C_{24}H_{36}O_9$: C, 61.52; H, 7.74. Found: C, 61.43; H, 7.87.

(1β,2β,5β,5aβ,6β,7aα,8α,9α,11β,11aβ,11bα,14α)-9-Bromo-1,6-Bis-(methoxymethoxy)-11-methoxy-1,6,7,7a,8,9,11a,11b-octahydro-8,11a,-14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,10-(5*H*,11*H*)-dione (39). A solution of ketone **38** (61 mg, 0.13 mmol) in tetrahydrofuran (2.6 mL, 0.05 M) was treated at –78 °C with lithium hexamethyldisilazide (868 μL of a freshly prepared 0.75 M solution in tetrahydrofuran). After the mixture was stirred for 1 h, chlorotrimethylsilane (116 μL, 0.91 mmol) was added. The reaction mixture was stirred at –78 °C for 10 min and at 0 °C for 45 min prior to the addition of *N*-bromosuccinimide (116 mg, 0.65 mmol). The yellow solution was stirred in the dark at 0 °C for 30 min before filtration through a plug of silica gel. The filtrate and washings were concentrated *in vacuo* to an oil, which, after column chromatography (elution with ethyl acetate–hexanes, 1:1), provided 87 mg (>100%) of crude **39** as a white solid [R_f 0.47 (diethyl ether–hexanes, 2:1); IR ($CHCl_3$) 2940 (m), 2900 (m), 2820 (w), 1770 (s), 1730 (s), 1450 (m), 1380 (m), 1370 (m), 1360 (m), 1310 (m), 1280 (m), 1220 (m), 1150 (s), 1130 (s), 1110 (s), 1030 (s), 990 (s), 940 (w), 920 (m), 910 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (AB q, 2H, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 29.38 Hz), 4.68 (AB q, 2H, J_{AB} = 7.4 Hz, $\Delta\nu_{AB}$ = 10.69 Hz), 4.50 (dd, 1H, J = 3.8, 1.0 Hz), 4.43 (s, 1H), 4.41 (d, 1H, J = 8.4 Hz), 4.28 (d, 1H, J = 3.6 Hz), 4.24 (t, 1H, J = 4.2 Hz), 4.16 (dd, 1H, J = 8.0, 1.6 Hz), 3.61 (dd, 1H, J = 12.2, 4.6 Hz), 3.43 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 2.95 (d, 1H, J = 0.8 Hz), 2.04 (ddd, 1H, J = 13.2, 4.4, 2.4 Hz), 1.93–1.84 (m, 1H), 1.84–1.74 (m, 1H), 1.82 (dd, 1H, J = 5.0, 1.4 Hz), 1.47 (s, 3H), 1.25–1.13 (m, 1H), 1.17 (s, 3H), 1.07 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.54, 173.66, 98.75, 96.63, 88.98, 85.80, 83.90, 79.93, 75.96, 69.98, 59.47, 58.29, 55.90, 55.57, 55.25, 53.96, 48.99, 47.54, 43.58, 33.59, 27.65, 21.18, 17.65, 11.53; high-resolution MS (CI) calcd for $C_{22}H_{30}O_8{}^{79}Br$ (M – C_2H_5O) m/e 501.1124, found 501.1136. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 185–188 °C], which was used directly in the next reaction.

(1β,2β,5β,5aβ,6β,7aα,11β,11aβ,11bα,14α)-1,6-Bis(methoxymethoxy)-1,6,7,7a,11a,11b-hexahydro-11-methoxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,10(5*H*,11*H*)-dione (40). A solution of bromide **39** from the above reaction (87 mg) in tetrahydrofuran (5.2 mL) was treated at 0 °C with tetra-*n*-butylammonium fluoride (286 μL of a 1.0 M solution in tetrahydrofuran). After 20 min at 0 °C and 1.5 h at room temperature, the reaction mixture was diluted with saturated aqueous sodium bicarbonate and diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to an orange solid, which was purified *via* chromatography on silica gel. Elution with ethyl acetate–hexanes (2:1) afforded 61 mg (100% over two steps) of pure enone **40** as a white solid: R_f 0.15 (diethyl ether–hexanes, 2:1); IR ($CHCl_3$) 2940 (m), 2900 (m), 2830 (m), 1770 (s), 1680 (s), 1640 (w), 1520 (w), 1470 (w), 1440 (m), 1380 (m), 1310 (m), 1280 (m), 1200 (s), 1180 (s), 1150 (s), 1140 (s), 1120 (s), 1030 (s), 980 (s), 950 (w), 900 (m), 830 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–5.95 (m, 1H), 4.81 (AB q, 2H, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 33.72 Hz), 4.69 (AB q, 2H, J_{AB} = 7.6 Hz, $\Delta\nu_{AB}$ = 34.37 Hz), 4.54 (d, 1H, J = 8.0 Hz), 4.49 (dd, 1H, J = 3.8, 1.0 Hz), 4.33 (t, 1H, J = 4.2 Hz), 4.21 (dd, 1H, J = 8.0, 1.6 Hz), 3.64 (dd, 1H, J = 11.8, 3.8 Hz), 3.61 (s, 3H), 3.52 (s, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 2.94 (d, 1H, J = 0.8 Hz), 2.41 (br d, 1H, J = 13.0 Hz), 2.32 (ddd, 1H, J = 13.2, 4.8, 2.4 Hz), 1.90 (br s, 3H), 1.87 (dd, 1H, J = 4.8, 1.6 Hz), 1.48 (s, 3H), 1.37 (q, 1H, J = 12.4 Hz), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.60, 173.70, 159.26, 126.63, 98.67, 96.69, 93.27, 85.87, 84.04, 79.56, 76.44, 70.23, 60.11, 55.93, 55.70, 55.21, 53.69, 48.91, 48.43, 47.94, 27.50, 22.36, 21.18, 10.73; high-resolution MS (CI) calcd for $C_{22}H_{29}O_8$ (M – C_2H_5O) m/e 421.1863, found 421.1876. An analytically pure sample was prepared *via* crystallization from ethyl acetate diethyl ether–hexanes, mp 191–193 °C. Anal. Calcd for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35. Found: C, 61.65; H, 7.28.

(1β,2β,5β,5aβ,6β,7aα,11β,11aβ,11bα,14α)-1,6-Dihydroxy-1,6,7,7a,-11a,11b-hexahydro-11-methoxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,10(5*H*,11*H*)-dione (41). A solution of aluminum trichloride (111 mg, 0.84 mmol) in acetonitrile (4.0 mL), cooled to 0 °C under argon in the dark, was treated with solid sodium iodide (125 mg, 0.84 mmol). After 10 min, enone **40** (39 mg, 0.084 mmol) was added dropwise as a solution in methylene chloride (2.0 mL). The reaction mixture was stirred at 0 °C for 35 min before being quenched with saturated aqueous sodium bicarbonate and diluted with brine and diethyl ether. The aqueous layer was extracted with diethyl ether. The combined ethereal extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to an oil, which was purified *via* chromatography on silica gel. Elution with ethyl acetate–hexanes (4:1) provided 28 mg (87%) of pure diol **41** as a white solid: R_f 0.29 (ethyl acetate–hexanes, 4:1); IR ($CHCl_3$) 3600–3200 (br, m), 3000 (m), 2920 (m), 2840 (w), 1770 (s), 1680 (s), 1640 (w), 1440 (w), 1380 (m), 1310 (m), 1150 (m), 1130 (s), 1100 (s), 1070 (m), 1000 (s), 890 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–5.95 (m, 1H), 4.51 (d, 1H, J = 8.4 Hz), 4.43–4.39 (m,

1H), 4.31 (dd, 1H, J = 3.8, 1.0 Hz), 4.25 (dd, 1H, J = 8.6, 1.4 Hz), 3.91 (dd, 1H, J = 11.8, 5.0 Hz), 3.71 (s, 3H), 3.58 (s, 1H), 3.54–3.40 (br s, 1H), 3.12 (d, 1H, J = 0.8 Hz), 2.50 (br d, 1H, J = 12.8 Hz), 2.50–2.35 (br, s, 1H), 2.19 (ddd, 1H, J = 13.2, 4.8, 2.4 Hz), 1.90 (br s, 3H), 1.74 (dd, 1H, J = 4.8, 1.6 Hz), 1.62–1.50 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.20, 173.61, 159.12, 126.67, 91.97, 86.16, 84.59, 70.36, 69.98, 69.35, 60.52, 55.40, 54.27, 49.05, 48.00, 47.38, 30.92, 22.20, 20.93, 12.03; high-resolution MS (CI) calcd for $C_{20}H_{27}O_7$ (M + 1) m/e 379.1757, found 379.1739. An analytically pure sample was prepared *via* crystallization from ethyl acetate, mp 248–250 °C.

(1β,2β,5β,5aβ,7aα,11β,11aβ,11bα,14α)-1-Hydroxy-1,7a,11a,11b-tetrahydro-11-methoxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,6,10(5*H*,7*H*,11*H*)-trione (42). A solution of oxalyl chloride (35 μL, 0.39 mmol) in methylene chloride (1.1 mL) under argon at –78 °C was treated dropwise with dimethyl sulfoxide (56 μL, 0.79 mmol). After 30 min, a solution of diol **41** (30 mg, 0.08 mmol) in methylene chloride–dimethyl sulfoxide (1.1 mL, 100 μL) was added dropwise. After 1.5 h, the reaction mixture was treated with triethylamine (111 μL, 0.79 mmol) and stirred at room temperature for 30 min before being quenched with diethyl ether and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a crude residue, which was chromatographed on silica gel. Elution with ethyl acetate–hexanes (1:1) provided 25 mg (83%) of pure keto enone **42** as a white solid: R_f 0.48 (ethyl acetate–hexanes, 4:1); IR ($CHCl_3$) 3540 (m), 3000 (m), 2940 (m), 2840 (w), 1800–1780 (br, s), 1690 (s), 1640 (m), 1450 (m), 1420 (m), 1390 (m), 1370 (m), 1330 (m), 1310 (m), 1280 (m), 1250–1200 (br, m), 1160 (m), 1130 (s), 1100 (s), 1080 (m), 1050 (m), 1000 (s), 950 (w), 900 (m), 860 (w), 830 (w), 650 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03–5.99 (m, 1H), 4.85 (d, 1H, J = 8.0 Hz), 4.42–4.36 (m, 1H), 4.33 (dd, 1H, J = 3.6, 1.2 Hz), 3.82 (dd, 1H, J = 8.0, 1.6 Hz), 3.76 (s, 3H), 3.74 (s, 1H), 3.63 (d, 1H, J = 1.2 Hz), 3.46 (d, 1H, J = 6.0 Hz), 2.98–2.89 (m, 1H), 2.94 (dd, 1H, J = 18.0, 4.4 Hz), 2.45 (dd, 1H, J = 18.0, 14.8 Hz), 2.19 (br, d, 1H, J = 4.4 Hz), 1.88 (br s, 3H), 1.56 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.44, 196.02, 171.96, 157.20, 126.80, 89.96, 87.42, 83.84, 75.61, 70.26, 60.71, 60.49, 56.28, 49.43, 48.15, 46.41, 38.78, 21.47, 20.55, 11.38; high-resolution MS (EI) calcd for $C_{20}H_{25}O_7$ (M + 1) m/e 377.1600, found 377.1590. An analytically pure sample was prepared *via* crystallization from ethyl acetate–hexanes, mp 246–250 °C.

Samaderin B, (1β,2β,5β,5aβ,7aα,11β,11aβ,11bα,14α)-1,11-Dihydroxy-1,7a,11a,11b-tetrahydro-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4,6,10(5*H*,7*H*,11*H*)-trione (2). A solution of methyl ether **42** (22 mg, 0.058 mmol) in methylene chloride (1.5 mL, 0.04 M) cooled to –45 °C under argon was treated dropwise with boron tribromide (877 μL of a freshly prepared 1.0 M solution in methylene chloride). After 1.5 h, the reaction was quenched at –45 °C with saturated aqueous sodium bicarbonate. The clear mixture was diluted with diethyl ether, and the aqueous layer was separated and extracted with diethyl ether–ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a yellow oil, which was purified by column chromatography. Elution with ethyl acetate–hexanes (2:1) furnished 12 mg (57%) of pure samaderin B (**2**) as a white solid [R_f 0.52 (ethyl acetate–hexanes, 4:1); FTIR ($CHCl_3$) 3667 (w), 3534 (m), 3453 (m), 3034 (w), 2990 (w), 2930 (w), 1788 (s), 1711 (s), 1676 (s), 1620 (w), 1379 (m), 1335 (m), 1308 (m), 1250 (s), 1221 (m), 1163 (s), 1121 (s), 1053 (m), 1003 (s), 893 (m), 831 (m), 758 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16–6.12 (m, 1H), 4.84 (d, 1H, J = 8.4 Hz), 4.80–4.75 (m, 1H), 4.54 (d, 1H, J = 1.6 Hz), 4.34 (dd, 1H, J = 3.4 , 1.0 Hz), 4.15 (d, 1H, J = 0.8 Hz), 3.83 (dd, 1H, J = 8.0, 1.6 Hz), 3.63 (d, 1H, J = 1.2 Hz), 3.56 (d, 1H, J = 6.8 Hz), 3.20–2.91 (m, 2H), 2.54–2.43 (m, 1H), 2.19 (dd, 1H, J = 4.4, 0.8 Hz), 1.94 (br s, 3H), 1.57 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6/$CDCl_3$) δ 205.04/203.33, 197.72/196.43, 171.90/171.91, 161.12/160.79, 124.28/124.40, 86.82/87.67, 83.57/83.74, 80.88/80.71, 74.60/75.48, 69.88/70.10, 60.39/60.53, 55.35/56.28, 48.47/49.44, 46.66/47.55, 46.63/46.91, 38.43/38.94, 21.38/21.91, 20.39/20.65, 9.94/10.60; high-resolution MS (CI) calcd for $C_{19}H_{23}O_7$ (M + 1) m/e 363.1444, found 363.1428. An analytically pure sample was prepared *via* crystallization from ethyl acetate, mp 230–233 °C dec obtained under argon in a sealed tube using a Thomas Hoover capillary melting point apparatus] along with 4 mg (16%) of recovered methyl ether **42**.

Transformation of (1β,2β,5β,5aβ,6β,7aα,8α,11β,11aβ,11bα,14α)-4β-Carbomethoxy-1,4,5,6,7,7a,8,9,10,11,11a,11b-dodecahydro-11-methoxy-1,6,4α-trihydroxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin (31) into (1β,2β,5β,5aβ,6β,7aα,8α,11β,11aβ,11bα,14α)-1,6-Dihydroxy-1,6,7,7a,8,9,10,11,11a,11b-decahydro-11-methoxy-8,11a,14-trimethyl-2*H*-5a,5,2-(methanoxymetheno)naphth[1,2-*d*]oxepin-4(5*H*)-one (29). A solution of hemiketal **31** (13.6 mg, 0.032 mmol) in tetrahydrofuran (200 μL) containing sodium acetate (84 mg, 1.024 mmol) was treated with acetic acid (116 μL) and 30% hydrogen peroxide (116 μL). The heterogeneous mixture was warmed to 60 °C. After 27 h at 60 °C the reaction mixture was diluted with diethyl ether–ethyl acetate and washed with a saturated aqueous sodium sulfite solution. The aqueous layer was separated and extracted with diethyl ether–ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a white solid, which was purified *via* chromatography on silica gel. Elution with ethyl acetate–hexanes (2:1), followed by ethyl acetate, provided 10.5 mg (90%) of γ-lactone **29**, along with 1.5 mg (10%) of recovered hemiketal **31**.

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