Total Synthesis of *d,l*-Isospongiadiol: An Intramolecular Radical Cascade Approach to Furanoditerpenes

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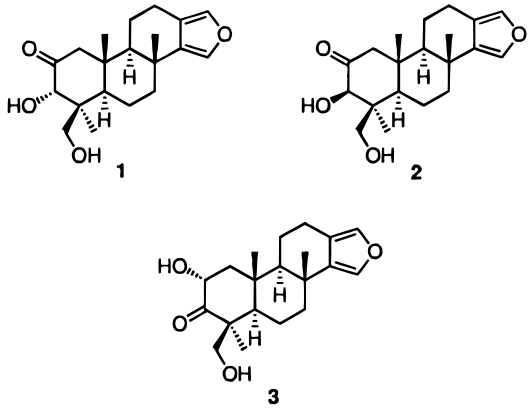
A stereoselective oxidative free-radical cyclization of β-keto ester polyenes **7** and **19** has been accomplished as a one-step entry to the tricarbocyclic synthons **8** and **21** which contain five and six stereogenic centers, respectively. These key synthons possessing an axial carboethoxy group at C-4 were ultimately converted to the spongian skeleton (**8** → **14** and **21** → **25** → **14**). The synthesis of *d,l*-isospongiadiol (**3**) from the common intermediate **14** was realized after introduction of the 2α-hydroxy group in the spongian A-ring *via* epoxidation of silyl enol ether **28** and subsequent desilylation.

Introduction

The furanoditerpenes, spongiadiol (**1**), epispongiadiol (**2**), and isospongiadiol (**3**), isolated[1] from the deep water Carribbean sponge, *Spongia linnaeus*, exhibit activity against Herpes simplex virus, type 1, and P 388 murine leukemia cells. Spongians **1** and **2** have also been previously isolated[2] from a *Spongia* species collected from the Great Barrier Reef in the Australian waters.

The synthesis of spongia-13(16), 14-diene, isolated[3] from *Spongia officinalis* collected near Laing Island, Papua New Guinea, from relay compounds *d,l*-lambda-8(20),13-dien-15-oic acid[4] and *d,l*-methyl isocopalate[5] has been reported. Recently, the synthesis of *d,l*-spongiadiosphenol,[6] a spongiaditerpenoid possessing an oxygenated A-ring was reported. We have also communicated[7,8] a stereoselective biomimetic-like oxidative free radical strategy as a facile entry to various spongiaditerpenes, and here we report the utilization of this methodology in the total synthesis of *d,l*-isospongiadiol (**3**).

Although enzyme-like polyene cationic cyclizations have been extensively studied, notably by Johnson,[9] little attention has been paid to analogous radical strategies[10] to similar polycyclic systems. During the past several years, we have focused in our laboratory on developing an alternative intramolecular oxidative free-radical approach to tri- and tetracyclic systems with the intent of utilizing this strategy as an approach to natural products.



Toward these ends it has been demonstrated that intramolecular oxidative radical cyclization of β-keto ester polyenes can be used to form tri- and tetracyclic systems in which five,[7] six,[8] or seven[11] chiral centers are introduced into the polycyclic system with a high degree of stereoselectivity. With respect to the synthesis of the aforementioned spongians, it seemed reasonable on the basis of our earlier work that cyclization of polyene **7** (Scheme 1) or polyene **19** (Scheme 3), containing all of the carbons present in the spongian skeleton, would be ideal to introduce five of the six chiral centers in the spongians and provide the necessary carboxyl precursor for the β-hydroxymethyl group at C-4 in one simple step. The application of this strategy in the total synthesis of *d,l*-**3** is detailed below.

Results and Discussions

Reaction of allylic alcohol **4**[11] (Scheme 1) with thionyl chloride[12] gave allyl chloride **5** and unrearranged allyl chloride **6** in an approximate 72:25 ratio, as determined by NMR analysis, in 74% yield. The mixture could be enriched in **5** (87:13) by chromatography, but this method could not provide pure **5**. Alkylation of this mixture with

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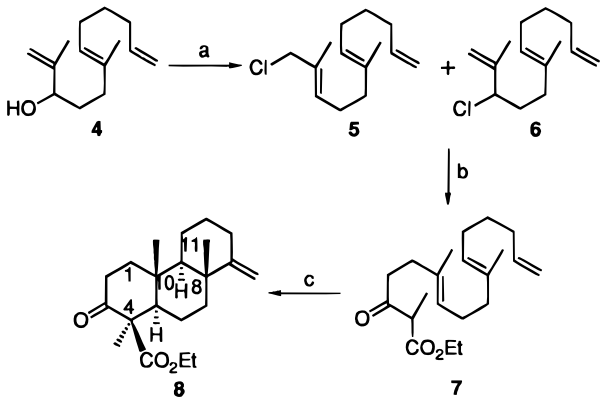
Scheme 1



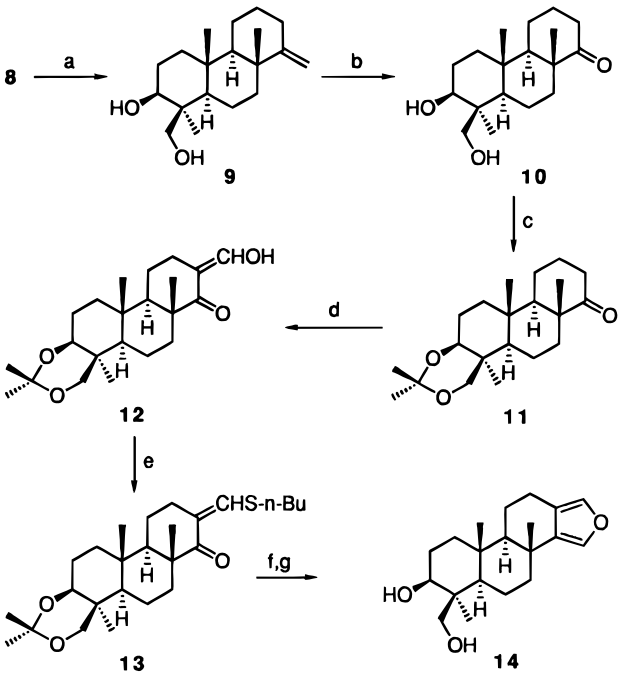
[a] Key: (a) $SOCl_2$, CCl_4; (b) $LiCH_2C(O)CMe(Na)CO_2Et$, HMPA, THF, 0 °C; then aqueous HCl; (c) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, HOAc.

the dianion[13] of ethyl 2-methylacetoacetate (generated from 1 equiv of NaH followed by 1 equiv of *n*-BuLi) gave *β*-keto ester **7** (66%), after chromatography. Subsequent oxidative free-radical cyclization[14] of **7** with a 2:1 ratio of $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in an 0.1 M solution of deaerated HOAc gave **8** in 43% yield.

The stereochemistry of the five generated chiral centers depicted in **8** was ascertained in the following manner. A series of COSY, RELAY, TOSCY, HMQC, and HMBC 2D NMR studies[15] was used to determine the assignment of each proton and carbon resonance signal in **8**. On the basis of these assignments, NOE difference spectra (NOEDS) of **8** revealed that irradiation of the C-10 angular methyl (*δ* 1.02) gave an enhancement of the C-2 axial proton (*δ* 2.94), C-6 axial proton (*δ* 2.11), C-11 axial proton (*δ* 1.48), and a methyleneoxy proton of the ester (*δ* 4.15). Likewise, irradiation of the C-8 angular methyl (*δ* 1.11) gave an enhancement of the C-13 axial proton (*δ* 2.30), C-11 axial proton (*δ* 1.48), C-6 axial proton (*δ* 2.11), and C-7 equatorial proton (*δ* 1.79), thus confirming the relative stereochemistry in **8**. With the stereochemistry in **8** firmly established, our attention turned to the construction of the spongian skeleton as delineated in Scheme 2. Hydride reduction of **8** with LAH gave diol **9** (95%, mp 165−166 °C). Ozonolysis of **9** followed by direct acetonide formation of crude keto diol **10**[16] with acetone in the presence of oxalic acid and calcium sulfate gave acetonide **11** (78%, two steps, mp 138−140 °C). Formylation of **11** afforded keto aldehyde **12** (90%), which was converted into the spongian skeleton **14** in three steps using Spencer's[17] methodology. Thus, reaction of **12** with *p*-TsCl in pyridine followed by addition of *n*-BuSH[18] yielded thioether **13** (73%). Subsequent treatment of **13** with dimethylsulfonium methylide gave an intermediate oxathioacetal which after reaction with $HgSO_4$ and concomitant hydrolysis of the acetonide protecting group gave spongian diol **14** in 57% overall yield from **11**.

In order to obtain a more direct entry to **14** *via* polyene **19**, possessing all of the carbons in the spongian skeleton,

Scheme 2[a]



[a] Key: (a) LAH, Et_2O; Δ; (b) O_3, CH_2Cl_2−MeOH, −78 °C; then Me_2S; (c) acetone, cat. oxalic acid, $CaSO_4$; (d) NaH, EtOCHO, cat. MeOH; then cold aqueous HCl, pH = 6−7; (e) *p*-TsCl, py, 0 °C; then *n*-BuSH, 0 °C; (f) DMSO, $Me_2S{=}CH_2$, THF, −5 °C → rt; (g) $HgSO_4$, Et_2O.

and to avoid the use of any complex trisubstituted olefin synthesis, it became apparent that alcohol **15**[19] (Scheme 3) obtained from selective allylic oxidation[20] of farnesyl acetate was an ideal starting material. Thus, reaction of alcohol **15** with MsCl and LiCl in the presence of 2,6-lutidine, following the procedure of Collington and Meyers,[21] gave allyl chloride **16**[8,22] (67%) while treatment of **15** with CBr_4 in the presence of triphenylphosphine gave bromide **17** (86%). Alkylation of **17** with the dianion[13] of ethyl 2-methylacetoacetate followed by reacylation of alcohol **18** afforded the desired keto ester **19** (77%, two steps), while an analogous sequence with **16** gave **19** in only 43% yield. Radical cyclization of **19** with a 2:1 molar ratio of $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in an 0.1 M solution of deaerated HOAc gave **21** (mp 106−107 °C) and **20** in an approximate 2:1 ratio in 35% yield as the major compounds, after chromatography.

The synthesis of the intact spongian skeleton **14** from **21** in four steps is detailed in Scheme 4. Cleavage of acetate **21** with ethanol in the presence of K_2CO_3 afforded alcohol **22** (96%, mp 147−148 °C). Epoxidation of **22** with *m*-chloroperoxybenzoic acid gave epoxide **23** (97%, mp 122−123 °C). The relative stereochemistry depicted in **23** was shown to be correct from the following considerations. The A/B and B/C ring junctures of **23** were shown to be trans on the basis of observed NOEs: (1) from the C-8 Me to H-11_{ax}, H-6_{ax}, H-7_{eq}, and C-10 Me and (2) from the C-10 Me to H-11_{ax}, H-1_{eq}, H-2_{ax}, H-6_{ax}, and C-8 Me. Irradiation of the C-10 Me also showed an enhancement of the methyleneoxy proton of the *β*-ester at C-4. The

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(16) Keto ester **10** proved to be difficult to elute from silica gel; it was found that a higher yield of **11** could be obtained by using crude **10** in the acetonide reaction.
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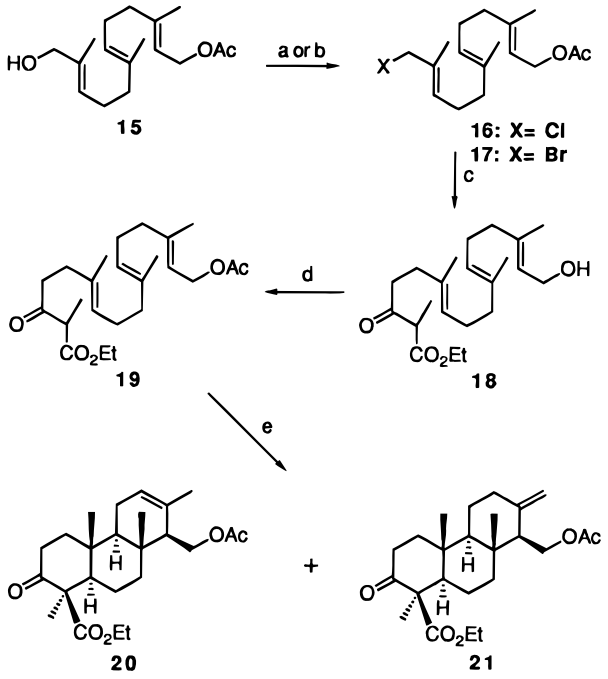
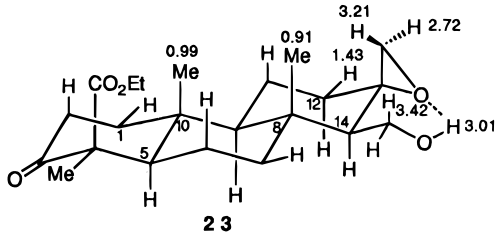
Scheme 3[a]



[a] Key: (a) MsCl, LiCl, 2,6-lutidine, DMF 0 °C → rt; (b) CBr_4, PPh_3, CH_2Cl_2; (c) $LiCH_2C(O)CMe(Na)CO_2Et$, HMPA, THF, 0 °C; (d) Ac_2O, py; (e) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, HOAc.

assignments of the α-configuration to the epoxy group at C-13 and the *β*-configuration to the C-14 hydroxymethyl substituent in **23** were based on both NOE and

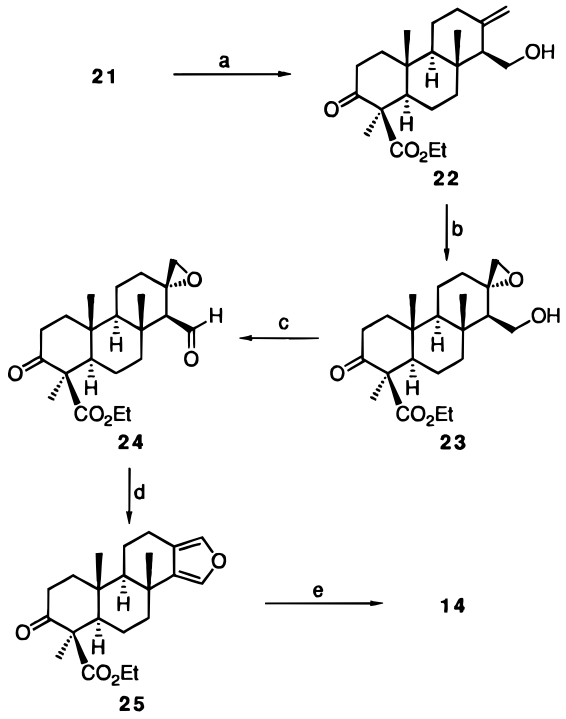


23

COSY studies. Irradiation of the C-8 Me (*δ* 0.91) showed enhancements of one of the diastereotopic protons of the epoxide (*δ* 3.21) and one of the hydroxymethyl protons (*δ* 3.42). While irradiation of the *δ* 3.21 epoxy proton showed enhancements of the C-8 Me (*δ* 0.91), hydroxymethyl proton (*δ* 3.42), epoxy proton (*δ* 2.72), and hydroxy proton (*δ* 3.01), irradiation of the epoxy proton at *δ* 2.72 showed only an enhancement of the epoxy proton at *δ* 3.21 and the C-12 equatorial proton at *δ* 1.43. A weak cross peak from four-bond coupling was also observed in the COSY spectrum from H-12_{ax} to the epoxy proton (*δ* 3.21) and this cross peak was enhanced in the long-range COSY spectrum.

Collins[23] oxidation of **23** gave aldehyde **24** (94%, mp 127−128 °C) and subsequent treatment of **24** with 5% *p*-TsOH in DMSO at 50 °C gave furan **25** (85%, mp 111−112 °C). Hydride reduction of **25** with LAH afforded **14** which was identical in all respects to **14** obtained from ketone **13**. Thus, the stereochemistry depicted in **21**, resulting from radical cyclization of **19**, was proven indirectly by NOE studies and directly by chemical transformation to **14**. The *β*-disposition of the substituent at C-14 in **21** was also shown to be correct, since irradiation of the C-8 Me (*δ* 0.81) showed a strong enhancement of one of the diastereotopic acetoxymethyl protons (*δ* 4.20), a weak enhancement of the other diastereotopic proton (*δ* 4.34), and an enhancement of the vinyl proton (*δ* 4.55).

Scheme 4[a]



[a] Key: (a) K_2CO_3, EtOH; (b) *m*-CPBA, CH_2Cl_2, 0 °C; (c) $CrO_3 \cdot 2py$, CH_2Cl_2; (d) 5% *p*-TsOH in DMSO, 50 °C; (e) LAH, Et_2O, Δ.

With the incorporation of the 4*β*-hydroxymethyl group in spongian skeleton **14**, our attention was next turned to modifying the A-ring and completing the synthesis of *d,l*-isospongiadiol (**3**) as outlined in Scheme 5. Preferential protection of the primary alcohol in **14** with *tert*-butyldimethylsilyl chloride[24] in the presence of a catalytic amount of 4-DMAP[25] gave the secondary alcohol **26** (95%), after chromatography. Collins[23] oxidation of **26** gave ketone **27** (80%, mp 141−142 °C). Reaction of **27** with LDA and subsequent treatment of the resulting lithuim enolate with trimethylsilyl chloride gave silyl enol ether **28** (88%). Epoxidation[26] of **28** with *m*-chloroperoxybenzoic acid afforded both **29** and **30**, after chromatography. The mixture of **29** and **30** was directly desilylated with *n*-tetrabutylammonium fluoride[24] to give *d,l*-isospongiadiol **3** (35% from **28**; mp 184−186 °C (lit.[1] mp 181−183 °C)), after chromatography. The ^{13}C NMR spectrum of *d,l*-**3** was identical to the spectrum of natural **3**.[1]

Experimental Section

General Procedures. NMR spectra were obtained at 200, 500, and 600 MHz. C and H microanalyses were obtained from Galbraith Laboratories. HRMS analyses were obtained from the Mass Spectroscopy Facility at UNC-CH. All melting points

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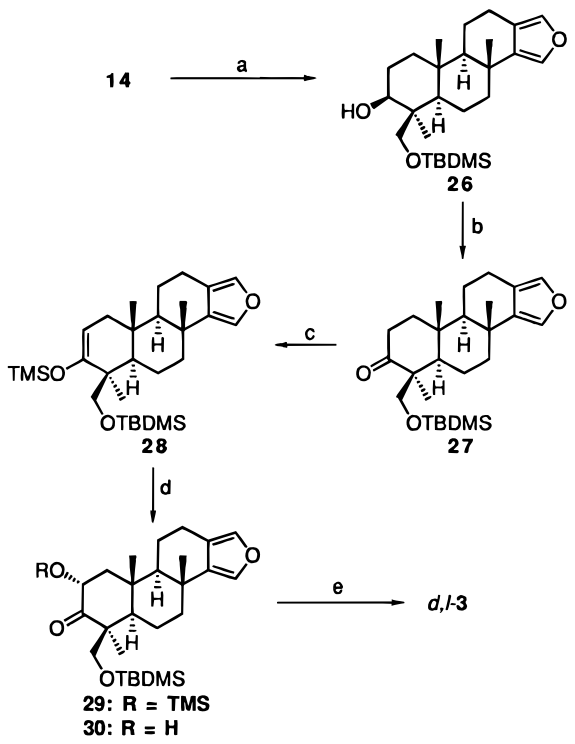
Scheme 5[a]



[a] Key: TBDMSCl, cat. 4-DMAP, Et_3N, CH_2Cl_2; (b) CrO_3·2Py, CH_2Cl_2; (c) LDA, THF, −78 °C; then TMSCl; (d) *m*-CPBA, CH_2Cl_2; (e) *n*-Bu_4NF, THF, 0 °C.

are uncorrected. Preparative chromatography was preformed on Merck silica gel G 60 (70−230 mesh) and Merck silica gel G (230−400 mesh, for pressure chromatography). TLC was preformed with Sybron/Brinkmann silica gel G/UV 254 plates, 0.25 mm (analytical). Compounds on chromatography plates were visualized by spraying with 4% phosphomolybdic acid in isopropyl alcohol followed by heating. THF was distilled from sodium benzophenone ketyl. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted.

(*E*)-2,6-Dimethyl-1,6,11-dodecatrien-3-ol (4). 2-Bromopropene (9.11 g, 75.3 mmol) in dry THF (80 mL) was added dropwise under N_2 to magnesium turnings (1.81 g, 75.4 mmol; covered with THF) with stirring at rt, and the reaction mixture was stirred for 1.5 h. (*E*)-4-Methyl-4,9-decadienal[11] (6.25 g, 37.7 mmol) in dry THF (50 mL) was then added dropwise, and the resulting reaction mixture was stirred at rt for an additional 1.5 h. The reaction mixture was filtered through Celite and the residue washed with CH_2Cl_2 (60 mL). The organic solution was acidified with 10% HCl, passed through Celite, concentrated, diluted with CH_2Cl_2 (110 mL), washed with H_2O, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. Distillation gave 6.3 g (81%) of **4**: bp 79−89 °C at 0.18 mm. A small amount of **4** was chromatographed on silica gel and elution with ethyl acetate−hexanes afforded an analytical sample of **4**:[11] ^{1}H NMR ($CDCl_3$) δ 5.70−5.92 (m, 1H), 5.12−5.22 (m, 1H), 4.81−5.05 (m, 4H), 4.04 (br t, 1H, J = 7 Hz), 1.91−2.10 (m, 6H), 1.72 (s), 1.60 (s) and 1.55−1.75 (m) and, 1.33−1.50 (m) [11H]; IR (neat) 3360 and 1640 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.87; H, 11.52.

(*E,E*)-1-Chloro-2,6-dimethyl-2,6,11-dodecatriene (5) and (*E*)-3-Chloro-2,6-dimethyl-1,6,11-dodecatriene (6). Thionyl chloride (23.6 g, 198 mmol) in CCl_4 (70 mL) was added dropwise over 65 min to alcohol **4** (10.3 g, 49.5 mmol) in CCl_4 (90 mL). The reaction mixture was stirred at rt for 3.5 h and then diluted with CH_2Cl_2 (80 mL). Saturated $NaHCO_3$ was carefully added dropwise with stirring. The organic solution was extracted with three (40 mL) portions of saturated $NaHCO_3$ and two (60 mL) portions of H_2O, dried (Na_2SO_4), and concentrated *in vacuo* to give a 75:25 ratio of **5** and **6** as determined by integration of the δ 5.52 and 4.36 resonance signals. Chromatography on silica gel and elution with ethyl acetate−hexanes gave 8.3 g (74%) in an 87:13 ratio of **5** and **6**: ^{1}H NMR ($CDCl_3$) δ 5.72−5.92 (m), 5.52 (t, 1H), 4.89−5.22 (m), 4.36 (t), 4.02 (s, 2H), 1.74 (s), and 1.59 (s). The mixture of **5** and **6** was not characterized further but submitted directly to the alkylation reaction.

(*E,E*)-Ethyl 2,6,10-Trimethyl-3-oxo-6,10,15-hexadecatrienoate (7). Ethyl 2-methylacetoacetate (92%, 6.47 g, 6.35 mL, 44.96 mmol) was added dropwise to a suspension of sodium hydride (50% in mineral oil, 2.16 g, 44.96 mmol) in THF (90 mL) at 0 °C under N_2. HMPA (4 mL) was added, and the reaction mixture was stirred for 30 min. *n*-BuLi (2.5 M in hexanes, 18 mL, 44.96 mmol) was added dropwise *via* a syringe, and the reaction mixture was stirred for an additional 30 min. An approximate 87:13 ratio of allyl chlorides **5** and **6** (5.08 g, 22.48 mmol) in dry THF (70 mL) was added dropwise, and stirring was continued for 2.5 h. The reaction mixture was acidified with 10% HCl and then diluted with CH_2Cl_2. The organic layer was extracted with three (60 mL) portions of H_2O and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. Two chromatographies on silica gel eluting with ethyl acetate−hexanes gave 4.3 g (66%) of **7**: ^{1}H NMR ($CDCl_3$) δ 5.72−5.93 (m, 1H), 4.90−5.20 (m, 4H), 4.20 (q, 2H, J = 7 Hz), 3.52 (q, 1H, J = 7 Hz), 2.49−2.78 (m, 2H), 1.92−2.46 (m, 11H), 1.59 (s, 6H), 1.33 (d, J = 7 Hz), 1.27 (t, J = 7 Hz) and 1.36−1.74 (13H); IR (neat) 1746, 1719 and 1650 cm^{-1}; HRMS calcd for $C_{21}H_{34}O_3$ (M^+) 334.2507, found 334.2509.

***d,l*-(1α,4aα,4b*β*,8aα,10a*β*)-Ethyl 1,4a,8a-Trimethyl-8-methylene-2-oxo-3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-1-phenanthrenecarboxylate (8).** A solution of keto ester **7** (5.03 g, 15.1 mmol) in HOAc (deaerated, 151 mL) was deaerated with Ar. $Mn(OAc)_3$·$2H_2O$ (8.09 g, 30.2 mmol) and $Cu(OAc)_2$·H_2O (3.02 g, 15.1 mmol) were added under Ar. The reaction mixture was stirred at rt for 24 h and then filtered through Celite and charcoal (salts were washed with CH_2Cl_2). The organic solution was extracted with two (60 mL) portions of saturated $NaHCO_3$, two (50 mL) portions of H_2O, and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a solid. The solid was triturated with hexane to give 1.01 g of **8** (mp 89.5−90.1 °C). An additional 1.13 g of **8** was obtained by chromatography of the filtrate on silica gel (elution with ethyl acetate−hexanes) to afford a total yield (43%) of **8**. An analytical sample was obtained from washing with hexanes to give pure **8**: mp 90−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (exo CH_2, m, 2H), 4.15 (CH_2O, m, 2H), 2.94 (H_{2ax}, 6 line ddd, 1H, J = 7, 15, 15 Hz), 2.37 (H_{2eq}, 1H, apparent dq, J = 2, 15 Hz), 2.30 (H_{13ax}, 1H, apparent dtt, J = ∼1, 5, 14 Hz), ∼2.11 (H_{6ax}, H_{13eq}) and 2.06 (H_{1eq}, ddd, J = 2, 7, 13 Hz) [3H], 1.90 (H_{12eq}) and 1.86 (H_{6eq}, apparent dq, partially resolved, J = 4, 14 Hz) [2H], 1.79 (H_{7eq}, 1H, apparent dt, J = 3, 13 Hz), 1.63 (H_{11eq}, 1H, m), 1.51 (H_{7ax}, partially resolved 6 line ddd, J = 4, 14, 14 Hz) and 1.48 (H_{11ax}, partially resolved 8 line dddd, J = 4, 13, 13, 13 Hz), 1.37 (C4-Me, s, 3H), ∼1.27 (CH_3CH_2, t, H_{5ax}, H_{1ax}, H_{12ax}) [6H], 1.11 (C8-Me, s, 3H), 1.02 (C10-Me, s, 3H), 0.89 (H_{9ax}, dd, 1H, J = 3, 12 Hz); ^{13}C NMR (500 MHz, 70.0, $CDCl_3$) δ 208.8 (C3), 173.7 (ester carbonyl), 159.6 (C14), 102.9 (exo CH_2), 61.0 (CH_2O), 58.1 (C5) , 57.6 (C4), 57.1 (C9), 40.6 (C1), 39.9 (C8), 38.6 (C7), 38.0 (C10), 36.7 (C2), 33.0 (C13), 28.5 (C12), 21.6 (C11), 21.0 (C8-Me), 20.9 (C4-Me), 20.5 (C6), 13.9 (ethyl CH_3), 13.8 (C10-Me); IR (KBr) 1722 and 1704 cm^{-1}. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.63; H, 9.49.

***d,l*-(1α,2α,4aα,4b*β*,8aα,10a*β*)-2-Hydroxy-1,4a,8a-trimethyl-8-methylene-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-1-phenanthrenemethanol (9).** Keto ester **8** (4.14 g, 12.5 mmol) in dry ether (70 mL) was added dropwise to a suspension of $LiAlH_4$ in ether (65 mL). The reaction mixture was refluxed for 3.0 h and then cooled to 0 °C, and the excess hydride was destroyed by dropwise addition of a saturated aqueous Na_2SO_4 solution. The mixture was diluted with CH_2Cl_2 (400 mL), washed with 10% HCl (100 mL) and saturated $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a solid. The solid was washed with hexanes followed by filtration. The filtrate in turn was concentrated,

and the resulting solid was washed with hexanes. This process was repeated again to afford 3.47 g (95%) of **9**. An analytical sample of pure **9** (mp 164−165 °C) was obtained by trituration of a 50 mg sample with ethyl acetate. Trituration with methanol gave **9**: mp 165−166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (exo CH_2, m, 2H), 4.20 (C*H*HOH, d, 1H, J = 11 Hz), 3.41 (H_{3ax}, dd, 1H, J = 4.5, 12 Hz), 3.37 (CH*H*OH, d, 1H, J = 11 Hz), 2.66 (br, OH) and 2.41 (br, OH) [2H], 2.27 (H_{13ax}, m, 1 H), 2.08 (H_{13eq}, m, 1H), 1.87 (H_{12eq}, m) and 1.82 (H_{2ax}, m) [2H], ~1.73 (H_{7eq}, H_{6eq}, H_{1eq}) and 1.72 (H_{2eq}) [m, 4H], 1.55 (H_{11eq}, H_{7ax}, m, 2H), 1.40 (H_{6ax}, partially resolved 8 line dddd, J = 2, 12, 12, 12 Hz) and 1.38 (H_{11ax}, partially resolved 8 line dddd, J = 4, 12.8, 12.8, 12.8 Hz) [overlapping, 2H], 1.24 (C4-Me, s) and (H_{12ax}, m) [4H], 1.02 (C8-Me, s, 3H), 0.93 (H_{1ax}, partially resolved 6 line ddd, J = 4, 13, 13 Hz), 0.90 (H_{5ax}, dd, J = 1.7, 12 Hz), 0.85 (H_{9ax}, dd, J = 2.5, 12.4 Hz) and 0.83 (C10-Me, s) [6H]; ^{13}C NMR (200 MHz, $CDCl_3$, 77.0) δ 160.4 (C14), 102.7 (exo CH_2), 80.8 (C3), 64.3 (CH_2O), 58.2 (C9), 56.0 (C5), 42.8 (C4), 40.0 (C10), 39.1 (C7), 38.0 (C1), 37.3 (C8), 32.9 (C13), 28.4 (C12), 27.6 (C2), 22.2 (C4-Me), 21.1 (C8-Me, C11), 18.3 (C6), 16.6 (C10-Me); IR (KBr) 3364 and 1636 cm^{-1}. Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.64; H, 10.81.

***d,l*-(1α,2α,4aα,4b*β*,8aα,10a*β*)-2-Hydroxy-1,4a,8a-trimethyl-8-oxo-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-1-phenanthrenemethanol (10).** Alkene diol **9** (992 mg, 3.40 mmol) in a solution of CH_2Cl_2−MeOH (125 mL:100 mL) was cooled to −78 °C, and ozone was passed into the reaction mixture until a light blue color was obtained (8 min). Nitrogen was then bubbled through the solution to remove excess ozone. Dimethyl sulfide (12.4 mL) was added, and the −78 °C bath was replaced with an ice−water bath. The reaction mixture was allowed to warm to rt and stirred an additional 18 h. The solvent was removed *in vacuo* to yield a solid. The solid was chromatographed on silica gel (25:1) with suction, and elution with ethyl acetate−hexanes gave 502 mg (50%) of **10**: mp 166−166.5 °C (triturated with EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (C*H*HO, d, 1H, J = 11Hz), 3.41 (H_{3ax}, dd, 1H, J = 4.3, 11.5 Hz), 3.36 (CH*H*O, d, 1H, J = 11 Hz), 2.65 (br, OH) and 2.54 (H_{13ax}, 6 line ddd, J = 7, 14, 14 Hz) [3H], 2.18 (H_{13eq}, m, 1H), 2.06 (H_{12eq}, m, 1H), ~1.83 (H_{2ax}), ~1.78 (H_{2eq}), ~1.74 (H_{1eq}, H_{6eq}), ~1.70 (H_{11eq}, H_{7eq}), ~1.61 (H_{11ax}, H_{7ax}), ~1.50 (H_{12ax}) [multiplets, 9H], 1.32 (H_{6ax}, 8 line dddd, 1H, J = 3, 13,13, 13 Hz), 1.23 (C4-Me, s, 3H), 1.12 (C8-Me, s, 3H), 1.05 (H_{9ax}, dd, 1H, J = 3, 12 Hz), 0.99 (H_{1ax}, 6 line ddd, 1H, J = 4, 12, 12 Hz), 0.90 (C10-Me, s, 3H), 0.87 (H_{5ax}, dd, 1H, J = 1.8, 12.4 Hz); ^{13}C NMR (500 MHz, $CDCl_3$, 77.0) δ 215.4 (CO), 80.6 (C3), 64.2 (CH_2O), 57.7 (C9), 55.5 (C5), 49.1 (C8), 42.9 (C4), 38.1 (C1), 37.9 (C10), 37.5 (C13), 34.7 (C7), 27.6 (C2), 26.1 (C12), 22.4 (C4-Me), 20.2 (C11), 19.6 (C8-Me), 17.8 (C6), 17.0 (C10-Me); IR (KBr) 3354 and 1702 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 72.90; H, 10.63. The keto diol **10** presumably was partially hydrated. It was found that **10** was difficult to chromatograph (very insoluble) and difficult to elute from silica gel. Direct use of crude **10** in the acetonide reaction gave a higher yield of **11**.

***d,l*-(4aα,6a*β*,6bα,10a*β*,12aα,12bα)-Dodecahydro-3,3,6a,10a,12b-pentamethyl-10*H*-phenanthro[2,1-*d*][1,3]-dioxan-10-one (11).** Calcium sulfate (5 g) was added to a solution of crude keto diol **10** (500 mg, 94%, 1.60 mmol), acetone (15 mL), and oxalic acid (120 mg) in CH_2Cl_2 (25 mL) and the resulting reaction mixture was stirred at rt for 26 h. The reaction mixture was filtered, and the residue was washed with CH_2Cl_2 (175 mL). The organic solution was extracted with two (100 mL) portions of saturated $NaHCO_3$ and two (100 mL) portions of brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a solid. Chromatography on silica gel and elution with 5% ethyl acetate−hexanes gave 33 mg of acetonide **9** and 446 mg (83%) of **11**: mp 138 −140 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (d, 1H, J = 11.4 Hz), 3.47 (dd, 1H, J = 3.2, 7.3 Hz), 3.20 (d, 1H, J = 11.4 Hz), 2.56 (6 line ddd, 1H, J = 7.0, 13.6, 13.6 Hz), 1.41 (s, 3H), 1.36 (s, 3H), 1.22 (s, 3H), 1.15 (s, 6H), 0.90 (dd, 1H, J = 1.9, 12.0 Hz); IR (KBr) 1705 cm^{-1}. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.20; H, 10.28.

***d,l*-(4aα,6a*β*,6bα,10a*β*,12aα,12bα)-Decahydro-9-(hydroxymethylene)-3,3,6a,10a,12b-pentamethyl-7*H*-phenanthro[2,1-*d*][1,3]dioxan-10-one (12).** The procedure of Spencer[17] was followed. NaH (50% in mineral oil, 320 mg, 6.67 mmol) followed by MeOH (2 drops) was added to a stirring solution of ketone **11** (446 mg, 1.34 mmol) in ethyl formate (13 mL) at −8 to −10 °C. The reaction mixture was stirred for 2.5 h, at which time Et_2O (15 mL) was added and stirring was continued for 4.5 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL), poured into ice−water, and acidified to pH = 6−7 with 10% HCl. The organic solution was washed with two (75 mL) portions of water and two (75 mL) portions of brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a solid. Addition of hexanes gave 437 mg (90%) of **12**: ^{1}H NMR ($CDCl_3$) δ 8.50 (d, 1H, J = 3.9 Hz), 3.96 (d, 1H, J = 11.5 Hz), 3.49 (dd, 1H, J = 3.6, 7.1 Hz), 3.20 (d, 1H, J = 11.5 Hz), 2.47 (ddd, 1H, J = 1.9, 6.3, 14.8 Hz), 2.27 (ddd, 1H, J = 6.6, 11.6, 15.1 Hz), 1.41 (s, 3H), 1.37 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.51) δ 194.3, 186.8, 106.4, 100.0, 75.9, 64.6, 54.1, 52.5, 42.8, 38.5, 36.9, 35.8, 35.7, 30.2, 26.8, 26.2, 25.6, 24.3, 21.8, 19.2, 18.5, 18.3. The keto aldehyde was not characterized futher but submitted directly to the next step.

***d,l*-(4aα,6a*β*,6bα,10a*β*,12aα,12bα)-Decahydro-9-[(*n*-butylthio)methylene]-3,3,6a,10a,12b-pentamethyl-7*H*-phenanthro[2,1-*d*][1,3]dioxan-10-one (13).** The procedure of Ireland and Marshall[18] was followed. *p*-Toluenesulfonyl chloride (121 mg, 0.635 mmol) was added to aldehyde **12** (192 mg, 0.530 mmol) in pyridine (3.5 mL) with stirring at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 2.5 h. *n*-Butylmercaptan (114 μL, 1.07 mmol) was added *via* a syringe, stirring was continued for 10 min at 0 °C, and then the reaction mixture was placed in a refrigerator (0 °C) for 60 h. The reaction mixture was poured into 1% NaOH (15 mL) and extracted with CH_2Cl_2. The organic solution was washed with H_2O, 25% KOH, H_2O, and brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a thick oil. Chromatography on silica gel and elution with 2% ethyl acetate−hexanes afforded 168 mg (73%) of **13**: ^{1}H NMR ($CDCl_3$) δ 7.49 (br s, 1H), 3.99 (d, 1H, J = 11.4 Hz), 3.51 (dd, 1H, J = 3.5, 7.1 Hz), 3.22 (d, 1H, J = 11.4 Hz), 2.86 (t, 2H, J = 7.4 Hz), 2.61 (m, 1H), 1.44 (s), 1.39 (s), 1.23 (s), 1.18 (s), 1.13 (s), 0.95 (t, 3H, J = 7.4 Hz). The vinyl thioether was used directly in the furan ring formation reaction.[17]

***d,l*-3*β*-Hydroxy-4*β*-(hydroxymethyl)-4α,8*β*,10*β*-trimethyl-13-nor-16-oxoandrosta-13,14-diene (14).** DMSO[27] (2 mL) was added to NaH (50% in mineral oil, 90.4 mg, 1.88 mmol, washed with hexanes), and the resulting reaction mixture was heated at 75 °C under N_2 with stirring for 40 min and then cooled to rt. THF (3 mL) was added, and the reaction mixture was cooled to −5 °C (ice−H_2O−salt). Trimethylsulfonium iodide (386 mg, 1.89 mmol) in DMSO (5 mL) was added over 2 min, and stirring was continued for an additional 2 min. Thioether **13** (422 mg, 0.972 mmol) in a solution of DMSO (4 mL) and THF (2 mL) was added over 5 min, and stirring was continued at −5 °C for 15 min and then at rt for 75 min. The orange reaction mixture was diluted with H_2O (30 mL) and extracted with two (50 mL) portions of CH_2Cl_2. The organic solution was washed with two (25 mL) portions of H_2O and two (35 mL) portions of brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield 426 mg of an oil. The oil was allowed to stand at rt for 2 days. $HgSO_4$ (282 mg, 0.952 mmol) was added to the oil in dry ether (4 mL), and the reaction mixture was stirred at rt for 35 min. The ether was decanted, and the residue was washed with ether. The organic solution was dried (Na_2SO_4), and concentrated *in vacuo* to give a solid. Crystallization from hexanes−ethyl acetate gave 237.4 mg and chromatography of the filtrate afforded an additional 11 mg, thus affording 248.4 mg (80%) of **14**: mp 207−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, 1H, J = 1.6 Hz), 7.04 (br dd, 1H, J = 1.6, ~2.8 Hz), 4.21 (d, 1H, J = 11 Hz), 3.44 (dd, J = 4, 11 Hz), and 3.39 (d, J = 11 Hz) [2H], 2.76 (dd, 1H, J = 6, 16 Hz), 1.24 (s, 3H), 1.18 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 137.1, 136.8, 135.1, 119.6, 80.7, 64.3, 56.1, 56.0, 42.9, 41.2, 38.1, 37.0, 34.1, 27.6, 26.1, 22.4, 20.6, 18.6, 18.4, 16.8; IR (KBr) 3535, 3408, 2997−2846, 1445, 1379, 1028, 901, 799, 593 cm^{-1};

(27) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. (b) Corey, E. J.; Chaykovsky, M. *Ibid.* **1965**, *87*, 1353.

HRMS calcd for $C_{20}H_{30}O_3$ (M^+) 318.2194, found 318.2175. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.74; H, 9.73.

(2*E*,6*E*,10*E*)-12-Hydroxy-3,7,11-trimethyl-2,6,10-octatrienyl Acetate (15). Farnesyl acetate (10 g, 37.9 mmol) in CH_2Cl_2 (15 mL) was added dropwise with stirring to a mixture of SeO_2 (1.05 g, 9.46 mmol) and *t*-BuOOH (90%, 4.17 g, 41.7 mmol) in CH_2Cl_2 (65 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h and diluted with Et_2O (100 mL). The organic layer was washed with brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. Chromatogrophy on silica gel and elution with 5% ethyl acetate−hexanes gave 2.83 g (27%) of **15**:[19] ^{1}H NMR ($CDCl_3$) δ 5.28−5.45 (m, 2H), 5.05−5.16 (m, 1H), 4.59 (d, 2H, J = 7 Hz), 4.00 (br s, 2H), 1.95−2.21 (m) and 2.06 (s) [11H], 1.71 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H).

(2*E*,6*E*,10*E*)-12-Bromo-3,7,11-trimethyl-2,6,10-dodecatrienyl Acetate (17). Carbon tetrabromide (7.11 g, 21.42 mmol) was added in small portions to alcohol **15** (4.0 g, 14.29 mmol) and Ph_3P (4.87 g, 18.59 mmol) in dry CH_2Cl_2 (80 mL) at rt with stirring. The reaction mixture was stirred for 1 h, and the CH_2Cl_2 was removed *in vacuo*. Hexanes (50 mL) was added, and the resulting solids were removed by filtration. Concentration of the filtrate, chromatography on silica gel, and elution with 5% ethyl acetate−hexanes gave 4.2 g (86%) of **17**:[22] ^{1}H NMR ($CDCl_3$) δ 5.52−5.63 (m, 1H), 5.28−5.40 (m, 1H), 5.04−5.16 (m, 1H), 4.59 (d, 2H, J = 7 Hz), 3.97 (br s, 2H), 1.97−2.20 (m) and 2.06 (s) [11H], 1.76 (s, 3H), 1.71 (s, 3H), 1.60 (s, 3H).

(6*E*,10*E*,14*E*)-Ethyl 16-Hydroxy-2,6,10,14-tetramethyl-3-oxo-6,10,14-hexadecatrienoate (18). Ethyl 2-methylacetoacetate (98%, 10.0 g, 9.81 mL, 68.1 mmol) was added *via* a syringe to a suspension of NaH (50% in mineral oil, 3.35 g, 69.8 mmol) and HMPA (4 mL) in dry THF (150 mL) at 0 °C under N_2 with stirring over 45 min. After addition the reaction became viscous, additional HMPA (3 mL) and THF (100 mL) were added, and stirring was continued for 1 h. *n*-BuLi (2.5 M in hexanes, 27.9 mL, 69.8 mmol) was added dropwise by syringe over 1 h, and stirring was continued at 0 °C for 1 h. Bromide **17** (5.84 g, 17.0 mmol) in THF (20 mL) was added dropwise over 30 min and stirring was continued for 1 h. HCl (10%, ∼50 mL) was added followed by addition of CH_2Cl_2 (30 mL). The organic solution was washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. Chromatography on silica gel and elution with ethyl acetate−hexanes gave 5.4 g (87%) of **18**: ^{1}H NMR ($CDCl_3$) δ 5.41 (m, 1H), 5.11 (m, 2H), 4.19 (q, J = 7 Hz) and 4.15 (d, J = 7 Hz) [4H], 3.53 (q, 1H, J = 7 Hz), 2.64 (m, 2H), 1.75−2.34 (m, 11H), 1.68 (s, 3H), 1.59 (s, 6H), 1.33 (d, J = 7 Hz) and 1.27 (t, J = 7 Hz) [6H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 205.5, 170.4, 139.0, 134.9, 133.1, 124.8, 123.8, 123.4, 61.1, 59.1, 52.7, 40.0, 39.4, 39.3, 33.1, 26.4, 26.1, 16.1, 15.9, 15.8, 13.9, 12.6; IR (neat) 3420, 2981−2856, 1743, 1715, 1659, 1449, 1377, 1194, 1017 cm^{-1}. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.67; H, 9.88.

(6*E*,10*E*,14*E*)-Ethyl 16-Acetoxy-2,6,10,14-tetramethyl-3-oxo-6,10,14-hexadecatrienoate (19). Alcohol **18** (2.8 g, 7.69 mmol), pyridine (1.46 g, 18.46 mmol), and acetic anhydride (1.18 g, 11.54 mmol) in CH_2Cl_2 (3 mL) was stirred overnight at rt. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. Chromatography on silica gel and elution with 4% ethyl acetate−hexanes afforded 2.74 g (88%) of **19**: ^{1}H NMR ($CDCl_3$) δ 5.36 (m, 1H), 5.12 (m, 2H), 4.59 (d, 2H, J = 7 Hz), 4.19 (q, 2H, J = 7 Hz), 3.52 (q, 1H, J = 7 Hz), 2.63 (m, 2H), 1.90−2.34 (m) and 2.06 (s) [15H], 1.71 (br s, 3H), 1.59 (br s, 6H), 1.33 (d, 3H, J = 7 Hz), 1.27 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 77.0) δ 205.4, 170.9, 170.4, 142.0, 135.1, 133.2, 124.9, 123.6, 118.2, 61.3, 61.2, 52.8, 40.0, 39.4 (2C), 33.2, 26.5, 26.1, 20.9, 16.3, 15.9, 14.0, 12.6; IR (neat) 2981−2856, 1741, 1717, 1448, 1372, 1234, 1024, cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.99; H, 9.39.

***d,l*-(1α,4aα,4bβ,8β,8aα,10aβ)- and *d,l*-(1α,4aα,4bβ,8β,8aα,10aβ)-Ethyl 8-(Acetoxymethyl)-1,4a,7,8a-tetramethyl-2-oxo-1,4,4a,4b,5,8,8a,9,10,10a-decahydro-1-phenanthrenecarboxylate (21 and 20).** To diester **19** (1.0 g, 2.46 mmol) in deaerated HOAc (25 mL) under Ar were added $Mn(OAc)_3\cdot 2H_2O$ (1.4 g, 4.93 mmol) and $Cu(OAc)_2\cdot H_2O$ (502 mg, 2.46 mmol). The reaction mixture was stirred at rt for 8 h and then passed through a bed of Celite and charcoal, washing with 50 mL of CH_2Cl_2. The organic solution was washed with two (30 mL) portions of 10% NaOH, H_2O (30 mL), and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. Chromatography on silica gel and elution with 5% ethyl acetate−hexanes gave 230 mg (23%) of **21** and 130 mg (13%) of an approximate 90:10 ratio of **20** and **21**. For **21**: mp 106−107 °C; IR (KBr) 2967−2853, 1737, 1711, 1649, 1235 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.87 (exo CH_2, d, 1H, J = 1 Hz), 4.55 (exo CH_2, s, 1H), 4.34 (C*H*HOAc, dd, 1H, J = 3.9, 11.1 Hz), 4.20 (CH*H*OAc, dd, 1H, J = 9.3, 11.1 Hz), 4.13 (m, 2H), 2.95 (6 line ddd, 1H, H_{2ax}, J = 6.6, 14.7, 14.7 Hz), 2.42 (partially resolved ddd, 1H, H_{12eq}, J = 2.5, 4.1, 13.3 Hz), 2.39 (partially resolved ddd, H_{2eq}, J = 2.3, 4.8, ∼14.8 Hz), 2.09 (ddd, 1H, H_{1eq}, J = 2.3, 6.6, 13.2 Hz), 2.02 (s, 3H), 1.91 (H_{7eq}, apparent dt, 1H, J = 3.3, 13.0 Hz), 1.84 (H_{6eq}, apparent dq, 1H, J = ∼3.2, 14.2 Hz), 1.72 (H_{11eq}, m, 1H), 1.42 (8 line dddd, 1H, H_{11ax}, J = 4.3, 13, 13, 13 Hz), 1.36 (C4-Me, s, 3H), 1.25 (t, 3H, J = 6.9 Hz), 1.09 (dd, 1H, H_{9ax}, J = 2.6, 12.4 Hz), 0.97 (C10-Me, s, 3H), 0.81 (C8-Me, s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$, 77.0) δ 208.6, 173.6, 171.4, 146.0, 107.6, 61.3, 61.0, 58.5, 57.8, 57.5, 54.8, 40.8, 40.3, 39.0, 37.9, 37.3, 36.6, 23.2, 21.1, 20.9, 20.8, 15.8, 13.9, 13.8. Irradiation of the C-8 Me (δ 0.81) showed a strong enhancement of the C-10 Me (δ 0.98), the H-11_{ax} (δ 1.42), one of the diastereotopic acetoxymethyl protons (δ 4.20), a weaker enhancement of the other diastereotopic acetoxymethyl proton (δ 4.34), and the vinyl proton (δ 4.45). Likewise irradiation of the C-10 Me showed enhancements of the C-8 Me (δ 0.81), H-11_{ax} (δ 1.42), H-2_{ax} (δ 2.96), and the methyleneoxy protons of the C-4 ester (δ 4.13). Pure **20** was obtained by treating a mixture of **20** and **21** with *p*-TsOH·H_2O in refluxing PhH followed by chromatography on silica gel. For **20**: ^{1}H NMR ($CDCl_3$) δ 5.47 (br s, 1H), 4.02−4.30 (m, 4H), 2.95 (6 line ddd, 1H, J = 6.5, 14.7, 14.7 Hz), 2.37 (apparent dq, 1H, J = 2.3, 15.0 Hz), 2.04 (s, 3H), 1.67 (br s, 3H), 1.36 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz), 1.05 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 208.6, 173.5, 171.1, 132.5, 122.8, 62.9, 61.0, 57.9, 57.5, 53.5, 53.4, 40.8, 40.5, 37.3, 36.5, 35.9, 22.9, 21.5, 21.2, 20.9, 20.5, 15.0, 13.9, 13.6; IR (neat) 2964−2856, 1739, 1713, 1236 cm^{-1}. Anal. Calcd for $C_{24}H_{36}O_5$ (**21**): C, 71.26; H, 8.97. Found: C, 71.26; H, 8.98. Anal. Calcd for $C_{24}H_{36}O_5$ (**20**): C, 71.26; H, 8.97. Found: C, 71.58; H, 9.23.

***d,l*-(1α,4aα,4bβ,8β,8aα,10aβ)-Ethyl 8-(Acetoxymethyl)-7-methylene-1,4a,8a-trimethyl-2-oxo-1,4,4a,4b,5,8,8a,9,10,10a-decahydro-1-phenanthrenecarboxylate (22).** A mixture of acetate **21** (500 mg, 1.24 mmol) and K_2CO_3 (612 mg, 6.19 mmol) in EtOH (20 mL) was stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with two (30 mL) portions of H_2O and brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a solid. Crystallization (hexanes−CH_2Cl_2) gave 432 mg (96%) of **22**: mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 4.96 (br s, 1H), 4.67 (br s, 1H), 4.13 (m, 2H), 3.81 (m, 2H), 2.96 (6 line ddd, J = 7, 15, 15 Hz), 1.36 (s), 1.25 (t), 1.08 (dd, 1H, J = 2.4, 12.3 Hz), 0.96 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 208.5, 173.5, 146.9, 106.7, 61.0, 59.0, 58.6, 58.4, 57.7, 57.4, 40.7, 40.2, 38.9, 37.8, 37.5, 36.5, 23.4, 20.8, 20.7, 15.9, 13.9, 13.8; IR (KBr) 3542, 3467, 1737, 1707, 1231, 1022 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.44; H, 9.26.

***d,l*-(1α,4aα,4bβ,7β,8aβ,10aβ)-Ethyl 7-(Epoxymethylene)-8-(hydroxymethyl)-1,4a,8a-trimethyl-2-oxo-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1-phenanthrenecarboxylate (23).** *m*-CPBA (80%, 913 mg, 4.22 mmol) was added to alcohol **22** (1.39 g, 3.84 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and then diluted with CH_2Cl_2 (100 mL). The organic solution was washed with two (50 mL) portions of a 0.1 N NaOH solution, H_2O (70 mL), and brine (70 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a solid. Trituration with hexanes gave 1.41 g (97%) of **23**: mp 122−123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.13 (m, 2H), 3.62 (6 line ddd, 1H, HC*H*OH, J = 3, 10.8, 10.8 Hz), 3.42 ("t", degenerate dd, 1H, *H*CHOH, J = 10.8 Hz), 3.21 (dd, 1H, epoxy H, J = 2, 3.6 Hz), 3.01 (d, 1H, OH, J

= 10.8 Hz), 2.95 (6 line ddd, 1H, H_{2ax}, J = 7, 15, 15 Hz), 2.72 (d, 1H, epoxy H, J = 3.6 Hz), 2.41 (ddd, 1H, H_{2eq}, J = 2, 5, 15 Hz), 2.09 (ddd, 1H, H_{1eq}, J = 2, 7, 13 Hz), 2.04 (m, 1H, H_{6ax}), 1.97 (12 line dddd, 1H, H_{12ax}, J = 13, 13, ~4, 2 Hz), 1.84 (m, 4H, H_{6eq}, H_{7eq}, H_{11eq}, H_{14ax}), 1.57 (8 line dddd, partially resolved, 1H, H_{11ax}, J = 4, 13, 13, 13, Hz), 1.43 (degenerate ddd, middle peaks coalesced, 1H, H_{12eq}, J = ~4, ~4, 13 Hz), 1.37 (s, 3H, C-4 Me), 1.33 (dd, 1H, H_{5ax}, J = 2, 12 Hz), ~1.36 and ~1.28 (m, H_{1ax}, H_{7ax}) [2H], 1.26 (t, 3H, J = 7 Hz), 1.04 (dd, 1H, H_{9ax}, J = 2, 13 Hz), 0.99 (s, 3H, C-10 Me), 0.91 (s, 3H, C-8 Me). On addition of D_2O the doublet at δ 3.01 disappeared and the 6 line ddd at δ 3.62 collapsed to a dd at δ 3.62 (J = 3, ~10.8 Hz); ^{13}C NMR ($CDCl_3$, 77.0) δ 208.2, 173.4, 61.3, 61.1, 58.7, 57.9, 57.5, 57.3, 54.4, 51.7, 40.7, 40.0, 39.1, 37.7, 36.5, 35.9, 21.0, 20.8, 20.2, 16.3, 13.9, 13.8; IR (KBr) 3511, 3449, 2983-2858, 1737, 1714, 1234, 1026, 875 cm^{-1}. NOE's for the A/B and B/C ring juncture of **23**: from the C-8 Me to H-11_{ax}, H-6_{ax}, H-7_{eq} and C-10 Me and from the C-10 Me to H-11_{ax}, H-1_{eq}, H-2_{ax}, H-6_{ax} and C-8 Me; Irradiation of the C-10 Me (δ 0.99) also showed an enhancement of the methyleneoxy protons of the C-4β-ester; Irradiation of the C-8 Me (δ 0.91) showed enhancements of one of the diastereotopic protons of the epoxide (δ 3.21) and one of the hydroxymethyl protons (δ 3.42). While irradiation of the δ 3.21 epoxy proton showed enhancements of the C-8 Me (δ 0.91), hydroxymethyl proton (δ 3.42), epoxy proton (δ 2.72), and OH (δ 3.01), irradiation of the epoxy proton at δ 2.72 showed only an enhancement of the epoxy proton at δ 3.21 and the C-12 equatorial proton at δ 1.43. Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.17; H, 9.02.

***d,l*-(1α,4aα,4b*β*,7*β*,8a*β*,10a*β*)-Ethyl 7-(Epoxymethylene)-8-formyl-1,4a,8a-trimethyl-2-oxo-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1-phenanthrenecarboxylate (24).** Collins reagent:[23] prepared from dry CrO_3 (1.06 g, 10.6 mmol) and pyridine (1.67 g, 21.2 mmol) in dry CH_2Cl_2 (30 mL) under N_2 with stirring for 30 min. The reagent was cooled to 0 °C, epoxide **23** (50 mg, 1.32 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 10 min, and stirring was continued for 4 h. The reaction mixture was passed through a silica gel column (230−400 mesh, 3 g) with 50 mL of CH_2Cl_2. The organic solution was concentrated *in vacuo*, and the pyridine was removed at 0.4 mm, 50 °C. The resulting solid was triturated with hexanes to give 465 mg (94%) of **24**: mp 127−128 °C; ^{1}H NMR ($CDCl_3$) δ 9.58 (d, 1H, J = 3.7 Hz), 4.14 (m, 2H), 3.16 (distorted dd, 1H, J = 1, 4 Hz), 2.96 (6 line ddd, 1H, J = 7, 15, 15 Hz), 2.73 (distorted dd, 1H, J = 1, 4 Hz), 1.36 (s), 1.263 (t) and 1.260 (s), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 208.0, 202.2, 173.3, 64.1, 61.1, 57.6, 57.5, 57.3, 57.2, 52.0, 40.5, 40.4, 40.0, 37.7, 36.4, 35.4, 20.8 (2C), 19.8, 16.7, 13.9, 13.8; IR (KBr) 1741, 1711, 1222, 1106 cm^{-1}; HRMS calcd for $C_{22}H_{32}O_5$ (M^+) 376.2249, found 376.2236.

***d,l*-4*β*-Carboethoxy-4α,8*β*,10*β*-trimethyl-2-oxo-13-nor-16-oxoandrosta-13,14-diene (25).** A solution of epoxide **24** (143 mg, 0.38 mmol) in DMSO (2 mL) containing *p*-TsOH·H_2O (100 mg) was heated at 50 °C for 12 h with stirring. The solvent was removed *in vacuo* (50 °C at 0.4 mm); the residue was chromatographed on silica gel, and elution with 5% ethyl acetate−hexanes gave 115 mg (85%) of **25**: mp 111−112 °C (triturated with hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (br d, 1H, J = 1.5 Hz), 7.05 (br dd, 1H, J = 1.5, 2.8 Hz), 4.15 (m, 2H), 2.99 (6 line ddd, 1H, J = 6.6, 14.8, 14.8 Hz), 2.79 (br dd, 1H, J = 6.2, 16.2 Hz), 2.45 (m, 2H), 2.17 (m, 3H), 1.83 (m, 2H), 1.68 (m, 1H), 1.37 (s, 3H), 1.27 (t) and 1.26 (s) [6H], 1.20 (br dd, 1H, J = 1.7, 11.8 Hz); ^{13}C NMR ($CDCl_3$, 77.0) δ 208.5, 173.5, 136.9, 136.7, 135.1, 119.4, 61.1, 57.7, 57.5, 54.9, 40.5 (2C), 37.6, 36.5, 33.9, 25.7, 20.9, 20.6, 20.5, 18.7, 13.9, 13.6; IR (KBr) 2960−2852, 1734, 1705, 1452, 1368, 1216, 1146, 1037, 889, 800, 600 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.88; H, 8.50.

***d,l*- 3*β*-Hydroxy-4*β*-hydroxymethyl-4α,8*β*,10*β*-trimethyl-13-nor-16-oxoandrosta-13,14-diene (14).** Keto ester **25** (200 mg, 0.56 mmol) in dry Et_2O (15 mL) was added dropwise to a suspension of LAH (53.1 mg, 1.40 mmol) in dry Et_2O (5 mL) with stirring over 10 min. The reaction mixture was refluxed for 2 h, cooled, quenched with saturated Na_2SO_4 (1.5 mL), and diluted with portions of CH_2Cl_2 (total 200 mL); the organic solvent was decanted, dried (Na_2SO_4), and concentrated *in vacuo* to afford a solid. Trituration with hexanes gave 152 mg (85%) of **14**: mp 207−208 °C. The ^{1}H NMR spectrum of **14** was identical to the spectrum of **14** obtained from thioether **13**.

***d,l*-3*β*-Hydroxy-4*β*-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-4α,8*β*,10*β*-trimethyl-13-nor-16-oxoandrosta-13,14-diene (26).** TBDMSCl (115.6 mg, 0.767 mmol) and 4-DMAP (17 mg, 0.139 mmol) were added to diol **14** (221.7 mg, 0.697 mmol) and Et_3N (107 μL, 0.769 mmol) in CH_2Cl_2 (15 mL) under N_2. The reaction mixture was stirred at rt for 28 h, diluted with CH_2Cl_2 (75 mL), washed with two (40 mL) portions of H_2O and two (40 mL) portions of brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a thick oil. Chromatography on silica gel (230−400 mesh, 6 g) and elution with 0.75% ethyl acetate−hexanes gave 286 mg (95%) of **26**: ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 1H, J = 1.5 Hz), 7.04 (br s, 1H), 4.28 (d, 1H, O*H*, J = 7.1 Hz), 4.21 (d, 1H, J = 10 Hz), 3.45 (d, 1H, J = 10 Hz), 3.28 (m, 1H), 2.76 (dd, 1H, J = 6.0, 16.2 Hz), 2.44 (m, 1H), 2.10 (m, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 0.91 (s, 9H), 0.87 (s, 3H), 0.093 (s) and 0.088 (s) [6H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 137.1, 136.8, 135.0, 119.6, 80.3, 65.3, 56.3, 56.2, 42.6, 41.4, 38.3, 37.1, 34.1, 28.0, 26.1, 25.8, 22.9, 20.6, 18.8, 18.4, 18.1, 17.1, −5.7, −5.8; IR (KBr) 3408, 2943, 2864, 1469, 1379, 1040, 799 cm^{-1}; HRMS calcd for $C_{26}H_{44}O_3Si$ (M^+) 432.3059 [$-C_4H_9$, calcd $C_{22}H_{35}O_3Si$, 375.2355], found 375.2323.

***d,l*-4*β*-[(*tert*-Butyldimethylsilyloxy)methyl]-4α,8*β*,10*β*-trimethyl-3-oxo-13-nor-16-oxoandrosta-13,14-diene (27).** A mixture of dry CrO_3 (397.2 mg, 3.97 mmol) and pyridine (627.6 mg, 7.94 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 15 min. Alcohol **26** (286 mg, 0.662 mmol) in dry CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred at rt for 2 h and passed through a short Celite−silica gel column, eluting with 30% ethyl acetate−hexanes. The organic solvent was removed *in vacuo*; the residue was chromatographed on silica gel (230−400 mesh, 6 g) and elution with 2% ethyl acetate−hexanes gave 229 mg (80%) of **27**: mp 141−142 °C; ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 1H, J = 1.5 Hz), 7.03 (br s, 1H), 3.84 (d, 1H, J = 10.0 Hz), 3.65 (d, 1H, J = 10.0 Hz), 2.77 (br dd, 1H, J =5.7, 16.2 Hz), 2.61 (ddd, 1H, J = 6.9, 12.7, 15.5 Hz), 2.44 (m) and 2.34 (ddd, J = 3.0, 6.0, 15.5 Hz) [2H], 2.10 (m, 2H), 1.23 (s, 3H), 1.08 (s, 6H), 0.85 (s, 9H), 0.001 (s, 6H); ^{13}C NMR ($CDCl_3$, 77.51) δ 214.9, 137.5, 137.4, 135.6, 120.1, 66.2, 57.6, 56.0, 54.6, 41.6, 40.2, 37.6, 35.5, 34.6, 26.5, 26.3, 21.8, 21.1, 20.7, 19.2, 18.7, 16.7, −5.1, −5.2; IR (KBr) 2954−2852, 1721, 1097, 838, 787, 602 cm^{-1}; HRMS calcd for $C_{26}H_{42}O_3Si$ (M^+) 430.2902 [$-CH_3$, $C_{25}H_{39}O_3Si$, calcd 415.2667], found 415.2691. Anal. Calcd for $C_{26}H_{42}O_3Si$: C, 72.51; H, 9.83. Found: C, 72.58; H, 10.09.

***d,l*-4*β*-[(*tert*-Butyldimethylsilyl)oxymethyl]-4α,8*β*,10*β*-trimethyl-3-[(trimethylsilyl)oxy]-13-nor-16-oxoandrosta-2,13,14-triene (28).** LDA was prepared from *n*-BuLi (2.5 M in hexanes, 251 μL, 0.628 mmol) and diisopropylamine (89 μL, 0.628 mmol) in dry THF (3 mL) at 0 °C under N_2. The solution was cooled to −78 °C, ketone **27** (180 mg, 0.419 mmol) in THF (9 mL) was added over 7 min, and stirring was continued for 30 min. Me_3SiCl (106 μL, 0.837 mmol) was added *via* a syringe, the reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to rt and stirred for 1.5 h. Direct chromatography on silica gel (230−400 mesh, 2 g) and elution with hexanes afforded 185 mg (88%) of **28**: ^{1}H NMR ($CDCl_3$) δ 7.10 (br s, 1H), 7.05 (br s, 1H), 4.66 (dd, 1H, J = 2, 6.6 Hz), 3.80 (d, 1H, J = 10 Hz), 3.49 (d, 1H, J = 10 Hz), 2.78 (m, 1H), 2.44 (m, 1H), 2.09 (m, 2H), 1.24 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.19 (s, 9H), 0.03 (s, 6H). The silyl enol ether was not characterized further but submitted directly to epoxidation.

***d,l*-4*β*-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4α,8*β*,10*β*-trimethyl-3-oxo-2α-trimethylsilyloxy-13-nor-16-oxoandrosta-13,14-diene (29) and *d,l*-4*β*-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2α-hydroxy-4α,8*β*,10*β*-trimethyl-3-oxo-13-nor-16-oxoandrosta-13,14-diene (30).** *m*-Chloroperoxybenzoic acid (80−90%, 26 mg, 0.12 mmol) was added to silyl enol ether **28** (52 mg, 0.10 mmol) in CH_2Cl_2 (1.5 mL) at rt. After the reaction mixture was stirred for 1 h, additional *m*-CPBA (5 mg) was added and stirring was continued for 30

min. Concentration of the reaction mixture *in vacuo*, chromatography on silica gel (230−400 mesh, 3 g), and elution with 5% ethyl acetate−hexanes afforded 26 mg of **29** and **30.** For pure **30**: ^{1}H NMR ($CDCl_3$) δ 7.05 (d, 1H, J = 1.5 Hz), 7.02 (br d, 1H, J = 1.5 Hz), 4.53 (ddd, 1H, H_{2ax}, J = 3.9, 6.5, 12.5 Hz), 4.02 (d, 1H, HC*H*OSi, J = 10.2 Hz), 3.66 (d, 1H, OH, J = 3.9 Hz), 3.45 (d, 1H, *H*CHOSi, J = 10.2 Hz), 2.77 (br dd, 1H, J = 5.8, 16.5 Hz), 2.59 (dd, J = 6.7, 12.5 Hz) and 2.58 (m) [2H], 2.13 (m, 1H), 1.25 (s), 1.23 (s), 1.22 (s) [9H], 0.82 (s, 9H), ~0.02 (s) and ~0.03 (s); ^{13}C NMR ($CDCl_3$, 77.50) δ 214.3, 137.5, 137.2, 135.6, 119.9, 70.5, 66.2, 59.0, 56.4, 55.2, 50.4, 41.7, 38.5, 34.8, 26.9, 26.2, 21.0, 20.7, 20.4, 19.3, 18.6, 18.1, −5.1. The mixture of **29** and **30** was submitted directly to desilylation.

***d,l*-Isospongiadiol (3).** *n*-Tetrabutylammonium fluoride (1.0 M in THF, 0.136 mmol, 136 μL) was added *via* a syringe to a mixture of **29** and **30** (26 mg) in THF (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and diluted with CH_2Cl_2 (30 mL); the organic solution was washed with H_2O (15 mL) and dried (Na_2SO_4), and concentration *in vacuo* gave a crude solid. Addition of CH_2Cl_2 and filtration gave semipure **3**. Concentration of the filtrate and chromatography on a silica gel sep-pack gave additional semipure **3**. Subsequent chromatography on a second silica gel sep-pack and elution with ethyl acetate−hexanes gave 12 mg (35% from **28**) of **3**: mp 184−186 °C (lit.[1] mp 181−183 °C); IR (KBr) 3529, 3402, 2967−2840, 1711, 1058, 605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 1.5 Hz) and 7.06 (d, J = 1.2 Hz) [2H], 4.62 (dd, 1H, J = 6.5, 12.3 Hz), 4.15 (d, 1H, J = 11.0 Hz), 3.66 (d, 1H, J = 11.0 Hz), 2.80 (dd, 1H, J = 6.1, 16.5 Hz), 2.64 (dd, 1H, J = 6.6, 12.6 Hz), 1.30 (s), 1.26 (s), and 1.25 (s) [9H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 214.1, 137.0, 136.6, 135.1, 119.3, 69.9, 65.6, 58.6, 55.8, 54.5, 49.5, 41.1, 38.0, 34.3, 26.4, 20.5, 20.0, 19.3, 18.8, 17.6. The ^{13}C NMR spectrum of *d,l*-**3** was identical to the spectrum of natural **3**.

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Supporting Information Available: ^{1}H NMR spectra (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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