Advanced Tetracycles in a Stereoselective Approach to *d,l*-Spongiatriol and Related Metabolites: The Use of Radicals in the Synthesis of Angular Electrophores

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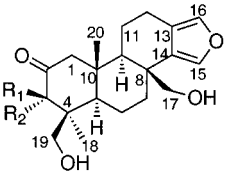
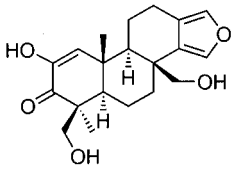
A stereoselective radical cascade cyclization of polyene **6**, containing an α,β-unsaturated cyano group, was employed to control six contiguous chiral centers and to introduce a C-8 angular CN group in tricycle **7**. The cyano group was ultimately utilized as an entry to a C-8 angular hydroxymethyl group. Compound **7** was converted into two key tetracycles **22** and **25**, respectively, each possessing an intact D-furan ring system and containing the necessary functionality for further chemical elaboration to the highly oxygenated spongians **1**-**5**.

Introduction

The highly oxygenated tetracyclic diterpenes spongiatriol (**1**)[1,2] and epispongiatriol (**2**) were isolated from a *Spongia* species off the Great Barrier Reef in the Australian waters. The diosphenol **3**,[3] a sponge metabolite, was isolated from the nudibranch *Casella* atromarginata, at Trincomallee, Sri Lanka. The source of the diterpenes from the nudibranch is presumed to be obtained indirectly from a sponge in the mollusk's diet. Two additional spongian metabolites (**4** and **5**) possessing an A-ring lactone system have also been isolated from a *Spongia* species from the Great Barrier Reef.[2] The latter metabolite (**5**) was shown to possess moderate cytotoxicity to P338 murine leukemia cells.



1: R_1 = H, R_2 = OH
2: R_1 = OH, R_2 = H



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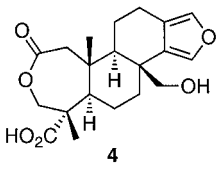

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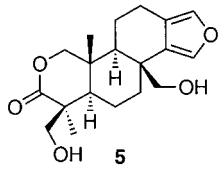

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Recently we[4] reported the synthesis of *d,l*-isospongiadiol using in part an intramolecular oxidative free-radical cyclization to introduce stereoselectively five of the six stereogenic centers present in the spongian.[5] We have also shown that an angular electrophore[6] can readily be introduced in polycycles via a radical cascade cyclization of a polyene containing an α,β-unsaturated cyano moiety and have extended this type of methodology in the synthesis of a D-homosteroid.[7] The combination of these two strategies (Scheme 1) should provide a stereoselective entry to spongiatriols **1**−**5** via the common intermediate **8**. Here, intramolecular oxidative radical cyclization of **6** can be effectively utilized to (1) control the desired 6-endo-trig mode in the second radical cyclization step; (2) stereoselectively introduce, in one step, six key chiral centers at C-4, 5, 8, 9, 10, and 14 in tricycle **7**; (3) provide an angular 8β-cyano group for further elaboration to a hydroxymethyl group; (4) introduce appropriate functionality in the A-ring system; and (5) provide a functional group in the termination step that can be used in the construction of the D-furan ring system. We describe here the application of this type of radical methodology in the synthesis of two advanced tetracycle intermediates that could ultimately be utilized in the total synthesis of the targeted spongians.

Results and Discussion

The synthesis of polyene **6** was achieved by using a similar protocol previously developed by us[6] as detailed in Scheme 2. Horner−Emmons reaction[8] of the potassium salt of cyano phosphonate **9**[6] with aldehyde **10** (eq 1) gave an 81:19 mixture of **11** and the corresponding

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(1) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Noack, K.; Oberhansli, W. E.; Schonholzer, P. *Aust. J. Chem.* **1979**, *32*, 867.
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(3) Sheuer, P. J.; de Silva, E. D. *Heterocyclics* **1982**, *17*, 167.
(4) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z.; Riberio, A. A. *J. Org. Chem.* **1996**, *61*, 1806.
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(6) Zoretic, P. A.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 1751.
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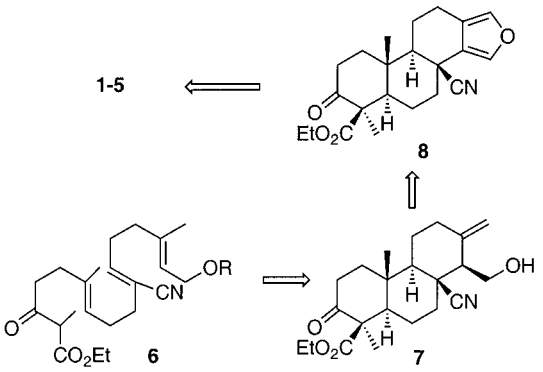
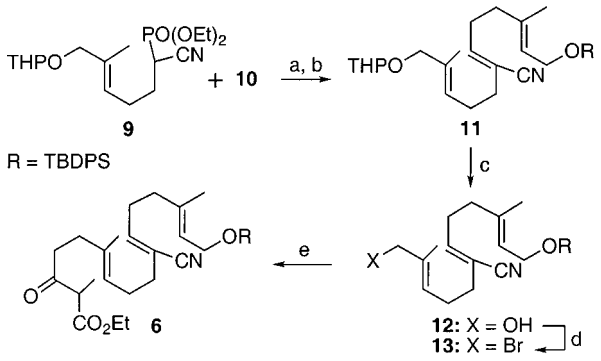
Scheme 1

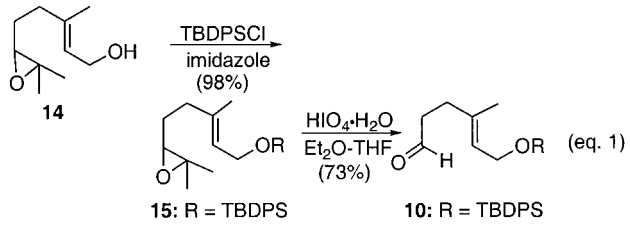


Scheme 2[a]



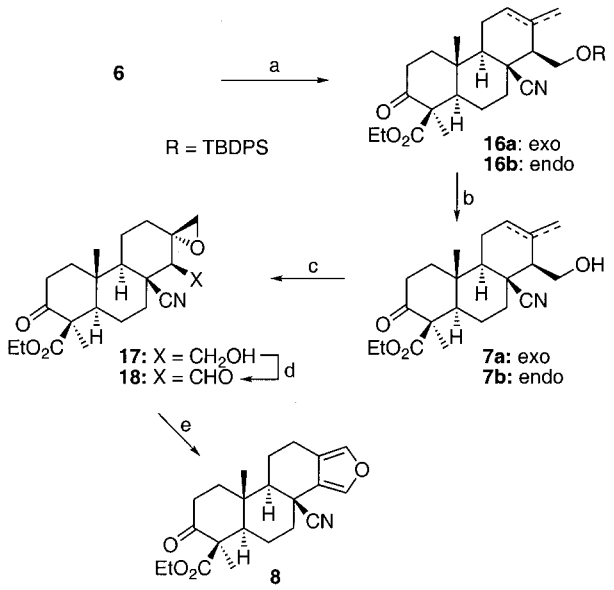
[a] Key: (a) $KN(SiMe_3)_2$, toluene, −78 °C; (b) **10**, −78 °C → rt, overnight; (c) MeOH, *p*-TsOH·py; (d) CBr_4, Ph_3P, CH_2Cl_2; (e) $LiCH_2C(O)CMe(Na)CO_2Et$, 0 °C, THF; then aqueous HCl.

2*E*,6*E*-isomer. The desired 2*E*,6*Z*-nitrile **11** was chromatographically separated from the isomer to afford pure **11** in 78% yield. Conversion of **11** to polyene **6** (44% overall yield) in three steps was realized by (1) cleavage of the THP protecting group in **11** to give alcohol **12**; (2) conversion of alcohol **12** to the corresponding bromide **13**; and (3) alkylation of **13** (inverse addition) with the dianion[9] of ethyl 2-methylacetoacetate.



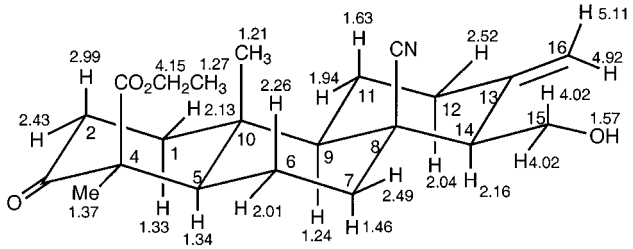
Intramolecular oxidative free-radical cyclization of **6** (Scheme 3) with a 2:1 ratio of $Mn(OAc)_3·2H_2O$ in tandem with $Cu(OAc)_2·H_2O$[10,11] in a 0.1 M solution of deaerated HOAc afforded an 81:19 ratio of **16a** and **16b** in 58% yield, after chromatography. Since it was determined that the exo and endo products could be separated more easily at the alcohol stage, the mixture of **16** was directly

Scheme 3[a]



[a] Key: (a) $Mn(OAc)_3·2H_2O$, $Cu(OAc)_2·H_2O$, HOAc, Ar; (b) *n*-Bu_4NF, THF; (c) *m*-CPBA, CH_2Cl_2; (d) $CrO_3·2py$, CH_2Cl_2; (e) *p*-TsOH·H_2O, DMSO, 50 °C.

desilylated with *n*-Bu_4NF[12] to give **7a** and **7b** in 88% yield. Subsequent chromatography on silica gel afforded pure **7a** (70%).



A series of 2D COSY, HMQC, HMBC, and 1D APT NMR studies was used to determine the assignment of each proton and carbon resonance signal in **7a**. Using these assignments, NOE difference spectra (NOEDS) of **7a** were used to confirm the stereochemistry derived from the cyclization process. Irradiation of the C-10 Me (*δ* 1.21) showed enhancements of the ester methylene protons (*δ* 4.15), C-2 axial proton (*δ* 2.99), C-6 axial proton (*δ* 2.26), C-1 equatorial proton (*δ* 2.13), and the C-11 axial proton (*δ* 1.63). Likewise irradiation of the C-9 axial proton (*δ* 1.24) gave a strong enhancement of the C-14 axial proton (*δ* 2.16), the C-5 axial proton (*δ* 1.34), and the C-1 axial proton (*δ* 1.33) and a weaker enhancement to the C-12 axial proton (*δ* 2.04), the C-7 axial proton (*δ* 1.46), and the C-11 equatorial proton (*δ* 1.94). Irradiation of both of the C-1 axial (*δ* 1.33) and the C-5 axial (*δ* 1.34) protons showed enhancements to the C-9 axial proton (*δ* 1.24), C-2 equatorial proton (*δ* 2.43), C-1 equatorial proton (*δ* 2.13), C-6 equatorial proton (*δ* 2.01), and the C-7 axial proton (*δ* 1.46), thus confirming the all-trans stereochemistry and the C-4 *β*-disposition of the carbethoxy group as shown in **7a**. It

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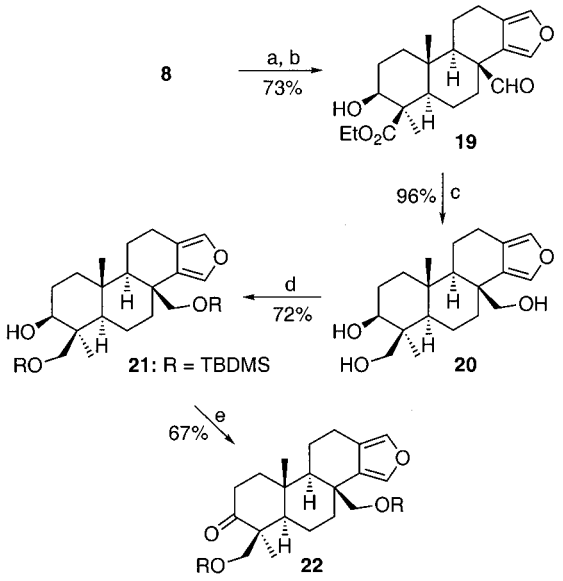
(11) For recent radical reviews, see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Malacria, M. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 289. (d) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (e) Melikyan, G. G. *Synthesis* **1993**, 833.
(12) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Scheme 4[a]



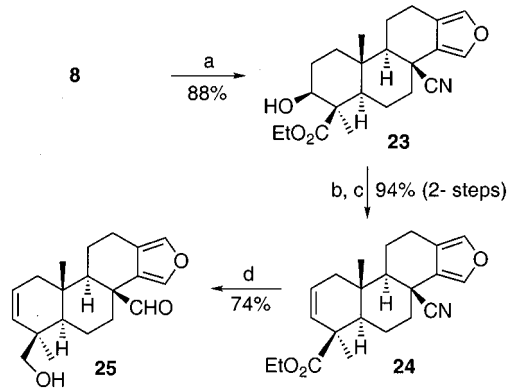
[a] Key: (a) 6.0 equiv of DIBALH, toluene, −78 °C; (b) 6% HOAc, saturated with NaOAc, −78 °C → rt; (c) LAH, THF, Δ; (d) 4.4 equiv of TBDMSCl, 4-DMAP, CH_2Cl_2, rt; (e) CrO_3·2py, CH_2Cl_2, rt.

is also noted that the large deshielding effect of the C-10 Me (δ 1.21) in **7a** is comparable to the chemical shift (δ 1.28) observed for an analogue[6] possessing an angular C-8 CN group which is consistent with the C-10 Me in **7a** being 1,3-diaxially disposed to the nitrile and in its deshielding cone. The stereospecificity derived in tetracycles **16** from cyclization of polyene **6** is presumably due to a stepwise process opposed to a concerted one in which the most stable ring system is formed at each cyclization stage in the radical cascade sequence.

The construction of the intact spongian skeleton **8** was realized from **7a** in three steps in 55% overall yield. Reaction of **7a** with *m*-CPBA gave epoxide **17**. The epoxide stereochemistry in **17** is tentatively assigned in analogy with that observed in a similar case.[4] It is also noted here that the C-13 center will ultimately be destroyed during the formation of the D-furan ring system. Thus, Collins oxidation of **17** followed by treatment of the resulting aldehyde **18** with *p*-TsOH·H_2O in DMSO gave tetracycle **8**.

With the spongian skeleton secured, our next objective was to introduce the desired hydroxymethyl group at C-8 and then to modify the A-ring system in an attempt to obtain two different intermediates that could be used in separate approaches to the afore-mentioned spongians. Toward these ends compounds **22** and **25** derivable from **8** were targeted. Reaction of **8** (Scheme 4) with 6.0 equiv of DIBALH in toluene at −78 °C and subsequent hydrolysis of the resulting imine with 6% HOAc saturated with NaOAc gave ester **19** in 73% yield, after chromatography. Presumably in the reduction of **8** the keto group is preferentially reduced to form an intermediate in which the generated C-3 β-diisobutylaluminum alkoxide group can chelate with the carbonyl of the ester, thus blocking complexation with a DIBALH molecule. Hydride reduction of **19** with LAH afforded triol **20** (96%). Preferential protection of the primary alcohols in the presence of the secondary alcohol was effected by reaction of **20** with TBDMSCl[12] in the presence of 4-DMAP[13] and

Scheme 5[a]



[a] Key: (a) $NaBH_4$, EtOH; (b) CF_3SO_2Cl, 4-DMAP, CH_2Cl_2, 0 °C; (c) 4-DMAP, CH_2Cl_2, Δ; (d) 3.3 equiv of DIBALH, −78 °C, toluene, then 6% HOAc saturated with NaOAc, −78 °C → rt.

triethylamine to give **21** (72%). Subsequent oxidation of **21** with Collins reagent yielded the targeted ketone **22** (67%).

A second intermediate **25** (Scheme 5) was also targeted, since it was anticipated that such a derivative should be suitable for further elaboration to metabolite **4**. The introduction of the $\Delta^{2,3}$-double bond in **25** was acheived in the following manner. Hydride reduction of **8** gave alcohol **23** (88%). Treatment of **23** with $POCl_3$ in refuxing pyridine afforded **24** in only 40% yield. However it was found that a two-step process produced **24** in excellent yield. Thus, reaction of alcohol **23** with trifluoromethanesulfonyl chloride at 0 °C in the presence of 4-DMAP gave a mixture of the corresponding sulfonated ester (major product) and a trace of **24**. Heating this mixture with 4-DMAP in refluxing CH_2Cl_2 yielded **24** (94%, two steps).

The introduction of the desired C-4β-hydroxymethyl group present in **25** appeared at first to be somewhat difficult. It is known that $LiBH_4$ in THF can selectively reduce an ester in the presence of a nitrile. Attempted $LiBH_4$ reduction of **24** in our case gave only partial reduction of the ester group. However, it was encouraging to find that reduction of **24** with 3.3 equiv of DIBALH at −78 °C in toluene followed by hydrolysis of the intermediate imine with 6% HOAc saturated with NaOAc gave the targeted hydroxy aldehyde **25** directly in 74% yield. The stereochemistry shown in **25** was proven to be correct on the basis of the following NOE study. Irradition of the 20-Me (δ 0.88) in **25** gave enhancements of the aldehydic proton (δ 9.86), the vinyl proton (δ 5.63), one of the hydroxymethyl protons (δ 3.36), the C-1 equatorial proton (δ 2.15), and the C-11 axial proton (δ 2.07). Indirectly this NOE study also confirms the assigned stereochemistry in tricycle **7a** vide supra.

Conclusion

In conclusion, a highly stereoselective radical cascade cyclization strategy was developed as a facile entry to various oxygenated spongiatriols. A key factor being the introduction of a latent angular electrophore at the cyclization stage which ultimately served as an entry to the desired angular hydroxymethyl group. In addition, the synthetic intermediates **22** and **25** can serve as key compounds en route to spongians **1**−**5**.

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Experimental Section

General Procedures. NMR spectra were obtained at 200, 300, 500, and 600 MHz. C and H microanalyses were obtained from Galbraith Laboratories. HRMS analyses were obtained from the Mass Spectroscopy Facility at Duke. All melting points 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 performed 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.

(2*E*,6*Z*,10*E*)-12-[(*tert*-Butyldiphenylsilyl)oxy]-6-cyano-2,10-dimethyl-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,6,10-dodecatriene (11). $KN(SiMe_3)_2$ (0.5 M in toluene, 31.8 mL, 15.9 mmol) was added dropwise to phosphonate **9** (5.95 g, 16.6 mmol) in dry toluene (60 mL) at −78 °C over 30 min under N_2. Stirring was continued for 1 h, aldehyde **10** (5.06 g, 13.8 mmol) in toluene (50 mL) was added over 1 h, stirring was continued for 4 h at −78 °C, and then the reaction mixture was gradually warmed to rt and stirred overnight. The reaction mixture was diluted with Et_2O, and the organic solution was washed with H_2O, brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel (70−230 mesh, 80 g) and elution with 2% and 5% EtOAc−hexanes gave 6.2 g (78%) of **11** and 450 mg of a mixture of **11** and the 2*E*,6*E*-isomer. For **11**: ^{1}H NMR ($CDCl_3$) δ 7.63−7.74 (m, 4H), 7.32−7.45 (m, 6H), 6.10 (t, 1H, J = 7.5 Hz), 5.32−5.45 (m, 2H), 4.59 (t, 1H, J = 3.2 Hz), 4.22 (d, 2H, J = 6.2 Hz), 4.10 (d, 1H, J = 11.8 Hz), 3.84 (d, J = 11.8 Hz) and 3.80−3.94 (m) [2H], 3.45−3.56 (m, 1H), 2.44 (m, 2H), 2.20−2.31 (m, 4H), 2.09 (m, 2H), 1.67 (s), 1.46 (s) and 1.41−1.90 (m) [12H], 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 77.0) δ 147.3, 135.5, 135.1, 133.9, 129.5, 127.6, 125.4, 124.8, 117.5, 114.3, 97.5, 72.4, 62.1, 60.9, 38.1, 34.0, 30.6, 29.5, 26.8, 26.3, 25.4, 19.4, 19.1, 16.1, 14.1; IR (neat) 2212 cm^{-1}. Anal. Calcd for $C_{36}H_{49}O_3NSi$: C, 75.61; H, 8.64; N, 2.45. Found: C, 75.74; H, 8.69; N, 2.53.

(2*E*,6*Z*,10*E*)-12-[(*tert*-Butyldiphenylsilyl)oxy]-6-cyano-2,10-dimethyl-2,6,10-dodecatrien-1-ol (12). A solution of nitrile **11** (1.00 g, 1.75 mmol) and *p*-TsOH·py (48 mg, 0.193 mmol) in MeOH (10 mL) was stirred for 10 h at rt. The solvent was removed in vacuo and the residue diluted with CH_2Cl_2. The organic solution was washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel (230−400 mesh, 20 g) and elution with 20% EtOAc−hexanes gave 0.70 g (82%) of **12**: ^{1}H NMR ($CDCl_3$) δ 7.65−7.74 (m, 4H), 7.33−7.45 (m, 6H), 6.11 (t, 1H, J = 7.5 Hz), 5.32−5.44 (m, 2H), 4.21 (d, 2H, J = 6.2 Hz), 3.99 (br s, 2H), 2.45 (m, 2H), 2.22−2.30 (m, 4H), 2.09 (m, 2H), 1.67 (s, 3H), 1.46 (br s, 4H, CH_3 and OH), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 77.0) δ 147.4, 136.5, 135.5, 135.0, 133.7, 129.5, 127.5, 125.3, 122.8, 117.6, 114.2, 68.3, 60.9, 38.0, 33.9, 29.4, 26.7, 26.3, 19.0, 16.0, 13.7; IR (neat) 3447, 2215 cm^{-1}. Anal. Calcd for $C_{31}H_{41}NO_2Si$: C, 76.34; H, 8.47; N, 2.87. Found: C, 75.99; H, 8.26; N, 3.26.

(2*E*,6*Z*,10*E*)-1-Bromo-12-[(*tert*-Butyldiphenylsilyl)oxy]-6-cyano-2,10-dimethyl-2,6,10-dodecatriene (13). Carbon tetrabromide (2.85 g, 8.58 mmol) was added in several portions to alcohol **12** (2.79 g, 5.73 mmol) and Ph_3P (1.95 g, 7.44 mmol) in dry CH_2Cl_2 (30 mL) at rt, and the reaction mixture was stirred for 1.5 h. The solvent was removed in vacuo. Hexanes (100 mL) was added to the residue, and the triphenylphosphine oxide was removed by filtration. Concentration of the filtrate and subsequent chromatography on silica gel (70−230 mesh, 20 g) eluting with 2% EtOAc−hexanes gave 2.95 g (94%) of **13**: ^{1}H NMR ($CDCl_3$) δ 7.63−7.74 (m, 4H), 7.32−7.46 (m, 6H), 6.10 (t, 1H, J = 7.5 Hz), 5.35−5.57 (m, 2H), 4.21 (d, 2H, J = 6.2 Hz), 3.94 (s, 2H), 2.45 (m, 2H), 2.20−2.34 (m, 4H), 2.10 (m, 2H), 1.77 (s, 3H), 1.46 (s, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 77.0) δ 147.8, 135.5, 135.0, 134.0, 133.8, 129.5, 128.4, 127.6, 125.4, 117.4, 113.8, 60.9, 40.9, 38.0, 33.6, 29.5, 26.8, 19.1, 16.1, 14.8; IR (neat) 2217 cm^{-1}. Anal. Calcd for $C_{31}H_{40}BrNOSi$: C, 67.62; H, 7.32; N, 2.54. Found: C, 67.22; H, 7.17; N, 2.34.

(*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-3,7-dimethyl-6,7-oxido-2-octene (15). Imidazole (7.89 g, 116.0 mmol), TBDPSCl (15.4 mL, 58.0 mmol), and **14** (7.59 g, 44.6 mmol) in DMF (40 mL) were stirred at rt for 2.5 h. The solvent was removed in vacuo (50 °C, 0.5 mm), and the residue was diluted with CH_2Cl_2. The organic solution was washed with H_2O, brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel (70−230 mesh, 100 g) eluting with 2% EtOAc−hexanes gave 17.9 g (98%) of **15**: ^{1}H NMR ($CDCl_3$) δ 7.63−7.74 (m, 4H), 7.32−7.45 (m, 6H), 5.39−5.50 (m, 1H), 4.23 (d, 2H, J = 6.2 Hz), 2.70 (t, 1H, J = 6.2 Hz), 2.02−2.19 (m, 2H), 1.47−1.61 (m, 2H), 1.46 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 77.0) δ 136.0, 135.5, 133.9, 129.5, 127.5, 124.5, 64.0, 61.0, 58.3, 36.0, 27.1, 26.8, 24.8, 19.1, 18.7, 16.3. The epoxide was not characterized further but submitted to oxidation.

(*E*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-4-methyl-4-hexenal (10). $HIO_4·2H_2O$ (10.4 g, 45.7 mmol) in THF (100 mL) was added to a solution of **15** (17.0 g, 41.6 mmol) in Et_2O (200 mL) at 0 °C over 1 h, and stirring was continued for an additional 1 h at 0 °C. The reaction mixture was diluted with Et_2O, washed with H_2O, saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (70−230 mesh) eluting with 2% EtOAc−hexanes gave 11.1 g (73%) of **10**: ^{1}H NMR ($CDCl_3$) δ 9.75 (t, 1H, J = 1.7 Hz), 7.63−7.74 (m, 4H), 7.32−7.45 (m, 6H), 5.34−5.43 (m, 1H), 4.21 (dd, 2H, J = 0.8, 6.2 Hz), 2.44−2.56 (m, 2H), 2.22−2.36 (m, 2H), 1.44 (s, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 77.0) δ 202.2, 135.5, 134.9, 134.7, 133.8, 129.5, 127.63, 127.56, 124.9, 60.9, 41.8, 31.4, 26.8, 26.5, 19.1, 16.4. Anal. Calcd for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25. Found: C, 75.25; H, 8.36.

Ethyl (6*E*,10*Z*,14*E*)-16-[(*tert*-Butyldiphenylsilyl)oxy]-10-cyano-2,6,14-trimethyl-3-oxo-6,10,14-hexadecatrienoate (6). Ethyl 2-methylacetoacetate (98%, 0.946 g, 6.44 mmol) was added via a syringe to a suspension of NaH (60% in mineral oil, 257 mg, 6.44 mmol) and HMPA (1 mL) in dry THF (20 mL) at 0 °C under N_2 over 15 min. The reaction mixture was stirred at 0 °C for 30 min. *n*-BuLi (2.5 M in hexanes, 2.57 mL, 6.44 mmol) was added via a syringe over 15 min, and stirring was continued for 30 min. The generated dianion of ethyl 2-methylacetoacetate was added to bromide **13** (2.95 g, 5.36 mmol) in dry THF (10 mL) at 0 °C over 45 min. The reaction mixture was stirred for 1 h at 0 °C, quenched with 10% HCl (pH = 7), and then diluted with CH_2Cl_2 (100 mL). The organic solution was washed with H_2O, brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (230−400 mesh, 20 g) and elution with 5% EtOAc−hexanes gave 2.18 g (66%) of **6**: ^{1}H NMR ($CDCl_3$) δ 7.63−7.74 (m, 4H), 7.32−7.45 (m, 6H), 6.09 (t, 1H, J = 7.4 Hz), 5.33−5.45 (m, 1H), 5.02−5.13 (m, 1H), 4.12−4.28 (m, 4H), 3.51 (q, 1H, J = 7.2 Hz), 2.57−2.71 (m, 2H), 2.36−2.53 (m, 2H), 2.04−2.32 (m, 8H), 1.60 (s, 3H), 1.46 (s, 3H), 1.33 (d, J = 7.2 Hz) and 1.27 (t, J = 7.2 Hz) [6H], 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 77.0) δ 205.4, 170.5, 147.3, 135.5, 135.4, 135.1, 133.9, 129.5, 127.6, 125.4, 122.7, 117.6, 114.4, 61.3, 60.9, 52.9, 39.9, 38.1, 34.2, 33.1, 29.5, 26.8, 26.7, 19.1, 16.1, 14.1, 12.8; IR (neat) 2214, 1743, 1716 cm^{-1}. Anal. Calcd for $C_{38}H_{51}NO_4Si$: C, 74.35; H, 8.37; N, 2.28. Found: C, 74.19; H, 8.32; N, 2.59.

***d,l*-(1α,4aα,4b*β*,8*β*,8a*β*,10a*β*)-Ethyl 8-[(*tert*-Butyldiphenylsilyl)oxy]-8a-cyano-1,4a-dimethyl-7-methylene-2-oxo-1,4,4a,4b,5,8,8a,9,10,10a-decahydro-1-phenanthrenecarboxylate (16a) and *d,l*-(1a,4aα,4b*β*,8*β*,8a*β*,10a*β*)-Ethyl 8-[(*tert*-Butyldiphenylsilyl)oxy]-8a-cyano-1,4a,7-trimethyl-2-oxo-1,4,4a,4b,5,8,8a,9,10,10a-decahydro-1-phenanthrenecarboxylate (16b).** To keto ester **6** (1.54 g, 2.51 mmol) in deaerated HOAc (25 mL) were added $Mn(OAc)_3·2H_2O$ (98%, 1.37 g, 5.02 mmol) and $Cu(OAc)_2·H_2O$ (97%, 0.52 g, 2.51 mmol). The reaction mixture was stirred at rt for 10 h and then passed through a bed of Celite (salts washed with 100 mL of CH_2-

Cl_2). The organic solution was washed with H_2O, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo gave a thick oil. Chromatography on silica gel (270−400 mesh, 20 g) and elution with 10% EtOAc−hexanes gave 887 mg (58%) of an 81:19 mixture of **16a** and **16b**. The ratio was determined by integration of the resonance signals at δ 5.55 (br s) and 4.99 (s) and 4.84 (s). It was found that the isomers could be more readily separated at the alcohol stage. Thus, the mixture was submitted directly to a desilylation reaction.

***d,l*-(1α,4aα,4bβ,8β,8aβ,10aβ)-Ethyl 8a-Cyano-8-(hydroxymethyl)-1,4a-dimethyl-7-methylene-2-oxo-1,4,4a,4b,5,8,8a,9,10,10a-decahydro-1-phenanthrenecarboxylate (7a) and *d,l*-(1α,4aα,4bβ,8β,8aβ,10aβ)-Ethyl 8a-Cyano-8-(hydroxymethyl)-1,4a,7-trimethyl-2-oxo-1,4,4a,4b,5,8,8a,9,10,10a-decahydro-1-phenanthrenecarboxylate (7b).** *n*-Bu_4NF (1.0 M in THF, 2.9 mL, 2.90 mmol) was added dropwise via a syringe to an 81:19 mixture of **16a** and **16b** (887 mg, 1.45 mmol) in dry THF (10 mL) at rt. The reaction mixture was stirred for 2 h and then diluted with CH_2Cl_2 (100 mL). The organic solution was washed with H_2O, and brine, dried (Na_2SO_4), and concentrated in vacuo to give a solid. Chromatography on silica gel (230−400 mesh, 20 g) and elution with 30% EtOAc−hexanes gave 94 mg (17%) of **7b** and 381 mg (70%) of **7a**. For **7a**: mp 176−177.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.11 (s, 1H), 4.92 (s, 1H), 4.15 (m, 2H, OCH_2CH$_3$), 4.02 (m, 2H, CH_2OH), 2.99 (6 line ddd, 1H, H_{2ax}, J = 6.5, 14.9, 14.9 Hz), 2.52 (apparent dt, H_{12eq}, J = ∼3.4, ∼13.1 Hz) and 2.49 (dt, H_{7eq}, J = 3.4, 13.5 Hz) [overlapping, 2H], 2.43 (dq, 1H, H_{2eq}, J = 2.4, 15.0 Hz), 2.26 (m, 1H, H_{6ax}), 2.16 (m, H_{14ax}) and 2.13 (ddd, H_{1eq}, J = 2.4, 6.6, 13.2 Hz) [overlapping, 2H], 2.04 (6 line ddd, H_{12ax}, J = 4.6, 13.1, 13.1 Hz) and 2.01 (dq, H_{6eq}, J = ∼3.4, ∼14.9 Hz) [overlapping, 2H], 1.94 (dp, 1H, H_{11eq}, J = ∼2.5, ∼13.5 Hz), 1.63 (8 line dddd, 1H, H_{11ax}, J = 4.1, 13.0, 13.0, 13.0 Hz), 1.57 (dd, OH, J = 4.2, 7.2 Hz, slow exchange), 1.46 (6-line ddd, 1H, H_{7ax}, J = 3.6, 13.6, 13.6 Hz), 1.37 (s, 3H, C4-Me), 1.34 (dd, H_{5ax}, J = 2.4, 12.5 Hz) and 1.33 (6-line ddd, H_{1ax}, J = ∼4.6, ∼13.6, ∼13.6 Hz) [overlapping, 2H], 1.27 (t, 3H, J = 7.1 Hz), 1.24 (dd, 1H, H_{9ax}, J = 2.8, 12.4 Hz), 1.21 (s, 3H, C10-Me); ^{13}C NMR ($CDCl_3$, 166 MHz) δ 207.6 (C3), 173.1 (ester CO), 144.0 (C13), 121.4 (CN), 110.0 (=CH_2), 61.4 (ethyl CH_2), 59.5 (CH_2OH), 57.2 (C4), 56.7 (C5), 56.3 (C9), 54.6 (C14), 43.6 (C8), 39.9 (C1), 38.2 (C10), 36.6 (C7), 36.4 (C2 and C12), 25.5 (C11), 21.6 (C6), 20.8 (C4-Me), 13.9 (ethyl CH_3), 12.7 (C10-Me); IR (KBr) 3446, 2223, 1746, 1701. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.35; H, 8.44; N, 3.62. For **7b**: mp 148−149 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65 (br s, 1H), 3.99−4.22 (m, 3H), 2.75 (dt, 1H, J = 3.3, 13.7 Hz), 2.42 (dq, 1H, J = 2.3, 14.9 Hz), 3.96 (dd, 1H, J = 4.7, 12.2 Hz), 2.98 (6 line ddd, 1H, J = 6.3, 14.7 Hz), 1.85−2.38 (m, 7H), 1.78 (br s, 3H), 1.38 (s), 1.28 (t, J = 7.0 Hz), 1.25 (s) and 1.17−1.41 (m) [13H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 207.7, 173.2, 130.9, 123.9, 123.1, 61.4, 60.6, 57.2, 56.8, 53.7, 51.2, 39.8, 38.4, 38.0, 37.6, 36.3, 23.3, 21.3, 21.2, 20.9, 13.9, 12.6; IR (KBr) 3500, 2229, 1740 (sh), 1709 cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.66; H, 8.50; N, 3.64.

***d,l*-(1α,4aα,4bβ,7β,8aβ,10aβ)-Ethyl 8a-Cyano-7,7-(epoxymethylene)-8-(hydroxymethyl)-1,4a-dimethyl-2-oxo-1,4, 4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1-phenanthrenecarboxylate (17).** *m*-CPBA (80%, 295 mg, 1.36 mmol) was added to **7a** (254 mg, 0.68 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred at rt for 1.5 h, diluted with CH_2Cl_2 (80 mL), washed with 0.1 N NaOH (2 × 30 mL), H_2O (30 mL), and brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a solid. The solid was recrystallized from EtOAc−hexanes to give 240 mg (91%) of **17**: ^{1}H NMR ($CDCl_3$) δ 4.16 (m, 2H), 3.69 (m, 2H), 3.34 (dd, 1H, J = 1.4, 3.1 Hz), 3.00 (6 line ddd, J = 6.4, 14.7 Hz), 2.80 (d, 1H, J = 3.4 Hz), 1.38 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 207.3, 173.0, 121.3, 61.4, 60.3, 58.5, 57.0, 56.3, 55.6, 51.1, 50.6, 41.6, 39.7, 38.0, 36.4, 36.2, 35.0, 22.8, 21.2, 20.8, 13.9, 12.5; IR (KBr) 3504, 2226, 1741, 1702 cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 68.06; H, 8.29; N, 3.55.

***d,l*-(1α,4aα,4bβ,7β,8aβ,10aβ)-Ethyl 8a-Cyano-7,7-(epoxymethylene)-8-formyl-1,4a-dimethyl-2-oxo-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1-phenanthrenecarboxylate (18).** Collins reagent: prepared from dry CrO_3 (308 g, 3.08 mmol) and pyridine (487 mg, 6.17 mmol) in dry CH_2Cl_2 (10 mL) under N_2 with stirring for 20 min. The reagent was cooled to 0 °C, alcohol **17** (200 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min, and stirring was continued for 45 min. The reaction mixture was passed through a short bed of Celite−silica gel, and the residue was washed with CH_2Cl_2. The solvent was removed in vacuo to afford crude aldehyde **18**: ^{1}H NMR ($CDCl_3$) δ 9.58 (d, 1H, J = 3 Hz), 4.17 (m, 2H), 3.08 (m) and 3.01 (6 line ddd, J = 6.4, 14.7, 14.7 Hz) [2H], 2.82 (m, 1H), 2.67 (br d, 1H, J = 2.6 Hz), 1.37 (s), 1.29 (t, 3H, J = 7.1 Hz), 1.28 (s, 3H). The aldehyde was not characterized further but was submitted directly to cyclization.

***d,l*-4β-Carbethoxy-8β-cyano-4α,10β-dimethyl-3-oxo-13-nor-16-oxoandrosta-13,14-diene (8).** The crude aldehyde **18** in 5% *p*-TsOH·H_2O in DMSO (5 mL) was heated at 50 °C for 20 h with stirring. The solvent was removed in vacuo (50 °C at 0.4 mm); the residue was diluted with CH_2Cl_2 and the organic solution was washed with saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and concentrated in vacuo to give a solid. Chromatography on silica gel (3 g, 270−400 mesh) eluting with 30% ethyl acetate−hexanes gave 114 mg (60%, two steps from **17**) of **8**: mp 182.6−183.8 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 1H, J = 1.3 Hz), 7.16 (s, 1H), 4.19 (m, 2H), 3.05 (6 line ddd, J = 6.5, 14.8, 14.8 Hz) and 2.90 (br dd, J = 5.4, 14.3 Hz) [2H], 2.69 (dt, 1H, J = 3.2, 13.2 Hz), 2.33−2.59 (m, 3H), 2.23 (ddd, 1H, J = 2.4, 6.5, 13.3 Hz), 1.75−2.13 (m, 3H), 1.63 (6 line ddd, 1H, J = 3.4, 13.5, 13.5 Hz), 1.39 (s, 3H), 1.30 (s, 3H and t, 3H, J = 7.2 Hz) and 1.18−1.47 (m) [3H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 207.4, 173.1, 138.3, 137.8, 125.8, 122.9, 118.8, 61.4, 57.3, 56.7, 54.2, 39.7, 37.8, 37.5, 36.2, 36.1, 21.5, 21.3, 20.8, 20.3, 13.9, 12.2; IR (KBr) 2225, 1721, 1707 (sh) cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.21; H, 7.67; N, 3.43.

***d,l*-4β-Carbethoxy-8β-formyl-3β-hydroxy-4α,10β-dimethyl-13-nor-16-oxoandrosta-13,14-diene (19).** DIBALH (1.0 M in toluene, 0.94 mL, 0.94 mmol) was added via a syringe to cyano ketone **8** (58.0 mg, 0.157 mmol) in dry toluene (6 mL) at −78 °C over a 25 min period under N_2. The reaction mixture was stirred at −78 °C for 25 min and then quenched with 6% HOAc saturated with NaOAc at −78 °C. The heterogeneous mixture was allowed to come to rt, stirred for 15 min, and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic solution was washed with water (10 mL), saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give a solid. Chromatography on silica gel (5 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 43 mg (73%) of **19**: mp 131.8−132.5 °C (EtOAc−hexanes 1:2); ^{1}H NMR ($CDCl_3$) δ 9.84 (d, 1H, J = 1.4 Hz), 7.18 (s, 1H), 7.15 (d, 1H, J = 1.3 Hz), 4.11 (q, 1H, J = 7.1 Hz), 3.45 (d, 1H, J = 12 Hz), 3.08 (6-line ddd, 1H, J = 4.3, 11.8, 11.8 Hz), 2.89 (m, 1H), 2.73 (dt, 1H, J = 3.3, 13.0 Hz), 2.52 (m, 1H), 1.41 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.10 (dd, 1H, J = 4.2, 11.4 Hz), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.36, 177.60, 139.56, 138.09, 123.60, 120.40, 78.00, 60.49, 56.01, 55.60, 48.88, 48.21, 38.08, 37.79, 33.61, 28.15, 23.49, 20.72, 20.57, 17.73, 13.95, 13.25. HRMS calcd for $C_{22}H_{30}O_5$ (M^+) 374.2093, found 374.2093. Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.43, H, 8.05. Found: C, 70.56; H, 8.07.

***d,l*-3β-Hydroxy-4,8-bis(hydroxymethyl)-4α,10β-dimethyl-13-nor-16-oxoandrosta-13,14-diene (20).** Aldehyde **19** (34.1 mg, 0.0912 mmol) in dry THF (1.5 mL) was added dropwise to a suspension of LAH (10.4 mg, 0.274 mmol) in dry THF (1.5 mL). The reaction mixture was refluxed for 2 h, cooled to 0 °C, carefully quenched with saturated Na_2SO_4 (10 mL), and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic solution was washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a solid. Chromatography on silica gel (5 g, 230−400 mesh) eluting with 50% and then 70% ethyl acetate−hexanes followed by ethyl acetate gave 29.2 mg (96%) of **20**: mp 185.0−186.1 °C (MeOH−

hexanes); ^{1}H NMR ($CDCl_3$) δ 7.17 (s, 2H), 4.20 (d, 1H, J = 11.4 Hz), 3.80 (overlapping d, J = 11.1 Hz) and 3.74 (overlapping d, J = 10.9 Hz) [2H], 3.44 (m, 3H), 2.75 (m, 2H), 2.49 (m, 3H), 1.59 (s, 3H), 1.24 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.00) δ 138.13, 137.20, 129.76, 119.74, 80.46, 64.17, 61.98, 56.28, 56.05, 42.83, 40.22, 38.07, 36.91, 34.69, 27.67, 22.42, 20.14, 18.05, 17.60, 17.24; HRMS calcd for $C_{20}H_{30}O_4$ (M^+) 334.2150, found 334.2144.

***d,l*-4β,8β-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-3β-hydroxy-4α,10β-dimethyl-13-nor-16-oxoandrostane-13,14-diene (21).** TBDMSCl (46.0 mg, 0.305 mmol) was added in one portion to triol **21** (23.2 mg, 0.0695 mmol) and 4-DMAP (18.7 mg, 0.153 mmol) in dry CH_2Cl_2 (3 mL) under N_2. The reaction mixture was stirred at rt for 48 h. Water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic solution was dried (Na_2SO_4) and concentrated in vacuo. Chromatography of the residue on silica gel (5 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 28 mg (72%) of **21**: mp 116.5−117.2 °C (from column); ^{1}H NMR ($CDCl_3$) δ 7.06 (s, 2H), 4.27 (d, 1H, J = 6.8 Hz), 4.20 (d, 1H, J = 10.1 Hz), 3.77 (d, 1H, J = 9.5 Hz), 3.47 (apparent t, 1H, J = 9.5 Hz), 3.21−3.34 (m, 1H), 2.68−2.82 (m, 1H), 2.36−2.57 (m, 2H), 1.20 (s), 0.91 (s), 0.84 (s), 0.87 (s), 0.095 (s), −0.15 (s), −0.18 (s); ^{13}C NMR ($CDCl_3$, 77.00) δ 137.92, 136.30, 130.83, 119.89, 80.18, 65.22, 64.30, 56.74, 56.34, 42.60, 39.63, 38.47, 37.06, 35.51, 28.11, 25.92, 25.79, 25.70, 20.48, 18.51, 18.06, 17.97, 17.80, 17.55, −3.60, −5.72, −5.77, −5.94; HRMS calcd for $C_{32}H_{58}O_4Si_2$ (M^+) 562.3875, found 562.3874.

***d,l*-4β,8β-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-4α,10β-dimethyl-3-oxo-13-nor-16-oxoandrosta-13,14-diene (22).** Jones reagent was prepared from pyridine (63 mg, 0.80 mmol) and dry CrO_3 (40.0 mg, 40.0 mmol) in dry CH_2Cl_2 (1 mL). Alcohol **21** (28 mg, 0.05 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise to the Jones reagent at rt. The reaction mixture was stirred for 2.5 h and then filtered through a pad of Celite and silica gel eluting with CH_2Cl_2. Concentration of the organic solution in vacuo and subsequent chromatography on silica gel (5 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 18.6 mg (67%) of **22**: mp 119.1−120.8 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (s, 2H), 3.91 (d, 1H, J = 9.5 Hz), 3.82 (d, 1H, J = 10 Hz), 3.74 (d, 1H, J = 10 Hz), 3.56 (d, 1H, J = 9.5 Hz), 2.73−2.86 (m, 1H), 2.33−2.71 (m, 4H), 1.33−1.56 (m, 1H), 2.13 (ddd, 1H, J = 3.1, 7.0, 13.1 Hz), 1.11 (s, 6H, 2-Me), 0.89 (s) and 0.86 (s) [18H], 0.046 (s, 6H), −0.11 (s) and −0.13 (s) [6H]; ^{13}C NMR ($CDCl_3$, 77.00) δ 214.44, 138.07, 136.39, 130.57, 119.79, 65.68, 64.12, 57.06, 55.96, 53.91, 39.75, 39.65, 36.95, 35.24, 35.05, 25.90, 25.85, 21.57, 20.60, 19.91, 18.24, 16.82, −5.58, −5.66, −5.66, −5.91; HRMS calcd for $C_{32}H_{56}O_4Si_2$ (M^+) 560.3722, found 560.3717.

***d,l*-4β-Carbethoxy-8β-cyano-3β-hydroxy-4α,10β-dimethyl-13-nor-16-oxo-androsta-13, 14-diene (23).** $NaBH_4$ (100 mg, 2.63 mmol) was added in several portions to keto ester **8** (90 mg, 0.24 mmol) in a 1:2 mixture of CH_2Cl_2 to EtOH (12 mL) at 0 °C. The reaction mixture was stirred for 1 h and then quenched with acetone. The solvent was removed in vacuo, and the residue was diluted with CH_2Cl_2 (40 mL). The organic solution was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a solid. The solid was triturated with hexanes and then recrystallized with CH_2Cl_2−hexanes to give 80 mg (88%) of **23**: ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1H, J = 1.3 Hz), 7.15 (d, 1H, J = 1.1 Hz), 4.18 (q, 2H, J = 7.2 Hz), 3.53 (d, 1H, J = 12.0 Hz), 3.08 (6-line ddd, 1H, J = 4.3, 12.0, 12.0 Hz), 2.87 (br dd, 1H, J = 5.5, 16.3 Hz), 2.65 (dt, 1H, J = 3.2, 13.3 Hz), 1.71−2.57 (m, 9H), 1.61 (6 line ddd, 1H, J = 3.6, 13.3, 13.3 Hz), 1.44 (s, 3H), 1.34 (t, 3H, J = 7.2 Hz), 1.17 (dd, 1H, J = 1.4, 11.5 Hz), ∼1.08 (m) and 1.04 (s) [4H]; ^{13}C NMR ($CDCl_3$, 77.00) δ 177.47, 138.20, 137.81, 126.06, 123.18, 119.05, 78.01, 60.76, 55.43, 54.70, 48.71, 38.40, 37.84, 37.81, 36.18, 27.85, 23.54, 21.38, 21.03, 20.38, 14.02, 12.58; IR (KBr) 3450, 2226, 1735 cm^{-1}. HRMS calcd for $C_{22}H_{29}NO_4$ (M^+) 371.2096, found 371.2094.

***d,l*-4β-Carbethoxy-8β-cyano-4α,10β-dimethyl-13-nor-16-oxoandrosta-2, 13, 14-triene (24).** Trifluoromethanesulfonyl chloride (51 μL, 79.5 mg, 0.47 mmol) was added via a syringe to alcohol **23** (70 mg, 0.19 mmol) and 4-DMAP (138 mg, 1.13 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and then diluted with CH_2Cl_2. The organic solution was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo afforded a mixture of the corresponding sulfonate ester, a trace amount of **24**, and 4-DMAP. 4-DMAP (50 mg) was then added to the three-component mixture in CH_2Cl_2 (5 mL). The reaction mixture was refluxed overnight and then diluted with CH_2Cl_2. The organic solution was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo to give a solid. Chromatography on a silica gel sep-pack and elution with 5% EtOAc−hexanes gave 63 mg (94%) of **24**: mp 126.5−128 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 1H, J = 1.3 Hz), 7.16 (d, 1H, J = 1.3 Hz), 5.65 (m, 2H), 4.14 (q, 2H, J = 7.1 Hz), 2.88 (br dd, 1H, J = 5.1, 16.1 Hz), 2.64 (dq, 1H, J = 3.2, 13.2 Hz), 1.32 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 175.0, 138.1, 137.9, 131.5, 126.0, 123.0, 122.9, 119.0, 60.7, 53.9, 52.4, 45.0, 40.4, 37.2, 36.3, 36.1, 27.7, 21.4, 21.2, 20.4, 14.1, 13.5; IR (KBr) 2225, 1734 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.53; H, 7.84; N, 3.79.

***d,l*-Formyl-4β-(hydroxymethyl)-4α,10β-dimethyl-13-nor-16-oxoandrosta-2,13,14-triene (25).** DIBALH (1.0 M in toluene, 0.47 mL, 0.47 mmol) was added via a syringe over 5 min to cyano ester **24** (50 mg, 0.14 mmol) in dry toluene (1.5 mL) at −78 °C under N_2, and stirring was continued for 1 h at −78 °C. The reaction mixture was quenched with 6% HOAc saturated with NaOAc, allowed to warm to rt, and then stirred for an additional 15 min. The reaction mixture was diluted with CH_2Cl_2, and the organic solution was washed with H_2O, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo to give a solid. Chromatography on a silica gel sep-pak and elution with 10% EtOAc−hexanes gave 33 mg (74%) of **25**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.86 (d, 1H, CHO, J = 1.5 Hz), 7.18 (s, 1H, H_{16}), 7.15 (d, 1H, H_{15}, J = 1.0 Hz), 5.63 (m, 2H, H_2 and H_3), 3.63 (d, 1H, C*H*HOH, J = 11.0 Hz), 3.47 (d, 1H, CH*H*OH, J = 10.7 Hz), 2.90 (dd, 1H, H_{12eq}, J = 5.0, 16.0 Hz), 2.73 (6-line ddd, 1H, H_{7eq}, J = 3.1, 3.1, 12.8 Hz), 2.54 (m, 1H, H_{12ax}), 2.15 (dd, 1H, H_{1eq}, J = 4.3, 16.8 Hz), 2.07 (8-line dddd, 1H, H_{1ax}, J = 5.4, 12.5, 12.5, 12.5 Hz), 1.92 (m, 1H, H_{11eq}), 1.76 (m, 2H, H_{1ax}, H_{6eq}), 1.59 (dd, H_{9ax}, J = 1.8, 12.5 Hz) and 1.53 (partially resolved 8-line dddd, H_{6ax}, J = 3.1, 13.1, 13.1, 13.1 Hz) [2H], 1.44 (dd, 1H, H_{5ax}, J = 2.7, 13.1 Hz), 1.36 (m, 1H, H_{7ax}), 1.09 (s, 3H, C-4 Me), 0.88 (s, 3H, C-10 Me); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.5 (CHO), 139.7 (C16), 138.1 (C15), 132.9 (C3), 123.7 (C14), 123.5 (C2), 120.5 (C13), 66.8 (CH_2OH), 55.4 (C9), 52.2 (C5), 48.6 (C8), 39.9 (C1), 39.5 (C4), 36.4 (C10), 33.4 (C7), 25.7 (C-4 Me), 20.7 (C12), 19.7 (C6), 17.9 (C11), 16.0 (C10).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **15**, **20**, **21**, **22**, **23**, **24**, and **25** and 2D COSY, HMQC, HMBC, and 1D APT spectra for **7a** (6 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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