Application of a Radical Methodology toward the Synthesis of *d,l*-5α-Pregnanes and Related Steroids: A Stereoselective Radical Cascade Approach

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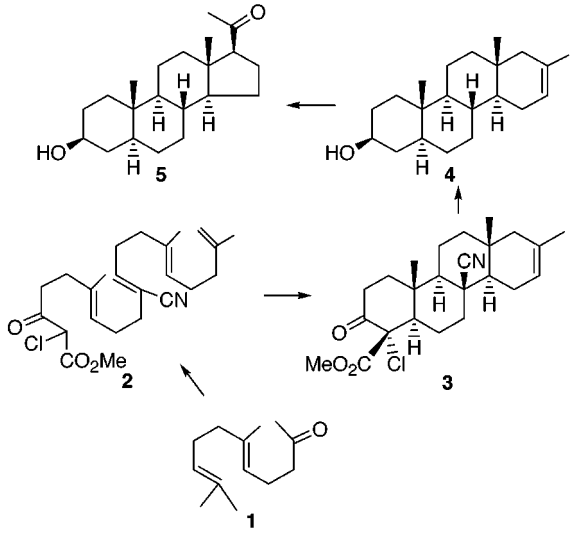
A stereoselective radical cascade cyclization to 5α-pregnanes is presented. Oxidative free radical cyclization of an appropriately substituted chloro cyano ester polyene was used to introduce the all trans stereochemistry in the steroid nucleus. The cyano group was utilized to introduce a C-8*β* angular hydrogen, while the chloro ester moiety served as an entry to the geminal hydrogens at C-4.

Introduction

A stereoselective one-step entry to tetracylic products[1,2] via a radical cascade cyclization[3,4] of polyenic substrates can now be achieved in favorable yields. Our laboratory has demonstrated that these tandem cyclizations can be used to introduce from five to seven stereogenic centers in a highly predictable manner in various polycyclic systems.[1,5] It has also been shown that a radical approach can be utilized in the synthesis of a methylated D-homosteroid.[1] To extend this radical methodology to natural steroids, two modifications of the polyene have to be addressed based on our earlier model. First, the polyene has to contain a functional moiety that could ultimately be used to introduce geminal hydrogens at C-4 or a C-4−C-5 double bond in the steroid nucleus. Second, the polyene has to be designed to yield a six membered D-ring system that can readily be degraded to the five-membered ring present in natural steroids. To develop a radical cascade approach to natural steroids, it was anticipated that oxidative radical cyclization of chloro cyano polyene **2** (Scheme 1) could be used to (1) control the necessary 6-*endo*-*trig* mode in the second cyclization step, (2) stereoselectively introduce in one step six of the chiral centers present in natural steroids, (3) provide an angular 8*β*-cyano group for further elaboration to an angular 8*β*-H, (4) utilize the 4-chloro-4-carbmethoxy moiety to introduce geminal hydrogens at C-4 or a C-4−C-5 double bond in the steroid nucleus, and (5) take advantage of the C-16−C-17 double bond in **4** to construct the D-ring system in natural steroids. Within we disclose the synthesis of D-homosteroid **4**, a precursor, to 5α-pregnane **5**, via a highly effective radical cascade cyclization of polyene **2**.

Scheme 1



Results and Discussion

Chloro polyene **2** was synthesized from commercial geranylacetone as outlined in Schemes 2 and 3. Reaction of **1** with NBS in aqueous THF gave bromohydrin **6**[6] (51%), after chromatography. Treatment of **6** with K_2CO_3 afforded the corresponding epoxide **7**[6] in 92% yield. Reaction of **7** with triphenylphosphonium methylide at low temperature yielded diene **8**[7] (61%) and subsequent

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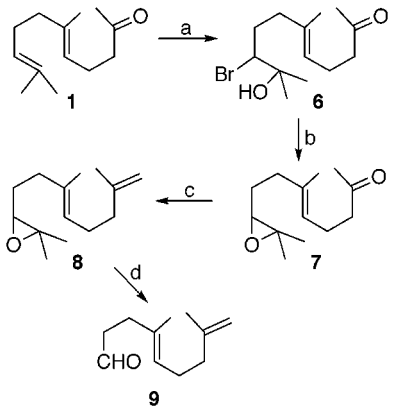
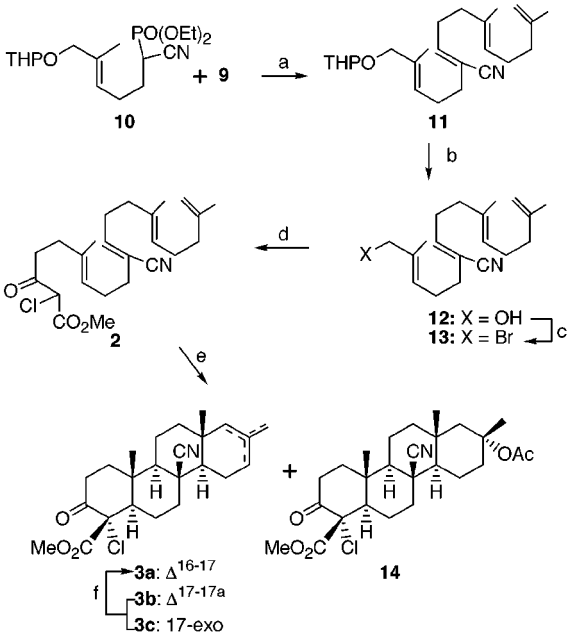
Scheme 2[a]



[a]Key: (a) NBS, THF, H_2O, (b) K_2CO_3, MeOH; (c) $Ph_3P{=}CH_2$, THF, -78 °C; (d) H_5IO_6, THF, H_2O.

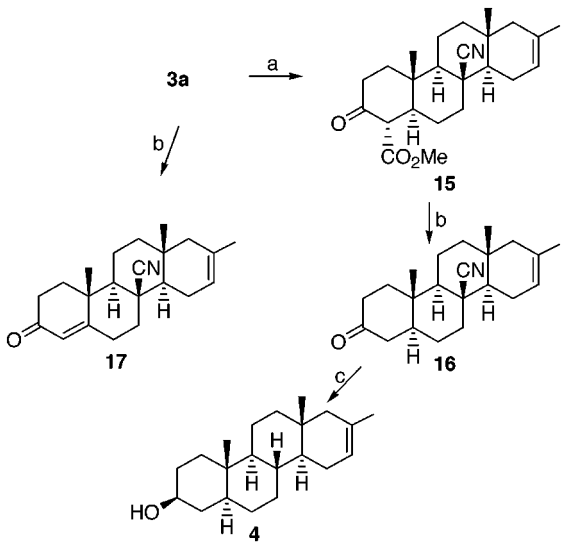
Scheme 3[a]



[a] Key: (a) $KN(SiMe_3)_2$, toluene, -78 °C, N_2; then **9**, 3h, -78 °C -> rt, 1h; (b) MeOH, *p*-TsOH·H_2O; (c) CBr_4, Ph_3P, CH_2Cl_2; rt, 3h; then 40-50 °C, 15 min; (d) $LiCH_2C(O)CCl(Na)CO_2Me$, THF, HMPA, 0 °C, inverse addition; then 10 % HCl; (e) $Mn(OAc)_3{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, HOAc, Ar; (f) CF_3CO_2H, rt, 1h.

cleavage of the epoxide group in **8** with periodic acid afforded the desired aldehyde **9**[8] in 94% yield. The *Z*-trisubstituted C-6−C-7 double bond in **11** (Scheme 3) was introduced utilizing a Horner−Emmons reaction.[9,10] Deprotonation of **10**[9] followed by reaction of the resulting potassium salt with aldehyde **9** gave an approximate 92:8 mixture of **11** and the corresponding 2*E*,6*E*,10*E* isomer. Chromatography on silica gel yielded pure **11** (52%) along with a 25% mixture of **11** and the 2*E*,6*E*,10*E* isomer in a 75:25 ratio. The synthesis of polyene **2** from **11** was accomplished as follows: (1) removal of the protecting group in **11** gave alcohol **12** (96%), (2) reaction of **12** with CBr_4 and Ph_3P[11] afforded bromide **13** (90%), and (3)

Scheme 4[a]



[a]Key: (a) Zn, HOAc, rt, 5h; (b) LiCl, DMSO, trace of H_2O, Δ; (c) excess Li, NH_3, -33 °C, N_2,13h; then EtOH.

alkylation of the dianion[12] of methyl 2-chloroacetoacetate with **13** (inverse addition) yielded the desired polyene **2** (75%), after chromatography.

Oxidative free-radical cyclization of **2**, as a 0.1 M solution in deaerated HOAc, with a 2:1 molar ratio of $Mn(OAc)_3{\cdot}2H_2O$[13] and $Cu(OAc)_2{\cdot}H_2O$ gave tetracycles **3** (61%) as D-ring double bond isomers, appearing as a single spot on TLC analysis, along with tetracyclic acetate **14** (5%), after chromatography. Subsequent isomerization of **3** with CF_3CO_2H at room temperature followed by chromatography gave pure **3a** (42%) and 31% of **3a** contaminated with a trace amount of **3b** and a trace amount of the corresponding C-17 fluoroacetate. The assignment of each proton and carbon resonance signal in **3a** was determined from a series of 2D COSY, long-range COSY, HMQC, and HMBC correlations. The relative stereochemistry depicted in **3a** was consistent with the following 2D NOESY and 1D NOEDS results: the C-10 Me (δ 1.26) showed NOE enhancements to the H_{2ax} (δ 3.01), H_{6ax} (δ ~2.35), H_{11ax} (δ ~1.72), and H_{1eq} (δ 2.68) protons and the methyl protons of the C-4 ester at δ 3.81. The H_{9ax} proton showed strong enhancements to the H_{1ax}, H_{5ax}, and H_{14ax} protons and a weaker enhancement to the overlapped H_{7ax} and H_{12ax} resonances. The C-13 Me gave enhancements to the H_{11ax}, H_{15ax}, and H_{17eq} protons and the overlapped H_{12eq} resonance.

Conversion of **3a** to D-homosteroid **4**, a precursor to 5α-pregnanes, was accomplished in three steps (Scheme 4). Thus, reduction of **3a** with zinc in HOAc gave keto ester **15** (96%). Decarbmethoxylation of **15** with LiCl in DMSO[14] containing a trace amount of H_2O afforded cyano ketone **16** (75%). Subsequent reductive removal of the C-8 angular cyano group and reduction of the C-3 carbonyl with excess Li[1,15] in NH_3 under N_2 yielded the known D-homosteroid **4**[16] (64%), after chromatography.

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The proton chemical shift values of the C-16 vinyl hydrogen (δ 5.34) and the two angular methyls at δ 0.79 and δ 0.76 in **4** were consistent with the reported δ values of 5.30, 0.79, and 0.76 for racemic **4**. The D-homosteroid can suffice as a precursor to 5α-pregnane **5**, since the C-16−C-17 double bond in **4** can be used to construct the trans five membered D-ring system in natural steroids in a straightforward manner by known[17] chemical reactions.

To develop a potential route to *d*,*l*-progesterone via common intermediate **3a**, a C-4−C-5 double bond must be introduced in the steroid nucleus. Although there are alternative chemical manipulations that could be utilized to achieve this objective, it was of interest to determine if the 4-chloro-4-carbmethoxy moiety could be converted to the desired enone system in a single step. In an initial experiment it was shown that reaction of **3a** with LiCl in refluxing DMSO afforded enone **17** directly albeit in 28% yield, after chromatography.

Conclusion

The presently reported radical cascade cyclization demonstrates an approach to 5α-pregnanes from a given polyenic system in which key stereogenic centers are introduced in a single step in a highly stereoselective and predictable manner.

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 Duke. All melting points are uncorrected. Preparative chromatography was performed on Merck silica gel G 60 (70−230 mesh) and Merck silica gel G (230−400 mesh, for pressure chromatography). TLC analysis 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.

(*E*)-9-Bromo-10-hydroxy-6,10-dimethyl-5-undecen-2-one (6). Two separate reactions were carried out and then combined. A total amount of NBS (5.96 g, 33.5 mmol) in a THF−H_2O solution (68:32, 200 mL) in freshly prepared 20 mL portions was added dropwise to geranylacetone (5.0 g, 25.8 mmol) in a THF−H_2O solution (68:32, 250 mL) over 3 h at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then diluted with $CHCl_3$ (300 mL). The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel eluting with ethyl acetate−hexanes gave 7.7 g (51%) of **6**:[6] ^{1}H NMR ($CDCl_3$) δ 5.09 (t, 1H, J = 6.7 Hz), 3.84 (dd, 1H, J = 1.7, 11.2 Hz), 2.07 (s, 3H), 1.54 (s, 3H), 1.27 (s, 6H, 2-Me); ^{13}C NMR ($CDCl_3$) δ 208.64, 134.28, 123.96, 72.21, 69.67, 43.31, 37.80, 31.55, 29.77, 26.15, 26.00, 22.18, 15.63.

(*E*)-9,10-Epoxy-6,10-dimethyl-5-undecen-2-one (7). K_2CO_3 (3.66 g, 26.5 mmol) was added to bromohydrin **6** (7.7 g, 26.5 mmol) in absolute MeOH (100 mL). The reaction mixture was stirred at room temperature for 30 min, diluted with H_2O, and extracted with CH_2Cl_2. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (100 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 5.13 g (92%) of **7**:[6] ^{1}H NMR ($CDCl_3$) δ 5.14 (m, 1H), 2.68 (t, 1H, J = 6.2 Hz), 2.48 (t, 2H, J = 6.9 Hz), 2.29 (m, 2H), 2.14 (s, 3H), 1.64 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.17, 135.10, 122.97, 63.74, 57.93, 43.28, 36.02, 29.65, 27.09, 24.60, 22.10, 18.48, 15.69; HRMS calc for $C_{13}H_{22}O_2$ (M^+) 210.1619, found 210.1622.

(*E*)-9,10-Epoxy-2,6,10-trimethyl-1,5-undecadiene (8). Methyltriphenylphosphonium bromide (32.6 g, 91.3 mmol) in dry THF (400 mL) was cooled to −78 °C under N_2. *n*-BuLi (2.6 M in hexanes, 35.0 mL, 91.0 mmol) was added dropwise via a syringe over 45 min. The reaction mixture was stirred at −78 °C for 2 h. Epoxy ketone **7** (15.3 g, 72.9 mmol) in dry THF (100 mL) was added over 30 s at −78 °C. The reaction mixture was stirred for an additional 10 min, quenched with H_2O (300 mL), and extracted with hexanes. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel (150 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 9.34 g (61%) of **8**:[7] ^{1}H NMR ($CDCl_3$) δ 5.18 (m, 1H), 4.64 (m, 2H), 2.70 (t, 1H, J = 6.3 Hz), 1.98−2.22 (m, 6H), 1.72 (s), 1.63 (s) and 1.55−1.77 (m) [8H], 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.45, 134.06, 124.55, 109.79, 63.97, 58.11, 37.62, 36.20, 27.30, 26.05, 24.76, 22.32, 18.62, 15.85. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.31; H, 11.94.

(*E*)-4,8-Dimethyl-4,8-nonadienal (9). $HIO_4 \cdot 2H_2O$ (10.9 g, 47.8 mmol) in THF (50 mL) was added dropwise to epoxide **8** (9.08 g, 43.7 mmol) in Et_2O (100 mL) at 0 °C under N_2 over 2 h. The reaction mixture was stirred at 0 °C for 20 min and then diluted with Et_2O (100 mL). The organic solution was washed with H_2O, saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel eluting with hexanes and ethyl acetate−hexanes gave 6.82 g (94%) of **9**:[8] ^{1}H NMR ($CDCl_3$) δ 9.76 (t, 1H, J = 1.7 Hz), 5.16 (m, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 2.52 (m, 2H), 2.32 (t, 2H, J = 7.3 Hz), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.78, 145.56, 133.09, 125.10, 109.92, 42.10, 37.57, 31.79, 26.04, 22.43, 16.08.

(2*E*,6*Z*,10*E*)-6-Cyano-2,10,14-trimethyl-1-[(tetrahydro-2*H*-pyran-2yl)oxy]-2,6,10,14-pentadecatetraene (11). KN($SiMe_3$)$_2$ (0.5 M in toluene, 92.4 mL, 46.2 mmol) was added to the cyano phosphonate **10**[9] (18.1 g, 50.6 mmol) in dry toluene (400 mL) at −78 °C under N_2 over 1 h, and stirring was continued for 30 min at −78 °C. Aldehyde **9** (6.97 g, 42.0 mmol) in dry toluene (20 mL) was added over 20 min, and the reaction mixture was stirred at −78 °C for an additional 3 h. The reaction mixture was then allowed to warm to room temperature, and stirring was continued for 1 h. H_2O was added, the organic solution was washed with brine and dried (Na_2SO_4), and the toluene was removed under reduced pressure to afford an oil. Chromatography on silica gel (300 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 8.14 g (52%) of **11** and 3.88 g (25%) of a mixture of **11** and the 2*E*,6*E*,10*E*-isomer in a 75:25 ratio as determined by integration of the resonance signals at δ 6.11 and 6.33. For **11**: ^{1}H NMR ($CDCl_3$) δ 6.11 (t, 1H, J = 7.6 Hz), 5.35 (m, 1H), 5.14 (t, 1H, J = 6.2 Hz), 4.71 (s, 1H), 4.67 (s, 1H), 4.60 (t, 1H, J = 3.2 Hz), 4.11 (d, 1H, J = 11.8 Hz), 3.84 (d, J = 11.8 Hz) and 3.91−3.98 (m) [2H], 3.51 (m, 1H), 2.45 (apparent q, 2H, J = 7.3 Hz), 2.25 (br s, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.68, 145.54, 133.77, 133.22, 125.43, 124.90, 117.57, 114.00, 109.84, 97.41, 72.44, 62.08, 36.24, 37.58, 33.94, 30.55, 29.75, 26.32, 26.01, 25.39, 22.38, 19.41, 15.76, 14.08. Anal. Calcd for $C_{24}H_{37}NO_2$: C, 77.58; H, 10.04; N, 3.77. Found: C, 78.05; H, 10.10; N, 3.91.

(2*E*,6*Z*,10*E*)-6-Cyano-2,10,14-trimethyl-2,6,10,14-pentadecatetraen-1-ol (12). *p*-TsOH·H_2O (2.04 g, 10.7 mmol) was added to nitrile **11** (7.96 g, 21.5 mmol) in MeOH (200 mL) at 0 °C. The ice bath was then removed, and the reaction mixture was stirred at room temperature for 3 h. Then 1 N NaOH (100 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic solution was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel (160 g, 230−400 mesh) eluting

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with ethyl acetate−hexanes gave 5.93 g, (96%) of **12**: ^{1}H NMR ($CDCl_3$) δ 6.13 (t, 1H, J = 7.5 Hz), 5.37 (m, 1H), 5.14 (t, 1H, J = 6.1 Hz), 4.71 (s, 1H), 4.68 (s, 1H), 4.01 (br s, 2H), 2.46 (apparent q, 2H, J = 7.3 Hz), 2.25 (br s, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.92, 145.64, 136.56, 133.26, 125.50, 123.18, 117.75, 114.02, 109.88, 68.55, 38.28, 37.63, 33.98, 29.77, 26.43, 26.05, 22.43, 15.81, 13.76. Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.30; H, 10.32; N, 4.97.

(2*E*,6*Z*,10*E*)-1-Bromo-6-cyano-2,10,14-trimethyl-2,6,10,-14-pentadecatetraene (13). Ph_3P (7.04 g, 26.9 mmol) and CBr_4 (10.3 g, 31.0 mmol) were added to alcohol **12** (5.93 g, 20.7 mmol) in dry CH_2Cl_2 (200 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h, warmed to 40−50 °C for 15 min, cooled to room temperature, diluted with hexanes (100 mL), and then concentrated to approximately 20 mL. The white slurry was directly chromatographed on silica gel (75 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 6.51 g (90%) of **13**: ^{1}H NMR ($CDCl_3$) δ 6.12 (t, 1H, J = 7.5 Hz), 5.52 (m, 1H), 5.14 (m, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 3.95 (s, 2H), 2.46 (apparent q, 2H, J = 7.3 Hz), 2.26 (m, 4H), 1.78 (s, 3H), 1.73 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.19, 145.61, 133.92, 133.25, 126.41, 125.50, 117.49, 113.53, 109.88, 40.98, 38.24, 37.63, 33.55, 29.78, 26.79, 26.05, 22.43, 15.81, 14.80. Anal. Calcd for $C_{19}H_{28}BrNO$: C, 65.14; H, 8.06; N, 4.00. Found: C, 65.12; H, 8.27; N, 3.99.

(6*E*,10*Z*,14*E*)-Methyl 2-Chloro-10-cyano-6,14,18-trimethyl-3-oxo-6,10,14,18-nonadecatetraenoate (2). NaH (60% in mineral oil, 1.11 g, 27.8 mmol) was added to HMPA (2 mL) in dry THF (50 mL) under N_2. The suspension was cooled to 0 °C. Methyl 2-chloroacetoacetate (4.18 g, 27.8 mmol) in dry THF (40 mL) was then added at 0 °C over a 30 min period. The yellow transparent reaction mixture was stirred for 30 min and *n*-BuLi (2.5 M in hexanes, 11.1 mL, 27.8 mmol) was added via a syringe over 30 min. The resulting pink-orange reaction mixture was stirred for an additional 30 min, then transferred via N_2 through a cannula into an addition funnel, and added dropwise to bromide **13** (4.86 g, 13.9 mmol) in dry THF (60 mL) over 45 min at 0 °C under N_2. The reaction mixture was stirred for 20 min at 0 °C, quenched with H_2O, neutralized with 10% HCl, and then extracted with Et_2O. The organic solution was washed with saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (120 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 4.36 g (75%) of **2**: ^{1}H NMR ($CDCl_3$) δ 12.31 (s, 0.52H), 6.10 (m, 1H), 5.13 (m, 2H), 4.82 (s, 0.48H), 3.85 (s) and 3.84 (s) [3H], 2.82 (m, 1H), 2.61 (m, 1H), 2.45 (apparent q, 2H, J = 7.4 Hz), 1.72 (s), 1.65 (s), and 1.63 (s) [9H]; ^{13}C NMR ($CDCl_3$) δ 198.26, 175.19, 169.71, 165.40, 147.71, 147.53, 145.51, 135.11, 134.64, 133.22, 125.41, 123.16, 123.08, 117.57, 114.07, 113.99, 109.82, 96.39, 60.59, 53.64, 52.66, 38.23, 37.57, 37.44, 35.24, 34.08, 32.93, 31.70, 29.72, 26.61, 26.53, 26.00, 22.35, 16.04, 15.91, 15.74. Anal. Calcd for $C_{24}H_{34}ClNO_3$: C, 68.64; H, 8.16; N, 3.33. Found: C, 69.15; H, 8.40; N, 3.38. The carbon was always slightly higher than the theoretical value. HRMS calcd for $C_{24}H_{34}Cl^{35}NO_3$ 419.2227, found 419.2241.

***d,l*-4α-Carbomethoxy-4α-chloro-8β-cyano-*D*-homo-5α-androst-16-en-3-one (3a).** To keto ester **2** (3.78 g, 9.03 mmol) in deaerated HOAc (100 mL) under Ar were added $Mn(OAc)_3 \cdot 2H_2O$ (4.84 g, 18.1 mmol) and $Cu(OAc)_2 \cdot H_2O$ (1.81 g, 9.05 mmol) at room temperature under Ar. The brown reaction mixture turned blue in 15 min, and stirring was continued at room temperature overnight. H_2O (100 mL) was added, and the resulting mixture was extracted with CH_2Cl_2. The organic solution was washed with 1 N NaOH, H_2O, and brine, dried (Na_2SO_4), and concentrated in vacuo to afford a thick oil. Chromatography on silica gel (120 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 2.31 g (61%) of a white solid as an isomeric mixture of **3a** (δ 5.34), **3b** (δ 5.08), and **3c** (δ 4.60 and 4.72), appearing as a single spot on TLC, along with 0.22 g (5%) of tetracyclic acetate **14**.

The three isomers of **3** (2.31 g, 5.53 mmol) in CF_3CO_2H (35 mL) were stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 and then washed with H_2O, saturated $NaHCO_3$, and brine. The organic solution was dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (110 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 964 mg (42%) of pure **3a** and 710 mg (31%) of **3a** contaminated with a trace amount of **3b** and a trace amount of the corresponding C-17 trifluoroacetate. For **3a**: mp 200.5−201.8 °C (CH_2Cl_2−hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.34 (m, 1H, H_{16}), 3.81 (s, 3H), 3.01 (dt, 1H, H_{2ax}, J = 6.5, 14.9 Hz), 2.68 (ddd, 1H, H_{2eq}, J = 2.5, 4.8, 15.1 Hz), 2.39 (dt, H_{7eq}, J = 3.4, ∼13.4 Hz) and ∼2.35 (m, H_{6ax} and H_{6eq}) [3H], 2.18 (ddd, H_{1eq}, J = 2.5, 6.4, 13.4 Hz) and ∼2.12 (m, H_{15ax} and H_{15eq}) [3H], 1.81 (d, 1H, H_{17ax}, J = 17.0 Hz), ∼1.72 (m, 4H, H_{11eq}, H_{11ax}, H_{5ax}, H_{12eq}), 1.60 (overlapped d, H_{17eq}, J = ∼17.0 Hz) and 1.63 (s, C-17 Me) [4H], ∼1.35 (m, H_{1ax}) and 1.31 (overlapped dd, H_{14ax}, J = 5.6, 11.5 Hz) [2H], 1.26 (s, 3H, C-10 Me), ∼1.17 (m, 2H, H_{7ax}, H_{12ax}), 1.12 (s, 3H, C-13 Me), 0.996 (dd, 1H, H_{9ax}, J = 2.9, 11.4 Hz); ^{13}C NMR ($CDCl_3$, 125.7 MHz, 77.00) δ 198.07 (C-3, C=O), 168.27 (*C*O_2Me), 132.23 (C-17), 123.28, (CN), 118.57 (C-16), ∼77.00 (C-4), 58.59 (C-5), 57.58, (C-9), 53.52 (OCH_3), 50.07 (C-14), 49.18 (17a), 41.56 (C-12), 40.11 (C-8), 39.61 (C-10), 39.41 (C-1), 37.73 (C-7), 36.38 (C-2), 33.38 (C-13), 24.24 (C-15), 23.54 (C-17 Me), 21.58 (C-6), 19.99 (C-11), 18.50 (C-13 Me), 12.40 (C-10 Me). For **3a**: Anal. Calcd for $C_{24}H_{32}ClNO_3$: C, 68.97; H, 7.72; N, 3.35. Found: C, 69.11; H, 7.93; N, 3.32. For **14**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.81 (s, 3H), 3.01 (6 line ddd, 1H, H_{2ax}, J = 6.5, 14.9, 14.9 Hz), 2.68 (ddd, 1H, H_{2eq}, J = 2.5, 4.6, 15.2 Hz), 2.45 (dt, 1H, H_{7eq}, J = 3.5, 13.3 Hz), ∼2.38 (m, H_{6ax} and H_{6eq}, 2H), 2.23 (dd, 1H, H_{17eq}, w-coupling to H_{16eq}, J = 2.3, 13.2 Hz), ∼2.16 (m, 2H, H_{1eq} and H_{16eq}), 1.94 (s, 3H), ∼1.82 (m, 1H, H_{15eq}), ∼1.73 (m, 2H, H_{5ax} and H_{11ax}), ∼1.65 (m, 2H, H_{11eq} and H_{15ax}), 1.64 (s, 3H, C-17 Me), ∼1.58 (m, 2H, H_{12eq} and H_{16ax}), 1.44 (d, 1H, H_{17ax}, J = 13.8 Hz), 1.34 (6 line ddd, 1H, H_{1ax}, J = 4.8, 14.0, 14.0 Hz), 1.25 (s, C-10 Me), 1.24 (s, C-13 Me), and ∼1.20 (m, H_{7ax}) [7H], ∼1.13 (dd, H_{14ax}, partially overlapped, J = ∼2.8, ∼12.0 Hz) and ∼1.13 (m, H_{12ax}) [2H], 0.99 (dd, 1H, H_{9ax}, J = 2.2, 12.5 Hz); ^{13}C NMR ($CDCl_3$, 125.7 MHz, 77.00) δ 197.96 (C-3, C=O), 170.17 [O(*C*O)CH_3], 168.21 (*C*O_2Me), 122.85 (CN), 81.99 (C-17), ∼77.02 (C-4), 58.71 (C-5), 57.93 (C-9), 54.63 (C-14), 53.71 (C-17a), 53.55 (OMe), 42.08 (C-12), 39.68 (C-10), 39.39 (C-1), 38.73 (C-8), 38.59 (C-16), 38.09 (C-7), 36.37 (C-2), 35.20 (C-13), 25.86 (C-17 Me), 22.57 (O(CO)*Me*), 21.54 (C-6), 20.45 (C-13 Me), 19.52 (C-15), 19.14 (C-11), 12.26 (C-10 Me). For **14**: Anal. Calcd for $C_{26}H_{36}ClNO_5$: C, 65.33; H, 7.59; N, 2.93. Found: C, 65.21; H, 7.68; N, 2.85.

***d,l*-4α-Carbomethoxy-8β-cyano-*D*-homo-5α-androst-16-en-3-one (15).** Zinc powder (960 mg, 14.7 mmol) was added to chloro ketone **3a** (450 mg, 1.08 mmol) in HOAc (50 mL) at room temperature. The reaction mixture was stirred under N_2 for 5 h and then passed through a Celite−silica gel pad by washing with CH_2Cl_2 (50 mL). The organic solution was washed with H_2O, 1 N NaOH, and brine, dried (Na_2SO_4), and concentrated in vacuo to give a solid. Recrystallization from ethyl acetate−hexanes gave 395 mg (96%) of **15**: mp 223.5−224.6 °C (CH_2Cl_2−hexanes); ^{1}H NMR ($CDCl_3$) δ 5.34 (m, 1H), 3.77 (s, 3H), 3.31 (d, 1H, J = 12.7 Hz), 1.63 (s, 3H), 1.33 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.08, 170.10, 132.22, 123.66, 118.51, 59.03, 56.03, 52.09, 50.02, 49.17, 47.70, 41.53, 39.97, 37.87, 36.95, 36.81, 36.28, 33.39, 24.13, 23.71, 23.55, 19.94, 18.50, 12.17. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65. Found: C, 75.38; H, 8.96; N, 3.65.

***d,l*-8β-Cyano-*D*-homo-5α-androst-16-en-3-one (16).** LiCl (29.5 mg, 0.697 mmol) and H_2O (5 drops) were added to keto ester **15** (46.7 mg, 0.122 mmol) in DMSO (3 mL). The reaction mixture was refluxed at 195−197 °C for 12 h under Ar. DMSO was removed in vacuo and the residue dissolved in CH_2Cl_2 (10 mL). The organic solution was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography of the residue on silica gel (8 g, 230−400 mesh) eluting with 4% ethyl acetate−hexanes gave 31.2 mg (79%) of **16**: mp 159.0−159.8 °C (EtOAc−hexanes); ^{1}H NMR ($CDCl_3$) δ 5.34 (m, 1H), 1.63 (s, 3H), 1.29 (s, 3H), 1.13 (s, 3H), ^{13}C NMR ($CDCl_3$) δ 210.88, 132.22, 123.83, 118.58, 56.12, 50.07, 49.24, 45.85, 43.93, 41.82, 40.17, 38.59, 37.43, 37.10, 36.44, 33.43, 25.83,

24.16, 23.55, 20.08, 18.52, 11.26. Anal. Calcd for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.22; H, 9.85; N, 4.20.

On a larger scale **15** (203 mg, 0.531 mmol), LiCl (128 mg, 3.03 mmol), and H_2O (17 drops) in DMSO (13 mL) gave 106 mg (62%) of **16**.

***d,l-D*-Homo-5α-androst-16-en-3*β*-ol (4).** Freshly cut Li (16 mg, 2.3 mmol) was added to a dry three-neck flask (10 mL) under N_2. Dry NH_3 (~6 mL) was transferred to the reaction flask fitted with a dry ice−acetone condenser under N_2. The blue-purple solution was stirred for 5 min and cooled to −78 °C under N_2, and then the cyano ketone **16** (37.5 mg, 0.115 mmol) in THF (2 mL) was added at −78 °C over 5 min. After stirring for an additional 5 min, the −78 °C bath was removed and the reaction mixture was allowed to stir at −33 °C for 13 h. The blue-purple color persisted throughout the reaction period. After addition of EtOH (1 mL) via a syringe, the reaction mixture was gradually allowed to warm to room temperature to remove the liquid ammonia. Et_2O (10 mL) was added, the organic solution was washed with H_2O and brine, and after back washing with Et_2O, the combined organic solution was dried (Na_2SO_4) and concentrated in vacuo to give a solid. Chromatography on silica gel (8 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 22.3 mg (64%) of **4**:[16] mp 150−150.5 °C (CH_2Cl_2−hexanes); ^{1}H NMR ($CDCl_3$) δ 5.32 (m, 1H), 3.59 (m, 1H), 1.62 (s, 3H), 0.79 (s, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 132.27, 119.91, 71.31, 53.90, 47.32, 45.75, 44.27, 41.41, 38.10, 36.84, 36.64, 35.60, 32.23, 31.45, 31.00, 28.71, 27.29, 23.76, 20.71, 17.44, 12.30; HRMS calcd for $C_{21}H_{34}O$ (M^+) 302.2609, found 302.2612.

A trace amount of *d*,*l*-8*β*-cyano-5α-androst-16-en-3-ol [^{1}H NMR ($CDCl_3$) δ 5.34 (br s, 1H), 3.61 (m, 1H), 2.24 (dt, J = 3.1, 13.1 Hz) and 2.12 (m) [3H], 1.62 (s, 3H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 132.22, 124.20, 118.74, 70.97, 56.76, 50.26, 49.37, 44.72, 41.80, 40.29, 37.66, 37.26, 37.26, 36.43, 33.43, 30.62, 25.69, 24.16, 23.59, 19.84, 18.57, 12.01; HRMS calcd for $C_{22}H_{33}NO$ (M^+) 327.2562, found 327.2560] and with trace amounts of three faster moving compounds (R_f's 0.73, 0.69, and 0.58; 30% EtOAc−hexanes) were also isolated. Each of these faster moving compounds was devoid of a resonance signal at δ 3.60 implicating an intact 3-keto group. These compounds have tentatively been assigned as *d*,*l-D*-homo-5α-androst-16-en-3-one[16] [R_f 0.73; ^{1}H NMR ($CDCl_3$) δ 5.33 (m, 1H), 1.62 (s, 3H), 0.99 (s, 3H), 0.79 (s, 3H)] and possible C-8−C-9 and C-8−C-14 double bond isomers.

***d,l*-8*β*-Cyano-*D*-homo-4,16-androstadien-3-one (17).** LiCl (298 mg, 7.04 mmol) and H_2O (39 drops) were added to chloro ester **3a** (514 mg, 1.23 mmol) in DMSO (30 mL). The reaction mixture was refluxed under Ar for 12 h. The solvent was removed in vacuo, and the residue was diluted with Et_2O (50 mL). The organic solution was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on silica gel (30 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 113 mg (28%) of **17**: mp 176−177 °C (CH_2Cl_2−hexanes); ^{1}H NMR ($CDCl_3$) δ 5.79 (s, 1H), 5.35 (s, 1H), 2.84 (m, 1H), 1.64 (s, 3H), 1.44 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.77, 167.50, 132.34, 124.88, 123.07, 118.37, 56.14, 49.55, 49.01, 41.43, 40.39, 38.97, 36.57, 36.26, 33.40, 33.24, 29.89, 24.23, 23.55, 19.85, 18.46, 17.17. Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.68; H, 9.04; N, 4.33.

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