104157-56-4; **11b**, 104157-57-5; **11c**, 104157-58-6; **11d**, 104157-59-7; **11d'**, 104157-60-0; **11e**, 104157-61-1; **11g**, 104157-62-2; **11i**, 104157-63-3; **11j**, 104157-64-4; 2-nitrobenzenesulfenyl chloride, 7669-54-7; 4-methylbenzenesulfenyl chloride, 933-00-6; *tert*-butyl isocyanide, 7188-38-7; isopropyl isocyanide, 598-45-8; benzyl isocyanide, 10340-91-7; isopropylsulfenyl thiocyanate, 104157-51-9; methanesulfenyl chloride, 5813-48-9; benzenesulfenyl chloride, 931-59-9.

Supplementary Material Available: Tables of positional parameters, bond distances, and angles of **11e** and **10e** (7 pages). Ordering information is given on any current masthead page.

Improved Preparation of (3β,5α,14α)-3-Hydroxy-14-methylcholest-7-en-15-one. Synthesis of Ergostenone and 20α-(Hydroxymethyl)pregnenone Analogues

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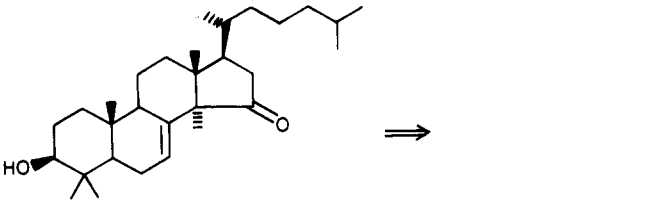
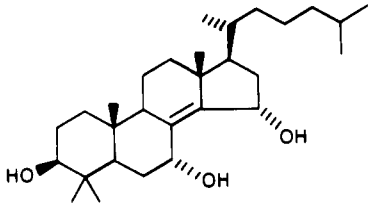
Reexamination of the synthesis of (3β,5α,14α)-3-hydroxy-14-methylcholest-7-en-15-one has led to an improved, large-scale preparation of this ketone. Noteworthy is the controlled outcome of a solvent effect observed during the pinacol-type rearrangement of vinyl epoxide **18** and the use of the ethoxyethyl ether protecting group at the C3 alcohol during alkylation. Preparative-scale routes to ergostenone derivatives **3** and **4** and pregnenone analogue **5** are described.

Certain 15-oxygenated sterol derivatives have been shown to be potent inhibitors of sterol biosynthesis.[1a-h] As a result of our current interest in this area we required multigram quantities of ketones **1**, **3**, **4**, and **5** (Schemes I and III) as synthetic intermediates. Nearly 30 years ago Woodward and co-workers described ketone **2** enroute to the first total synthesis of lanostenol via the chemical modification of cholesterol.[2a,b] The key step in this preparation of **2** was the vinylogous pinacol rearrangement of triol **6** to the corresponding 8(14)-en-15-one,[2c] which was subsequently methylated at C14.



2



6

Analogous synthetic strategies have since been employed by others for the construction of **1** with some success.[3,4] Our reinvestigation of these reactions for preparative purposes has led to an improved synthesis of ketone **1**, readily adaptable to large scale. We also report the first synthesis of (3β,5α,14α)-3-hydroxy-14-methylergost-7-en-15-one (**3**), its corresponding 4,4-dimethyl analogue **4**, and on an efficient preparation of the pregnenone analogue **5**.

Results and Discussion

4,4-Dimethylergosterol **10** was conveniently prepared in 55% overall yield via an oxidation, methylation, and reduction sequence on a 500-g scale using modified literature procedures[5,6] employing ergosterol[7] **7** as starting material (Scheme I). Subsequent benzoylation using 2 equiv of benzoyl chloride in pyridine furnished the crystalline benzoate **14** in 97% yield (Scheme I). Similar benzoylations of 7-dehydrocholesterol[7] **11** and ergosterol **7** furnished benzoates **12** and **13** in 95% and 92% yield, respectively. These latter two benzoylations were easily carried out on a kilogram scale, and isolation of the products was straightforward (Scheme I).

The first of several problems arose during initial attempts to generate large quantities of the 7,14-diene **15a** and 7,14,22-trienes **16a** and **17a** as products from the acid-catalyzed migration of the corresponding 5,7-diene congeners **12**–**14** (Scheme I). The literature procedures[4,8,9]

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(2) (a) Woodward, R. B.; Patchett, A. A.; Barton, D. H. R.; Ives, D. A. J.; Kelly, R. B. *J. Am. Chem. Soc.* **1954**, *76*, 2852. (b) Woodward, R. B.; Patchett, A. A.; Barton, D. H. R.; Ives, D. A. J.; Kelly, R. B. *J. Chem. Soc.* **1957**, 1131. (c) For the classical approach to the introduction of the 15-keto function, also see: Barton, D. A. R.; Laws, G. F. *J. Chem. Soc.* **1954**, 52.

(3) Spike, T. E.; Martin, J. A.; Huntoon, S.; Wang, A. H.; Knapp, F. F.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids* **1978**, *21*, 31.

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(6) Lakeman, J.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron Lett.* **1967**, 3699.

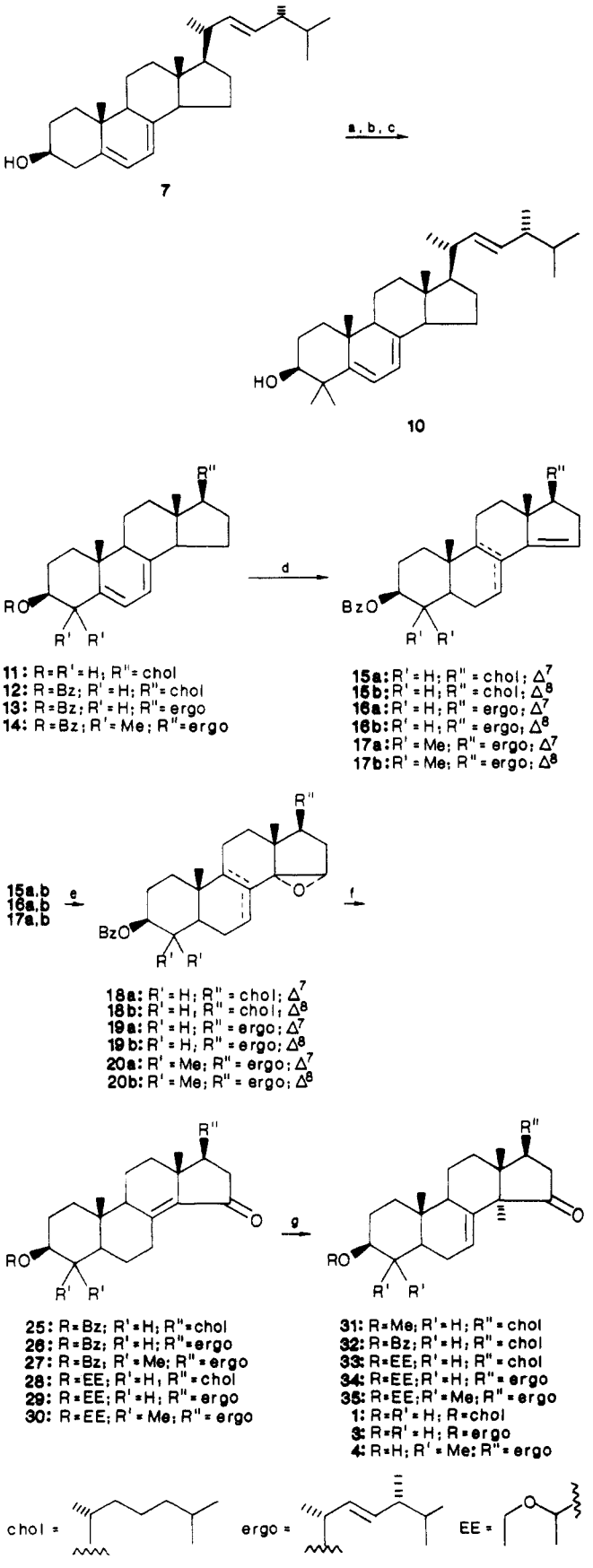
(7) 7-Dehydrocholesterol ($900/kg) and ergosterol ($710/kg) were obtained from Vitamins Inc., Chicago, IL.

(8) Parish, E. J.; Spike, T. E.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids*, **1977**, *18*, 233.

(9) (a) For a discussion of the isomerization reaction, see: Fieser, L.; Fieser, M. *Steroids*; Reinhold: New York, 1959; pp 111–122. (b) Rhodium-catalyzed isomerization: Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans 1* **1977**, 359.

0022-3263/86/1951-4047$01.50/0

Scheme I. Synthesis of 14-Methylcholest-7-en-15-one and 14-Methyergost-7-en-15-ones[a]



[a] Reagents and conditions: (a) PhMe, $C_6H_{10}O$, $Al(OiPr)_3$; (b) *t*-BuOK/*t*-BuOH, MeI; (c) LAH, THF; (d) HCl; (e) mCPBA, Et_2O, 0 °C; (f) EtOH, $CHCl_3$, HCl (15:3:1), reflux; (g) *t*-BuOK/*t*-BuOH, MeI and then THF, 5% HCl (4:1).

suggest a continual treatment of a relatively dilute solution of **12** in chloroform with dry HCl gas at low temperature for an extended period of time. During a detailed investigation of this isomerization, we found temperature to be an important factor and constant purging by HCl to be unnecessary. It was discovered that purging methylene chloride slurries of either diene **12** or trienes **13** or **14** for only 15 min at −30 to −40 °C followed by stirring at that temperature for 2 h was satisfactory. This protocol allows for maximum concentration of substrate in methylene chloride (1 g/10 mL) and furnished an easily isolated product (ca. 75% yield), which consisted of a 3:1 mixture of dienes **15a,b** or trienes **16a,b** or **17a,b**.[10]

Increased reaction times, a large excess of HCl, or higher temperatures all resulted in decreased isolated yields of the 7,14 dienes. Temperatures below −40 °C led to incomplete isomerization. Furthermore, whereas previous product isolation involved dilution with two to three volumes of ether and washing with saturated sodium bicarbonate, it was found that product isolation on a large scale was most easily accomplished by washing the cold reaction mixture with aqueous NH_4OH followed by concentration. Trituration of the residual slurry with cold methanol afforded crystalline mixtures (ca. 3:1) of **15a,b**, **16a,b**, or **17a,b** in 75–80% yield. Although pure **15a**, **16a**, or **17a** could be obtained by repeated recrystallization of these mixtures of isomers, this proved unnecessary as the mixtures were readily converted to enones **25**, **26**, and **27**, respectively, and easily purified to homogeneity at this stage.

The regioselective epoxidation of the 14,15 double bond in **15a,b**, **16a,b**, and **17a,b** with *m*-chloroperbenzoic acid was found to be quite rapid (ca. 1 h) in contrast to previous reports.[2b,4,8] Examination of a number of solvents including toluene, methylene chloride, diethyl ether, and ethyl acetate established that maximum regioselectivity occurred with diethyl ether[2b,4,8] at an optimum reaction temperature of 0 °C. Epoxides so generated were not isolated or purified but were used directly in the subsequent rearrangement.

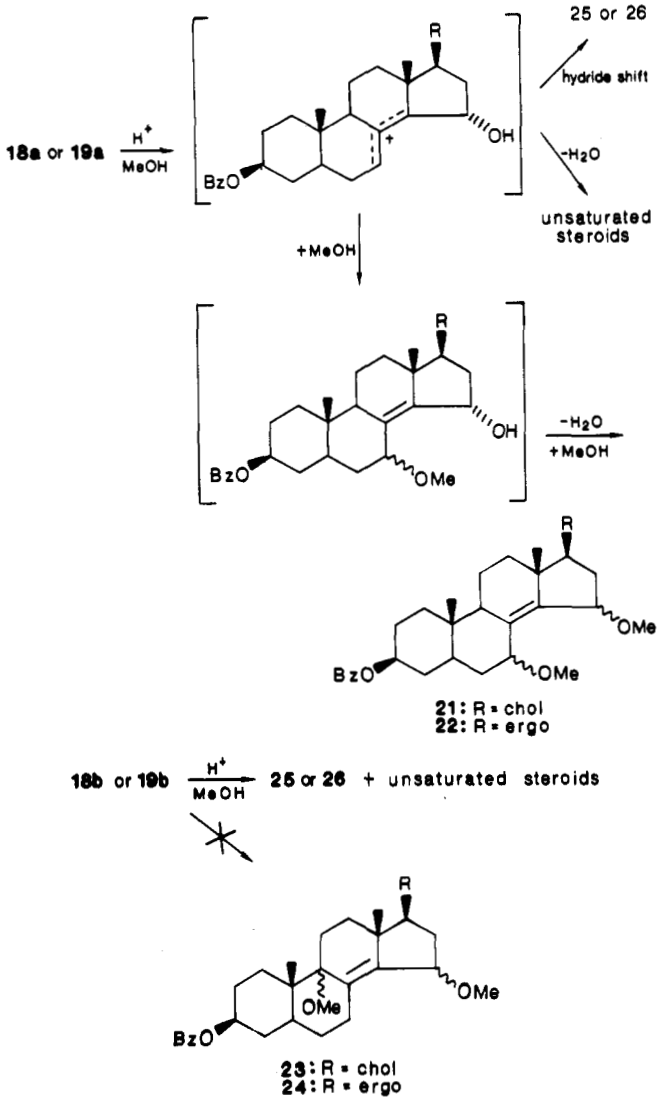
Pinacol-type rearrangement of the crude epoxides **18**, **19**, and **20** in methanolic HCl produced enones **25**, **26**, and **27**, respectively, as had been previously reported;[4,8] however, in our hands with these rearrangement conditions the desired products were isolated in only 20–30% yield following chromatography. TLC on the crude reaction mixtures (silica, CH_2Cl_2) indicated the presence of two byproducts, a material that was less polar (R_f 0.95; 45% yield) and a material that was slightly more polar (R_f 0.39; 25% yield) than the desired enones (R_f 0.5). In the case of the pinacol rearrangements of epoxides **18** and **19** these byproducts were examined further.[11]

Analysis of the higher R_f side product by ^1H NMR revealed an extremely complex vinylic region (δ 5.5–6.5) while GC/mass spectral data established this material to be a complex mixture of polyunsaturated steroids, i.e., dehydration products. A high-field ^1H NMR analysis of the more polar byproduct showed two anomalous methoxy resonances at δ 3.1 and 3.2, two methine protons at δ 4.25, and an absence of the H-7β anisotropic effect which is characteristic of a carbonyl at C15.[8] Further analysis suggested structures **21** and **22** (Scheme II), methanol addition products, as the more polar contaminants.

(10) ^1H NMR analysis of the crystalline product was facilitated by presence of the C7 vinylic proton (δ5.8) in **15a**, **16a**, and **17a** and its absence in **15b**, **16b**, and **17b**.

(11) Byproducts from the acid-catalyzed rearrangement of epoxide **20** were presumed to be analogous to those generated during the rearrangement of epoxides **18** and **19**.

Scheme II. Postulated Acid-Catalyzed Rearrangement of α,β-Unsaturated Epoxides in Methanol[13]



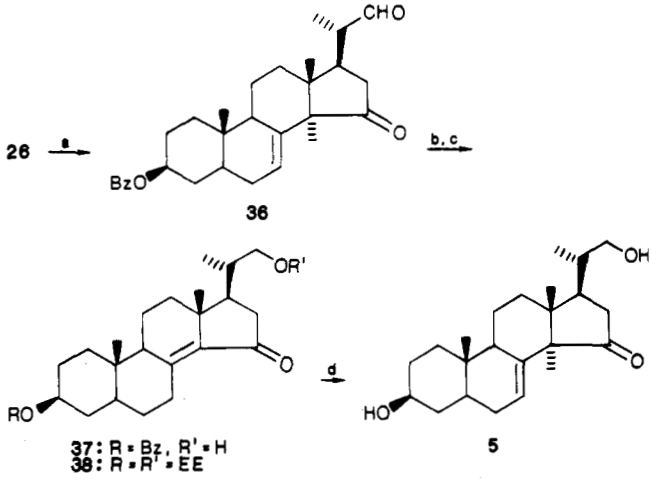
The undesired side products presumably arise via the acid-catalyzed E1 dehydration of the epoxide(s) as illustrated in Scheme II or, in the case of addition products **21** and **22**, interception of the incipient allylic carbocation(s) with methanol.[12] No evidence was found for the formation of addition products such as **23** or **24** from **18b** or **19b**, supporting an observation that epoxides in the Δ^8 series give rise to enones and elimination products only.[13] Stereochemistries of the methoxy groups in **21** and **22** were not rigorously established; however, the literature precedent argues for the α-configurations.[2a,b]

When ethanol was employed in place of methanol as solvent in the rearrangement, a complete absence of solvent addition products and an attenuation of E1 elimination products resulted. Enones **25–27** were thus obtained in 55–65% yields. The decreased nucleophilicity of ethanol is no doubt responsible for the observed change in product distribution. Although the elimination products could not be efficiently removed from the enone(s) via crystallization, a large R_f difference between the two products (ΔR_f = 0.8, silica, 30% petroleum ether in CH_2Cl_2) allowed a trivial purification simply by filtering through silica gel.

Repeating the suggested literature procedures[3,4] for the methylation of enone **25** using excess *t*-BuOK/*t*-BuOH (18 equiv) and methyl iodide (90 equiv) under anhydrous conditions did result in the formation of alkylated benzoate **32** (Scheme I), but this was accompanied by methyl ether **31**[14] (25%) and **1** (30%). No evidence was found to suggest the formation of di- or trimethylated products. Furthermore, it was our experience that the enone must first be powdered and the reaction mixture heated to 50–60 °C before dissolution and reaction would occur. This operation proved impractical (as well as destructive to **25–27**) on a preparative scale.

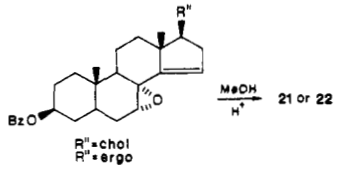
An obvious solution to the problem encountered during the alkylation would be the introduction of a different protecting group for the hydroxyl moiety at C3 which would be inert to the basic reaction conditions. Exchange of the benzoate in **25** for the ethoxyethyl ether (EE) protecting group[15,16] (K_2CO_3, MeOH, CH_2Cl_2; then ethyl vinyl ether, 2 equiv; pyridinium *p*-toluenesulfonate (PPTS), catalyst) furnished ether **28**. This exchange was quantitative and could be readily accomplished in essentially one pot. Subsequent methylation (12 equiv of *t*-BuOK, 75 equiv of MeI) provided (3β,5α,14α)-3-(1-ethoxyethoxy)-14-methylcholest-7-en-15-one (**33**) in 85% isolated yield.

Scheme III. Synthesis of Pregn-7-en-15-one 5[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C, and then Me_2S; (b) *t*-$BuNH_2$·BH_3, CH_2Cl_2, 0 °C; (c) K_2CO_3, MeOH, and then EVE, PPTS, CH_2Cl_2; (d) *t*-BuOK/*t*-BuOH, MeI and then THF, 5% HCl (4:1).

(12) These addition products may also arise from the isomeric epoxide:



(13) It has been reported that the epoxides generated from the 8-(9),14(15)-diene give rise to the respective enone and elimination/rearrangement products: (a) Anastasia, M.; Allevi, P.; Fiecchi, A.; Scala, A. *Lipids* **1982**, *17*, 226. (b) Anastasia, M.; Allevi, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1981**, *46*, 3265.

(14) Analogous ether formation was noted during the *t*-BuOK alkylation of **25** with ethyl iodide: Parish, E. J.; Tsuda, M.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids*, **1979**, *24*, 209.

(15) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104.

(16) Use of the benzyl vs. benzoate group as the initial protecting function at C3 was also investigated. Although the desired chemistry (isomerization, epoxidation, pinacol rearrangement, and alkylation) could be carried out with the benzyl-protected material, the benzyl group drastically altered the solubility properties of the steroid intermediates. Flash chromatography became necessary at each step, and this proved too laborious for the large-scale preparation of intermediates. Likewise the acetate at C3 also proved inferior as a protecting group.

In an analogous fashion, **26** and **27** were converted to **29** and **30**, respectively, and then alkylated to give (3β,5α,14α)-3-(1-ethoxyethoxy)-14-methylergost-7-en-15-one (**34**) and the 4,4-dimethyl analogue **35** in 88% overall yield. Treatment of **33–35** in THF containing 5% aqueous HCl (4:1) for 10 min at ambient temperature afforded the respective alcohols **1**, **3**, and **4** in quantitative yield. The regiochemical outcome of the methylation reaction was obvious from spectroscopic analysis of both intermediates **33–35** and the products **1**, **3**, and **4**. Thus upon alkylation the NMR signal characteristic of the 7β-H disappeared to be replaced by a new signal corresponding to the vinyl proton at 7. In addition, in the IR of the alkylated, deconjugated products the C15 carbonyl group absorbed at 1730 cm^{-1}. Precedent for α-diastereofacial selectivity upon alkylation of enones **28–30** is based on a reported X-ray crystallographic analysis of a derivative of **1**.[3]

In order to further extend the utility of this synthetic sequence to 14α-methyl-15-oxo steroids bearing modified side chains, selective ozonolysis of the 22,23 double bond in enone **26** was studied (Scheme III). Treatment of **26** with a slight excess of ozone in CH_2Cl_2 at −78 °C followed by reduction with methyl sulfide afforded the corresponding aldehyde **36** in 72% yield. The α,β-unsaturated ketone group proved relatively resistant to ozonolysis, and thus a carefully controlled addition of 1 equiv of ozone was found to be unnecessary. The ^1H and ^{13}C NMR spectra unequivocally established aldehyde **36** as a single diastereomer.[17]

Chemoselective reduction of the aldehyde moiety in **36** was carried out by using *tert*-butylamine–borane complex[18] in CH_2Cl_2 at 0 °C to furnish alcohol **37** as the sole product. Debenzoylation and ethoxyethyl ether formation gave the bisacetal **38** which was subsequently alkylated. Formation of a monoalkylated product was apparent from mass spectral and NMR data for the methylated ketone. That alkylation had occurred regiochemically at C14 with deconjugation was obvious from the presence of a vinyl proton signal as well as the disappearance of the characteristic 7β-hydrogen present in the starting material **38**. It is assumed, by analogy with the known methylation of **25**, that introduction of the C14 methyl group occurred selectively from the less hindered α-face. Removal of the protecting groups under previously described conditions provided pregnenone derivative **5** in 85% overall yield from aldehyde **36**.

In summary, a large-scale, improved preparation of ketone **1** has been successfully completed. Notable improvements over the existing literature preparations of **1** include (1) definition of controlled 5,7- to 7,14-diene isomerization and simplified workup, (2) identification of side products generated during the allylic epoxide to enone rearrangement and inhibition thereof (thus nearly doubling the isolated yield of enone **25**), and (3) establishing the 1-ethoxyethyl ether as the preferred protecting group for the 3-hydroxyl group during alkylation at C14. Also described are the first syntheses of ergostenone analogues **3** and **4** and 20(*S*)-(hydroxymethyl)pregnenone **5** using these modifications. Thus, ketones **1**, **3**, **4**, and **5** were prepared in 30%, 25%, 15%, and 14% overall yields from commercially available 7-dehydrocholesterol and ergosterol.

(17) No epimerization at C20 was observed following ozonolysis of enone **26**. (a) Barton, D. H. R.; Shioiri, T.; Widdowson, D. A. *J. Chem. Soc. C* **1971**, 1968. (b) Slomp G., Jr.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.

(18) (a) Lane, C. F.; *Aldrichimica Acta* **1973**, *6*, 51. (b) Crawford, T. C.; Andrews, G. C. *Tetrahedron Lett.* **1980**, 693, 697.

Experimental Section

General Methods. Tetrahydrofuran was dried over 4A molecular sieves for 24 h before use. *tert*-Butyl alcohol was dried over K_2CO_3 for 24 h and then freshly distilled from *t*-BuOK. All other solvents and reagents were used without purification. Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. Thin-layer chromatography was conducted on Analtech Uniplate 200μ silica gel plates, and Baker 40-μm "flash" silica gel was used for flash chromatography. Infrared (IR) spectra ($CHCl_3$ thin films) were recorded on a Perkin-Elmer 727 spectrometer. ^1H NMR were recorded at 90 MHz (Varian EM 390) and/or 270 MHz (JEOL GX 270), and ^{13}C NMR were recorded at 67.8 MHz on the latter instrument. Mass spectra were recorded on a Finnigan Model 3625 mass spectrometer equipped with chemical ionization capability. High-resolution mass spectra (FAB) were determined on a VG-SAB at the Mass Spectrometry Resource facility in the SK&F Analytical, Physical and Structural Chemistry Department. Elemental analyses and optical rotations were also performed in this department.

(22*E*)-Ergosta-4,7,22-trien-3-one (8). A mixture of ergosterol[7] (**7**) (397 g, 1 mol), toluene (5 L), and cyclohexanone (1.3 L) was heated at reflux in a 12-L flask equipped with a Dean–Stark trap, condenser, and mechanical stirrer until water ceased to collect in the trap (ca. 2 h). The solution was cooled to 80–90 °C, and aluminum triisopropoxide (113 g, 0.56 mol) was added in one portion. The reaction was heated at reflux for 15–20 min, then cooled to 10 °C, and poured into 2 N HCl (5 L). The organic layer was separated and washed with 2 N HCl (2 × 1 L). The combined acid washes were back-extracted with diethyl ether (2 × 500 mL), and the organic extracts were combined and washed sequentially with water (3 × 1 L) and brine (2 × 500 mL) and then dried (Na_2SO_4). Toluene and ether were removed in vacuo [50 °C (20 torr)], leaving a syrup of **8** in cyclohexanone. Further concentration of the syrup in vacuo [70 °C (5 torr)] gave a dark red crystalline mass of crude **8**. Recrystallization from acetone (1 g/6 mL) yielded **8** (296 g, 75%) as yellow needles. An analytical sample was prepared by flash chromatography (70% CH_2Cl_2 in petroleum ether): mp 130–131 °C (lit.[5] mp 128–130 °C; lit.[6] mp 128–131 °C); R_f 0.35 (CH_2Cl_2); $[\alpha]^{25}_D$ −16.34° (*c* 1.06, CH_2Cl_2) [lit.[5] $[\alpha]_D$ −9° ($CHCl_3$)]; IR 2960, 2870, 1660, 1620, 970 cm^{-1}; NMR δ 5.81 (s, 1 H, H-4), 5.15 (m, 3 H, H-7,22,23), 3.2–0.6 (m, 38 H, remaining H); mass spectrum *m/e* 395 (M + H), 379, 267, 125.

Anal. Calcd for $C_{28}H_{42}O$: C, 85.22; H, 10.73. Found: C, 84.93; H, 10.58.

(22*E*)-4,4-Dimethylergosta-5,7,22-trien-3-one (9). To a solution of *t*-BuOH (5 L) containing *t*-BuOK (226 g, 2 mol, Aldrich) at 40–50 °C was added a solution of **8** (200 g, 0.508 mol) in THF (500 mL) in one portion. After 10 min, methyl iodide (250 mL, 4 mol) was added, and the reaction was stirred at 45 °C for 30 min, then concentrated in vacuo to one-third its original volume, poured into ice–water (10 L), and extracted with ether containing 10% CH_2Cl_2 (2.5 L). The organic extract was washed sequentially with water (5 × 1 L) and brine (2 × 1 L) and dried ($MgSO_4$). Removal of solvent in vacuo gave essentially pure **9** (182 g, 85%). An analytical sample was prepared by flash chromatography (30% CH_2Cl_2 in petroleum ether): mp 163–164 °C (lit.[6] mp 163–165 °C); R_f 0.47 (50% CH_2Cl_2 in petroleum ether); $[\alpha]^{25}_D$ −28.1° (*c* 1.0, CH_2Cl_2); IR 2960, 2870, 1710, 1380 cm^{-1}; NMR δ 5.80 (m, 1 H, H-6), 5.52 (m, 1 H, H-7), 5.17 (m, 2 H, H-22,23), 2.5–0.5 (m, 43 H, remaining H); mass spectrum, *m/e* 423 (M + H), 407, 299, 125.

Anal. Calcd for $C_{30}H_{46}O$: C, 85.25; H, 10.97. Found: C, 85.57; H, 11.02.

(3β,22*E*)-4,4-Dimethylergosta-5,7,22-trien-3-ol (10). A solution of **9** (200 g, 0.474 mol) in THF (4 L) was added to a stirred solution of $LiAlH_4$ (9 g, 0.242 mol) in THF (500 mL) over a 30-min period at room temperature. After 30 min, excess $LiAlH_4$ was destroyed by the addition of 1:1 H_2O–THF. The solution was dried with $MgSO_4$ and filtered through Celite. The solvent was removed to give crude **10** (197 g, 98%). An analytical sample was prepared by flash chromatography (50% CH_2Cl_2 in petroleum

ether): mp 183–184 °C; R_f 0.25 (50% CH_2Cl_2 in petroleum ether); $[\alpha]^{25}_D$ −185.7° (c 1.12, CH_2Cl_2); IR 3400, 2960, 2870, 1460, 1380 cm^{-1}; NMR δ 5.95 (d, 1 H, J = 6.5 Hz, H-6), 5.55 (m, 1 H, H-7), 5.20 (m, 2 H, H-22,23), 3.30 (m, 1 H, H-3), 2.00–0.50 (m, 43 H, remaining H); mass spectrum, m/e 425 (M + H), 424 (M^+), 423 (M − H), 407 (M + H −H_2O), 125.

Anal. Calcd for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found: C, 84.62; H, 11.34.

(3β,22*E*)-4,4-Dimethylergosta-5,7,22-trien-3-ol Benzoate (14). A solution of alcohol **10** (250 g, 0.589 mol) in pyridine (2.5 L) was cooled at 10 °C during the addition (5 min) of benzoyl chloride (two 70-mL portions, 1.2 mol). The reaction was stirred at ambient temperature for 5 h and then poured into ice–water (5 L). The precipitate was collected, washed with ice-cold acetone (2 × 200 mL), recrystallized from CH_2Cl_2/MeOH, and dried [25 °C (0.1 torr)] for 12 h to give **14** (286 g, 92%): mp 147–148 °C; R_f 0.80 (20% CH_2Cl_2 in petroleum ether); $[\alpha]^{25}_D$ −63.4° (c 0.6, CH_2Cl_2); IR 2960, 2870, 1710, 1260, 1120, 910 cm^{-1}; NMR δ 8.10 and 7.51 (m, 5 H, Ar), 5.96 (d, 1 H, J = 9.0 Hz, H-6), 5.55 (m, 1 H, H-7), 5.24 (m, 2 H, H-22,23), 4.85 (t, 1 H, J = 11.0 Hz, H-3), 2.10–0.60 (m, 42 H, remaining H); mass spectrum, m/e 528 (M^+), 407, 125, 105.

Anal. Calcd for $C_{37}H_{52}O_2$: C, 84.04; H, 9.91. Found: C, 84.02; H, 9.84.

(3β)-Cholesta-5,7-dien-3-ol Benzoate (12). 7-Dehydrocholesterol[7] (**11**) (1 kg, 2.6 mol) was dissolved in pyridine (7.5 L) with warming. Benzoyl chloride (four 225-mL portions, 7.7 mol) was then added (15 min) to the cooled (10–15 °C) solution. The reaction was stirred for 6 h at ambient temperature and then poured into ice–water (15 L). The precipitate was collected and washed with ice-cold acetone (3 × 500 mL) and dried [25 °C (0.1 torr)] to yield **12** (1.2 kg, 93%), which was used without further purification. An analytical sample was prepared by recrystallization (CH_2Cl_2/MeOH): mp 138–139 °C (lit.[19] mp 139–140 °C); R_f 0.51 (30% CH_2Cl_2 in petroleum ether); $[\alpha]^{25}_D$ −61.6° (c 0.6, CH_2Cl_2) [lit.[19] $[\alpha]^{20}_D$ −53.2° ($CHCl_3$)]; IR: 2980, 2870, 1710, 1280 cm^{-1}; NMR δ 8.10 and 7.45 (m, 5 H, Ar) 5.60 (d, 1 H, J = 9.0 Hz, H-6), 5.35 (m, 1 H, H-7), 4.90 (m, 1 H, H-3), 2.50–0.60 (m, 40 H, remaining H); mass spectrum, m/e 489 (M + H), 395, 367, 199, 123.

Anal. Calcd for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90. Found: C, 83.45; H, 10.04.

(3β,22*E*)-Ergosta-5,7,22-trien-3-ol Benzoate (13). Ergosterol[7] **7** (500 g, 1.26 mol) was benzoylated as in the preparation of **11** to give **13** (600 g, 95%). An analytical sample of **13** was prepared by recrystallization (CH_2Cl_2/MeOH): mp 169–171 °C (lit.[18] mp 169–171 °C); R_f 0.51 (30% CH_2Cl_2 in petroleum ether); $[\alpha]^{25}_D$ −61.6° (c 1.0, CH_2Cl_2) [lit.[20] $[\alpha]^{20}_D$ −71° ($CHCl_3$)]; IR 2960, 2860, 1710, 1280 cm^{-1}; NMR δ 8.10 and 7.45 (m, 5 H, Ar), 5.60 (m, 1 H, H-6), 5.40 (m, 1 H, H-7), 5.20 (m, 2 H, H-22,23), 4.92 (m, 1 H, H-3), 2.50–0.60 (m, 38 H, remaining H); mass spectrum, m/e 501 (M + H), 407, 379, 363, 125.

Anal. Calcd for $C_{35}H_{48}O_2$: C, 83.95; H, 9.66. Found: C, 83.88; H, 9.75.

(3β,5α)-Cholesta-7,14-dien-3-ol and -8,14-dien-3-ol Benzoates (15a,b). A slurry of **12** (300 g, 0.614 mol) in CH_2Cl_2 (3 L) was cooled to −30 to −40 °C. HCl gas was passed into the slurry at a moderate rate for 15 min to produce a deep clear purple solution which was kept at −30 to −40 °C for 2 h and then poured into ice–cold 8 N NH_4OH[21] (6 L) contained in a separatory funnel. The mixture was shaken, and the resulting yellow organic layer was separated and washed sequentially with 18 N NH_4OH (3 × 3 L), water (3 L), and brine (2 × 2 L). The CH_2Cl_2 solution was dried ($MgSO_4$),[22] concentrated in vacuo (30 °C) to 2 L (ca. one-third its original volume), and triturated with methanol[23] (7 L). The resulting crystalline product was filtered and dried overnight [25 °C (0.1 torr)] to give a 3:1 mixture of dienes **15a** and **15b** (225 g, 75%), which was used without further purification: mp 146–150 °C (lit.[8] mp 148–150 °C); R_f 0.51 (30% CH_2Cl_2 in petroleum ether); IR 2960, 1710, 1280 cm^{-1}; NMR δ 8.15 and 7.50 (m, 5 H, Ar), 5.80 (br s, 0.77 H, H-7), 5.60 (br s, 0.77 H, H-15), 5.40 (br s, 0.23 H, H-15), 5.00 (m, 1 H, H-3), 2.50–0.80 (m, remaining H); mass spectrum m/e 489 (M + H), 395, 367, 199, 123.

Anal. Calcd for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90. Found: C, 83.92; H, 9.86.

(3β,5α,22*E*)-Ergosta-7,14,22-trien-3-ol and -8,14,22-trien-3-ol Benzoates (16a,b). Benzoate **13** (400 g, 0.8 mol) in CH_2Cl_2 (4 L) was isomerized as in the preparation of **15** to give a 3:1 mixture of benzoates **16a** and **16b** (296 g, 74%): mp 179–184 °C; R_f 0.51 (30% CH_2Cl_2 in petroleum ether); IR 2960, 2860, 1710, 1280 cm^{-1}; NMR δ 8.15 and 7.50 (m, 5 H, Ar), 5.75 (br s, 0.77 H, H-7), 5.50 (br s, 0.77 H, H-15), 5.20 (m, 2.23 H, H-22,23,15), 4.90 (m, 1 H, H-3), 2.4–0.70 (m, remaining H); mass spectrum, m/e 501 (M + H), 407, 379, 363, 125.

Anal. Calcd for $C_{35}H_{48}O_2$: C, 83.95; H, 9.66. Found: C, 84.12; H, 9.60.

(3β,5α,22*E*)-4,4-Dimethylergosta-7,14,22-trien-3-ol and -8,14,22-trien-3-ol Benzoates (17a,b). Benzoate **14** (200 g, 0.378 mol) in CH_2Cl_2 (2 L) was isomerized as in the preparation of **15** to provide a 3:1 mixture of trienes **17a** and **17b** (144 g, 72%): mp 169–173 °C; R_f 0.80 (50% CH_2Cl_2 in petroleum ether); IR 2960, 2860, 1710, 1280 cm^{-1}; NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.80 (br s, 0.77 H, H-7), 5.50 (br s, 0.77 H, H-15), 5.20 (m, 2.23 H, H-22,23,15), 4.75 (m, 1 H, H-3), 2.40–0.70 (m, remaining H); mass spectrum, m/e 528 (M^+), 407, 125, 105.

Anal. Calcd for $C_{37}H_{52}O_2$: C, 84.04; H, 9.91. Found: C, 84.12; H, 9.95.

(3β,5α,15α)-14,15-Epoxycholest-7-en-3-ol Benzoate (18). The 3.5:1 mixture of dienes **15a** and **15b** (400 g, 0.820 mol) was dissolved in diethyl ether (15 L) with gentle warming. The solution was stirred and cooled to ca. 15 °C, and a solution of *m*-chloroperbenzoic acid (*m*-CPBA)[24] (336 g, 1.9 mol) in diethyl ether (2 L) was added (30 min). The epoxide **18** began to separate from the reaction mixture within 10 min following the *m*-CPBA addition. The reaction was cooled to −5 °C (salt–ice bath) for approximately 3 h and then filtered[25,26] to afford a mixture of epoxides **18a** and **18b** (297 g, 72%), which was used directly: mp 180–195 °C (lit.[8] mp 200–201 °C, pure **18a**); R_f 0.38 (35% ethyl acetate in CH_2Cl_2).

(3β,5α,15α,22*E*)-14,15-Epoxyergosta-7,22-dien-3-ol Benzoate (19) and the 4,4-Dimethyl Analogue 20. A mechanically stirred solution of the 3.5:1 mixture of trienes **16a** and **16b** (300 g, 0.600 mol) in diethyl ether (9 L) was cooled to 10 °C. A solution of *m*-CPBA (240 g, 1.4 mol) in diethyl ether (500 mL) was added (20 min), and the reaction was stirred for 1 h at 0 °C.[27] Excess *m*-CPBA was destroyed with dimethyl sulfide (ca. 20 mL), and the solution was washed sequentially with 3 N NH_4OH (4 × 2.5 L), water (2 × 1.5 L), and brine (1 L). Drying ($MgSO_4$) and removal of solvents in vacuo furnished crude epoxides **19a** and **19b** (254 g, 82%) as a yellow foam, which was used without purification: R_f 0.42 (35% ethyl acetate in CH_2Cl_2).

Epoxide 20. A solution of trienes **17a,b** (2.8:1 mixture, 200 g, 0.378 mol) in diethyl ether (2 L) was treated with *m*-CPBA (110.7 g, 0.645 mol) at 0 °C for 1 h as in the preparation of **19** to yield the crude epoxides **20a,b** as a yellow foam (164 g, 80%): R_f 0.69 (30% ethyl acetate in CH_2Cl_2).

(3β,5α)-3-(Benzoyloxy)cholest-8(14)-en-15-one (25). Method A. Crude epoxide mixture **18a,b** (5 g, 9.92 mmol) was dissolved in MeOH/$CHCl_3$/12 N HCl (420 mL of a 15:5:1 solution) and heated at reflux for 15 min. The dark yellow reaction mixture

(19) *The Merck Index*, 10th ed.; Windholz, M., Ed.; Merck & Co.: Rahway, NJ, 1983; p 2846.

(20) See ref 19, p 3602.

(21) Some fuming is observed upon quenching the acidic reaction mixture with NH_4OH; however, the neutralization has no tendency to become violent.

(22) Success of this reaction depends on the complete removal of HCl from the CH_2Cl_2 solution before concentration, hence the need for several NH_4OH washings. A few drops of pyridine were added to the dried ($MgSO_4$) CH_2Cl_2 extract before concentration and trituration with MeOH.

(23) For best results, addition of five 400-mL portions of MeOH with vigorous swirling until crystallization (precipitation) initiates and then addition of the remaining MeOH (5 L) in two or three portions.

(24) *m*-CPBA was the technical grade (80–85%) from Aldrich.

(25) The epoxidation is complete within 1 h (TLC). Additional reaction times at −5 °C ensures nearly complete precipitation from solvent.

(26) Additional epoxides (10%) can be recovered from the mother liquor via standard workup; however, this was found to be counterproductive on a large scale.

(27) Separation of epoxides **19a,b** and **20a,b** from the reaction did not occur.

was cooled and then diluted with water (1 L). The organic layer was separated, washed sequentially with saturated aqueous $NaHCO_3$ (2 × 50 mL), water (50 mL), and brine (100 mL), and then dried ($MgSO_4$). The solvent was removed in vacuo, and the crude enone was purified by flash chromatography (CH_2Cl_2) to afford a complex mixture of unsaturated steroids (2.3 g, 45%), desired enone **25** (1.5 g, 30%), and the 7,15-dimethoxy-8(14)-cholestene **21** (1.2 g, 25%). The dehydrated steroid mixture was recrystallized ($CHCl_3$/MeOH): mp 139–146 °C; R_f 0.50 (30% CH_2Cl_2 in petroleum ether); IR 2960, 2870, 1710, 1280, 1120 cm^{-1}; NMR δ 8.10 and 7.50 (m, 5 H, Ar), 6.25–5.32 (m, 4 H total), 5.00 (m, 1 H, H-3), 2.50–0.70 (m, remaining H); GC/mass spectrum, *m/e* 486 (M^+).

Recrystallization (CH_2Cl_2/MeOH) of **25** yielded the product as a white solid: mp 156–157 °C (lit.[8] mp 157–158 °C; lit.[4] mp 156–158 °C); R_f 0.43 (CH_2Cl_2); $[\alpha]^{25}_D$ + 112.7° (*c* 1.0, CH_2Cl_2) (lit.[4] $[\alpha]^{26}_D$ +98° ($CHCl_3$); lit.[2b] $[\alpha]^{25}_D$ +103° ($CHCl_3$)]; IR 2960, 2860, 1710, 1620, 1280 cm^{-1}; NMR δ 8.15 and 7.50 (m, 5 H, Ar), 5.10 (m, 1 H, H-3), 4.15 (m, 1 H, H-7β), 2.5–0.80 (m, 41 H, remaining H); mass spectrum, *m/e* 505 (M + H), 383, 355.

Anal. Calcd for $C_{34}H_{48}O_3$: C, 80.91; H, 9.59. Found: C, 80.57; H, 9.37.

Dimethyl ether 21: oil; R_f 0.26 (CH_2Cl_2); $[\alpha]^{25}_D$ +0.04° (*c* 0.25, CH_2Cl_2); IR 2970, 2860, 1710, 1380 cm^{-1}; NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.00 (m, 1 H, H-3), 4.25 (m, 2 H, H-7,15), 3.25 and 3.18 (2 × s, 3 H each, OMe), 2.5–0.80 (m, 40 H, remaining H); mass spectrum, *m/e* 551 (M + H), 534, 518, 276; high-resolution FAB mass spectrum, calcd for $C_{36}H_{54}O_4$ 550.0123, found 550.0125.

Method B. A solution of epoxides **18a** and **18b** (275 g, 0.546 mol, crude from the epoxidation of the corresponding dienes **15a** and **15b**) in absolute EtOH/$CHCl_3$/12 N HCl (2 L of a 15:3:1 solution) was heated at reflux for 15 min on a steam bath and then cooled to ambient temperature. The solution was diluted with CH_2Cl_2 (400 mL) and washed sequentially with water (2 × 4 L), saturated aqueous $NaHCO_3$ (2 × 500 mL), and brine (500 mL) and then dried ($MgSO_4$). Evaporation of solvents afforded crude enone **25** as a mixture with unidentified dehydrated steroids. Flash chromatography (70% petroleum ether in CH_2Cl_2) of the mixture gave pure enone **25** (181 g, 66%), identical in all respects with the enone obtained by method A.

(3β,5α,22*E*)-3-(Benzoyloxy)ergosta-8(14),22-dien-15-one (26). Method A. Epoxides **19a,b** (4 g, 7.75 mmol) were treated with MeOH/$CHCl_3$/12 N HCl (400 mL of a 15:5:1 solution) in exactly the same manner as epoxides **18a,b** to yield polyunsaturated steroids (1.92 g, 48%), enone **26** (1.12 g, 28%) and the dimethoxy compound **22** (0.8 g, 20%). Enone **26** crystallized (CH_2Cl_2/MeOH) as colorless crystals: mp 175–176 °C; R_f 0.54 (CH_2Cl_2); $[\alpha]^{25}_D$ +62.2° (*c* 0.75, CH_2Cl_2); IR 2960, 2880, 1710, 1620, 1280 cm^{-1}; NMR δ 8.15 and 7.45 (m, 5 H, Ar), 5.20 (m, 2 H, H-22,23), 4.90 (m, 1 H, H-3), 4.20 and 4.05 (m, 1 H, H-7β), 2.40–0.80 (m, 39 H, remaining H); mass spectrum, *m/e* 517 (M + H), 395, 271, 125.

Anal. Calcd for $C_{35}H_{48}O_3$: C, 81.35; H, 9.36. Found: C, 81.37; H, 9.37.

Dimethyl ether 22: crystallized (CH_2Cl_2, MeOH) as a white solid; mp 146–147 °C; R_f 0.43 (CH_2Cl_2); $[\alpha]^{25}_D$ −31.3° (*c* 1.0, CH_2Cl_2); IR 2970, 1710, 1280 cm^{-1}; NMR δ 8.15 and 7.50 (m, 5 H, Ar), 5.25 (m, 2 H, H-22,23), 4.95 (m, 1 H, H-3), 4.25 (m, 2 H, H-7,15), 3.20 and 3.15 (2 s, 3 H each, OMe), 2.50–0.80 (m, 40 H, remaining H); mass spectrum, *m/e* 562 (M^+), 531, 515, 409, 377, 285, 125.

Anal. Calcd for $C_{37}H_{54}O_4$: C, 78.96; H, 9.67. Found: C, 78.76; H, 9.68.

Method B. Epoxides **19a,b** (300 g, 0.58 mol) were rearranged in absolute EtOH/CH_2Cl_2/12 N HCl (2.5 L of a 15:3:1 solution) in the same fashion as epoxides **18a,b** to provide enone **26** (164 g, 55%), identical in all respects with the material obtained by method A.

(3β,5α,22*E*)-3-(Benzoyloxy)-4,4-dimethylergosta-8(14),22-dien-15-one (27). A solution of the epoxides **20a,b** (280 g, 0.51 mol) in absolute EtOH/$CHCl_3$/12 N HCl (3 L of a 15:3:1 solution) was heated at reflux for 15 min and then cooled to room temperature. Dilution with CH_2Cl_2 and workup as described above for **26** furnished enone **27** (162 g, 58%) after flash chromatography (50% CH_2Cl_2 in petroleum ether) and recrystallization (CH_2Cl_2/MeOH): mp 178–179 °C; R_f 0.68 (CH_2Cl_2); $[\alpha]^{25}_D$ +92.4° (*c* 0.83, CH_2Cl_2); IR 2960, 1710, 1700, 1620, 1280, 1120 cm^{-1}; NMR δ 8.15 and 7.50 (m, 5 H, Ar), 5.25 (m, 2 H, H-22,23), 4.80 (m, 1 H, H-3), 4.20 (m, 1 H, H-7β), 2.40–0.80 (m, 43 H, remaining H); mass spectrum, *m/e* 545 (M + H), 423, 395, 299, 125.

Anal. Calcd for $C_{37}H_{52}O_3$: C, 81.57; H, 9.62. Found: C, 81.74; H, 9.50.

(3β,5α,14α)-3-(Benzoyloxy)-14-methylcholest-7-en-15-one (32). A solution of *t*-BuOH (500 mL) containing *t*-BuOK (40.3 g, 0.36 mol) was stirred under argon as a solution of enone **25** (10 g, 20 mmol) in THF (60 mL) was added in one portion. After the reaction was stirred for 10 min, methyl iodide (100 mL, 1.6 mol) was added (5 min), and the resulting reaction mixture was stirred for 2 h. The milky white reaction mixture was poured into water (2 L), and ether (200 mL) was added. The organic layer was separated and washed sequentially with water (4 × 500 mL) and brine (100 mL) and then dried ($MgSO_4$). Solvents were removed in vacuo, and the resulting residue was purified by flash chromatography (CH_2Cl_2) to give alkylated benzoate **32** (2.7 g, 26%), the corresponding methyl ether **31** (2.5 g, 25%), and keto alcohol **1** (3.1 g, 30%). Recrystallization (CH_2Cl_2/MeOH) yielded benzoate **32**: mp 146–147 °C (lit.[3,4] mp 146–148 °C; lit.[2b] 145–147 °C); R_f 0.78 (CH_2Cl_2); $[\alpha]^{25}_D$ + 53.5° (*c* 1.0, CH_2Cl_2) [lit.[4] $[\alpha]^{25}_D$ +56° ($CHCl_3$); lit.[2b] $[\alpha]^{25}_D$ +51° ($CHCl_3$)]; IR 2960, 1730, 1710, 1280, 1120 cm^{-1}; NMR δ 8.15 and 7.50 (m, 5 H, Ar), 6.50 (m, 1 H, H-7), 5.00 (m, 1 H, H-3), 2.50–0.80 (m, 43 H, remaining H); mass spectrum, *m/e* 519 (M + H), 501, 461, 397, 379.

Anal. Calcd for $C_{35}H_{50}O_3$: C, 81.03; H, 9.72. Found: C, 81.17; H, 9.75.

Methyl ether 31: crystallized (ether/MeOH) as a white solid; mp 84–85 °C (lit.[2b] mp 86–87 °C); R_f 0.40 (CH_2Cl_2); $[\alpha]^{25}_D$ +16.4° (*c* 1.0, CH_2Cl_2) [lit.[2b] $[\alpha]_D$ + 56° ($CHCl_3$)]; IR 2940, 1730, 1470, 1380, 1110 cm^{-1}; NMR δ 6.45 (m, H-7, 1 H), 3.30 (s, OMe, 3 H), 3.15 (m, H-3; 1 H), 2.5–0.80 (m, 43 H, remaining H); mass spectrum, *m/e* 429 (M + H), 411, 397, 371.

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25, H, 11.29. Found: C, 81.63; H, 11.24.

(3β,5α)-3-(1-Ethoxyethoxy)cholest-8(14)-en-15-one (28). To a solution of benzoate **25** (100 g, 0.2 mol) in toluene (1 L) and MeOH (4 L) was added finely powdered anhydrous K_2CO_3 (300 g). The suspension was stirred for 24 h at 60 °C and filtered through Celite, and the Celite was washed with ether (200 mL). The filtrate was diluted with water (4 L), the organic layer was separated and washed sequentially with water (3 × 500 mL) and brine (500 mL) and dried ($MgSO_4$). After concentration of the solution under reduced pressure to one-half the original volume, ethyl vinyl ether (190 mL, 1.98 mol) and pyridinium *p*-toluenesulfonate (PPTS, 5.0 g, 20.0 mmol) were added. The etherification was complete in 10 min with stirring at room temperature. The reaction mixture was washed sequentially with saturated aqueous $NaHCO_3$ (4 × 400 mL) and brine (400 mL) and dried ($MgSO_4$). Removal of solvents in vacuo and flash chromatography (1% ethyl acetate in CH_2Cl_2) to remove methyl benzoate furnished the ethoxyethyl ether **28** (91.7 g, 98%): mp 93–94 °C; R_f 0.59 (1% ethyl acetate in CH_2Cl_2); IR 2960, 2870, 1690, 1620, 1380, 910 cm^{-1}; NMR δ 4.80 (q, 1 H, *J* = 9.0 Hz, $CH(OR)_2$), 4.15 (d, 1 H, *J* = 16.0 Hz, H-7β), 3.50 (m, 3 H, H-3, CH_2O), 2.50–0.80 (m, 47 H, remaining H); mass spectrum, *m/e* 473 (M + H), 457, 427, 401, 383, 355, 115.

Anal. Calcd for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09. Found: C, 78.95; H, 11.24.

(3β,5α,22*E*)-3-(1-Ethoxyethoxy)ergosta-8(14),22-dien-15-one (29) and (3β,5α,22*E*)-3-(1-Ethoxyethoxy)-4,4-dimethylergosta-8(14),22-dien-15-one (30). Deprotection of the benzoyl group in ergostenone analogues **26** and **27** with MeOH/toluene (4:1) and powdered K_2CO_3 and reprotection as the ethoxyethyl ether was conducted in an identical fashion as for **25**.

Ethoxyethyl ether 29: mp 114–116 °C; R_f 0.63 (1% EtOAc in CH_2Cl_2); IR 2960, 2880, 1690, 1620, 1380, 910 cm^{-1}; NMR δ 5.20 (m, 2 H, H-22,23), 4.75 (q, 1 H, *J* = 9.0 Hz, $CH(OR)_2$), 4.10 (m, 1 H, H-7β), 3.50 (m, 3 H, CH_2O), 2.5–0.70 (m, 45 H, remaining H); mass spectrum, *m/e* 485 (M + H), 469, 441, 413, 395, 367, 125.

Anal. Calcd for $C_{32}H_{52}O_3$: C, 79.29; H, 10.81. Found: C, 79.16; H, 10.93.

Ethoxyethyl ether 30: mp 145–147 °C; R_f 0.78 (CH_2Cl_2); IR 2980, 2870, 1690, 1620, 1380 cm^{-1}; NMR δ 5.20 (m, 2 H, H-22,23),

4.85 (m, 1 H, $CH(OR)_2$), 4.10 (d, 1 H, J = 16.0 Hz, H-7β), 3.5 (m, 2 H, CH_2OR), 3.0 (m, 1 H, H-3), 2.50–0.80 (m, remaining H); mass spectrum, m/e 513 (M + H), 467, 441, 423, 125; high-resolution FAB mass spectrum, calcd for $C_{34}H_{56}O_3$: 512.0177, found 512.0176.

(3β,5α,14α)-3-Hydroxy-14-methylcholest-7-en-15-one (1). Ethoxyethyl ether **28** (106 g, 0.225 mol) in THF (500 mL) was added in one portion to a mechanically stirred solution of *t*-BuOH (6 L) containing *t*-BuOK (300 g, 2.7 mol) under argon. After 10 min, methyl iodide[28] (1050 mL, 16.9 mol) was added, and the resulting solution was stirred for 3 h. The reaction was concentrated in vacuo to one-third its original volume and then poured into a separatory funnel containing ice–water (12 L), and ether (1 L) was added. The organic extract was washed sequentially with water (5 × 8 L) and brine (1 L) and dried ($MgSO_4$). The solvents were removed in vacuo,[29] and the residue was dissolved in THF containing 5% aqueous HCl (1 L of a 4:1 solution) and the resulting solution was stirred at ambient temperature for 10 min. The reaction mixture was diluted with water (5 L) and extracted with ether (3 × 200 mL). The ether extracts were combined and washed sequentially with water (300 mL), saturated aqueous $NaHCO_3$ (3 × 300 mL), and brine (300 mL) and then dried ($MgSO_4$). Either flash chromatography (3% ethyl acetate in CH_2Cl_2) or recrystallization of the residue (CH_2Cl_2/MeOH) gave alcohol **1** (79.2 g, 85%): mp 133–134 °C; R_f 0.26 (5% ethyl acetate in CH_2Cl_2); $[\alpha]^{25}_D$ +14.1° (*c* 1.0, CH_2Cl_2); IR 3600, 3400, 2940, 1730, 1480, 1380, 1020 cm^{-1}; ^1H NMR δ 6.51 (m, 1 H, H-7), 3.55 (m, 1 H, H-3), 2.10–0.80 (m, 44 H, remaining H); ^{13}C NMR δ 137.7 (C8), 120.1 (C7), 70.8 (C3), 56.9 (C14), 22.7, 22.5, 21.2, 19.1, 15.9, and 12.6 (CH_3); mass spectrum, m/e 415 (M + H), 397, 379, 259.

Anal. Calcd for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.01; H, 11.03.

(3β,5α,14α,22*E*)-3-Hydroxy-14-methylergost-7-en-15-one (3) and (3β,5α,14α,22*E*)-3-Hydroxy-4,4,14-trimethylergost-7-en-15-one (4). Alkylation of the enones **29** and **30** was performed in the same fashion as for **28** to afford alcohols **3** (87%) or **4** (83%) following deprotection in THF/5% HCl. Alcohol **3** was recrystallized (methanol/ether): mp 160–161 °C; R_f 0.28 (5% ethyl acetate in CH_2Cl_2); $[\alpha]^{25}_D$ +39.0° (*c* 0.12, CH_2Cl_2); IR 3600, 3450, 2960, 2880, 1730, 910 cm^{-1}; ^1H NMR δ 6.44 (m, 1 H, H-7), 5.19 (m, 2 H, H-22,23), 3.60 (m, 1 H, H-3), 2.40–0.80 (m, 42 H, remaining H); ^{13}C NMR δ 217.7 (C15), 137.8 (C8), 134.6 and 133.3 (C22,23), 120.2 (C7), 70.9 (C3), 57.1 (C14), 21.5, 21.3, 19.9, 17.7, 16.3, and 12.5 (CH_3); mass spectrum, m/e 427 (M + H), 426 (M^+), 409, 369, 301, 285, 125.

Anal. Calcd for $C_{29}H_{46}O_2 \cdot {}^1/_2H_2O$: C, 79.95; H, 10.87. Found: C, 80.28; H, 10.63.

Alcohol **4** was recrystallized (methanol/ether): mp 188–189 °C; R_f 0.28 (CH_2Cl_2); $[\alpha]^{25}_D$ + 36.1° (*c* 0.21, CH_2Cl_2); IR 3600, 3450, 2970, 2880, 1730, 910 cm^{-1}; ^1H NMR δ 6.50 (m, 1 H, H-7), 5.20 (m, 2 H, H-22,23), 3.21 (m, 1 H, H-3), 2.40–0.80 (m, 46 H, remaining H); ^{13}C NMR δ 217.7 (C15), 136.9 (C8), 134.9 and 134.6 (C22,23), 120.6 (C7), 79.1 (C3), 56.9 (C14), 21.6, 21.4, 21.3, 19.9, 19.6, 17.7, 16.2, 15.4, and 14.2 (CH_3); mass spectrum, m/e 455 (M + H), 437, 397, 313.

Anal. Calcd for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 82.13; H, 11.11.

(3β,5α,20*S*)-3-(Benzoyloxy)-15-oxopregn-8(14)-ene-20-carboxaldehyde (36). A solution of ergostenone **26** (25.5 g, 49.4 mmol) in CH_2Cl_2 (1 L) was cooled to −78 °C. Ozone was passed into the solution until a slight excess of the oxidant had been added (light gray solution). Excess dimethyl sulfide (approximately 60 mL) was then added, and the solution was brought to room temperature. The solution was concentrated in vacuo, and the residue was purified by flash chromatography (3% ethyl acetate in CH_2Cl_2) to give pure aldehyde **36** (15.9 g, 72%). A sample was recrystallized (ether/hexane): mp 185–187 °C; R_f 0.46 (3% ethyl acetate in CH_2Cl_2); IR 3020, 2960, 2870, 1710, 1620, 1280, 1120 cm^{-1}; ^1H NMR δ 9.68 (d, 1 H, J = 3.5 Hz, CHO), 8.10 and 7.50 (m, 5 H, Ar), 5.05 (m, 1 H, H-3), 4.20 (d, 1 H, J = 16.0 Hz, H-7β), 2.80–0.80 (m, 21 H, remaining H); ^{13}C NMR δ 205.9 (C15), 203.4 (CHO), 151.5 (C8), 138.7 (C14), 73.7 (C3), 19.2, 13.9, 12.9 (Me): mass spectrum, m/e 449 (M + H), 431, 391, 327.

Anal. Calcd for $C_{29}H_{36}O_4$: C, 77.65; H, 8.09. Found: C, 77.37, H, 8.13.

(3β,5α,20*S*)-3-(Benzoyloxy)-20-(hydroxymethyl)pregn-8-(14)-en-15-one (37). A solution of aldehyde **36** (15 g, 33.5 mmol) in CH_2Cl_2 (200 mL) at 0 °C was treated with *tert*-butylamine–borane complex[18] (1.9 g, 22.1 mmol). After 15 min the reaction was diluted with 5% HCl (200 mL) and stirred vigorously at 0 °C for an additional 20 min. The organic layer was separated, washed sequentially with 5% HCl (100 mL), water (100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), and brine (100 mL), and dried ($MgSO_4$). Removal of solvent in vacuo and purification by flash chromatography (10% ethyl acetate in CH_2Cl_2) gave **37** (15.1 g, 100%): mp 185–186 °C; R_f 0.42 (35% ethyl acetate in CH_2Cl_2); $[\alpha]^{25}_D$ +118.1° (*c* 0.44, CH_2Cl_2); IR 3600, 3400, 2970, 2870, 1710, 1280 cm^{-1}; NMR δ 8.10 and 7.55 (m, Ar, 5 H), 5.00 (m, 1 H, H-3), 4.20 (d, 1 H, J = 16.0 Hz, H-7β), 3.60 (m, 2 H, CH_2O), 2.50–0.80 (m, 20 H, remaining H); mass spectrum, m/e 451 (M + H), 433, 329, 311, 123.

Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.30; H, 8.50. Found: C, 77.07; H, 8.51.

(3β,5α,20*S*)-3-(1-Ethoxyethoxy)-20-[(1-ethoxyethoxy)-methyl]pregn-8(14)-en-15-one (38). A solution of **37** (10.0 g, 22.2 mmol) in $CHCl_3$ (50 mL) and methanol (150 mL) was treated with powdered K_2CO_3 (20 g) for 24 h as described above for the debenzoylation of **25**. Filtration and workup gave a residue (10 g), which was dissolved in methylene chloride (100 mL) and treated with ethyl vinyl ether (10.7 mL, 111.1 mmol) and PPTS (0.8 g, 3.1 mmol). After approximately 10 min the reaction mixture was washed sequentially with saturated aqueous $NaHCO_3$ (2 × 30 mL) and brine (30 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography (3% ethyl acetate in CH_2Cl_2) of the oily residue provided bis(ethoxyethyl ether) **38** (10.6, 98%): oil; R_f 0.47 (3% ethyl acetate in CH_2Cl_2); IR 2970, 2860, 1710, 1620, 1280 cm^{-1}; NMR δ 4.70 (m, 3 H, H-3, 2 × $CH(OR)_2$), 3.50 (m, 4 H, 2 × CH_2OR), 2.30–0.80 (m, 43 H, remaining H); mass spectrum, m/e 491 (M + H), 462, 385, 290; high-resolution FAB mass spectrum, calcd for M + H, $C_{30}H_{51}O_5$ 491.3740, found 491.3739.

(3β,5α,14α,20*S*)-3-Hydroxy-20-(hydroxymethyl)-14-methylpregn-7-en-15-one (5). The ether **38** (6.8 g, 13.8 mmol) was methylated with *t*-BuOK (18.7 g, 166.2 mmol) and methyl iodide (65.0 mL, 1.0 mol) in *t*-BuOH (400 mL) in a fashion analogous to that of ether **28**. Deprotection in THF containing 5% aqueous HCl (50 mL of a 4:1 solution) provided diol **5** (5.4 g, 78%) following workup (ethyl acetate extraction) and flash chromatography (35% ethyl acetate in CH_2Cl_2). Compound **5** was recrystallized (methanol/ether): mp 221–222 °C; R_f 0.23 (35% ethyl acetate in CH_2Cl_2); $[\alpha]^{25}_D$ +113.0° (*c* 0.22, MeOH); IR 3600, 3400, 2980, 1730, 1280 cm^{-1}; NMR δ 6.45 (m, 1 H, H-7), 3.45 (m, 4 H, H-3, CH_2OH), 2.5–0.80 (m, 31 H, remaining H); ^{13}C NMR δ 217.6 (C15), 138.0 (C8), 119.6 (C7), 69.9 (C3), 66.4 (C22), 56.6, 44.4, 43.6, 41.3, 40.5, 39.8, 38.3, 37.2, 37.0, 34.2, 30.6, 30.4, 29.3, and 20.4 (CH_3), 19.9, 16.6 (CH_3), 15.3 (CH_3), 11.6 (CH_3); mass spectrum, m/e 343 (M + H − H_2O), 325, 303, 285, 229, 155.

Anal. Calcd for $C_{23}H_{36}O_3 \cdot H_2O$: C, 72.98; H, 10.12. Found: C, 73.28; H, 10.10.

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Registry No. **1**, 64768-24-7; **3**, 103751-23-1; **4**, 103751-24-2; **5**, 103775-98-0; **7**, 57-87-4; **8**, 17398-57-1; **9**, 17398-58-2; **10**, 25843-03-2; **11**, 434-16-2; **12**, 1182-06-5; **13**, 5035-30-3; **14**, 103751-11-7; **15a**, 34227-12-8; **15b**, 74524-23-5; **16a**, 36959-80-5; **16b**, 53639-76-2; **17a**, 103751-12-8; **17b**, 103751-13-9; **18a**, 62324-19-0; **18b**, 103751-14-0; **19a**, 103751-15-1; **19b**, 103751-16-2; **20a**, 103751-17-3; **20b**, 103751-18-4; **21**, 103751-25-3; **22**, 103751-26-4; **25**, 7654-37-7; **26**, 36071-76-8; **27**, 103751-19-5; **28**, 103751-20-8; **29**, 103751-21-9; **30**, 103751-22-0; **31**, 64768-25-8; **32**, 26313-82-6; **36**, 103775-97-9; **37**, 103751-27-5; **38**, 103751-28-6.

(28) A moderate exotherm was noted upon the addition of methyl iodide. Temperature was maintained at ca. 30 °C.

(29) The ethoxyethyl ethers can be isolated at this point via flash chromatography.