Further Studies on the Synthesis of 24(*S*),25-Epoxycholesterol. A New, Efficient Preparation of Desmosterol

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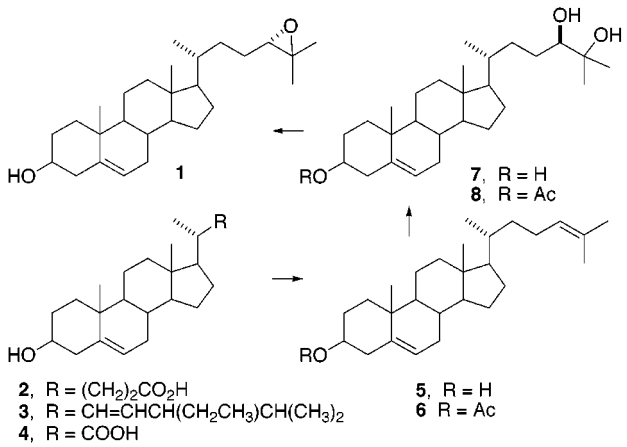
Efforts to improve the synthesis of 24(*S*),25-epoxycholesterol (**1**) from stigmasterol (**3**) have included identification of 6α-hydroxy-*i*-steroid **11** as a byproduct from the ozonolysis of **9** and an attempt to effect conversion of sulfone **14** to diol **18** via Payne rearrangement and nucleophilic trapping of epoxide **25**, which led instead to **27** and **28** (97% yield). A more efficient synthesis of **1** was achieved via coupling of cuprate **21** with allylic acetate **31** to give 73% of **16**, in the most efficient conversion yet of a C22 intermediate to desmosterol (**5**) or its acetate **6**.

Substantial evidence has been accumulated that 24(*S*),25-epoxycholesterol (**1**), formed enzymatically via squalene 2,3(*S*),22(*S*),23-dioxide,[1,2] participates in the natural regulation of cholesterol metabolism.[3−6] In particular, it has recently been found that in response to **1** the nuclear LXRα receptor subtype regulates transcription of the gene encoding cholesterol 7α-hydroxylase,[7] the enzyme that catalyzes the rate-limiting step in conversion of cholesterol to bile acids. This increasing evidence of the biological importance of **1** has made access to substantial quantities of this epoxide essential and has dictated development of stereoselective syntheses of **1**. We have described syntheses of **1** starting from cholenic acid (**2**)[8] and from stigmasterol (**3**),[8] and Corey and Grogan[9] have described a synthesis of **1** from bisnorcholenic acid (**4**) (Scheme 1). Each of these approaches relies on Sharpless asymmetric dihydroxylation[10] of the key intermediate desmosterol (**5**)[9] or its acetate **6**,[8] followed by mesylation of resulting diol **7**[9] or **8**[8] and base-catalyzed epoxide formation.

Scheme 1



In this paper we describe efforts to improve our synthesis of **1** from stigmasterol (**3**), the least costly of the steroidal starting materials. These efforts include identification of a curious byproduct from ozonolysis of intermediate **9** and an unsuccessful attempt to achieve in one step both addition of a prenyl moiety to a C22 intermediate such as **13** and introduction of the 24*R*,25-diol functionality of **8**, thus bypassing formation and dihydroxylation of **6**. We have succeeded, however, in improving the overall yield of **1** by discovery of the best method to date for prenylation of **13**, en route to desmosterol acetate (**6**).

Our synthesis of **1** from **3** (Scheme 2)[8] begins with the sequence initially reported by Partridge,[11] involving preparation of *i*-steroid **9** and ozonolysis to **10**. Treatment of **9** with ozone and then $NaBH_4$ yields up to 81% of **10**,[8,12] but also consistently affords another, more polar, apparently previously unreported, product, which we chose to

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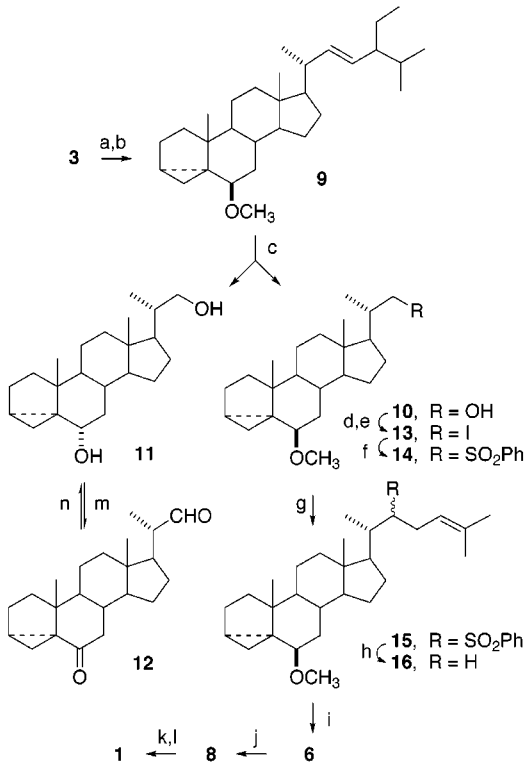
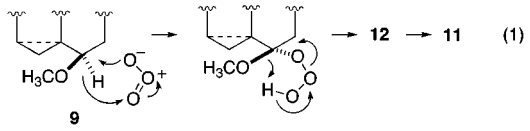
Scheme 2[a]



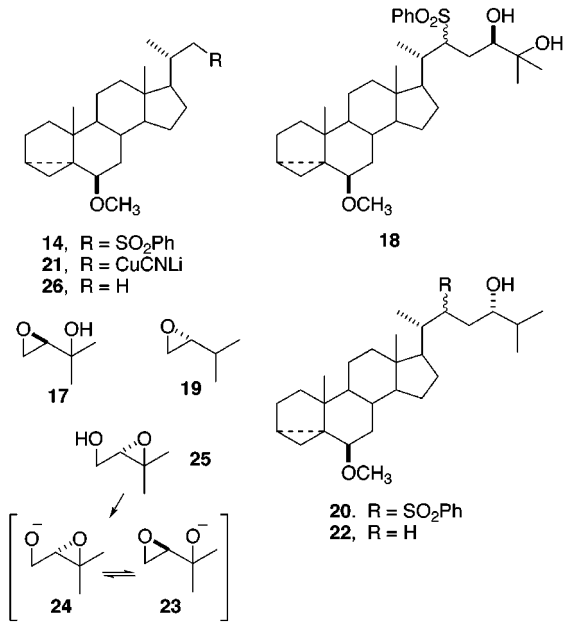
[a] Reagents: (a) TsCl, py; (b) CH_3OH, Δ; (c) (1) O_3, CH_2Cl_2; (2) $NaBH_4$; (d) TsCl, py; (e) KI, acetone, Δ; (f) $PhSO_2Na$, DMF, Δ; (g) (1) BuLi; (2) 4-bromo-2-methyl-2-butene; (h) Li, NH_3; (i) HOAc, Δ; (j) AD-mix-*β*, $CH_3SO_2NH_2$; (k) CH_3SO_2Cl, py; (l) K_2CO_3, $CH_3OH{\cdot}H_2O$; (m) Swern; (n) $NaBH_4$.

characterize with the hope of learning how to improve the yield of **10**. This compound was determined to be 6α-hydroxy-*i*-steroid **11** on the basis of its elemental composition and its ^1H and ^{13}C NMR properties, in particular signals at high field indicating the presence of the cyclopropyl group and at δ 3.91 (dd, $J = 11.4$, 4.2 Hz) for the 6*β*-H.[13] Compound **11** is presumably formed by $NaBH_4$ reduction of ketone **12**,[14] a type of product often observed upon ozonolysis of ethers.[15−17] Such ketone formation has been rationalized by the type of mechanism shown in eq 1[15−17] and tends to occur in cases, such as **9**,



in which carbocation formation at the site of oxidation is relatively favorable.[15,17,18] Hydride reduction of 3α,5-cyclocholestan-6-one has previously been shown to afford exclusively the 6α-alcohol,[13,19−21] and we confirmed that $NaBH_4$ reduction of **12**, prepared in 68% yield by Swern oxidation of **11**, likewise gave only the 6α-hydroxy compound. If ozonolysis of **9** is allowed to proceed for 12 h, 22% of **11** (plus 69% of **10**) can be obtained; ozonolysis for the minimum time (5 min) required to consume **9** affords ca. 2% of **11**.

A key step in our previous preparation of **1** from **3** is prenylation of *i*-steroid sulfone **14**.[8] If the anion of **14** could be used instead to react with epoxide **17** (presumably also as its anion) to give **18**, both the construction of the requisite cholestane skeleton and the stereoselective introduction of the 24*R*,25-diol functionality would be accomplished in one step. Ourisson[22] and Moriarty[12] have used the anion of **14** in reaction with the simpler chiral epoxide **19** to provide **20**, and we have shown that cyanocuprate **21** can be similarly used with **19** to give 56% of **22**,[23] so this potentially highly efficient strategy seemed promising. Unfortunately, chiral epoxide **17** is not readily available, because Sharpless asymmetric epoxidation is ineffective for tertiary allylic alcohols,[24,25] such as 2-methyl-3-buten-2-ol. However, it seemed that the desired electrophile **23** might be accessible via Payne rearrangement of anion **24** formed from the readily prepared isomeric epoxide **25**.[26] If deprotonation of **25** established the equilibrium **24** ⇄ **23**[27] in the presence of a suitable nucleophile, such as **21** or the anion of **14**, reaction at the least substituted epoxide carbon to give



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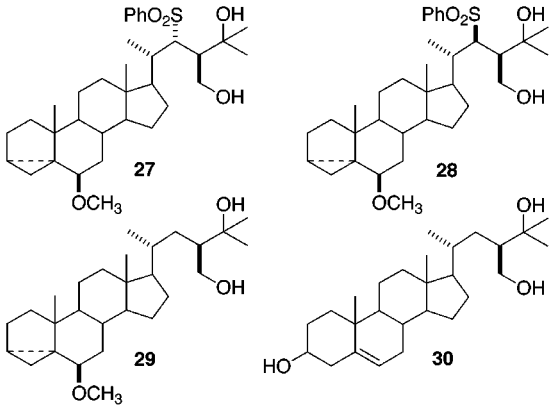
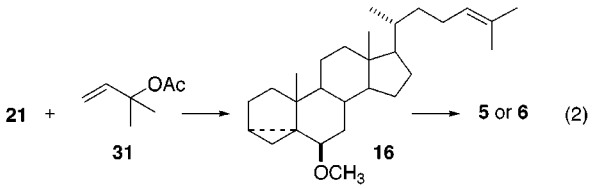
18 would be expected.[28] This type of Payne rearrangement−nucleophilic trapping has been conducted successfully,[28] although usually under basic aqueous conditions that facilitate epoxide isomerization but preclude the use of a carbon nucleophile.[27] Only a few examples of such reactions under aprotic conditions have been reported.[29−31] Sutherland and co-workers[30,31] have conducted a study of solvents, Lewis acid isomerization catalysts, and carbon nucleophiles in an effort to develop optimized conditions for such reactions. Their study suggested that saturated solutions of LiCl in THF offer the best prospects for trapping rearranged epoxide with cyanocuprates.

This strategy was first tried using as nucleophile cyanocuprate **21**, which was prepared from iodide **13** via the lithio derivative[32] according to the procedure of Acker.[33] Unfortunately, treatment of **21** with the anion formed from **25** with 1 equiv of BuLi in THF in the presence of excess LiCl led only to formation of **26** (30%) and alcohol **10** (53%). Although this reaction was run under N_2, adventitious O_2 seems the likely source of **10**. When the more stable anion of sulfone **14** was used as nucleophile with the anion of **25** under the same conditions, carbon−carbon coupling was indeed effected, but, disappointingly, the product was a 5:1 mixture of epimers **27** and **28**, formed in 97% yield, presumably by reaction at the less substituted end of unrearranged **24**. The



structural assignments to **27** and **28** were based on HRMS analysis and NMR spectra. One peak in the ^{1}H NMR spectra in $CDCl_3$ at δ 3.75 for **27** and δ 3.94 for **28** was initially puzzling, but 2D NMR experiments with **27** indicated that it is probably the C22 proton geminal to the phenylsulfonyl group appearing unexpectedly far downfield.[34] Confirmation of structure and assignment of C22 stereochemistry was obtained by X-ray crystal structure determination on **27**.[35] Reaction of either **27** or **28** with Li in NH_3 afforded **29**. This *i*-steroid was in turn converted by treatment with aqueous acid to **30**, which is being evaluated as a structurally novel ligand for the LXR receptors.[36]

Having failed to effect direct formation of a diol such as **18** via the Payne rearrangement strategy, we turned to efforts to improve the prenylation of a C22 intermediate, such as iodide **13**. We had previously employed prenylation of sulfone **14** only because considerable effort to effect efficient coupling of C22 electrophiles, such as **13**, or nucleophiles, such as **21**, with, respectively, prenyl nucleophiles or electrophiles had not been rewarding. One variation of this approach that had not been attempted was the coupling of organocuprate **21** with 3-acetoxy-3-methyl-1-butene (**31**).[37] Gratifyingly, this reaction afforded 73% of **16** (eq 2), the same intermediate



encountered in our earlier synthesis of **6** after prenylation of sulfone **14** to give **15** and removal of the C22 phenylsulfonyl group (Scheme 2). Compound **16** has been readily converted to either desmosterol (**5**)[38] or its acetate **6**,[8] and the 73% yield of **16** obtained from the reaction of **21** with **31** effects the most efficient synthesis yet of the desmosterol structure from C22 intermediates, bettering the 65% yield reported for $Ni(CO)_4$-catalyzed coupling of **13** with prenyl bromide.[38] The coupling of **21** with **31** also increases the overall yield in our conversion of stigmasterol (**3**) to 24(*S*),25-epoxycholesterol (**1**) from 16% in 12 steps[8] to 21% in 10 steps.

Experimental Section

Unless otherwise specified, NMR spectra were taken at 300 MHz in $CDCl_3$. The ^{1}H and ^{13}C chemical shifts are reported in units of δ. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone. Acetone was distilled from calcium carbonate onto 3 Å molecular sieves. Pyridine was distilled from calcium hydride onto 4 Å molecular sieves. Methanol was distilled from magnesium and iodine onto 3 Å molecular sieves. Acetic acid was distilled from acetic anhydride. All reactions were magnetically stirred. Melting point determinations were made with a Thomas-Hoover melting point apparatus and are uncorrected.

Flash column chromatography was carried out on EM Reagent silica gel 60 (230−400 mesh). Thin-layer chromatography (TLC) was conducted on EM plastic sheets precoated with silica gel 60 F-245. Visualization was obtained by exposure to 5% phosphomolybdic acid in 2-propanol. All solvents were dried over $MgSO_4$. All reagents, unless otherwise noted, were obtained from Aldrich Chemical Co.

3α,5-Cyclo-22-hydroxy-5α-23,24-bisnorcholan-6*β*-ol 6-Methyl Ether (10) and 3α,5-Cyclo-22-hydroxy-5α-23,24-bisnorcholan-6α-ol (11). A solution of 9.5 g (22.8 mmol) of ***9*** in 450 mL of 2:1 dry CH_2Cl_2/methanol at −78 °C was treated with ozone for 12 h. The mixture was bubbled with oxygen for 5 min to remove excess ozone, warmed to 0 °C, and treated with 100 mL of 95% ethanol, and 8.6 g (230 mmol) of $NaBH_4$ was added slowly. The resulting mixture was warmed to room

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(34) The C22 protons in **14** are at δ 3.12 and 2.83, and the C22 protons in the epimers of **15** are at δ 3.07 and 3.05.[8]
(35) Atomic coordinates, bond lengths and angles, and thermal parameters for **27** have been deposited at the Cambridge Crystallographic Data Centre, with registration no. 135903.
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temperature, stirred overnight, and then poured slowly onto 100 mL of 5% HCl solution at 0 °C. The aqueous layer was extracted five times with CH_2Cl_2, and the combined organic layers were condensed to 150 mL, washed with saturated $NaHCO_3$ solution and brine, dried, filtered, and evaporated to give 8.0 g of residue, which was chromatographed (3:17 EtOAc/hexane) to give 5.4 g (69%) of **10** and 1.7 g (22%) of **11** (mp 157.5−160.0 °C). Compound **10**: ^{1}H NMR 3.65 (dd, J = 10.5, 3.3 Hz, 1H), 3.38 (dd, J = 10.5, 6.9 Hz, 1H), 3.33 (s, 3H), 2.78 (t, J = 2.7 Hz, 1H), 1.05 (d, J = 6.6 Hz, 3H), 1.03 (s, 3H), 0.75 (s, 3H), 0.66 (m, 1H), 0.44 (dd, J = 8.1, 5.1 Hz, 1H); ^{13}C NMR 82.6, 68.3, 56.8, 56.5, 52.8, 48.2, 43.6, 43.1, 40.3, 39.0, 35.3, 33.5, 30.7, 28.0, 25.2, 24.5, 23.9, 23.0, 21.7, 19.5, 17.0, 13.3, 12.5. Compound **11**: after recrystallization from CH_2Cl_2/hexane, mp 163.4−164 °C; IR ν_{max} 3330 cm^{-1}; ^{1}H NMR 3.91 (dd, J = 11.4, 4.2 Hz, 1H), 3.64 (dd, J = 10.5, 3.0 Hz, 1H), 3.37 (dd, J = 10.5, 6.9 Hz, 1H), 1.05 (d, J = 6.6 Hz, 3H), 0.92 (s, 3H), 0.72 (s, 3H), 0.61 (dd, J = 8.1, 4.5 Hz, 1H), 0.26 (m, 1H); ^{13}C NMR 68.2, 67.4, 56.2, 52.7, 47.8, 45.2, 43.0, 40.4, 40.1, 40.0, 39.0, 35.2, 33.0, 27.9, 25.3, 24.5, 23.3, 18.9, 18.2, 16.9, 12.4, 6.83; EI-HRMS (M^+) calcd for $C_{22}H_{36}O_2$, 332.2715, found 332.2724.

20(*S*)-6-Oxo-3α,5-cyclo-5-pregnane-20-carboxaldehyde (12). According to a procedure by Swern,[39] to a solution of 0.3 mL (3.3 mmol) of oxalyl chloride in 2 mL of CH_2Cl_2 at −78 °C was added 0.5 mL (6.5 mmol) of DMSO in 1 mL of CH_2Cl_2. After the resulting mixture was stirred for 2 min, 99.4 mg (0.300 mmol) of **11** was added and the mixture was stirred for 15 min before 1.8 mL (12.8 mmol) of Et_3N was added. The mixture was stirred at −78 °C for 20 min, warmed to room temperature, stirred for 5 h, diluted with 10 mL of H_2O, and extracted thrice with CH_2Cl_2. The combined organic layers were washed with 1% HCl, H_2O, 5% $NaHCO_3$, H_2O, and brine, dried, filtered, and evaporated to give 151 mg of residue, which was chromatographed (1:4 EtOAc/hexane) to afford 66.9 mg (68%) of **12**: mp 106−107.5 °C (lit.[14] 105−106 °C); IR ν_{max} 1728, 1692 cm^{-1}; ^{1}H NMR 9.55 (d, J = 3.3 Hz, 1H), 1.11 (d, J = 6.9 Hz, 3H), 0.98 (s, 3H), 0.73 (s, 3H); ^{13}C NMR 209.4, 204.9, 56.3, 51.1, 49.5, 46.8, 46.4, 46.1, 44.7, 43.4, 39.5, 35.5, 34.8, 33.6, 27.1, 26.0, 24.5, 22.9, 19.8, 13.5, 12.5, 11.8.

Conversion of 12 to 11. To a solution of 86.1 mg (0.263 mmol) of **12** in 2.5 mL of CH_2Cl_2 and 1 mL of MeOH, and 1 mL of 90% EtOH in water at 0 °C was added 90.3 mg (2.39 mmol) of $NaBH_4$. The resulting mixture was stirred at room temperature for 3 h, treated with 5 mL of 1 N HCl at 0 °C, and extracted with 4 × 10 mL of CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried, filtered, and evaporated to give 128.2 mg of residue in which no ^{1}H NMR signal for the 6α-H of the 6β-hydroxy isomer could be detected and which crystallized from CH_2Cl_2/hexane to give 69.5 mg (80%) of **11**: mp 163−164 °C.

3α,5-Cyclo-22(*S* and *R*)-phenylsulfonyl-23(*R*)-hydroxymethyl-5α-26,27-bisnorergost-6β,24-diol 6-Methyl Ether (27 and 28). To a solution of 262 mg (0.56 mmol) of **14** in 2 mL of THF was added dropwise 0.22 mL (0.56 mmol) of 2.5 M *n*BuLi in pentane at −78 °C with stirring under N_2. After being stirred for 15 min, the yellow solution was treated dropwise at −78 °C with a solution previously prepared by treating 157 mg (1.54 mmol) of **25**, prepared according to a modification of the procedure of Gao et al.,[40] in 2 mL of THF with 0.62 mL (1.54 mmol) of 2.5 M *n*BuLi in pentane at −78 °C with stirring under nitrogen for 5 min and then allowed to warm slowly over 10 min before being added to the anion of **14**. The resulting mixture was allowed to warm to room temperature over 4 h, and stirring was continued for 12 h. The solvent was evaporated, and the residue was dissolved in 20 mL of CH_2Cl_2 and washed with 20 mL of water. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried, filtered, and evaporated to afford 398 mg of yellow residue. Fractional recrystallization from 4:1 CH_2Cl_2/EtOAc afforded 234 mg (81%) of the less polar **27** and 46 mg (16%) of the more polar **28**. Compound **27**: mp 230−231 °C; ^{1}H NMR (4:1 $CDCl_3$/CD_3OD) 7.84−7.78 (m, 2H), 7.62−7.47 (m, 3H), 4.23−4.16 (dd, J = 12, 6 Hz, 1H), 3.88−3.81 (dd, J = 12, 6 Hz, 1H), 3.5 (br s, 1H), 3.18 (s, 3H), 2.65 (br, 1H), 2.48−2.42 (br, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.23 (d, J = 9 Hz, 3H), 0.88 (s, 3H), 0.41 (s, 3H); ^{13}C NMR 139.3, 134.16, 129.7, 129.1, 82.9, 73.8, 68.3, 66.8, 61.5, 56.7, 56.5, 48.1, 43.6, 43.5, 40.2, 36.8, 35.5, 35.0, 33.6, 30.8, 29.3, 29.1, 28.6, 25.2, 24.2, 23.0, 22.0, 19.3, 15.8, 13.2, 11.4. Anal. Calcd for $C_{34}H_{52}O_5S\cdot H_2O$: C, 69.12; H. 9.21. Found: C, 69.12, H. 9.21. FAB-HRMS (MH^+): calcd for $C_{34}H_{53}O_5S$ 573.3614, found 573.3612. X-ray analysis was performed on a crystal grown from 4:1 CH_2Cl_2/EtOAc. Compound **28**: mp 195−197 °C; ^{1}H NMR 8.00−7.95 (m, 2H), 7.72−7.56 (m, 3H), 4.25−4.19 (dd, J = 12, 6 Hz, 1H), 4.12−4.06 (dd, J = 12, 6 Hz, 1H), 3.94 (br s, 1H), 3.24 (s, 3H), 2.70 (t, J = 3 Hz, 1H), 1.36 (d, J = 6 Hz, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.96 (s, 3H), 0.60 (s, 3H); ^{13}C NMR 139.2, 134.2, 129.4, 128.8, 82.5, 73.7, 68.6, 61.1, 58.6, 56.6, 56.4, 48.0, 45.4, 43.6, 43.4, 40.4, 35.6, 35.2, 33.6, 30.8, 30.2, 30.1, 27.8, 25.2, 24.2, 22.9, 21.8, 19.4, 14.8, 13.2, 11.4; IR 3424, 2961, 1446, 1083, 1020, 800 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{34}H_{53}O_5S$ 573.3614, found 573.3612.

3α,5-Cyclo-23(*R*)-hydroxymethyl-5α-26,27-bisnorergost-6β,24-diol 6-Methyl Ether (29). A solution of 72 mg (10.5 mmol) of lithium in 30 mL of 3:1 ammonia/THF at −78 °C was treated dropwise with a suspension of 211 mg (0.37 mmol) of **27** in 10 mL of THF and 0.5 mL of ethanol. The blue solution was stirred for 25 min at −78 °C, then quenched by dropwise addition of acetone until the solution became colorless. The mixture was allowed to warm slowly to room temperature over 2 h to allow the ammonia to evaporate. The residue remaining as a suspension in THF was treated with 10 mL of EtOAc, and this organic layer was washed with 10 mL of water. The aqueous layer was washed with EtOAc, and the combined EtOAc layers were washed with saturated NH_4Cl solution and brine, dried, filtered, and evaporated to afford 156 mg of residue that was chromatographed on silica gel (1:3 EtOAc/hexane) to afford 123 mg (77%) of colorless, oily **29**: ^{1}H NMR 3.76−3.62 (m, 2H), 3.30 (s, 3H), 2.75 (t, J = 3 Hz, 1H), 1.28 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H), 0.93 (d, J = 6 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR 82.6, 66.3, 57.8, 56.8, 56.6, 48.2, 43.6, 43.1, 40.5, 37.8, 35.4, 35.3, 34.9, 33.6, 30.7, 30.4, 28.8, 25.2, 24.4, 23.0, 21.7, 19.5, 13.3, 12.4; IR 3382, 2933, 1467, 1381, 1261, 1070, 1019 cm^{-1}; EI-HRMS (M^+) calcd for $C_{28}H_{48}O_3$ 432.3603, found 432.3601. Using the same procedure, 20 mg of **28** was converted to 8 mg (55%) of **29**.

23(*R*)-Hydroxymethyl-26,27-bisnorergost-5-en-3β,24-diol (30). According to a modification of a procedure by Partridge et al.,[11] a solution of 74 mg (0.17 mmol) of **29** and 3.0 mg (0.017 mmol) of *p*-toluenesulfonic acid monohydrate in 6 mL of 25% aqueous dioxane was heated (oil bath temp 75 °C) for 6 h. The mixture was cooled to room temperature and quenched with 5 mL of water, and the colorless precipitate was collected by suction filtration and washed four times with water. The solid was dried under vacuum to afford 61 mg (86%) of colorless **30**: mp 222−224 °C. Recrystallization of a 26 mg sample from 1:1 methanol/acetone gave 18 mg of **30**: mp 230−232 °C; ^{1}H NMR (3:1 DMSO/CD_3OD) 5.24 (m, 1H), 3.52−3.44 (dd, J = 12, 6 Hz, 1H), 3.38−3.32 (dd, J = 12, 6 Hz, 1H), 3.29−3.17 (m, 1H), 1.07 (s, 3H), 1.03 (s, 3H), 0.91 (s, 3H), 0.89 (d, J = 9 Hz, 3H), 0.63 (s, 3H); ^{13}C NMR (DMSO) 141.2, 120.4, 72.6, 70.0, 63.7, 57.2, 56.2, 49.6, 48.3, 42.2, 42.0, 36.9, 36.7, 36.1, 34.4, 31.5, 31.4, 31.2, 29.0, 28.8, 27.9, 26.5, 23.9, 20.6, 19.2, 19.1, 11.7; IR 3316, 2926, 1463, 1367, 1260, 1063, 1022; FAB-HRMS (MNa^+) calcd for $C_{27}H_{46}NaO_3$ 441.3339, found 441.3345.

3α,5-Cyclo-5α-cholest-24-en-6β-ol 6-Methyl Ether (16). According to a procedure by Bailey[32] and a modification of a procedure by Acker,[33] to a solution of 456 mg (1.00 mmol) of **13** in 1 mL of dry ether at −78 °C was added dropwise to 2.1 mL (2.247 mmol) of 1.07 M *t*BuLi in pentane with stirring under N_2. After 15 min, the mixture was allowed to warm slowly and stand at room temperature for 1 h, cooled again to −78 °C, and then added dropwise to a solution of 104 mg (1.16 mmol) of CuCN in 1 mL of dry ether at −78 °C. The resulting

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mixture was stirred for 5 min, then warmed slowly until most of the CuCN was dissolved (~20−30 min), and recooled to −78 °C. Then a solution of 502 mg (3.92 mmol) of **31**, prepared in 48% yield from 2-methyl-3-buten-2-ol according to a procedure by Bergstrom,[37] in 1 mL of dry ether over 3 Å molecular sieves was added dropwise. The resulting mixture was stirred at −78 °C for 3 h, warmed to room temperature, and stirred under N_2 overnight. A mixture of 10 mL of saturated NH_4Cl solution and 1 mL of NH_4OH was added to the mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and evaporated to give 546 mg of yellow residue, which was chromatographed (3:20 EtOAc/hexane) to give 290 mg (73%) of colorless, oily **16**. A 216 mg sample was crystallized from acetone/methanol to afford 163 mg of colorless **16**: mp 60−61 °C (lit.[38] mp 64−66 °C); ^{1}H NMR 5.09 (t, J = 7.2 Hz, 1H), 3.33 (s, 3H), 2.77 (t, J = 2.7 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.03 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR 131.1, 125.4, 82.6, 56.7, 56.5, 48.2, 43.6, 43.0, 40.5, 36.3, 35.8, 35.5, 35.3, 33.6, 30.7, 28.5, 25.9, 25.2, 24.9, 24.4, 23.0, 21.7, 19.5, 18.8, 17.8, 13.3, 12.5.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds and for **10**, for which spectra have not previously been reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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