Steroidal Ethers. Analogues of 7-Ketocholesterol

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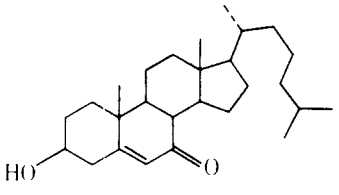
Several investigators have demonstrated that 7-ketocholesterol (1) inhibits β-hydroxy-β-methylglutaryl CoA reductase (EC 1.1.1.34) in vitro but not in vivo, presumably because of metabolic degradation. In an attempt to prepare analogues of 1 which might be more resistant to catabolism, a series of 7-ketocholesterol analogues having an oxygen atom in place of the carbon atoms at positions 20, 22, 23, and 24 of the cholesterol side chain has been synthesized. In addition, the corresponding analogues having a methyl group in place of the hydrogen atom at C-25 have also been prepared. One of the compounds, 7-keto-21-nor-20-oxacholesterol (**5b**), has exhibited potent in vitro inhibition of HMG CoA reductase as well as inhibition of acyl coenzyme A/cholesterol acyltransferase (ACAT) (EC 2.3.1.26), an enzyme involved in the accumulation of cholesterol esters in the artery wall. However, **5b** does not significantly inhibit HMG CoA reductase or lower serum cholesterol levels in rats when administered orally.

Several investigators[1-5] have demonstrated that oxygenated cholesterol derivatives such as 7-ketocholesterol (**1**) and 25-hydroxycholesterol (**2**) inhibit the activity of β-hydroxy-β-methylglutaryl CoA (HMG CoA) reductase (EC 1.1.1.34), the rate-limiting enzyme in the biosynthesis of cholesterol, in various in vitro test systems.



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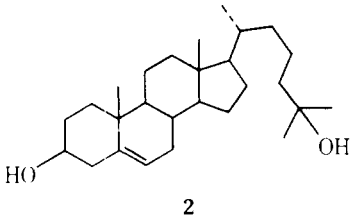

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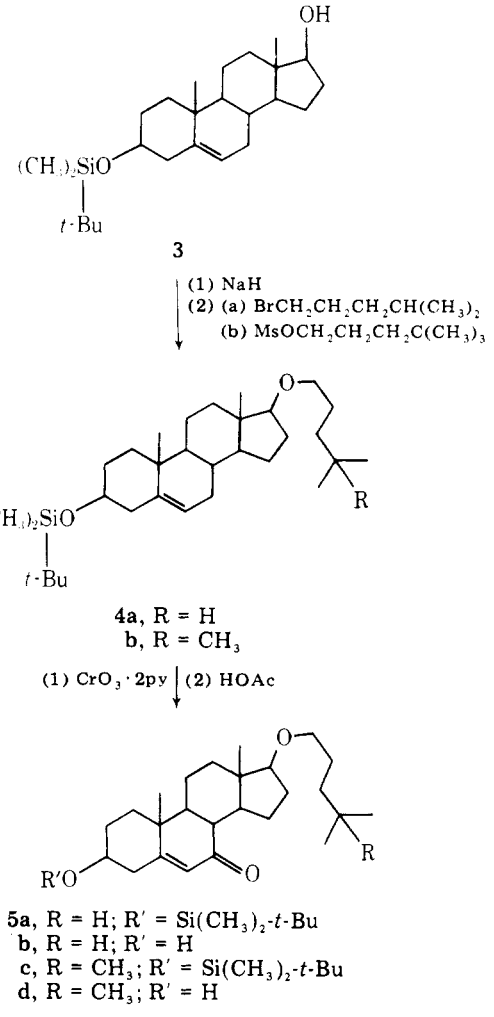
Counsell and co-workers,[6] however, have observed that **1** does not significantly lower cholesterol levels or inhibit HMG CoA reductase activity in vivo and have postulated that catabolism of **1** in the intact rat may account for the lack of in vivo activity.

Gould and co-workers[7] have observed that **1** produces a transient inhibition of HMG CoA reductase in vivo along with a concomitant elevation in the levels of liver total cholesterol and microsomal cholesterol esters. Upon prolonged treatment, the animals rapidly developed a tolerance to **1**, presumably due to the buildup of polar metabolites.

Kandutsch and co-workers[8] have also reported a transient effect of **1** and **2** upon intestinal sterol synthesis in mice which decreased upon prolonged feeding.

Thus, it appears that oxygenated cholesterol derivatives such as **1** and **2** will not find clinical utility due to their rapid metabolism. Since metabolism of **1** most likely occurs via degradation of the aliphatic side chain, one possible approach to the problem would be appropriate modification of the side chain. As part of a program designed to prepare analogues of **1** which might retain the hypolipidemic activity while being more resistant to catabolism, we have prepared a series of 7-ketocholesterol analogues having an oxygen atom in place of carbons 20, 22, 23, and 24 of the cholesterol side chain. In addition, we have also prepared the corresponding analogues in which the hydrogen atom at C-25 has been replaced with a methyl group.

Scheme I



Results and Discussion

The synthesis of the 7-keto-21-nor-20-oxacholesterol analogues is outlined in Scheme I.

Alkylation of androst-5-en-3β,17β-diol 3-dimethyl-*tert*-butylsilyl ether (**3**)[9] using sodium hydride and 1-bromo-4-methylpentane in refluxing xylene afforded **4a**. Substitution of the mesylate of 4,4-dimethyl-1-pentanol for 1-bromo-4-methylpentane in the alkylation reaction gave **4b**. Treatment of **4a** and **4b** with a solution of CrO_3·pyridine complex in methylene chloride according to the procedure of Fullerton and Chen[10] afforded the 7-keto analogues **5a** and **5c**, respectively. Hydrolysis of the protecting group with a mixture of HOAc–THF–water gave 7-keto-21-nor-20-oxacholesterol (**5b**)

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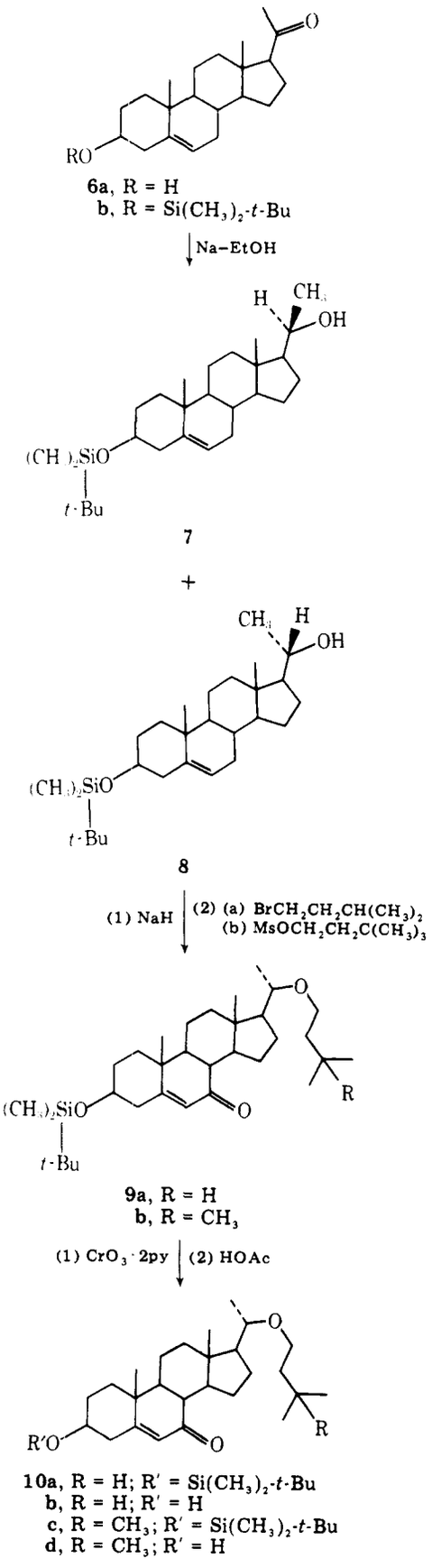
Scheme II



and 7-keto-25-methyl-21-nor-20-oxacholesterol (**5d**).

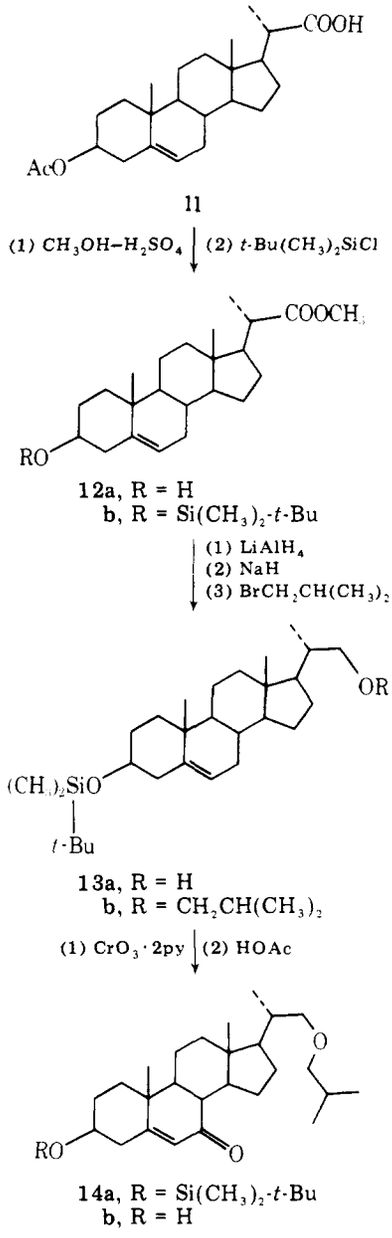
The synthesis of the 7-keto-22-oxacholesterol analogues is outlined in Scheme II.

Pregnenolone (**6a**) was treated with dimethyl-*tert*-butylsilyl chloride in DMF–Et_2O in the presence of imidazole to give **6b**. Reduction of **6b** with sodium in refluxing ethanol afforded a mixture of **7** (28%) and **8** (45%) which was separated via low pressure chromatography on silica gel. Assignment of the stereochemistry at C-20 for compounds **7** and **8** was based on the chemical shifts observed for the C-21 methyl resonances for each compound. Robinson and Hofer[11] reported that for a series of C-20 substituted pregnanes the C-21 methyl resonance for the 20α epimer was shifted downfield by 0.07–0.11 ppm relative to the 20β epimer. Compound **7**, which had a methyl resonance at δ 1.14 (J = 6 Hz), was assigned as the 20β epimer, and compound **8**, which had a methyl resonance at δ 1.22 (J = 6 Hz), was assigned as the 20α epimer.

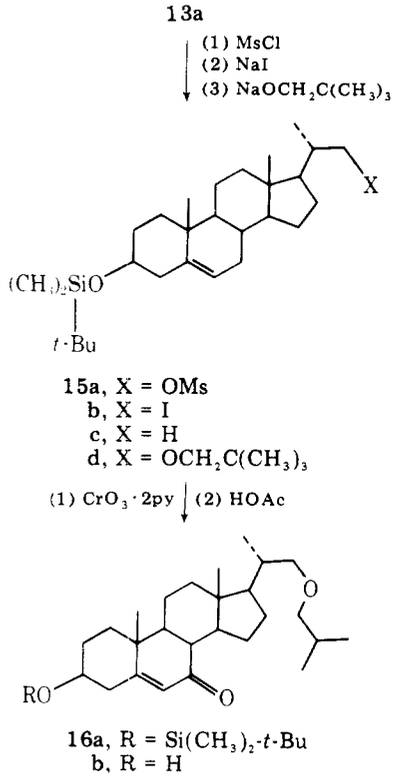
Alkylation of **8** with sodium hydride and 1-bromo-3-methylbutane in refluxing xylene gave **9a**. Substitution of the mesylate of 3,3-dimethyl-1-butanol for 1-bromo-3-methylbutane in the alkylation reaction gave **9b**. Oxidation of **9a** and **9b** with a solution of CrO_3·pyridine complex in methylene chloride afforded the 7-keto analogues **10a** and **10c**, respectively, which were hydrolyzed with a mixture of HOAc–THF–water to give 7-keto-22-oxacholesterol (**10b**) and 7-keto-25-methyl-22-oxacholesterol (**10d**).

The synthesis of the 7-keto-23-oxacholesterol analogues is outlined in Schemes III and IV.

Scheme III



Scheme IV

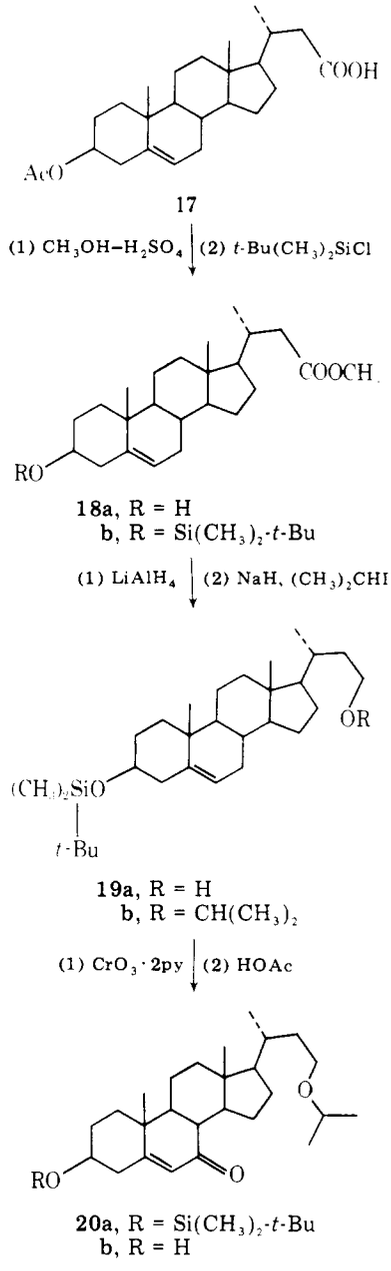


A methanol solution of 3β-acetoxybisnor-5-cholenic acid (11)[12] was refluxed in the presence of sulfuric acid to give methyl 3β-hydroxybisnor-5-cholenate (**12a**).[13] The hydroxy group in **12a** was protected as its *tert*-butyldimethylsilyl ether, and the ester function in **12b** was reduced with lithium aluminum hydride in tetrahydrofuran to give the C-22 alcohol (**13a**). To ensure that epimerization at C-20 had not occurred during any of the steps involved in the conversion of **11** into **13a**, noise-decoupled ^{13}C NMR spectra were obtained on compounds **11**, **12a**, **12b**, and **13a**. In each case the number of ^{13}C NMR signals was equal to or less than the number of carbon atoms in the proposed structures, indicating the presence of only one epimer. Alkylation of **13a** with sodium hydride and 1-bromo-2-methylpropane in refluxing xylene afforded **13b**. Oxidation of **13b** with CrO_3·pyridine complex in methylene chloride gave the 7-keto analogue **14a**, which was hydrolyzed with a mixture of HOAc–THF–water to give 7-keto-23-oxacholesterol (**14b**).

We anticipated that the alkylation of **13a** with 1-bromo-2,2-dimethylpropane would be difficult if not impossible since this would involve nucleophilic attack on a neopentyl carbon atom. In order to circumvent this potential problem, we used the sequence of reactions depicted in Scheme IV to prepare the desired 25-methyl analogue.

Treatment of **13a** with methanesulfonyl chloride in pyridine gave the mesylate **15a**, which was converted into the iodide **15b** by heating with sodium iodide in butan-2-one. Refluxing the iodide **15b** with a suspension of sodium neopentoxide in xylene for 40 h resulted in the formation of two products which were separated via low pressure chromatography. The less polar material, isolated in 9% yield, was identified as **15c**, which presumably arises via homolytic thermolysis of the carbon–iodine bond followed by hydrogen atom abstraction from the solvent. The more polar material, isolated in 66% yield, was the desired alkylation product **15d**. Oxidation of **15d** with CrO_3·pyridine complex in methylene chloride gave the 7-keto analogue **16a**, which was converted into 7-keto-25-methyl-23-oxacholesterol (**16b**) by treatment with HOAc–THF–water.

Scheme V



The synthesis of the 7-keto-24-oxacholesterol analogues is outlined in Schemes V and VI.

3β-Acetoxynor-5-cholenic acid (**17**) was prepared from **11** according to the procedure of Sax and Bergmann.[14] Refluxing a methanolic solution of **17** in the presence of a catalytic amount of sulfuric acid resulted in hydrolysis of the acetate and concomitant esterification of the acid function to give the methyl ester **18a**.[15] The hydroxy group in **18a** was protected as its *tert*-butyldimethylsilyl ether, and the ester function was reduced with lithium aluminum hydride in tetrahydrofuran to give **19a**. Alkylation of **19a** with sodium hydride and 2-iodopropane in refluxing xylene was sluggish. Consequently, the reaction mixture had to be recycled three times to effect a satisfactory conversion to **19b**. Dehydrohalogenation of 2-iodopropane by the anion of **19a** presumably competes with the alkylation reaction, thus accounting for the need to recycle several times. Allylic oxidation of **19b** with CrO_3·pyridine complex followed by acid hydrolysis of the protecting group afforded 7-keto-24-oxacholesterol (**20b**).

The corresponding 25-methyl analogue was prepared as outlined in Scheme VI.

Reduction of **17** with a solution of borane in tetrahydrofu-

Scheme VI

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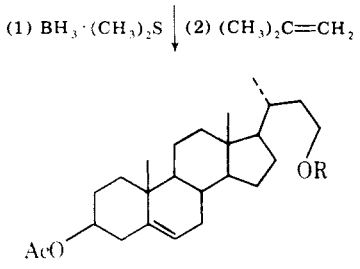
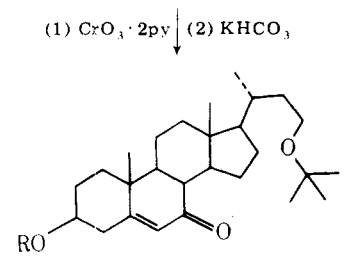


21a, R = H
21b, R = $C(CH_3)_3$



22a, R = $C(=O)CH_3$
b, R = H

ran at 0 °C gave 3β-acetoxy-23-hydroxynorchol-5-ene (**21a**)[16] in approximately 50% yield. Treatment of **21a** with a cold solution of isobutylene in methylene chloride in the presence of a catalytic amount of sulfuric acid afforded the *tert*-butyl ether derivative **21b**. Allylic oxidation of **21b** with CrO_3·pyridine complex followed by hydrolysis with methanolic potassium bicarbonate gave 7-keto-25-methyl-24-oxacholesterol (**22b**).

Several of the 7-ketocholesterol analogues have shown significant inhibition of HMG CoA reductase in human fibroblasts.[17] One of the most potent compounds in this series, **5b**, has been evaluated by Brown and co-workers[18] in their human fibroblast assay. These authors demonstrated that **5b** was a potent inhibitor of both HMG CoA reductase and acyl coenzyme A/cholesterol acyltransferase (ACAT) (EC 2.3.1.26), an enzyme which plays an important role in the accumulation of cholesterol esters within smooth muscle cells in the artery wall during the development of atherosclerosis. The combination of activities exhibited by **5b** would appear to be highly desirable in the treatment of atherosclerosis. Unfortunately, we[19] have not been able to demonstrate either inhibition of HMG CoA reductase or reduction of serum cholesterol levels when **5b** was administered either orally or subcutaneously to intact rats. Although our results do not conclusively rule out the possibility that **5b** may be inactive due to poor absorption, the fact that **5b** was inactive when administered subcutaneously indicates that the lack of in vivo activity is probably not due to poor absorption of the compound.

Experimental Section

Melting points were taken on a Thomas-Hoover unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-12 grating spectophotometer. UV spectra were obtained in methanol on a Beckman DK-2A instrument. NMR spectra were recorded on Varian A-60A, T-60, FT80A, or XL100-15 spectrometers using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Chromatographic separations were performed via gravity column using EM-100 silica or via low pressure chromatography using Altex glass columns packed with Woelm silica (30–60 μm) or EM-60 silica. Large samples were chromatographed on a Waters Preparative LC-500 instrument using Waters silica cartridges. Elemental analyses were performed by the microanalytical group at Searle Laboratories.

Procedure A. Alkoxide Alkylations. A mixture of the appropriate alcohol (1.0 equiv), sodium hydride (1.4–3.6 equiv), which was washed twice with hexane, and 10–25 mL of xylene was refluxed for 1–2 h and cooled to room temperature. The appropriate alkylating agent (1.6–9.0 equiv) was added, and the mixture was refluxed for 8–48 h until TLC indicated no further reaction. The mixture was cooled, diluted with an equal volume of ether, and filtered through Celite. The solvents were removed in vacuo and the residue purified as indicated for each specific compound.

Procedure B. Allylic Oxidations. Allylic oxidations were carried out via a slight modification of the procedure of Fullerton and Chen.[10] Chromium trioxide (15–20 equiv), which had previously been dried over phosphorus pentoxide in a desiccator, was added to a solution of pyridine (30–40 equiv; analytical reagent grade dried over molecular sieves) in 35–75 mL of methylene chloride (spectral grade dried over molecular sieves), and the mixture was stirred at room temperature for 20 min. The appropriate steroid (1.0 equiv) was added, and the mixture was stirred at room temperature under nitrogen for 6–18 h until TLC indicated no further reaction. The mixture was decanted and the tarry residue washed with methylene chloride. The combined organic phases were concentrated in vacuo, and the residue was leeched several times with hot ether. The ether phase was filtered through Florisil (60 mesh) and the solvent removed in vacuo. The residue was purified as indicated for each specific compound.

Procedure C. Hydrolysis of *tert*-Butyldimethylsilyl Ethers. A solution of the steroid in acetic acid, tetrahydrofuran, and water (see specific examples for ratios of reagents) was gently heated on a steam bath until hydrolysis was complete as evidenced by TLC. Addition of a few drops of 12 N hydrochloric acid greatly accelerated the rate of hydrolysis. The mixture was poured onto water and extracted with ether. The extracts were washed with 5% aqueous potassium bicarbonate and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified as indicated for each specific compound.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-17β-(4-methylpentyloxy)androst-5-ene (4a). Alkylation of **3**[9] (10.1 g, 25.0 mmol) with NaH (2.00 g, 41.6 mmol) and 1-bromo-4-methylpentane (6.60 g, 40.0 mmol) in 200 mL of xylene according to procedure A followed by recrystallization from ether–CH_3OH gave **4a** (9.98 g, 82%): mp 137–138 °C; NMR δ 0.77 (s, 3 H), 0.89 (d, J = 6 Hz, 6 H), 1.01 (s, 3 H).

Anal. Calcd for $C_{31}H_{56}O_2Si$: C, 76.16; H, 11.55. Found: C, 76.23; H, 11.52.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-17β-(4,4-dimethylpentyloxy)androst-5-ene (4b). Alkylation of **3**[9] (10.1 g, 25.0 mmol) with NaH (2.20 g, 45.8 mmol) and the mesylate of 4,4-dimethylpentan-1-ol (6.25 g, 35.7 mmol) in 200 mL of xylenes was accomplished according to procedure A. The crude product was impregnated on 20 g of silica using CH_2Cl_2 and chromatographed on 250 g of silica using 50% Skellysolve B–50% benzene as eluant. The pure fractions were recrystallized from ether–CH_3OH to give **4b** (7.66 g, 61%): mp 138–139 °C; NMR δ 0.78 (s, 3 H), 0.88 (s, 9 H), 1.02 (s, 3 H).

Anal. Calcd for $C_{32}H_{58}O_2Si$: C, 76.43; H, 11.63. Found: C, 76.60; H, 11.60.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-17β-(4-methylpentyloxy)androst-5-en-7-one (5a). Oxidation of **4a** (8.85 g, 18.1 mmol) was accomplished with CrO_3 (36.0 g, 360 mmol) and pyridine (57.2 g, 720 mmol) in 1 L of CH_2Cl_2 according to procedure B. The crude product was impregnated on 20 g of silica using CH_2Cl_2 and chromatographed on 250 g of silica using benzene and increasing amounts of EtOAc as eluant. The pure fractions were combined to give **5a** (5.91 g, 65%). Recrystallization from ether–CH_3OH gave an analytical sample of **5a**: mp 143–145 °C; NMR δ 0.77 (s, 3 H), 0.88 (d, J = 6 Hz, 6 H), 1.18 (s, 3 H).

Anal. Calcd for $C_{31}H_{54}O_3Si$: C, 74.04; H, 10.83. Found: C, 74.09; H, 10.44.

3β-Hydroxy-17β-(4-methylpentyloxy)androst-5-en-7-one (5b). Hydrolysis of **5a** (5.86 g, 11.3 mmol) with 30 mL of HOAc, 20 mL of water, and 100 mL of THF according to procedure C gave a crude product which was impregnated on 20 g of silica using CH_2Cl_2 and chromatographed on 250 g of silica using 20% EtOAc–80% benzene as eluant. The pure fractions were combined and recrystallized from ether–Skellysolve B to give **5b** (3.09 g, 68%): mp 133.5–134.5 °C; IR (KBr) 1660 cm^{-1}; UV λ_{max} 238 nm (ε 13 900); NMR δ 0.78 (s, 3 H), 0.88 (d, J = 6 Hz, 6 H), 1.20 (s, 3 H), 5.69 (s, 1 H).

Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.27; H, 10.38. Found: C, 77.07; H, 10.34.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-17β-(4,4-dimethylpentyloxy)androst-5-en-7-one (5c). Oxidation of **4b** (2.01 g, 4.00 mmol) was accomplished with CrO_3 (8.00 g, 80.0 mmol) and pyridine

(12.7 g, 160 mmol) in 300 mL of CH_2Cl_2 according to procedure B. The crude product was impregnated on 3 g of silica using CH_2Cl_2 and chromatographed on 30 g of silica using Skellysolve B and increasing amounts of benzene as eluant. The pure fractions were combined and recrystallized from ether–CH_3OH to give **5c** (1.11 g, 54%): mp 155–156 °C; NMR δ 0.78 (s, 3 H), 0.89 (s, 9 H), 1.20 (s, 3 H).

Anal. Calcd for $C_{32}H_{56}O_3Si$: C, 74.36; H, 10.92. Found: C, 74.26; H, 10.52.

17β-(4,4-Dimethylpentyloxy)-3β-hydroxyandrost-5-en-7-one (5d). Hydrolysis of **5c** (1.05 g, 2.03 mmol) with 10 mL of HOAc, 5 mL of water, and 25 mL of THF according to procedure C gave a crude product which was chromatographed on 30 g of silica using benzene and increasing amounts of EtOAc as eluant. The pure fractions were combined and recrystallized from acetone–Skellysolve B to give 5d (0.593 g, 73%): mp 203–205 °C; IR (KBr) 1660 cm^{-1}; UV λ_{max} 237 nm (ε 13 100); NMR δ 0.77 (s, 3 H), 0.88 (s, 9 H), 1.21 (s, 3 H), 5.71 (s, 1 H).

Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.46; H, 10.53.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]pregn-5-en-20-one (6b). A mixture of pregnenolone (31.6 g, 100 mmol), *tert*-butyldimethylchlorosilane (17.5 g, 116 mmol), imidazole (19.7 g, 290 mmol), and 200 mL of ether–200 mL of DMF was stirred at room temperature for 2.5 h. The mixture was poured onto water and extracted with ether and then with CH_2Cl_2 because of the relative insolubility of the product in ether. The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was recrystallized from CH_2Cl_2–CH_3OH to give **6b** (34.6 g, 81%): mp 162–164 °C; NMR δ 0.63 (s, 3 H), 1.00 (s, 3 H), 2.10 (s, 3 H).

Anal. Calcd for $C_{27}H_{46}O_2Si$: C, 75.28; H, 10.77. Found: C, 75.21; H, 10.71.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]pregn-5-en-20(*R*)-ol (7) and 3β-[(1,1-Dimethylethyl)dimethylsilyloxy]pregn-5-en-20(*S*)-ol (8). Sodium metal (150 g, 6.52 mol) was added portionwise to a refluxing solution of **6b** (29.7 g, 69.0 mmol) in 2200 mL of EtOH at such a rate as to maintain reflux without heating. After all of the sodium had been consumed, the mixture was concentrated to 1500 mL by distillation and poured onto 2000 mL of water. The gelatinous mixture was filtered through Celite, and the resulting cake was air-dried overnight. The cake was extracted with hot CH_2Cl_2 and filtered. The organic phase was washed with water, dried over $MgSO_4$, and filtered. Solvent removal gave a crude product mixture which was chromatographed via low pressure chromatography on 1800 g of silica using 5% EtOAc–95% toluene as eluant. Pure fractions containing the first major product to be eluted were combined and the solvents removed in vacuo. The residue was recrystallized from ether–CH_3OH to give **7** (8.50 g, 28%): mp 141–143 °C; NMR δ 0.77 (s, 3 H), 1.02 (s, 3 H), 1.14 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{27}H_{48}O_2Si$: C, 74.93; H, 11.18. Found: C, 74.60; H, 10.90.

Pure fractions containing the second major product to be eluted were combined and concentrated in vacuo, and the residue was recrystallized from ether–CH_3OH to give **8** (13.3 g, 45%): mp 162–164 °C; NMR δ 0.68 (s, 3 H), 1.00 (s, 3 H), 1.22 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{27}H_{48}O_2Si$: C, 74.93; H, 11.18. Found: C, 74.78; H, 10.94.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-20(*S*)-(3-methylbutoxy)pregn-5-ene (9a). Alkylation of **8** (5.00 g, 11.6 mmol) with NaH (1.92 g, 40.0 mmol) and 1-bromo-3-methylbutane (9.06 g, 60.0 mmol) in 300 mL of xylene according to procedure A followed by recrystallization from ether–CH_3OH gave **9a** (5.09 g, 87%): mp 120–122 °C; NMR δ 0.66 (s, 3 H), 0.89 (d, J = 6 Hz, 6 H), 1.01 (s, 3 H), 1.15 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{32}H_{58}O_2Si$: C, 76.43; H, 11.63. Found: C, 76.68; H, 11.59.

20(*S*)-(3,3-Dimethylbutoxy)-3β-[(1,1-dimethylethyl)dimethylsilyloxy]pregn-5-ene (9b). Partial alkylation of **8** (5.00 g, 11.6 mmol) with NaH (2.00 g, 41.7 mmol) and the mesylate of 3,3-dimethylbutan-1-ol (5.20 g, 28.8 mmol) in 300 mL of xylene was accomplished according to procedure A. The crude product was impregnated on 10 g of silica using ether and chromatographed on 250 g of silica using 5% toluene–95% Skellysolve B as eluant. Pure fractions of the first major product to be eluted were combined and the solvents removed in vacuo to give **9b** (2.15 g, 36%). Recrystallization from ether–CH_3OH gave an analytical sample of **9b:** mp 137–139 °C; NMR δ 0.67 (s, 3 H), 0.88 (s, 9 H), 1.00 (s, 3 H), 1.15 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{33}H_{60}O_2Si$: C, 76.67; H, 11.70. Found: C, 76.97; H, 11.67.

Further elution of the column with 30% EtOAc–70% Skellysolve B afforded unreacted **8** (2.05 g, 41%).

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-20(*S*)-(3-methylbutoxy)pregn-5-en-7-one (10a). Oxidation of **9a** (4.55 g, 9.05 mmol) was accomplished with CrO_3 (14.0 g, 140 mmol) and pyridine (22.1 g, 280 mmol) in 500 mL of CH_2Cl_2 according to procedure B. The crude product was chromatographed on 250 g of silica using 2% EtOAc–98% toluene as eluant. The pure fractions were combined to give **10a** (2.45 g, 52%). Recrystallization from ether–CH_3OH gave an analytical sample of **10a:** mp 162–164 °C; NMR δ 0.68 (s, 3 H), 0.89 (d, J = 6 Hz, 6 H), 1.15 (d, J = 6 Hz, 3 H), 1.19 (s, 3 H).

Anal. Calcd for $C_{32}H_{56}O_3Si$: C, 74.36; H, 10.92. Found: C, 74.62; H, 11.04.

3β-Hydroxy-20(*S*)-(3-methylbutoxy)pregn-5-en-7-one (10b). Hydrolysis of **10a** (1.63 g, 3.15 mmol) with 25 mL of HOAc, 10 mL of HOH, and 50 mL of THF according to procedure C gave a crude product which was chromatographed on 90 g of silica using 20% EtOAc–80% toluene as eluant. The pure fractions were combined and recrystallized from ether–Skellysolve B to give **10b** (1.11 g, 88%): mp 123–125 °C; IR (KBr) 1668 cm^{-1}; UV λ_{max} 237 nm (ε 13 900); NMR δ 0.68 (s, 3 H), 0.89 (d, J = 6 Hz, 6 H), 1.16 (d, J = 6 Hz, 3 H), 1.20 (s, 3 H).

Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.48, H, 10.25.

20(*S*)-(3,3-Dimethylbutoxy)-3β-[(1,1-dimethylethyl)dimethylsilyloxy]pregn-5-en-7-one (10c). Oxidation of **9b** (1.94 g, 3.75 mmol) was accomplished with CrO_3 (6.00 g, 60.0 mmol) and pyridine (9.49 g, 120 mmol) in 250 mL of CH_2Cl_2 according to procedure B. The crude product was chromatographed on 250 g of silica using 2% EtOAc–98% toluene as eluant. The pure fractions were combined and the solvents removed in vacuo to give **10c** (1.17 g, 59%). Recrystallization from ether–CH_3OH gave an analytical sample of **10c:** mp 188–190 °C; NMR δ 0.68 (s, 3 H), 0.88 (s, 9 H), 1.16 (d, J = 6 Hz, 3 H), 1.20 (s, 3 H).

Anal. Calcd for $C_{33}H_{58}O_3Si$: C, 74.66; H, 11.01. Found: C, 74.84, H, 11.01.

20(*S*)-(3,3-Dimethylbutoxy)-3β-hydroxypregn-5-en-7-one (10d). Hydrolysis of **10c** (1.00 g, 1.88 mmol) with 25 mL of HOAc, 10 mL of water, 50 mL of THF, and 0.10 mL of HCl according to procedure C gave a crude product which was recrystallized from ether–Skellysolve B to give **10d** (0.500 g, 64%): mp 143–145 °C; IR (KBr) 1672 cm^{-1}; UV λ_{max} 237 nm (ε 13 300); NMR δ 0.68 (s, 3 H), 0.92 (s, 9 H), 1.10 (d, J = 6 Hz, 3 H), 1.21 (s, 3 H).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.62; H, 10.60.

Methyl 3β-Hydroxypregn-5-en-20(*S*)-carboxylate (12a). A mixture of **11** (10.0 g, 25.7 mmol) in 200 mL of CH_3OH was treated with 3 mL of H_2SO_4 and refluxed for 36 h. The solution was cooled and poured onto 1000 mL of 5% $KHCO_3$, and the product was collected and air-dried. Recrystallization from CH_2Cl_2–Skellysolve B afforded **12a** (7.95 g, 86%), mp 140–142 °C (lit.[12] mp 140 °C).

Methyl 3β-[(1,1-Dimethylethyl)dimethylsilyloxy]pregn-5-en-20(*S*)-carboxylate (12b). A mixture of **12a** (7.95 g, 22.1 mmol), *tert*-butyldimethylsilyl chloride (3.77 g, 25.0 mmol), imidazole (3.40 g, 50.0 mmol), 100 mL of anhydrous ether, and 150 mL of DMF was stirred overnight at room temperature. The ether was removed in vacuo, and the resulting slurry was poured onto 1 L of water. The product was collected by filtration, washed with water, and air-dried. Recrystallization from ether–CH_3OH gave **12b** (9.58 g, 91%): mp 150–151 °C; NMR δ 0.70 (s, 3 H), 1.00 (s, 3 H), 1.19 (d, J = 6.5 Hz, 3 H), 3.64 (s, 3 H).

Anal. Calcd for $C_{29}H_{50}O_3Si$: C, 73.36; H, 10.62. Found: C, 73.38; H, 10.72.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-20(*S*)-methylpregn-5-en-21-ol (13a). A solution of **12b** (9.50 g, 20.0 mmol) in 70 mL of THF was added dropwise to a stirred suspension of $LiAlH_4$ (0.760 g, 20.0 mmol) in 130 mL of THF. After 30 min, the mixture was hydrolyzed by the dropwise addition of 3.0 mL of water. The mixture was filtered and the filtrate concentrated in vacuo to give **13a** (8.80 g, 98%). Recrystallization from ether–Skellysolve B gave an analytical sample of **13a:** mp 153.5–155.5 °C; NMR δ 0.71 (s, 3 H), 1.01 (s, 3 H), 1.05 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{28}H_{50}O_2Si$: C, 75.27; H, 11.28. Found: C, 74.90; H, 11.44.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-20(*S*)-methyl-21-(2-methylpropoxy)pregn-5-ene (13b). Alkylation of **13a** (2.00 g, 4.48 mmol) with NaH (0.480 g, 10.0 mmol) and 1-bromo-2-methylpropane (5.48 g, 40.0 mmol) in 50 mL of xylene was accomplished according to procedure A. The crude product was chromatographed on 250 g of silica using 20% $CHCl_3$–80% Skellysolve B as eluant. The pure fractions were combined, and the solvents were removed in vacuo to give **13b** (1.98 g, 88%). Recrystallization from ether–CH_3OH gave

an analytical sample of **13b:** mp 162–164 °C; NMR δ 0.70 (s, 3 H), 0.90 (d, J = 6 Hz, 6 H), 1.02 (s, 3 H), 1.03 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{32}H_{58}O_2Si$: C, 76.43; H, 11.63. Found: C, 76.75; H, 11.61.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-20(*S*)-methyl-21-(2-methylpropoxy)pregn-5-en-7-one (14a). Oxidation of **13b** (1.45 g, 2.88 mmol) was accomplished with CrO_3 (6.00 g, 60.0 mmol) and pyridine (9.50 g, 120 mmol) in 150 mL of CH_2Cl_2 according to procedure B. The crude product was impregnated on 3 g of silica and chromatographed on 90 g of silica using 2% EtOAc–98% Skellysolve B as eluant. The pure fractions were combined, and the solvent was removed in vacuo to give **14a** (0.812 g, 55%). Recrystallization from ether–Skellysolve B gave an analytical sample of **14a:** mp 116–118 °C; NMR δ 0.70 (s, 3 H), 0.89 (d, J = 6 Hz, 6 H), 1.03 (d, J = 6 Hz, 3 H), 1.18 (s, 3 H).

Anal. Calcd for $C_{32}H_{56}O_3Si$: C, 74.36; H, 10.92. Found: C, 74.28; H, 11.00.

3β-Hydroxy-20(*S*)-methyl-21-(2-methylpropoxy)pregn-5-en-7-one (14b). Hydrolysis of **14a** (0.765 g, 1.48 mmol) with 10 mL of HOAc, 1 mL of water, 5 mL of THF, and 0.10 mL of 12 N HCl was accomplished according to procedure C. The crude product was chromatographed on 15 g of silica using $CHCl_3$ as eluant. The pure fractions were combined to give **14b** (0.563 g, 94%). Recrystallization from ether–Skellysolve B gave an analytical sample of **14b:** mp 139.5–141.5 °C; UV λ_{max} 238 nm (ε 12 700); NMR δ 0.70 (s, 3 H), 0.89 (d, J = 6 Hz, 6 H), 1.03 (d, J = 6 Hz, 3 H), 1.22 (s, 3 H).

Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.37; H, 10.68.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-20(*S*)-methylpregn-5-en-21-ol Methanesulfonate (15a). Methanesulfonyl chloride (0.700 g, 6.11 mmol) was added dropwise to a stirred solution of **13a** (2.12 g, 4.75 mmol) in 30 mL of pyridine at 0 °C. After addition was complete, the mixture was warmed to room temperature, stirred for 1.5 h, and poured onto 150 mL of water. The solid which precipitated was collected, washed with water, and air-dried to give **15a** (2.45 g, 98%), which was used without further purification.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-21-iodo-20(*S*)-methylpregn-5-ene (15b). A mixture of **15a** (2.45 g, 4.67 mmol), NaI (4.50 g, 30.0 mmol), and 100 mL of butan-2-one was refluxed for 4 h and poured onto 600 mL of water, and the product was collected and air-dried. Recrystallization from ether–acetone gave **15b** (2.45 g, 94%), mp 184.5–186.5 °C.

Anal. Calcd for $C_{28}H_{49}OISi$: C, 60.41; H, 8.87. Found: C, 60.43; H, 9.00.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-20-methylpregn-5-ene (15c) and 3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-21-(2,2-dimethylpropoxy)-20(*S*)-methylpregn-5-ene (15d). Alkylation of 2,2-dimethylpropanol (0.880 g, 10.0 mmol) with NaH (0.580 g, 12.0 mmol) and **15b** (2.40 g, 4.31 mmol) in 50 mL of xylene was accomplished according to procedure A. The crude product was impregnated on 3 g of silica and chromatographed on 250 g of silica using Skellysolve B as eluant. Fractions containing the less polar product were combined to give **15c** (0.268 g, 14%). Recrystallization from ether–Skellysolve B gave an analytical sample of **15c:** mp 169–170 °C; NMR δ 0.67 (s, 3 H), 0.84 (d, J = 6 Hz, 3 H), 0.94 (d, J = 6 Hz, 3 H), 1.00 (s, 3 H).

Anal. Calcd for $C_{28}H_{50}OSi$: C, 78.07; H, 11.70. Found: C, 77.85; H, 11.87.

Further elution with Skellysolve B afforded the major product **15d** (1.46 g, 66%). Recrystallization from ether–CH_3OH gave an analytical sample of **15d:** mp 185.5–187.5 °C; NMR δ 0.70 (s, 3 H), 0.88 (s, 18 H), 1.00 (s, 3 H), 1.02 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{33}H_{60}O_2Si$: C, 76.67; H, 11.70. Found: C, 76.40; H, 11.72.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-21-(2,2-dimethylpropoxy)-20(*S*)-methylpregn-5-en-7-one (16a). Oxidation of **15d** (1.26 g, 2.44 mmol) was accomplished with CrO_3 (5.00 g, 50.0 mmol) and pyridine (7.91 g, 100 mmol) in 125 mL of CH_2Cl_2 according to procedure B. The crude product was impregnated on 3 g of silica and chromatographed on 90 g of silica using 1% EtOAc–99% Skellysolve B as eluant. The pure fractions were combined to give **16a** (0.683 g, 53%). Recrystallization from ether–Skellysolve B gave an analytical sample of **16a:** mp 229–231 °C; NMR δ 0.70 (s, 3 H), 0.90 (s, 18 H), 1.03 (d, J = 6 Hz, 3 H), 1.19 (s, 3 H).

Anal Calcd for $C_{33}H_{58}O_3Si$: C, 74.66; H, 11.01. Found: C, 74.48; H, 10.93.

21-(2,2-Dimethylpropoxy)-3β-hydroxy-20(*S*)-methylpregn-5-en-7-one (16b). Hydrolysis of **16a** (0.560 g, 1.11 mmol) with 6 mL of HOAc, 1 mL of water, 3 mL of THF, and 0.10 mL of 12 N HCl according to procedure C gave a crude product which was chromatographed on 30 g of silica using $CHCl_3$ as eluant. The pure fractions were combined to give **16b** (0.390 g, 84%). Recrystallization from ether–Skellysolve B gave an analytical sample of **16b:** mp 168–169 °C; IR (KBr) 1665 cm^{-1}; UV λ_{max} 238 nm (ε 13 100); NMR δ 0.70 (s, 3 H), 0.90 (s, 9 H), 1.02 (d, J = 6 Hz, 3 H), 1.20 (s, 3 H).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.85; H, 10.79.

3β-(Acetyloxy)-24-norchol-5-en-23-oic acid (17) was prepared from **11**[12] according to the procedure of Sax and Bergmann.[14]

Methyl 3β-Hydroxy-24-norchol-5-en-23-oate (18a). A mixture of **17** (5.07 g, 12.6 mmol) in 100 mL of CH_3OH was treated with 1 mL of H_2SO_4 and refluxed for 2 days. The mixture was poured onto 600 mL of water and extracted with CH_2Cl_2. The extracts were washed with 5% $KHCO_3$, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, and the residue was recrystallized from ether–Skellysolve B to give **18a** (3.82 g, 81%), mp 141–142 °C (lit.[15] mp 141–142 °C).

Methyl 3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-24-norchol-5-en-23-oate (18b). A mixture of **18a** (3.43 g, 9.16 mmol), *tert*-butyldimethylsilyl chloride (1.51 g, 10.0 mmol), imidazole (1.36 g, 20.0 mmol), and 100 mL of DMF was stirred overnight at room temperature. The mixture was poured onto 600 mL of water, and the product was collected, washed with water, and air-dried. Recrystallization from ether–CH_3OH gave **18b** (4.06 g, 91%): mp 168–169 °C; NMR δ 0.72 (s, 3 H), 0.97 (d, J = 6 Hz, 3 H), 1.00 (s, 3 H), 3.65 (s, 3 H).

Anal. Calcd for $C_{30}H_{52}O_3Si$: C, 73.71; H, 10.72. Found: C, 73.73; H, 10.86.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-24-norchol-5-en-23-ol (19a). A solution of **18b** (4.00 g, 8.18 mmol) in 50 mL of THF was added dropwise to a stirred suspension of $LiAlH_4$ (0.400 g, 10.6 mmol) in 50 mL of THF. The mixture was stirred at room temperature for 30 min and hydrolyzed by the dropwise addition of 1.6 mL of water. The mixture was filtered, and the filtrate was concentrated in vacuo to give **19a** (3.60 g, 96%). Recrystallization from ether–Skellysolve B gave an analytical sample of **19a:** mp 158–160 °C; NMR δ 0.70 (s, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.02 (s, 3 H).

Anal. Calcd for $C_{29}H_{52}O_2Si$: C, 75.59; H, 11.38. Found: C, 75.20; H, 11.73.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-23-(1-methylethoxy)-24-norchol-5-ene (19b). Alkylation of **19a** (3.58 g, 7.77 mmol) with NaH (1.00 g, 20.8 mmol) and 2-iodopropane (4.25 g, 25.0 mmol) in 150 mL of xylene was accomplished according to procedure A with the following modifications. After the mixture was refluxed for 18 h, additional NaH (2.00 g, 41.6 mmol) and 2-iodopropane (4.00 g; 23.5 mmol) were added and refluxing was continued for 4 h, at which time more 2-iodopropane (4.00 g, 23.5 mmol) was added and refluxing was continued for 18 h. The mixture was worked up as described in procedure A, and the crude product was impregnated on 10 g of silica and chromatographed on 250 g of silica using 25% $CHCl_3$–75% Skellysolve B as eluant. The pure fractions were combined to give **19b** (1.62 g, 41%). Recrystallization from ether–CH_3OH gave an analytical sample of **19b:** mp 144–147 °C; NMR δ 0.68 (s, 3 H), 1.00 (s, 3 H), 1.13 (d, J = 6 Hz, 6 H).

Anal. Calcd for $C_{32}H_{58}O_2Si$: C, 76.43; H, 11.63. Found: C, 76.56; H, 11.80.

3β-[(1,1-Dimethylethyl)dimethylsilyloxy]-23-(1-methylethoxy)-24-norchol-5-en-7-one (20a). Oxidation of **19b** (1.11 g, 2.21 mmol) was accomplished with CrO_3 (4.50 g, 45.0 mmol) and pyridine (7.12 g, 90.0 mmol) in 75 mL of CH_2Cl_2 according to procedure B. The crude product was chromatographed on 90 g of silica using 2% EtOAc–98% toluene as eluant. The pure fractions were combined to give **20a** (0.565 g, 49%). Recrystallization from ether–CH_3OH gave an analytical sample of **20a:** mp 202.5–205.5 °C; NMR δ 0.68 (s, 3 H), 1.13 (d, J = 6 Hz, 6 H), 1.18 (s, 3 H).

Anal. Calcd for $C_{32}H_{56}O_3Si$: C, 74.36; H, 10.92. Found: C, 74.08; H, 10.92.

3β-Hydroxy-23-(1-methylethoxy)-24-norchol-5-en-7-one (20b). Hydrolysis of **20a** (0.512 g, 0.991 mmol) with 13 mL of HOAc, 6 mL of THF, and 1 mL of water according to procedure C gave a crude product which was chromatographed on 30 g of silica using $CHCl_3$ as eluant. The pure fractions were combined to give **20b** (0.347 g, 87%). Recrystallization from ether gave an analytical sample of **20b:** mp 146.5–148.5 °C; IR (KBr) 1668 cm^{-1}; UV λ_{max} 237 nm (ε 12 900); NMR δ 0.68 (s, 3 H), 0.94 (d, J = 6 Hz, 3 H), 1.13 (d, J = 6 Hz, 6 H), 1.18 (s, 3 H).

Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.28; H, 10.42.

24-Norchol-5-ene-3β,23-diol 3-Acetate (21a). A solution of 10.2 M borane-dimethyl sulfide complex (5.0 mL, 51 mmol) was added via

syringe to a solution of **17** (17.4 g, 45.0 mmol) in 250 mL of THF at −50 °C under N_2. The mixture was slowly warmed to room temperature and allowed to stand overnight under N_2. The mixture was poured onto 1200 mL of water, and the product was collected, washed with water, and air-dried. The crude product was chromatographed on 500 g of silica using 5% EtOAc–95% toluene as eluant. The pure fractions were combined to give **21a** (6.91 g, 41%). Recrystallization from benzene–Skellysolve B gave a sample having mp 153.5–155.5 °C (lit.[16] mp 154–156 °C).

23-(1,1-Dimethylethoxy)-24-norchol-5-en-3β-ol Acetate (21b). Approximately 100 mL of isobutylene was condensed into a solution of **21a** (2.79 g, 7.18 mmol) in 80 mL of CH_2Cl_2 at −40 °C. H_2SO_4 (2 mL) was added, and the solution was allowed to reflux at 5 °C for 7 h. An additional 100 mL of CH_2Cl_2 was added, and the isobutylene was allowed to evaporate off overnight. The mixture was washed with water, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo. The crude product was impregnated on 10 g of silica using CH_2Cl_2 and chromatographed on 250 g of silica using 2% EtOAc–98% benzene as eluant. The pure fractions were combined to give **21b** (1.56 g, 49%). Recrystallization from ether–CH_3OH gave an analytical sample of **21b:** mp 134–135 °C; NMR δ 0.68 (s, 3 H), 0.93 (d, J = 6 Hz, 3 H), 1.02 (s, 3 H), 1.17 (s, 9 H), 2.02 (s, 3 H).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.16; H, 11.02.

3β-(Acetyloxy)-23-(1,1-dimethylethoxy)-24-norchol-5-en-7-one (22a). Oxidation of **21b** (1.75 g, 4.49 mmol) was accomplished with CrO_3 (9.00 g, 90.0 mmol) and pyridine (14.2 g, 180 mmol) in 300 mL of CH_2Cl_2 according to procedure B. The crude product was chromatographed on 30 g of silica using benzene and increasing amounts of EtOAc as eluant. The pure fractions were combined to give **22a** (1.36 g, 66%). Recrystallization from ether–Skellysolve B gave an analytical sample of **22a:** mp 169–170 °C; NMR δ 0.69 (s, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.17 (s, 9 H), 1.43 (s, 3 H), 2.03 (s, 3 H).

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 75.73; H, 9.72.

23-(1,1-Dimethylethoxy)-3β-hydroxy-24-norchol-5-en-7-one (22b). A mixture of **22a** (0.960 g, 2.09 mmol), $KHCO_3$ (0.500 g, 5.00 mmol), 45 mL of CH_3OH, and 5 mL of water was gently heated on a steam bath for 1 h. The mixture was concentrated in vacuo to about 20 mL and was poured onto 100 mL of water. The solid was collected, washed thoroughly with water, and air-dried. The product was chromatographed on 90 g of silica using 20% EtOAc–80% benzene as eluant. The pure fractions were combined, and the solvents were removed in vacuo to give **22b** (0.810 g, 93%). Recrystallization from ether–Skellysolve B gave an analytical sample of **22b:** mp 145–147 °C; IR (KBr) 1670 cm^{-1}; UV λ_{max} 235 nm (ε 13 700); NMR δ 0.70 (s, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.17 (s, 9 H), 1.44 (s, 3 H).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.58; H, 10.36.

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