Synthesis of 15β-Hydroxy-24-oxocholesterol and 15β,29-Dihydroxy-7-oxofucosterol

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3β-Acetoxyandrost-5-en-17-one has been converted into 15β-hydroxy-24-oxocholesterol. Reaction of (17*E*)-3β-(dimethyl-t-butylsilyloxy)-15β,16β-epoxypregna-5,17(20)-diene with the magnesium cyanocuprate derivative of 3-(1,3-dioxolan-2-yl)-4-methylpentyl bromide gave (20*R*)-3β-(dimethyl-t-butylsilyloxy)-15β-hydroxy-24-oxocholesta-5,16-diene 24-ethylene acetal in 80% yield, and this was converted into the target compound in high yield by catalytic hydrogenation followed by removal of the protecting groups. Reaction of 3β,15β-diacetoxycholest-5-en-24-one with the anion of diethyl cyanomethylphosphonate and reduction of the resulting nitrile with DIBAL-H, gave 15β,29-dihydroxyfucosterol. This was converted into the 3,29-diacetate 15-formate and oxidized with chromium trioxide–3,5-dimethylpyrazole. Removal of the acetate and formate groups with aqueous potassium carbonate afforded 15β,29-dihydroxy-7-oxofucosterol.

The synthesis of steroids containing functional side chains continues to attract the efforts of organic chemists. Many of these compounds have important biological properties and are not readily accessible by synthetic approaches involving modification of naturally occurring steroids possessing an intact side chain.

Marino and Abe have reported reactions of $\Delta^{17(20)}$-steroidal vinyl oxiranes with alkylcyanocuprates which resulted in the stereospecific synthesis of steroids possessing a 15β-hydroxy substituent and a side chain with the natural configuration at C-20.[1] Thus didehydroepiandrosterone (**1a**) was converted into 15β-hydroxycholesterol by a series of high-yielding steps.

This method seemed an attractive way to prepare oogoniol and 24,28-didehydro-oogoniol, female-activating hormones of the aquatic fungus *Achlya*.[2] We recently completed a synthesis of didehydro-oogoniol from 11α,15β-dihydroxyprogesterone, but this method suffered from two drawbacks. One was that the starting material, 11α,15β-dihydroxyprogesterone, had to be prepared by fermentation of progesterone with *Aspergillus giganteus* and was not readily available. The other problem was in the construction of the side chain, which resulted in mixtures of C-20 epimers, so that about half the valuable starting steroid was lost.[3] For synthesis of didehydro-oogoniol by the Marino approach, a suitable starting steroid would be androst-4-ene-3,11,17-trione, which is commercially available. In this paper we describe experiments in which the analogue of didehydro-oogoniol lacking the 11α-hydroxy group was synthesized from the readily available didehydroepiandrosterone (**1a**).

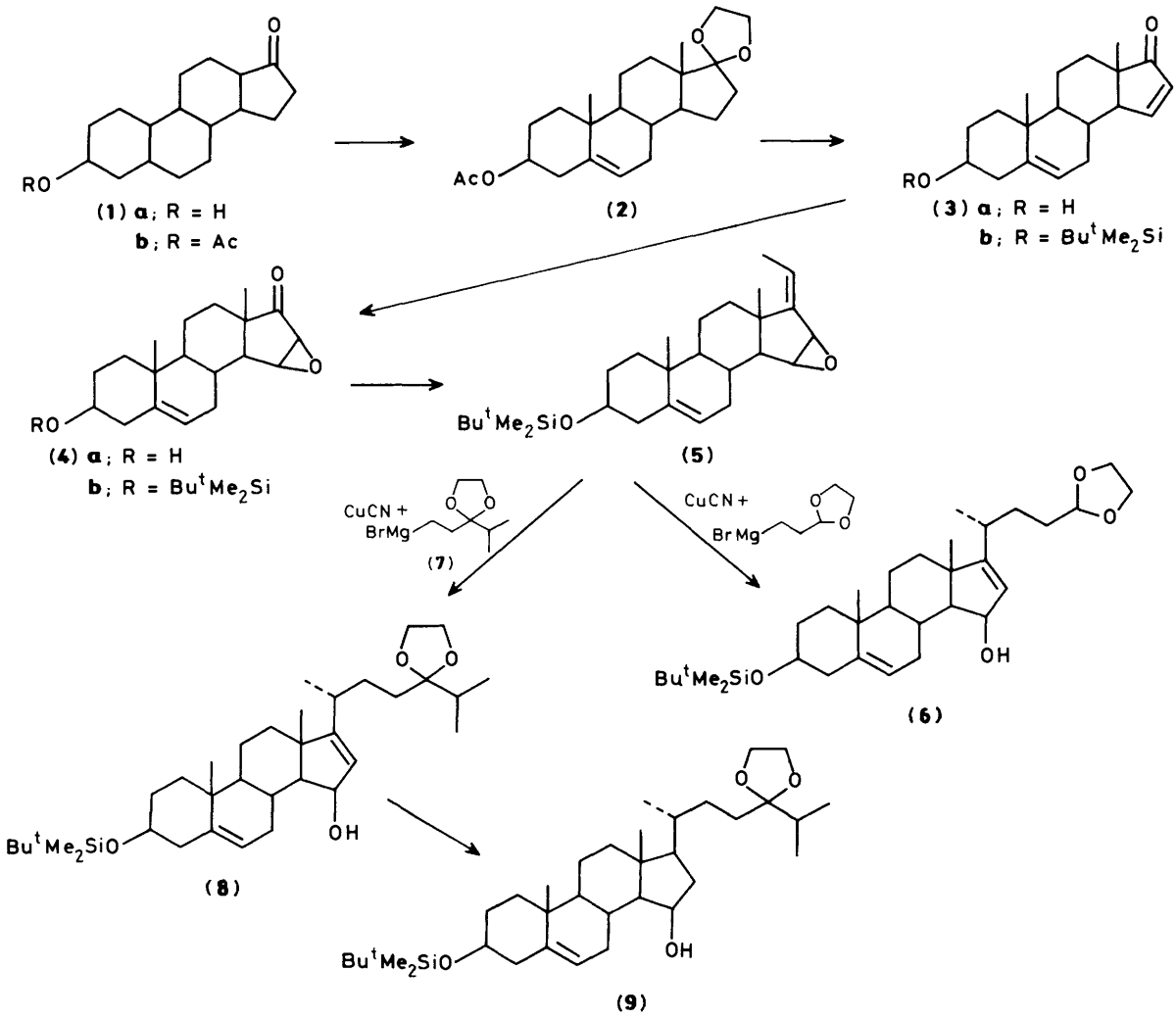
Didehydroepiandrosterone acetate (**1b**) was first converted into the acetal (**2**) in almost quantitative yield by a known procedure.[4] Bromination of the acetal with pyridinium bromide perbromide in tetrahydrofuran (THF) followed by treatment with sodium iodide, then sodium thiosulphate in aqueous pyridine, afforded the 16α-bromo acetal in 90% yield. Dehydrobromination was effected in 78% yield with potassium t-butoxide in dimethyl sulphoxide at 40 °C overnight. Acid-catalysed hydrolysis then gave 3β-hydroxyandrosta-5,15-dien-17-one (**3a**).[4]

Epoxidation of (**3a**) with 30% hydrogen peroxide and 4M sodium hydroxide[1] was not entirely satisfactory since appreciable amounts of side products, resulting from opening of the epoxide ring, were obtained. Also, when the reaction was carried out at room temperature some α-epoxide was formed in addition to the desired β-epoxide. However, when a solution of (**3a**) in pyridine was treated with a slight excess of sodium hypochlorite at room temperature for 36 h, n.m.r. analysis indicated that only the β-epoxide was formed.[5] This compound was then converted into the *O*-dimethyl(t-butyl)silyl derivative in a yield of 50% for the two steps. Alternatively, the enone (**3a**) was converted into the silyl derivative before epoxidation.

A Wittig reaction of (**4b**) with the ylide generated from ethyltriphenylphosphonium bromide with lithium di-isopropylamide (LDA) in tetrahydrofuran furnished the (*E*)-alkylidene epoxide (**5**) in 80% yield. Compound (**5**) was isolated by recrystallisation from hexane since it decomposed on attempted purification by silica gel chromatography. The instability of (**5**) has been noted recently by Tsuji and his co-workers.[6] Furthermore, although only the *E*-isomer was isolated when the reaction was performed at 0 °C, some of the *Z*-isomer was also obtained when the reaction temperature was raised quickly above 0 °C after addition of the ylide to the epoxy ketone.

We planned to construct the didehydro-oogoniol side chain in stepwise fashion from the intermediate alkylidene epoxide (**5**). Thus the readily available 2-(2-bromoethyl)-1,3-dioxolane was treated with t-butyl-lithium at −78 °C to exchange the halogen for lithium, and the product was added to butylethynylcopper to generate the mixed cuprate. The steroid intermediate (**5**) dissolved in ether was then added, and the reaction of the two afforded the pure 1,4-adduct (**6**) in 70% yield. However, this reaction proved to be capricious and the yield was not reproducible. Attempts to carry out the reaction with the lithium cyanocuprate gave similar results. The magnesium cyanocuprate was prepared more readily and we were delighted to obtain a high yield of the 1,4-adduct routinely. The reason for the difficulty encountered with the lithium cuprates is not clear, but it may have been incomplete halogen–metal exchange. In preparing the Grignard reagent, it was necessary to filter the bromo compound through a short column of alumina (activity I) immediately before treatment with magnesium.

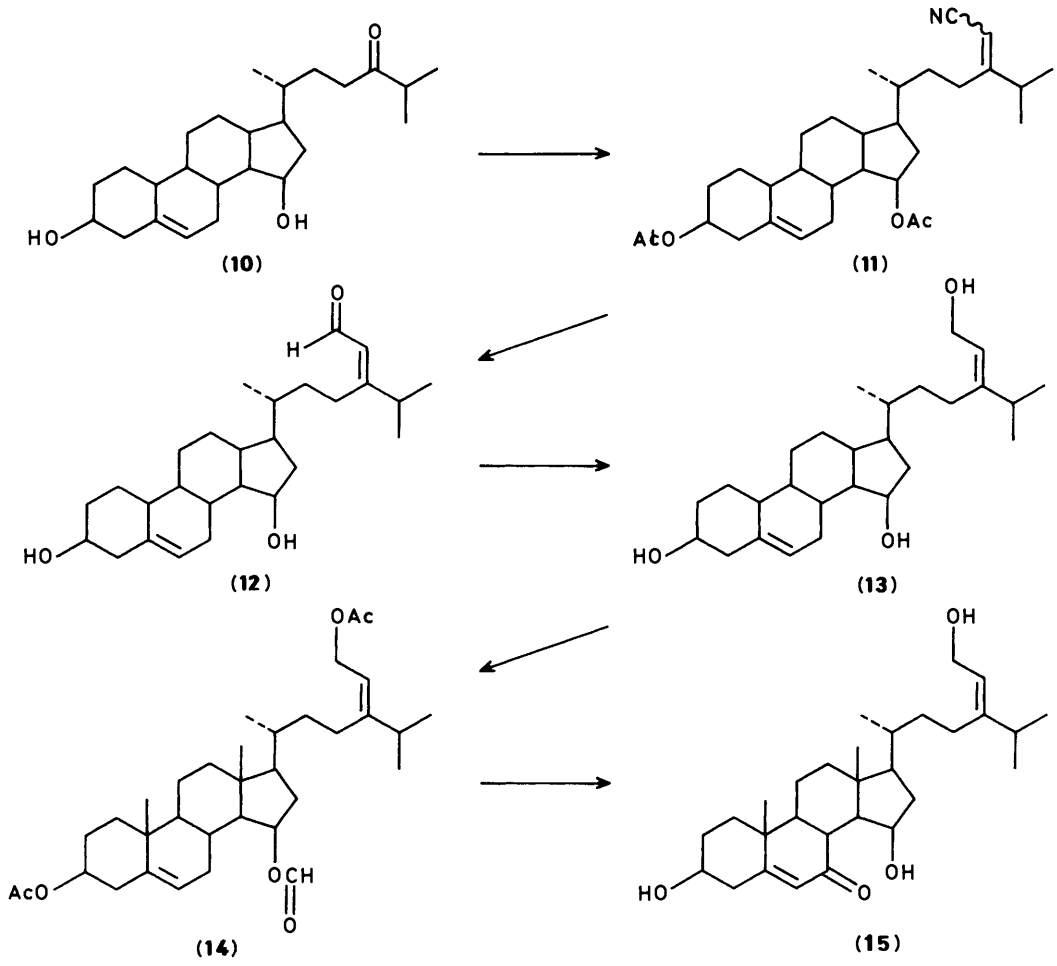
Having succeeded in adding a three-carbon chain, we proceeded to prepare 2-(2-bromoethyl)-2-isopropyl-1,3-dioxolane (**7**) from ethyl 4-methyl-3-oxopentanoate. The latter was converted into the acetal, after which the ester was reduced to the alcohol with lithium aluminium hydride. Mesylation followed by treatment with lithium bromide gave (**7**) in about 50% overall yield from the starting ester. The magnesium cyanocuprate prepared from (**7**) reacted with the alkylidene epoxide



(**5**) to give an 80% yield of the desired 1,4-adduct (**8**). Regioselective hydrogenation of (**8**) over platinum on carbon gave an almost quantitative yield of the dihydro compound (**9**), which on hydrolysis afforded 15β-hydroxy-24-oxocholesterol (**10**). The ^{1}H n.m.r. spectrum of (**10**) showed a doublet at δ 0.92 (21-H), expected for the natural 20*R*-configuration. The signal for the 21-H in the 20*S*-isomer would be expected at higher field, δ *ca.* 0.84.[7] This configuration was confirmed by converting the intermediate (**9**) into the 6α-alcohol with BH_3–THF followed by hydrogen peroxide and sodium hydroxide. After removal of the silyl and acetal groups, the compound was oxidized to the 3,6,15,24-tetraketone. Wolff-Kishner reduction of the latter gave a product the n.m.r. spectrum of which closely resembled that of authentic 5α-cholestane. [A similar series of reactions was carried out with cholesterol, *i.e.* conversion into 5α-cholestane-3,6-dione followed by Wolff-Kishner reduction, to give a product identical (n.m.r.) with authentic 5α-cholestane.] The cholestane derived from the tetraketone was therefore examined by g.l.c. It showed one major peak with the same retention time as authentic 5α-cholestane and a minor peak (about one tenth the area of the major peak) with slightly shorter retention time. G.l.c. of the tetraketone itself gave similarly a major and a minor peak. The identity of the minor peak was not determined. It might have been due to the C-20 epimer of (**10**) formed in the Grignard reaction with the alkylidene epoxide, indicating that the reaction of the magnesium cyanocuprate was not completely stereoselective.

Completion of the synthesis involved acetylation of (**10**) followed by Horner-Emmons reaction with diethyl cyanomethylphosphonate to give the nitrile (**11**) as a mixture of isomers (*E*:*Z* 4:1). The nitrile was converted into the allylic aldehyde (**12**) by reduction with (DIBAL-H) followed by hydrolysis, and further reduction of the aldehyde with DIBAL-H gave the triol (**13**). The *E*- and *Z*-isomers of the aldehyde were readily distinguished in the n.m.r. spectrum.

In order to convert the triol (**13**) into 15β,29-dihydroxy-7-oxofucosterol, it was first acetylated and the triacetate was oxidized with chromium trioxide–3,5-dimethylpyrazole in dichloromethane to give a good yield of the 7-ketone. Treatment of the product with K_2CO_3 in aqueous methanol resulted in hydrolysis of the 3β- and 29-acetates, but not the 15β-acetate. More forcing conditions (dilute KOH in methanol at 45 °C) caused extensive elimination of the 3β-hydroxy group. This problem was overcome by converting the triol into the 3β,29-diacetate by short treatment (1 h) with acetic anhydride–pyridine. The less reactive 15β-hydroxy group was then formylated with formic acetic anhydride (a small amount of the 3,15,29-triacetate was also formed). Oxidation of the diacetate formate (**14**) gave the 7-ketone, which was smoothly converted into the target compound (**15**) with K_2CO_3 in aqueous methanol. A by-product was the corresponding 15β-acetate, which was not hydrolysed under these conditions. The two compounds were well separated by h.p.l.c. on μ-Bondapak C18 with 55% methanol–water as eluant.



Experimental

M.p.s were determined with a Kofler hot-stage apparatus. Spectra were obtained on the following instruments: Varian EM 390, (^{1}H n.m.r., 90 MHz); General Electric QE-300 console with an Oxford magnet and a Nicolet computer system (^{1}H n.m.r. 300 MHz; ^{13}C n.m.r., 75.48 MHz); Perkin-Elmer 1330 i.r. spectrophotometer; UVikon 819 Kontron u.v. spectrophotometer. ^{1}H N.m.r. spectra were taken for solutions in $CDCl_3$ with Me_4Si as internal standard. High resolution mass spectra were determined at the University of Minnesota Mass Spectrometry Service Laboratory and microanalyses were carried out by Galbraith Laboratories Inc., Knoxville, Tennessee.

Unless otherwise indicated, all solvents and reagents were of commercial grade. Dry tetrahydrofuran (THF) was obtained by heating the liquid at reflux, under nitrogen, in a recirculating still over potassium. Pyridine was distilled from sodium hydroxide. All reactions using water-sensitive reagents were carried out in flame-dried glassware under argon or nitrogen. In work-up, the drying agent ($MgSO_4$) was removed by filtering the mixture through a sintered glass funnel, and the solvent was then removed under reduced pressure.

Column chromatography was carried out with silica gel 60 (70—230 mesh or finer than 200 mesh; EM Laboratories, Elmsford, N.Y.). Analytical t.l.c. was carried out on Merck 60 F-254 silica gel plates. Reactions were routinely monitored by t.l.c.

3β-*Acetoxy*-17-*ethylenedioxyandrost*-5-*ene* (**2**).—Toluene-*p*-sulphonic acid (476 mg, 2.50 mmol), 3β-acetoxyandrost-5-en-17-one (**1b**) (25 g, 75.7 mmol), ethylene glycol (14.3 ml, 260 mmol), and triethyl orthoformate (35.7 ml, 214 mmol) were stirred together at 90 °C and refluxed under anhydrous conditions. After 1 h, the solvent was slowly distilled off and the distillation was continued until the temperature of the mixture reached 110 °C. The hot mixture was poured cautiously into hot methanol (285 ml) containing pyridine (4 ml). Water (72 ml) was then added and the solution allowed to cool slowly to room temperature. The crystals were filtered off and dried to give the acetal (**2**) (27 g, 96%), m.p. 142 °C (lit.,[4] 143—144 °C); δ_H 0.86 (s, 3 H), 1.03 (s, 3 H), 2.03 (s, 3 H), 3.75—4.05 (m, 4 H, 17-acetal), 4.48—4.73 (m, 1 H), and 5.38 (br d, 1 H, *J* 4.5 Hz); δ_C 170.34, 139.45, 122.24, 119.30, 73.73, 65.03, 64.38, 50.38, 49.73, 45.56, 37.95, 36.85, 36.47, 34.04, 31.97, 31.08, 30.38, 27.60, 22.62, 21.27, 20.29, 19.19, and 14.05; $\nu_{max.}(CH_2Cl_2)$ 2 950, 2 900, and 1 725 cm^{-1}.

3β-*Hydroxyandrosta*-5,15-*dien*-17-*one* (**3a**).—The acetal (**2**) (25 g, 66.8 mmol) was dissolved in freshly distilled anhydrous THF (75 ml). Pyridinium bromide perbromide (50 g, 156 mmol) in THF (75 ml) was added and the resulting mixture stirred for 2 h. Sodium iodide (37.5 g, 250 mmol) was added and stirring continued for 30 min. A solution of sodium thiosulphate (50 g, 201 mmol) in water (75 ml) and pyridine (15 ml) was added and the resulting solution stirred for 2 h. The mixture was diluted with water (150 ml) and the THF evaporated off under reduced pressure. The crystalline material was filtered off, washed well with water, dried and recrystallized from aqueous ethanol to give the 16α-bromo derivative (27.2 g, 90%); δ_H 0.90 (s, 3 H), 1.02 (s, 3 H), 2.03 (s, 3 H), 3.85—4.05 (m, 2 H), 4.10—4.20 (m, 1 H), 4.20—4.30 (m, 1 H), 4.50—4.70 (m, 1 H), 4.50—4.60, (dd, J_1

10.50, J_2 4.50 Hz, 1 H), and 5.36 (br d, 1 H); δ_C 170.27, 139.49, 121.83, 116.62, 73.54, 66.30, 65.97, 65.16, 64.06, 55.18, 49.43, 44.99, 37.87, 36.67, 36.41, 35.28, 31.46, 30.68, 27.51, 21.24, 19.88, 19.16, and 14.31; $\nu_{max.}(CH_2Cl_2)$ 2 940, 2 895, and 1 720 cm^{-1}.

The bromo acetal (25 g, 55 mmol), was dissolved in hot benzene (100 ml) and hot methanol (1 l) was added. The solution was heated to reflux and a solution of potassium hydroxide (20 g, 500 mmol) in water (150 ml) was added. The resulting solution was refluxed for 3 h, then 100 ml of solvent was distilled off and the mixture allowed to cool to room temperature. The product was filtered off, washed with methanol, and dried. Recrystallization from aqueous methanol gave the 3β-hydroxy compound (20.8 g, 92%), m.p. 179—181 °C; δ_H 0.90 (s, 3 H), 1.00 (s, 3 H), 3.45—3.60 (m, 1 H), 3.90—4.10 (m, 2 H), 4.05—4.20 (m, 1 H), 4.20—4.30 (m, 1 H), 4.54 (dd, J_1 8.7, J_2 3.6 Hz, 1 H), and 5.35 (br d, 1 H); δ_C 140.62, 120.85, 116.65, 71.33, 66.29, 65.97, 64.06, 55.25, 49.50, 45.07, 41.97, 36.89, 36.07, 35.27, 31.49, 31.29, 30.68, 30.23, 19.92, 19.23, and 14.31; $\nu_{max.}(CH_2Cl_2)$ 3 600, 3 440, 2 940, and 2 900 cm^{-1}.

The hydroxy compound (9.5 g, 23 mmol) was dissolved in dry dimethyl sulphoxide (120 ml) at 40 °C. Dry potassium t-butoxide (5.5 g, 49 mmol) was added under nitrogen and the mixture left at 40 °C for 15 h. The solution was then poured into dry ether (1 l) and agitated to dissolve any solids. Water was added and the ethereal solution was washed with water followed by saturated brine. The solution was dried ($MgSO_4$) and evaporated to dryness. Recrystallization of the residue from aqueous ethanol gave the diene (6.6 g, 86%), m.p. 157—159 °C; δ_H 0.94 (s, 3 H), 1.05 (s, 3 H), 3.46—3.63 (m, 1 H), 3.79—4.08 (m, 4 H), 5.37 (br d, 1 H), 5.71 (dd, J 3.3 Hz, 1 H), and 6.13 (br d, J 4.8 Hz, 1 H); δ_C 140.97, 136.25, 131.92, 120.89, 119.40, 71.43, 65.09, 63.96, 56.55, 50.43, 49.15, 42.51, 37.34, 36.96, 31.81, 31.61, 29.84, 29.55, 20.46, 19.69, and 16.09; $\nu_{max.}(CH_2Cl_2)$ 3 650, 3 400, 2 930, and 1 600 cm^{-1}.

The diene (10 g, 30.3 mmol) was dissolved in acetone (500 ml). A solution of toluene-*p*-sulphonic acid (500 mg, 2.6 mmol) in water (50 ml) was added, and the resulting solution was kept at 15 °C for 19 h. Water (150 ml) was added and the solution was concentrated to half its volume under reduced pressure. The solid was filtered off, washed well with water, and dried *in vacuo* to give the dienone (**3a**) (8 g, 92%), m.p. 187—190 °C; δ_H 1.09 (s, 3 H), 1.59 (s, 3 H), 3.50—3.60 (m, 1 H), 5.41 (m, 1 H), 6.05 (dd, J 3 and 6 Hz, 1 H), and 7.51 (br d, J 6 Hz, 1 H); δ_C 216.00, 158.51, 141.43, 131.67, 120.12, 71.24, 57.14, 51.09, 50.57, 42.00, 36.83, 36.67, 31.30, 30.45, 28.87, 28.67, 19.98, 19.85, and 19.20; $\nu_{max.}(CH_2Cl_2)$ 3 580, 3 410, 2 900, 2 850, and 1 690 cm^{-1}; $\lambda_{max.}$(MeOH) 230 nm (ε 15 100).

3β-(*Dimethyl-t-butylsilyloxy*)*androsta*-5,15-*dien*-17-*one* (**3b**).—To the dienone (**3a**) (1 g, 3.5 mmol) in dichloromethane (25 ml) were added dimethyl(t-butyl)silyl chloride (1.5 g, 9.7 mmol), dry triethylamine (1.1 ml, 7.9 mmol; distilled from CaH), and 4-dimethylaminopyridine (914 mg, 7.5 mmol). The mixture was stirred at room temperature for 15 h, then added to water (300 ml), and the resulting mixture was extracted with dichloromethane. The organic layer was washed with 10% aqueous NH_4Cl and saturated brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed with chloroform to give pure silylated product (**3b**) in 76% yield; δ_H 1.06 (s, 6 H), 3.20—3.60 (m, 1 H), 5.38 (d, 1 H), 6.03 (dd, J 3 H and 6 Hz, 1 H), and 7.47 (br d, J 6 Hz, 1 H).

15β,16β-*Epoxy*-3β-*hydroxyandrost*-5-*en*-17-*one* (**4a**).—*Method A*. To a solution of 3β-hydroxyandrosta-5,15-dien-17-one (**3a**) (1.44 g, 5 mmol) in t-butyl alcohol (100 ml) at 15—20 °C was added dropwise an ice-cold mixture of 4M NaOH (2.5 ml, 10 mmol) and 30% H_2O_2 (5.67 ml, 50 mmol). The mixture was stirred for 3 h at 15—20 °C. Ether (300 ml) was added and the mixture was vigorously stirred for 10 min. The ethereal layer was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was recrystallized from methanol to yield the product, consisting of the desired β-epoxide (**4a**) and the isomeric α-epoxide in the ratio 9 : 1. The product was purified by chromatography; m.p. 163—165 °C; δ_H 1.06 (s, 3 H), 1.17 (s, 3 H), 3.30 (d, J 2.4 Hz, 1 H, 15-H), 3.36—3.48 (m, 1 H), 3.82 (d, J 2.9 Hz, 1 H, 16-H), and 5.39 (br s, 1 H).

Method B. To a solution of the dienone (**3a**) (2 g, 7.02 mmol) in pyridine (15 ml) was added sodium hypochlorite (Chlorox; 5.25%; 14 ml, 9.93 mmol) and the mixture was stirred at room temperature for 36 h. To the resulting clear, red solution was added sodium hydrogen sulphite (315 mg, 3 mmol), and the solvent was evaporated off under reduced pressure at 85 °C, leaving a brown oil. Water (25 ml) was added to the residue and the aqueous mixture was extracted with ether. The combined ethereal layer was washed with saturated brine, dried ($MgSO_4$), and evaporated, leaving the product β-epoxide (**4a**) and a small amount of pyridine.

3β-(*Dimethyl-t-butylsilyloxy*)-15,16-*epoxyandrost*-5-*en*-17-*one* (**4b**).—*Method A*. To the crude epoxide (**4a**) dissolved in dichloromethane (15 ml) were added dimethyl(t-butyl)silyl chloride (1.2 g, 8 mmol), 4-dimethylaminopyridine (282 mg, 2.3 mmol), and dry triethylamine (1.2 ml, 8.4 mmol) and the mixture was stirred at room temperature for 15 h. More dichloromethane (200 ml) was added and the solution was washed with water and saturated brine, dried ($MgSO_4$), and evaporated. The crude product was chromatographed with 5% ethyl acetate in hexane to give pure (**4b**) (1.44 g, 49%), m.p. 139—140 °C; δ_H 0.064 (s, 6 H), 0.893 (s, 9 H), 1.05 (s, 3 H), 1.17 (s, 3 H), 3.30 (br d, J 4 Hz, 1 H, 15-H), 3.40—3.55 (m, 1 H), 3.81 (br d, J 4 Hz, 1 H, 16-H), and 5.39 (br s, 1 H); δ_C 210.40, 140.07, 116.86, 72.23, 55.56, 53.29, 52.97, 51.11, 42.64, 41.81, 37.01, 36.79, 32.72, 31.82, 30.10, 28.49, 25.80, 19.86, 19.15, 18.81, 18.11, and −4.70; $\nu_{max.}$ 2 930, 2 850, and 1 735 cm^{-1}.

Method B. To a solution of the dienone (**3b**) (312 mg, 0.78 mmol) in pyridine (1 ml) was added sodium hypochlorite (5.25%; 1.5 ml, 1 mmol) and the mixture was stirred at room temperature for 36 h. Ether was added, the solution was washed with aqueous 10% HCl, aqueous $NaHCO_3$, and saturated brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed with 5% ethyl acetate in hexane to give pure (**4b**) (276 mg; 85%), m.p. 139—141 °C.

(17E)-3β-(*Dimethyl-t-butylsilyloxy*)-15β,16β-*epoxypregna*-5,17(20)-*diene* (**5**).—To a solution of dry di-isopropylamine (0.7 ml, 5 mmol) in anhydrous THF (15 ml) at 0 °C under nitrogen BuLi (5 mmol) in hexane was added dropwise. The mixture was stirred at 0 °C for 15 min and then was transferred *via* a cannula to dry ethyltriphenylphosphonium bromide (1.86 g, 5 mmol) suspended in anhydrous THF (15 ml) at 0 °C. (The phosphonium salt was dried over P_2O_5 at 100 °C under vacuum overnight prior to use.) The mixture was stirred for 15 min at 0 °C to give a clear orange-red ylide solution.

The silylated epoxide (**4b**) (0.83 g, 2.131 mmol) in anhydrous THF (10 ml) was added dropwise to the ylide and the mixture was stirred for 1 h at 0 °C and then for 15 h at room temperature under nitrogen. The reaction was quenched with saturated aqueous NH_4Cl and THF was removed under reduced pressure at 30 °C. The residue was extracted with ether and the ethereal layer was washed with saturated brine, dried ($MgSO_4$), and evaporated. The residue was recrystallized from hexane to yield pure alkylidene epoxide (**5**) (0.64 g, 80%), m.p. 191—193 °C; δ_H 0.06 (s, 6 H), 0.89 (s, 9 H), 1.05 (s, 3 H), 1.14 (s, 3 H), 1.75 (d, J 6.9 Hz, 3 H), 3.40—3.60 (m, 1 H), 3.48 (d, J 3.0 Hz, 1 H, 16α-H), 3.60 (d, J 3.0 Hz, 1 H, 15α-H), 5.36 (br s, 1 H), and 5.70 (q, J 6.9 Hz, 1 H, 20-H); δ_C 146.18, 141.94, 121.70, 120.24, 72.38,

58.86, 57.72, 57.04, 51.09, 42.68, 39.31, 37.92, 37.11, 36.73, 31.90, 31.19, 28.09, 25.82, 22.30, 20.81, 19.10, 18.15, 13.40, and −4.68; $\nu_{max.}$ 2 930 and 2 850 cm^{-1}.

(20R)-3β-(*Dimethyl-t-butylsilyloxy*)-24-*ethylenedioxy*-15β-*hydroxychola*-5,16-*diene* (**6**).—*Method A*. A solution of t-butyllithium was standardized by adding it to a solution of 1,3-diphenylpropan-2-one tosylhydrazone (Alfa) (380 mg, 1 mmol) in dry THF (10 ml) at 0 °C, dropwise *via* a syringe until the colour of the solution turned to a light brown (end-point).

A solution of 2-(2-bromoethyl)-1,3-dioxolane (0.13 ml, 1.11 mmol) in anhydrous ether (20 ml) was forced through a short column of alumina (activity I) under argon just prior to use. To this bromide solution at −78 °C was added freshly standardized Bu^{t}Li (2.22 mmol). The solution was stirred for 2 h at −78 °C. The alkyl-lithium solution was transferred *via* a cannula to a clear yellow solution of either butylethynylcopper (162 mg, 1.11 mmol) or copper (I) cyanide (99 mg, 1.11 mmol) in anhydrous ether (5 ml) and hexamethylphosphoric triamide (0.6 ml, 3.30 mmol) at −30 °C, and the resulting solution was stirred for 30 min. A solution of the alkylidene epoxide (**5**) (200 mg, 0.47 mmol) in anhydrous ether (5 ml) was added dropwise, by syringe, to the greenish-yellow cuprate solution at −30 °C, which was then stirred for 2.5 h at −30 °C. The mixture was quenched with ice-cold, saturated aqueous $(NH_4)_2SO_4$ and stirred until the solution turned blue. More ether (25 ml) was added and the ethereal layer was shaken with ice-cold 2% H_2SO_4 in water. The entire mixture was filtered through a Celite pad. The organic layer of the filtrate was washed with aqueous $NaHCO_3$ (4%) and saturated brine, dried ($MgSO_4$), and evaporated and the residue was recrystallized from methanol to yield (**6**) (170 mg, 70%), m.p. 159—161 °C; δ_H 1.02 (d, *J* 6.9 Hz, 3 H), 1.08 (s, 3 H), 1.12 (s, 3 H), 3.40—3.56 (m, 1 H), 3.80—4.00 (m, 4 H), 4.39 (m, 1 H), 4.85 (t, *J* 4.2 Hz, 1 H), 5.35 (br s, 1 H), and 5.55 (d, *J* 3.0 Hz, 1 H, 16-H); δ_C 165.74, 141.72, 123.25, 120.69, 104.58, 73.59, 72.47, 64.77, 59.86, 51.09, 47.14, 42.71, 37.18, 36.82, 35.17, 32.16, 31.92, 30.82, 30.39, 27.54, 25.83, 22.98, 21.78, 20.51, 19.15, 18.16, and −4.00; $\nu_{max.}$ 3 600, 2 920, and 2 850 cm^{-1}.

Method B. A solution of 2-(2-bromoethyl)-1,3-dioxolane (0.1 ml, 0.8 mmol) in dry THF was forced through a column of alumina (activity I) under argon. Most of the THF was removed under reduced pressure and the bromide was added *via* a syringe to magnesium turnings (17 mg, 0.7 mmol) in anhydrous THF (5 ml). The mixture was heated at 45 °C with stirring until all the magnesium turnings had dissolved. The resulting Grignard reagent was added to CuCN (63 mg, 0.69 mmol) in THF (2 ml). The mixture was stirred at room temperature until a deep black colour was observed (about 2 h), then cooled to 0 °C. A solution of the alkylidene epoxide (**5**) (100 mg, 0.23 mmol) in THF (2 ml) was added and the black mixture was stirred at room temperature overnight. Aqueous NH_4Cl was added and the mixture was stirred for 15 min, then filtered through a Celite pad. The THF was distilled off and the residue was extracted with ether and dried ($MgSO_4$). Column chromatography with hexane–ethyl acetate (5:1) yielded an oil, which crystallized from methanol to give pure (**6**) (100 mg, 82%), m.p. 159—161 °C.

Ethyl 3-(1,3-*Dioxolan*-2-*yl*)-4-*methylpentanoate*.—A mixture of ethylene glycol (30 ml) and dry benzene (100 ml) was refluxed (vigorous stirring) and water was azeotropically removed with a Dean-Stark trap. Ethyl 4-methyl-3-oxopentanoate (10 ml, 0.06 mol) and toluene-*p*-sulphonic acid (1.3 g, 6.8 mmol) were added and the mixture was refluxed overnight. The cooled mixture was neutralized with solid $NaHCO_3$. The ethylene glycol layer was separated and the benzene layer was dried ($MgSO_4$) and evaporated. The residue was distilled to give the pure acetal (9.79 g), b.p. 80—81 °C at 0.350 mmHg; δ_H 0.95 (d, *J* 6 Hz, 6 H), 1.27 (t, *J* 7 Hz, 3 H), 1.90—2.30 (m, 1 H), 2.65 (br s, 2 H), 3.80—4.20 (m, 4 H), and 4.13 (q, *J* 6 Hz, 2 H).

3-(1,3-*Dioxolan*-2-*yl*)-4-*methylpentan*-1-*ol*.—$LiAlH_4$ (2.28 g, 0.06 mol) in dry ether (15 ml) was stirred in an ice-bath under nitrogen for 15 min. To this mixture was slowly added dropwise a solution of the foregoing ester in dry ether (5 ml), using a syringe (exothermic reaction). The mixture was stirred for 3.5 h, then quenched with water (1.1 ml), 15% NaOH (1.1 ml) in water, and water (3.3 ml) to yield a greyish precipitate. Dry ether (75 ml) was added and the mixture was stirred vigorously for 10 min. It was then filtered through a pad of Celite. The ether was evaporated off under reduced pressure giving a colourless oil (8.5 g), b.p. 70 °C at 0.20 mmHg; δ_H 0.93 (d, *J* 7 Hz, 6 H), 1.86 (m, 3 H), 2.85—3.15 (m, 1 H, OH), 3.50—3.80 (m, 2 H), and 3.90—4.00 (br s, 4 H, acetal).

3-(1,3-*Dioxolan*-2-*yl*)-4-*methylpentyl Methanesulphonate*.—To a solution of the foregoing crude alcohol (0.06 mol) in dry pyridine (40 ml) at 0 °C under nitrogen was added mesyl chloride (9.29 ml, 0.12 mol) and the mixture was stirred for 7 h at 0 °C. Ether (200 ml) was added to the mixture, which was then washed with water, saturated aqueous $NaHCO_3$, and saturated brine. The ether layer was dried ($MgSO_4$) and evaporated and THF was added to the residue. The insoluble material was removed by filtration and the filtrate evaporated under reduced pressure to give the product as a white solid (8 g) which was unstable at room temperature and was immediately transformed into the bromide; δ_H 0.93 (d, *J* 6 Hz, 6 H), 1.70—2.10 (m, 1 H), 2.10 (t, *J* 8 Hz, 2 H), 2.90 (s, 3 H), 3.93 (br s, 4 H), and 4.30 (t, *J* 7 Hz, 2 H).

3-(1,3-*Dioxolan*-2-*yl*)-4-*methylpentyl Bromide* (**7**).—A solution of the crude methanesulphonate (2 g, 8.4 mmol) in dry THF (100 ml) was added to dry LiBr (5.1 g, 59 mmol) and the mixture was refluxed under nitrogen for 4 h, cooled, and filtered. The filtrate was evaporated to give a yellow oil. This was redissolved in chloroform and washed well with water and saturated brine, and dried ($MgSO_4$). The oily product was chromatographed with 2% ethyl acetate in hexane to yield the bromide (**7**) (1.59 g); δ_H 0.90 (d, *J* 7 Hz, 6 H), 1.60—2.00 (m, 1 H), 2.20 (t, *J* 7 Hz, 3 H), 3.30 (t, *J* 7 Hz, 2 H), and 3.87 (s, 4 H).

(20R)-3β-(*Dimethyl-t-butylsilyloxy*)-15β-*hydroxy*-24-*oxocholesta*-5,16-*diene* 24-*Ethylene Acetal* (**8**).—The experiment was carried out as for the preparation of (**6**) (method B), but with the bromide (**7**) (0.5 ml, 4 mmol), magnesium turnings (72 mg, 3 mmol), CuCN (270 mg, 3 mmol), and (**5**) (380 mg, 0.9 mmol). The yield of product (**8**) after chromatography was 409 mg (80%); m.p. 126—128 °C; δ_H 0.06 (s, 6 H), 0.89 (s, 9 H), 0.92 (d, *J* 6.0 Hz, 6 H), 1.01 (d, *J* 6.9 Hz, 3 H), 1.07 (s, 3 H), 1.12 (s, 3 H), 3.50 (m, 1 H), 3.95 (s, 4 H), 4.45 (m, 1 H), 5.35 (br s, 1 H), and 5.55 (d, *J* 3.0 Hz, 1 H); δ_C 166.32, 141.73, 123.10, 120.69, 113.75, 73.59, 72.47, 65.23, 20.55, and 19.15; $\nu_{max.}(CH_2Cl_2)$ 3 420 and 1 460 cm^{-1}.

(20R)-3β-(*Dimethyl-t-butylsilyloxy*)-15β-*hydroxy*-24-*oxocholest*-5-*ene* 24-*Ethylene Acetal* (**9**).—A solution of compound (**8**) (1.7 g, 3.3 mmol) in ethyl acetate and platinum (10%) on carbon (250 mg) was stirred at room temperature under hydrogen at atmospheric pressure for 8.5 h, during which 45 ml of H_2 was absorbed. The solvent was removed under reduced pressure, giving (**9**) in early quantitative yield as a partly crystalline compound; δ_H 0.06 (s, 6 H), 0.89 (s, 9 H), 0.92 (d, *J* 6.9 Hz, 6 H), 0.95 (s, 3 H), 1.03 (s, 3 H), 3.52 (m, 1 H), 3.95 (s, 4 H), 4.22 (m, 1 H), and 5.35 (br s, 1 H); δ_C 141.60, 120.51, 113.92, 72.48, 70.26, 65.23, 20.85, and 19.18; $\nu_{max.}$ 3 420 and 1 460 cm^{-1}.

15β-*Hydroxy*-24-*oxocholesterol* (**10**).—Compound (**9**) (400 mg) and toluene-*p*-sulphonic acid (100 mg) were dissolved in acetone–water (5:1). The solution was refluxed with stirring for 3 h. Most of the acetone was removed under reduced pressure, the residue was dissolved in ether, and the solution was washed with aqueous $NaHCO_3$, then saturated brine, and dried ($MgSO_4$). Removal of the ether and chromatography of the residue gave the crystalline product (**10**) (320 mg, 95%); m.p. 153—155 °C; δ_H 0.92 (d, *J* 6.6 Hz, 3 H), 0.95 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.10 (s, 3 H), 3.52 (m, 1 H), 4.18 (m, 1 H), and 5.35 (br s, 1 H); δ_C 215.26, 140.75, 121.64, 71.86, 70.73, 20.77, and 19.01; $\nu_{max.}$ 3 400 and 1 710 cm^{-1}; *m/z* 416.3275 (M^+, 3.4%), 398 (69.7), 383 (14.6), 380 (10.2), 365 (23.9), 312 (22.6), 271 (25.6), and 71 (100).

Acetylation of (**10**) with pyridine and acetic anhydride for 48 h gave an almost quantitative yield of the *diacetate*, which was recrystallized from methanol; m.p. 161—163 °C (Found: C, 73.8; H, 9.5. $C_{31}H_{48}O_5 \cdot 0.25CH_3OH$ requires C, 73.8; H, 9.5%).

To the solution of the diacetate (85 mg, 0.17 mmol) in dry THF (4 ml) was added BH_3–THF complex (0.5 mmol) at 0 °C during 10 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 6 h. It was again cooled to 0 °C and water was added to destroy the excess of diborane, followed by aqueous 5% $NaHCO_3$ (3 ml) and H_2O_2 (1 ml). After 15 min, the mixture was allowed to warm to room temperature and stirred for 45 min, then saturated aqueous NaCl was added, the mixture was extracted with $CHCl_3$, and the extract was dried and evaporated. The 6α-hydroxy diacetate was dissolved in 5% KOH–methanol (5 ml) and stirred for 2 days at room temperature. Work-up gave 3β,6α,15β-trihydroxy-24-oxocholestane (65 mg, 88%); δ_H 0.80 (br s, 6 H), 0.90 (br s, 6 H), 1.20 (s, 3 H), 3.10—3.70 (m, 4 H), and 4.10 (m, 1 H).

To the solution of the trihydroxyoxocholestane (63 mg, 0.15 mmol) in dry CH_2Cl_2 (2 ml) was added pyridinium dichromate (246 mg, 0.65 mmol). The mixture was stirred under N_2 for 60 h, then filtered through a short column of silica gel. Removal of the solvent left semi-crystalline 3,6,15,24-tetraoxocholestane (40 mg, 65%); δ_H 0.79 (s, 3 H), 0.97 (s, 3 H), 1.00 (d, *J* 6.0 Hz, 3 H), and 1.10 (d, *J* 6.9 Hz, 6 H); $\nu_{max.}$ 1 745, 1 715, and 1 260 cm^{-1}.

A mixture of the tetraketone (30 mg), K_2CO_3 (240 mg), hydrazine hydrate (85%; 0.5 ml) and triethylene glycol (2 ml) in a condenser-equipped flask was heated at 150 °C for 1 h. The temperature was increased to 220 °C, and the condenser was removed. After 30 min the condenser was replaced and the temperature was kept at 220 °C for a further 5 h. The black mixture was partitioned between hexane and aqueous 10% HCl. The organic layer was washed with aqueous 10% HCl, water, and saturated aqueous $NaHCO_3$, then dried ($MgSO_4$). Removal of the solvent and column chromatography (hexane) of the residue gave the product (20 mg), with i.r. and n.m.r. spectra similar to those of authentic 5α-cholestane.

A sample of pure cholesterol was converted into 3,6-dioxo-5α-cholestane in the same way as described for the tetraketone. Wolff-Kishner reduction of the diketone gave a product the i.r. and n.m.r. spectra of which were identical with those of authentic 5α-cholestane. The cholestane sample from the tetraketone and authentic 5α-cholestane were therefore compared by g.l.c. analysis (1% SE 30 on Chromosorb W). The sample was injected into the column at 200 °C and the temperature was programmed to rise at 2° min^{-1}. The flow rate of He carrier gas was 30 ml min^{-1}. 5α-Cholestane gave a single peak with retention time 3.6 min. The product from reduction of the tetraketone gave a major peak at 3.6 min and a minor peak, one tenth the area of the major peak, at 3.4 min. The tetraketone itself similarly gave two peaks on g.l.c.

3β,15β-*Diacetoxystigmasta*-5,24(28)-*diene*-29-*nitrile* (**11**).—To a suspension of NaH (1.72 mmol) in anhydrous THF (2 ml) was added diethyl cyanomethylphosphonate (425 mg, 2.4 mmol) in THF (2 ml), and the resulting mixture was stirred for 40 min, then cooled to −78 °C. The diacetate of 15β-hydroxy-24-oxocholesterol (100 mg, 0.2 mmol) in THF (2 ml) was added, and the mixture was stirred at room temperature for 3 h, then refluxed for 2 h. After cooling, water was added, THF was removed under reduced pressure, and the residue was taken up in ether, washed with water, and dried ($MgSO_4$). Removal of the ether and chromatography of the residue with hexane–ethyl acetate (5:1) gave the crystalline product (**11**) (81.6 mg, 80%), m.p. 139—141 °C; δ_H 0.92 (s, 3 H), 1.06 (s, 3 H), 1.06 (d, *J* 7.5 Hz, 6 H), 2.00 (s, 3 H), 2.02 (s, 3 H), 4.60 (m, 1 H), 5.00—5.09 (s + m, 2 H), and 5.36 (m, 1 H); $\nu_{max.}$ 2 220 and 1 720 cm^{-1}.

3β,15β-*Dihydroxystigmasta*-5,24(28)-*dien*-29-*al* (**12**).—To a solution of the nitrile (**11**) (750 mg, 1.44 mmol) in dry toluene (20 ml) was added DIBAL-H in hexane (5.6 mmol). The mixture was stirred at room temperature for 150 min, then cooled to 0 °C, and aqueous 7% acetic acid–THF–methanol (1:1:1; 105 ml) was added dropwise over 20 min with vigorous stirring. The mixture was allowed to warm to room temperature, $CHCl_3$ (15 ml) was added, and stirring was continued overnight. Two clear phases formed. Water (140 ml) was added, and the product was extracted with $CHCl_3$ (3 × 20 ml). The combined extract was washed with aqueous $NaHCO_3$ and saturated brine and dried ($MgSO_4$). Removal of the solvent left partly crystalline aldehyde (**12**) (595 mg, 95%); δ_H 1.09 (s, 3 H), 1.11 (s, 3 H), 3.20—3.60 (m, 1 H), 4.10 (m, 1 H), 5.35 (br s, 1 H), 5.77 (d, *J* 8.4 Hz, 0.2 H, *Z*-isomer), 5.83 (d, *J* 8.1 Hz, 0.8 H, *E*-isomer), 9.98 (d, *J* 8.1 Hz, 0.8 H, *E*-isomer), and 10.09 (d, *J* 8.4 Hz, 0.2 H, *Z*-isomer); $\nu_{max.}(CH_2Cl_2)$ 3 420 and 1 650 cm^{-1}. Acetylation with pyridine—acetic anhydride gave the partly crystalline diacetate in nearly quantitative yield.

3β,15β,29-*Trihydroxystigmasta*-5,24(28)-*diene* (**13**).—To a solution of the diacetate of (**12**) (620 mg, 1.18 mmol) in dry toluene (15 ml) was added DIBAL-H in hexane (12 mmol) at 0 °C. The mixture was stirred at room temperature under N_2 for 5 h. Water was added, the mixture was extracted with chloroform, and the extract was dried ($MgSO_4$) and evaporated. The *triol* (**13**) was obtained crystalline from ethyl acetate and was recrystallized from ethyl acetate (yield 420 mg, 80%); m.p. 176—178 °C; δ_H 0.91 (s, 3 H), 0.93 (d, *J* 7 Hz, 6 H), 1.04 (s, 6 H), 2.78 (m, 0.1 H, 25-H of *Z*-isomer), 3.30—3.70 (m, 1 H), 4.15 (br d, *J* 7.0 Hz, 3 H, 15- and 29-H), and 5.35 (br t, *J* 7.0 Hz, 2 H, 6-and 28-H); δ_C 150.33, 140.85, 120.82, 105.3, 70.11, 61.16, 59.34, 55.84, 50.24, 42.13, 40.91, 35.92, 34.47, 31.11, 27.41, 26.24, and 20.84; *m/z* 426.3519 ($M^+ - H_2O$, 24%), 408 (29), 393 (19), 330 (45), and 215 (100); $\nu_{max.}$ 3 450 and 1 600 cm^{-1} (Found: C, 76.6; H, 10.7. $C_{29}H_{48}O_3 \cdot 0.5CH_3CO_2C_2H_5$ requires C, 76.2; H, 10.7%).

The triol (100 mg, 0.23 mmol) was treated with acetic anhydride (3 ml) and dry pyridine (3 ml) at room temperature for 1 h. The 3β,29-diacetate was obtained in nearly quantitative yield; δ_H 0.90 (s, 3 H), 0.91 (s, 3 H), 1.00 (s, 6 H), 1.90 (s, 3 H), 1.92 (s, 3 H), 4.10 (br t, *J* 6.0 Hz, 1 H), 4.50 (br d, *J* 7.0 Hz, 3 H), and 5.22 (m, 2 H).

To the solution of the diacetate in dry pyridine (1.5 ml) was added formic acetic anhydride (1.5 ml) at 0 °C, and the mixture was stirred at room temperature overnight. The 15β-formate 3β,29-diacetate (**14**) was obtained in nearly quantitative yield; δ_H 0.80 (s, 3 H), 0.85 (s, 3 H), 0.95 (s, 6 H), 1.90 (s, 3 H), 1.95 (s, 3 H), 4.50 (br d, *J* 7.0 Hz, 3 H), 5.10—5.40 (m, 3 H), and 7.90 (s, 1 H).

3β,15β,29-*Trihydroxystigmasta*-5,24(28)-*dien*-7-*one* (15β,29-*Dihydroxy*-7-*oxofucosterol*) (**15**).—To a suspension of CrO_3 (920 mg, 9.2 mmol) in dry CH_2Cl_2 (15 ml) at −20 °C, 3,5-dimethylpyrazole (920 mg, 9.2 mmol) was added as quickly as

possible. The resulting deep brown mixture was stirred at −25 to −15 °C for 30 min. Then the solution of the formate diacetate (125 mg, 0.22 mmol) in CH_2Cl_2 (3 ml) was added, and the mixture was stirred under N_2 at −25 to −15 °C for 4.5 h. Aqueous NaOH (20%) was added and the mixture stirred at 0 °C for 1 h and extracted with CH_2Cl_2. The organic layer was washed with aqueous 15% HCl, aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). Column chromatography [ethyl acetate–light petroleum (1:4 initially, ranging to pure ethyl acetate)] gave the crystalline ketone (80 mg, 64%); δ_H 0.82 (s, 3 H), 0.92 (s, 3 H), 1.00 (s, 3 H), 1.26 (s, 3 H), 2.00 (s, 6 H), 4.50 (br d, *J* 7.0 Hz, 3 H), 5.22 (t, *J* 7.0 Hz, 1 H), 5.65 (s, 1 H), 5.70 (m, 1 H), and 7.90 (s, 1 H).

To a solution of the ketone (60 mg, 0.11 mmol) in methanol (4 ml) was added aqueous 10% K_2CO_3 (0.8 ml). The mixture was stirred at room temperature for 20 h. The solvent was removed and the residue was extracted with ethyl acetate and CH_2Cl_2. Removal of the solvent left a solid which on recrystallization from ethyl acetate yielded the *trihydroxy ketone* (**15**) (48 mg, 95%), m.p. 180—182 °C; $\lambda_{max.}$(MeOH) 236 nm (ε 12 000); δ_H 0.90 (s, 3 H), 0.94 (s, 3 H), 0.96 (s, 3 H), 1.12 (s, 3 H), 3.64 (m, 1 H), 4.09 (d, *J* 6.9 Hz, 2 H), 4.50 (m, 1 H), 5.29 (t, *J* 6.9 Hz, 1 H), and 5.72 (s, 1 H); *m/z* 440.3295 (M^+ − water, 9%), 422 (90), 407 (30), 379 (6), 361 (14), 323 (21), and 283 (100); $\nu_{max.}$ 3 600, 3 450, 1 640, and 1 255 cm^{-1}.

H.p.l.c. analysis was performed with a Waters Associates M-45 instrument (30 × 4 cm i.d. prepacked μ-Bondapak C 18 column). The mobile phase was 55% MeOH–water and the flow rate was 2 ml min^{-1} at 2 500 lb in^{-2}. Three peaks with retention times 3 min 5 s, 3 min 35 s, and 5 min 30 s were observed (ratio of areas *ca.* 35:1:3). The major component was determined by n.m.r. to be (**15**) (m.p. 183—184 °C), and the minor component to be the 15β-acetate, which could be distinguished by the chemical shift of the 15-acetate group: δ_H 0.80 (s, 3 H), 0.85 (s, 3 H), 0.90 (s, 3 H), 1.12 (s, 3 H), 1.90 (s, 3 H), 3.50 (br s, 1 H), 4.05 (d, *J* 6.9 Hz, 2 H), 4.40—4.65 (br s, 2 H), 5.20 (t, *J* 6.9 Hz, 1 H), and 5.72 (s, 1 H).

Acknowledgements

This work was supported by grant AM25625 from the National Institutes of Health.

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Received 10*th November* 1987; *Paper* 7/1994