Photoinduced Molecular Transformations. Part 112.[1] Transformation of Steroids into Ring-A-Aromatized Steroids and 19-Norsteroids involving a Regioselective β-Scission of Alkoxyl Radicals; Synthesis of Two Marine Natural Products, 19-Nor-5α-cholestan-3β-ol and 19-norcholest-4-en-3-one, and New Synthesis of Estrone and 19-Nortestosterone[2]

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A new transformation of steroids into 19-norsteroids and ring-A-aromatized steroids is described. The transformation method involves the removal of the 10β-methyl group by a regioselective β-scission of alkoxyl radicals. Cholesterol was transformed into two marine natural products, 19-nor-5α-cholestan-3β-ol and 19-norcholest-4-en-3-one, and into 19-norcholesta-1,3,5(10)-trien-3-ol. Transformations of 3β-hydroxyandrost-5-en-17-one into 19-nortestosterone, estrone, and the related estranes are also described.

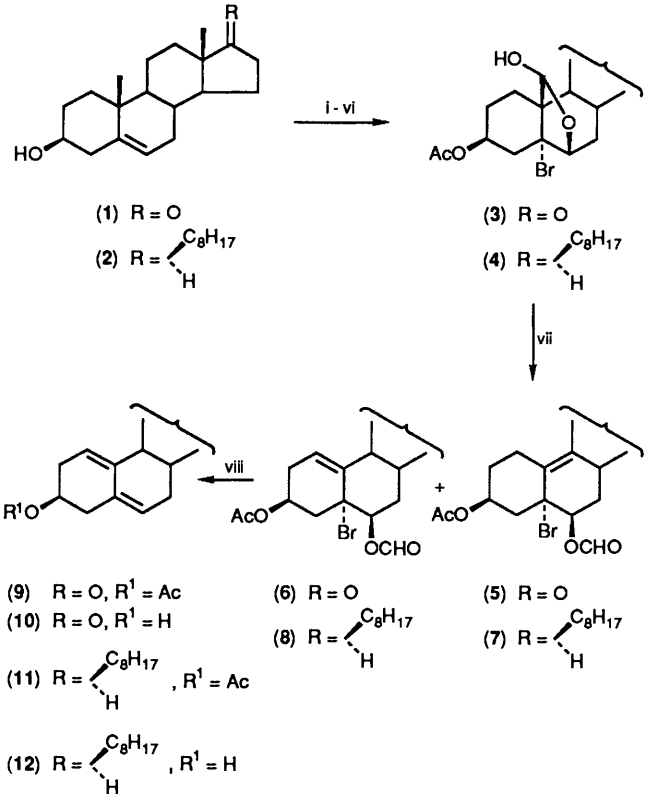
19-Norsteroids occupy a significant position in steroids, since the group contains a number of compounds which have pronounced biological activity and are of importance as gestogens.[3] A variety of 19-norsteroids has also been isolated from marine creatures.[4] A number of methods for the transformation of steroids into their 19-nor derivatives has been reported.[5] Most of these involve an initial functionalization of the inactive 10β-methyl group of steroids, followed by the removal of the functionalized 10β-carbon.

In this paper we report on a new transformation of steroids into 19-norsteroids and into ring-A-aromatized steroids based on the removal of the 10β-methyl group involving a selective β-scission of alkoxyl radicals as the key step. The investigation was carried out as one application of the reactions of alkoxyl radicals to synthetic problems which had extensively been carried out in this laboratory.[6]

Results

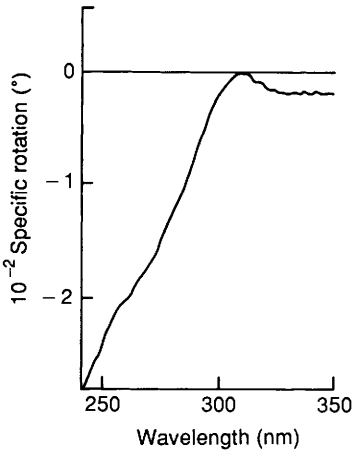
Preparations of 3β-*Hydroxyestra- and -cholesta*-1(10),5-*diene* (**10**) *and* (**12**) *by the Removal of the* 10β-*Methyl Group of the Steroids involving a Regioselective* β-*Scission of Alkoxyl Radicals* (*Scheme* 1).—Commercially available 3β-hydroxyandrost-5-en-17-one (**1**) was transformed into a cyclic hemiacetal (**3**) *via* a 5-step sequence according to the procedure of Akhtar and Barton.[7] The cyclic hemiacetal (**3**) was subjected to our regioselective β-scission through photolysis of the corresponding hypoiodite to give a 5:1 mixture of 5-bromo-17-oxo-5α-estr-9-ene-3β,6β-diol 3-acetate 6-formate (**5**) and 5-bromo-17-oxo-5α-estr-1(10)-ene-3β,6β-diol 3-acetate 6-formate (**6**) in 74% yield. A mixture of these two formates (**5**) and (**6**) was then subjected to reductive elimination by treatment with zinc in acetic acid[8] at 100–120 °C for 0.5 h to give 17-oxoestra-1(10),5-dien-3β-yl acetate (**9**)[9] in 89% yield. The acetate (**9**) was then subjected to hydrolysis with potassium hydroxide in a mixture of methanol and ethanol at room temperature for 4 h to give the corresponding crystalline 3β-ol (**10**) in 78% yield.

Cholesterol (**2**) was then similarly transformed into a dienol (**12**). Thus, the cyclic hemiacetal (**4**) derived in 5 steps from cholesterol (**2**) according to Barton's procedure[7] gave a 5:1 mixture of 5-bromo-19-nor-5α-cholest-9-ene-3β,6β-diol 3-acetate 6-formate (**7**) and 5-bromo-19-nor-5α-cholest-1(10)-ene-3β,6β-diol 3-acetate 6-formate (**8**) in 75% yield *via* selective β-scission of the alkoxyl radical. A reductive elimination of a mixture of the two formates (**7**) and (**8**) in acetic acid with zinc under the conditions used for the androstane series gave 19-norcholesta-1(10)-dien-3β-yl acetate (**11**)[10] in 89% yield; hydrolysis of this product with potassium hydroxide at room temperature for 4 h gave the corresponding crystalline 3β-ol (**12**) in 67% yield.



Scheme 1. *Reagents and conditions:* i, Ac_2O–pyridine; ii, NBS–$HClO_4$–dioxane; iii, NOCl–pyridine; iv, *hv*, toluene or 1:1 MeOH–PhH; v, $(Me)_2CHOH$, neat; vi, $NaNO_2$–AcOH–dioxane; vii, HgO–I_2–PhH, *hv*; viii, Zn–AcOH, neat.

Synthesis of Estrone (**14**) *and* 19-*Norcholesta*-1,3,5(10)-*trien*-3-*ol* (**15**) *from the Dienes* (**10**) *and* (**12**) (*Scheme* 2).—Oxidation of



dienes (**10**) and (**12**) with pyridinium chlorochromate (PCC)[11] in dichloromethane, with chromium(VI) oxide–H_2SO_4–acetone (the Jones reagent), or with aluminium alkoxides in acetone (the Oppenauer oxidation) failed to aromatize their A-ring. Irradiation of the diene pyruvates[12] also failed to give the ring-A-aromatized steroids. Oxidation of dienol (**10**) in dichloromethane with dimethyl sulphoxide–trifluoroacetic anhydride (TFAA) at −78 °C according to the procedure devised by Swern,[13] however, successfully gave estrone (**14**)[14] and 17-oxoestra-1(10),5-diene-3β-yl trifluoroacetate (**13**) in 53 and 20% yield, respectively. Swern oxidation of dienol (**12**) similarly gave 19-norcholesta-1,3,5(10)-trien-3-ol (**15**)[15] in 35% yield.

Transformation of Dienol Acetate (**11**) *into* 19-*Nor*-5α-*cholestan*-3β-*ol* (**20**), *a Marine Natural Product, its* 10-*Epimer* (**19**), *and* 19-*Norcholest*-4-*en*-3-*one* (**30**) (*Scheme* 2).—A number of 19-norsteranols, including 19-nor-5α-cholestan-3β-ol (**20**), have been found to be the constituents of a sponge, *Axinella polypoides*.[4a,4b] 19-Norcholest-4-en-3-one (**30**), synthesized from cholesterol *via* 7 steps by Tanabe *et al.* in 1967,[16] has recently been isolated as a constituent of the Californian gorgonian, *Muricea californica*, by Djerassi[4c] who synthesized this enone by Oppenauer oxidation of 19-norcholesterol.[4c]

The dienol acetate (**11**) is an excellent starting material for the synthesis of these marine steroids. Thus, catalytic hydrogenation of dienol acetate (**11**) in glacial acetic acid with platinum as catalyst gave a mixture of 19-nor-5α,10α-cholestan-3β-yl acetate (**16**), 19-nor-5α-cholestan-3β-yl acetate (**17**), and a small amount of some 19-norsteroids devoid of the 3β-acetoxy group. Treatment of a mixture of acetates (**16**) and (**17**), isolated by preparative TLC (PLC), with potassium hydroxide in ethanol at room temperature for 1 h resulted in a selective hydrolysis of the 3β-acetoxy group of the A/B *trans* acetate (**17**) to give 19-nor-5α,10α-cholestan-3β-yl acetate (**16**) (52%) as well as the corresponding 3β-ol (**19**) (3%) and 19-nor-5α-cholestan-3β-ol (**20**) (22%). The m.p. and mass and ^{1}H NMR spectral data of this 19-norsteroid were in agreement with those of 19-nor-5α-cholestan-3β-ol isolated from the sponge *Axinella polypoides*.[4a,4b] The stereochemistry of the A/B ring junctions of isomeric 3β-ols (**19**) and (**20**) was determined by means of the ORD and CD curves, as assigned. Oxidation of 3β-ols (**19**) and (**20**) with PCC, respectively, gave the corresponding 3-ones (**28**) and (**29**). The ORD curve (Figure) of ketone (**28**) in methanol was quite different from that of 5β-cholestan-3-one,[17] as has already been reported for 5α,10α-estran-3-one,[18] and the CD curve showed a positive Cotton effect. The ORD curve of ketone (**29**) showed a positive Cotton effect at 306 nm, a result parallel with the reported ORD of 5α-cholestan-3-one.[19] The CD spectrum indicated a positive Cotton effect at 287.5 nm.

Catalytic hydrogenation of dienol acetate (**11**) in ethyl acetate with 10% Pd–C as catalyst, however, gave 19-norcholest-5(10)-en-3β-ol acetate (**18**) as the major product with accompanying formation of 19-nor-5α,10α-cholestan-3β-yl acetate (**16**), and 19-nor-5α,10β-cholestan-3β-ol acetate (**17**). Treatment of this mixture with methanolic potassium hydroxide at room temperature for 24 h gave a product which was subjected to PLC to give 19-norcholest-5(10)-en-3β-ol (**21**)[16] (37%), acetate (**16**) (22%), 19-nor-5α,10α-cholestan-3β-ol (**19**) (2%), and its 10β-epimer (**20**) (8%). Oxidation of 19-norcholest-5(10)-en-3β-ol (**21**) with PCC gave 19-norcholest-4-en-3-one (**30**) in 33% yield.

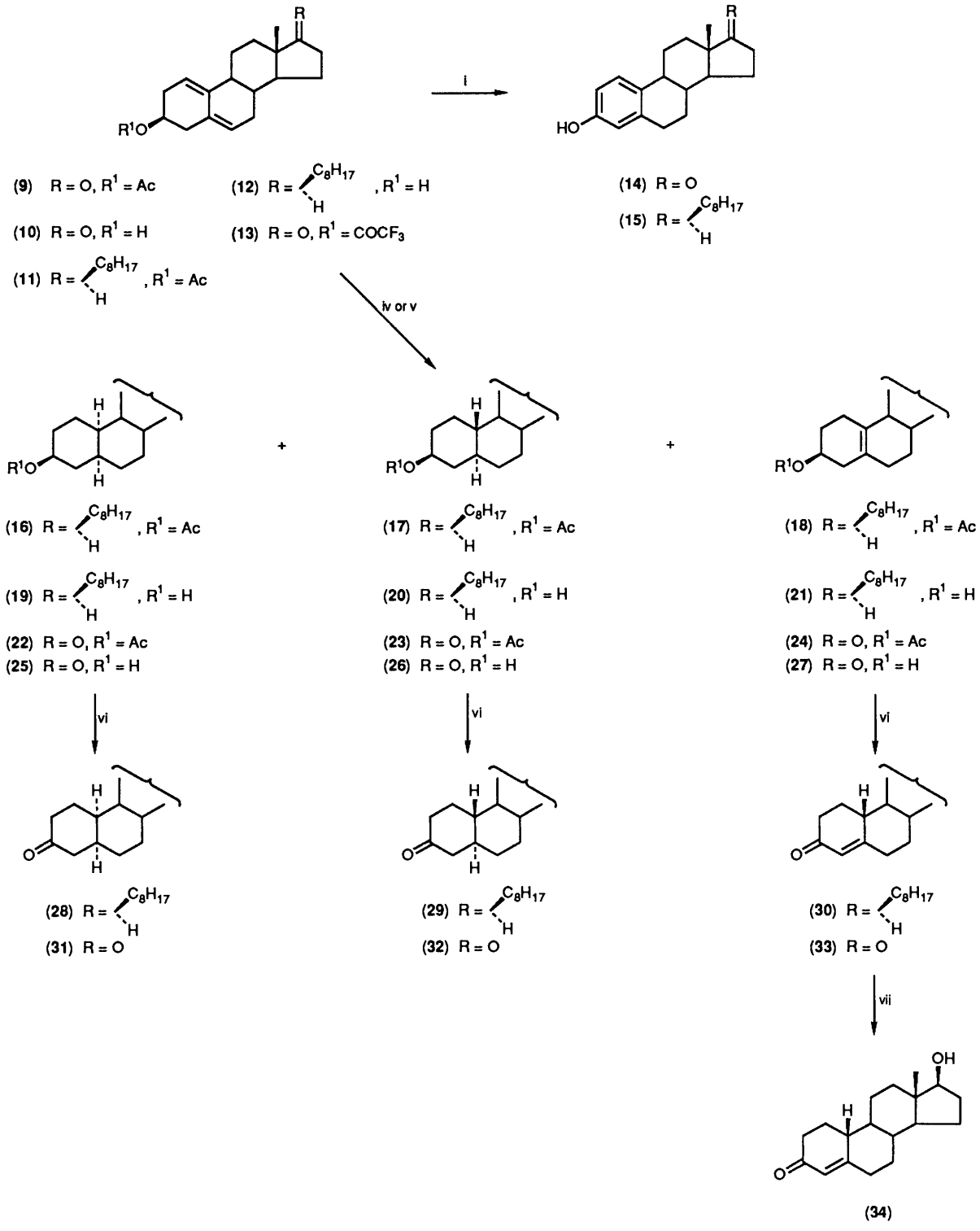
Transformations of Dienol Acetate (**9**) *into* 5α,10α-*Estran*-17-*ones and* 19-*Nortestosterone* (*Scheme* 2).—Several estranes and 19-nortestosterone (**34**)[20] can be obtained from dienol acetate (**9**). Thus, catalytic hydrogenation of dienol acetate (**9**) with 10% Pd–C as catalyst resulted in nearly parallel results to those in the hydrogenation of dienol (**12**) and gave three 3β-hydroxyestrane acetates: (**22**), (**23**), and (**24**). The mixture was subjected to hydrolysis with methanolic potassium hydroxide to give a mixture of 3β-hydroxyestranes (**25**), (**26**), and (**27**). The mixture was then subjected to PLC to separate 3β-hydroxy-5α,10α-estran-17-one (**25**)[21] (30%) and a mixture of 3β-hydroxy-5α-estran-17-one (**26**) and 3β-hydroxyestr-5(10)-en-17-one (**27**). This mixture was then oxidized with PCC in dichloromethane to give a mixture of 5α-estrane-3,17-dione (**32**)[19,22] and estr-4-ene-3,17-dione (**33**).[16] The two diones (**32**) (15%) and (**33**) (12%) were separated by PLC. 5α-Estrane-3,17-dione (**32**) has been obtained by oxidation of 17β-hydroxy-5α-estran-3-one which was prepared by the reduction of 19-nortestosterone with lithium and liquid ammonia.[19] A similar oxidation of 3β-ol (**25**) with PCC gave 5α,10α-estrane-3,17-dione (**31**).[21] The *cis*-dione (**31**) has been synthesized by catalytic hydrogenation of estrone or estradiol over a ruthenium catalyst, followed by oxidation of the resulting 5α,10α-estrane-3β,17β-diol.[18,21] The selective reduction of the 17-carbonyl group of 3,17-dione (**33**) with sodium borohydride in dichloromethane–methanol gave 19-nortestosterone (**34**) in 75% yield.

Experimental

M.p.s were recorded with a Yanagimoto m.p. apparatus. IR spectra were determined for Nujol mulls with a JASCO IR 810 IR spectrophotometer, unless stated otherwise. The ^{1}H NMR spectra were determined with a JEOL JNM-FX 270 spectrometer (270 MHz) (Faculty of Pharmaceutical Sciences of this University) or with a Hitachi R-90H spectrometer (90 MHz) for solution in $CDCl_3$ with $SiMe_4$ as internal reference. TLC was carried out on Merck Kieselgel 60-PF_{254}. The high- and low-resolution mass spectra were determined with a JEOL JMS-300 spectrometer (70 eV) (Faculty of Pharmaceutical Sciences of this University). Elemental analyses were performed at the analytical Laboratory of the Faculty of Pharmaceutical Sciences. The ORD and CD spectra were determined with a JASCO J-20A (Faculty of Agriculture of this University). Light petroleum refers to the fraction boiling in the range 30–70 °C.

5-*Bromo*-3β,19-*dihydroxy*-6β,19-*epoxy*-5α-*androstan*-17-*one* 3-*Acetate* (**3**).—This hemiacetal was prepared from 3β-hydroxyandrost-5-en-17-one (**1**) according to a procedure reported by Akhtar and Barton.[7] δ(270 MHz) 0.88 and 0.93 (3 H, s, 18-H_3 of the two isomers), 2.03 (3 H, s, OAc), 2.72 (1 H, dd, *J* 13.2 and 11.4 Hz, 4β-H), 3.32 (1 H, br d, *J* 4 Hz, OH), 4.20 and 4.30 (each 1 H, each d, *J* 4.5 Hz, 6α-H of the two isomers), 5.29 and 5.85 (each 1 H, each d, *J* 4 Hz, 19-H of the two isomers), and 5.15–5.40 (1 H, m, 3α-H).

Photoreaction of Hypoiodite of Lactol (**3**).—A solution of



Scheme 2. *Reagents:* i, DMSO–TFAA–Et_3N–CH_2Cl_2; ii, H_2–PtO_2–AcOH–Et_2O; iii, H_2–PtO_2–AcOH–Et_2O then KOH–MeOH; iv, H_2–Pd/C, AcOEt; v, H_2–Pd/C, AcOET then KOH–MeOH; vi, PCC–CH_2Cl_2; vii, $NaBH_4$–CH_2Cl_2–MeOH.

lactol (**3**) (280 mg, 0.63 mmol) in benzene (32 ml) containing mercury(II) oxide (275 mg, 1.27 mmol) and iodine (322 mg, 1.27 mmol) was flushed with nitrogen. The solution was irradiated with Pyrex-filtered light generated by a 100-W high-pressure mercury arc lamp for 3 h and 45 min. The solution was filtered and the filtrate was washed successively with 5% aq. sodium thiosulphate and then with saturated brine, and was dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was subjected to PLC [silica gel; benzene–diethyl ether (1:1)] to give a 7:1 mixture of formates (**5**), and (**6**) (208 mg, 74%), ν_{max}(neat) 1 739 and 1 720 (OAc and OCHO), 1 369, 1 241, and 1 164 cm^{-1}; δ(270 MHz) 0.91 [3 H, s, 18-H_3 of 1(10)-ene], 0.93 (3 H, s, 18-H_3 of 9-ene), 2.05 (3 H, s, OAc), 5.09 (1 H, m, 3α-H), 5.27 (1 H, br s, 1-H of 1(10)-ene], 8.13 (1 H, s,

OCHO), and 8.17 (1 H, s, OCHO); *m/z* 440 (M^+, 0.19%), 438 (M^+, 0.19), 254 [$(M - Br - OCHO - AcOH)^+$, 100], and 104 (44).

Reductive Elimination of Formates (**5**) *and* (**6**) *with Zinc in Glacial Acetic Acid.*—A mixture of formates (**5**) and (**6**) (157 mg, 0.36 mmol) in glacial acetic acid (6.4 ml) containing zinc powder (321 mg, 4.91 mmol) was heated under reflux for 1 h. After an additional amount of zinc (30 mg, 0.46 mmol) was added, the solution was heated under reflux for 15 min. The solution was filtered and diethyl ether was added to the filtrate. The solution was washed successively with 5% aq. sodium hydrogen carbonate, water, and saturated brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was subjected to PLC [silica gel; benzene–diethyl ether (4:1)] to give the diene (**9**) (100 mg, 89%), m.p. 86–92 °C (from MeOH), [lit.,[9] 115 °C (from benzene–diethyl ether)] (Found; C, 76.3; H, 8.4. Calc. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33%); ν_{max}(Nujol) 1 743 and 1 728 cm^{-1} (OAc, C=O), 1 692, and 1 242 cm^{-1}; δ(270 MHz) 0.89 (3 H, s, 18-H_3), 2.05 (3 H, s, OAc), 5.01 (1 H, m, 3α-H), 5.42 (1 H, br s, 1-H), and 5.51 (1 H, br d, *J* 5.86 Hz, 6-H); *m/z* 314 (M^+, 2.4%), 270 (15.4), 254 [$(M - AcOH)^+$, 100], and 104 (75).

Hydrolysis of Diene (**9**).—To a solution of the diene acetate (**9**) (100 mg, 0.32 mmol) in ethanol (2 ml) was added potassium hydroxide (18 mg, 0.32 mmol) in methanol (3 ml) and the solution was stirred for 4 h. The solvent was evaporated off to give a product, which was dissolved in diethyl ether. The solution was then washed successively with 2M hydrochloric acid, water, and saturated brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was subjected to PLC [silica gel; benzene–diethyl ether (1:1)] to give the 3β-*ol* (**10**) (68 mg, 78%). An analytical sample was obtained by recrystallization from hexane–acetone, m.p. 134.5–135.5 °C (Found: M^+, 272.1786. $C_{18}H_{24}O_2$ requires *M*, 272.1777); ν_{max}(Nujol) 3 498 (OH), 1 733 (C=O), 1 220, 1 076, and 1 061 cm^{-1}; δ(270 MHz) 0.89 (3 H, s, 18-H_3), 3.9–4.2 (1 H, m, 3α-H), 5.41 (1 H, br s, 1-H), and 5.58 (1 H, br d, *J* 5.5 Hz, 6-H); *m/z* 272 (M^+, 100%), 254 [$(M - H_2O)^+$, 19], 197 (22), and 129 (20).

Synthesis of Estrone (**14**).—A mixture of dimethyl sulphoxide (DMSO) (24 ml) and dichloromethane (135 ml) was stirred at −78 °C (solid CO_2–MeOH) for 30 min. To this solution was added a solution of the diene (**10**) (20 mg, 0.074 mmol) in dichloromethane (500 ml) during 5 min. After the solution had been stirred for 100 min, triethylamine (68 ml) was added and the solution was stirred for another 30 min at −78 °C. The temperature of the stirred solution was then raised to room temperature and water was added. The solution was extracted with dichloromethane (× 3). The combined organic layers were washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was subjected to PLC [silica gel; benzene–diethyl ether (2:1)] to give three fractions in order of mobility on the TLC plate. The most mobile fraction A (5.3 mg, 20%) was 17-*oxo*-19-*norandrost*-1(10),5-*dien*-3β-*yl trifluoroacetate* (**13**), m.p. 108–111 °C (from MeOH) (Found: M^+, 368.1588. $C_{20}H_{23}F_3O_3$ requires *M*, 368.1599); ν_{max}(Nujol) 1 781 ($OCOCF_3$), 1 739 (C=O), 1 220, and 1 173 cm^{-1}; δ(270 MHz) 0.90 (3 H, s, 18-H), 5.19–5.27 (1 H, m, 3α-H), 5.41 (1 H, br s, 1-H), and 5.57 (1 H, br d, *J* 5.49 Hz, 6-H); *m/z* 368 (M^+, 26%), 254 [$(M - CF_3CO_2H)^+$, 100], and 104 (83).

The next mobile fraction (5.9 mg, 30%) was estrone (**14**), which was identical with an authentic specimen in every respect.

The most polar fraction (4.8 mg, 24%) was the starting diene. The yield of estrone based on the converted diene was 40%.

5-*Bromo*-3β,19-*dihydroxy*-6β,19-*epoxy*-5α-*cholestane* 3-*Acetate* (**4**).—5-Bromo-19-hydroxyimino-5α-cholestane-3β,6β-diol 3-acetate, prepared according to the procedure reported by Akhtar and Barton,[7] was converted into the lactol (**4**) as described for the preparation of lactol (**3**). The crude lactol (**4**) was purified by PLC [silica gel; benzene–diethyl ether (3:1)] to give the *pure lactol* (**4**) (980 mg, 87%), m.p. 160–162 °C (from hexane–acetone) (Found: C, 64.5; H, 8.9; Br, 14.8. $C_{29}H_{47}BrO_4$ requires C, 64.55; H, 8.78; Br, 14.81%); ν_{max}(Nujol) 3 380 (OH), 1 738 (C=O), 1 242, 1 167, 1 130, 1 094, and 1 035 cm^{-1}; δ(270 MHz) 0.66 and 0.71 (each s, 18-H_3), 2.03 (3 H, s, OAc), 2.70 (1 H, dd, *J* 11.35 and 13.19 Hz, 4β-H), 4.14 and 4.24 (each 0.5 H, each d, *J* 4.4 Hz, 6α-H), 5.29 (1 H, m, 3α-H), 5.28 and 5.81 (each 0.5 H, each d, *J* 4 and 5 Hz, 19-H); *m/z* 413 [$(M - OH - Br - CHO)^+$, 3.3%], 3.70 [$(M - Br - CHO - AcOH)^+$, 18.8], and 353 [$(M - OH - Br - CHO - AcOH)^+$, 100].

Photoreaction of Hypoiodite of Lactol (**4**).—A solution of lactol (**4**) (250 mg, 0.46 mmol) in benzene (28 ml) containing mercury(II) oxide (201 mg, 0.93 mmol) and iodine (235 mg, 0.93 mmol) was flushed with nitrogen and then irradiated with Pyrex-filtered light for 3 h. The solution was worked up as in the case of the hypoiodite of lactol (**3**). The product was purified by PLC [silica gel; benzene–diethyl ether (10:1)] to give a mixture of formates (**7**) and (**8**) (187 mg, 75%), ν_{max}(neat) 1 736 (OAc), 1 720 (OCHO), 1 238, 1 168, and 1 033 cm^{-1}; δ(270 MHz) 0.72 (s, 18-H_3 of 9-ene), 0.68 [s, 18-H_3 of 1(10)-ene], 2.05 (3 H, s, OAc), 5.06 (1 H, m, 3α-H), 5.22 (br s, 6α-H of 9-ene), 5.34 [br s, 6α-H of 1(10)-ene], 5.71 [br s, 1-H of 1(10)-ene], 8.11 (1 H, s, OCHO of 9-ene), and 8.15 [1 H, s, OCHO of 1(10)-ene]. The ratio of the 9-ene to 1(10)-ene was 5 to 1; *m/z* 412 [$(M - Br - OCHO)^+$, 1.4%], 352 [$(M - Br - OCHO - AcOH)^+$, 100], 197 (58), 144 (82), and 135 (60).

Reductive Elimination of Formates (**7**) *and* (**8**) *with Zinc in Glacial Acetic Acid.*—The mixture of formates (432 mg, 0.80 mmol) in glacial acetic acid (14.4 ml) containing zinc powder (864 mg, 13.2 mmol) was heated under reflux for 30 min. The solution was then worked up as in the case of formates (**5**) and (**6**). The product was purified by PLC (silica gel; benzene) to give the diene acetate (**11**) (296 mg, 89%), m.p. 72–74 °C (from MeOH) (lit.,[9] 74–76 °C; lit.,[10] 74–75 °C) [Found: $(M - AcOH)^+$, 352.3135. Calc. for $C_{26}H_{40}$: *m/z*, 352.3130]; ν_{max}(neat) 1 734 (OAc) 1 248, and 1 033 cm^{-1}; δ(270 MHz) 0.68 (3 H, s, 18-H_3), 5.00 (1 H, m, 3α-H), 5.37 (1 H, br s, 1-H), and 5.48 (1 H, br d, *J* 5.1 Hz, 6-H); *m/z* 412 (M^+, 0.3%), 352 [$(M - AcOH)^+$, 100], 197 (70), and 135 (77).

Hydrolysis of the Diene Acetate (**11**).—To a solution of the diene acetate (**11**) (510 mg, 1.2 mmol) in ethanol (8 ml) was added a solution of sodium hydroxide (269 mg) in methanol (13 ml). The solution was stirred for 4 h at room temperature and worked up as in the case of the androstane series. The product was purified by PLC (silica gel). The plates were developed three times with (10:1) benzene–diethyl ether to give *dienol* (**12**) (306 mg, 67%), m.p. 69.5–71.5 °C (from MeOH) (Found: *M*, 370.3264. $C_{26}H_{42}O$ requires *M*, 370.3236); ν_{max}(neat) 3 280 (OH), 1 658, 1 468, and 1 031 cm^{-1}; δ(270 MHz), 0.68 (3 H, s, 18-H_3), 4.05 (1 H, br s, 3α-H), 5.35 (1 H, br s, 1-H), and 5.55 (1 H, br d, *J* 5.13 Hz, 6-H); *m/z* 371 [$(M + H)^+$, 32%], 370 (M^+, 100), 352 [$(M - H_2O)^+$, 10], 357 (23), 239 (19) and 197 (26).

Synthesis of 19-*Norcholesta*-1,3,5(10)-*trien*-3-*ol* (**15**).—A solution of DMSO (24 ml) in dichloromethane (135 ml) was stirred for 15 min at −78 °C. To this solution was added TFAA (37 ml). After the mixture had been stirred for 30 min, a solution of the dienol (**12**) (50 mg, 0.14 mmol) in dichloromethane (500 ml) was added dropwise to the mixture at −65 °C; the mixture was

then stirred for 1.5 h and triethylamine (68 ml) was then added. The solution was stirred for 1 h at −65 °C, and the solution was allowed to warm to room temperature. Water was added to the reaction mixture, and the solution was extracted with dichloromethane. The extract was washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue, which was subjected to PLC [silica gel; benzene–diethyl ether (10:1)] to give the cholestatrienol (**15**) [14.5 mg, 35% based on converted 3-ol (**12**)] and recovered starting material (**12**) (8.1 mg). The title compound showed m.p. 114–116 °C (from MeOH) (lit.,[15] 113–115 °C); ν_{max} 3 566 and 3 282 (OH), 1 611, 1 508, 1 367, 1 241, 1 159, and 867 cm^{-1}; δ(90 MHz) 0.70 (3 H, s, 18-H_3), 2.78 (2 H, br s, 6-H_2), 6.55 (1 H, s, 4-H), 6.65 (1 H, d, *J* 2.64 Hz, 2-H), and 7.14 (1 H, d, *J* 7.91 Hz, 1-H); *m/z* 369 [$(M + H)^+$, 30%], 368 (M^+, 100), 213 (72), and 160 (54).

Catalytic Hydrogenation of 19-*Norcholesta*-1(10),5-*dien*-3β-*yl Acetate* (**11**) *with Platinum Oxide*.—The diene acetate (**11**) (217 mg, 0.53 mmol) in a stirred mixture of acetic acid (4 ml) and diethyl ether (4 ml) containing platinum(IV) oxide (20 mg) was hydrogenated under hydrogen at room temperature. After hydrogenation was complete, the catalyst was removed by filtration. The solution was washed successively with 5% aq. sodium hydrogen carbonate, water, and saturated brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue, which was subjected to PLC (silica gel; benzene) to give two fractions, A (16 mg) and B (184 mg), in order of polarity. Fraction A was an oily mixture of the stereoisomers of 19-norcholestane (Found: *M*, 358.3620. Calc. for $C_{26}H_{46}$: *M*, 358.3599); δ(270 MHz) 0.64 and 0.66 (each s, each 3 H, 18-H_3); ν_{max}(neat), 2 922, 2 860, 1 365, 1 448, 1 380, and 1 363 cm^{-1}; *m/z* 358 (M^+, 94%), 343 [$(M - Me)^+$, 4.5], and 203 (100).

Fraction B was a mixture of products, which was dissolved in ethanol (5 ml) containing potassium hydroxide (20 mg) and methanol (5 ml). The solution was stirred for 1 h at room temperature and the solvent was evaporated on a rotary evaporator. The residue was dissolved in diethyl ether and the solution was washed successively with dil. hydrochloric acid, water, and saturated brine, and then dried over anhydrous sodium sulphate. Evaporation of the solvent left a residue, which was subjected to PLC [silica gel; hexane–ethyl acetate (3:1)] to give three fractions. The most mobile fraction (113 mg, 52%) was 19-*nor*-5α,10α-*cholestan*-3β-*yl acetate* (**16**), which was recrystallized from methanol, m.p. 106–107.5 °C; δ(270 MHz) 0.66 (3 H, s, 18-H_3), 2.03 (3 H, s, OAc), and 5.01 (1 H, t, *J ca.* 3 Hz, 3α-H) (Found; C, 80.6; H, 11.75. $C_{28}H_{48}O_2$ requires C, 80.71; H, 11.61%); ν_{max} 1 737 and 1 728 (C=O), 1 238, 1 018, and 956 cm^{-1}; *m/z* 417 [$(M + H)^+$, 2.3%], 416 (M^+, 6.5), 358 [$(M - AcOH)^+$, 87], 216 (49), 202 (100), and 201 (97).

The next mobile fraction (6 mg, 3%) was 19-*nor*-5α,10α-*cholestan*-3β-*ol* (**19**), which was recrystallized from methanol, m.p. 136–138.5 °C (Found: C, 83.2; H, 12.5. $C_{26}H_{46}O$ requires C, 83.35; H, 12.38%); ν_{max} 3 310 and 3 240 (OH), 1 027, and 959 cm^{-1}; δ(270 MHz) 0.65 (3 H, s, 18-H) and 4.08 (1 H, t, *J ca.* 3 Hz, 3α-H); *m/z* 375 [$(M + H)^+$, 13], 374 (M^+, 43), 356 [$(M - H_2O)^+$, 26], 219 (40), 216 (36), and 201 (100).

The most polar fraction (42 mg, 22%) was 19-nor-5α-cholestan-3β-ol (**20**), which was recrystallized from methanol to yield a specimen for analysis, m.p. 107.5–109 °C (lit.,[4b] 107–108 °C). The spectral data of this product were in agreement with those reported for the natural product (Found: *M*, 374.3538. Calc. for $C_{26}H_{46}O$: *M*, 374.3548); ν_{max} 3 372 (OH), 1 171, 1 058, and 1 036 cm^{-1}; δ(270 MHz) 0.66 (3 H, s, 18-H_3) and 3.46–3.67 (1 H, m, 3α-H); *m/z* 375 [$(M + H)^+$, 14%], 374 (M^+, 45), 356 [$(M - H_2O)^+$, 45], 220 (51), and 201 (100).

Oxidation of 19-*Nor*-5α, 10α-*cholestan*-3β-*ol* (**19**) *with PCC*.—A solution of PCC (27 mg) in dichloromethane (2 ml) was added to a solution of 19-nor-5α,10α-cholestan-3β-ol (**19**) (47 mg, 0.13 mmol) in dichloromethane (4 ml). The solution was stirred for 5 h at room temperature, treated with diethyl ether, and filtered, and the filtrate was washed successively with water and saturated brine, and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was recrystallized from methanol to yield the *ketone* (**28**) (22 mg, 47%), m.p. 123.0–125.5 °C. The solvent was evaporated from the mother liquor and the residue was subjected to PLC [silica gel; benzene–diethyl ether (10:1)] to yield a further crop (17 mg) of the ketone (total yield 83%) (Found: C, 83.6; H, 12.0. $C_{26}H_{44}O$ requires C, 83.80; H, 11.90%); ν_{max} 1 720 (C=O), 1 332, 1 293, 1 245, and 1 172 cm^{-1}; δ(270 MHz) 0.64 (3 H, s, 18-H_3) and 2.59 (1 H, dd, *J* 6.2 and 13.9 Hz, 4α-H); *m/z* 372 (M^+, 100%), 218 (66), 217 (75), 199 (40), and 108 (68); ORD—see the Figure; CD Δε +0.085 (*c* 0.106, MeOH).

Oxidation of 19-*Nor*-5α-*cholestan*-3β-*ol* (**20**) *with PCC*.—A solution of PCC (18 mg) in dichloromethane (2 ml) was added to a solution of 19-nor-5α-cholestan-3β-ol (**20**) (32 mg, 0.086 mmol) in dichloromethane (3 ml). The solution was stirred for 48 h at room temperature and worked up as in the oxidation of the 5α,10α-isomer, to give the 3-one (**29**) (27 mg, 85%), which was recrystallized from methanol, m.p. 74.0–76.5 °C (Found: M^+, 372.3378. Calc. for $C_{26}H_{44}O$: *M*, 372.3391); ν_{max} 1 719 (C=O), 1 263, 1 200, 1 173, 1 084, and 956 cm^{-1}; δ(270 MHz) 0.69 (3 H, s, 18-H_3); *m/z* 372 (M^+, 50), 357 [$(M - Me)^+$, 2], 217 (100), and 162 (27%); $[\alpha]_{250}$ −356.4°, $[\alpha]_{267}$ −613.6° (min), $[\alpha]_{275}$ +524.9°, $[\alpha]_{300}$ −823.5°, $[\alpha]_{306}$ +951.6° (max), $[\alpha]_{325}$ +542.3°, $[\alpha]_{350}$ +298.6°. (23 °C; *c* 0.104, MeOH); CD Δε +1.270 (*c* 0.104, MeOH).

Catalytic Hydrogenation of 19-*Norcholesta*-1(10),5-*dien*-3β-*yl Acetate* (**11**) *over* Pd-C.—The diene acetate (**11**) (135 mg, 0.33 mmol) was dissolved in ethyl acetate (13 ml) containing 10% Pd-C catalyst (30 mg) and hydrogenated in the stirred solution under hydrogen. After hydrogenation was complete (TLC), the catalyst and the solvent were removed. The residue was dissolved in ethanol (3 ml) containing potassium hydroxide (20 mg). The solution was stirred for 24 h at room temperature. After evaporation of the solvent on a rotory evaporator, diethyl ether was added to the residue. The solution was washed successively with dil. hydrochloric acid, water, and saturated brine; it was then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a mixture of products, which was subjected to PLC [silica gel; benzene–diethyl ether (3:1)] to give four fractions in order of mobility. Fraction A (30 mg, 22%) was 19-nor-5α,10α-cholestan-3-β-yl acetate (**16**), identical with the specimen obtained above. Fraction B (2 mg, 2%) was 19-nor-5α,10α-cholestan-3β-ol (**19**), identical with an authentic specimen.

Fraction C (47 mg, 37%) was 19-norcholest-5(10)-en-3β-ol (**21**). An analytical sample, m.p. 106.5–108.0 °C (lit.,[16] 108–109 °C), was obtained by recrystallization from methanol; ν_{max} 3 276 (OH), 1 336, 1 252, 1 053, and 962 cm^{-1}; *m/z* 372 (M^+, 100), 354 [$(M - H_2O)^+$, 85], 339 (20), 259 (30), 241 (52), and 215 (61%); δ(270 MHz) 0.68 (3 H, s, 18-H_3) and 4.0–4.1 (1 H, br m, 3α-H).

Fraction D (37 mg) was a mixture, which was subjected twice to PLC [benzene–diethyl ether (2:1) and then benzene–diethyl ether (3:1)] to give 19-nor-5α-cholestan-3β-ol (**20**) (10 mg, 8%).

Oxidation of 19-*Norcholest*-5(10)-*en*-3β-*ol* (**21**) *with PCC*.—A solution of PCC (40 mg) in dichloromethane (5 ml) was added to a solution of 19-norcholest-5(10)-en-3β-ol (**21**) (70 mg, 0.19 mmol) in dichloromethane. After the solution had been stirred for 14 h at room temperature, additional PCC (20 mg) in

dichloromethane (2 ml) was added and the solution was stirred for a further 2 h. After diethyl ether had been added, the solution was filtered. The filtrate was washed successively with water and saturated brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was dissolved in methanol (15 ml). After the addition of conc. hydrochloric acid (0.2 ml) the solution was stirred for 1.5 h at room temperature. The solvent was then removed and the residue was dissolved in diethyl ether. The solution washed successively with water and saturated brine, and it was then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to PLC [silica gel; benzene–diethyl ether (3:1)] to give oily 19-norcholest-4-en-3-one (**30**) (23 mg, 33%) (lit.,[4c,16] oil); ν_{max} 1 683, 1 615 (COC=C). 1 259, and 1 205 cm^{-1}; δ 0.72 (3 H, s, 18-H_3) and 5.82 (1 H, s, 4-H); *m/z* 371 [$(M + H)^+$, 30%], 370 (M^+, 100), 355 [$(M - Me)^+$, 6], 352 (5), 215 (61), and 110 (51).

Catalytic Hydrogenation of 17-*Oxoestra*-1(10),5-*dien*-3β-*yl Acetate* (**9**).—A solution of the diene acetate (**9**) (308 mg, 0.75 mmol) in ethyl acetate (30 ml) containing 10% Pd-C catalyst (65 mg) was stirred under hydrogen at room temperature. After the hydrogenation was complete (TLC), the solvent was evaporated off to give a mixture of products, which was dissolved in methanol containing potassium hydroxide (5%). The solution was heated under reflux for 1.5 h and the solvent was then evaporated off. The residue was dissolved in diethyl ether, and the solution was washed successively with dil. hydrochloric acid, water, and saturated brine; it was then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product mixture, which was subjected to PLC [silica gel; benzene–diethyl ether (2:3)] to yield two fractions. The more mobile fraction (82 mg, 30%) was 3β-hydroxy-5α,10α-estran-17-one (**25**) which, after recrystallization from light petroleum–acetone, melted at 154–155 °C (lit.,[21] 152–154 °C); ν_{max} 3 550 and 3 486 (OH), 1 726 (C=O), 1 202, 1 109, 1 050, 961, and 922 cm^{-1}; δ(270 MHz) 0.86 (3 H, s, 18-H), 2.44 (1 H, dd, *J* 8.4 and 10.3 Hz, 16-H), and 4.10 (1 H, t, *J ca.* 3 Hz, 3α-H); *m/z* 276 (M^+, 100%), 258 [$(M - H_2O)^+$, 40], 202 (38), 108 (51), and 67 (63).

The less mobile fraction (132 mg) was a mixture of 3β-hydroxyestran-17-one (**26**) and 3β-hydroxyestr-5(10)-en-17-one (**27**). This fraction was dissolved in dichloromethane (5 ml) and a solution of PCC (103 mg) in dichloromethane (5 ml) was added. After the solution had been stirred for 16 h, additional PCC (60 mg) in dichloromethane (3 ml) was added and the solution was stirred for a further 3 h, and was then worked up as in the oxidation of 19-norcholest-5(10)-en-3β-ol. The product was subjected to PLC [silica gel; benzene–diethyl ether (2:3)] to give two fractions. The more mobile fraction (41 mg, 15%) was estrane-3,17-dione (**32**) which was recrystallized from aq. methanol, m.p. 70–72 °C (lit.,[21] 73–75 °C); ν_{max} 1 737 and 1 720 (C=O), 1 187, 1 097, 1 051, and 996 cm^{-1}; *m/z* 274 (M^+, 100%), 256 (24), and 230 (49).

The less mobile fraction (31 mg, 12%) was estr-4-ene-3,17-dione (**33**), which was recrystallized from methanol m.p. 163–165 °C (lit.,[16] 163–167 °C); ν_{max} 1 744 (C=O), 1 674, 1 621 (conjugated C=O), 1 251, and 1 044 cm^{-1}; δ(90 MHz) 0.94 (3 H, s, 18-H_3) and 5.85 (1 H, s, 4-H); *m/z* 272 (M^+, 100%), 244 (23), 228 (28), 110 (55), and 41 (56).

5α,10α-*Estrane*-3,17-*dione* (**31**).—A solution of PCC (94 mg, 0.437 mmol) in dichloromethane (5 ml) was added to a solution of 3β-hydroxy-5α,10α-estran-17-one (**25**) (12 mg, 0.438 mmol) in dichloromethane (5 ml). The solution was stirred for 18 h, treated with diethyl ether, and filtered; the filtrate was washed successively with water and saturated brine, and was then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue, which was recrystallized from methanol to give the dione (**31**) (78 mg, 65%), m.p. 159–162 °C (lit., 163–165 °C; lit.,[22] 164 °C; lit.,[21] 158–161 °C). A further crop of the dione (32 mg) was obtained from the mother liquor by PLC [benzene–diethyl ether (2:3)]; ν_{max} 1 748 (17-carbonyl) and 1 722 cm^{-1}; δ(90 MHz) 0.86 (3 H, s, 18-H_3).

Synthesis of 19-*Nortestosterone* (**34**) *by Reduction with Sodium Borohydride*.—Sodium borohydride (30 mg) was added to a solution of estr-4-en-3,17-dione (**33**) (29 mg, 0.107 mmol) in 1:1 dichloromethane–methanol (7.2 ml) at −78 °C (solid CO_2–MeOH). The solution was stirred for 6 h and dichloromethane was added to the solution, which was then washed successively with 1M-sodium hydroxide and water; it was then dried over anhydrous sodium sulphate. Evaporation of the solvent gave crude 19-nortestosterone (**34**), which was purified by PLC [benzene–diethyl ether (1:2)] and then recrystallization from light petroleum–acetone to give pure material, m.p. 112–113 °C (lit.,[20] 122–123 °C); ν_{max} 3 368 (OH), 1 656, 1 620 (conjugated C=O), 1 263, 1 203, and 1 056 cm^{-1}; δ(90 MHz) 0.81 (3 H, s, 18-H_3), 3.75 (1 H, t, *J* 7.9 Hz, 17α-H), and 5.82 (1 H, br s, 4-H); *m/z* 275 [$(M + H)^+$, 28%], 274 (M^+, 100), 256 [$(M - H_2O)^+$, 19], and 110 (90).

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