Preparation of Antiandrogenic 17-Hydroxy-3,6-cyclo-4-nor-3,5-seco-6β-androstan-3-one by Deoxygenation of the Corresponding 5-Hydroxy Derivatives

Jiří Polman and Alexander Kasal *
Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6, Czechoslovakia

This paper reports on three alternative procedures for the preparation of antiandrogenic 17β-hydroxy-3,6-cyclo-4-nor-3,5-seco-6β-androstan-3-one **15**. The key step represents the removal of the oxygen functional group from position 5 which was effected by radical deoxygenation of thioesters of type **13**. The variant of choice was the deoxygenation of the 5-thioimidazolide **29** prepared from diketone **5**. The 3-keto group was selectively protected during hydride reduction by conversion into the corresponding silyl enol ether.

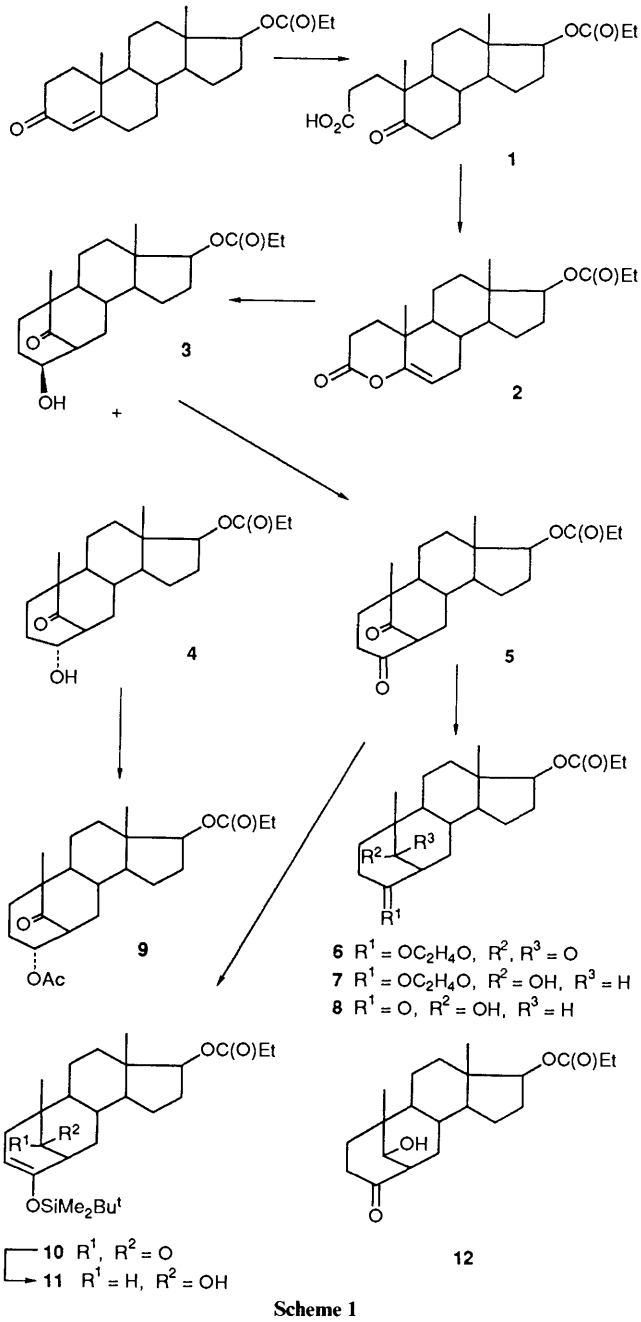
During our search for a new type of therapeutically usable antiandrogen we found[1] a relatively high activity for 17β-hydroxy-3,6-cyclo-4-nor-3,5-seco-6β-androstan-3-one **15** prepared by deoxygenation of the corresponding 5-keto derivative. Attempts to achieve deoxygenation of the 5-hydroxy derivatives *via* reduction of the corresponding methanesulphonates by hydride reagents yielded,[1,2] similarly to Huang-Minlon reduction of the 5-ketone, merely the 3,5-seco products of type **25** or alternatively **30**. Reduction by zinc and sodium iodide in the presence of water gave rise to elimination products with rearrangement[1] [unsaturated 1(10→6)*abeo*-6β(H)-4-nor-derivatives **26** and **27**]. In this study we present the results of our investigation of deoxygenations realized under conditions of radical reactions during which the formation of rearranged products is usually suppressed.[3]

The starting compounds were prepared from commercial testosterone propionate which was oxidized[4] to keto acid **1**; the latter was converted[5,6] into enol lactone **2** (see Scheme 1). The reduction of the enol lactone[7] by lithium tri-t-butoxyaluminium hydride afforded β-hydroxy ketones **3** and **4**. Ketone **4** was used in further experiments after its acylation to compound **9**, and both hydroxy ketones were also oxidized to afford diketone **5**. The corresponding 5-alcohols were obtained by reduction of 5-ketones whose oxygen function at position 3 was protected by acetylation (compound **9**), acetalization (compound **6**) or silylation (compound **10**). The reaction of diketone **5** with an excess of t-butyldimethylsilyl chloride in triethylamine–dimethylformamide (DMF) afforded enol silyl ether **10**. All the compounds prepared showed characteristics (such as IR and NMR spectra) which were analogous to those of products prepared in earlier experiments.[1]

The stereochemical course of the reduction of the 5-carbonyl group by hydrides (lithium tri-t-butoxyaluminium hydride[1] and sodium borohydride) was in accord with our previous data.[1] We made a new observation with the reduction of trimethylsilyl enol ether **10** by lithium tri-t-butoxyaluminium hydride; according to our expectations, the (5*R*)-alcohol **11** was the only product formed.

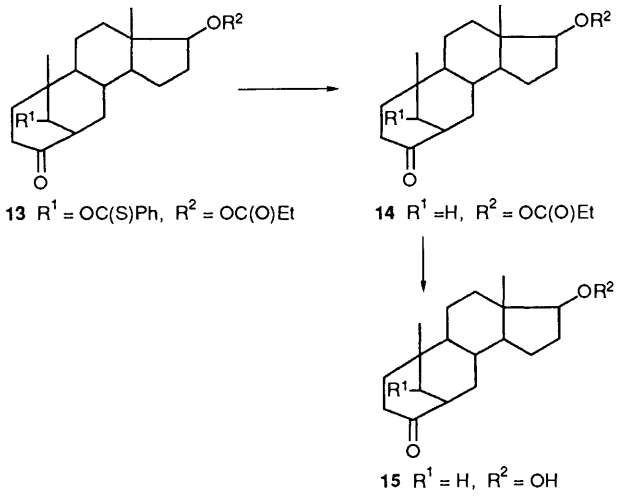
The selective protection of the 3-keto group of diketone **5** *via* silyl enol ether **10** was superior in many respects to protection by acetalization which is paralleled by formation of a product resulting from opening of ring A and which, moreover, is more difficult to monitor (both the starting ketone **5** and the monoacetal required **6** show identical behaviour during TLC on silica gel).

The deoxygenation of the (5*S*)-alcohols was realized first with 3-keto derivative **8** whose hydroxy group is located axially with respect to ring A and equatorially to ring B. Acylation of this



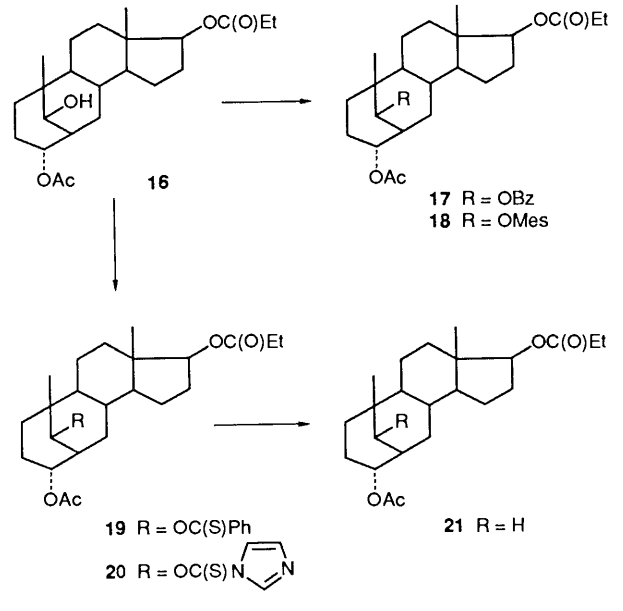
Scheme 1

group was possible only when the reaction time was prolonged and a considerable excess of reagents was used. Even under such conditions, however, the yield of the thioacylation product was merely 21%. Likewise the deoxygenation of thiobenzoate **13** gave only a low yield. Similar results were obtained with thioimidazolylation of compound **8** and its reduction. The preparation of hydroxy ketone **15** was therefore paralleled by considerable losses (Scheme 2).



Scheme 2

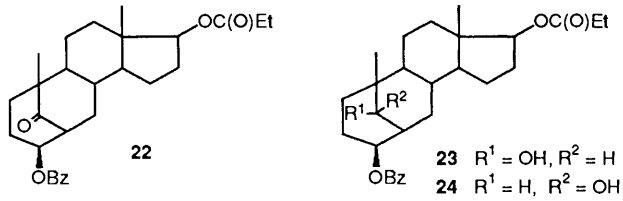
Acylation of (5*R*)-3α-acetoxy alcohol **16** (see Scheme 3) by the corresponding reagents afforded benzoate **17**, methanesulphonate **18** and thioesters **19** and **20**. The reactions of methanesulphonate **18** were used to confirm the configuration on carbon 5; compound **18** afforded diol **25** after treatment with lithium aluminium hydride and *endo*- and *exo-abeo* compounds **26** and **27** by reaction with zinc and sodium iodide. The 5-epimeric methanesulphonate should obviously give rise to other products.[1] Both thioesters **19** and **20** have the configuration which favours skeletal rearrangements on reaction under ionic conditions. On reduction under radical conditions (slow addition to a boiling solution of tributyltin hydride in benzene), however, the compounds yielded the desired product, deoxy compound **21**. The structure of compound **21** was confirmed by its hydrolysis to known[1] diol **28**. (It is important that a high



Scheme 3 Mes = $S(O)_2Me$

temperature be maintained constantly during the entire reduction period; see the isolation of the 5-hydroxy derivative by deoxygenation of compound **20** in the Experimental section).

Reduction of compound **22** gave rise to a mixture of alcohols **23** and **24** which, however, we could not either separate or derivatize for steric reasons (Scheme 4).

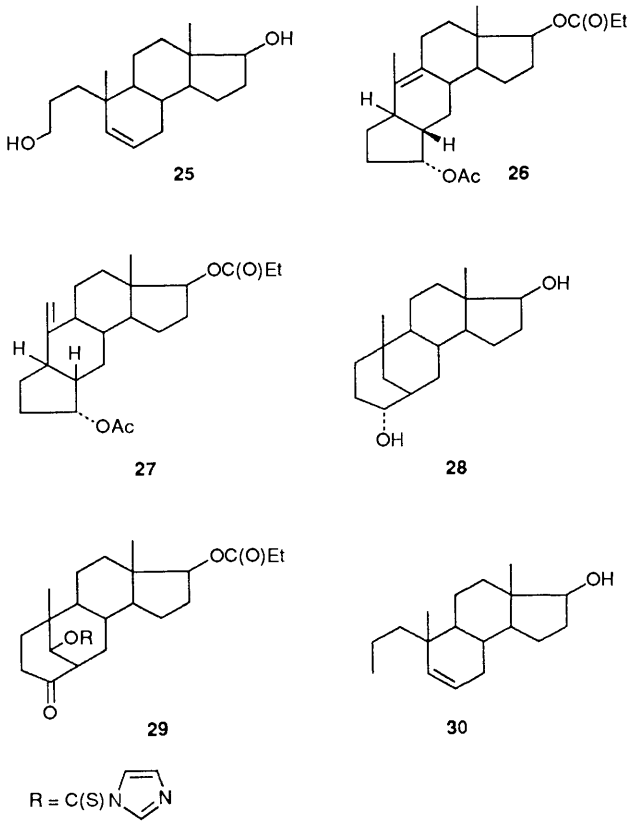


Scheme 4

We made an effort to deoxygenate the (5*R*)-hydroxy group of the enol silyl ether **11**; under the conditions of derivatization of this hydroxy group the enol silyl ether protecting group was removed. Thiobenzoylation of keto alcohol **12** did not occur even when a large excess of the reagents was used at 60 °C. In contrast the thioimidazolylation proceeded relatively smoothly when ketone **12** was refluxed with thiocarbonyldiimidazole in toluene in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Thioimidazolide **29** itself was readily deoxygenated by being refluxed with a solution of tributyltin hydride in toluene in the presence of azoisobutyronitrile (AIBN).

We attempted to remove the keto group of the enol silyl ether **10** *via* reduction to the hydroxy group. We were not successful, however, with attempted modified Kizhner–Wolf reduction;[8] we were able to prepare the corresponding tosylhydrazone, yet its reduction by lithium aluminium hydride afforded merely 5-(*p*-tolylsulphonylimino)-3,6-cyclo-4-nor-3,5-seco-6β-androstan-3α,17β-diol.[9]

The data presented in this report show that the most



advantageous approach for the preparation of 17β-hydroxy-3,6-cyclo-4-nor-3,5-seco-6β-androstan-3-one **15** should use selective enolsilylation of the 3-carbonyl group of diketone **5**, giving rise to compound **10** in which the 5-keto group can be reduced to give the (5*R*)-hydroxy derivative **11**. The deoxygenation itself was performed after the regeneration of the 3-oxo group, by conversion of alcohol **12** into the corresponding thioimidazolide **29** and by reduction with tributyltin hydride. The total yield of compound **15** in this sequence starting with enol lactone **2** is 15.8%, whereas the procedure originally reported,[1,10] *i.e.* the reduction of the dithiolane derivatives by Raney nickel, gave a yield of only 5.9%. The losses during this procedure are due predominantly to the fact that derivatization to the thioacetal could be performed only with the 3α-hydroxy 5-ketone of type **4**. In contrast, this novel synthetic procedure makes use also of the 3β-hydroxy 5-ketone **3** since both alcohols **3** and **4** yield the identical diketone **5** when oxidized according to Jones' procedure.

Experimental

M.p.s were measured on a Kofler block and are not corrected. Analytical samples were dried over phosphorus pentaoxide at 50 °C/100 Pa. Optical rotation and IR were measured in chloroform at 23–25 °C. IR spectra were measured on a UR-20 Zeiss Jena spectrometer for solutions in tetrachloromethane. ^{1}H NMR spectra were measured in deuteriochloroform ($SiMe_4$ as internal standard) on a Tesla BS-497 (100 MHz; FT mode) or a Varian 200 (200 MHz; FT mode) spectrometer. For analytical and preparative TLC (PLC), silica gel containing 5% gypsum was used. Extracts of organic compounds were dried over sodium sulphate. Light petroleum refers to that fraction boiling in the range 60–90 °C.

5-*Oxo*-17β-*propionyloxy*-4-*nor*-3,5-*secoandrostan*-3-*oic Acid* **1**.—To a solution of testosterone propionate (20 g, 58.06 mmol) in 2-methylpropan-2-ol (1200 cm^3) were added aq. solutions of potassium carbonate (12.3 g in 350 cm^3), potassium permanganate (175 mg in 22 cm^3) and sodium periodate (17.5 g in 220 cm^3). The mixture was stirred for 30 min at room temperature and aq. sodium periodate (70.5 g in 880 cm^3) and several crystals of potassium permanganate were added. The solution was stirred for a further 4 h at room temperature and then aq. sodium pyrosulphate was added until the solution became colourless. The resulting solution was partially evaporated, sulphuric acid (36 cm^3; 50%) was added, and the organic substance was taken up into diethyl ether. The ethereal layer was washed with brine, dried and evaporated. The product was *acid* **1** (20 g, 94%) $[\alpha]_D$ +17° (*c* 1.9) (Found: C, 69.5; H, 8.5. $C_{21}H_{32}O_5$ requires C, 69.20; H, 8.8%); ν_{max}/cm^{-1} 1741 and 1196 (OProp), 1720 (C=O), 3400, 2500 and 1710 (CO_2H); δ_H 0.86 (3 H, s, 18-H_3), 1.14 (3 H, t, *J* 7.6 Hz, OCOCH$_2$*Me*), 1.28 (3 H, s, 19-H_3), 2.33 (2 H, q, *J* 7.6 Hz, OCOC*H*$_2$Me), 4.63 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H) and 5.21 (1 H, s, CO_2H).

17β-*Propionyloxy*-4-*oxaandrost*-5-*en*-3-*one* **2**.—A mixture of seco acid **1** (9.5 g, 26.03 mmol), ethyl acetate (600 cm^3), acetic anhydride (80 cm^3, 0.84 mmol) and perchloric acid (80%; 0.14 cm^3) was allowed to react for 10 min and was then poured into aq. potassium hydrogen carbonate. The organic layer was washed successively and several times with aq. sodium hydrogen carbonate and water, and evaporated. The residue was dissolved in acetone (40 cm^3)–pyridine (40 cm^3), and the solution was kept for 10 min and then poured into water–ice. The precipitate was filtered off and crystallized from acetone–heptane. The product was *enol lactone* **2** (8.6 g, 95%), m.p. 145–146 °C; $[\alpha]_D$ −87° (*c* 2.6) (Found: C, 72.9; H, 8.6. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.73%); ν_{max}/cm^{-1} 1766, 1699 and 1164 (lactone), and 1741, 1200 and 1191 (OProp); δ_H 0.83 (3 H, s, 18-H_3), 1.14 (3 H, s, 19-H_3), 1.16 (3 H, t, *J* 7.6 Hz, OCOCH$_2$*Me*), 2.33 (2 H, q, *J* 7.6 Hz, OCOC*H*$_2$Me), 2.64 (2 H, dd, J_1 5, J_2 9 Hz, 1-H_2), 4.63 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H) and 5.26 (1 H, dd, J_1 2, J_2 5 Hz, 6-H); *m/z* 346 (M^+, 100%) and 290 M − C_3H_4O, 20).

3β-*Hydroxy*-17β-*propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-5-*one* **3**.—A solution of enol lactone **2** (43 g, 124.1 mmol) in tetrahydrofuran (THF) (150 cm^3) was stirred at −80 °C and then a suspension of lithium tri-t-butoxyaluminium hydride (40 g, 157 mmol) in THF (115 cm^3) was added. The temperature was allowed to rise to 0 °C within 1 h. The mixture was then poured into aq. sodium potassium tartrate, the product was taken up in chloroform, and the organic layer was washed successively with aq. sodium carbonate and water, dried over magnesium sulphate, and evaporated. Crystallization from acetone–heptane yielded compound **3** (13 g, 30%).

The residue (17 g) was chromatographed on silica gel [1000 g; benzene–diethyl ether (8:2) and then diethyl ether] to give the less polar hydroxy ketone **4** (see below) and a further portion of the more polar *hydroxy ketone* **3** (6.1 g, 14%), m.p. 188–189 °C (from acetone–heptane); $[\alpha]_D$ −36° (*c* 1.4) (Found: C, 72.5; H, 9.0. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.36%); ν_{max}/cm^{-1} 3620 and 1039 (OH), 1740 and 1196 (OCOR) and 1720 (C=O); δ_H 0.75 (3 H, s, 18-H_3), 0.98 (3 H, s, 19-H_3), 1.16 (3 H. t, *J* 7.6 Hz, OCOCH$_2$*Me*), 2.33 (2 H, q, *J* 7.6 Hz, OCOC*H*$_2$Me), 4.20 (1 H, dd, J_1 2, J_2 4 Hz, 3-H) and 4.63 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H); *m/z* 348 (100%, M^+) and 292 (15, M − C_3H_4O).

3α-*Hydroxy*-17β-*propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-5-*one* **4**.—The less polar, minor product from the preceding experiment was crystallized from acetone–heptane. The product was *hydroxy ketone* **4** (7.55 g, 18%), m.p. 119–120 °C; $[\alpha]_D$ −13° (*c* 1.6) (Found: C, 72.7; H, 9.1%); ν_{max}/cm^{-1} 3620 (OH), 1736 and 1196 (OCOR) and 1720 (C=O); δ_H 0.75 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 1.17 (3 H, t, *J* 7.6 Hz, OCOCH$_2$*Me*), 2.33 (2 H, q, *J* 7.6 Hz, OCOC*H*$_2$Me), 2.85 (1 H, q, *J* 5 Hz, 6-H), 3.92 (1 H, p, *J* 5 Hz, 3-H) and 4.61 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H).

17β-*Propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3,5-*dione* **5**.—A solution of hydroxy ketone **3** (4.2 g, 12.05 mmol) in acetone (20 cm^3) was treated with Jones' reagent. The solution was worked up as usual. After evaporation of the solvent the residue was crystallized from acetone–heptane to afford *diketone* **5** (4 g, 96%), m.p. 117 °C; $[\alpha]_D$ +14° (*c* 2.9) (Found: C, 73.0; H, 8.8. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%); ν_{max}/cm^{-1} 1739 and 1196 (OProp) and 1716 (C=O); δ_H 0.76 (3 H, s, 18-H_3), 1.11 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, *Me*CH$_2$CO$_2$), 2.31 (2 H, q, *J* 7.6 Hz, MeC*H*$_2$CO$_2$) and 4.58 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H).

Similarly, diketone **5** can be prepared from the crude mixture of hydroxy ketones **3** and **4**. Thus, Jones' oxidation of the above mentioned mixture (3.2 g) gave diketone **5** (3 g, 94%).

(5S)-5-*Hydroxy*-17β-*propionyloxy*-3,6-*cyclo*-4-*nor*-3.5-*seco*-6β-*androstan*-3-*one* **8**.—A solution of diketone **5** (3.75 g, 10.05 mmol) and toluene-*p*-sulphonic acid (PTSA) hydrate (750 mg) in benzene (700 cm^3) was refluxed with ethane-1,2-diol (150 cm^3, 2.67 mol). Water was eliminated by means of a Dean–Stark adapter. After 8 h the reaction was quenched by addition of aq. potassium hydroxide (500 mg in 20 cm^3) and then washed successively with aq. potassium hydrogen carbonate and water; ν_{max}/cm^{-1} 1741 and 1197 (OProp), 1730infl. (C=O), and 1130, 1087, 1063 and 1030 (acetal); δ_H 0.74 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, *Me*CH$_2$CO$_2$), 2.31 (2 H, q, *J* 7.6 Hz, MeC*H*$_2$CO$_2$), 3.89 and 4.16 (each 2 H, each m, OCH$_2$CH$_2$O) and 4.59 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H).

The azeotropic mixture (250 cm^3) was distilled off from a solution of the mixture of ketone **5** and acetal **6** (3.7 g) in toluene (750 cm^3), and lithium tri-t-butoxyaluminium hydride (8.5 g) was added. The mixture was refluxed for 90 min and was then poured into aq. potassium sodium tartrate. The organic layer was washed with water, dried and evaporated under reduced pressure. PTSA monohydrate (630 mg) was added to a solution of the above mentioned residue in acetone (45 cm^3). After 18 h at room temperature the solution was poured into aq. potassium hydrogen carbonate and the organic layer was washed with water. The product was applied to a column of silica gel (100 g) and eluted with light petroleum–ethyl acetate (9:1) to give *compound* **8** (650 mg, overall yield 19%), m.p. 173–174 °C (from acetone–heptane); $[\alpha]_D$ +34° (*c* 1.2) (Found: C, 72.5; H, 9.3. $C_{21}H_{32}O_4$ requires C, 72.4, H, 9.3%); ν_{max}/cm^{-1} 3630, 3620 and 1038 (OH), 1736 and 2294 (OProp) and 1715 (C=O); δ_H 0.79 (3 H, s, 18-H_3), 1.06 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, *Me*CH_2CO_2), 2.31 (2 H, q, *J* 7.6 Hz, MeCH_2CO_2), 3.93 (1 H, d, *J* 2.5 Hz, 5-H) and 4.58 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H).

(5S)-17β-*Propionyloxy*-5-*thiobenzoyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-3-*one* **13**.—The imidoyl chloride methochloride[11] (prepared from *N*,*N*-dimethylbenzamide and phosgene) (5 cm^3) was added dropwise under argon to a refluxing solution of compound **8** (250 mg, 0.72 mmol) in THF (2.1 cm^3). The reaction mixture was stirred at room temperature for 25 h, then pyridine (0.5 cm^3) was added, hydrogen sulphide was bubbled for 15 min through the solution and the mixture was stored for 80 h before being diluted with dichloromethane, washed successively with aq. potassium hydrogen carbonate and water, dried and evaporated under reduced pressure. The crude product was chromatographed on silica gel in light petroleum–ethyl acetate (17:3). The following substances were eluted:

(i) *N*,*N*-Dimethylthiobenzamide (1 g); (ii) *thiobenzoate* **13** (70 mg, 21%) (Found: C, 71.8; H, 6.65; S, 6.9. $C_{28}H_{36}O_4S$ requires C, 71.8; H, 6.8; S, 6.84%); δ_H 0.74 (3 H, s, 18-H_3), 1.12 (3 H, s, 19-H_3), 1.12 (3 H, t, *J* 7.6 Hz, *Me*$_2CH_2CO_2$), 2.31 (2 H, q, *J* 7.6 Hz, MeCH_2CO_2), 4.58 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H), 5.72 (1 H, d, *J* 2.5 Hz, 5-H) and 7.27–7.40 and 8.00–8.27 (5 H, ABC system, ArH); (iii) the starting alcohol **8** (62 mg recovery).

17β-*Propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-3-*one* **14**.—(a) *Deoxygenation of thiobenzoate* **13**. A solution of thiobenzoate **13** (50 mg, 0.11 mmol) in toluene (0.6 cm^3) was added dropwise to a refluxing solution of tributyltin hydride in benzene (1 mol dm^{-3}; 0.6 cm^3). The mixture was refluxed under argon for 8 h and then separated on preparative chromatographic plates [benzene–diethyl ether (8:2)] to give *ketone* **14** (20 mg, 55%), m.p. 106 °C (from MeOH); $[\alpha]_D$ +29° (*c* 1.9) (Found: C, 75.8; H, 9.7. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%); ν_{max}/cm^{-1} 1738 (OProp) and 1710 (C=O); δ_H 0.81 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, *Me*CH_2CO_2), 2.31 (2 H, q, *J* 7.6 Hz, MeCH_2CO_2) and 4.59 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H); *m*/*z* (FAB) 331 (M^+, 25%) and 257 (M − $CH_3CH_2CO_2H$, 100).

(b) *Deoxygenation of thioimidazolide* **29**. A solution of thioimidazolide **29** (770 mg, 1.68 mmol) in toluene (20 cm^3) was added dropwise to a refluxing solution of tributyltin hydride (1.4 g) and AIBN (15 mg) in toluene (20 cm^3). The mixture was refluxed for 2 h, then evaporated, and the residue was applied to a column of silica gel [light petroleum–ethyl acetate (9:1)]. The product (464 mg, 83%) was identical with an authentic sample of **14**.

17β-*Hydroxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-3-*one* **15**.—To a solution of compound **14** (8 mg, 0.02 mmol) in THF (0.3 cm^3) was added hydrochloric acid (0.06 cm^3; 15%) and the mixture was stirred at room temperature for 18 h. The product was purified by chromatography on preparative plates. The product **15** (2.5 mg) was identical with an authentic sample [IR, NMR (200 MHz)].

3α-*Acetoxy*-17β-*propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-5-*one* **9**.—Acetic anhydride (6.2 cm^3, 64 mmol) was added to a solution of hydroxy ketone **4** (1.9 g, 5.45 mmol) in pyridine (25 cm^3) and the mixture was stored overnight at room temperature and poured into 1% aq. hydrochloric acid, and the precipitate was taken up into diethyl ether. The extract was washed successively with dil. hydrochloric acid (5%), aq. potassium hydrogen carbonate and water, dried, and evaporated to afford *compound* **9** (2 g, 95%), m.p. 103 °C (from EtOAc); $[\alpha]_D$ +13° (*c* 2) (Found: C, 71.0; H, 8.3. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%); ν_{max}/cm^{-1} 1747 and 1240 (OAc), 1747 and 1196 (OProp) and 1726 (C=O); δ_H 0.75 (3 H, s, 18-H_3), 0.97 (3 H, s, 19-H_3), 1.11 (3 H, t, *J* 8 Hz, OCOCH_2*Me*), 2.09 (3 H, s, OAc), 2.30 (2 H, q, *J* 8 Hz, OCOCH_2Me), 2.96 (1 H, q, *J* 5 Hz, 6-H), 4.61 (1 H, dd, J_1 7.5, J_2 9 Hz, 17-H) and 4.86 (1 H, p, *J* 5 Hz, 3-H).

(5R)-3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3α,5,17β-*triol* 3-*Acetate* 17-*Propionate* **16**.—(a) *Reduction of ketone* **9** *with sodium borohydride*. Sodium borohydride (200 mg, 5.29 mmol) was added to a stirred solution of ketone **9** (1 g, 2.57 mmol) in ethanol (40 cm^3)–ethyl acetate (30 cm^3) at 0 °C. After 20 h at −5 °C the mixture was poured onto ice–water, and the precipitate was filtered off and dissolved in diethyl ether. The ethereal solution was washed successively with 5% aq. hydrochloric acid, aq. potassium hydrogen carbonate and water, and was evaporated to give *compound* **16** (950 mg, 95%), m.p. 135–136 °C (from acetone–heptane); $[\alpha]_D$ +24° (*c* 1.9) (Found: C, 70.6; H, 8.9. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%); ν_{max}/cm^{-1} 3630 (OH), 1740 and 1246 (AcO) and 1740 and 1196 (PropO); δ_H(200 MHz) 0.82 (3 H, s, 18-H_3), 1.00 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, OCOCH_2*Me*), 2.04 (3 H, s, AcO), 2.33 (2 H, q, *J* 7.6 Hz, OCOCH_2Me), 3.19 (1 H, t, *J* 5.8 Hz, 5-H), 4.61 (1 H, dd, $J_{17\alpha,16\alpha}$ 7.3, $J_{17\alpha,16\beta}$ 9.3 Hz, 17-H) and 4.75 (1 H, m, 3-H).

(b) *Reduction of ketone* **9** *with lithium tri-t-butoxyaluminium hydride*. A solution of lithium tri-t-butoxyaluminium hydride (850 mg, 3.34 mmol) in THF (5 cm^3) was added dropwise to a stirred solution of ketone **9** (420 mg, 1.08 mmol) in THF (5 cm^3) at room temperature. After 20 h the mixture was poured onto ice–water, and the precipitate was filtered off and dissolved in diethyl ether. The ethereal solution was washed successively with 5% aq. hydrochloric acid, aq. potassium hydrogen carbonate, and water, and was then evaporated. The product **16** was purified by crystallization from methanol (400 mg, 95%).

(5R)-3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-3α,5,17β-*triol* 3-*Acetate* 5-*Benzoate* 17-*Propionate* **17**.—Compound **16** (20 mg, 0.05 mmol) was dissolved in pyridine (0.25 cm^3) containing benzoyl chloride (0.06 cm^3) and after 18 h the solution was poured onto ice. The precipitated product was taken up into benzene, and the solution was washed successively with dil. hydrochloric acid and aq. potassium hydrogen carbonate and dried. After removal of the solvent the *product* **17** was purified on preparative plates in benzene–diethyl ether (8:2) (15 mg) (Found: C, 73.0; H, 7.8. $C_{30}H_{38}O_6$ requires C, 72.85; H, 7.7%); δ_H 0.94 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), 1.15 (3 H, t, *J* 7.6 Hz, OCOCH$_2$*Me*), 2.05 (3 H, s, AcO), 2.33 (2 H, q, *J* 7.6 Hz, OCOCH_2Me), 4.61 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H), 4.72 (1 H, d, *J* 3 Hz, 5-H), 4.93 (1 H, m, 3-H) and 7.50–7.75 and 7.95–8.25 (5 H, ABC system, ArH).

3β-*Benzyloxy*-17β-*propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-5-*one* **22**.—Compound **3** (2 g, 5.74 mmol) was dissolved in pyridine (25 cm^3) containing benzoyl chloride (6 cm^3, 51.4 mmol) and after 18 h the solution was poured onto ice.

The precipitated product was taken up into benzene, and the solution was washed successively with dil. hydrochloric acid and aq. potassium hydrogen carbonate, dried and evaporated. *Benzoate* **22** (2 g, 77%) was obtained, m.p. 136 °C (from MeOH); $[\alpha]_D$ −7° (*c* 1.4) (Found: C, 74.35; H, 8.2. $C_{28}H_{36}O_5$ requires C, 74.3; H, 8.0%); ν_{max}/cm^{-1} 1738 and 1193 (OProp), 1724 and 1274 (OBz) and 1724 infl. (C=O); δ_H 0.76 (3 H, s, 18-H_3), 1.06 (3 H, s, 19-H_3), 1.14 (3 H, t, *J* 7.6 Hz, OCOCH$_2$*Me*), 2.32 (2 H, q, *J* 7.6 Hz, OCOC*H*$_2$Me), 4.63 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H) and 5.42 (1 H, dd, J_1 3, J_2 7 Hz, 3-H).

(5S) **23** *and* (5R)-3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3β,5,17β-*triol* 3-*Benzoate* 17-*Propionate* **24**.—Lithium tri-t-butoxyaluminium hydride (4.3 g, 16.9 mmol) was added to a solution of ketone **22** (2.5 g, 5.52 mmol) in diethyl ether (25 cm^3). The mixture was stirred at room temperature for 46 h and was then poured onto ice–water, diluted with diethyl ether, and the ethereal layer was washed successively with hydrochloric acid, sodium hydrogen sulphate, and water, dried, and evaporated under reduced pressure. Most of the starting ketone (1.3 g) was isolated by crystallization from methanol. The mother liquor was applied to a column of silica gel (120 g) and eluted by light petroleum–ethyl acetate (8:2). The following compounds were eluted:

(i) Starting material **22** (870 mg recovery); (ii) compounds **23** and **24** (251 mg) which are not separable; δ_H 0.78 (3 H, s, 18-H_3), 0.97 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, *Me*CH$_2$CO$_2$), 2.29 (3 H, q, *J* 7.6 Hz, MeC*H*$_2$CO$_2$), 3.05 (0.5 H, d, *J* 3.5 Hz, OH, decreased after extraction with D_2O), 3.46 (0.5 H, d, *J* 9 Hz, OH decreased after extraction with D_2O), 3.72 (1 H, d, *J* 3 Hz, 5-H), 4.58 (1 H, dd, $J_1$7.3, J_2 9.3 Hz, 17-H) and 5.39 (1 H, m, 3-H).

(5R)-3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3α,5,15β-*triol* 3-*Acetate* 5-*Methanesulphonate* 17-*Propionate* **18**.—Compound **16** (260 mg, 0.67 mmol) was dissolved in a mixture of pyridine (1 cm^3) and mesyl chloride (0.3 cm^3) at 0 °C and after 18 h the solution was poured onto ice. The product which had precipitated, was taken up in diethyl ether, and the solution was successively washed with 5% hydrochloric acid, aq. potassium hydrogen carbonate, and water, dried and evaporated to afford *compound* **18** (271 mg, 86%), m.p. 116 °C (decomp.) (from diethyl ether–heptane); $[\alpha]_D$ +2° (*c* 1.8) (Found: C, 61.5; H, 7.7; S, 7.0. $C_{24}H_{36}O_7S$ requires C, 61.5; H, 7.7; S, 6.8%); ν_{max}/cm^{-1} 1741 and 1241 (OAc and OProp) and 1364 and 1188 (MesO); δ_H 0.82 (3 H, s, 18-H_3), 1.05 (3 H, s, 19-H_3), 1.16 (3 H, t, *J* 8 Hz, OCOCH$_2$*Me*), 2.03 (3 H, s, AcO), 2.31 (2 H, q, *J* 8 Hz, OCOC*H*$_2$Me), 3.02 (3 H, s, MeSO$_3$), 4.18 (1 H, d, *J* 2.5 Hz, 5-H) and 4.67 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H).

4-*Nor*-3,5-*secoandrost*-5-*ene*-3,17β-*diol* **25**.—Methanesulphonate **18** (15 mg, 0.03 mmol) was added to a solution of lithium aluminium hydride (10 mg) in dioxane (0.5 cm^3) and the mixture was refluxed for 5 h. Then several drops of water were added, and the crude product was applied to preparative plates, which were developed with diethyl ether. The main product (4 mg) was identical with an authentic sample of compound **25** (TLC, IR, ^{1}H NMR).

1(10→6)abeo-4-*Nor*-5β,6β-*androst*-9-*ene*-1α,17β-*diol* 1-*Acetate* 17-*Propionate* **26**.—Methanesulphonate **18** (240 mg, 0.51 mmol) was added to a refluxing mixture of zinc powder (1.5 g) and sodium iodide (300 mg) in 1,2-dimethoxyethane (15 cm^3) and the mixture was refluxed for 5 h. The inorganic compounds were filtered off and the mother liquors were diluted with toluene (80 cm^3), washed successively with aq. sodium thiosulphate and water and evaporated under reduced pressure. The crude product was applied to preparative plates. *Compound* **26** (89 mg) was purified, m.p. 78 °C (from MeOH); $[\alpha]_D$ +58° (*c* 1.6) (Found: C, 73.7; H, 9.2. $C_{23}H_{34}O_4$ requires C, 73.76; H, 9.15%); ν_{max}/cm^{-1} 1741 and 1250 (OAc) and 1741 and 1197 (OProp); δ_H 0.88 (3 H, s, 18-H_3), 1.14 (3 H, t, *J* 8 Hz, OCOCH$_2$*Me*), 1.61 (3 H, s, 19-H_3), 2.05 (3 H, s, OAc), 2.31 (2 H, q, *J* 8 Hz, OCOC*H*$_2$Me), 4.60 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H) and 5.16 (1 H, dd, *J* 7.5, 16 Hz, 1-H).

1(10→6)abeo-4-*Nor*-5β,6β-*androst*-10(19)-*ene*-1α,17β-*diol* 1-*Acetate* 17-*Propionate* **27**.—The more polar fraction from the preceding chromatography yielded *ester* **27** (8 mg) (Found: C, 73.55; H, 9.15%); ν_{max}/cm^{-1} 3090, 1650, 1640 and 898 (C=C), 1740 and 1250 (OAc) and 1740 and 1196 (OProp); δ_H 0.80 (3 H, s, 18-H_3), 1.14 (3 H, t, *J* 8 Hz, OCOCH$_2$*Me*), 2.03 (3 H, s, OAc), 2.31 (2 H, q, *J* 8 Hz, OCOC*H*$_2$Me), 4.64 (1 H + 2 H, m, 17-H and 19-H_2) and 5.16 (1 H, dd, J_1 7.5, J_2 16 Hz, 1-H).

(5R)-3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3α,5,17β-*triol* 3-*Acetate* 17-*Propionate* 5-*Thiobenzoate* **19**.—The imidoyl chloride methochloride[11] (prepared from *N*,*N*-dimethylbenzamide and phosgene) (6 cm^3) was added dropwise under argon to a refluxing solution of compound **16** (730 mg, 1.87 mmol) in THF (7 cm^3). The reaction mixture was stirred at room temperature for 20 h, then pyridine (0.5 cm^3) was added, hydrogen sulphide was bubbled through the solution for 15 min, and the mixture was kept for 2h before being diluted with dichloromethane, washed successively with aq. potassium hydrogen carbonate and water, dried, and evaporated under reduced pressure. The crude product was chromatographed on silica gel in light petroleum–ethyl acetate (9:1). The following substances were eluted:

(i) *Thiobenzoate* **19** (500 mg, 52%) (Found: C, 70.45; H, 7.5; S, 6.3. $C_{30}H_{38}O_5S$ requires C, 70.6; H, 7.5; S, 6.3%); ν_{max}/cm^{-1} 1749, 1245 and 1045 (AcO), 1748 and 1199 (PropO) and 1264, 1230 and 690 (PhCSO); δ_H 0.94 (3 H, s, 18-H_3), 1.00 (3 H, s, 19-H), 1.16 (3 H, t, *J* 8 Hz, OCOCH$_2$*Me*), 2.03 (3 H, s, AcO), 2.31 (2 H, q, *J* 8 Hz, OCOC*H*$_2$Me), 4.67 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H), 4.98 (1 H, m, 3-H) and 5.35 (1 H, d, *J* 3 Hz, 5-H); *m*/*z* 512 (3%, M$^+$), 314 (280) and 241 (100); (ii) starting material **16** (106 mg, 15% recovery).

3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3α,17β-*diol* 3-*Acetate* 17-*Propionate* **21**.—A solution of thiobenzoate **19** (400 mg, 0.78 mmol) in toluene (1.6 cm^3) was added dropwise to a refluxing solution of tributyltin hydride (3 cm^3; 1 mol dm^{-3} solution of tributyltin hydride in benzene) and AIBN (3 mg). After the mixture had been refluxed for 4 h the solvent was evaporated off, and the residue was applied to a column of silica gel (50 g), which was then eluted with light petroleum–ethyl acetate (19:1). *Diester* **21** (200 mg, 69%) was obtained, $[\alpha]_D$ +8° (*c* 2.2) (Found: C, 73.95; H, 9.2. $C_{23}H_{34}O_4$ requires C, 73.8; H, 9.15%); ν_{max}/cm^{-1} 1750 and 1199 (OProp) and 1750, 1245 and 1045 (OAc); δ_H 0.82 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 1.14 (3 H, t, *J* 8 Hz, OCOCH$_2$*Me*), 2.03 (3 H, s, AcO), 2.31 (2 H, q, *J* 8 Hz, OCOC*H*$_2$Me) and 4.62 (2 H, m, 17- and 3-H).

3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3α,17β-*diol* **28**.—Diester **21** (15 mg) was added to a suspension of lithium aluminium hydride (10 mg) in dioxane (0.5 cm^3) and the mixture was refluxed for 5 h. Several drops of water were added to the reaction mixture and the residue was applied to preparative plates and developed with benzene–diethyl ether (8:2). Diol **28** (7 mg) was identical with an authentic sample (TLC, IR, ^{1}H NMR).

(5R)-3,6-*Cyclo*-4-*nor*-3,5-*seco*-6β-*androstane*-3α,5,17β-*triol* 3-*Acetate* 5-(1H-*Imidazole*-1-*carbothioate*) 17-*Propionate* **20**.—Thiocarbonyldiimidazole (17 mg) was added to a refluxing solution of compound **16** (200 mg, 0.39 mmol) in 1,2-dichloro-

ethane (2 cm^3). After 5 h the reaction mixture was applied to preparative plates, which were then developed with benzene–diethyl ether (8:2); starting material (64 mg) and *thioimidazolide* **20** (109 mg) were eluted (Found: C, 64.3; H, 7.5; N, 5.55; S, 6.4. $C_{27}H_{38}N_2O_5S$ requires C, 64.58; H, 7.63; N, 5.58; S, 6.37%); δ_H 0.90 (3 H, s, 18-H_3), 1.00 (3 H, s, 19-H_3), 1.16 (3 H, t, *J* 8 Hz, $OCOCH_2Me$), 2.04 (3 H s, AcO), 2.31 (2 H, q, *J* 8 Hz, $OCOCH_2Me$), 4.67 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H), 4.90 (1 H, m, 3-H), 5.15 (1 H, d, *J* 3 Hz, 5-H), 7.07 (1 H, s, 4′-H), 7.63 (1 H, s, 5′-H) and 8.33 (1 H, s, 2′-H).

3-*t*-*Butyldimethylsiloxy*-17-*propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androst*-2-*en*-5-*one* **10**.—To a solution of diketone **5** (4.2 g, 12.12 mmol) in DMF (5 cm^3) and triethylamine (10 cm^3, *ca.* 100 mmol) was added t-butyldimethylsilyl chloride (7 g, 46.4 mmol) and the solution was heated at 150 °C for 48 h. Crystals of the ammonium salt were filtered off and the solution was diluted with ethyl acetate. This solution was washed successively with brine and aq. potassium hydrogen carbonate, dried and evaporated. The mixture was applied to a column of silica gel (350 g) and was eluted with light petroleum–ethyl acetate (97:3). The following compounds were separated:

(i) *t*-*Butyldimethylsilyl enol ether* **10** (3.85 g, 69%), m.p. 106 °C (from MeOH); $[\alpha]_D$ −111° (*c* 1.9) (Found: C, 70.4; H, 9.6. $C_{27}H_{44}O_4Si$ requires C, 70.4; H, 9.6%); ν_{max}/cm^{-1} 3050, 1680 and 1664 (C=C), 1740 and 1194 (OProp), 1740 (C=O) and 1259, 1194 and 855 (Si–O); δ_H 0.14 (3 H, s, MeSi), 0.17 (3 H, s, MeSi), 0.74 (3 H, s, 18-H_3), 0.92 (9 H, s, Bu^{t}Si), 1.12 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, $MeCH_2CO_2$), 2.31 (2 H, q, *J* 7.6 Hz, $MeCH_2CO_2$) and 4.47–4.73 (2 H, m, 17- and 2-H); (ii) starting diketone **5** (600 mg, 15% recovery).

(5R)-3-*t*-*Butyldimethylsiloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androst*-2-*ene*-5,17β-*diol* 17-*Propionate* **11**.—A solution of lithium tri-t-butoxyaluminium hydride (2.13 g, 8.38 mmol) in THF (12 cm^3) was added dropwise to a solution of ketone **10** (1.05 g, 2.28 mmol) in THF (12.5 cm^3). The mixture was stirred at room temperature for 30 min, diluted with diethyl ether, and rapidly washed successively with 1.5% hydrochloric acid, aq. potassium hydrogen carbonate and water, dried (magnesium sulphate), and evaporated. *Compound* **11** (850 mg, 81%) was obtained, m.p. 105–106 °C (from MeOH); $[\alpha]_D$ −99° (*c* 1.9) (Found: C, 7.1; H, 10.0. $C_{27}H_{46}O_4Si$ requires C, 7.1; H, 10.0%); ν_{max}/cm^{-1} 3635 and 1060 (OH), 3050, 1680 and 1665 (C=C), 1765, 1741 and 1202 (OProp) and 1289, 1220, 1202, 859 and 845 (SiO); δ_H 0.14 (6 H, s, MeSi), 0.83 (3 H, s, 18-H_3), 0.97 (9 H, s, Bu^{t}Si), 1.09 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, $MeCH_2CO_2$), 2.31 (2 H, q, *J* 7.6 Hz, $MeCH_2CO_2$), 3.55 (1 H, d, *J* 4.2 Hz, 5-H) and 4.47–4.73 (2 H, m, 17- and 2-H).

(5R)-5-*Hydroxy* 17β-*propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-3-*one* **12**.—A solution of tetrabutylammonium fluoride (10 cm^3; 1 mol dm^{-3} in THF) was added to a stirred solution of silyl enol ether **11** (5.1 g, 11 mmol) in THF (18 cm^3) and the mixture was kept at room temperature for 5 min before being diluted with toluene and adsorbed on a short column of silica gel. The column was eluted with benzene–ether (9:1) the eluate was evaporated. The residue was applied to a second column of silica gel (120 g) and eluted with light petroleum–ethyl acetate (75:25) to afford *ketone* **12** (3.5 g, 91%), m.p. 143 °C (from acetone–heptane); $[\alpha]_D$ +39° (*c* 1.8) (Found: C, 72.4; H, 9.4. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%); ν_{max}/cm^{-1} 3630 and 1084 (OH) 1738 and 1202 (OProp) and 1700 (C=O); δ_H 0.82 (3 H, s, 18-H_3), 1.09 (3 H, s, 19-H_3), 1.13 (3 H, t, *J* 7.6 Hz, $MeCH_2CO_2$), 2.31 (2 H, q, *J* 7.6 Hz, $MeCH_2CO_2$), 3.57 (1 H, d, *J* 4.2 Hz, 5-H) and 4.57 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H).

5-(1H-*Imidazole*-1-*thiocarbonyloxy*)-17β-*propionyloxy*-3,6-*cyclo*-4-*nor*-3,5-*seco*-6β-*androstan*-3-*one* **29**.—Thiocarbonyldiimidazole (2 g, 11.2 mmol) was added to a solution of compound **12** (2 g, 5.74 mmol) and a catalytic amount of DMAP in toluene (15 cm^3). The mixture was refluxed for 4 h and then evaporated under reduced pressure. The residue was applied to a column of silica gel (120 g) and eluted with light petroleum–ethyl acetate (19:1). The following compounds were eluted:

(i) *Imidazole thioester* **29** (1.86 g, 63%); $[\alpha]_D$ −43° (*c* 2.28) (Found: C, 65.4; H, 7.5; N, 6.1; S, 7.0. $C_{25}H_{34}N_2O_4S$ requires C, 65.5; H, 7.5; N, 6.1; S, 7.0%); ν_{max}/cm^{-1} 1740 and 1300 (OProp), 1720 (C=O) and 1392, 1240 and 900 (N–C=S); δ_H 0.87 (3 H, s, 18-H_3), 1.10 (3 H, s, 19-H_3), 1.14 (3 H, t, *J* 7.6 Hz, $MeCH_2CO_2$), 2.33 (2 H, q, *J* 7.6 Hz, $MeCH_2CO_2$), 4.62 (1 H, dd, J_1 7.3, J_2 9.3 Hz, 17-H), 5.62 (1 H, d, *J* 4.2 Hz, 5-H), 7.10 (1 H, s, 4′-H), 7.64 (1 H, s, 5′-H) and 8.31 (1 H, s, 2′-H); (ii) starting alcohol **13** (100 mg, 5% recovery).

Acknowledgements

We thank Dr. J. Smolíková for IR spectra, Dr. Y. Malát and Dr. T. Waisar for mass spectral measurements and Mrs. J. Jelinková for NMR spectra. The elemental analyses were performed (Dr. V. Pechanec) in the analytical department of this Institute.

References

1 A. Kasal, *Collect. Czech. Chem. Commun.*, 1979, **44**, 1619.
2 A. Kasal, unpublished results.
3 J. Polman and A. Kasal, *Collect. Czech. Chem. Commun.*, 1990, **55**, 1783.
4 J. T. Edward, D. Holder, W. H. Lunn and I. Puskas, *Can. J. Chem.*, 1961, **39**, 599.
5 B. E. Edwards and P. N. Rao. *J. Org. Chem.*, 1966, **31**, 324.
6 B. E. Edwards and P. N. Rao, USP 3 329, 688 (*Chem. Abstr.*, 1967, **67**, 108854).
7 J. Martin, W. Parker, B. Shroot and T. Stewart, *J. Chem. Soc. C*, 1967, 101.
8 E. J. Corey and K. Achiva, *Tetrahedron Lett.*, 1969, 1837.
9 J. Polman, unpublished results.
10 A. Kasal, *Collect. Czech. Chem. Commun.*, 1978, **43**, 1778.
11 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.

Paper 0/03420G
Received 26*th July* 1990
Accepted 6*th September* 1990