Synthesis of 4-Hydroxy-15-oxaandrost-4-en-3-one and other Potential Aromatase Inhibitors from Sandaracopimaric Acid

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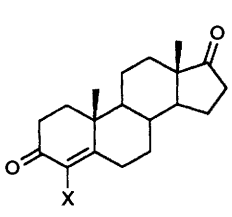
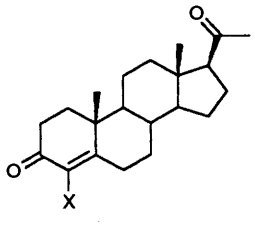
The stereoselective synthesis of 4-substituted androstenes (8β,14α) **30** and **36** related to inhibitors of the enzyme aromatase and 5α-reductase has been achieved in a short-step sequence from sandaracopimaric acid. The synthetic strategy is the stereoselective construction of ring D, and the appropriate modification of the A-ring diterpene functionality to the enone system found in the aromatase inhibitors. A parallel sequence is developed to obtain the isomers (8α,14β) **31** and **41**.

Inhibition of the enzyme aromatase, which catalyses the final stages of estrogen biosynthesis by some 4-substituted androstenones **1**–**3**, is a valuable strategy in the therapeutic treatment of neoplastic diseases such as breast cancer.[1] In addition, it has recently been shown that some 4-substituted progestagens **4** and **5** are inhibitors of the enzyme 5α-reductase[2] involved in the conversion of the male hormone testosterone into dihydrotestosterone, which has been implicated in prostate enlargement in later life. Reduction of dihydrotestosterone by inhibition of 5α-reductase could be a strategy for the control of prostatic hyperplasia and prostatic cancer.



1 X = OH
2 X = OMe
3 X = OAc



4 X = F
5 X = CN

In this context some recent work has been done on the synthesis of analogues of 4-hydroxyandrost-4-ene-3,17-dione **1**, one of the most potent aromatase inhibitors known, with the aim of enhancing the antineoplastic activity.[3] This encouraged us to prepare related compounds starting from sandaracopimaric acid **6**, a readily available and inexpensive naturally occurring diterpenoid.

Results and Discussion

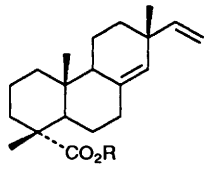
We were interested in the functionality shown by compounds **30** and **36**, in which the D ring has been altered by replacement of the methylene group C-15 by an oxygen atom and of the hydroxy or keto functions of C-17 by hydrogen atoms. These modifications in functionality would be justified by the higher oral activity shown by 15-oxasteroids and the low affinity shown by some receptors for 17-hydroxysteroids.

Sandaracopimaric acid **6** is a useful starting material for the synthesis of novel steroidal derivatives due to its suitable structural characteristics.[4] Transformation of sandaracopimaric acid **6** to the target molecule required: (i) building the D ring; (ii) removing the methoxycarbonyl group attached to C-4 and in some cases the methyl group on C-4; (iii) introducing the required functionality in the A ring.

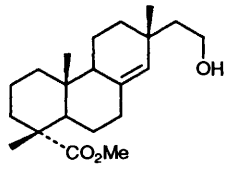
We approach two types of transformation: **7** ⟶ **10** ⟶ **14** ⟶ **19** ⟶ **21** ⟶ **30**, and **7** ⟶ **19** ⟶ **23** ⟶ **32** ⟶ **35** ⟶ **36**.

Construction of the D ring common to both transformations requires functionalization of carbons C-14 and C-16, and cyclization.

The first step was accomplished by hydroboration of methyl sandaracopimarate **7** with diborane generated '*in situ*' from sodium boranuide and boron trifluoride–diethyl ether in diglyme.[5] With a reagent:substrate ratio of 3:1 (3 h; room temp.), followed by the usual oxidative work-up, a mixture of monohydroxylated products **8** and **9** (23%) was obtained; dihydroxylated products **10** and **11** (56%); and trihydroxylated compounds **12** and **13** (14%). The **10**:**11** ratio was 30:70. When a six-fold excess of 1 mol dm^{-3} diborane solution in tetrahydrofuran (THF) was added to methyl sandaracopimarate **7**, and the reaction time was 1 h, the mixture obtained was the following: **8** and **9** (24%); **10** and **11** (70%); and **12** and **13** (4%). The **10**:**11** ratio was the same as above. While the minor diol **10** possesses the right configuration (8β,14α) for access to *trans-anti-trans* androstanes, the major diol **11** has the inverse configuration (8α,14β). This fact prompted us to



6 R = H
7 R = Me



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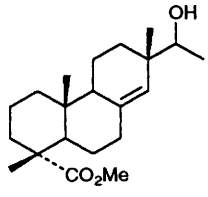

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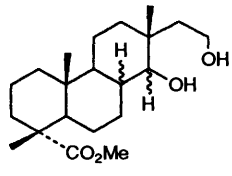
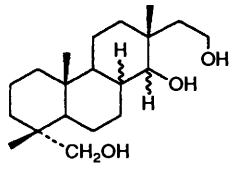
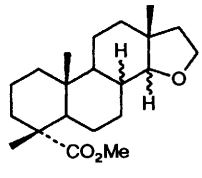


10 (8β, 14α)
11 (8α, 14β)



12 (8β, 14α)
13 (8α, 14β)



14 (8β, 14α)
15 (8α, 14β)

Table 1 Products obtained on allylic oxidation of the androstene **21**

Conditions	Products, yield (%)			
	21	**30**	**29**	Others
SeO_2, EtOH, 100 °C, 22 h	48			40
CrO_3, AcOH, 100 °C, 1 h		30		56
NBS, $CaCO_3$, dioxane–water, 25 °C, 2 h		34		20
Na_2CrO_4, Ac_2O–AcOH–AcONa, 50 °C, 23 h	11	40	11	28
$CrO_2(OBu^t)_2$, Ac_2O–AcOH–CCl_4, 80 °C, 17 h		29	17	10
CrO_3, DMP, CH_2Cl_2, −25 °C, 2 h		51	13	9

transform compound **11** (8α,14β) into **10** (8β,14α); however, we considered it interesting to perform the transformation into androstanes from both diols.

Cyclodehydration of diols **10** and **11** separately to oxolanes (tetrahydrofurans) **14** and **15**[6] was carried out firstly with toluene-*p*-sulfonyl chloride in pyridine, with 18% and 36% yield, respectively; a better yield (43%) was obtained with boron trifluoride–diethyl ether. The best conditions for the cyclization of diols **10** and **11** were attained with toluene-*p*-sulfonic acid (PTSA) in refluxing benzene, which afforded 15-oxaandrostanes **14** and **15** in quantitative yield. In practice, the cyclization is better to be carried out with the diol mixture because the separation of ethers **14** and **15** is easier than that of diols **10** and **11**.

The transformation of diol **11** (8α,14β) into the ether **14** (8β,14α) was carried out by the sequence **11** ⟶ **16** ⟶ **17** ⟶ **17a** ⟶ **18** ⟶ **14**. Selective protection of the primary alcohol of diol **11** was achieved quantitatively with trityl chloride in dimethylformamide (DMF)[7] at 25 °C. The oxidation of protected compound **16** with chromium trioxide in pyridine yielded ketone **17** (96%). Treatment with sodium methoxide in methanol epimerized **17** to compound **17a** in quantitative yield. The reduction of compound **17a** with sodium boranuide afforded a 7:3 mixture of hydroxy derivatives **18** and **18a** in 93% yield. Finally, deprotection of the primary hydroxy group of compound **18** with PTSA succeeded with concomitant formation of a THF derivative, to give compound **14** in quantitative yield.

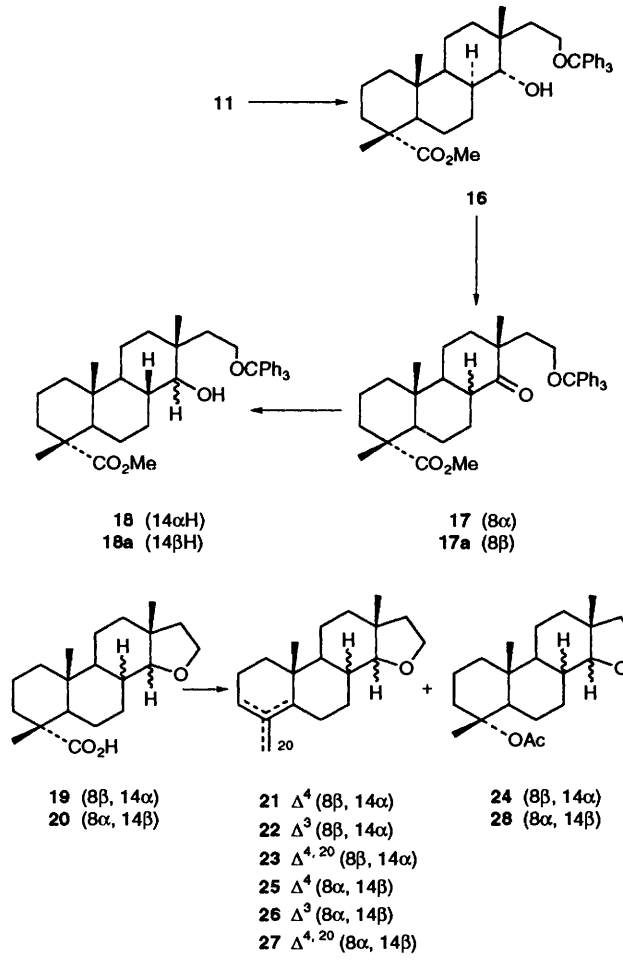
For the elimination of the carboxylic and methyl groups at C-4, hydrolysis of the ester group is required; this was accomplished in quantitative yield with potassium hydroxide in ethylene glycol under reflux for both isomers **14** and **15** individually.

Oxidative decarboxylation of acid **19** with lead tetraacetate (LTA) in benzene gave a 31:36:33 mixture of olefinic ethers **21**–**23** (66%) and the acetate **24** (24%). Pyrolysis of compound **24** quantitatively afforded a 2:1:2 mixture of ethers **21**–**23**. The absolute yield of olefinic ethers **21**, **22** and **23** from acid **19** were 29, 31 and 31%, respectively. The same process carried out with acid **20** afforded the olefinic ethers **25**, **26** and **27** in 26, 31 and 30% yield, respectively.

Our first target, compound **30**, required a two-step sequence from the mixture of olefinic ethers **21**–**23**. Treatment of the mixture with iodine in refluxing benzene[8] afforded the tetrasubstituted olefinic **21** after half an hour, in quantitative yield. Allylic oxidation of androstene **21** was attempted with several reagents with the results shown in Table 1.

The best yield of enone **30** was obtained with the complex chromium trioxide–dimethylpyrazole.[9] The mild conditions and short reaction time reduce the proportion of polar-product oxidation. However, the epoxide **29** was obtained in 13% yield. A lower reaction temperature (−78 °C) did not improve the yield of compound **30**. The high sensitivity of the oxolane ring of compound **21** to oxidants was responsible for the low yields obtained in some oxidations.

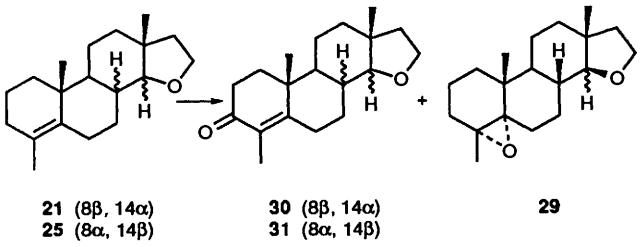
Allylic oxidation of *trans-anti-cis* isomer **25** with sodium chromate afforded a very low yield (6%) of enone **31** and a complex mixture of polar products. However, with the complex chromium trioxide–dimethylpyrazole a 53% yield of enone **31** was obtained. No epoxide was found this time.

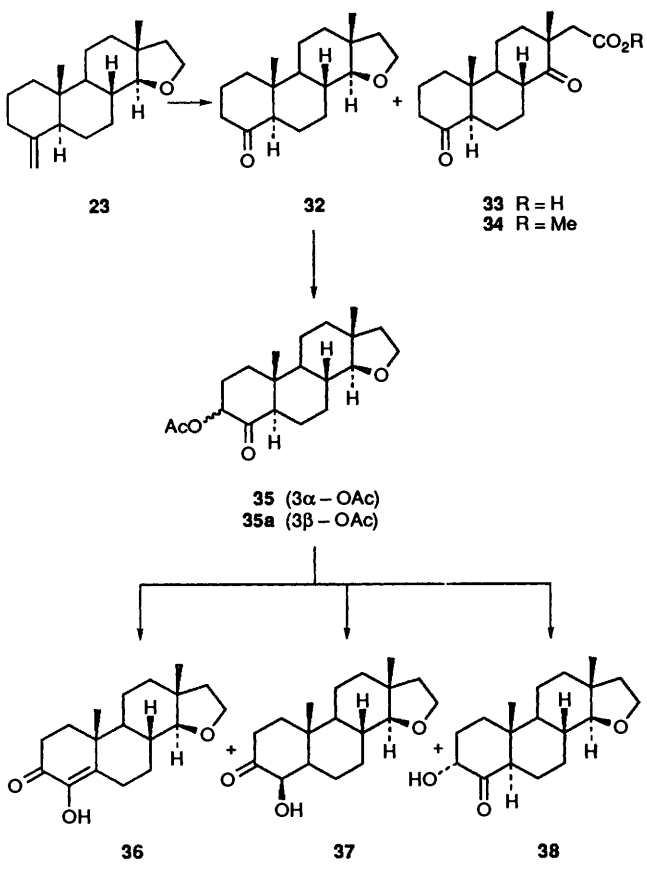


The second target, compound **36**, was obtained in three steps from the antrostene **22**. Oxidative cleavage of the compound **23** exocyclic double bond carried out with ruthenium tetraoxide, generated '*in situ*' from ruthenium dioxide and sodium periodate,[10] gave the keto ether **32** (36%) and the diketone **33** (34%). The fast rate of oxidation at the α-carbon to the oxygen in the oxolane ring was a drawback in obtaining high yields of the desired products by this simple method. Ozonolysis of compound **23** afforded only keto ether **32** in 85% yield.

Regioselective α-acetoxylation of compound **32** was achieved with LTA[11] at room temperature in benzene to give a 14:1 mixture of epimers **35** and **35a** in 60% yield.

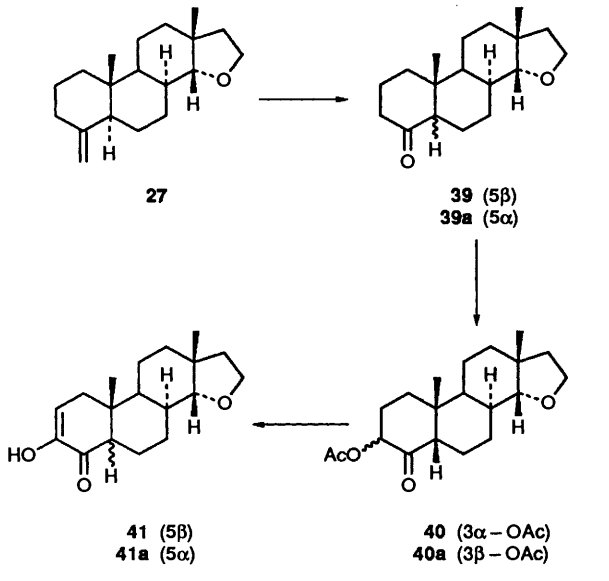
Treatment of α-acetate **35** with potassium hydroxide in ethanol–water under reflux[12] for 3 h, the last step in the sequence, afforded the target compound **36** and two epimeric hydroxy ketones **37** and **38**, in 5:2:1 proportions and 70% yield.



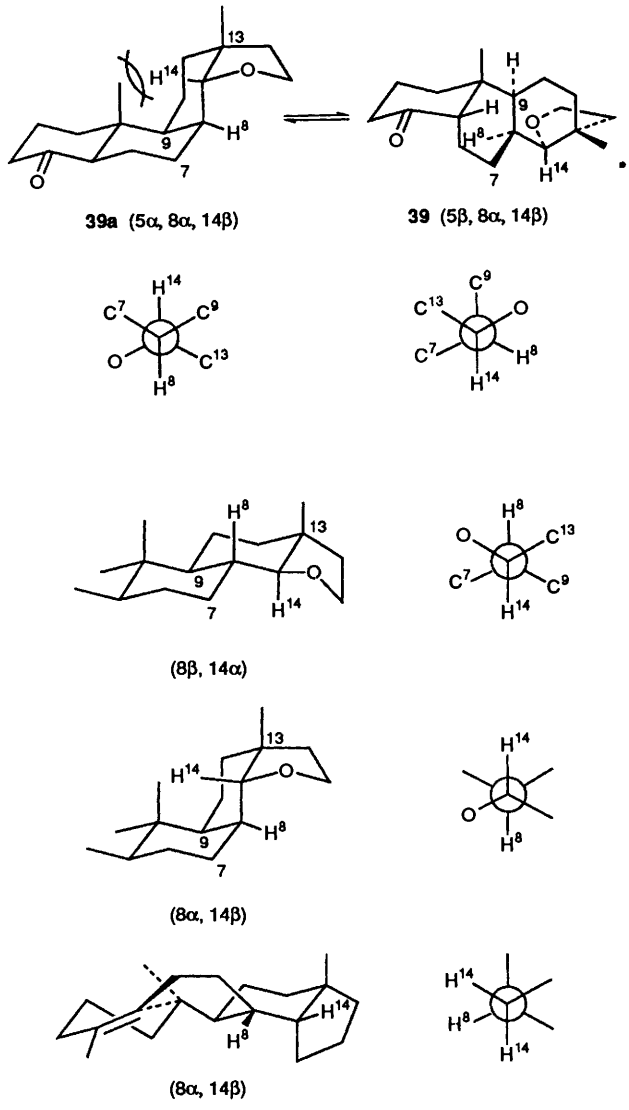


The described three-step sequence was applied to the *trans-anti-cis* androstene **27**. Oxidative cleavage of the double bond was carried out with potassium permanganate–dicyclohexyl-18-crown-6 [13] in a benzene–water mixture over 95 h to give the 4-oxo androstane **39** in 65% yield. The easy epimerization of C-5α ⟷ C-5β of the cleavage product and the conformational change of the molecule must be promoted by the release of the 1,3-diaxial interaction observed in 5α isomer **39a**.

Treatment of ketone **39** with LTA in refluxing benzene regioselectively afforded a 1:1 mixture of acyl acyloins **40** and **40a** in 68% yield. The lack of stereoselectivity in this case must be due to steric requirements; both faces of the enolized ring A of substrate **39** showed an axial substituent.



The last step in the sequence carried out with potassium hydroxide in ethanol–water [12] converted the mixture of acyloins **40** and **40a** into the single hydroxy ketone **41**, in almost quantitative yield. The result obtained in the latter reaction is coherent with the higher thermodynamic stability of the 5β-isomer **41** as compared with that of the potential isomer **41a**.



Experimental

General.—Mps were determined on a Kofler hot-stage apparatus and are not corrected. IR spectra were recorded on a Beckman 33-IR spectrophotometer, for film samples. The ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker WP-200-SY spectrometer. Spectra were measured in deuteriochloroform. Chemical shifts are given in ppm downfield from tetramethylsilane. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra; *J* values are given in Hz. Optical rotations were measured on a digital Perkin-Elmer 241 polarimeter in a 1-dm cell, and are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured on a V.G. TS-250 apparatus. Microanalyses were performed using a Carlo Erba 1106 elemental analyser.

Solvents were distilled before use and were dried, as necessary, by literature procedures. Work-up of solutions involved evaporation under reduced pressure at below 40 °C. Reactions were carried out under nitrogen. Silica gel for column chromatography refers to Merck Kieselgel 60.

Hydroboration of Methyl Sandaracopimarate **7**.—*Method* (*a*): *With diborane generated* in situ. To a solution of compound **7** (21 g, 66.4 mmol) in diglyme (55 cm^3) was added first a solution of sodium boranuide (5.8 g, 154 mmol) in diglyme (110 cm^3) and then, dropwise, boron trifluoride (27 g, 192 mmol) in diglyme (27 cm^3). The mixture was stirred for 3 h at room temperature after which was added gradually at 0 °C, ice–water (13 cm^3), 3 mol dm^{-3} aq. NaOH (66 cm^3) and 30% H_2O_2 (66 cm^3). After the reaction mixture had been stirred for 1 h it was left overnight at room temperature. Then it was poured into ice–water (1 dm^3) and extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4) and evaporated. The crude mixture was chromatographed on silica gel (350 g). With hexane–diethyl ether (1 : 1) as eluent a mixture of monohydroxylated compounds **8** and **9** (5.1 g, 23%) was obtained.

With hexane–diethyl ether (1 : 3) as eluent, a mixture of compounds **10** and **11** was given in the ratio ~30 : 70 (13.1 g, 56%). Crystallization from hexane–diethyl ether gave *methyl* 14α,16-*dihydroxy*-8α-*isopimarate* **11**, mp 145–146 °C; $[\alpha]_D^{20}$ +28.6 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 3300, 1740 and 1255; δ_H 1.06 (6 H, s), 1.19 (3 H, s), 3.54 (1 H, d, *J* 12), 3.67 (3 H, s) and 3.70 (2 H, m); δ_C 16.84 (C-19), 17.90 (C-11), 19.27 (C-20), 19.94 (C-6), 21.07 (C-2), 26.32 (C-17), 26.32 (C-12), 36.20 (C-15), 36.79 (C-3), 37.85 (C-8), 37.87 (C-10), 38.57 (C-7), 38.73 (C-13), 39.86 (C-1), 47.62 (C-4), 49.76 (C-9), 50.05 (C-5), 51.57 (OMe), 58.60 (C-16), 75.26 (C-14) and 179.50 (C-18) (Found: C, 71.6; H, 10.2%; M^+, 352. $C_{21}H_{36}O_4$ requires C, 71.59; H, 10.23%; M, 352). Concentration of the mother liquors gave *methyl* 14β,16-*dihydroxyisopimarate* **10**, $[\alpha]_D^{20}$ −13.4 (*c* 1.6, $CHCl_3$); ν_{max}/cm^{-1} 3300, 1735 and 1245; δ_H 0.88 (6 H, s), 1.18 (3 H, s), 2.94 (1 H, d, *J* 10), 3.62 (3 H, s) and 3.69 (2 H, m); δ_C 14.47 (C-20), 15.52 (C-17), 16.58 (C-19), 18.03 (C-11), 19.38 (C-2), 23.90 (C-6), 23.90 (C-12), 31.02 (C-7), 36.14 (C-10), 36.88 (C-15), 37.85 (C-13), 38.08 (C-3), 38.08 (C-8), 46.41 (C-1), 47.52 (C-4), 49.54 (C-5), 51.68 (OMe), 54.42 (C-9), 58.25 (C-16), 81.43 (C-14) and 179.32 (C-18) (Found: C, 71.6; H, 10.2%; M^+, 352).

With diethyl ether as eluent, a mixture of the triols **12** and **13** (3.0 g, 14%) was obtained.

Method (*b*): *With a solution of borane in tetrahydrofuran*. To a stirred solution of compound **7** (5.48 g, 17.4 mmol) in THF (25 cm^3) at 0 °C was added dropwise a solution of borane in THF (104 cm^3; 1 mol dm^{-3}). The mixture was then stirred at 0 °C for 1 h and at room temperature overnight after which were added successively to the reaction mixture water (15 cm^3), 3 mol dm^{-3} aq. NaOH (20 cm^3) and, at 0 °C, 30% H_2O_2 (20 cm^3). The mixture was heated at 50 °C for 1 h, after which it was cooled at room temperature and extracted with diethyl ether. The extract was dried (Na_2SO_4) and evaporated. The crude mixture was chromatographed on silica gel (100 g). With hexane–diethyl ether (3 : 1) as eluent, a mixture of monohydroxylated compounds **8** and **9** (1.43 g, 24%) was obtained.

With hexane–diethyl ether (1 : 1) as eluent, a mixture of the diols **10** and **11** (4.3 g, 70%) was obtained.

With diethyl ether as eluent, a mixture of the triols **12** and **13** (0.2 g, 4%) was obtained.

Methyl 4β-*Methyl*-15-*oxaandrostane*-4α-*carboxylate* **14**.—To a solution of compound **10** (8.11 g, 23.0 mmol) in benzene (811 cm^3) was added PTSA (0.81 g, 4.22 mmol). The mixture was heated under reflux for 40 h after which it was cooled to room temperature and washed successively with saturated aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give the ester **14** (7.70 g, 100%), mp 85–86 °C; $[\alpha]_D^{20}$ −8.7 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 1715 and 1235; δ_H 0.81 (3 H, s), 0.90 (3 H, s), 1.15 (3 H, s), 2.71 (1 H, d, *J* 10.7), 3.62 (3 H, s) and 3.83 (2 H, m); δ_C 14.62 (C-19), 16.60 (CH_3, 4β), 17.49 (C-18), 18.12 (C-11), 19.96 (C-6), 23.70 (C-2), 31.07 (C-12), 34.52 (C-17), 35.42 (C-8), 36.34 (C-10), 36.93 (C-3), 38.34 (C-1), 39.88 (C-7), 40.07 (C-13), 47.62 (C-4), 50.09 (C-5), 51.69 (OMe), 54.60 (C-9), 65.48 (C-16), 89.78 (C-14) and 179.18 (CO_2H) (Found: C, 75.5; H, 10.2%; M^+, 334. $C_{21}H_{34}O_3$ requires C, 75.45, H, 10.18%; M, 334).

Methyl 4β-*Methyl*-15-*oxa*-8α,14β-*androstane*-4α-*carboxylate* **15**.—To a solution of the diol **11** (8.11 g, 23.0 mmol) in benzene (811 cm^3) was added PTSA (0.81 g, 4.22 mmol). The mixture was heated under reflux for 40 h after which it was cooled to room temperature and washed successively with saturated aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give the *title compound* **15** (7.70 g, 100%), mp 179 °C; $[\alpha]_D^{20}$ +23.4 (*c* 1.7, $CHCl_3$); ν_{max}/cm^{-1} 1715 and 1235; δ_H 0.94 (3 H, s), 1.08 (3 H, s), 1.18 (3 H, s), 3.56 (1 H, d, *J* 10), 3.65 (3 H, s) and 3.76 (2 H, m); δ_C 16.93 (CH_3, 4β), 17.87 (C-19), 17.87 (C-11), 20.00 (C-6), 21.05 (C-2), 26.58 (C-12), 27.19 (C-18), 33.08 (C-17), 37.02 (C-3), 37.70 (C-8), 37.70 (C-10), 39.54 (C-1), 39.73 (C-7), 40.55 (C-13), 47.49 (C-4), 48.43 (C-9), 49.44 (C-5), 51.82 (OMe), 64.62 (C-16), 84.04 (C-14) and 179.35 (CO_2H) (Found: C, 75.5; H, 10.2%; M^+, 334).

Methyl 14α-*Hydroxy*-16-*triphenylmethoxy*-8α-*isopimarate* **16**.—To a solution of the diol **11** (800 mg, 2.3 mmol) in DMF (10 cm^3) were added successively triethylamine (0.56 cm^3, 4.0 mmol), 4-dimethylpyridine (21 mg, 0.2 mmol) and triphenylmethyl chloride (1.26 g, 4.5 mmol); the reaction mixture was stirred at room temperature for 2 h after which was added a further portion of triphenylmethyl chloride (1.26 mg, 4.5 mmol); after three such treatments the reaction mixture was stirred for 1 h and extracted with dichloromethane. The extract was washed successively with saturated aq. NH_4Cl and water, dried (Na_2SO_4), and evaporated. The crude mixture was chromatographed on silica gel.

With hexane–diethyl ether (70 : 30) as eluent, *compound* **16** (1.07 g, 78%) was obtained; $[\alpha]_D^{20}$ +37.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3400, 3110, 3050, 1735, 770 and 710; δ_H 0.74 (3 H, s), 0.95 (3 H, s), 1.11 (3 H, s), 3.58 (3 H, s) and 7.16–7.32 (15 H, m); δ_C 16.85 (C-19), 17.97 (C-11), 19.32 (C-20), 20.13 (C-6), 21.17 (C-2), 26.50 (C-12), 26.50 (C-17), 31.98 (C-7), 36.94 (C-15), 36.99 (C-10), 37.69 (C-3), 38.12 (C-8), 38.62 (C-13), 39.96 (C-1), 47.67 (C-4), 49.80 (C-9), 50.12 (C-5), 51.71 (OMe), 60.76 (C-16), 75.91 (C-14), 87.56 (C-benzyl), 126.93 (Ar), 127.76 (Ar), 128.57 (Ar), 143.95 (Ar) and 179.42 (C-18) (Found: C, 80.8; H, 8.4%; M^+, 594. $C_{40}H_{50}O_4$ requires C, 80.81; H, 8.42%; M, 594).

Methyl 14-*Oxo*-16-*triphenylmethoxy*-8α-*isopimarate* **17**.—To a stirred solution of pyridine (2.9 cm^3) in dichloromethane (50 cm^3) was added CrO_3 (2.02 g, 20.2 mmol). After 15 min compound **16** (1.98 g, 3.3 mmol) was added in one portion and the reaction mixture was stirred for 30 min. The mixture was filtered, the filtrate was evaporated, the residue was dissolved in diethyl ether, and the solution was washed successively with 6% hydrochloric acid, 5% aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated. The crude mixture was chromatographed on silica gel. Elution with hexane–diethyl ether (90 : 10) gave *compound* **17** (1.6 g, 82%), mp 151–152 °C; $[\alpha]_D^{20}$ +38.0 (*c* 1.3, $CHCl_3$); ν_{max}/cm^{-1} 3030, 3060, 1725, 1710, 730 and 705; δ_H 0.61 (3 H, s), 0.87 (3 H, s), 1.05 (3 H, s), 3.55 (3 H, s) and 7.15–7.32 (15 H, m); δ_C 15.77 (C-20), 16.84 (C-19), 17.60 (C-11), 19.21 (C-2), 21.64 (C-6), 22.20 (C-17), 24.27 (C-12), 35.43 (C-7), 36.95 (C-3), 38.09 (C-10), 38.91 (C-15), 40.56 (C-1), 43.51 (C-9), 46.38 (C-13), 47.24 (C-4), 49.28 (C-5), 51.11 (C-8), 51.76 (OMe), 59.97 (C-16), 87.02 (C-benzyl), 126.85 (Ar), 127.67 (Ar), 128.59 (Ar), 144.15 (Ar), 179.23 (C-18) and 218.98 (C-14) (Found: C, 81.1; H, 8.1%; M^+, 592. $C_{40}H_{48}O_4$ requires C, 81.08; H, 8.11%; M, 592).

Methyl 14-*Oxo*-16-(*triphenylmethyoxy*)*isopimarate* **17a**.—A solution of sodium methoxide (336 mg, 6.2 mmol) in methanol

(4 cm^3) was added to a solution of compound **17** (1.47 g, 2.5 mmol) in methanol (30 cm^3); the mixture was heated under reflux for 1 h after which it was cooled to room temperature and evaporated; the residue was dissolved in water, the aqueous solution was extracted with diethyl ether, and the extract was washed with brine, dried (Na_2SO_4), and evaporated to give *compound* **17a** (1.47 g, 100%), $[\alpha]_D^{20}$ −14.2 (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1} 3060, 3020, 1730, 1700, 1250, 1070, 760 and 705; δ_H 0.85 (3 H, s), 0.95 (3 H, s), 1.07 (3 H, s), 3.55 (3 H, s) and 7.15–7.38 (15 H, m); δ_C 14.01 (C-20), 16.66 (C-19), 18.04 (C-11), 19.52 (C-2), 23.26 (C-6), 23.27 (C-17), 26.44 (C-12), 36.71 (C-7), 36.86 (C-10), 36.95 (C-3), 37.76 (C-15), 38.10 (C-1), 44.72 (C-9), 46.43 (C-13), 47.38 (C-4), 48.77 (C-5), 51.66 (OMe), 56.70 (C-8), 60.27 (C-16), 86.40 (C-benzyl), 126.63 (Ar), 127.51 (Ar), 128.66 (Ar), 144.42 (Ar), 178.78 (C-18) and 215.73 (C-14) (Found: C, 81.1; H, 8.1%; M^+, 592).

Methyl 14β-*Hydroxy*-16-(*triphenylmethoxy*)*isopimarate* **18**. —To a stirred solution of the ketone **17a** (2.0 g, 3.4 mmol) in methanol (75 cm^3) was added a solution of sodium boranuide (128 mg, 3.4 mmol) in methanol (12 cm^3). After 30 min the reaction mixture was evaporated, the residue was dissolved in water, and the aqueous solution was extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was chromatographed on silica gel (50 g). Elution with hexane–diethyl ether (90:10) gave *methyl* 14α-*hydroxy*-16-(*triphenylmethoxy*)*isopimarate* **18a** (565 mg, 28%), mp 199–200 °C; $[\alpha]_D^{20}$ −1.7 (*c* 0.8, $CHCl_3$); ν_{max}/cm^{-1} 3500, 3080, 3050, 1710, 1205, 1045, 750 and 695; δ_H 0.55 (3 H, s), 0.74 (3 H, s), 1.07 (3 H, s), 2.96 (1 H, s, $w_{h1/2}$ 4.5 Hz), 3.53 (3 H, s) and 7.15–7.34 (15 H, m); δ_C 14.76 (C-20), 17.47 (C-19), 18.86 (C-11), 20.32 (C-2), 21.50 (C-17), 24.79 (C-6), 30.68 (C-12), 33.48 (C-7), 36.08 (C-8), 36.67 (C-10), 37.39 (C-13), 37.53 (C-15), 38.82 (C-3), 41.17 (C-1), 48.17 (C-4), 48.34 (C-9), 49.69 (C-5), 52.16 (OMe), 60.60 (C-16), 76.00 (C-14), 88.12 (C-benzyl), 127.51 (Ar), 128.35 (Ar), 129.06 (Ar), 144.49 (Ar) and 179.73 (C-18) (Found: C, 80.8; H, 8.4%; M^+, 594. $C_{40}H_{50}O_4$ requires C, 80.81; H, 8.42%; M, 594).

Elution with hexane–diethyl ether (85:15) gave compound **18** (1.31 g, 65%), mp 188–189 °C; $[\alpha]_D^{20}$ +13.3 (*c* 1.3, $CHCl_3$); ν_{max}/cm^{-1} 3420, 3080, 3020, 1720, 1245, 1065, 750 and 700; δ_H 0.64 (3 H, s), 0.76 (3 H, s), 1.07 (3 H, s), 2.83 (1 H, d, *J* 9.5), 3.56 (3 H, s) and 7.16–7.32 (15 H, m); δ_C 14.54 (C-20), 16.70 (C-19), 16.99 (C-11), 16.99 (C-17), 18.15 (C-6), 19.42 (C-2), 24.01 (C-12), 36.28 (C-10), 36.88 (C-7), 37.04 (C-15), 37.55 (C-8), 37.96 (C-3), 38.24 (C-13), 42.55 (C-1), 47.62 (C-4), 49.78 (C-5), 51.87 (OMe), 54.58 (C-9), 60.30 (C-16), 80.78 (C-14), 87.58 (C-benzyl), 126.90 (Ar), 127.74 (Ar), 128.83 (Ar), 144.09 (Ar) and 179.29 (C-18) (Found: C, 80.8; H, 8.4%; M^+, 594).

Treatment of Compound **18** *with Toluene*-p-*sulfonic Acid*.—To a solution of compound **18** (1.6 g, 2.7 mmol) in benzene (160 cm^3) was added PTSA (160 mg, 0.8 mmol). The mixture was heated under reflux for 29 h after which it was cooled to room temperature and washed successively with saturated aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give compound **14** (0.90 g, 100%).

4β-*Methyl*-15-*oxaandrostane*-4α-*carboxylic Acid* **19**.—A solution of KOH (1.92 g, 34.2 mmol) in ethylene glycol (39 cm^3) was added to the ester **14** (4.60 g, 13.7 mmol). The mixture was heated under reflux for 21 h after which it was cooled to room temperature. The solution was acidified with 2 mol dm^{-3} hydrochloric acid and extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give the *acid* **19** (4.40 g, 99%), mp 190–191 °C; $[\alpha]_D^{20}$ +4.5 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1} 3200, 1700, 1260 and 1140; δ_H 0.84 (3 H, s), 0.91 (3 H, s), 1.15 (3 H, s), 2.84 (1 H, d, *J* 10.7) and 3.87 (2 H, m); δ_C 14.56 (C-19), 16.41 (CH_3, 4β), 17.45 (C-18), 18.08 (C-11), 19.92 (C-6), 23.34 (C-2), 30.84 (C-12), 34.54 (C-17), 35.35 (C-8), 36.28 (C-3), 36.62 (C-10), 38.41 (C-1), 39.73 (C-13), 40.02 (C-7), 47.19 (C-4), 50.06 (C-5), 54.64 (C-9), 65.43 (C-16), 89.81 (C-14) and 183.09 (CO_2H) (Found: C, 75.0; H, 10.0%; M^+, 320. $C_{20}H_{32}O_3$ requires C, 75.00; H, 10.00%; M, 320).

4β-*Methyl*-15-*oxa*-8α,14β-*androstane*-4α-*carboxylic Acid* **20**. —A solution of KOH (2.38 g, 42.5 mmol) in ethylene glycol (48 cm^3) was added to the ester **15** (5.7 g, 17 mmol). The mixture was heated under reflux for 17 h after which it was cooled to room temperature. The solution was acidified with 2 mol dm^{-3} hydrochloric acid and extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give the *acid* **20** (5.36 g, 98%), mp 198–199 °C; $[\alpha]_D^{20}$ +20.2 (*c* 0.8, $CHCl_3$); ν_{max}/cm^{-1} 3200, 1710 and 1285; δ_H 0.95 (3 H, s), 1.07 (3 H, s), 1.18 (3 H, s), 3.60 (1 H, d, *J* 10) and 3.75 (2 H, m); δ_C 16.66 (CH_3, 4β), 17.78 (C-11), 17.89 (C-19), 19.97 (C-6), 20.99 (C-2), 26.54 (C-12), 27.17 (C-18), 32.98 (C-17), 36.94 (C-8), 37.02 (C-3), 37.57 (C-10), 39.42 (C-1), 39.46 (C-7), 40.52 (C-13), 47.15 (C-4), 48.41 (C-9), 49.12 (C-5), 64.56 (C-16), 84.05 (C-14) and 184.65 (CO_2H) (Found: C, 75.0; H, 10.0%; M^+, 320).

Decarboxylation of the Acid **19**.—LTA (9.96 g, 22.5 mmol) was added to a stirred solution of the acid **19** (5.3 g, 16.7 mmol) in pyridine (10 cm^3)–benzene (440 cm^3). The mixture was heated under reflux for 3.5 h after which it was cooled to room temperature. The reaction mixture was washed successively with 2 mol dm^{-3} hydrochloric acid, 5% aq. sodium hydrogen carbonate, and brine, dried (Na_2SO_4), concentrated and chromatographed. Elution with hexane–diethyl ether (96:4) gave a mixture of the olefins **21**, **22** and **23** (2.40 g, 66%) in the proportions ~28:41:31 and an *acetoxy compound* **24** (1.10 g, 24%), $[\alpha]_D^{20}$ −32.1 (*c* 0.8, $CHCl_3$); ν_{max}/cm^{-1} 1750, 1265, 1070 and 1030; δ_H 0.83 (3 H, s), 0.93 (3 H, s), 1.43 (3 H, s), 1.90 (3 H, s), 2.71 (1 H, m) and 3.82 (2 H, m) (Found: C, 75.5; H, 10.2%; M^+, 334. $C_{21}H_{34}O_3$ requires C, 75.45; H, 10.18%; M, 334).

The olefinic mixture was rechromatographed on silica gel–$AgNO_3$ (80:20; 60 g) with hexane–diethyl ether (98:2) as eluent to give: 4-*methyl*-15-*oxaandrost*-4-*ene* **21** (672 mg, 18.5%), $[\alpha]_D^{20}$ +70.0 (*c* 0.8, $CHCl_3$); ν_{max}/cm^{-1} 2920, 1460 and 1380; δ_H 0.84 (3 H, s), 0.99 (3 H, s), 1.56 (3 H, s), 2.69 (1 H, d, *J* 10.5) and 3.84 (2 H, m); δ_C 17.30 (C-18), 19.00 (C-11), 19.33 (4-Me), 19.38 (C-19), 20.91 (C-6), 24.36 (C-2), 30.97 (C-12), 32.66 (C-3), 34.55 (C-17), 35.73 (C-8), 37.09 (C-10), 38.16 (C-1), 39.77 (C-7), 39.82 (C-13), 52.62 (C-9), 65.10 (C-16), 89.33 (C-14), 123.30 (C-4) and 136.00 (C-5) (Found: C, 83.1; H, 10.9%; M^+, 274. $C_{19}H_{30}O$ requires C, 83.12; H, 10.95%; M, 274).

4-*Methyl*-15-*oxaandrost*-3-*ene* **22** (984 mg, 27%), ν_{max}/cm^{-1} 2950, 1450 and 1380; δ_H 0.77 (3 H, s), 0.82 (3 H, s), 1.56 (3 H, s), 2.75 (1 H, d, *J* 10.5), 3.81 (2 H, m) and 5.24 (1 H, s); δ_C 12.09 (C-19), 17.52 (C-18), 20.60 (C-11), 21.14 (4-Me), 22.68 (C-6), 22.92 (C-20), 30.58 (C-12), 34.31 (C-17), 35.27 (C-8), 37.17 (C-10), 38.21 (C-1), 39.97 (C-7), 40.04 (C-13), 48.58 (C-5), 62.25 (C-16), 89.58 (C-14), 120.26 (C-3) and 134.52 (C-4) (Found: C, 83.1; H, 11.0%; M^+, 274).

4-*Methylidene*-15-*oxaandrostane* **23** (744 mg, 20%), $[\alpha]_D^{20}$ +46.8 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3100, 1660, 900 and 860; δ_H 0.68 (3 H, s), 0.80 (3 H, s), 2.73 (1 H, d, *J* 10.5), 3.77 (2 H, m), 4.41 (1 H, s) and 4.66 (1 H, s); δ_C 12.64 (C-19), 17.31 (C-18), 20.77 (C-11), 23.34 (C-2), 23.42 (C-6), 29.86 (C-12), 34.50 (C-17), 35.15 (C-8), 36.51 (C-3), 38.91 (C-1), 39.74 (C-7), 39.84 (C-10), 39.91 (C-13), 51.21 (C-5), 52.47 (C-9), 65.06 (C-16), 89.24 (C-14), 105.68 (CH_2=) and 150.08 (C-4) (Found: C, 83.1; H, 10.9%; M^+, 274).

Pyrolysis of compound **24**.—Compound **24** (1.10 g, 3.30 mmol) was heated at 220 °C, at 14 mmHg, for 15 min, after which it was cooled to room temperature and dissolved in

diethyl ether. The solution was washed successively with 5% aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give a mixture of the olefins **21**, **22** and **23** (860 mg, 95.4%) in the proportions ~ 39:23:38, respectively.

Decarboxylation of the Acid **20**.—LTA (12.27 g, 27.7 mmol) was added to a stirred solution of the acid **20** (5.36 g, 16.7 mmol) in pyridine (13 cm^3)–benzene (558 cm^3). The mixture was heated under reflux for 3.5 h after which it was cooled to room temperature and washed successively with 2 mol dm^{-3} hydrochloric acid, 5% aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), concentrated and chromatographed. Elution with hexane–diethyl ether (90:10) gave a mixture of the olefins **25**, **26** and **27** (3.0 g, 65%) in the proportions ~ 22:40:38, and an *acetoxy compound* **28** (1.3 g, 23%), $[\alpha]_D^{20}$ −5.0 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 1730 and 1250; δ_H 0.90 (3 H, s), 1.08 (3 H, s), 1.45 (3 H, s), 1.91 (3 H, s) and 3.60 (3 H, m) (Found: C, 75.5; H, 10.2%; M^+, 334. $C_{21}H_{34}O_3$ requires C, 75.45; H, 10.18%; M, 334).

The olefinic mixture was rechromatographed on silica gel–$AgNO_3$ (80:20; 75 g). Elution with hexane–diethyl ether (99.5:0.5) gave 4-*methyl*-15-*oxa*-8α,14β-*androst*-4-*ene* **25** (0.66 g, 14.4%), $[\alpha]_D^{20}$ +39.3 (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1} 2950, 1475 and 1390; δ_H 1.00 (3 H, s), 1.10 (3 H, s), 1.57 (3 H, s), 3.47 (1 H, d, *J* 5.7) and 3.80 (2 H, m); δ_C 19.22 (C-11), 19.30 (C-19), 20.36 (C-6), 23.51 (C-2), 24.61 (4-Me), 24.81 (C-18), 24.87 (C-12), 32.37 (C-17), 33.67 (C-3), 36.55 (C-8), 37.30 (C-10), 39.14 (C-7), 39.62 (C-13), 40.99 (C-1), 43.67 (C-9), 64.85 (C-16), 86.30 (C-14), 124.63 (C-4) and 135.49 (C-5) (Found: C, 83.1; H, 11.0%; M^+, 274. $C_{19}H_{30}O$ requires C, 83.12; H, 10.95%; M, 274).

Hexane–diethyl ether (98:2) as eluent gave 4-*methyl*-15-*oxa*-8α,14β-*androst*-3-*ene* **26** (1.20 g, 26%), $[\alpha]_D^{20}$ +19.5 (*c* 0.9, $CHCl_3$); ν_{max}/cm^{-1} 2940, 1450 and 1370; δ_H 0.82 (3 H, s), 1.09 (3 H, s), 1.60 (3 H, d, *J* 1.6), 3.62 (1 H, d, *J* 9), 3.81 (2 H, m) and 5.30 (1 H, s); δ_C 16.20 (C-19), 20.40 (C-6), 20.28 (C-11), 21.39 (4-Me), 22.81 (C-2), 26.44 (C-12), 26.51 (C-18), 32.79 (C-17), 35.85 (C-1), 36.09 (C-8), 36.42 (C-10), 39.33 (C-7), 40.12 (C-13), 44.70 (C-5), 47.25 (C-9), 64.54 (C-16), 85.13 (C-14), 120.59 (C-3) and 135.20 (C-4) (Found: C, 83.1; H, 11.0%; M^+, 274. $C_{19}H_{30}O$ requires C, 83.12; H, 10.95%; M, 274).

Hexane–diethyl ether (95:5) as eluent gave 4-*methylidene*-15-*oxa*-8α,14β-*androstane* **27** (1.14 g, 25%), $[\alpha]_D^{20}$ +85.5 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3080, 1635, 965 and 875; δ_H 0.74 (3 H, s), 1.07 (3 H, s), 3.63 (1 H, d, *J* 10), 3.80 (2 H, m), 4.47 (1 H, s) and 4.72 (1 H, s); δ_C 17.01 (C-19), 20.39 (C-11), 20.93 (C-6), 23.31 (C-2), 26.21 (C-12), 27.59 (C-18), 32.66 (C-17), 36.78 (C-3), 37.23 (C-8), 38.33 (C-1), 39.56 (C-10), 40.29 (C-7), 40.43 (C-13), 46.54 (C-9), 51.59 (C-5), 64.50 (C-16), 83.75 (C-14), 106.13 (CH_2=) and 150.11 (C-4) (Found: C, 83.1; H, 10.9%; M^+, 274. $C_{19}H_{30}O$ requires C, 83.12; H, 10.95%; M, 274).

Pyrolysis of Compound **28**.—Compound **28** (1.3 g, 3.9 mmol) was heated at 220 °C at 14 mmHg for 10 min after which it was cooled to room temperature and dissolved in diethyl ether. The solution was washed with 5% aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give a mixture of the olefins **25**, **26** and **27** (1.2 g, 92%) in the proportions ~ 41:30:29.

Isomerization with Iodine.—A solution of the olefinic mixture **21**–**23** (1.0 g, 3.60 mmol) in benzene (100 cm^3) containing a small amount of iodine (70 mg) was heated at 110 °C for 30 min after which it was cooled to room temperature and washed successively with 40% aq. sodium hydrogen sulfite and brine, dried (Na_2SO_4), concentrated and chromatographed. Elution with hexane–diethyl ether (95:5) gave compound **21** (987 mg, 99%).

4-*Methyl*-15-*oxaandrost*-4-*en*-3-*one* **30**.—To a stirred suspension of CrO_3 (4.04 g, 40.4 mmol) in dichloromethane (34 cm^3) at −25 °C was added 3,5-dimethylpyrazole (3.9 g, 40.4 mmol); after 15 min, compound **21** (925 mg, 3.4 mmol) was added. The mixture was stirred for 2 h, after which it was warmed to 0 °C and 5 mol dm^{-3} aq. NaOH (17 cm^3) was added. The mixture was stirred for 1 h after which it was diluted with dichloromethane (10 cm^3) and the two layers were separated. The organic layer was washed successively with 2 mol dm^{-3} hydrochloric acid, water and brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on silica gel (25 g). Elution with hexane–diethyl ether (95:5) gave 4α,5α-*epoxy*-4β-*methyl*-15-*oxaandrostane* **29** (133 mg, 14%), mp 153–154 °C; $[\alpha]_D^{20}$ +14.5 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 2960, 1470 and 1390; δ_H 0.82 (3 H, s), 0.98 (3 H, s), 1.31 (3 H, s), 2.77 (1 H, d, *J* 10) and 3.80 (2 H, m); δ_C 11.28 (C-19), 16.51 (4-Me), 17.32 (C-18), 20.75 (C-11), 25.44 (C-2), 26.95 (C-6), 29.67 (C-12), 32.94 (C-3), 34.34 (C-17), 34.91 (C-8), 37.11 (C-10), 39.76 (C-7), 40.03 (C-1), 40.26 (C-13), 49.01 (C-9), 65.18 (C-4), 65.54 (C-16), 72.53 (C-5) and 88.79 (C-14) (Found: C, 78.6; H, 10.35%; M^+, 290. $C_{19}H_{30}O_2$ requires C, 78.62; H, 10.34%; M, 290).

Hexane–diethyl ether (90:10) as eluent gave 4-*methyl*-15-*oxaandrost*-4-*en*-3-*one* **30** (498 mg, 51%), mp 109–110 °C; $[\alpha]_D^{20}$ +60.4 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 1670 and 1615; δ_H 0.82 (3 H, s), 1.12 (3 H, s), 1.69 (3 H, d, *J* 1.4), 2.30 (2 H, m), 2.68 (1 H, d, *J* 10.6) and 3.83 (2 H, m); δ_C, see Table 2 (Found: C, 79.2; H, 9.7%; M^+, 288. $C_{19}H_{28}O_2$ requires C, 79.17; H, 9.72%; M, 288).

Isomerization with Iodine.—A solution of the olefinic mixture **25**–**27** (2.5 g, 9.1 mmol) in benzene (250 cm^3) containing a small amount of iodine (70 mg) was heated under reflux for 2.5 h after which it was cooled to room temperature and washed successively with 40% aq. sodium hydrogen sulfite and brine, dried (Na_2SO_4), concentrated and chromatographed. Elution with hexane–diethyl ether (95:5) gave compound **25** (2.0 g, 80%).

4-*Methyl*-15-*oxa*-8α,14β-*androst*-4-*en*-3-*one* **31**.—To a stirred suspension of CrO_3 (4.52 g, 45.2 mmol) in dichloromethane (38 cm^3) at −25 °C was added 3,5-dimethylpyrazole (4.34 g, 45.2 mmol); after 15 min compound **25** (1.3 g, 4.7 mmol) was added. The mixture was stirred for 2 h after which it was warmed at 0 °C and 5 mol dm^{-3} aq. NaOH (19 cm^3) was added. The mixture was stirred for 1 h after which it was diluted with dichloromethane (10 cm^3) and the two layers were separated. The organic layer was washed successively with 2 mol dm^{-3} hydrochloric acid, water and brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on silica gel (25 g), with hexane–diethyl ether (85:15) as eluent, to give *compound* **31**, $[\alpha]_D^{20}$ +41.7 (*c* 1.6, $CHCl_3$); ν_{max}/cm^{-1} 1670 and 1625; δ_H 1.11 (3 H, s), 1.15 (3 H, s), 1.70 (3 H, s), 3.41 (1 H, d, *J* 5.6) and 3.80 (2 H, m); δ_C, see Table 2 (Found: C, 79.2; H, 9.73%; M^+, 288. $C_{19}H_{28}O_2$ requires C, 79.17; H, 9.72%; M, 288).

15-*Oxaandrostan*-4-*one* **32**.—A mixture of the alkene **23** (690 mg, 2.5 mmol), CCl_4 (5 cm^3), MeCN (5 cm^3), water (7.7 cm^3), $NaIO_4$ (2.21 g, 10.3 mmol) and RuO_2 (7 mg, 0.055 mmol) was stirred for 24 h at room temperature, after which it was extracted with dichloromethane. The extract was washed with brine, dried (Na_2SO_4), concentrated and chromatographed. Elution with hexane–diethyl ether (75:25) gave *compound* **32** (250 mg, 36%), mp 97 °C; $[\alpha]_D^{20}$ +7.6 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 1720; δ_H 0.76 (3 H, s), 0.83 (3 H, s), 2.76 (1 H, d, *J* 10) and 3.85 (2 H, m); δ_C 13.47 (C-19), 17.31 (C-18), 19.63 (C-11), 20.86 (C-6), 22.33 (C-2), 28.76 (C-12), 34.29 (C-17), 34.91 (C-8), 37.43 (C-3), 39.65 (C-7), 39.93 (C-13), 40.78 (C-1), 42.07 (C-10), 52.17 (C-9), 58.72 (C-5), 65.27 (C-16), 89.03 (C-14) and 211.98 (C-4) (Found: C, 78.3; H, 10.1%; M^+, 276. $C_{18}H_{28}O_2$ requires C, 78.26; H, 10.14%; M, 276).

Hexane–diethyl ether (50:50) as eluent gave the acid **33** (266 mg, 34%) which was methylated by addition of ethereal

Table 2 ^{13}C Chemical shifts

	30	31	35	36	40	40a	41
C-1	35.12	36.58	32.36	34.93	41.54	42.46	42.40
C-2	33.56	34.16	27.91	31.79	23.62	27.96	114.98
C-3	198.28	186.73	75.98	193.26	74.54	72.66	144.68
C-4	128.11	128.91	207.31	139.10	207.22	207.34	198.43
C-5	162.65	164.71	54.57	141.39	55.46	55.46	50.63
C-6	26.93	23.68	20.86	22.42	23.00	23.97	23.11
C-7	39.67	41.39	39.90	40.11	29.20	29.46	32.36
C-8	35.29	35.37	34.80	35.35	35.54	35.12	35.69
C-9	52.16	43.22	52.22	52.39	39.91	41.23	41.01
C-10	38.82	38.59	42.94	37.79	38.89	38.35	38.24
C-11	20.46	20.19	19.11	20.56	18.61	17.97	17.50
C-12	30.16	26.31	28.57	29.70	26.60	27.03	28.07
C-13	39.99	39.96	39.60	39.88	39.08	39.45	38.41
C-14	89.07	86.61	88.89	89.24	86.25	86.99	86.87
C-16	65.61	65.26	65.26	65.72	64.64	64.59	64.52
C-17	34.31	33.63	34.20	34.44	33.50	33.78	33.74
C-18	17.33	25.01	17.26	17.35	26.00	23.52	24.62
C-19	17.56	21.16	12.98	17.14	23.97	22.76	22.75
4-Me	10.93	10.68					
3-OCOMe			169.23		169.40	169.70	
3-OCO*Me*			20.60		20.77	20.51	

diazomethane. Evaporation of the solvent afforded the ester **34**, mp 93–94 °C; $[\alpha]_D^{20}$ −21.7 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1} 1760, 1725 and 1210; δ_H 0.65 (3 H, s), 1.10 (3 H, s) and 3.49 (3 H, s) (Found: C, 71.25; H, 8.75%; M^+, 320. $C_{19}H_{28}O_4$ requires C, 71.25; H, 8.75%; M, 320).

Ozonolysis of the Alkene **23**.—A mixture of the alkene **23** (175 mg, 0.64 mmol) in methanol (11 cm^3) was exhaustively ozonolysed at −78 °C. The solution was flushed with nitrogen for 30 min, before addition of dimethyl sulfide (1 cm^3). The solution was stirred at −78 °C for 2 h and at room temperature overnight. After concentration under reduced pressure, the residue was taken up in diethyl ether (5 cm^3), and the organic phase was washed successively with water and brine, dried (Na_2SO_4), and evaporated. Purification by silica gel [elution with hexane–diethyl ether (50:50)] gave the ketone **32** (150 mg, 85%).

4-*Oxo*-15-*oxaandrostan*-3α-*yl Acetate* **35**.—LTA (1.07 g, 2.4 mmol) and boron trifluoride–diethyl ether (0.87 cm^3) were added successively to a solution of the ketone **32** (240 mg, 0.9 mmol) in benzene (60 cm^3), and the mixture was stirred at room temperature for 23 h after which it was washed successively with water and brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on silica gel, with hexane–diethyl ether (75:25), to give *compound* **35** (171 mg, 56%), $[\alpha]_D^{20}$ +1.1 (*c* 1.6, $CHCl_3$); ν_{max}/cm^{-1} 1750, 1725 and 1235; δ_H 0.77 (3 H, s), 0.82 (3 H, s), 2.12 (3 H, s), 2.75 (1 H, d, *J* 10), 3.85 (2 H, m) and 4.78 (1 H, t, *J* 2); δ_C, see Table 2 (Found: C, 71.9; H, 9.1%; M^+, 334. $C_{20}H_{30}O_4$ requires C, 71.85; H, 8.98%; M, 334).

Hexane–diethyl ether (70:30) as eluent gave 4-oxo-15-oxaandrostan-3β-yl-acetate **35a** (12 mg, 4%), δ_H 0.77 (3 H, s), 0.84 (3 H, s), 2.11 (3 H, s), 2.83 (1 H, d, *J* 10), 3.86 (2 H, m) and 5.14 (1 H, dd, J_1 2, J_2 8).

4-*Hydroxy*-15-*oxaandrost*-4-*en*-3-*one* **36**.—To a mixture of aq. KOH (52 mg, 0.9 mmol in 0.17 cm^3) and ethanol (1.1 cm^3) was added compound **35** (86 mg, 0.2 mmol); the mixture was heated under reflux for 3 h, after which it was cooled to room temperature and evaporated; the residue was dissolved in water and the aqueous solution was extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on silica gel. Elution with hexane–diethyl ether (80:20) gave the *acyloin* **36** (26 mg, 45%), mp 167 °C; $[\alpha]_D^{20}$ +77.0 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3400, 1670, 1660, 1645, 1635 and 1220; δ_H 0.90 (3 H, s), 1.20 (3 H, s), 2.76 (1 H, d, *J* 10), 3.88 (2 H, m) and 6.07 (1 H, s); δ_C, see Table 2 (Found: C, 74.5; H, 8.95%; M^+, 290. $C_{18}H_{26}O_3$ requires C, 74.48; H, 8.96%; M, 290).

Hexane–diethyl ether (75:25) as eluent gave 4β-*hydroxy*-15-*oxaandrostan*-3-*one* **37** (10 mg, 17%), mp 185 °C; $[\alpha]_D^{20}$ −18.1 (*c* 0.8, $CHCl_3$); ν_{max}/cm^{-1} 3360 and 1720; δ_H 0.84 (3 H, s), 1.06 (3 H, s), 2.78 (1 H, d, *J* 10), 2.90 (1 H, m) and 3.86 (2 H, m) (Found: C, 74.0; H, 9.6%; M^+, 292. $C_{18}H_{28}O_3$ requires C, 73.97; H, 9.59%; M, 292).

Hexane–diethyl ether (70:30) as eluent gave 3α-hydroxy-15-oxaandrostan-4-one **38** (5 mg, 8.5%), ν_{max}/cm^{-1} 3380, 1720 and 1705; δ_H 0.75 (3 H, s), 0.85 (3 H, s), 2.71 (1 H, d, *J* 10), 3.86 (2 H, m) and 4.12 (1 H, t, *J* 10).

15-*Oxa*-5β,8α,14β-*androstan*-4-*one* **39**.—Aq. dicyclohexyl-18-crown-6 (0.14 g, 0.4 mmol)–$KMnO_4$ (1.55 g, 9.8 mmol) (in 12 cm^3) was added to a stirred solution of the alkene **27** (1.04 g, 3.8 mmol) in benzene (56 cm^3). After 24 h, further aq. dicyclohexyl-18-crown-6 (10 mg, 0.02 mmol) and $KMnO_4$ (200 mg, 1.3 mmol) (in 2 cm^3) was added; after two such treatments the reaction mixture was stirred for 24 h after which an excess of sodium hydrogen sulfite was added and the filtrate was decanted, the aqueous layer was extracted with diethyl ether, and the combined organic layers were dried (Na_2SO_4), concentrated, and applied to short-column chromatography. Elution with hexane–diethyl ether (75:25) gave *compound* **39** (679 mg, 65%), mp 129 °C; $[\alpha]_D^{20}$ +23.3 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 1720; δ_H 0.89 (3 H, s), 1.08 (3 H, s), 3.30 (1 H, d, *J* 1.8) and 3.84 (2 H, m); δ_C 17.86 (C-11), 21.84 (C-6), 23.01 (C-19), 23.69 (C-18), 24.31 (C-2), 26.69 (C-7), 27.52 (C-12), 33.96 (C-17), 35.24 (C-8), 36.38 (C-3), 38.54 (C-10), 39.27 (C-13), 41.77 (C-9), 42.65 (C-1), 56.06 (C-5), 64.80 (C-16), 87.32 (C-14) and 212.54 (C-4) (Found: C, 78.3; H, 10.1%; M^+, 276. $C_{18}H_{28}O_2$ requires C, 78.26; H, 10.14%; M, 276).

4-*Oxo*-15-*oxa*-5β,8α,14β-*androstan*-3α-*yl Acetate* **40** *and* -3β-*yl Acetate* **40a**.—LTA (1.82 g, 4.1 mmol) and boron trifluoride–diethyl ether (1.48 cm^3) were added successively to a solution of the ketone **39** (410 mg, 1.5 mmol) in benzene (100 cm^3). The mixture was stirred at room temperature for 17 h, after which it was washed successively with water and brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on

silica gel. Elution with hexane–diethyl ether (85:15) gave *compound* **40** (170 mg, 34%); $[\alpha]_D^{20}$ +36.7 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 1760, 1725 and 1235; δ_H 0.96 (3 H, s), 1.05 (3 H, s), 2.05 (3 H, s), 3.35 (1 H, d, *J* 4.8), 3.78 (2 H, m) and 5.02 (1 H, t, *J* 7); δ_C, see Table 2 (Found: C, 72.0; H, 9.2%; M^+, 334. $C_{20}H_{30}O_4$ requires C, 71.85; H, 8.98%; M, 334).

Hexane–diethyl ether (80:20) as eluent gave compound **40a** (170 mg, 34%), mp 163 °C; $[\alpha]_D^{20}$ −9.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 1760, 1730 and 1240; δ_H 0.83 (3 H, s), 1.00 (3 H, s), 2.05 (3 H, s), 3.23 (1 H, d, *J* 1.8), 3.74 (2 H, m) and 5.50 (1 H, dd, J_1 6, J_2 8); δ_C, see Table 2 (Found: C, 71.9; H, 9.0%; M^+, 334).

3-*Hydroxy*-15-*oxa*-5β,8α,14β-*androst*-2-*en*-4-*one* **41**.—To a mixture of aq. KOH (76 mg, 1.3 mmol in 0.28 cm^3) and ethanol (1.4 cm^3) was added an isomeric mixture **40** and **40a** (113 mg, 0.34 mmol); the reaction mixture was heated under reflux for 3 h, after which it was cooled to room temperature and evaporated; the residue was dissolved in water and the aqueous solution was extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give the *acyloin* **41** (89 mg, 94%), $[\alpha]_D^{20}$ −6.3 (*c* 1.8, $CHCl_3$); ν_{max}/cm^{-1} 3440, 1685 and 1660; δ_H 0.93 (3 H, s), 1.01 (3 H, s), 3.24 (1 H, d, *J* 1.8), 3.74 (2 H, m) and 5.82 (1 H, dd, J_1 2, J_2 4); δ_C, see Table 2 (Found: C, 74.5; H, 8.95%; M^+, 290. $C_{18}H_{26}O_3$ requires C, 74.48; H, 8.96%; M, 290).

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