Synthesis of 8β-Methyltestololactone

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The stereoselective synthesis of (+)-8β-methyltestololactone has been achieved in a thirteen-step process from (+)-*O*-15-methyl agathate. The synthetic strategy is the stereoselective construction of ring D by electrophilic cyclization induced by acids, and the appropriate modification of the A-ring diterpene functionality to the enone system common among steroidal hormones.

Testosterone propionate (**1**) was one of the first drugs used in treatment of breast cancer; dromostanolone (**2**), calusterone (**3**), and testolactone (**4**) were introduced later in an attempt to decrease secondary effects such as virilizing activity and to extend the period of effectiveness; the methyl groups at C-2 and C-7 and the extra oxygen in ring D, respectively could be responsible for diminishing the reported undesired effects.[1] While nowadays the drugs of choice for the treatment of breast cancer are non-steroidal[1b] (*e.g.*, Tamoxifen), the structure–activity relationship of methyl steroids has not been studied in detail. In some cases it has been observed that methyl-group insertion in the steroid skeleton contributes to resistance to metabolism. Also, the combination of structural enhancement factors has proved to be additive.[2]

These considerations prompted us to design an approach to the synthesis of 8β-methyl steroids, a relatively unknown type of compound, whose physiological properties have received little attention and which deserve further work regarding their synthesis and biological properties.[3]

In this paper we approach the synthesis of 8β-methyltestololactone (**5**) from a very common diterpenoid, *O*-15-methyl agathate (**6**), an inexpensive and readily available starting material.

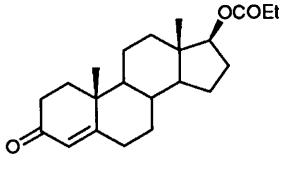
Upon reaction of mono ester (**6**) with formic acid at 70 °C, quantitatively stereospecific cyclization[4] occurred, giving the tricyclic *O*-15-methyl isoagathate (**7**) (Scheme 1). This was reduced with $LiAlH_4$ in diethyl ether at room temperature to give the hydroxy acid (**8**), which after treatment with an ethereal solution of diazomethane afforded ester (**9**), m.p. 127 °C. The latter compound was next transformed into the unsaturated diester (**12**) by a series of standard reactions in which a two-carbon chain was added, while the ester group attached to carbon C-4 remained unaffected. Thus, the hydroxy ester (**9**) was converted into the tosyl derivative (**10**) by treatment with toluene-*p*-sulphonyl chloride in pyridine at 0 °C; condensation of the tosyl ester (**10**) with sodium diethyl malonate in refluxing toluene afforded a separable mixture of the diene (**22**) (15%) and the triester (**11**) (85%). Treatment of triester (**11**) with a mixture of sodium chloride, dimethyl sulphoxide (DMSO), and water at 180 °C gave the diester (**12**) in 60% overall yield from diester (**6**).

Table 1. Products obtained on acid treatment of ester acid (**13**).

Conditions	Product, yield (%) (**15**)	(**23**)	(**24**)
$AcOH–H_2SO_4$; 5 °C	74	21	
$AcOH–H_2SO_4$; 20 °C		67	27
p-TsOH; 90 °C		95	
HCO_2H; 70 °C	50	50	
$BF_3·Et_2O$; 20 °C	90		

A key step in our synthesis is the stereoselective construction of ring D; this was achieved by electrophilic cyclization induced by acids. The cyclization substrate (**13**) was obtained by selective hydrolysis of the diester (**12**) in nearly quantitative yield.

Table 1 shows the results obtained by treatment of compound (**13**) with several acids. Only the Lewis acid reaction gave stereospecifically the desired lactone (**15**) (in excellent yield), while the other protonic acids afforded the lactone (**23**) or mixture of products. While the reaction catalysed by proton-donating acids gave a localized carbocation prone to re-arrangement, followed by electrophilic attack at the carboxylic oxygen, Lewis acid catalysis would occur through a complex non-localized cation followed by a cyclic *cis*-addition process of



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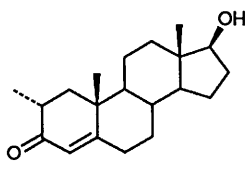

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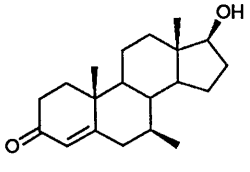

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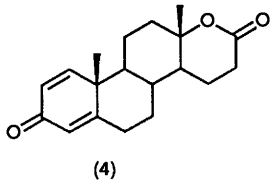

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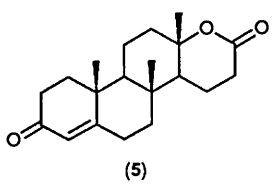

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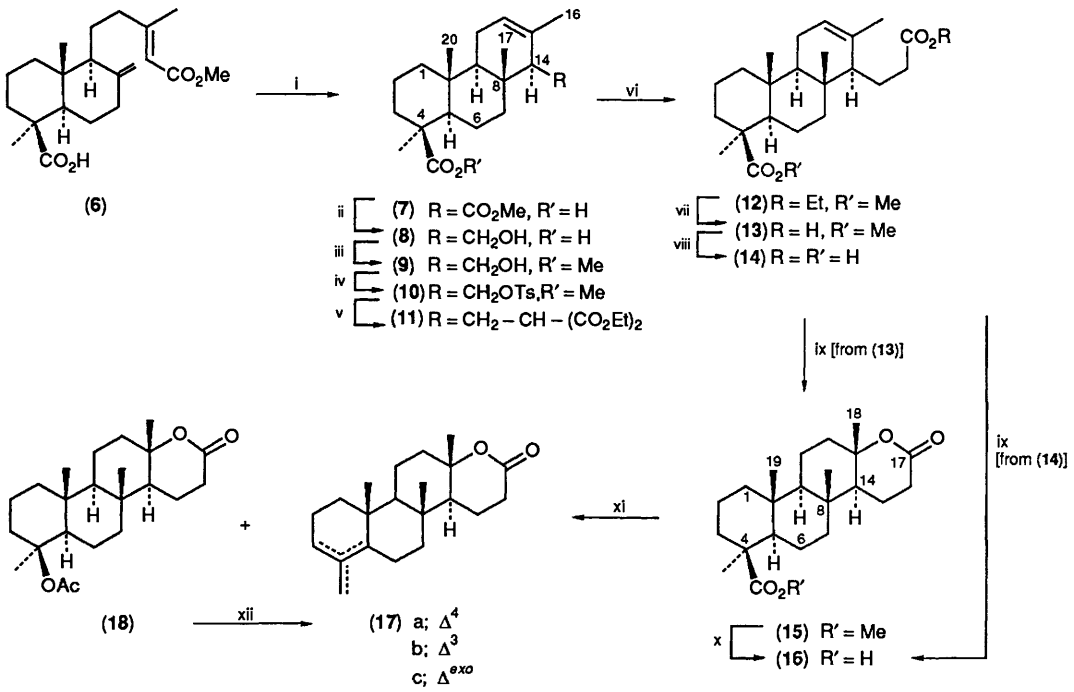
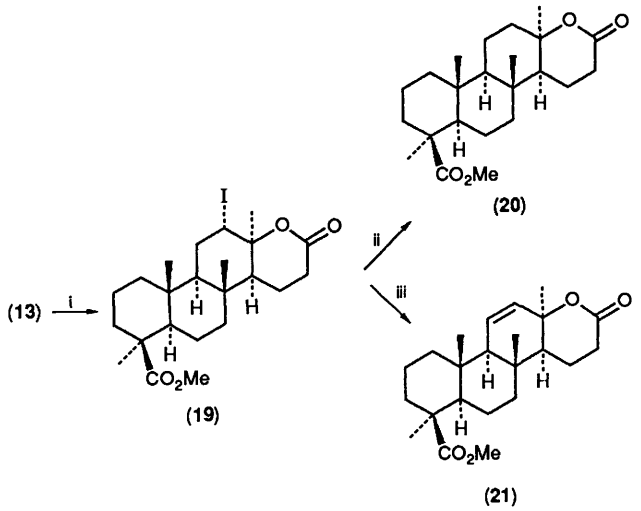


Scheme 1. *Reagents and conditions:* i, HCO_2H; ii, $LiAlH_4$, Et_2O; iii, CH_2N_2; iv, *p*-TsCl, pyridine; v, diethyl malonate, Na, toluene; vi, NaCl, aq. DMSO; vii, KOH, aq. EtOH; viii KOH, ethylene glycol; ix, BF_3·Et_2O, benzene; x, DBN, *o*-xylene; xi, LTA, benzene–pyridine; xii, 210 °C.



Scheme 2. *Reagents:* i, I_2, KI, $NaHCO_3$, water; ii, Bu_3SnH, benzene; iii, DBN, *o*-xylene.

the protonated carboxylic function to the Δ^{13}-double bond. This mechanistic difference could account for the results obtained.[5] The structure of the undesired lactone (**23**) is based on the spectroscopic properties obtained for stypodiol.[6] The rearranged product, which has been formulated tentatively as (**24**), is in accord with its spectral properties (Table 2); the signal at δ_C 28.28 assigned to CH_3 (C-4) in the ^{13}C NMR spectrum rules out the Δ^4 isomer, for which it would appear at higher field.[7]

The structure of the δ-lactone (**15**), described by us elsewhere, has been established by comparison of its spectral properties with those of the closely related testololactone and analogues.[8] The configuration of the newly created chiral centre at C-13 is opposite that obtained from model compounds, which have the *cis* stereochemistry for trisubstituted cyclohexenes, whereas the tetrasubstituted isomers still have the *trans* stereochemistry.[9] A simple explanation of our results could be the previous double-bond $\Delta^{12} \longrightarrow \Delta^{13}$ isomerization which in some cases would also account for the formation of the lactone (**23**).

To confirm the stereochemical aspects related to the lactone (**15**), we prepared the C-13 epimer (**20**) by an halogenolactonization process—carried out with compound (**13**)—through the iodo lactone (**19**) (Scheme 2). In the *anti*-addition, the iodine must be preferentially α orientated due to steric requirements. This fact was demonstrated by a triplet at δ 4.69, *J* 3 Hz, in the ^1H NMR spectrum of compound (**19**), which revealed the presence of the iodine atom in an axial position. Reduction of compound (**19**) with tributyltin hydride[10] in benzene at 20 °C afforded the lactone (**20**) at almost quantitative yield. Comparative ^{13}C NMR spectral analysis of compounds (**15**) and (**20**) showed a significant difference for C-18 ($\Delta^\delta \approx 6$ ppm). The downfield displacement for compound (**20**) indicated the equatorial position of the methyl group bonded to C-13 and also the *cis* ring C/D fusion. Treatment of the iodo lactone (**19**) with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[11] in refluxing

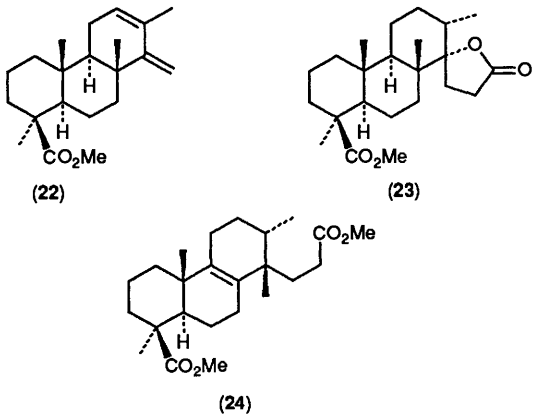


Table 2. ^{13}C Chemical shifts.

	(15)	(24)	(20)	(21)	(17c)	(25)	(26)	(29)	(30)	(5)
C-1	40.24	38.11	40.37	39.64	39.41	38.16	37.85	40.08	40.41	36.86
C-2	19.20	19.66	19.15	19.51	23.09	22.09	27.81	22.87	25.61	33.20
C-3	37.82	37.68	38.11	38.07	36.38	40.61	76.00	36.68	28.91	198.45
C-4	43.90	43.80	43.85	43.80	150.44	212.49	212.00	71.98	120.50	124.42
C-5	57.11	53.65	57.20	56.71	52.23	59.34	55.21	50.71	143.36	169.20
C-6	18.78	20.28	17.02	16.78	19.16	16.19	16.48	16.51	18.62	28.66
C-7	41.52	27.42	41.51	39.69	39.09	37.97	33.58	39.07	38.75	38.71
C-8	37.82	131.36	38.11	37.36	37.49	37.28	37.29	37.77	37.30	37.33
C-9	54.01	140.48	49.78	49.85	53.89	53.81	53.73	53.81	53.65	53.20
C-10	37.50	39.08	37.74	37.11	39.41	43.04	43.96	36.49	37.65	38.50
C-11	17.08	25.39	15.37	127.83	15.76	15.77	15.75	15.56	15.86	15.72
C-12	41.40	29.36	41.65	131.34	41.83	41.20	41.10	41.07	41.23	40.79
C-13	83.54	33.77	81.74	79.90	83.62	83.33	83.27	83.49	83.59	82.66
C-14	60.01	40.30	58.75	58.06	56.45	58.30	58.33	59.38	58.65	57.53
C-15	19.64	27.42	19.47	18.82	20.66	19.37	19.37	17.91	19.30	18.90
C-16	29.05	30.40	26.34	27.89	28.95	28.87	28.85	28.77	29.02	28.90
C-17	171.50	174.50	172.50	172.17	171.50	171.29	171.25	171.26	171.45	170.68
C-18	22.84	28.28	28.91	30.50	22.89	22.89	22.87	22.59	22.88	22.67
C-19	14.03	16.10	13.99	14.21	13.53	13.96	13.68	16.00	20.32	17.57
Me(C-4)	28.64	28.28	28.57	28.48	105.27 (=CH_2)					
Me(C-8)	15.82		16.31	14.89	16.00	15.94	16.05	16.12	14.99	14.56
Me(C-14)		21.07								
CO(carboxy C-4)	177.60	177.76	177.00	177.42						
Me(methoxy C-4)	51.11	50.89	51.09	51.14						
Me(methoxy C-17)		51.33								
CO(acetyl)							177.36			
Me(acetyl)							20.98			

o-xylene yielded the unsaturated lactone (**21**) (67%), a useful intermediate for the synthesis of C-11- or C-12-functionalized analogues.

Compound (**16**) is an ideal substrate for the conversion of ring A to an enone system, common among the steroidal hormones. To accomplish this transformation the following operations are required: (1) Elimination of the carboxylic and methyl groups at C-4; (2) oxidation of carbon C-3, and (3) introduction of a Δ^4-double bond. Substrate (**16**) was obtained in two ways: (a) from compound (**15**), by selective hydrolysis of the ester group bonded to C-4, accomplished in 81% yield with DBN in refluxing *o*-xylene; (b) from diester (**12**) by hydrolysis of the ester groups, followed by cyclization of the diacid intermediate (**14**) with $BF_3{\cdot}Et_2O$ in 88% overall yield. Oxidative decarboxylation of acid (**16**) with lead tetra-acetate (LTA) in benzene gave a 1:2:2.7 mixture of the olefinic lactones (**17a–c**) (50%) and the acetate (**18**) (20%). Pyrolysis of compound (**18**) afforded (quantitatively) a 1.5:1:1.5 mixture of the olefinic lactones (**17a–c**).

The 4-oxo lactone (**25**) was obtained in 62% yield by oxidative cleavage of the (**17c**) exocyclic double bond, carried out with $KMnO_4$–dicyclohexyl-18-crown-6 in a benzene–water mixture during 24 h. The chosen sequences to the target compound (**5**) from ketone (**25**) are shown in Scheme 3. We first attempted the transformation (**25**) ⟶ (**28**) by the following steps: (a) oxidation at carbon C-3; (b) reduction of the 4-oxo group to the 4-hydroxy derivative, and (c) dehydration. Treatment of ketone (**25**) with LTA in refluxing benzene afforded the acyl acyloin (**26**) (61%) exclusively. The α-axial acetate group is justified by the triplet centred at δ_H 4.79 (*J* 3 Hz) assigned to 3-H. Reduction of the 4-oxo group in compound (**26**) was achieved with $NaBH_4$ in methanol at room temperature. The β-axial orientation of the 4-hydroxy group in the only compound obtained, (**27**) was justified on the basis of the broad singlet at δ_H 3.75 for 4-H.

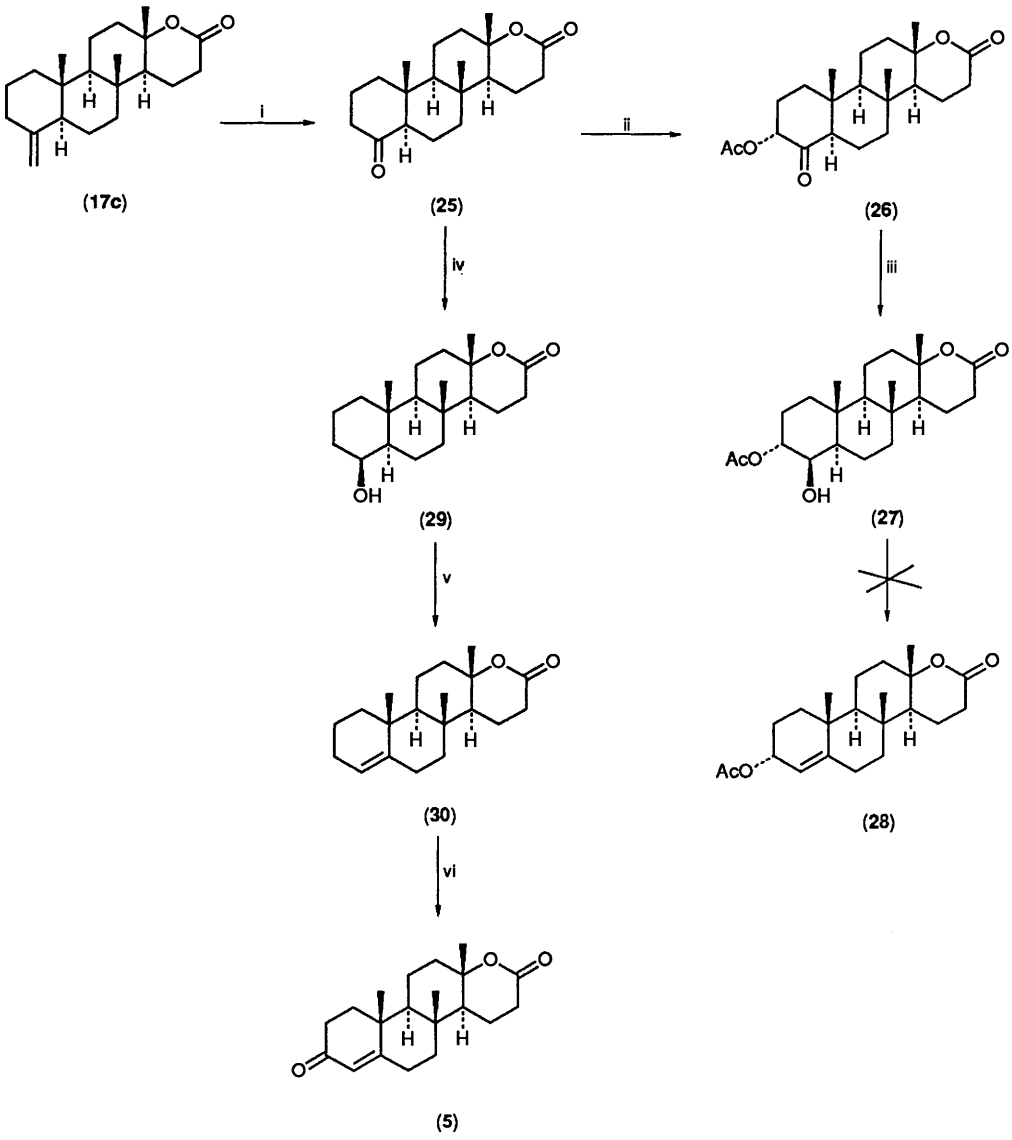
The last step in the sequence failed after several dehydration attempts, probably due to steric hindrance of the acetate group. After this frustrating result, we changed the order of the sequence into the following and successful synthetic route. Reduction of ketone (**25**) with $NaBH_4$ in methanol stereospecifically afforded the alcohol (**29**) in 90% yield, which after treatment with $MeSO_2Cl$ in dimethylformamide (DMF)–*s*-collidine[12] gave the unsaturated lactone (**30**) (75%). Finally, allylic oxidation at the C-3 position with Na_2CrO_4 gave the target compound (**5**) in 73% yield.

Experimental

General.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Beckman 33-IR spectrophotometer for films. ^1H 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 downfield from tetramethylsilane Chemical shifts and coupling constant were obtained from a first-order analysis of the spectra. Optical rotations were measured on a digital Perkin-Elmer 241 polarimeter in a 1-dm cell. 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 <40 °C. Reactions were carried out under nitrogen. Silica gel for column chromatography refers to Merck Kieselgel 60. Light petroleum refers to that fraction boiling in the range 40–60 °C.

O-15-*Methyl Isoagathate* (**7**).—A solution of compound (**6**) (34 g, 97.7 mmol) and 98% aq. formic acid (272 ml) was heated to 70 °C and stirred for 7 h. The formic acid was removed under reduced pressure to give an oily residue, which was chromatographed (5% light petroleum in diethyl ether) to afford pure *compound* (**7**) (32.6 g, 99%); $[\alpha]_D^{20}$ + 13.90 (*c* 1.05, $CHCl_3$)



Scheme 3. *Reagents:* i, $KMnO_4$, aq. benzene; ii, LTA, BF_3·Et_2O, benzene; iii $NaBH_4$, MeOH; iv, $NaBH_4$, MeOH; v, $MeSO_2Cl$, *s*-collidine–DMF; vi, Na_2CrO_4, AcOH–Ac_2O.

(Found: C, 72.5; H, 9.2%; M^+, 348. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.2%; *M*, 348); ν_{max} 3 640–3 100 and 1 720 cm^{-1}; δ_H 0.80 (3 H, s), 0.91 (3 H, s), 1.21 (3 H, s), 1.56 (3 H, s), 2.80 (1 H, br s), 3.58 (3 H, s), and 5.30 (1 H, br s).

ent-*Methyl* 15-*Hydroxyisocopal*-12-*en*-19-*oate* (**9**).—Lithium aluminium hydride (5.3 g, 139 mmol) was added in small portions to a stirred solution of the tricyclic ester (**7**) (19 g, 54.6 mmol) in dry diethyl ether (400 ml), the mixture was stirred for 4 h at room temperature, after which it was carefully quenched with water, and the solution was acidified with 1M-sulphuric acid. The mixture was extracted with diethyl ether and the extract was washed with brine, dried (Na_2SO_4), and evaporated.

The crystalline residue was then methylated by addition of ethereal diazomethane. Evaporation of the solvent afforded the *title compound* (**9**) (14 g, 91%) as a crystalline solid, m.p. 127 °C; $[\alpha]_D^{20}$ +33.96° (*c* 1.75, $CHCl_3$); *m*/*z* 334 (M^+, 19%), 236 (85), 178 (87), 121 (86), 81 (91), and 55 (100) (Found: C, 75.5; H, 10.3. $C_{21}H_{32}O_2$ requires C, 75.45; H, 10.2%); ν_{max} 3 500 and 1 730 cm^{-1}; δ_H 0.70 (3 H, s), 0.82 (3 H, s), 1.17 (3 H, s), 1.75 (3 H, s), 3.60 (3 H, s), 3.75 (2 H, br s), and 5.45 (1 H, br s).

Tosyl Ester (**10**) *of* ent-*Methyl* 15-*Hydroxyisocopal*-12-*en*-19-*oate* (**9**).—Toluene-*p*-sulphonyl chloride (6.6 g, 35 mmol) was added to a solution of the hydroxy ester (**9**) (8.7 g, 26.0 mmol) in dry pyridine (166 ml) and the mixture was kept at 0 °C for 2 days. Ice–water (250 ml) was added to afford a solution, which was extracted with diethyl ether. The organic layer was washed with 2M-hydrochloric acid, brine, dried (Na_2SO_4), and evaporated to give the corresponding tosyl ester (**10**) (12 g, 98%); ν_{max} 1 750, 1 610, and 1 460 cm^{-1}; δ_H 0.68 (3 H, s), 0.37 (3 H, s), 1.15 (3 H, s), 1.58 (3 H, s), 2.43 (3 H, s), 3.60 (3 H, s), 4.10 (2 H, t, *J* 6 Hz), 5.40 (1 H, br s), 7.28 (2 H, d, *J* 9 Hz), and 7.75 (2 H, d, *J* 9 Hz).

ent-*Methyl* 15-[*Bis*(*ethoxycarbonyl*)*methyl*]*isocopal*-12-*en*-19-*oate* (**11**).—To a solution of sodium diethyl malonate, prepared from sodium (2.5 g, 110 mmol) and diethyl malonate (18.9 g, 118 mmol) in toluene (110 ml), was added a solution of the tosyl ester (**10**) (12.5 g, 25.6 mmol) in toluene (90 ml). After 30 h reflux the mixture was cooled, the solid was filtered off, and the filtrate was evaporated. The residue was chromatographed (5% light petroleum in diethyl ether) to afford the *diene* (**22**) (1.2

g, 15%) (Found: C, 79.8; H, 10.25%; M^+, 316. $C_{21}H_{32}O_2$ requires C, 79.75; H, 10.1%; *M*, 316); ν_{max} 1 735 and 890 cm^{-1}; δ_H 0.77 (3 H, s), 0.95 (3 H, s), 1.12 (3 H, s), 1.75 (3 H, s), 3.60 (3 H, s), 4.70 (2 H, s), and 5.60 (1 H, br s).

Further elution (10% light petroleum in diethyl ether) afforded the *triester* (**11**) (10.3 g, 85%) as a crystalline compound, m.p. 70 °C; $[\alpha]_D^{20}$ +30.27° (*c* 1.29, $CHCl_3$) (Found: C, 70.65; H, 9.3%; M^+, 476. $C_{28}H_{44}O_6$ requires C, 70.6; H, 9.25%; *M*, 476); ν_{max} 1 750 cm^{-1}; δ_H 0.63 (3 H, s), 0.70 (3 H, s), 1.10 (3 H, s), 1.20 (6 H, t, *J* 7 Hz), 1.69 (3 H, s), 3.55 (3 H, s), 4.15 (4 H, complex, *J* 7 Hz), 5.30 (1 H, br s).

ent-*Methyl* 15-(*Ethoxycarbonylmethyl*)*isocopal*-12-*en*-19-*oate* (**12**).—To a solution of the triester (**11**) (8.5 g, 17.8 mmol) in DMSO (17.8 ml) were added water (0.64 ml, 35.7 mmol) and sodium chloride (2.1 g, 35.7 mmol). The suspension was heated at 180 °C for 4 h, after which it was diluted with ethyl acetate (500 ml). The solution was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed (5% light petroleum in diethyl ether) to yield the *unsaturated diester* (**12**) (5.9 g, 81%), $[\alpha]_D^{20}$ +32.07° (*c* 1.93, $CHCl_3$) (Found: C, 74.35; H, 9.95%; M^+, 404. $C_{25}H_{40}O_4$ requires C, 74.25; H, 9.9%; *M*, 404); ν_{max} 1 730 cm^{-1}; δ_H 0.70 (3 H, s), 0.76 (3 H, s), 1.15 (3 H, s), 1.27 (3 H, t, *J* 7 Hz), 1.65 (3 H, s), 3.59 (3 H, s), 4.05 (2 H, complex, *J* 7 Hz), and 5.30 (1 H, br s).

ent-*Methyl* 15-(*Carboxymethyl*)*isocopal*-12-*en*-19-*oate* (**13**).—The unsaturated diester (**12**) (1.17 g, 2.89 mmol) was refluxed for 4 h in a mixture of ethanol (7.5 ml) and water (1.1 ml) containing potassium hydroxide (0.37 g). After cooling and removal of the solvent, the residual solid was dissolved in water, acidified with 2M-hydrochloric acid, and the solution was extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), filtered, and evaporated to afford the *title compound* (**13**) (1.01 g, 93%) as a crystalline solid, m.p. 150–152 °C; $[\alpha]_D^{20}$ +25.99° (*c* 1.88, $CHCl_3$) (Found: C, 73.5; H, 9.6%; M^+, 376. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.55%; *M*, 376); ν_{max} 3 700–2 500 and 1 730 cm^{-1}; δ_H 0.69 (3 H, s), 0.77 (3 H, s), 1.16 (3 H, s), 1.67 (3 H, s), 3.62 (3 H, s), and 5.37 (1 H, br s).

Methyl 4α,8β-*Dimethyl*-17-*oxo*-D-*homo*-17a-*oxa*-*androstane*-4β-*carboxylate* (**15**).—To a solution of compound (**13**) (0.7 g, 1.86 mmol) in dry benzene (105 ml) was added boron trifluoride–diethyl ether (0.7 ml) and the reaction mixture was stirred at room temperature for 2 h. Water (400 ml) was added and the layers were separated. The aqueous phase was extracted with diethyl ether and the combined organic extracts were washed with brine, and dried (Na_2SO_4). Evaporation of the solvent afforded the *title compound* (**15**) (0.69 g, 90%) as a crystalline solid, m.p. 214–215 °C; $[\alpha]_D^{20}$ +12.2° (*c* 1.16, $CHCl_3$) (Found: C, 73.5; H, 9.65%; M^+, 376. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.55%; *M*, 376); ν_{max} 1 715 cm^{-1}; δ_H 0.65 (3 H, s), 0.86 (3 H, s), 1.17 (3 H, s), 1.37 (3 H, s), and 3.64 (3 H, s).

Methyl 12α-*Iodo*-4α,8β-*dimethyl*-17-*oxo*-D-*homo*-17a-*oxa*-13α-*androstane*-4β-*carboxylate* (**19**).—To a solution of the unsaturated acid (**13**) (0.3 g, 0.79 mmol) in 0.5M-aq. sodium hydrogen carbonate (0.5 ml) was added a solution of iodine (0.43 g, 1.69 mmol) and potassium iodide (0.85 g, 5.12 mmol) in water (2.5 ml). The mixture was kept at room temperature for 48 h and then was extracted with methylene dichloride. The extract was washed successively with aq. sodium thiosulphate, water, and aq. sodium chloride and was then dried and concentrated. Chromatography of the residue (25% light petroleum in diethyl ether) gave the iodo lactone (**19**) (0.17 g, 45%), ν_{max} 1 740 cm^{-1}; δ_H 0.65 (3 H, s), 0.91 (3 H, s), 1.19 (3 H, s), 1.63 (3 H, s), 3.63 (3 H, s), and 4.69 (1 H, t, *J* 3 Hz).

Methyl 4α,8β-*Dimethyl*-17-*oxo*-D-*homo*-17a-*oxa*-13α-*androstane*-4β-*carboxylate* (**20**).—Tributyltin hydride (32 mg, 0.11 mmol) was added dropwise to a cooled (5 °C) solution of the iodo lactone (**19**) (64 mg, 0.12 mmol) in benzene (0.5 ml). The resulting solution was stirred at room temperature for 36 h. Water (10 ml) was added and the mixture was extracted with diethyl ether. The extract was washed with aq. sodium chloride, dried (Na_2SO_4), and concentrated. The residue was chromatographed (30% light petroleum in diethyl ether) to give *compound* (**20**) (34 mg, 98%) as a crystalline solid, m.p. 203–205 °C; $[\alpha]_D^{20}$ +31.29° (*c* 1.62, $CHCl_3$) (Found: C, 73.5; H, 9.65%; M^+, 376. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.5%; *M*, 376); ν_{max} 1 730 cm^{-1}; δ_H 0.65 (3 H, s), 0.88 (3 H, s), 1.16 (3 H, s), 1.34 (3 H, s), and 3.62 (3 H, s).

Methyl 4α,8β-*Dimethyl*-17-*oxo*-D-*homo*-17a-*oxa*-13α-*androst*-11-*ene*-4β-*carboxylate* (**21**).—A solution of DBN (82 mg, 0.66 mmol) and the iodo lactone (**19**) (113 mg, 0.22 mmol) in *o*-xylene (0.5 ml) was heated for 27 h at 165 °C. The reaction mixture was cooled, and diluted with diethyl ether. The solution was washed successively with 5% aq. sodium carbonate and water, dried (Na_2SO_4), and evaporated. Chromatography of the residue (30% light petroleum in diethyl ether) gave the *title compound* (**21**) (55 mg, 67%) as a crystalline solid, m.p. 156 °C; $[\alpha]_D^{20}$ +84.55° (*c* 0.68, $CHCl_3$); *m/z* 374 (M^+, 28%), 360 (81), 122 (72), 82 (64), 70 (69), and 56 (100) (Found: C, 73.8; H, 9.1. $C_{23}H_{34}O_4$ requires C, 73.75; H, 9.05%); ν_{max} 1 720 cm^{-1}; δ_H 0.71 (3 H, s), 0.84 (3 H, s), 1.18 (3 H, s), 1.45 (3 H, s), 3.64 (3 H, s), and 5.76 (2 H, s).

4α,8β-*Dimethyl*-17-*oxo*-D-*homo*-17a-*oxa*-*androstane*-4β-*carboxylic Acid.* (**16**).—A solution of DBN (0.081 ml, 0.65 mmol) and the lactone (**15**) (50 mg, 0.13 mmol) in *o*-xylene (0.12 ml) was heated for 2 h at 165 °C. The reaction mixture was cooled, acidified with 2M-hydrochloric acid, and extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), filtered, and evaporated to afford the *title compound* (**16**) (42 mg, 97%) as a crystalline solid, m.p. 266–268 °C; $[\alpha]_D^{20}$ +32.68° (*c* 2.01, $CHCl_3$) (Found: C, 73.0; H, 9.4%; M^+, 362. $C_{22}H_{34}O_4$ requires C, 72.9; H, 9.35%; *M*, 362); ν_{max} 3 400–2 500 and 1 720 cm^{-1}; δ_H 0.76 (3 H, s), 0.86 (3 H, s), 1.23 (3 H, s), and 1.37 (3 H, s).

ent-15-(*Carboxymethyl*)*isocopal*-12-*en*-19-*oic Acid* (**14**).—Unsaturated diester (**12**) (8.1 g, 20 mmol) was refluxed for 24 h in ethylene glycol (56 ml) containing potassium hydroxide (4.5 g). Dilution with ice–water (500 ml) afforded a clear solution, which was acidified with 2M-hydrochloric acid and extracted with diethyl ether. The extract was dried (Na_2SO_4) and evaporated to give the *title compound* (**14**) (7.0 g, 96%) as a crystalline solid, m.p. 112–115 °C; $[\alpha]_D^{20}$ +20.58° (*c* 1.02, $CHCl_3$) (Found: C, 72.8; H, 9.45%; M^+, 362. $C_{22}H_{34}O_4$ requires C, 72.93; H, 9.3%; *M*, 362); ν_{max} 3 500–2 500 and 1 700 cm^{-1}; δ_H 0.77 (3 H, s), 0.82 (3 H, s), 1.24 (3 H, s), 1.68 (3 H, s), and 5.40 (1 H, br s).

Alternative Preparation of Compound (**16**).—To a solution of the unsaturated diacid (**14**) (7.0 g, 20 mmol) in dry benzene (110 ml) was added boron trifluoride–diethyl ether (7 ml), and the reaction mixture was stirred at room temperature for 2 h. Water (400 ml) was added and the usual work-up gave compound (**16**) (6.5 g, 92%), identical with that obtained earlier *via* a different route.

Oxidative Decarboxylation of Acid (**16**).—A mixture of the acid lactone (**16**) (6.3 g, 17.6 mmol), dry benzene (552 ml), pyridine (12 ml), and freshly crystallized LTA (12.1 g) was stirred at reflux for 6 h. The cooled mixture was filtered and the filtrate was washed consecutively with 2M-hydrochloric acid, aq.

sodium hydrogen carbonate, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (25% light petroleum in diethyl ether) to afford an alkene fraction of the compounds (**17**) (2.87 g, 50%).

Further elution (30% light petroleum in diethyl ether) gave the *acetate* (**18**) (13 g, 20%) as a crystalline solid, m.p. 192–194 °C; $[\alpha]_D^{20}$ −46.16° (*c* 0.73, $CHCl_3$) (Found: C, 73.45; H, 9.5%; M^+, 376. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.6%; *M*, 376); ν_{max} 1 740 cm^{-1}; δ_H 0.79 (3 H, s), 0.83 (3 H, s), 1.34 (3 H, s), 1.38 (3 H, s), and 1.90 (3 H, s).

The alkene mixture was chromatographed on silver nitrate–silica gel. Initial 40% light petroleum in diethyl ether eluates afforded 4,8β-*dimethyl*-D-*homo*-17a-*oxa*-*androst*-4-*en*-17-*one* (**17a**) (0.43 g, 17%), m.p. 148 °C; $[\alpha]_D^{20}$ +27.66° (*c* 0.77, $CHCl_3$) (Found: C, 79.8; H, 10.2%; M^+, 316. $C_{21}H_{32}O_2$ requires C, 79.75; H, 10.1%; *M*, 316); ν_{max} 1 740 cm^{-1}; δ_H 0.94 (3 H, s), 0.96 (3 H, s), 1.40 (3 H, s), and 1.62 (3 H, s).

50% Light petroleum in diethyl ether eluates gave 4,8β-*dimethyl*-D-*homo*-17a-*oxa*-*androst*-3-*en*-17-*one* (**17b**) (0.95 g, 37%), m.p. 124–126 °C; $[\alpha]_D^{20}$ −8.12° (*c* 1.39, $CHCl_3$) (Found: C, 79.8; H, 10.2%; M^+, 316), ν_{max} 1 730 cm^{-1}; δ_H 0.71 (3 H, s), 0.89 (3 H, s), 1.38 (3 H, s), 1.63 (3 H, s), and 5.28 (1 H, br s).

80% Light petroleum in diethyl ether eluates gave 8β-*methyl*-4-*methylene*-D-*homo*-17a-*oxa*-*androstan*-17-*one* (**17c**) (1.17 g, 46%), m.p. 142–144 °C; $[\alpha]_D^{20}$ +44.76° (*c* 1.07, $CHCl_3$) (Found: C, 79.7; H, 10.2%; M^+, 316); ν_{max} 1 740 and 990 cm^{-1}; δ_H 0.64 (3 H, s), 0.87 (3 H, s), 1.38 (3 H, s), 4.47 (1 H, s), and 4.71 (1 H, s).

Pyrolysis of 4β,8β-*Dimethyl*-17-*oxo*-D-*homo*-17a-*oxa*-*androstan*-4α-*yl Acetate* (**18**).—The acetate (**18**) (1 g, 2.68 mmol) was heated at 210 °C under reduced pressure (17 mmHg) for 10 min. The residue was cooled and dissolved in diethyl ether, and the extract was washed successively with aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give the unsaturated lactones (**17**) (0.82 g, 98%).

8β-*Methyl*-D-*homo*-17a-*oxa*-*androstane*-4,17-*dione* (**25**).—An aqueous solution of potassium permanganate (1.20 g, 7.59 mmol in 10 ml) was added to a solution of the unsaturated lactone (**17c**) (0.98 g, 3.10 mmol) in benzene (45 ml) containing dicyclohexyl-18-crown-6 (0.11 g, 0.29 mmol) and the mixture was stirred at room temperature for 24 h. Excess of permanganate was destroyed by addition of aq. sodium sulphite. The mixture was filtered to remove manganese oxide and the benzene layer was separated. The aqueous layer was extracted with diethyl ether and the combined organic solutions were washed with aq. sodium chloride, and were then dried (Na_2SO_4). Evaporation of the solvent gave crystalline *compound* (**25**) (0.47 g, 62%), m.p. 160–163 °C; $[\alpha]_D^{20}$ −5.11° (*c* 0.90, $CHCl_3$) (Found: C, 75.5; H, 9.5%; M^+, 318. $C_{20}H_{30}O_3$ requires C, 75.45; H, 9.4%; *M*, 318); ν_{max} 1 720 cm^{-1}; δ_H 0.73 (3 H, s), 0.88 (3 H, s), and 1.39 (3 H, s).

8β-*Methyl*-4,17-*dioxo*-D-*homo*-17a-*oxa*-*androstan*-3α-*yl Acetate* (**26**).—A mixture of the ketone (**25**) (0.54 g, 1.70 mmol) and LTA (0.73 g, 1.65 mmol) in benzene (100 ml) containing boron trifluoride–diethyl ether (0.5 ml) was refluxed for 3 h. Water was added and the benzene layer was separated. The aqueous layer were extracted with diethyl ether and the combined organic phases were washed successively with aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and concentrated. Chromatography of the residue (80% light petroleum in diethyl ether) gave the title compound (**26**) (0.39 g, 61%); ν_{max} 1 730 and 1 720 cm^{-1}; δ_H 0.73 (3 H, s), 0.88 (3 H, s), 1.39 (3 H, s), 2.13 (3 H, s), and 4.79 (1 H, t, *J* 3 Hz).

4β-*Hydroxy*-8β-*methyl*-17-*oxo*-D-*homo*-17a-*oxa*-*androstan*-3α-*yl Acetate** (**27**).—A solution of compound (**26**) (132 mg, 0.35 mmol) in methanol (3 ml) was treated with a solution of sodium borohydride (13 mg, 0.34 mmol) in methanol (2 ml). The reaction mixture was stirred for 15 min at room temperature. Water was added and the mixture was concentrated to half volume, diluted with water, and extracted with diethyl ether. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed (75% light petroleum in diethyl ether) to afford compound (**27**) (80 mg, 60%); ν_{max} 3 500 and 1 730 cm^{-1}; δ_H 0.90 (3 H, s), 0.97 (3 H, s), 1.35 (3 H, s), 2.05 (3 H, s), 3.75 (1 H, br s), and 4.75 (1 H, br s).

4β-*Hydroxy*-8β-*methyl*-D-*homo*-17a-*oxa*-*androstan*-17-*one* (**29**).—To a solution of the keto lactone (**25**) (170 mg, 2 mmol) in methanol (6.5 ml) was added sodium borohydride (20.5 mg, 0.54 mmol). The mixture was stirred for 10 min at room temperature. Water was added and the mixture was concentrated to half volume, diluted with water, and extracted with diethyl ether. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give the *title compound* (**29**) (162 mg, 90%), $[\alpha]_D^{20}$ −7.62 (*c* 1.60, $CHCl_3$) (Found: C, 74.9; H, 10.1%; M^+, 320. $C_{20}H_{32}O_3$ requires C, 75.0; H, 10.0%; *M*, 320); ν_{max} 3 500 and 1 720 cm^{-1}; δ_H 0.82 (3 H, s), 0.90 (3 H, s), 1.29 (3 H, s), 3.61 (3 H, s), and 3.75 (1 H, br s).

8β-*Methyl*-D-*homo*-17a-*oxa*-*androst*-4-*en*-17-*one* (**30**).—A solution of the hydroxy lactone (**29**) (140 mg, 0.43 mmol) in a mixture of (natural) *s*-collidine (0.43 ml) and DMF (1 ml) was cooled to 0 °C. The cooling bath was removed and methanesulphonyl chloride (0.11 ml) containing 3.5% by weight of anhydrous sulphur dioxide was added to the clear solution. The reaction mixture was stirred for 5 h at 40 °C. Water was added and the mixture was extracted with diethyl ether. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue (50% light petroleum in diethyl ether) afforded *compound* (**30**) (100 mg, 75%) as a crystalline solid, m.p. 181–184 °C; $[\alpha]_D^{20}$ +12.66° (*c* 1.20, $CHCl_3$) (Found: C, 79.5; H, 9.8%; M^+, 302. $C_{20}H_{30}O_2$ requires C, 79.45; H, 9.9%; *M*, 302); ν_{max} 1 725 cm^{-1}; δ_H 0.96 (6 H, s), 1.40 (3 H, s), and 5.37 (1 H, br s).

8β-*Methyl*-D-*homo*-17a-*oxa*-*androst*-4-*ene*-3,17-*dione* (**5**).—A solution of the unsaturated lactone (**30**) (80 mg, 0.26 mmol) in a mixture of benzene (0.7 ml), acetic acid (0.4 ml), and acetic anhydride (0.4 ml) was warmed to 40 °C and anhydrous sodium chromate (72 mg) was added. The mixture was stirred for 15 h at 40 °C after which ice–water (10 ml) was added. The solution was extracted with diethyl ether and the extract was washed successively with 10% aq. sodium carbonate and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed (80% light petroleum in diethyl ether) to afford *compound* (**5**) (60 mg, 73%) as a crystalline solid, m.p. 219 °C; $[\alpha]_D^{20}$ +3.88° (*c* 0.90, $CHCl_3$) (Found: C, 75.8; H, 8.9%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75.95; H, 8.85%; *M*, 316); ν_{max} 1 730 and 1 680 cm^{-1}; δ_H 1.03 (3 H, s), 1.13 (3 H, s), 1.42 (3 H, s), and 5.70 (1 H, d, *J* 1.5 Hz).

Acknowledgements

We thank the 'Ministerio de Educación y Ciencia,' Spain, for a Doctoral Fellowship to R. R. G.

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Paper 0/00522C
Received 5*th February* 1990
Accepted 11*th April* 1990