17a-OXA-17a-HOMOBRASSINOSTEROID ANALOGUES*

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Synthesis of a 17a-oxa-17a-homobrassinosteroids, *i.e.* brassinosteroids having two lactone rings, is described. In the bean second internode bioassay, dilactone **16** was the most effective of the compounds synthesized. In the same test, the castasterone analogue **12** exhibited a growth-retarding effect.
Key words: Steroids; Brassinolide analogues; Brassinosteroid dilactones; Second bean internode bioassay; Brassinolide activity.

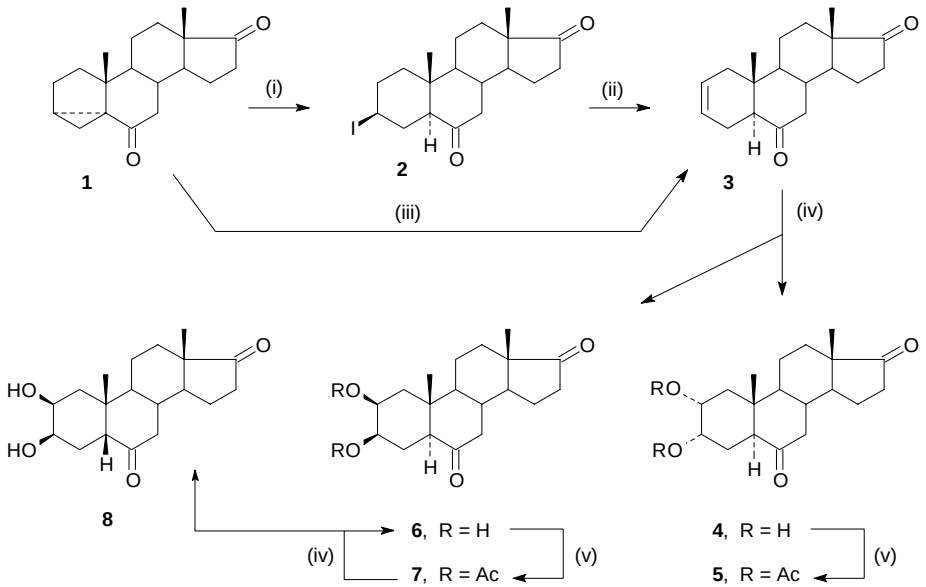
A great number of studies on brassinolide analogues pay attention to the structure–activity relationships[2,3] because some biological activities of these compounds are very interesting[4,5]. In our previous papers[6–8] dealing with structure–activity relationships of brassinosteroids, we prepared various brassinolide analogues differing from the natural brassinolide mainly in the side chain or in the substituent in position 17.

In the present communication[9] we describe the synthesis of compounds having the D-homo ring with an oxygen atom. First we prepared a derivative with the A ring of brassinolide structure and then we oxidized both the keto groups in the rings B and D using the Baeyer–Villiger oxidation.

Our synthesis (Scheme 1) started from 3α,5-cyclo-5α-androstane-6,17-dione[10] (**1**) which was converted into 2,3-olefin **3** by two methods. In the first, compound **1** was treated with hydrogen iodide and the obtained iodo derivative **2** reacted with lithium bromide in DMF in the presence of lithium carbonate to give the required alkene **3**. In the second method, cyclo derivative **1** was treated with lithium bromide in DMF in the presence of pyridinium 4-toluenesulfonate at 160 °C. This reaction afforded directly alkene **3** and proved to be much better than the first route, giving the desired 5α-androst-2-ene-6,17-dione (**3**) in a yield of 57%, compared with 21% obtained in the preparation *via* the iodo derivative **2**.

* Part CCCXCV in the series On Steroids; Part CCCXCIV see ref.[1].

Hydroxylation of the double bond in compound **3** with osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide gave a mixture of two diols in which the 2α,3α-dihydroxy derivative **4** predominated, in accord with the literature data[7]. Compound **4** crystallized pure from the reaction mixture whereas the 2β,3β-isomer **6** remained in the mother liquor.



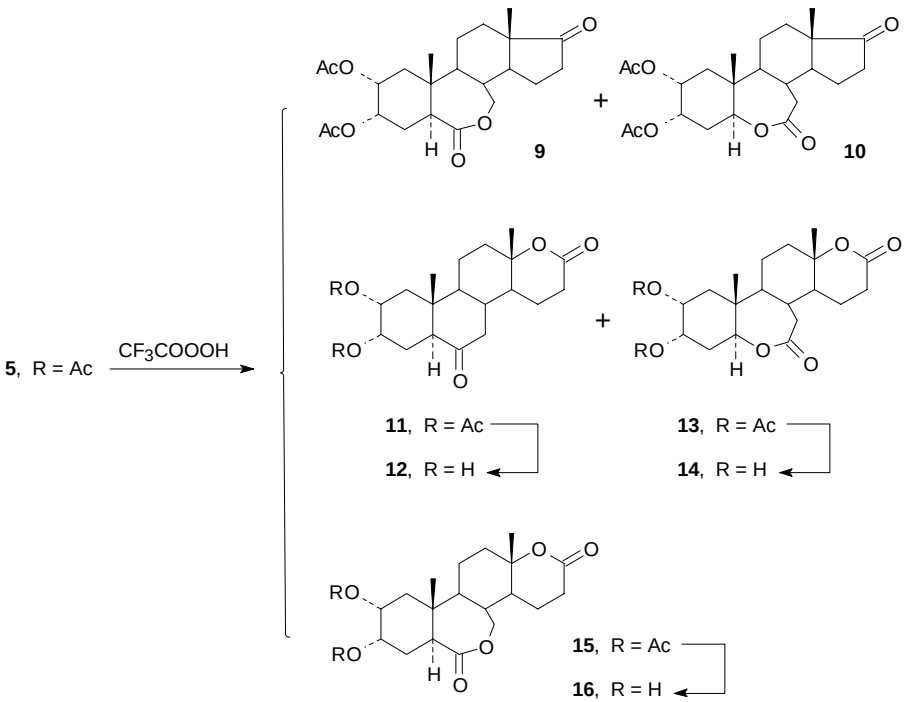
(i) HI, AcOH; (ii) LiBr, Li_2CO_3, DMF; (iii) LiBr, Py.TsOH;
(iv) OsO_4, *N*-methylmorpholine *N*-oxide, H_2O; (v) Ac_2O, Py; (vi) KOH, MeOH

SCHEME 1

Chromatographic separation of the two isomers present in the mother liquor was very difficult because their R_F was practically identical; better separation was achieved in the form of their acetates **5** and **7**. Acetates **5** and **7** were assigned configuration by comparing the observed ^{1}H NMR chemical shifts of the 18-H and 19-H signals (compound **5**: 0.87 and 0.87 (H-19 and H-18, respectively); compound **7**: 0.96 and 0.86 (H-19 and H-18, respectively)) with the values calculated[11] for both isomers (**5**: 0.88 and 0.91 (H-19 and H-18); **7**: 0.96 and 0.90 (H-19 and H-18)). The assigned structures were confirmed by alkaline hydrolysis of the acetate groups in diacetate **7** leading to 5α-diol **6** together with 5β-diol **8**. Both the diols were unequivocally identified by comparison with literature data[12] (see Experimental).

Diketone **5** with brassinolide structure of the ring A was subjected to the Baeyer–Villiger reaction (Scheme 2). The reaction mixture contained products with one and two lactone groups. Using careful column and preparative thin-layer chromatography, we identified

five reaction products: two lipophilic and three more polar. Although the two lipophilic products could not be separated, spectral data indicated their structure: both were 17-oxo compounds and in one (**9**) the ring B had a "normal" 6-oxo-7-oxa lactone structure (*i.e.*, the same as in natural brassinolide) whereas the other contained a "reverse", 6-oxa-7-oxo lactone grouping (**10**). This assignment was confirmed by the Baeyer–Villiger oxidation of a mixture of compounds **9** and **10** which afforded a mixture of two products, identical with two of the three more polar products mentioned above. All the three polar products had a lactone grouping in the ring D and differed in the structure of ring B: one compound contained a 6-oxo group (**11**), the second had "normal", 6-oxo-7-oxa lactone grouping (**15**) and the third "reverse", 6-oxa-7-oxo lactone grouping (**13**). The structure of all the product follows from ^{1}H NMR spectral analysis. In the ^{1}H NMR spectrum of



SCHEME 2

compound **11**, we identified only the H-2β and H-3β protons. The spectrum of lactone **13** exhibited, in addition, a one-proton multiplet (H-5α) in the region 4.48–4.60 whereas in the spectrum of compound **15**, the H-5α signal appeared as doublet of doublet of doublet at 3.08 and the spectrum exhibited a two-proton multiplet in the region 4.10–4.37 due to the H-7a protons. Also, the mass spectra showed that ketone **11**

contains one oxygen atom less than lactones **13** and **15**. The assigned structures were then confirmed by the Baeyer–Villiger oxidation of ketone **11** which afforded a mixture of lactones **13** and **15**.

The corresponding hydroxy derivatives **12**, **14** and **16** were prepared by alkaline hydrolysis of the acetates and subsequent acidification of the reaction mixture which brought about recyclization of the lactone ring.

The brassinolide activity was measured by a modified bean second internode bioassay[13]. Of all the compounds tested in this study, compound **16** was the most active and, surprisingly, a similar activity has also been found for its diacetate **15**. The other compounds tested (**3–11**, **13** and **14**; **9** and **10** as a 1 : 1 mixture) were less active. Worth mentioning is also the activity of compound **12** which, at higher concentrations, (10^{-6} to 10^{-9} mol/l per plant) retarded the second internode growth (Table I).

EXPERIMENTAL

Melting points were determined on a melting point microapparatus Electrothermal (U.S.A.). Infrared spectra were recorded on a Bruker IFS 88 spectrometer in tetrachloromethane (unless stated otherwise); wavenumbers are given in cm^{-1}. ^1H NMR spectra were taken on a Varian XL-200 (FT mode, 200 MHz) instrument at 23 °C in deuteriochloroform with tetramethylsilane as internal reference unless stated otherwise. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and multiplet half-widths ($W_{1/2}$) in Hz. Mass spectra were obtained with a ZAB-EG spectrometer at 70 eV. Optical rotations were measured in chloroform. The identity of the prepared samples was checked by IR and ^1H NMR spectra, mixed melting points and thin-layer chromatography (TLC) on silica gel G (ICN Biochemicals, detection by spraying with sulfuric acid and heating). Preparative TLC was carried out on 200 × 200 mm plates coated with a 0.7 mm thick layer of silica gel Woelm DC. Column chromatography was performed on 60–120 μm neutral silica gel (Service Laboratories of the Institute). "Usual work-up" of a solution denotes extraction with an organic solvent, washing the organic phase with 5% hydrochloric acid, water, 5% aqueous potassium hydrogen carbonate, water, drying over an-

TABLE I
Elongation of bean second internode relative to a control (in mm)

Compound	Applied amount, μmol					
	1	$1 . 10^{-1}$	$1 . 10^{-2}$	$1 . 10^{-3}$	$1 . 10^{-4}$	$1 . 10^{-5}$
15	1.4	9.9	11.0	9.0	4.6	5.5
16	6.4	12.4	10.0	4.4	1.9	0
12	–4.8	–0.8	–6.1	–7.5	1.1	1.1
24-epiBR[a]	[b]	[b]	20.4	30.8	32.3	18.6

[a] 24-Epibrassinolide ((22*R*,23*R*,24*R*)-2α,3α,22,23-tetrahydroxy-24-methyl-7-oxa-7a-homo-5α-cholestan-6-one); [b] not measured.

hydrous sodium sulfate, filtration and evaporation of the solvent to dryness *in vacuo*. The light petroleum was a fraction boiling at 40–62 °C.

Bean Second Internode Bioassay. Bean seeds (*Phaseolus vulgaris* L. cv. Pinto) were germinated for two days. Selected germinated seeds were planted into pots containing perlite and modified Hoagland's solution (half concentration, pH 5.7). The pots were placed in a light-controlled cultivation room (25 to 27 °C, light: 48 W/m^2, light/dark period: 16 h/8 h). Groups of eight 7-days old bean seedlings with 1–2 mm long second internodes were treated with different amounts of the tested compounds in lanolin (2 μl). The control plants were treated with lanolin alone. The measurements were taken after 5 days. The difference in the length of the second internode of the treated and control plants was used as a measure of the activity.

3β-Iodo-5α-androstane-6,17-dione (**2**)

A solution of 3α,5-cyclo-5α-androstane-6,17-dione[10] (**1**; 10.0 g, 34.9 mol) in acetic acid (200 ml) was treated with hydroiodic acid (67%; 24.0 g, 125 mmol) at room temperature overnight. The mixture was partitioned between water and ether and worked up in the usual manner. The residue was crystallized from tetrachloromethane to give 4.65 g (32%) of iodo compound **2**, m.p. 210–212 °C. ^{1}H NMR spectrum: 0.84 s, 3 H (3 × H-19); 0.875 s, 3 H (3 × H-18); 4.00 m, 1 H, $W_{1/2}$ = 26 (H-3α). IR spectrum: 1 738 (17-ketone C=O); 1 714 (6-ketone C=O). For $C_{19}H_{27}IO_2$ (414.3) calculated: 55.08% C, 6.57% H, 30.63% I; found: 55.31% C, 6.31% H, 30.41% I.

Androst-2-ene-6,17-dione (**3**)

A. From 3β-iodo-5α-androstane-6,17-dione (**2**): Lithium bromide (10.0 g, 115 mmol) and Li_2CO_3 (10.0 g, 135 mmol) were added to a solution of iodo compound **2** (20 g, 48 mmol) in *N*,*N*-dimethylformamide (200 ml). After heating at 140 °C for 2 h under nitrogen, the mixture was cooled, and poured into water; the product was taken up in ether and the ethereal layer was worked up as usual. The residue was chromatographed on silica gel (500 g) in benzene–ethyl ether (9 : 1) to give 13.1 g of product which on crystallization from ethanol afforded 9.11 g (66%) of alkene **3**, m.p. 193–194 °C, $[\alpha]_D^{20}$ +113° (*c* 1.1), in accord with the literature[12]. ^{1}H NMR spectrum: 0.74 s, 3 H (3 × H-19); 0.875 s, 3 H (3 × H-18); 5.57 m, 2 H, $W_{1/2}$ = 4.5 (H-2 and H-3). IR spectrum: 3 030, 1 658 (C=C–H), 1 744 (17-ketone C=O); 1 714 (6-ketone C=O).

B. From 3α,5-cyclo-5α-androstane-6,17-dione (**1**): Lithium bromide (12.0 g, 13.8 mmol) and pyridinium 4-toluenesulfonate (240 mg, 1.00 mmol) were added to a solution of cyclo derivative[10] **1** (3.0 g, 10.5 mmol) in *N*,*N*-dimethylacetamide (90 ml). After heating at 160 °C under nitrogen for 6 h, the mixture was cooled, partitioned between water and ether, and worked up in the usual manner. The residue (2.7 g) was chromatographed on silica gel (60 g) in light petroleum–ether (4 : 1) to give 2.1 g of product which was crystallized from ethanol. Yield 1.72 g (57%) of alkene **3**, identical with the product obtained by method *A*.

2α,3α-Dihydroxy-5α-androstane-6,17-dione (**4**)

A solution of osmium tetroxide (180 mg, 0.71 mmol) in 2-methyl-propan-2-ol (6.0 ml) was added to a solution of alkene **3** (3.6 g, 12 mmol) in acetone (180 ml). A solution of *N*-methylmorpholine *N*-oxide (3.6 g, 31 mmol) in water (6.0 ml) was added, the mixture was stirred under nitrogen for 5 h and filtered. The filtrate was concentrated *in vacuo* to about one third and a sodium sulfite solution (10 ml, 10%) was added. The mixture was stirred for 30 min, poured into water, extracted with chloroform and the extract was worked up as usual. The residue was purified by chromatography on silica gel (80 g) in ether–chloroform (1 : 1). The work-up of the product fractions and crystallization from

methanol afforded 1.89 g (47%) of diol **4**, m.p. 166–170 °C (modification change at 142–150 °C), $[\alpha]_D^{20}$ +80° (*c* 1.3). ^{1}H NMR spectrum: 0.78 s, 3 H (3 × H-19); 0.87 s, 3 H (3 × H-18); 3.74 m, 1 H, $W_{1/2}$ = 21 (H-2β); 4.03 m, 1 H, $W_{1/2}$ = 6 (H-3β). IR spectrum: 3 613, 3 568, 3 469 (O–H); 1 734 (17-ketone C=O); 1 707 (6-ketone C=O); 1 055, 1 039, 1 006 (diol C–O). For $C_{19}H_{28}O_4$ (320.4) calculated: 71.22% C, 8.81% H; found: 70.47% C, 9.12% H.

6,17-Dioxo-5α-androstane-2α,3α-diyl Diacetate (**5**)

Acetic anhydride (6.0 g, 59 mmol) was added to a solution of diol **4** (2.0 g, 6.2 mmol) in pyridine (10 ml), the mixture was set aside at room temperature for 2 days, then poured into water, extracted with ether and worked up in the usual manner. The residue was purified by chromatography on silica gel (100 g) in benzene–ether (2 : 1). Crystallization from methanol afforded 1.13 g (45%) of diacetate **5**, m.p. 188–190 °C, $[\alpha]_D^{20}$ +53° (*c* 0.7). ^{1}H NMR spectrum: 0.86 s, 3 H and 0.88 s, 3 H (3 × H-18 and 3 × H-19); 1.97 and 2.06 2 s, 2 × 3 H (2 × CH_3COO); 4.93 m, 1 H, $W_{1/2}$ = 22 (H-2β); 5.35 m, 1 H, $W_{1/2}$ = 7.5 (H-3β). IR spectrum: 1 744 (17-ketone C=O); 1 718 (6-ketone C=O); 1 744 (acetate C=O); 1 245, 1 046 (acetate C–O). Mass spectrum, *m/z*: 404 (M^+), 344 (404 – HOAc), 284 (404 – 2 × HOAc), 269 (284 – CH_3). For $C_{23}H_{32}O_6$ (404.5) calculated: 68.29% C, 7.97% H; found: 68.11% C, 8.10% H.

2β,3β-Dihydroxy-5α-androstane-6,17-dione (**6**)

Potassium hydroxide (400 mg, 7.13 mmol) was added to diacetate **7** (280 mg, 0.69 mmol) in methanol (18 ml). After reflux for 40 min, the mixture was poured into water and the product was taken up in chloroform. The usual work-up afforded 220 mg of a residue which was chromatographed on 8 preparative plates of silica gel in chloroform–ether (1 : 1). Lipophilic fractions afforded 21 mg (10%) of diol **6**, m.p. 241–243 °C (ethyl acetate–heptane), $[\alpha]_D^{20}$ +66° (*c* 0.6) (reported[12] m.p. 243–244.5 °C, $[\alpha]_D^{20}$ +66°). ^{1}H NMR spectrum: 0.91 s, 3 H (3 × H-18); 1.04 s, 3 H (3 × H-19); 3.60 m, 1 H, $W_{1/2}$ = 21 (H-3α); 4.07 dd, 1 H, J = 3, J' = 6.5 (H-2α). IR spectrum: 3 625, 3 250 (O–H); 1 741 (17-ketone C=O); 1 708 (6-ketone C=O).

6,17-Dioxo-5α-androstane-2β,17β-diyl Diacetate (**7**)

Acetylation of the mother liquor (1.45 g, 4.53 mmol) from crystallization of diol **4** was carried out similarly to the preparation of diacetate **5**. Chromatography of the reaction product on a column of silica gel in light petroleum–chloroform–ether (3 : 1 : 1) afforded, in addition to the lipophilic diacetate **5** (0.7 g, 38%), the polar diacetate **7** (0.49 g, 34%), m.p. 283–290 °C (ethanol), $[\alpha]_D^{20}$ +67° (*c* 1.0). ^{1}H NMR spectrum: 0.87 s, 3 H (3 × H-18); 0.97 s, 3 H (3 × H-19); 2.00 s and 2.08 s, 2 × 3 H (2 × CH_3COO); 4.80 m, 1 H, $W_{1/2}$ = 21 (H-3α); 5.31 m, 1 H, $W_{1/2}$ = 6 (H-2α). IR spectrum: 1 745 (17-ketone and acetate C=O); 1 718 (6-ketone C=O); 1 243, 1 042 (acetate C–O). Mass spectrum, *m/z*: 404 (M^+), 344 (404 – HOAc). For $C_{23}H_{32}O_6$ (404.5) calculated: 68.29% C, 7.97% H; found: 68.01% C, 8.11% H.

2β,3β-Dihydroxy-5β-androstane-6,17-dione (**8**)

Work-up of polar fractions from the TLC preparation of diol **6** afforded 138 mg (62%) of diol **8**, m.p. 213–215 °C (ethyl acetate–hexane), $[\alpha]_D^{20}$ 0° (*c* 0.7) (reported[12] m.p. 214–216 °C, $[\alpha]_D^{20}$ –4.5°). ^{1}H NMR spectrum: 0.89 s, 3 H (3 × H-18); 0.95 s, 3 H (3 × H-19); 3.81 dm, 1 H, J = 12, $W_{1/2}$ = 21 (H-2α); 4.07 dd, 1 H, J = 3, J' = 6 (H-3α). IR spectrum: 3 161 (O–H); 1 736 (17-ketone C=O); 1 704 (6-ketone C=O); 1 058, 1 046 (C–O).

Baeyer–Villiger oxidation of ketone **5**

To a solution of diacetate **5** (0.9 g, 2.2 mmol) in dichloromethane (20 ml) was added a solution of trifluoroperoxyacetic acid, prepared from trifluoroacetic anhydride (2.45 g, 11.7 mmol) and 50% hydrogen peroxide (0.36 g, 10.6 mmol) in dichloromethane (20 ml). After standing at room temperature for 2 h, the same amount of the trifluoroperoxyacetic acid solution in dichloromethane was added and the mixture was set aside at room temperature for another 2 h. The reaction mixture was carefully poured into water, the product was taken up in chloroform, the chloroform extract was successively washed with water, aqueous potassium hydrogen carbonate solution, water, and dried over sodium sulfate. Evaporation of the solvent afforded 1.5 g of material which was separated on a column of silica gel into a lipophilic fraction (153 mg, 16%) containing an unseparable mixture of two lipophilic products **9** and **10**, and into three fractions containing polar products (in the order of increasing polarity, compounds **11**, **13** and **15**).

6,17-Dioxo-7-oxa-7a-homo-5α-androstane-2α,3α-diyl diacetate (**9**) *and 7,17-dioxo-6-oxa-7a-homo-5α-androstane-2α,3α-diyl diacetate* (**10**). The lipophilic fraction (mixture of **9** and **10**) had the following ^{1}H NMR spectrum: 0.90 s, 1.5 H and 0.92 s, 1.5 H (H-18); 1.02 s, 1.5 H and 1.04 s, 1.5 H (H-19); 2.00 s, 3 H (CH_3COO); 2.12 s, 1.5 H and 2.11 s, 1.5 H (CH_3COO); 4.04–4.28 m, 1.5 H (1 × H-7, lactone **10** and 0.5 × H-5, lactone **9**); 4.47–4.57 m, 1.5 H (0.5 × H-5, lactone **10** and 1 × H-7, lactone **9**); 4.89 m, 1 H (H-2β); 5.39 m, 1 H (H-3β). IR spectrum: 1 736 (17-ketone C=O); 1 715–1 736 (6-ketone and 7-ketone and acetate C=O); 1 251, 1 108, 1 043 (acetate C–O). Both spectra correspond to a mixture of compounds **9** and **10**.

6,17-Dioxo-17a-oxa-17a-homo-5α-androstane-2α,3α-diyl Diacetate (**11**)

Further chromatographic elution in the above Baeyer–Villiger oxidation experiment afforded 461 mg of material which on crystallization from ethanol gave lactone **11** (97 mg, 10.4%), m.p. 233 °C, $[\alpha]_D^{20}$ +33° (*c* 1.1). ^{1}H NMR spectrum: 1.33 s, 3 H (3 × H-18); 0.81 s, 3 H (3 × H-19); 2.00 s, 3 H and 2.08 s, 3 H (2 × CH_3COO); 4.94 m, 1 H, $W_{1/2}$ = 22 (H-2β); 5.39 m, 1 H, $W_{1/2}$ = 6 (H-3β). IR spectrum ($CHCl_3$): 1 740 (acetate C=O); 1 725, 1 713 (lactone C=O); 1 267 (acetate C–O). Mass spectrum, *m/z*: 420 (M^+), 360 (M^+ – HOAc). For $C_{23}H_{32}O_7$ (420.5) calculated: 65.70% C, 7.67% H; found: 65.41% C, 7.41% H.

2α,3α-Dihydroxy-17a-oxa-17a-homo-5α-androstane-6,17-dione (**12**)

A solution of sodium hydroxide (100 mg, 2.5 mmol in 0.2 ml water) was added to a solution of diacetate **11** (390 mg, 0.76 mmol) in methanol (10 ml) and the mixture was refluxed under nitrogen for 1 h. Tetrahydrofuran (15 ml) and aqueous hydrochloric acid (6 mol/l, 6 ml) were added and boiling under nitrogen was continued for 30 min. After cooling, the mixture was partitioned between water and chloroform and the chloroform layer was worked up in the usual manner to give 270 mg of a residue which was crystallized from ethanol. The yield was 115 mg of diol **12**. Repeated crystallizations of the mother liquor afforded 196 mg (76%) of diol **12**, m.p. 255–257 °C, $[\alpha]_D^{20}$ –21° (*c* 0.9). ^{1}H NMR spectrum: 1.35 s, 3 H (3 × H-18); 0.74 s, 3 H (3 × H-19); 3.70 m, 1 H, $W_{1/2}$ = 24 (H-2β); 4.00 m, 1 H, $W_{1/2}$ = 6 (H-3β). IR spectrum (KBr): 3 435, 3 405 (O–H); 1 713, 1 716 (C=O); 1 238, 1 221, 1 112, 1 070, 1 052 (C–O). For $C_{19}H_{28}O_5$ (336.4) calculated: 67.83% C, 8.39% H; found: 67.71 % C, 8.19% H.

7,17-Dioxo-6,17a-dioxa-7a,17a-dihomo-5α-androstane-2α,3α-diyl Diacetate (**13**)

A. From 2α,3α-diacetoxy-5α-androstane-6,17-dione (**5**): Further product from the chromatography in the preparation of compounds **9**, **10** and **11**, was dilactone **13** (97 mg, 10%), m.p. 281–285 °C

(ethanol), $[\alpha]_D^{20}$ –19° (*c* 1.7). ^{1}H NMR spectrum: 1.00 s, 3 H (3 × H-18); 1.00 s, 3 H (3 × H-19); 2.00 s, 3 H (CH_3COO); 2.12 s, 3 H (CH_3COO); 4.48–4.60 m, 1 H (H-5); 4.91 ddd, 1 H, J = 12.5, J' = 2.75, J'' = 3 (H-2β); 5.40 dm, 1 H, J = 2.75, $W_{1/2}$ = 10 (H-3β). IR spectrum ($CHCl_3$): 1 736 (C=O); 1 249, 1 045 (acetate C–O). Mass spectrum, *m/z*: 436 (M^+), 421 (M^+ – 15), 376 (M^+ – HOAc). For $C_{23}H_{32}O_8$ (436.5) calculated: 63.29% C, 7.39% H; found: 63.11% C, 7.21% H.

B. From 2α,3α-diacetoxy-17a-oxa-17a-homo-5α-androstane-6,17-dione (**11**): To a solution of compound **11** (194 mg, 0.46 mmol) in dichloromethane (5 ml) was added a solution of trifluoroperoxyacetic acid prepared from trifluoroacetic anhydride (0.48 g, 2.33 mmol) and 50% hydrogen peroxide (72 mg, 2.12 mmol) in dichloromethane (4 ml). After standing at room temperature for 4 h, the reaction mixture was poured into water and the product was taken up in chloroform. The chloroform extract was washed with water, aqueous solution of potassium hydrogen carbonate, water, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue chromatographed on 8 preparative plates of silica gel in chloroform–propan-2-ol (9 : 1). The lipophilic zones gave 72 mg (35%) of lactone **13**, identical with the product obtained by method *A*.

C. From a mixture of 2α,3α-diacetoxy-7-oxa-7a-homo-5α-androstane-6,17-dione (**9**) and 2α,3α-diacetoxy-6-oxa-7a-homo-5α-androstane-7,17-dione (**10**): A mixture of ketones **9** and **10** (60 mg, 0.14 mmol) was allowed to stand with trifluoroperoxyacetic acid, freshly prepared as described in experiment *B*. After standing at room temperature for 48 h, the reaction mixture contained no starting material and was worked up as described under *B*. Crystallization of the lipophilic fractions from ethanol gave 22 mg (18%) of lactone **13**, identical with the compound obtained by method *A*.

2α,3α-Dihydroxy-6,17a-dioxa-7a,17a-dihomo-5α-androstane-7,17-dione (**14**)

Potassium hydroxide (50 mg, 0.89 mmol) was added to diacetate **13** (90 mg, 0.21 mmol) in methanol (10 ml) and the mixture was boiled under reflux for 60 min. Tetrahydrofuran (10 ml) and concentrated hydrochloric acid (1 ml) were added and boiling was continued for further 30 min. The reaction mixture was poured into water, the product was extracted with chloroform and the extract was worked up in the usual manner. The residue (79 mg) was crystallized from acetone–light petroleum to give 24 mg (33%) of diol **14**, m.p. 295 °C (decomp.). ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD): 1.34 s, 3 H (3 × H-18); 0.91 s, 3 H (3 × H-19); 3.61–3.79 m, 1 H (H-2β); 3.99 bs, 1 H, $W_{1/2}$ = 8 (H-3β); 4.63–4.75 m, 1 H (H-5α). IR spectrum (KBr): 3 520, 3 413 (O–H); 1 732, 1 711 (C=O); 1 042, 969 (diol C–O). Mass spectrum, *m/z*: 352 (M^+), 334 ($M^+ - H_2O$), 316 ($M^+ - 2 \times H_2O$). For $C_{19}H_{28}O_6$ (352.4) calculated: 64.75% C, 8.01% H; found: 64.51% C, 8.11% H.

6,17-Dioxo-7,17a-dioxa-7a,17a-dihomo-5α-androstane-2α,3α-diyl Diacetate (**15**)

A. From 2α,3α-diacetoxy-5α-androstane-6,17-dione (**5**): Further product, obtained in the preparation of compounds **9**, **10**, **11** and **13**, was dilactone **15** (106 mg, 11%), m.p. 221–226 °C (ethanol). ^{1}H NMR spectrum: 1.36 s, 3 H (3 × H-18); 0.76 s, 3 H (3 × H-19); 2.00 s, 3 H (CH_3COO); 2.17 s, 3 H (CH_3COO); 3.08 dd, 1 H, J = 6, J' = 14 (H-5α); 4.10–4.37 m, 2 H (2 × H-7a); 4.84 dm, 1 H, $W_{1/2}$ = 12 (H-2β) and 5.38 m, 1 H, $W_{1/2}$ = 7 (H-3β). IR spectrum ($CHCl_3$): 1 737 (C=O); 1 251, 1 047 (acetate C–O). Mass spectrum, *m/z*: 436 (M^+), 376 (M^+ – HOAc), 316 ($M^+ - 2 \times$ HOAc). For $C_{23}H_{32}O_8$ (436.5) calculated: 63.29% C, 7.39% H; found: 63.19% C, 7.10% H.

B. From ketone **11**: The work-up of zones with the polar product from preparative TLC in the preparation of compound **13** by method *B* afforded 30 mg (15%) of crystalline lactone **15**, identical with the product prepared by method *A*.

C. From a mixture of ketones **9** and **10**: The work-up of fractions from preparative TLC in the preparation of compound **13** according to method *C* afforded 10.3 mg (8.5%) of a residue which was identical with the compound prepared by method *A*.

2α,3α-Dihydroxy-7,17a-dioxa-7a,17a-dihomo-5α-androstane-6,17-dione (**16**)

Potassium hydroxide (60 mg, 1.07 mmol) was added to diacetate **15** (80 mg, 0.18 mmol) in methanol (10 ml) and the mixture was refluxed for 160 min. Tetrahydrofuran (7 ml) and concentrated hydrochloric acid (1.5 ml) were added and boiling was continued for further 30 min. The reaction mixture was poured into water and the product was extracted with chloroform and worked up as usual. The residue (75 mg) was purified by preparative TLC on two plates of silica gel in chloroform–acetone (3 : 1). Yield 37 mg (60%) of diol **16**, m.p. 128–130 °C. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD): 1.35 s, 3 H (3 × H-18); 0.91 s, 3 H (3 × H-19); 3.10 m, 1 H (H-5α); 3.75 dm, 1 H, J = 14, $W_{1/2}$ = 9 (H-2β); 4.04 m, 1 H, $W_{1/2}$ = 8 (H-3β); 4.08–4.33 m, 2 H (2 × H-7a). IR spectrum (KBr): 3 534, 3 415 (O–H); 1 715 (C=O); 1 037, 969 (C–OH). Mass spectrum, *m/z*: 352 (M^+), 334 ($M^+ - H_2O$), 316 ($M^+ - 2 \times H_2O$). For $C_{19}H_{28}O_6$ (352.4) calculated: 64.75% C, 8.01% H; found: 64.51% C, 8.19% H.

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