Recl. Trav. Chim. Pays-Bas **105**, 111–115 (1986) 0165–0513/86/04111–05$1.75

An alternative synthesis of 17β-hydroxy-7α-methyl-19-nor--17α-pregn-5(10)-en-20-yn-3-one (Org OD 14)

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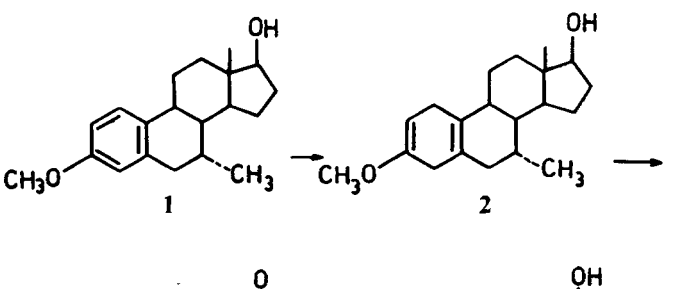
(Received August 14th, 1985)

Abstract. The title compound (**4**) was prepared starting from 17β,19-dihydroxyandrosta-4,6-dien-3--one 17,19-diacetate (**5**). Copper-catalyzed conjugate addition of methylmagnesium iodide gave, after hydrolysis, 17β,19-dihydroxy-7α-methylandrost-4-en-3-one (**8a**), which was converted by oxidation and deacylation into 7α-methylestr-5(10)-ene-3,17-dione (**11**). Selective protection of the 3-keto group as the dimethyl acetal, followed by ethynylation and deacetalization, gave the desired product **4**. The 7β-methyl adduct, a by-product in the Grignard reaction, was removed after the oxidation step. Its structure was confirmed by an independent synthesis of the 7β-methyl-19-aldehyde **9b**.

Introduction

The steroid 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)--en-20-yn-3-one **4** is of great interest in the treatment of menopausal complaints[1]. It was first synthesized by our group[2], and independently by others[3], using *Birch* reduction of 3-methoxy-7α-methylestra-1,3,5(10)-trien-17β-ol **1**, followed by *Oppenauer* oxidation to the 17-ketone **3**, ethynylation and mild hydrolysis of the enol ether group (Scheme 1).



Scheme 1

The starting material for this synthesis (**1**) was obtained by methylation of the corresponding 3-hydroxyl compound or by reduction of the 17-ketone[3], both compounds having been prepared by elaborate routes[4,5]. A stereoselective total synthesis of racemic 3-methoxy-7α-methylestra-1,3,5(10)-trien--17-one has recently been reported[6].

We now wish to describe a synthesis of **4** starting from 17β,19-dihydroxyandrosta-4,6-dien-3-one 17,19-diacetate (**5**), which can be prepared in good yield from 3β-hydroxyandrost-5-en-17-one 3-acetate[7,8].

Synthesis of the title compound

Copper-catalyzed conjugate addition of methylmagnesium iodide to dienone **5** (Scheme 2) at −40 °C yielded a mixture of the two enolates **6a** and **6b**, which, after protonation under equilibrating conditions[9], gave a mixture of the 7α- and 7β-methylandrost-4-en-3-ones **7a** and **7b**, respectively. At higher temperatures, attack on the ester functions together with other side-reactions became more pronounced. Mild saponification of the reaction mixture to prevent a retro-aldol reaction gave **8a** and **8b** in a ratio of about 4/1. This ratio, determined by integration of the 4-H signals in the 200-MHz ^{1}H NMR spectrum (Table I), is not significantly different from that found for similar methyl-Grignard additions to 19-unsubstituted androsta-4,6-dien-3-ones[5]. A lesser degree of stereoselectivity has been reported for the 1,6-addition of lithium dimethylcuprate to dienones of the latter type[10,12]. The very slight difference in polarity between **7a** and **7b** and between **8a** and **8b** rendered chromatographic separation of both epimeric mixtures impractical. Although the 7α-isomer **8a** could be obtained in poor yield by repeated crystallization of the **8a/8b** mixture, it proved more economic to carry out a limited purification (crystallization) and to oxidize the

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[1] *R. Lindsay, D. M. Hart* and *A. Kraszewski*, Br. Med. J. **280**, 1207 (1980); *P. Franchimont, F. Franchi, M. Luisi* and *P. M. Kicovic*, Reproduccion **6**, 61 (1982); *J. Cittadini, J. Ben, A. R. Badano, H. J. Denari, S. Quiroga, A. E. Marcus, I. Schlaen* and *P. R. Figueroa Casas*, Reproduccion **6**, 69 (1982); *P. M. Kicovic, J. Cortes–Prieto, M. Luisi, S. Milojevic* and *F. Franchi*, Reproduccion **6**, 81 (1982); *R. Trévoux, P. Dieulangard* and *A. Blum*, Maturitas **5**, 89 (1983); *J. Nevinny–Stickel*, Arch. Gynecol. **234**, 27 (1983).

[2] *Organon*, Neth. Patent Application 6,406,797; Chem. Abstr. **64**, 12759b (1966).

[3] *P. Wieland and G. Anner*, Helv. Chim. Acta **50**, 1453 (1967).

[4] *J. Kalvoda, Ch. Krähenbühl, P. A. Desaulles* and *G. Anner*, Helv. Chim. Acta **50**, 281 (1967).

[5] *P. Wieland* and *G. Anner*, Helv. Chim. Acta **50**, 289 (1967).

[6] *M. B. Groen* and *F. J. Zeelen*, Recl. Trav. Chim. Pays-Bas **97**, 301 (1978).

[7] *Ciba–Geigy* A.G. Belgian Patent 620225; Chem. Abstr. **59**, 7612f (1963).

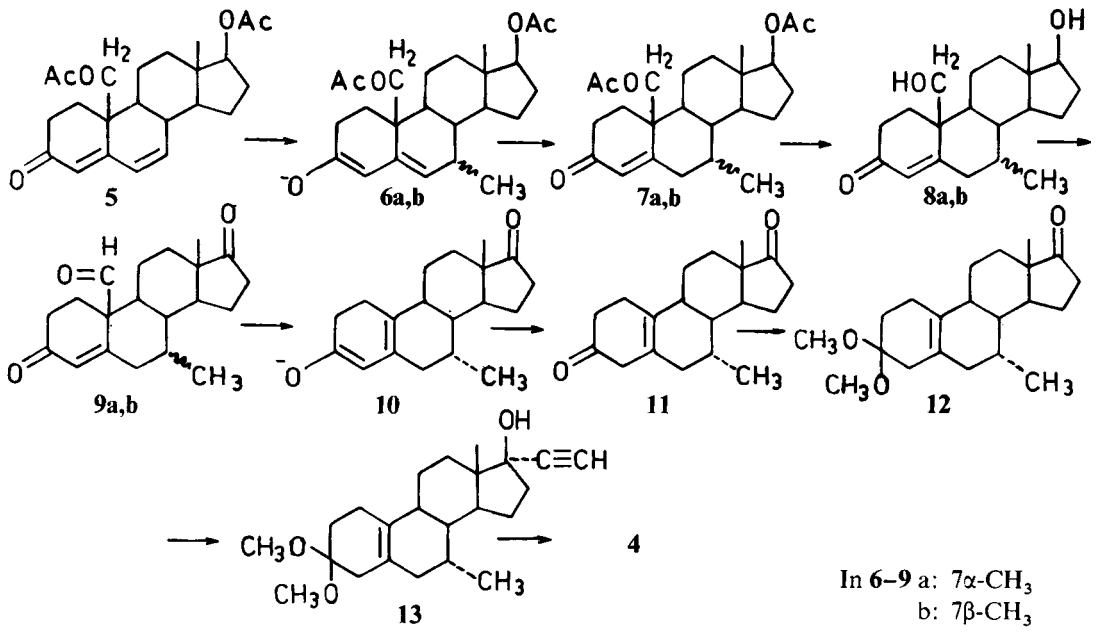
[8] *K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner* and *A. Wettstein*, Experientia **18**, 464 (1962).

[9] Kinetic protonation would have yielded the corresponding androst-5-en-3-one derivatives[10].

[10] *J. F. Grunwell, H. D. Benson, J. O'Neal Johnston* and *V. Petrow*, Steroids **27**, 759 (1976).

[11] *J. Pfister, H. Wehrli* and *K. Schaffner*, Helv. Chim. Acta **50**, 166 (1967).

[12] *F. Gasparrini, S. Cacchi, L. Caglioti, D. Misiti* and *M. Giovannoli*, J. Chromatogr. **194**, 239 (1980).



Scheme 2

product with chromic acid to the epimeric 19-aldehydes **9a** and **9b**. At this stage, the pure 7α-isomer **9a** could be isolated by column chromatography in 30% yield based on **5**.

The 7β-isomer **9b** could not be fully separated from **9a**. It was obtained as a ≈4/1 mixture with the latter compound (200-MHz ^{1}H NMR). Comparison of this spectrum with that of pure **9b**, prepared via an independent route *(vide infra)*, confirmed the assigned structure. The relevant ^{1}H NMR data of **8a**, **8b**, **9a** and **9b** are in good agreement with the literature data on related 7α- and 7β-methylandrost-4-en-3-ones (see Table I). The characteristic difference in δ values of the 7α- and 7β-methyl substituents is caused by deshielding of the equatorial 7β-methyl group by steric interaction with the C(15) methylene group.

The 19-aldehyde **9a** was subjected to deacylation by treatment with magnesium methoxide in liquid ammonia followed by kinetic protonation of the resulting enolate ion **10**[13]. The crude dione **11**, thus obtained, was treated with methanol and malonic acid to protect the 3-keto function as the dimethyl acetal[14]. Subsequent ethynylation with potassium acetylide gave pure **13**, isolated from the reaction product in 77% yield based on **9a**. Removal of the protecting group with aqueous oxalic acid gave, in 79% yield, **4**, which was identical (m.p., $[\alpha]_D$, TLC, IR, ^{1}H NMR) with the product obtained earlier by a different route[2]. Thus, the overall yield based on **5** was 18%.

The ^{1}H NMR spectrum of **4** is in accordance with the assigned structure. The signal for the 7α-methyl substituent at δ 0.84 (d, *J* 7 Hz) is in the expected range (Table I). A sample of the 7β-isomer 17β-hydroxy-7β-methyl-19-nor-17α--pregn-5(10)-en-20-yn-3-one (**20**)[15]), prepared from 19-alde-

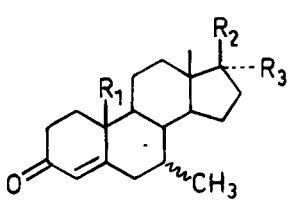
[13] *C. M. Siegmann* and *M. S. de Winter*, Recl. Trav. Chim. Pays-Bas **89**, 442 (1970).

[14] *H. Ueberwasser, K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner* and *A. Wettstein*, Helv. Chim. Acta **46**, 344 (1963).

[15] This compound has been previously mentioned in a patent application[16] although no physical constants were reported. Our product, crystallized from diisopropyl ether, had a m.p. 136–138°C, $[\alpha]_D$ +161 ($CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.90 (s, 3, 13-CH_3), 0.99 (d, *J* 6 Hz, 3, 7β-CH_3), 2.47 (m, 4, 1- and 2-H's), 2.61 (s, 1, C≡CH), 2.74 (m, 2, 4-H's). IR (CH_2Cl_2): 3595 (OH), 3300 (C≡CH), 1715 (C=O), 1060 and 1040 cm^{-1}.

[16] *J. C. Babcock* and *A. Campbell*, Ger. Pat. Appl. 2,043,404; Chem. Abstr. **75**, 20798t (1971).

Table I Relevant ^{1}H NMR data[a] of 7-methylandrost-4-en-3-ones.



Compound	7α-isomer 7α-CH_3	4-H	7β-isomer 7β-CH_3	4-H
8a,b R_1 = CH_2OH; R_2 = OH; R_3 = H	0.78 (d, *J* 7)[b]	5.93 (d, *J* 2)[b]	1.08 (d, *J* 6)[c]	5.91 (s)[c]
9a,b R_1 = CHO; $R_2 + R_3$ = O	0.88 (d, *J* 7)	6.01 (d, *J* 2)	1.19 (d, *J* 6)	5.98 (s)
R_1 = CH_3; R_2 = OH; R_3 = H[10]	0.77 (d, *J* 6)	5.75 (m)	1.17 (d, *J* 6)	5.75 (m)
R_1 = CH_3; R_2 = OAc; R_3 = H[11]	0.78 (d, *J* 7)	5.71 (b.s.)	1.06 (d, *J* 6)	5.69 (s)
R_1 = CH_3; R_2 = OAc; R_3 = H[12]	0.81 (d, *J* 7)	5.72 (d, *J* 1.8)	1.03 (d, *J* 5)	5.70 (b.s.)
R_1 = CH_3; R_2 = OH; R_3 = CH_3[12]	0.75 (d, *J* 7)	5.73 (d, *J* 1.8)	1.03 (d, *J* 5)	5.70 (b.s.)

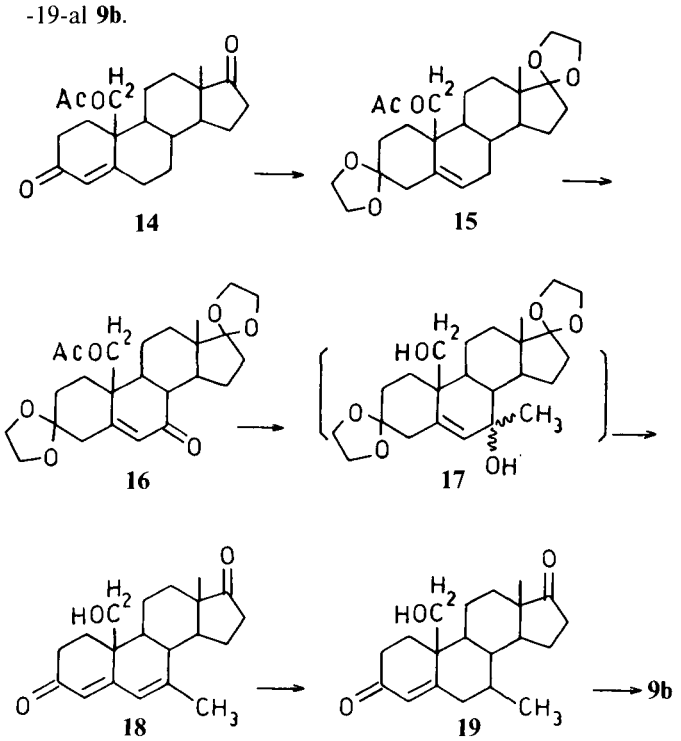
[a] $CDCl_3$solution; chemical shifts are given in ppm relative to TMS. Coupling constants are in Hz. [b] In $CDCl_3$ + 10% CD_3OD. [c] From **8a/8b** mixture in $CDCl_3$ + 10% CD_3OD.

hyde **9b** using the sequence of reactions described for **4**, showed a 7β-methyl signal at δ 0.99 (d, *J* 6 Hz). The shift to lower field and the smaller coupling constant are also in accordance with Table I. Recently, an independent proof of the structure of **4** was obtained from a single-crystal X-ray structure analysis[17].

Synthesis of the 7β-methyl-19-aldehyde 9b

Pure 19-aldehyde **9b** was prepared via an independent route involving catalytic hydrogenation of a 7-methylandrosta-4,6--dien-3-one as a key step[18] (Scheme 3). 19-Hydroxyandrost-4--ene-3,17-dione 19-acetate **14**[19] was converted to the bis-(ethylene acetal) **15**[20] and then oxidized to the conjugated 7-ketone **16** using sodium chromate in acetic acid/acetic anhydride[21]. The ethylene acetal groups were insufficiently stable under these severe reaction conditions, with the result that **16** was isolated as an impure product. It could, however, be used for the Grignard reaction to give, after acid treatment and chromatography, pure dienone **18** in 8.5% overall yield. No attempt was made to improve this yield by using more stable acetals as protecting groups. The use of milder oxidizing agents such as the chromium trioxide/pyridine complex[22] resulted in much lower yields.

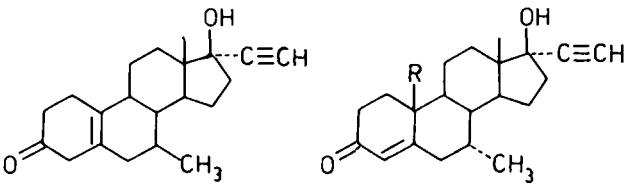
Catalytic hydrogenation of **18** proceeded from the less hindered α-side[18] to produce 19-hydroxy-7β-methylandrost-4--ene-3,17-dione **19**, which, upon oxidation with chromium trioxide, gave the desired 7β-methyl-3,17-dioxoandrost-4-en--19-al **9b**.



Scheme 3

Potential impurities in 4

Since dimethyl acetal **13** gave **4** when deprotected under weakly acidic conditions, but produced the conjugated isomer **21** on treatment with strong acids[23], the latter compound is a potential impurity in **4**. Other impurities containing an α,β-unsaturated keto group which one may expect are 10β-hydroperoxy-17β-hydroxy-7α-methyl-19-nor--17α-pregn-4-en-20-yn-3-one (**22**) and 10β,17β-dihydroxy--7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one (**23**), arising from oxidation of the β,γ-unsaturated ketone **4**[24]. Samples of these potential impurities were prepared. Photosensitized oxygenation[25] of **4** gave **22**, which, upon reduction[26], yielded **23**.



20

21 R = H
22 R = OOH
23 R = OH

The batches of **4** produced thus far showed, on thin-layer chromatography, only small amounts of three impurities. These were identified by isolation from the mother liquors and proved to be identical, both chromatographically and spectroscopically (^{1}H NMR, IR and UV), with the reference compounds **21**, **22** and **23**. These were used in the quantitative thin-layer chromatography of **4** on silica gel 60 F_{254} pre-coated plates (Merck) with benzene/ethyl acetate/pyridine (70/20/2, v/v) as eluent. In typical samples we found less than 1% each of **21** and **22** and only traces (<0.1%) of **23**.

Acknowledgements

We wish to thank Dr. *M. B. Groen*, Mr. *G. N. Wagenaars* and Mr. *E. M. van Doornum* for their help in interpreting the spectral data. We are also indebted to Mr. *J. G. C. Vermeer* for technical assistance and to Mr. *A. W. Blokland* for carrying out the quantitative TLC.

Experimental

General remarks

Melting points, determined in capillary tubes, are uncorrected. Unless otherwise stated, optical rotations were determined in chloroform solution ($c \approx 1\%$) at 20°C using a Perkin-Elmer 141 polarimeter. ^{1}H NMR spectra were recorded with TMS (δ = 0) as internal standard on a Bruker HX-90E or WP 200 instrument. IR

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[17] *J.-P. Declercq, M. Van Meerssche* and *F. J. Zeelen*, Recl. Trav. Chim. Pays-Bas **103**, 145 (1984).

[18] *C. H. Robinson, O. Gnoj, W. Charney, M. L. Gilmore* and *E. P. Oliveto*, J. Am. Chem. Soc. **81**, 408 (1959); *J. A. Zderic, H. Carpio* and *H. J. Ringold*, J. Am. Chem. Soc. **81**, 432 (1959).

[19] *L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Velarde* and *J. A. Edwards*, J. Org. Chem. **30**, 2198 (1965).

[20] *M. Mousseron-Canet, B. Labeeuw* and *J. C. Lanet*, Bull. Soc. Chim. Fr. 2125 (1968).

[21] *C. W. Marshall, R. E. Ray, I. Laos* and *B. Riegel*, J. Am. Chem. Soc. **79**, 6308 (1957).

[22] *W. G. Dauben, M. Lorber* and *D. S. Fullerton*, J. Org. Chem. **34**, 3587 (1969).

[23] A different synthesis of **21** has been described by *J. A. Campbell, S. Lyster, G. W. Duncan* and *J. C. Babcock*, Steroids **1**, 317 (1963), although no physical constants were given. The corresponding Belgian patent 610,385; Chem. Abstr. **57**, 13834c (1962), gives a m.p. 197–199.5°C. Our product had a m.p. 200–202°C; $[\alpha]_D$ −9.4 ($CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.78 (d, *J* 7 Hz, 3, 7α-CH_3), 0.92 (s, 3, 13-CH_3), 2.57 (s, 1, C≡CH), 5.84 (br.s., 1, 4-H). IR (CH_2Cl_2): 3595 (OH), 3300 (C≡**CH**), 1665 (C=O), 1620 (C=C), 1035 (C−OH) cm^{-1}. UV (EtOH): λ_{max} 240 nm, ε 1780 m^2/mol.

[24] *E. L. Shapiro, T. Legatt* and *E. P. Oliveto*, Tetrahedron Lett. 663 (1964); *E. L. Shapiro, L. Finckenor* and *H. L. Herzog*, J. Org. Chem. **33**, 1673 (1968).

[25] *N. Furutachi, Y. Nakadaira* and *K. Nakanishi*, Chem. Commun. 1625 (1968); *M. Maumy* and *J. Rigaudy*, Bull. Soc. Chim. Fr. 2021 (1976).

[26] *M. S. Kharash, R. A. Mosher* and *I. S. Bengelsdorf*, J. Org. Chem. **25**, 1000 (1960).

spectra were recorded on a Perkin-Elmer 357 or 580 grating spectrophotometer. UV spectra were recorded on a Perkin-Elmer 124 UV/VIS spectrophotometer. Microanalyses were provided by Dr. *W. McMeekin*, Analytical Department, Organon Laboratories, Newhouse, Scotland. All reactions were carried out in a nitrogen atmosphere.

17β,19-Dihydroxy-7α-methylandrost-4-en-3-one (**8a**)

Dry THF (200 ml) was added to a solution of methylmagnesium iodide prepared from magnesium (10.0 g, 0.41 mol), methyl iodide (25.6 ml, 0.41 mol) and anhydrous ether (200 ml). At −5°C, cupric acetate monohydrate (4.0 g, 0.02 mol) in dry THF (200 ml) was added with stirring. The mixture was cooled to −40°C and at this temperature a solution of **5** (20.0 g, 0.05 mol) in dry THF (160 ml) was added over 2 h. Stirring was continued at −40°C for 30 min. The mixture was worked up by pouring into cold 2N H_2SO_4 (800 ml), stirring for 2 h and extracting with CH_2Cl_2 (3 ×). The combined extracts were washed with brine, dried over anhydr. Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in methanol (300 ml), and KOH (30.0 g) in water (80 ml) was added. The resulting mixture was stirred at 0°C for 4 h and worked up by pouring into water and extracting with CH_2Cl_2 (3 ×). The combined extracts were washed with water, dried over anhydr. Na_2SO_4 and evaporated to dryness *in vacuo*. The crude mixture of **8a** and the 7β-isomer **8b** (≈4/1 by ^1H NMR) was crystallized from ethyl acetate to give 10.4 g (65%) of **8a** containing 17 ± 3% of **8b** (^1H NMR), m.p. 178–200°C, $[\alpha]_D$ +94.
Repeated crystallization from CH_2Cl_2/ethyl acetate gave **8a** containing 1–2% of **8b**, m.p. 197–199°C, $[\alpha]_D$ +102. $C_{20}H_{30}O_3$ (318.44) calcd.: C 75.43, H 9.50, O 15.07; found: C 75.2, H 9.5, O 15.2. ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ 0.78 (s, 3,13-CH_3), 0.78 (d, *J* 7 Hz, 3,7α-CH_3), 3.86 and 4.03 (2 × d, *J* 11 Hz, 2, 10-CH_2OH), 5.93 (d, *J* 2 Hz, 1, 4-H). IR (KBr): 3450 (OH), 1665 (C=O) and 1620 (C=C) cm^{-1}. UV (EtOH) λ_{max} 244 nm, ε 1580 m^2/mol.

7α-Methyl-3,17-dioxoandrost-4-en-19-al (**9a**)

At 30°C, an aqueous solution of CrO_3 (36.0 ml; 233 g/l CrO_3 + 175 ml/l conc. H_2SO_4) was added over 45 min to a vigorously stirred suspension of **8a** (10.0 g, 0.03 mol, containing 17 ± 3% of **8b**) in CH_2Cl_2 (100 ml). Stirring was then continued at reflux temperature (40°C) for 2 h. The mixture was cooled, poured into water and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined extracts were washed successively with aqueous Na_2SO_3, aqueous $NaHCO_3$ and water and dried over anhydr. Na_2SO_4. The solvent was removed *in vacuo*. The residue was crystallized from CH_2Cl_2/diisopropyl ether to give 8.0 g (81%) of **9a** containing 8 ± 3% of **9b**, m.p. 154–159°C. Subsequent preparative HPLC over Merck silica gel 60 (0.040–0.063 mm, 1 kg, 73 × 6 cm, p ≈ 5 bar, elution with CH_2Cl_2/acetone 97.5/2.5 v/v, detection by TLC), followed by crystallization from CH_2Cl_2/diisopropyl ether, gave **9a** (<1% of **9b**) in 46% yield, m.p. 162 – 164°C, $[\alpha]_D$ +307. $C_{20}H_{26}O_3$ (314.41) calcd.: C 76.40, H 8.34; found: C 76.2, H 8.3. ^1H NMR ($CDCl_3$): δ 0.88 (d, *J* 7 Hz, 3, 7α-CH_3), 0.91 (s, 3, 13-CH_3), 6.01 (d, *J* 2 Hz, 1, 4-H), 9.96 (s, 1, CHO). IR (CH_2Cl_2): 2720 (HC=O), 1735 (C=O), 1710 (HC=O), 1675 (C=O), 1625 (C=C), 1405 (CH_2C=O), 860 (4-en-3-one) cm^{-1}. UV (EtOH) λ_{max} 248 nm, ε 1090 m^2/mol. The combined final fractions, most enriched in **9b**, were crystallized from MeOH to give a 1/4 mixture of **9a** and **9b**, m.p. 104–112°C. ^1H NMR ($CDCl_3$); δ 0.88 (d, *J* 7 Hz, *ca.* 0.6, 7α-CH_3), 0.91 (s, *ca.* 0.6, 13-CH_3 in **9a**), 0.92 (s, *ca.* 2.4, 13-CH_3 in **9b**), 1.19 (d, *J* 6 Hz, *ca.* 2.4, 7β-CH_3), 5.98 (s, *ca.* 0.8, 4-H in **9b**), 6.01 (d, *J* 2 Hz, *ca.* 0.2, 4-H in **9a**), 9.94 (s, *ca.* 0.8, CHO in **9b**), 9.96 (s, *ca.* 0.2, CHO in **9a**).

19-Hydroxyandrost-5-ene-3,17-dione 19-acetate 3,17-bis(ethylene acetal) (**15**)

A mixture of **14** (57.0 g, 0.16 mol), *p*-toluenesulphonic acid monohydrate (2.5 g), 1,2-ethanediol (260 ml) and benzene (1300 ml) was heated under reflux for 16 h, water being removed via a separator. After cooling, the mixture was poured into 5% aqueous $NaHCO_3$ (1000 ml). The aqueous layer was extracted with ether (3 ×) and the combined organic phases were washed with water and dried over anhydr. Na_2SO_4. Evaporation of the solvents *in vacuo* left **15** (70.0 g, 98%) as an oil, which was used in the next step without purification. IR (CH_2Cl_2): 1735 (C=O, acetate), 1370 (CH_3, acetate), 1240 (C–O, acetate), 1105 and 950 (C–O, acetal) cm^{-1}.

19-Hydroxyandrost-5-ene-3,7,17-trione 19-acetate 3,17-bis(ethylene acetal) (**16**)

To a stirred solution of **15** (63.0 g, 0.15 mol) in a mixture of benzene (650 ml), acetic acid (690 ml) and acetic anhydride (500 ml) was added anhydr. sodium acetate (53.5 g) and (portionwise) anhydr. sodium chromate (69.0 g, 0.43 mol), while maintaining the temperature in the range 25–35°C. Stirring was continued for 70 h at 20°C. The benzene was then distilled off *in vacuo* and the residue poured into ice water (11 l). The resulting mixture was extracted with CH_2Cl_2 (4 ×). The combined extracts were then washed with 5% aqueous $NaHCO_3$ and with water until neutral, dried over anhydr. Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and filtered over Al_2O_3 (350 g). Evaporation of the solvent *in vacuo* gave crude **16** (42.0 g, 63%) as an oil, which was used in the next step without further purification. IR (CH_2Cl_2): 1740 (C=O, acetate), 1675 (C=O), 1370 (CH_3, acetate), 1235 (C–O, acetate), 1105 and 950 (C–O, acetal) cm^{-1}.

19-Hydroxy-7-methylandrosta-4,6-dien-3,17-dione (**18**)

At 20°C, a solution of crude **16** (42.0 g, 0.09 mol) in dry THF (500 ml) was added to a 1M solution of methylmagnesium bromide (800 ml) in diethyl ether/THF 1/1. Ether was distilled off and replaced by dry THF until the b.p. reached 60°C. The mixture was heated under reflux for 2½ h, then cooled and poured into ice water (5 l) containing NH_4Cl (130 g). The resulting mixture was extracted with CH_2Cl_2 (3 ×) and the combined extracts were washed with water, dried over anhydr. Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in acetone (600 ml), conc. HCl (4.5 ml) was added and the mixture was heated under reflux for 1 h. After cooling, pyridine (10 ml) was added and the mixture was concentrated *in vacuo* to a small volume and poured into ice water (1 l). The resulting mixture was extracted with CH_2Cl_2 (3 ×), the combined extracts were washed with water until neutral, dried over anhydr. Na_2SO_4 and the solvent was evaporated *in vacuo*. Chromatography of the residue (SiO_2, toluene/acetone 1/1) and crystallization from diethyl ether/acetone gave **18** (3.9 g, 13%) m.p. 200–204°C, $[\alpha]_D$ +350. $C_{20}H_{26}O_3$ (314.41) calcd.: C 76.40, H 8.34, O 15.27; found: C 76.5, H 8.4, O 14.9. ^1H NMR ($CDCl_3$): δ 0.99 (s, 3, 13-CH_3), 1.99 (s, 3, 7-CH_3), 3.80 (s, 2, 10-CH_2OH), 5.70 (s, 1, 4-H), 6.03 (s, 1, 6-H). IR (CH_2Cl_2): 3570 (OH), 3400 (OH associated), 1735 and 1655 (C=O), 1620 and 1580 (C=C), 1405 (CH_2C=O), 905 and 890 (HC= of dienone) cm^{-1}. UV (EtOH): λ_{max} 283 nm, ε 2600 m^2/mol.

19-Hydroxy-7β-methylandrost-4-ene-3,17-dione (**19**)

To a suspension of 2% Pd/$SrCO_3$ catalyst (1.0 g) in a mixture of THF (9 ml) and benzene (175 ml), saturated with hydrogen, was added **18** (5.0 g, 16 mmol). The mixture was then hydrogenated until the theoretical amount of H_2 had been consumed. The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. Crystallization of the residue from acetone gave **19** (3.6 g, 71%), m.p. 167–170°C. The analytical sample (from acetone) had a m.p. 170–172°C, $[\alpha]_D$ +175. $C_{20}H_{28}O_3$ (316.42) calcd.: C 75.91, H 8.92, O 15.17; found: C 75.8, H 9.0, O 15.1. ^1H NMR ($CDCl_3$): δ 0.91 (s, 3, 13-CH_3), 1.15 (d, *J* 6 Hz, 3, 7β-CH_3), 3.86 and 4.08 (2 × d, *J* 11 Hz, 2, 10-CH_2OH), 5.90 (s, 1, 4-H). IR (CH_2Cl_2): 3585 (OH), 3415 (OH associated), 1735 and 1665 (C=O), 1625 (C=C), 1405 (CH_2C=O), 865 (4-en-3-one) cm^{-1}. UV (EtOH): λ_{max} 243, ε 1495 m^2/mol.

7β-Methyl-3,17-dioxoandrost-4-en-19-al (**9b**)

Using the method given for the preparation of **9a**, compound **19** was oxidized to give **9b** in 52% yield after crystallization from MeOH, m.p. 117.5–120°C, $[\alpha]_D$ +244. $C_{20}H_{26}O_3$. 1/4 CH_3OH (322.42) calcd.: C 75.43, H 8.44, O 16.12; found: C 75.8, H 8.4, O 16.1. ^1H NMR ($CDCl_3$): δ 0.92 (s, 3, 13-CH_3), 1.19 (d, *J* 6 Hz, 3, 7β-CH_3), 5.98 (s, 1, 4-H), 9.94 (s, 1, CHO). IR (CH_2Cl_2): 2725 (HC=O), 1740 (C=O), 1720 (HC=O), 1675 (C=O), 1625 (C=C), 1405 (CH_2C=O), 860 (4-en-3-one) cm^{-1}. UV (EtOH): λ_{max} 247 nm, ε 1000 m^2/mol.

7α-Methylestr-5(10)-ene-3,17-dione (**11**)

A solution of **9a** (10.0 g, 32 mmol) in dry THF (50 ml) was added to a suspension of freshly prepared magnesium methoxide (3.5 g, 41 mmol) in liquid NH_3 (250 ml). After stirring at −35°C for 1 h, NH_4Cl (14 g, 0.26 mol) was cautiously added followed by CH_2Cl_2 (200 ml) and water (600 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 ×). The combined extracts were washed with water, dried over anhydr. Na_2SO_4 and evaporated *in vacuo* to give crude **11** (9.0 g, 98%) which was used

without further purification in the next reaction. The analytical sample was obtained by crystallization from acetone/hexane, m.p. 112–114°C, $[\alpha]_D$ + 239. $C_{19}H_{26}O_2$ (286.40) calcd.: C 79.68, H 9.15, O 11.17; found: C 79.3, H 9.2, O 11.2. ^{1}H NMR ($CDCl_3$): δ 0.88 (d, *J* 7 Hz, 3, 7α-CH_3), 0.90 (s, 3, 13-CH_3), 2.46 (m, 4, 1- and 2-H's), 2.76 (br.s., 2, 4-H's). IR (CH_2Cl_2): 1740 and 1715 (C=O). UV (EtOH): λ 240 nm, ε 26 m²/mol.

3,3-Dimethoxy-7α-methylestr-5(10)-en-17-one (**12**)

Crude **11** (10.0 g, 35 mmol) and malonic acid (5.7 g, 55 mmol) were dissolved in MeOH (150 ml). After stirring at 20°C for 24 h, aqueous $NaHCO_3$ (5%, 200 ml) was added and the mixture was extracted (5×) with hexane containing 0.1% of pyridine. The combined extracts were washed with water, dried over anhydr. Na_2SO_4 and evaporated *in vacuo* to give crude **12** (10.1 g, 86%) which was used without further purification in the next reaction. The analytical sample was obtained by crystallization from ether/hexane containing a trace of pyridine[27], m.p. 126.5–127.5°C, $[\alpha]_D$ + 166. $C_{21}H_{32}O_3$ (332.47) calcd.: C 75.86, H 9.70, O 14.44; found: C 75.9, H 9.8, O 14.5. ^{1}H NMR ($CDCl_3$): δ 0.82 (d, *J* 7 Hz, 3, 7α-CH_3), 0.88 (s, 3, 13-CH_3), 3.23 (s, 3, OCH_3), 3.27 (s, 3, OCH_3). IR (CH_2Cl_2): 1740 (C=O), 1410 (CH_2C=O), 1055 (C–O) cm^{-1}.

3,3-Dimethoxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-17β-ol (**13**)

At 0°C, acetylene was passed through a stirred solution of potassium *tert*-butoxide (8.5 g, 75 mmol) in dry THF (100 ml) for 2 h. At −10°C, crude **12** (10.0 g, 30 mmol) was added over 20 min. Passage of acetylene through the reaction mixture was continued at 0°C for a further 2 h. Ice water (300 ml) was then added slowly and the mixture was concentrated *in vacuo*. A further amount of water was added and, after 1 h at 0°C, the precipitate was filtered off, washed thoroughly with water and dried. Crystallization from diisopropyl ether containing a trace of pyridine[27] gave **13** (9.8 g, 91%), m.p. 142–144°C, $[\alpha]_D$ + 66. $C_{23}H_{34}O_3$ (358.50) calcd.: C 77.05, H 9.56, O 13.39; found: C 77.2, H 9.5, O 13.4. ^{1}H NMR ($CDCl_3$): δ 0.78 (d, *J* 7 Hz, 3, 7α-CH_3), 0.87 (s, 3, 13-CH_3), 2.58 (s, 1, C≡CH), 3.23 (s, 3, OCH_3), 3.27 (s, 3, OCH_3). IR CH_2Cl_2): 3595 (OH), 3300 (C≡CH), 2835 (OCH_3), 1100 (OCH_3), 1045 (C–OH) cm^{-1}.

17β-Hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one (**4**)

A solution of oxalic acid dihydrate (3.0 g, 24 mmol) in water (40 ml) was added to a solution of **13** (10.0 g, 28 mmol) in ethanol (220 ml). The mixture was stirred at 20°C for 2 h. A 5% aqueous $NaHCO_3$ solution was added until the solution was weakly alkaline. The resulting mixture was diluted with water (800 ml) and the precipitate was collected, washed with water and dried. Crystallization from diisopropyl ether containing a trace of pyridine[27]) gave **4** (6.9 g, 79%), m.p. 166–169°C [lit.[3] 166–169°C], $[\alpha]_D$ + 103 [lit.[3] + 105]. ^{1}H NMR ($CDCl_3$): δ 0.84 (d, *J* 7 Hz, 3, 7α-CH_3), 0.87 (s, 3, 13-CH_3), 2.44 (m, 4, 1- and 2-H's), 2.58 (s, 1, C≡CH), 2.74 (br.s., 2, 4-H's). IR (CH_2Cl_2): 3590 (OH), 3300 (C≡CH), 1700 (C=O), 1040 (C–OH) cm^{-1}. UV (EtOH): λ 240 nm, ε 26 m²/mol.

10β-Hydroperoxy-17β-hydroxy-7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one (**22**)

Hematoporphyrin (0.20 g) was added to a solution of **4** (10.0 g, 32 mmol) in pyridine (600 ml). Oxygen was passed through the stirred mixture under irradiation with a 125 W high-pressure mercury lamp (Philips 57236/E70). The lamp was installed in a double-walled water-cooled jacket (Duran 50 glass) immersed in the reaction mixture. The temperature was maintained at *ca.* 20°C. The reaction was monitored using TLC. After 1 h, most of the starting material had been converted. The reaction mixture was concentrated *in vacuo* to *ca.* 100 ml, diluted with toluene (100 ml), treated with activated charcoal, filtered over Hyflo Supercel and evaporated to dryness *in vacuo*. The residue was filtered over a short silica-gel column with toluene/ethyl acetate 1/1 and crystallized from MeOH/diisopropyl ether to give **22** (5.0 g, 45%), m.p. 208–209°C, $[\alpha]_D$ + 1.4 (MeOH, $c \approx 1$). $C_{21}H_{28}O_4$ (344.44) calcd.: C 73.22, H 8.19; found: C 73.3, H 8.1. ^{1}H NMR ($CDCl_3$ + 20% CD_3OD): δ 0.81 (d, *J* 7 Hz, 3, 7α-CH_3), 0.88 (s, 3, 13-CH_3), 2.60 (s, 1, C≡CH), 5.97 (d, *J* 2 Hz, 1, 4-H). IR (KBr): 3610 (OH), 3520 (OOH), 3310 (C≡CH), 3270 (OH and OOH associated), 2115 (C≡C), 1655 (C=O), 1630 (C=C), 1045 (C–OH), 870 (4-en-3-one) cm^{-1}. UV (EtOH): λ_{max} 236.5 nm, ε 1560 m²/mol.

10β,17β-Dihydroxy-7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one (**23**)

At 0°C, triethyl phosphite (6.0 ml, 35 mmol) was added dropwise to a suspension of **22** (10.0 g, 29 mmol) in dry ethanol (50 ml). After stirring at 20°C for 1 h, 15% hydrogen peroxide (30 ml) was added slowly and stirring was continued at 20°C for a further hour. The mixture was diluted with water and the precipitate was filtered off, washed with water and dried. Chromatography over alumina (Woelm N, activity grade 1) with toluene/THF 1/1, followed by crystallization from acetone/diisopropyl ether, gave **23** (7.0 g, 73%), m.p. 221–222°C, $[\alpha]_D$ + 0.6. $C_{21}H_{28}O_3$ (328.44) calcd.: C 76.79, H 8.59; found: C 76.7, H 8.7. ^{1}H NMR ($CDCl_3$ + 5% CD_3OD): δ 0.79 (d, *J* 7 Hz, 3, 7α-CH_3), 0.92 (s, 3, 13-CH_3), 2.59 (s, 1, C≡CH), 5.79 (d, *J* 2 Hz, 1, 4-H). IR (CH_2Cl_2): 3610 (OH), 3310 (C≡CH), 1670 (C=O), 1625 (C=C), 1040 and 945 (C–OH), 865 (4-en-3-one) cm^{-1}. UV (EtOH): λ_{max} 236.5 nm, ε 1540 m²/mol.

[27] By way of precaution, pyridine was added to protect the acid-sensitive compound during crystallization.