Synthesis of hydroxylated steroid hormones via conjugate addition of a silyl-cuprate reagent

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The synthesis of several hydroxylated steroids via conjugate addition of Fleming's silyl-cuprate reagent, $(PhMe_2Si)_2CuLi$, a masked hydroxyl group, to the appropriate enone was studied. By this means 7α-hydroxytestosterone (**7**) *was obtained in good yield from 17β-hydroxyandrosta-4,6-dien-3-one* (**1a**), *though similar reactions on 17β-hydroxyandrosta-1,4-dien-3-one* (**8**) *gave a low yield of 1α-hydroxytestosterone* (**13**) *chiefly through the poor conversion of the phenylsilyl intermediate into the halogenosilane. 3β,16α-Dihydroxy-5α-pregnan-20-one* (**18b**) *was obtained in a similar manner from 3β-hydroxy-5α-pregn-16-en-20-one and 5α-cholestane-1α,3α-diol* (**17**) *was produced from the 1-en-3-one* (**14**) *via conjugate addition of the silyl group, reduction of the carbonyl function, and oxidative removal of the silyl group.* (*Steroids* **59**:702–711, 1994)

Keywords: hydroxylated steroids; 7α-hydroxytestosterone; 1α-hydroxytestosterone; 3β,16α-dihydroxy-5α-pregnan-20-one; 5α-cholestane-1α,3α-diol

Introduction

Steroid hormones, in particular testosterone, androstenedione, and progesterone, are hydroxylated, mainly by liver enzymes, at positions C-1, 2, 6, 7, 14, 15, and 16, but very few such derivatives are available commercially. The 2α/β-, 6α/β-, and 16α-hydroxy derivatives are reasonably accessible by chemical methods, but the 1α/β-, 7α/β-, 15α/β-, and 16β-hydroxy derivatives have only been obtained chemically by tedious and inefficient routes, if at all. For example, some 1α-hydroxy-4-en-3-ones have been obtained by selective epoxidation followed by selective reduction of 1,4,6-trien-3-ones.[1] Experience has shown, however, that both steps are difficult to control; the first step tends to over-oxidize, opening ring A, and the second step tends to over-reduce, saturating the 4-ene. The same difficulties and other problems also apply to the best known route to 7α-hydroxy-4-en-3-ones.[2] In neither case is there any known modification which would afford the β-isomer. Such compounds have only been obtained microbiologically. A recent report,[3] however, gave a procedure for the chemical synthesis of 1β-hydroxytestosterone. The method is very long and as a consequence of a multi-step synthesis the yield is diminished. Existing chemical routes to 15β-hydroxy androgens usually involve the conjugate addition of alcohols, HOR (where R = alkyl, aryl, or allyl), to steroidal 15-en-17-ones.[4] Cleavage of the R-group, however, is not easy and is often incompatible with the rest of the functionality in the molecule. Consequently, this investigation of the synthesis of hydroxylated steroids by the conjugate addition of silyl-cuprate reagents[5] was commenced.

Experimental

M.p.s. were determined on a Reichert melting point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded, in deuterated chloroform, at 250, 400, 500, and 600 MHz, using a Bruker AM-250, a Bruker WH-400, a Bruker AM-500 and a Varian UNITY-600, respectively, at 303 K. Chemical shifts derived from 250 MHz spectra are included with the preparative details. ^1H NMR spectra recorded on the higher field instruments have been resolved with the aid of the COSY method and are listed in Table 1. Infra red (IR) spectra were taken on a Perkin-Elmer 1600 FT-IR, using KBr discs. Mass spectra were taken on a Kratos MS-50 RF machine. Thin-layer chromatography (TLC) was carried out on 0.2 mm silica gel plates, using as the developing solvent, ethyl acetate and light petroleum. Flash column chromatography used Sorbsil Silica Gel C60-H 40/60 and a solvent gradient of ethyl acetate and light petroleum with an air pressure of 0.4 Kg/cm^2. All light petroleum refers to the fraction of boiling range 60–80°C.

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Table 1 ^{1}H NMR chemical shifts of steroid derivatives

Compound												
Proton	1b[a]	2[b]	3[c]	5[b]	7[c]	9[c]	10[c]	21[a]	22[b]	25[b]	27[c]	29[c]
1α	1.72	1.53	0.99	1.05	1.79	–[d]	1.93	1.04	1.02	2.43	1.73	2.43
1β	2.03	2.00	1.87	1.71	2.05	1.85	–	1.80	1.79	1.90	1.90	2.29
2α	2.45	2.33	2.22	2.09	2.37	2.53	2.62	2.18	1.71	1.84	2.38	6.02
2β	2.59	2.39	2.43	2.41	2.43	2.84	2.27	1.70	1.54	1.53	2.42	–
3α	–	–	–	–	–	–	–	3.48	3.46	3.54	–	–
4α	5.68	5.69	2.81	5.68	5.81	5.68	5.77	2.18	2.16	2.32	5.77	–
4β	–	–	3.33	–	–	–	–	2.23	2.25	2.24	–	–
6α	6.11	2.57	5.41	5.44	2.43	2.31	2.13	5.32	5.29	5.23	2.38	6.89
6β	–	2.39	–	–	2.64	2.31	2.46	–	–	–	2.48	–
7α	6.11	–	–	–	–	0.92	0.94	1.63	1.44	2.24	1.23	2.26
7β	–	1.47	1.83	2.02	3.97	1.72	1.93	2.02	1.94	2.00	2.15	1.86
8β	2.24	1.90	1.11	1.96	1.63	?[e]	1.65	?	1.44	2.18	2.18	1.50
9α	1.20	1.27	?	1.13	?	?	1.50	?	0.86	1.01	1.08	1.31
11α	1.61	1.49	1.13	1.41	1.65	?	?	1.59	1.57	1.68	1.76	1.64
11β	1.45	1.37	1.42	1.35	1.46	1.12	?	1.52	1.36	1.50	1.62	1.47
12α	1.06	0.89	0.86	0.85	1.10	1.09	?	1.30	?	1.84	1.58	1.47
12β	1.84	1.75	1.72	1.69	1.85	1.23	?	2.40	1.93	1.69	1.93	1.69
14α	1.20	1.05	?	1.04	?	0.74	1.35	1.40	0.86	–	2.28	1.80
15α	?	1.14	?	1.17	1.72	1.53	?	2.03	1.44	5.39	6.07	2.14
15β	?	1.09	1.09	1.03	1.36	1.23	?	2.32	1.60	–	–	2.05
16α	1.96	1.55	1.54	1.48	2.13	1.85	1.86	6.70	–	2.62	7.52	–
16β	1.50	1.30	1.26	1.24	1.49	1.40	1.42	–	2.09	2.38	–	4.54
17α	3.60	3.40	3.38	3.35	3.71	3.35	3.53	–	2.46	–	–	–
18-CH_3	0.80	0.68	0.64	0.62	0.80	0.64	0.68	0.92	0.60	1.04	1.12	0.92
19-CH_3	1.13	1.18	1.16	0.98	1.21	1.29	1.12	1.04	0.97	1.10	1.25	1.12
21-CH_3	–	–	–	–	–	–	–	2.25	1.92	–	–	–
Si*Me$_2$t*-Bu	0.02	0.00, 0.01	0.00, 0.01	−0.01, −0.02	–	−0.01, −0.02	0.00, −0.01	0.06	0.05	–	–	–
SiMe$_2$*t-Bu*	0.89	0.88	0.87	0.85	–	0.87	0.87	0.88	0.88	–	–	–
Si*Me$_2$*Ph	–	0.36, 0.38	0.33, 0.37	0.34, 0.35	–	0.26, 0.35	0.26, 0.36	–	0.19, 0.21	–	–	–
SiMe$_2$*Ph*	–	7.33, 7.48	7.30, 7.46	7.32, 7.49	–	7.32, 7.47	7.33, 7.45	–	7.33, 7.48	–	–	–
CH_2-ketal	–	–	–	–	–	–	–	–	–	3.93	–	3.94, 4.10, 4.26
O−CO−CH_3	–	–	–	2.12	–	–	–	–	–	–	–	–

[a]400 MHz, [b]500 MHz, [c]600 MHz, [d]not applicable, [e]not identified

Dilute sulphuric acid refers to a solution of 5 mL of concentrated sulphuric acid in 95 mL of water, while dilute hydrochloric acid refers to a solution of 20 mL of concentrated hydrochloric acid in 80 mL of water. 'A solution' implies an aqueous medium, unless otherwise stated. Copper(I) iodide was dried at 120°C overnight before use.

Experiments that had to be anhydrous and kept free of atmospheric conditions were done under a positive atmosphere of argon. All glassware and syringes were dried in an oven overnight at 120°C and glassware was flame-dried and flushed with nitrogen or argon immediately prior to use. Transfer of reagents was performed by syringes equipped with stainless steel needles that were flushed with argon or nitrogen and kept under a positive argon or nitrogen pressure until use. Teflon-coated magnetic stirring bars were used.

17β-(t-Butyldimethylsilyloxy)-androsta-4,6-dien-3-one (1b)

17β-Hydroxyandrosta-4,6-dien-3-one **1a** (0.1944 g; 1 Eq) was placed in a pre-dried, argon-flushed flask where it was dissolved in dry dimethylformamide (DMF; 5 mL). Imidazole (0.1925 g; 4 Eq) was added, followed by *t*-butyldimethylsilyl chloride (TBDMSCl; 0.2432 g; 2.3 Eq) and the solution was stirred at room temperature, under an atmosphere of argon, for 24 h. The reaction was quenched by adding water (20 mL). The product was extracted with ether (3 × 20 mL) and the combined ether extracts were washed with dilute hydrochloric acid (20 mL), water (20 mL), and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the yellow solid was purified using flash column chromatography with an eluting solvent of 0–15% ethyl acetate in light petroleum, to give cream crystals of 17β-(*t*-butyldimethylsilyloxy)-androsta-4,6-dien-3-one **1b** (0.2570 g; 94%), m.p. 118–120°C (ethyl acetate/light petroleum). Found: C, 75.02; H, 10.23, $C_{25}H_{40}O_2Si$ requires C, 74.94; H, 10.06%. IR (KBr): 2933–2856, 1665, 1620, and 1600 cm^{-1}; ^{1}H NMR in Table 1.

17β-(t-Butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-4-en-3-one (2)

Dimethylphenylsilyllithium (9 mL of a 0.3816 M solution in tetrahydrofuran (THF; 14 Eq) was added to a slurry of purified copper(I) iodide (0.3400 g; 7 Eq), in anhydrous THF (2 mL), under an atmosphere of argon at −23°C (CCl_4/CO_2) and was stirred under these conditions for 4 h to produce a red mixture of the silyl-cuprate reagent. A solution of 17β-(*t*-butyldimethylsilyloxy)-androsta-4,6-dien-3-one **1b** (0.1000 g; 1 Eq; previously kept at 60°C overnight), in anhydrous THF (2 mL), was cooled and added to the cold reagent. The mixture was stirred under the same conditions as before, for a further 30 min. The mixture was quenched by adding cooled dilute hydrochloric acid (35 mL). The black mixture was left to stir

overnight and the products were extracted with ether (6 × 30 mL). The combined extracts were filtered, washed with water (30 mL) and a saturated solution of sodium chloride (30 mL), and dried ($MgSO_4$). 17β-(*t*-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-4-en-3-one **2** was separated from excess reagent and unreacted starting steroid **1b** using flash column chromatography with an eluting solvent of 0–10% ethyl acetate in light petroleum to give white crystals (0.0405 g; 30%), m.p. 115–118°C (light petroleum/ether). Mass spectrum, m/z: M^+ 536, 537. $C_{33}H_{52}O_2Si_2$ requires 536. Found: C, 73.60; H, 9.75. $C_{33}H_{52}O_2Si_2$ requires C, 73.81; H, 9.76. IR (KBr): 2931, 1675, and 1252 cm^{-1}. ^1H NMR in Table 1.

17β-(t-Butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-5-en-3-one (3)

The silyl-cuprate reagent was prepared by the same procedure as in the preparation of **2** from dimethylphenylsilyllithium (2.62 mL of a 0.3816 M solution in THF; 4 Eq) and purified copper(I) iodide (0.1010 g; 2 Eq), at −23°C (CCl_4CO_2). A solution of 17β-(*t*-butyldimethylsilyloxy)-androsta-4,6-dien-3-one **1b** (0.1000 g; 1 Eq; previously kept at 60°C overnight), in anhydrous THF (1 mL), was cooled and added to the reagent. The mixture was stirred under the same conditions as before, for a further 1.5 h and then quenched by adding a solution of saturated ammonium chloride (35 mL), followed by stirring for 10 min.[6] The products were extracted with ether (6 × 20 mL) and the combined extracts were filtered, washed with water (30 mL) and a saturated solution of sodium chloride (30 mL), and dried ($MgSO_4$). The yellow oil was chromatographed using flash column chromatography with an eluting solvent of 0–5% ethyl acetate in light petroleum to separate 17β-(*t*-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-5-en-3-one **3** from the excess reagent and unreacted starting steroid **1b**, to yield a white powder (0.0710 g; 53%), m.p. 130–134°C (light petroleum/ether). Mass spectrum, m/z M^+ 536.3492. $C_{33}H_{52}O_2Si_2$ requires 536.3506. IR (KBr): 2960, 1718, and 1249 cm^{-1}. ^1H NMR in Table 1.

3β-Acetoxy-17β-(t-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androsta-3,5-diene (5)

The silyl-cuprate reagent was prepared, by the same procedure as in the preparation of **2**, from dimethylphenylsilyllithium (5.60 mL of a 0.357 M solution in THF; 4 Eq) and purified copper(I) iodide (0.1959 g; 2 Eq) at −23°C (CO_2/CCl_4). 17β-(*t*-Butyldimethylsilyloxy)-androsta-4,6-dien-3-one **1b** (0.1959 g; 1 Eq; which had been kept overnight at 60°C), dissolved in anhydrous THF (1 mL), was added to the reagent, and stirring was continued for a further 40 min before acetyl chloride (0.22 mL; 6 Eq) was added. The reaction was allowed to continue for another 10 min and then it was quenched by stirring it with a cold saturated solution of ammonium chloride (25 mL) for 10 min. The product was extracted with ether (3 × 30 mL) and the combined ether extracts were washed with water (30 mL), a saturated solution of sodium hydrogen carbonate (30 mL), water (30 mL), and a saturated solution of sodium chloride (30 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a deep yellow oil, from which the trapped enolate **5** was separated from excess reagent using flash column chromatography with an eluting solvent of 0–3% ethyl acetate in light petroleum to give a white solid (0.2336 g; 81%), m.p. 99–103°C (light petroleum/ether). Mass spectrum, m/z: M^+ 578. $C_{35}H_{54}O_3Si_2$ requires 578. Found: C, 72.25; H, 9.69. $C_{35}H_{54}O_3Si_2$ requires C, 72.60; H, 9.40. IR (KBr) 1759, 1663, 1625, and 1215 cm^{-1}. ^1H NMR in Table 1.

Acid-catalyzed isomerization of the 5-en-3-one (3) to the 4-en-3-one (2)

17β - (*t* - Butyldimethylsilyloxy) - 7α - (dimethylphenylsilyl) - androst-5-en-3-one **3** (0.0353 g) was dissolved in acetone (50 mL). Dilute hydrochloric acid (1 drop) was added to the solution which was stirred for 1 h at room temperature. TLC showed complete conversion of the 5-ene **3** into the 4-ene **2**. A saturated solution of sodium hydrogen carbonate (10 mL) was added to the reaction mixture, and the product was extracted with ether (3 × 20 mL). The combined ether extracts were washed with water (20 mL) and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). The oil obtained after the solvents had been evaporated was recrystallized from light petroleum/ether to give white crystals of 17β-(*t*-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-4-en-3-one (**2**; 0.0351 g; 99%), m.p. 114–118°C. IR and ^1H NMR spectra were identical to the previous data for the 4-en-3-one **2**.

7α-(Dimethylfluorosilyl)-17β-hydroxyandrost-4-en-3-one (6)

17β - (*t* - Butyldimethylsilyloxy) - 7α - (dimethylphenylsilyl) - androst-4-en-3-one **2** (0.0164 g) to be protodesilylated was dissolved in chloroform (2 mL) and stirred. Tetrafluoroboric acid diethyl ether complex (1 mL) was added and stirring was continued overnight at room temperature for 20 h. TLC showed complete conversion of the starting material into product and the reaction was quenched with a cooled 5% potassium hydroxide solution (5 mL). The product was extracted with chloroform (1 × 15 mL, 2 × 5 mL) and the combined chloroform extracts were washed with a saturated solution of sodium chloride (2 × 10 mL), and dried (Na_2SO_4). The yellow oil was cleaned using flash column chromatography with an eluting solvent of 25% ethyl acetate in light petroleum, to give 7α-(dimethylfluorosilyl)-17β-hydroxyandrost-4-en-3-one **6** (0.0137 g; 97%) as a pale yellow oil. NMR (250 MHz): 0.25 and 0.28 (2xd, J = 1.25 Hz, $SiMe_2F$), 0.81 (s, 18-CH_3), 1.25 (s, 19-CH_3), 3.68 (t, J = 10 and 10 Hz, 17α-H), and 5.73 ppm (dJ = 1.25 Hz, 4-H).

7α-Hydroxytestosterone (7)

Potassium fluoride (0.0070 g; 3 Eq) was placed in a pre-dried argon-flushed flask, followed by a solution of 7α-(dimethylfluorosilyl)-17β-hydroxyandrost-4-en-3-one **6** (0.0152 g; 1 Eq), in dry DMF (2 mL). The mixture was stirred and a solution of purified *m*-chloroperoxybenzoic acid (0.0286 g; 4 Eq), in dry DMF (1 mL), was added. The clear solution was stirred at room temperature for 5 h under an argon atmosphere. TLC showed only one product which corresponded in polarity to an authentic sample of 7α-hydroxytestosterone. The reaction was quenched by pouring it into water (30 mL) and extracting it with ether (5 × 10 mL). The combined ether extracts were washed with a saturated solution of sodium hydrogen sulphite (10 mL), a saturated solution of sodium hydrogen carbonate (3 × 10 mL), and water (10 mL), and dried (Na_2SO_4). 7α-Hydroxytestosterone **7** was purified using flash column chromatography with an eluting solvent of ethyl acetate to yield white crystals (0.0125 g; 98%), m.p. 219–223°C (lit.[7] 221–223°C). Mass spectrum, m/z: M^+ 304.2019. $C_{19}H_{28}O_3$ requires 304.2038. IR (KBr): 3372 and 1654 cm^{-1}. ^1H NMR in Table 1.

17β-(t-Butyldimethylsilyloxy)-androsta-1,4-dien-3-one (8b)

1-Dehydrotestosterone **8a** (1.3241 g; 1 Eq) was converted into the product **8b** by the use of imidazole (1.2573 g; 4 Eq) and

TBDMSCl (1.6049 g; 2.3 Eq) by the procedure for the preparation of **1b**. After removal of the ether solvent, 17β-(*t*-butyldimethylsilyloxy)-androsta-1,4-dien-3-one **8b** was purified, using flash column chromatography with an eluting solvent of 10% ethyl acetate in light petroleum, to give white crystals (1.6528 g; 89%), m.p. 161–163°C (ether/ethyl acetate). Mass spectrum, m/z: M^+ 400.2797. $C_{25}H_{40}O_2Si$ requires 400.2798. IR (KBr) 2939, 1656, 1615, 1603, and 1250 cm^{-1}; NMR (250 MHz); 0.00 (2 × s, OSiMe_2*t*-Bu), 0.77 (s, 18-CH_3), 0.88 (s, OSiMe_2*t-Bu*), 1.23 (s, 19-CH_3), 3.54 (t, J = 7.5 and 7.5 Hz, 17α-H), 6.06 (t, J = 1.25 and 1.25 Hz, 4-H), 6.22 (dd, J = 10 and 2.5 Hz, 2-H), and 7.06 ppm (d, J = 10 Hz, 1-H).

17β-(t-Butyldimethylsilyloxy)-1α-(dimethylphenylsilyl)-androst-4-en-3-one (9) and 17β-(t-butyldimethylsilyloxy)-1β-(dimethylphenylsilyl)-androst-4-en-3-one (10)

The silyl-cuprate reagent was prepared, by the same procedure as in the preparation of **2**, from dimethylphenylsilyllithium (22.5 mL of a 0.399 M solution in THF; 12 Eq) and purified copper(I) iodide (0.8571 g; 6 Eq) at −23°C (CO_2/CCl_4). 17β-(*t*-Butyldimethylsilyloxy)-androsta-1,4-dien-3-one **8b** (0.2988 g; 1 Eq; which had been kept overnight at 60°C) was dissolved in dry toluene, which was then removed, dissolved in anhydrous THF (1 mL), and added to the reagent mixture. Stirring was continued at −23°C under argon for 1/2 h before the reaction was quenched by the addition of dilute hydrochloric acid (1 mL), followed by stirring in water (20 mL). The two products formed were extracted with ether (3 × 20 mL) and the combined ether extracts were washed with a saturated solution of sodium hydrogen carbonate (20 mL), water (20 mL), and a saturated solution of sodium chloride (3 × 20 mL), and dried ($MgSO_4$). The 1α- and 1β-isomers **9** and **10**, respectively, were separated using flash column chromatography with an eluting solvent of 0–2% ethyl acetate in light petroleum. 17β-(*t*-Butyldimethylsilyloxy)-1β-(dimethylphenylsilyl)-androst-4-en-3-one **10** eluted first from the column and appeared as white crystals (0.1386 g; 35%), m.p. 118–121°C (ether). Mass spectrum, m/z: M^+ 536.3487. $C_{33}H_{52}O_2Si_2$ requires 536.3506. IR (KBr) 1659 and 1250 cm^{-1}. ^1H NMR in Table 1. 17β-(*t*-Butyldimethylsilyloxy)-1α-(dimethylphenylsilyl)-androst-4-en-3-one **9** was a colorless oil, containing excess reagent, and the yield could not be accurately quantified but it was the major product. IR (KBr) 3384, 1663, and 1252 cm^{-1}. ^1H NMR in Table 1.

1α-(Dimethylfluorosilyl)-17β-hydroxyandrost-4-en-3-one (11)

Tetrafluoroboric acid diethyl ether complex (0.1 mL; 2 Eq) was added to a stirred solution of 17β-(*t*-butyldimethylsilyloxy)-1α-(dimethylphenylsilyl)-androst-4-en-3-one **9** (~200 mg; 1 Eq), in anhydrous chloroform (2 mL), under an atmosphere of argon. The yellow solution was stirred at room temperature for 20 h when more tetrafluoroboric acid (0.5 mL) was added and stirring was continued for 3 days. A further amount of tetrafluoroboric acid (1 mL) was added to the mixture over 4 more days, until TLC showed only a single product. The reaction was quenched by adding a cold 5% potassium hydroxide solution (2 mL) and the product was extracted with chloroform (3 × 10 mL). The combined chloroform extracts were washed with water (10 mL) and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). The product was cleaned using flash column chromatography with an eluting solvent of 25% ethyl acetate in light petroleum to yield 1α-(dimethylfluorosilyl)-17β-hydroxyandrost-4-en-3-one **11** (0.0142 g; ~10%) as a colorless oil. NMR (250 MHz): 0.21 and 0.25 (2 × d, J = 7.5 Hz, SiMe_2F), 0.82 (s, 18-CH_3), 1.36 (s, 19-CH_3), 3.69 (t, J = 7.5 and 7.5 Hz, 17α-H), and 5.71 ppm (1 H, s, 4-H).

1β-(Dimethylfluorosilyl)-17β-hydroxyandrost-4-en-3-one (12)

A solution of 17β-(*t*-butyldimethylsilyloxy)-1β-(dimethylphenylsilyl)androst-4-en-3-one **10** (0.0329 g; 1 Eq), in chloroform (1 mL), was stirred with tetrafluoroboric acid diethyl ether complex (3 drops; excess) at room temperature for 3 days. The reaction was quenched with a cold 5% potassium hydroxide solution (2 mL) and the product was extracted with chloroform (3 × 10 mL). The combined chloroform extracts were washed with a saturated solution of sodium chloride (20 mL) and dried ($MgSO_4$). The product was cleaned, using flash column chromatography with an eluting solvent of 25% ethyl acetate in light petroleum, to yield the fluorosilane **12** and testosterone 3:1 (0.0075 g; 34%) as a pale yellow oil. NMR (250 MHz): 0.23 and 0.26 (2 × d, J = 2.5 Hz, SiMe_2F), 0.79 (s, 18-CH_3), 0.08 (s, 18-$CH_{3(test)}$), 1.19 (s, 19-$CH_{3(test)}$), 1.25 (s, 19-CH_3), 3.65 (t, J = 7.5 and 7.5 Hz, 17α-H and 17α-$H_{(test)}$), 5.73 (s, 4-$H_{(test)}$), and 5.80 ppm (s, 4-H).

1α-Hydroxytestosterone (13)

Potassium fluoride (0.0113 g; 5 Eq) was placed in a pre-dried argon-flushed flask where a solution of 1α-(dimethylfluorosilyl)-17β-hydroxyandrost-4-en-3-one **11** (0.0133 g; 1 Eq), in dry DMF (2 mL), was added, followed by a solution of purified *m*-chloroperoxybenzoic acid (0.0272 g; 4 Eq), in dry DMF (2 mL). The mixture was stirred under argon at room temperature for 21 h. TLC showed only one product so the reaction was quenched by pouring it into water (10 mL). The reaction mixture was extracted with ether (5 × 15 mL), and the combined ether extracts were washed with a saturated solution of sodium hydrogen sulphite (10 mL), a saturated solution of sodium hydrogen carbonate (3 × 10 mL), and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). The product was purified using flash column chromatography, with an eluting solvent of 100% ethyl acetate, to give white crystals of 1α-hydroxytestosterone **13** (0.0099 g; 89%), m.p. 248–253°C (lit.[7] 250–254°C) (acetone). Mass spectrum, m/z: M^+, 304.2038. $C_{19}H_{28}O_3$ requires M, 304.2061. IR (KBr): 3449, 1658, and 1625 cm^{-1}. NMR (250 MHz): 0.80 (s, 18-CH_3), 1.21 (s, 19-CH_3), 2.56 (ddd, J = 17.5, 3.75 and 1.25 Hz, 2α-H), 2.75 (dd, J = 17.5 and 3.5 Hz, 2β-H), 3.66 (t, J = 8.75 and 8.75 Hz, 17α-H), 4.09 (m, $w_{1/2}$ 6.25 Hz, 1β-H), and 5.79 ppm (s, 4-H).

1α-(Dimethylphenylsilyl)-5α-cholestan-3-one (15)

The silyl-cuprate reagent was prepared, by the same procedure as in the preparation of **2**, from dimethylphenylsilyllithium (2.65 mL of a 0.393 M solution in THF; 4 Eq) and purified copper(I) iodide (0.1002 g; 2 Eq) at −23°C (CO_2/CCl_4). A solution of cholest-1-en-3-one **14** (0.1003 g; 1 Eq; previously kept at 60°C overnight and dissolved in dry toluene which was then removed), in anhydrous THF (2 mL), was added to the reagent. Stirring was continued, under the same conditions, for 20 min until TLC showed only one product and no more starting steroid **14**. The reaction was quenched by adding dilute hydrochloric acid (2 mL) and then the mixture was stirred in water (20 mL). The product was extracted with ether (3 × 15 mL) and the combined ether extracts were washed with a saturated solution of sodium hydrogen carbonate (20 mL), water (20 mL), and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). The product was separated from

excess reagent using flash column chromatography with an eluting solvent of 0–3% ethyl acetate in light petroleum and then recrystallized from acetone/light petroleum to give white crystals of 1α-(dimethylphenylsilyl)-5α-cholestan-3-one **15** (0.1269 g; 93%), m.p. 138–141°C. IR (KBr): 1705 (C=O) and 1253 cm^{-1} (Si-Me). Mass spectrum, m/z: M^+, 520.4093. $C_{35}H_{56}OSi$ requires 520.4100. NMR (400 MHz): 0.36 and 0.41 (6 H, s, Si*Me*$_2$Ph), 0.64 (3 H, s, 18-CH_3), 0.88 (3 × 3 H, d, J = 6 Hz, 21-, 26-, and 27-CH_3), 1.09 (3 H, s, 19-CH_3), 1.68 (1 H, d, J = 8 Hz, 1β-H), 1.76 (1 H, m, $w_{1/2}$ 20 Hz, 4β-H), 2.12 (1 H, m, $w_{1/2}$ 12 Hz, 4α-H), 2.42 (1 H, d, J = 16 Hz, 2α-H), 2.63 (1 H, dd, J = 16 and 8 Hz, 2β-H), 7.34 (3 H, m, $w_{1/2}$ 8 Hz, aromatic-H), and 7.51 ppm (2 H, m, $w_{1/2}$ 12 Hz, aromatic-H). ^{13}C NMR ($CDCl_3$; 400 MHz): 128.0, 129.0, 134.0, and 139.5 (4 × aromatic-C), and 212.5 ppm (C-3).

1α-(Dimethylphenylsilyl)-5α-cholestan-3-ol (16)

1α-(Dimethylphenylsilyl)-5α-cholestan-3-one **15** (0.1995 g) was dissolved in cold methanol (100 mL) and stirred with sodium borohydride (0.0481 g; 3 Eq) at room temperature for 1 h. TLC showed no change. Sodium hydroxide pellets were added to bring the mixture to pH 10 (to prevent the $NaBH_4$ reacting with the MeOH) and more sodium borohydride was added. The reaction was left to stir overnight and when TLC still showed no change the reaction was quenched with water (50 mL). The product was extracted with ether (3 × 50 mL) and the combined ether extracts were washed with dilute hydrochloric acid (50 mL), water (50 mL), and a saturated solution of sodium chloride (50 mL), and dried ($MgSO_4$). The product was separated from traces of a more polar product, using flash column chromatography with an eluting solvent of 3–10% ethyl acetate in light petroleum, to give a colorless oil, which ^1H NMR spectra showed to be 1α-(dimethylphenylsilyl)-5α-cholestan-3-ol **16** (0.1709 g; 85%). The product had the same polarity as the starting steroid on TLC. IR (KBr): 3262 (OH) and 2941 (CH). Mass spectrum, m/z: M^+ 522.4247. $C_{35}H_{58}OSi$ requires 522.4257. NMR (250 MHz): 0.49 and 0.53 (6 H, s, Si*Me*$_2$Ph), 0.63 (3 H, s, 18-CH_3), 0.88 (9 H, m, $w_{1/2}$ 10 Hz, 21-, 26-, and 27-CH_3), 0.90 (3 H, s, 19-CH_3), 3.93 (1 H, bt, J = 2.5 and 2.5 Hz, 3β-H), 7.30 (3 H, m, $w_{1/2}$ 7.5 Hz, aromatic-H), and 7.53 ppm (2 H, m, $w_{1/2}$ 10 Hz, aromatic-H).

5α-Cholestane-1α,3α-diol (17)

Mercuric acetate (0.1198 g; 1.5 Eq) was added to a stirred solution of 1α-(dimethylphenylsilyl)-5α-cholestan-3-ol **16** (0.1305 g; 1 Eq) in peracetic acid (1.6 mL of a 32% by weight solution in acetic acid; 26.7 Eq) and acetic acid (6 mL).[8] The mixture was stirred at room temperature for 23 h. TLC showed that the starting steroid had been consumed and that there was a single product which did not absorb UV light. Ether (60 mL) was added and the ether solution was washed with sodium thiosulfate solution (3 × 20 mL), water (20 mL), a saturated solution of sodium hydrogen carbonate (3 × 20 mL), and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). The product was purified using flash column chromatography with an eluting solvent of 10–30% ethyl acetate in light petroleum. The resulting white solid was recrystallized from ether/ethanol to give white needles of 5α-cholestane-1α,3α-diol **17** (0.1010 g; 72%), m.p. 208–212°C (lit.[9] 210°C). IR (KBr): 3240 (OH) and 2936, 1467, and 1383 cm^{-1} (C—H). Mass spectrum, m/z: M^+, 404.3636. $C_{27}H_{48}O_2$ requires 404.3654. NMR (250 MHz): 0.65 (3 H, s, 18-CH_3), 0.74 (3 H, s, 19-CH_3), 0.86 (6 H, d, J = 7.5 Hz, 26- and 27-CH_3), 0.89 (3 H, d, J = 7.5 Hz, 21-CH_3), 3.73 (1 H, s, 1β-H), and 4.07 ppm (1 H, t, J = 2.5 and 2.5 Hz, 3β-H).

3β-(t-Butyldimethylsilyloxy)-5α-pregn-16-en-20-one (18a)

3β-Hydroxy-5α-pregn-16-en-20-one (0.2130 g; 1 Eq) was converted into the product **18a** by the use of imidazole (0.1910 g; 4 Eq) and TBDMSCl (0.2320 g; 2.3 Eq) by the procedure for the preparation of **1b** until TLC showed that no starting steroid was left, when the reaction was worked up as for **1b**. The ether solvent was removed under reduced pressure to yield white crystals of 3β-(*t*-butyldimethylsilyloxy)-5α-pregn-16-en-20-one **18a** (0.2580 g; 89%). The compound was recrystallized from ethyl acetate and light petroleum, m.p. 185–188°C. Mass spectrum, m/z: M^+ 430.3285. $C_{27}H_{46}O_2Si$ requires 430.3267. NMR (250 MHz): 0.04 (6 H, s, *t*-Bu*Me*$_2$SiO), 0.83 (3 H, s, 18-CH_3), 0.88 (12 H, s, 19-CH_3 and *t*-*Bu*Me$_2$SiO), 2.24 (3 H, s, 21-CH_3), 3.54 (1 H, m, $w_{1/2}$ 22.5 Hz, 3α-H), and 6.67 ppm (1 H, dd, J = 2.5 and 1.25 Hz, 16-H).

3β-(t-Butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-5α-pregnan-20-one (19)

The silyl-cuprate reagent was prepared, by the same procedure as in the preparation of **2**, from dimethylphenylsilyllithium (4.32 mL of a 0.302 M solution in THF; 4 Eq) and purified copper(I) iodide (0.1269 g; 2 Eq) at −23°C (CCl_4/CO_2). A solution of 3β-(*t*-butyldimethylsilyloxy)-5α-pregn-16-en-20-one **18a** (0.1406 g; 1 Eq), in anhydrous THF (3 mL), was added to the reagent and stirring was continued for a further 1.5 h, under an argon atmosphere, at −23°C. TLC showed no more starting steroid **18a** and the reaction was quenched by the addition of dilute hydrochloric acid (1 mL). The reaction mixture was transferred to a separating funnel where water (20 mL) was added. The products were extracted with chloroform (3 × 20 mL) and the combined organic extracts were filtered, washed with dilute hydrochloric acid (20 mL), water (20 mL), a saturated solution of sodium hydrogen carbonate (20 mL), water (20 mL), and a saturated solution of sodium chloride (20 mL), and dried (Na_2SO_4). 3β-(*t*-butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-5α-pregnan-20-one **19** was separated from excess reagent using flash column chromatography with an eluting solvent of 0–1% ethyl acetate in light petroleum. The white solid was recrystallized from ethyl acetate/light petroleum to yield pure 3β-(*t*-butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-5α-pregnan-20-one **19** (0.1180 g; 64%), m.p. 128–131°C. Found C 74.32, H 10.37%. $C_{35}H_{58}O_2Si_2$ requires C 74.14, H 10.31. Mass spectrum, m/z: M^+ 566. 552 (MH^+-CH_3), 510 (MH^+-*t*Bu) and 490 (MH^+-Ph). $C_{35}H_{58}O_2Si_2$ requires M^+ 566. NMR (250 MHz): 0.05 (6 H, s, *t*-Bu*Me*$_2$SiO), 0.19 and 0.21 (2 × 3 H, s, SiMe$_2$Ph), 0.57 (3 H, s, 18-CH_3), 0.77 (3 H, s, 19-CH_3), 0.85 (14α-H), 0.89 (9 H, s, *t*-*Bu*Me$_2$SiO), 1.32 (12α-H), 1.43 and 1.60 (15-H_2), 1.90 (3 H, s, 21-CH_3), 2.05 (1 H, td, J = 10, 10 and 2.5 Hz, 16β-H), 2.45 (1 H, d, J = 10 Hz, 17α-H), 3.53 (1 H, m, $w_{1/2}$ 22.5 Hz, 3α-H), 7.34 (3 H, m, $w_{1/2}$ 7.5 Hz, aromatic-H), and 7.48 ppm (2 H, m, $w_{1/2}$ 10 Hz, aromatic-H).

3β,16α-Dihydroxy-5α-pregnan-20-one (18b)

Mercuric acetate (0.0141 g; 1.5 Eq) was added to a stirred solution of 3β-(*t*-butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-5α-pregnan-20-one **19** (0.0180 g; 1 Eq) in peracetic acid (0.2 mL of a 32% by weight solution in acetic acid; 26.7 Eq) with additional acetic acid (1 mL) as a solvent. The mixture was stirred at room temperature, in the dark, for 3 h. Ether (10 mL) was added to the reaction mixture, and washed with a solution of sodium thiosulfate (10 mL), water (10 mL), a saturated solution of sodium hydrogen carbonate (10 mL), and

a saturated solution of sodium chloride (10 mL), and dried ($MgSO_4$). A product was separated from the remaining starting steroid **19**, using flash column chromatography with an eluting solvent of 40–100% ethyl acetate in light petroleum. This yielded white crystals of 3β,16α-dihydroxy-5α-pregnan-20-one **18b** (0.0062 g; 58%) which were recrystallized from methanol/ethyl acetate; m.p. 260–264°C (lit.[7] 260–262°C). The melting point of an authentic sample was 260–263°C and a mixed melting point was 260–264°C. IR (KBr): 3331 (OH), 1702 (C=O), 1354 cm^{-1} (O—H), 1043 (C—O). NMR ($CDCl_3$/DMSO; 250 MHz): 0.56 (3 H, s, 18-CH_3), 0.74 (3 H, s, 19-CH_3), 2.10 (3 H, s, 21-CH_3), 2.47 (1 H, d, J = 6.25 Hz, 17α-H), 3.52 (1 H, m, $w_{1/2}$ 22.5 Hz, 3α-H), and 4.72 ppm (1 H, td, J = 7.5, 7.5 and 2.5 Hz, 16β-H).

3β-(t-Butyldimethylsilyloxy)-pregna-5,16-dien-20-one (21)

16-Dehydropregnenolone **20** (6.5120 g; 1 Eq) was converted into the product **21** by the use of imidazole (5.6731 g; 4 Eq) and TBDMSCl (7.1936 g; 2.3 Eq) by the procedure for the preparation of **1b**. The reaction mixture was quenched with water (20 mL) and the product was extracted with ether (3 × 20 mL). The combined ether extracts were dried over anhydrous sodium sulfate before the ether was removed under reduced pressure. Excess TBDMSCl was removed from the product using flash column chromatography with an eluting solvent of 10% ethyl acetate in light petroleum. The product was recrystallized from ethyl acetate/light petroleum to yield white crystals of the protected steroid, 3β-(t-butyldimethylsilyloxy)-pregna-5,16-dien-20-one **21** (8.3561 g; 94%); m.p. 149–155°C. IR (KBr): 2938 (C—H) and 1656 cm^{-1} (α,β-unsaturated C=O). Mass spectrum, m/z: M^+ 428.3093. $C_{27}H_{46}O_2Si$ requires 428.3111. ^1H NMR in Table 1.

3β-(t-Butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-pregn-5-en-20-one (22)

The silyl-cuprate reagent was prepared, by the same procedure as in the preparation of **2**, from dimethylphenylsilyllithium (60 mL of a 0.2903 M solution in THF; 4 Eq) and purified copper(I) iodide (1.667 g; 2 Eq) at −23°C (CCl_4/CO_2). A solution of 16-dehydropregnenolone TBDMS ether **21** (1.8790 g; 1 Eq; dissolved in dry toluene, which was then removed under reduced pressure) in anhydrous THF (30 mL) was added to the reagent. Stirring was continued for a further 45 min, under an atmosphere of argon, keeping the temperature at −23°C. The reaction was quenched by the addition of dilute hydrochloric acid (4 mL), when TLC showed no more starting steroid **21**. Water was added (20 mL) and the product was extracted with chloroform (3 × 60 mL). The combined chloroform extracts were filtered, washed with dilute hydrochloric acid (40 mL), water (40 mL), a saturated solution of sodium hydrogen carbonate (40 mL), and water (40 mL), and dried (Na_2SO_4). Flash column chromatography was used to separate the only product from excess reagent, using an eluting solvent of 0–5% ethyl acetate in light petroleum, to yield white crystals of 3β-(t-butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-pregn-5-en-20-one **22** (1.7451 g; 70%). The product was recrystallized from ethyl acetate/light petroleum m.p. 145–149°C. Found C 74.41, H 9.91. $C_{35}H_{56}O_2Si_2$ requires C 74.40, H 9.99. Mass spectrum, m/z: M^+ 564, 487. $C_{35}H_{56}O_2Si_2$ requires 564, 487 (M^+-Ph). IR (KBr): 2942-2853 (C—H), 1702 (C=O), 1245 (Si—Me), 1093 (C—O), and 772 cm^{-1} (monosubstituted benzene ring). UV λ_{max} (ε): ($CHCl_3$) 238 (378), 253 (332), 259 (401), and 265 nm (386). ^1H NMR in Table 1.

17,17-Ethylenedioxy-3β-hydroxyandrosta-5,15-diene (24) and 17,17-ethylenedioxy-3β-hydroxyandrosta-5,14-diene (25)

16α-Bromo-17,17-ethylenedioxyandrost-5-en-3β-ol **23** (0.8893 g; 1 Eq) was dissolved in dry dimethyl sulfoxide (14 mL) and placed in a pre-dried flask, under an atmosphere of nitrogen. Potassium-t-butoxide (0.5959 g; ~2 Eq) was added to the steroid solution which was then stirred at 40°C. After 18 h, TLC showed that some starting steroid was still present, so more potassium-t-butoxide (0.4963 g; 2 Eq) was added and stirring was continued for a further 20 h. The reaction mixture was allowed to cool and the solution was poured into dry ether (30 mL). The ether was washed with water (3 × 20 mL) and a saturated solution of sodium chloride (30 mL), and dried ($MgSO_4$). The resulting white solid was separated into its components using flash column chromatography with an eluting solvent of 20–40% ethyl acetate in light petroleum. The prolonged reaction time had led to a second product, 17,17-ethylenedioxyandrosta-5,14-dien-3β-ol, in addition to the desired 15-ene **24**. 17,17-Ethylenedioxyandrosta-5,14-dien-3β-ol **25** was recrystallized from ethyl acetate/light petroleum to give white crystals (0.1681 g; 24%), m/p. 171–174°C. 17,17-Ethylenedioxy-3β-hydroxyandrosta-5,15-diene **24** was recrystallized from acetone/hexane to also give white crystals (0.3126 g; 44%), m.p. 158–162°C (lit.[10] 158–161°C). 5,15-diene **24**. IR (KBr): 3448 (OH), and 1102 and 1049 cm^{-1} (C—O). NMR ($CDCl_3$; 250 MHz): 0.93 (3 H, s, 18-CH_3), 1.04 (3 H, s, 19-CH_3), 3.52 (1 H, m, $w_{1/2}$ 22.5 Hz, 3α-H), 3.91 (4 H, m, $w_{1/2}$ 22.5 Hz, 2 × CH_2-ketal), 5.37 (1 H, m, $w_{1/2}$ 7.5 Hz, 6-H), 5.69 (1 H, dd J = 5 and 2.5 Hz, 15-H), and 6.12 ppm (1 H, dd, J = 5 and 1.25 Hz, 16-H). 5,14-diene **25**. IR (KBr): 3266 (OH), 1610 (diene), and 1110 and 1054 cm^{-1} (C—O). Mass spectrum, m/z: M^+ 330.2206. $C_{21}H_{30}O_3$ requires 330.2195. ^1H NMR in Table 1.

3β-Hydroxyandrosta-5,15-dien-17-one (26)

17,17-Ethylenedioxy-3β-hydroxyandrosta-5,15-diene **24** (0.2941 g; 1 Eq), was treated with toluene-p-sulfonic acid (0.0160 g; 1/11 Eq) under the conditions employed by Kelly and Sykes.[10] After 20 h, TLC showed that about half of the starting steroid had been converted into the ketone **26**, and that there was also a trace of a more polar product beginning to appear. The reaction was quenched with water (5 mL) and the products were extracted with ether (3 × 15 mL). The combined ether extracts were washed with water (15 mL) and dried ($MgSO_4$). The two main components were separated using flash column chromatography and an eluting solvent of 20–30% ethyl acetate in light petroleum. ^1H NMR spectra showed the products to be recovered starting steroid **24** (0.1402 g) and the desired 3β-hydroxyandrosta-5,15-dien-17-one **26** (0.0942 g; 37% or 71% based on starting materials used). The ketone **26** was recrystallized from ethyl acetate and light petroleum to give white crystals, m.p. 201–205°C (lit.[10] 202–205°C). IR (KBr): 3440 (OH), 1693 (α,β-unsaturated C=O), 1560 (C=C), 1050 (C—O), and 825 cm^{-1}. NMR ($CDCl_3$; 250 MHz): 1.09 (6 H, s, 18- and 19-CH_3), 3.55 (1 H, m, $w_{1/2}$ 30 Hz, 3α-H), 5.43 (1 H, m, $w_{1/2}$ 8.75 Hz, 6-H), 6.06 (1 H, dd, J = 5 and 2.5 Hz, 15-H), and 7.52 ppm (1 H, d, J = 6.25 Hz, 16-H).

Androsta-4,15-diene-3,17-dione (27)

3β-Hydroxyandrosta-5,15-dien-17-one **26** (0.0893 g; 1 Eq) was dissolved in anhydrous toluene (4 mL) and heated under reflux, using a condenser protected with a drying tube. Cyclohexanone

(0.6 mL) was added and heating was continued. A solution of aluminium isopropoxide (0.0342 g; 0.5 Eq), in anhydrous toluene (1 mL), was added and the yellow solution was heated under reflux for 4 h. TLC showed no more starting steroid was left, so the reaction mixture was allowed to cool and then quenched with a saturated solution of potassium sodium tartrate (30 mL). The product was extracted with chloroform (5 × 10 mL) and the combined chloroform extracts were washed with water (20 mL) and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). The product was separated from the impurities using flash column chromatography with an eluting solvent of 20–30% ethyl acetate in light petroleum to give white crystals of androsta-4,15-diene-3,17-dione **27** (0.0293 g; 33%), m.p. 153–156°C (lit.[11] 158°C) (chloroform). Mass spectrum, m/z: M^+ 284.1789. $C_{19}H_{24}O_3$ requires 284.1776. IR (KBr): 2932, 1706 and 1654, 1560, 849, and 820 cm^{-1}. ^1H NMR in Table 1.

16α-Bromo-17,17-ethylenedioxyandrost-4-en-3-one (28)

16α-Bromo-17,17-ethylenedioxyandrost-5-en-3β-ol **23** (0.8698 g; 1 Eq) was dissolved in anhydrous toluene (10 mL) and the solution was heated under reflux, using a condenser protected with a drying tube. Cyclohexanone (4 mL) was added to the boiling solution, followed by a solution of aluminium isopropoxide (0.2182 g; 0.5 Eq) in anhydrous toluene (4 mL). The resulting solution was heated under reflux for 1 h, and then allowed to cool. The reaction was quenched by adding a saturated solution of potassium sodium tartrate (20 mL; to keep the aluminium ions in solution) and the product was extracted with chloroform (5 × 20 mL). The combined chloroform extracts were washed with water (30 mL) and a saturated solution of sodium chloride (30 mL), and dried ($MgSO_4$). The resulting yellow oil was separated from the impurities seen on TLC, using flash column chromatography with an eluting solvent of 10–15% ethyl acetate in light petroleum. The white crystals of 16α-bromo-17,17-ethylenedioxyandrost-4-en-3-one **28** were recrystallized to give the pure product in good yield (0.7788 g; 90%); m.p. 188–190°C. IR (KBr): 1671 (C=O), 1063 (C—O). Mass spectrum, m/z: M^+, 410.1294, 408.1312. $C_{21}H_{29}O_3Br$ requires 410.1279, 408.1299. NMR (250 MHz): 0.94 (3 H, s, 18-CH_3), 1.18 (3 H, s, 19-CH_3, 3.93 (2 H, m, $w_{1/2}$ 7.5 Hz, CH_2-ketal), 4.20 (2 H, m, $w_{1/2}$ 40 Hz, CH_2-ketal), 4.53 (1 H, dd, J = 10 and 5 Hz, 16β-H), and 5.73 ppm (1 H, s, 4-H).

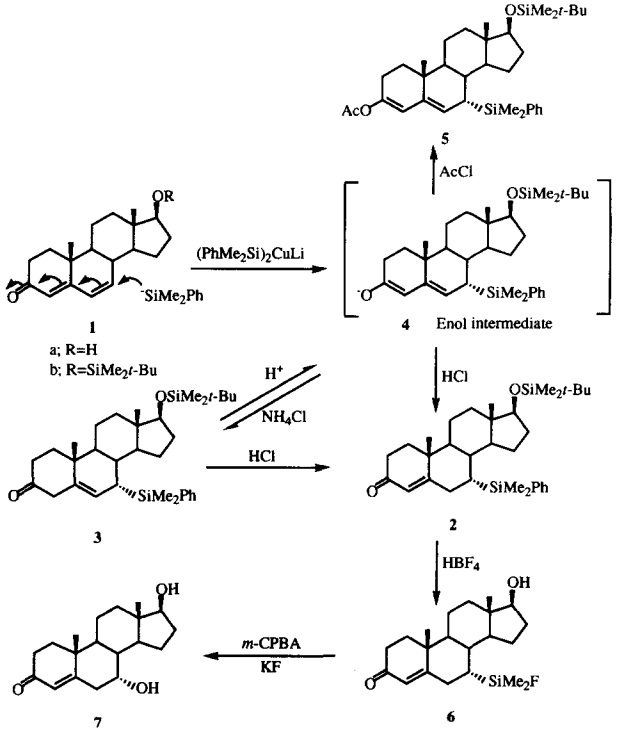
16α-Bromo-17,17-ethylenedioxy-3-hydroxyandrosta-2,5-dien-4-one (29)

16α-Bromo-17,17-ethylenedioxyandrost-4-en-3-one **28** (0.1064 g; 1 Eq) was dissolved in dry dimethyl sulfoxide (5 mL). Potassium-*t*-butoxide (0.0589 g; 2 Eq) was added to the steroid solution, under an atmosphere of nitrogen, and the mixture was left to stand at 40°C overnight. The dark brown solution was poured into dry ether (20 mL) and the resulting yellow solution was washed with water (3 × 10 mL) and a saturated solution of sodium chloride (20 mL), and dried ($MgSO_4$). The product obtained was separated from impurities, seen by TLC, using flash column chromatography with an eluting solvent of 10% ethyl acetate in light petroleum. The product was recrystallized from ethyl acetate/light petroleum to give white crystals of 16α-bromo-17,17-ethylenedioxy-3-hydroxy-androsta-2,5-dien-4-one **29** (0.0166 g; 15%), m.p. 192–196°C. IR (KBr): 3423 (OH), 2883 (C—H), 1654 (C=O), 1606 (C=C), 1105 (C—O), and 627 cm^{-1} (C-Br). Mass spectrum, m/z: M^+ 424.1073, 422.1094. $C_{21}H_{27}BrO_4$ requires 424.1073, 422.1093. ^1H NMR in Table 1.

Results and discussion

7α-Hydroxytestosterone (7)

The 17β-hydroxy group of 17β-hydroxyandrosta-4,6-dien-3-one **1a** was protected as the silyl ether, using *t*-butyldimethylsilyl chloride (TBDMSCl) to give 17β-(*t*-butyldimethylsilyloxy)-androsta-4,6-dien-3-one **1b**. Treatment of this conjugated ketone with $(PhMe_2Si)_2$-CuLi,[12] led to one of two products, depending on the method of workup; quenching the reaction with dilute hydrochloric acid led to 17β-(*t*-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-4-en-3-one **2** (Scheme 1), whilst quenching with aqueous ammonium chloride resulted in the product, 17β-(*t*-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-5-en-3-one **3**. Addition of the dimethylphenylsilyl anion, however, appeared to be reversible as much starting steroid **1a** was recovered. [Trapping the enolate intermediate **4** with acetyl chloride led to an 81% yield of 3β-acetoxy-17β-(*t*-butyldimethylsilyloxy) - 7α - (dimethylphenylsilyl) - androsta - 3,5-diene **(5)**, showing that the initial addition worked well, but in the presence of protons, the reverse reaction occurred.] The polarity of the 4-en-3-one product **2** was very similar to the starting steroid **1b**, which made separation of the two difficult. The 5-en-3-one product **3**, however, was easily separated from the recovered 4,6-dien-3-one **1b** and led to a 53% yield of the addition product. Acid catalysed isomerization of 17β-(*t*-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-5-en-3-one **3** with hydrochloric acid gave the desired product, 17β-(*t*-butyldimethylsilyloxy)-7α-(dimethylphenylsilyl)-androst-4-en-3-one **2**, in a good yield. Thus the conversion of the dienone **1b** into the dimethylphenylsilyl



Scheme 1

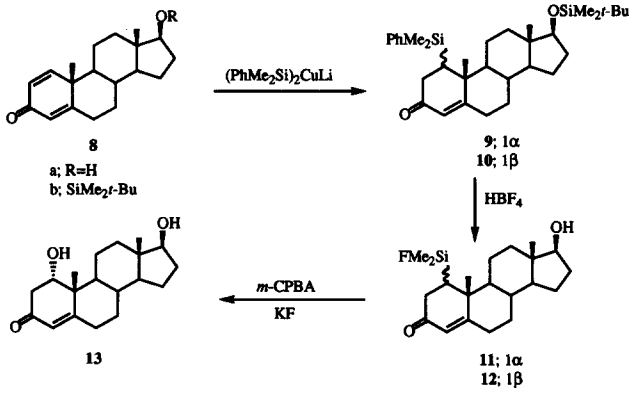
derivative **2** is best achieved via the intermediate isolation of the non-conjugated ketone **3**.

The dimethylphenylsilyl group can be converted, in two steps, with retention of configuration, into a hydroxyl function.[4] The first step of the conversion requires the phenyl group to be substituted with a fluorine atom,[4,13] in a protodesilylation reaction, to give a fluorosilane. This was done by treating 17β-(*t*-butyldimethylsilyloxy) - 7α - (dimethylphenylsilyl) - androst-4-en-3-one **2** with tetrafluoroboric acid diethyl ether complex, giving the fluorosilane, 17β-hydroxy-7α-(dimethylfluorosilyl)-androst-4-en-3-one **6** (Scheme 1). A peracid mediated rearrangement reaction of the fluorosilane, first discovered by Buncel and Davies[14] and developed by Kumada and colleagues,[15] with *m*-chloroperoxybenzoic acid and potassium fluoride, gave 7α-hydroxy-testosterone **7** in an overall yield of 50% in this conversion.

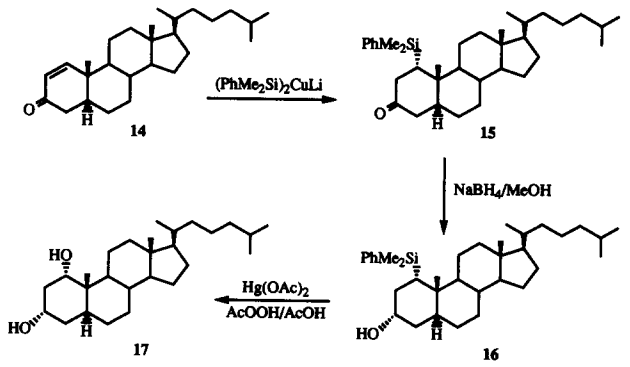
1α-Hydroxytestosterone (13)

The same procedure, addition of the dimethyl-phenylsilyl group using the silyl-cuprate reagent, $(PhMe_2Si)_2CuLi$, followed by its two-step conversion into a hydroxyl group, was applied to 17β-(*t*-butyldimethylsilyloxy)-androsta-1,4-dien-3-one **8b**. The addition of the silyl-cuprate reagent resulted in two products, 17β-(*t*-butyldimethylsilyloxy)-1α-(dimethylphenylsilyl)-androst-4-en-3-one **9** and 17β-(*t*-butyldimethylsilyloxy)-1β-(dimethylphenylsilyl)-androst-4-en-3-one **10** (Scheme 2). The 1β-isomer was unexpected, but welcome, and was produced in a 35% yield as the minor product. The yield of the 1α-isomer was unquantified, due to the inability to separate it completely from silyl reagent, but it was the major product and no starting steroid was left unreacted.

Assignment of the 1α- and 1β-conformations to the two products, **9** and **10**, was confirmed by several differences in the features of the ^1H NMR spectra caused by the dimethylphenylsilyl group at the 1β-position requiring ring A to adopt a half-chair conformation.[16,17] The NOE difference ^1H NMR spectrum of the 1β-isomer showed the expected NOE enhancement at the phenyl group but not at the 2β-proton when the 19-methyl group was irradiated. A similar experiment on the



Scheme 2



Scheme 3

1α-isomer showed the opposite enhancement. Additionally, in the 1β-isomer the carbonyl group at C-3 caused anisotropic shielding of the 19-methyl protons while in the 1α-isomer the carbonyl group caused deshielding. Also the 6α/β proton shifts are very close to each other in the 1α-isomer but in the 1β-isomer they are separated by 0.33 ppm which is a similar situation to 2α/β-hydroxytestosterone where the β-isomer has a half-chair structure for ring A.[18]

Preparation of the 1α- and 1β-fluorosilanes **11** and **12** (Scheme 2), using tetrafluoroboric acid diethyl ether complex, gave the products in poor yields, often resulting in the elimination of the silyl-group, leading to the 1,4-dien-3-one **8a**. Other methods of desilylation, however, were even less successful. Treatment of the 1α- and 1β-isomers **9** and **10**, with iodine monochloride which should yield a chlorosilyl derivative[19–21] and also with bromine where a bromosilyl product should be formed[22] gave none of the expected product, since both eliminated the C-1 silyl group completely. Oxidation of the 1α-isomer, 17β-hydroxy-1α-(dimethylfluorosilyl)-androst-4-en-3-one **11**, with *m*-chloroperoxybenzoic acid, using potassium fluoride as the catalyst, as before, gave 1α-hydroxytestosterone **13**. The analogous reaction with the 1β-isomer, however, did not yield 1β-hydroxy-testosterone, but the method still has potential.

A one-pot oxidation[8] of the dimethylphenylsilyl group into a hydroxyl was tried in both the 1α and 7α syntheses, but it was found to be incompatible with the 4-en-3-one system present in the substrates, resulting in Baeyer-Villiger oxidations, phenyl migrations, and ring rearrangements.

5α-Cholestane-1α,3α-diol (17)

It was also possible to introduce the hydroxyl function at the 1-position in the cholestane series. Treatment of 5α-cholest-1-en-3-one **14** with the silyl-cuprate reagent in the usual way resulted in complete conversion of the starting steroid into 1α-(dimethylphenylsilyl)-5α-cholest-3-one **15** (Scheme 3). The one-pot oxidation procedure[8] for conversion of the dimethylphenylsilyl group into hydroxyl failed as it did in the previously mentioned syntheses at the 1α- and 7α-positions for similar reasons. In this case the first step of the two-step method, which was previously successful also failed due to phenyl migration to C-3 induced by the protonated lactone

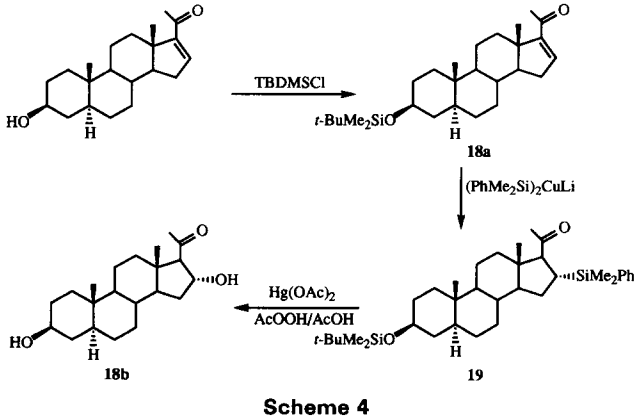
produced by Baeyer-Villiger oxidation of **15**. Reaction of the ketone **15** at C-3 with sodium borohydride to the alcohol, 1α-(dimethylphenylsilyl)-5α-cholestan-3-ol **16** followed by oxidation by the one-pot method did successfully introduce the 1α-hydroxyl function, since the product 5α-cholestane-1α,3α-diol **17** had two sharp ^{1}H NMR signals at 3.73 and 4.07 ppm for the 1β- and 3β-protons and the melting point coincides with the literature value.[9]

3β,16α-Dihydroxy-5α-pregnan-20-one (18b)

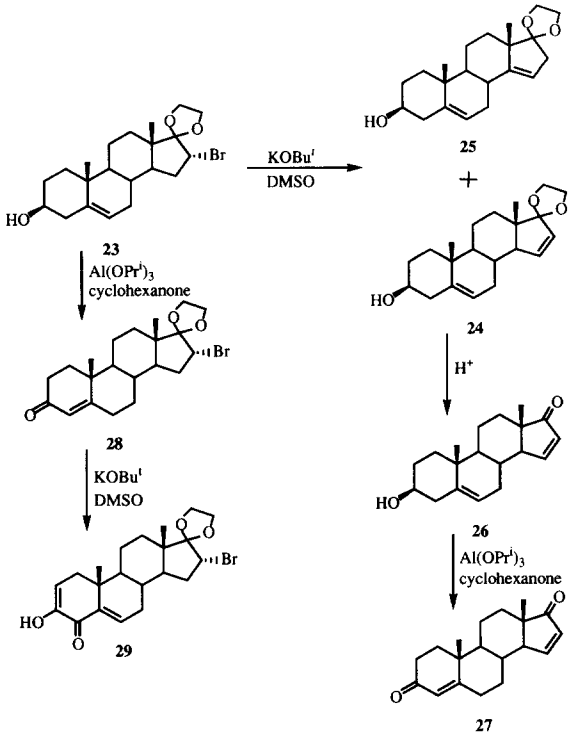
The silyl-cuprate reagent also afforded a route to the already accessible 16α-hydroxysteroids. The hydroxyl group of 3β-hydroxy-5α-pregn-16-en-20-one was protected by a 1-butyldimethylsilyl group to give the protected alcohol **18a** before reaction with the silyl-cuprate reagent to yield 3β-(*t*-butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-5α-pregnan-20-one **19** in good yield (Scheme 4). The one-pot oxidation procedure using mercuric acetate in peracetic acid was successful in this case giving the required alcohol, 3β,16α-dihydroxy-5α-pregnan-20-one **18b** in a reasonable yield. The product was identical to an authentic specimen by m.p. and mixed m.p., TLC, IR, and ^{1}H NMR. In a similar manner, the analogous compound, 16-dehydropregnenolone **20**, was protected by a *t*-butyldimethylsilyl group, yielding **21**, when it was reacted with the silyl-cuprate reagent to give 3β-(*t*-butyldimethylsilyloxy)-16α-(dimethylphenylsilyl)-pregn-5-en-20-one **22** (Scheme 4 structures with 5,6 double bond). However, in this case the one-pot method was unable to convert the dimethylphenylsilyl group into a hydroxy group, due to the presence of the unsaturation at C-5.

Androsta-4,15-diene-3,17-dione (27)

A novel route to androsta-4,15-diene-3,17-dione **27**, a suitable α,β-unsaturated steroid ketone precursor for the addition of the silyl-cuprate reagent to the C-15 position, was found, so that work could begin at applying the new method to preparing 15-hydroxyandrostanes. It was based on the method of Kelly and Sykes[10] for the preparation of 3β-hydroxyandrost-5,15-diene-17-one **26**, followed by an Oppenauer oxidation[2,3] to give the 4,15-diene-3,17-dione **27** (Scheme 5). The product of the



Scheme 4



Scheme 5

dehydrobromination of 16α-bromo-17,17-ethylenedioxyandrost-5-en-3β-ol **23** proved to be a chromatographically separable mixture of the 17,17-ethylenedioxy-3β-hydroxyandrosta-5,15-diene **24** which was purified by Kelly and Sykes and its isomer 17,17-ethylenedioxy-3β-hydroxyandrosta-5,14-diene **25** as shown by its ^{1}H NMR spectrum.

The sequence of three reactions starting from **23**, dehydrobromination, deketalization, and oxidation of the 3β-hydroxy group could have been attempted in a different order to produce the dienedione **27**. Oppenauer oxidation of the 16α-bromo-17,17-ethylenedioxyandrost-5-en-3β-ol **23** produced the ketone **28** in good yield but attempts to dehydrobrominate this ketone in dimethyl sulfoxide solution with potassium *t*-butoxide resulted in oxidation of ring A to afford a low yield of 16α-bromo-17,17-ethylenedioxy-3-hydroxyandrosta-2,5-diene-4-one **29**.

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References

1. Pelc B, Kodicek E (1971). A simple preparation of 1α,2α-epoxy-3-oxo-Δ^4-steroids. *J Chem Soc (C)* 1568.
2. Hossan AMM, Kirk DN, Mitra G (1976). A synthesis of 7α-hydroxyandrost-4-ene-3,17-dione. *Steroids* **27**:603–608.

3. Sharma PK, Akhila A (1991). A facile synthesis of 1β-hydroxytestosterone. *Indian J Chem (B)* **30B**:554–556.
4. Corrie JET (1979). Synthesis of 15β,17β-dihydroxyandrost-4-en-3-one and its 17-monoacetate. *J Chem Res (M)* 201–203.
5. Fleming I, Henning R, Plaut H (1984). The phenyldimethylsilyl group as a masked form of the hydroxyl group. *J Chem Soc Chem Commun* 29–31.
6. Marshall JA, Rudem RA, Hirsch LK, Phillipe M (1971). Regioselectivity in the conjugate addition of lithium dimethylcopper to cyclohexadienones. *Tetrahedron Lett* **41**:3795–3798.
7. Hill RA, Kirk DN, Makin HLJ, Murphy GM (eds) (1991). In: *Dictionary of Steroids*. Chapman and Hall, London, pp. 263, 270.
8. Fleming I, Sanderson PEJ (1987). A one-pot conversion of the phenyldimethylsilyl group into a hydroxyl group. *Tetrahedron Lett* **28**:4229–4232.
9. Streibel P, Tamm C (1954). 1-Ketocholestan. Steroide, 8. Mitteilung. *Helv Chim Acta* **37**:1094–1112.
10. Kelly RW, Sykes PJ (1968). Synthetic steroids. Part III. The preparation of 3β,15β,17β-trihydroxyandrost-5-ene and the attempted preparation of 3β,15α,17β-trihydroxyandrost-5-ene. *J Chem Soc (C)* 416–421.
11. Magiwara H, Sugiyama I (1962). Microbiological oxidation of Reichstein substance S by *Corticum Sasakii*; isolation of 15α-hydroxy-substance S. *Takeda Kenkyusho Nempo* **21**: 102–108.
12. Ager DJ, Fleming I, Patel SK (1981). The conjugate addition of a silyl group to enones and its removal with copper(II) bromide: a protecting group for the $\alpha\beta$ unsaturation of $\alpha\beta$-unsaturated ketones. *J Chem Soc Perkin Trans 1* 2520–2526.
13. Tamao K, Ishida N (1984). Silafunctional compounds in organic synthesis. XXVI Silyl groups synthetically equivalent to the hydroxy group. *J Organometallic Chem* **269**:C37–C39.
14. Buncel E, Davies AG (1958). Peroxides of elements other than carbon. Part I. The preparation and reactions of peroxysilanes. *J Chem Soc* 1550–1556.
15. Tamao K, Kakui T, Akita M, Iwahara T, Karatani R, Yoshida J, Kumada M (1983). Oxidative cleavage of silicon-carbon bonds in organosilicon fluorides to alcohols. *Tetrahedron* **39**:983–990.
16. Crabbé P (1965). In: *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*. Holden-Day, San Francisco, pp. 194–196.
17. Wechter WJ, Stomp G, MacKellar FA, Wiechert R, Kerb U (1965). Configuration and conformation of the A-ring of 1-methyl steroids. *Tetrahedron* **21**:1625–1634.
18. Kirk DN, Toms HC, Douglas C, White KA, Smith KE, Latif S, Hubbard RWP (1990). A survey of the high-field ^{1}H NMR spectra of steroid hormones, their hydroxylated derivatives, and related compounds. *J Chem Soc Perkin Trans* **2**:1567–1594.
19. Eaborn C, Bott RW (1968). Synthesis and reactions of the silicon carbon bond. In: MacDiarmid AG (ed), Organometallic Compounds of the Group IV Elements. Vol I. Part I. Marcell Dekker, Inc., New York, pp. 106–536.
20. Weber WP (1983). Arylsilanes. In: Silicon Reagents for Organic Synthesis, Ch. 8. Springer-Verlag, Berlin, pp. 114–128.
21. Félix G, Dungogues J, Pisciotti F, Clas R (1977). Regiospecific synthesis of mono- and polyiodo derivatives of benzene. *Angew Chem Int Ed Engl* **16**:488–489.
22. Hillard III RL, Volkhardt KPC (1977). Substituted benzocyclobutenes, indans and tetralins via cobalt-catalysed cooligomerization of α,ω-diynes with substituted acetylenes. Formation and synthetic utility of trimethylsilylated benzocycloalkenes. *J Am Chem Soc* **99**:4058–4069.
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23. Eastham JF, Teranishi R (1963). Δ^4-Cholestan-3-one. *Org Synth Coll* **IV**:192–195.