THE SYNTHESIS OF A-HOMO-B-NORANDROSTANES: THE EFFECT OF A HYDROXYL ON THE COURSE OF HYDROGENATION OF THE Δ^9-DOUBLE BOND*

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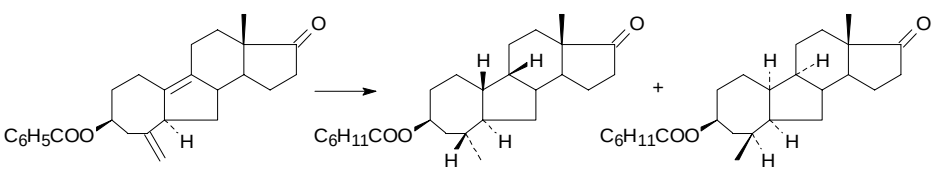
Acetolysis of 6β-mesyloxy-5-methyl-19-nor-5β-steroids (*e.g.* **10**) was proved to yield 4a-homo-7,19-dinor compounds (*e.g.* **9**) with a hydroxy group in the position 4aα. Hydrogenation of these compounds affords 9β,10β-dihydro derivatives (*e.g.* **12**) predominantly, corresponding 9α,10α isomers (*e.g.* **13**) are only formed in low yields. This sequence was used for the synthesis of analogues of androgen hormones 4aα-hydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-androstane-3,17-dione (**27**), 4aα,17β-dihydroxy-4aβ,17α-dimethyl-4a-homo-7,19-dinor-5α,9β,10β-androstan-3-one (**28**) and 4aα,17β-dihydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-androstan-3-one (**29**).

Key words: NOE experiments; Hormone analogues; Steroid skeletal rearrangement; Ketone circular dichroism; Steroids.

In a search for new types of antiandrogens we[2] had to deal with the problem of hydrogenation of Δ^9-unsaturated 4a-homo-7,19-dinor steroids (*e.g.* compound **1**, Scheme 1):



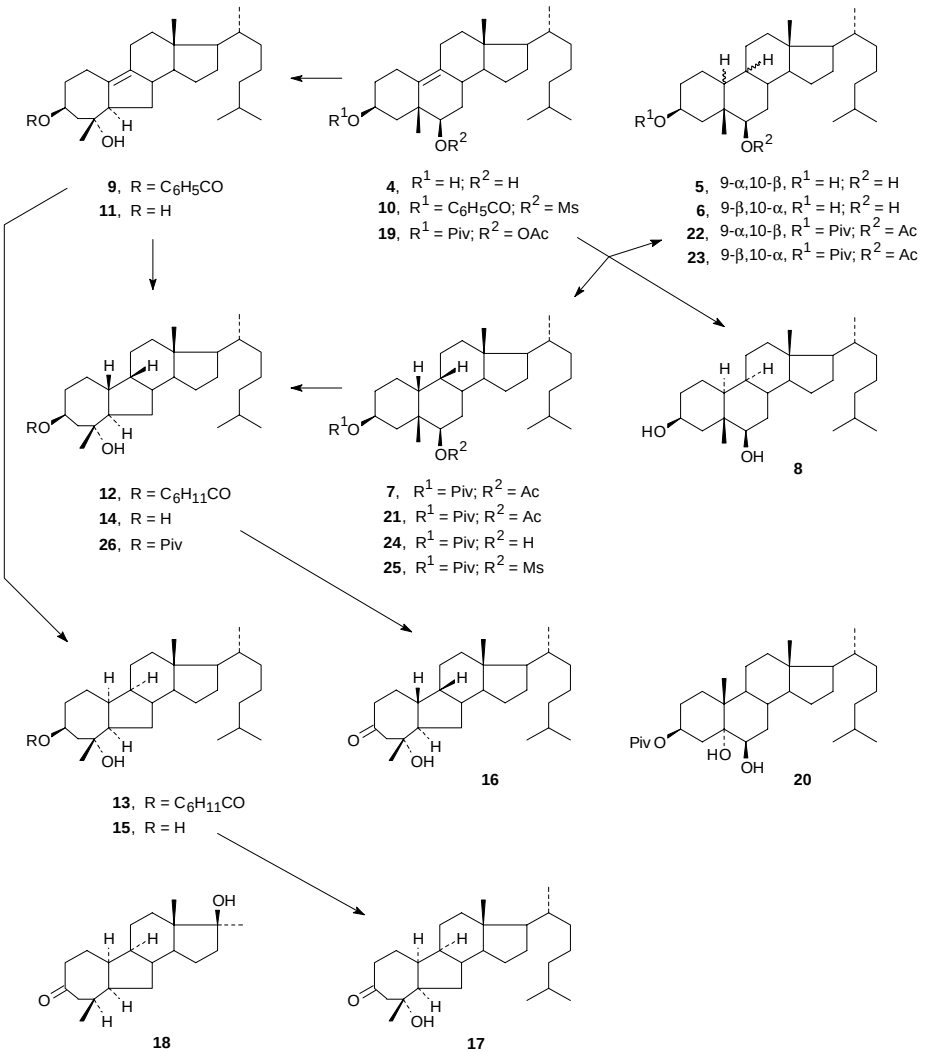
SCHEME 1

two products of *cis* addition of hydrogen (**2** and **3**) were formed in comparable yields, though the same reaction in Δ^9-unsaturated 19-nor steroids **4** (Scheme 2) yielded pre-

* Part CCCXC in the series On Steroids; Part CCCLXXXIX see ref.[1].

dominantly[3] products of *trans* addition of hydrogen, compounds **5** and **6** in addition to their *cis* isomer **7**. The fourth isomer **8** is only available by diimide reduction[3].

Here we report on our experiments to influence the above product distribution by placing a hydroxy group into a homoallylic 4a position. Compound **9** was prepared[4] by acetolysis of mesylate **10**. This reaction was first carried out by Mousseron-Canet[5],



SCHEME 2

though, the product formed was given a formula of a 4,5-seco-4,6-cyclo derivative[5]. Its skeleton was later corrected[4]. Here we are correcting a configuration of the 4a hydroxy group: as no intramolecular hydrogen bond[6] exists in diol **11** nor its ester **9**, the α-configuration of the 4a hydroxyl is more likely. Experimental evidence has been obtained from ^{1}H NMR spectra of an androstane analogue of ester **9** (*vide infra*).

Catalytic hydrogenation of **9** produced a mixture of perhydro products **12** and **13** in a proportion of 7.6 : 1. They were hydrolyzed to 3β-hydroxy derivatives **14** and **15** and oxidized to ketones **16** and **17** (ref.[4]). Circular dichroism of these ketones settled the question of their 9 and 10 configurations: the strong positive Cotton effect of the latter isomer ($\Delta\varepsilon_{286}$ +3.04) is close to the value for 17β-hydroxy-4aβ,17-dimethyl-4a-homo-7,19-dinor-5α,10α-androstan-3-one[7] (**18**, $\Delta\varepsilon_{288}$ +3.55). The strong negative Cotton effect for ketone **16** ($\Delta\varepsilon_{293}$ –2.9) suggests the 9β,10β configuration.

A direct proof of the suggested structures was now carried out as follows: Westphalen diol ester **19**, prepared from diol **20**, was hydrogenated and a 9β,10β-dihydro derivative **21** was easily separated from a mixture and identified: it was the only one of the four possible isomers that had an equatorial (Table I) 3β-acyloxy group (isomers **22** and **23**, with an axial 3β-acyloxy group, have very similar chromatographic properties but differ from compound **21**). Mesylate of the 9β,10β isomer, compound **25** was solvolyzed to yield a 4a-homo-7-nor compound **26**. Its hydrolysis and oxidation afforded ketone **16** identical with the sample prepared above.

The experience gained was used for the synthesis of analogues of androgen hormones **27**, **28** and **29**. Mesylate **30** (ref.[7], Scheme 3) yielded a mixture of diene **1** and a hydroxy derivative **31** on solvolysis with potassium acetate in aqueous acetone. Detailed analysis of proton 1D, 2D-COSY and 2D-NOESY spectra of compound **31** resulted in a complete structural assignment of all protons in the molecule (see Experimental). Figure 1 shows schematically the observed non-trivial NOE contacts.

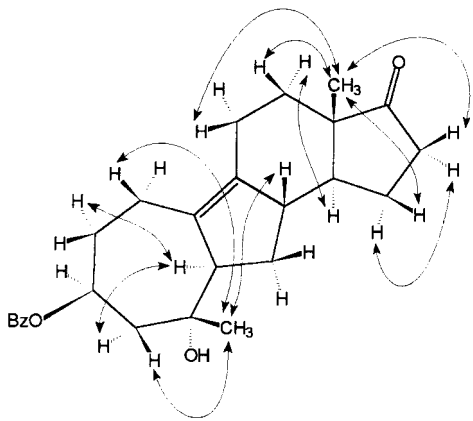


FIG. 1
The observed "non-trivial" NOE contacts (indicated with arrows) in ester **31**

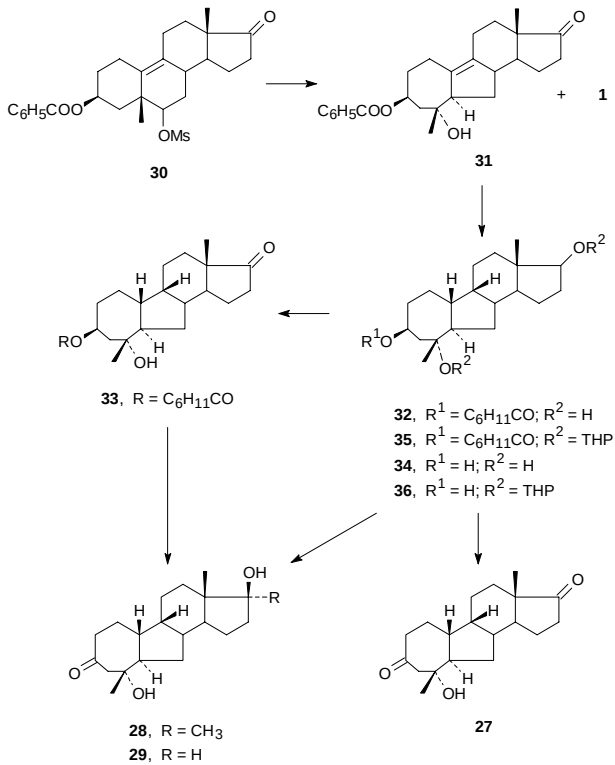
TABLE I
Characteristic parameters of the ^{1}H NMR spectra (in $CDCl_3$)

Compound	H-18[a]	4a-Me[a]	H-3[b]	H-17[c]	Other signals
9[d,e]	0.75	1.22	5.48[f]	–	2.87[g]
11[d]	0.73	1.16	4.25[f]	–	2.74[g]
12[d]	0.66	1.12	5.03	–	–
13[d]	0.66	1.21	5.18	–	–
14[d]	0.66	1.14	4.07	–	–
15[d]	0.65	1.22	4.15	–	–
16[d]	0.71	1.14	–	–	2.63[h] and 2.93[h]
17[d]	0.65	1.24	–	–	2.35[i] and 3.19[i]
19[d]	0.79	–	5.08[j]	–	1.23[k], 1.24[l], 2.05[m], 3.76[n]
20[d]	0.68	–	5.13[o]	–	1.17[k], 1.20[p], 3.54[q]
21[d]	0.65	–	4.69[r]	–	1.16[k], 1.06[l], 2.08[m], 5.15[s]
24[d]	0.65	–	4.80[r]	–	0.98[l], 1.17[k], 3.92[s]
25[d]	0.65	–	4.83[r]	–	1.07[l], 1.15[k], 3.12[t], 4.89[u]
26[d]	0.66	1.13	5.02	–	1.17[k]
27	0.94	1.16	–	–	2.61[v] and 2.97[v]
28	0.91	1.16	–	–	2.69[w] and 2.89[w], 1.22[x]
29	0.80	1.16	–	3.69	2.69[w] and 2.91[w]
31	0.97	1.24	5.48	–	–
32	0.73	1.11	5.00	3.62	–
33	0.88	1.15	4.99	–	–
34	0.61	1.07	3.95	3.56	–

[a] Singlet, 3 H; [b] broad triplet (J = 10.7) or m (W = 31.0), unless stated otherwise; [c] dd (J = 8.5 and 7.5); [d] cholestane side chain: 0.86 d, 3 H, J = 6.7 (3 × H-26 and 3× H-27) and 0.92 d, 3 H, J = 6.4 (3 × H-21); [e] multiplets of aromatic protons at 7.43 (H-2′, H-6′), 7.54 (H-4′) and 8.00 (H-3′, H-5′); [f] m, W = 29.1; [g] d, J = 8.7, 1 H, H-5a; [h] AB system, 2 × H-4, J = 11.6; [i] AB system, 2 × H-4, J = 14.0; [j] m, W = 20.0; [k] s, 9 H, $(CH_3)_3CCOO$; [l] s, 3 H, 5β-CH_3; [m] s, 3 H, CH_3COO; [n] dd, J = 4.0 and 11.6, 1 H, H-6; [o] m, W = 40; [p] s, 3 H, 3 × H-19; [q] m, W = 18, 1 H, H-6; [r] tt, J = 4.0 and 11.6; [s] t, J = 8,2, 1 H, H-6; [t] s, 3 H, CH_3SO_2O; [u] overlapping signal of H-6; [v] AB system, J = 12.1, 2 × H-4; [w] AB system, J = 11.6, 2 × H-4; [x] s, 3 H, 17a-CH_3.

The NOE cross-peaks between 4a-methyl group and protons in position 2β, 4β and 8β clearly indicate the 4aα-OH, 4aβ-CH_3 configuration at carbon C-4a.

Compound **31** was hydrogenated using a platinum catalyst in acetic acid. The lipophilic fraction, a product of hydrogenation and hydrogenolysis[8], was oxidized to a mixture of ketones **2** and **3**. The major fraction yielded a single compound **32** whose properties (see Experimental) were compatible with the structure of 4aα,17β-dihydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-androstan-3β-yl cyclohexanecarboxylate. Ketone **33**, derived from compound **32**, had a strong positive Cotton effect ($\Delta\varepsilon_{298}$ +2.30) which compares well with a CD curve of the corresponding 4a-deoxy compound – ketone **2** (ref.[7], $\Delta\varepsilon_{297}$ +2.78).



SCHEME 3

Ketone **33** was treated with methylmagnesium iodide and oxidized to yield compound **28**, an analogue of methyltestosterone. Triol **34**, obtained from ester **32**, was oxidized to another analogue, diketone **27**.

Alternatively, hydroxy groups of 17β-alcohol **32** were protected by tetrahydropyranylation and a mixture of isomers produced (**35**) was subjected to lithium alumi-

nium hydride treatment which resulted in a hydrolysis of the ester group. 3β-Alcohol formed (**36**) was oxidized and after deprotection, a testosterone analogue **29** was produced.

In summary, platinum-catalyzed hydrogenation of the Δ^9-double bond in B-nor steroids (*i.e.* types **1** and **31**) yields products of *syn* addition of hydrogen from the α and β sides. The homoallylic 4aα-hydroxy group favours the approach of hydrogen from the opposite (*i.e.* β) side under the formation of 9β,10β-dihydro products. For example the cholestane 9β,10β isomer **12** is formed in 88% yield, in the androstane series the excess of the 9β,10β isomer (*i.e.* **32**) seems to be even higher.

This directing effect of a homoallylic hydroxy group on the catalytic hydrogenation of olefins has manifested itself in increased addition of hydrogen from the site of the hydroxyl: *e.g.* the 19-hydroxyl increased the yield of 5β-steroids[9,10]. The "hydroxyl group effect" was observed with platinum[11], palladium[12] and rhodium[13] catalysts. The discrepancy between earlier findings and our results may be explained in terms of steric factors: the homoallylic hydroxyl in olefins of the type **9** is a tertiary hydroxyl group while the most convincing examples of the above hydroxyl group effect are based on the effect of primary hydroxyl groups[9,12].

Preliminary receptor tests of compound **28** revealed no significant binding to androgen receptors (rat prostates) nor to human gestagen, glucocorticoid, mineralocorticoid and estrogen receptors. Compound **28** did not affect the mammary gland[14] of male or female mice. Because of the negative results of these tests, the other analogues **27** and **29** were withdrawn from the testing.

EXPERIMENTAL

Melting points were determined on a melting point micro apparatus Boetius (Germany) and are uncorrected. Analytical samples were dried over phosphorus pentoxide at 50 °C/100 Pa. Optical rotations were measured in chloroform, circular dichroism in methanol. IR spectra of chloroform solutions (unless stated otherwise) were recorded on a Bruker IFS 88 spectrometer. Wavenumbers are given in cm^{-1}. ^1H NMR spectra of prepared compounds were measured on a Varian UNITY-200 (at 200 MHz) spectrometer at 23 °C in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants and width of multiplets in Hz (see Table I). Proton 1D, 2D-COSY and 2D-NOESY spectra of compound **9** were run on a Varian UNITY-500 (at 500 MHz) under the same conditions. Mass spectra were recorded on a VG Analytical ZAB-EQ spectrometer (energy of ionizing electrons 70 eV, ion source temperature 180–220 °C). Thin-layer chromatography (TLC) was done on silica gel (ICN Biochemicals). Preparative thin-layer chromatography (PLC) was carried out on 200 × 200 mm plates coated with a 0.7 mm layer of the same material. For column chromatography silica gel 60–120 μm was used. Whenever aqueous solutions of hydrochloric acid, potassium hydrogen carbonate and potassium carbonate are used, their concentration is always 5%.

4aβ-Methyl-4a-homo-7,19-dinor-5α-cholest-9-ene-3β,4aα-diol (**11**)

A solution of compound[4] (**9**; 150 mg, 0.30 mmol) in tetrahydrofuran (5 ml) was refluxed with lithium aluminium hydride (*ca* 50 mg, 1.3 mmol). After 2 h, an excess of hydride was destroyed with

acetone, the mixture was acidified with hydrochloric acid (5%, 1 ml) and a precipitate was extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated in a vacuum. Crystallization of the residue from acetone afforded 95 mg (80%) of compound **11**, m.p. 126–128 °C. IR spectrum: 3 609, 3 378 (OH); 1 025 (C–O). Mass spectrum, *m/z* (%): 402 (M^+, 70), 384 (M – H_2O, 100). For $C_{27}H_{46}O_2$ (402.7) calculated: 80.54% C, 11.51% H; found: 80.27% C, 11.45% H.

4aα-Hydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-cholestan-3-one (**16**)

a) From compound **9**. A solution of olefin **9** (3.1 g, 6.12 mmol) in acetic acid (40 ml) was stirred with a platinum catalyst (450 mg) in a hydrogen atmosphere at laboratory temperature for 18 h. The solvent was evaporated in a vacuum. The residue was dissolved in chloroform, washed with the potassium carbonate solution and water, and dried. The residue, *i.e.* a mixture of compounds **12** and **13**, was dissolved in tetrahydrofuran (25 ml) and treated with lithium aluminium hydride (*ca* 150 mg, *ca* 4 mmol) at reflux. After 2 h, the mixture was worked up as in the preparation of diol **11**. The residue was purified on a column of silica gel (100 g, benzene–ether, 1 : 1). The major product (**14**; 2.05 g, 83%), identical with the earlier prepared sample[4], was dissolved in acetone (10 ml) and Jones reagent was added dropwise under stirring at 0 °C. After 10 min, an excess of the oxidant was destroyed by a few drops of methanol, inorganic products were filtered out and the solution was concentrated in a vacuum. The residue was partitioned between ether and the potassium hydrogen carbonate solution. The organic layer was washed with water, dried over sodium sulfate and evaporated in a vacuum. The residue (**16**; 1.99 g, 81% from compound **9**) crystallized from acetone, m.p. 118–119 °C, $[\alpha]_D$ –48° (*c* 1.0). CD: $\Delta\varepsilon_{293}$ –2.95. IR spectrum: 3 601 (OH); 1 693 (C=O). Mass spectrum, *m/z* (%): 402 (M^+, 71), 384 (100), 369 (41), 344 (53). For $C_{27}H_{46}O_2$ (402.7) calculated: 80.54% C, 11.51% H; found: 80.49% C, 11.54% H.

b) From diol **14**. Jones reagent (0.5 ml) was added to a solution of diol **14** (65 mg, 0.16 mmol) in acetone (1 ml). The mixture was worked up and crystallized as above to yield 48 mg (74%) of ketone **16**, identical with the above sample.

4aα-Hydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,10α-cholestan-3-one (**17**)

Compound **15** (260 mg, 0.64 mmol), the minor product from the chromatography of compound **16**, was oxidized to **17** according to the preceding experiment. Ketone **17** (235 mg, 91% from alcohol **15** or 9% from olefin **9**) crystallized from acetone, m.p. 154–156 °C, $[\alpha]_D$ +72° (*c* 0.9). CD: $\Delta\varepsilon_{286}$ +3.04. IR spectrum (carbon tetrachloride): 3 610, 3 598 (OH); 1 702 (C=O). Mass spectrum, *m/z* (%): 402 (100). For $C_{27}H_{46}O_2$ (402.7) calculated: 80.54% C, 11.51% H; found: 80.29% C, 11.44% H.

5,6β-Dihydroxy-5α-cholestan-3β-yl Pivalate (**20**)

Sodium hydrogen phosphate (40.3 g, 0.284 mol) and peracetic acid (32 wt.% solution in dilute acid, 105 ml, 38 mmol) were added to a solution of cholest-5-en-3β-yl pivalate[15] (51.89 g, 110 mmol) in chloroform (250 ml). The mixture was stirred for 2 h, washed with water, the potassium hydrogen carbonate solution, water, and dried over sodium sulfate. The solvent was evaporated in a vacuum. The residue was dissolved in dioxane (1 040 ml) and acetone (700 ml). Perchloric acid (5%, 175 ml, 207.5 mmol) was added to the solution under stirring at laboratory temperature. After 3 h the mixture was concentrated to a quarter of its volume and washed with brine. The product was extracted with chloroform, dried and the solvent was evaporated in a vacuum. Crystallization of the residue from toluene afforded compound **20** (37 g, 67%), m.p. 230–232 °C, $[\alpha]_D$ –8° (*c* 1.3). IR spectrum: 3 632, 3 598 (OH); 1 723 (C=O); 1 170, 1 157 (C–O). For $C_{32}H_{56}O_4$ (504.8) calculated: 76.14% C, 11.18% H; found: 76.38% C, 11.33% H.

5-Methyl-19-nor-5β-cholest-9-ene-3β,6β-diyl 3-Pivalate 6-Acetate (**19**)

From a solution of compound **20** (37 g, 73.3 mmol) in acetic anhydride (810 ml) volatile products (156 ml) were distilled off at atmospheric pressure. Concentrated sulfuric acid (1 ml, 18.76 mmol) was added dropwise into the stirred mixture below 30 °C. After 2 h the reaction mixture was diluted with brine (5.5 l). A precipitate was filtered off, dissolved in toluene and washed with the potassium carbonate solution and brine. An organic layer was filtered over silica gel (30 g) and the solvent was evaporated. Crystallization of the residue from methanol yielded compound **19** (26.68 g, 69%), m.p. 156–157 °C, $[\alpha]_D$ +84° (*c* 1.3). IR spectrum: 1 739, 1 725 (C=O); 1 242, 1 029, 1 158 (C–O). For $C_{34}H_{56}O_4$ (528.8) calculated: 77.22% C, 10.67% H; found: 77.47% C, 10.70% H.

5-Methyl-19-nor-5β,9β,10β-cholestane-3β,6β-diyl 3-Pivalate 6-Acetate (**21**)

Compound **19** (100 mg, 0.19 mmol) was hydrogenated on platinum oxide (80 mg) in acetic acid (30 ml) at 70 °C for 8 h. The catalyst was filtered off and the filtrate was evaporated in a vacuum. The residue was purified by PLC (3 plates): elution with petrolether–ether (9 : 1) afforded compound **21** (51 mg, 51%) and a mixture of *trans* dihydro derivates **22** and **23** (47 mg, 47%). Compound **21** crystallized from methanol (43 mg), m.p. 129–131 °C, $[\alpha]_D$ +3° (*c* 1.3). IR spectrum: 1 739, 1 725 (C=O); 1 240, 1 036, 1 172 (C–O). For $C_{34}H_{58}O_4$ (530.8) calculated: 76.93% C, 11.01% H; found: 77.12% C, 11.23% H.

5-Methyl-6β-hydroxy-19-nor-5β,9β,10β-cholestan-3β-yl Pivalate (**24**)

A solution of sodium methoxide in methanol (0.87 M, 0.84 ml, 0.73 mmol) was added to a solution of compound **21** (258 mg, 0.49 mmol) in ethanol (1 ml) and the reaction mixture was refluxed for 1.5 h. The solvent was evaporated in a vacuum, the residue was dissolved in chloroform, washed with water and dried. After evaporation, compound **24** (213.8 mg, 90%) did not crystallize, $[\alpha]_D$ +15° (*c* 1.3). IR spectrum: 3 629, 3 466 (OH); 1 722, 1 710 sh (C=O); 1 172 (C–O); 1 054 (C–OH). For $C_{32}H_{56}O_3$ (488.8) calculated: 78.63% C, 11.55% H; found: 78.51% C, 11.48% H.

5-Methyl-19-nor-5β,9β,10β-cholestane-3β,6β-diyl 3-Pivalate 6-Methanesulfonate (**25**)

Methanesulfonyl chloride (0.8 ml, 10.34 mmol) was added to a solution of **24** (500 mg, 1.0 mmol) in pyridine (8 ml) at 0 °C. After 2.5 h, the reaction mixture was diluted with ice water, the product was extracted with chloroform, washed with aqueous hydrochloric acid, water, the potassium hydrogen carbonate solution, water and dried. Evaporation of the solvent afforded compound **25** (540 mg, 93%). IR spectrum: 1 723 (C=O); 1 363, 1 354, 1 340 (SO_2); 1 175, 1 160 (C–O). For $C_{33}H_{58}O_5S$ (566.9) calculated: 69.92% C, 10.31% H, 5.66% S; found: 69.85% C, 10.14% H, 5.50% S.

4aα-Hydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-cholestan-3β-yl Pivalate (**26**)

A solution of potassium acetate (400 mg, 4.1 mmol) in water (10 ml) was added to a solution of mesylate **25** (250 mg, 0.44 mmol) in dioxane (30 ml) and the mixture was refluxed in a nitrogen atmosphere. After 6 h, the solvent was evaporated in a vacuum, the residue was dissolved in toluene, washed with the potassium carbonate solution and water, and dried. After evaporation of the solvent, the residue was purified by PLC (4 plates, benzene–ether, 95 : 5). Compound **26** (90 mg, 42%) did not crystallize, $[\alpha]_D$ +24° (*c* 1.6). IR spectrum: 3 613, 3 503 (OH); 1 722 (C=O); 1 176 (C–O). For $C_{32}H_{56}O_3$ (488.8) calculated: 78.63% C, 11.55% H; found: 78.57% C, 11.71% H.

4aβ-Methyl-4a-homo-7,19-dinor-5α,9β,10β-cholestane-3β,4aα-diol (**14**)

Lithium aluminum hydride (100 mg, 2.7 mmol) was added to a solution of compound **26** (130 mg, 0.27 mmol) in tetrahydrofuran (5 ml) and the mixture was refluxed for 1 h. After cooling, a solution of sodium sulfate was added (1 ml), the mixture was filtered over sodium sulfate and the solvent was evaporated. The residue crystallized from acetone–heptane, m.p. 90–92 °C (75 mg, 70%), $[\alpha]_D$ +31° (*c* 1.1). IR spectrum: 3 613, 3 371 (OH); 1 022 (C–OH). The compound was identical (IR spectrum) with a sample prepared before[4] (for compound XVII the lit.[4] gives the following values: m.p. 90–92 °C, $[\alpha]_D$ +34°).

4aα-Hydroxy-4aβ-methyl-17-oxo-4a-homo-7,19-dinor-5α-androst-9-en-3β-yl Benzoate (**31**)

a) A solution of 5-methyl-17-oxo-19-nor-5β-androst-9-en-3β,6β-diyl 3-benzoate 6-methanesulfonate[7] (**30**; 4.13 g, 8.5 mmol) and potassium acetate (4.13 g, 42.1 mmol) in aqueous acetone (500 ml, 27%) was refluxed in a nitrogen atmosphere. After 5 h, the solvent was evaporated in a vacuum. The residue was dissolved in toluene and washed successively with the potassium carbonate solution and water, and dried. The product was purified by chromatography on a column of silica gel (150 g). Elution with toluene yielded diene **1** (1.13 g, 34%) identical with the authentic sample[7]. Elution with ethyl acetate–toluene (1 : 5) yielded compound **31** (2.42 g, 61%), $[\alpha]_D$ +90° (*c* 0.9). IR spectrum: 3 597 (OH); 1 731, 1 712 (C=O); 1 602, 1 585, 1 452 (arom.); 1 278 (C–O). ^{1}H NMR spectrum (500 MHz): 0.96 s, 3 H (3 × H-18); 1.19 dt, 1 H, *J*(12α,12β) = 12.8, *J*(12α,11β) = 13.2, *J*(12α,11α) = 5.6 (H-12α); 1.24 s, 3 H (4a-Me); 1.29 ddd, 1 H, *J*(14,8) = 11.6, *J*(14,15α) = 5.8, *J*(14,15β) = 12.6 (H-14); 1.62 ddd, 1 H, *J*(6α,5) = 9.4, *J*(6α,6β) = 13.6, *J*(6α,8) = 6.7 (H-6α); 1.64 tt, 1 H, *J*(15β,15α) = *J*(15β,14) = 12.6, *J*(15β,16α) = *J*(15β,16β) = 9.0 (H-15β); 1.85 ddd, 1 H, *J*(12β,12α) = 12.8, *J*(12β,11α) = 1.8, *J*(12β,11β) = 5.6 (H-12β); 1.95 m, 1 H (H-15α); 1.98 m, 1 H (H-2β); 2.00 dd, 1 H, *J*(4α,4β) = 14.6, *J*(4α,3) = 3.6 (H-4α); 2.05 m, 1 H (H-11β); 2.09 ddd, 1 H, *J*(16α,16β) = 19.0, *J*(16α,15α) = 10.0, *J*(16α,15β) = 9.0 (H-16α); 2.12 m, 1 H (H-2α); 2.21 ddd, 1 H, *J*(6β,6α) = 13.6, *J*(6β,5) = 2.6, *J*(6β,8) = 7.9 (H-6β); 2.23 dd, 1 H, *J*(4β,4α) = 14.6, *J*(4β,3) = 5.5 (H-4β); 2.25 m, 1 H (H-1α); 2.47 bddd, 1 H, *J*(11α,11β) = 14.8, *J*(11α,12α) = 5.6, *J*(11α,12β) = 1.8 (H-11α); 2.47 ddd, 1 H, *J*(16β,16α) = 19.0, *J*(16β,15α) = 1.1, *J*(16β,15β) = 9.0 (H-16β); 2.50 m, 1 H (H-1β); 2.67 m, 1 H (H-8); 2.94 m, 1 H (H-5); 5.48 tdd, 1 H, *J*(3,2α) = *J*(3,4α) = 3.6, *J*(3,2β) = 7.3, *J*(3,4β) = 5.5 (H-3); 7.44 m, 2 H (H-3 of benzoate); 7.56 m, 1 H (H-4 of benzoate); 8.00 m, 2 H (H-2 of benzoate). For $C_{26}H_{32}O_4$ (408.5) calculated: 76.44% C, 7.90% H; found: 76.14% C, 8.12% H.

b) A solution of mesylate **30** (200 mg, 0.4 mmol) and silver tetrafluoroborate (400 mg, 2.1 mmol) in toluene (4 ml) was stirred at 20 °C in the dark. After 40 h, the mixture was diluted with chloroform, washed with water and dried over sodium sulfate. The residue was resolved by PLC (3 plates, ether–benzene, 1 : 1) into two products: **1** (51 mg, 32%) and **31** (63 mg, 38%).

Hydrogenation of 4aα-Hydroxy-4aβ-methyl-17-oxo-4a-homo-7,19-dinor-5α-androst-9-en-3β-yl Benzoate (**31**)

Compound **31** (2.60 g, 6.24 mmol) was hydrogenated in acetic acid (40 ml) with a platinum catalyst (460 mg) at laboratory temperature for 24 h. The catalyst was filtered off. The filtrate was evaporated in a vacuum. The residue (2.6 g) was applied on a column of silica gel (200 ml). Toluene–ethyl acetate (3 : 1) eluted successively.

Lipophilic fraction (711 mg, 28%), according to ^{1}H NMR spectrum it is a mixture of 4a-deoxy compounds. Its Jones oxidation afforded a mixture of compounds **2** and **3**.

4aα,17β-Dihydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-androstan-3β-yl cyclohexanecarboxylate (**32**; 1.65 g, 63%) crystallized from acetone–heptane, m.p. 121–123 °C, $[\alpha]_D$ +10° (*c* 1.0).

IR spectrum (carbon tetrachloride): 3 631, 3 617 (OH); 1 723 (C=O); 1 249, 1 192, 1 174 (C–O); 1 134, 1 041 (C–OH). Mass spectrum, *m/z* (%): 418 (M^+, 0.3), 290 (100), 272 (84). For $C_{26}H_{42}O_4$ (418.6) calculated: 74.60% C, 10.11% H; found: 74.59% C, 10.08% H.

4aβ-Methyl-4a-homo-7,19-dinor-5α,9β,10β-androstane-3β,4aα,17β-triol (**34**)

Lithium aluminium hydride (*ca* 30 mg, *ca* 0.8 mmol) was added to a solution of ester **32** (74 mg, 0.18 mmol) in tetrahydrofuran (3 ml) and the mixture was refluxed for 5 min. After 1 h standing at room temperature, an excess reagent was decomposed by water. The mixture was saturated with anhydrous sodium sulfate. Inorganic material was filtered off and washed with hot chloroform. The extract was concentrated in a vacuum and crystallized from acetone. Yield 45 mg (83%), m.p. 211–213 °C, $[\alpha]_D$ +22° (*c* 0.9). IR spectrum: 3 608, 3 340, 3 232 (OH); 1 075, 1 043, 1 021, 1 013 (C–OH). For $C_{19}H_{32}O_3$ (308.5) calculated: 73.98% C, 10.46% H; found: 73.78% C, 10.39% H.

4aα-Hydroxy-4aβ-methyl-17-oxo-4a-homo-7,19-dinor-5α,9β,10β-androstan-3β-yl Cyclohexanecarboxylate (**33**)

Compound **32** (370 mg, 0.88 mmol) was oxidized by Jones reagent in acetone as above. A product was purified by PLC (5 plates, benzene–ether, 3 : 1) and crystallized from acetone–heptane. Yield 257 mg (69%), m.p. 144–147 °C, $[\alpha]_D$ +54° (*c* 1.2). CD: $\Delta\varepsilon_{298}$ +2.30. Mass spectrum, *m/z*: 416 (M^+), 288 (M – $C_6H_{11}COOH$), 270 (288 – H_2O). For $C_{26}H_{40}O_4$ (416.6) calculated: 74.96% C, 9.68% H; found: 74.80% C, 9.72% H.

4aα,17β-Dihydroxy-4aβ,17α-dimethyl-4a-homo-7,19-dinor-5α,9β,10β-androstan-3-one (**28**)

Ketone **33** (4.9 g, 11.8 mmol) was dissolved in benzene (150 ml) and added to a solution of freshly prepared methylmagnesium iodide in ether, prepared from magnesium (1.0 g, 41.1 mmol) and methyl iodide (2.0 ml, 32.1 mmol) in ether (50 ml). After the addition, ether was distilled off, the mixture was refluxed for 3 h and poured onto ice (200 g) with concentrated hydrochloric acid (15 ml). The precipitate was filtered off and dissolved in chloroform. The solution was washed with a sodium thiosulfate solution (5%), water and the potassium hydrogen carbonate solution. The solution was evaporated in a vacuum and oxidized with Jones reagent as above. Ketone **28** crystallized from toluene. Yield 2.30 g (64%), m.p. 201–203 °C, $[\alpha]_D$ –94° (*c* 1.1). CD: $\Delta\varepsilon_{294}$ –2.16. IR spectrum: 3 604, 3 457 (OH); 1 695 (C=O). For $C_{20}H_{32}O_3$ (320.5) calculated: 74.96% C, 10.06% H; found: 74.68% C, 10.06% H.

4aα-Hydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-androstane-3,17-dione (**27**)

Jones reagent was added dropwise into a solution of **34** (198 mg, 0.64 mmol) in acetone (5 ml) under stirring at 20 °C. After 10 min, an excess of the reagent was reduced with a few drops of methanol, the inorganics were filtered off and the filtrate was evaporated in a vacuum. The residue was dissolved in chloroform and washed with the potassium carbonate solution and water, and dried. Crystallization of the residue from acetone–heptane afforded 98 mg (50%) of compound **27**, m.p. 202–204 °C, $[\alpha]_D$ +26° (*c* 0.7). CD: $\Delta\varepsilon_{300}$ +0.52. IR spectrum: 3 600 (OH); 1 732, 1 685 (C=O); 1 040 (C–O). Mass spectrum, *m/z* (%): 304 (M^+), 286 (100); high resolution, for $C_{19}H_{28}O_3$ calculated: 304.203845, found: 304.201800. For $C_{19}H_{28}O_3$ (304.4) calculated: 74.96% C, 9.27% H; found: 74.80% C, 9.19% H.

4aα,17β-Dihydroxy-4aβ-methyl-4a-homo-7,19-dinor-5α,9β,10β-androstan-3-one (**29**)

A solution of 17β-hydroxy derivative **32** (100 mg, 0.24 mmol) in dichloromethane (20 ml) and 3,4-dihydro-2*H*-pyran (*ca* 200 mg, *ca* 2.4 mmol) was treated with 4-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) at ambient temperature. After 2 h, the mixture was washed with the potassium hydrogen carbonate solution and dried over magnesium sulfate. The residue (compound **35**) was refluxed in a solution of sodium methoxide in methanol (4.7%, 5 ml, 4.4 mmol). After 5 h, the solution was concentrated in a vacuum and the product was precipitated by and addition of brine (10 ml). The precipitate was taken up in toluene. The extract was washed with brine and concentrated in a vacuum. The residue was dissolved in dichloromethane (1 ml) and added in one portion to a stirred suspension of pyridinium chlorochromate (130 mg, 0.6 mmol) and sodium acetate (50 mg, 0.61 mmol) in the same solvent (3 ml). After 3 h, the mixture was diluted with ether (20 ml) and stirred for another 10 min. The supernatant was decanted and the dark solid was washed twice with ether (5 ml). The solution was filtered through a short column of silica gel (1.5 g). The filtrate was evaporated and the residue was treated with 4-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) in acetone (3 ml) at ambient temperature. After 18 h, potassium hydrogen carbonate was added (10 mg, 0.1 mmol) and the mixture was concentrated in a vacuum. The residue was dissolved in chloroform, washed with water, dried and purified by PLC (one plate, benzene–ether, 1 : 1). Compound **29** (21 mg, 29%) melts at 180–182 °C (acetone–heptane), $[\alpha]_D$ –73° (*c* 0.8). IR spectrum: 3 604, 3 464 (OH); 1 696 (C=O); 1 404 (CH_2 next to C=O). For $C_{19}H_{33}O_3$ (306.4) calculated: 74.47% C, 9.87% H; found: 74.26% C, 9.73% H.

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