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Analogues of androgen hormones with inverted configuration at carbons 5, 9, and 10

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Abstract

On catalytic hydrogenation of Δ^9-steroids (e.g. 3β-hydroxy-5-methyl-19-nor-5β-androst-9-en-17-one), four isomers were formed: 9α,10α-, 9α,10β-, 9β,10α- and 9β,10β-adducts. The product distribution was affected by the nature of the C-3 substituent. A chair conformation of A, B, and C rings was found in all of the products with the exception of the 9α,10α-adduct whose B ring adopts a twist boat conformation. The products were utilized for the synthesis of dihydrotestosterone analogues.

Keywords: Catalytic hydrogenation; Trans addition; Rearrangement; NMR spectroscopy; HPLC

1. Introduction

In a search for new types of antihormones [1], we produced [2] Westphalen-type [3] isomers of testosterone, whose angular methyl group in position 10 and double bond in the A ring were swapped (e.g. 17β-hydroxy-5-methyl-19-nor-5β-androst-9-en-3-one). A similar idea was conceived by Covey [4], who prepared similar compounds in a different way. In a further attempt to modify this structure, we considered hydrogenation of the 9(10) double bond to substantially alter the overall conformation of the molecule. The reduction is generally claimed to proceed as a *cis* addition of hydrogen; though, in cholestane analogues, like **1,** products of *trans* hydrogenation were also produced (see Snatzke [5]). The finding was based on circular dichroism [6] and very simple ^{1}H NMR techniques that were available in the sixties. Snatzke [6] argued that the hydrogenation proceeded after a preliminary migration of the C = C double bond (see Scheme 1). Thus, 9β,10β-dihydro derivatives (type **2**) were accompanied by *trans* adducts, i.e. 9α,10β, and 9β,10α isomers (types **3** and **4**). The idea of a preliminary isomerization of the Δ^9-double bond was first formulated by Grob [7], who achieved the isomerization to a $\Delta^{9\,(11)}$-product and also proposed its 10βH-configuration.

Snatzke [5] claimed the chair conformation of the C ring for his dihydro products **2** and **4.** Recently, however, we found [8] a boat conformation of the C ring for 8β,9β-steroids. Therefore we decided to fully analyze NMR spectra of these products in order to re-examine the earlier results.

2. Experimental

Melting points were determined on a Boetius micro melting point apparatus (Germany) and are uncorrected. Analytical samples were dried over phosphorus pentoxide at 50°C/100 Pa. Circular dichroism was measured on a Mark V apparatus in CH_3OH, optical rotations, and IR spectra were measured in chloroform. IR spectra (wave numbers in cm^{-1}) were recorded on a Bruker IFS 88 spectrometer in $CHCl_3$ (if not specified otherwise). ^{1}H NMR spectra were measured on a Varian UNITY-200 (at 200 MHz) spectrometer at 23°C in $CDCl_3$ with TMS as the internal standard. Chemical shifts are given in ppm (δ-scale), and coupling constants and widths of multiplets are given in Hz. ^{1}H and ^{13}C NMR spectra of diols **6**, **11**, keto alcohols **15**, **17**, **16**, **18**, and diketones **13**, **33**, **14**, **34** were measured on a Varian UNITY-500 (^{1}H at 500 MHz; ^{13}C at 125.7 MHz). 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 performed on silica gel (ICN Biochemicals), and prepar-

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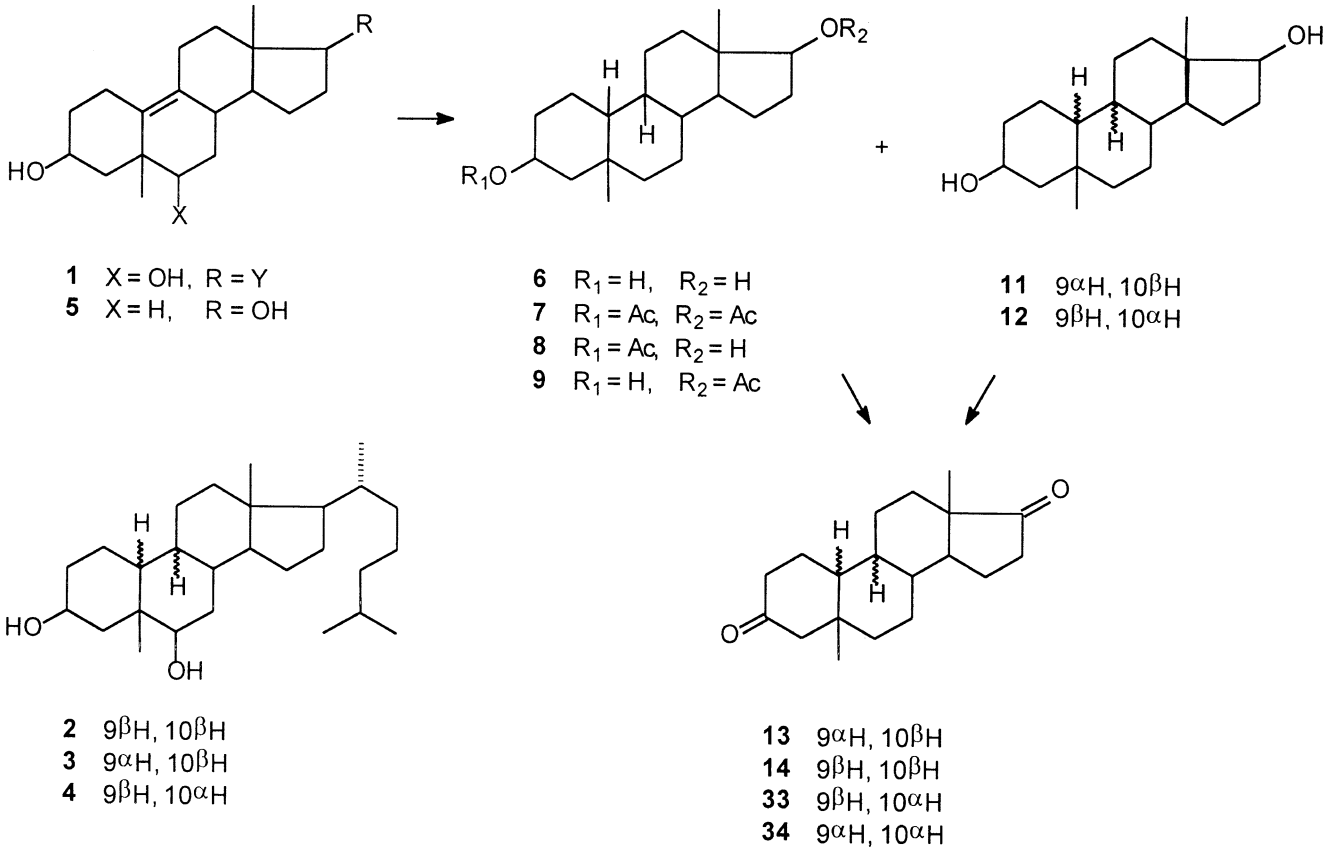


Scheme 1.

ative TLC (PLC) was carried out on 200 × 200 mm plates coated with a 0.6 mm thick layer of the same material.

HPLC separations were performed on a Spectra-Physics chromatograph consisting of a SP8800 ternary pump, a SP8450 UV/VIs detector, a SP4270 programmable integrator, and a Rheodyne 7125/7161 sampling valve with an electronic integrator start up. A Tessek Separon SGX C18 10 m (4 × 250 mm) column was used for analyses, and a 7 m (8 × 250 mm) column was used for preparation. Samples were prepared in methanol solutions (c = 1 mg/ml for analysis, saturated solution for preparation). The flow rate was 1 ml/min in all cases. Eluents (HPLC grade, J.T. Baker) were degassed by sonication and He degassing. Isocratic chromatography in methanol water (75/25 w/w) was used in all cases. Detection was performed at 294 nm.

Hydrogenation experiments were carried out by stirring a solution of olefin (ca 3 mmol) in a mixture of acetic acid (30 ml) and ethanol (3 ml) at 70°C in a hydrogen atmosphere with Adams catalyst (350–400 mg) for 18 h. Platinum was filtered out and washed with toluene and ethanol, and the filtrate was evaporated in a vacuum. For column chromatography, silica gel 60–12 058 was used. Whenever aqueous solutions of hydrochloric acid, potassium hydrogen carbonate, and potassium carbonate were used, their concentration was always 5%. Prior to evaporation on a rotary evaporator in vacuo (bath temperature 50°C), solutions in organic solvents were dried over anhydrous sodium sulfate. Compounds purified by chromatography are presented according to their increasing polarity.

Unless otherwise stated, the conversion of hydrogenation products into a mixture of diketones for ^{1}H NMR spectroscopy was carried out as follows: Part of the mixture of saturated hydroxy esters (e.g. **35** and **40**) (cca 20 mg) was refluxed in a solution of sodium methoxide in methanol (4.7%, 2 ml) under nitrogen. After 2 h, the solution was concentrated in a vacuum, diluted with brine (10 ml), and the precipitate was extracted into chloroform. After evaporation, the residue was dissolved in acetone (2 ml) and oxidized with Jones reagent at 20°C. After 5 min, the excess of the reagent was reduced with a few drops of methanol, a solution of potassium hydrogen carbonate (10 ml) was added, and the precipitate was extracted with chloroform. The extract was purified by PLC, and the product was analyzed by ^{1}H NMR.

2.1. Hydrogenation of 5-methyl-19-nor-5β-androst-9-ene-3β,17β-diol (5)

Diol [2] (**5**, 900 mg, 3.10 mmol) was hydrogenated as described above. Solvents were evaporated under vacuum, and the residue was treated with methanol (20 ml) and a solution of sodium methoxide in methanol (4.7%, 4 ml, 3.5

mmol) for 30 min. The solution was evaporated under vacuum, and the residue was separated between brine and chloroform. The organic layer was washed with water, dried, and evaporated under vacuum. Chromatography on silica gel (50 g, 10% acetone in petrolether) yielded the following two compounds:

5-methyl-19-nor-5β,9α,10β-androstane-3β,17β-diol (**11**, 260 mg, 29%). Crystallization from acetone-heptane afforded 160 mg (18%) of compound **11**, m.p. 158–161°C; $[\alpha]_D$ +21° (c 1.2); ^{1}H and ^{13}C NMR - Tables 3 and 4. For $C_{19}H_{32}O_2$ (292.4): calculated: 78.03% C, 11.03% H; found: 77.75% C, 10.92% H.

5-methyl-19-nor-5β,9β,10β-androstane-3β,17β-diol (**6**, 550 mg, 61%). Crystallization from acetone afforded 370 mg of compound **6**, m.p. 209–210°C; $[\alpha]_D$−7° (c 1.1); ^{1}H and ^{13}C NMR - Tables 3 and 4. For $C_{19}H_{32}O_2$ (292.4): calculated: 78.03% C, 11.03% H; found: 77.81% C, 11.09% H.

*2.2. Partial acetylation of 5-methyl-19-nor-5β,9β,10β-androstane-3β,17β-diol (**6**)*

A solution of compound **6** (310 mg, 1.1 mmol) in pyridine (1.5 ml), toluene (2.5 ml), and acetic anhydride (0.9 ml, 9.5 mmol) was left standing at ambient temperature for 4 h. The solution was poured onto ice, the precipitate was extracted with ether and washed successively with aqueous hydrochloric acid, water, potassium carbonate solution, and water, and then dried. The residue was separated by PLC (8 plates), and the products were identified by NMR as:

5-Methyl-19-nor-5β,9β,10β-androstane-3β,17β-diacetate (**7**, 158 mg, 40%), m.p. 97–98°C, $[\alpha]_D$–10° (c 1.1); IR spectrum: 1724 (C = O), 1257, 1044, 1024 (C-O); ^{1}H NMR spectrum: 4.65 m (3-H), 4.82 t (*J*∼8.5, 17-H), 2.01 s, 2.03 s (OAc), 1.01 s (5-Me), 0.79 s (13-Me). For $C_{23}H_{36}O_4$ (376.5): calcd: 73.37% C, 9.64% H; found: 72.49% C, 9.77% H.

3β-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstane-17β-yl acetate (**9**, 97 mg, 27%), $[\alpha]_D$−7° (c 1.0); IR spectrum: 3621 and 3466 (OH), 1733 (C = O), 1248, 1034, 1023 (C-O); ^{1}H NMR spectrum: 3.71 m (3-H), 4.64 t (*J*∼8.5, 17-H), 2.04 s (OAc), 1.01 s (5-Me), 0.79 s (13-Me). For $C_{21}H_{34}O_3$ (334.5) calcd: 75.41% C, 10.25% H: found: 75.12% C, 9.98% H.

17β-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstane-3β-yl acetate (**8**, 65 mg, 18%), $[\alpha]_D$−4° (c 1.2); IR, spectrum: 3629 and 3511 (OH), 1736 and 1720 sh (C = O), 1248, 1061, 1044, 1025 (C-O); ^{1}H NMR spectrum: 4.78 m (3-H), 3.66 t (*J*∼8.5, 17-H), 2.01 s (OAc), 1.03 s (5-Me), 0.74 s (13-Me). For $C_{21}H_{34}O_3$ (334.5) calcd: 75.41% C, 10.25% H: found: 75.16% C, 10.31% H; and the *starting diol* **6** (37 mg, 12%).

*2.3. 5-Methyl-19-nor-5β,9α,10β-androstane-3,17β-dione (**13**)*

Diol **11** (99 mg, 0.34 mmol) was oxidized as above. The product (92 mg, 94%) was crystallized from acetone-heptane. M.p. 151–152°C (ref. [4]: 141–143°C); $[\alpha]_D$ +114° (c 1.2); CD: $\Delta\epsilon_{298}$ +3.90; IR spectrum: 1733 and 1407 (a cyclopentanone system), 1705 (a cyclohexanone system); ^{1}H and ^{13}C NMR - Tables 3 and 4. For $C_{19}H_{28}O_2$ (288.4) calculated: 79.12% C, 9.78% H; found: 79.09% C and 9.80% H.

*2.4. 5-Methyl-19-nor-5β,9β,10β-androstane-3,17β-dione (**14**)*

a) Diol **6** (75 mg, 0.26 mmol) was dissolved in acetone (5 ml) and treated with Jones reagent at 0°C while stirring. After 10 min, excess reagent was reduced with methanol, the solution was concentrated under vacuum, and potassium hydrogen carbonate solution was added. The resulting precipitate was extracted with chloroform, and the extract was washed with water and dried. The residue (69 mg, 93%) crystallized from acetone gave dione **14**, m.p. 96–99°C; $[\alpha]_D$ +74° (c 1.1); CD: $\Delta\epsilon_{297}$ +2.78; IR spectrum: 1731 and 1406 (a cyclopentanone system), 1707 (a cyclohexanone system); ^{1}H and ^{13}C NMR - Tables 3 and 4. For $C_{19}H_{28}O_2$ (288.4) calculated: 79.12% C, 9.78% H; found: 79.02% C and 9.71% H.

b) Hydroxy ketone **15** (12 mg, 0.04 mmol) was oxidized as above. The resulting product was purified by PLC, and its IR spectrum was found to be identical with that of the sample prepared above.

*2.5. 3β-Hydroxy-5-methyl-19-nor-5β,9β,10α-androstan-17-one (**17**)*

The mother liquor after crystallization of ketone **16** (289 mg) was subjected to re-chromatography on silica gel (75 g) in ethyl acetate-ligroin (1:10), and the content of individual fractions was checked by ^{1}H NMR spectroscopy. The following compounds were isolated:

3β-Hydroxy-5-methyl-19-nor-5β,9β,10α-androstane-17-one (**17**, 17 mg, 2%), m.p. 161–163°C (acetone-heptane); $[\alpha]_D$ +63° (c 1.1); CD: $\Delta\epsilon_{296}$ +2.71; IR spectrum: 3615 and 3446 (OH), 1731 (C = O), 1407 (CH_2-CO), 1050 (C-OH); ^{1}H and ^{13}C NMR - Tables 3 and 4. EI-MS, m/z (%): 290 (M^+, 100), 272 (19), 257 (16), 246 (40), 231 (20), 228 (16), 219 (16), 215 (15); HR-MS for $C_{19}H_{30}H_2$ required 290.224580, found 290.218700. A 1:1 mixture of compounds **17** and **16** (97 mg, 13%). 3β-Hydroxy-5-methyl-19-nor-5β,9α,10β-androstan-17-one (**16**, 49 mg, 7%), m.p. 192–193°C, identical with the sample prepared above.

*2.6. 3β-Hydroxy-5-methyl-19-nor-5β,9α,10α-androstan-17-one (**18**)*

The mother liquor after crystallization of ketone **16** (a repeated experiment, 80 mg), containing isomers **16**, **17**, and **18** in 52:39:9 ratio (HPLC) were separated on a preparative HPLC column (see Table 2). Transfer from the analytical to the preparative scale brought about a slight

broadening of peaks. In repeated runs, retention times of components varied slightly with an overall difference of less than 5%. Individual fractions were dissolved in chloroform, washed with water, and dried over sodium sulfate. They were identified by ^{1}H NMR spectroscopy as:

3β-Hydroxy-5-methyl-19-nor-5β,9β,10α-androstane-17-one (**17**, 24 mg), 3β-Hydroxy-5-methyl-19-nor-5β,9α,10β-androstane-17-one (**16**, 60 mg), and 3β-Hydroxy-5-methyl-19-nor-5β,9α,10α-androstane-17-one (**18**, 4 mg). M.p. 158–160°C (acetone-heptane); CD: $\Delta\epsilon_{296}$ +3.43; ^{1}H and ^{13}C NMR - Tables 3 and 4. EI-MS, m/z (%): 290 (M^+, 100), 272 (19), 257 (23), 246 (42), 231 (13), 228 (13), 219 (27), 215 (32); HR-MS for $C_{19}H_{30}O_2$ required 290.22458, found 290.22450.

*2.7. Hydrogenation of 5-methyl-17-oxo-19-nor-5β-androst-9-en-3β-yl acetate (**19**)*

Compound **19** ([2], 850 mg, 2.6 mmol) was hydrogenated as above. The residue was dissolved in acetone (5 ml) and treated with Jones reagent as above. The residue was then dissolved in methanol (15 ml) and treated with a solution of sodium methoxide in methanol (4.7%, 5 ml, 4.4 mmol) for 90 min. The solution was concentrated under vacuum, brine (20 ml) was added, and the resulting precipitate was extracted with chloroform. The extract was washed with water, dried, and evaporated under vacuum. Chromatography on silica gel (50 g, 10% acetone in petroleum ether) yielded successively:

3β-Hydroxy-5-methyl-19-nor-5β,9α,10β-androstan-17-one (**16**, 291 mg, 39%). Crystallization from acetone-heptane afforded 109 mg (15%) of compound **16**, m.p. 192–193°C (ref. [7]: 192–194°C); $[\alpha]_D$ +104° (c 1.0); CD: $\Delta\epsilon_{296}$ +2.51; IR spectrum: 3614 (OH), 1732 (C = O), 1406 (cyclopentanone), 999 (C-OH); ^{1}H and ^{13}C NMR - Tables 3 and 4. EI-MS, m/z (%): 290 (M^+, 100), 272 (24) 257 (28), 246 (40), 231 (11), 228 (7), 219 (37), 215 (16). For $C_{19}H_{30}O_2$ (292.4): calculated: 78.57% C, 10.41% H; found: 78.53% C, 10.43% H.

3β-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-17-one (**15**, 453 mg, 61%). Crystallization from acetone-heptane afforded 320 mg (30%) of compound **15**, m.p. 114–116°C; $[\alpha]_D$ +66° (c 1.0); CD: $\Delta\epsilon_{297}$ +1.89; IR spectrum: 3606 (OH), 1730 (C = O), 1406 (cyclopentanone), 1065, 1034, 1014 (C-OH); ^{1}H and ^{13}C NMR - Tables 3 and 4. EI-MS, m/z (%): 290 (M^+, 26), 272 (100), 257 (41), 246 (17), 231 (26), 228 (15), 219 (24), 215 (32). For $C_{19}H_{30}O_2$ (292.4): calculated: 78.57% C, 10.41% H; found: 78.50% C, 10.45% H.

*2.8. 5-Methyl-17-oxo-19-nor-5β,9α,10β-androstan-3β-yl acetate (**20**)*

Hydroxy compound **16** (100 mg, 0.34 mmol) was treated with acetic anhydride (0.2 ml, 2.1 mmol) in pyridine (0.2 ml) at laboratory temperature for 20 h. The mixture was worked up as above (see the preparation of compound **9**). After evaporation, compound **20** crystallized from acetone-heptane. M.p. 161–162°C (72 mg, 63%; ref [7] gives 163–164°C); $[\alpha]_D$ +98° (c 1.2); IR spectrum: 1729 (C = O), 1272, 1258, 1247 (C-O), 1406 (cyclopentanone); ^{1}H NMR spectrum: 5.09 m (3-H), 2.05 s (OAc), 1.13 s (5-Me), 0.88 s (13-Me). For $C_{21}H_{32}O_3$ (332.5): calculated: 75.86% C, 9.70% H; found: 75.74% C, 9.76% H.

*2.9. 5,17-Dimethyl-19-nor-5β,9β,10β-androstane-3β,17β-diol (**21**)*

A solution of methyl magnesium iodide was prepared from magnesium turnings (1.5 g, 61.7 mmol) and methyl iodide (4.7 ml, 75.4 mmol) in ether (16 ml). A solution of ketone **15** (718 mg, 2.47 mmol) in benzene (50 ml) was added, and the ether was distilled off. The reaction mixture was refluxed for 4 h. The mixture was poured onto ice (70 ml) acidified with hydrochloric acid (7 ml, 84.0 mmol). The precipitate was extracted with chloroform, and the extract was successively washed with an aqueous sodium thiosulfate solution (5%), potassium hydrogen carbonate solution, and water. After evaporation, the product was applied onto a column of silica gel. Benzene-ethyl acetate (10:1) eluted the starting ketone **15** (72 mg, 10%) and diol **21** (523 mg, 69%). M.p. 157–158°C (acetone-heptane); $[\alpha]_D$ –29° (c 1.3); IR spectrum: 3609, 3448 (OH), 1087, 1029, 1013, 940, 932 (C-O); ^{1}H NMR spectrum: 3.73 m (3-H), 1.23 s (17-Me), 1.02 s (5-Me), 0.86 s (13-Me). For $C_{20}H_{34}O_2$ (306.5) calculated: 78.38% C, 11.18% H; found: 78.12% C, 11.36% H.

*2.10. 5,17-Dimethyl-19-nor-5β,9α,10β-androstane-3β,17β-diol (**22**)*

Analogously, ketone **16** (133 mg, 0.46 mmol) was treated with methyl magnesium iodide. PLC (3 plates, benzene-ether, 1:1) afforded the starting ketone **16** (4 mg, 3%) and diol **22** (99 mg, 71%); $[\alpha]_D$ –4° (c 1.1); IR spectrum: 3615, 3462 (OH), 1092, 1000, 946, 931 (C-O); ^{1}H NMR spectrum: 4.16 m (3-H), 1.21 s (17-Me), 1.20 s (5-Me), 0.85 s (13-Me). For $C_{20}H_{34}O_2 \cdot H_2O$ (324.5) calculated: 74.03% C, 11.18% H; found: 74.18% C, 11.07% H.

*2.11. 17β-Hydroxy-5,17-dimethyl-19-nor-5β,9β,10β-androstan-3-one (**23**)*

Diol **21** (380 mg, 1.37 mmol) was oxidized with Jones reagent as in the preparation of compound **14**. The product (380 mg) was purified by PLC (6 plates, benzene-ether 1:1). Ketone **23** (336 mg, 89%) crystallized from acetone-heptane. M.p. 136°C; $[\alpha]_D$ –24° (c 1.2); IR spectrum: 3613, 3477 (OH), 1707 (C = O), 1092, 944, 932 (C-O); ^{1}H NMR spectrum: 1.20 (17-Me), 1.10 s (5-Me), 0.87 s (13-Me). For $C_{20}H_{34}O_2$ (306.5) calculated: 78.38% C, 11.18% H; found: 78.58% C, 11.20% H.

*2.12. 17β-Hydroxy-5,17-dimethyl-19-nor-5β,9α,10β-androstan-3-one (**24**)*

Analogously, diol **22** (114 mg, 0.37 mmol) was oxidized, and the product (114 mg) was purified by PLC. Ketone **23** (92 mg, 81%) crystallized from acetone-heptane. M.p. 156–157°C; $[\alpha]_D$ −6° (c 1.1); IR spectrum: 3612, 3480 (OH), 1704 (C = O), 1093, 946, 932 (C-O); ^{1}H NMR spectrum: 1.24 s (17-Me), 0.95 s (5-Me), 0.89 s (13-Me). For $C_{20}H_{34}O_2$ (306.5) calculated: 78.38% C, 11.18% H; found: 78.29% C, 11.06% H.

*2.13. Reduction of 5-methyl-19-nor-3-oxo-5β-androst-9-en-17β-yl benzoate (**25**)*

While stirring, sodium borohydride (400 mg, 10.6 mmol) was added to a cool (0°C) solution of compound **25** (ref. [2], 2.2 g, 5.1 mmol) in a mixture of ethanol (25 ml), dichloromethane (8 ml), and ethyl acetate (8 ml). After 1 h, the mixture was poured onto a solution of acetic acid (1 ml, 17.5 mmol) in brine (200 ml). The precipitate was filtered off, dissolved in chloroform, washed with water, and dried. The chloroform solution was evaporated under vacuum, and the residue was applied onto a column of silica gel (100 g). Ethyl acetate-toluene (3:97) eluted successively:

3β-Hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl benzoate (**27**, 1.15 g, 52%). M.p. 137–139°C (methanol); $[\alpha]_D$+142° (c 1.0); IR spectrum: 3613 (OH), 1711 (C = O), 1281, 966 (C-O), 1602, 1451 (arom.), 1039, 1016, 995 (C-OH); ^{1}H NMR spectrum: 8.00 m, 7.54 m and 7.43 m (OBz), 4.87 t (*J*∼8.5, 17-H), 4.14 m (3-H), 1.23 s (5-Me), 1.06 s (13-Me). For $C_{26}H_{34}O_3$ (394.6) calculated: 79.15% C, 8.69% H; found: 79.03% C, 8.74% H.

3α-Hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl benzoate (**29**, 1.01 g, 46%); $[\alpha]_D$ +220° (c 1.0); IR spectrum: 3619 (OH), 1720 (C = O), 1603, 1451 (arom.), 1247, 968 (C-O), 1042, 1018, 996 (C-OH); ^{1}H NMR spectrum: 8.00 m, 7.54 m and 7.43 m (OBz), 4.87 t (*J*∼8.5, 17-H), 4.01 m (3-H), 1.06 s (5-Me), 1.06 s (13-Me). For $C_{26}H_{34}O_3$ (394.6) calcd: 79.15% C, 8.69% H; found: 78.89% C, 8.54% H.

*2.14. Reduction of 5-methyl-19-nor-3-oxo-5β-androst-9-en-17β-yl acetate (**26**)*

Ketone **26** (700 mg, 2.12 mmol) was reduced as above, and chromatography on silica gel (50 ml) in benzene-ether (20:1) yielded successively:

3β-Hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl acetate (28, 388 mg, 55%), m.p. 146–148°C, identical with an authentic sample [2].

3α-Hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl acetate (**30**, 290 mg, 41%). M.p. 125–126°C (acetone-heptane); $[\alpha]_D$ +81° (c 1.0); IR spectrum: 3607, 1027, 1048 (OH), 1723, 1258, 1036 (AcO); ^{1}H NMR spectrum: 4.60 t (*J*∼8.5, 17-H), 4.00 m (3-H), 2.05 s (OAc); 1.05 s (5-Me), 0.91 s (13-Me). For $C_{21}H_{32}O_3$ (332.5) calcd: 75.86% C, 9.70% H; found: 75.62% C, 9.76% H.

*2.15. Hydrogenation of 3β-hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl benzoate (**27**)*

Compound **27** (678 mg, 1.7 mmol) was hydrogenated as above. Chromatography of the product on silica gel (150 g, 2%-ethyl acetate in toluene) yielded successively:

A mixture of 3β-hydroxy-5-methyl-19-nor-5β,9α,10β-androstan-17β-yl cyclohexanecarboxylate (**35**) and 3β-hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-17β-yl cyclohexanecarboxylate (**37**, 310 mg, 44%). On repeated crystallization from acetone-heptane, the mixture yielded compound **35** (106 mg, 15%); m.p. 121–123°C; $[\alpha]_D$ +28° (c 0.8); IR spectrum: 3615 (OH), 1718 (C = O), 1249, 1196, 1176 (C-O), 1003 (C-OH); ^{1}H NMR spectrum: 4.60 t (*J*∼8.5, 17-H), 4.16 m (3-H), 1.20 s (5-Me), 0.79 s (13-Me). For $C_{26}H_{42}O_3$ (402.6) calcd: 77.56% C, 10.51% H; found: 77.49% C, 10.52% H.

3β-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-17β-yl cyclohexanecarboxylate (**37**) (366 mg, 53%), $[\alpha]_D$ +8° (c 1.1); IR spectrum (CCl_4): 3620 (OH), 1729 (C = O), 1171, 1033 (C-O). ^{1}H NMR spectrum: 4.64 t (*J*∼8.5, 17-H), 3.72 m (3-H), 1.01 s (5-Me), 0.80 s (13-Me). EI-MS, m/z (%): 384 (27), 274 (53), 256 (100), 241 (36), 215 (26); HR-MS (FAB) for $C_{26}H_{43}O_3$ required 403.321221, found 403.315500. For $C_{26}H_{42}O_3$ (402.6) calculated: 77.56% C, 10.51% H; found: 77.28% C, 10.36% H.

*2.16. Hydrogenation of 3β-hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl acetate (**28**)*

Compound **28** (380 mg, 1.14 mmol) was hydrogenated as above, and chromatography on a column of silica gel (30 g, toluene-ether 3:1) yielded:

A mixture of compounds **38** and **39** (114 mg, 33%); ^{1}H NMR spectra compound **38**: 4.60 t (*J*∼8.5, 17-H), 4.16 m (3-H), 2.04 s (OAc), 1.03 s (5-Me), 0.79 s (13-Me); compound **39**: 4.64 t (*J*∼8.5, 17-H), 4.11 m (3-H), 2.04 s (OAc), 1.09 s (5-Me), 0.81 s (13-Me).

3β-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-17β-yl acetate (9, 186 mg, 53%), identical with the sample prepared above.

*2.17. Hydrogenation of 3α-hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl benzoate (**29**)*

a) With a low amount of catalyst: Compound **29** (103 mg, 0.26 mmol) was hydrogenated as above, using 15 mg of Adams catalyst. ^{1}H NMR spectrum of the crude product indicated the presence of olefins (C = C-H signal around δ 5.44).

b) Under standard conditions (see Experimental): Compound **29** (196 mg, 0.50 mmol) was hydrogenated as above using 200 mg of Adams catalyst in ethanol (2 ml) and acetic

acid (10 ml). The product was applied onto 5 PLC plates that were developed with benzene-ether (5:1). The following compounds were isolated:

3α-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-17β-yl cyclohexanecarboxylate (**42**) (10 mg, 5%), m.p. 136–138°C (acetone-heptane); $[\alpha]_D$ +2° (c 0.9); IR spectrum (CCl_4): 3619 (OH), 1730 (C = O), 1171, 1041 (C-O). ^{1}H NMR spectrum: 4.68 t (*J*~8.5, 17-H), 4.08 m (3-H), 0.97 s (5-Me), 0.82 s (13-Me). EI-MS, m/z (%): 384 (64), 369 (14), 274 (31), 256 (100), 241 (28), 215 (28); HR-MS (FAB): for $C_{26}H_{43}O_3$ required 403.321221, found 403.315100.

A mixture of 3α-hydroxy-5-methyl-19-nor-5β,9α,10β-androstan-17β-yl cyclohexanecarboxylate (**40**) and 3α-hydroxy-5-methyl-19-nor-5β,9β,10α-androstan-17β-yl cyclohexanecarboxylate (**41**, 168 mg, 84%); $[\alpha]_D$ +24° (c 0.9); ^{1}H NMR spectra, compound **40**: 4.62 t (*J*~8.5, 17-H), 3.91 m (3-H), 0.99 s (5-Me), 0.80 s (13-Me) and compound **41**: 4.71 t (*J*~8.5, 17-H), 3.85 m (3-H), 0.86 s (5-Me), 0.82 s (13-Me).

*2.18. Hydrogenation of 3α-hydroxy-5-methyl-19-nor-5β-androst-9-en-17β-yl acetate (**30**)*

Compound **30** (80 mg, 0.24 mmol) was hydrogenated as above, PLC (4 plates, benzene-ether 4:1) yielded the following fractions:

3α-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-17β-yl acetate (**45**, 6 mg, 7%), oil; ^{1}H NMR spectrum: 4.68 t (J~8.5, 17-H), 4.06 m (3-H), 0.96 s (5-Me), 0.80 s (13-Me).

3α-Hydroxy-5-methyl-19-nor-5β,9α,10β-androstan-17β-yl acetate (**43**, 59 mg, 70%), m.p. 160–161°C (acetone-heptane); $[\alpha]_D$ +30° (c 0.7); IR spectrum: 3606 (OH), 1724 (C = O), 1259, 1045 (C-O), 1025 (C-OH); ^{1}H NMR spectrum: 4.60 t (*J*~8.5, 17-H), 3.90 m (3-H), 2.03 s (OAc), 0.97 s (5-Me), 0.78 s (13-Me). For $C_{21}H_{34}O_3$ (334.5) calcd: 75.41% C, 10.25% H; found: 75.26% C, 10.22% H.

3α-Hydroxy-5-methyl-19-nor-5β,9β,10α-androstan-17β-yl acetate (**44**, 19 mg, 23%), oil; ^{1}H NMR spectrum: 4.71 t (*J*~8.5, 17-H), 2.04 s (OAc), 3.83 m (3-H), 0.85 s (5-Me), 0.81 s (13-Me).

*2.19. 5-Methyl-19-nor-5β-androst-9-ene-3β,17β-diyl 3-pivalate 17-acetate (**31**)*

Trimethylacetylchloride (1.5 ml, 12.18 mmol) was added to a solution of compound **28** (900 mg, 2.69 mmol) in pyridine (3 ml) at 0°C. The solution was left aside for 8 h at 20°C and then poured onto ice. The resulting precipitate was extracted into chloroform and washed successively with a solution of hydrochloric acid, water, potassium hydrogen carbonate solution, and water. The product crystallized from ethanol, m.p. 111–113°C (838 mg, 74%); $[\alpha]_D$ +69° (c 1.2); ^{1}H NMR spectrum: 5.06 m (3-H), 4.60 t (*J*~8.5, 17-H), 1.22 s (Piv); 1.21 s (5-Me), 0.91 s (13-Me). For $C_{26}H_{40}O_4$ (416.6) calcd: 74.96% C, 9.68% H; found: 74.96% C, 9.60% H.

*2.20. 5-Methyl-19-nor-5β-androst-9-ene-3α,17β-diyl 3-pivalate 17-acetate (**32**)*

Compound **30** (260 mg, 0.78 mmol) was treated with trimethylacetylchloride in pyridine as in the preceding experiment. The product was purified by PLC (9 plates, benzene-ether 20:1). Yield: 297 mg (91%); $[\alpha]_D$ +69° (c 0.9); IR spectrum: 1716 (C = O), 1398, 1365, 1172 (t-butyl), 1388, 1373 (methyl), 1288, 1258, 1030 (C-O); ^{1}H NMR spectrum: 5.07 (3-H), 4.61 m t (*J*~8.5, 17-H), 2.04 s (OAc), 1.17 s (Piv), 1.09 s (5-Me), 0.91 s (13-Me). For $C_{26}H_{40}O_4$ (416.6) calcd: 74.96% C, 9.68% H; found: 74.56% C, 9.46% H.

*2.21. Hydrogenation of 5-methyl-19-nor-5β-androst-9-ene-3β,17β-diyl 3-pivalate 17-acetate (**31**)*

Compound **31** (502 mg, 1.20 mmol) was hydrogenated as above, and PLC plates (11) were developed with benzene-ether (20:1). The following compounds were isolated: 5-Methyl-19-nor-5β,9β,10β-androstane-3β,17β-diyl 3-pivalate 17-acetate (**10**) (259 mg, 51%), m.p. 118–119°C (CH_3OH); $[\alpha]_D$ –5° (c 0.9); IR spectrum: 1716, 1725 (C = O), 1287, 1257 (C-O), 1374 (CH_3 in CH_3COO), 1178, 1160 (CH_3 in $(CH_3)_3COO$); ^{1}H NMR spectrum: 4.77 m (3-H), 4.65 t (*J*~8.5, 17-H), 2.03 s (OAc), 1.17 s (Piv), 1.01 s (5-Me), 0.79 s (13-Me). For $C_{26}H_{42}O_4$ (418.6) calcd: 74.60% C, 10.11% H; found: 74.80% C, 10.28% H.

A mixture of 5-methyl-19-nor-5β,9α,10β-androstane-3β,17β-diyl 3-pivalate 17-acetate (**46**) and 5-methyl-19-nor-5β,9β,10α-androstane-3β,17β-diyl 3-pivalate 17-acetate (**47**) (199 mg, 39%). ^{1}H NMR spectra, compound **46**: 5.08 m (3-H), 4.60 dd t (*J*~8.5, 17-H), 2.04 s (OAc), 1.19 s (Piv), 1.14 s (5-Me), 0.79 s (13-Me); compound **47**: 5.04 m (3-H), 4.71 t (*J*~8.5, 17-H), 2.04 s (OAc), 1.19 s (Piv), 1.02 s (5-Me), 0.81 s (13-Me).

*2.22. Hydrogenation of 5-methyl-19-nor-5β-androst-9-ene-3α,17β-diyl 3-pivalate 17-acetate (**32**)*

Compound **32** (270 mg, 0.65 mmol) was hydrogenated as above, and the product was applied onto 8 PLC plates, which were developed with benzene-ether (20:1). The following compounds were isolated:

A mixture of 5-methyl-19-nor-5β,9α,10β-androstane-3,17β-diyl 3α-pivalate 17-acetate (**48**) and 5-methyl-19-nor-5β,9β,10α-androstane-3α,17β-diyl 3-pivalate 17-acetate (**49**) (175 mg, 65%); ^{1}H NMR spectra, compound **48**: 4.92 m (3-H), 4.61 t (*J*~8.5, 17-H), 2.04 s (OAc), 1.18 s (Piv), 1.03 s (5-Me), 0.78 s (13-Me) and compound **49**: 4.97 m (3-H), 4.70 t (*J*~8.5, 17-H), 2.04 s (OAc), 0.90 s (5-Me), 0.80 s (13-Me).

5-Methyl-19-nor-5β,9β,10β-androstane-3α,17β-diyl 3-pivalate 17-acetate (**50**) (67 mg, 25%), m.p. 99–100°C (acetone-heptane); $[\alpha]_D$–1° (c 1.2); IR spectrum: 1716 (C = O), 1374 (CH_3 in CH_3COO), 1288, 1257 (C-O), 1173, 1155

(CH_3 in $(CH_3)_3COO$); ^1H NMR spectrum: 4.96 m (3-H), 4.66 t (J~8.5, 17-H), 2.05 s (Ac), 1.21 s (Piv), 0.98 s (5-Me), 0.81 s (13-Me). For $C_{26}H_{42}O_4$ (418.6) calcd: 74.60% C, 10.11% H; found: 74.22% C, 10.19% H.

*2.23. 5-Methyl-19-nor-5β,9β,10α-androstane-3,17β-dione (**33**)*

Compound **17** (9 mg, 0.03 mmol) was oxidized as above, and the resulting product was purified by PLC (40 × 200 × 0.7 mm) and crystallized from heptane. M.p. 133–134°C (6 mg, 67%); $[\alpha]_D$ +24° (c 0.6); IR spectrum: 1741, 1720 (C = O); CD: $\Delta\epsilon_{304}$ +1.01; EI-MS, m/z (%): 288 (M^+, 100), 273 (6), 270 (17), 255 (14), 244 (44), 229 (26), 217 (23); HR-MS for $C_{19}H_{28}O_2$ required 288.208930, found 288.206800; ^1H and ^{13}C NMR - Tables 3 and 4.

*2.24. 5-Methyl-19-nor-5β,9α,10α-androstane-3,17β-dione (**34**)*

Compound **18** (4 mg, 0.014 mmol) was oxidized as above, and the resulting product was purified by PLC (40 × 200 × 0.7 mm) and crystallized from heptane. M.p. 127–129°C (3 mg, 74%); $[\alpha]_D$ +54° (c 0.2); CD: $\Delta\epsilon_{302}$ +1.19; IR spectrum: 1742, 1721 (C = O); EI-MS, m/z (%): 288 (M^+, 100), 275 (8), 273 (8), 255 (10), 244 (58), 229 (22), 217 (30), 199 (11); HR-MS for $C_{19}H_{28}O_2$ required 288.208930, found 288.201200; ^1H and ^{13}C NMR - Tables 3 and 4.

*2.25. 17β-Hydroxy-5-methyl-19-nor-5β,9α,10β-androstan-3-one (**51**)*

A solution of sodium methoxide in methanol (4.7%, 1 ml, 0.87 mmol) was added to a solution of oxo ester **54** (40 mg, 0.1 mmol) in the same solvent (2 ml). The mixture was refluxed under a nitrogen atmosphere. After 3 h, the solution was concentrated under vacuum, and the product was precipitated by addition of brine (5 ml), filtered off, and purified by PLC (2 plates, benzene-ether, 1:1). Compound **51** (24 mg, 83%) crystallized from acetone-heptane, m.p. 159–160°C; $[\alpha]_D$ +37° (c 1.1); IR spectrum: 3614 (OH), 1705 (C = O), 1069, 1053 (C-OH); ^1H NMR spectrum: 3.65 m (3-H), 0.95 s (5-Me), 0.78 s (13-Me). For $C_{19}H_{30}O_2$ (290.4) calcd: 78.57% C, 10.41% H; found: 78.51% C, 10.39% H.

*2.26. 17β-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-3-one (**52**)*

A solution of 17β-ester **55** (490 mg, 1.22 mmol) was dissolved in methanol (5 ml) and treated with sodium methoxide in methanol (4 ml, 4.7%, 3.5 mmol) at 70°C under nitrogen. After 4 h, the solvent was evaporated under vacuum. The residue was diluted with brine, and the resulting precipitate was dissolved in chloroform, washed with water, and dried. The product was purified by PLC (4 plates, ether-toluene 1:3). Yield 323 mg (91%). Crystallization of the residue from acetone afforded 313 mg (88%) of compound **52**, m.p. 166–167°C; $[\alpha]_D$ +6° (c 1.3); CD: $\Delta\epsilon_{288}$ -0.3; IR spectrum: 3613, 3457 (OH), 1705 (C = O), 1059 (C-O) $cm^{-1;}$ ^1H NMR spectrum: 3.64 t (J~8.5, 17-H), 1.10 s (5-Me), 0.76 s (10-Me). For $C_{19}H_{30}O_2$ (290.4) calcd.: 78.57% C, 10.41% H; found: 78.74% C, 10.65% H.

*2.27. 17β-Hydroxy-5-methyl-19-nor-5β,9β,10β-androstan-3β-yl pivalate (**53**)*

A solution of sodium methoxide in methanol (4.7%, 1 ml, 0.87 mmol) was added to a solution of acetate **10** (150 mg, 0.36 mmol) in ethanol (2 ml). After 2 h, brine (5 ml) was added to the mixture, and the precipitate formed was filtered out, washed with water, and dissolved in chloroform. The chloroform solution was washed with water and dried. After evaporation, the residue crystallized from acetone. M.p. 182–183°C (103 mg, 76%); $[\alpha]_D$ –7° (c 1.1); IR spectrum: 3614, 3491, 1061 (OH), 1714, 1398, 1288, 1178, 1160 (OPiv); ^1H NMR spectrum: 4.80 m (3-H), 3.69 t (J~8.5, 17-H), 1.19 s (Piv), 1.04 s (5-Me), 0.77 s (13-Me). For $C_{24}H_{40}O_3$ (376.6) calculated: 76.55% C, 10.71% H; found: 76.51% C, 10.68% H.

*2.28. 3-Oxo-5-methyl-19-nor-5β,9α,10β-androstan-17β-yl cyclohexanecarboxylate (**54**)*

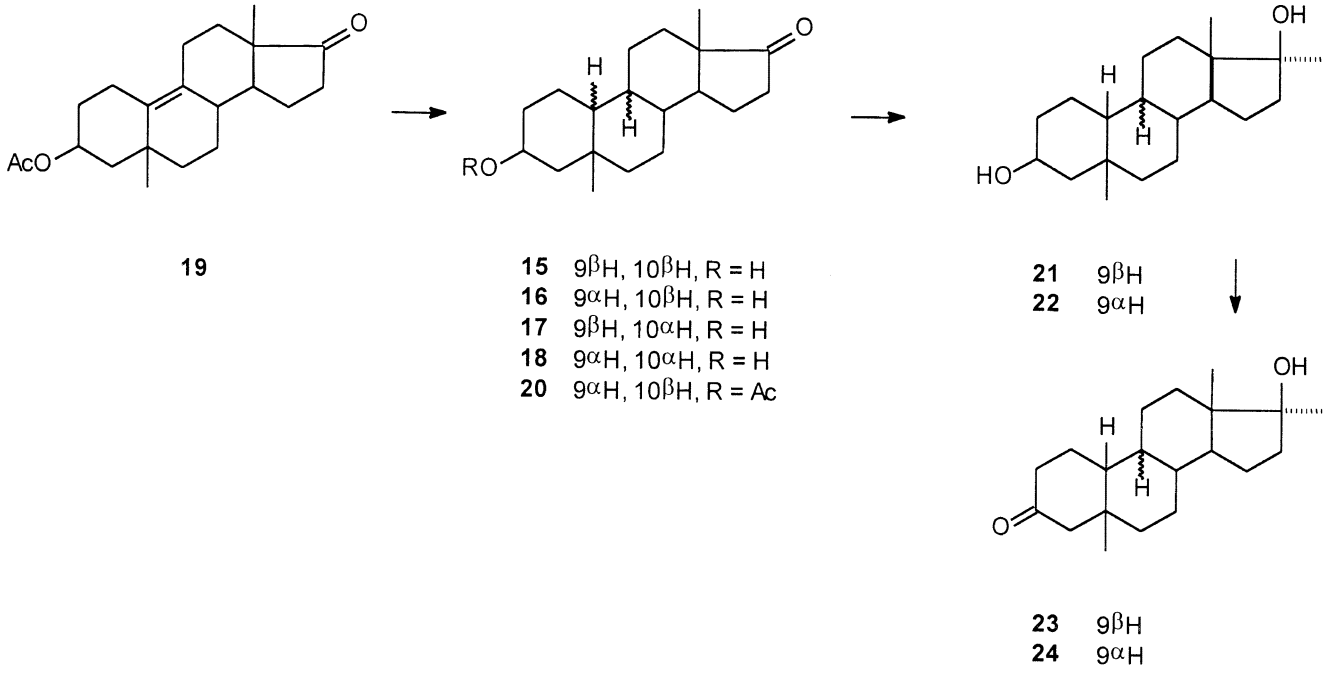
The above mixture of hydroxy esters **40** and **35** (117 mg, 0.29 mmol) was oxidized with Jones reagent as above (see the preparation of **14**). Product **54** was purified by PLC (2 plates, benzene-ether, 9:1) and crystallized from acetone-heptane. M.p. 124–126°C (48 mg, 41%); $[\alpha]_D$ +32° (c 1.1); ^1H NMR spectrum: 4.62 (3-H), 0.95 s (5-Me), 0.83 s (13-Me). For $C_{26}H_{40}O_3$ (400.6) calcd: 77.95% C, 10.06% H; found: 77.90% C, 10.11% H.

*2.29. 5-Methyl-19-nor-3-oxo-5β,9β,10β-androstan-17β-yl cyclohexanecarboxylate (**55**)*

Hydroxy compound **37** (280 mg, 0.70 mmol) was dissolved in acetone (4 ml) and treated with Jones reagent at 0°C. After 10 min, the mixture was worked up as above. The product **55** (254 mg, 91%) did not crystallize from common solvents. $[\alpha]_D$ +7° (c 0.9); IR spectrum (CCl_4): 1727 (C = O), 1170 (C-O); ^1H NMR spectrum: 4.63 t (J~8.5, 17-H), 1.09 s (5-Me), 0.81 s (13-Me). For $C_{26}H_{40}O_3$ (400.6) calcd: 77.95% C, 10.06% H; found: 77.57% C, 10.26% H.

*2.30. 3-Oxo-5-methyl-19-nor-5β,9,10β-androstan-17β-yl acetate (**56**)*

Compound **43** (30 mg, 0.09 mmol) was oxidized in acetone with Jones reagent at 20°C. After 10 min, the reaction was worked up as above, and the crude product was



Scheme 2.

purified by TLC (1 plate, benzene-ether 3:1). Ketone **56** (24 mg, 80%) crystallized from acetone-heptane. M.p. 163–164°C; $[\alpha]_D$ +26° (c 0.9); IR spectrum: 1736, 1246, 1046 (AcO), 1714 (C = O); ^{1}H NMR spectrum: 4.62 t (J~8.5, 17-H), 2.05 s (OAc), 0.95 s (5-Me), 0.83 s (13-Me). For $C_{21}H_{32}O_3$ (332.5) calcd: 75.86% C, 9.70% H; found: 75.82% C, 9.66% H.

3. Results and discussion

3.1. Synthesis of compounds

Hydrogenation of Δ^9-steroids had to be carried out in the presence of a large amount of catalyst (ca 0.5 equivalent); when a 'catalytic' amount (e.g. 0.1 equivalent and less) was used, starting material was recovered together with another olefinic derivative (a doublet of C = CH at δ 5.44, J = 1.8 Hz in ^{1}H NMR).

Hydrogenation of 5-methyl-19-nor-5β-androst-9-en-3β,17β-diol (**5**) yielded two major products. The polar product could easily be identified as the 9β,10β-isomer **6** by ^{1}H NMR spectroscopy because the 9β,10β-adduct was the only isomer with a 3β-hydroxyl in an equatorial configuration (clean separation of C*H*OR signals was achieved by conversion to ester **7**, see Experimental). Crystallization of the lipophilic product yielded a 9α,10β-dihydro diol **11** as proved by oxidation to a known [4] dione **13**, while diol **6** was oxidized to another dione **14**. According to the presence of angular methyl group signals in the ^{1}H NMR spectra of the mother liquor of compound **11**, yet another isomer (probably **12**) was present in the mixture; it could not be isolated in a pure state.

Slightly better separation of hydrogenation products was achieved with corresponding 17-oxo derivatives **15**, **17**, **16**, and **18** (Scheme 2). They were prepared by hydrogenation of 5-methyl-19-nor-3-oxo-5β-androst-9-en-3β-yl acetate [2] (**19**), followed by re-oxidation of the 17-alcohols formed, and hydrolysis of acetates. For structural assignment, the hydroxy ketones **15** and **16** were oxidized to diketones; the former product afforded the above diketone **14**, and the latter gave a diketone with properties described [4] for compound **13**. Properties of compounds **16**, **20**, and **13** were in agreement with compounds [4] prepared from steroids with known configuration in positions 8, 9, and 10. Another hydroxy ketone **17** could be partly isolated by repeated chromatography of a mixture of compounds **16** and **17**. Only HPLC and ^{1}H NMR spectra of their mother liquor showed evidence of the presence of yet another isomer **18**. Eventually, all three isomers with an axial hydroxyl in position 3β (**16**, **17**, and **18**) were separated by preparative HPLC and identified (see Table 1). Their structures were established by detailed NMR analysis (see the next paragraph). Hydroxy ketones **15** and **16** were converted to analogues of 'methyltestosterone' on reaction with methyl magnesium iodide, and they afforded homologous diols **21** and **22**, which were oxidized to target compounds **23** and **24**, respectively.

In an attempt to avoid the complex hydrogenation mixture, we examined a possible directing effect of substituents on the hydrogenation course. Esters [2] **25** and **26** (Scheme 3) were reduced by sodium borohydride to afford their

Table 1
HPLC separation of ketones **15–18**

Compound	Retention time[a]	
	Analytical column[b]	Preparative column[c]
15	8.2	26.6
16	10.7	29.9
17	9.8	27.5
18	11.4	31.8

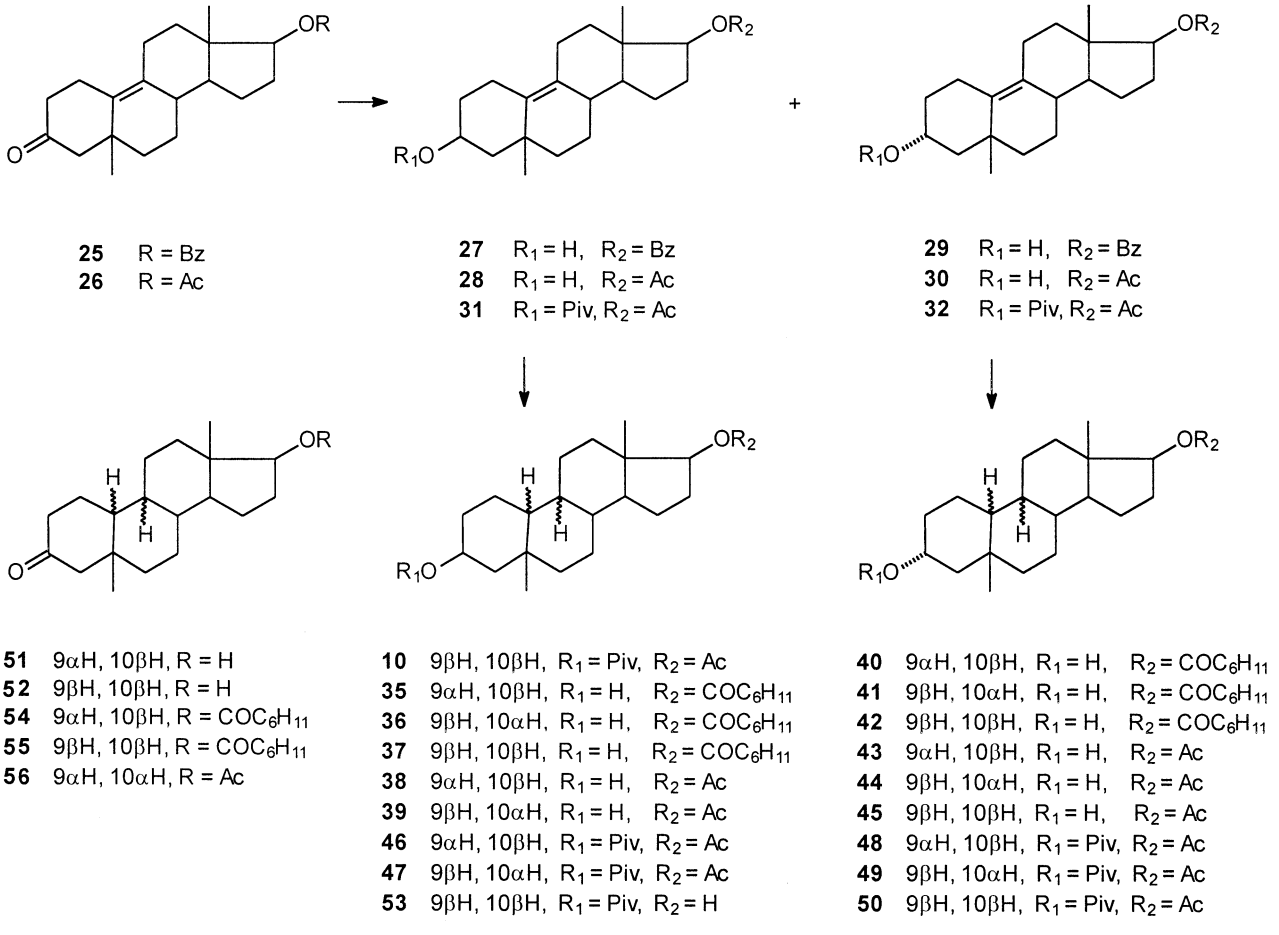
[a] Isocratic chromatography (CH_3OH + H_2O 75:25) was used, and detection was performed at 294 nm.
[b] Separon SGX C 18 (4 × 250 mm, 10 m).
[c] Separon SGX C 18 (8 × 250 mm, 7 m).

corresponding 3β-alcohols (**27**, **28**) and 3α-alcohols (**29**, **30**), respectively. A large group was then introduced to positions 3β and 3α by acylation with pivaloyl chloride (compounds **31** and **32**). After hydrogenation, chromatography on silica gel was used to separate 9β,10β-products from the other three isomers with identical chromatographic properties. The composition of the mixtures was recognized from ^{1}H NMR spectra of the mixtures and of diketones **13**, **33,** and **34** obtained by hydrolysis and oxidation. The results, summarized in Table 2, suggest that 9β,10β-dihydro derivatives constitute the major products in all substrates with an oxygen group in position 3β (i.e. in compounds **27**, **28**, **31**, and **19**), while 9α,10β-dihydro products prevail in hydrogenation of free 3α-hydroxy derivatives (**29** and **30**).

The results were used for the preparation of some analogues of testosterone and methyltestosterone using the conventional combination of ester hydrolysis, Grignard reaction, and oxidation. The 9β,10β-products were easily obtained by chromatography. The 9α,10β-products were obtained by chromatography and repeated crystallization, which sometimes was not sufficient to rid the main product of its isomers. The biologic activity of analogues **52**, **51**, **23**, and **24** will be reported elsewhere.

3.2. Configuration and conformation of 9,10-isomers

The configuration and conformation of the 9,10-isomers were studied in detail on three series of compounds: 3β,17β-diols **6**, **11**, 3β-hydroxy-17-oxo derivatives **15** –**18**, and 3,17-diketones **13**, **14**, **33**, **34** by NMR spectroscopy. The typical NMR parameters used in the solution of stereochemical problems are vicinal coupling constants related to torsion angles and NOE as a function of interatomic distances. The necessary condition for successful applica-



25 R = Bz
26 R = Ac

27 R_1 = H, R_2 = Bz
28 R_1 = H, R_2 = Ac
31 R_1 = Piv, R_2 = Ac

29 R_1 = H, R_2 = Bz
30 R_1 = H, R_2 = Ac
32 R_1 = Piv, R_2 = Ac

51 9αH, 10βH, R = H
52 9βH, 10βH, R = H
54 9αH, 10βH, R = COC_6H_{11}
55 9βH, 10βH, R = COC_6H_{11}
56 9αH, 10αH, R = Ac

10 9βH, 10βH, R_1 = Piv, R_2 = Ac
35 9αH, 10βH, R_1 = H, R_2 = COC_6H_{11}
36 9βH, 10αH, R_1 = H, R_2 = COC_6H_{11}
37 9βH, 10βH, R_1 = H, R_2 = COC_6H_{11}
38 9αH, 10βH, R_1 = H, R_2 = Ac
39 9βH, 10αH, R_1 = H, R_2 = Ac
46 9αH, 10βH, R_1 = Piv, R_2 = Ac
47 9βH, 10αH, R_1 = Piv, R_2 = Ac
53 9βH, 10βH, R_1 = Piv, R_2 = H

40 9αH, 10βH, R_1 = H, R_2 = COC_6H_{11}
41 9βH, 10αH, R_1 = H, R_2 = COC_6H_{11}
42 9βH, 10βH, R_1 = H, R_2 = COC_6H_{11}
43 9αH, 10βH, R_1 = H, R_2 = Ac
44 9βH, 10αH, R_1 = H, R_2 = Ac
45 9βH, 10βH, R_1 = H, R_2 = Ac
48 9αH, 10βH, R_1 = Piv, R_2 = Ac
49 9βH, 10αH, R_1 = Piv, R_2 = Ac
50 9βH, 10βH, R_1 = Piv, R_2 = Ac

Scheme 3.

Table 2
Relative yields[a] of 9,10-isomers after hydrogenation of Δ^9-olefins

Compound	Substituent	Yield of		
		9α,10β adduct	9β,10α adduct	9β,10β adduct
19[b]	3β-OAc	16 (23%)	17 (13%)	15 (61%)
27	3β-OH	35 (30%)	36 (7%)	37 (53%)
28	3β-OH	38 (29%)	39 (8%)	9 (63%)
31	3β-OPiv	46 (35%)	47 (9%)	10 (56%)
32	3β-OPiv	48 (41%)	49 (31%)	50 (28%)
30	3α-OH	43 (70%)	44 (23%)	45 (7%)
29	3α-OH	40 (77%)	41 (19%)	42 (4%)

[a] Yields are based on the weight of crude 9β,10β-isomers and on ^{1}H NMR analysis of diketones obtained from unseparable mixtures of the other three isomers

[b] After hydrolysis, compound **18** (2%) was obtained by preparative HPLC.

tion of both parameters is structural assignment of the involved atoms which must be done first. This was not an easy task in the rather complex molecules of our disubstituted steroids, even at a high magnetic field (11.4 T). All ring hydrogen atoms of these molecules formed just one spin system (only in the case of 3,17-diketones **13**, **14**, **33**, **34** there were two hydrogen atoms in position 4 isolated with a 3-oxo group). To solve this problem, we applied a general strategy [9] based on a combination of 1D and 2D-techniques (proton COSY, J-resolved and NOESY or ROESY spectra and heteronuclear ^{1}H-^{13}C-correlated HMQC and HMBC spectra). The resulting complete structural assignments of protons and carbons in compounds **6**, **11**, **13–18**, **33**, and **34** are given in Tables 3 and 4. The relative configurations of methylene protons were derived from characteristic values of vicinal couplings and/or NOE contacts (vide infra).

Since the determination of configuration was closely connected with conformation of the molecule, we first analyzed possible conformations of all 9,11-isomers qualita-

Table 3
Proton NMR parameters of 9,10-isomers[a]

Proton	9βH,10βH			9αH,10βH			9βH,10αH		9αH,10αH	
	6	**15**	**14**	**11**	**16**	**13**	**17**	**33**	**18**	**34**
1α	1.50 dq	1.48 dq	1.87 dq	1.53	1.54	2.05 ddt	1.27	2.05 dddd	1.43	1.98 dddd
1β	1.82 dq	1.81 dq	2.12 m	1.98 tt	2.00 tt	1.95 tt	1.47	1.35 dq	1.71	1.72 dq
2α	2.00 m	1.98 m	2.32 m	1.44	1.45	2.21 dt	1.54	2.26 dddd	1.53	2.26 dddd
2β	1.03 dddd	1.03 m	2.24 tdd	1.55	1.54	2.16 dp	1.86	2.41 ddt	1.86 ddq	2.42 ddt
3α	3.71 tt	3.71 tt	—	4.15 m	4.16 m	—	4.11 p	—	4.07 p	—
4α	1.68 ddd	1.71 ddd	2.12 dd	1.91 bdd	1.91 bdd	2.71 bd	1.30 ddd	2.195 dp	1.29	~2.15
4β	1.14 dd	1.16 dd	2.26 dd	1.10	1.13	1.77 dt	1.59 dt	2.07 dd	1.74	~2.15
6α	1.59 bdt	1.64 dt	1.46 bdt	1.35 dt	1.42 dt	1.43 ddd	1.14	1.47 dt	1.56	1.61 ddd
6β	0.86 m	0.93 m	1.07 dtd	1.17 dt	1.22 dt	1.46 ddd	1.17	1.22 dt	1.38	~1.58
7α	1.42	1.55 m	1.57 m	0.96	1.08	1.19 m	1.82	~1.57	1.74	~1.75
7β	1.75	1.83 ddt	1.82 m	1.41	1.55	1.68 dq	1.45	1.75 tt	1.36	~1.32
8	1.74	1.89 m	1.94 m	1.04	1.10	1.34	1.93 dddd	1.98 dtd	1.82	~1.78
9	2.22 bq	2.28 bq	2.35 bq	1.03	1.20	1.34	1.73 dtd	1.72 dddd	1.66	1.54
10	1.18 m	1.21 m	1.65 m	1.08	1.11	1.26	1.81	1.95 dt	1.36	2.16 ddd
11α	1.42	1.49	1.55 m	1.80	1.83	1.90	1.45	1.81 dm	1.61	~1.73
11β	1.90 tdd	1.92	2.00 tdd	1.07	1.08	1.20	1.50	1.61 tdd	1.22 dddd	1.37 dq
12α	1.30 bdt	1.49	1.47 bdt	1.05	1.27	1.35	1.27	1.38 bdt	1.24	1.26 bdt
12β	1.61	1.62 ddd	1.67 ddd	1.74	1.81	1.87 ddd	1.48	1.56 dt	1.81 dt	1.82 ddd
14	1.46 dt	1.79 dt	1.71 dt	1.00	1.34 ddd	1.42 ddd	2.02 dt	2.05 dt	1.35	~1.33 td
15α	1.61 m	1.97 dddd	1.96 dddd	1.59 m	1.94 dddd	1.98 dddd	1.91 dddd	1.93 dddd	1.88 dddd	1.93 dddd
15β	1.13 dq	1.39 tt	1.40 tt	1.25 dq	1.51 tt	1.55 tt	1.45 tt	1.49 tt	1.54 tt	1.55 tt
16α	2.04 ddt	2.08 dt	2.08 dt	2.06 dddd	2.08 dt	2.11 dt	2.08 dt	2.11 dt	2.06 dt	2.08 dt
16β	1.38 dddd	2.43 ddd	2.44 ddd	1.42 dddd	2.45 ddd	2.48 ddd	2.45 ddd	2.48 ddd	2.43 ddd	2.45 ddd
17α	3.66 t	—	—	3.64 t	—	—	—	—	—	—
Me-18	0.741 s	0.879 s	0.892 d	0.737 s	0.870 s	0.907 s	0.895 d	0.923 s	0.900 d	0.886 d
Me-19	1.015 s	1.038 s	1.120 s	1.202 s	1.225 s	0.973 d	1.115 s	0.834 d	1.286 s	0.992 s

[a] In cases where multiplicity of a signal is not given, the position of the signal was determined from 2D-COSY or HMQC spectra, and multiplicity could not be obtained due to heavy overlap of signals or second order effects.

Table 4
Carbon-13 chemical shifts of 9,10-isomers

Carbon	9βH,10βH			9αH,10βH			9βH,10αH		9βα,10αH	
	6	**15**	**14**	**11**	**16**	**13**	**17**	**33**	**18**	**34**
1	27.35	27.29	28.92	17.13	17.09	22.77	18.92	25.78	19.61	24.60
2	37.03	36.94	41.97	26.64	26.58	36.20	34.37	41.39	34.33	41.69
3	67.13	67.04	212.09	67.82	67.65	212.75	67.47	211.53	67.60	211.51
4	51.49	51.29	55.61	37.66	37.52	48.09	48.29	56.90	50.37	58.79
5	35.92	35.87	39.66	32.83	32.85	38.98	33.83	38.41	33.32	37.66
6	26.94	26.91	28.30	41.65	41.44	39.46	36.59	35.85	39.22	36.77
7	22.48	21.80	22.00	26.66	25.89	25.87	21.53	22.52	23.82	23.54
8	33.60	33.23	32.96	39.53	39.61	40.03	35.30	35.09	35.60	34.45
9	31.54	31.74	31.66	41.32	40.71	40.85	35.30	36.10	41.27	43.10
10	48.16	48.01	48.11	46.08	46.02	45.50	40.24	38.51	45.97	41.07
11	26.37	25.88	25.86	25.85	25.45	25.54	22.14	22.43	23.40	24.24
12	35.18	30.09	30.20	36.86	31.63	31.54	26.86	26.92	32.73	32.27
13	43.33	48.16	47.98	42.89	47.71	47.64	48.16	48.12	49.20	48.48
14	43.59	44.42	45.08	50.34	50.74	50.61	40.91	41.06	51.91	52.26
15	24.22	22.58	22.56	23.21	21.61	21.57	21.53	21.47	21.33	21.45
16	29.83	35.44	35.40	30.59	35.88	35.82	35.27	35.23	35.84	35.78
17	82.57	221.90	221.38	82.08	221.61	220.91	221.45	220.80	221.33	220.65
18	10.06	12.76	12.82	10.98	13.70	13.74	12.95	12.99	14.81	14.40
19	27.53	27.49	27.38	31.52	31.43	29.24	18.31	17.04	26.84	23.97

tively on models and then minimized the energy of individual conformers by molecular mechanics (MM2+ method). The calculation showed that in all isomers, the lowest energy conformers had rings A, B, and C in the chair form (except ring B in the 9αH,10αH-derivatives **18** and **34** which adopted a twist-boat form). The alternative conformations of B/C cis-anneled 9βH,10βH- and 9βH,10αH-isomers containing one or two boat (or twist-boat) forms of rings B and C showed substantially higher energy. The calculated energetically preferred conformers for the series of 9,10-isomeric 3β-hydroxy-17-oxo derivatives **15** –**18** are shown in Fig. 1.

The general molecular shape of the individual isomers showed an increasing extent of bending to the α-side of the steroid molecule in the following order: 9αH,10αH-, 9αH,10βH-, 9βH,10αH-, 9βH,10βH-isomer, resulting in the different numbers and types of observable non-trivial NOE contacts (between protons separated by more than 3 bonds) on both the α- and β-sides of the molecule. These NOE contacts could be divided into three categories: [1] NOEs that were common for all 9,10-isomers (mainly between protons of C and D rings), [2] NOEs that were absent in one or two 9,10-isomers, and [3] NOEs that were specific (unique) for just one 9,10-isomer. Only specific NOEs are indicated with arrows in Fig. 1. The experimental observation of the expected NOEs had been used as an argument for the configuration in positions 9 and 10 in studied compounds. Although in some cases the observation and/or unequivocal assignment of the NOE contact was difficult due to distribution of signals, the majority of expected NOE contacts for individual isomers could be identified or at least not excluded. The observation of the above-mentioned specific NOEs, together with the absence of unexpected ones, strongly supported the suggested configurations and preferred conformations of the individual 9,10-isomers as well.

Additional arguments could be derived from chemical shifts and interproton coupling constants. Chemical shifts of most protons, although rather variable (except for protons in ring D), were not easily interpretable in the sense of the 9,10-configurations. Furthermore, their identification (ex-

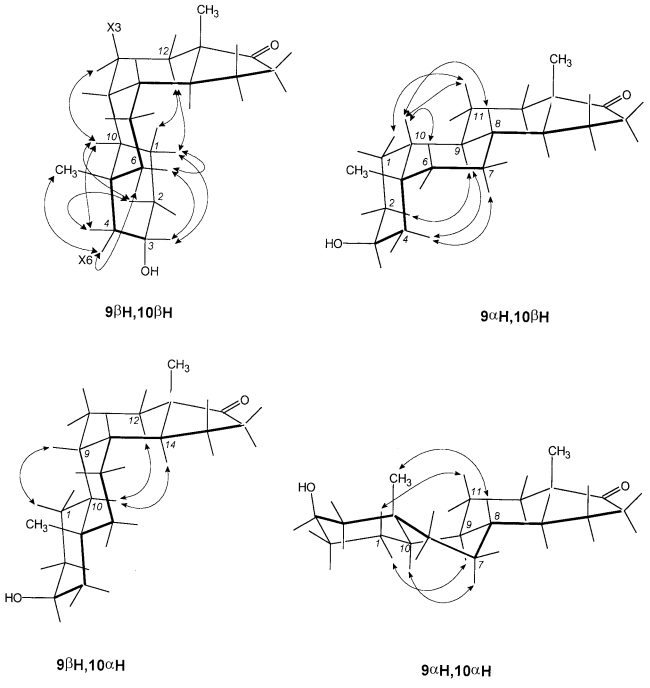


Fig. 1. Schematic representation of calculated lowest energy conformations of compounds **15–18** and NOE contacts characteristic for each isomer.

Table 5
Some characteristic NMR parameters of 9,10-isomers of hydroxy ketones **15–18** and diketones **13**, **14**, **33**, and **34**. Parameters that are specific for hydroxy ketones only are given in italics

	9βH,10βH-	9αH,10βH-	9βH,10αH-	9αH,10αH-
		Specific NOEs		
Protons	*1αH ↔ 3αH*	1αH ↔ 11βH	1βH ↔ 9βH	1αH ↔ 9αH
	1αH ↔ 6αH	2αH ↔ 9αH	10αH ↔ 12αH	1βH ↔ 11βH
	1αH ↔ 12αH	4αH ↔ 7αH	10αH ↔ 14αH	7αH ↔ 10αH
	1βH ↔ 12αH	4αH ↔ 9αH		8βH ↔ 19Me
	2βH ↔ 4βH	6βH ↔ 10βH		
	2βH ↔ 10βH	10βH ↔ 8βH		
	3αH ↔ 6αH	10βH ↔ 11βH		
	4αH ↔ 6βH			
	4αH ↔ 19Me			
	4βH ↔ 10βH			
	10βH ↔ 11αH			
		Proton chemical shifts		
H-3	*3.71 tt (ΣJ ≈ 30 Hz)*	*4.16 m (ΣJ ≈ 13 Hz)*	*4.11 m (ΣJ ≈ 13 Hz)*	*4.07 m (ΣJ ≈ 13 Hz)*
19-Me	*1.04* 1.12	*1.22* 0.97	*1.12* 0.83	*1.29* 0.99
		Vicinal couplings of protons 9 and 10 (calculated torsion angles)		
J(9,8)	6.0 (−44°)	* (−176°)	4.5 (−50°)	11.6 (168°)
J(9,10)	6.0 (46°)	* (176°)	12.0 (175°)	10.3 (27°)
J(9,11α)	<2 (−76°)	* (53°)	2.0 (−68°)	* (58°)
J(9,11β)	7.2 (37°)	* (170°)	4.5 (45°)	≈13.0 (176°)
J(10,1α)	13.2 (172°)	3.3 (60°)	3.7 (−59°)	3.7 (−61°)
J(10,1β)	4.2 (53°)	≈4.5 (52°)	12.9 (177°)	13.5 (179°)
		Characteristic observable long-range couplings of protons		
	J(2α,4α)			
		J(2β,4β)	J(2β,4β)	J(2β,4β)
		J(2β,10β)		
		J(4β,10β)		
	J(6β,8β)		J(6β,8β)	
	J(6β,10β)			
	J(8β,10β)			
	J(9β,12β)		J(9β,12β)	
		Carbon-13 chemical shifts		
C-4	*51.29* 55.61	*37.52* 48.09	*48.29* 56.90	*50.37* 58.79
C-6	*26.91* 28.30	*41.44* 39.46	*36.59* 35.85	*39.22* 36.77
C-9	*31.74* 31.66	*40.71* 40.85	*35.30* 36.10	*41.27* 43.10
C-10	*48.01* 48.11	*46.02* 45.50	*40.24* 38.51	*45.97* 41.07
C-14	*44.42* 45.08	*50.74* 50.61	*40.91* 41.06	*51.91* 52.26
C-19	*27.49* 27.38	*31.43* 29.24	*18.31* 17.04	*26.84* 23.97

* J-value was not determined.

cept methyl protons and H-3) required detailed analysis based on a combination of 2D-NMR techniques. The upfield shift (~0.4 ppm) of H-3 and vicinal couplings of this proton in compounds **6** and **15** indicated its axial position (which appeared only in the 9βH,10βH-isomer), while in other compounds (**11**, **16**, **17**, and **18**) this proton adopted an equatorial position. Configurations in positions 9 and 10 were directly reflected in the vicinal couplings of these protons. The observed *J*-values of protons H-9 and H-10 and the corresponding torsion angles calculated for the preferred conformation of each 9,10-isomer are summarized in Table 5. Other interproton coupling constants, except those not obtainable due to heavy overlap and/or second order spectral pattern in strongly coupled spin systems, are summarized in Table 6.

As follows from inspection of the models, the 9,10-isomers differed in number and type of proton long-range couplings over four bonds in a planar 'zig-zag' arrangement. Characteristic couplings (1–3 Hz) that were expected (and mostly observed either as fine splitting or line broad-

Table 6
Observed coupling constants and calculated torsion angles of the corresponding hydrogen atoms (in parentheses) in the lowest energy conformations of 9,10-isomers shown in Fig. 1

	9βH,10βH			9αH,10βH			9βH,10αH		9αH,10αH	
J(H,H)	3β,17β-diOH	3β-OH,17-oxo	3.17-dioxo	3β,17β-diOH	3β-OH,17-oxo	3.17-dioxo	3β-OH,17-oxo	3.17-dioxo	3β-OH,17-oxo	3.17-dioxo
	6[a]	**15**[b]	**14**[c]	**11**	**16**[d]	**13**[e]	**17**[f]	**33**[g]	**18**[h]	**34**[i]
1α,1β	13.3	13.2	~13	~15	14.1	14.3	[j]	12.9	~12.9	13.3
1α,2α	3.3 (−56)	3.3 (−56)	4.4 (−53)	[j] (59)	3.3 (60)	6.0 (58)	[j] (55)	7.4 (52)	[j] (54)	7.2 (52)
1α,2β	13.2 (−174)	11.8 (−174)	13.2 (−173)	[j] (−57)	3.3 (−57)	2.8 (−61)	[j] (−61)	1.9 (−66)	~2.6 (−62)	~2 (−66)
1α,10	13.0 (175)	13.2 (175)	13.1 (175)	[j] (60)	3.3 (61)	2.4 (62)	[j] (−62)	3.7 (−59)	3.3 (−64)	3.7 (−63)
1β,2α	4.8 (59)	~3.8 (59)	2.8 (62)	~11.3 (172)	11.6 (172)	13.7 (170)	[j] (170)	12.9 (167)	~12.9 (171)	12.6 (168)
1β,2β	3.6 (−59)	3.5 (−59)	5.8 (−58)	~3.9 (56)	3.7 (56)	4.7 (52)	[j] (54)	5.1 (49)	3.4 (54)	5.0 (50)
1β,10	4.2 (56)	4.2 (56)	3.9 (56)	~3.9 (−54)	6.6 (−54)	~4.5 (−52)	[j] (−179)	12.9 (−177)	~12.9 (178)	13.5 (180)
2α,2β	11.8	13.3	13.8	[j]	14.1	14.3	[j]	14.9	14.2	14.8
2α,3	4.2 (57)	4.2 (57)	—	~3 (−51)	~3 (−51)	—	~3 (−51)	—	~3 (−53)	—
2β,3	11.2 (175)	11.3 (175)	—	~3 (65)	~3 (65)	—	~3 (65)	—	~2.6 (64)	—
3,4α	4.2 (−58)	4.2 (−58)	—	4.0 (49)	4 (49)	—	3.8 (52)	—	~3 (53)	—
3,4β	11.2 (−173)	11.3 (−172)	—	~3 (−65)	~3 (−66)	—	2.5 (−63)	—	~3 (−62)	—
4α,4β	12.5	12.7	13.5	15.0	14.5	14.2	14.5	13.5	14.8	[j]
6α,6β	13.5	13.4	13.6	13.6	13.2	13.9	[j]	13.3	14.5	13.9
6α,7α	4.0 (−58)	4.2 (−58)	~4.0 (−57)	3.2 (57)	~3.1 (57)	4.7 (57)	[j] (−56)	~3.8 (−57)	2.6 (41)	9.0 (40)
6α,7β	~13.5 (−172)	13.6 (−172)	13.2 (−171)	3.2 (−60)	~3.1 (−60)	~3.0 (−60)	[j] (−171)	~13.6 (−172)	2.6 (−77)	4.5 (−78)
6β,7α	2.6 (57)	2.8 (57)	3.8 (58)	13.5 (171)	13.5 (171)	12.1 (172)	[j] (59)	~3.3 (58)	[j] (153)	[j] (153)
6β,7β	4.3 (−56)	4.4 (−56)	4.4 (−55)	4.0 (55)	4.2 (55)	3.9 (55)	[j] (−55)	~3.6 (−57)	[j] (36)	[j] (35)
7α,7β	[j]	13.5	14.4	[j]	[j]	13.3	[j]	~14	[j]	[j]
7α,8	[j] (−74)	~1 (−74)	2.2 (−75)	[j] (−176)	[j] (−177)	~11 (−177)	4.2 (−68)	~4.5 (−67)	13.2 (174)	[j] (173)
7β,8	[j] (40)	6.5 (40)	6.9 (39)	[j] (−59)	[j] (−60)	~3.0 (−59)	5.2 (46)	~4.5 (48)	2.9 (−68)	[j] (−69)
8,9	~6 (−43)	~6 (−43)	~6.0 (−42)	[j] (−177)	[j] (−176)	[j] (−177)	4.5 (−51)	2.0 (−51)	11.6 (167)	[j] (168)
8,14	~12 (−179)	12.4 (−177)	12.4 (−178)	[j] (−178)	[j] (−177)	10.6 (−176)	12.3 (−176)	12.4 (−175)	13.2 (−173)	[j] (−173)
9,10	5.8 (47)	~6 (47)	~5.0 (48)	[j] (179)	[j] (179)	[j] (178)	12.0 (180)	~11.5 (179)	[j] (27)	10.3 (26)
9,11α	<1 (−78)	<2 (−79)	~5.1 (−80)	[j] (54)	[j] (52)	[j] (52)	2.0 (−65)	4.9 (−66)	[j] (61)	[j] (61)
9,11β	7.6 (35)	~7.2 (34)	7.7 (34)	[j] (171)	[j] (169)	~13.5 (169)	4.5 (47)	4.5 (47)	[j] (178)	~13 (178)
11α,11β	14.5	[j]	~13.5	[j]	11.5	11.4	[j]	14.6	12.7	~13
11α,12α	4.8 (−54)	[j] (−54)	2.9 (−54)	[j] (−55)	4.5 (−54)	[j] (−54)	[j] (−61)	3.4 (−61)	4.0 (−55)	4.0 (−54)
11α,12β	[j] (62)	1.4 (62)	2.2 (63)	[j] (62)	2.6 (63)	~2.5 (63)	[j] (56)	~3.1 (56)	~3 (62)	2.7 (62)
11β,12α	13.3 (−167)	[j] (−167)	13.5 (−167)	[j] (−169)	~12.8 (−168)	~13.5 (−169)	[j] (−173)	13.7 (−173)	~12.8 (−170)	12.8 (−170)
11β,12β	5.4 (−51)	5.5 (−50)	5.7 (−50)	[j] (−53)	3.7 (−52)	~3.8 (−52)	[j] (−56)	~3.5 (−56)	~3 (−54)	3.6 (−54)
12α,12β	13.3	12.6	13.2	[j]	13.2	~13	[j]	13.7	12.8	12.9
14,15α	~7 (−42)	5.7 (−47)	5.7 (−47)	3.5 (−42)	5.7 (−47)	5.6 (−47)	5.7 (−48)	5.6 (−49)	5.8 (−47)	5.8 (−47)
14,15β	12.0 (−162)	12.2 (−169)	12.2 (−168)	11.5 (−163)	12.2 (−168)	12.5 (−168)	12.4 (−169)	12.0 (−170)	12.5 (−168)	12.2 (−168)
15α,15β	12.0	12.2	12.2	13.0	12.2	12.0	12.4	12.0	12.2	12.3
15α,16α	~9.2 (10)	9.0 (27)	9.0 (27)	9.5 (11)	8.9 (27)	~8.9 (27)	8.9 (26)	~8.9 (26)	8.9 (26)	8.9 (26)
15α,16β	3.6 (−109)	1.2 (−95)	1.0 (−96)	3.4 (−109)	1.3 (−96)	1.1 (−96)	1.2 (−97)	1.2 (−97)	1.2 (−96)	1.2 (−96)
15β,16α	5.7 (130)	9.0 (148)	9.0 (148)	5.8 (131)	9.1 (148)	~9.0 (148)	8.9 (147)	~8.9 (147)	8.9 (148)	9.2 (148)
15β,16β	12.0 (11)	9.2 (25)	9.0 (26)	11.8 (12)	8.9 (25)	8.7 (25)	9.0 (24)	9.0 (24)	8.8 (25)	8.9 (25)
16α,16β	13.4	19.3	19.1	13.5	19.0	19.1	19.0	19.3	19.2	19.3
16α,17α	9.2 (21)	—	—	9.2 (21)	—	—	—	—	—	—
16α,17β	8.2 (141)	—	—	8.0 (140)	—	—	—	—	—	—

[a] J(2α,4α) = 2.7, J(6β,10β) = 1.6 Hz; [b] J(6β,10β) = 1.6, J(2α,4α) = 2.8 Hz; [c] J(2β,4α) = 2.2, J(2α,4β) = 1.2, J(6β,10β) = 1.4, J(12α,18) = 1.0 Hz; [d] J-values obtained in C_6D_6, J(4α,19) = 0.8, J(2β,4β) ≠ 0, J(4β,10β) ≠ 0; [e] J(2β,4β) = 1.8, J(2β,10β) ≠ 0, J(4α,19) = 0.8, J(4β,10β) ~ 1.5 Hz; [f] J(2α,4α) = 0.8, J(2β,4β) = 2.5, J(12α,18) = 0.5 Hz; [g] J(2α,4α) = 0.9, J(2β,4β) = 2.4, J(12α,18) = 0.7 Hz; [h] J(2β,4β) ~ 2.6, J(12α,18) = 0.8 Hz; [i] J(2β,4β) ~ 1.6, J(12α,18) = 0.7 Hz; [j] J-value could not be determined.

ening in 1D spectra and confirmed in 2D-Long-range COSY spectra) in individual isomers are given in Table 5. Additional long-range couplings were observed for 18- and 19-Me protons in some compounds (see Table 6).

Carbon-13 chemical shifts are sensitive to molecular geometry. Comparison of chemical shifts of individual carbons within the series of 9,10-isomers (hydroxy ketones **15–18** and diketones **13**, **14**, **33**, **34**) showed the largest differences (> 8 ppm in both groups) in positions 4, 6, 9, 10, 14, and 19 (see Table 5). These differences can be explained (on a semiquantitative level) by upfield shifts resulting from the interaction between two proton-bearing carbons in a *γ-gauche* orientation. For each of the above-mentioned carbons, the most upfield shift appeared in the

9,10-isomer that had the highest number of γ-*gauche* interactions.

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