trans-HYDRINDANES BY REDUCTION: SYNTHESIS OF DIHYDRO-B-NORTESTOSTERONE*

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Dedicated to Professor Jaroslav Podlaha on the occasion of his 60th birthday.

Reduction with diimide was employed in the synthesis of potential antiandrogens – 17β-hydroxy-B-nor-5α-androstan-3-one (**26**) and its 17α-methyl derivative (**25**). Other methods of reduction (hydroboration, catalytic hydrogenation) were less effective.

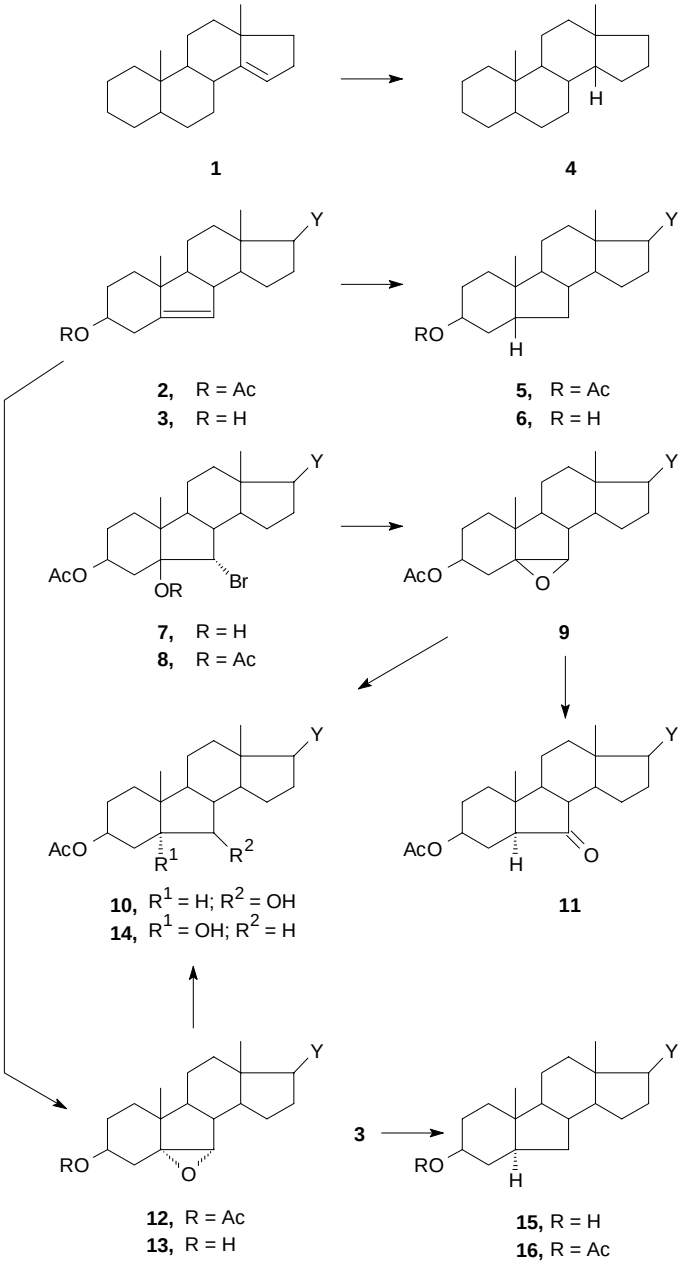
Key words: Diimide reduction; Stereochemistry; Catalytic hydrogenation.

In the formation of hydrindanes from unsaturated derivatives (e.g., by hydrogenation), *cis*-hydrindanes are known[2,3,4] to be the preferred products; e.g., on addition, Δ^{14}-unsaturated steroids (type **1**) as well as Δ^{5}-unsaturated B-norsteroids (type **2** and **3**) yield mainly C/D *cis* (type **4**) or A/B *cis* (type **5** and **6**) products, respectively. This preference affected the total synthesis of steroids even 40 years ago[5].

trans-Hydrindanes could, however, be obtained by indirect routes[6]: hypobromous acid and their derivatives were found to approach the double bond from the less hindered α-side[7–9] yielding bromohydrine derivatives (e.g., **7** and **8**) which were converted into β-epoxides (e.g., **9**). These were either hydrogenated to 6β-hydroxy-B-nor-5α-steroids **10** or isomerized by Lewis acids to 6-oxo-B-nor-5α-steroids **11**. Alternatively[10], complex hydride reduction of 5α,6α-epoxides (e.g., **12** and **13**) afforded 5-hydroxy-B-nor-5α-steroid (e.g., **14**). Conversion of these intermediates into deoxy products like **15** would pose some problems. A straightforward approach is described here.

The major hindrance to the 5β-approach of a reagent was recently[11,12] attributed to the presence of an angular methyl group. If relative yields of 5α- and 5β-epoxides indicate the relative steric hindrance of the double bonds involved, the Δ^{5}-double bond

* Part CCCLXXXV in the series On Steroids; Part CCCLXXXIV: see ref.[1].


1
4
2, R = Ac
3, R = H
5, R = Ac
6, R = H
7, R = H
8, R = Ac
9
10, R1 = H; R2 = OH
14, R1 = OH; R2 = H
11
12, R = Ac
13, R = H
15, R = H
16, R = Ac
3
Y = CH(CH3)(CH2)3CH(CH3)2, (20R)-cholestane side chain

SCHEME 1

in B-norsteroids is much more accessible than the same double bond in normal steroids to an electrophilic attack of reagents from the α-side leading to substituted *trans*-hydrindanes (see Table I and Scheme 1) .

This steric factor was not manifest in reversible reactions, however, stereospecific addition reactions proceeding in a four-centre mechanism (e.g., hydroboration, reduction with diimide[13]), which does not allow for internal rotation or inversion of intermediates, should produce even better yields of 5α-adducts (i.e., A/B *trans* products) in the B-nor series than in corresponding classical steroids with six-membered rings A and B. Recent results of this more direct approach to such B-nor-5α-steroids are presented here.

Hydroboration, followed by oxidation, of Δ^{14}-olefins was[14,15] successfully utilized in the synthesis of 15α-hydroxy steroids. Now we used a similar sequence in the transformation of B-norcholesterol (**3**). Its hydroboration and treatment of borane formed with propionic acid[16] yielded B-nor-5α-cholestan-3β-ol (**15**, yield 9%). ^{1}H NMR spectrum of the product confirms an axial character of the 3α-proton (multiplet, ΣJ = 32 Hz, see Table II). No 5β-isomer **6** was found in the mixture either by NMR spectroscopy of the crude reaction product, or by TLC analysis. The authentic sample of **6**, for comparison, was prepared by catalytic hydrogenation of B-norcholesterol **3**, its ^{1}H NMR spectrum indicated the equatorial nature of the 3α-proton (a narrow multiplet, ΣJ = 16 Hz).

Low yields of the hydroboration sequence were not due to partial addition of diborane: TLC showed the complete conversion of the starting material into a borane intermediate, however, its acidolysis proceeded mainly with the formation of the starting olefin **3** (identified after epoxidation to compound **13**).

The best reagent for the desired reduction of Δ^5-B-norsteroids to A/B *trans* products was found to be diimide[17]. Treatment of olefins (e.g., **2** and **3**) with 4-toluenesulfonhydrazide in boiling diglyme yielded 5α-dihydro derivatives (**15** and **16**) in fair yields (ca 60%). Unreacted starting material (15–20%) was removed by epoxidation with 3-chloroperoxybenzoic acid: the epoxides formed (e.g., **12** and **13**) could easily be separated from the expected products.

In an attempt to increase the yields, the diimide reduction was carried out without solvent, by heating olefins to 140 °C in an excess of 4-toluenesulfonhydrazide. This method worked well with less sensitive compounds. However, compounds with a free

TABLE I
Yields of epoxides formed from Δ^5-unsaturated steroids

Starting olefin	5α,6α-Epoxide, %	5β,6β-Epoxide, %
Δ^5-steroid	62	38
Δ^5-B-steroid	>95	<5

secondary hydroxy group suffered partial dehydration when heated either without solvent or in boiling diglyme or dioxane; the structure of the side product was not studied, the elimination mentioned is supported by the presence of olefinic protons at δ 5.60 in its ^{1}H NMR spectrum.

The best conditions for the reduction with diimide were found in the heating of reactants in 2,4,6-collidine to 150 °C. Under these conditions olefins **2** and **3** were hydrogenated without decomposition to yield compounds **16** and **15** (yield 89 and 95%, respectively).

These results have opened the way to the synthesis of 5α-dihydro derivatives of B-nortestosterone (see Scheme 2): while testosterone is an androgen hormone in testes

TABLE II
Characteristic parameters of the ^{1}H NMR spectra of B-norsteroidal derivatives

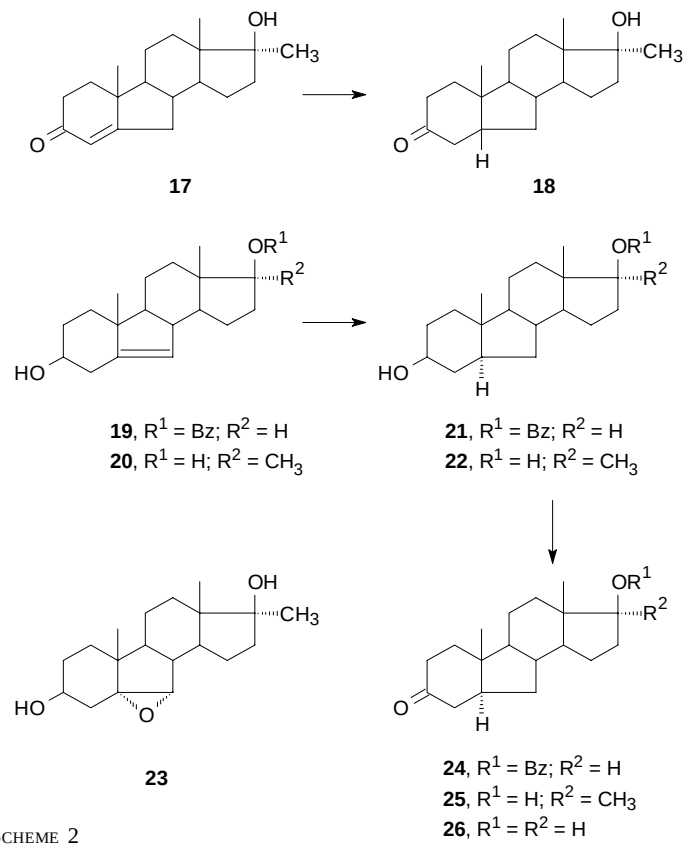
Compound	H-18[a]	H-19[a]	H-3	H-17	Other signals
2[b]	0.67	0.89	4.62[c]	–	2.04[d], 2.62[e], 5.38[f]
3[b]	0.68	0.88	3.57[c]	–	5.36[f]
5[b]	0.64	0.85	5.01[g]	–	2.03[d]
6[b]	0.64	0.86	4.02[g]	–	–
12[b]	0.63	0.90	4.99[c]	–	2.03[d], 3.26[h]
13[b]	0.63	0.89	3.96[c]	–	3.26[h]
15[b]	0.64	0.72	3.61[i]	–	–
16[b]	0.65	0.74	4.71[i]	–	2.03[d]
17	0.92	1.10	–	–	1.25[a], 5.80[j]
18	0.87	0.96	–	–	1.23[a]
19	0.91	0.98	3.69[c]	4.89[k]	2.62[e], 5.40[h], 7.48[m], 8.05[n]
20	0.85	0.87	3.52[c]	–	1.20[a], 2.56[e], 5.34[f]
21	0.75	0.94	3.65[i]	4.87[k]	2.30[l], 7.48[m], 8.05[n]
22	0.74	0.86	3.63[i]	–	1.22[a]
23	0.84	0.91	3.95[c]	–	1.23[a], 3.28[h]
24	0.92	0.96	–	4.89[k]	7.48[m], 8.05[m]
25	0.88	0.92	–	–	1.24[a]
26	0.76	0.91	–	3.68[k]	–

[a] Singlet, 3 H. [b] Signal of cholestane side chain: 0.90 d, 3 H, J = 6.5 (3 × H-21) and 0.86 s, 6 H (3 × H-26 and 3 × H-27). [c] tt, 1 H (J = 11.0 and 8.9). [d] s, 3 H (Ac). [e] ddd, 1 H (J = 13.7 and 4.9 and 1.8) 4α-H. [f] bs, 1 H, 6-H. [g] m, 1 H (W = 26). [h] s, 1 H, 6-H. [i] m, 1 H (W = 42). [j] s, 1 H, H-4; [k] dd (J = 8.5 and 7.5); [l] m, 1 H (ΣJ = 44), H-16β. [m] m, 3 H (H-3, H-4 and H-5 of C_6H_5COO). [n] m, 2 H (H-2 and H-6 of C_6H_5COO).

only and in many tissues has to be reduced to a hormone proper – "5α-dihydrotestosterone" (17β-hydroxy-5α-androstan-3-one)[18], B-nortestosterone and its derivatives (e.g., **17**) act as antiandrogens[19,20]. However, the biological activity of their 5α-dihydro derivatives has not been thoroughly studied yet because of the difficult approach to these compounds (both catalytic hydrogenation and Birch reduction afford the 5β-isomer **18**).

The 2,4,6-collidine modification of the reduction of compounds **19** and **20**, followed by evaporation of the solvent and chromatography on silica gel yielded less polar fractions (products of decomposition accompanied with 4-methylbenzenesulfinic acid[21]) and major (i.e., polar) components of the mixture, i.e., compounds **21** and **22**, respectively. When a smaller excess of the reducing reagent was employed, the starting material had to be removed from the product by epoxidation (leading, e.g., to compound **23**).

On oxidation, compounds **21** and **22** afforded ketones **24** and **25**. The latter represents the sought-for 5α-dihydro derivative of 17-methyl-B-nortestosterone, the former was hydrolyzed to the 5α-dihydro derivative of B-nortestosterone **26**.



SCHEME 2

The best method of identifying the A/B ring junction of steroids is circular dichroism: Joska, Fajkos and Sorm[22] studied ORD curves of 3-oxo-B-nor-5α- and 3-oxo-B-nor-5β-steroids and found a positive Cotton effect for the former isomer and a negative one for the latter within the $n \rightarrow \pi^*$ absorption band of the chromophore. In a latter work on CD of ketones, Kirk[23] reported Δε +2.5 and –1.3 for B-nor-5α- and B-nor-5β-cholestan-3-ones, respectively. We found a strong Cotton effect (Δε +1.88 and +1.63, respectively) in **24** and **25** and a negative effect (Δε –1.50) in **18**. Significant differences between 5α and 5β isomers **25** and **18** were also found in their ^{13}C NMR spectra (see Table III): as in parent compounds with the classical steroid skeleton[24], C-19 of the 5β-isomer is shifted to a lower field than the same signal of the 5α-isomer.

The biological properties of compounds **25** and **26** will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (Germany) and are uncorrected. Analytical samples were dried over phosphorus pentoxide at 50 °C/100 Pa. Optical rotations were measured in chloroform, IR spectra of chloroform solutions were recorded on a Bruker IFS 88 spectrometer, wavenumbers are given in cm^{-1}. ^{1}H NMR spectra were measured on a Varian UNITY-200 (200 MHz, FT mode) and ^{13}C NMR spectra on a Varian UNITY-500 (125.7 MHz, FT mode) spectrometer at 23 °C in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and width of multiplets (*W*) in Hz. The data were interpreted as the first-order spectra. Thin-layer chromatography (TLC) was performed on silica gel (ICN Biochemicals), preparative TLC was carried out on 200 × 200 mm plates coated with an 0.5 mm thick layer of the same material. For column chromatography silica gel 60–120 μm

TABLE III
^{13}C NMR spectral parameters of 5α and 5β isomers **25** and **18**. Measured in $CDCl_3$, for other conditions see Experimental

Carbon	**25**	**18**	Carbon	**25**	**18**
1	34.91	35.20	12	31.86	31.66
2	37.49	37.93	13	47.67	46.78
3	212.42	214.81	14	50.59	50.37
4	42.83	44.19	15	23.61	23.56
5	48.18	44.12	16	39.13	39.12
6	28.65	32.21	17	81.34	81.34
8	41.04	4.70	18	14.31	14.02
9	58.87	55.04	19	12.15	24.93
10	40.84	39.46	17a	26.06	25.88
11	20.98	20.90			

was used. When aqueous solutions of hydrochloric acid, potassium hydrogen carbonate and potassium carbonate are used, their concentration is always 5%.

3β-Acetoxy-B-nor-5β-cholestane (**5**)

A solution of 3β-acetoxy-B-norcholest-5-ene[22] **2** (100 mg, 0.24 mmol) in tetrahydrofuran (4 ml) and acetic acid (2 ml) was stirred under hydrogen in the presence of Adams catalyst (20 mg). After 1 h at ambient temperature the catalyst was filtered off and the solution evaporated. ^{1}H NMR spectrum was consistent with the spectra of compounds **5** and **16** in the proportion 82 : 18. The mixture could be separated by TLC (benzene–ether, 5 : 1) only after hydrolysis (1% sodium methoxide in methanol) to 3β-hydroxy derivatives **6** (69.7 mg, 77%) and **15** (16.2 mg, 18%). Re-acetylation of **6** (69.7 mg, acetic anhydride–pyridine, 18 h) afforded pure **5** (70 mg, 91%). $[\alpha]_D$ +17° (*c* 0.9). Dauben[25] could not crystallize the compound either.

B-Nor-5α-cholestan-3β-ol (**15**)

a) A solution of sodium borohydride (200 mg, 5.29 mmol) in tetrahydrofuran (6 ml) was added into a solution of boron trifluoride etherate (0.7 ml, 5.61 mmol) in the same solvent (2 ml). The diborane generated was passed into the solution of olefin **2** (125 mg, 0.30 mmol) in tetrahydrofuran (4 ml). After 30 min, the solution was concentrated in a vacuum, the residue was dissolved in propionic acid (5 ml) and refluxed for 2 h. The solution was evaporated in a vacuum, dissolved in chloroform and washed with an aqueous potassium hydrogen carbonate solution and water. The extract was concentrated in a vacuum to 2 ml and 3-chloroperoxybenzoic acid (60%, 100 mg, 0.35 mmol) was added. After 18 h, the solution was washed with the potassium hydrogen carbonate solution, concentrated in a vacuum and hydrolyzed by standing in a solution of sodium methoxide in methanol (3 ml, *c* = 0.86 mol/l). After 18 h the solution was concentrated in a vacuum, the product was precipitated with brine and extracted with chloroform. The extract was applied on 2 TLC plates. The polar fraction was identified as epoxide **13** (20 mg, 15%): its IR spectrum was identical with that of the sample prepared directly from olefin **3**. The lipophilic fraction consisted of compound **15** (10 mg, 8%), m.p. 130–131 °C (methanol). Literature[22] records 130–131 °C.

b) A suspension of compound **3** (122 mg, 0.33 mmol) and 4-toluenesulfonhydrazide (386 mg, 3.22 mmol) in 2,4,6-collidine (3 ml) was heated to 150 °C for 3 h. The solvent was evaporated in a vaccum, the residue was dissolved in chloroform and washed with aqueous hydrochloric acid (5%), water, potassium carbonate and water, and dried. Preparative TLC of the product afforded compound **15** (116 mg, 95%), m.p. 130–131 °C (92 mg, methanol).

3β-Acetoxy-B-nor-5α-cholestane (**16**)

a) Reduction in diglyme: compound **2** (69 mg, 0.17 mmol) and 4-toluenesulfonhydrazide (300 mg, 1.61 mmol) in diglyme (2 ml) were heated under reflux. After 3 h the mixture was diluted with brine (15 ml), the precipitate was extracted with ether and the extract was washed with the potassium hydrogen carbonate solution, water and evaporated. The residue was purified by preparative TLC (silica gel, benzene), the major product (49 mg) was identified by its NMR spectrum as an 88 : 12 mixture of **16** and **2**. 3-Chloroperoxybenzoic acid (60%, 50 mg, 0.17 mmol) was added to the solution of the mixture in chloroform (1 ml). After 18 h the mixture was worked up as above. Preparative TLC yielded 6 mg (8%) of **12** (identical with an authentic sample) and 41 mg (59%) of **16**, m.p. 67–69 °C (methanol). Literature[22] records 68–69 °C.

b) Reduction without solvent: compound **2** (25 mg, 0.06 mmol) and 4-toluenesulfonhydrazide (85 mg, 0.46 mmol) were thoroughly mixed in a tube which was heated in a bath to 140 °C. After 2 h the

mixture was dissolved in ether, washed with a potassium carbonate solution (10%) and applied on a thin layer of silica gel. The plate was developed with benzene and the major product was eluted with ether. Yield 18 mg (72%) of **16**.

c) Reduction in 2,4,6-collidine: compound **2** (125 mg, 0.30 mmol) and 4-toluenesulfonhydrazide (400 mg, 2.15 mmol) in 2,4,6-collidine (2 ml) were heated at 150 °C. After 3 h, volatile components were distilled off in a vacuum, the residue was dissolved in toluene and washed with aqueous hydrochloric acid, water and the potassium carbonate solution and water. The dried solution was evaporated in a vacuum and the residue was oxidized with 3-chloroperoxybenzoic acid (60%, 50 mg, 0.17 mmol) in chloroform (1 ml). After 18 h the solution was washed with the potassium carbonate solution and water, concentrated in a vacuum and applied on 3 preparative TLC plates which were developed with benzene. The major component of the mixture, compound **16** (112 mg, 89%) was identical with the above sample.

17β-Hydroxy-17α-methyl-B-nor-5β-androstan-3-one (**18**)

17β-Hydroxy-17α-methyl-B-norandrost-5-en-3-one[26] (**17**, 160 mg, 0.52 mmol) in tetrahydrofuran (20 ml) was added dropwise into a stirred solution prepared by dissolving lithium (200 mg, 28.8 mmol) in liquid ammonia (150 ml) and 2-methylpropan-2-ol (10 ml). After an additional 30 min, the reagent was decomposed with a saturated aqueous solution of ammonium chloride (30 ml). Ammonia was distilled off, the aqueous layer was extracted with ethyl acetate (4 × 20 ml) and combined organic extracts were washed successively with the aqueous hydrochloric acid solution, water, the saturated potassium hydrogen carbonate solution and water. The dried extract was concentrated in a vacuum and applied on a column of silica gel. A mixture of toluene and ether (9 : 1) afforded 63 mg (39.1%) of compound **18**, m.p. 127–130 °C (ether), $[\alpha]_D$ −23° (*c* 0.4). IR spectrum: 931 (OH); 1 707 (C=O); 3 611 (OH). CD: $\Delta\varepsilon_{288}$ −1.50 (methanol). For $C_{19}H_{30}O_2$ (290.4) calculated: 70.57% C, 10.41% H; found: 70.36% C, 10.42% H.

17β-Benzoyloxy-B-nor-5α-androstan-3β-ol (**21**)

A suspension of 17β-benzoyloxy-B-nor-5α-androstan-3β-ol[26] (**19**, 200 mg, 0.53 mmol) and 4-toluenesulfonhydrazide (600 mg, 3.22 mmol) in 2,4,6-collidine (3 ml) was heated to 150 °C for 3 h. The solvent was evaporated in a vaccum. The residue was dissolved in chloroform and washed successively with aqueous hydrochloric acid, water, the potassium carbonate solution and water, and dried. Crystallization of the residue from acetone afforded 126 mg (63%) of compound **21**, m.p. 190–191 °C, $[\alpha]_D$ +21° (*c* 1.2), literature[22] records m.p. 189–190 °C, $[\alpha]_D$ +23.5°). Mother liquors were purified by preparative TLC yielding an additional crop of the product **21** (the total yield 178 mg; 88%). IR spectrum (chloroform): 3 608 (OH); 1 709 (C=O); 1 603, 1 589 (arom); 1 281, 1 033 (C–O). Lipophilic admixture consisted of products of steroid decomposition (12.0 mg). ^{1}H NMR spectrum (after hydrolysis of this mixture): 0. 67 s, 3 H (3 × H-18); 0.75 s, 3 H (3 × H-19); 3.63 t, 1 H, J = 8.0 (H-17β); 5.82 m, 2 H, W = 42 (H-2 and H-3).

17α-Methyl-B-nor-5α-androstane-3β,17β-diol (**22**)

a) Attempted reduction with diimide without solvent: 17α-methyl-B-nor-5α-androstane-3β,17β-diol[26] (**20**, 100 mg, 0.34 mmol) was treated with 4-toluenesulfonhydrazide (300 mg, 1.61 mmol) without solvent at 150 °C for 2 h. TLC separation (8 plates) of the mixture afforded 4-toluenesulfinic acid (207 mg, m.p. 67–71 °C) and a mixture of dehydrated steroids (40 mg). ^{1}H NMR spectrum: 3.62 m, 1 H, W = 42 (H-3α); 2.52 t, J = 5.6 and 2.75 m, W = 42 (possibly allylic protons of 17,17-dimethyl-18-norsteroids). No compound **22** could be isolated from the mixture.

b) Reduction in 2,4,6-collidine: 200 mg of olefin **20** (0.69 mmol) was treated according to the preparation of compound **21**. After usual work-up, 186 mg (92%) of compound **22** was obtained. M.p. 159–160 °C (acetone), $[\alpha]_D$ –33° (*c* 0.9, methanol). For $C_{19}H_{32}O_2$ (292.5) calculated: 78.03% C, 11.03% H; found: 78.09% C, 11.06% H.

5,6α-Oxido-17α-methyl-B-nor-5α-androstane-3β,17β-diol (**23**)

When a lower excess of 4-toluenesulfonhydrazide (twofold to threefold molar excess) was used for the preparation of compound **22**, the starting olefin had to be removed by epoxidation with 3-chloroperoxybenzoic acid. A polar reaction product **23** was obtained in 5 to 10% yields, m.p. 160–161 °C (acetone); $[\alpha]_D$ –51° (*c* 1.1). For $C_{19}H_{30}O_3$ (306.5) calculated: 74.47% C, 9.87% H; found: 74.32% C, 9.92% H.

17β-Benzoyloxy-B-nor-5α-androstan-3-one (**24**)

3β-Hydroxy derivative **21** (199 mg, 0.52 mmol) was oxidized in acetone (8 ml) with Jones reagent at 0 °C. After 10 min the excess reagent was destroyed by methanol, the acids present were neutralized by the potassium hydrogen carbonate solution (6%, 1.0 ml) and the reaction mixture was concentrated in a vacuum. The product was precipitated by another lot of the potassium hydrogen carbonate solution and extracted with chloroform. Crystallization of the product from acetone–heptane, afforded compound **24** (158 mg, 80%), m.p. 185.5–186 °C, $[\alpha]_D$ +72° (*c* 1.1), $\Delta\varepsilon_{289}$ +1.80 (methanol). Literature[22] gives m.p. 185–186 °C and $[\alpha]_D$ +80°).

17β-Hydroxy-17α-methyl-B-nor-5α-androstan-3-one (**25**)

3β-Alcohol **22** (220 mg, 0.75 mmol) was oxidized according to the preparation of compound **24**. Crystallization of the product from acetone afforded 156 mg (72%) of compound **25**, m.p. 168–168.5 °C, $[\alpha]_D$ +5° (*c* 1.4). For $C_{19}H_{30}O_2$ (290.4) calculated: 78.03% C, 11.03% H; found: 77.89% C, 11.17% H.

17β-Hydroxy-B-nor-5α-androstan-3-one (**26**)

A solution of benzoate **24** (196 mg, 0.52 mmol) in methanol (18 ml) containing sodium methoxide (280 mg, 5.2 mmol) was refluxed under nitrogen for 2 h. Most of the solvent was removed in a vacuum, the product was precipitated with brine, filtered and washed with water. Crystallization of the residue from acetone–heptane afforded compound **26** (104 mg, 73.0%), m.p. 176.5–177 °C, $[\alpha]_D$ +29° (*c* 1.3), $\Delta\varepsilon_{291}$ +1.63 (methanol). Literature records m.p. 173–174 °C and $[\alpha]_D$ +38°.

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