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Synthesis of 5-azaandrostane-3β,17β-diol protected at the 17β-hydroxyl group*

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Abstract: In the present paper, the preparation of 3β-hydroxy-17β-dimethyl-*tert*-butylsilyloxy-5-azaandrostane (**15**) in fourteen steps is described. B-nor-17-oxoandrost-5-en-3β-yl acetate (**1**)[1,2] was used as the starting material, which was transformed to the key intermediate of the synthesis, B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-4-en-3β-yl acetate (**7**).

Keywords: 5-azasteroids, B-nor-17-oxoandrost-5-en-3β-yl acetate, 3β-hydroxy-17β-dimethyl-*tert*-butylsilyloxy-5-azaandrostane.

INTRODUCTION

5-Azasteroids, the nitrogen analogs of natural steroids which contain the six-membered rings A and B, deserve particular attention. Due to their structural similarity with non-modified steroids, it can be assumed that the 5-aza analogs of biologically active natural steroids could also possess potential biological activity.

In connection with such a possibility, it was assumed that 3β,17β-dihydroxy-5-aza derivatives with 17β-hydroxyl group protected could be useful substrates for the preparation of the above-mentioned 5-aza derivatives. The structure of such substrates enables the selective functionalization of the C(3)- and C(17)-position, which is necessary in most of the syntheses of biologically active steroid compounds.

RESULTS AND DISCUSSION

The starting 17-oxo derivative **1** was reduced with a methanolic solution of sodium borohydride to produce the 17β-alcohol **2** (in about 95 % yield). Upon treat-

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ment with *tert*-butyldimethylsilyl chloride in dimethyl formamide in the presence of imidazole, the alcohol **2** was transformed to the crystalline *tert*-butyldimethylsilyl derivative **3** (in ≈ 97 % yield) (Scheme 1). Its ^{1}H-NMR spectrum (singlet, 12H, at δ 0.86 ppm for $(CH_3)_3C$ and $CH_3(19)$), and ^{13}C-NMR spectrum (singlet at 18.1 ppm for Me_3C, and two quartets at – 4.5 and – 4.9 ppm for the two *Me*Si) are characteristic for compounds containing the dimethyl-*tert*-butylsilyloxy group.

Scheme 1. **a**. $NaBH_4$/MeOH, **b**. TBDMSCl, imidazole, dimethyl formamide, **c**. KOH/MeOH, **d**. Oppenauer oxidation, **e**. $NaBH_4$/MeOH, **f**. Ac_2O/Py.

For the desired modification of the steroid moiety, it was necessary to shift the double bond from the C(5)–C(6) to the C(4)–C(5) position. This was done by saponification of the 3β-acetoxy derivative **3** with a 5 % methanolic solution of potassium hydroxide to give the alcohol **4** (in 95.6 % yield). The Oppenauer oxidation of the alcohol in dry toluene and cyclohexanone in the presence of aluminium isopropoxide gave the conjugated 3-oxo-Δ^4-derivative **5** (in 93.6 % yield). Its reduction with a methanolic sodium borohydride solution gave the allylic alcohol **6** (in 88.6 % yield), which upon acetylation with acetic anhydride in pyridine at room temperature, was converted to the required intermediate, the 3β-acetoxy derivative **7** (in 86.7 % yield).

The spectral and analytical data obtained for the compounds **2–7** were in complete agreement with their structures presented in Scheme 1 (see Experimental).

The further steps leading from the allylic acetate **7** to the 5-aza derivative **15** (shown in Scheme 2) are based on the approach designed by Rodewald *et al.* for the synthesis of 5-azasteroids of the cholestane[3] and androstane[4] series. It consisted of the following.

Cleavage of the olefinic Δ^4-double bond in the 3β-acetoxy derivative **7** by ozonolysis in dichloromethane solution at – 75 ºC, followed by reductive opening of

Scheme 2. **a**. 1. O_3, 2. $(CH_3)_2S$, **b**. $KMnO_4$, $^tBuOH/NaH_2PO_4$, **c**. Ph_2CN_2, **d**. $NH_2OH/EtOH$, e. $SOCl_2$/ether, **f**. 1. KOH/MeOH, 2. HCl, **g**. Ac_2O/Py, h. $LiAlH_4$/dioxane.

the ozonide bridge with dimethyl sulfide, affording the 4,5-seco-ketoaldehyde **8** (in 99.5 % yield). This product was treated with 5 % aqueous potassium permanganate solution in *tert*-butylalcohol to give B-nor-4,5-seco-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-5-on-4-oic acid **9** which was isolated as an oil (in 97.8 % yield). Due to the instability of the ketoaldehyde **8** and the carboxylic acid **9**, they were used in the next steps without purification. However, their spectral data were consistent with the structures given in Scheme 2 (see Experimental).

Esterification of the acid **9** with diphenyldiazomethane and column chromatography of the obtained mixture on SiO_2 afforded the corresponding ester **10** (in 63.8 % yield). Its treatment with hydroxylamine hydrochloride in ethanol/pyridine solution gave the (*E*)-oxime **11** (in 96.7 % yield).

In the next, step the oxime **11** was subjected to the Beckmann rearrangement (performed in cold (–20 ºC) anhydrous diethyl ether solution with thionyl chloride) to give a complex mixture from which, after column chromatography on silica gel, diphenylmethyl 4,5-seco-5-aza-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-6-on-4-oate **12** was obtained (however in only 34.1 % yield). The low yield of the lactam **12** is partly due to a competing process by which the $\Delta^{1(10)}$-unsaturated cyanide of the partial structure **i** (Scheme 3) is formed (in about 20 % yield).

Upon saponification of the lactam **12**, both the acetoxy and benzhydrilic groups were removed, producing (3*S*)-hydroxy-17β-dimethyl-*tert*-butylsilyloxy-4,5-seco-5-azaandrostan-6-on-4-oic acid (**13**) (in 94.8 % yield). Treatment of a cooled

Scheme 3.

solution (0 ºC) of the acid **13** with acetic anhydride in pyridine, resulted in simultaneous cyclization and acetylation affording 17β-dimethyl-*tert*-butylsilyloxy-5-azaandrostane-4,6-dion-3β-yl acetate **14** (in 84.5 %). Reduction of the diimide **14** was performed with an excess of lithium aluminium hydride in boiling dioxane. Under these conditions, both the C-4 and C-6 oxo functions were reduced to methylene groups and the 3β-acetoxy function to the 3β-hydroxyl group, affording the desired 17β-dimethyl-*tert*-butylsilyloxy-5-azaandrostan-3β-ol (**15**) in 90.7 % yield (and after recrystallization from acetone/methanol in 76.5 % yield).

Analytical ($C_{24}H_{45}O_2NSi$) and spectral data (IR, ^{1}H- and ^{13}C-NMR, see Experimental) of the obtained 5-aza derivative **15** showed that protection of the 17β-hydroxyl was preserved during all steps of the synthesis. The total yield of **15** starting from compound **1** was about 9 %.

EXPERIMENTAL

General

Column chromatography: silica gel 0.04–0.063 mm. TLC: control of reactions and separation of products on silica gel G (Stahl), detection with aq. 50 % H_2SO_4 soln. M.p.: uncorrected. IR spectra: Perkin-Elmer-337 and Varian Gemini FT- 80A spectrophotometers; ν in cm^{-1}. NMR spectra: [a]Varian Gemini 200 and [b]Varian Gemini FT-80 (^{1}H at 200 and 80 MHz; ^{13}C at 50 MHz); $CDCl_3$ soln. at r.t.; $SiMe_4$ as internal standard; δ in ppm, J in Hz. Mass spectra: Finnigan-MAT 8230; m/z (rel. intensity in %); ionization energy 70 eV.

B-Nor-17-oxoandrost-5-en-3β-yl acetate (**1**)[1,2]

M.p. 134–135 ºC (lit.[2] m.p. 135–136 ºC), $[\alpha]_D = -43.5$ ($c = 1.0$, $CHCl_3$); lit.[2] $[\alpha]_D = -50 \pm 2$ ($c = 2.4$, $CHCl_3$). IR (neat): 1745, 1244, 1049. ^{1}H-NMR[a]: 0.91 (*s*, 3H, Me(18)), 0.92 (*s*, 3H, Me(19)), 2.05 (*s*, 3H, AcO), 2.45 (2 × *m*, 2H), 2.66 (*ddd*, 1H, $J = 13.6$, 4.6, 2.0 Hz, H_β–C(4)), 4.64 (*m*, 1H, H–C(3)), 5.47 (*br.s*, 1H, H–C(6)). ^{13}C-NMR: 220.1 (*s*, C(17)), 170.3 (*s*, MeCOO), 148.7 (*s*, C(5)), 124.1 (*d*, C(6)), 73.3 (*d*, C(3)), 62.3 (*d*, C(9)), 49.4 (*d*, C(14)), 49.1 (*s*, C(13)), 45.5 (*d*, C(8)), 44.5 (*s*, C(10)), 36.6 (*t*, C(1)), 35.6 (*t*, C(16)), 32.6 (*t*, C(4)), 31.6 (*t*, C(12)), 27.7 (*t*, C(2)), 22.2 (*t*, C(15)), 21.2 (*q*, *Me*COO), 19.9 (*t*, C(11)), 14.8 (*q*, C(19)), 13.9 (*q*, C(18)). Anal: calcd. for $C_{20}H_{28}O_3$ (316.444): C 75.91, H 8.92; found: C 75.68, H 9.00.

*Sodium borohydride reduction of B-nor-17-oxoandrost-5-en-3β-yl acetate (**1**)*

To a stirred soln. of **1** (50.0 g) in MeOH (350 ml) cooled in an ice-water bath, $NaBH_4$ (4.0 g) was added portion-wise during 20 min. The mixture was poured into vigorously stirred ice cold water acidified with acetic acid. The precipitate was filtered off, thoroughly washed with water and air-dried to give B-nor-17β-hydroxy-androst-5-en-3β-yl acetate (**2**) (50.0 g, 99.5 %), which was recrystallized from acetone/methanol (47.6 g, 94.6 %). M.p. 148–150 ºC (lit.[5] m.p. 151–152 ºC). IR (KBr): 3300, 1735, 1240, 1054, 1036. ^{1}H-NMR[a]: 0.77 (*s*, 3H, Me-(18)), 0.90 (*s*, 3H, Me-(19)), 2.04 (*s*, 3H, AcO), 2.63 (*ddd*, 1H, $J = 13.6$, 5.0, 2.0 Hz, H_β–C(4)), 3.69 (*t*, 1H, $J = 7.6$ Hz, H–C(17)), 4.63

(*m*, 1H, H–C(3)), 5.38 (*br.s*, 1H, H–C(6)). ^{13}C-NMR: 170.6 (*s*, Me*C*OO), 148.0 (*s*, C(5)), 125.6 (*d*, C(6)), 81.3 (*d*, C(17)), 73.6 (*d*, C(3)), 62.4 (*d*, C(9)), 49.1 (*d*, C(14)), 46.1 (*d*, C(8)), 44.9 (*s*, C(13)), 44.6 (*s*, C(10)), 36.9 (*t*, C(1)), 36.8 (*t*, C(16)), 32.7 (*t*, C(4)), 30.6 (*t*, C(12)), 27.9 (*t*, C(2)), 23.7 (*t*, C(15)), 21.3 (*q*, *Me*COO), 20.5 (*t*, C(11), 14.9 (*q*, C(19)), 11.3 (*q*, C(18)). Anal: calcd. for $C_{20}H_{30}O_3$ (381.460): C 75.43, H 9.50; found: C 75.37, H 9.49.

Dimethyl-tert-*butylsilylation of B-nor-17β-hydroxy-androst-5-en-3β-yl acetate (**2**)*

To a stirred soln. of **2** (47.0 g) in dimethylformamide (330 ml) cooled in an ice-water bath, dimethyl-*tert*-butylsilyl chloride (34.04 g) and imidazole (31.6 g) were added. The stirring was continued first at r.t. (30 min) and then at 45–50 ºC until consumption of the substrate (TLC control) (≈2 h). The mixture was poured into crushed ice-water (≈ 2 l) with vigorous stirring. The precipitate was filtered off, thoroughly washed with water and air-dried to give B-nor-17β-dimethyl-*tert*-butylsilyloxy-androst-5-en-3β-yl acetate (**3**) (62.0 g, 97.1 %). M.p. 83–87 ºC. $[\alpha]_D = -76.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 1736, 1242, 1129, 1088, 1033, 837, 777. ^{1}H-NMR^b: 0.70 (*s*, 3H, Me(18)), 0.86 (*s*, 12H, Me_3C, Me(19)), 2.01 (*s*, 3H, AcO), 2.62 (*dd*, 1H, $J = 13.6$, 5.0 Hz, H_β–C(4)), 3.58 (*m*, 1H, H–C(17)), 4.60 (*m*, 1H, H–C(3)), 5.34 (*br.s*, 1H, H–C(6)). ^{13}C-NMR: 170.6 (*s*, Me*C*OO), 147.9 (*s*, C(5)), 125.8 (*d*, C(6)), 81.2 (*d*, C(17)), 73.7 (*d*, C(3)), 62.7 (*d*, C(9)), 48.8 (*d*, C(14)), 46.3 (*d*, C(8)), 45.3 (*s*, C(13)), 44.6 (*s*, C(10)), 37.3 (*t*, C(1)), 36.9 (*t*, C(16)), 32.7 (*t*, C(4)), 31.1 (*t*, C(12)), 28.0 (*t*, C(2)), 25.8 (*q*, Me_3C), 23.9 (*t*, C(15)), 21.4 (*q*, *Me*COO), 20.6 (*t*, C(11)), 18.1 (*s*, Me_3*C*), 15.0 (*q*, C(19)), 11.5 (*q*, C(18)), –4.5 (*q*, MeSi), –4.9 (*q*, MeSi). Anal: calcd. for $C_{26}H_{44}O_3Si$ (432.724): C 72.17, H 10.25; found: C, 72.03, H, 10.34.

Saponification of B-nor-17β-dimethyl-tert-*butylsilyloxyandrost-5-en-3β-yl acetate (**3**)*

A soln. of **3** (105.5 g) in MeOH (600 ml) and 5 % methanolic KOH (100 ml) was refluxed for 1 h. After cooling at r.t., the mixture was diluted with water. The precipitate was filtered off, thoroughly washed with water and air-dried to give B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-5-en-3β-ol (**4**) (91.1 g, 95.6 %). M.p. 141–143 ºC. $[\alpha]_D = -58.0$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3412, 3267, 1461, 1251, 1131, 1106, 1097, 1088, 1063, 1044, 858, 835, 774. ^{1}H-NMR^b: 0.72 (*s*, 3H, Me(18)), 0.86 (*s*, 12H, Me_3C, Me(19)), 2.58 (*dd*, 1H, $J = 13.6$, 5.2 Hz, H_β–C(4)), 3.56 (2 × *m*, 2H, H–C(3), H–C(17)), 5.32 (*br.s*, 1H, H–C(6)). ^{13}C-NMR: 149.2 (*s*, C(5)), 124.9 (*d*, C(6)), 81.3 (*d*, C(17)), 71.7 (*d*, C(3)), 62.8 (*d*, C(9)), 49.0 (*d*, C(14)), 46.3 (*d*, C(8)), 45.3 (*s*, C(13)), 44.6 (*s*, C(10)), 37.4 (*t*, C(1)), 37.2 (*t*, C(16)), 36.6 (*t*, C(4)), 32.0 (*t*, C(12)), 31.1 (*t*, C(2)), 25.8 (*q*, Me_3C), 23.9 (*t*, C(15)), 20.6 (*t*, C(11)), 18.1 (*s*, Me_3*C*), 15.1 (*q*, C(19)), 11.5 (*q*, C(18)), –4.5 (*q*, MeSi), –4.9 (*q*, MeSi)). Anal: calcd. for $C_{24}H_{42}O_2Si$ (390.686): C 73.78, H 10.84; found: C 73.76, H 10.96.

Oppenauer oxidation of B-nor-17β-dimethyl-tert-*butylsilyloxyandrost-5-en-3β-ol (**4**)*

To a distilling soln. of **4** (91.0 g) in dry toluene (2 l) and cyclohexanone (500 ml), a soln. of Al-isopropoxide (28 g) in toluene (400 ml) was slowly added through a dropping funnel at a rate which corresponded to the rate of solvent distillation. When the addition was completed and the substrate consumed (TLC control), the distillation was continued until *ca.* 1200 ml solvent had been distilled off. The rest was transferred to a separatory funnel, treated with a saturated aq. K,Na-tartrate soln. (400 ml) and after vigorous shaking the separated aq. layer was discarded. The organic layer was diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), filtered off and evaporated to dryness under reduced pressure to give B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-4-en-3-one (**5**) (84.7 g, 93.6 %), which was recrystallized from MeOH (76.9 g, 84.9 %). M.p. 101–103 ºC. $[\alpha]_D^{25} = -0.60$ ($c = 1.0$, $CHCl_3$). IR (KBr): 1673, 1620, 1262, 1251, 1108, 1097, 1077, 879, 841, 777. ^{1}H-NMR^a: 0.013 (*s*, 3H, Me–Si), 0.018 (*s*, 3H, Me–Si), 0.76 (*s*, 3H, Me(18)), 0.89 (*s*, 9H, Me_3C), 1.08 (*s*, 3H, Me(19)), 3.61 (*t*, 1H, $J = 7.8$ Hz, H–C(17)), 5.78 (*br.s*, 1H, H–C(4)). ^{13}C-NMR: 199.6 (*s*, C(3)), 179.0 (*s*, C(5)), 122.5 (*d*, C(4)), 81.1 (*d*, C(17)), 58.4 (*d*, C(9)), 50.3 (*d*, C(14)), 45.0 (*s*, C(13)), 43.8 (*s*, C(10)), 38.4 (*d*, C(8)), 36.6 (*t*, C(2)), 35.2 (*t*, C(16)), 34.2 (*t*, C(1)), 33.5 (*t*, C(6)), 30.9 (*t*, C(12)), 25.8 (*q*, Me_3C), 23.9 (*t*, C(15)), 20.4 (*t*, C(1)), 18.0 (*s*, Me_3*C*), 17.4 (*q*, C(19)), 11.6 (*q*, C(18)), –4.6 (*q*, MeSi), –4.9 (*q*, MeSi). Anal: calcd. for $C_{24}H_{40}O_2Si$ (388.670): C 74.17, H 10.37; found: C 74.28, H 10.22.

*Sodium borohydride reduction of B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-4-en-3-one (**5**)*

A solution of **5** (90.0 g) in MeOH (800 ml) was reduced with $NaBH_4$ (≈11 g) at r.t. (TLC control) and the mixture worked up as previously described. The isolated crystalline solid (88.0 g, 97.3 %) was recrystallized twice from MeOH to give B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-4-en-3β-ol (**6**) (80.2 g, 88.6 %). M.p. 123–126 ºC. IR (KBr): 3416, 1473, 1251, 1155, 1102, 877, 838, 774. ^{1}H-NMR^a: 0.000 (*s*, 3H, Me–Si), 0.005 (*s*, 3H, Me–Si), 0.73 (*s*, 3H, Me(18)), 0.88 (*s*, 9H, Me_3C), 0.96 (*s*, 3H, Me(19)), 2.43 (*dd*, 1H, *J* = 17.4, 9.6 Hz, H_β–C(6)), 3.57 (*t*, 1H, *J* = 7.6 Hz, H–C(17)), 4.26 (*m*, 1H, H–C(3)), 5.30 (*s*, 1H, H–C(4)). ^{13}C-NMR: 152.9 (*s*, C(5)), 121.6 (*d*, C(4)), 81.3 (*d*, C(17)), 68.8 (*d*, C(3)), 59.2 (*d*, C(9)), 50.5 (*d*, C(14)), 45.1 (*s*, C(13)), 42.1 (*s*, C(10)), 37.9 (*d*, C(8)), 36.9 (*t*, C(2)), 35.3 (*t*, C(16)), 31.9 (*t*, C(1)), 30.9 (*t*, C(6)), 29.3 (*t*, C(12)), 25.8 (*q*, *Me*$_3$C), 24.0 (*t*, C(15)), 20.5 (*t*, C(11), 18.5 (*q*, C(19)), 18.0 (*s*, Me$_3$*C*), 11.7 (*q*, C(18)), –4.6 (*q*, MeSi), –5.0 (*q*, MeSi). Anal: calcd. for $C_{24}H_{42}O_2Si$ (390.686): C 73.78, H 10.84; found: C 73.75, H 10.67.

*Acetylation of B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-4-en-3β-ol (**6**)*

A solution of **6** (80.0 g) in pyridine (425 ml) was acetylated with acetic anhydride (275 ml) at r.t. for 16 h. The mixture was poured into crushed ice-water under stirring. The precipitate was filtered off, thoroughly washed with water and air-dried to give B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-4-en-3β-yl acetate (**7**) (87.3 g, 98.5 %), which was recrystallized from acetone/methanol (76.8 g, 86.7 %). M.p. 72–73 ºC. $[\alpha]_D$ = –62.3 (*c* = 1.0, $CHCl_3$). IR (KBr): 1736, 1240, 1101, 907, 879, 838,. 778. ^{1}H-NMR^b: 0.00 (*s*, 6H, Me_2Si), 0.72 (*s*, 3H, Me(18)), 0.88 (*s*, 9H, *Me*$_3$C), 0.98 (*s*, 3H, Me(19)), 2.05 (*s*, 3H, AcO), 3.58 (*t*, 1H, *J* = 7.8 Hz, H–C(17)), 5.26 (*br.s*, 1H, H–C(4)), 5.35 (*m*, 1H, H–C(3)). ^{13}C-NMR: 171.1 (*s*, Me*C*OO), 155.5 (*s*, C(5)), 117.3 (*d*, C(4)), 81.2 (*d*, C(17)), 71.2 (*d*, C(3)), 59.1 (*d*, C(9)), 50.5 (*d*, C(14)), 45.1 (*s*, C(13)), 42.0 (*s*, C(10)), 37.9 (*d*, C(8)), 36.9 (*t*, C(2)), 35.2 (*t*, C(16)), 32.2 (*t*, C(1)), 30.9 (*t*, C(6)), 25.8 (*q*, *Me*$_3$C), 24.9 (*t*, C(12)), 24.0 (*t*, C(15)), 21.4 (*Me*COO), 20.1 (*t*, C(11)), 18.5 (*q*, C(19)), 18.0 (*s*, Me$_3$*C*), 11.7 (*q*, C(18)), –4.6 (*q*, MeSi), –4.9 (*q*, MeSi). Anal: calcd. for $C_{26}H_{44}O_3Si$ (432.724): C 72.17, H 10.25; found: C 71.96, H 9.89.

*Ozonolysis of B-nor-17β-dimethyl-*tert*-butylsilyloxyandrost-4-en-3β-yl acetate (7) (reductive procedure)*

A solution of **7** (12.5 g) in CH_2Cl_2 (365 ml) and MeOH (1.82 ml) was ozonized at –75 ºC till blue color appeared (≈7.7 h). While still at –75 ºC, the solution was flushed with argon for 45 min and treated with dimethyl sulfide (13 ml). The mixture was left at –75 ºC for 1 h and at 0 ºC for 4 h. Then it was transferred to a separatory funnel, diluted with CH_2Cl_2 (200 ml), washed with water, saturated aq. $NaHCO_3$ soln., water, dried (Na_2SO_4) and evaporated to dryness affording B-nor-4,5-seco-4,5-dioxo-17β-dimethyl-*tert*-butylsilyloxyandrostan-(3*S*)-yl acetate (**8**) (13.35 g, 99.5 %), as an oil. It was used in the next step without purification.* IR (neat): 1738, 1249, 1134, 1101, 1075, 1044, 836, 775, 758. ^{1}H-NMR^a: –0.01 (*s*, 3H, Me–Si), – 0.03 (*s*, 3H, Me–Si), 0.78 (*s*, 3H, Me(18)), 0.89 (*s*, 9H, Me_3C), 0.90 (*s*, 3H, Me(19)), 2.17 (*s*, 3H, AcO), 2.34 (*dd*, 1H, *J* = 15.6, 4.4 Hz, H_β–C(6)), 3.63 (*t*, 1H, *J* = 7.8 Hz, H–C(17)), 4.91 (*dd*, 1H, *J* = 7.6, 4.2 Hz, H–C(3)), 9.49 (*s*, 1H, HCO). ^{13}C-NMR: 221.9 (*s*, C(5)), 198.1 (*d*, C(4)), 170.5 (*s*, Me*C*OO), 81.0 (*d*, C(17)), 78.2 (*d*, C(3)), 52.1 (*d*, C(9)), 50.1 (*d*, C(14)), 50.0 (*s*, C(13)), 44.7 (*s*, C(10)), 42.9 (*t*, C(2)), 36.6 (*t*, C(16)), 36.5 (*d*, C(8)), 31.3 (*t*, C(1)), 30.7 (*t*, C(6)), 25.7 (*q*, *Me*$_3$C), 23.9 (*t*, C(12)), 23.6 (*t*, C(15)), 20.7 (*q*, *Me*COO), 20.4 (*t*, C(11)), 17.9 (*s*, Me$_3$*C*), 17.5 (*q*, C(19)), 11.5 (*q*, C(18)), –4.7 (*q*, *Me*Si), –5.0 (*q*, *Me*Si). $C_{26}H_{44}O_5Si$ (464.724). CI-MS: 465 (M + 1, 12 %), 405 (465 – CH_3COOH, 100 %).

*Potassium permanganate oxidation of B-nor-4,5-seco-4,5-dioxo-17β-dimethyl-*tert*-butylsilyloxyandrostan-(3*S*)-yl acetate (**8**)*

To a solution of **8** (13.30 g) in *tert*-BuOH (172 ml) and aq. 5 % Na_2HPO_4 soln. (115 ml), an aq. 1 M $KMnO_4$ soln. (172 ml) was gradually added with vigorous stirring at r.t. After 45 min (TLC control), the reaction was quenched with cold (0 ºC) dilute HCl (to pH 3). The mixture was extracted with diethyl ether, the organic layer washed with saturated aq. NaCl soln. until neutral, dried

* For analyses a small amount of this product was chromatographed on a SiO_2 column.

(Na_2SO_4) and evaporated to dryness under reduced pressure to give B-nor-4,5-seco-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-5-on-4-oic acid (**9**) (13.45 g, 97.8 %), as an oil. It was used in the next step without purification.* IR (neat): 3650–3200, 1740, 1250, 1135, 1075, 836, 776. ^{1}H-NMR^a: 0.02 (*s*, 3H, Me–Si), 0.03 (*s*, 3H, Me–Si), 0.78 (*s*, 3H, Me(18)), 0.89 (*s*, 9H, Me_3C), 0.92 (*s*, 3H, Me(19)), 2.14 (*s*, 3H, AcO), 2.36 (*dd*, 1H, *J* = 15.6, 4.4 Hz, H_β–C(6)), 3.64 (*t*, 1H, *J* = 7.2 Hz, H–C(17)), 4.94 (*dd*, 1H, *J* = 7.4, 4.4 Hz, H–C(3)), 8.20–8.6 (*br.s*, 1H, COOH). ^{13}C-NMR: 222.5 (*s*, C(5)), 174.9 (*s*, *C*OOH), 170.6 (*s*, Me*C*OO), 81.0 (*d*, C(17)), 71.9 (*d*, C(3)), 52.3 (*d*, C(9)), 50.1 (*d*, C(14)), 50.0 (*s*, C(13)), 44.7 (*s*, C(10)), 43.0 (*t*, C(2)), 36.7 (*t*, C(16)), 36.5 (*d*, C(8)), 31.6 (*t*, C(1)), 30.7 (*t*, C(6)), 26.0 (*t*, C(12)), 25.7 (*q*, *Me*$_3$C), 23.9 (*t*, C(15)), 20.8 (*q*, *Me*COO), 20.5 (*t*, C(11)), 17.9 (*s*, Me_3*C*), 17.5 (*q*, C(19)), 11.5 (*q*, C(18)), –4.7 (*q*, MeSi), –5.0(*q*, MeSi). $C_{26}H_{44}O_6Si$ (480.724). CI-MS: 481 (M + 1, 100 %), 421 (M – CH_3COOH, 21 %).

*Esterification of B-nor-4,5-seco-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-5-on-4-oic acid (**9**) with diphenyldiazomethane*

A stirred solution of **9** (13.40 g) in dry benzene (250 ml) was treated with diphenyldiazomethane (5 g) in benzene (50 ml) dropwise at r.t. until a persistent violet colour was obtained. The mixture was evaporated to dryness and the residue chromatographed on SiO_2 column (450 g). Elution with benzene/EtOAc (94:6 and 95:5) eluted diphenylmethyl B-nor-4,5-seco-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-5-on-4-oate (**10**) (11.5 g, 63.8 %), as an oil. IR (neat): 1746, 1472, 1455, 1250, 1100, 1075, 836, 758, 701. ^{1}H-NMR^a: 0.025 (*s*, 3H, Me–Si), 0.037 (*s*, 3H, Me–Si), 0.76 (*s*, 3H, Me(18)), 0.82, (*s*, 3H, Me(19)), 0.90 (*s*, 9H, Me_3C), 2.11 (*s*, 3H, AcO), 2.29 (*dd*, 1H, *J* = 16.4, 5.4 Hz, H_β–C(6)), 3.61 (*t*, 1H, *J* = 7.2 Hz, H–C(17)), 5.06 (*dd*, 1H, *J* = 7.0, 5.2 Hz, H–C(3)), 7.00 (*s*, 1H, (OC*H*$(Ph)_2$), 7.26–7.41 (*m*, 10H, arom.). ^{13}C-NMR: 221.9 (*s*, C(5)), 170.4 (*s*, Me*C*OO), 169.2 (*s*, *C*OOCHPh_2), 139.5 (*s*, arom. *C*–CH), 139.3 (*s*, arom. *C*–CH), 129.6–126.9 (*doublets*, arom *C*H), 81.1 (*d*, C(17)), 77.8 (*d*, O*C*HPh_2), 72.4 (*d*, C(3)), 52.5 (*s*, C(9)), 50.2 (*d*, C(14)), 49.8 (*s*, C(13)), 44.7 (*s*, C(10)), 43.0 (*t*, C(2)), 36.8 (*t*, C(16)), 36.6 (*d*, C(8)), 31.4 (*t*, C(1)), 30.8 (*t*, C(6)), 26.0 (*t*, C(12)), 25.8 (*q*, *Me*$_3$C), 24.0 (*t*, C(15)), 20.7 (*q*, *Me*COO), 20.6 (*t*, C(11)), 18.0 (*s*, Me_3*C*), 17.4 (*q*, C(19)), 11.6 (*q*, C(18)), – 4.6 (*q*, MeSi), – 4.9 (*q*, MeSi). Anal: calcd. for $C_{39}H_{54}O_6Si$ (646.947): C 72.41, H 8.41; found: C 72.29, H 8.59. CI-MS: *m*/*z* = 647 (M + 1).

*Oximation of diphenylmethyl B-nor-4,5-seco-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-5-on-4-oate (**10**)*

A solution of **10** (9.20 g) and hydroxylamine hydrochloride (9.20 g) in ethanol (150ml) and pyridine (36 ml) was heated at reflux for 1.5 h. The solvent was removed by distillation *in vacuo* and the residue diluted with diethyl ether. The ethereal layer was thoroughly washed with water, dried (Na_2SO_4) and evaporated to dryness. The resulting product was chromatographed on SiO_2 column (100 g). Elution with benzene/EtOAc (95:5) afforded diphenylmethyl B-nor-4,5-seco-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-5-on-4-oate oxime (**11**) (9.1 g, 96.7 %), as an oil.+ IR (neat): 3442, 1748, 1249, 1103, 1079, 836, 776, 700. ^{1}H-NMR^a: 0.019 (*s*, 3H, Me–Si), 0.030 (*s*, 3H, Me–Si), 0.71 (*s*, 3H, Me(18)), 0.89 (*s*, 9H, Me_3C), 0.91 (*s*, 3H, Me(19)), 2.10 (*s*, 3H, AcO), 3.59 (*t*, 1H, *J* = 7.6 Hz, H–C(17)), 5.06 (*t*, 1H, *J* = 5.6 Hz, H–C(3)), 6.91 (*s*, 1H, OC*H*Ph_2), 7.24–7.34 (*m*, 10H, arom.), 7.82 (*br.s*, 1H, NO*H*). ^{13}C-NMR: 170.6 (*s*, Me*C*OO), 170.0 (*s*, C(5)), 169.4 (*s*, *C*OOCHPh_2), 139.7 (*s*, arom. *C*–CH), 139.5 (*s*, arom, *C*–CH), 128.5–126.9 (*doublets*, arom. *C*H), 81.2 (*d*, C(17)), 77.6 (*d*, COO*C*HPh_2), 72.7 (*d*, C(3)), 53.6 (*d*, C(9)), 50.2 (*d*, C(14)), 45.7 (*s*, C(13)), 44.8 (*s*, C(10)), 37.6 (*d*, C(8)), 36.7 (*t*, C(2)), 33.0 (*t*, C(16)), 31.2 (*t*, C(1)), 30.9 (*t*, C(6)), 26.2 (*t*, C(12)), 25.8 (*q*, *Me*$_3$C), 23.8 (*t*, C(15)), 21.2 (*q*, *Me*COO), 20.5 (*t*, C(11)), 18.1 (*s*, Me_3*C*), 11.6 (*q*, C(18)), – 4.6 (*q*, MeSi), – 4.9 (*q*, MeSi).Anal: calcd. for $C_{39}H_{55}NO_6Si$ (661.962): C 70.76, H 8.38; found: C 71.19, H 8.77. CI-MS: *m*/*z* = 662 (M + 1, 30 %).

* For analyses a small amount of this product was chromatographed on a SiO_2 column.

\+ For analysis a small amount of this product was rechromatographed.

*Beckmann rearrangement of diphenylmethyl B-nor-4,5-seco-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-5-on-4-oate oxime (**11**)*

To a cooled solution (–20 ºC) of **11** (9.05 g) in dry diethyl ether (500 ml), a soln. of freshly distilled $SOCl_2$ (24 ml) in dry diethyl ether (250 ml) was added dropwise under stirring. The mixture was stirred for an additional 30 min, poured into crushed ice, carefully neutralized with saturated aq. $NaHCO_3$ soln. and extracted with diethyl ether. The ethereal layer was dried and evaporated to give an oily mixture (about 9 g), which was separated by column chromatography on silica gel (300 g). Elution with benzene afforded a mixture (1.75 g, ≈ 20 %) in which the undesired cyano derivative prevailed (IR: 2240 cm^{-1} (CN); ^{1}H-NMR: δ = 1.60 ppm (Me at the olefinic double bond), ≈ 5.00 (olefinic proton)).* Elution with benzene/EtOAc (95:5, 90:10 and 85:15) gave a complex mixture (2.6 g), which was not further investigated. Elution with benzene/Et_2O gave diphenylmethyl 4,5-seco-5-aza-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-6-on-4-oate (**12**) (3.09 g, 34.1 %), as an oil. IR (neat): 3194, 1747, 1660, 1451, 1377, 1249, 1198, 1092, 876, 837, 757, 700. ^{1}H-NMR^a: 0.014 (*s*, 3H, Me–Si), 0.023 (*s*, 3H, Me–Si), 0.70 (*s*, 3H, Me(18)), 0.89 (*s*, 9H, Me_3C), 1.01 (*s*, 3H, Me(19)), 2.13 (*s*, 3H, AcO), 3.56 (*t*, 1H, *J* = 8.4 Hz, H–C(17)), 5.13 (*t*, 1H, *J* = 5.8 Hz, H–C(3)), 5.39 (*s*, 1H, NH), 6.95 (*s*, 1H, COOC*H*Ph_2), 7.30–7.40 (*m*, 10H, arom.). ^{13}C-NMR: 171.7 (*s*, C(6)), 170.3 (*s*, Me*C*OO), 168.9 (*s*, *C*OOCHPh_2), 139.5 (*s*, arom. *C*–CH), 139.1 (*s*, arom. *C*–CH), 128.7–126.9 (*doublets*, arom. CH), 81.2 (*d*, C(17)), 77.9 (*d*, COO*C*HPh_2) 71.7 (*d*, C(3)), 57.3 (*s*, C(10)), 50.3 (*d*, C(14)), 43.6 (*d*, C(9)), 43.1 (*s*, C(13)), 36.6 (*t*, C(12)), 36.3 (*t*, C(7)), 35.2 (*t*, C(1)), 31.3 (*d*, C(8)), 30.6 (*t*, C(16)), 25.8 (*q*, *Me*$_3$C), 25.7 (*q*, C(19)), 24.7 (*t*, C(15)), 23.1 (*t*, C(2)), 21.2 (*t*, C(11)), 20.6 (*q*, *Me*COO), 18.0 (*s*, Me_3*C*), 11.2 (*q*, C(18)), – 4.6 (*q*, MeSi), – 4.9 (*q*, MeSi). Anal: calcd. for $C_{39}H_{55}NO_6Si$ (661.962): C 70.76, H 8.38, N 2.12; found: C 70.81, H, 7.98, N 2.07. CI-MS: *m*/*z* = 662 (M + 1).

*Saponification of diphenylmethyl 4,5-seco-5-aza-(3*S*)-acetoxy-17β-dimethyl-*tert*-butylsilyloxyandrostan-6-on-4-oate (**12**)*

A solution of **12** (3.0 g) in MeOH (100 ml) and 5 % methanolic potassium hydroxide (25 ml) was refluxed for 2 h (TLC control) and poured onto crushed ice. The mixture was transferred to a separatory funnel and washed with diethyl ether. The aqueous layer was cooled to – 10 ºC, acidified with 10 % hydrochloric acid to pH 1 and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to dryness to give (3*S*)-hydroxy-17β-dimethyl-*tert*-butylsilyloxy-4,5-seco-5-aza-androstan-6-on-4-oic acid (**13**) (1.95 g, 94.8 %), which was used in the next step without purification. IR (neat): 3600–3150, 1708, 1641, 1451, 1407, 1251, 1142, 875, 837, 816, 774, 668. 1H-NMR: 0.00 (*s*, 3H, Me–Si), 0.010 (*s*, 3H, Me–Si), 0.72 (*s*, 3H, Me(18)), 0.88 (*s*, 9H, Me_3C), 1.26 (*s*, 3H, Me(19)), 3.58 (2 × *m*, 2H, H–C(3), H–C(17)), 5.15 (*br.s*, 2H, NH, HO–C(3)), 7.45 (*br. m*, 1H, COOH). $C_{24}H_{45}NO_5Si$ (453.701). CI-MS: *m*/*z* = 454 (M + 1, 50 %).

*Cyclization of (3*S*)-hydroxy-17β-dimethyl-*tert*-butylsilyloxy-4,5-seco-5-azaandrostan-6-on-4-oic acid (**13**)*

To a cold (0 ºC) solution of **13** (1.90 g) in pyridine (50 ml), acetic anhydride (25 ml) was added and the mixture left overnight in a refrigerator. Then it was poured onto crushed ice and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to dryness leaving an oil (about 2 g) which was recrystallized from methanol to give 17β-dimethyl-*tert*-butylsilyl-5-azaandrostane-4,6-dion-3β-yl acetate (**14**) (1.69 g, 84.5 %). M.p. 166–168 ºC. $[\alpha]_D$ = – 53.4 (*c* = 1.0, $CHCl_3$). IR (KBr): 1773, 1757, 1669, 1474, 1461, 1371, 1252, 1229, 1137, 1099, 1079, 877, 835, 775. ^{1}H-NMR^b: 0.70 (*s*, 3H, Me(18)), 0.85 (*s*, 9H, Me_3C), 1.28 (*s*, 3H, Me(19)), 2.23 (*s*, 3H, AcO), 3.56 (*t*, 1H, *J* = 8.0 Hz, H–C(17)), 5.25 (*m*, 1H, H–C(3)). ^{13}C-NMR: 174.5, 173.3 (two *s*, C(4), C(6)), 170.6 (*s*, Me*C*OO), 81.2 (*d*, C(17)), 71.5 (*d*, C(3)), 58.3 (*s*, C(10)), 50.2 (*d*, C(14)), 43.6 (*d*, C(9)), 43.2 (*s*, C(13)), 36.2 (*t*, C(12)), 35.4 (*t*, C(7)), 35.0 (*t*, C(1)), 30.7 (*d*, C(8)), 25.8 (*q*, *Me*$_3$C), 25.0 (*q*, C(19)), 24.8 (*t*, C(15)), 23.1 (*t*, C(2)), 21.3 (*t*, C(11)), 20.7 (*q*, *Me*COO), 18.0 (*s*, Me_3*C*), 11.2 (*q*, C(18)), – 4.6 (*q*, MeSi), – 4.9 (*q*, MeSi). Anal: calcd. for $C_{26}H_{43}NO_5Si$ (477.723): C 65.37, H 9.07, N 2.93; found: C 65.24, H 9.29, N 3.16. CI-MS: *m*/*z* = 478 (M + 1).

* This compound was not properly purified for a correct analysis.

Lithium aluminium hydride reduction of 17β-dimethyl-tert-*butylsilyl-5-azaandrostane-4,6-dion-3β-yl acetate (**14**)*

To a refluxed suspension of $LiAlH_4$ (12 g) in dioxane (distilled over Na) (190 ml), a soln. of **14** (1.90 g) in dry dioxane (190 ml) was dropwise added during 3 h, and the heating continued for an additional 14 h. The usual alkaline work-up afforded a crude reaction product (1.47 g, 90.7 %) which was recrystallized from acetone/methanol to give 17β-dimethyl-*tert*-butylsilyloxy-5-azaandrostan-3β-ol (**15**) (1.24 g, 76.5 %). M.p. 158–159 ºC. $[\alpha]_D$ = + 4.3 (*c* = 1.0, $CHCl_3$). IR (KBr): 3338, 1473, 1390, 1374, 1250, 1156, 1133, 1095, 1070, 896, 834, 775. ^{1}H-NMR^b: 0.71 (*s*, 3H, Me(18)), 0.86 (*s*, 9H, Me_3C), 0.92 (*s*, 3H, Me(19)), 2.20–2.80 (*m*, 4H, $H_2C(4)$, $H_2C(6)$), 3.58 (*t*, 1H, *J* = 8.0 Hz, H–C(17)), 3.75 (*m*, 1H, H–C(3)). ^{13}C-NMR: 81.6 (*d*, C(17)), 68,0 (*d*, C(3)), 57.1 (*t*, C(4)), 55.4 (*s*, C(10)), 53.3 (*d*, C(14)), 50.1 (*d*, C(9)), 49.8 (*t*, C(6)), 43.1 (*s*, C(13)), 37.0 (*t*, C(12)), 36.1 (*t*, C(1)), 34.3 (*d*, C(8)), 30.9 (*t*, C(7)), 30.6 (*t*, C(16)), 29.9 (*t*, C(15)), 25.8 (*q*, Me_3C), 23.2 (*t*, C(2)), 21.7 (*t*, C(11)), 18.0 (*s*, Me_3C), 11.3 (*q*, C(18)), 7.12 (*q*, C(19)), – 4.6 (*q*, MeSi), – 4.9 (*q*, MeSi)). Anal: calcd. for $C_{24}H_{45}NO_2S$ (407.717): C 70.70, H, 11.12; found: C 70.88, H 11.40. CI-MS: *m*/*z* = 408 (M + 1).

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ИЗВОД

СИНТЕЗА 5-АЗААНДРОСТАН-3β,17β-ДИОЛА ЗАШТИЋЕНОГ НА 17β-ХИДРОКСИЛНОЈ ГРУПИ

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У овом раду је описано добијање 3β-хидрокси-17β-диметил-*tert*-бутилсилилокси-5-азаандростана (**15**) у 14 фаза. Као полазно једињење употребљен је B-нор-17-оксоандрост-5-ен-3β-ил-ацетат (**1**) који је трансформисан у кључни интермедијер синтезе, B-нор-17β-диметил-*tert*-бутилсилилоксиандрост-4-ен-3β-ил-ацетат (**7**).

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