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Synthesis of 13,14-secotestosterone derivatives

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Abstract

A number of testosterone analogs with a 13,14-secosteroidal fragment have been prepared from (13*S*)-13-iodo-6β-methoxy-3α, 5-cyclo-13,14-seco-5α-androstan-14,17-dione. The key steps involved stereoselective deiodination of the starting compound with triphenylphosphine and selective protection of the 17-keto group with trimethylsilylcyanide. Removal of iodine at C-13 proceeded with inversion of the configuration at C-13, which has been established by X-ray crystallography. 13,14-Secotestosterone analogues substituted and non-substituted at C-14 have been prepared. The obtained compounds containing flexible CD ring fragments are of great interest for comparative studies in biological tests together with testosterone and other steroids with a rigid tetracyclic skeleton.
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1. Introduction

Secosteroids have attracted considerable interest because of the broad range of biological activities of many naturally occurring representatives, such as Vitamins D [1], with anolides [2], and marine steroids [3,4]. Apart from Vitamins D with their innumerable biological effects [5], secosteroids with cytotoxic [6–8], antihistamine [9], and anticancer [10] activity should be mentioned as compounds with great potential for drug development. The activity of seco analogs of normal steroidal hormones in humans and higher animals is a matter of scientific interest as well. Some of these compounds were prepared synthetically and showed hormonal or antihormonal activity [11–18]. It is evident that the higher conformational flexibility of seco steroids in comparison with normal steroids may result in novel, pharmaceutically useful compounds. As part of our continuing interest in the synthesis of secosteroids [19,20], we report here on the preparation of 13,14-seco analogs of testosterone.

2. Experimental

The detailed description of experimental details is given in our previous article [20]. Crystal data and numerical details of the structure determination are given in Table 1.

2.1. (13S)-6β-Methoxy-3α,5-cyclo-13,14-seco-5α-androstan-14,17-dione (2)

Iodo ketone **l** (15 g, 33.8 mmol) [19] was added to a solution of triphenylphosphine (13.6 g, 51.9 mmol) in THF (50 ml). After 10 min, the precipitate was filtered off, and the filtrate was evaporated. The residue was chromatographed on SiO_2 (hexane–EtOAc = 5:1) to give diketone **2** (10 g, 93%) as an oil. IR (cm^{-1}): 1710, 1465, 1450, 1390, 1110, 1090. ^{1}H NMR δ: 1.00 (s, 3H, 19-H), 1.06 (d, J 7 Hz, 3H, 18-H), 2.32–2.60 (m, 2H, 15-H), 2.70–2.78 (m, 2H, 16-H), 2.82 (m, 1H, 6-H), 3.34 (s, 3H, OMe). ^{13}C NMR δ: 13.1,

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Table 1
Crystal data and structure refinement details for (13*S*,17*R*)-17-acetoxy-13,14-seco-androst-4,14(*E*)-dien-3-one **26a**

Empirical formula	$C_{21}H_{30}O_3$
Formula weight	330.45
Temperature (K)	293(2)
Wavelength (Å)	0.71069
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	A = 7.936(2) Å, $\alpha = 90^\circ$ B = 18.272(5) Å, $\beta = 100.80(2)^\circ$ C= 13.138(3) Å, $\gamma = 90^\circ$
Volume (Å^3)	1871.4(8)
Z	4
Calculated density (Mg/m^3)	1.173
Absorption coefficient (mm^{-1})	0.076
F(0 0 0)	720
Theta range for data collection	1.58–27.57
Index ranges	$0 \le h \le 10$, $0 \le k \le 23$, $-17 \le l \le 16$
Reflections collected	4931
Independent reflections	4473 [R(int) = 0.0179]
Completeness to theta = 30.06°	100.0%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4473/1/439
Goodness-of-fit on F^2	1.030
Final R indices [$I > 2$ sigma(I)]	$R_1 = 0.0456$, $wR_2 = 0.1221$
R indices (all data)	$R_1 = 0.0527$, $wR_2 = 0.1289$
Absolute structure parameter	−0.2(14)
Largest diffraction peak and hole (e Å^{-3})	0.229 and −0.210

15.9, 18.6, 21.3, 24.6, 27.1, 30.8, 32.7, 33.2, 34.4, 34.7, 40.5, 45.3, 46.0, 48.7, 49.2, 56.7, 81.1, 216.4, 217.9.

*2.2. (13S)-6β-Methoxy-14-oxo-l7-trimethylsilyloxy-3α, 5-cyclo-13,14-seco-5α-androstan-17-carbonitrile (**3**)*

Triphenylphosphine (25 g, 95.4 mmol) and trimethylsilyl cyanide (8.9 ml, 66.5 mmol) were added to a solution of diketone **2** (10 g, 31.5 mmol) in THF (40 ml). The reaction mixture was kept at RT for 16 h. THF was partly evaporated, the mixture was cooled down, the precipitate was filtered off, and the filtrate was evaporated. The residue was chromatographed on SiO_2 (hexane–EtOAc = 7:1) to give the silylated cyanohydrin **3** (8.7 g, 66%) as single oily product of unknown configuration at C-17. ^{1}H NMR δ: 0.24 (s, 9H, $SiMe_3$), 1.04 (s, 3H, 19-H), 1.10 (d, J 6 Hz, 18-H), 3.36 (s, 3H, OMe). ^{13}C NMR δ: 1.2, 13.4, 17.2, 19.6, 21.4, 26.2, 26.9, 27.6, 34.2, 34.5, 35.7, 37.4, 38.5, 42.3, 44.5, 45.7, 48.2, 56.7, 75.9, 81.0, 122.4, 218.4. HRMS Calc. for $C_{24}H_{40}NO_3Si$ (M + H) 418.2771; found 418.2772.

*2.3. (13S,14R)-14-Hydroxy-6β-methoxy-17-trimethylsilyloxy-3α,5-cyclo-13,14-seco-5α-androstan-17-carbonitrile (**4**)*

$NaBH_4$ (355 mg, 9.35 mmol) was added in three portions to a solution of **3** (2.6 g, 6.24 mmol) and $CaCl_2$ (1.03 g, 9.35 mmol) in EtOH (50 ml). The suspension was stirred for 5 min, then the solids were filtered off, and the filtrate was concentrated in vacuo. The residue was chromatographed on SiO_2 (hexane–EtOAc = 1:1) to give alcohol **4** (2.3 g, 88%) as an oil. ^{1}H NMR δ: 1.00 (s, 3H, 19-H), 1.08 (d, J 7 Hz, 3H, 18-H), 2.82 (m, 1H, 6-H), 3.32 (s, 3H, OMe), 3.83 (dd, J 6, 4 Hz, 1H, 14-H). ^{13}C NMR δ: 1.2, 12.7, 18.5, 20.2, 21.7, 24.7, 27.7, 30.0, 32.3, 33.4, 35.3, 35.9, 37.4, 39.4, 42.0, 47.1, 49.0, 56.6, 76.0, 76.6, 82.0, 122.5.

*2.4. (13S)-14,17-Oxido-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstan-17-ol (**7**)*

A 1 M solution of Bu_4NF in THF (0.42 ml, 0.42 mmol) was added to a solution of the silylated cyanohydrin **3** (90 mg, 0.21 mmol) in THF (1 ml). After 5 min, the solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 1:1) to give hemiacetal **7** (60 mg, 87%) as an oil. ^{1}H NMR δ: 0.88 (d, J 8 Hz, 3H, 18-H), 0.92 (s, 3H, 19-H), 2.71 (m, 1H, 6-H), 3.23 (s, 3H, OMe), 4.36–4.48 (m, 1H, 14-H). ^{13}C NMR δ: 13.1, 18.4, 18.8, 21.8, 24.8, 25.9, 28.7, 32.0, 32.8 33.5, 35.5, 35.8, 36.3, 45.3, 45.9, 46.4, 56.4, 82.0, 83.4, 111.0.

*2.5. (13S,14R)-14-Acetoxy-6β-methoxy-17-trimethylsilyloxy-3α,5-cyclo-13,14-seco-5α-androstan-17-carbonitrile (**5**)*

Ac_2O (10 ml) and a catalytic amount of DMAP (84 mg, 0.69 mmol) were added to a solution of alcohol **4** (5.8 g, 13.8 mmol) in pyridine (50 ml). The reaction mixture was left at RT for 16 h. Then, the solvents were partially evaporated, water was added, and the mixture was extracted with EtOAc. The solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 1:10) to give acetate **5** (5.1 g, 80%) as an oil. ^{1}H NMR δ: 0.76 (s, 3H, 19-H), 0.87 (d, J 8 Hz, 3H, 18-H), 1.84 (s, 3H, OAc), 2.56 (m, 1H, 6-H), 3.08 (s, 3H, OMe), 4.75 (m, 1H, 14-H). ^{13}C NMR δ: 0.12, 11.6, 17.6, 18.5, 20.2, 20.6, 23.5, 26.5, 27.2, 31.1, 32.4, 33.5, 34.0, 34.2, 36.4, 41.6, 45.5, 47.3, 55.4, 74.8, 76.1, 80.6, 121.3, 168.9.

*2.6. (13S,14R)-14-Acetoxy-6β-methoxy-3α,5-cyclo-13, 14-seco-5α-androstan-17 one (**8**)*

A 1 M solution of Bu_4nf in THF (14 ml, 14 mmol) was added to a solution of silylated cyanhydrin **5** (5.1 g, 11.1 mmol) in THF (50 ml). After 5 min, the solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 3:1) to give ketone **8** (3.6 g, 90%) as an oil. IR (cm^{-1}): 1745, 1710, 1460, 1370, 1260, 1100, 1090, 750. ^{1}H NMR δ: 0.97 (s, 3H, 19-H), 0.98 (d, J 8 Hz, 3H, 18-H), 2.00 (s, 3H, OAc), 2.76 (m, 1H, 6-H), 3.29 (s, 3H, OMe), 4.77 (dt, J 10.5, 3 Hz, 14-H). ^{13}C NMR δ: 13.3, 13.4, 20.7, 21.0, 21.5, 22.5, 24.6, 28.4, 29.0, 31.8, 32.9, 33.9, 34.5, 34.8, 43.2, 45.7, 48.3, 56.4, 73.8, 81.7, 170.1, 216.1.

2.7. (13S,14R,17R)-14-Acetoxy-6β-methoxy-3α, 5-cyclo-13,14-seco-5α-androstan-17-ol (9)

A 1 M solution of L-selectride (8 mmol, 8 ml) was added to a solution of ketone **8** (1.9 g, 5.2 mmol) in THF (20 ml) at −60 °C under argon. After 40 min, acetone (3 ml) was added to the reaction mixture, it was allowed to warm to room temperature, and the solvents were evaporated. The residue was dissolved in $CHCl_3$, and then, water was added. The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on SiO_2 (hexane–EtOAc = 1:1) to give alcohol **9** (1.5 g, 79%) as an oil. IR (cm^{-1}): 1740, 1460, 1380, 1255, 1100, 1090, 960. ^{1}H NMR δ: 0.92 (d, *J* 1 Hz, 3H, 18-H), 0.98 (s, 3H, 19-H), 2.04 (s, 3H, OAc), 2.76 (m, 1H, 6-H), 3.32 (s, 3H, OMe), 4.00 (m, 1H, 17-H), 5.60 (m, 1H, 14-H). ^{13}C NMR δ: 12.9, 17.3, 18.7, 21.3, 21.5, 24.7, 25.0, 31.9, 32.9, 33.6, 33.9, 34.8, 36.9, 37.3, 39.5, 45.9, 49.5, 56.6, 76.5, 77.7, 82.0, 171.0. HRMS Calc. for $C_{22}H_{37}O_4$ (M + H) 365.2686; found 365.2678.

2.8. (13S,14R,17R)-3β, 17-Dihydroxy-14-acetoxy-13, 14-seco-androst-5-ene (10)

A solution of ether **9** (1.0 g, 2.5 mmol), TsOH (100 mg, 0.53 mmol) in dioxane (10 ml) and water (2.5 ml) was heated at 80 °C for 1 h. The solvents were evaporated, and the residue was chromatographed on SiO_2 to give the alcohol **10** (0.8 g, 86%) as an oil. ^{1}H NMR δ: 0.93 (d, *J* 6 Hz, 3H, 18-H), 0.95 (s, 3H, 19-H), 3.50 (m, 1H, 3-H), 4.05 (m, 1H, 17-H), 5.10 (m, 1H, 14-H), 5.32 (d, *J* 6 Hz, 6-H). ^{13}C NMR δ: 16.8, 18.0 21.3, 22.4, 30.1, 31.4, 32.0, 33.2, 36.4, 36.5, 37.1, 38.9, 41.1, 41.8, 52.2, 71.7, 76.3, 78.9, 121.2, 140.5, 171.0.

2.9. (13S,14R)-17-Hydroxyimine-14-acetoxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstane (11)

$NH_2OH{\cdot}HC1$ (200 mg, 6.12 mmol) was added to a solution keto acetate **8** (120 mg, 0.33 mmol) in pyridine (3 ml). The reaction mixture was kept at RT for 16 h. Then, the solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 3:1) to give oxime **11** (120 mg, 96%) as an oil. IR (cm^{-1}): 1735, 1470, 1380, 1250, 1100, 950, 760. ^{1}H NMR δ: 0.99 (s, 3H, 19-H), 1.07 (d, *J* 8 Hz, 3H, 18-H), 2.05 (s, 3H, OAc), 2.79 (m, 1H, 6-H), 3.33 (s, 3H, OMe), 4.95 (t, *J* 6 Hz, 1H, 14-H). ^{13}C NMR δ: 13.3, 17.3, 20.0, 21.2, 21.5, 23.5, 23.7, 24.7, 31.0, 32.2, 32.9, 34.4, 34.7, 36.3, 39.5, 45.8, 56.5, 77.0, 82.0, 165.1, 170.6.

2.10. (13S,14R)-17-Acetoxyimine-14-acetoxy-6β-methoxy-3α, 5-cyclo-13,14-seco-5α-androstane (12)

Ac_2O (0.4 ml) and a catalytic amount of DMAP (2 mg, 0.016 mmol) were added to a solution of oxime **11** (120 mg, 0.32 mmol) in pyridine (1.6 ml). The reaction mixture was left at RT for 16 h, and then, the solvents were evaporated. The residue was chromatographed on SiO_2 (hexane–EtOAc = 3:1) to give diacetate **12** (95 mg, 71%); mp 95–96 °C (hexane–EtOAc). IR (cm^{-1}): 1780, 1740, 1550, 1380, 1250, 1220, 1100, 930. ^{1}H NMR δ: 0.98 (s, 3H, 19-H), 1.22 (d, *J* 8 Hz, 3H, 18-H), 2.05 (s, 3H, OAc), 2.17 (s, 3H, OAc), 2.79 (m, 1H, 6-H), 3.33 (s, 3H, OMe), 4.89 (m, 1H, 14-H). ^{13}C NMR δ: 13.2, 17.9, 19.5, 19.8, 21.2, 21.4, 24.4, 24.7, 24.8, 31.9, 32.6, 34.1, 34.6, 35.1, 37.8, 39.6, 45.9, 47.3 56.6, 77,6, 81.8, 169.0, 170.5, 173.3.

2.11. (13S)-6β-Methoxy-3α,5-cyclo-13, 14-seco-5α-androst-14(E)-en-17-one (15)

$SOCl_2$ (1.3 ml) was added dropwise to a solution of alcohol **4** (1.5 g, 3.6 mmol) in pyridine (24 ml) at 0 °C. The reaction mixture was stirred at RT for 1 h. Then, the solvents were evaporated without warming. The residue was chromatographed on SiO_2 (hexane–EtOAc = 10:1) to give an oily product (1.1 g). This was used without further purification for the next step.

A 1 M solution of Bu_4NF (0.47 ml) was added to a solution of the product from the previous step (1.1 g) in THF (12 ml). After 5 min, the solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 15:1) to give olefin **15** (425 mg, 39%); mp 90–92 °C (hexane). IR (cm^{-1}): 1710, 1565, 1380, 1350, 1200, 1115, 1100. ^{1}H NMR δ: 0.99 (s, 3H, 19-H), 1.01 (d, *J* 8 Hz, 3H, 18-H), 2.77 (m, 1H, 6-H), 3.33 (s, 3H, OMe),. 5.40 (dd, *J* 15, 10 Hz, 1H, 15-H), 5.70 (m, 1H, 14-H). ^{13}C NMR δ: 12.8, 18.6, 18.9, 21.5, 24.7, 31.6, 34.3, 34.8, 35.1, 38.0, 41.4, 44.9, 45.3, 50.4, 53.7, 56.7, 81.8, 120.0, 145.5, 213.0. HRMS Calc. for $C_{20}H_{31}O_2$ (M + H) 303.2318; found 303.2317.

2.12. (13S,17R)-17-Hydroxy-6β-methoxy-3α,5-cyclo-13, 14-seco-5α-androst-14(E)-ene (16a)

Enone **15** was converted into the unsaturated alcohol **16a** using the procedure reported for the preparation of compound **9**. Compound **16a** was isolated as an oil in 63% yield. ^{1}H NMR δ: 0.96 (d, *J* 8 Hz, 3H, 18-H), 0.98 (s, 3H, 19-H), 2.78 (m, 1H, 6-H), 3.33 (s, 3H, OMe), 3.92 (s, 1H, 17-H), 5.20-5.46 (m, 2H, 14- and 15-H). ^{13}C NMR δ: 12.5, 18.2, 18.6, 19.2, 21.7, 23.7, 27.8, 34.4, 34.6, 37.4, 39.5, 41.1, 42.6, 45.0, 51.3, 56.6, 73.2, 82.3, 125.8, 138.4.

2.13. (13S,17R)-17-Hydroxy-6β-methoxy-3α,5-cyclo-13, 14-seco-5α-androstane (16b)

A suspension of homoallylic alcohol **16a** (150 mg, 0.49 mmol) and 10% Pd/$BaSO_4$ (50 mg) in EtOH (5 ml) was stirred under hydrogen for 18 h. Then, the suspension was filtered, the solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 5:1) to give alcohol **16b** (100 mg, 67%); mp 122–123 °C

(hexane–EtOAc). ^{1}H NMR δ: 0.94 (s, 3H, 19-H), 1.04 (d, *J* 8 Hz, 3H, 18-H), 2.81 (m, 1H, 6-H), 3.32 (s, 3H, OMe), 3.62 (m, 1H, 17-H). ^{13}C NMR δ: 12.5, 17.9, 21.5, 21.7, 24.7, 28.8, 30.3, 32.0, 32.5, 33.6, 34.0, 35.4, 35.7, 39.1, 46.9, 50.4, 56.6, 76.6, 83.1.

2.14. Isomerization of (8)

A mixture of **8** (370 mg, 1.02 mmol), TsOH (40 mg, 0.21 mmol), dioxane (5 ml), and water (0.3 ml) was heated for 1 h at 90 °C. Then, the mixture was concentrated in vacuo, and the residue chromatographed on SiO_2 (hexane–EtOAc = 1:1) to give (*13ξ,14R)-3β-hydroxy-14-acetoxy-13,14-seco-androst-5-ene-17-one* **17** (270 mg, 76%).

A 1 M solution of L-selectride (2.5 ml) was added to a solution of ketones **17** (300 mg, 0.86 mmol) in THF (10 ml) at −60 °C under argon. After 40 min, acetone was added to the reaction mixture, and the solvents were evaporated. The residue was chromatographed on SiO_2 (hexane–EtOAc = 1:2) to give: (a) (*13R,14R,17R)-3β,17-dihydroxy-14-acetoxy-13,14-seco-androst-5-ene* **18** (94 mg, 31%) as an oil. ^{1}H NMR δ: 0.98 (s, 3H, 19-H), 1.00 (d, *J* 7 Hz, 3H, 18-H), 2.04 (s, 3H, OAc), 3.52 (m, 1H, 3-H), 3.80 (m, 1H, 17-H), 4.96 (m, 1H, 14-H), 5.32 (brs, 1H, 6-H). ^{13}C NMR δ: 18.4, 18.7, 18.9, 21.3, 23.4, 24.2, 28.5, 29.4, 30.5, 31.3, 33.5, 37.3, 39.4, 41.7, 47.0, 71.5, 74.8, 75.5, 121.0, 141.4, 170.6; b) (*13S,14R,17R)-3β,17-dihydroxy-14-acetoxy-13,14-seco-androst-5-ene* **10** (170 mg, 56%) as an oil. Its NMR data corresponded to those obtained for the compound derived from **9**.

2.15. (13S,14R,17R)-14,17-Diacetoxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstane (19)

Ac_2O (25 ml) and a catalytic amount of DMAP (8.6 mg, 0.07 mg) were added to a solution of alcohol **9** (500 mg, 1.37 mmol) in pyridine (10 ml). The reaction mixture was left at RT for 16 h. Then, the solvents were partially evaporated, water was added, and the mixture was extracted with ether. The organic layer was dried, and evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 3:1) to give diacetate **19** (418 mg, 75%) as an oil. IR (cm^{-1}): 1730, 1610, 1580, 1470, 1380, 1280, 1130, 1070, 750. ^{1}H NMR δ: 0.88 (d, *J* 8 Hz, 3H, 18-H), 0.99 (s, 3H, 19-H), 2.03 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.76 (m, 1H, 6-H), 3.36 (s, 3H, OMe), 5.08 (m, 2H, 14- and 17-H). ^{13}C NMR δ: 13.0, 16.6, 18.7, 21.3, 21.5, 24.3, 24.7, 28.6, 33.0, 33.6, 34.4, 34.7, 34.8, 37.1, 39.5, 45.9, 49.3, 56.6, 77.1, 77.7, 82.0, 170.5.

2.16. (13S,14R,17R)-3β-Hydroxy-14,17-diacetoxy-13,14-seco-androst-5-ene (20)

Compound **19** was converted into alcohol **20** using the procedure reported for the preparation of compound **10**. The alcohol **20** was isolated as an oil in 78% yield. ^{1}H NMR δ: 0.88 (d, *J* 8 Hz, 3H,C_{18}), 0.99 (s, 3H, 19-H), 2.03 (s, 3H, OAc), 2.04 (s, 3H, OAc), 3.50 (m, 1H, 3-H), 5.06 (m, 2H, 14- and 17-H), 5.32 (m, 1H, 6-H). ^{13}C NMR δ: 16.0, 18.0, 21.3, 21.4. 21.7, 28.5, 30.6, 31.4, 33.8, 34.3, 36.4, 36.8, 38.9, 41.2, 41.8, 52.0, 71.7, 78.7, 79.2, 121.2, 140.5, 170.58, 170.63.

2.17. Oppenauer oxidation of (10)

A solution of diol **10** (190 mg, 0.53 mmol) in toluene (8 ml) and cyclohexanone (0.7 ml) was heated under reflux. After 2 ml of toluene were distilled off, $Al(O^iPr)_3$ (40.85 mg, 0.2 mmol) was added. The reaction mixture was refluxed for 20 min, and then the solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 1:2, 1:4) to give: (a) *(13S,14R,17R)-17-hydroxy-14-acetoxy-13,14-seco-androst-4-en-3-one* **22** (42 mg, 25%) as an oil. ^{1}H NMR δ: 0.94 (d, *J* 8 Hz, 3H, 18-H), 1.13 (s, 3H, 19-H), 4.00 (m, 1H, 17-H), 4.88 (m, 1H, 14-H), 5.66 (s, 1H, 4-H). ^{13}C NMR δ: 17.7, 21.2, 24.1, 28.8, 31.2, 32.3, 32.8, 33.7, 34.5, 35.0, 37.7, 40.0, 44.9, 53.7, 75.5, 77.3, 123.8, 170.1, 170.6, 199.3; b) (*13S,14R)-14-acetoxy-13,14-seco-androst-4-en-3,17-dione* **23** (48 mg, 26%) as an oil. ^{1}H NMR δ: 1.04 (d, *J* 8 Hz, 3H, 18-H), 1.16 (s, 3H, 19-H), 4.85 (m, 1H, 14-H), 5.66 (m, 4-H). ^{13}C NMR δ: 14.4, 20.1, 21.1, 21.8, 27.6, 28.6, 29.7, 31.8, 33.6, 34.4, 35.8, 39.5, 40.1, 47.5, 49.1, 73.2, 123.9, 169.7, 170.2, 199.0, 216.5. HRMS Calc. for $C_{21}H_{31}O_4$ (M + H) 347.2216; found 347.2206.

2.18. (13S,14R,17R)-14,17-Diacetoxy-13,14-seco-androst-4-en-3-one (21)

Using the procedure reported for the Oppenauer oxidation of **10**, alcohol **20** was converted into enone **21** (84%), which was isolated as an oil. ^{1}H NMR δ: 0.88 (d, *J* 8 Hz, 3H, 18-H), 1.12 (s, 3H, 19-H), 2.04 (s, 3H, OAc), 2.05 (s, 3H, OAc), 4.98 (m, 1H, 14- or 17-H), 5.10 (m. 1H, 17- or 14-H), 5.71 (s, 1H, 4-H). ^{13}C NMR δ: 16.7, 17.6, 21.20, 21.25, 23.0, 27.9, 29.0, 32.4, 33.68, 33.73, 35.0, 35.1, 35.3, 40.0, 45.1, 54.0, 77.3, 77.8, 123.9, 169.8, 170.3, 170.7, 199.2.

2.19. (13S,17R)-17-Acetoxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androst-14(E)-ene (24a)

Using the procedure reported for the acetylation of **9**, alcohol **16a** was converted into acetate **24a** (83%), which was obtained as white crystals, mp 113–116 °C (hexane–toluene). ^{1}H NMR δ: 0.91 (d, *J* 8 Hz, 3H, 18-H), 0.98 (s, 3H, 19-H), 2.05 (s, 3H, OAc), 2.77 (m, 1H, 6-H), 3.32 (s, 3H, OMe), 5.00 (q, *J* 4 Hz, 15-H), 5.35 (m, 1H, 14-H). ^{13}C NMR δ: 12.7, 18.6, 18.9, 21.4, 21.7, 24.8, 27.4, 31.2, 34.5, 35.1, 35.2, 37.3, 41.3, 45.1, 51.2, 56.7, 75.1, 82.2, 125.3, 139.4, 170.6.

*2.20. (13S,17R)-3β-Hydroxy-17-acetoxy-13,14-seco-androst-5,14(E)-diene (**25a**)*

Using the procedure reported for the preparation of compound **10**, ether **24a** was converted into alcohol **25a** (85%), which was isolated as an oil. ^{1}H NMR δ: 0.92 (d, J 8 Hz, 3H, 18-H), 0.93 (s, 3H, 19-H), 2.05 (s, 3H, OAc), 3.52 (m, 1H, 3-H), 5.00 (m, 1H, 17-H), 5.25–5.50 (m, 3H, 6-, 14- and 15-H). ^{13}C NMR δ: 18.0, 18.2, 21.4, 24.3, 31.4, 31.9, 34.1, 35.0, 36.6, 37.8, 38.1, 39.1, 42.1, 53.7, 71.7, 74.4, 121.2, 125.6, 139.4, 140.9, 170.5.

*2.21. (13S,17R)-17-Acetoxy-13,14-seco-androst-4,14(E)-dien-3-one (**26a**)*

Using the procedure reported for Oppenauer oxidation of **10**, alcohol **25a** was converted into enone **26a** (81%), which was obtained as white crystals, mp 115–117 °C (hexane–toluene). ^{1}H NMR δ: 0.94 (d, J 8 Hz, 3H, 18-H), 1.10 (s, 3H, 19-H), 2.06 (s, 3H, OAc), 5.00 (q, 1H, J 3 Hz, 17-H), 5.24 (dd, J 17, 8 Hz, 1H, 14- or 15-H), 5.44 (dd, J 8, 5 Hz, 1H, 15- or 14-H), 5.76 (s, 1H, 4-H). ^{13}C NMR δ: 17.0, 19.0, 21.3, 25.5, 31.4, 32.8, 33.6, 34.4, 34.6, 36.0, 37.3, 40.0, 47.1, 56.6, 74.6, 124.6, 126.3, 137.9, 170.1, 170.6, 199.5. HRMS Calc. for $C_{21}H_{31}O_3$ (M + H) 331.2267; found 331.2259.

*2.22. (13S,17R)-17-Hydroxy-13,14-seco-androst-4,14(E)-dien-3-one (**27a**)*

Acetoxyenone **26a** (60 mg, 0.18 mmol) was dissolved in a solution of 5% KOH/MeOH (1 ml). After l h at RT, dilute AcOH was added to the reaction mixture. The solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 1:1) to give hydroxyenone **27a** (45 mg, 86%) as an oil. ^{1}H NMR δ: 0.97 (d, J 8 Hz, 3H, 18-H), 1.10 (s, 3H, 19-H), 3.90 (m, 1H, 17-H), 5.30 (m, 2H, 14- and 15-H), 5.78 (brs, 1H, 4-H). ^{13}C NMR δ: 17.0, 19.6, 26.1, 31.6, 32.8, 33.6, 33.8, 35.9, 37.2, 39.6, 39.8, 46.9, 46.9, 56.8, 73.1, 124.5, 126.7, 136.9, 170.4, 200.0.

*2.23. (13S)-13,14-Seco-androst-4,14(E)-dien-3,17-dione (**28a**)*

A solution of hydroxy enone **27a** (30 mg, 0.10 mmol) in pyridine (1 ml) was added to a suspension of CrO_3 (100 mg, 1 mmol) in pyridine (1 ml). After 20 min, isopropanol was added to the reaction mixture, and it was diluted with dry THF. The reaction mixture was filtered, and the filtrate was evaporated. The residue was chromatographed on SiO_2 (hexane–EtOAc = 1:1) to give dienone **28a** (26 mg, 87%); mp 133–136 °C (hexane–toluene). ^{1}H NMR δ: 1.00 (d, J 8 Hz, 3H, 18-H), 1.08 (s, 3H, 19-H), 5.36 (dd, J 15, 10 Hz, 1H, 14- or 15-H), 5.44 (dd, J 9, 6 Hz, 1H, 15- or 14-H), 5.76 (s, 1H, 4-H). ^{13}C NMR δ: 17.0, 18.6, 29.6, 31.2, 32.4, 33.8, 35.8, 37.5, 39.9, 44.9, 47.1, 50.4, 58.9, 121.1, 124.7, 143.8, 169.4, 199.2.

*2.24. (13S,17R)-17-Acetoxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstane (**24b**)*

Using the procedure for the acetylation of **9**, alcohol **16b** was converted into acetate **24b** (93%), which was isolated as an oil. IR (cm^{-1}): 1745, 1470, 1380, 1250, 1100, 1020, 970, 960, 870. ^{1}H NMR δ: 0.92 (d, J 8 Hz, 3H, 18-H), 0.96 (s, 3H, 19-H), 2.03 (s, 3H, OAc), 2.82 (m, 1H, 6-H), 3.32 (s, 3H, OMe), 4.90 (m, 1H, 17-H). ^{13}C NMR δ: 12.5, 17.9, 20.7, 21.2, 21.7, 21.8, 24.8, 28.3, 30.6, 30.7, 32.4, 33.6, 34.0, 35.4, 36.0, 37.5, 46.8, 50.4, 56.6, 78.9, 83.0, 170.7.

*2.25. (13S,17R)-3β-Hydroxy-17-acetoxy-13,14-seco-androst-5-ene (**25b**)*

Using the procedure for the preparation of compound **10**, ether **24b** was converted into alcohol **25b** (94%), which was isolated as an oil. IR (cm^{-1}): 1735, 1450, 1380, 1250, 1070, 1020, 760. ^{1}H NMR δ: 0.92 (s, 3H, 19-H), 0.94 (d, J 8 Hz, 3H, 18-H), 2.01 (s, 3H, OAc), 3.50 (m, 1H, 3-H), 4.98 (m, 1H, 17-H), 5.40 (brs, 1H, 6-H). ^{13}C NMR δ: 17.7, 19.9, 21.2, 21.7, 25.5, 29.4, 29.9, 31.4, 31.8, 34.0, 34.9, 36.9, 39.8, 42.1, 54.5, 71.8, 78.4, 122.0, 141.0, 170.7.

*2.26. (13S,17R)-17-Acetoxy-13,14-seco-androst-4-en-3-one (**26b**)*

Using the procedure for Oppenauer oxidation of **10**, alcohol **25b** was converted into the enone **26b** (95%), which was isolated as an oil. ^{1}H NMR δ: 0.93 (d, J 8 Hz, 3H, 18-H), 1.07 (s, 3H, 19-H), 2.02 (s, 3H, OAc), 4.90 (m, 1H, 17-H), 5.75 (brs, 1H, 4-H). ^{13}C NMR δ: 20.5, 21.2, 21.7, 24.2, 25.5, 26.2, 30.2, 30.4, 33.4, 33.7, 35.1, 37.4, 37.43, 38.8, 40.8, 55.87, 78.2, 123.9, 170.7, 171.0, 200.0.

*2.27. (13S,17R)-17-Hydroxy-13,14-seco-androst-4-en-3-one (**27b**)*

Using the procedure for the saponification of **26a**, acetate **26b** was converted into alcohol **27b** (66%), which was isolated as an oil. ^{1}H NMR δ: 1.03 (d, J 8 Hz, 3H, 18-H), 1.05 (s, 3H, 19-H), 3.65 (m, 1H, 17-H), 5.75 (brs, 1H, 4-H). ^{13}C NMR δ: 16.3, 21.3, 26.8, 29.8, 31.9, 33.7, 33.9, 35.06, 35.09, 38.5, 40.9, 55.7, 77.7, 123.9, 171.3, 200.0. HRMS Calc. for $C_{19}H_{31}O_2$ (M + H) 291.2318; found 291.2287.

*2.28. (13S)-13,14-Seco-androst-4-en-3,17-dione (**28b**)*

Using the procedure for oxidation of **27a**, alcohol **27b** was converted into ketone **28b** (88%), which was isolated as white crystals, mp 103–104 °C (hexane–toluene). ^{1}H NMR δ: 1.00 (d, J 8 Hz, 3H, 18-H), 1.07 (s, 3H, 19-H), 5.68 (brs,

1H, 4-H). ^{13}C NMR δ: 15.5, 19.0, 21.8, 23.8, 30.5, 31.3, 32.9, 33.5, 33.7, 35.5, 35.6, 39.6, 40.3, 49.0, 49.7, 123.3, 170.9, 199.3, 218.6.

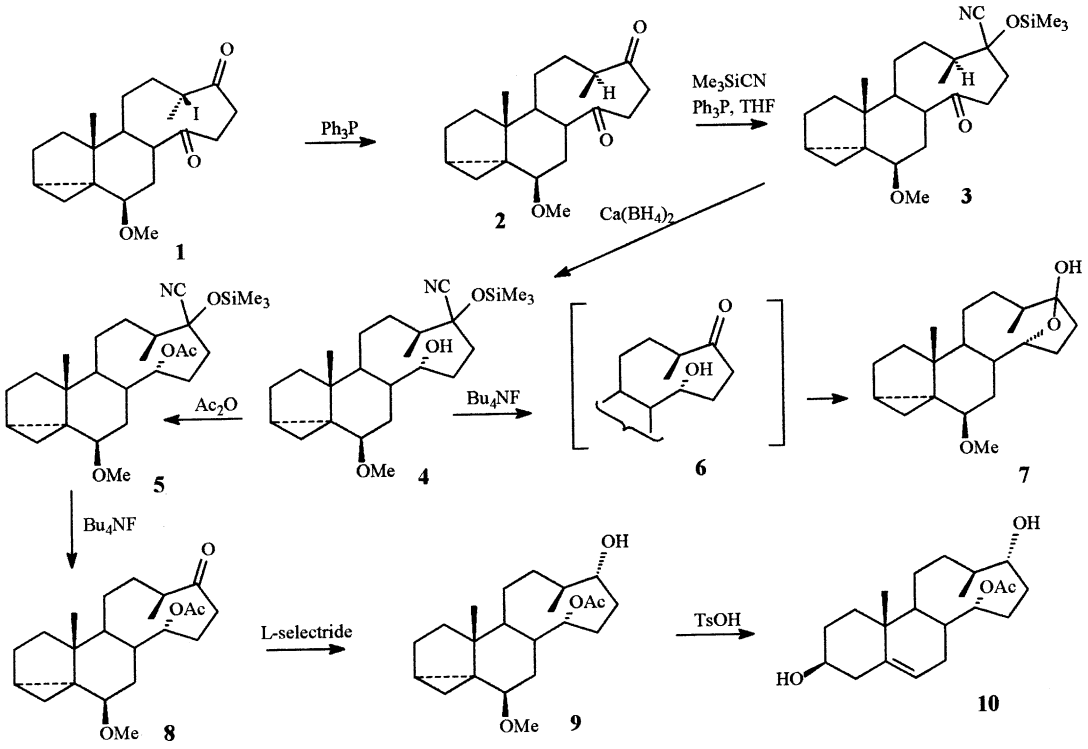
3. Results and discussion

3.1. Synthesis of 13,14-secosteroids containing a functional group at C-14

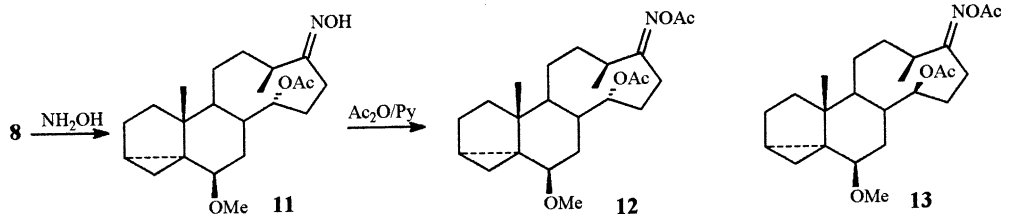
Recently, we reported that the reaction of steroid **1** with hydroxylamine can be used to remove the iodide and to differentiate the carbonyl groups at C-14 and C-17 [20]. However, better results can be obtained in this respect with the successive treatment of **1** with triphenylphosphine and trimethylsilylcyanide (Scheme 1). The first reaction was carried out in up to 93% yield to give diketone **2**. Similar to the reaction with hydroxylamine, the deiodination of **1** was stereoselective and led to inversion of the configuration at C-13. The selective protection of the carbonyl group at C-17 proceeded in a reasonable yield to afford single product of unknown configuration at C-17.

Reduction of the unprotected carbonyl group at C-14 in ketone **3** with $Ca(BH_4)_2$ produced the alcohol **4**. Deprotection of the carbonyl group at C-17 in **4** was achieved by treatment with Bu_4nf, but a transannular reaction with the unprotected alcohol at C-14 led to hemiacetal **7**. Acetylation of the hydroxy group prior to treatment with BU_4NF smoothly afforded the desired ketone **8** as a single product. Its reduction with $Ca(BH_4)_2$ proceeded with the formation of a mixture of diastereomers at C-17, but reduction with L-selectride gave only one product **9**.

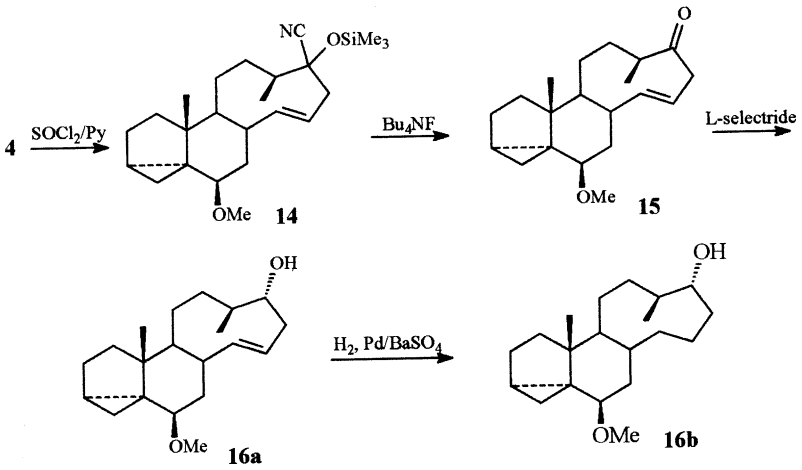
At this stage, the stereochemistry at C-13, C-14, and C-17 was not clear. The unambiguous assignment of the structure could be done only after X-ray analysis of an appropriate sample. A number of steroids, including **10** and its corresponding 4-iodobenzoates, have been crystallized, but unfortunately, none of them produced crystals suitable for X-ray analysis. The problem was solved later by using compound **26a**, which did give the necessary crystals. This study



Scheme 1.



Scheme 2.



Scheme 3.

allowed for the establishment of the configuration at C-13 and C-17 of all compounds of this series. Additional experiments were necessary to determine the stereochemistry at C-14 because compound **26a** has no substituent at this position.

In our previous article [20], we described the preparation of diacetoxy oxime **13** with the *S*-configuration at C-14. Formation of **13** was also expected from **8** given that the stereochemistry at C-14 was the same (Scheme 2). However, comparison of the NMR spectra of **12** and **13** showed that these compounds are different despite the fact that they contained the same set of functional groups. There is also another possibility to compare compounds from both series. It is expedient taking into account an opportunity of syn/anti-isomerism for oximes. Thus, comparison of NMR spectra showed that compound **8** differed from the corresponding 14-epimer [20]. For these reasons, it was concluded that acetoxy ketone **8** and diacetoxy oxime **12** as well as all related compounds **4**–**10** of this series have the *R*-configuration at C-14.

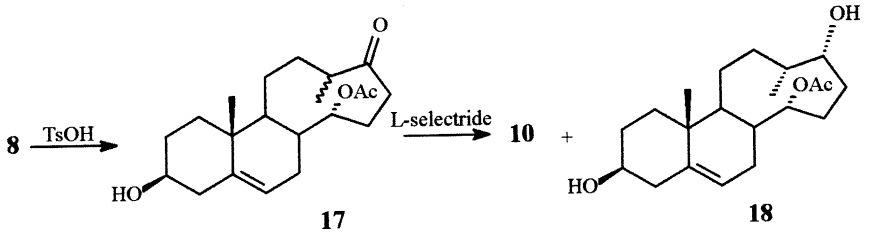
3.2. Synthesis of 14-unfunctionalized 13,14-secosteroids

Various approaches were studied to develop a synthetic route to 14-unsubstituted 13,14-secosteroids. The hydroxy group at C-14 in **4** is rather hindered and tosylation could not be achieved at all, although the corresponding mesylate and the thiocarbonate could be prepared. Under radical deoxygenation conditions, the thiocarbonate gave mainly the Δ^{14}-olefin **14** (Scheme 3). This compound could also be prepared by elimination of the 14-mesylate group, but both approaches gave significant amounts of other unidentified compounds. Ultimately, the reaction of **4** with $SOCl_2$ in pyridine afforded the expected Δ^{14}-olefin **14** in a reasonable yield. Deprotection of the C-17 carbonyl group was effected smoothly by Bu_4NF without isomerization of the adjacent methyl group. Treatment of ketone **15** with L-selectride proceeded with formation of one unsaturated alcohol **16a**. Hydrogenation of the double bond in this compound afforded the saturated alcohol **16b**.

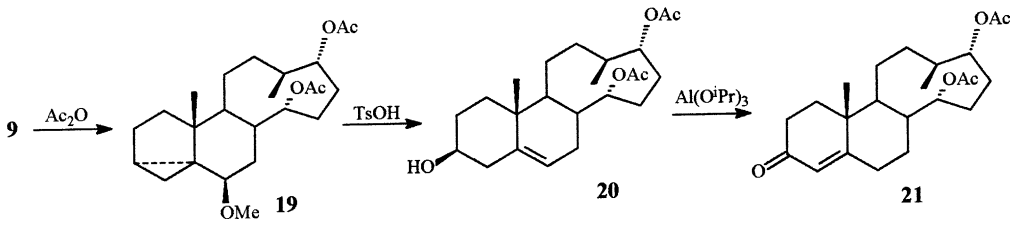
Ketone **8** was also used to elaborate a synthetic methodology for 13,14-secosteroids with an opposite stereochemistry at C-13 (Scheme 4). Hydrolytic treatment of **8** with TsOH in aqueous dioxane led to isomerization at C-13, but also to transformation of the AB-cyclic part of the steroidal skeleton [21], and an epimeric mixture (1:2) of ketones **17** was formed. This mixture was reduced with L-selectride to give alcohols **10** and **18**, which could be separated by column chromatography. In this way, the construction of 13,14-secosteroids with the *R*-configuration at C-13 could be achieved and applied for the preparation of the corresponding final compounds with a suitably functionalized A-ring.

3.3. Synthesis of Δ^4-3-keto-13,14-secosteroids

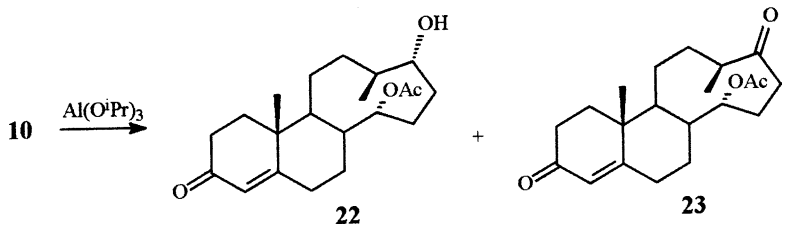
The transformation of 3α,5-cyclo-6β-methoxy derivatives into Δ^4-3-ketones was achieved using well known steroid



Scheme 4.



Scheme 5.

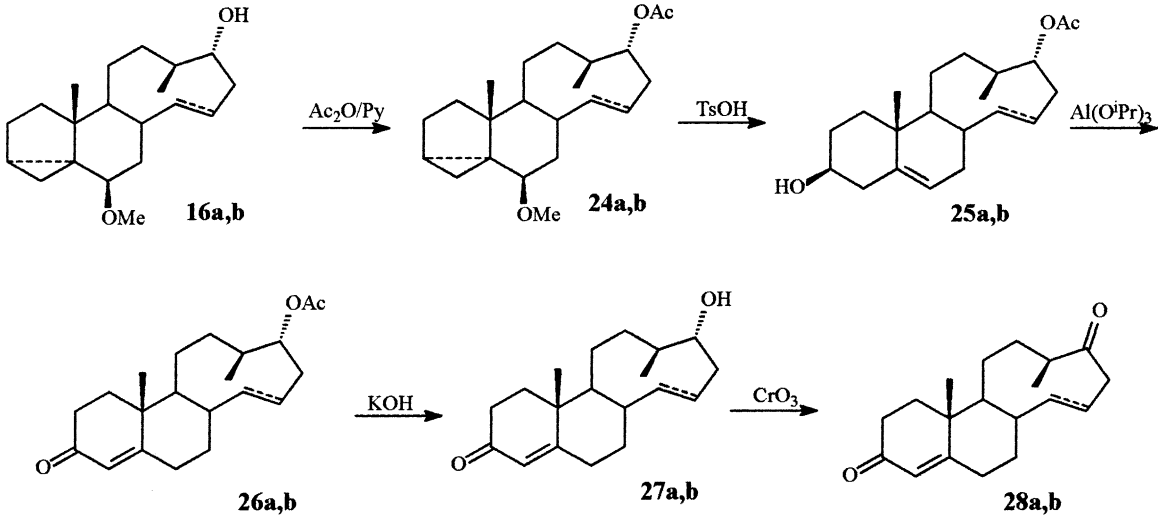


Scheme 6.

chemistry [22]. Thus, acetylation of **9** followed by treatment of the corresponding diacetate **19** with TsOH in dioxane produced the 3β-hydroxy-Δ^5-diacetate **20** (Scheme 5). Oppenauer oxidation of the hydroxy group in **20** gave the expected Δ^4-3-ketone **21**. In the case of diol **10**, a moderate regioselectivity was observed, which allowed us to obtain **23** in addition to **22** (Scheme 6). Similar reaction sequences were found with **16a** and **16b**, which have no functional group or a double bond at C-14, respectively (Scheme 7).

Secosteroid **26a** ultimately gave good crystals for X-ray analysis, which greatly helped in the structural elucidation of all compounds of this series (Table 1). There are two symmetry-independent molecules of **26a** in the asymmetric unit, one of which is shown in Fig. 1. Some difference can be seen from Fig. 2, representing the fitting of these molecules, although in general their geometries are very similar. It should be noted that the bond distances and angles of the composing fragments are close to those observed previously [23].

Thus, a number of analogs of testosterone with a 13,14-secosteroidal fragment have been prepared. Their biological testing is currently in progress, and the results will be presented elsewhere.



a: Δ^{14}-olefins
b: 14,15-saturated compounds

Scheme 7.

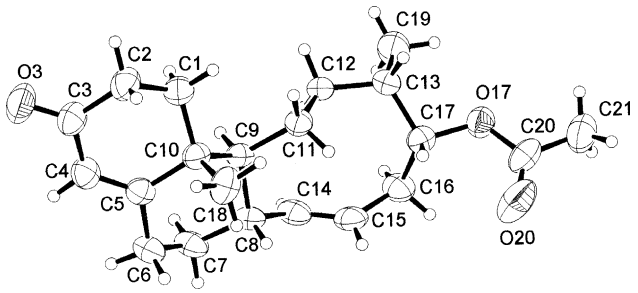


Fig. 1. ORTEP ([24]) drawing of one molecule of (13*S*,17*R*)-17-acetoxy-13,14-seco-androst-4,14(*E*)-dien-3-one **26a** with atom numbering. Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as spheres of arbitrary radii.

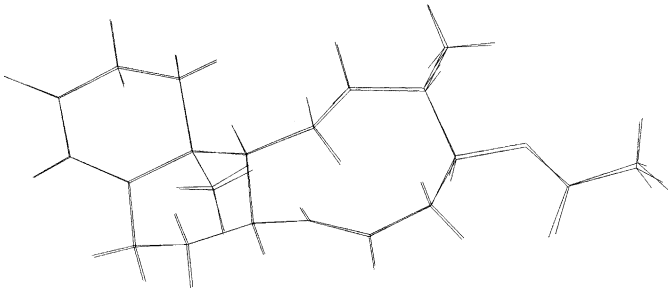


Fig. 2. PLATON [25] fitting plot of the two symmetry independent molecules of **26a**.

Acknowledgements

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