SYNTHESIS OF 17β-ISOXAZOLYL STEROIDS AND SPIRO[STEROID-17,2′-FURANONE]S

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Received May 5, 1998
Accepted July 3, 1998

This paper is dedicated to Dr Jan Fajkos on the occasion of his 1998 jubilee and his significant contribution to chemistry of natural products.

Synthesis of 17β-isoxazolyl steroids and their transformations into the corresponding spiro[steroid-17,2′-furanone]s are described. The reaction sequence consists of the 1,3-dipolar cycloaddition of a nitrile oxide to mestrenol, dehydration, epoxidation or dihydroxylation, cleavage of the isoxazole moiety and cyclization of intermediate enamino ketones.

Key words: Steroids; Isoxazoles; Spiro[steroid-17,2′-furanone]s; Steroidal spirofuranones; Nitrile oxides.

At present, only a few 17-isoxazolyl steroids are known[1–4] and there are no data in the literature on 17α-hydroxy-17-isoxazolyl steroids. To our best knowledge, only one attempt was undertaken to open the heterocycle ring in 17-isoxazolyl steroids[5]. We describe here a new approach to 17β-isoxazolyl steroids and the cleavage of their heterocyclic moiety to the corresponding spirofuranones. A number of (17*R*)- and (17*S*)- steroidal spirofuranones can be found in literature, but they were prepared *via* intramolecular condensation of derivatives of 17-hydroxypregnenolone[6–8] or mercury-catalyzed cyclization of 17-diyne steroids[9].

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EXPERIMENTAL

Melting points are uncorrected. Infrared spectra (wavenumbers in cm^{-1}) were recorded on a UR-20 spectrometer and only characteristic absorptions are reported. ^1H NMR spectra were measured in deuteriochloroform solutions with residual $CHCl_3$ as internal standard on Bruker AC-200, operating at 200 MHz. ^{13}C NMR spectra were recorded on Bruker AC-200 operating at 50 MHz. Chemical shifts are reported in ppm (δ-scale) and coupling constants (*J*) are in Hz. MS data were determined at 70 eV on a Shimadzu QP-5000 mass spectrometer. The ratios *m/z* are indicated for the significant peaks. Optical rotations were recorded in chloroform on a JASCO-20 polarimeter at 20 °C and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed on Merck silica gel 60. All reactions were carried out under a positive pressure of nitrogen. Reactions were monitored by TLC silica gel plates (Merk Kieselgel 60 F-254) and visualization of the compounds was accomplished by UV light, and/or spraying with an acidic cerium ammonium sulfate solution.

3-Methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)-trien-17β-ol (**2**)

To a stirred suspension of *N*-chlorosuccinimide (9.35 g, 70 mmol) in $CHCl_3$ (60 ml), pyridine (0.1 ml) and acetaldehyde oxime (4.54 g, 77 mmol) were added. The mixture was stirred for 15 min until it became clear. A solution of mestrenol (**1**) (6.2 g, 20 mmol) in $CHCl_3$ (70 ml) was added to the mixture. After stirring of the resulting mixture for 5 min a solution of Et_3N (8.24 g, 77 mmol) in $CHCl_3$ (30 ml) was added dropwise during 10 h. The mixture was washed with water and dried over Na_2SO_4. The solvent was evaporated. The residue was chromatographed on silica gel (toluene–AcOEt 20 : 90) to afford **2** (6.53 g, 89%), m.p. 157–159°C (MeOH–CH_2Cl_2) (literature[1] gives 155–157 °C). ^1H NMR spectrum: 1.03 s, 3 H (3 × H-18); 2.32 s, 3 H (Me-3′); 3.78 s, 3 H (OMe); 6.03 s, 1 H (H-4′); 6.62 d, 1 H, *J* = 2 (H-4); 6.70 dd, 1 H, J_1 = 8, J_2 = 2 (H-2); 7.16 d, 1 H, *J* = 8 (H-1). IR spectrum (KBr): 3 410, 2 935, 1 605, 1 590.

3-Methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10),16-tetraene (**3**)

To a stirred solution of **2** (336 mg, 0.92 mmol) and pyridine (0.3 ml, 3.68 mmol) in THF (20 ml), thionyl chloride (0.33 ml, 1.84 mmol) in THF (5 ml) was added at –50 °C. The temperature was allowed to rise to ambient for 1 h and 5% $NaHCO_3$ was added. The organic phase was extracted with ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained oil was chromatographed on silica gel (toluene–AcOEt 95 : 5) to give **3** (270 mg, 84%), m.p. 141–143 °C (MeOH–CH_2Cl_2), $[\alpha]_D$ –65 (*c* 1.10). ^1H NMR spectrum: 1.01 s, 3 H (3 × H-18); 2.33 s, 3 H (Me-3′); 2.95 m, 2 H (2 × H-6); 3.79 s, 3 H (OMe); 6.07 s, 1 H (H-4′); 6.43 brs, 1 H (H-16); 6.68 d, 1 H, *J* = 2.6 (H-4); 6.73 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.22 d, 1 H, *J* = 8.8 (H-1). ^{13}C NMR spectrum: 12.1 q, 17.1 q, 27.2 t, 28.4 t, 30.3 t, 32.4 t, 35.8 t, 37.8 d, 44.8 d, 47.6 s, 55.9 q, 56.6 d, 100.9 d, 112.1 d, 114.5 d, 126.7 d, 133.1 d, 133.2 s, 138.5 s, 142.6 s, 158.2 s, 160.4 s, 167.2 s. IR spectrum (KBr): 1 620, 1 605, 1 570, 1 550, 1500. Mass spectrum: 349 [M^+], 334.

17β-(3-Amino-1-oxobut-2-en-1-yl)-3-methoxyestra-1,3,5(10)-triene (**4**)

To a stirred solution of nickel chloride hydrate (226 mg, 1 mmol) in methanol (5 ml), compound **3** (175 mg, 0.5 mmol) in THF (7 ml) was added. The resulting mixture was cooled to 0 °C and sodium borohydride (76 mg, 2 mmol) was added portionwise. Aqueous ammonia was added in 10 min and the solution was evaporated to a small volume. The organic phase was extracted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated. The obtained oil was crystallized to give enaminoketone **4** (94 mg, 53%), m.p. 182–184 °C (MeOH), $[\alpha]_D$ +106 (*c* 0.48). ^1H NMR spec-

trum: 0.62 s, 3 H (3 × H-18); 1.91 s, 3 H (H-4′); 2.88 m, 2 H (2 x H-6); 3.78 s, 3 H (OMe); 4.90 brs, 1 H (NH); 5.03 s, 1 H (H-2′); 6.62 d, 1 H, J = 2 (H-4); 6.70 dd, 1 H, J_1 = 8.5, J_2 = 2 (H-2); 7.16 d, 1 H, J = 8.5 (H-1); 9.78 brs, 1 H (NH). ^{13}C NMR spectrum: 13.4 q, 22.6 q, 22.7 t, 24.3 t, 26.7 t, 27.8 t, 29.9 t, 38.9 t, 38.9 d, 43.9 d, 44.8 s, 55.2 q, 55.7 d, 62.2 d, 100.0 d, 111.5 d, 113.7 d, 126.3 d, 132.8 s, 138.1 s, 157.4 s, 159.8 s, 199.1 s. IR spectrum (KBr): 3 400, 2 940, 1 610, 1 520. Mass spectrum: 353 [M^+], 310, 268.

Cleavage of Isoxazole **3** with $Mo(CO)_6$

A solution of **3** (524 mg, 1.5 mmol) and hexacarbonyl molybdenum (436 mg, 1.65 mmol) in acetonitrile (35 ml) and water (0.6 ml) was refluxed for 1 h. The solution was then cooled and the solvent was evaporated. The brown residue was dissolved in chloroform (5 ml) and silica gel was added. Then the solvent was evaporated and the residue absorbed on silica gel, was chromatographed on a silica gel column (toluene–AcOEt 95 : 5).

17-(3-Hydroxy-1-oxobut-2-en-1-yl)-3-methoxyestra-1,3,5(10),16-tetraene (**6**) (168 mg, 32%), m.p. 120–121 °C (MeOH). ^{1}H NMR spectrum: 0.92 and 1.00 s, 3 H (3 × H-18); 2.12 and 2.25 s, 3 H (H-4′); 2.88 m, 2 H (2 × H-16); 3.78 s, 3 H (OMe); 5.87 s, 1 H (H-2′); 6.64 m, 2 H (H-4 and H-16); 6.70 dd, 1 H, J_1 = 8.5, J_2 = 2 (H-2); 7.16 d, 1 H, J = 8.5 (H-1); 15.66 brs, 1 H (OH). IR spectrum (KBr): 1 730, 1 660, 1 610, 1 600, 1 510. ^{13}C NMR spectrum: 15.9 and 16.3 q, 25.6 and 30.3 q, 26.4 and 26.5 t, 27.7 t, 29.6 t, 31.9 and 32.3 t, 34.7 and 35.1 t, 37.0 d, 44.1 d, 46.7 s, 55.1 q, 55.5 and 55.9 d, 97.7 d, 111.4 d, 113.9 d, 126.1 d, 132.6 s, 137.8 s, 140.1 d, 151.9 s, 157.5 s, 182.0 s, 192.2 s. Mass spectrum: 352 [M^+], 337.

17-(3-Amino-1-oxobut-2-en-1-yl)-3-methoxyestra-1,3,5(10),16-tetraene (**5**) (299 mg, 57%), m.p. 200–202 °C (MeOH), $[\alpha]_D$ +66 (*c* 0.56). ^{1}H NMR spectrum: 1.02 s, 3 H (3 × H-18); 1.91 s, 3 H (H-4′); 2.88 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.00 brs, 1 H (NH); 5.38 s, 1 H (H-2′); 6.43 brs, 1 H (H-16); 6.62 d, 1 H, J = 2 (H-4); 6.70 dd, 1 H, J_1 = 8.5, J_2 = 2 (H-2); 7.16 d, 1 H, J = 8.5 (H-1); 9.80 br s, 1 H (NH). IR spectrum (KBr): 3 430, 1 610, 1 520, 1 510.

16α,17α-Epoxy-3-methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)-triene (**7**)

A solution of **3** (450 mg, 1.29 mmol), 3-chloroperoxy benzoic acid (267 mg, 1.55 mmol), and $NaHCO_3$ (236 mg, 2.8 mmol) in dichloromethane (50 ml) was stirred at room temperature. After 4 h, it was treated with a solution of $Na_2S_2O_3$. The organic phase was diluted with dichloromethane, washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The obtained residue was chromatographed on silica gel (toluene–AcOEt 95 : 5) to give the starting material **3** (113 mg) followed by epoxide **7** (269 mg, 57 %), m.p. 179–181 °C (MeOH–CH_2Cl_2), $[\alpha]_D$ +96 (*c* 1.59). ^{1}H NMR spectrum: 0.92 s, 3 H (3 × H-18); 2.29 s, 3 H (Me-3′); 2.88 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 3.88 s, 1 H (H-16β); 6.16 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum: 12.1 q, 16.3 q, 26.7 t, 27.7 t, 28.2 t, 30.3 t, 32.4 t, 37.5 d, 43.5 s, 44.7 d, 45.1 d, 55.9 q, 61.7 d, 64.4 s, 105.2 d, 112.2 d, 114.6 d, 126.7 d, 132.9 s, 138.3 s, 158.3 s, 160.3 s, 168.5 s. IR spectrum (KBr): 1 600, 1 500, 1 235. Mass spectrum: 365 [M^+], 322.

3-Methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)trien-16α,17α-diol (**8**)

A mixture of **3** (1.222 g, 3.5 mmol), OsO_4 (79 mg, 0.31 mmol), and 4-methylmorpholine *N*-oxide (747 mg, 5.6 mmol) in acetone (50 ml) and water (2.5 ml) was stirred at room temperature for 18 h. Then the solvent was evaporated and the residue was dissolved in ethyl acetate. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. Crystallization of the obtained ma-

terial from aqueous methanol and chromatography on silica gel of the mother liquor gave diol **8** (1.099 g, 82%), m.p. 191–192 °C (EtOAc). ^{1}H NMR spectrum: 0.66 s, 3 H (3 × H-18); 2.21 s, 3 H (Me-3′); 2.86 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.08 dd, 1 H, J_1 = 10, J_2 = 3 (H-16 β); 6.10 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). IR spectrum (KBr): 3 590; 1 600, 1 500. Mass spectrum: 383 [M^+], 365.

17α-Hydroxy-3-methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)-trien-16α-yl Acetate (**9**)

A mixture of diol **8** (958 mg, 2.5 mmol) and Ac_2O (0.4 ml, 3.9 mmol) in pyridine (8 ml) reacted for 15 h at 20 °C. Then it was poured into ice water and extracted with ethyl acetate. The organic phase was washed with 1 M HCl, saturated $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The obtained oil was purified on a short silica gel column (toluene–AcOEt 80 : 20) to give acetate **9** (1.02 g, 96%), m.p. 215–217 °C (EtOAc), $[\alpha]_D$ –12 (*c* 1.34). ^{1}H NMR spectrum: 0.68 s, 3 H (3 × H-18); 2.10 s, 3 H, (OAc); 2.30 s, 3 H (Me-3′); 2.86 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.81 dd, 1 H, J_1 = 10, J_2 = 3 (H-16β); 6.10 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum: 11.5 q, 15.5 q, 21.1 q, 25.6 t, 27.8 t, 29.5 t, 29.8 t, 32.1 t, 38.7 d, 43.5 d, 47.8 d, 49.0 s, 55.2 q, 81.2 s, 103.4 d, 111.5 d, 113.6 d, 126.2 d, 132.3 s, 137.8 s, 157.5 s, 159.6 s, 169.6 s, 172.7 s. IR spectrum (KBr): 3 450, 1 730, 1 600, 1 500, 1 250. Mass spectrum: 425 [M^+], 365.

17α-Hydroxy-3-methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)-trien-16α-yl Benzoate (**10**)

A mixture of diol **8** (502 mg, 1.31 mmol), benzoyl chloride (0.38 ml, 2.62 mmol) and 4-dimethylaminopyridine (425 mg, 3.93 mmol) in dichloromethane (15 ml) reacted for 48 h at room temperature. The precipitate was filtered off, and the mother liquor was washed with water, dried (Na_2SO_4), evaporated and the residue was crystallized from methanol to give the second crop. Both crops were combined to afford benzoate **10** (531 mg, 83%), m.p. 262–264 °C (MeOH), $[\alpha]_D$ –27 (*c* 0.64). ^{1}H NMR spectrum: 0.77 s, 3 H (3 × H-18); 2.30 s, 3 H (Me-3′); 2.86 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 6.10 dd, 1 H, J_1 = 10, J_2 = 3 (H-16β); 6.15 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1); 7.42 and 7.55 and 8.00 m, 5 H (Ph). IR spectrum (KBr): 3 540, 1 710, 1 600, 1 500, 1 250.

17α-Hydroxy-3-methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)-trien-16-one (**11**) and
3-Methoxy-17α-(methylsulfanyl)methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)-trien-16-one (**12**).

To a stirred solution of oxalyl chloride (127 mg, 1.0 mmol) in dichloromethane (3 ml) at –70 °C, dimethyl sulfoxide (117 mg, 1.5 mmol) in dichloromethane (3 ml) was added dropwise. After stirring for 20 min, diol **8** (192 mg, 0.5 mmol) in dichloromethane (5 ml) was added and stirring was continued for 20 min. Subsequently, triethylamine (505 mg, 5.0 mmol) was added, the temperature was risen slowly to 20 °C and stirring was continued for another hour. Then the mixture was poured in saturated $NaHCO_3$ and extracted with chloroform. The extract was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (toluene–AcOEt 1 : 1) to give following compounds.

Ether **12** as oil (46 mg, 21%). ^{1}H NMR spectrum: 0.62 s, 3 H (3 × H-18); 2.14 s, 3 H (CH_3S); 2.33 s, 3 H (Me-3′); 2.90 m, 2 H (H-6); 3.80 s, 3 H (OMe); 4.38 d, 2 H, J = 3 (OCH_2S); 6.42 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.18 s, 1 H, J = 8.8 (H-1). IR spectrum (KBr): 1 740, 1 600, 1 500, 1 040. Mass spectrum: 441 [M^+], 394, 380.

Ketone **11** (120 mg, 63%), m.p. 221–222 °C (benzene–EtOAc), $[\alpha]_D$ –138 (*c* 0.84). ^{1}H NMR spectrum: 0.66 s, 3 H (3 × H-18); 2.29 s, 3 H (Me-3′); 2.90 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 6.25 s, 1 H

(H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.18 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum (C_5D_5N): 11.2 q, 15.6 q, 26.0 t, 28.5 t, 30.0 t, 30.0 t, 37.1 t, 38.4 d, 43.9 d, 44.2 d, 47.2 s, 55.2 q, 80.4 s, 105.2 s, 112.2 d, 114.2 d, 126.7 d, 132.6, 138.0 s, 158.3 s, 159.2 s, 171.3 s, 212.4 s. IR spectrum (KBr): 3 450, 1 740, 1 605, 1 500. Mass spectrum: 381 [M^+], 227.

17α-Hydroxy-3-methoxy-17-(3-methylisoxazol-5-yl)estra-1,3,5(10)-trien-16β-yl Acetate (**13**)

To a stirred solution of ketone **11** (70 mg, 0.18 mmol) in THF (7 ml) lithium tri-*tert*-butoxyaluminiumhydride (127 mg, 0.5 mmol) was added portionwise. The resulting solution was stirred at room temperature for 1 h and water (0.1 ml) was added. The slurry was filtered through a plug with Na_2SO_4 and the precipitate was washed several times with chloroform. The filtrate and the washings were combined and evaporated. The residue was chromatographed on silica gel (toluene–AcOEt 80 : 20) to give diol (60 mg, 87%), which was acetylated to acetate **13** as described above, m.p. 107–110 °C (MeOH–water), $[\alpha]_D$ +22.5 (*c* 1.02). ^{1}H NMR spectrum: 0.88 s, 3 H (3 × H-18); 2.08 s, 3 H, (OAc); 2.32 s, 3 H (Me-3′); 2.88 m, 2 H (2 × H-6); 3.80 s, 3 H (OMe); 5.20 dd, 1 H, J_1 = 8, J_2 = 6 (H-16α); 6.12 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum: 11.4 q, 14.9 q, 21.1 q, 25.7 t, 27.8 t, 29.7 t, 30.4 t, 32.8 t, 38.6 d, 43.3 d, 46.3 d, 48.5 s, 55.2 q, 82.0 d, 83.0 s, 103.8 d, 111.5 d, 113.8 d, 126.3 d, 132.3 s, 137.8 s, 157.5 s, 159.2 s, 170.7 s, 172.2 s. IR spectrum (KBr): 3 450, 1 730, 1 600, 1 500, 1 250. Mass spectrum: 425 [M^+], 365.

Cleavage of Epoxide **7**

To a stirred solution of epoxide **7** (114 mg, 0.31 mmol) in THF (10 ml), perchloric acid (46%, 0.6 ml) was added, and the resulting mixture was stirred for 20 h at room temperature. Saturated $NaHCO_3$ was added and the mixture was evaporated to 10% of its original volume. The organic material was extracted with chloroform and the organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (toluene–AcOEt 70 : 30) to give two isoxazoles (96 mg, 85%).

3-Methoxy-17-methyl-17α-(3-methylisoxazol-5-yl)-18-nor-8α,13α,14β-estra-1,3,5(10),9(11)-tetraen-16α-ol (**15**), m.p. 176–179 °C (EtOAc). ^{1}H NMR spectrum: 1.46 s, 3 H (Me-17); 2.26 s, 3 H (Me-3′); 2.85 m, 2 H (H-6); 3.78 s, 3 H (OMe); 4.15 m, 1 H (H-16β); 5.71 m, 1 H (H-11); 5.98 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1).

3-Methoxy-17-methyl-17α-(3-methylisoxazol-5-yl)-18-norestra-1,3,5(10),13-tetraen-16α-ol (**14**), m.p. 188–190 °C (MeOH–CH_2Cl_2), $[\alpha]_D$ –11 (*c* 1.09). ^{1}H NMR spectrum: 1.46 s, 3 H (Me-17); 2.26 s, 3 H (Me-3′); 2.95 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 4.27 t, 1 H, J = 7 (H-16β); 5.88 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). IR spectrum (KBr): 3 350, 1 600, 1 585, 1 500. Mass spectrum: 365 [M^+].

3-Methoxy-17-methyl-17α-(3-methylisoxazol-5-yl)-18-norestra-1,3,5(10),13-tetraen-16α-yl Acetate (**16**)

Title compound was prepared from **14** by the above described procedure in 83% yield, m.p. 119–120 °C (aqueous MeOH), $[\alpha]_D$ +12 (*c* 0.26). ^{1}H NMR spectrum: 1.53 s, 3 H (3 × H-18); 1.94 s, 3 H (OAc); 2.29 s, 3 H (Me-3′); 2.87 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.30 t, 1 H, J = 7 (H-16β); 5.83 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum: 11.6 q, 20.9 q, 21.5 q, 22.4 t, 26.3 t, 26.8 t, 29.9 t, 36.7 t, 39.6 d, 40.9 d, 53.1 s, 55.2 q, 80.7 d, 102.8 d, 111.4 d, 114.0 d, 125.8 d, 132.1 s, 136.5 s, 137.6 s, 138.0 s, 157.7 s, 159.4 s, 170.9 s, 173.7 s. IR spectrum (KBr): 1 740, 1 600, 1 500, 1 270, 1050. Mass spectrum: 407 [M^+], 347.

3-Methoxy-17-methyl-17α-(3-methylisoxazol-5-yl)-18-nor-8α,13α,14β-estra-1,3,5(10),9(11)-tetraen-16α-yl Acetate (**17**)

Title compound was prepared from **15** by the above described procedure in 84% yield, m.p. 157–159 °C ($MeOH–CH_2Cl_2$). ^1H NMR spectrum: 1.52 s, 3 H (Me-17); 1.87 s, 3 H (OAc); 2.28 s, 3 H (Me-3′); 2.85 obsc m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.18 dd, 1 H, J_1 = 6, J_2 = 3 (H-16β); 5.71 m, 1 H (H-11); 5.95 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum: 11.5 q, 20.9 q, 24.9 q, 27.8 t, 29.9 t, 32.7 t, 34.8 t, 39.7 d, 42.9 d, 45.1 d, 49.9 s, 55.2 q, 81.0 d, 102.6 d, 112.1 d, 113.4 d, 120.8 d, 127.5 d, 131.9 s, 137.7 s, 146.1 s, 157.4 s, 159.2 s, 170.3 s, 174.9 s. IR spectrum (KBr): 1 740, 1 600, 1 500, 1 270, 1 050. Mass spectrum: 407 [M^+], 346.

17β-(3-Amino-1-oxobut-2-en-1-yl)-16α,17α-epoxy-3-methoxyestra-1,3,5(10)-triene (**18**)

A solution of compound **7** (435 mg, 1.19 mmol), $Mo(CO)_6$ (333 mg, 1.26 mmol) and water (0.5 ml) in acetonitrile (30 ml) was refluxed for 1 h. The solution then was cooled and the solvent was evaporated. The brown residue was dissolved in chloroform (5 ml) and silica gel was added. Then the solvent was evaporated *in vacuo* and the residue absorbed on silica gel, was purified on a silica gel column (toluene–AcOEt 90 : 10) to give enamino ketone **18** (301 mg, 69%), m.p. 222–224 °C ($MeOH–CH_2Cl_2$), $[\alpha]_D$ + 109 (*c* 0.51). ^1H NMR spectrum: 1.11 s, 3 H (3 × H-18); 1.95 s, 3 H (H-4′); 2.84 m, 2 H (2 × H-6); 3.62 s, 1 H (H-16β); 3.78 s, 3 H (OMe); 5.08 brs, 2 H (H-2′ and NH); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1); 9.82 brs, 1 H (NH). IR spectrum (KBr): 3 280, 1 610, 1 550.

Spiro [((17*R*)-16β-bromo-3-methoxyestra-1,3,5(10)-triene)-17,2′-(5′-methylfuran-3′(2′*H*)-one)] (**19**)

To a stirred solution of compound **18** (130 mg, 0.35 mmol) in THF (5 ml), HBr (48%, 0.2 ml) was added at 0 °C. In 1 h the temperature was allowed to rise to ambient and stirring was continued for 24 h. The solution was diluted with ethyl acetate, washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The obtained material was purified on a silica gel column (toluene–AcOEt 90 : 10) to give product **19** (136 mg, 90%), m.p. 177–180 °C ($MeOH–CH_2Cl_2$), $[\alpha]_D$ +43 (*c* 0.56). ^1H NMR spectrum: 1.21 s, 3 H (3 × H-18); 2.26 s, 3 H (Me-5′); 2.86 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 4.32 t, 1 H, J = 7 (H-16α); 5.45 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum: 14.0 q, 17.1 q, 26.1 t, 28.5 t, 30.3 t, 31.3 t, 38.7 d, 40.0 t, 43.9 d, 49.0 d, 50.2 s, 51.2 d, 55.9 q, 97.2 s, 106.6 d, 112.3 d, 114.4 d, 126.9 d, 132.4 s, 138.3 s, 158.3 s, 187.2 s, 200.0 s. IR spectrum (KBr): 1 700, 1 620, 1 510. Mass spectrum: 430 and 432 [M^+], 351, 253, 227.

Spiro[((17*R*)-3-methoxyestra-1,3,5(10)-triene)-17,2′-(5′-methylfuran-3′(2′*H*)-one)] (**20**)

A solution of compound **19** (64 mg, 0.15 mmol), tributylstannane (87 mg, 0.3 mmol) and AIBN (98 mg, 0.6 mmol) in benzene (2 ml) was refluxed for 1 h. The solution then was cooled and the solvent was evaporated. The obtained material was purified on a silica gel column (toluene–AcOEt 90 : 10) to give product **20** (50 mg, 95%), m.p. 169–170 °C ($MeOH–CH_2Cl_2$), $[\alpha]_D$ +139 (*c* 1.11). ^1H NMR spectrum: 0.96 s, 3 H (3 × H-18); 2.25 s, 3 H (Me-5′); 2.88 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.42 s, 1 H (H-4′); 6.63 d, 1 H, J = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.20 d, 1 H, J = 8.8 (H-1). ^{13}C NMR spectrum: 13.6 q, 17.3 q, 24.9 t, 26.6 t, 28.5 t, 30.5 t, 30.8 t, 33.8 t, 39.3 d, 44.0 d, 50.5 s, 52.4 d, 55.9 q, 101.4 s, 106.0 d, 112.2 d, 114.4 d, 126.9 d, 132.9 s, 138.5 s, 158.1 s, 187.7 s, 204.8 s. IR spectrum (KBr): 1 690, 1 610, 1 510. Mass spectrum: 352 [M^+].

Spiro[((17*S*)-16α-acetoxy-3-methoxyestra-1,3,5(10)-triene)-17,2′-(5′-methylfuran-3′(2′*H*)-one)] (**21**)

To a stirred solution of nickel chloride hydrate (135 mg, 0.6 mmol) in methanol (5 ml), compound **9** (107 mg, 0.25 mmol) in THF (10 ml) was added. The resulting mixture was cooled to 0 °C and sodium borohydride (70 mg, 1.8 mmol) was added portionwise. Aqueous ammonia was added in 10 min and the solution was evaporated to a small volume. The organic phase was extracted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated. The obtained oil was dissolved in ethanol (7 ml) contained HCl (0.1 ml) and the solution was stirred at room temperature. After 24 h, the solvent was evaporated to 10% of its original volume and silica gel was added. Then the rest of solvent was evaporated *in vacuo* and the residue absorbed on silica gel, was purified on a silica gel column (toluene–AcOEt 80 : 20) to give acetate **21** (72 mg, 70%), m.p. 187–190 °C (MeOH–CH_2Cl_2), $[\alpha]_D$ +87 (*c* 1.0). ^{1}H NMR spectrum: 1.04 s, 3 H (3 × H-18); 2.00 s, 3 H (OAc); 2.29 s, 3 H (Me-5′); 2.86 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.44 s, 1 H (H-4′); 5.48 obsc m, 1 H (H-16β); 6.63 d, 1 H, *J* = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.18 d, 1 H, *J* = 8.8 (H-1). IR spectrum (KBr): 1 735. 1 685, 1 600, 1 500, 1 250. Mass spectrum: 410 [M^+], 350.

Spiro[((17*S*)-16α-benzoyloxy-3-methoxyestra-1,3,5(10)-triene)-17,2′-(5′-methylfuran-3′(2′*H*)-one)] (**22**)

A solution of compound **10** (325 mg, 0.67 mmol), $Mo(CO)_6$ (195 mg, 0.74 mmol) and water (0.8 ml) in acetonitrile (60 ml) was refluxed for 1 h. The solution was cooled and concentrated hydrochloric acid (0.3 ml) was added. A resulted mixture was refluxed for another hour, cooled and the solvent was evaporated. The brown residue was dissolved in chloroform (5 ml) and silica gel was added. Then the solvent was evaporated *in vacuo* and the residue adsorbed on silica gel was purified on a silica gel column to give benzoate **22** (288 mg, 91%), m.p. 182–183 °C (MeOH–CH_2Cl_2), $[\alpha]_D$ +54 (*c* 0.99). ^{1}H NMR spectrum: 1.13 s, 3 H (3 × H-18); 2.29 s, 3 H (Me-5′); 2.86 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 5.46 s, 1 H (H-4′); 5.84 m, 1 H (H-16β); 6.63 d, 1 H, *J* = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.18 d, 1 H, *J* = 8.8 (H-1); 7.42 and 7.55 and 8.00 m, 5 H (Ph). IR spectrum (KBr): 1 730, 1 700, 1 600, 1 500, 1 250. Mass spectrum: 472 [M^+], 350.

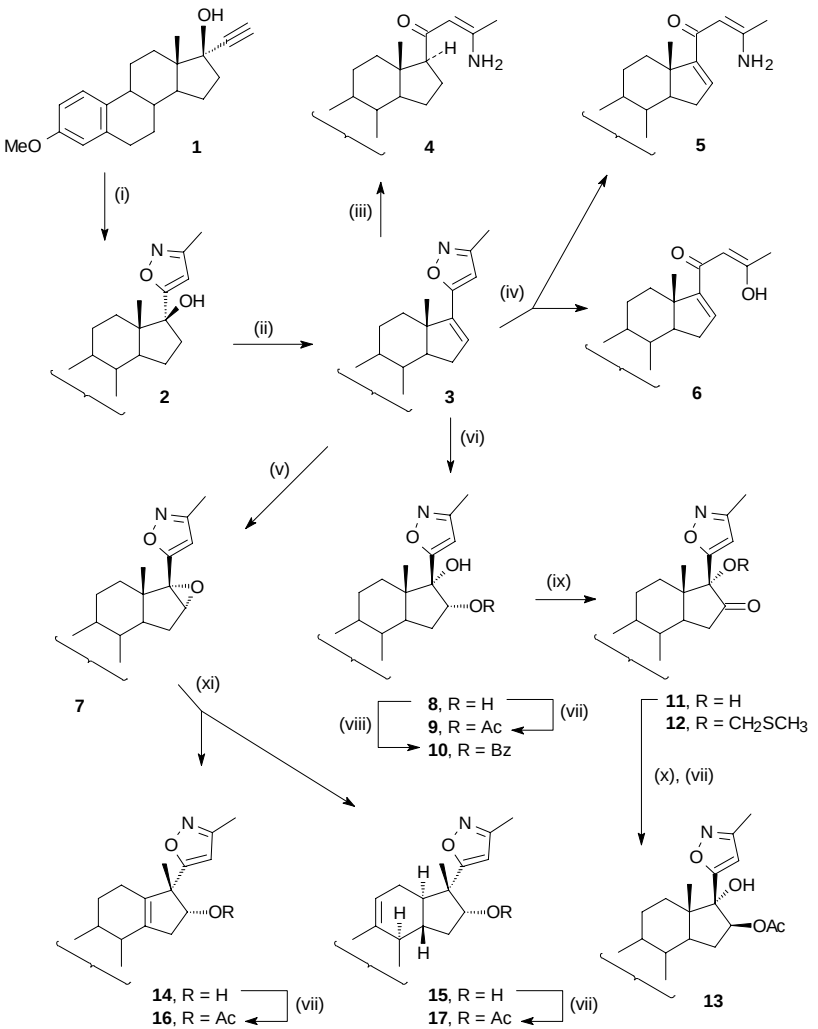
Spiro[((17*S*)-16α-hydroxy-3-methoxyestra-1,3,5(10)-triene)-17,2′-(5′-methylfuran-3′(2′*H*)-one)] (**23**)

To a stirred solution of compound **21** (68 mg, 0.17 mmol) in methanol (10 ml), 1 M KOH in methanol (0.5 ml) was added. After stirring for 20 min, 5% aqueous HCl (0.5 ml) was added and the mixture was evaporated to a small volume. The organic material was extracted with chloroform. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (toluene–AcOEt 50 : 50) to give product **23** (42 mg, 67%), m.p. 209–211 °C (aqueous MeOH), $[\alpha]_D$ +74 (*c* 0.65). ^{1}H NMR spectrum: 1.03 s, 3 H (3 × H-18); 2.33 s, 3 H (Me-5′); 2.86 m, 2 H (2 × H-6); 3.78 s, 3 H (OMe); 4.72 m, 1 H (H-16β); 5.49 s, 1 H (H-4′); 6.63 d, 1 H, *J* = 2.6 (H-4); 6.70 dd, 1 H, J_1 = 8.8, J_2 = 2.6 (H-2); 7.18 d, 1 H, *J* = 8.8 (H-1). ^{13}C NMR spectrum: 13.7 q, 17.3 q, 26.1 t, 28.5 t, 30.9 t, 31.1 t, 35.6 t, 38.9 d, 44.0 d, 50.4 s, 51.2 d, 55.9 q, 77.4 d, 100.2 s, 107.3 d, 112.3 d, 114.5 d, 126.8 d, 132.7 s, 138.5 s, 158.2 s, 188.7 s, 203.9 s. Mass spectrum: 368 [M^+], 350.

RESULTS AND DISCUSSION

Our approach is based on the elimination of the 17-hydroxy group in mestrenol (**1**) and introduction of the chiral center at C-17 bearing in mind that the attack of the reagent will take place from the α-side of the steroid skeleton. However, direct dehydration of

mestrenol did not give the desired enyne as it was also reported previously[10]. However, elimination of water from hydroxyisoxazole **2** with thionyl chloride was successful and led to alkene **3** exclusively in 84% yield (Scheme 1). No products of skeletal rearrangement were detected. The cleavage of the isoxazole ring was effected by reduction with



Bz = benzoyl

(i) $CH_3C{=}NOH$, N-chlorosuccinimide, $Et_3N/CHCl_3$; (ii) $SOCl_2$, pyridine/THF, -50 °C; (iii) $NiCl_2$, $NaBH_4$/THF; (iv) $Mo(CO)_6/CH_3CN$, H_2O, reflux; (v) 3-chloroperoxybenzoic acid, $NaHCO_3/CH_2Cl_2$; (vi) OsO_4, 4-methylmorpholine *N*-oxide/Me_2CO, H_2O; (vii) Ac_2O/pyridine; (viii) benzoyl chloride, DMAP/CH_2Cl_2; (ix) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, -70 °C; (x) $LiAlH(tBuO)_3$/THF; (xi) $HClO_4$, H_2O/THF

SCHEME 1

nickel boride, but in these conditions, the saturation of the Δ^{16}-bond also occurred, giving enaminoketone **4**. To avoid this reduction, the cleavage with $Mo(CO)_6$ was employed. The reaction of alkene **3** with $Mo(CO)_6$ afforded enamino ketone **5** along with compound **6** in a good yield. From the ^1H and ^{13}C NMR spectra, it could be concluded that diketone **6** exists in solution mostly in its 22-en-23-ol tautomeric form. Unfortunately, all further attempts to electrophilic and free-radical cyclization of compounds **5** or **6** into a spirofurane were unsuccessful. This turned us to try the formation of the chiral center at C-17 before opening of the ring.

Two approaches were examined for this purpose, dihydroxylation and epoxidation.

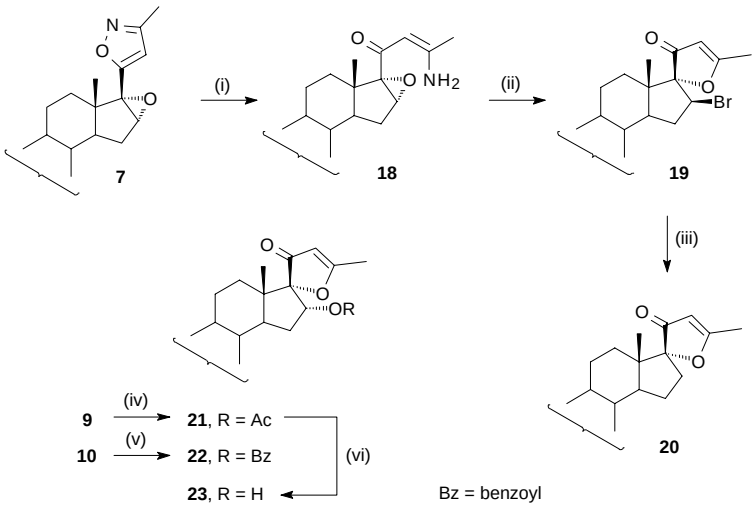
It is known that the attack of a reagent on the Δ^{16}-bond usually occurs from the α-side and also in our reactions, only epimers **7** and **8** were isolated. The epoxidation route was not entirely satisfactory since appreciable amounts of side products, resulting from opening of the epoxide ring and further rearrangements, were obtained. Thus, when epoxide **7** was treated with perchloric acid in THF, compounds **14** and **15** were isolated in a 3 : 1 ratio. Such backbone rearrangement induced by boron trifluoride is known for 5α,6α- and 16α,17α-epoxy steroids[11,12]. Because of their low solubility, compounds **14** and **15** were converted in their acetates **16** and **17** for spectroscopic correlations. The assignment of the structure of acetate **17** was based on analysis of its ^{13}C NMR spectrum[13,14].

The dihydroxylation gave a better yield (82% *vs* 57% for the epoxide) but also required a strict control of conditions. It was found that excess of oxidant (4-methylmorpholine *N*-oxide) led to oxidative cleavage of diol **8**. The secondary hydroxy group in diol **8** was protected as esters **9** or **10** to ensure the formation of spirofurans after cleavage of the isoxazole ring and to prevent the cyclization at C-16. In an attempt to prepare the 16β-epimer of diol **8**, we examined its oxidation to ketone **11**. It was found that chromium reagents were unsuitable for this oxidation and led to complex mixtures due to cleavage of the D ring of the steroid. Swern oxidation afforded the desired ketone in 63% yield along with some ketone **12** as a result of the Pummerer rearrangement. Finally, the reduction of ketone **11** with the bulky lithium tri-*tert*-butoxyaluminiumhydride followed by acetylation gave acetate **13** exclusively.

In acidic conditions, epoxide **7** suffered from rearrangement and therefore we decided to open the epoxy ring after cleavage of the isoxazole ring. Indeed, compound **18** treated with HBr in THF was converted smoothly and without rearrangement to bromofuranone **19** in 90% yield, *via trans*-opening of the epoxy ring[8,15–18] followed by intramolecular cyclization (Scheme 2).

Debromination of bromofuranone **19** was performed with tributylstannane and product **20** was isolated in a good yield. Comparison of the spectral data of compound **20** with those of analogs given in literature[6,9] unambiguously confirms the 17*R*-configuration of the chiral center at C-17. The signals of the protons at C-18 and C-4′ in the ^1H NMR spectra are the most suitable for structure assignment. Thus, for furanone **20**, the sig-

nals of the protons at C-18 resonate at higher field in comparison with those of the 17-epimer (*ca* 0.07 ppm) and the signal of the proton at C-4′ appears at lower field (*ca* 0.11 ppm).



(i) $Mo(CO)_6/CH_3CN$, H_2O, reflux; (ii) 48% aq. HBr/THF; (iii) tributylstannane, AIBN/benzene, reflux; (iv) $NiCl_2$, $NaBH_4$/THF, MeOH; (v) a) $Mo(CO)_6/CH_3CN$, H_2O, reflux, b) 37% aq. HCl/THF; (vi) KOH/MeOH

SCHEME 2

The 16-substituted spirofuranones **21** and **22** were prepared from the corresponding isoxazoles **9** and **10**. The cleavage of isoxazole **9** was carried out with nickel boride and, after cyclization, furanone **21** was isolated in 70% yield. The protection of the C-16 hydroxy group as benzoate and the use of $Mo(CO)_6$ as reducing agent allowed to obtain furanone **22** in 91% yield after cyclization. Cyclization of the enamino ketones was performed with HCl in ethanol. Hydrolysis of the acetate in furanone **21** with KOH in methanol gave alcohol **23** in 67% yield along with some by-products.

We are grateful to the Laboratory for Physical and Chemical Analysis of the Institute of Bioorganic chemistry for the acquisition of spectral data.

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