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Steroids 66 (2001) 117–126

Steroids

Synthesis of (3α,7β,17α)-7-methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol, a metabolite of ORG OD14, and its 7-epimer

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Received 17 February 2000; received in revised form 4 April 2000; accepted 12 April 2000

Abstract

The syntheses of the 7β-hydroxy metabolite of ORG OD14 (Livial®), (3α,7β,17α)-7-methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol (**35**), and its 7-epimer, (3α,7α,17α)-7-methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol (**11**), are described.

Keywords: Tibolone; Livial; ORG OD14; 7-Hydroxy steroids

1. Introduction

Livial® is of great interest in hormone replacement therapy in menopausal women at risk of osteoporosis [1,2]. The active principle of Livial® is ORG OD14 (generic name: tibolone, scientific name: (7α,17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one) **I** [3]. Recently, the metabolism of ORG OD14 in rat and human hepatocytes has been reported [4]. In both rat and human hepatocytes the metabolism of this steroid was found to be virtually complete. Among the metabolites detected, the 7-hydroxy derivative **III** is a result of phase II metabolism (sulfate conjugation) of its precursor **35,** which is produced by phase I metabolism (hydroxylation) of **II** (Scheme 1). Cytochrome P450 enzymes [5] are known to be involved in the phase I 7-hydroxylation of endogenous steroids, such as cholesterol, pregnenolone and dehydroepiandrosterone. Although not proven, these enzymes are candidates for the conversion of **II** into **35.**

The 7-hydroxy derivative **III** has been found in an in vivo metabolism study of ORG OD14 in rat, but it could not be detected in human. Structure verification as well as an understanding of the pharmacology of this drug metabolite urged us to develop the synthesis of **35** as described below.

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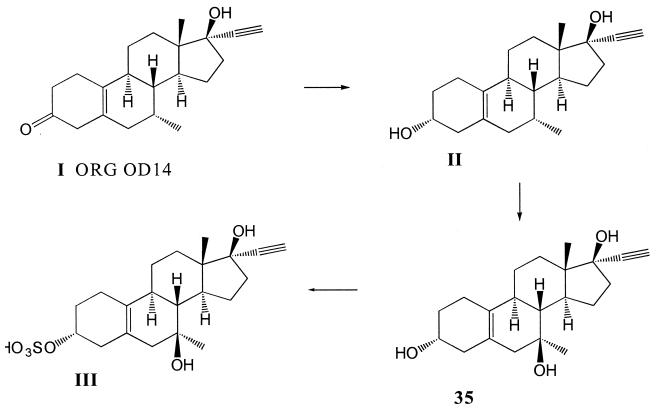
2. Experimental

2.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (200 MHz, 400 and 600 MHz) with deuteriochloroform was as the solvent unless stated otherwise. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard, and coupling constants are expressed in Hertz. Thin layer chromatography was performed on pre-coated Merck Silica gel 60 F_{254} plates and visualized with UV light and/or with sulfuric acid in ethanol solution or the Usui reagent. Column chromatography was performed on Merck Silica gel 60 (230–400 mesh or 400–600 mesh). Melting points were determined on a Büchi 535 apparatus and are uncorrected. Fast atom bombardment (FAB) mass spectra were recorded with a Finnigan MAT 90 mass spectrometer (Finnigan MAT, Bremen, FRG). Samples were dissolved in methanol and mixed with the matrix compounds on standard stainless steel targets. Exact masses of the protonated molecular ions were determined with the peak matching technique at a mass resolution of $>$ 7500 (10% valley definition) in the positive ion mode using reference masses 369 and 461 from glycerol. Average exact masses were calculated from at least 10 computer-controlled measurements using the bracketing method.

0039-128X/01/$ – see front matter
PII: S0039-128X(00)00111-2



Scheme 1.

*2.1.1. 3-Methoxyestra-1,3,5(10),6-tetraen-17-one cyclic 1,2-ethanediyl acetal **(2)***

Triethyl orthoformate (66 ml) and p-toluenesulphonic acid (990 mg) were added to a solution of **1** (33.1 g, 117 mM) in ethylene glycol (330 ml) and CH_2Cl_2 (50 ml). After stirring at room temperature for 6 h, the reaction mixture was poured into sodium bicarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness to give **2** (42.5 g, 100% crude). R_f 0.8 [toluene/ethyl acetate (8:2 v/v)]. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H, 18CH_3), 3.80 (s, 3H, Ar-OCH_3), 3.93 (m, 4H, ketal), 6.01 (dd, J = 2Hz, 1H, 7-H), 6.45 (dd, J = 3 Hz, 1H, 6-H), 6.65 (d, 1H, Ar-4H), 6.74 (dd, 1H, Ar-2H), 7.16 (d, 1H, Ar-1H).

*2.1.2. (6α,7α)-6,7-Epoxy-3-methoxyestra-1,3,5(10) -trien-17-one cyclic 1,2-ethanediyl acetal **(3)***

3-Chloroperoxybenzoic acid (44.4 g, 260 mM) was added to a solution of **2** (42 g, crude) in ethyl acetate (420 ml) under nitrogen was added and stirred at room temperature for 6 h. Then, the reaction mixture was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate. The extract was washed with ammonium chloride solution, treated with sodium thiosulfate solution, filtered, washed with brine, and evaporated to dryness to give **3** (48.4 g, 100% crude). R_f 0.5 [toluene/ethyl acetate (8:2 v/v)]. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H, 18CH_3), 3.58 (d, 1H, 7-H), 3.82 (s, 3H, Ar-OCH_3), 3.85 (d, 1H, 6-H), 3.95 (m, 4H, ketal), 6.85 (dd, 1H, Ar-2H), 6.97 (d, 1H, Ar-4H), 7.16 (d, 1H, Ar-1H).

*2.1.3. (7α)-7-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal **(4)***

A solution of **3** (48.4 g, crude) in tetrahydrofuran (480 ml) to a suspension of lithium aluminum hydride (25.7 g, 678 mM) in tetrahydrofuran (300 ml), was added dropwise. The mixture was heated to reflux. After stirring for 1.5 h, the mixture was cooled to −15°C and quenched with ethyl acetate whereas maintaining the temperature below 10°C. Water (250 ml) was added. After stirring for 1 h, the mixture was filtered over a Decalite pad and extracted with ethyl acetate. The extract was successively washed with ammonium chloride, sodium bicarbonate solution, and brine. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography [heptane/ethyl acetate (8:2)] to give **4** (24.9 g, 72.3 mM, 51%). R_f 0.55 [toluene/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H, 18CH_3), 2.43 (m, 1H, 9αH), 2.63 (m, 1H, 8βH), 2.91 (m, 1H, 6-H), 3.12 (m, 1H, 6-H), 3.78 (s, 3H, Ar-OCH_3), 3.93 (m, 4H, ketal), 4.15 (m, 1H, 7βH), 6.64 (d, 1H, Ar-4H), 6.75 (dd, 1H, Ar-2H), 7.25 (d, 1H, Ar-1H).

*2.1.4. 3-Methoxyestra-1,3,5(10)-triene-7,17-dione cyclic 17-(1,2-ethanediyl acetal) **(5)***

Chromic acid (3 ml, 8N, 24 mM) was added to a solution of **4** (2 g, 5.8 mM) in acetone (30 ml) at −20°C. The reaction was stirred for 6 h, whereas the temperature raised to 20°C. Ethanol (10 ml) was added, and the mixture was poured into a saturated solution of sodium bicarbonate. Then, the mixture was filtered over a Decalite pad, extracted with ethyl acetate, and washed successively with sodium bicarbonate, ammonium chloride, water, and brine. The organic layer was dried (Na_2SO_4) and evaporated to dryness. Purification by column chromatography [heptane/ethyl acetate (8:2)] gave **5** (1.31 g, 3.8 mM, 66%). R_f 0.7 [toluene/ethyl acetate (1:1 v/v)] ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.87 (s, 3H, 18CH_3), 2.65 (m, 1H, 8βH), 3.59 (s, 2H, 6-H), 3.80 (s, 3H, Ar-OCH_3), 3.93 (m, 4H, ketal), 6.67 (d, 1H, Ar-4H), 6.81 (dd, 1H, Ar-2H), 7.24 (d, 1H, Ar-1H).

*2.1.5. (7α)-7-Hydroxy-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal **(6)***

Cerium(III) chloride heptahydrate (560 mg, 1.5 mM) was finely ground in a mortar and placed into in a 50 ml necked flask. The flask was put in an oil bath, evacuated, and heated to 140°C, whereas the powder was stirred with a magnetic stirring bar for 16 h. Then, while the flask was still hot, nitrogen was introduced, the flask was cooled to 0°C, and tetrahydrofuran (5 ml) was added. The flask was put in an ultrasound bath, and the suspension was stirred for 1 h. After cooling to 0°C, methylmagnesium chloride (0.75 ml of a 2.0-M solution in tetra- hydrofuran, 1.5 mM) was added to the suspension. After stirring for 1.5 h at 0°C, a solution of **5** (356 mg, 1 mM) in tetrahydrofuran (3 ml) was added to the mixture. After 0.5 h of stirring at 0°C, the reaction mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The extract was washed successively sodium bicarbonate, water, and brine. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give the crude product. Purification by column chromatography [heptane/ethyl acetate (7:3)] gave **6** (190 mg, 0.5 mM, 53%). R_f 0.5 [toluene/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H, 18CH_3), 1.32

(s, 3H, 7-CH_3), 2.33 (m, 1H, 9αH), 2.48 (m, 1H, 8βH), 2.72 (d, J = 16 Hz, 1H, 6αH), 2.94 (d, J = 16Hz, 1H, 6βH), 3.78 (s, 3H, Ar-OCH_3), 3.92 (m, 4H, ketal), 6.64 (d, 1H, Ar-4H), 6.76 (dd, 1H, Ar-2H), 7.22 (d, 1H, Ar-1H).

*2.1.6. (7α)-7-Hydroxy-3-methoxy-7-methylestra-2,5(10)-dien-17-one cyclic 1,2-ethanediyl acetal **(7)***

Lithium metal (1.1 g, 158 mM) was cut into small pieces and dissolved in liquid ammonia (90 ml). After stirring for 0.5 h at −65°C, a solution of **6** (4.53 g, 11.67 mM) in tetrahydrofuran (45 ml) was added dropwise. After stirring at −35°C for 4.5 h, ethanol (40 ml) was added. After evaporation of the ammonia, the reaction mixture was poured into a saturated ammonium chloride solution and extracted with ethyl acetate. The extract was washed successively with sodium bicarbonate, water, and brine. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give **7** (4.83 g, 100% crude). R_f 0.45 [heptane/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.88 (s, 3H, 18CH_3), 1.31 (s, 3H, 7-CH_3), 3.54 (s, 3H, 3-OCH_3), 3.90 (m, 4H, ketal), 4.64 (m, 1H, 2-H).

*2.1.7. (7α)-7-Hydroxy-7-methylestr-5(10)-ene-3,17-dione cyclic 17-(1,2-ethanediyl acetal) **(8)***

Oxalic acid (1.17 g, 13.0 mM) was added to a solution of **7** (4.83 g, crude) in acetone (120 ml) and water (30 ml). After stirring for 6 h, the mixture was poured into a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The extract was washed successively with sodium bicarbonate, water, and brine. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give the crude product. Purification by column chromatography [heptane/ethyl acetate (1:1)] gave **8** (2.21 g, 6.4 mM, 49%). R_f 0.3 [heptane/ethyl acetate (4:6 v/v)].^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.89 (s, 3H, 18CH_3), 1.32 (s, 3H, 7-CH_3), 2.65 (d, 1H, 4-H), 2.78 (d, 1H, 4-H), 3.92 (m, 4H, ketal).

*2.1.8. (3α,7α)-3,7-Dihydroxy-7-methylestr-5(10)-en-17-one cyclic 1,2-ethanediyl acetal **(9)***

A suspension of lithium tri-*tert*-butoxy aluminum hydride (3.69 g, 14.52 mM) in THF (30 ml) was added dropwise to a solution of **8** (2.21 g, 6.3 mM) in THF (20 ml) under nitrogen and at room temperature. After 3 h, the reaction mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The extract was washed successively with water, brine and dried (Na_2SO_4), and evaporated to dryness to give **9** (2.18 g, 6.3 mM, 98%). R_f 0.2 [heptane/ethyl acetate (2:8 v/v)].^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.88 (s, 3H, 18CH_3), 1.29 (s, 3H, 7-CH_3), 3.83 (m, 1H, 3βH), 3.92 (m, 4H, ketal).

*2.1.9. (3α,7α)-3,7-Dihydroxy-7-methylestr-5(10)-en-17-one **(10)***

Hydrochloric acid (5 ml of a 0.1N HCl solution) was added to a solution of **9** (2.18 g, 6.3 mM) in acetone (20 ml) and water (2 ml). After 4 h, the reaction mixture was poured into a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed successively with sodium bicarbonate, water, and brine, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized (dichloro methane/acetone) to give **10** (1.07 g, 3.5 mM, 56%) as white crystals; m.p. 247°C. R_f 0.8 [ethanol/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 600 MHz) δ 0.90 (s, 3H, 18-CH_3), 1.28 (m, 1H, 11βH), 1.31 (m, 1H, 12αH), 1.36 (s, 3H, 7-CH_3), 1.53 (m, 1H, 2βH), 1.80 (m, 1H, 12βH), 1.81 (m, 1H, 14αH), 1.82 (m, 1H, 6αH), 1.82 (m, 1H, 15βH), 1.83 (m, 1H, 4βH), 1.89 (m, 1H, 9αH), 1.91 (m, 1H, 2αH), 1.97 (m, 1H, 1βH), 2.08 (m, 1H, 11αH), 2.11 (m, 1H, 16αH), 2.16 (m, 1H, 1αH), 2.21 (m, 1H, 4αH), 2.24 (m, 1H, 6βH), 2.30 (m, 1H, 15αH), 2.45 (m, 1H, 16βH), 3.85 (m, 1H, 3βH). ^{13}C-NMR ($CDCl_3$, 150 MHz) 14.6 (q, 18-CH_3), 25.1 (t, C11), 25.4 (t, C15), 26.3 (t, C1), 29.5 (q, 7-CH_3), 31.8 (t, C2), 31.9 (t, C12), 36.0 (t, C16), 39.3 (t, C4), 43.3 (d, C9), 46.6 (d, C8), 46.6 (d, C14), 47.9 (t, C6), 49.4 (s, C13), 67.1 (d, C3), 71.0 (s, C7), 123.4 (s, C5), 129.2 (s, C10), 222.2 (s, C17).

*2.1.10. (3α,7α,17α)-7-Methyl-19-norpregn-5(10)-en-20-yne-3,7,17-diol **(11)***

Acetylene gas was passed through a suspension of potassium *tert*-butoxide (1.49 g, 13.3 mM) in tetrahydrofuran (5 ml) at 0°C. After 0.5 h, a suspension of **10** (0.9 g, 2.96 mM) in tetrahydrofuran (10 ml) was added, and the mixture was stirred for 1 h at 0°C. Then, nitrogen was passed through the suspension. The reaction mixture was extracted with ethyl acetate, the extract was washed successively with sodium bicarbonate and brine, dried (Na_2SO_4) and evaporated to dryness. Purification by column chromatography [methylene chloride/acetone (8:2)], followed by crystallization from ethyl acetate/acetone gave **11** (580 mg, 1.76 mM, 59%), m.p. 197°C. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H, 18-CH_3), 1.23 (m, 1H, 11βH), 1.27 (s, 3H, 7-CH_3), 1.41 (m, 1H, 8βH), 1.51 (m, 1H, 2βH), 1.60 (m, 1H, 12βH), 1.63 (m, 1H, 15βH), 1.77 (m, 1H, 6αH), 1.78 (m, 1H, 12αH), 1.83 (m, 1H, 4βH), 1.87 (m, 1H, 9αH), 1.93 (m, 1H, 2αH), 1.96 (m, 1H, 16βH), 1.97 (m, 1H, 14αH) 1.98 (m, 1H, 1βH), 1.98 (m, 1H, 15αH), 2.05 (m, 1H, 11αH), 2.17 (m, 1H, 1αH), 2.19 (m, 1H, 4αH), 2.19 (m,1H, 6βH), 2.25 (m, 1H, 16αH), 2.58 (s, 1H, C ≡ CH), 3.83 (m, 1H, 3β H). $_{13}$C-NMR ($CDCl_3$, 100 MHz) 13.5 (q, 18-CH_3), 25.7 (t, C11), 26.6 (t, C15), 26.9 (t, C1), 29.9 (q, 7-CH_3), 32.3 (t, C2), 33.2 (t, C12), 39.1 (t, C16), 39.7 (t, C4), 43.1 (d, C9), 45.4 (d, C14), 47.7 (d, C8), 48.1 (t, C6), 49.0 (s, C13), 67.6 (d, C3), 71.6 (s, C7), 74.4 (d, C-H ≡CH), 78.9 (s, C17), 88.0 (s, C≡CH), 123.5 (s, C5), 129.8 (s, C10). Exact mass calculated for $[M+H+Glyc.]^+$ is 423.2747, Found: 423.2745.

*2.1.11. (17β)-17-Hydroxy-3-methoxyestra-1,3,5(10)-trien-6-one **(13)***

19-Nortestosterone **12** (46 g, 168 mM) and potassium acetate (25g, 255 mM) were dissolved in dry DMF (500 ml)

and heated to 120°C. The solution was stirred for 6 h whereas oxygen gas was passed through. The reaction mixture was cooled to room temperature, potassium carbonate (138 g, 1 mol) and methyl iodide (80 ml, 1.29 mol) were added and the solution was stirred for 18 h at room temperature. The reaction mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give the crude product that was purified by column chromatography [silica gel, heptane/ethyl acetate (9:1 v/v)], to give **13** (37.7 g, 125 mM, 75%). R_f 0.5 [heptane/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 600 MHz) δ 0.79 (s, 3H, 18CH_3), 1.34 (m, 1H, 14αH), 1.34 (m, 1H, 15βH), 1.35 (m, 1H, 12αH), 1.50 (m, 1H, 16βH), 1.61 (m, 1H, 11βH), 1.68 (m, 1H, 15αH), 1.94 (m, 1H, 8βH), 2.02 (m, 1H, 12βH), 2.14 (m, 1H, 16αH), 2.21 (dd, J = 13.4 Hz, 1H, 7αH), 2.39 (m, 1H, 11αH), 2.48 (m, 1H, 9αH), 2.75 (dd, J = 3.2 Hz, 1H, 7βH), 3.75 (t, 1H, 17αH), 3.75 (s, 3H, Ar-OCH_3), 7.10 (dd, 1H, Ar-2H), 7.34 (d, 1H, Ar-1H), 7.56 (d, 1H, Ar-4H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 11.3 (q, C18), 23.2 (t, C15), 25.9 (t, C11), 30.8 (t, C16), 36.7 (t, C12), 40.5 (d, C8), 43.4 (d, C9), 43.5 (s, C13), 44.4 (t, C7), 50.3 (d, C14), 55.9 (q, Ar-OCH_3), 81.9 (d, C17), 110.0 (d, C1), 122.0 (d, C4), 127.0 (d, C2), 133.8 (s, C10), 140.0 (s, C5), 158.6 (s, C3), 198.4 (s, C6).

*2.1.12. (17β)-17-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxyestra-1,3,5(10)-trien-6-one **(14)***

Imidazole (26.6 g, 391 mM) was added to a solution of **13** (65.3 g, 217 mM) in methylene chloride (500 ml). *tert*-Butyldimethylsilylchloride (54 g, 358 mM) was added, and the orange reaction mixture was stirred for 4 h at room temperature. The solution was poured into saturated ammonium chloride solution, extracted with ethyl acetate, and dried (Na_2SO_4). During evaporation of the solvent, the product crystallized. The crystals were collected by filtration and dried in vacuo to give **14** (46.9 g, 113 mM, 52%). R_f 0.85 [heptane/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.05 (d, 6H), 0.75 (s, 3H, 18CH_3), 0.9 (s, 9H), 2.20 (dd, J = 13.4 Hz, 1H, 7αH), 2.74 (dd, J = 3.2 Hz, 1H, 7βH), 3.66 (t, 1H, 17αH), 3.85 (s, 3H, Ar-OCH_3), 7.10 (dd, 1H, Ar-2H), 7.34 (d, 1H, Ar-1H), 7.56 (d, 1H, Ar-4H).

*2.1.13. (7α,17β)-17-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-trien-6-one **(15)***

Potassium *tert*-butoxide (10.3 g, 91.5 mM) was added to a solution of **14** (37.5 g, 90.6 mM) in dimethoxyethane (500 ml). Methyl iodide (13 g, 91.5 mM), dissolved in dimethoxyethane (50 ml), was added to the red solution over in 30-min interval. The reaction mixture was stirred for 1 h at room temperature. Then, the solution was poured into 2N HCl, extracted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography [silica gel, heptane/ethyl acetate (9:1 v/v)] to give **15** (24 g, 56.1 mM, 63%). R_f 0.3 [heptane/ethyl acetate (9:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 600 MHz) δ 0.01 (s, 6H), 0.75 (s, 3H, 18CH_3), 0.90 (s, 9H), 1.09 (d, J = 8 Hz, 3H, 7-CH_3), 1.25 (m, 1H, 12αH), 1.31 (m, 1H, 15βH), 1.42 (m, 1H, 14αH), 1.49 (m, 1H, 16βH), 1.56 (m, 1H, 11βH), 1.58 (m, 1H, 15αH), 1.91 (m, 1H, 12βH), 1.95 (m, 1H, 16αH), 2.04 (m, 1H, 8βH), 2.40 (m, 1H, 11αH), 2.64 (m, 1H, 7βH), 2.67 (m, 1H, 9αH), 3.68 (t, 1H, 17αH), 3.84 (s, 3H, Ar-OCH_3), 7.10 (dd, 1H, Ar-2H), 7.34 (d, 1H, Ar-1H), 7.57 (d, 1H, Ar-4H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.9 (q, CH_3Si), 9.7 (q, 7-CH_3), 11.0 (q, C18), 18.5 (s, C-TBDMS), 21.9 (t, C15), 25.9 (q, CH_3-TBDMS), 26.1 (t, C11), 30.6 (t, C16), 36.0 (d, C9), 36.7 (t, C12), 41.8 (d, C8), 43.1 (d, C7), 43.8 (s, C13), 45.0 (d, C14), 55.0 (q, Ar-OCH_3), 81.2 (d, C17), 109.3 (d, C4), 121.2 (d, C2), 126.6 (d, C1), 132.6 (s, C10), 139.5 (s, C5), 158.5 (s, C3), 202.4 (s, C6). Exact mass calculated for $[M+H]^+$ is 429.2825, Found: 429.2833.

*2.1.14. (6α,7α,17β)-17-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-trien-6-ol **(16)***

Compound **15** (31 g, 72.4 mM), dissolved in dry THF (170 ml), was added dropwise over 1 h to a suspension of lithium aluminumhydride (11 g, 290 mM) in dry THF (120 ml). After 0.5 h of stirring at room temperature, saturated sodium sulfate solution was added dropwise until the excess of $LiAlH_4$ was quenched. Water was added, and the reaction mixture was extracted with ethyl acetate, dried (Na_2SO_4), and evaporated to dryness to give **16** (32 g, 100% crude). R_f 0.2 [heptane/ethyl acetate (8:2 v/v)]. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.01 (d, 6H), 0.76 (s, 3H, 18CH_3), 0.80 (d, J = 7.2 Hz), 7-CH_3) 0.90 (s, 9H), 3.66 (t, 1H, 17αH), 3.81 (s, 3H, Ar-OCH_3), 4.87 (m, 1H, 6-H) 6.78 (dd, 1H, Ar-2H), 7.18 (d, 1H, Ar-1H), 7.20 (d, 1H, Ar-4H).

*2.1.15. (17β)-17-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10),6-tetraene **(17)***

Compound **16** (20 g, 46.4 mM) was dissolved in toluene (2 liters), and Amberlyst 15 (4 g) was added. The mixture was heated to reflux for 5 h. The reaction mixture was cooled to room temperature, filtered and evaporated to dryness. The crude product was dissolved in methylene chloride (90 ml), and imidazole (6 g, 88 mM) was added. Then, *tert*-butyldimethylsilylchloride (54 g, 358 mM) was added, and the reaction mixture was stirred for 18 h at room temperature. The solution was poured into water, extracted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer was dried (Na_2SO_4), evaporated to dryness, and purified by column chromatography [silica gel, heptane/ethyl acetate (98:2 v/v)] to give **17** (11.8 g, 28.6 mM, 67%). R_f 0.85 [heptane/ethyl acetate (8:2 v/v)].

^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.05 (d, 6H), 0.74 (s, 3H, 18CH_3), 1.00 (s, 9H), 1.95 (s, 3H, 7-CH_3), 3. 61 (t, 1H, 17α-H), 3.78 (s, 3H, Ar-OCH_3), 6.20 (s, 1H, H-6), 6.56 (d, 1H, Ar-4H), 6.69 (dd, 1H, Ar-2H), 7.16 (d, 1H, Ar-1H).

2.1.16. (6β,7β,17β)-17-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6,7-epoxy-3-methoxy-7-methylestra-1,3,5(10)-triene ***(19)***

Compound **17** (21g, 51 mM) was dissolved in THF (170 ml). Water (20 ml) was added, and the solution was cooled to 0°C. *N*-chlorosuccinimide (6.8 g, 51 mM) was added, and the reaction mixture was stirred for 18 h at room temperature. Then, water was added, and the solution was extracted with ethyl acetate, dried (Na_2SO_4), and evaporated to dryness to give crude (6β,7α,17β)-7-chloro-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5 (10)-trien-6-ol **18** (R_f 0. 5 [heptane/ethyl acetate (8:2 v/v)], which was used in the next step without further purification. Crude **18** (25 g) was dissolved in THF (330 ml), potassium *tert*-butoxide (5.7 g, 51 mM) was added, and the reaction mixture was stirred for 1.5 h at room temperature. Then, the solution was poured into water, extracted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give the crude product **19** [R_f 0.6 (heptane/ethyl acetate (8:2 v/v)]. Purification by column chromatography (silica gel, heptane/ethyl acetate 9/1 (v/v) gave **19** (1 g, 2.3 mM, 5%) ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.05 (d, 6H), 0.67 (s, 3H, 18CH_3), 0.89 (s, 9H), 1.52 (s, 3H, 7-CH_3), 3.4 (s, 1H, H-6), 3. 65 (t, 1H, 17α-H), 3.81 (s, 3H, Ar-OCH_3), 6.84 (dd, 1H, Ar-2H), 7.06 (d, 1H, Ar-2H), 7.17 (d, 1H, Ar-1H). Further elution gave an additional 4 g of a more polar compound, characterized as (6α,7β,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-triene-6,7-diol **20** (4g, 9.0 mM, 20%). R_f 0.15 [heptane/ethyl acetate (8:2 v/v)]. ^{1}H NMR: (DMSO, 600 MHz) δ 0.01 (s, 6H), 0.71 (s, 3H, 18CH_3), 0.83 (s, 3H, 7-CH_3), 0.86 (s, 9H) 1.19 (m, 1H, 12α-H), 1.30 (m, 1H, 16β-H), 1.33 (m, 1H, 14α-H), 1.38 (m, 1H, 11β-H), 1.65 (m, 1H, 15β-H), 1.72(m, 1H, 12β-H), 1.81 (m, 1H, 15α-H), 1.82 (m, 1H, 16α-H), 1.88 (m, 1H, 8β-H), 2.11 (m, 1H, 9α-H), 2.28 (m, 1H, 11α-H), 3.61 (t, 1H, 17α-H), 3.70 (s, 3H, Ar-OCH_3), 3.90 (d, 1H, H6) 6.76 (d, 1H, Ar-4H), 6.78 (dd, 1H, Ar-2H), 7.20 (dd, 1H, Ar-1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.8 (q, CH_3Si), 11.7 (q, C18), 18.2 (s, C-TBDMS), 18.8 (q, 7-CH_3), 25.9 (q, CH_3-TBDMS), 26.1 (t, C15), 27.5 (t, C11), 31.3 (t, C16), 37.6 (t, C12), 41.6 (d, C8), 43.2 (d, C9), 45.0 (s, C13), 45.6 (d, C14), 55.5 (q, Ar-OCH_3), 73.6 (s, C7), 77.1 (d, C6), 81.6 (d, C17), 115.4 (d, C2), 115.7 (d, C4), 127.7 (d, C1), 131.2 (s, C10), 137.4 (s, C5), 158.5 (s, C3).

2.1.17. (7β,17β)-17-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxy-7-methylestra-1,3,5(10)-trien-7-ol ***(22)***

2.1.17.1. From 19. Compound **19** (320 mg, 0.75 mM), dissolved in dry THF (3 ml), was added to a suspension of lithium aluminum hydride (136 mg, 3.6 mM) in dry THF (3 ml). The reaction mixture was heated to reflux for 1.5 h. Then, saturated sodium sulfate solution was added dropwise until the excess of $LiAlH_4$ was quenched. Water was added, and the reaction mixture was extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to dryness to give **22** (300 mg, 0.70 mM, 93%). Data are shown below.

2.1.17.2. From 20. Mesyl chloride (3.7 g, 32.6 mM) was added to a cooled (0°C) solution of **20** (3.6 g, 8.1 mM) and triethylamine (3.3 g, 32.6 mM) in methylene chloride (50 ml). The reaction mixture was stirred for 1.5 h at 0°C and then for3 h at room temperature. Then, the mixture was poured into a saturated solution of ammonium chloride, extracted with methylene chloride, dried (Na_2SO_4), and evaporated to dryness to give crude 6α-*O*-mesylate **21.** R_f 0.55 [heptane/ethyl acetate (8:2 v/v)]. Crude **21**(5 g), dissolved in dry THF (45 ml), was added to a suspension of lithium aluminum hydride (1.48 g, 39.1 mM) in dry THF (45 ml). The reaction mixture was heated to reflux for 1.5 h. Then, saturated sodium sulfate solution was added, dropwise until the excess of $LiAlH_4$ was quenched. Water was added and the reaction mixture was extracted with ethyl acetate and washed with saturated sodium chloride solution. The organic portion was dried (Na_2SO_4) and evaporated to dryness to give the crude product, which was purified by column chromatography [silica gel, heptane/ethyl acetate (9:1 v/v)] to give **22** (1.8 g, 4.2 mM, 51%). R_f 0.35 [heptane/ethyl acetate (8:2 v/v)] ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.05 (d, 6H), 0.79 (s, 3H, 18CH_3), 0.90 (s, 9H),1.14 (s, 3H, 7-CH_3), 2.77 (d, J = 16.2 Hz, 1H, 6α-H), 2.96 (d, J = 16.2 Hz, 1H, 6β-H), 3. 63 (t, 1H, 17α-H), 3.77 (s, 3H, Ar-OCH_3), 6.57 (d, 1H, Ar-4H), 6.73 (dd, 1H, Ar-2H), 7.20 (d, 1H, Ar-1H).

2.1.18. (7β,17β)-3-Methoxy-7-methylestra-1,3,5(10)-triene-7,17-diol ***(23)***

Hydrochloric acid (2N, 3.5 ml) was added to a solution of **22** (1.75 g, 4.1 mM) in acetone (25 ml), and the reaction mixture was stirred at room temperature for 5 h. Aqueous sodium bicarbonate was added, and the solution was extracted with ethyl acetate. The organic portion was dried (Na_2SO_4) and evaporated to dryness to give the crude product, which was purified by column chromatography [silica gel, heptane/ethyl acetate (9:1–7:3 v/v)] to give **23** (1.15 g, 3.63 mM, 89%). R_f 0.2 [heptane/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 600 MHz) δ 0.81 (s, 3H, 18-CH_3), 1.14 (s, 3H, 7-CH_3), 1.28 (m, 1H, 12α-H), 1.40 (m, 1H, 14α-H), 1.48 (m, 1H, 16β-H), 1.55 (m, 1H, 11β-H), 1.72 (m, 1H, 8β-H), 1.75 (m, 1H, 15β-H), 1.88 (m, 1H, 15α-H), 1.94 (m, 1H, 12β-H), 2.10 (m, 1H, 16α-H), 2.28 (m, 1H, 9α-H), 2.35 (m, 1H, 11α-H), 2.78 (d, J = 16.2 Hz, 1H, 6α-H), 2.97 (d, J = 16.2 Hz, 1H, 6β-H), 3.70 (t, 1H, 17α-H), 3.77 (s, 3H, Ar-OCH_3), 6.57 (d, 1H, Ar-4H), 6.74 (dd, 1H, Ar-2H), 7.19 (d,

1H, Ar-1H). ^{13}C-NMR ($CDCl_3$, 150 MHz) 11.7 (q, 18-CH_3), 21.5 (q, 7-CH_3), 26.2 (t, C15), 28.1 (t, C11), 31.1 (t, C16), 37.5 (t, C12), 43.8 (d, C9) 44.7 (s, C13), 46.8 (d, C14), 48.0 (t, C6), 48.5 (d, C8), 55.6 (q, Ar-OCH_3), 72.6 (s, C7), 81.7 (d, C17) 112.7 (d, C4), 113.9 (d, C2), 127.4 (d, C1), 130.5 (s, C10), 136.9 (s, C5), 158.1 (s, C3).

*2.1.19. (7β)-7-Hydroxy-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one **(24)***

Compound **23** (1.15 g, 3.6 mM) and *N*-methylmorpholine-*N*-oxide (1.1 g, 9.5 mM) were dissolved in acetone (50 ml). A catalytic amount of tetra-n-propylammonium perruthenate(VII) (70 mg, 0.2 mM) was added, and the reaction mixture was stirred for 1.5 h at room temperature. The solution was filtered over dicalite, rinsed with ethyl acetate, evaporated to dryness, and filtered over a short silica gel column using heptane/ethyl acetate (8:2 v/v) as eluent to give **24** (1.0 g, 3.2 mM 88%). R_f 0.3 [heptane/ethyl acetate (1:1 v/v)]. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.96 (s, 3H, 18CH_3), 1.21 (s, 3H, 7-CH_3), 2.82 (d, J = 16 Hz, 1H, 6αH), 3.01 (d, J = 16 Hz, 1H, 6βH), 3.78 (s, 3H, Ar-OCH_3), 6.58 (d, 1H, Ar-4H), 6.74 (dd, 1H, Ar-2H), 7.21 (d, 1H, Ar-1H).

*2.1.20. (7β)-7-Hydroxy-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal **(28)***

Compound **24** (1 g, 3.2 mM), ethylene glycol (4 ml), and p-toluenesulfonic acid (30 mg) were dissolved in triethylorthoformate (7 ml) and stirred for 30 min at 60°C. Water was added, and the mixture was extracted with ethyl acetate and washed successively with water and saturated sodium chloride solution. The organic portion was dried (Na_2SO_4), evaporated to dryness, and filtered over a short silica gel column using heptane/ethyl acetate 9/1 (v/v) as eluent to give crude 3-methoxy-7-methylestra-1,3,5(10),6-tetraen-17-one cyclic 1,2-ethanediyl acetal **25**, R_f 0.85 [heptane/ethyl acetate (8:2 v/v)]. **25** (1 g, crude) was dissolved in THF (10 ml). Water (1 ml) was added, and the solution was cooled to 0°C. *N*-Chlorosuccinimide (400 mg, 3 mM) was added, the ice bath was removed, and the reaction mixture was stirred for 18 h at room temperature. Then, water was added, and the solution was extracted with ethyl acetate, dried (Na_2SO_4), and evaporated to dryness to give crude (6β,7α)-7-chloro-6-hydroxy-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal **26** (R_f 0.15 [heptane/ethyl acetate (8:2 v/v)], which was used in the next step without further purification. Crude **26** (1.2 g) was dissolved in THF (20 ml), potassium *tert*-butoxide (337 mg, 3 mM) was added and the reaction mixture was stirred for 1 h at room temperature. Then, another portion potassium *tert*-butoxide (300 mg, 2.7 mM) was added, and the reaction mixture was stirred for another hour. The solution was poured into water, extracted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give crude (6β,7β)-6,7-epoxy-3-methoxy-7-methylestra-1,3,5(10) -trien-17-one cyclic 1,2-ethanediyl acetal **27** (770 mg, crude), R_f 0.3 [heptane/ethyl acetate (8:2 v/v)]. **27** (770 mg, crude), dissolved in dry THF (7 ml), was added to a suspension of lithium aluminum hydride (569 mg, 15 mM) in dry THF (15 ml). The reaction mixture was heated to reflux for 0.5 h. Then, saturated sodium sulfate solution was added dropwise until the excess of $LiAlH_4$ was quenched. Water was added, and the reaction mixture was extracted with ethyl acetate and washed with saturated sodium chloride solution. The organic portion was dried (Na_2SO_4) and evaporated to dryness to give the crude product, which was purified by column chromatography [silica gel, heptane/ethyl acetate 8/2 (v/v)] to give **28** (280 mg, 0.78 mM, 26%), R_f 0.1 [heptane/ethyl acetate (8:2 v/v)]. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H, 18CH_3), 1.18 (s, 3H, 7-CH_3), 2.77 (d, J = 16 Hz, 1H, 6αH), 2.97 (d, J = 16 Hz, 1H, 6βH), 3.77 (s, 3H, Ar-OCH_3), 3.92 (m, 4H, ketal) 6.57 (d, 1H, Ar-4H), 6.73 (dd, 1H, Ar-2H), 7.21 (d, 1H, Ar-1H).

*2.1.21. (7β)-7-Hydroxy-7-methylestr-5(10)-ene-3,17-dione cyclic 17-(1,2-ethanediyl acetal) **(30)***

Ammonia (ca. 20 ml) was condensed in a three-necked flask equipped with a thermometer, dry ice cooler and addition funnel. Lithium (342 mg, 49 mM) was added, and the blue solution was stirred for 20 min at −78°C. **28** (280 mg, 0.78 mM) dissolved in THF (5 ml), was added to the blue solution over a 5 min interval. The dry ice bath was removed, and the reaction mixture was refluxed at −35°C for 3 h. Then, isopropanol (± 10 ml) was added over 15 min until the color of the reaction mixture changed from blue to white. The excess ammonia evaporated upon standing, water was added, and the reaction mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to dryness to give (7β)-7-Hydroxy-3-methoxy-7-methylestra-2,5(10) -dien-17-dione cyclic (1,2-ethanediyl acetal) **29** (258 mg, 0.72 mM, 92%), R_f 0.5 [heptane/ethyl acetate (1:1 v/v)]. **29** (256 mg, 0.71 mM) was dissolved in methylene chloride (3 ml) and SiO_2 (49 mg) was added. Then, a solution of oxalic acid (63 mg, 0.7 mM) and 1 drop of water in methanol (1 ml) was added, and the reaction mixture was stirred for 15 min at room temperature. The suspension was filtered and rinsed with methylene chloride, and the filtrate was washed successively with saturated $NaHCO_3$ solution and saturated sodium chloride solution. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give 240 mg of a 1/1 mixture of **30,** R_f 0.25 [heptane/ethyl acetate (1:1 v/v)], and (7β)-7-hydroxy-7-methylestr-5(10)-ene-3,17-dione **31**, R_f 0.15 [heptane/ethyl acetate (1:1 v/v)]. This mixture was used in the next step without further purification.

*2.1.22. (3α,7β)-3,7-Dihydroxy-7-methylestr-5(10)-en-17-one **(34)***

Lithium tri-*tert*-butoxy aluminum hydride (406 mg, 1.6 mM) in THF (4 ml) was added dropwise to a solution of **30**

and **31** (240 mg, 0.7 mM) dissolved in THF (4 ml). The reaction mixture was stirred for 1.5 h at room temperature, poured into saturated ammonium chloride solution, and extracted two times with ethyl acetate. The combined organic layers were washed successively with water and saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to dryness to give 236 mg of a 1/1 mixture of (3α,7β)-3,7-Dihydroxy-7-methylestr-5(10)-en-17-one cyclic 1,2-ethanediyl acetal **33**, R_f 0.55 (ethyl acetate), and (3α,7β,17β)-7-methylestr-5(10)-ene-3,7,17-triol **32**, R_f 0.4 (ethyl acetate). This mixture was dissolved in acetone (5 ml), and a 0.1 N HCl (0.5 ml) solution was added. The solution was stirred for 5 h at room temperature, saturated sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give the crude product mixture, which was separated by column chromatography [silica gel, toluene/ethanol 95/5 (v/v)] to give **34 (**75 mg, 0.25 mM, 37%), R_f 0.35 [toluene/ethanol (8:2 v/v)]. ^{1}H NMR: (CD_3OD, 400 MHz) δ 0.92 (s, 3H, 18-CH_3), 1.11 (s, 3H, 7-CH_3), 3.70 (m, 1H, 3βH), exact mass calculated for $[M+H]^+$ is 305.2117, Found: 305.2090, and **32** (25 mg, 0.08 mM, 12%), R_f 0.2 [toluene/ethanol (8:2 v/v)], m.p. 202°C. ^{1}H NMR: (CD_3OD, 400 MHz) δ 0.78 (s, 3H, 18-CH_3), 1.03 (s, 3H, 7-CH_3), 1.10 (m, 1H, 12αH), 1.20 (m, 1H, 11βH), 1.29 (m, 1H, 14αH), 1.36 (m, 1H, 2αH), 1.42 (m, 1H, 16βH), 1.53 (t, 1H, 8βH), 1.60 (m, 1H, 9αH), 1.67 (m, 1H, 15βH), 1.77 (m, 1H, 4αH), 1.82 (m, 1H, 6αH), 1.83 (m, 1H, 12βH), 1.85 (m, 1H, 15αH), 1.90 (m, 1H, 1αH), 1.92 (m, 1H, 2βH), 1.93 (m, 1H, 11αH), 1.95 (m, 1H, 16αH), 2.11 (m, 1βH), 2.12 (m, 1H, 6βH), 2.14 (m, 1H, 4βH), 3.58 (t, 1H, 17αH), 3.70 (m,1H, 3βH). ^{13}C-NMR (CD_3OD, 100 MHz) 12.2 (q, 18-CH_3), 20.7 (q, 7-CH_3), 26.7 (t, C15), 27.2 (t, C11), 31.3 (t, C16), 33.6 (t, C2), 38.4 (t, C1), 38.8 (t, C12), 40.9 (t, C4), 45.8 (s, 13C), 47.9 (d, C14), 48.4 (d, C9), 48.6 (d, C8), 49.7 (t, C6), 68.9 (d, C3), 72.9 (s, C7), 82.6 (d, C17), 126.4 (s, C5), 130.1 (s, C10). Exact mass calculated for $[M+H+Glyc.]^+$ is 399.2747, Found: 399.2740.

*2.1.23. (3α,7β,17α)-7-Methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol **(35)***

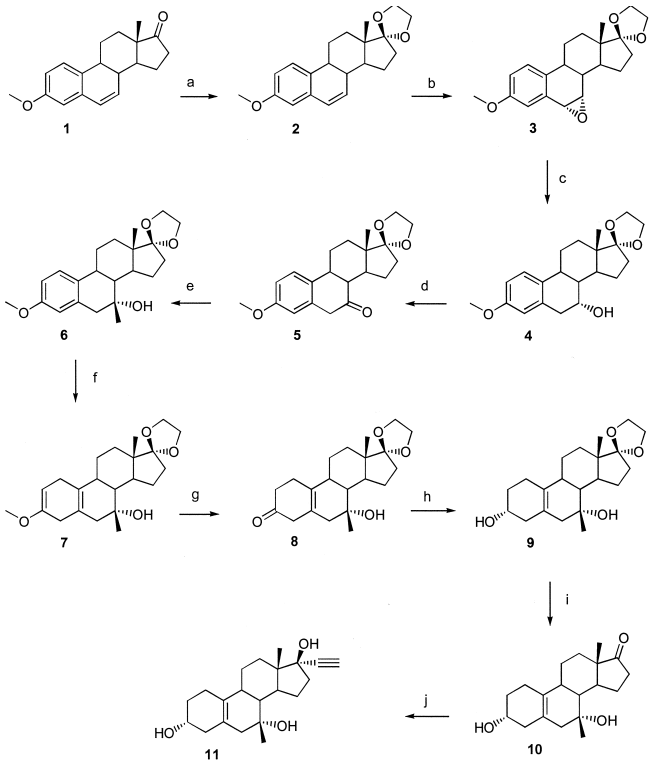
Potassium *tert*-butoxide (258 mg, 2.3 mM) was dissolved in dry THF (3 ml). The solution was cooled to 0°C and stirred for 30 min whereas nitrogen was passed through. Then, although the temperature was kept at 0°C, acetylene was passed through the solution for 1 h. **34** (70 mg, 0.23 mM), dissolved in THF (3 ml), was added to the white suspension, and the reaction mixture was stirred for 1 h at 0°C. Then, the yellow suspension was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give the crude product, which was purified by column chromatography [silica gel, toluene/ethanol 95/5 (v/v)] to give **35** (40 mg, 0.12 mM, 53%), R_f 0.3 [toluene/ethanol (8:2 v/v)], m.p. 175°C. ^{1}H NMR: ($CDCl_3$, 600 MHz) δ 0.86 (s, 3H, 18-CH_3), 1.03 (s, 3H, 7-CH_3), 1.19 (m, 1H, 11βH), 1.38 (m, 1H, 2βH), 1.52 (t, 1H, 8βH), 1.58 (m, 1H, 9αH),1.61 (m, 1H, 12βH), 1.73 (m, 1H, 15βH), 1.78 (m, 1H, 4βH), 1.82 (m, 1H, 12αH), 1.83 (dd, 1H, 6αH), 1.86 (m, 1H, 14αH), 1.90 (m, 1H, 15αH), 1.90 (m, 1H, 16βH), 1.92 (m, 1H, 1βH), 1.92 (m, 1H, 2αH), 1.99 (m, 1H, 11αH), 2.13 (m, 1αH), 2.13 (dd, 1H, 6βH), 2.15 (m, 1H, 4αH), 2.20 (m, 1H, 16αH), 2.87 (s,1H, C≡CH), 3.7 (m, 1H, 3βH). ^{13}C-NMR (CD_3OD, 150 MHz) 13.9 (q, 18-CH_3), 20.8 (q, 7-CH_3), 26.3 (t, C15), 27.4 (t, C11), 28.6 (t, C1), 33.7 (t, C2), 34.8 (t, C12), 40.6 (t, C16), 41.1 (t, C4), 47.0 (d, C9), 47.6 (d, C14), 49.3 (s, C13), 49.5 (d, C8), 49.6 (t, C6), 68.5 (D, C3), 73.0 (t, C7), 75.1 (d, ≡CH), 80.2 (s, C17), 89.4 (s, C≡), 126.4 (s, C5), 130.0 (s, C10). Exact mass calculated for $[M+H+Glyc.]^+$ is 423.2747, Found: 423.2748.

3. Results and discussion

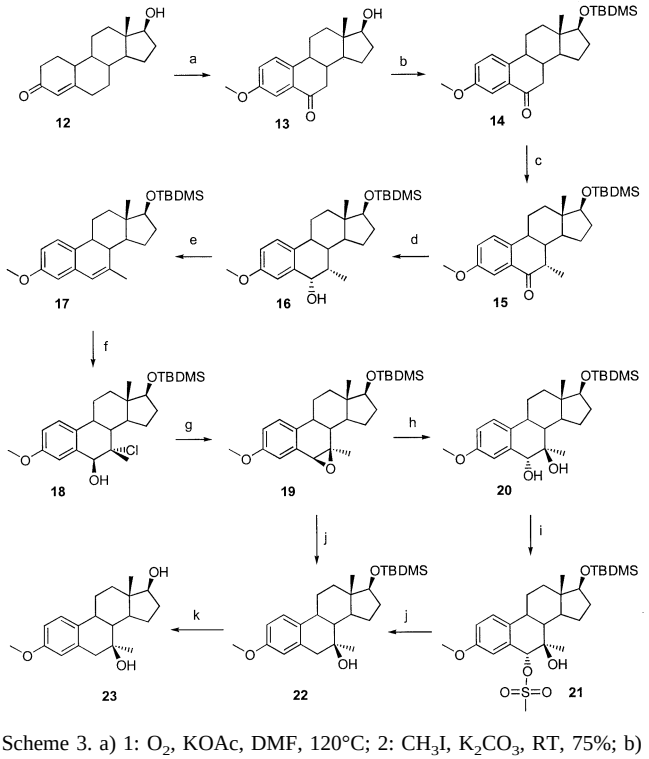
Here, we describe our approaches toward the synthesis of the 7-β-hydroxy metabolite of Org OD 14, **35**, as well as its isomeric 7-α-hydroxy derivative **11.**

*3.1. Synthesis of (3α,7α,17α)-7-methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol **(11)***

In our first approach toward 7-hydroxy Org OD 14 derivatives, a synthetic route via the key intermediate **5** was elaborated commencing with the Δ^6-estrone derivative **1** (Scheme 2). Ketalization of the readily available starting material **1** gave the corresponding 17-acetal **2**. Epoxidation of the Δ^6-double bond, using 3-chloro-peroxybenzoic acid as a reagent, gave the (6α,7α)-6,7-epoxy-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal **(3)**. Ring opening of the epoxy function, using lithium aluminum hydride as a reagent, gave the (7α)-7-hydroxy-3-methoxyestra-1,3,5 (10)-trien-17-one cyclic 1,2-ethanediyl acetal **(4)**. Oxidation of 4, using the Jones reagent, gave the desired 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-7-one (**5**) in moderate yield. Attempts to introduce a methyl group at the 7-keto position of derivative **5**, either using methyllithium or methylmagnesium chloride as reagents, failed in that no reaction occurred. This failure may be attributed to complete enolization of the keto function under these conditions. Application of a modified method [6] gave the desired addition product 17,17-ethylenedioxy-3-methoxy-7β-methylestra-1,3,5(10)-trien-7α-ol **(6)** in 55% yield. The stereochemistry observed (7α-OH, 7β-Me) was surprising and could not be rationalized with the Felkin–Anh principle [7,8]. Birch reduction of **6** gave **7**, which upon mild, selective hydrolysis, gave 17,17-ethylenedioxy-7α-hydroxy-7β-methylestr-5(10)-en-3-one **(8).** Reduction of the 3-ketofunction of **8,** using lithium tri-*tert*-butoxy aluminum hydride as a reagent, gave the 3α-hydroxy derivative **9**. Finally, deprotection of the 17-ketal function, gave



Scheme 2. a) glycol, PTSA, TEOF (95%) b) mCPBA, EtOAc (90%); c) $LiAlH_4$, THF (50%); d) CrO_3, acetone (55%); e) $CeCl_3$, CH_3MgCl, THF (55%); f) Li, NH_3, THF (90%); g) oxalic acid, acetone, water (50%); h) Li(*tert*-BuO)$_3$AlH, THF (80%); i) HCl, acetone (85%); j) ethyne, KO*t*Bu (62%).



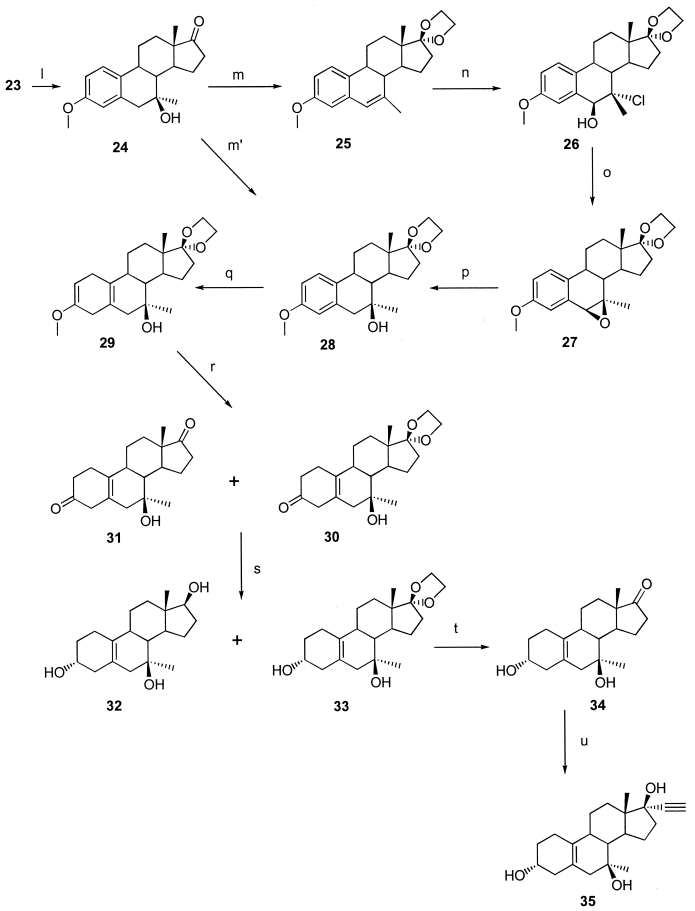
Scheme 3. a) 1: O_2, KOAc, DMF, 120°C; 2: CH_3I, K_2CO_3, RT, 75%; b) TBDMS-Cl, CH_2Cl_2, 52%; c) KOtBu, CH_3I, DME, RT, 63%; d) $LiAlH_4$, THF, RT, 100%; e) 1: Amberlyst 15, toulene, reflux; 2: TBDMS-Cl, CH_2Cl_2, 67%; f) N-chlorosuccinimide, THF, H_2O; g) KOtBu, THF; h) column chromatography; i) Mesylchloride, TEA, CH_2Cl_2; j) $LiAlH_4$, THF, **22** from **19** 93%, **22** from **20** 51%; k) 2n HCl, acetone, 90%.

10, which upon ethynylation, gave the desired (3α,7α,17α)-7-methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol **(11)**.

3.2. Synthesis of (3α,7β,17α)-7-methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol (35)

In our second approach toward 7-hydroxy Org OD 14 derivatives, a route commencing with 17β-hydroxyestr-4-en-3-one (**12,** 19-nortestosterone) was devised (Scheme 3) [9]. The oxidation of **12** with oxygen in dimethylformamide, followed by in situ methylation with methyliodide, gave 17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-6-one **(13)**. Protection of the 17-hydroxy function of **13** with the *tert*-butyldimethylsilyl group gave 17β-(*tert*-butyldimethylsilyl)oxy-3-methoxyestra-1,3,5(10)-trien-6-one **(14).** Selective methylation at the 7-position, using methyliodide in dimethoxyethane as a reagent, gave 17β-(*tert*-butyldimethylsilyl)oxy-3-methoxy-7α-methyl-estra-1,3,5(10)-trien-6-one **(15)**. Reduction of the keto function of **15** with lithium aluminum hydride gave 17β-(*tert*-butyldimethylsilyl)oxy-3-methoxy-7α-methyl-estra-1,3,5(10)-trien-6α-ol **(16)**. Dehydration of **16** into 17β-(*tert*-butyldimethylsilyl)oxy-3-methoxy-7-methylestra-1,3,5(10),6-tetraene **(17)** was carried out using Amberlyst 15 in refluxing toluene at high dilution. This was necessary to prevent the formation of dimers e.g. these dimers are formed in concentrated solution as a result of the attack of the intermediate formed carbocation at the 6-position with the A-ring aromat. Reaction of the Δ^6-double bond of **17** with *N*-chlorosuccinimide in aqueous THF gave 17β-(*tert*-butyldimethylsilyl)oxy-7α-chloro-3-methoxy-7β-methyl-estra-1,3,5(10)-trien-6β-ol **(18)**. Ring closure of **18** gave the 17β-(*tert*-butyldimethylsilyl)oxy-3-methoxy-7α-methyl-6β,7β-epoxyestra-1,3,5(10)-triene **(19).** In small-scale experiments, the epoxide **19** was isolated after column chromatography in 30% yield. In larger scale experiments, only 5% of **19** was isolated, whereas the major portion of the epoxide underwent ringopening during column chromatography to give 17β-(*tert*-butyldimethylsilyl)oxy-3-methoxy-7α-methyl-estra-1,3,5(10)-trien-6α,7β-diol **(20)**. Epoxide **19** was found to be unstable at room temperature. Reduction of the epoxide function of **19,** using lithium aluminum hydride as a reagent, gave 17β-(*tert*-butyldimethylsilyl)oxy-3-methoxy-7α-methylestra-1,3,5(10)-trien-7β-ol **(22).** Alternatively, **22** was prepared from **20** by mesylation and subsequent reduction of **21**. Deprotection of **22** gave 3-methoxy-7α-methylestra-1,3,5(10)-trien-7β,17β-diol **(23).**

Oxidation of **23,** using *N*-methylmorpholine *N*-oxide and a catalytic amount of tetra-n-propylammonium perruthenate (VII) as reagents, gave 7β-hydroxy-3-methoxy-7α-methylestra-1,3,5(10)-trien-17-one **(24)** (Scheme 4). Ketalization of **24,** at 60°C using ethylene glycol and a catalytic



Scheme 4. 1) NMO, TPAP, acetone, 80%; m) glycol, PTSA, TEOF; n) N-chlorosuccinimide; THF, H_2O; o) KOtBu, THF; p) $LiAlH_4$, THF, **28** from **25** 26%; q) Li, NH_3, THF, 92%; r) oxalic acid, SiO_2, MeOH, H_2O, CH_2Cl_2; s) Li(*tert*-BuO)$_3$A1H, THF; t) 0.1N HCl, acetone, **34** 37%; u) ethyne, KOtBu, 52%.

amount of p-toluene sulfonic acid in triethylorthoformate as reagents, led to the undesired elimination of the 7-hydroxy moiety and gave a mixture of 17,17-ethylenedioxy-3-methoxy-7-methyl-estra-1,3,5(10),6-tetraene **(25),** the 7-exomethylene derivative, and other alkenes. Because of the observed liability of the reaction intermediates (viz. 17 → 19), the alkene **25** was converted into the 7α-chloro-17,17-ethylenedioxy-3-methoxy-7β-methyl-estra-1,3,5(10)-trien-6β-ol **(26)** 6,7β-epoxy-17,17-ethylenedioxy-3-methoxy-7α-methyl-estra-1,3,5(10)-triene **(27)** and 17,17-ethylenedioxy-3-methoxy-7α-methyl-estra-1,3,5(10)-trien-7β-ol **(28)**, according to the sequence described above. Later, the ketalization of **24** into **28** was successfully carried out using 1,2-bis-((trimethylsilyl)oxy)ethane and a catalytic amount of trimethylsilyl triflate in methylene chloride at −78°C.

Birch reduction of **28** gave 17,17-ethylenedioxy-3-methoxy-7α-methyl-estra-2,5(10)-dien-7β-ol **(29).** Hydrolysis of the ketal function of **29,** using oxalic acid in the presence of silica gel [10], gave a 1:1 mixture of 17,17-ethylenedioxy-7β-hydroxy-7α-methyl-estra-5(10)-en-3-one **(30)** and 7β-hydroxy-7α-methyl-estra-5(10)-diene-3,17-dione **(31).** This mixture was reduced with lithium tri-*tert*-butoxy aluminum hydride to 17,17-ethylenedioxy-7α-methyl-estr-5(10)-ene-3α,7β-diol **(33)** and 7α-methyl-estr-5(10)-ene-3α,7β,17β-triol **(32).** Hydrolysis of **33** gave 7α-methyl-estr-5(10)-en-3α,7β-diol-17-one **(34)**, and finally, ethynylation gave the desired target molecule (3α,7β,17α)-7-methyl-19-norpregn-5(10)-en-20-yne-3,7,17-triol **(35).**

The pharmacological properties of the 7-hydroxy derivatives of ORG OD14, namely **11** and **35,** will be described elsewhere.

Acknowledgments

We wish to thank F. Martens, R. Aspers (NMR-spec.), and G. Schmeits (Mass-spec.) for their help in interpretation of the spectral data.

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