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Article *in* Steroids · May 2007

DOI: 10.1016/j.steroids.2006.12.007 · Source: PubMed

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Published in final edited form as:
Steroids. 2007 April ; 72(4): 351–359. doi:10.1016/j.steroids.2006.12.007.

A Facile Total Synthesis of *ent*-17β-Estradiol and Structurally–Related Analogues

Zu Yun Cai and **Douglas F. Covey***
Department of Molecular Biology and Pharmacology Washington University School of Medicine Campus Box 8103 660 S. Euclid Ave. St. Louis, MO 63110

Abstract

A facile six-step synthesis (15.2% yield) of *ent*-17β-estradiol from readily accessible precursors is described. The preparation of analogues with 2-alkyl substitutents, double bond unsaturation in the C-ring, a *cis* C, D-ring fusion and modified substituents at C_{17} is also reported.

Keywords

ent-17β-estradiol; enantiomer; neuroprotectants; antioxidants; estradiol analogues

1. Introduction

Phenolic compounds are free-radical scavengers and have antioxidant activity. Estrone and 17β-estradiol, as well as other steroids containing a phenolic A-ring, are antioxidants with neuroprotective properties that are potentially useful for the treatment of Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases [1-6]. Since the antioxidant properties of 17β-estradiol are not dependent on the absolute configuration of this steroid, *ent*-17β-estradiol also has neuroprotective properties [7]. Additionally, *ent*-17β-estradiol lacks the feminizing actions of 17β-estradiol [7-9] so that neuroprotection is possible without the complications of feminization or other undesirable actions attributable to the hormonal actions of 17β-estradiol (e.g., stimulation of estrogen-dependent breast cancer). Many different routes have been published for the total syntheses of natural or racemic estrogens [10-23]. However, only two enantioselective syntheses of *ent*-estrogens have been published. Hutchinson and Money used (+)-3-bromocamphor as a starting material for the synthesis of *ent*-estrone [24]. We previously reported [7], without discussion of the chemistry methods, that *ent*-17β-estradiol can be obtained by the aromatization of *ent*-19-nortestosterone (Scheme 1).

Herein we describe an alternative method for the synthesis of *ent*-17β-estradiol (**3**, Scheme 2) that does not proceed by aromatization of a 19-norsteroid intermediate. This synthetic route is based on literature analogies used for the synthesis of 7-substituted analogues of 17β-estradiol [25,26]. The synthesis of several structurally related analogues (Scheme 3, **12a,b**; Scheme 4, **14a,b**; Scheme 5, **17a,b**; Scheme 6, **20**; Scheme 7, **22**) that were part of a previously published structure–activity study [27] is also reported.

*Corresponding author. Telephone: 314-362-1726 FAX: 314-362-7058 dcovey@molecool.wustl.edu.

2. Experimental methods

2.1 General Methods

Melting points were determined on a Kofler micro hot stage and were uncorrected. NMR spectra were recorded in $CDCl_3$, or $(CD_3)_2CO$ at 300MHz (^1H) or 75MHz (^{13}C). Chemical shifts (δ) were reported downfield from internal Me_4Si (δ: 0.00). Mass spectra were obtained using mass spectrometry facilities located at either the Univ. of Wisconsin or Washington University. IR spectra were recorded either as films on a NaCl plate or in KBr. Elemental analyses were carried out by M-H-W laboratories. Phoenix AZ. Chromatography was performed using flash chromatography grade silica gel (32–63μm) purchased from Scientific Adsorbents, Atlanta, GA. Organic extracts were dried over anhydrous Na_2SO_4.

2.1.1. 2-(3-Methoxyphenyl) ethanol (5a) [28]—To a suspension of $LiAlH_4$ (4.93 g, 123 mmol) in anhydrous Et_2O (100 ml), *m*-methoxyphenylacetic acid (17 g, 102 mmol) dissolved in anhydrous Et_2O (100 ml) was added dropwise over 1.5 h at room temperature. Stirring was continued overnight and the reaction flask was cooled with an ice bath, H_2O (15 ml) was cautiously added dropwise over 30 min, and then 2 N H_2SO_4 (200 ml) was added to bring the aqueous layer to neutral pH. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with brine and dried. Solvent removal gave the crude product (16.2 g), which was purified by vacuum distillation to yield alcohol **5a** (bp 133 °C/6 mm Hg, 14.6 g, 94%).

2.1.2 Toluene-4-sulfonic acid 2-(3-methoxyphenyl)ethyl ester (5b) [29]—To a solution of *m*-methoxyphenylethanol (**5a**, 3 g, 19.7 mmol) in anhydrous pyridine (16 ml), was added *p*-toluenesulfonyl chloride (4.15 g) at 0 °C. After 30 min, the reaction flask was placed in a cold room (5 °C) and stirred overnight. The reaction mixture was poured onto ice, neutralized with 6 N HCl and extracted with EtOAc. The combined extracts were again washed with 6 N HCl, washed with brine and dried. Solvent removal gave a thick oil (5.6 g) which was purified by chromatography (20% EtOAc in hexanes) to yield compound **5b** (4.73 g, 78%): ^1H NMR($CDCl_3$) δ 2.41 (s, 3H, Ar-*CH*$_3$), 2.91 (t, *J* = 7.2 Hz, 2H), 3.74 (s, 3H, OCH_3), 4.20 (t, *J* = 7.2 Hz, 2H), 6.62 (s, 1H, Ar-*H*), 6.69 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 6.73–6.77 (dd, J = 8.4 Hz, 1.5 Hz, 1H, Ar-*H*), 7.16 (t, *J* = 8.1 Hz, 1H, Ar-*H*), 7.25–7.28 (d, J = 8.4 Hz, 2H, Ar-*H*), 7.66–7.69 (d, J = 8.1 Hz, 2H, Ar-*H*).

2.1.3. (1R,7aR)-1-(1,1-dimethylethoxy)-1,2,3,6,7,7a-hexhydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-5H-inden-5-one (6)—Under N_2, a 60% suspension of NaH (1.21 g, 30.3 mmol) in mineral oil was washed with anhydrous hexanes (2 × 10 ml) to remove the mineral oil. After removal of the hexanes, anhydrous DME (48 ml) and then indenone **4** (4.5 g, 20.3 mmol) were added. The reaction mixture was heated and stirred at 65 °C for 20 h during which time it turned dark brown. Tosylate (**5b**, 7.09 g, 23.2 mmol) dissolved in DME (40 ml) was then added over 15 min and the reaction mixture was further heated at 65 °C for 20 h. After cooling the reaction flask with an ice bath, saturated aqueous NaH_2PO_4 (50 ml) was added and the resultant red orange solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried. Solvent removal gave deep orange crude product **6** (9.01 g), which was purified by chromatography (6% EtOAc in hexanes). Product **6** (4.33 g, 60%) was obtained as a colorless oil: $[\alpha]^{20}_D$ −41.8 (c = 0.46, $CHCl_3$); UV λmax (EtOH) 251nm (ε =15100); IR (neat, cm^{-1}) 1661, 1584, 1258, 1195, 1098; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H, CH_3), 1.20 (s, 9H, $C(CH_3)_3$), 3.48–3.43 (q, *J* = 10.2 Hz, 7.5 Hz, 1H, HC-O^{t}Bu), 3.83 (s, 3H, OCH_3), 6.72–6.75 (m, 1H, Ar-*H*), 6.75–6.80 (m, 2H, Ar-*H*), 7.21 (t, *J* = 7.8 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 198.69, 169.65, 159.42, 143.74, 131.51, 129.02, 121.34, 114.73, 110.84, 79.66, 72.77, 54.98, 44.52, 34.45, 33.93,

33.46, 29.55, 28.45, 27.51, 25.13, 15.54; MS m/z 356 (M^+), 300, 222, 179, 166, 148, 135, 122, 107, 91, 57.

2.1.4. (1R,3aR,4S,7aR)-1-(1,1-Dimethylethoxy)octahydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-5H-inden-5-one (7a)—To a solution of compound **6** (3.76 g, 10.6 mmol) in EtOH (360 ml) was added 10% Pd/C (0.96 g) and the reaction mixture was hydrogenated (H_2, 3.4 atm) for 1 h. After filtration to remove the catalyst, the solvent was removed and the crude product was purified by chromatography (3.5% EtOAc in hexanes) to yield product **7a** (1.96 g, 52%) as a colorless oil: $[\alpha^{20}]_D$ −24.7 (c = 0.22, EtOH); UV (EtOH) λ max 280 nm (ε = 1800), 273 nm (ε = q930); IR (neat, cm^{-1}) 1705, 1602, 1585, 1259, 1194, 1153, 1118, 1046; ^{1}H NMR ($CDCl_3$) δ 1.01(s, 3H, CH_3), 1.13(s, 9H, $C(CH_3)_3$), 3.38 (t, *J* = 8.4 Hz, HC-O*t*Bu), 3.79 (s, 3H, OCH_3), 6.72–6.78 (m, 3H, Ar-*H*), 7.17–7.22 (m 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 215.38, 159.68, 143.41, 129.35, 120.91, 114.32, 111.13, 79.60, 72.45, 55.03, 52.86, 47.56, 41.47, 36.06, 34.98, 31.28, 29.20, 28.53, 28.42, 21.67, 12.53; MS m/z 358 (M^+), 302, 224, 181, 167, 147, 134, 122, 107, 93, 57.

2.1.5. (1R,3aR,4R,7aR)-1-(1,1-Dimethylethoxy)octahydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-5H-inden-5-one (7b)—Compound **7b** (100 mg) was obtained as an oil from the chromatographic separation that yielded compound **7a**. Compound **7b** had: IR (neat, cm^{-1}) 1706, 1602, 1585, 1259, 1194, 1152, 1119, 1077; ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 3H, CH_3), 1.14 (s, 9H, $C(CH_3)_3$), 3.45 (t, *J* = 8.7 Hz, HC-O*t*Bu), 3.80 (s, 3H, OCH_3), 6.72–6.81 (m, 3H, Ar-*H*), 7.19 (t, *J* = 7.8 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 213.07, 159.74, 144.59, 129.31, 120.89, 114.08, 111.16, 79.40, 72.51, 55.09, 49.99, 49.65, 42.75, 38.01, 35.91, 33.46, 31.70, 28.57, 28.39, 24.48, 11.03; MS m/z 358 (M^+), 301, 245, 224, 181, 167, 134, 121, 93, 57.

2.1.6. (8α,13α,14β,17α-17-(1,1-Dimethylethoxy)-3-methoxyestra-1,3,5(10),9(11)-tetraene (8a)—Compound **7a** (1.21 g, 3.38 mmol) was dissolved in MeOH (30 ml) and cooled to 0 °C with and ice/salt bath. 10 N HCl (3.2 ml) was quickly added and stirring was continued at 0 °C for 4 h and then at room temperature for an additional 4 h. Product **8a** formed as a white precipitate during this time. The reaction was then moved to a cold room (5 °C) and stirring was continued overnight. Filtration gave crude product **8a** (0.91g, mp 124–126 °C, this material contains minor amounts of the isomeric tetraene **8b**), which was removed by recrystallization from MeOH/CH_2Cl_2. Product **8a** (0.83 g, 72%) had: mp 128–129 °C; $[\alpha]^{20}_D$ −109.9 (c = 0.36, $CHCl_3$); UV λ max (EtOH) 263 nm (ε = 14900); IR (KBr, cm^{-1}) 1626, 1604, 1568, 1255, 1197, 1116; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H, C_{18}-CH_3), 1.17 (s, 9H, $C(CH_3)_3$), 3.54 (t, *J* = 8.7 Hz, C_{17}-H), 3.79 (s, 3H, C_3-OCH_3), 6.12 (d, *J* = 5.4 Hz, C_{11}-H), 6.59 (d, *J* = 2.7 Hz, C_4-H), 6.71 (dd, *J* = 8.7 Hz, 2.7 Hz, 1H, C_2-H), 7.53 (d, *J* = 8.7 Hz, 1H, C_1-H); ^{13} C NMR ($CDCl_3$) δ 158.34, 137.57, 135.06, 127.70, 125.15, 118.02, 113.29, 112.63, 80.79, 72.22, 55.15, 47.30, 41.08, 39.49, 38.89, 31.17, 30.09, 28.68, 28.15, 24.29, 11.55. Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47; Found: C, 81.26; H, 9.47.

Compound **7b** (140 mg) was similarly converted to product **8a** (100 mg, 75%).

2.1.7. (13α,14β,17α)-17-(1,1-Dimethylethoxy)-3-methoxyestra-1,3,5(10),8-tetraene (8b)—The solid (150 mg) recovered from the mother liquors from recrystallizations of several preparations of compound **8a** contained both *ent*-steroids **8a** and **8b** (~2:3 ratio). Chromatography (successive elution with 1%, 1.5%, 2% and 2.5% Et_2O in hexanes) gave product **8b** (90 mg eluted in the 2% Et_2O fractions after compound **8a** eluted): mp 82–83 °C; $[\alpha]^{25}_D$ = −118.1 (c = 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3H, C_{18}-CH_3), 1.17 (s, 9H, $C(CH_3)_3$), 2.71 (t, *J* = 8 Hz, 2H, C_6-CH_2), 3.56 (t, 1H, C_{17}-H), 3.79 (s, 3H, OCH_3), 6.68 (s, 1H, C_4-H), 6.71 (d, *J* = 8.7 Hz, 1H, C_2-H), 7.12 (d, J = 8.7 Hz, 1H,

C_1-H); ^{13}C NMR ($CDCl_3$) δ 157.83, 137.16, 135.11, 129.77, 123.97, 122.81, 113.41, 110.84, 78.69, 72.61, 55.19, 48.96, 42.46, 33.20, 30.44, 28.86, 28.76, 28.59, 28.03, 22.38, 20.18.

2.1.8. (8α,9β,13α,14β,17α)-17-(1,1-Dimethylethoxy)-3-methoxyestra-1,3,5(10)-triene (9a)—Compound **8a** (1.08 g, 3.18 mmol) in EtOAc (74 ml) was hydrogenated in a Parr hydrogenator (H_2, 3.4 atm) using a 10% Pd/C (200 mg) catalyst for 6 h. Solvent removal gave a crude product (1.27 g) that was a mixture of products **9a** and **9b**. Chromatography (1% ether in hexanes) gave product **9a** (0.88 g, 81%): mp 90–91 °C; [α^{20}_D −61.9 (c = 0.49, $CHCl_3$); UV λmax (EtOH) 273nm (ε = 2310), 277 nm (ε = 2330), 287 nm (ε = 2050); IR (KBr, cm^{-1}) 1611, 1575, 1198; ^{1}H NMR($CDCl_3$) δ 0.75 (s, 3H, C_{18}-CH_3), 1.15 (s, 9H, $C(CH_3)_3$, 2.82–2.86 (m, 2H, C_6-CH_2), 3.45(t, *J* = 7.8 Hz, C_{17}-H), 3.78 (s, 3H, OCH_3), 6.63 (d, *J* = 2.7 Hz, C_4-H), 6.72 (dd, J = 8.7 Hz, 2.7 Hz, C_2-H), 7.22 (d, *J* = 8.4 Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 157.49, 138.17, 132.99, 126.44, 113.80, 111.47, 80.84, 72.17, 55.15, 49.96, 44.05, 42.69, 38.68, 37.16, 31.14, 29.82, 28.68, 27.19, 26.30, 23.40, 11.49.

2.1.9. (8α,9α,13α,14β,17α)-17-(1,1-Dimethylethoxy)-3-methoxyestra-1,3,5(10)-triene (9b)—Chromatography of the mixture of products **9a** and **9b** also yielded pure product **9b** (200 mg, 18%): [α^{20}_D +20.2 (c = 0.51, $CHCl_3$); UV λ max (EtOH) 288 nm (ε = 1580), 279 nm (ε = 1910); IR (KBr, cm^{-1}) 1608, 1575, 1267, 1079, 1059; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H, C_{18}-CH_3), 1.06 (s, 9H, $C(CH_3)_3$, 3.23 (t, *J* = 7.8 Hz, C_{17}-H), 3.77 (s, 3H, OCH_3), 6.62 (d, *J* = 2.4 Hz, C_4-H), 6.72 (dd, *J* = 8.7 Hz, 2.7 Hz, C_2-H), 7.27 (d, *J* = 8.4 Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 157.15, 139.04, 130.75, 127.51, 113.71, 111.80, 80.87, 72.10, 55.00, 42.63, 41.26, 37.27, 33.92, 32.78, 30.52, 28.61, 25.92, 25.28, 24.46, 23.42, 11.09.

2.1.10. (8α,9β,13α,14β,17α)-3-Methoxyestra-1,3,5(10)-trien-17-ol (10)—6 N HCl (3 ml) was added to a solution of compound **9a** (0.31 g, 0.91 mmol) dissolved in THF (3 ml) and EtOH (3 ml). The mixture, which became turbid, was refluxed 35 min during which time a clear solution was obtained. After cooling with an ice bath, 6 N NaOH (3 ml) was added. The THF was removed on a rotary evaporator and the remaining aqueous phase was extracted with EtOAc. The combined EtOAc extracts were washed with brine and dried to yield crude product. This material was converted to *ent*-17β-estradiol (**3**) without purification. Product **10** had: ^{1}H NMR ($CDCl_3$) δ 0.77 (s, 3H, C_{18}-CH_3), 2.85 (m, 2H, C_6-CH_2), 3.77 (s, 3H, OCH_3), 6.63 (d, *J* = 2.7 Hz, 1H, C_4-H), 6.69–6.74 (dd, *J* = 8.7 Hz, 2.7 Hz, C_2-H), 7.21 (d, *J* = 8.4Hz, C_1-H).

2.1.11. (8α,9β,13α,14β,17α)-Estra-1,3,5(10)-trien-3,17-diol (3, ent-17β-estradiol)—Unpurified compound **10** dissolved in anhydrous toluene (8 ml) was added to a 1 M solution of DIBALH (8 ml, 8 mmol) in hexanes under N_2. Then the reaction solution was refluxed for 24 h during which time it became pale yellow. After cooling to room temperature, the reaction solution was poured onto ice (50 g). After the oily product **3** solidified, the water was acidified with 3 N HCl and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine and dried. Solvent removal gave crude product **3**. Chromatography (30% EtOAc in hexanes) and recrystallization from acetone/hexanes gave purified product **3** (200 mg, 84% from compound **9a**): mp 176–177 °C; lit [7] mp 176–177 °C; lit [30] mp 177–178 °C; after second recrystallization, [α^{25}_D −82 (c = 0.28, dioxane); UV (EtOH) λ max 281 nm (ε = q250); IR (KBr, cm^{-1}) 3434, 1610, 1586, 1500, 1250, 1056, 1012; $^{\delta}$H NMR ($CDCl_3$/acetone-d_6) δ 0.79 (s, 3H, C_{18}-CH_3), 2.78–2.756 (m, 2H, C_6-CH_2), 2.96 (s, 1H, OH), 3.60 (d, *J* = 5.1 Hz, C_9-H), 3.69 (m, 1H, C_{17}-H), 6.53(d, *J* = 2.1 Hz, C_4-H), 6.60 (dd, *J* = 8.4 Hz, 2.7 Hz C_2-H), 7.09 (d, *J* = 8.7 Hz, C_1-H), 7.90 (d, *J* = 5.1 Hz, 1H, OH); ^{13}CNMR($CDCl_3$/acetone-d_6) δ 154.03, 136.67, 130.33,

125.24, 114.15, 111.75, 80.07, 48.97, 42.95, 42.13, 38.00, 35.74, 29.04, 26.19, 25.28, 21.88, 9.77. Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88; Found: C, 79.20; H, 8.95.

2.1.12. (8α,9β,13α,14β,17α)-Estra-1,3,5(10)-trien-3,17-diol 17-acetate (11)—To a solution of compound **10** (70 mg, 0.25 mmol) in glacial HOAc (1.5 ml) was added 48% HBr (0.7 ml). A white solid formed. The reaction mixture was then heated under N_2 for 1 h to yield a yellow solution. After cooling to room temperature, ice was added and a pink precipitate formed. The mixture was extracted with Et_2O and the combined organic extracts were washed with water, aqueous $NaHCO_3$, brine and dried. Solvent removal gave a crude product, which was purified by chromatography (20% EtOAc in hexanes) to give crystalline product **11** (60 mg, 78%). Further elution (30% EtOAc in hexanes gave compound **3** (10 mg). Product **11** had: ^{1}H NMR ($CDCl_3$/acetone-d_6) δ 0.84 (s, 3H, C_{18}-CH_3), 2.03 (s, 3H, $OCOCH_3$), 2.77–2.79 (m, 2H, C_6-CH_2), 4.66 (t, J = 8.1 Hz, C_{17}-H), 6.55 (s, 1H, C_4-H), 6.60 (d, J = 8.4 Hz, C_2-H), 7.09 (d, J = 8.4 Hz, C_1-H), 7.87 (br s, C_3-OH); ^{13}C NMR ($CDCl_3$/acetone-d_6) δ 170.14, 154.12, 137.02, 130.61, 125.57, 114.61, 112.20, 81.96, 49.16, 43.18, 42.24, 38.08, 36.31, 29.86, 27.00, 26.61, 25.59, 22.52, 20.16, 11.29.

2.1.13. (8α,9β,13α,14β,17α)-2-(1,1-Dimethylethyl)estra-1,3,5(10)-trien-3,17-diol (12a)—A suspension of compound **3** (30 mg, 0.11 mmol) and 2-methyl-2-propanol (0.06 ml, 0.63 mmol) in anhydrous pentane (1 ml) was stirred at room temperature for 15 min and at 0 °C to −5 °C for 20 min. BF_3–EtOEt (0.07 ml, 0.56 mmol) was added, stirring was continued at 0 °C to −5 °C for 20 min and then at room temperature. The reaction mixture first became a homogeneous solution and after 15 min a yellow solid formed on the flask wall. After stirring an additional 15 min at room temperature, ice was added. The solid product was filtered, washed with water and dried over P_2O_5 overnight in a vacuum desiccator. Chromatography (18% EtOAc in hexanes) and recrystallization from acetone/hexanes gave product **12a** (20 mg, 55%): mp 177–179 °C; $[\alpha]^{25}_D$ −91.3 (c = 0.23, $CHCl_3$); IR (film, cm^{-1}) 3368, 1612, 1511, 1214, 1058, 1011; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H, C_{18}-CH_3), 1.40 (s, 9H, $C(CH_3)_3$) , 2.74–2.75 (m, 2H, C_6-CH_2), 3.74 (t, J = 8.4 Hz, C_{17}-H), 6.41 (s, 1H, C_4-H), 7.19 (s, 1H, C_1-H); ^{13}C NMR ($CDCl_3$) δ 152.05, 135.33, 133.37, 131.81, 124.04, 116.55, 81.98, 50.03, 44.23, 43.26, 38.98, 36.78, 34.47, 30.57, 29.74, 28.91, 27.22, 26.38, 23.12, 11.07; MS m/z 328 (M^+), 313, 271, 253, 213, 185, 159, 147, 129, 115, 107, 91, 81, 69; Anal Calcd. for: $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.41, H, 9.62.

2.1.14. (8α,9β,13α,14β,17α)-2-(1-adamantyl)estra-1,3,5(10)-trien-3,17-diol (12b)—A suspension of compound **3** (40 mg, 0.15 mmol) and 1-adamantanol (20 mg, 0.13 mmol) in anhydrous pentane (1 ml) was stirred at room temperature for 20 min and then at −5 °C for 15 min. BF_3–EtOEt (0.05 ml, 0.40 mmol) was added, stirring was continued at 0 °C to −5 °C for 20 min and gave a pale yellow solution. Stirring was continued at room temperature and after 15 min a precipitate formed on the flask wall. After 45 min, ice was added. The solid product was filtered, washed with water and dried over P_2O_5 in a vacuum desiccator. Crude product **12b** (50 mg) was purified by chromatography (20% EtOAc in hexanes). Product **12b** (40 mg, 67%) was recrystallized from CH_2Cl_2/hexanes and had: mp174–176 °C; $[\alpha]^{24}_D$ −198 (c = 0.1, $CHCl_3$); IR (film, cm^{-1}) 3368, 1613, 1511, 1249, 1215, 1121, 1052, 1011; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H, C_{18}-CH_3); 1.77 (br s, 6H, adamantyl-H), 2.07 (br s, 3H, adamantyl-H), 2.11 (br s, 6H, adamantyl-H), 2.75–2.76 (m, 2H, C_6-CH_2); 3.78 (t, J = 8 Hz, 1H, C_{17}-H); 6.39 (s, 1H, C_4-H) 7.15 (s, 1H, C_1-H); ^{13}C NMR ($CDCl_3$) δ 152.16, 135.16, 133.73, 132.13, 124.02, 116.81, 81.98, 50.08, 44.31, 43.29, 40.82, 39.01, 37.10, 36.81, 36.64, 30.65, 29.10, 28.87, 27.22, 26.44, 23.14, 11.07; MS m/z 406 (M^+), 306, 293, 271, 253, 183, 159, 135, 107, 91, 79, 67. Anal Calcd. for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.88; H, 9.31.

2.1.15. (8α,13α,14β,17α)-3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-ol (13a)—To a stirred solution of compound **8a** (100 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (4 ml) at −10 °C, was quickly added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.38 ml). After 15min, water (4 ml) was added and the heterogeneous solution was extracted with CH_2Cl_2. The combined extracts were washed with brine and dried. Solvent removal gave crude product **13a** (90 mg) as a solid, which was used without further purification. Product **13a** had: ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3H, C_{18}-CH_3), 2.84 (m, 2H, C_6-CH_2), 3.79 (s, 3H, OCH_3), 3.82 (m, 1H, C_{17}-H), 6.13 (t, 1H, *J* = 2.1 Hz, C_{11}-H), 6.60 (d, 1H, *J* = 2.7 Hz, C_4-H), 6.72 (dd, 1H, *J* = 2.7 Hz, 8.7 Hz, C_2-H), 7.54 (d, 1H, *J* = 8.7 Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 158.47, 137.58, 135.12, 127.57, 125.23, 117.54, 113.35, 112.69, 82.02, 55.18, 47.35, 41.50, 38.91, 38.80, 30.71, 30.02, 28.15, 23.87, 10.85.

2.1.16. (13α,14β,17α)-3-Methoxyestra-1,3,5(10),8-tetraen-17-ol (13b)—To a solution of compound **8b** (90 mg, 0.27 mmol) in anhydrous CH_2Cl_2 (3 ml) at −5 °C was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.30 ml, 0.30 mmol). The reaction solution became orange. After 5 min, water was added and the heterogeneous solution was extracted with CH_2Cl_2. The combined extracts were washed with brine and dried. Solvent removal gave crude product **13b** (70 mg) as a solid, which was used without further purification. Product **13b** had: ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 3H, C_{18}-CH_3), 2.73 (t, *J* = 8.1 Hz, 2H, C_6-CH_2), 3.84 (t, *J* = 6 Hz, 1H, C_{17}-H), 6.69 (s, 1H, C_4-H), 6.73 (dd, *J* = 2.7 Hz, 8.1 Hz, C_2-H), 7.13 (d, *J* = 8.1Hz, C_1-H).

2.1.17. (8α,13α,14β,17α)-Estra-1,3,5(10),9(11)-tetraene-3,17-diol (14a)—A solution of compound **13a** (120 mg, 0.42 mmol) in anhydrous toluene (4 ml) under N_2 was added to DIBALH (1.5 M in toluene, 3 ml, 4.5 mmol). The reaction was refluxed overnight, cooled to room temperature and ice was added. The reaction mixture was then acidified with 3 N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried. Solvent removal gave a crude product which was purified by chromatography (35% EtOAc in hexanes) and crystallized from CH_2Cl_2/hexanes to give product **14a** (70 mg, 61%) as white crystals: mp 191–192 °C; lit [31] mp 186-191 °C ; $[\alpha^{25}_D$ −138.4 (c = 0.31, dioxane), UV (EtOH) λmax 265 nm (ε = 11900); IR (KBr, cm^{-1}) 3421, 1630, 1614, 1578, 1287, 1246, 1055; ^{1}H NMR ($CDCl_3$/acetone-*d_6*) δ 0.81 (s, 3H, C_{18}-CH_3), 2.77–2.82 (m, 2H, C_6-CH_2), 3.35 (d, 1H, *J* = 5.1 Hz, C_8-H) 3.80 (m, 1H, C_{17}-H), 6.08 (d, 1H, *J* = 5.1 Hz, C_{11}-H), 6.56 (d, 1H, *J* = 2.7 Hz, C_4-H), 6.65 (dd, 1H, J = 8.7 Hz, 2.7 Hz, C_2-H), 7.45 (d, *J* = 8.7Hz, C_1-H); ^{13}C NMR ($CDCl_3$/acetone-*d_6*) δ 155.28, 130.92, 134.67, 125.97, 124.55, 116.25, 114.44, 113.16, 80.82, 46.79, 40.87, 38.39, 38.30, 29.83, 28.29, 27.59, 23.20, 10.18; MS m/z: 270 (M^+), 211, 181, 169, 157, 149, 129, 111, 97, 83.69.

2.1.18. (13α,14β,17α)-Estra-1,3,5(10),8-tetraene-3,17-diol (14b)—A solution of compound **13b** (70 mg, 0.25 mmol) in anhydrous toluene (3 ml) under N_2 was added to DIBALH (1.5 M in toluene, 1.5 ml, 2.25 mmol). The reaction was refluxed overnight, cooled to room temperature and ice was added. The reaction mixture was then acidified with 2.5 N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried. Solvent removal gave a pale yellow oil (80 mg), which was purified by chromatography (30% EtOAc in hexanes) to give product **14b** (40 mg, 60%) as an oil, which later solidified to a red orange solid that could not be further purified. Product **14b** had: mp 86–96 °C; lit [31] mp 130–132 °C; $[\alpha]^{25}_D$ −99.5 (c = 0.37, $CHCl_3$), UV (EtOH) λ max 273 nm (ε = 16200); IR (KBr, cm^{-1}) 3447, 1678, 1649, 1615, 1260, 1194, 1098; ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 3H, C_{18}-CH_3), 2.68 (t, *J* = 7.6 Hz, 2H, C_6-CH_2), 3.86 (t, *J* = 5.4 Hz, 1H, C_{17}-H), 5.83 (s, OH), 6.61 (s, 1H, C_4-H), 6.64 (dd, *J* = 2.7 Hz, 8.1 Hz, 1H, C_2-H), 7.06 (d, *J* = 8.1 Hz, 1H, C_1-H); ^{13}C NMR ($CDCl_3$) δ 153.87, 137.27, 134.28, 129.30, 123.82, 122.97, 114.52, 112.59, 80.86, 48.09, 43.56, 32.17, 29.63, 29.16, 28.72, 28.24,

22.24, 18.49; MS m/z 270 (M^+), 237, 227, 211, 197, 181, 172, 157, 145, 137, 129, 111, 97, 81, 69.

2.1.19. (8α,9β,13α,14β,17β)-3-Methoxyestra-1,3,5(10)-trien-17-ol p-nitrobenzoate (15a)—The mixture of compound **10** (80 mg, 0.28 mmol), *p*-nitrobenzoic acid (0.12 g, 0.72 mmol), triphenylphosphine (0.15 g, 0.57 mmol) and diethylazodicarboxylate (0.13 g, 0.75 mmol) in anhydrous toluene (2 ml) was heated at 80 °C for 3.5 h. Solvent removal followed by chromatography (10% EtOAc in hexanes) gave product **15a** (70 mg, 58%) as a solid: ^{1}H NMR ($CDCl_3$) δ 0.79 (s, 3H, C_{18}-CH_3), 2.80 (m, 2H, C_6-CH_2), 3.69 (s, 3H, OCH_3) 5.07 (d, 1H, *J* = 6 Hz, C_{17}-H), 6.56 (d, 1H, J = 2.4 Hz, C_4-H), 6.62 (dd, J = 8.7 Hz, 2.7 Hz, C_2-H), 7.11 (d, 1H, *J* = 8.7 Hz, C_1-H), 8.12–8.23 (m, 4H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 164.34, 157.60, 150.55, 137.93, 136.25, 132.35, 130.68, 126.39, 123.59, 113.84, 111.54, 83.82, 55.09, 49.49, 45.39, 43.54, 38.96, 32.08, 30.09, 29.74, 27.94, 25.98, 24.29, 16.60.

2.1.20. (8α,13α,14β,17β)-3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-ol p-nitrobenzoate (15b)—A mixture of compound **13a** (0.24 g, 0.85 mmol), *p*-nitrobenzoic acid (305 mg, 1.84 mmol), triphenylphosphine (0.49 g, 1.87 mmol) and diethylazodicarboxylate (0.45 g, 2.58 mmol) in anhydrous toluene (7 ml) was heated at 80 °C for 6 h. Solvent removal and chromatography (10% EtOAc in hexanes) gave product **15b** (150 mg, 41%) as a solid: ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H, C_{18}-CH_3), 2.87–2.89 (m, 2H, C_6-CH_2), 3.80 (s, 3H, OCH_3), 5.21 (d, *J* = 6 Hz, C_{17}-H), 6.15 (m, 1H, C_{11}-H), 6.62 (d, 1H, *J* = 2.7 Hz, C_4-H), 6.72 (dd, 1H, *J* = 8.7 Hz, 2.7 Hz, C_2-H), 7.55 (d, 1H, *J* = 8.7 Hz, C_1-H), 8.18–8.31(m, 4H, Ar-*H*).

2.1.21. (8α,9β,13α,14β,17β)-3-Methoxyestra-1,3,5(10)-trien-17-ol (16a)—Compound **15a** (70 mg, 0.16 mmol) dissolved in THF (2 ml) was stirred with 2.8% methanolic KOH (3 ml) at room temperature for 2 h. Solvent removal and chromatography (15% EtOAc in hexanes) gave product **16a** (40 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 3H, C_{18}-CH_3), 2.84–2.87 (m, 2H, C_6-CH_2), 3.78 (s, 3H, OCH_3), 3.82 (m, 1H, C_{17}-H), 6.64 (d, 1H, C_4-H), 6.72 (dd, *J* = 8.7 Hz, 2.7 Hz, C_2-H), 7.23 (d, *J* = 8.7 Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 157.57, 138.17, 132.87, 126.45, 113.88, 111.53, 80.08, 55.16, 47.71, 45.51, 43.55, 39.03, 32.36, 31.41, 29.84, 27.99, 26.14, 24.18, 16.96.

2.1.22. (8α,13α,14β,17β)-3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-ol(16b)—Compound **15b** (150 mg, 0.35 mmol) dissolved in THF (4 ml) was stirred with 3% methanolic KOH (6 ml) at room temperature for 1h. After acidification with 3 N HCl, and solvent removal, the residue was chromatographed (20% EtOAc in hexanes) to give product **16b** (60 mg, 61%) as a solid: ^{1}H NMR ($CDCl_3$) δ 0.71 (s, 3H, C_{18}-CH_3), 2.82–2.84 (m, 2H, C_6-CH_2), 3.78 (s, 3H, OCH_3), 3.84–3.86 (d, 1H, *J* = 5.1 Hz, C_{17}-H), 6.17 (t, 1H, *J* = 2.7 Hz, C_{11}-H), 6.60 (d, 1H, *J* = 2.4 Hz, C_4-H), 6.71 (dd, 1H, *J* = 8.7 Hz, 2.4 Hz, C_2-H), 7.54 (d, 1H, *J* = 8.7 Hz, C_1-H). ^{13}C NMR ($CDCl_3$) δ 158.31, 137.55, 134.79, 127.66, 125.15, 117.90, 113.27, 112.63, 79.49, 55.13, 45.43, 43.89, 38.98, 33.08, 32.66, 30.09, 29.09, 24.92, 17.37.

2.1.23. (8α,9β,13α,14β,17β)-estra-1,3,5(10)-triene-3,17-diol (17a)—A solution of compound **16a** (40 mg, 0.14 mmol) in anhydrous toluene (3 ml) under N_2 was added to DIBALH (1.5 M in toluene, 1.5 ml, 2.25 mmol). The reaction was refluxed overnight, cooled to room temperature and ice was added. The reaction mixture was then acidified with 3 N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried. Solvent removal, chromatography (20% EtOAc in hexanes) and recrystallization from acetone/hexanes gave product **17a** (30 mg, 79%): mp 224–225 °C; [α^{22}_D −54.9 (c = 0.40, dioxane); IR (KBr, cm^{-1}) 3421, 1611, 1587, 1252, 1234, 1035; ^{1} D H NMR ($CDCl_3$/

acetone-d_6) δ 0.70 (s, 3H, C_{18}-CH_3), 2.77–2.78 (m, 2H, C_6-CH_2), 3.75 (q, J = 6 Hz, 1H, C_{17}-H), 6.54 (d, 1H, J = 2.4 Hz, C_4-H), 6.59 (dd, 1H, J = 8.4 Hz, 2.4 Hz, C_2-H), 7.10 (d, 1H, J = 8.4 Hz, C_1-H); ^{13}C NMR ($CDCl_3$/acetone-d_6) δ 154.02, 136.72, 130.50, 125.29, 114.18, 111.78, 78.14, 46.51, 44.39, 42.72, 38.30, 31.18, 30.53, 29.01, 27.12, 25.27, 23.08, 15.77. Anal Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.18; H, 8.62.

2.1.24. (8α,13α,14β,17β)-Estra-1,3,5(10),9(11)-tetraene-3,17-diol (17b)—A solution of compound **16b** (60 mg, 0.21 mmol) in anhydrous toluene (3 ml) under N_2 was added to DIBALH (1.5 M in toluene, 1.5 ml, 2.25 mmol). The reaction was refluxed overnight, cooled to room temperature and ice was added. The reaction mixture was then acidified with 3 N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried. Solvent removal, chromatography (20% EtOAc in hexanes) and recrystallization from acetone/hexanes gave product **17b** (40 mg, 70%): mp 239–241 °C; [α^{25}_D −131.3 (c = 0.27, dioxane); UV (EtOH) λmax 263 nm (ε = 15100); IR (KBr, cm^{-1}) 3482, 1634, 1581, 1284, 1236, 1158, 1027; ^{1}H NMR (CD_3OD) δ 0.72 (s, 3H, C_{18}-CH_3), 3.76 (d, 1H, J = 6 Hz, C_{17}-H), 6.12 (t, 1H, J = 2.4 Hz, C_{11}-H), 6.47 (d, 1H, J = 2.4 Hz, C_4-H), 6.55 (dd, 1H, J = 8.7 Hz, 2.4 Hz, C_2-H), 7.43 (d, 1H, J = 8.7 Hz, C_1-H); ^{13}C NMR (CD_3OD) δ 157.41, 138.94, 136.71, 128.10, 126.46, 118.39, 116.07, 114.91, 80.53, 47.01, 45.30, 40.88, 34.54, 33.16, 31.24, 30.82, 26.24, 18.13. Anal Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.77; H, 8.37.

2.1.25. (8α,9β,13α,14β,17β)-17-Iodo-3-methoxyestra-1,3,5(10)-triene (18)—To the stirred solution of compound **10** (120 mg, 0.42 mmol) and triphenylphosphine (140 mg, 0.53 mmol) in anhydrous toluene (3 ml) was added diethylazodicarboxylate (140 mg, 0.80 mmol) and then CH_3I (130 mg, 0.92 mmol) dissolved in toluene (1 ml). A precipitate formed. The reaction was stirred at room temperature for 30 min and then refluxed for 15 min. Solvent removal gave a dark brown oil and chromatography (5% EtOAc in hexanes) gave product **18** (70 mg, 41%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H, C_{18}-CH_3), 2.84–2.89 (m, 2H, C_6-CH_2), 3.77 (s, 3H, OCH_3), 4.42 (d, 1H, J = 6.9 Hz, - CHI), 6.63 (d, 1H, J = 1.8 Hz, C_4-H), 6.71 (dd, 1H, J = 8.4 Hz, 2.4 Hz, C_2-H), 7.21 (d, 1H, J = 8.4 Hz, C_1-H).

2.1.26. (8α,9β,13α,14β)-3-Methoxyestra-1,3,5(10)-triene (19)—Under N_2, AIBN (14 mg, 85 μmol) and $(Bu)_3SnH$ (0.3 ml, 1.12 mmol) were added to a solution of compound **18 (** 90 mg, 0.22 mmol) in anhydrous benzene (3 ml). The reaction was refluxed for 1.5 h. Solvent removal and chromatography (5% EtOAc in hexanes) gave product **19** (70 mg) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H, C_{18}-CH_3), 2.83–2.85 (m, 2H, C_6-CH_2), 3.72 (s, 3H, OCH_3), 6.63 (d, 1H, J = 2.7 Hz, C_4-H), 6.71 (dd, 1H, J = 8.7 Hz, 2.7 Hz, C_2-H), 7.22 (d, 1H, J = 8.7 Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 157.50, 138.15, 133.19, 126.40, 113.82, 111.44, 55.11, 53.49, 43.97, 41.00, 40.44, 39.10, 38.75, 29.87, 28.02, 26.67, 25.09, 20.46, 17.43.

2.1. 27. (8α,9β,13α,14β)-Estra-1,3,5(10)-trien-3-ol (20)—A solution of compound **19** (70 mg, 0.26 mmol) in anhydrous toluene (3 ml) was added to DIBALH (1.5 M in toluene, 1.5 ml, 2.25 mmol) under N_2. The reaction was refluxed overnight, cooled to room temperature and ice was added. The reaction mixture was then acidified with 3 N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried. After solvent removal, chromatography (20% EtOAc in hexanes) gave product **20** (40 mg, 60%): mp 130–131 °C (recrystallized from EtOAc/hexanes); lit [32] mp 134–135 °C; [α^{25}_D −100.5 (c = 0.19, $CHC1_3$); lit [32] [α^{20}_D −92 (c = 1, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H, C_{18}-CH_3), 2.80–2.81 (m, 2H, C_6-CH_2), 4.63 (s, OH), 6.56 (s, 1H, C_4-H), 6.63 (d, J = 8.4 Hz, C_2-H), 7.17 (d, 1H, J = 8.4 Hz, C_1-H); ^{13}C NMR ($CDCI_3$) δ 153.27, 138.51, 133.33, 126.64, 115.26, 112.62, 53.51, 43.96, 41.00, 40.46, 39.08, 38.76, 29.68, 27.97, 26.69, 25.11, 20.47, 17.45.

2.1.28. (8α,9α,13α,14β,17α)-3-Methoxyestra-1,3,5(10)-trien-17-ol (21)—To a solution of compound **9b** (0.41 g, 1.2mmol) in THF (4 ml) and EtOH (4 ml) was added 6 N HCl (4 ml). The reaction was heated with an oil bath to 100 °C for 1 h, then cooled with an ice bath and neutralized with 6 N NaOH (3.5 ml). The THF was removed and the remaining solution was extracted with EtOAc. The combined extracts were dried and the solvent removed to give crude product **21** as a pale brown solid (0.36 g), which was immediately converted to compound **22** without purification or characterization.

2.1.29. (8α,9α,13α,14β,17α)-Estra-1,3,5(10)-triene-3,17-diol (22)—A solution of compound **21** (90 mg, 0.32 mmol) in anhydrous toluene (4 ml) under N_2 was added to DIBALH (1.5 M in toluene, 3 ml, 4.5 mmol). The reaction was refluxed overnight, cooled to room temperature and ice was added. The reaction mixture was then acidified with 3 N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried. Solvent removal and chromatography (30% EtOAc in hexanes) gave product **22** (70 mg, 82%): mp 223–224 °C (crystallized from acetone/hexanes); $[\alpha^{25}_D$ +55.3 (c = 0.34, dioxane); IR (KBr, cm^{-1}) 3393, 1610, 1505, 1239, 1230, 1044; ^{1}H NMR ($CDCl_3$/acetone-d_6) δ 0.86 (s, 3H, C_{18}-CH_3), 3.21 (d, 1H, J = 5.1 Hz, C_9-H), 3.5 (m, 1H, C_{17}-H), 6.56 (d, 1H, J = 2.4 Hz, C_4-H), 6.63 (dd, J = 2.4 Hz, 8.4 Hz, C_2-H), 7.16 (d, J = 8.4 Hz, C_1-H). ^{13}C NMR ($CDCl_3$/acetone-d_6) δ 153.84, 138.07, 128.49, 126.64, 114.67, 112.54, 80.69, 42.44, 40.59, 36.47, 33.46, 31.65, 29.70, 24.95, 24.64, 23.84, 22.34, 9.85. Anal Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.10; H, 8.68.

3. Results and Discussion

3.1. Synthesis of ent-17β-estradiol

Indenone **4** [33], the C,D-ring synthon, was treated with NaH in ethylene glycol dimethyl ether and reacted with tosylate **5b** [29] to afford compound **6** (60%). Hydrogenation of compound **6** gave a 52% yield of the indenones **7a** (major isomer) and **7b** (minor isomer). Treatment of compound **7a** with 10 N HCl at 0 °C results in epimerization of the (methoxyphenyl)ethyl group to give **7b** and subsequent cyclization leads to $\Delta^{9(11)}$ *ent*-steroid **8a** (72%) and a small amount of the isomeric Δ^8 *ent*-steroid **8b** as products. Under these reaction conditions, compound **7b** also yields products **8a** and **8b**. The *trans* ring fusion of the C,D-rings of *ent*-steroid **8a** was established initially by ^{1}H NMR and ^{13}C NMR spectroscopy. The chemical shifts of the 18-Me group protons (δ = 0.78) and the carbon resonance of this group (δ = 11.55) are both characteristic of the *trans* C,D-ring fusion of *ent*-steroid **8a** [34]. Hydrogenation of compound **8a** produced *ent*-steroids **9a** (81%, major product) and **9b** (minor product). Removal of the *tert*-butyl protecting group from the oxygen atom at C_{17} using 6 N HCl in THF/EtOH converts compound **9a** to *ent*-steroid **10**, which was used without purification. Removal of the methyl protecting group from the oxygen atom at C_3 using DIBALH [35] converts compound **10** to *ent*-17β-estradiol **3** (84% yield overall for the **9a** to **3** conversion). Alternatively, methyl group removal from the oxygen atom at C_3 using 48% HBr [36] in glacial acetic acid gave a mixture of *ent*-steroids **3** (minor product) and **11** (major product). The overall yield for the conversion of indenone **4** to *ent*-17β-estadiol is 15.2%.

3.2. Synthesis of ent-17β-estradiol analogues

We have previously shown that 2-(1-adamantyl)-estrogens bind very poorly to estrogen receptors and are more potent neuroprotective agents than estrogens lacking the adamantyl subsitutent [37]. In part, at least, increased neuroprotective potency may be attributed to increased antioxidant potency. The bulky electron donating substituent increases the stability of the free-radical phenoxy radical. This effectively makes it easier for homolytic cleavage of the phenolic OH bond to occur and increases the rate of formation of the hydrogen radical

needed to quench lipid hydoperoxy radicals [38]. To extend these studies of the effect of bulky 2-subsitutents on neuroprotective potency into the *ent*-estrogen series, either *t*-butyl alcohol or 1-adamantanol in the presence of BF_3–EtOEt were reacted with steroid **3** to obtain steroids **12a** (55%) and **12b** (67%), respectively (Scheme 3).

Since extended conjugation can also increase the stability of a phenoxy radical, we used the $\Delta^{9(11)}$ and Δ^8 intermediates **8a** and **8b**, respectively, to prepare *ent*-17β-estadiol analogues having an additional double bond conjugated to the phenol ring. The *t*-butyl group was removed from *ent*-steroids **8a** and **8b** with $TiCl_4$ to yield compounds **13a** and **13b**, and these products were then converted without purification into products **14a** (61%) and **14b** (60%) by cleavage of the C_3 methoxy group with DIBALH (Scheme 4).

Also of interest to us are *ent*-estrogens in which the D-ring C_{17} substituent is varied. Previous studies with estrogens having the natural absolute configuration show that the substituent at C_{17} has a minor effect on neuroprotective activity [1,39] and we sought to verify this for the corresponding *ent*-estrogens. Using a Mitsunobu reaction [40] the C_{17} α-OH groups of compounds **10** and **13a** were inverted to the epimeric *p*-nitrobenzoates of compounds **15a** (58%) and **15b** (41%), the esters were hydrolyzed to obtain compounds **16a** (87%) and **16b** (61%), and the C_3 methoxy groups were cleaved with DIBALH to obtain compounds **17a** (79%) and **17b** (70%) (Scheme 5).

Since estra-1,3,5(10)-trien-3-ol is an effective neuroprotective agent [2], we also removed the C_{17} substituent to obtain its enantiomer, *ent*-steroid **20**. Compound **10** was first converted into the C_{17} β-iodo compound **18** (41%) using DEAD, Ph_3P, MeI, the iodo group was removed with Bu_3SnH and AIBN [41,42] and the C_3 methoxy group was cleaved with DIBALH to obtain *ent*-steroid **20** [32] (60%) (Scheme 6).

Finally, we used compound **9b** to obtain *ent*-steroid **22** (82%), which has a *cis* B,C-ring fusion, *via* compound **21** by the previously described two step acid hydrolysis, DIBALH reaction sequence (Scheme 7).

3.3. Biological evaluation

The estrogen receptor binding, antioxidant and neuroprotective properties of compounds **3**, **12a,b**, **14a,b**, **17b**, **20**, and **22** have been reported in detail elsewhere [27,43]. All of the evaluated *ent*-steroids bound more weakly to estrogen receptors (α and β forms) than 17β-estradiol. Compounds **12a,b** were particularly weak estrogen receptor ligands because of the bulky substituents at C_2. All of the *ent*-steroids were antioxidants and neuroprotective agents. Compounds **12a,b**, because of the steric and electronic properties of the C_2 substituents, were the most potent antioxidants. Thus, neuroprotection correlated with antioxidant activity rather than with estrogen receptor binding.

5. Conclusion

Starting with indenone **4**, *ent*-17β-estradiol is obtained in six steps with an overall yield of 15.2%. No hazardous Li/liquid NH_3 reduction or expensive reagents are used in the reaction sequence and *ent*-estrogens containing the $\Delta^{9(11)}$-bond are also accessible via this synthetic route.

Acknowledgments

This research was supported by a research grant from Apollo Biopharmaceutics, Inc., prior to its acquisition by MIGENIX Corp. and by NIH grant AG10485.

References and Notes

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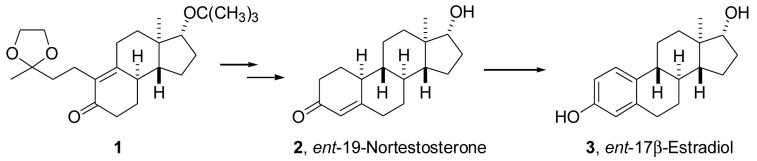
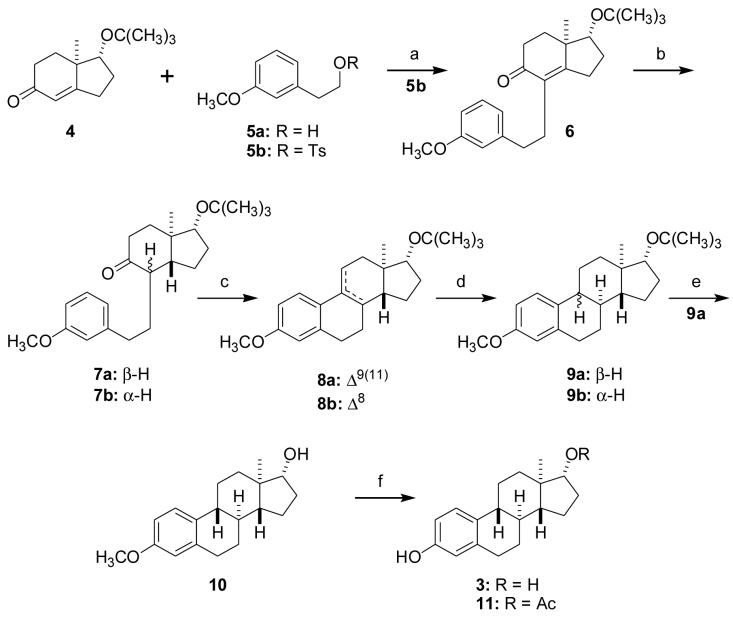
[43]. The designation of compounds in this paper (compound numbers) is different than that used in reference 18 (abbreviations and code numbers) which reports the details of their biological evaluation. For the reader's convenience, the designations for the compounds in the two publications are as follows: **3** (*ent*-E2), **12a** (ZYC34), **12b** (ZYC33), **14a** (ZYC10), **14b** (ZYC27), **17b** (ZYC12), **20** (ZYC13), **22** (ZYC9).



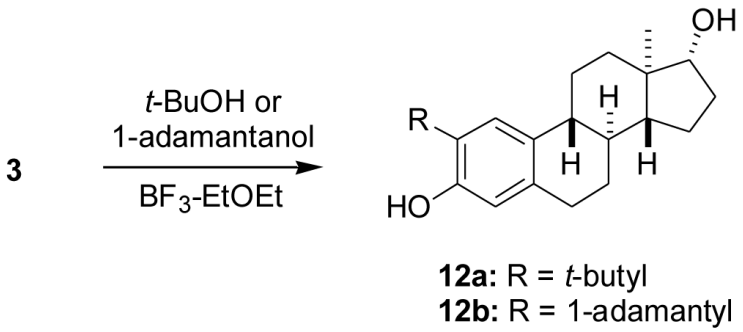
1 **2**, *ent*-19-Nortestosterone **3**, *ent*-17β-Estradiol

Scheme 1.

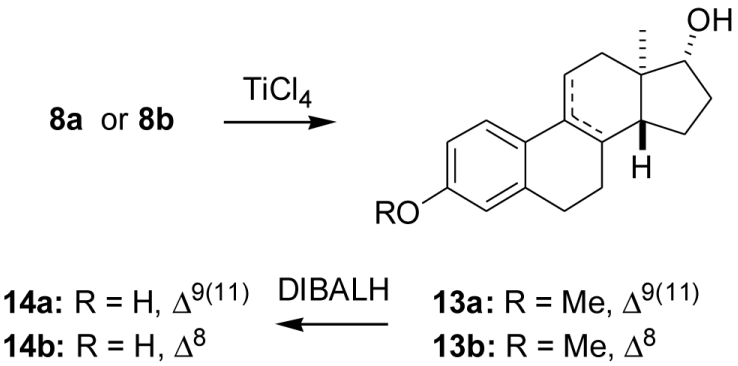


a: NaH, DME, 60%; b: H_2 (3.4 atm), 10% Pd/C, EtOH, 52%; c: 10 N HCl, 0 °C, 72%; d: H_2 (3.4 atm), 10% Pd/C, EtOAc, 81%; e: 6 N HCl, EtOH, THF; f: 48% HBr, HOAc or DIBALH.

Scheme 2.



Scheme 3.



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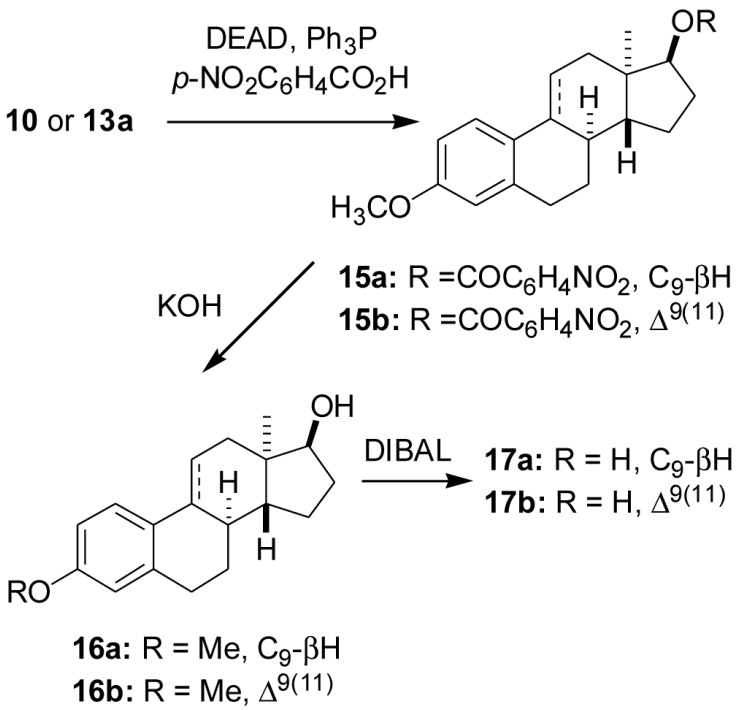
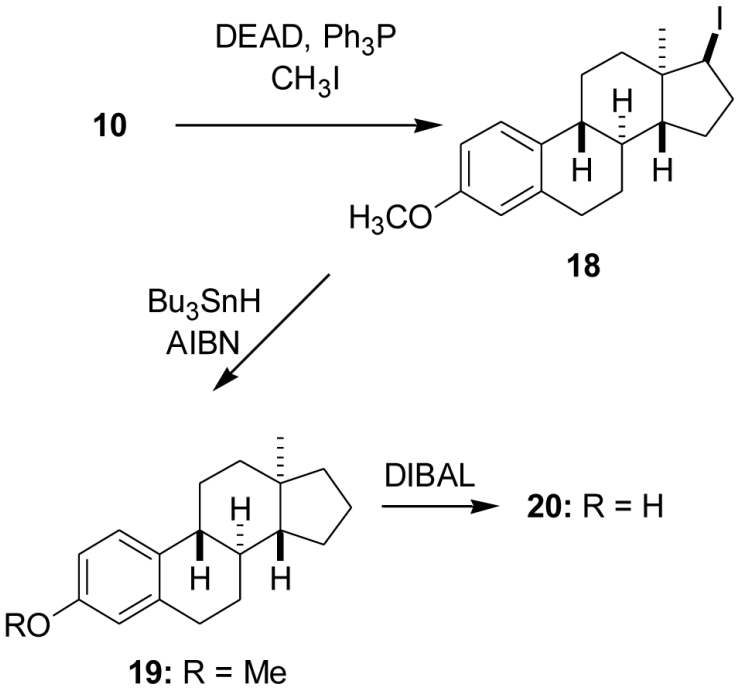
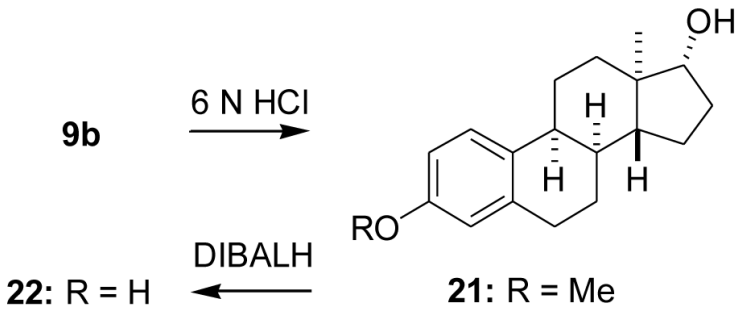


Scheme 5.



Scheme 6.



Scheme 7.