7α-Alkoxyestra-1,3,5(10)-trienes

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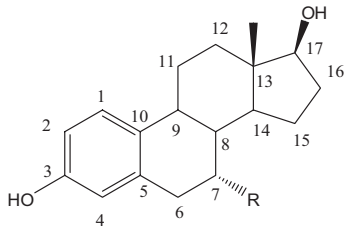
α-Alkoxyestradiols were prepared through $LiAlH_4$ reduction of a suitably protected 6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one, alkylation of the resultant 7α-hydroxyestra-1,3,5(10)-trien-3-ol-17-one derivative and subsequent transformation of the C17 functionality.

Keywords: steroids, estradiol, ethers

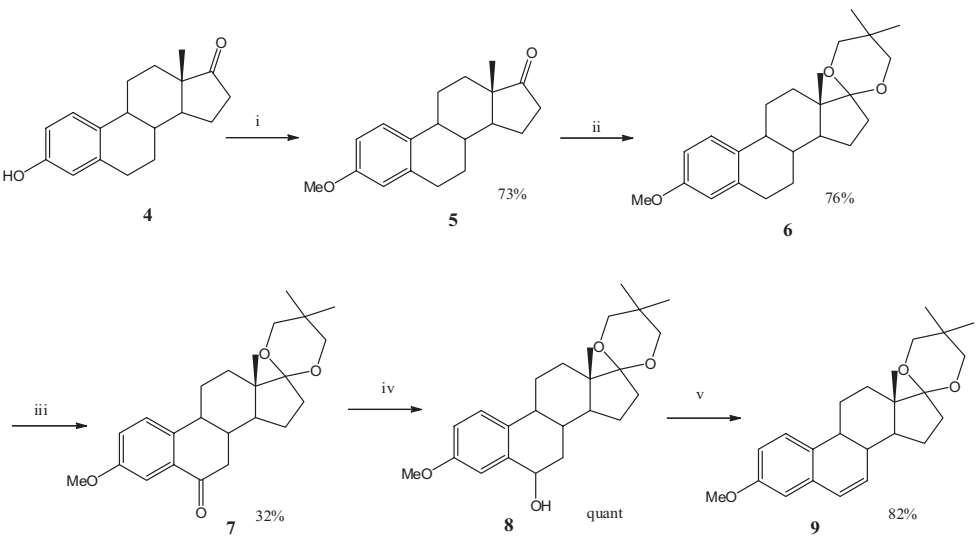
In 60–70% of breast cancer cases, the estrogen receptor ERα is over-expressed in the cell nucleus.[1] The relative abundance of estrogen receptors in ERα positive breast cancer cells *vis*-a-*vis* healthy breast tissue may provide potential leverage in the diagnosis and treatment of minimal ER-positive breast cancer. A prerequisite is a good binding affinity of the potential diagnostic or therapeutic agent to the estrogen receptor. A number of synthetic steroidal and non-steroidal derivatives have been studied as to their suitability as drug-delivery systems for anti-tumour compounds in the form of steroidal hybrids with known cytotoxic residues,[2-5] as antiestrogens[6-8] or selective estrogen modulators,[9] or as potential diagnostic agents in form of radiolabelled estradiol derivatives,[10-12] all targeting the estrogen receptor. The general influence of the substitution pattern in estradiol derived molecules on the binding behaviour of the molecules to the estrogen receptor has been established.[13] Substitution of estradiol at either C7,[14] C11,[15] or C16[18,19] and at C17[20,22] is tolerated, often without reducing significantly the binding affinity of the steroid to the receptor. The best known steroidal based antiestrogens, molecules that bind competitively to the estrogen receptor but do not activate transcription that would lead to cell division, are C7α-substituted estradiols such as ICI 164384 (**2**) and ICI 182780 (**3**) (Fig. 1). In our quest for novel estradiol based ligands for the estrogen receptor ERα,[23-29] that could ultimately be radiolabelled, we have synthesised a number of 7α-alkoxyestradiol derivatives.



1: R = H (Estradiol)
2: R = $(CH_2)_{10}CON(n\text{-}C_4H_9)CH_3$ (ICI 164384)
3: R = $(CH_2)_9SO(CH_2)_3CF_2CF_3$ (ICI 182780)

Fig. 1

It was decided to prepare 7α-alkoxyestradiols via a common intermediate, 6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one derivative **10**, which was to be prepared from estra-1,3,5,(10), 6-tetraene **9**. At the start of the reaction sequence, the phenolic function at C3 of the starting material estrone **4,** was protected as its methyl ether by treatment of **4** with NaOH in DMSO followed by subsequent alkylation of the phenoxide with methyl iodide to give **5**.[30] Acetalisation of the C17 keto function in **5** was carried out with neopentyl glycol (NPG) under standard conditions[31,32] to give the fully protected **6** (Scheme 1). In order to access the C7-position in estranes of type **6** it was necessary to activate C6. For this purpose, C6 was oxidised. The direct oxidation of estrane derivatives to 6-ketoestranes has been described



Scheme 1 i. KOH, DMSO,MeI; ii. NPG, *p* -TsOH, benzene, ref l., iii. $KMnO_4$, Adogen 464, $NaHCO_3$, benzene, H_2O; iv. $NaBH_4$, MeOH,Et_2O; v. *p*-TsOH, NPG, benzene.

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previously. Among the reagents used are CrO_3, CH_2Cl_2, 2,5-dimethylpyrazole,[33] AcOH, CrO_3, H_2O,[34-36] pyridinium chlorochromate (PCC), benzene[37] and CrO_3, H_2SO_4.[38] In our hands, however, the direct oxidation of fully protected **6** to **7** could best be achieved with $KMnO_4$ under PTC conditions (Adogen 464, benzene, aq. $NaHCO_3$).[24] Next, **7** was reduced with $NaBH_4$ in a mixture of MeOH/Et_2O to give **8** (Scheme 1). **8** can be prepared alternatively by lithiation of **6**, reaction of the benzylic anion of **6** with trimethyl borate, and oxidative cleavage of the boronic ester with H_2O_2[24,39] according to a method reported by R. Tedesco *et al.*,[40] **8** was subjected to dehydration with *p*-TsOH (benzene, reflux) to give 3-methoxy-estra-1,3,5(10),6(7)-tetraen-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**9**) (Scheme 1). In this reaction, some neopentylglycol was added in order to maintain the protecting group at C17.[24]

Compound **9** was reacted with *m*-chloroperbenzoic acid in a phosphate buffer. The reaction is stereoselective and gives the 6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one derivative **10**. The stereochemistry at C6/C7 was determined by a NOE experiments. In order to assign the proton signals, a ^1H–^1H COSY experiment was carried out beforehand.

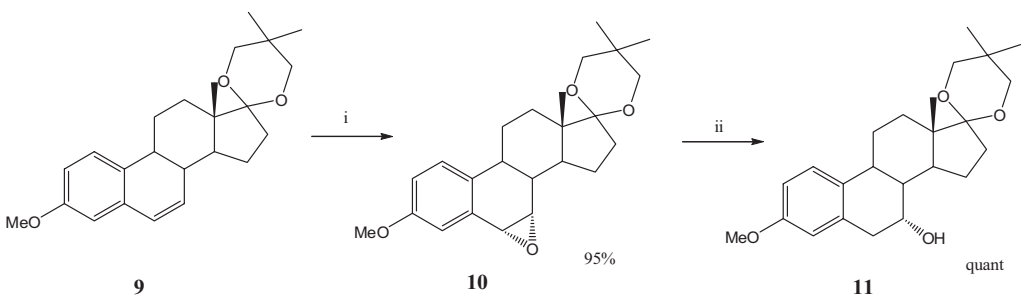
Benzocycloalkene 1,2-oxides are known to undergo regioselective reductive ring opening with complex hydrides.[41-43] While reactions of **10** with carbon nucleophiles such as $(n\text{-Bu})_2Cu(CN)Li_2$ were found to be not completely regioselective,[44] the reaction of **10** with $LiAlH_4$ led exclusively to estra-1,3,5(10)-trien-3,7-diol-17-one **11** (Scheme 2). Again, the stereochemistry of **11** at C7 was determined by NOE experiments, and the compound was shown to be the 7α-hydroxy derivative.[45] Additionally, the coupling constants ^3J of H(C7) at δ 4.13 (in $CDCl_3$) with Hα/Hβ(C6) and H(C8) are very small, indicative of H(C7) at an equatorial position. Larger coupling constants would be expected between neighbouring axially positioned protons for a discussion see ref. 46.

Etherification of **11** was carried out using NaH as base and alkyl halides such as methyl iodide or benzyl bromide as alkylating agents (Scheme 3). The use of the reaction system NaOH/DMSO/RI[30] failed to give ethers as did the use of Ag_2O, MeI.[47] Due to its axial nature, steric constraints may influence the reactivity of the 7α-hydroxy group. However, use of excess NaH and long reaction times provided the protected 7α-alkoxyestrone derivatives **12** in excellent yield (Scheme 3).

Steroidal ethers **12** were deprotected at C17 to ketones **13** by transacetalisation (acetone, *p*-TsOH, rt) (Scheme 3). In order to utilise derivatives of the steroidal ethers **13** as potential radioligands for the estrogen receptor ERα, the estrones were converted to estradiols. In the present case, an ethynyl group was chosen as the 17α-substituent in the desired estradiols, *i.e.*, as found in **14**/**15**. The ethynyl group can enhance the binding affinity of the steroid to the receptor,[20,22] but more importantly, the 17α-ethynyl group can be used as a precursor of a 17α-halovinyl group.[39,48-50] At a later stage, a radiohalide such as ^{125}I or ^{123}I can be incorporated in such a halovinyl function. An exemplary ethynylation was carried out with **13a** and trimethylsilylacetylene and led to desired **15** after F^- induced desilylation of the ethynyl function in **14** (Scheme 4).

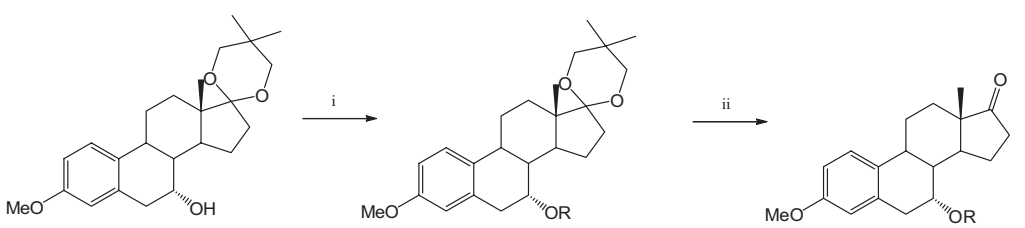
The use of 4-bromobenzyl bromide as an alkylating agent provided possibilities for the further modification of the ether side chain. Thus, the C7 substituent of **13f** can be derivatised simply by Suzuki–Miyaura cross coupling reaction with an aryl boronic acid [$Pd(PPh_3)_2Cl_2$, PPh_3, DME, aq. Na_2CO_3][51-53] (Scheme 5).

In summary, it has been shown that 7α-alkoxyestranes are readily accessible via the 6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one derivative **10**. Transformation of the 17-keto group and further functionalisation of the C7α side chain provide an easy derivatisation of these molecules. Currently, 7α-alkoxyestranes are being synthesised with the tetrahydropyranyl function as a removable protective group at (C3-O). These compounds will be tested as to their binding affinity to the estrogen receptor ERα and *in vivo* biodistribution assays will be carried out.



9 **10** **11**

Scheme 2 i. *m*-CPBA, Na_2HPO_4, NaH_2PO_4, CH_2Cl_2, ii. $LiAlH_4$, THF.

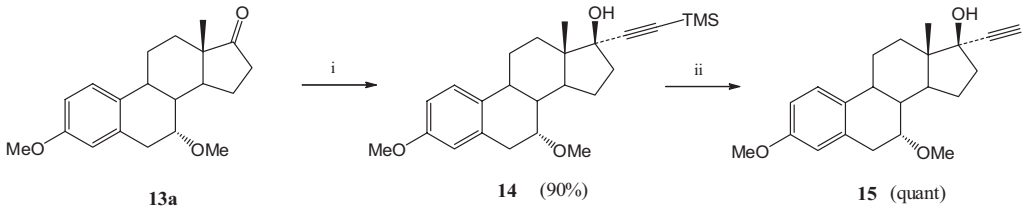


11

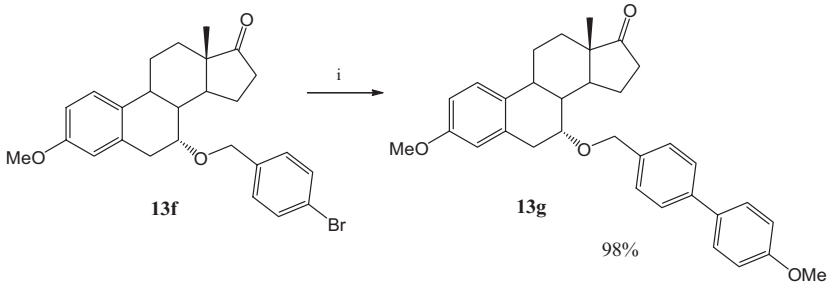
12a: RX = MeI; R = Me (56%)
12b: RX = PrI; R = Pr (73%)
12c: RX = AmI; R = Am (99%)
12d: RX = HexI; R = Hex (quant)
12e: RX = BenzylBr; R = Benzyl (quant)
12f: RX = 4-Br-benzylBr; R = 4-Br-benzyl (75%)

13a: R = Me (quant)
13b: R = Pr (quant)
13c: R = Am (96%)
13d: R = Hex (80%)
13e: R = Benzyl (96%)
13f: R = 4-Br-benzyl (78%)

Scheme 3 i. NaH, THF, RX; ii. *p*-TsOH, acetone, room temperature.



Scheme 4 i. LDA, THF, TMS-acetylene; ii.Bu_4NF, THF.



Scheme 5 i. 4-MeO-Ph-$B(OH)_2$, $Pd(PPh_3)_2Cl_2$, PPh_3, DME, aq. Na_2CO_3.

Experimental

General

Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. IR spectra were measured with JASCO IR-700 and Nippon Denshi JIR-AQ2OM machines. ^1H and ^{13}C NMR spectra were recorded with a JEOL EX-270 spectrometer. The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Partly, the interpretation of the ^{13}C NMR data was aided by DEPT (distortionless enhancement by polarisation transfer) experiments: (+) denotes primary and tertiary, (–) secondary and C_{quat} quaternary carbons. Mass spectra were measured with a JMS-01-SG-2 spectrometer [electron impact mode (EI), 70 eV or fast atom bombardment (FAB)]. Column chromatography was carried out on Wakogel 300 or on silica gel 60N (spherical, neutral, Kanto Chemicals). Estrone (estra-1,3,5(10)-trien-3-ol-17-one, **4**) was obtained commercially from Wako and from Aldrich. Compounds **5**,[30] **6**,[24] **7**,[54] **8**,[55] and **9**[24] were prepared according to literature procedures.

3-O-Methyl-6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]) (**10**): To a mixture of 3-*O*-methylestra-1,3,5(10),6-tetraene-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**9**, 355 mg, 1.0 mmol) in a mixture of CH_2Cl_2 (20 ml) and phosphate buffer (the buffer was prepared by adding sufficient aqueous 0.1 M Na_2HPO_4 to 0.1 M NaH_2PO_4 until pH 8 was reached) was added *m*-chloroperbenzoic acid (173 mg, 1.0 mmol) in small portions at 0°C. The reaction mixture was stirred at rt for 5 h and the organic layer was separated, washed with saturated sodium thiosulfate and water and dried over anhydrous $MgSO_4$. Concentration of the solution *in vacuo* and column chromatography gave **10** (365 mg, 95%) as a colourless solid, m.p. 93°C; (Found: M^+, 384.2298. $C_{24}H_{32}O_4$ requires M, 384.2301); ν_{max} (KBr)/cm^{-1} 2946, 1616, 1504, 1470, 1395, 1311, 1257, 1147, 1104, 1040, 860, 839, 749, 687, 643, 603, 557; ^1H δ_H (270 MHz, CD_2Cl_2) 0.64 (3H, s, CH_3), 0.74 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.42–2.03 (7H, m), 3.27–3.63 (7H, m), 3.71 (1H, s), 6.61 (1H, d, ^4J = 2.4 Hz), 6.73 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz), 7.23 (1H, d, ^3J = 8.4 Hz); δ_C (67.8 MHz, CD_2Cl_2, DEPT 90, DEPT 135) 13.7 (+, CH_3), 22.1 (+, CH_3), 23.6 (+, CH_3), 24.5 (–), 27.4 (-), 29.4 (C_{quat}), 30.6 (–), 36.5 (+, CH), 38.1 (+, CH), 45.3 (+, CH), 48.4 (C_{quat}), 53.8 (+, CH), 55.6 (+, OCH_3), 56.3 (+, CH), 70.9 (–), 73.0 (–), 108.5 (C_{quat}), 113.3 (+, CH), 115.6 (+, CH), 125.5 (+, CH), 132.7 (C_{quat}), 134.1 (C_{quat}), 158.4 (C_{quat}); MS (EI, 70 eV) *m/z* (%) = 384 (55) [M^+], 368 (14), 141 (100).

3-O-Methyl-estra-1,3,5(10)-trien-3,7α-diol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**11**): To a suspension of $LiAlH_4$ (98 mg, 2.6 mmol) in dry THF (3 ml) was added **10** (500 mg, 1.3 mmol) in THF (1 ml) at 0°C and under an Ar atmosphere. After the addition, the solution was stirred for 3 h. Ethyl acetate (1 ml) was added to quench the remaining $LiAlH_4$. Aqueous NH_4Cl was added until a pH of 3 was reached, and the mixture was extracted with ether. The organic phase was washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **11** (502 mg, quant) as a colourless solid; m.p. 90°C; (Found: M^+, 386.2459. $C_{24}H_{34}O_4$ requires M, 386.2457); ν_{max} (KBr)/cm^{-1} 3350 (bs, OH), 1609, 1501, 1467, 1285, 1238, 1104, 1037, 961, 927, 880, 849, 817, 755; δ_H (270 MHz, CD_2Cl_2) 0.72 (3H, s, CH_3), 0.81 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.18–1.98 (9H, m), 2.27–2.58 (3H, m), 2.83 (1H, d, ^2J = 16.8 Hz), 3.05–3.12 (1H, m), 3.34–3.50 (3H, m), 3.65–3.78 (4H, m), 6.60 (1H, d, ^4J = 2.6 Hz), 6.70 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.6 Hz), 7.23 (1H, d, ^3J = 8.6 Hz); δ_H (270 MHz, $CDCl_3$) 0.73 (3H, s, CH_3), 0.83 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 6.62 (1H, d, ^4J = 2.7 Hz), 6.73 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 7.24 (1H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.9, 22.0, 22.5 (2C), 26.2, 27.0, 29.4, 30.4, 35.6, 38.6, 42.6, 43.2, 47.4, 55.2, 66.0, 70.6, 72.7, 108.4, 112.1, 114.5, 126.6, 131.7, 134.4, 157.7; MS (EI, 70 eV) *m/z* (%) = 386 (32) [M^+], 282 (33), 243 (27), 141 (100).

3-O-Methyl-7α-methoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12a**): To a solution of **11** (100 mg, 0.26 mmol) in dry THF (1.5 ml) was added NaH (19 mg, 0.78 mmol) and then MeI (50 μL, 0.78 mmol). The resulting reaction mixture was stirred at ambient temperature for 20 h. Then the mixture was poured into cold water and extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 5:1:1) to give **12a** (58 mg, 56%) as a colourless solid; m.p. 72°C (Found: M^+, 400.2617. $C_{25}H_{36}O_4$ requires M, 400.2614); ν_{max} (KBr)/cm^{-1} 2950, 1275, 1240, 820, 757; δ_H (270 MHz, $CDCl_3$) 0.73 (3H, s, CH_3), 0.81 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.34–2.43 (10H, m), 2.67 (1H, m), 2.82 (1H, dd, ^2J = 18.1 Hz, ^3J = 4.1 Hz), 3.09 (1H, d, ^2J = 18.1 Hz), 3.35 (3H, s, OCH_3), 3.35–3.43 (2H, m), 3.48 (1H, d, ^2J = 10.8 Hz), 3.50 (1H, m), 3.65 (1H, d, ^2J = 11.1 Hz), 3.77 (3H, s, OCH_3), 6.61 (1H, d, ^4J = 2.7 Hz), 6.71 (1H, dd, ^3J = 8.6 Hz, ^4J 2.7 Hz), 7.23 (1H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.7, 22.1, 22.6, 23.0, 26.4, 27.1, 29.4, 30.4, 33.4, 36.1, 42.7, 43.0, 47.4, 55.2, 56.9, 70.6, 72.7, 75.0, 108.6, 111.8, 114.4, 126.6, 132.6, 135.0, 157.4; MS (EI, 70 eV) *m/z* (%) = 400 (22) [M^+], 385 (28) [M^+-CH_3], 368 (27), 141 (100).

3-O-Methyl-7α-propoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12b**): To a solution of **11** (100 mg, 0.26 mmol) in dry THF (1.5 ml) was added NaH (208 mg, 60w% in oil, 5.2 mmol) and thereafter iodopropane (442 mg, 2.6 mmol). The resulting reaction mixture was stirred under reflux for 20 h. Then the mixture was poured into cold water and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 10:1:1) to give **12b** (82 mg, 73%) as a colourless solid; m.p. 53°C; (Found: M^+ H^+, 429.3010. $C_{27}H_{41}O_4$ requires M, 429.3005); ν_{max} (KBr)/cm^{-1} 2965, 1280, 1255; δ_H (270 MHz, $CDCl_3$) 0.73 (3H, s, CH_3), 0.80 (3H, s, CH_3), 0.84 (3H, t, ^3J = 7.3 Hz), 1.16 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 6.61 (1H, d, ^3J = 2.7 Hz), 6.71 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.7 Hz); δ_C (67.8 MHz, $CDCl_3$) 10.7, 13.8, 22.0, 22.5, 23.0, 23.3, 26.3, 27.1, 29.3, 30.4, 34.2, 35.9, 42.8, 42.9, 47.3, 55.2, 70.6, 70.9, 72.7, 73.1, 108.7, 111.5, 114.3, 126.5, 133.0, 135.4, 157.3; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 429 (23) [MH^+], 385 (24), 368 (35), 265 (38).

3-O-Methyl-7α-pentoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12c**): To a solution of **11** (100 mg, 0.26 mmol) in dry THF (1.5 ml) was added NaH (208 mg, 60w% in oil, 5.2 mmol) and thereafter iodopentane (515 mg, 2.6 mmol). The resulting reaction mixture was stirred under reflux for 20 h. Thereafter, the mixture was poured into cold water and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 10:1:1) to give **12c** (118 mg, 99%) as a colourless oil; (Found: MH^+, 457.3314. $C_{29}H_{45}O_4$ requires MH, 457.3318 [FAB]); ν_{max} (neat)/cm^{-1} 2967, 1257, 1230, 805; ^1H NMR (270 MHz, $CDCl_3$) δ 0.72 (3H, s, CH_3), 0.80 (3H, s, CH_3), 0.85 (3H, t, ^3J = 6.7 Hz, CH_3), 1.16 (3H, s, CH_3), 1.23–2.42 (17H, m), 2.71 (1H, m), 2.82 (1H, dd, ^2J = 18.6 Hz, ^3J 4.1 Hz), 3.03 (1H, d, ^2J = 18.6 Hz), 3.25–3.68 (7H, m), 3.76 (3H, s, OCH_3), 6.60 (1H, d, ^4J = 2.7 Hz), 6.70 (1H, dd, ^3J = 8.6 Hz, ^4J 2.7 Hz), 7.23 (1H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.8, 14.1, 22.0, 22.5, 22.5, 23.0, 26.3, 27.1, 28.4, 29.4, 29.7, 30.4, 34.2, 35.9, 42.8, 42.9, 47.3, 55.2, 69.1, 70.6, 72.7, 73.2, 108.6, 111.5, 114.4, 126.5, 133.0, 135.4, 157.4; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 457 (1.9) [MH^+], 385 (1.9), 369 (3.1), 345 (1.7).

3-O-Methyl-7α-hexoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12d**): To a solution of **11** (100 mg, 0.26 mmol) in dry THF (1.5 ml) was added NaH (208 mg, 60w% in oil, 5.2 mmol) and thereafter iodohexane (551 mg, 2.6 mmol). The resulting reaction mixture was stirred under reflux for 20 h. Then the mixture was poured into cold water and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 10:1:1) to give **12c** (122 mg, quant) as a colourless solid; (Found: MH^+, 471.3481. $C_{30}H_{47}O_4$ requires MH, 471.3474, FAB); ν_{max} (KBr)/cm^{-1} 2955, 1273, 1247; δ_H (270 MHz, $CDCl_3$) 0.73 (3H, s, CH_3), 0.80 (3H, s, CH_3), 0.91 (3H, m), 1.16 (3H, s, CH_3), 1.24–2.47 (18H, m), 2.72 (1H, m), 2.80 (1H, dd, ^2J = 18.1 Hz, ^3J = 3.9 Hz), 3.04 (1H, d, ^2J = 18.1 Hz), 3.35–3.63 (7H, m), 3.76 (3H, s, CH_3), 6.61 (1H, d, ^4J = 2.7 Hz), 6.71 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 7.23 (1H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.8, 14.0, 14.1, 22.0, 22.5, 22.6, 22.7, 25.9, 26.3, 27.0, 29.3, 29.9, 30.4, 31.6, 34.2, 35.9, 42.9, 47.3, 55.2, 69.0, 70.6, 72.7, 73.1, 108.6, 111.5, 114.3, 126.5, 132.9, 135.4, 157.5; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 471 (13) [MH^+], 385 (20), 369 (31).

3-O-Methyl-7α-benzyloxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12e**): To a solution of **11** (100 mg, 0.26 mmol) in dry THF (3.0 ml) was added NaH (208 mg, 60 w%, 5.2 mmol) and then benzyl bromide (445 mg, 2.6 mmol). The resulting reaction mixture was stirred under reflux for 20 h. Then the mixture was poured into cold water and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 10:1:1) to give **12e** (124 mg, quant) as a colourless, slowly solidifying oil; (Found: M^+ H^+, 477.3000. $C_{31}H_{41}O_4$ requires M, 477.3005); ν_{max} (KBr)/cm^{-1} 3012, 2967, 1277, 1240, 815, 760; δ_H (270 MHz, $CDCl_3$) 0.72 (3H, s, CH_3), 0.78 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.24–2.43 (10H, m), 2.80 (1H, m), 2.85 (1H, dd, ^2J = 17.0 Hz, ^3J = 3.2 Hz), 3.10 (1H, d, ^2J = 17.0 Hz), 3.43 (3H, m), 3.65 (1H, d, ^2J = 11.3 Hz), 3.75 (1H, m), 3.76 (3H, s, OCH_3), 4.44 (1H, d, ^2J = 12.4 Hz), 4.67 (1H, d, ^2J = 12.4 Hz), 6.60 (1H, d, ^4J = 2.4 Hz), 6.72 (1H, dd, ^3J = 8.9 Hz, ^4J = 2.4 Hz), 7.23–7.33 (6H, m); δ_C (67.8 MHz, $CDCl_3$) 13.8, 22.0, 22.5, 22.7, 26.3, 27.1, 29.3, 30.3, 34.2, 36.0, 42.8 (2C), 47.3, 55.2, 70.5, 70.6, 72.4, 72.6, 108.6, 111.6, 114.4, 126.6, 127.2, 127.6 (2C), 128.1 (2C), 132.9, 135.1, 139.3, 157.5; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 477 (5.6) [MH^+], 385 (25), 369 (8.4).

3-O-Methyl-7α-(4-bromobenzyloxy)estra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12f**): To a solution of **11** (100 mg, 0.26 mmol) in dry THF (3.0 ml) was added NaH (208 mg, 60w% in oil, 5.2 mmol) and then a solution of 4-bromobenzyl bromide (650 mg, 2.6 mmol) in dry THF (1.0 ml). The resulting reaction mixture was stirred under reflux for 20 h. Then the mixture was poured into cold water and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 10:1:1) to give **12f** (112 mg, 78%) as a colourless solid; (Found: M^+ H^+, 555.2106. $C_{31}H_{40}O_4{}^{79}Br$ requires M, 555.2110); ν_{max} (KBr)/cm^{-1} 3010, 2973, 2930, 1270, 1245, 807; δ_H (270 MHz, $CDCl_3$) 0.74 (3H, s, CH_3), 0.79 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.22–1.43 (10H, m), 2.78 (1H, m), 2.86 (1H, dd, ^2J = 18.1 Hz, ^3J = 3.8 Hz), 3.07 (1H, d, ^2J = 18.1 Hz), 3.35–3.49 (3H, m), 3.66 (1H, d, ^2J = 11.3 Hz), 3.73 (1H, m), 3.77 (3H, s, OCH_3), 4.39 (1H, d, ^2J = 12.4 Hz), 4.62 (1H, d, ^2J = 12.4 Hz), 6.59 (1H, d, ^4J = 2.4 Hz), 6.73 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz), 7.16 (2H, d, ^3J = 8.4 Hz), 7.25 (1H, d, ^3J = 8.6 Hz), 7.40 (2H, d, ^3J = 8.4 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.8, 22.0, 22.5, 22.8, 26.2, 27.0, 29.3, 30.4, 34.2, 36.0, 42.7, 42.8, 47.3, 55.2, 69.9, 70.6, 72.6, 73.0, 108.5, 111.7, 114.3, 121.0, 126.6, 129.2, 131.1, 132.8, 134.9, 138.4, 157.5; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 557 (6.5) [$^{81}BrMH^+$], 555 (7.7) [$^{79}BrMH^+$], 385 (100).

3-O-Methyl 7α-methoxyestra-1,3,5(10)-trien-3-ol-17-one (**13a**): A solution of **12a** (49 mg, 0.12 mmol) and *p*-TsOH (10 mg, 0.052 mmol) in acetone (10 ml) was stirred at room temperature for 15 h. Then the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **13a** (38 mg, quant) as a colourless solid; m.p. 169°C ν_{max} (KBr)/cm^{-1} 3002, 2976, 1737, 1261, 1241; (Found: M^+, 314.1879. $C_{20}H_{26}O_3$ requires M, 314.1882); δ_H (270 MHz, $CDCl_3$) 0.89 (3H, s, CH_3), 1.48–2.52 (10H, m), 2.69 (1H, m), 2.87 (1H, dd, ^2J = 17.8 Hz, ^3J = 3.2 Hz), 3.17 (1H, d, ^2J = 17.8 Hz), 3.39 (3H, s, OCH_3), 3.69 (1H, m), 3.78 (3H, s, OCH_3), 6.65 (1H, d, ^4J = 2.4 Hz), 6.74 (1H, d, ^3J = 8.6 Hz), 7.23 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.6, 21.4, 26.0, 31.4, 32.9, 35.8, 36.3, 42.0, 45.8, 47.8, 55.2, 56.8, 74.2, 111.9, 114.5, 126.5, 131.6, 134.7, 157.7, 220.7 (CO); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 314 (41) [M^+], 282 (74).

3-O-Methyl 7α-propoxyestra-1,3,5(10)-trien-3-ol-17-one (**13b**): A solution of **12b** (75 mg, 0.175 mmol) and *p*-TsOH (13 mg, 0.068 mmol) in acetone (13 ml) was stirred at room temperature for 15 h. Then the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **13b** (60 mg, quant) as a colourless solid; (Found: M+, 342.2200; $C_{22}H_{30}O_3$ requires M, 342.2195); ν_{max} (KBr)/cm^{-1} 2978, 1735, 1261, 1241; δ_H (270 MHz, $CDCl_3$) 0.86 (3H, t, ^3J = 7.6 Hz, CH_3), 0.88 (3H, s, CH_3), 1.47–2.23 (12H, m), 2.76 (1H, m), 2.87 (1H, dd, ^2J = 17.8 Hz, ^3J = 3.8 Hz), 3.13 (1H, d, ^2J = 17.8 Hz), 3.27 (1H, dd, ^2J = 8.9 Hz, ^3J = 6.7 Hz), 3.62 (1H, dt, ^2J = 8.9 Hz, ^3J = 6.2 Hz), 3.76 (1H, m), 6.64 (1H, d, ^4J = 2.7 Hz), 6.73 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.7 Hz), 7.22 (1H, d, ^3J = 8.4 Hz); δ_C (67.8 MHz, $CDCl_3$) 10.7, 13.5, 21.4, 23.2, 25.9, 31.4, 33.7, 35.8, 36.1, 42.1, 45.8, 47.8, 55.2, 70.7, 72.4, 111.6, 114.4, 126.3, 131.9, 135.1, 157.6, 220.9; MS (EI, 70 eV) *m/z* (%) = 342 (23) [M^+], 282 (100).

3-O-Methyl 7α-pentoxyestra-1,3,5(10)-trien-3-ol-17-one (**13c**): A solution of **12c** (27 mg, 0.059 mmol) and *p*-TsOH (4.5 mg, 0.024 mmol) in acetone (4.5 ml) was stirred at room temperature for 15 h. Then the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **13c** (21 mg, 96%) as a colourless solid; m.p. 88°C; (Found: M^+, 370.2504. $C_{24}H_{34}O_3$ requires M, 370.2508); ν_{max} (KBr)/cm^{-1} 2978, 2860, 1735, 1240, 821; δ_H (270 MHz, $CDCl_3$) 0.78 (3H, t, ^3J = 6.5 Hz, CH_3), 0.81 (3H, s, CH_3), 1.17–2.48 (16H, m), 2.67 (1H, m), 2.80 (1H, dd, ^2J = 17.8 Hz, ^3J = 3.8 Hz), 3.05 (1H, d, ^2J = 17.8 Hz), 3.24 (1H, dt, ^2J = 8.9 Hz, ^3J = 7.0 Hz), 3.58 (1H, dt, ^2J = 8.9 Hz, ^3J = 6.2 Hz), 3.69 (1H, m), 3.71 (3H, s, OCH_3), 6.56 (1H, d, ^4J = 2.7 Hz), 6.66 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 7.15 (1H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.6, 14.1, 21.5, 22.5, 25.9, 28.5, 29.7, 31.4, 33.7, 35.9, 36.2, 42.1, 45.8, 47.8, 55.2, 69.0, 72.4, 111.7, 114.5, 126.4, 131.9, 135.2, 157.6, 221.0 (CO); MS (EI, 70 eV) *m/z* (%) = 370 (22) [M^+], 282 (100).

3-O-Methyl 7α-hexoxyestra-1,3,5(10)-trien-3-ol-17-one (**13d**): A solution of **12d** (115 mg, 0.24 mmol) and *p*-TsOH (18 mg, 0.097 mmol) in acetone (18 ml) was stirred at room temperature for 15 h. Then the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N 8 hexane/ether/$CHCl_3$ 4:1:1) gave **13d** as a colourless solid; (75 mg, 80%); m.p. 119°C; (Found: M^+, 384.2659. $C_{25}H_{36}O_3$ requires M, 384.2664); ν_{max} (KBr/cm^{-1}) 2926, 2855, 1739, 1212; δ_H (270 MHz, $CDCl_3$) 0.85 (3H, t, ^3J = 6.5 Hz), 0.88 (3H, s, CH_3), 1.24–2.49 (18H, m), 2.75 (1H, m), 2.87 (1H, dd, ^2J = 17.8 Hz, ^3J = 3.5 Hz), 3.13 (1H, d, ^2J = 17.8 Hz), 3.31 (1H, dt, ^2J = 9.2 Hz, ^3J = 6.8 Hz), 3.65 (1H, dt, ^2J = 9.2 Hz, ^3J = 6.5 Hz), 3.77 (1H, m), 3.78 (3H, s, OCH_3), 6.64 (1H, d, ^4J = 2.7 Hz), 6.73 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 7.22 (1H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.6, 14.0, 21.4, 22.6, 25.9 (2C), 29.9, 31.4, 31.6, 33.6, 35.8, 36.1, 42.0, 45.8, 47.8, 55.2, 69.0, 72.3, 111.6, 114.4, 126.4, 131.9, 135.1, 157.7, 221.0; MS (EI, 70 eV) *m/z* (%) = 384 (12) (M^+), 282 (100).

3-O-Methyl 7α-benzyloxyestra-1,3,5(10)-trien-3-ol-17-one (**13e**): A solution of **12e** (23 mg, 0.048 mmol) and *p*-TsOH (3.6 mg, 0.019 mmol) in acetone (3.6 ml) was stirred at room temperature for 15 h. Then the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **13e** (18 mg, 96%) as a colourless solid; m.p. 178°C; (Found: M^+, 390.2195. $C_{26}H_{30}O_3$ requires M, 390.2195); ν_{max} (KBr)/cm^{-1} 3010, 2928, 2853, 1739, 813; δ_H (270 MHz, $CDCl_3$) δ 0.85 (3H, s, CH_3), 1.45–2.48 (10H, m), 2.82 (1H, m), 2.91 (1H, dd, ^2J = 18.1 Hz, ^3J = 3.2 Hz), 3.20 (1H, d, ^2J = 18.1 Hz), 3.78 (3H, s, OCH_3), 3.88 (1H, m), 4.43 (1H, d, ^2J = 11.9 Hz), 4.73 (1H, d, ^2J = 11.9 Hz), 6.65 (1H, d, ^4J = 2.7 Hz), 6.74 (1H, dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz), 7.22–7.32 (6H, m); δ_C (67.8 MHz, $CDCl_3$) 13.6, 21.1, 25.9, 31.4, 36.6, 35.8, 36.2, 42.0, 45.7, 47.8, 55.2, 70.3, 71.4, 111.8, 114.5, 126.5, 127.6, 127.8 (2C), 128.3 (2C), 131.8, 134.8, 138.8, 157.6, 220.9 (CO); MS (EI, 70 eV) *m/z* (%) = 390 (12) [M^+], 370 (11), 299 (30), 282 (100).

3-O-Methyl-7α-(4-bromobenzyloxy)estra-1,3,5(10)-trien-3-ol-17-one (**13f**): A solution of **12f** (107 mg, 0.19 mmol) and *p*-TsOH (15 mg, 0.079 mmol) in acetone (15 ml) was stirred at room temperature for 15 h. Then the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **13f** (66 mg, 74%) as a colourless solid; m.p. 189°C; (Found: M^+, 468.1298. $C_{26}H_{29}O_2{}^{79}Br$ requires M, 468.1300); ν_{max} (KBr/cm^{-1}) 2924, 2852, 1739, 821; δ_H (270 MHz, $CDCl_3$) 0.87 (3H, s, CH_3), 1.47–2.50 (10H, m), 2.80 (1H, m), 2.92 (1H, dd, ^2J = 18.1 Hz, ^3J = 3.8 Hz), 3.17 (1H, d, ^2J = 18.1 Hz), 3.78 (3H, s, OCH_3), 3.88 (1H, m), 4.40 (1H, d, ^2J = 12.2 Hz), 4.66 (1H, d, ^2J = 12.2 Hz), 6.63 (1H, d, ^4J = 2.7 Hz), 6.75 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 7.14 (2H, d, ^3J = 8.4 Hz), 7.24 (1H, d, ^3J = 8.6 Hz), 7.43 (2H, d, ^3J = 8.4 Hz); δ_C (67.8 MHz, $CDCl_3$) 13.6, 21.2, 25.9, 31.4, 33.6, 35.7, 36.2, 42.1, 45.7, 47.8, 55.2, 69.7, 72.0, 111.8, 114.5, 121.3, 126.5, 129.2 (2C), 131.4 (2C), 131.7, 134.6, 137.9, 157.7, 220.7; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 470 (0.8) [$^{81}BrM^+$], 468 (0.76) [$^{79}BrM^+$].

3-O-Methyl-7α-(4-(4-methoxyphenyl)benzyloxy)estra-1,3,5(10)-trien-3-ol-17-one (**13g**): A mixture of **13f** (60 mg, 0.13 mmol), 4-methoxyphenylboronic acid (97 mg, 0.64 mmol), $Pd(PPh_3)_2Cl_2$ (9.0 mg, 1.28×10^{-5} mol) and triphenylphosphine (8 mg, 3.05×10^{-5} mol) in DME (3.0 ml) and aq. Na_2CO_3 (232 mg Na_2CO_3 in 1.5 ml H_2O) was kept at reflux for 24 h. Then the solution was diluted with water (30 ml) and extracted with chloroform (3 × 15 ml). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/$CHCl_3$/ether 2:1:1) to give **13g** (63 mg, 98%) as a colourless solid; m.p. 261°C; (Found: M^+, 496.2613. $C_{33}H_{36}O_4$ requires M, 496.2614); ν_{max} (KBr/cm^{-1}) 2924, 2852, 1739, 1300, 1275, 825; δ_H (270 MHz, $CDCl_3$) 0.85 (3H, s, CH_3), 1.48–2.48 (10H, m), 2.85 (1H, m), 2.94 (1H, dd, ^2J = 19.7 Hz, ^3J = 3.2 Hz), 3.23 (1H, d, ^2J = 19.7 Hz), 3.78 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.90 (1H, m), 4.46 (1H, d, ^2J = 12.5 Hz), 4.75 (1H, d, ^2J = 12.5 Hz), 6.65 (1H, d, ^4J = 2.4 Hz), 6.75 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz), 6.97 (2H, d, ^3J = 8.6 Hz), 7.24 (1H, d, ^3J = 8.4 Hz), 7.33 (2H, d, ^3J = 8.1 Hz), 7.50 (4H, 2d, ^3J = 8.4 Hz [2H], ^3J = 8.1 Hz [2H]); δ_C (67.8 MHz, $CDCl_3$) 13.6, 21.1, 25.9, 31.4, 33.7, 35.8, 36.2, 42.0, 45.7, 47.8, 55.2, 55.3, 70.1, 71.4, 111.8, 114.2 (2C), 114.5, 126.5, 126.6 (2C), 128.0 (2C), 128.3 (2C), 131.8, 133.3, 134.9, 137.2, 140.2, 157.6, 159.2, 220.8; MS (EI, 70 eV) *m/z* (%) = 496 (12) (M^+), 299 (100), 288 (83).

3-O-Methyl 7α-methoxy-17α-trimethylsilylethynylestra-1,3,5(10)-trien-3,17β-diol (**14**): To a solution of trimethylsilylacetylene (32 mg, 0.33 mmol) in dry THF (1 ml) was added at –78°C lithium diisopropylamide (solution in THF/ethylbenzene/heptanes, 2 M, 0.17 ml, 0.34 mmol), and the resulting mixture was stirred at –78°C for 30 min, thereafter 30 min at 0°C. Then, the reaction mixture was cooled again to –78°C and a solution of **13a** (35 mg, 0.11 mmol) in dry THF (1 ml) was added. The mixture was allowed to warm overnight (15 h). Then, NH_4Cl (2N, 10 ml) was added and the mixture was extracted with ether (3 × 50 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) to give **14** (41 mg, 90%) as a slowly crystallising, colourless solid; (Found: M^+, 412.2429. $C_{25}H_{36}O_3Si$ requires M, 412.2434); ν_{max} (neat/cm^{-1}) 3420, 2924, 2163, 1200; δ_H (270 MHz, $CDCl_3$) 0.19 (9H, s, $SiMe_3$), 0.85 (3H, s, CH_3), 1.37–2.47 (11H, m), 2.64 (1H, m), 2.85 (1H, dd, ^2J = 17.3 Hz, ^3J = 3.0 Hz), 3.10 (1H, d, ^2J = 17.3 Hz), 3.39 (3H, s, OCH_3), 3.55 (1H, m), 3.78 (3H, s, OCH_3), 6.64 (1H, d, ^4J = 1.8 Hz), 6.73 (1H, dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz), 7.24 (1H, d, ^3J = 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 0.0, 12.5, 22.7, 26.6, 32.7, 33.6, 36.1, 38.9, 43.1, 44.8, 47.3, 55.2, 57.2, 75.0, 80.1, 90.3, 109.5, 111.8, 114.4, 126.6, 132.0, 134.9, 157.6; MS (EI, 70 eV) *m/z* (%) = 412 (35) [M^+], 380 (100), 365 (36), 240 (80).

3-O-Methyl 7α-methoxy-17α-ethynylestra-1,3,5(10)-trien-3,17β-diol (**15**): To **14** (24 mg, 0.058 mmol) in THF (1 ml) was added tetrabutylammonium fluoride (TBAF, 30 mg, 0.115 mmol) at –10°C. The reaction mixture was stirred at rt for 2 h. Then ether (10 ml) was added, and the mixture was extracted with H_2O. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) to give **15** (20 mg, quant) as a colourless solid; m.p. 71°C; (Found: M^+, 340.2036. $C_{22}H_{28}O_3$ requires M, 340.2038); ν_{max} (KBr/cm^{-1}) 3460, 2965, 1261; δ_H (270 MHz, $CDCl_3$) 0.86 (3H, s, CH_3), 1.26–2.48 (11H, m), 2.62 (1H, s), 2.66 (1H, m), 2.84 (1H, dd, ^2J = 17.6 Hz, ^3J = 3.5 Hz), 3.11 (1H, d, ^2J = 17.6 Hz), 3.36 (3H, s, OCH_3), 3.55 (1H, m), 3.77 (3H, s, OCH_3), 6.63 (1H, d, ^4J = 2.7 Hz), 6.72 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 7.23 (1H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 12.4, 22.6, 26.6, 32.6, 33.3, 35.9, 38.9, 43.1, 44.8, 47.2, 55.2, 57.0, 74.3, 74.9, 79.8, 87.3, 111.8, 114.4, 126.6, 132.1, 134.9, 157.5; MS (EI, 70 eV) *m/z* (%) = 340 (37) [M^+], 308 (100).

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