Articles

11β-Substituted Estradiol Derivatives, Potential High-Affinity Carbon-11-Labeled Probes for the Estrogen Receptor: A Structure–Affinity Relationship Study

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In view of their possible development as carbon-11-labeled receptor-based radiotracers for imaging estrogen-responsive breast tumors, we have synthesized a series of estradiols (**1**), estriols (**2**), 11β-ethylestradiols (**3**), 11β-ethylestriols (**4**), 11β-methoxyestradiols (**5**), and 11β-methoxyestriols (**6**), differing in the type of substituent R present at the 17α-position (**a**, -H; **b**, $-CH_3$; **c**, -C≡CH; **d**, $-C{\equiv}CCH_3$; **e**, -Ph; **f**, -CH=CHMe cis), and measured their binding affinity for the estrogen receptor relative to estradiol (RBA). As expected, all the derivatives having an 11β-ethyl substituent have good binding properties (**3a–d**, **4a–d**, RBA (25 °C): 109–3000%), and among them there are several promising candidates for carbon-11 labeling. Moxestrol (RBA (25 °C) = 185%) and its corresponding estriol derivative (**4c**, RBA (25 °C) = 20%) were the analogs having the highest affinity in the 11β-methoxyestradiol (**5a–f**) and 11β-methoxyestriol (**6a–e**) series, respectively; other analogs (R = Me, C≡CMe, Ph, or *cis*-CH=CHMe) had uniformly lower RBA values.

Introduction

In the development of receptor-binding radiopharmaceuticals, suitable for imaging breast tumors and for the assessment of estrogen receptor levels in vivo, halogens (such as fluorine-18, bromine-77 and -84m, iodine-123 and -125) have been the radionuclides most frequently used.[1–4] This preference for radiohalogens reflects the ease with which they are produced and can be introduced into organic compounds. However, although halogenated estradiols include ligands for the estrogen receptor that have very high affinity, a number of them have shown only moderate stability in vivo, a factor which seriously limits their practical application.[1–4] More recently, technetium-99m, the most widely used radionuclide in nuclear medicine, has been investigated for labeling steroid receptor ligands, despite the difficult task of designing metal complexes that combine a high chemical stability with a high affinity for the receptor.[5] By contrast, surprisingly little use has been made of carbon-11,[6] despite its unique suite of characteristics in terms of (a) the quality of the radiation emitted (positron), (b) the availability of the chemical precursor and ease of its preparation in high specific activity, (c) the possibility of converting the radionuclide derivative into either electrophilic or nucleophilic reagents with consequent versatility in the labeling procedures, and (d) the stability of the bond between the radioactive label and the rest of the molecular probe. While the short half-life of carbon-11 ($t_{1/2}$ = 20 min) presents a challenge to the widespread use of this radionuclide, particularly in the labeling of complex molecules, rapid decay of radioactivity can be an attractive property in a radiopharmaceutical, if repeat injection protocols are required and there is concern about patient radiation exposure.

We wish to report here the results of a study of structure–affinity relationships encompassing the six groups of estradiol derivatives **1–6** (see Table 1), part of which were designed as high-affinity ligands for the estrogen receptor that could be readily labeled by reaction of an appropriate precursor with either [^{11}C]-methyl iodide or [^{11}C]methyllithium. Estradiols **1b,d** constitute probably the most straightforward choice of derivatives one can consider for the introduction of ^{11}C-methyl groups. Small groups in the 17α-position are known to be well tolerated, and with some of them enhanced binding affinities can even result.[1b] The methyl derivative **1b** is actually the only estradiol derivative which has already been radiolabeled in high specific activity with ^{11}C and used in a study of tissue distribution.[6]

The estriols **2b,d** were designed as in vivo receptor probes that might be endowed with better pharmacodynamic properties compared to the estradiols **1b,d**. When dealing with receptor-based imaging agents labeled with especially short-lived radionuclides such as carbon-11, a rapid clearance from the plasma and nontarget areas is crucial for contrast to develop between target and surrounding areas, during the useful lifetime of the radionuclide. From this point of view, estriols **2b,d** were expected to undergo a particularly rapid metabolic clearance, as the presence a 16α-hydroxy group provides a site for the direct conjugation

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with sulfuric or glucuronic acid (direct phase II metabolism),[7] thereby obviating the need for a preliminary oxidation step (phase I metabolism), which may be required for the clearance and elimination of derivatives of the parent estradiol. Pharmacokinetic studies of estrogens in humans have demonstrated that, compared to estradiol, the more polar estriol has a larger initial volume of distribution,[7] a greater metabolic clearance rate,[7] and a more rapid and complete urinary excretion.[8]

The rationale for choosing derivatives **3b,d** and **4b,d** bearing an 11β-ethyl group is that such a substituent (as well as other short carbon chains) generally imparts very good binding properties to estradiol derivatives.[9] Thus, it was expected that these compounds would be endowed with higher relative binding affinity (RBA) values than the corresponding 11β-unsubstituted estradiols 1 and **2** discussed above.

11β-Methoxy-substituted estradiols **5** and **6** are the class of compounds best represented in this study because the 11β-methoxy group provides an obvious site for the introduction of the ^{11}C-methyl group. Furthermore, the 11β-methoxy group, despite its moderate depressive effect on receptor binding, imparts to estradiol derivatives favorable properties by improving the selectivity of their uptake by target tissues.[10] Since the reduced binding due to an 11β-methoxy group can be largely compensated by introducing an ethynyl group in the 17α-position (moxestrol, **5c**, is actually a most powerful synthetic hormonal agent),[11] we sought in this study to find alternatives to the ethynyl group as an enhancer of receptor binding, with a 2-fold goal: (a) to improve further the binding properties of these estrogen derivatives and (b) to investigate alternatives to the 11-methoxy group as sites for an easy incorporation of a carbon-11 methyl group.

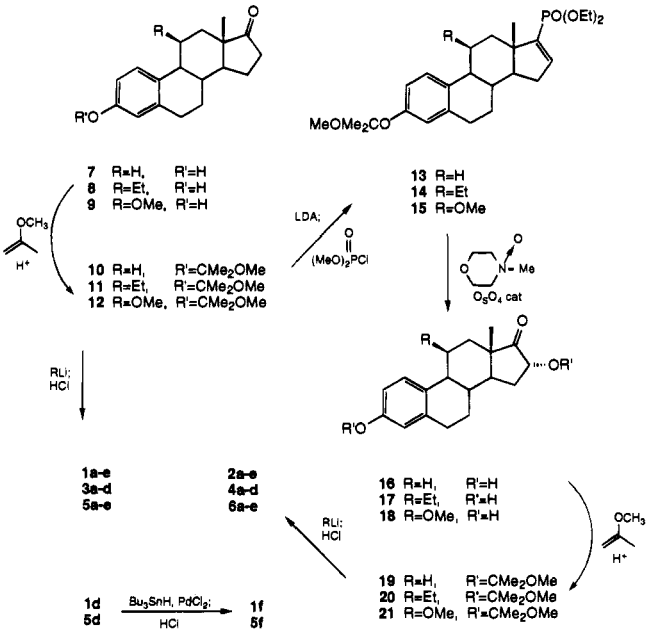
A number of the compounds in the series **1**–**6** are not amenable for labeling with a ^{11}C-methyl group in an obvious way. These were included in this study of structure–affinity relationships for sake of completeness, in order to provide us with a better understanding of how substituents introduced at positions 11β, 16α, and 17α affect the binding affinity of estradiol derivatives for the estrogen receptor.

Results and Discussion

Synthesis. Estrones **7**–**9** were the starting materials for the synthesis of compounds **1**–**6** (Scheme 1). 11β-Ethylestrone (**8**) was prepared by hydrogenation and hydrolysis of 11β-vinylestrone acetate.[12] 11β-Methoxyestrone (**9**) was prepared as reported.[13] Addition of 2-methoxypropene (benzene, picric acid) to the estrones **7**–**9** gave the corresponding crude O-protected derivatives **10**–**12**, which were allowed to react with the appropriate organometallic reagents to afford target estradiols **1b**–**e**, **3b**–**d**, and **5b**–**e**, respectively, after removal of the protecting group. Propenyl derivatives **1f** and **5f** were obtained from the corresponding propynyl derivative **1d** and **5d** by a two-step reduction involving palladium-catalyzed hydrostannation of the triple bond[14] followed by protolysis (hydrochloric acid in methanol) of the intermediate vinylstannane.

Elaboration of the estriol series **2**, **4**, and **6** required the introduction of a 16α-hydroxy into the D-ring of estrones **7**–**9**. The direct oxidation of the metal enolate from ketones **10**–**12** by means of currently employed

Scheme 1. Synthesis of Estrogen Derivatives **1**–**6**

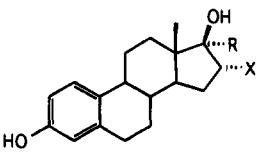


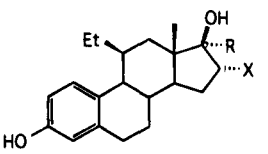
reagents (such as oxaziridine[15] or molybdenum peroxide[16]) gave unsatisfactory results (incomplete reaction, impure product). However, oxidation of the 16α-position was more efficiently accomplished by a two-step procedure consisting of the conversion of protected ketones **10**–**12** into the corresponding enol phosphates **13**–**15** (reaction with lithium diisopropylamide and quenching with diethyl chlorophosphate) followed by a standard dihydroxylation procedure (*N*-methylmorpholine *N*-oxide and osmium tetraoxide), as reported for similar substrates.[17] Because of their instability in the chromatographic purification, the mono-protected derivatives resulting from the above sequence were not isolated but directly deprotected to give hydroxyestrones **16**–**18**. Addition of 2-methoxypropene gave crude, fully protected hydroxyestrones **19**–**21**, which underwent reaction with the appropriate organometallic reagent to give (after removal of the O-protecting groups) target compounds **2a**–**e**, **4a**–**d**, and **6a**–**e**, respectively. The α stereochemistry at carbon-16 was verified on the basis of the appearance of the multiplet attributable to the 16-Hb[2a,17,18] in the ^{1}H-NMR spectrum.

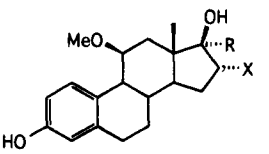
Receptor Binding Affinity. Table 1 summarizes the estrogen receptor binding data of the compounds prepared in this study, along with that for a few others obtained from the literature. Determination of these relative binding affinity (RBA) values was done with a radiometric competitive binding assay, as described previously.[19] Two clear trends can be recognized; all the rest being the same, (a) the binding affinity increases going from 11β-methoxy-substituted (**5**, **6**) to 11β-unsubstituted (1, **2**) to 11β-ethyl-substituted (**3**, **4**) derivatives and (b) estradiols (1, **3**, **5**) are better ligands than the corresponding estriols (**2**, **4**, **6**). In these series, at least, affinity is thus apparently directly related to the lipophilicity of the ligand.

Less consistent is the way substituents at the 17α-position modulate the RBA, as this seems to be also dependent on the nature of the group at 11β. Thus, with 11β-unsubstituted derivatives **1** and **2** and 11β-methoxyestradiols **5** and **6**, only the ethynyl group results in significant enhancement of binding. Other groups of

Table 1. Relative Binding Affinities (RBA) of Estradiol Derivatives 1–6 for the Estrogen Receptor of Lamb Uterine Cytosol at 0 and 25 °C[a]







			RBA			RBA			RBA	
X	R	compd	0 °C	25 °C	compd	0 °C	25 °C	compd	0 °C	25 °C
H	H	**1a**	100	100	**3a**	400	3000	**5a**	8	80
H	Me	**1b**	57	46	**3b**	83	1096	**5b**	6	28
H	C≡CH	**1c**	112	270	**3c**	88	946	**5c**	14	185
H	C≡CMe	**1d**	47	14	**3d**	66	562	**5d**	18	15
H	Ph	**1e**	30	5				**5e**	15	5
H	*cis*-CH=CHMe	**1f**	100	67				**5f**	26	26
OH	H	**2a**	21	5	**4a**	28	263	**6a**	1	1
OH	Me	**2b**	14	7	**4b**	85	434	**6b**	4	2
OH	C≡CH	**2c**	20	20	**4c**	79	177	**6c**	1	20
OH	C≡CMe	**2d**	5	0.5	**4d**	18	109	**6d**	0.8	0.5
OH	Ph	**2e**	8	1				**6e**	5	1.3

[a] Determined by methods previously described.[19]

varying size and steric hindrance have a generally deleterious effect on binding. Particularly interesting is the reduction in binding that results from homologation of the 17α-ethynyl group to a 1-propynyl group (compare the ***Xc*** and ***Xd*** compounds in each of the six series). Also, in contrast with the precedents for the good binding behavior of *cis*-2-halovinyl groups in the 17α-position,[1b] the presence of a *cis*-propenyl group has little positive effect on the binding.

When an ethyl group is present at the 11β-position (compounds **3** and **4**), introduction of groups at 17α invariably lowers the binding affinity, even in the case of the ethynyl group, which has a beneficial effect on the binding of the other two series (**1**, **2**, **5**, **6**). Although a cooperative effect on the binding might in principle be expected from these two groups, each of which alone is capable of significantly improving the binding of an estradiol derivative, their combined behavior is similar to that observed for substituents in 11β-vinyl-17α-(halovinyl)estradiols,[1b] which is the following: the binding affinity of 11β,17α-disubstituted estradiols is dominated by the group that, if present alone, would behave as a better enhancer of the binding; the other group, even if it enhances binding by itself, will counteract the effect of the first substitutent; as a consequence, the affinity of the disubstituted steroid is lower than that of the steroid with just the better substituent alone. The reason for this lack of cooperativity in the binding of the disubstituted estrogens is unclear. Regardless of the precise mechanism, the ethyl group at 11β is, however, such a strong promoter of the binding affinity that most of the other modifications required to provide a site for C-11 labeling (e.g., 17α-methyl) and pharmacodynamic enhancement (e.g., 16α-hydroxyl) can be introduced without causing the binding to drop to unacceptably low levels.

In conclusion, we have synthesized a number of estradiol and estriol derivatives through which we have begun to probe sites on the ligand structure where substitutents may effect an increase in binding affinity or provide a site for facile steroid conjugation and clearance. Among the compounds studied are those which constitute promising candidates as high-affinity receptor-based imaging agents to be labeled by incorporation of a carbon-11 methyl group. Further work is continuing with the specific compounds 11β-ethyl-17α-methylestradiol (**3b**) and 11β-ethyl-17α-propynylestradiol (**3d**) and the corresponding estriols **4b**,**d**, as these compounds combine high affinity for the estrogen receptor and/or direct phase II metabolism and clearance, with potential sites for facile radiolabeling with carbon-11.

Experimental Section

Chemical Synthesis. General. Melting points were taken with either a Hoover capillary melting point apparatus or a Kofler hot plate apparatus and are uncorrected. For analytical thin-layer chromatography, Merck silica gel F-254 glass-backed plates were used; for the visualization of the spots, the plates were soaked with an ethanol solution containing phosphomolybdic acid (5%) and sulfuric acid (5%) and heated by means of a heat gun. For column chomatography, the technique described by Still was adopted using, unless otherwise stated, mixtures of hexane (H) and ethyl acetate (EA) as eluants.[20] ^{1}H NMR (200 MHz) spectra were obtained using either a Varian XL200 or a Bruker AC200 instrument; chemical shifts (δ) are relative to tetramethylsilane as internal standard. High-resolution electron impact mass spectra (HREIMS) were obtained with a Varian MAT 731 mass spectrometer. All the reactions involving organometallic reagents were performed under nitrogen in solvents distilled from sodium benzophenone ketyl.

Compounds **1a**,**c**, **2a**, and **7** were purchased from Sigma. Compound **8** was synthesized from 11β-vinylestrone acetate[12] by catalytic hydrogenation (PtO_2) followed by removal of the acetyl group in methanolic NaOH. Compound **9** was obtained as reported.[2a,c] 17α-Unsubstituted estradiol derivatives **4a** and **6a** were obtained from the corresponding 17-ketones by reduction with sodium borohydride. RBA data of compounds **3a**,**c** and **5a** were taken from the literature.[2c]

General Conditions for the Conversion of Estrones (7–9) and 16α-Hydroxyestrones (16–18) to the Respective O-Protected Derivatives (10–12, 19–21). A mixture containing the estrone derivative (10 mmol), picric acid (a few crystals), and 2-methoxypropene (10 mL; added after picric acid had been dissolved) in benzene (100 mL) was heated at 50 °C with rapid stirring in a stoppered flask until the starting material was completely consumed. Triethylamine (a few drops) was added; the mixture was diluted with ether and filtered through a short pad of silica gel. The eluate, once evaporated, left a residue of crude product which was carried on to the subsequent step without further purification.

3-[(2-Methoxy-2-propyl)oxy]estra-1,3,5(10)-trien-17-

one (10): oil which solidified on standing; mp 124–125 °C; ^{1}H-NMR ($CDCl_3$) δ 0.91 (s, 3H, 18-H), 1.47 (s, 6H, CMe_2), 2.89 (m, 2H), 3.41 (s, 3H, OMe), 6.82 (d, J = 2.5 Hz, 1H, 4-H), 6.90 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.17 (d, J = 8.5 Hz, 1H, 1-H).

11β-Ethyl-3-[(2-methoxy-2-propyl)oxy]estra-1,3,5(10)-trien-17-one (11): oil which solidified on standing; mp 98–100 °C; ^{1}H-NMR ($CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.02 (s, 3H, 18-H), 1.45 (s, 6H, CMe_2), 3.41 (s, 3H, OMe), 6.78 (d, J = 2.5 Hz, 1H, 4-H), 6.87 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.02 (d, J = 8.5 Hz, 1H, 1-H).

11β-Methoxy-3-[(2-methoxy-2-propyl)oxy]estra-1,3,5(10)-trien-17-one (12): oil, ^{1}H-NMR ($CDCl_3$) δ 1.10 (s, 3H, 18-H), 1.47 (s, 6H, CMe_2), 3.31 (s, 3H, 11-OMe), 3.40 (s, 3H, CMe_2OMe), 4.22 (m, 1H, 11-H), 6.83 (d, J = 2.5 Hz, 1H, 4-H), 6.92 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.03 (d, J = 8.5 Hz, 1H, 1-H).

3,16α-Bis[(2-methoxy-2-propyl)oxy]estra-1,3,5(10)-trien-17-one (19): oil which solidified on standing; mp 128–130 °C; ^{1}H-NMR ($CDCl_3$) δ 0.97 (s, 3H, 18-H), 1.36 and 1.43 (s, 2 × 3H, 16-$OCCMe_2$), 1.47 (s, 6H, 3-$OCMe_2$), 2.85 (m, 2H), 3.34 and 3.40 (s, 2 × 3H, CMe_2OMe), 4.50 (d, J = 8 Hz, 1H, 16-H), 6.81 (d, J = 2.5 Hz, 1H, 4-H), 6.89 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.14 (d, J = 8.5 Hz, 1-H).

11β-Ethyl-3,16α-bis[(2-methoxy-2-propyl)oxy]estra-1,3,5(10)-trien-17-one (20): glass; ^{1}H-NMR ($CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.10 (s, 3H, 18-H), 1.36 and 1.42 (s, 2 × 3H, 16-$OCCMe_2$), 1.46 (s, 6H, 3-$OCMe_2$), 3.34 and 3.41 (s, 2 × 3H, CMe_2OMe), 4.56 (d, J = 8 Hz, 1H, 16-H), 6.77 (d, J = 2.5 Hz, 1H, 4-H), 6.88 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.02 (d, J = 8.5 Hz, 1-H).

11β-Methoxy-3,16α-bis[(2-methoxy-2-propyl)oxy]estra-1,3,5(10)-trien-17-one (21): glass; ^{1}H-NMR ($CDCl_3$) δ 1.17 (s, 3H, 18-H), 1.36 and 1.42 (s, 2 × 3H, 16-$OCCMe_2$), 1.46 (s, 6H, 3-$OCMe_2$), 3.30, 3.34, 3.39 (s, 3 × 3H, OMe), 4.20 (m, 1H, 11-H), 4.54 (d, J = 8.5 Hz, 1H, 16-H), 6.81 (d, J = 2.5 Hz, 1H, 4-H), 6.91 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.02 (d, J = 8.5 Hz, 1-H).

General Conditions for the Oxidation of Protected Estrones 10–12 to the Corresponding Hydroxyestrones 16–18. The transformation was accomplished in two steps, namely: conversion of the 17-ketone into its enol phosphate followed by oxidation with osmium tetraoxide and *N*-methylmorpholine *N*-oxide, as decribed for analogus substrates.[17] The protected estrone (10 mmol) was added to a cooled (−78 °C) THF solution (20 mL) of lithium diisopropylamide obtained by combining diisopropylamine (3 mL, 20 mmol) and 1.6 M butyllithium in hexane (10 mL). After 1 h, diethyl chloroformate (2.75 g, 2.35 mL, 16 mmol) was added and the reaction mixture was allowed to warm to room temperature and then partitioned between ethyl acetate and a saturated solution of sodium bicarbonate. The organic phase was dried over sodium carbonate and evaporated to afford crude enol phosphate, which was used in the subsequent step without further purification.

Compound 13: ^{1}H-NMR ($CDCl_3$) δ 5.25 (m, 1H, 16-H), 0.95 (s, 3H, 18-H).

Compound 14: ^{1}H-NMR ($CDCl_3$) δ 5.19 (m, 1H, 16-H), 1.12 (s, 3H, 18-H).

Compound 15: ^{1}H-NMR ($CDCl_3$) δ 5.23 (m, 1H, 16-H), 1.18 (s, 3H, 18-H).

The enol phosphate from the above step was dissolved in acetone (20 mL) containing *N*-methylmorpholine *N*-oxide (1.5 g) and osmium tetraoxide (0.5 mL of a 2.5 M solution in *tert*-butyl alcohol). The mixture was monitored until the starting material was consumed and then acidified by addition of 1 M methanolic HCl. After 10 min of stirring, the mixture was partitioned between ethyl acetate and brine. The organic phase was washed with 10% sodium hydrogen carbonate solution, dried over magnesium sulfate, and evaporated to afford a residue from which hydroxyestrones **16** (mp 241–245 °C (lit.[21] mp 221–226 °C)), **17** (mp 205–208 °C (lit.[2d] mp 200–202 °C)), and **18** (mp 241–243 °C (lit.[2c] mp 250 °C)) were obtained by chromatography.

General Conditions for the Preparation of 17α-Substituted Estradiol Derivatives (Xb–e) by Addition of Carbon Nucleophiles to Protected Estrones 10–12 or 19–21. The appropriate carbon nucleophile was added to a solution of the protected estrone **10–12**, or **19–21** (1 mmol) in THF (20 mL) at −78 °C. Methyllithium in ether (0.5 M, 2-fold excess) was used for compounds **1b–6b**; solid lithium acetylide ethylenediamine complex (10-fold excess) was used to obtain compounds **1c–6c**; 1-lithio-1-propyne (4-fold excess), used to prepare compounds **1d–6d**, was generated by mixing 2-bromopropene and lithium diisopropylamide (2 equiv) in THF at −78 °C and allowing the mixture to react for 20 min at room temperature; phenyllithium (2 M in cyclohexane/ether) was used to obtain compounds **1e**, **5e**, **2e**, and **6e**. After the addition of the organometallic reagent, the reaction mixture was allowed to warm to the room temperature, and after 3 h, it was partitioned between ethyl acetate and 10% sodium bicarbonate. The organic phase was washed with water, evaporated to afford the crude addition product which was dissolved in methanol (20 mL) containing a few drops of acetyl chloride, and allowed to react until the starting material was converted to a more polar compound. The reaction mixture was partitioned between ethyl acetate and 10% aqueous bicarbonate; the organic phase was washed with water and evaporated to afford a residue from which the desired compound was obtained by chromatography.

17α-Methylestra-1,3,5(10)-triene-3,17β-diol (1b): mp 185–188 °C (lit.[22] mp 188–90 °C).

17α-(1-Propynyl)estra-1,3,5(10)-triene-3,17β-diol (1d): mp 130–134 °C (lit.[23] mp 134 °C).

17α-Phenylestra-1,3,5(10)-triene-3,17β-diol (1e): mp 216–218 °C (lit.[24] mp 225 °C).

17α-(*cis*-1-Propenyl)estra-1,3,5(10)-triene-3,17β-diol (1f). The compound was obtained in two steps consisting of palladium-catalyzed addition of tributylstannane to the triple bond[14] followed by protolysis. Thus, to a THF (3 mL) solution containing **1d** (24 mg, 0.07 mmol) and $PdCl_2(PPh_3)_2$ (4 mg), stirred in an ice bath under nitrogen, was added a solution of tributylstannane (76 mg, 70 mL, 0.35 mmol) in THF (1 mL) over 30 min. The solvent was evaporated, and the residue was chromatographed (H/EA, 7:3) to give 17α-[(2-(tributylstannyl)-*cis*-1-propenyl)estra-1,3,5(10)-triene-3,17β-diol as an oil: ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 9H, $Sn(CH_2)_3CH_3$), 0.93 (s, 3H, 18-H_3), 2.12 (d, J = 2.5 Hz, 3H, CH=C(Sn)CH_3), 5.68 (m, $J_{H\text{-}Sn}$ = 76 Hz, 1H, CH=C(Sn)CH_3), 6.56 (d, J = 2.5 Hz, 1H, 4-H), 6.63 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.16 (d, J = 8.5 Hz, 1H, 1-H).

A methanol solution of the above stannane (3 mL) was mixed with a solution obtained by dissolving acetyl chloride (20 mL) in methanol (2 mL), and the reaction was monitored by TLC (H/EA, 6.5:3.5) until the starting material was consumed (30 min). The solution was then partitioned between ethyl acetate and sodium bicarbonate; the organic phase was washed with brine, dried over magnesium sulfate, and evaporated to give a residue from which **1f** (16 mg, 75%) was obtained by chromatography (H/EA, 6.5:3.5): mp 149–150 °C; ^{1}H-NMR ($CDCl_3$) δ 0.93 (s, 3H, 18-H_3), 1.86 (d, J = 5.3 Hz, 3H, CH=CHCH_3), 5.50–5.70 (m, 2H, CH=CHCH$_3$), 6.56 (d, J = 2.5 Hz, 1H, 4-H), 6.61 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.28 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{21}H_{28}O_2$ 312.2089, found 312.2088.

17α-Methylestra-1,3,5(10)-triene-3,16α,17β-triol (2b): mp 275 °C; ^{1}H-NMR ($CDCl_3$/DMSO-d_6) δ 0.91 (s, 3H, 18-H), 1.21 (s, 3H, 17-Me), 4.29 (dd, J = 5 and 11.5 Hz, 1H, 16-H), 6.56 (d, J = 2.5 Hz, 1H, 4-H), 6.63 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.09 (d, J = 8.5 Hz, 1H, 1-H); HRMS (EI) calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1882.

17α-Ethynylestra-1,3,5(10)-triene-3,16α,17β-triol (2c): mp 235–237 °C dec; ^{1}H-NMR ($CDCl_3$/DMSO-d_6) δ 0.91 (s, 3H, 18-H), 2.77 (m, 2H), 4.28 (dd, J = 3 and 8 Hz, 1H, 16-H), 6.57 (d, J = 2.5 Hz, 1H, 4-H), 6.64 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.10 (d, J = 8.5 Hz, 1H, 1-H); HRMS (EI) calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1736.

17α-(1-Propynyl)estra-1,3,5(10)-triene-3,16α,17β-triol (2d): mp 240–243 °C; ^{1}H-NMR ($CDCl_3$/DMSO-d_6) δ 0.89 (s, 3H, 18-H), 1.97 (s, 3H, C≡CMe), 4.21 (dd, J = 4 and 8 Hz, 1H, 16-H), 6.57 (d, J = 2.5 Hz, 1H, 4-H), 6.64 (dd, J = 2.5 and

8.5 Hz, 1H, 2-H), 7.10 (d, J = 8.5 Hz, 1H, 1-H); HRMS (EI) calcd for $C_{21}H_{26}O_3$ 326.1882, found 326.1889.

17α-Phenylestra-1,3,5(10)-triene-3,16α,17β-triol (2e): mp 217–220 °C dec; ^{1}H-NMR ($CDCl_3$/DMSO-d_6) δ 0.57 (dt, J_d = J_t = 10 Hz, 1H, 12a-H), 1.08 (s, 3H, 18-H), 4.76 (dd, J = 4 and 11 Hz, 1H, 16-H), 6.51–6.60 (m, 2H, 2-H and 4-H), 6.95 (d, J = 8.5 Hz, 1H, 1-H); HRMS (EI) calcd for $C_{24}H_{28}O_3$ 364.2038, found 364.2048.

11β-Ethyl-17α-methylestra-1,3,5(10)-triene-3,17β-diol (3b): mp 241–244 °C; ^{1}H-NMR (acetone-d_6) δ 0.87 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.02 (s, 3H, 18-H), 1.24 (s, 3H, 17-Me), 6.50 (d, J = 2.5 Hz, 1H, 4-H), 6.60 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.99 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{21}H_{30}O_2$ 314.2246, found 314.2249.

11β-Ethyl-17α-(1-propynyl)estra-1,3,5(10)-triene-3,17β-diol (3d): mp 115 °C; ^{1}H-NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.00 (s, 3H, 18-H), 1.88 (s, 3H, C≡CMe), 6.54 (d, J = 2.5 Hz, 1H, 4-H), 6.64 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.04 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{20}H_{30}O_2$ 338.2246, found 338.2248.

11β-Ethylestra-1,3,5(10)-triene-3,16α,17β-triol (4a): mp 138–140 °C; ^{1}H-NMR (methanol-d_6) δ 0.90 (t, J = 7.3 Hz, 3H, CH_2CH_3), 0.92 (s, 3H, 18-H), 3.43 (d, J = 5 Hz, 1H, 17-H), 4.03 (dd, J = 5 and 7.5 Hz, 1H, 16-H), 6.46 (d, J = 2.5 Hz, 1H, 4-H), 6.55 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.95 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2040.

11β-Ethyl-17α-methylestra-1,3,5(10)-triene-3,16α,17β-triol (4b): mp 257–259 °C; ^{1}H-NMR (methanol-d_6) δ 0.88 (s, 3H, 18-H), 0.90 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.18 (s, 3H, 17-Me), 4.08 (dd, J = 5 and 9 Hz, 1H, 16-H), 6.46 (d, J = 2.5 Hz, 1H, 4-H), 6.56 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.96 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{21}H_{30}O_3$ 330.4714, found 330.4715.

11β-Ethyl-17α-ethynylestra-1,3,5(10)-triene-3,16α,17β-triol (4c): mp 193–195 °C; ^{1}H-NMR (methanol-d_6) δ 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.04 (s, 3H, 18-H), 2.76 (s, 3H, C≡CH), 4.44 (d, J = 9 Hz, 1H, 16-H), 6.45 (d, J = 2.5 Hz, 1H, 4-H), 6.55 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.97 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2039.

11β-Ethyl-17α-(1-propynyl)estra-1,3,5(10)-triene-3,16α,-17β-triol (4d): ^{1}H-NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.05 (s, 3H, 17-Me), 1.98 (s, 3H, C≡CMe), 2.50–2.80 (m, 3H), 4.24 (m, 1H, 16-H), 6.54 (d, J = 2.5 Hz, 1H, 4-H), 6.64 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.03 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2196.

11β-Methoxyestra-1,3,5(10)-triene-3,17β-diol (5a): mp 240 °C (lit.[25] mp 245–246 °C).

11β-Methoxy-17α-methylestra-1,3,5(10)-triene-3,17β-diol (5b): mp 219–223 °C; ^{1}H-NMR ($CDCl_3$/DMSO-d_6) δ 1.09 (s, 3H, 18-H), 1.26 (s, 3H, 17-Me), 2.19 (dd, J = 2.5 and 14 Hz, 1H), 2.36 (bd, J = 10 Hz, 1H), 3.28 (s, 3H, OMe), 4.17 (m, 1H, 11-H), 6.56 (d, J = 2.5 Hz, 1H, 4-H), 6.66 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.97 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{20}H_{28}O_3$ 316.2034, found 316.2039.

11β-Methoxy-17α-ethynylestra-1,3,5(10)-triene-3,17β-diol (moxestrol, 5c): mp 275 °C (lit.[25] mp 280 °C).

11β-Methoxy-17α-(1-propynyl)estra-1,3,5(10)-triene-3,17β-diol (5d): mp 280 °C; ^{1}H-NMR (methanol-d_6) δ 0.98 (s, 3H, 18-H_3), 1.10–1.60 (m, 2H), 1.82 (s, 3H, C≡CCH_3), 2.55–2.90 (m, 2H), 3.25 (s, 3H, OCH_3), 4.21 (m, 1H, 11-H), 6.46 (d, J = 2.5 Hz, 1H, 4-H), 6.55 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.00 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{22}H_{30}O_3$ 342.2194, found 342.2193.

11β-Methoxy-17α-phenylestra-1,3,5(10)-triene-3,17β-diol (5e): mp 264–265 °C dec; ^{1}H-NMR ($CDCl_3$) δ 0.47 (dd, J = 3 and 14 Hz, 1H, 12a-H), 1.30 (s, 3H, 18-H), 3.27 (s, 3H, OMe), 3.92 (s, 3H, OMe), 6.50 (d, J = 2.5 Hz, 1H, 4-H), 6.57 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.85 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{25}H_{30}O_3$ 378.2194, found 378.2196.

11β-Methoxy-17α-(*cis*-1-propenyl)estra-1,3,5(10)-triene-3,17β-diol (5f): mp 216–218 °C; ^{1}H-NMR ($CDCl_3$) δ 1.14 (s, 3H, 18-H_3), 1.88 (d, J = 5.3 Hz, 3H, CH=$CHCH_3$), 2.24 (dd, J = 2 and 14 Hz, 1H), 2.35 (d, J = 10 Hz, 1 H), 2.63–2.98 (m, 2H), 3.30 (s, 3H, OCH_3), 4.16 (m, 1H, 11-H), 5.50–5.70 (m, 2H, CH=$CHCH_3$), 6.51 (d, J = 2.5 Hz, 1H, 4-H), 6.60 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.99 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{22}H_{30}O_3$ 342.2194, found 342.2193.

The compound was obtained from **5e**, as described for the conversion of **1e** into **1f**, by a two-step sequence involving the palladium-catalyzed addition of tributyltin hydride to the triple bond followed by protolysis in methanolic hydrochloric acid of the intermediate 17α-[2-(tributylstannyl)-*cis*-1-propenyl]-estra-1,3,5(10)-triene-3,17β-diol: oil; ^{1}H-NMR ($CDCl_3$) δ 0.87 (t, 12H, $Sn(CH_2)_3CH_3$ and 18-H), 2.14 (d, J = 2.5 Hz, 3H, CH=C(Sn)CH_3), 2.63–2.98 (m, 2H), 3.26 (s, 3H, OCH_3), 4.16 (m, 1H, 11-H), 5.63 (d, $J_{H\text{-}H}$ = 1.5 Hz, $J_{H\text{-}Sn}$ = 78 Hz, 1H, CH=C(Sn)CH_3), 6.48 (d, J = 2.5 Hz, 1H, 4-H), 6.55 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.97 (d, J = 8.5 Hz, 1H, 1-H).

11β-Methoxyestra-1,3,5(10)-triene-3,16α,17β-triol (6a): mp 218–223 °C (lit.[25] mp 228 °C).

11β-Methoxy-17α-methylestra-1,3,5(10)-triene-3,16α,-17β-triol (6b): mp 254–256 °C; ^{1}H-NMR ($CDCl_3$/DMSO-d_6) δ 0.91 (s, 3H, 18-H), 1.17 (s, 3H, 17-Me), 3.28 (s, 3H, OMe), 4.09 (m, 1H, 16-H), 4.19 (m, 1H, 11-H), 6.55 (d, J = 2.5 Hz, 1H, 4-H), 6.64 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.97 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{20}H_{28}O_4$ 332.1987, found 332.1974.

11β-Methoxy-17α-(1-ethynyl)estra-1,3,5(10)-triene-3,16α,-17β-triol (6c): mp 216–217 °C; ^{1}H-NMR (methanol-d_4) δ 1.07 (s, 3H, 18-H), 2.29 (dd, J = 2.5 and 11.5 Hz, 1H), 2.35–2.45 (m, 1H), 2.65–2.75 (m, 2H), 3.04 (s, 1H, C≡CH), 3.27 (s, 3H, OMe), 4.23 (m, 2H, 16-H and 11-H), 6.48 (d, J = 2.5 Hz, 1H, 4-H), 6.58 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.00 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1830.

11β-Methoxy-17α-(1-propynyl)estra-1,3,5(10)-triene-3,16α,17β-triol (6d): mp 217–221 °C dec; ^{1}H-NMR ($CDCl_3$) δ 1.12 (s, 3H, 18-H), 1.98 (s, 3H, C≡CMe), 2.29 (dd, J = 2.5 and 14 Hz, 1H), 2.45 (bd, J = 9 Hz, 1H), 2.65–2.98 (m, 2H), 3.29 (s, 3H, OMe), 4.15–4.29 (m, 2H, 16-H and 11-H), 6.53 (d, J = 2.5 Hz, 1H, 4-H), 6.64 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 7.00 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{22}H_{28}O_4$ 356.1987, found 356.1989.

11β-Methoxy-17α-phenylestra-1,3,5(10)-triene-3,16α,-17β-triol (6e): mp 270 °C; ^{1}H-NMR ($CDCl_3$/DMSO-d_6) δ 0.41 (dd, J = 3 and 14 Hz, 1H, 12a-H), 1.32 (s, 3H, 18-H), 3.22 (s, 3H, OMe), 3.87 (m, 1H, 11-H), 4.76 (dd, J = 4 and 11 Hz, 1H, 16-H), 6.51 (d, J = 2.5 Hz, 1H, 4-H), 6.57 (dd, J = 2.5 and 8.5 Hz, 1H, 2-H), 6.78 (d, J = 8.5 Hz, 1H, 1-H); HREIMS calcd for $C_{25}H_{30}O_4$ 394.2144, found 394.2149.

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