Novel Stereoselective Synthesis of 11β-Carbon-Substituted Estradiol Derivatives

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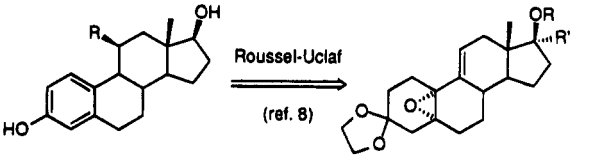
Estradiol derivatives of general structure **1** encompass a variety of interesting and valuable compounds. Those bearing small carbon substituents at the 11β-position (R = ethyl,[1] chloromethyl,[2] vinyl[3]) are the best known ligands for the estrogen receptor, their affinity being more then 10 times higher than that of estradiol, the natural ligand. Thus, in the design of estradiol derivatives designed as probes for the estrogen receptor, the inclusion of one of such groups (particularly the ethyl and chloromethyl) is often used to secure high binding affinities.[4,5] In fact, the specific structural modifications of the estradiol molecule that are needed to incorporate suitable kinds of labels (radioactive, fluorescent, or photoaffinity) and to impart a favorable metabolism typically have a deleterious effect on the binding affinity of the probe. Also, appropriate substitution at the 11β-position results in compounds endowed with pure antiestrogenic activity.[6]

Except for the case of the chloromethyl derivative, which is elaborated *via* the hydroboration of an 11-methylene group,[7] the stereospecific introduction of 11β-carbon substituents is presently limited to the copper-catalyzed conjugate addition of organometallic reagents to vinyloxyrane **2**.[8] Although it has proved to be wide in scope, this approach suffers from a number of problems: (a) It is quite lengthy when commercially available estradiol 3-methyl ether is the starting material, if one considers that most of the steps required to achieve the functionalization at C(11) involve the destruction and the reconstruction of the aromaticity of ring A. (b) The key intermediate **2** is not very stable, and (c) it is obtained by oxidation of the corresponding diene by a process which is not completely stereoselective.[9] Finally, (d) the method gave particularly poor results when we tried to open **2** with a variety of stannylvinyl cuprate reagents, in an attempt to obtain 11β-alkynylestradiol **1a**.[10] In the



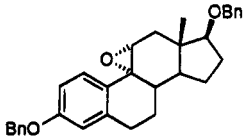
1 **2**

hopes of finding a more direct and convenient approach, we set out to introduce 11β-carbon substituents into estradiol by manipulating only ring C functionality and starting from derivatives with an aromatic ring A.

We report here on a novel approach to 11β-carbon-substituted estradiols, which is particularly well-suited for the introduction of unsaturated substituents. It involves the addition of lithium or Grignard reagents to the 11-carbonyl group of an estradiol derivative, followed by the stereoselective deoxygenation of the resulting 11-hydroxy steroids by means of an ionic hydrogenation.

Results and Discussion

Because of the presence of the 18-methyl group, the approach of nucleophiles to the 11-position from the β face is quite difficult when dealing with estranes. This was apparent from our many unsuccessful attempts to induce the opening of the unstable 9α,11α-epoxide derivative **3** with a variety cuprate reagents and to displace an 11α-sulphonate group from **4** (R = Me or Ph) by acetylides.



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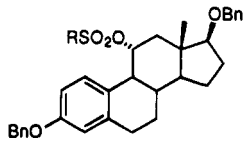

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Ionic hydrogenation is an effective method to reduce, under acidic conditions, tertiary carbinols, which could not be attacked by any nucleophilic hydride source.[11] Ionic hydrogenation has already been used in the stereoselective reduction of hydroxylated and unsaturated estradiol derivatives.[12] On the basis of these precedents, we envisaged that 11-hydroxy derivatives, bearing an additional carbon substituent at the 11-position capable of stabilizing a carbocation, would be ideal substrates for ionic hydrogenation. Concerning the stereochemical outcome of the reduction, we expected that the approach of the hindered trialkylsilane to the 11-carbocation would

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(1) Pomper, M. G.; VanBrocklin, H.; Thieme, A. M.; Thomas, R. D.; Kiesewetter, D. O.; Carlson, K. E.; Mathias, C. J.; Welch, M. J.; Katzenellenbogen. J. A. *J. Med. Chem.* **1990**, *33*, 3143–3155.

(2) (a) Bindal, R. D.; Carlson, K. E.; Reiner, G. C. A.; Katzenellenbogen, J. A. *J. Steroid Biochem.* **1987**, *28*, 361–370. (b) Sasson, S.; Katzenellenbogen, J. A. *J. Steroid Biochem.* **1989**, *33*, 859–865.

(3) Hanson, R. N.; Napolitano, E.; Fiaschi, R. *J. Med. Chem.* **1990**, *33*, 3155–3160.

(4) Top, S.; Vessieres, A.; Jaouen, G. *J. Chem. Soc., Chem. Commun.* **1994**, 453–454.

(5) Napolitano, E.; Fiaschi, R.; Carlson, K. E.; Katzenellenbogen J. A. *J. Med. Chem.* **1995**, *38*, 429.

(6) (a) Nique, F.; Van De Velde, P.; Brémaud, J.; Hardy, M.; Philibert, D.; Teutsch, G. *J. Steroid Biochem. Mol. Biol.* **1994**, *50*, 609. (b) Claussner, A.; Nedelec, L.; Nique, F.; Philibert, D.; Teutsch, G.; Van De Velde, P. *J. Steroid Biochem. Mol. Biol.* **1992**, *41*, 609. (c) Maudelonde, T. *Ann. Endocrinol.* **1991**, *52*, 387.

(7) (a) Zeicher, M.; Quivy, J. Eur. Pat. Appl. EP 365421 A1 900425 *Chem. Abstr.* **1991**, *114*, 139123. (b) Ratajczak, T.; Atrache, V.; Antes, P.; Comber, M.; Hähnel, R. *Steroids* **1988**, *51*, 499–518. (c) Van den Broek, A. J.; Leemhuis, J.; De Winter, M. S.; Zeelen, F. J. *Pharm. Weekbl., Sci. Ed.* **1983**, *5*, 182–183.

(8) (a) Teutsch, G.; Belanger, A. *Tetrahedron Lett.* **1979**, 2051–2054. (b) Teutsch, G.; Belanger, A.; Philibert, D.; Tournemine, C. *Steroids* **1982**, *39*, 607. (c) Teutsch, G. *Tetrahedron Lett.* **1982**, *23*, 4697–4700. (d) Belanger, A.; Philibert, D.; Teutsch, G. *Steroids* **1981**, *37*, 361. For a recent synthesis of 11β-ethynylestranes, which is not amenable for the synthesis of estradiols in an obvious way, see: Ottow, E.; Rohde, R.; Schwede, W.; Wiechert, R. *Tetrahedron Lett.* **1993**, *34*, 5253–5256. Schwede, W.; Cleve, A.; Ottow, E.; Wiechert, R. *Tetrahedron Lett.* **1993**, *34*, 5257–5260.

(9) Napolitano, E.; Fiaschi, R.; Hanson, R. *Gazz. Chim. Ital.* **1990**, *120*, 323.

(10) Napolitano, E.; Fiaschi, R.; Carlson, K. E.; Katzenellenbogen J. A. *J. Med. Chem.*, submitted for publication.

(11) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651.

(12) (a) Peters, R. H.; Crowe, D. F.; Avery, M. A.; Chong, W. K. M.; Tanabe, M. *J. Med. Chem.* **1989**, *32*, 2306–2310. (b) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239–1244.

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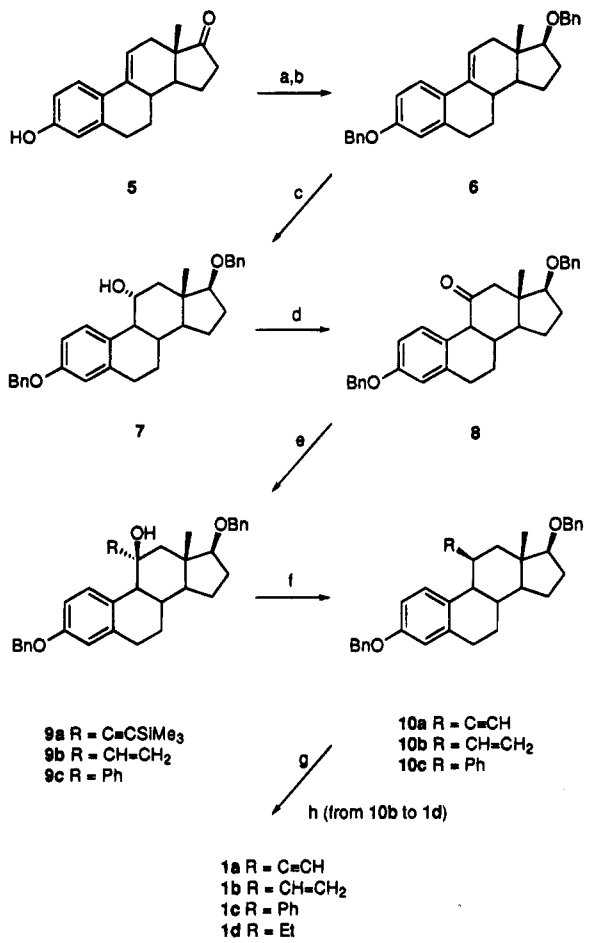
Scheme 1



[a] Key: (a) $NaBH_4$, MeOH; (b) NaH, BnBr, DMF; (c) (1) catechol borane, $LiBH_4$, THF; (2) NaOOH; (d) pyridinium chlorochromate, CH_2Cl_2; (e) lithium (trimethylsilyl)acethylide, vinylmagnesium bromide, or phenyllithium for **9a**, **9b**, or **9c**, respectively; (f) $HSiEt_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (g) BCl_3, CH_2Cl_2; (h) H_2, $Pd(OH)_2$, ethyl acetate. Bn = benzyl.

occur from the less hindered α face, leading to a product with the carbon substituent having the desired 11β-configuration.

The protected 11-ketoestradiol derivative **8**, the precursor common to all of the 11-carbon-substituted derivatives **9** we have synthesized, was readily prepared by utilizing literature procedures, as detailed in Scheme 1. Thus, the the 9(11)-unsaturated derivative **5** (contaminated with some estrone precursor from which it is difficult to separate)[13] was reduced with sodium borohydride and benzylated (sodium hydride and benzyl bromide) to give the protected unsaturated estradiol **6** containing some of the saturated analogue. The removal of this impurity was best accomplished after the hydroboration/oxidation, which converted **6** to the more polar 11α-hydroxy derivative **7**. The best yields in the hydroboration step were obtained using catechol borane and lithium borohydride.[14] Pyridinium chlorochromate oxidation of **7** finally gave **8**, the key intermediate in our synthesis.

Ketone **8** underwent clean addition of either lithium (trimethylsilyl)acetylide, vinylmagnesium bromide, or phenyllithium to give the respective carbinols **9a–c** as single stereoisomers. On the basis of the strong effect of the unsaturated group on the chemical shift of C(1)–H in the NMR spectra of **9a–c**, we believe that the addition of these carbon nucleophiles occurs preferentially from the α-face of the carbonyl group.

In agreement with our expectation, the 11-hydroxyestradiol derivatives **9a–c** were cleanly reduced by treatment with triethylsilane and boron trifluoride etherate, furnishing the desired 11β-substituted estradiol derivatives **10a–c**. It is interesting to note that derivative **9a** undergoes desilylation under deoxygenation conditions. The stereochemistry of the ethynyl and the vinyl derivatives **10a** and **10b** was unambiguously determined by their conversion to the respective known estradiol derivatives **1a** and **1b**, by cleavage of the benzyl groups with boron trichloride in methylene chloride.[15] The stereochemistry of the phenyl derivative **1c** is based on the strong shielding effect that the phenyl group has on the 18-methyl. 11β-Ethylestradiol **1d** was most conveniently obtained in a single step by catalytic hydrogenation of **10b** in the presence of palladium hydroxide on charcoal.

In conclusion, a novel approach to 11β-carbon-substituted estradiol derivatives starting with commercially available estrone has been found, which makes this class of interesting and valuable compounds more readily available than before. We hope that this approach will assist those researchers interested in the development of probes for the estrogen receptor endowed with improved receptor-binding characteristics.

Experimental Section

Melting points were taken with a Kofler hot plate apparatus and are uncorrected. For analytical thin-layer chromatography, Merck silica gel F-254 on aluminum plates was 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.[16] ^{1}H-NMR (200 MHz) spectra were obtained using a Bruker AC200 instrument for samples disolved in $CDCl_3$, unless otherwise stated; chemical shifts (δ) are relative to tetramethylsilane as internal standard. Elemental analyses were performed by the microanalytical laboratory of the Faculty of Pharmacy of the University of Pisa. All the reactions involving organometallic reagents were performed under nitrogen in solvents distilled from sodium benzophenone ketyl. Unless otherwise stated, solutions were dried with magnesium sulfate and evaporated in a rotary evaporator under diminished pressure.

3,17β-Bis(benzyloxy)estra-1,3,5(10),9(11)-tetraene (6). To an ice-cooled solution of **5** (5 g, 18.5 mmol, containing 10% of estrone) in methanol (70 mL) was added sodium borohydride (1.5 g, 39.5 mmol), and the mixture was stirred at room temperature for 2 h. Most of the solvent was evaporated, and the crude intermediate 1,3,5(10),9(11)-tetraene 3,17β-diol (5 g, 100%) was precipitated by the addition of 10% aqueous acetic acid. The solid that formed was collected by filtration, dried *in vacuo* over concentrated sulfuric acid, and carried to the next step without further purification: ^{1}H-NMR δ 0.80 (s, 3 H), 2.81 (m, 2 H), 3.83 (t, J = 8 Hz, 1 H), 6.11 (m, 1 H), 6.54 (d, J = 2.5 Hz, 1 H), 6.64 (dd, J = 2.5 and 8.5 Hz, 1 H), 7.49 (d, J = 8.5 Hz, 1 H) (the material contained 15% of estradiol, as evaluated from relative intensity of the signals relative to 1-H protons). Sodium hydride (1.7 g of an 80% suspension in Vaseline, 72 mmol) was washed free from oil with hexane under nitrogen and then suspended in dry dimethylformamide (20 mL). A solution of the crude estradiol from the above step (5 g, 18.5 mmol) in dry

(13) Collins, J. D.; Sjovall, J. *Aust. J. Chem.* **1983**, *36*, 339–360.
(14) Arase, A.; Nunokawa, Y.; Masuda, Y.; Hoshi, M. *J. Chem. Soc., Chem. Commun.* **1991**, *4*, 205–206.
(15) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923–1925.
(16) Still, W. C.; Kahn, M.; Mitra, A. P. *J. Org. Chem.* **1978**, *43*, 2923–2925.

tetrahydrofuran (20 mL) was then added cautiously in order to control the evolution of H_2. Benzyl bromide (7.7 g, 5.35 mL, 45 mmol) was added and the mixture stirred for 18 h. Water was added dropwise in order to decompose the excess of sodium hydride (H_2 evolution). When the solid was completely dissolved, the resulting mixture was partitioned between ether and water. The ether phase was washed several times with water, dried, and evaporated to leave a residue which was triturated in methanol to give **6** (6.9 g, 83% yield) as a solid: mp 74–80 °C; ^{1}H-NMR δ 0.88 (s, 3 H), 2.70–2.97 (m, 2 H), 3.58 (t, J = 8 Hz, 1 H), 4.57, 5.04 (2 s, 2 × 2 H), 6.10 (m, 1 H), 6.67 (d, J = 2.5 Hz, 1 H), 6.78 (dd, J = 2.5 and 8.5 Hz, 1 H), 7.24–7.44 (m, 10 H), 7.53 (d, J = 8.5 Hz, 1 H).

3,17β-Bis(benzyloxy)estra-1,3,5(10)-trien-11α-ol (7). A solution of **6** (1.5 g, 3.3 mmol), catechol borane (10 mL of a 1 M tetrahydrofuran solution), and lithium borohydride (100 mg) was stirred under nitrogen for 18 h. The reaction mixture was then added in portions to an ice cold mixture of 33% sodium hydroxide (1.5 g), ethanol (15 mL), and 32% hydrogen peroxide (10 mL). After 6 h of stirring at room temperature, the reaction mixture was partitioned between water and ethyl acetate; the organic phase was washed several times with water, dried, and evaporated to afford a residue from which **7** (1.1 g, 72%) was obtained as a glass after chromatography (H/EA, 3:1): ^{1}H-NMR δ 0.82 (s, 3 H), 2.76 (m, 2 H), 3.48 (t, J = 8 Hz, 1 H), 4.14 (m, 1 H), 4.54, 4.99 (2s, 2 × 2 H), 6.71 (d, J = 2.5 Hz, 1 H), 6.77 (dd, J = 2.5 and 8.5 Hz, 1 H), 7.16–7.47 (m, 10 H), 7.85 (d, J = 8.5 Hz, 1 H). Anal. Calcd for $C_{32}H_{36}O_3$: C, 82.02; H, 7.74. Found: C, 82.22; H, 8.01.

3,17β-Bis(benzyloxy)estra-1,3,5(10)-trien-11-one (8). A mixture of pyridinium chlorochromate (2.5 g, 12 mmol) and alcohol **7** (1.4 g, 3 mmol) in methylene chloride (50 mL) was stirred until the starting material was almost completely converted to a less polar compound (18 h, TLC monitoring; H/EA, 4:1). The mixture was diluted with carbon tetrachloride (200 mL); the decanted solution was filtered through a short pad of silica gel which was washed with ether. Combined eluates were evaporated to give a residue from which **8** (800 mg, 57% yield) was obtained as a solid by chromatography (H/EA, 4:1): mp 133–135 °C; ^{1}H-NMR δ 0.86 (s, 3 H), 2.44, 2.50, 2.65, 2.71 (ABq, 2 H), 2.73–2.87 (m, 2 H), 3.46 (d, J = 9 Hz, 1 H), 3.72 (t, J = 8 Hz, 1 H), 4.54, 5.03 (2s, 2 × 2 H), 6.70 (d, J = 2.5 Hz, 1 H), 6.82 (dd, J = 2.5 and 8.5 Hz, 1 H), 7.22–7.41 (m, 11 H). Anal. Calcd for $C_{32}H_{34}O_3$: C, 82.37; H, 7.34. Found: C, 82.43; H, 7.69.

General Conditions for the Addition of Carbon Nucleophiles to 8 (9a–c). The appropriate organometallic compound was added to a solution of **8** (500 mg, 1 mmol) in tetrahydrofuran (20 mL) stirred at −15 °C. The reaction was allowed to take place under the conditions of time and temperature given for the individual compounds. The reaction was quenched with saturated ammonium chloride (containing some ammonia) and the mixture partitioned between water and ether. The organic phase was washed, dried over sodium carbonate, and evaporated to afford a residue from which **9a–c** were obtained by chromatography.

3,17β-Bis(benzyloxy)-11α-[(trimethylsilyl)ethynyl]estra-1,3,5(10)-trien-11β-ol (9a). The organometallic reagent was lithium (trimethylsilyl)acetylide, freshly prepared as follows: butyllithium (7 mL of a 1.4 M hexane solution) and (trimethylsilyl)acetylene (1.4 mL, 0.98 g, 10 mmol) were added in turn to an ice cold solution of diisopropylamine (1 g, 1.4 mL, 10 mmol) in tetrahydrofuran (10 mL), and the solution was used after 20 min. The reaction with **8** was quenched after 1.5 h of stirring at room temperature; the compound was chromatographed using 9:1 H/EA: solid (85% yield); mp 145–148 °C; ^{1}H-NMR δ 0.19 (s, 9 H), 1.05 (s, 3 H), 2.55–3.00 (m, 4 H), 3.49 (t, J = 8 Hz, 1 H), 4.49, 4.55, 4.57, 4.63 (ABq, 2 H), 5.02 (s, 2 H), 6.73 (d, J = 2.5 Hz, 1 H), 6.80 (dd, J = 2.5 and 8.5 Hz, 1 H), 7.20–7.44 (m, 10 H), 8.63 (d, J = 8.5 Hz, 1 H). Anal. Calcd for $C_{37}H_{44}O_3Si$: C, 78.68; H, 7.85. Found: C, 78.70; H, 7.90.

3,17β-Bis(benzyloxy)-11α-ethenylestra-1,3,5(10)-trien-11β-ol (9b) was obtained by reaction of **8** with vinylmagnesium bromide (14 mL of a 1 M tetrahydrofuran solution (Aldrich), 14 mmol). The reaction was quenched after 1.5 h at room temperature; the compound was chromatographed using 4:1 H/EA: solid (72% yield); mp 63–67 °C; ^{1}H-NMR δ 1.12 (s, 3 H), 2.54 (d, J = 10.5 Hz, 1 H), 2.65–2.95 (m, 2 H), 3.45 (t, J = 8 Hz, 1 H), 4.46, 4.52, 4.55, 4.61 (ABq, 2 H), 5.01 (s, 2 H), 5.17 (dd, J = 10.5 and 1.1 Hz, 1 H), 5.44 (dd, J = 17.3 and 1.1 Hz, 1 H), 6.28 (dd, J = 17.3 and 10.5 Hz, 1 H), 6.67 (dd, J = 2.5 and 8.5 Hz, 1 H), 6.73 (d, J = 2.5 Hz, 1 H), 7.24–7.43 (m, 10 H), 7.84 (d, J = 8.5 Hz, 1 H). Anal. Calcd for $C_{34}H_{38}O_3$: C, 82.55; H, 7.74. Found: C, 82.50; H, 7.38.

3,17β-Bis(benzyloxy)-11α-phenylestra-1,3,5(10)-trien-11β-ol (9c) was obtained by reaction of **8** with phenyllithium (0.7 mL of a 2 M solution). The reaction was quenched after 15 min at −15 °C; the compound was chromatographed using 85:15 H/EA: glass (52% yield); ^{1}H-NMR δ 1.18 (s, 3 H), 2.28 (d, J = 14 Hz, 1 H), 2.72–3.05 (m, 2 H), 3.27 (d, J = 10.3 Hz, 1 H), 3.46 (t, J = 8 Hz, 1 H), 4.35, 4,41, 4.48, 4.53 (ABq, 2 H), 4.92 (s, 2 H), 6.36 (dd, J = 2.5 and 8.5 Hz, 1 H), 6.52 (d, J = 8.5 Hz, 1 H), 6.71 (d, J = 2.5 Hz, 1 H), 7.19–7.42 (m, 15 H). Anal. Calcd for $C_{38}H_{40}O_3$: C, 83.79; H, 7.40. Found: C, 83.82; H, 7.38.

General Conditions for the Deoxygenation of 9a–c (10a–c). To a solution of **9** (0.1 mmol) and triethylsilane (0.5 mL, 3 mmol) in methylene chloride (10 mL) cooled at −5 °C was added dropwise boron trifluoride etherate (1 mL, 8 mmol). The solution was stirred until **9** was completely converted to a less polar compound (monitored by TLC). The solution was partitioned between ether and 10% sodium carbonate. The ethereal phase was washed with brine, dried, and evaporated to afford a residue from which **10** was obtained after chromatography.

3,17β-Bis(benzyloxy)-11β-ethynylestra-1,3,5(10)-triene (10a) was isolated by chromatography with 1:1 H/CH_2Cl_2: oil (65% yield); ^{1}H-NMR δ 1.14 (s, 3 H), 1.85 (d, J = 2 Hz, 1 H), 2.30–2.45 (m, 2 H), 2.63–2.96 (m, 2 H), 3.37 (dd, J = 7.5 and 8.5 Hz, 1 H), 3.44 (m, 1 H), 4.49, 4.95 (2s, 2 × 2 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.75 (dd, J = 2.5 and 8.5 Hz, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.20–7.40 (m, 10 H). Anal. Calcd for $C_{34}H_{36}O_2$: C, 85.67; H, 7.61. Found: C, 85.72; H, 7.78.

3,17β-Bis(benzyloxy)-11β-ethenylestra-1,3,5(10)-triene (10b) was isolated by chromatography with 3:2 H/CH_2Cl_2 (64% yield): oil (lit.[3] mp 62–64 °C). The spectral data were identical with those reported.

3,17β-Bis(benzyloxy)-11β-phenylestra-1,3,5(10)-triene (10c) was isolated by chromatography with 3:2 H/CH_2Cl_2: solid (85% yield); mp 145–148 °C; ^{1}H-NMR δ 0.41 (s, 3 H), 2.66 (dd, J = 13 and 2 Hz, 1 H), 2.67–3.12 (m, 3 H), 3.46 (t, J = 8 Hz, 1 H), 3.96 (m, 1 H), 4.54, 4.95 (2s, 2 × 2 H), 6.54 (dd, J = 2.5 and 8.5 Hz, 1 H), 6.72 (d, J = 2.5 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H), 6.10–7.10 (m, 5 H), 7.18–7.41 (m, 10 H). Anal. Calcd for $C_{38}H_{40}O_2$: C, 86.32; H, 7.63. Found: C, 86.15; H, 7.72.

General Conditions for the Debenzylation of 10a–c (1a–c). Boron trichloride (1.5 mL of a 1 M methylene chloride solution) was added dropwise to a solution of **10** (0.5 mmol) in methylene chloride (10 mL). After the mixture was stirred for 45 min at 0 °C, methanol was added and most of the solvent evaporated. The residue was partitioned between ethyl acetate and 10% sodium hydrogen carbonate solution, and the organic phase was washed with brine, dried, and evaporated to afford a residue from which **1** was obtained by chromatography (H/EA, 2:1).

11β-Ethynylestra-1,3,5(10)-triene-3,17β-diol (1a): solid; mp 155–158 °C (lit.[10] mp 153–158 °C).

11β-Ethenylestra-1,3,5(10)-triene-3,17β-diol (1b): solid; mp 197–200 °C (lit.[3] mp 196–198 °C).

11β-Phenylestra-1,3,5(10)-triene-3,17β-diol (1c): solid; mp 220–223 °C; ^{1}H-NMR δ 0.31 (s, 3 H), 2.56 (dd, J = 2 and 13 Hz, 1 H), 2.78–3.15 (m, 3 H), 3.69 (m, 1 H), 3.99 (m, 1 H), 6.39 (dd, J = 2.5 and 8.5 Hz, 1 H), 6.58 (d, J = 2.5 Hz, 1 H), 6.82 (d, J = 8.5 Hz, 1 H), 6.90–7.18 (m, 5 H). Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.57; H, 8.25.

11β-Ethylestra-1,3,5(10)-triene-3,17β-diol (1d) was obtained in quantitative yield by hydrogenation of **10b** in ethyl acetate in the presence of palladium hydroxide on charcoal: mp 222–224 °C (lit.[17] mp 224–226 °C).

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(17) Baran, J. S.; Langford, D. D.; Laos, I.; Liang, C. D. *Tetrahedron* **1977**, *33*, 609–616.