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Chemical synthesis of two novel diaryl ether dimers of estradiol-17β

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Abstract

We recently detected the formation of estradiol-17β (estradiol) dimers, linked together through a diaryl ether bond between the C-3 phenolic oxygen of one estradiol molecule and the 2- or 4-position aromatic carbon of another estradiol, following incubations of [^{3}H]estradiol with human liver microsomes or cytochrome P450 enzymes in the presence of NADPH. Using estradiol as the starting material, we designed a four-step method for the chemical synthesis of these two estrogen dimers with the Ullmann condensation reaction as a key step. Step 1: Synthesis of 2- or 4-bromoestradiol from estradiol. Step 2: Protection of the C-3 phenolic hydroxyl group of the 2- or 4-bromoestradiol. Step 3: The Ullmann condensation reaction between the phenol-protected bromoestradiol and the estradiol potassium salt under our modified reaction conditions (with a 41% product yield). Step 4: Removal of the C-3 benzyl group by catalytic hydrogenation. The chromatographic and various spectrometric properties of the two synthesized compounds were identical to those metabolically formed by human cytochrome P450 3A4.

Keywords: Estradiol; Nonpolar estrogen metabolites; Estrogen dimers

1. Introduction

The endogenous estrogens such as estradiol-17β (estradiol) and estrone are important female gonadal hormones that have very diverse physiological and pathophysiological actions. Although many of the biological actions of endogenous estrogens are believed to be directly mediated by the estrogen receptors (namely, the ER-α and/or ER-β subtypes), there is also mounting experimental evidence suggesting that some of the unique biological actions of the endogenous estrogens are exerted by their metabolites. For instance, 4-hydroxyestradiol is a genotoxic/mutagenic estrogen metabolite [1–3], and it also appears to have its own signal-transduction pathway that is different from the classical ERα-mediated pathways [4]. This catechol estrogen metabolite has been suggested to play an important role in hormonal carcinogenesis in animal models and humans [3]. In addition, a few other hydroxyestrogen metabolites (such as 2-hydroxyestradiol, 15α-hydroxyestradiol, and 16α-hydroxyestrone) have also been suggested to have unique biologic properties [5,6]. In addition to these polar estrogen metabolites, 2-methoxyestradiol and estradiol-17-fatty acid esters are two examples of nonpolar estrogen metabolites that also have unique biological properties. It is known that 2-methoxyestradiol has strong growth-inhibitory, apoptotic, and antiangiogenic actions [7]. Recent results have suggested that the naturally occurring lipoidal estradiol-17-stearate appeared to have a strong, preferential growth-stimulatory and carcinogenic activity in the fat-rich mammary tissues over other target organs (such as the uterus and pituitary), which is different from the parent hormone estradiol [8,9].

During our recent study of the NADPH-dependent metabolism of [^{3}H]estradiol by human liver microsomes and fifteen selectively expressed human CYP isoforms, we detected ≥20 nonpolar radioactive metabolite peaks (designated as M1–M20), in addition to a large number of hydroxylated or keto metabolites (Lee et al., submitted for publication). Among ∼20 nonpolar estradiol metabolites detected, M15 and M16 were only selectively formed by a few of the human CYP isoforms (predominantly CYP3A4 and CYP3A5). The formation of these two representative nonpolar estrogen metabolites by human CYP isoforms did not correlate with their overall catalytic activity for the oxidative metabolism of estradiol. The structures of the metabolically formed M15 and M16 were identified to be the dimers of estradiol, linked

Abbreviations: Estradiol, estradiol-17β; HPLC, high-pressure liquid chromatography; TLC, thin-layer chromatography; CYP, cytochrome P450; NMR, nuclear magnetic resonance

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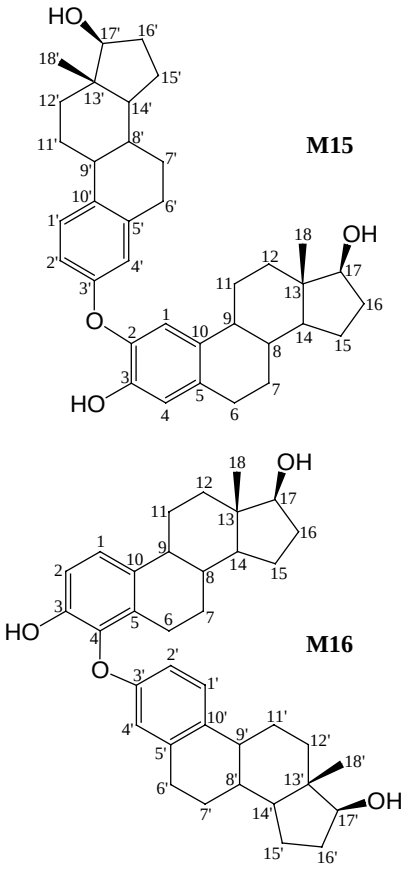

Fig. 1. Structures of M15 and M16, two novel diaryl ether dimers of estradiol-17β that were metabolically formed by human CYP enzymes in the presence of NADPH.

together through a diaryl ether bond between a phenolic oxygen atom of one estradiol molecule and the 2- or 4-position aromatic carbon of another estradiol (structures shown in Fig. 1). We report here an efficient method for the chemical synthesis of these two novel estradiol dimers.

2. Experimental

2.1. Chemicals and reagents

N-Bromosuccinimide, benzyl bromide, potassium carbonate (K_2CO_3, anhydrous), 4-picoline (4-methylpyridine), copper (II) oxide (CuO), anhydrous sodium sulfate (Na_2SO_4), 10% palladium on carbon (Pd-C), and Celite were of ACS grades and purchased from ACROS (through Fisher Scientific, Atlanta, GA). Estradiol (in ∼50 g of quantity, used as the starting material for chemical synthesis) and very small amounts (5 mg) of 2-bromoestradiol and 4-bromoestradiol (used as reference standards) were purchased from Steraloids (Newport, RI). Methanol-d_4 (CD_3OD) was obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA).

2.2. Spectrometric analyses

Mass spectra were recorded by using a VG70S analytical mass spectrometer. An aliquot of the ethanol solution of the test compound was used for the direct-probe mass analysis. The NMR spectra were recorded on a Varian Inova 500 spectrometer operating at a proton frequency of 500.21 MHz and a carbon frequency of 125.79 MHz. Chemical shifts were given as δ values with reference to CD_3OD as an internal standard.

2.3. Synthesis

2.3.1. 4-Bromoestradiol (compound **2**) and 2-bromoestradiol (compound **3**) [10]

A solution of estradiol (1.5 g, 5.5 mmol) in chloroform (250 ml) was treated with *N*-bromosuccinimide (1.05 g, 5.9 mmol) dissolved in chloroform (150 ml). The mixture was refluxed for an hour and the solvent was then removed in vacuo to yield a solid. The crude product was dissolved in methanol (25 ml) and precipitated by addition of water (200 ml). The solid was filtered and dried in vacuo. Upon crystallization from ethanol, 4-bromoestradiol was separated as short needles which, after recrystallization, afforded the product with a melting point (m.p.) of 209–211 °C in 34% (yield 654 mg) (literature m.p. value: 213.5–215 °C [9]). After separation of 4-bromoestradiol, the ethanol solution was dried and the residues were dissolved in acetonitrile. 2-Bromoestradiol was obtained as long rods in 23% yield (437 mg) with an m.p. of 200–207 °C (literature value: 197–198 °C [11]).

2.3.2. 4-Bromoestradiol 3-O-benzyl ether (compound **4**)

A 50-ml round-bottom flask was charged with 4-bromoestradiol (527 mg, 1.5 mmol), anhydrous K_2CO_3 (1.382 g, 10 mmol) and 25 ml acetonitrile, and then 180 μl of benzyl bromide (1.5 mmol) was also added. The reaction mixture was refluxed with stirring for 1 h. The hot reaction mixture was then filtered under a reduced pressure, and the filtrate was concentrated. 4-Bromoestradiol 3-*O*-benzyl ether was crystallized as long needles: 463 mg (70% yield); m.p. 163–164 °C; R_f of 0.47 on Silica gel TLC (toluene/chloroform/ethyl acetate, 1/10/2); molecular weight (*m/z*) 440.1342 (440.1351 calculated for $C_{25}H_{29}BrO_2$, with 2.0 ppm error); ^{1}H NMR (CD_3OD): 2nd order phenyl (benzyl) multiplets at 7.473 (2H, for H-*ortho*), 7.355 (2H, for H-*meta*), 7.283 (1H, for H-*para*), 7.228 (d, $J = 8.5$ Hz, 1H, for H-1), and 6.683 (d, $J = 8.5$ Hz, 1H, for H-2) ppm (δ).

2.3.3. M16 3-O-benzyl ether (compound **5**) [12]

A mixture of 4-bromoestradiol 3-*O*-benzyl ether (441 mg, 1.0 mmol), estradiol (272 mg, 1.0 mmol), anhydrous K_2CO_3 (290 mg, 2.1 mmol) in 4-picoline (5 ml) was incubated at 130 °C for 3 h, and then CuO (40 mg, 0.5 mmol) was added. The reaction mixture was heated at 155–160 °C with stirring under argon for 72 h, cooled to room temperatures, diluted

with 50 ml ethyl acetate, and vacuum-filtered through Celite. The filtrate was extracted with 1 N HCl (50 ml) twice to remove 4-picoline. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography eluting with a gradient from 33% ethyl acetate in hexanes to 100% ethyl acetate. The fractions were combined, concentrated, and further purified by column chromatography eluting with 33% ethyl acetate in hexanes. The fractions were combined and concentrated and the residues were purified by crystallization from ethanol. M16 3-benzyl ether was obtained as colorless needles: 262 mg (41% yield); m.p. 142–144 °C; R_f of 0.22 on Silica gel TLC (50% ethyl acetate/hexanes); molecular weight (*m/z*) 632.3864 (632.3866 calculated for $C_{43}H_{52}O_4$, 0.3 ppm error); ^{1}H NMR (CD_3OD): overlapped region 7.100–7.197 (5H, for H-1′, H-*meta*, and H-*ortho*), overlapped region 6.999–7.022 (2H, for H-1 and H-*para*), 6.903 (d, $J = 8.6$ Hz, 1H, for H-2), 6.517 (dd, $J = 8.6$ and 2.6 Hz, 1H, for H-2′), and 6.444 (d, $J = 2.6$ Hz, 1H, for H-4′) ppm (δ).

2.3.4. M16

Into a Parr flask, M16 3-benzyl ether (240 mg, 0.38 mmol) in 100 ml ethanol and Pd-C (500 mg) were added. The reaction mixture was subjected to hydrogen at 40 psi for 4 h and the catalyst was removed by vacuum filtration through Celite. The filtrate was concentrated and the residue was dissolved in hot acetonitrile. During the concentration of the acetonitrile solution with heating, white amorphous powder was obtained as M16: 136 mg (66% yield); R_f of 0.22 on Silica gel TLC (50% ethyl acetate/hexanes); molecular weight (*m/z*) 542.3387 (542.3396 calculated for $C_{36}H_{46}O_4$, 1.7 ppm of error); ^{1}H NMR (CD_3OD): 7.140 (d, $J = 8.5$ Hz, 1H, for H-1′), 7.040 (d, $J = 8.5$ Hz, 1H, for H-1), 6.740 (d, $J = 8.5$ Hz, 1H, for H-2), 6.530 (dd, $J = 8.5$ and 2.5 Hz, 1H, for H-2′), and 6.470 (d, $J = 2.5$ Hz, 1H, for H-4′) ppm (δ).

2.3.5. 2-Bromoestradiol 3-*O*-benzyl ether (compound **6**)

A 50-ml round-bottom flask was charged with 2-bromoestradiol (527 mg, 1.5 mmol) and anhydrous K_2CO_3 (1.382 g, 10 mmol) in 25 ml acetonitrile, and then benzyl bromide (180 μl, 1.5 mmol) was added. The reaction mixture was refluxed with stirring for 1 h. The hot reaction mixture was then filtered under a reduced pressure, and the filtrate was concentrated. 2-Bromoestradiol 3-*O*-benzyl ether was obtained as white powder (539 mg, 82%). Although TLC analysis showed a single spot (Silica gel, toluene/chloroform/ethyl acetate, 1/10/2, $R_f = 0.49$), further mass spectrometric analysis showed two molecular weights: one corresponding to 2-bromoestradiol 3-*O*-benzyl ether (compound **6**), with a molecular weight (*m/z*) of 440.1339 (440.1351 calculated for $C_{25}H_{29}BrO_2$, 2.7 ppm error), and the other one corresponding to 2,4-dibromoestradiol 3-*O*-benzyl ether, with *m/z* 520 (its high-resolution mass was not determined).

2.3.6. M15 3-*O*-benzyl ether (compound **7**) [12]

Into a 50-ml round-bottom flask, 441 mg of crude 2-bromoestradiol 3-*O*-benzyl ether (containing 2,4-dibromoestradiol 3-*O*-benzyl ether), estradiol (272 mg, 1.0 mmol), and anhydrous K_2CO_3 (290 mg, 2.1 mmol) in 5 ml 4-picoline were added. The mixture was first incubated at 130 °C for 3 h, and then CuO (40 mg, 0.5 mmol) was added. The reaction mixture was heated at 155–160 °C with stirring under argon for 72 h, cooled to room temperatures, diluted with ethyl acetate, and vacuum-filtered through Celite. The filtrate was extracted with 1 N HCl (50 ml) twice to remove 4-picoline. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under a reduced pressure. The residue was purified by column chromatography eluting with 50% ethyl acetate in hexanes. The residue was purified again by column chromatography eluting with 33% ethyl acetate in hexanes. The fractions were combined and concentrated and the yellow-colored residues were not further purified.

2.3.7. M15

Into a Parr flask, crude M15 3-*O*-benzyl ether in 100 ml ethanol and Pd-C (500 mg) were added. The reaction mixture was subjected to hydrogen at 40 psi for 4 h and the catalyst was removed by vacuum filtration through Celite. The filtrate was concentrated and the residue was dissolved in hot acetonitrile. During the concentration of acetonitrile solution with heating, white amorphous powder was obtained as M15: 39 mg; R_f of 0.25 on Silica gel TLC (50% ethyl acetate/hexanes); molecular weight (*m/z*) 542.3407 (542.3396 calculated for $C_{36}H_{46}O_4$, 2.0 ppm of error); ^{1}H NMR (CD_3OD): 7.178 (d, $J = 8.5$ Hz, 1H, for H-1′), 6.773 (s, 1H, for H-1), 6.639 (dd, $J = 8.5$ and 2.3 Hz, 1H, for H-2′), 6.612 (s, 1H, for H-4), and 6.564 (d, $J = 2.3$ Hz, 1H, for H-4′) ppm (δ).

3. Results and discussion

The key structural characteristic of M15 and M16 (structures shown in Fig. 1) is the presence of a diaryl ether bond between two estradiol moieties. The method commonly used for preparation of a diaryl ether linkage has been the reaction between an alkali metal phenolate and a halogenated benzene in the presence of copper (or a copper salt) as catalyst, which was originally developed by Ullmann and is widely known as the Ullmann condensation reaction [13–15]. Accordingly, a four-step synthetic scheme (depicted in Fig. 2) for the synthesis of M15 and M16 was designed with the Ullmann condensation reaction as a key step. Step 1: Synthesis of 2- or 4-bromoestradiol from estradiol. Step 2: Protection of the C-3 phenolic hydroxyl group of the 2- or 4-bromoestradiol. Step 3: The Ullmann condensation reaction of the phenol-protected bromoestradiol and the estradiol potassium salt under our modified reaction conditions (with a 41% product yield). Step 4: Removal of the C-3 benzyl group by catalytic hydrogenation.

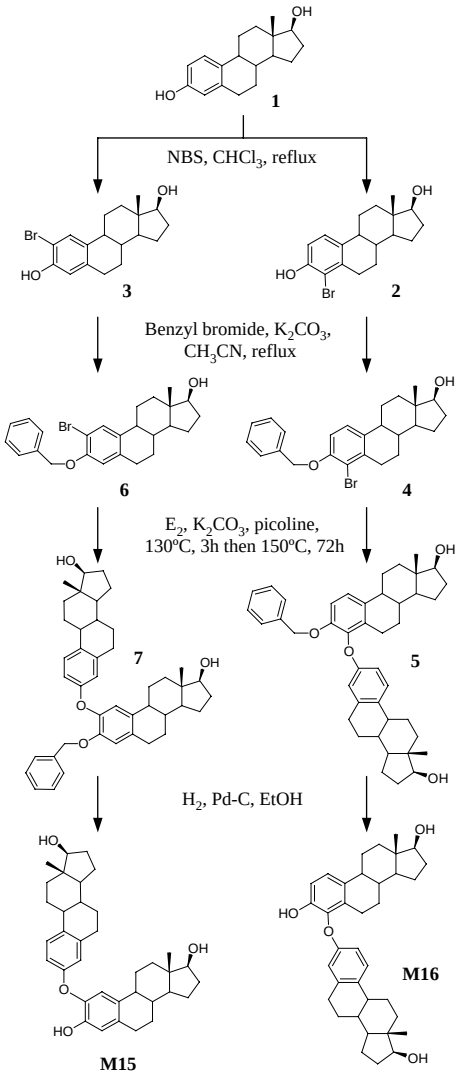

Fig. 2. Synthetic scheme for M15 and M16.

In Step 1, estradiol was brominated at the C-2 or C-4 position by reaction of estradiol with *N*-bromosuccinimide [10]. Briefly, the chloroform solution of estradiol and *N*-bromosuccinimide was refluxed and the solvent was evaporated to yield a white solid. This solid was then dissolved in methanol and precipitated upon addition of water. After two times of recrystallization, 4-bromoestradiol (compound **2**) was obtained first as short needles. The resulting ethanol solution was dried and the residue was redissolved in acetonitrile. 2-Bromoestradiol (compound **3**) was crystallized as long rods. Both compounds were identified by comparing their m.p. and R_f values on the TLC with those of the reference standards. The reaction of estradiol with *N*-bromosuccinimide for the preparation of 2- and 4-bromoestradiol was repeated multiple times to obtain sufficient quantities for the next step of synthesis.

To prevent the formation of side products during the Ullmann condensation reaction, the phenolic hydroxyl group (i.e. at the C-3 position) of 2- or 4-bromoestradiol was protected in Step 2. We selected benzyl ether as the protecting group for the following reasons: (i) its stability under the alkaline conditions required for the Ullmann condensation reaction; (ii) its easy removal; and (iii) that the reaction condition has little or no effect on other parts of the product. It should be noted that the hydroxyl group at the C-17 position of 2- or 4-bromoestradiol was not protected since it is known that the secondary alkyl hydroxyl group is not ionized during the Ullmann condensation reaction. For protection, benzyl bromide (in equivalent amount) and K_2CO_3 (in excess) were added to an acetonitrile solution containing 2- or 4-bromoestradiol and refluxed. Upon recrystallization, 3-*O*-benzyl ethers of 2- or 4-bromoestradiol (compound **6** or **4**) were obtained as powder or long needles, respectively, and their yields were 70–81%. The structures of the products were confirmed by analyzing their high resolution mass and ^{1}H NMR spectra (aromatic protons). 4-Bromoestradiol 3-*O*-benzyl ether (compound **4**) was highly pure according to TLC, mass, and ^{1}H NMR analyses. However, the mass and NMR spectra of 2-bromoestradiol 3-*O*-benzyl ether (compound **6**) showed that there were small amounts of 2,4-dibromoestradiol 3-*O*-benzyl ether present as impurity.

In Step 3, 3-*O*-benzyl ethers of M16 or M15 (compound **5** or **7**) were synthesized by using the Ullmann condensation reaction between estradiol 3-potassium salt and the 3-*O*-benzyl ether of 4- or 2-bromoestradiol. It has been documented that the Ullmann condensation usually requires high temperatures (up to 300 °C), long reaction time (up to 3 days), and strong polar solvents [16,17]. Notably, these harsh reaction conditions often produce competitive side products such as dehalogenated arene and homocoupled diaryls [17]. Although the overall yield of this reaction usually is around 40–50%, much lower yields have often been reported in cases involving substituted reactants [12]. Since the reactants used for chemical synthesis of M15 and M16 are bulky (2- or 4-bromoestradiol 3-*O*-benzyl ether and the potassium salt of estradiol), we had chosen to carry out the Ullmann condensation reaction at 150 °C for 3 days in the presence of CuO as a catalyst [12]. This modified procedure was adopted after review of the literature on the synthesis of other similar compounds. Also, 4-picoline was used here as a solvent since it has a higher boiling point (145 °C) and basicity ($pK_a = 7.96$) than the commonly used pyridine (boiling point = 115 °C and $pK_a = 5.19$). Under these reaction conditions and with 4-bromoestradiol 3-*O*-benzyl ether (compound **4**) as the starting material, a benzyl derivative of M16 (compound **5**) was obtained with a moderate yield (41%) even after two steps of column chromatography and recrystallization. The structure of the product was confirmed by high resolution mass and ^{1}H NMR (aromatic protons). The benzyl derivative of M15 (compound **7**) was synthesized under the same reaction conditions.

In the final procedure (Step 4), the benzyl group was removed by catalytic hydrogenation in the presence of Pd-C. The reaction mixture was subjected to hydrogen at 40 psi for 4 h and the catalyst was then removed by vacuum filtration

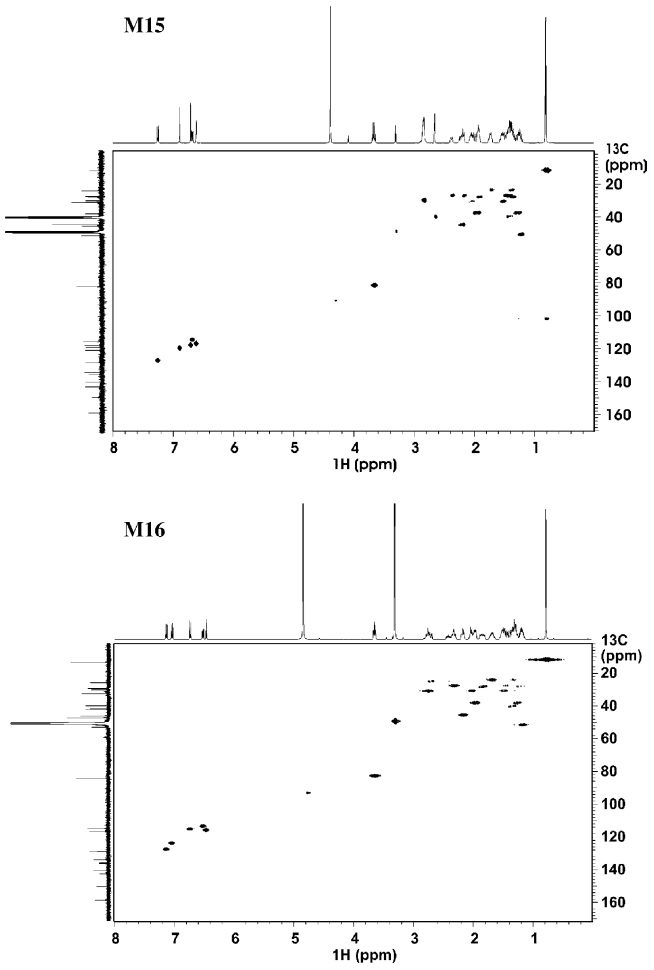

Fig. 3. Gradient-enhanced heteronuclear multiple quantum coherence-(gHMQC) spectra of the synthesized M15 and M16. The NMR spectra were recorded on a Varian Inova 500 spectrometer operating at a proton frequency of 500.21 MHz and a carbon frequency of 125.79 MHz. Chemical shifts are given as δ values with reference to CD_3OD (for M16) or CD_3OD and DMSO-d_6 (for M15) as internal standard. Parameters for the two-dimensional experiments included 4000 Hz ^1H (F2) spectral window collected with 2K complex data points. A 200 ppm F1 window for ^{13}C was used for the gHMQC experiments.

through Celite. Both M15 and M16 were obtained as powder from acetonitrile solution upon concentration. Their structures were confirmed through analysis of their high resolution mass and the ^1H NMR spectra of their aromatic protons. The ^1H and ^{13}C NMR spectra of M15 and M16 were shown in Fig. 3 as gHMQC spectra. It is of note that the chemically synthesized M15 and M16 showed identical ^1H NMR peaks to those of enzymatically formed M15 and M16 (*data not shown*). HPLC analysis of the enzymatically and chemically prepared M15 or M16 showed the same retention times, and co-injection of metabolically formed and chemically synthesized M15 or M16 into HPLC showed a single peak.

In summary, two novel diaryl ether dimers of estradiol were chemically synthesized by using estradiol as the starting material. After appropriate protection of the phenolic hydroxyl groups of 2- or 4-bromoestradiol, the Ullmann condensation reaction (with 4-picoline as a solvent) was used to generate the corresponding diaryl ether product, with a moderate yield of 41%. The chromatographic and spectrometric properties of the two synthesized compounds (M15 and M16) were identical to the enzymatically formed M15 and M16. The ready availability of sufficient amounts of these estrogen dimers makes it possible for us to further determine any biological activities that may be associated with this novel class of nonpolar estrogen metabolites.

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