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Synthesis of 4-Formyl Estrone Using a Positional Protecting Group and Its Conversion to Other C-4-Substituted Estrogens

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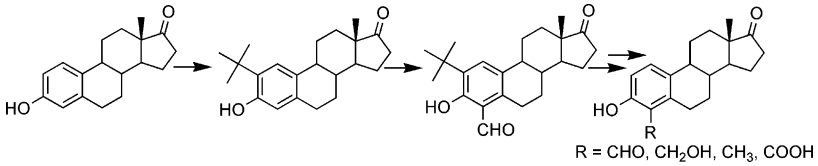

4-Formyl estrone was synthesized in overall good yield in three steps starting from estrone. This was achieved by conducting an electrophilic aromatic substitution reaction using formaldehyde, triethylamine, and $MgCl_2$ on 2-*tert*-butyl estrone, which was readily prepared in 96% yield from estrone using *tert*-butyl alcohol and BF_3OEt_2. The *tert*-butyl group acted as a positional protecting group to prevent reaction at the 2-position. The *tert*-butyl group was readily removed in good yield using $AlCl_3$ in dichloromethane/CH_3NO_2. To our knowledge, this represents the first use of a positional protecting group for the synthesis of a C-4-modified estrogen. 4-Formyl estrone was used as a common precursor to obtain a variety of other C-4 modified estrogens in very high yields such as 4-methylestrone and 4-hydroxymethylestrone as well as the novel estrogen 4-carboxyestrone. The syntheses of 4-formyl, -methyl-, and -hydroxymethyl estrone represent dramatic improvements over previously reported syntheses of these compounds.

Introduction

Estrogens, such as estrone (**1**, E1) and estradiol (**2**, E2), have key roles in many biological processes. Numerous derivatives have been made from these two steroids, and some are used as drugs for treatment of a variety of medical conditions.[1] Thus, improved methods for preparing estrogen derivatives and the synthesis of new estrogen derivatives is of considerable importance. Our interest in E1 and E2 derivatives is a result of our work on developing inhibitors of steroid sulfatase (STS), an enzyme that catalyzes the desulfation of estrone sulfate to estrone. STS is now considered to be an important target for the treatment of various forms of steroid-dependent cancers.[2−4] We were specifically interested in constructing E1 derivatives bearing substituents attached to C-4 by a C−C bond such as compounds **3**−**6** (Figure 1). Some of these (**3**, **4**, and **6**) are known compounds, and several have been shown to be useful as intermediates in the synthesis of biologically active estrogen derivatives.[5−9] However, their syntheses were achieved in poor yields (16% or less),[5−9] and these low yields reflect the

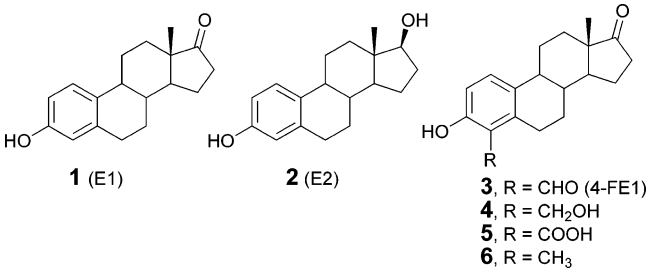

FIGURE 1. Structures of estrone, estradiol, and targeted estrogen derivatives **3**−**6**.

(1) Fullerton, D. S. *Textbook of Organic, Medicinal and Pharmaceutical Chemistry*; Delgado, J. N., Remers, W. A., Eds.; Lippincott Williams & Wilkins: New York, 1998; Chapter 23.

(2) For a review of the biology and regulation of STS, see: Reed, M. J.; Purohit, A.; Woo, L. W.; Newman, S. P.; Potter, B. V. *Endocr. Rev.* **2005**, *26*, 171.

(3) For a review on STS inhibitors see: Nussbaumer, P.; Billich, A. *Med. Res. Rev.* **2004**, *24*, 529.

(4) For a review on aryl sulfatases, see: Hanson, S. R.; Best, M. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5736.

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(6) Pert, D. J.; Ridley, D. D. *Aust. J. Chem.* **1989**, *42*, 405.

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(8) Singh, V.; Lahiri, S.; Kane, V. V.; Stey, T.; Stalke, D. *Org. Lett.* **2003**, *5*, 2199.

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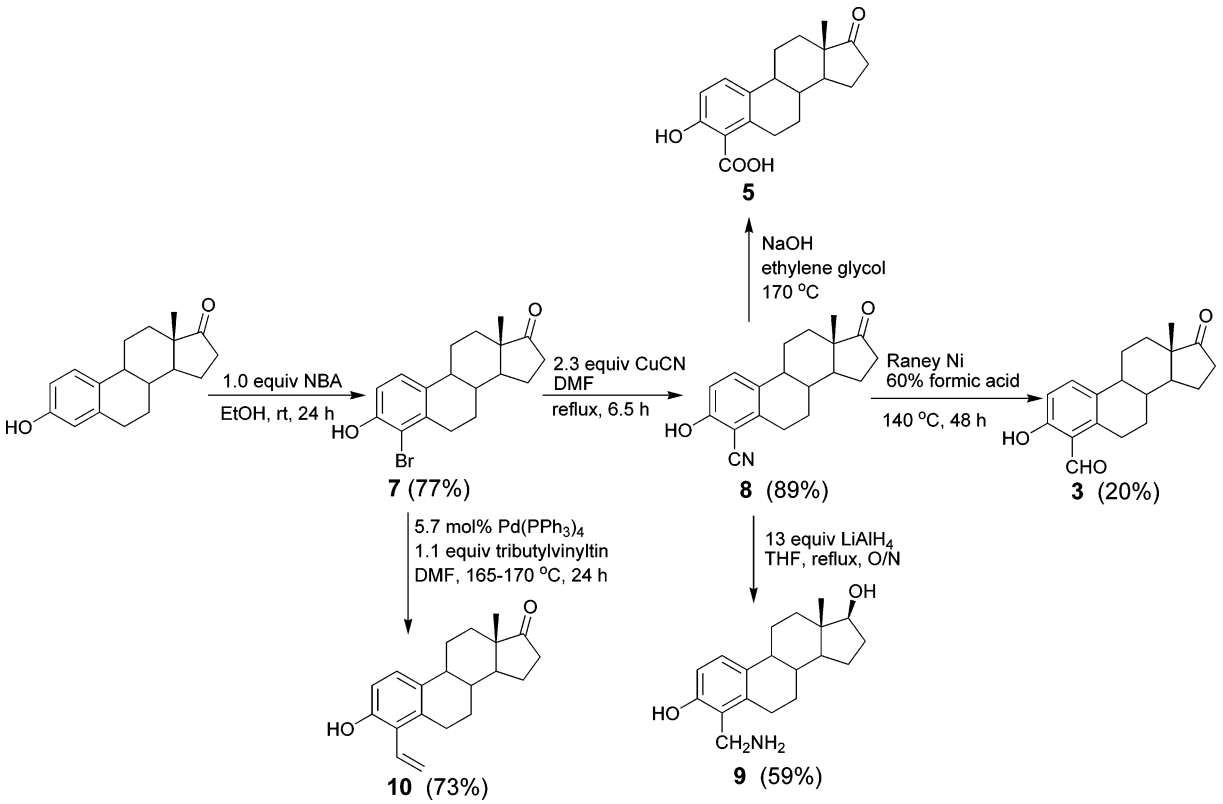
SCHEME 1. Synthesis of Estrogens 3, 5, and 9 from Nitrile 8



difficulties in preparing E1 derivatives modified at the 4-position. Here, we report the synthesis of these and other C-4-modified estrogen derivatives in good yield from a common precursor and using a positional protecting group.

Results and Discussion

We envisioned preparing 4-formyl estrone (**3**, 4-FE1) and then either oxidizing or reducing the aldehyde group to obtain compounds **4**−**6**. The first synthesis of 4-FE1 appeared in the patent literature and was achieved by reacting E1 with NaOH, $CHCl_3$ in EtOH with heating (Reimer−Tiemann reaction).[5a,b] This gave a mixture of 2-formyl estrone (2-FE1) and 4-FE1 in an unspecified yield. However, Pert and Ridley later reported that they were only able to obtain a 9% yield of the mixture using this approach.[6] However, by making slight modifications to the amount of base and chloroform and performing the reaction in the presence of catalytic benzyltriethylammonium chloride, these workers were able to obtain 4-FE1 in a 16% yield after careful chromatographic separation from a small amount of 2-FE1 that was also produced in the reaction.[6] These workers also constructed 4-formylestradiol (4-FE2) by first protecting the phenolic and 17-OH groups in 4-bromoestradiol with the MEM moiety followed by lithium−bromine exchange and formylation of the resulting carbanion with N-methylformamide.[6] Removal of the MEM groups gave 4-FE2. Although this was a potential route to 4-FE1 by oxidation of the 17-OH in 4-FE2,[7] the overall yield of 4-FE2 from 4-bromoestradiol was only 19%. Moreover, when including the additional steps of E2 bromination[10] and oxidation of the 17-OH,[7] an overall yield of 14% for 4-FE1 can be estimated.[11]

Our initial route to 4-FE1 was to prepare 4-cyanoestrone (**8**), which is easily obtained in good yield,[12] and then convert the cyano group to the desired functional group (Scheme 1). Pert and Ridley had previously attempted to prepare 4-FE2 from 4-cyanoestradiol using a variety of methodologies.[6] However, only when Raney nickel/formic acid was used was the desired product obtained and in only a 9% yield. Nevertheless, we reasoned that optimization of the Raney nickel reaction or other methods that are available for converting nitriles to aldehydes would yield 4-FE1 in good yield. Thus, E1 was reacted with NBA in EtOH to give 4-bromoestrone (**7**) in 77% yield.[10,13] Compound **7** was then converted into nitrile **8** in 89% yield using CuCN in refluxing DMF.[12] However, after many reactions of **8** with various amounts of Raney Ni and formic acid and at various temperatures the best yield of 4-FE1 we were able to obtain was only 20% (Ra/Ni, 60% formic acid, 140 °C, 48 h) and the purification was difficult. Other reagents were examined for converting **8** in to 4-FE1 such as DIBAL, PtO_2 in refluxing formic acid,[14] ($MeNHCH_2CH_2NHMe$)−$LiAlH_4$[15] however, only trace amounts of 4-FE1 and/or 4-FE2 were formed. Protection

(9) Holt, D. A.; Levy, M. A.; Ladd, D. L.; Oh, H-J.; Erb, J. M.; Heaslip, J. I.; Brandt, M.; Metcalf, B. W. *J. Med. Chem.* **1990**, *33*, 937.

(10) Utne, T.; Jobson, R. B.; Landgraf, F. W. *J. Org. Chem.* **1968**, *33*, 1654.

(11) This assumes a yield of 93% for the oxidation step (see ref 7) and 80% for the bromination (see ref 10).

(12) Labrie, F.; Provencher, L.; Gauthier, S. Int. Appl. WO2004089971, 2004; *Chem. Abstr*. **2004**, *141*, 366369.

(13) This high level of selectivity for the 4-position is unusual for an electrophilic aromatic substitution (EAS) on E1. All other reported EAS reactions on E1 (not just bromination) always give mixtures of the 2- and 4-isomeric products (plus disubstituted product) and the 2-isomer usually dominates. Other brominating agents do not give the same degree of selectivity as NBA. See: Numazawa, M.; Ogura, Y.; Kimura, K.; Nagaoka, M. *J. Chem. Res., Syn.* **1985**, *11*, 348. No explanation has been put forth to explain the high level of selectivity obtained with NBA.

(14) Xi, F.; Kamal, F.; Schenerman, M. A. *Tetrahedron Lett.* **2002**, *43*, 1395.

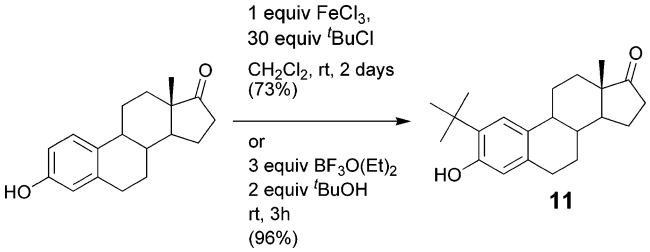
of the 3-OH group as a methyl ether did not help. Reaction of nitrile **8** with $LiAlH_4$ in refluxing THF gave amine **9** in 59% yield.[16] Direct oxidation of **9** using refluxing $(CH_2)_6N_4$ in HOAc/H_2O[18] failed to give 4-FE1. Nitrile **9** proved to be remarkably inert to hydrolysis. Acidic hydrolysis in 70% sulfuric acid did not proceed at all. Basic hydrolysis using NaOH in ethylene glycol at 170 °C did yield acid **5** however many unidentified byproducts were formed and we were never able to isolate **5** in pure form.

Since bromo compound **7** was readily obtained, we envisioned preparing 4-FE1 by converting **7** to vinyl derivative **10** followed by oxidation of the alkene. Stille coupling of **7** with 1.1 equiv of tributylvinyltin in degassed DMF in the presence of 5.7 mol % of $Pd(PPh_3)_4$ at 165−170 °C for 24 h gave **10** in 73% yield. However, attempts to convert alkene **10** into 4-FE1 using ozonolysis or $NaIO_4/OsO_4$ yielded either complex mixtures or only trace amounts of 4-FE1.

One route by which formylated phenols are frequently prepared is by electrophilic aromatic substitution (EAS) of unprotected phenols using formaldehyde equivalents, such as hexamethylenetetramine (HMT), in the presence of an acid, such as TFA,[19] or using formaldehyde itself in the presence of a metal salt catalyst.[20] The former approach was used by Cushman et al.[21] and Peters et al.[7] for the synthesis of formylated E2 directly from E2. Not surprisingly, this gave a mixture of 2-formylestradiol (2-FE2) and 4-FE2, which were difficult to separate, and the yields were poor ranging from 13 to 25% for 2-FE2 and 4−13% for 4-FE2. Clearly, the issues of both yield and regioselectivity would have to be addressed for EAS to be a practical approach to 4-FE1. We reasoned that the formaldehyde/metal salt approach could be used to address the yield issue since these procedures generally proceed in good yield and that the selectivity issue could be dealt with using a positional protecting group at C-2.

Although regioselectivity has long been a problem in the synthesis of C-4-substituted estrogens by EAS, to our knowledge, the use of a positional protecting group has never been examined as a means of getting around this issue. The *tert*-butyl group has been used as a positional protecting group for the ortho position of substituted phenols for over 50 years.[22] It is usually removed using Lewis acids such as $AlCl_3$ in an acceptor solvent such as benzene, toluene, or nitromethane.[23] 2-*tert*-Butylestrone (**11**) was first synthesized in 1968 by Lunn and Farkas by passing a slow stream of BF_3 over a solution of

SCHEME 2. Synthesis of 2-*tert*-Butylestrone (11)



E1 and 6 equiv of *tert*-butyl alcohol in *n*-pentane.[24] What was particularly significant about this was the high yield of the reaction (89%) and, due to the large size of the *tert*-butyl group, no reaction occurred at the 4-position. Later, Goendoes et al. reported that **11** could be prepared in an 81% yield using Friedel−Crafts (F−C) chemistry (*tert*-butyl chloride, $FeCl_3$).[25] The high selectivity and yields of these reactions, coupled with the knowledge that the *tert*-butyl group can be removed from phenolic derivatives in high yield using Lewis acids, suggested to us that it could be used as a positional protecting group during the synthesis of 4-FE1.

We examined both of the above methods for preparing compound **11**. Using the F−C chemistry we found that although the major product was the desired 2-isomer, some of the undesired 4-isomer was also obtained and after chromatography and recrystallization, **11** was obtained in a 73% yield (Scheme 2). Therefore, we examined Lunn and Farkas' approach. However, rather than use gaseous BF_3, we elected to use $BF_3(OEt)_2$ which is easier to handle. It was found that by subjecting E1 to 3.0 equiv of $BF_3(OEt)_2$ and 2.0 equiv of *tert*-butyl alcohol in dry CH_2Cl_2 for 3 h, a 96% yield of **11** could be obtained. None of the 4-isomer was detected.

For the formylation of **11** we chose to use the method of Hofslokken and Skattebol.[20d,26] This is a convenient and generally high-yielding procedure for the selective ortho formylation of phenols using paraformaldehyde, anhydrous $MgCl_2$, and anhydrous trimethyl amine in refluxing anhydrous acetonitrile or THF. Employing the reagent quantities and conditions reported by Hofslokken and Skattebol (2 equiv of $MgCl_2$, 3 equiv of paraformaldehyde, 2 equiv of Et_3N, oil bath at 75 °C, 4 h), we obtained three products (Scheme 3).[27] One was the desired aldehyde product **12**, which could not be separated using silica gel chromatography from another product, ether **13**. The ratio of aldehyde **12** to ether **13** was 3.1:1.0 as determined by ^1H NMR of the chromatographed mixture. A yield of 30% was calculated for aldehyde **12**. The third product was dimer **14**, which was readily separated from compounds **12** and **13**. The ratio of aldehyde **12** to dimer **14** was 1.2:1.0 as determined by the ^1H NMR of the crude reaction mixture after aqueous workup. In their original paper, Hofslokken and Skattebol reported the formation of methyl ether byproducts in only a few of the

(15) Cha, J. S.; Jang, S. H.; Kwon, S. Y. *Bull. Korean Chem. Soc.* **2002**, *23*, 1697.

(16) This synthesis of **9** (33% in three steps from E1) is a considerable improvement over the literature synthesis of **9** which was accomplished in a 21% yield over 6 steps starting from estradiol. See ref 17.

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(22) Kulka, M. *J. Am. Chem. Soc.*, **1954**, *76*, 5469.

(23) For a review on the de-*tert*-butylation of substituted arenes, see: Saleh, S. A.; Tashtoush, H., I. *Tetrahedron*, **1998**, *53*, 14157.

(24) Lunn, W. H. W.; Farkas, E. *Tetrahedron* **1968**, *24*, 6773.

(25) Goendoes, G.; Dombi, G. *Monatsh. Chem.* **2002**, *133*, 1279.

(26) We also attempted the formylation of **11** by a Reimer−Tiemann reaction employing the conditions used by Pert and Ridley for the formylation of E1 (1.0 mmol compound **11**, 2.5 mL $CHCl_3$, 2.5 mL of 1.5 M NaOH, 20 mg benzyltriethylammonium chloride in 2.5 mL 95% ethanol then reflux for 20 h. See ref 6). However, even after 24 h reflux, most of the starting material remained unreacted and only a 9% yield of 4-formylated product was obtained. Adding additional base or chloroform at various time intervals and increasing the reaction times did not result in improved yields.

(27) We found that subjecting E1 to these conditions yields a mixture of 2-FE1 (major) and 4-FE1 (minor) as well as unidentified byproducts.

SCHEME 3. Formylation of 11 with Paraformaldehyde, Triethylamine, and Magnesium Chloride

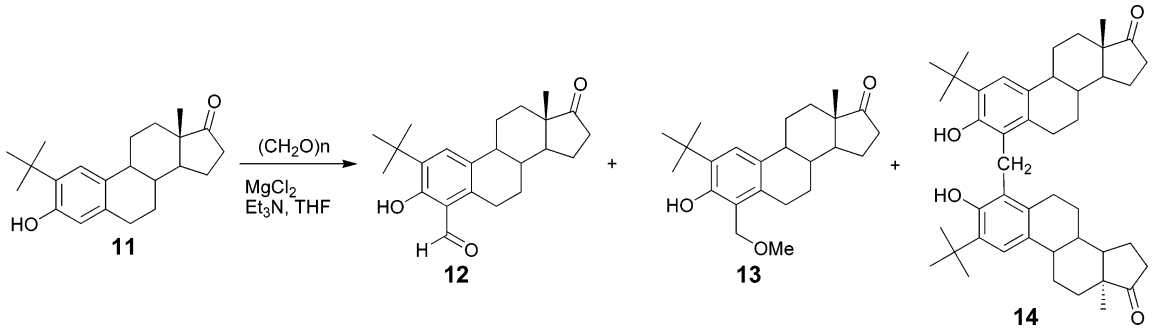
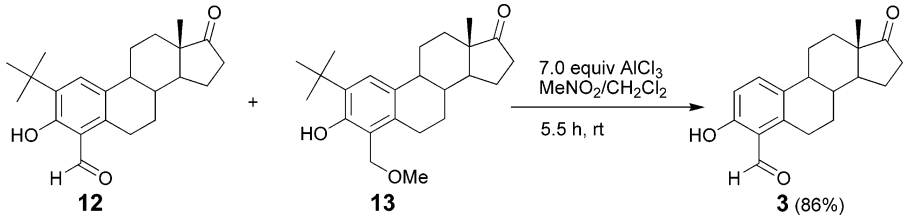


TABLE 1. Formylation of 11 Using Paraformaldehyde, Magnesium Chloride, and Triethylamine

entry[a]	$(CH_2O)_n$[b]	$MgCl_2$[b]	Et_3N[b]	*T* (°C)	time (h)	**12**:**13**	**12**:**14**[e]	% yield of **12**[c]
1	3.0	2.0	2.0	75	5	3.1:1.0[d]	1.2:1.0	30
2	3.0	2.0	2.0	40	6	5.9:1.0[d]	7.7:1.0	47
3[g]	3.0	2.0	2.0	33	16	7.1:1.0[e]	9.0:1.0	ND
4[h]	3.0	2.0	2.0	40−54	36		1.25:1.0	ND
5	7.0	6.0	6.0	40	3.5	6.5:1.0[d]	11.6:1.0	53
6	5.0	4.0	4.0	40	4.5	7.5:1.0[d]	13.4:1.0	60
7[i]	5.0	4.0	4.0	40	4	7.5:1.0[d]	12.5:1.0	68
8[j]	5.0	4.0	4.0	40	8	8.0:1.0[e]	4.5:1.0	ND

[a] Entry 1 was performed using 326 mg of **11** in 5 mL of THF. Entries 2−6 were performed using 200 mg of **11** in 10 mL of THF. [b] Equivalents of reagent compared to compound **11**. [c] Compound **12** was obtained as a mixture with compound **13** after chromatography. The yield of **12** was calculated using the ratio of **12**:**13** shown in column 7. [d] Ratio determined by ^{1}H NMR after chromatography. [e] Ratio determined by ^{1}H NMR after aqueous workup. [f] 2.0 equiv of HMPA added. [g] 17% of unreacted **11** remained after 16 h. [h] 23% unreacted **11** remained after 36 h. [i] Performed using 2 g of **11** in 100 mL of THF. [j] Reaction performed using 200 mg of **11** in 30 mL of THF and under a slight vacuum. THF was replenished at various time intervals.

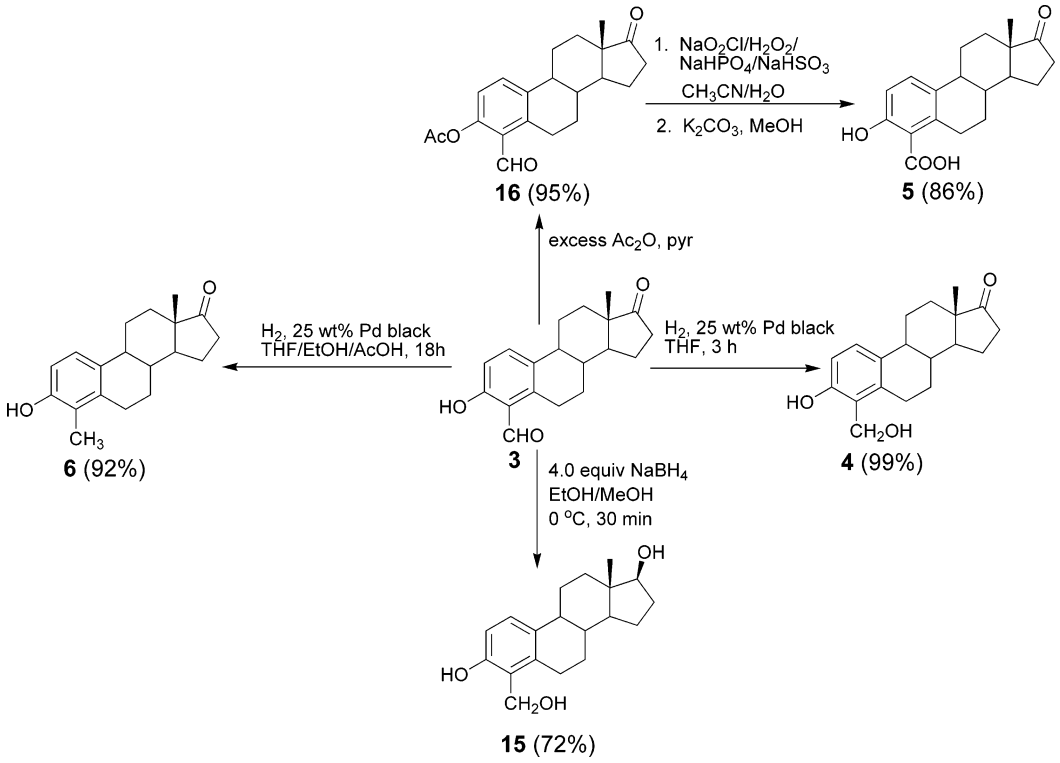
SCHEME 4. Synthesis of 4-FE1 (3) by De-*tert*-butylation of 12



phenols they examined as substrates and in amounts usually well under 9%. No dimer formation was reported. However, dimer formation was observed in the reaction between paraformaldehyde and magnesium phenoxides formed from ethyl magnesium bromide[20b] or magnesium methoxide.[20c] Formation of both the ether and dimer byproducts was attributed to the attack of methanol, a byproduct of the reaction, and the phenol derivative on a quinone methide which is produced as a transient byproduct.[20b−d] Optimization studies were undertaken to try and improve the yield of **12** (Table 1). It was found that the reaction proceeded within 6 h at 40 °C (entry 2), but lowering the temperature even further to 33 °C did not result in complete reaction even after 16 h (entry 3). The amount of dimer and ether byproducts decreased at the lower temperatures, and at 40 °C, the yield of aldehyde **12** increased 47%. It was reported that by adding HMPA to the reaction when using ethyl magnesium bromide to generate the magnesium phenoxide that dimer formation could be suppressed.[20b] However, when the reaction was performed using $MgCl_2/Et_3N$ at 40 °C in the presence of 2.0 equiv of dry HMPA the reaction was very slow and after 16 h little reaction had occurred. Increasing the temperature to 54 °C and letting the reaction proceed for a further 24 h gave aldehyde **12** and dimer **14** in almost equal amounts, though almost no ether was formed and 23% of unreacted compound **11** remained (entry 4). Increasing the amount of paraformaldehyde to 7.0 equiv and the amount of Et_3N and $MgCl_2$ to 6.0 equiv gave the aldehyde in 53% yield with an aldehyde to ether ratio of 6.5:1.0 and a aldehyde to dimer ratio of 11.6:1 (entry 5). Using 5.0 equiv of paraformaldehyde and 4.0 equiv of Et_3N and $MgCl_2$, the aldehyde was obtained in a 60% yield and the amount of ether and dimer byproducts again decreased (entry 6). Using the same number of equivalents but performing the reaction on a 10-fold larger scale resulted in a 68% yield of aldehyde and with similar ratios of aldehyde to byproduct (entry 7). In an attempt to remove the methanol that is formed during the reaction and thereby reduce ether formation, the reaction was performed at 40 °C under a slight vacuum that allowed solvent and methanol to distill off slowly during the reaction (entry 8). The solvent was replenished at various time intervals during the reaction. Although this resulted in a slight increase in the aldehyde to ether ratio, the aldehyde to dimer ratio decreased significantly and the reaction was not complete even after 8 h.

Since **12** and **13** were inseparable, the deprotection was performed on the mixture. Subjecting a mixture of **12** and **13** (ratio of 7.5:1.0, entry 7, Table 1) to 8.5 equiv of anhydrous aluminum chloride in nitromethane−CH_2Cl_2 at room temperature for 5.5 h gave 4-FE1 in 86% yield (Scheme 4). 4-FE1 was easily isolated by column chromatography, and the product resulting from de-*tert*-butylatation of methyl ether **13** was not detected, suggesting that compound **13** was decomposing to an identified byproduct during the reaction and aq. acidic workup.

SCHEME 5. Synthesis of Compounds 4−6 and 15 from 4-FE1



The yield of 4-FE1 starting from compound **11** was 58% (two steps) and a respectable 56% starting from E1.

We found that 4-FE1 could be readily converted into the other estrone derivatives that we required (Scheme 5). Not surprisingly, selective reduction of the aldehyde moiety in 4-FE1 was not possible using $NaBH_4$, and triol **15** was obtained in 72% yield using this reagent.[28] However, it was found that by subjecting 4-FE1 to hydrogenation using 25 wt % Pd black/H_2 (balloon pressure) in THF the desired hydroxymethyl derivative **4** could be obtained in 99% yield (Scheme 5).[29] No reduction of the ketone at the 17-position was detected. Performing the hydrogenation in THF/EtOH/AcOH gave the 4-methyl derivative **6** in 92% yield.[30] We were unable to obtain acid **5** directly from 4-FE1. Conditions that have been shown to be effective for converting salicylaldehyde derivatives to salicylic acid derivatives, such as NaO_2Cl in the presence of either NaOMe in DMSO[31] or sulfamic acid in THF/H_2O/DMSO,[32] were ineffective with 4-FE1. We believed that this was partly due to solubility issues since 4-FE1 is insoluble in most polar solvents as DMSO and H_2O. Therefore, 4-FE1 was acetylated in 95% yield using Ac_2O/pyr. The resulting ester **16** was soluble in most organic solvents, and we were able to oxidize the aldehyde moiety in **5** to the corresponding acid using NaO_2Cl/H_2O_2/$NaHPO_4/NaHSO_3$ in acetonitrile/water.[33] The crude acid was subjected to methanolysis which gave acid **5** in 86% yield (two steps).

In summary, an effective synthesis of 4-FE1 was achieved. Key to the success of this synthesis was the use of the *tert*-butyl group as a positional protecting group and we believe that this represents the first use of a positional protecting group for the synthesis of a C-4 modified estrogen. 4-FE1 could be converted to a variety of other C-4-modified estrogens in very high yield.[34] These syntheses represent dramatic improvements over literature procedures. The first synthesis of 4-carboxyestrone (**5**) was also achieved. We expect that this approach will find widespread use in the synthesis of other C-4-modified estrogens.

Experimental Section

4-Formylestra-1,3,5(10)-trien-17-one (3). To a solution of **12** and **13** (100 mg, ratio of **12**:**13** was 7.5:1, 0.247 mmol compound **12**) in CH_2Cl_2 (4.0 mL) was added nitromethane (2.0 mL, 151 equiv). The resulting mixture was cooled to 0 °C, and anhydrous $AlCl_3$ (280 mg, 2.1 mmol, 8.5 equiv) was added. After being stirred for 5.5 h at rt, the reaction was quenched with ice−water and 1 N HCl and the reaction stirred for 10 min. The mixture was extracted with EtOAc, and the combined extracts were washed with H_2O and brine and then dried (Na_2SO_4) and concentrated. Purifica-

(28) Triol **15** has been prepared previously by Lovely et al. in five steps starting from E2 in an overall yield of 13% (see ref 17). We have achieved its synthesis in 4 steps starting from E1 in 33% yield and we have not attempted to optimize the reduction reaction.

(29) Compound **4** was obtained by Singh et al. as a byproduct in the synthesis of 2-hydroxymethyl estrone. This was achieved by hydroxymethylation of estrone protected at the 17-position with a 1,3-dioxolane ketal followed by removal of the ketal protecting group. The hydroxymethylation gave a 35% yield of the 2- and 4-isomers in a 5:1 ratio which could not be separated until the ketal protecting group was removed. The overall yield of **4** was 6%. See ref 8. We have prepared compound **4** in a 55% yield starting from E1.

(30) This synthesis of **6** (50% from E1) represents a dramatic improvement over the literature procedure which has been prepared by a multistep procedure in less than 3% yield starting from expensive 19-nortestosterone. See ref 9 and references therein.

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(34) Inhibition studies with compounds **3**−**6** and steroid sulfatase are in progress. The results of these studies will be reported elsewhere.

tion of the residue by chromatography (methylene chloride) gave compound **3** as a yellow solid (63 mg, 86%). NMR spectra corresponded to those reported in the literature:[7] mp 234−236 °C (lit.[7] mp 234−237 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.96 (s, 1H), 10.34 (s, 1H), 7.44 (d, J = 8.9 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 3.34 (dd, J = 17.1 Hz, J = 5.7 Hz, 1H), 3.19−3.07 (m, 1H), 2.48 (dd, J = 18.9 Hz, J = 9.3 Hz, 1H), 2.36−1.90 (m, 6H), 1.67−1.35 (m, 6H), 0.89 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.4, 195.5, 161.5, 139.3, 135.4, 131.0, 117.4, 115.8, 50.7, 47.8, 43.8, 37.4, 35.8, 31.5, 26.1, 26.0, 25.4, 21.4, 13.8.

4-Hydroxymethylestra-1,3,5(10)-trien-17-one (4). To a solution of **3** (300 mg, 1.01 mmol) in dry THF (60 mL) was added Pd black (75 mg). The flask was flushed with H_2 and fitted with a balloon filled with H_2. The mixture was stirred for 6 h and filtered through Celite and the filtrate concentrated, which gave compound **4** as a white solid (300 mg, 99%): mp 201−202 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.03 (s, 1H), 6.98 (d, J = 7.2 Hz, 1H, H-1), 6.50 (d, J = 7.2 Hz, 1H, H-2), 4.64 (s, 1H), 4.48 (s, 2H), 2.99−2.70 (m, 2H), 2.47−1.92 (m, 6H), 1.73−1.70 (m, 1H), 1.55−1.27 (m, 6H), 0.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 220.2, 153.8, 137.1, 130.7, 125.4, 125.1, 113.3, 55.0, 50.8, 47.7, 44.3, 37.8, 35.9, 31.9, 26.6, 26.3, 26.0, 21.6, 13.9; LRMS (EI) m/z 300 (M^+, 63), 299 (43), 282 ($M-H_2O$, 100), 240 (14), 225 (18); LRMS (EI) m/z 300 (M^+, 64), 282, (100), 255 (15); HRMS (EI) calcd for $C_{19}H_{24}O_3$ 300.1725, found 300.1715.

4-Carboxyestra-1,3,5(10)-trien-17-one (5). To a solution of 80% sodium chlorite (312 mg, 2.73 mmol), sodium hydrogen phosphate (528 mg, 4.41 mmol), and hydrogen peroxide (0.225 mL, 30% in water) in water (6 mL) at 0 °C was added portionwise sodium hydrogen sulfite (143 mg, 1.2 mmol) with stirring. This solution was added dropwise to a solution of **16** (436 mg, 1.27 mmol) in CH_3CN (15 mL) at room temperature and the resulting yellow biphasic solution vigorously stirred for 1.5 h. The reaction was quenched with satd sodium sulfite (5 mL) and extracted with EtOAc (5 × 15 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a white solid. This solid was dissolved in MeOH (12 mL), and potassium carbonate (800 mg) was added. The mixture was stirred for 2.5 h and then acidified with 1 N HCl (pH 2 by pH paper) and diluted with water (40 mL). The resulting suspension was stored at −20 °C for 3 h and then filtered and the filter cake washed with cold water. The filter cake was collected and dried over high vacuum to give acid **5** as a slightly off-white solid (345 mg, 86%): mp 236−238 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.12 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.7 Hz, 1H), 2.72 (broad d, J = 5.5 Hz, 2H), 2.28−2.42 (m, 2H), 1.68−2.13 (m, 5H), 1.21−1.60 (m, 6H), 0.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 220.1, 173.0, 158.3, 137.7, 129.6, 128.0, 119.8, 114.1, 50.1, 47.7, 44.4, 37.7, 35.9, 31.9, 28.5, 26.7, 26.4, 21.6, 14.0; LRMS (neg ESI) m/z 313 (M − 1, 100); HRMS (neg ESI) calcd for $C_{19}H_{21}O_4$ (M − 1) 313.1450, found 313.1440.

4-Methylestra-1,3,5(10)-trien-17-one (6). Compound **3** (50 mg, 0.168 mmol) was dissolved in dry THF (10 mL). This required some gentle heating with a heat gun. Absolute ethanol (10 mL) was added followed by Pd black (12.5 mg, 25 wt %). The flask was purged with H_2 and then fitted with a balloon filled with H_2. After 2 h, glacial AcOH was added (3 mL) and the solution stirred for a further 16 h. The mixture was filtered through Celite and the filtrate concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane, 1:4) to give **6** as a white solid (43.9 mg, 92%): mp 216−217 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (d, J = 8.7 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 4.63 (s, 1H), 1.90−2.90 (m, 12H), 1.36−1.71 (m, 6H), 0.83 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 220.0, 153.2, 136.0, 130.5, 123.2, 121.8, 112.5, 50.8, 47.7, 44.2, 37.7, 35.8, 31.8, 27.4, 26.8, 26.3, 21.6, 13.9, 11.5; LRMS (EI) m/z 284 (M^+, 100), 199.1 (18), 160 (15); HRMS (EI) calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1776.

4-Cyanoestra-1,3,5(10)-trien-17-one (8). This was prepared according to the procedure of Labrie et al. with slight modifications.[12] A mixture of **7**[10] (500 mg, 1.44 mmol) and CuCN (300 mg. 3.33 mmol, 2.3 equiv) in DMF (12 mL) was refluxed for 6.5 h. After the mixture was cooled to rt, $FeCl_3$ (1 g) and concd HCl (1 mL) were added, and the mixture was heated at 55 °C for 30 min, cooled to rt, and treated with H_2O (20 mL). The mixture was extracted with ethyl acetate, and combined organics were washed with H_2O and brine and then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane 1:2 to 1:1.5) to give **8** as a white solid (375 mg, 89%): ^{1}H NMR corresponded to that reported in the literature;[12] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.68 (s, 1H), 7.34 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 2.92−2.70 (m, 2H), 2.39 (dd, J = 18.6 Hz, J = 8.1 Hz, 1H), 2.27−2.25 (m, 1H), 2.13−1.85 (m, 4H), 1.69 (d, J = 8.4 Hz, 1H), 1.54−1.25 (m, 6H), 0.76 (s, 3H, CH_3).

4-(Aminomethyl)-17β-hydroxylestra-1,3,5(10)-triene (9). To a suspension of $LiAlH_4$ (300 mg, 8.82 mmol, 13 equiv) in THF (20 mL) at 0 °C was added a solution of **8** (200 mg, 0.678 mmol) in THF (20 mL). After addition, the resulting mixture was stirred for 20 min at rt and then gently refluxed overnight (oil bath temperature 70 °C). The mixture was cooled to rt and poured onto ice−water, and the mixture was filtered through a pad of Celite. The filtrate was extracted with Et_2O, and the combined extracts were washed with brine and then dried (Na_2SO_4), filtered, and concentrated. The residue was subjected to chromatography (ethyl acetate/methanol, 2:1) to give pure **9** as a yellow solid (120 mg, 59%): NMR spectra corresponded to that reported in the literature;[17] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.94 (d, 1H), 6.43 (d, 1H), 5.00 (brs, 4H), 3.79 (s, 2H), 3.47 (s, 1H), 2.70−2.45 (m, 2H), 2.20−1.10 (m, 13H), 0.61 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.6, 134.5, 130.4, 124.7, 123.3, 113.9, 80.5, 50.0, 44.4, 43.1, 39.6, 39.1, 37.1, 30.4, 27.6, 26.9, 26.7, 23.2, 11.7.

4-Vinylestra-1,3,5(10)-trien-17-one (10). To a solution of **7** (2.10 g, 6.05 mmol) and tributylvinyltin (2.0 mL, 6.8 mmol, 1.1 equiv) in DMF (40 mL) was added $Pd(PPh_3)_4$ (400 mg, 0.347 mmol, 5.7 mol %). The resulting mixture was degassed seven times using liquid nitrogen and high vacuum before heating at 165−170 °C for 24 h. After cooling to rt, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined organics were washed with H_2O and brine and then dried (Na_2SO_4), filtered, and concentrated. The residue was subjected to chromatography (ethyl acetate/hexane, 1:3 to 1:2.5) to give **10** as a white solid (1.31 g, 73%): mp 188−189 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (dd, J = 8.7 Hz, J = 3.0 Hz, 1H), 6.79 (dd, J = 8.7 Hz, J = 3.3 Hz, 1H), 6.62 (ddd, J = 18.3 Hz, J = 12.7 Hz, J = 3.0 Hz, 1H), 5.70 (dd, J = 11.4 Hz, J = 1.8 Hz, 1H), 5.53 (t, J = 3.0 Hz, 1H), 5.52 (dd, J = 18.0 Hz, J = 1.8 Hz, 1H), 2.82−2.59 (m, 2H), 2.54−2.33 (m, 2H), 2.30−1.89 (m, 5H), 1.66−1.32 (m, 6H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 221.2, 150.8, 135.3, 132.4, 131.5, 125.6, 123.4, 120.5, 113.0, 50.4, 47.9, 44.2, 37.7, 35.9, 31.6, 27.9, 26.6, 26.1, 21.6, 12.8; LRMS (EI) m/z 296 (M^+, 100), 281 (2), 239 (8), 211 (12), 172 (10); HRMS (EI) calcd for $C_{20}H_{24}O_2$ 296.1776, found 296.1780.

2-*tert*-Butylestra-1,3,5(10)-trien-17-one (11). To a solution of E1 (7.00 g, 25.9 mmol) and *tert*-butyl alcohol (4.95 mL, 51.8 mmol, 2.0 equiv) in dry methylene chloride (300 mL) was added BF_3-$(OEt)_2$ (9.80 mL, 77.3 mmol, 3.0 equiv) over a period of 1 h by syringe pump. After being stirred for 2 h, the reaction was quenched with satd aq $NaHCO_3$, and the layers were separated. The organic layer was washed with water and brine and then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (methylene chloride) to give **11** as a white solid (8.1 g, 96%): NMR spectra corresponded to those reported in the literature;[25] mp 241−242 °C (lit.[24] mp 244−245 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (s, 1H), 6.44 (s, 1H), 5.09 (s, 1H), 2.87−2.75 (m, 2H), 2.53−2.40 (m, 2H), 2.30−1.90 (m, 5H), 1.70−1.40 (m, 15H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 221.5, 152.2, 135.1, 133.6, 131.2, 124.0, 116.6, 50.4, 48.1, 44.3, 38.5, 35.9, 34.5, 31.6, 29.7, 28.8, 26.5, 26.0, 21.6, 13.9.

2-*tert*-Butyl-4-formylestra-1,3,5(10)-trien-17-one (12), 2-*tert*-Butyl-4-(methoxymethyl)estra-1,3,5(10)-trien-17-one (13), and Bis(2-*tert*-butylestra-1,3,5(10)-trien-17-one)-3-ylmethane (14). Compound **11** (2.0 g, 6.13 mmol), dry paraformaldehyde (915 mg, 30.7 mmol, 5.0 equiv), and dry $MgCl_2$ beads (2.33 g, 24.5 mmol, 4.0 equiv) were added to a dry 500 mL round-bottom flask under Ar and then fitted with an unused septum. To this was added dry THF (100 mL) followed by dry triethylamine (3.4 mL, 24.5 mmol, 4.0 equiv). The resulting stirred mixture was heated at 40 °C for 4.0 h (a blast shield was positioned in front of the flask). It was then cooled to rt, diluted with ethyl acetate, and acidified with 1 N HCl, and the resulting mixture was stirred 10 min and then extracted with ethyl acetate. The combined extracts were washed with H_2O and brine and then dried (Na_2SO_4), filtered, and concentrated. ^{1}H NMR of the resulting solid revealed that the ratio of **12**:**13** was 7.9:1 and the ratio of **12**:**14** was 12.5:1. Subjecting the residue to flash chromatography (ethyl acetate/hexane 1:4) gave **12** and **13** as an inseparable yellow solid mixture (1.68 g total or 1.47 g aldehyde **12**, 68%). ^{1}H NMR of the mixture revealed that the ratio of **12**:**13** after chromatography was 7.5:1. Dimer **14** was isolated as a yellow solid (324 mg). Characteristic ^{1}H NMR assignments for **12**: ($CDCl_3$, 300 MHz) δ 12.80 (s, 1H), 10.34 (s, 1H), 7.47 (s, 1H); HRMS (EI) calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2187. Characteristic ^{1}H NMR assignments for **13**: ($CDCl_3$, 300 MHz) δ 8.16 (s, 1H), 7.20 (s, 1H), 4.73 (d, J = 12.4 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 3.45 (s, 3H); HRMS (EI) calcd for $C_{24}H_{34}O_3$ 370.2508, found 370.2518. Characterization data for **14**: mp dec >170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (s, 2H), 5.40 (s, 2H), 4.02 (s, 2H), 3.04 (dd, J = 16.8 Hz, J = 4.8 Hz, 2H), 2.90−2.79 (m, 2H), 2.55−2.29 (m, 6H), 2.21−1.97 (m, 8H), 1.67−1.23 (m, 18H), 0.93 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.9, 152.8, 134.7, 133.5, 132.2, 123.4, 121.6, 50.5, 47.9, 44.7, 37.6, 35.9, 34.8, 31.7, 29.7, 27.6, 27.0, 26.9, 25.2, 21.6, 13.9; LRMS (EI) *m*/*z* 664 (M^+, 38), 339 (57), 326 (100), 311 (50); HRMS (EI) calcd for $C_{45}H_{60}O_4$ 664.4492, found 664.4498.

17β-Hydroxy-4-(hydroxymethyl)estra-1,3,5(10)-triene (15). To a solution of **3** (100 mg, 0.336 mmol) in EtOH/THF (30 mL, 2:1, heated to make a solution then cooled) at 0 °C was added $NaBH_4$ (51 mg, 1.34 mmol, 4.0 equiv). The reaction mixture was stirred for 30 min at 0 °C. The solvent was removed in vacuo at 30 °C (water bath), and the residue was acidified with 1 N HCl at 0 °C and extracted with ethyl acetate. The combined extracts were washed with H_2O and brine then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane, 1:2 to 1:1) to give **15** as a white solid (72 mg, 72%): the ^{1}H NMR corresponded to that reported in the literature;[17] ^{1}H NMR (CD_3OD, 300 MHz) δ 7.05 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 4.58 (s, 2H), 3.63 (t, J = 8.5 Hz, 1H), 3.00−2.93 (m, 1H), 3.00−2.72 (m, 1H), 2.28−1.10 (m, 13H), 0.74 (s, 3H).

3-Acetyl-4-formylestra-1,3,5(10)-trien-17-one (16). To a solution of compound **3** (400 mg, 1.34 mmol) in dry pyridine (7 mL) was added acetic anhydride (0.189 mL, 2.01 mmol, 1.5 equiv) and the reaction mixture stirred. After 1.5 h, additional acetic anhydride (0.063 mL, 0.5 equiv) was added, the mixture stirred for 1 h followed by the addition of another 0.5 equiv of acetic anhydride, and the reaction mixture stirred for 4 h. The mixture was concentrated and the residue purified by flash chromatography (ethyl acetate/hexane, 1:4) to give compound **16** as a white foam (436 mg, 95%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.39 (s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.31−3.39 (m, 1H), 3.09−3.21 (M, 1H), 1.90−2.60 (m, 10H), 1.34−1.71 (m, 6H), 0.90 (s, 3H); ^{13}C NMR (75 MHz) δ 220.2, 190.3, 169.5, 150.8, 140.5, 139.0, 131.8, 125.4, 120.6, 50.2, 47.6, 44.3, 36.8, 35.8, 31.5, 27.1, 26.0, 21.4, 20.8, 13.7.; LRMS (EI) *m*/*z* 340 (M^+, 20), 298 (100), 241 (5); HRMS (EI) calcd for $C_{21}H_{24}O_4$ 340.1675, found 340.1671.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **3**−**6**, **10**, **14**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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