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ortho-Formylation of estrogens. Synthesis of the anti-cancer agent 2-methoxyestradiol

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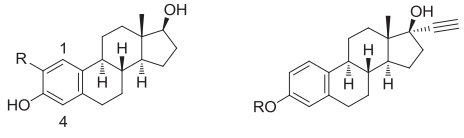
ABSTRACT

Several estrogens were mono-formylated using a mixture of paraformaldehyde, $MgCl_2$, and Et_3N in refluxing THF. In all cases, the 2-isomer was formed as the major product with high regioselectivity compared to the 4-isomer. Excellent to high yields were obtained in all examples except one. The method was applied for an efficient synthesis of the anti-cancer agent 2-methoxyestradiol.

1. Introduction

Estrogens exhibit many interesting biological activities and several are used as pharmaceuticals (Fig. 1). The synthesis of estrogens and their derivatives continues to attract interest as it is evident from the numerous studies that have been reported over the last five decades.[1,2]



2-Methoxyestradiol (**1**): R = OMe
Estradiol (**2**): R = H

Ethinylestradiol (**3**): R = H
Mestranol (**4**): R = Me

Fig. 1. Examples of bioactive estrogens.

One example of a bioactive estrogen is 2-methoxyestradiol (**1**) that exhibits promising anti-cancer activity and has entered clinical trials.[3] Several syntheses of **1** have been reported;[4] however, most of them are hampered by problems, such as low yields and formation of both 2- and 4-regioisomers by protocols that are not easily adaptable for large scale preparations. Hence, improved synthetic routes are still desired. One attractive approach for a preparative scale synthesis of 2-methoxyestradiol (**1**) is by regioselective *ortho*-formylation of estradiol (**2**) to its 2-substituted salicylaldehyde. Salicylaldehydes are accessible from the corresponding phenols by several classical formylation reactions.[5] Unfortunately, the yields are often only moderate and the lack of regioselectivity is apparant.[6] Moreover, the reaction conditions are quite harsh and often environmentally disagreeable reagents must be employed. The recently reported regioselective *ortho*-formylation of substituted phenols using the $MgCl_2$–Et_3N base system and paraformaldehyde yields salicylaldehydes in excellent yields.[7] This method has been employed for the preparation of useful intermediates and natural products.[8] We wanted to investigate if this methodology could be applied in regioselective formylation of estrogens. Taylor and coworkers have used this method for the synthesis of 4-substituted salicylaldehydes of estrone derivatives that were protected in the 2-position; however, the regioselectivity was not an issue for these examples.[9] Herein a practical, regioselective, and operationally simple procedure for the formylation of estrogens **2**, **6**–**12** is reported. Furthermore, this procedure was applied in a practical and scalable synthesis of 2-methoxyestradiol (**1**).

2. Results and discussion

When estradiol (**2**) was reacted with 4 equiv of paraformaldehyde in the presence of 3 equiv of both $MgCl_2$ and Et_3N, the regioisomeric aldehydes **13a** and **13b** were obtained in an excellent 92% yield (Table 1). According to LC/MS and ^1H NMR analyses the regioisomeric ratio was determined to be 13:1 in favor of the 2-substituted aldehyde **13a**. The aldehydes **14a** and **14b** were obtained in 86% yield when 17α ethinyl estradiol (**6**) was reacted under the same conditions; in this case the regioisomeric ratio was 6:1 in favor of **14a**.

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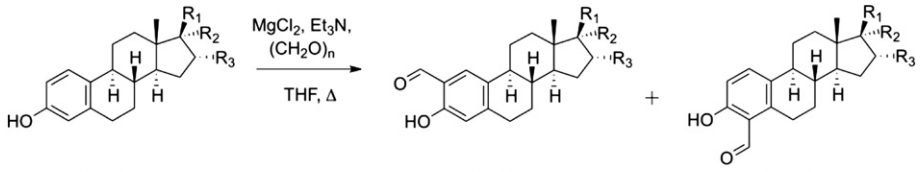
Table 1
ortho-Formylation of estrogens



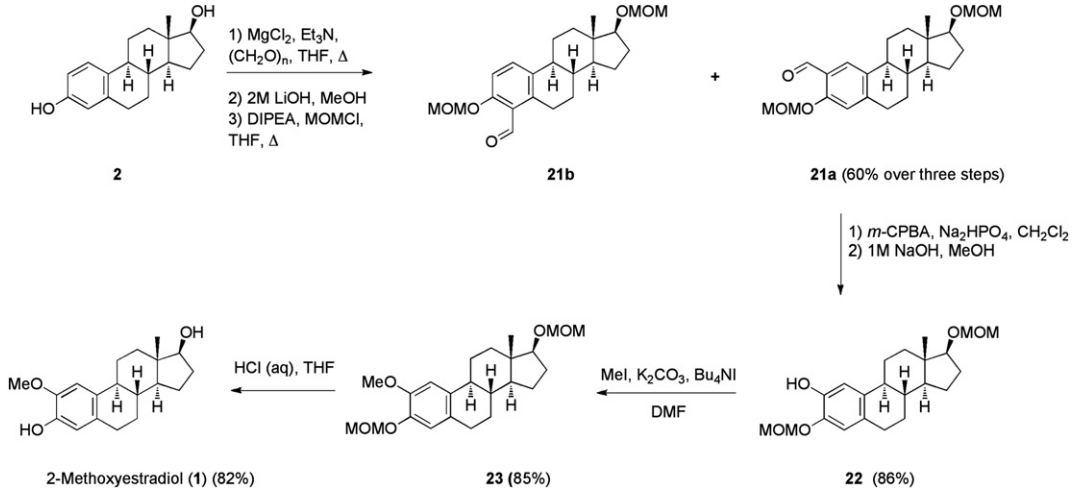
Estrogen	R_1	R_2	R_3	Product	Regioisomeric ratio[a]	Yield[c] %
2	OH	H	H	**13a**:**13b**	13:1	92
6	OH	CCH	H	**14a**:**14b**	6:1	86
7	OH	CH_2CH_3	H	**15a**:**15b**	12:1	90
8	H	OH	H	**16a**:**16b**	13:1	85
9	OAc	H	H	**17a**:**17b**	8:1	90
10	OH	H	OH	**18a**:**18b**	n.d.[b]	15
11	=O		H	**19a**:**19b**	9:1	90
12		OCH_2CH_2O	H	**20a**:**20b**	12:1	74[d]

[a] The regioisomeric ratios of the salicylaldehydes were determined by LC/MS analysis.
[b] Not determined.
[c] The yields and regioisomeric ratios are based on three experiments. The regioisomeric ratios were constant in all experiments.
[d] A 12:1 regioisomeric mixture of **19a** and **19b** was also obtained in 14% isolated yield.

Reacting 17α ethyl estradiol (**7**) under the aforementioned conditions afforded the two regioisomers **15a** and **15b** in 90% yield in a 12:1 ratio, respectively.

The 17α epimer **8** yielded comparable results using this *ortho*-formylation protocol, affording **16a** and **16b**. When the 17β-acetate **9** was formylated with the $MgCl_2$/Et_3N-base system, aldehydes **17a** and **17b** were formed as 8:1 mixture in a combined 90% yield. Again the 2-substituted aldehyde was the major product. Disappointingly, estriol (**10**) yielded only 15% yield of the two aldehydes **18a** and **18b**. On the other hand, when estrone (**11**) was subjected to the aforementioned formylation conditions, a mixture of the isomers **19a** and **19b** was formed in a combined 90% yield. Formylation of the acetal protected estrone **12** afforded a regioisomeric ratio of 12:1 in favor of the 2-substituted regioisomer **20a**. Deprotection of the acetal group in **12** occurred under the slightly acidic work-up conditions; the aldehydes **19a** and **19b** were also isolated in a combined 14% yield after chromatography (Table 1). Increasing the amount of $MgCl_2$, Et_3N or paraformaldehyde did not alter the regioisomeric outcome in any of the reactions. Changing the solvent resulted in complex reaction mixtures and significantly lower yields of the *ortho*-formylated products. In the *ortho*-formylation of estradiol (**2**) and its epimer **8** less than 10% of the corresponding 17-formate esters were also observed in the reaction mixture. These esters were identified by LC/MS and ^1H NMR analyses and were easily hydrolyzed with aqueous LiOH in methanol before work-up and chromatography yielded the target salicylaldehydes. Several other groups have also observed the formation of these esters in much higher yields when a combination of EtMgBr, HMPA, and paraformaldehyde in benzene at reflux was employed,[10] rendering support for the advantages for our protocol. Structural assignments of all products were based on spectral data and by comparison with literature values.[4j,6b,10a,11]

The *ortho*-formylation procedure with the $MgCl_2$/Et_3N-base system was employed in an efficient synthesis of the anti-cancer agent 2-methoxyestradiol (**1**). Again, formylation of estradiol (**2**) afforded a 13:1 mixture of **13a** and **13b**. This mixture of aldehydes was converted to the MOM-protected aldehydes **21a** and **21b** under standard conditions.[12] Separation by column chromatography yielded **21a** in 60% isolated yield over the three steps. Applying the Dakin oxidation[13] conditions to **21a** gave the corresponding phenol **22** in 86% yield with physical and spectral data in accord with those previously reported.[4j] Methylation of the phenol **22** under known conditions yielded compound **23** that was deprotected[14] to 2-methoxyestradiol (**1**) in 70% yield over the two last steps (Scheme 1). Thus, starting from **2**, a synthesis of **1** was achieved in 36% overall yield.



Scheme 1. Synthesis of 2-methoxyestradiol (**1**).

3. Conclusion

In conclusion, the experimentally simple and regioselective *ortho*-formylation protocol of phenols was extended to several estrogens. All but one of the formylations occurred with high to excellent yields. In all cases, formation of the 2-isomer was highly preferred. The practical use of this method was proven with an efficient synthesis of the anti-cancer agent 2-methoxyestradiol (**1**). Our synthesis compares favorably with respect to simplicity, yield and especially regioselectivity with those reported.[4]

4. Experimental section

4.1. General

All reagents and solvents were used as purchased without further purification unless stated otherwise. Melting points are uncorrected. Analytical TLC was performed using silica gel 60 F_{254} glass plates (Merck). Flash column chromatography was performed on silica gel 60 Geduran (35–75 mm, EM Science). IR spectra were obtained on a Perkin–Elmer Spectrum BX series FT-IR spectrophotometer only selected peaks are reported. NMR spectra were recorded on a Bruker Avance DPX-300 MHz or DPX200 spectrometer for ^{1}H NMR and 75 or 50 MHz for ^{13}C NMR, respectively. Coupling constants (*J*) are reported in hertz, and chemical shifts are reported in parts per million relative to $CDCl_3$ (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C) and DMSO-d_6 (2.50 ppm for ^{1}H, 39.52 ppm for ^{13}C). Mass spectra were recorded at 70 eV with Fission's VG Pro spectrometer. High resolution mass spectra were performed with a VG Prospec mass spectrometer and with a Micromass Q-TOF-2™. The LC/MS analyses were performed on an Agilent Technologies 1200 Series (Eclipse XDB-C18 5 μm 4.6×150 mm), coupled with an Agilent 6310 ion Trap.

4.2. General procedure for the *ortho*-formylation of estrogens

To a solution of the estrogen (1 mmol) in dry THF (10 mL), anhydrous $MgCl_2$ (285 mg, 3 mmol), Et_3N (0.42 mL, 3 mmol), and paraformaldehyde (120 mg, 4 mmol) were added under an argon atmosphere. The reaction mixture was heated to reflux for 1–2 h, and monitored by TLC (hexane/EtOAc, 7:3). After complete consumption of the estrogen, the reaction mixture was cooled and quenched (1 M HCl, 10 mL). The aqueous phase was extracted with EtOAc (3×10 mL) and the combined organic phases were washed with brine and then dried ($MgSO_4$). Analytical pure samples were obtained by column chromatography or recrystallization.

*4.2.1. (8R,9S,13S,14S,17R)-17-Ethynyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthrene-2-carbaldehyde (**14a**).* Purification by recrystallization from Et_2O afforded a colorless solid (209 mg, 65%) with mp 201–202 °C (Et_2O) (lit.[10a] mp 210–215 °C); R_f 0.51 (hexane/acetone, 6:4); IR (KBr, cm^{-1}) ν: 3488, 3255, 2102, 1659; ^{1}H NMR (300 MHz, $CDCl_3$) δ=10.75 (s, 1H), 9.79 (s, 1H), 7.40 (s, 1H), 6.67 (s, 1H), 2.86 (s, 2H), 2.59 (s, 1H), 2.45–2.10 (m, 3H), 2.10–1.24 (m, 11H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=196.1, 159.2, 148.0, 132.6, 130.5, 118.9, 116.9, 87.4, 79.7, 74.1, 49.4, 47.0, 42.9, 39.0, 38.9, 32.5, 30.1, 26.7, 26.2, 22.7, 12.6; LC/MS [M$^{\bullet+}$−1] 323; $[\alpha]_D^{20}$ −27.0 (*c* 0.50, THF).

*4.2.2. (8R,9S,13S,14S,17R)-17-Ethynyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthrene-4-carbaldehyde (**14b**).* ^{1}H NMR (200 MHz, $CDCl_3$) δ=11.97 (s, 1H), 10.36 (s, 1H), 7.47 (d, *J*=8.9 Hz, 1H), 6.77 (d, *J*=9.2 Hz, 1H).

*4.2.3. (8R,9S,13S,14S,17S)-17-Ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]-phenanthrene-2-carbaldehyde (**15a**).* Purification by chromatography (hexane/EtOAc, 9:1–8:2) afforded a colorless solid (131 mg, 80%) with mp 157–158 °C ($CHCl_3$) (lit.[4b] mp 156–157 °C); R_f 0.26 (hexane/EtOAc, 8:2); IR (KBr, cm^{-1}) ν: 3487, 3413, 3318, 1653; ^{1}H NMR (300 MHz, $CDCl_3$) δ=10.74 (s, 1H), 9.77 (s, 1H), 7.38 (s, 1H), 6.65 (s, 1H), 2.91–2.78 (m, 2H), 2.31 (m, 1H), 2.11 (m, 1H), 2.03–1.92 (m, 1H), 1.92–1.81 (m, 1H), 1.69–1.18 (m, 12H), 0.98 (t, *J*=7.3 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=196.1, 159.2, 148.1, 132.8, 130.4, 118.9, 116.9, 83.4, 49.5, 46.5, 43.2, 39.2, 33.6, 31.3, 30.2, 28.8, 27.0, 26.2, 23.3, 14.4, 7.8; LC/MS [M$^{\bullet+}$−1] 327; $[\alpha]_D^{20}$ +51.8 (*c* 0.50, THF).

*4.2.4. (8R,9S,13S,14S,17S)-17-Ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-4-carbaldehyde (**15b**).* ^{1}H NMR (200 MHz, $CDCl_3$) δ=11.96 (s, 1H), 10.34 (s, 1H), 7.45 (d, *J*=9.0 Hz, 1H), 6.75 (d, *J*=8.9 Hz, 1H).

*4.2.5. (8R,9S,13S,14S,17S)-2-Formyl-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthren-17-yl acetate (**17a**).* An analytical sample was made according to Peters et al.:[10e] mp 181–182 °C (hexane/EtOAc) (lit.[11] mp 184–185 °C); R_f 0.50 (hexane/EtOAc, 2:1); IR (KBr, cm^{-1}) ν: 3427, 1728, 1652; ^{1}H NMR (300 MHz, $CDCl_3$) δ=10.74 (s, 1H), 9.78 (s, 1H), 7.38 (s, 1H), 6.66 (s, 1H), 4.67 (t, *J*=8.4 Hz, 1H), 2.93–2.75 (m, 2H), 2.37–2.08 (m, 3H), 2.04 (s, 3H), 1.95–1.81 (m, 2H), 1.79–1.63 (m, 1H), 1.61–1.16 (m, 8H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=196.0, 171.1, 159.2, 147.9, 132.5, 130.5, 118.9, 116.9, 82.5, 49.7, 43.2, 42.8, 38.1, 36.6, 30.0, 27.5, 26.7, 26.0, 23.2, 21.1, 12.0; LC/MS [M$^{\bullet+}$−1] 341; $[\alpha]_D^{20}$ +52.6 (*c* 0.50, THF).

*4.2.6. (8R,9S,13S,14S,17S)-4-Formyl-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthren-17-yl acetate (**17b**).* ^{1}H NMR (200 MHz, $CDCl_3$) δ=11.90 (s, 1H), 10.27 (s, 1H), 7.38 (d, *J*=9.0 Hz, 1H), 6.68 (d, *J*=8.8 Hz, 1H).

*4.2.7. (8R,9S,13S,14S)-3-Hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthrene-2-carbaldehyde (**19a**).* Purification by chromatography (hexane/EtOAc, 9:1–8:2) afforded a colorless solid (459 mg, 77%) with mp 164–165 °C (hexane/EtOAc) (lit.[6b,10a] mp 158–160 °C ($CHCl_3$)); R_f 0.26 (hexane/EtOAc 7:3); IR (KBr, cm^{-1}) ν: 3449, 1736, 1651; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.76 (s, 1H), 9.79 (s, 1H), 7.40 (s, 1H), 6.69 (s, 1H), 3.01–2.79 (m, 2H), 2.50 (dd, *J*=18.4, 8.3 Hz, 1H), 2.39 (s, 1H), 2.29–1.92 (m, 5H), 1.69–1.34 (m, 6H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=196.5, 159.7, 148.1, 132.5, 130.9, 119.4, 117.5, 50.8, 48.3, 43.8, 38.4, 36.2, 31.8, 30.4, 26.5, 26.2, 22.0, 14.2. LC/MS [M$^{\bullet+}$−1] 297; $[\alpha]_D^{20}$ +130 (*c* 0.50, THF), $[\alpha]_D^{20}$ +85.0 (*c* 0.50, $CHCl_3$) (lit.[11a] $[\alpha]_D$ +151 ($CHCl_3$)).

*4.2.8. (8R,9S,13S,14S)-3-Hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthrene-4-carbaldehyde (**19b**).* Purification by chromatography (hexane/EtOAc, 9:1–8:2) yellow solid (36 mg, 6%) with mp 244–247 °C (decomp., EtOAc) (lit.[6b] mp 244–246 °C (EtOAc)); R_f 0.26 (hexane/EtOAc 7:3); IR (KBr, cm^{-1}) ν: 3440, 1734, 1644; ^{1}H NMR (300 MHz, $CDCl_3$) δ=11.99 (s, 1H), 10.40 (s, 1H), 7.48 (d, *J*=8.9 Hz, 1H), 6.81 (d, *J*=8.9 Hz, 1H), 3.38 (dd, *J*=16.9, 5.7 Hz, 1H), 3.27–3.07 (m, 1H), 2.52 (dd, *J*=18.3, 8.5 Hz, 1H), 2.42–1.86 (m, 6H), 1.76–1.35 (m, 7H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=195.5, 161.6, 139.3, 135.4, 131.1, 117.5, 115.9, 50.1, 47.8, 43.9, 37.5, 35.8, 31.5, 26.1, 26.0, 25.4, 21.5, 13.8; LC/MS [M$^{\bullet+}$−1] 297; $[\alpha]_D^{20}$ +123 (*c* 0.50, THF).

*4.2.9. (8R,9S,13S,14S)-3-Hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]-phenanthrene-17,2′-[1,3]dioxolane]-2-carbaldehyde (**20a**).* Purification by chromatography (hexane/EtOAc, 9:1–8:2) afforded a colorless solid (67 mg, 64%) with mp 128–129 °C; (lit.[10a] mp 129–131 °C) R_f 0.43 (hexane/acetone, 1:3);

IR (KBr, cm^{-1}) ν: 3420, 1653; ^1H NMR (200 MHz, $CDCl_3$) δ=10.74 (s, 1H), 9.78 (s, 1H), 7.38 (s, 1H), 6.66 (s, 1H), 4.01–3.78 (m, 4H), 3.11 (m, 1H), 2.93–2.73 (m, 2H), 2.24 (m, 2H), 2.09–1.15 (m, 11H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=196.0, 159.2, 148.1, 132.8, 130.5, 119.2, 118.9, 116.9, 65.2, 64.5, 49.3, 46.0, 43.0, 38.6, 34.1, 30.4, 30.1, 26.5, 26.0, 22.3, 14.3; LC/MS [$M^{\bullet+}-1$] 341; $[\alpha]_D^{20}$ +60.2 (*c* 0.50, THF).

*4.2.10. (8R,9S,13S,14S)-3-Hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]-phenanthrene-17,2′-[1,3]dioxolane]-4-carbaldehyde (**20b**).* ^1H NMR (200 MHz, $CDCl_3$) δ=11.95 (s, 1H), 10.34 (s, 1H), 7.45 (d, *J*=8.9 Hz, 1H), 6.75 (d, *J*=8.8 Hz, 1H).

4.3. Hydrolysis of 17-formate esters

The crude reaction mixture was suspended in methanol (33 mg/mL) and LiOH (2 M, 1 mL) was added and an exothermic reaction occurred. The reaction mixture became instantly yellow. The reaction mixture was stirred for 15 min before HCl (1 M) was added until the reaction mixture became acidic, where after the reaction mixture was extracted with EtOAc (2×10 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). LC/MS- and ^1H NMR-analyses showed complete hydrolysis of the 17-formate. The hydrolysis did not change the 2- and 4-regioisomeric ratio.

*4.3.1. (8R,9S,13S,14S,17S)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]-phenanthrene-2-carbaldehyde (**13a**).* Purification by chromatography (hexane/THF, 5:1–3:2) afforded a colorless solid (1.23 g, 82%) with mp 232–234 °C (hexane/THF) (lit.[6b,10a] mp 231–233 °C (EtOH)); R_f 0.48 (hexane/THF, 3:2); IR (KBr, cm^{-1}) ν: 3358, 1657; ^1H NMR (300 MHz, $CDCl_3$) δ=10.75 (s, 1H), 9.79 (s, 1H), 7.40 (s, 1H), 6.68 (s, 1H), 3.78–3.63 (m, 1H), 2.96–2.76 (m, 2H), 2.33 (ddd, *J*=12.9, 6.9, 4.0 Hz, 1H), 2.23–2.03 (m, 2H), 2.03–1.93 (m, 1H), 1.93–1.82 (m, 1H), 1.78–1.61 (m, 1H), 1.46 (s, 9H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=196.1, 159.2, 148.1, 132.7, 130.5, 119.0, 117.0, 81.8, 50.0, 43.4, 43.2, 38.4, 36.5, 30.6, 30.1, 26.7, 26.2, 23.1, 11.0; LC/MS [$M^{\bullet+}-1$] 299; $[\alpha]_D^{20}$ +89.0 (*c* 0.50, THF), $[\alpha]_D^{20}$ +140 (*c*1.00, dioxane) (lit.[11b] $[\alpha]_D^{20}$ +88.0 (*c* 1.00, dioxane)).

*4.3.2. (8R,9S,13S,14S,17S)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]-phenanthrene-4-carbaldehyde (**13b**).* Purification by chromatography (hexane/THF, 5:1–3:2) afforded pale yellow crystals (71 mg, 5%) with mp 150–151 °C ($CHCl_3$) (lit.[6b] mp 144–145 °C (MeOH)); R_f 0.48 (hexane/THF, 3:2); IR (KBr, cm^{-1}) ν: 3451, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ=11.99 (s, 1H), 10.37 (s, 1H), 7.48 (d, *J*=8.8 Hz, 1H), 6.79 (d, *J*=8.8 Hz, 1H), 3.74 (t, *J*=8.1 Hz, 1H), 3.32 (dd, *J*=16.9, 5.1 Hz, 1H), 3.24–2.99 (m, 1H), 2.40–1.08 (m, 15H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=195.7, 161.4, 139.5, 135.5, 131.6, 117.5, 115.6, 81.7, 49.7, 43.8, 43.1, 37.9, 36.6, 30.6, 26.7, 26.5, 25.5, 23.0, 11.0; LC/MS [$M^{\bullet+}-1$] 299; $[\alpha]_D^{20}$ +94.8 (*c* 0.25, THF).

*4.3.3. (8R,9S,13S,14S,17R)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-2-carbaldehyde (**16a**).* Purification by chromatography (hexane/THF, 9:1–8:2) afforded a colorless solid (50 mg, 69%) with mp 181–182 °C (hexane/THF); R_f 0.30 (hexane/acetone, 3:1); IR (KBr, cm^{-1}) ν: 3339, 1655; ^1H NMR (300 MHz, $CDCl_3$) δ=10.75 (s, 1H), 9.79 (s, 1H), 7.42 (s, 1H), 6.68 (s, 1H), 3.80 (d, *J*=5.8 Hz, 1H), 2.96–2.75 (m, 2H), 2.45–2.32 (m, 1H), 2.29–2.12 (m, 2H), 1.99–1.71 (m, 3H), 1.71–1.13 (m, 9H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=196.1, 159.2, 148.2, 132.8, 130.5, 118.9, 116.9, 79.9, 47.7, 45.5, 43.1, 38.7, 32.5, 31.3, 30.3, 27.6, 26.1, 24.2, 17.0; LC/MS [$M^{\bullet+}-1$] 299; $[\alpha]_D^{20}$ +27.0 (*c* 1.00, THF); HRMS calcd for $C_{19}H_{23}O_3$ [$M^{\bullet+}$]: 300.1725. Found 300.1729.

*4.3.4. (8R,9S,13S,14S,17R)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthrene-4-carbaldehyde (**16b**).* ^1H NMR (200 MHz, $CDCl_3$) δ=11.92 (s, 1H), 10.31 (s, 1H), 7.41 (d, *J*=9.0 Hz, 1H), 6.72 (d, *J*=8.7 Hz, 1H).

*4.3.5. (8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthrene-2-carbaldehyde (**21a**).* The mixture of aldehydes **13a** and **13b** obtained from the *ortho*-formylation reaction of estradiol (**2**, 1 mmol) was dissolved in dry THF (3 mL) in a flame dried round bottle flask. Diisopropylethylamine (1 mL, 6.4 mmol) and chloromethyl methyl ether (400 μL, 5.3 mmol) was added. The reaction mixture was heated to reflux for 4 h before being cooled to room temperature where upon H_2O (10 mL) was added and the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic phases were washed with aqueous AcOH (10%, 5 mL) and aqueous $NaHCO_3$ solution (10 mL), dried ($MgSO_4$) and concentrated. Purification by chromatography (heptane/EtOAc, 9:1 to 6:4) yielded **21a** as a yellow semi solid (232 mg, 60% over two steps). R_f 0.43 (hexane/acetone, 3:1); IR (KBr, cm^{-1}) ν: 3417, 1675, 1607; ^1H NMR (300 MHz, $CDCl_3$) δ=10.40 (s, 1H), 7.74 (s, 1H), 6.88 (s, 1H), 5.24 (s, 2H), 4.69–4.57 (m, 2H), 3.59 (t, *J*=8.4 Hz, 1H), 3.49 (s, 3H), 3.35 (s, 3H), 2.92–2.81 (m, 2H), 2.36 (ddd, *J*=12.8, 6.9, 3.7 Hz, 1H), 2.22–1.77 (m, 4H), 1.77–1.03 (m, 8H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=189.5, 157.5, 146.3, 134.5, 125.3, 123.3, 115.0, 96.0, 94.6, 86.4, 56.4, 55.2, 50.0, 43.7, 42.9, 38.3, 37.0, 30.4, 28.0, 26.8, 26.1, 23.1, 11.7; $[\alpha]_D^{20}$ +60.2 (*c* 0.50, THF); HRMS calcd for $C_{23}H_{32}O_5$ [$M^{\bullet+}$]: 388.2250. Found 388.2265.

*4.3.6. (8R,9S,13S,14S,17S)-3,17-Bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthren-2-ol (**22**).* A solution of *m*-chloroperbenzoic acid (77%, 360 mg, 1.6 mmol) in CH_2Cl_2 (5 mL) was added drop wise to a solution of **21a** (320 mg, 0.8 mmol) in a mixture of CH_2Cl_2 (7 mL) and sodium hydrogenphosphate dihydrate (425 mg, 2.4 mmol). The resulting mixture was stirred at room temperature for 24 h, the reaction mixture was poured into H_2O (25 mL) and the product was extracted with Et_2O (3×40 mL). The organic layers were washed with saturated $NaHCO_3$ solution (25 mL), brine (2×25 mL), and then combined. The organic phases were dried ($MgSO_4$), and evaporation afforded a yellow oil that was dissolved in MeOH (5 mL). Then 1 M NaOH (3 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The solution was neutralized to pH 7 with 1:1 $NaHCO_3$/AcOH solution (15 mL), then methanol was removed under reduced pressure, and the residue was transferred into a mixture of EtOAc and water (1:1, 50 mL). The aqueous phase was extracted with a second portion of EtOAc (20 mL). The combined EtOAc fractions were dried ($MgSO_4$) and evaporated. The product (270 mg, 90%) was pure by ^1H NMR analysis, but was further purified by chromatography on silica gel (heptane/EtOAc 9:1 to 7:3) affording compound **22** as a colorless oil (258 mg, 86%). R_f 0.35 (heptane/EtOAc, 3:2); IR (KBr, cm^{-1}) ν: 3545; ^1H NMR (300 MHz, $CDCl_3$) δ=6.87 (s, 1H), 6.77 (s, 1H), 5.95 (s, 1H), 5.13 (s, 2H), 4.65 (s, 2H), 3.59 (t, *J*=8.4 Hz, 1H), 3.49 (s, 3H), 3.36 (s, 3H), 2.75 (dd, *J*=10.6, 4.5 Hz, 2H), 2.23–1.95 (m, 3H), 1.90–1.76 (m, 1H), 1.75–1.06 (m, 8H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.0, 142.3, 135.0, 128.2, 115.8, 112.3, 95.9, 86.5, 56.2, 55.0, 49.9, 44.0, 42.8, 38.4, 37.2, 29.0, 28.0, 27.3, 26.2, 23.0, 11.6; $[\alpha]_D^{20}$ +48.8 (*c* 0.50, THF); HRMS calcd for $C_{22}H_{32}O_5$ [$M^{\bullet+}$]: 376.2250. Found 376.2253.

*4.3.7. (8R,9S,13S,14S,17S)-2-Methoxy-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (**23**).* A solution of **22** (380 mg, 1 mmol) in anhydrous DMF (15 mL) containing anhydrous K_2CO_3 (1.38 g, 10 mmol) was stirred at

room temperature for 10 min. Iodomethane (781 mg, 5.5 mmol) was introduced into the reaction mixture, followed by the addition of *tetra*-butylammoniumiodide (8.5 mg, 0.03 mmol). The resulting mixture was stirred at room temperature for 5 h and then another portion of iodomethane (781 mg, 5.5 mmol) was introduced. After 20 h, the reaction mixture was poured into brine (20 mL) and the products were extracted with EtOAc (3×10 mL). The EtOAc layers were washed with brine (20 mL) and several portions of H_2O, combined, dried ($MgSO_4$), and evaporated to dryness. Purification by flash chromatography (heptane/EtOAc, 9:1 to 7:3) gave **23** (331 mg, 85%) as a colorless oil. R_f 0.50 (heptane/EtOAc, 1:1). Recrystallization from MeOH yielded a colorless solid with mp 68–70 °C (MeOH) (lit.[4j] mp 69–70 °C (MeOH)); IR (KBr, cm^{-1}) ν: 3435; ^1H NMR (300 MHz, $CDCl_3$) δ=6.87 (s, 1H), 6.84 (s, 1H), 5.19 (s, 2H), 4.70–4.62 (m, 2H), 3.85 (s, 3H), 3.62 (t, J=8.4 Hz, 1H), 3.51 (s, 3H), 3.38 (s, 3H), 2.89–2.72 (m, 2H), 2.33–1.95 (m, 4H), 1.95–1.79 (m, 1H), 1.77–1.11 (m, 8H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=147.5, 144.2, 134.0, 128.8, 116.7, 109.3, 95.8, 95.4, 86.4, 55.9, 55.9, 54.9, 49.8, 44.2, 42.8, 38.4, 37.1, 28.9, 28.0, 27.1, 26.3, 22.9, 11.6; $[\alpha]_D^{20}$ +64.0 (*c* 0.50, THF); HRMS calcd for $C_{23}H_{34}O_5$ [$M^{\bullet+}$]: 390.2406. Found 390.2400.

*4.3.8. (8R,9S,13S,14S,17S)-2-Methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta-[a]phenanthrene-3,17-diol (**1**).* To a solution of **23** (206 mg, 0.53 mmol) in THF (3 mL) was added HCl (6 M, 3 mL) at room temperature and the resulting solution was stirred at room temperature for 5 h. The reaction mixture was poured into brine (20 mL) and the products were extracted with EtOAc (3×20 mL). The EtOAc layers were washed with saturated $NaHCO_3$ solution (10 mL) and brine (20 mL), then combined, dried ($MgSO_4$), and evaporated. Purification by chromatography (CH_2Cl_2/EtOAc 9:1) gave **1** (131 mg, 82%) and recrystallization from $CHCl_3$ yielded a colorless solid with mp 185–186 °C ($CHCl_3$) (lit.[4a] mp 184–186 °C ($CHCl_3$)); IR (KBr, cm^{-1}) ν: 3426, 3198, 1607; ^1H NMR (300 MHz, DMSO) δ=8.55 (s, 1H), 6.75 (s, 1H), 6.43 (s, 1H), 4.47 (d, J=4.8 Hz, 1H), 3.71 (s, 3H), 3.58–3.44 (m, 1H), 2.74–2.54 (m, 2H), 2.34–2.17 (m, 1H), 2.15–2.00 (m, 1H), 1.97–1.80 (m, 2H), 1.80–1.70 (m, 1H), 1.64–1.49 (m, 1H), 1.47–0.99 (m, 7H), 0.66 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ=145.5, 144.3, 130.4, 128.3, 115.6, 109.7, 80.1, 55.8, 49.5, 43.9, 42.8, 38.7, 36.6, 29.9, 28.4, 27.1, 26.2, 22.8, 11.3; $[\alpha]_D^{20}$ +108 (*c* 0.50, THF); HRMS calcd for $C_{19}H_{26}O_3$ [$M^{\bullet+}$]: 302.1991. Found 302.1880.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.005.

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