Acid catalysed reaction of estrones with neopentyl glycol under forced conditions

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Upon reaction with an excess of 2,2-dimethylpropane-1,3-diol (neopentyl glycol) under acid catalysis, estrones form 17-*O*-[2′,2′-dimethyl-2′-(5′′,5′′-dimethyl-1′′,3′′-dioxanyl)ethyl] substituted estra-3,17β-diols. The reaction represents a formal reduction of a keto function under acidic conditions in the absence of a metal.

Keywords: estrone, reductive etherification, acid catalysis

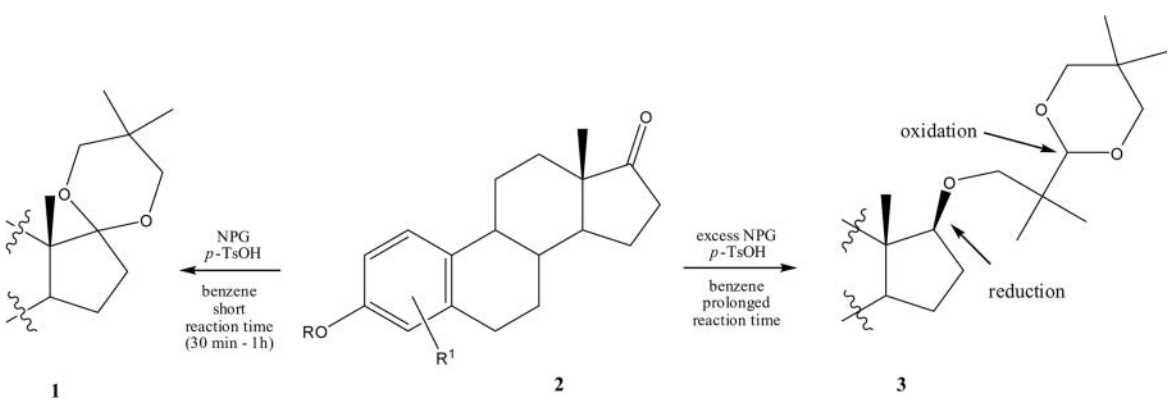
The protection of keto compounds as 1,3-dioxanes by reaction with 1,3-diols is a commonly used method.[1] Among the 1,3 diols that are used is 2,2-dimethylpropane-1,3-diol (neopentyl glycol), and 5,5-dimethyl-1,3-dioxanes[2,3] are obtained as the protected molecules. Due to the smell of some of these compounds, especially of those prepared from cyclic ketones, the perfume industry has expressed interest in them.[4,5] In the preparation of acetals derived from steroidal ketones with neopentyl glycol,[6–8] the authors have often noted side products, which were not easily separated from the desired acetals. The following contribution details the structural identification and the targeted synthesis of these side products.

The reaction of estrones **2** with neopentyl glycol (NPG) in refluxing benzene with the azeotropic removal of the water that was formed, gave the corresponding acetals **1** in good yield within 30 min. However, when estrones **2** were heated with an excess of neopentyl glycol in refluxing benzene or in toluene over a prolonged period, 17-*O*-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl)ethyl] steroidal ethers **3** were formed (Schemes 1 and 2).

The reaction involves a formal reduction of the C-17 keto functionality of the steroidal ketones **2**. This is of interest as few reduction methods have been reported to date that do not involve a metal, a metal hydride or hydrazine as reductant.[9] Alcohols as reductants of ketones are known, but these mostly involve the Meerwein–Ponndorf–Verley reduction, using aluminum,[10–13] lithium,[14,15] lanthanum[16] or samarium alkoxides.[16] The proposed mechanism of the current reaction is shown in Scheme 2. The reduction of the keto function is stereospecific. X-ray crystal structural analysis of **3e** shows that ethers of estra-3,17β-diols are formed exclusively.[17] It is believed that the key step in the mechanism is the intramolecular hydride transfer from the terminal alcohol of the neopentyl glycol tether to the C17 keto group. While the keto group is reduced, the terminal alcohol function of the tether is concomitantly oxidised. The carbaldehyde which is formed undergoes acetalisation immediately (Scheme 2). 1,3-Dioxane-type acetals of aldehydes are much more stable than the corresponding spiroacetals of cyclic ketones. The known spiroacetals **1** of the steroidal ketones are probably formed initially, even under the more extreme reaction conditions employed here. The spiroacetals, however, ring open in a back reaction to hemiacetals **A**. In this equilibrium of ring closure to the spiroacetal and ring opening, some of the material then undergoes the intramolecular hydride transfer to **C** (Scheme 3). Indeed, during the deacetalisation of **1a** (*p*-TsOH, acetone) small amounts of **3a** were observed as a side product.

Previously, a hydride transfer under acidic conditions has been noted in the case of the reaction of tetralones with pentane-2,4-diol.[18] A rearrangement of *m*-dioxanes to β-alkoxyaldehydes has also been reported previously, albeit at the high reaction temperature of 350−400 °C over a pumice catalyst[19–22] or over zeolite[23,24] as has the analogous rearrangement of an *m*-dioxane with sulfuric acid to a 2,2-dimethyl-2-(5′,5′-dimethyl-1′,3′-dioxanyl)ethyl alkyl ether.[25]

In the present case, it could not be established experimentally whether the hydride transfer is the rate determining step of the reaction. When the reaction was carried out with deuterated neopentyl glycol (**4**), in order to measure a potential isotope effect, only acetal **5** was formed (Scheme 4). This



Scheme 1 Reaction of estrones with neopentyl glycol under different conditions.

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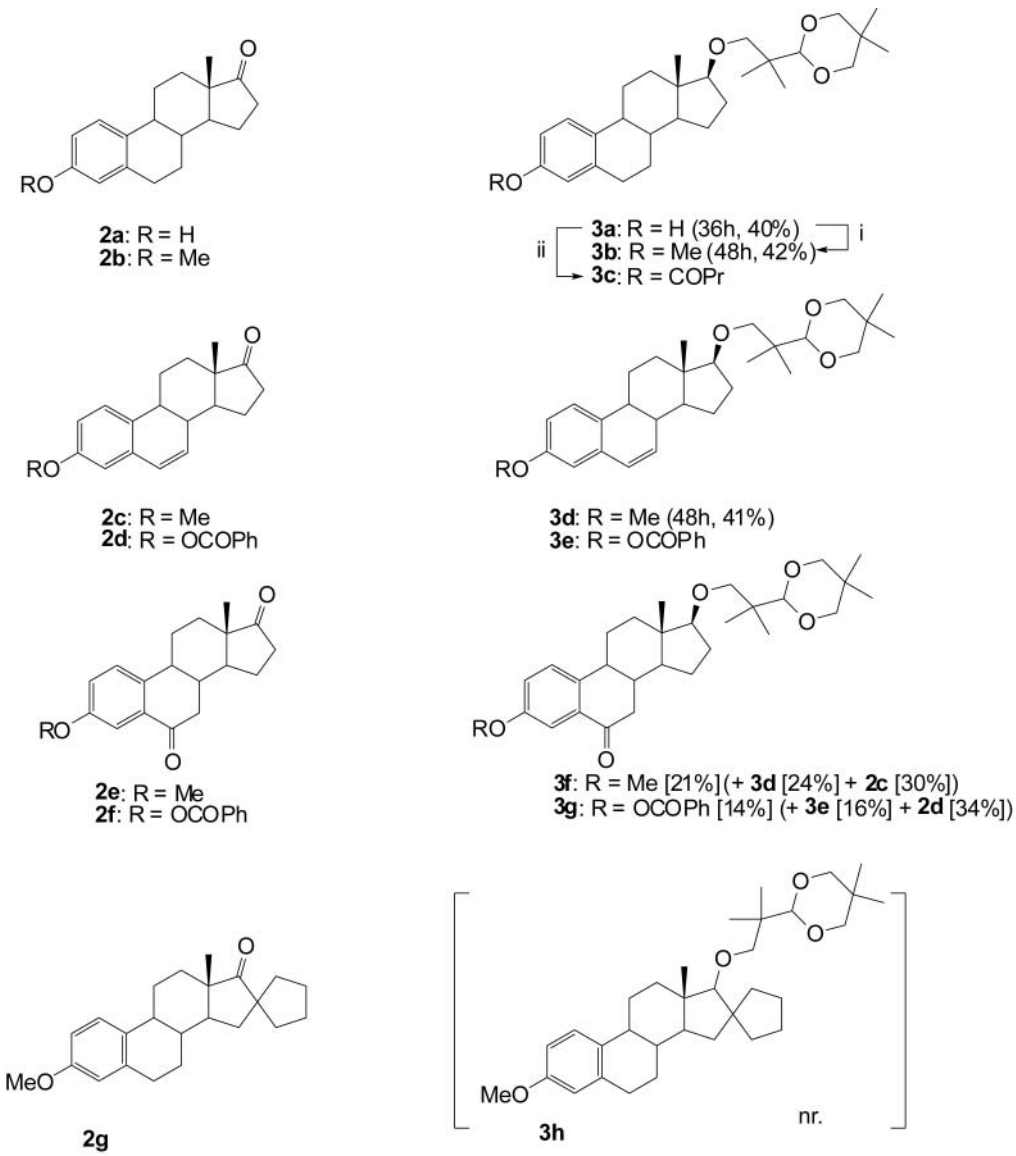
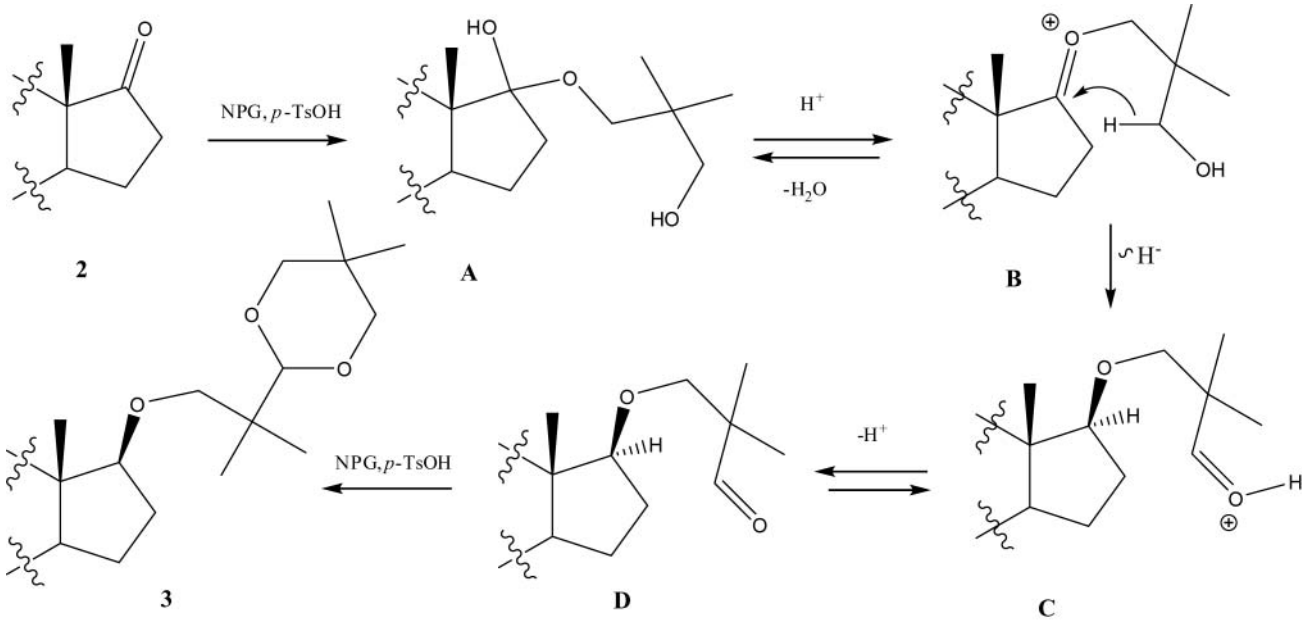
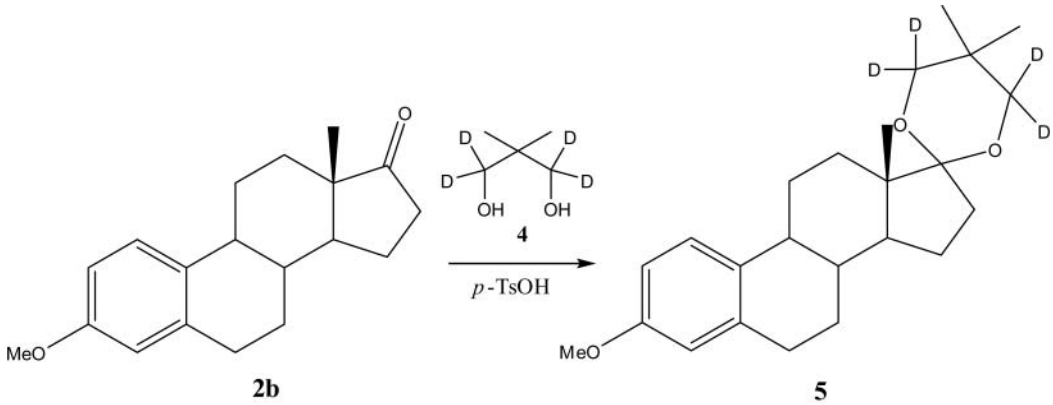


Scheme 2 i, KOH MeI (yield 70%); ii, CH3CH=2COCl, Et_3N, CH_2Cl_2 (80%).
17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl)]-3,17β-diols from estrones. nr., no reaction.



Scheme 3 Mechanism of formation of 17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl)ethyl]estra-3,17β-diols.



Scheme 4 Acetalisation of estrone with d⁴-neopentylglycol under forced conditions.

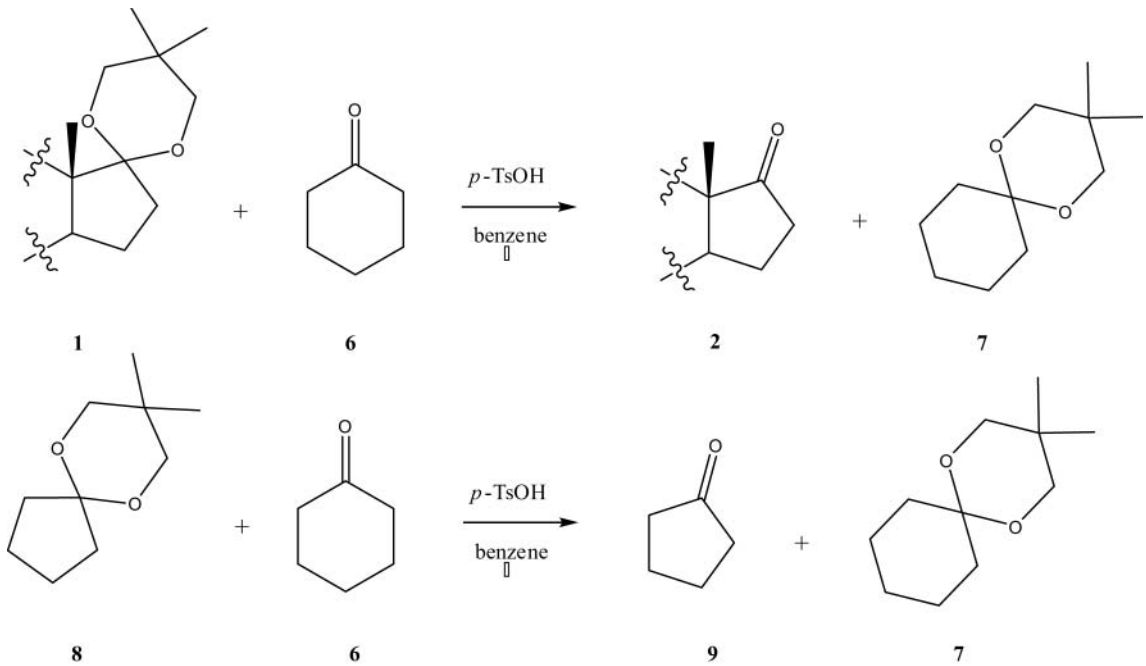
suggests that an isotope effect operates, but its value could not be ascertained. Further elevation of the temperature led to partial decomposition of the material.

Note that steric characteristics of the atoms neighbouring to the carbonyl function play a role not only in the stability of the acetals and but also influence the kinetics of the ring closure–ring opening equilibrium. While it is known, that spiroacetals of five-membered cycloalkanones possess a different stability in comparison to the six-membered cycloalkanones, this fact seems not to be the overriding factor for the course of the reaction discussed here, *i.e.* acetal formation versus hydride migration. Thus, reaction of cyclohexanone and of cyclopentanone under the normal reaction conditions used (NPG, *p*-TsOH, benzene, reflux 36h; then acetone, *p*-TsOH, RT, 12h) furnishes only the corresponding acetals. It is interesting that acid-catalysed reaction of the spiroacetal of cyclopentanone **8** with cyclohexanone (**6**) leads to a much smaller amount of *trans* acetalisation, than that of steroidal 17,17-spiroacetals **1** with cyclohexanone (**6**), where the reaction leads to a complete conversion to the ketosteroids **2** within short reaction times (Scheme 5). Again this reveals that the different stability of the spiroacetals is due to different steric requisites of the starting materials.

A further increase of the steric demand of the neighbouring atoms suppresses acetal formation. Thus, spiro compound **2g** does not form the corresponding acetal with NPG under these conditions. Also, no trace of the ether-acetal could be detected (Table 1). 6-Ketoestrones **2c** and **2d** yield a separable mixtures of 17-*O*-[2,2-dimethyl-2-(5′,5′-dimethyl-1′,3′-dioxanyl)ethyl-6-ketoestra-3,17β-diols **3f/3g**, 17-*O*-[2,2-dimethyl-2-(5′,5′-dimethyl-1′,3′-dioxanyl)ethyl-estra-1,3,5(10),6-tetraene-3,17β-diols **3d/3e**, and estratetraen-3-ol-17-one**s 2c/2d** (Scheme 2). Estratetraenes **2c**, **2d**, **3d**, and **3e** are formed by a reductive etherification–elimination reaction of the benzylic keto function. This is a general reaction found for indanones and tetralones reacted with NPG under forced acidic conditions (unpublished data), similar to the reaction of tetralones with pentane-2,4-diol.[18]

The ether-acetals **3** are stable under various conditions and can be transformed further as seen in typical reactions of **3a** to **3b** and **3c** (Scheme 2).

In conclusion, it was found that estrones are reduced to 17-*O*-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl)ethyl] steroidal ethers by a prolonged reaction with neopentyl glycol under acidic conditions. The benzylic keto function in a 6-oxoestra-1,3,5(10)-trien-17-one is converted to a 6,7-ene.



Scheme 5 Transacetalisation of cyclopentanone spriroacetals with cyclohexanone (**6**).

Experimental

Melting points were measured on a Yanaco microscopic Hotstage and are uncorrected. IR spectra were measured with JASCO IR-700 and Nippon Denshi JIR-AQ2OM instruments. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-270 spectrometer (^{1}H at 270 MHz, ^{13}C at 67.8 MHz) and a JEOL Lambda 400 FT-NMR spectrometer (^{1}H at 395.7 MHz, ^{13}C at 99.45 MHz). The assignments of the carbon signals were aided by DEPT 90 and DEPT 135 experiments (DEPT = Distortionless Enhancement by Polarisation Transfer). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer. Column chromatography was carried out on Wakogel 300.

Estrone (WAKO) was acquired commercially. 3-*O*-Methylestrone (**2b**)[26] and **2g**[27] were synthesised according to literature procedures. Estra-1,3,5(10),6-tetraen-3-ol-17-ones **2c** and **2d** were prepared via the corresponding 6-ketoestra-1,3,5(10)-trien-17-one 17,17-acetals **2e** and **2f**.[6]

17-O-[2′,2′-Dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl)ethyl]-estra-1,3,5(10)-trien-3,17-diol (**3a**); *general procedure A*: A solution of estrone (**2a**, 1.0 g, 3.7 mmol), neopentylglycol (462 mg, 4.4 mmol) and *p*-TsOH monohydrate (100 mg, 0.53 mmol) in benzene (30 mL) was refluxed for 36h with the azeotropic removal of water. Then, the solution was concentrated *in vacuo* and acetone (20 mL) was added to the residue. The resulting solution was stirred for 14h at RT. The solution was concentrated *in vacuo* and the residue was separated by column chromatography on silica gel (ether/hexane/$CHCl_3$ 1:1:1) to yield **3a** (654 mg, 40%) as a slowly crystallising, low melting solid. (Found: M$^+$, 442.3085. $C_{28}H_{42}O_4$ requires M$^+$, 442.3083). ν_{max} (KBr/cm^{-1}) 3324 (OH), 2938, 2854, 1611, 1587, 1504, 1475, 1212, 1138, 1103, 1033, 1020, 1006, 989, 927; δ_H 0.70 (3H, s, CH_3), 0.76 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.29–2.20 (13H, m), 2.78–2.82 (2H, m), 3.19–3.31 (3H, m), 3.38 (2H, d, ^2J = 11.1 Hz), 3.60 (2H, d, ^2J = 11.1 Hz), 4.29 (1H, s), 4.58 (1H, s), 6.55 (1H, ^4J = 2.7 Hz), 6.62 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.7 Hz), 7.15 (1H, d, ^3J = 8.4 Hz); δ_C (99.45 MHz) 11.6, 19.5, 19.8, 21.7, 22.9, 23.2, 26.5, 27.2, 27.9, 29.7, 30.3, 37.9, 38.6, 39.3, 43.4, 44.0, 75.6, 89.2, 104.9, 112.6, 115.2, 126.5, 132.9, 138.3, 153.2; MS (EI, 70 eV) *m/z* (%) = 442 (6) [M$^+$], 115 (100).

3-O-Methyl-17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl) ethyl]-estra-1,3,5(10)-trien-3,17-diol (**3b**) *A*: **2b** was reacted according *General procedure A* and **3b** obtained as a slowly crystallising, low melting, colourless solid; (Found: M$^+$, 456.3246. $C_{29}H_{44}O_4$ requires M$^+$, 456.3240). ν_{max} (KBr/cm^{-1}) 2950, 2846, 1612, 1501, 1468, 1392, 1256, 1237, 1140, 1112, 1042; δ_H 0.70 (3H, s, CH_3), 0.77 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.96 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.31–2.20 (13H, m), 2.85 (2H, m), 3.23 (1H, d, ^2J = 8.5 Hz), 3.29 (1H, d, ^2J = 8.5 Hz), 3.33 (1H, m), 3.41 (2H, d, ^2J = 10.8 Hz), 3.61 (2H, ^2J = 10.8 Hz), 3.77 (3H, s, OCH_3), 4.28 (1H, s), 6.62 (1H, d, ^4J = 2.7 Hz), 6.72 (1H, dd, ^3J = 7.6 Hz, ^4J = 2.7 Hz), 7.21 (1H, d, ^3J = 7.6 Hz); δ_C (99.45 MHz, $CDCl_3$) 11.6, 19.5, 19.8, 21.7, 22.9, 23.2, 26.5, 27.3, 27.9, 29.9, 30.2, 37.9, 38.7, 39.3, 43.4, 44.0, 50.2, 55.2, 75.6, 77.3, 89.2, 104.9, 111.4, 113.7, 126.3, 132.8, 138.0; MS (EI, 70 eV) m/z (%) = 456 (6) [M$^+$], 269 (10), 173 (31), 147 (20), 115 (69), 85 (33), 69 (100).

B. Finely ground KOH (51 mg, 0.91 mmol) was added to DMSO (1 mL) and the resulting mixture was stirred for 25 min at RT. Then, **3a** (100 mg, 0.23 mmol) was added and the mixture was stirred for a further 20 min at RT. Then the methyl iodide (28 µL, 64 mg, 0.45 mmol) was added. The mixture was stirred for 10 min at RT. Then, it was poured into water (10 mL) and extracted with chloroform (3 × 10 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/ether/$CHCl_3$ 4:1:1) to give **3b** (73 mg, 70%).

3-O-Propanoyl-17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl) ethyl]-estra-1,3,5(10)-trien-3,17-diol (**3c**): To a solution of **3a** (100 mg, 0.23 mmol) in dry CH_2Cl_2 (5 mL) was added dry triethylamine (114 mg, 157 µL) and then propionyl chloride (104 mg, 97 µL). The reaction mixture was stirred at RT for 20 min. It was poured into cold water (15 mL) and extracted immediately with chloroform (3 × 15 mL). The organic phase was washed with a 2N aq. Na_2CO_3 solution, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **3c** (92 mg, 80%) as a slowly solidifying oil. (Found: M$^+$, 498.3347. $C_{31}H_{46}O_5$ requires M$^+$, 498.3345). ν_{max} (neat/cm^{-1}) 2950, 2866, 1762 (C=O), 1493, 1460, 1111; δ_H (400 MHz) 0.71 (3H, s, CH_3), 0.77 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.13–1.69 (8H, m), 1.18 (3H, s, CH_3), 1.24 (3H, t, ^3J = 7.5 Hz, CH_3), 1.84–1.88 (2H, m), 1.95–2.04 (2H, m), 2.17–2.29 (2H, m), 2.57 (2H, q, ^3J = 7.5 Hz), 2.83–2.87 (2H, m), 3.21 (1H, d, J = 8.4 Hz), 3.27 (1H, d, J = 8.4 Hz), 3.33 (2H, d, ^2J = 10.6 Hz), 3.60 (2H, d, ^2J = 10.6 Hz), 4.29 (1H, s), 6.78 (1H, d, ^4J = 2.2 Hz), 6.83 (1H, dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz), 7.27 (1H, d, ^3J = 8.5 Hz); δ_C (99.45 MHz) 9.2, 11.6, 19.5, 19.8, 21.7, 22.9, 23.2, 26.3, 27.1, 27.8, 27.9, 29.6, 30.3, 31.6, 37.9, 38.3, 39.3, 43.4, 44.2, 50.3, 75.7, 89.1, 104.9, 118.5, 121.4, 126.3, 138.1, 148.4, 173.3; MS (EI, 70 eV) m/z (%) = 498 (2.3) [M$^+$], 115 (100).

3-O-Methyl-17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl) ethyl]-estra-1,3,5(10),6-tetraen-3,17-diol (**3d**): **2c** was reacted according to *General procedure A*, and **3d** was obtained as a slowly crystallising, low melting, colourless solid. (Found: M$^+$, 454.3090. $C_{29}H_{42}O_4$ requires M+, 454.3083). ν_{max} (neat/cm^{-1}) 3018, 2924, 1603, 1570, 1476, 1258, 1214, 1113, 1043, 757; δ_H 0.69 (3H, s, CH_3), 0.78 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.96 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.28–2.41 (11H, m), 3.23 (1H, d, ^2J = 8.5 Hz), 3.29 (1H, d, ^2J = 8.5 Hz), 3.33 (1H, m), 3.41 (2H, d, ^2J = 10.8 Hz), 3.61 (2H, ^2J = 10.8 Hz), 3.80 (3H, s, OCH_3), 4.29 (1H, s), 5.98 (1H, dd, ^3J = 9.3 Hz, J = 1.7 Hz), 6.44 (1H, dd, ^3J = 9.3 Hz, J = 2.7 Hz), 6.64 (1H, ^4J = 2.7 Hz), 6.74 (1H, dd, ^3J = 8.7 Hz, ^4J = 2.7 Hz), 7.17 (1H, d, ^3J = 8.7 Hz); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 11.4 (+, CH_3), 19.5 (+, CH_3), 19.8 (+, CH_3), 21.7 (+, CH_3), 22.9 (+, CH_3), 23.1 (−), 24.3 (−), 27.8 (−), 30.3 (C_{quat}), 37.4 (−), 38.6 (+, CH), 39.3 (C_{quat}), 42.1 (+, CH), 44.0 (C_{quat}), 48.5 (+, CH), 55.3 (+, OCH_3), 75.7 (–), 77.3 (–), 77.4 (–), 88.9 (+, CH), 104.9 (+, CH), 111.7 (+, CH), 111.8 (+, CH), 124.3 (+, CH), 127.7 (+, CH), 131.6 (C_{quat}), 133.2 (+, CH), 135.4 (C_{quat}), 158.0 (C_{quat}); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 454 (25) [M$^+$].

Reaction of **2f** *with NPG under forced conditions*: A solution of **2f** (386 mg, 1.0 mmol), *p*-TsOH (104 mg, 0.54 mmol) and NPG (574 mg, 5.5 mmol) in toluene (25 mL) was stirred under reflux for 12 h. The solvent was then evaporated, and acetone (50 mL) was added. The reaction mixture was stirred at RT. After 4 h, the solvent was evaporated and a 10% aq. $NaHCO_3$ solution (50 mL) was added, and the mixture was extracted with $CHCl_3$ (2 x 50 mL). The organic phase was washed with water (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was chromatographed on silica gel (hexane/ether/$CHCl_3$ 1:1:1) to afford **3e** (73 mg, 14%), **3g** (90 mg, 16%) and **2d** (125 mg, 34 %). *3-O-benzoyl-17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl)ethyl]-estra-1,3,5(10), 6-tetraene-3,17β-dio*l (**3e**): Colourless solid, m.p. 153–157 °C. (Found: M$^+$, 544.3188. $C_{35}H_{44}O_5$ requires M$^+$, 544.3189). ν_{max} (KBr/cm^{-1}) 2938, 2848, 1738, 1477, 1450, 1260, 1235, 1145, 1116, 1080, 1063, 1027, 703; δ_H (270 MHz, $CDCl_3$) 0.70 (3H, s, CH_3), 0.78 (3H, s, CH_3), 0.95 (6H, s, 2 CH_3), 1.16 (3H, s, CH_3), 1.25–2.49 (10H, m), 3.20–3.62 (7H, m), 4.28 (1H, s), 6.01 (1H, dd, J = 1.7 Hz, J = 9.5 Hz, H7), 6.46 (1H, dd, ^4J = 2.6 Hz, ^3J = 9.5 Hz, H6), 6.91 (1H, d, J = 2.1 Hz), 7.01 (dd, 1H, J = 2.1 Hz, J = 8.1 Hz), 7.27–1.30 (2H, m), 7.50–6.63 (3H, m), 8.18–8.21 (2H, m); δ_C (67.8 MHz, $CDCl_3$) 11.4, 19.5, 19.8, 21.7, 22.9, 23.1, 24.2, 27.8, 30.3, 37.3, 38.2, 39.3, 42.3, 24.0, 48.6, 75.7, 88.9, 104.9, 118.8, 119.5, 124.4, 127.3, 128.5 (2C), 129.7, 130.2 (2C), 133.5, 133.6, 135.8, 136.9, 149.4, 165.3; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 544 (7.3) [M$^+$], 105 (100); *3-O-benzoyl-17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl)ethyl]-6-oxo-estra-1,3,5(10)-triene-3,17β-diol* (**3g**): Colourless solid, mp. 120–124 °C. (Found: MH$^+$, 561.3217. $C_{35}H_{45}O_6$ requires MH$^+$, 561.3216). ν_{max} (KBr/cm^{-1}) 2950, 2846, 1739, 1682, 1603, 1483, 1253, 1193, 1112, 1080, 704; δ_H (270 MHz, $CDCl_3$) 0.71 (3H, s, CH_3), 0.79 (3H, s, CH_3), 0.95 (6H, s, 2 CH_3), 1.16 (3H, s, CH_3), 1.25–2.65 (12H, m), 2.75 (1H, dd, J = 3.2 Hz, J = 16.8 Hz, H7), 3.23–3.62 (7H, m), 4.28 (1H, s), 7.4 (1H, dd, J = 2.4 Hz, J = 8.1 Hz), 7.48–7.70 (5H, m), 7.87 (1H, d, J = 2.4 Hz), 8.19 (1H, d, J = 8.1 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.4, 19.6, 19.7, 21.7, 22.9, 25.6, 27.7, 30.2, 37.4, 39.3, 39.7, 43.2, 43.3, 44.0, 50.2, 70.1, 75.7, 88.7, 104.9, 120.0, 126.8, 127.0, 128.6 (2C), 129.3, 130.2 (2C), 133.7, 133.8, 144.7, 149.6, 165.3, 197.2; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 561 (16) (MH$^+$), 105 (100); *3-O-benzoyl-estra-1,3,5(10),6-tetraen-3-ol-17-one* (**2d**): Colourless solid; mp. 188–191 °C. (Found: MH$^+$, 373.1803. $C_{25}H_{25}O_3$ requires MH$^+$, 373.1804). ν_{max} (KBr/cm^{-1}) 2920, 2856, 1736, 1648, 1603, 1451, 1267, 1236, 1063; δ_H (270 MHz, $CDCl_3$) 0.93 (3H, s, CH_3), 1.43–2.62 (11H, m), 6.11 (1H, d, J = 9.6 Hz, H7), 6.54 (1H, dd, ^4J = 2.7 Hz, ^3J = 9.6 Hz, H6), 6.95 (1H, d, J = 2.4 Hz), 7.05 (1H, dd, J = 2.4 Hz, J = 8.1 Hz), 7.30 (1H, d, J = 8.1 Hz), 7.48–7.54

(2H, m), 7.61–7.64 (1H, m), 8.18–8.22 (2H, m); δ_C (67.8 MHz, $CDCl_3$) 13.6, 21.6, 23.6, 31.0, 35.7, 37.8, 42.3, 48.5, 48.8, 119.1, 119.9, 124.5, 128.6 (2C), 130.2, 133.6, 128.1, 131.5, 135.6, 136.2, 149.5, 220.2; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 373 (MH^+) (36), 105 (100).

*3-O-Methyl-17-O-[2′,2′-dimethyl-2′-(5″,5″-dimethyl-1″,3″-dioxanyl) ethyl]-6-ketoestra-1,3,5(10)-trien-3,17*β*-diol* (**3f**): This was obtained from **2e** using a method analogous to the reaction of **2f** (see above) as a colourless solid, m.p. 136 °C. (Found: MH^+, 471.3113. $C_{29}H_{43}O_5$ requires MH^+, 471.3110 [FAB]). ν_{max} (KBr/cm^{-1}) 2954, 2870, 1675, 1608, 1495, 1473, 1335, 1321, 1288, 1254, 1110, 1034; δ_H 0.71 (3H, s, CH_3), 0.78 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.20–2.53 (11H, m), 2.21 (1H, dd, ^2J = 16.3 Hz, ^3J = 13.2 Hz), 2.74 (1H, dd, ^2J = 16.3 Hz, ^3J = 3.6 Hz), 3.23 (1H, d, ^2J = 8.7 Hz), 3.28 (1H, d, ^2J = 8.7 Hz), 3.31 (1H, dd, ^3J = 8.2 Hz, ^3J = 8.2 Hz), 3.39 (2H, d, ^2J = 11.3 Hz), 3.60 (2H, d, ^2J = 11.3 Hz), 3.84 (3H, s, OCH_3), 4.28 (1H, s), 7.10 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 7.34 (1H, d, ^3J = 8.6 Hz), 7.56 (1H, d, ^4J = 2.7 Hz); δ_C (67.8 MHz, DEPT 90, DEPT 135) 11.5 (+, CH_3), 19.6 (+, CH_3), 19.7 (+, CH_3), 21.7 (+, CH_3), 22.9 (−), 25.7 (−), 27.7 (−), 30.3, 37.4, 39.3, 40.0, 43.0, 43.2, 44.1 (−), 50.1 (+, OCH_3), 55.5 (C_{quat}), 75.7 (−), 77.3 (−), 88.8 (+, CH), 104.9 (+, CH), 109.5 (+, CH), 121.5 (+, CH), 126.6 (+, CH), 133.4 (C_{quat}), 140.0 (C_{quat}), 158.2 (C_{quat}), 198.1 (C_{quat}); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 471 (81) [MH^+]. **3d** and **2c** are also produced in the reaction.

d^4-Neopentylglycol (**4**). To a suspension of $LiAlD_4$ (1.0 g, 25 mmol) in dry ether (100 mL) was added dimethyl malonate (1.0 g, 6.25 mmol) within 10 min at 0 °C. The reaction mixture was heated under reflux for 1h. Ethanol (10 mL) was then added, and the mixture was stirred at RT for 30 min. The solvents were removed *in vacuo*, and the residue was extracted with ether (3 × 50 mL). The combined organic phase was dried over anhydrous $MgSO_4$. Concentration of the organic layer led to crystallisation of d^4- neopentyl glycol (**4**, 332 g, 49.5%), colourless solid; m.p. 115 °C; ν_{max} (KBr/cm^{-1}) 3308, 2958, 2866, 2210, 2092, 1469, 1376, 1115, 1101, 974, 716; δ_H 0.89 (6H, s, 2 CH_3), 3.02–3.29 (2H, bs, 2 OH); δ_C (67.8 MHz) 21.2, 36.1, 70.8 (quint, $2J_{C\text{-}D}$ = 20.7 Hz); MS (EI, 70 eV) *m/z* (%) = 108 (M^+) (11).

3-O-Methylestra-1,3,5(10)-trien-3-ol-17-one 17,17-O,O-[2′-(4′,4′,6′,6′-tetradeuterio-5″,5″-dimethyl-1″,3″-dioxane)] (**5**): 3-Methoxyestrone (**2b**, 175 mg, 0.61 mmol), d^4-neopentylglycol (**4**, 150 mg, 2.5 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg) in benzene (20 mL) were heated under reflux for 15 hours with the continuous azeotropic removal of water (Dean–Stark condenser). The reaction was cooled to room temperature, poured into a saturated aqueous Na_2CO_3 solution and the organic layer was separated. The organic layer was washed with brine, and dried over anhydrous $MgSO_4$. Concentration of the solution *in vacuo* and column chromatography (ether hexane/1:1) to give **5** (95 mg, 41%); δ_H 0.72 (3H, s, CH_3), 0.83 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.25–1.76 (10H, m), 1.85–1.96 (1H, m), 2.22–2.27 (2H, m), 2.81–2.87 (2H, m), 3.77 (3H, m), 6.62 (1H, d, ^4J = 3.0 Hz), 6.70 (1H, dd, ^3J = 8.6 Hz, ^4J = 3.0 Hz), 7.21 (1H, d, ^3J = 8.6 Hz); MS (70 eV) *m/z* (%) = 374 (35) [M^+], 312 (23), 266 (88), 145 (100).

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