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Synthesis of functionalised enantiopure steroids from estrone and cholestanone through organolithium intermediates

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Abstract—The reaction of epoxides **1** and **8** derived from estrone and cholestanone, respectively, with an excess of lithium and a catalytic amount of DTBB (7 mol%) in THF at −78°C led to formation of the corresponding β-oxido-functionalised organolithium intermediates **2** and **9**, respectively, in a regio- and stereoselective manner. Treatment of these intermediates with different electrophiles [H_2O, D_2O, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, CO_2] at −78 to 20°C afforded, after hydrolysis with water, enantiomerically pure derivatives **3** and **10**, respectively. When protected ketones **5** and **6** derived from D-glucose and D-fructose were used as the electrophile, the reaction with **2** gave the expected mixed products **3g** and **3h**, respectively, which consist of a steroid and a carbohydrate fragment. The reaction of *O*-protected estrone **4** as the electrophilic component and intermediate **2** afforded the C_2-symmetric steroid dimer **3f**. The stereochemistry of the products was unambiguously determined by correlation with X-ray data for compound **3d** and by comparison with the known compound **6a**. Finally, the addition of the dianions **13**, resulting from the DTBB-catalysed lithiation of phthalan **12a** and isochroman **12b**, to the *O*-protected estrone **4** and to cholestanone **9** led to the formation of the diols **14**, **15** and **16**. Diols **14** were cyclised under Mitsunobu reaction conditions to the corresponding heterocycles **17**.

1. Introduction

It is well-known that steroids are very important biologically active molecules and are widely represented in both the plant and animal kingdoms, their biosynthesis being almost the same in both cases.[1a] In spite of the fact that steroids have many common structural features, small changes in the functionalities attached to the steroid skeleton can cause marked changes in their biological activity.[1b] For this reason, it is interesting to selectively transform naturally occurring steroids to new functionalised structures which may as a consequence have new bioactivity and possible therapeutic applications. This strategy would be a typical example of EPC (enantiomerically pure compounds) synthesis,[2] which takes advantage of the chiral pool of natural products for elaboration to more sophisticated chiral molecules.

Over the last decade we have used an arene-catalysed lithiation[3–6] for the preparation of very reactive organolithium compounds under very mild conditions. Among these intermediates we find especially interesting functionalised organolithium compounds,[7] which on reaction with electrophilic reagents undergo functionality transfer to the electrophile, giving polyfunctionalised molecules in a single step. Of precursors to this class of organolithium reagent, heterocyclic compounds[8] such as epoxides are of interest as ring opening can be carried out in a stoichiometric[9] or a catalytic[10] arene-promoted lithiation reaction.

Herein, we report arene-catalysed lithiation of epoxides derived from estrone or cholestanone for the generation of functionalised organolithium intermediates, which are used in turn to introduce different electrophilic fragments to the steroid skeleton. In this way, functionalised steroid and steroid-like molecules are readily prepared.[11]

2. Results and discussion

The reaction of the epoxy steroid **1** derived from estrone **7** with an excess of lithium (1:16 molar ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 1:0.14 molar ratio, 7 mol%) in THF at −78°C for 2 h gave a solution of the corresponding β-oxido organolithium intermediate **2**, which by treatment with different electrophiles [H_2O, D_2O, PhCHO, Me_2CO, $(CH_2)_5CO$, **4**, **5**, **6** (Fig. 1), CO_2] at the same temperature for 10 min led, after hydrolysis with water (or

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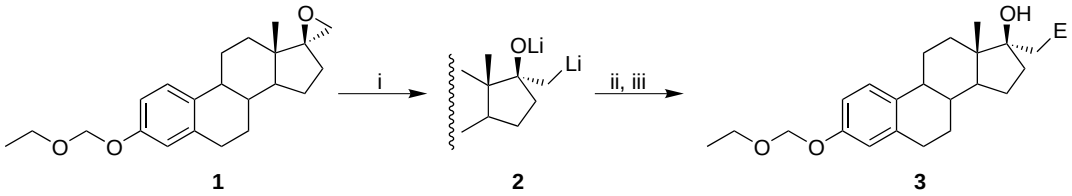


Scheme 1. *Reagents and conditions*: (i) Li, DTBB (7 mol%), THF, −78°C, 2 h; (ii) $E^+ = H_2O$, D_2O, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, **4**, **5**, **6**, CO_2, −78°C, 10 min; (iii) H_2O, −78 to 20°C or 0.1 M HCl, −78 to 20°C.

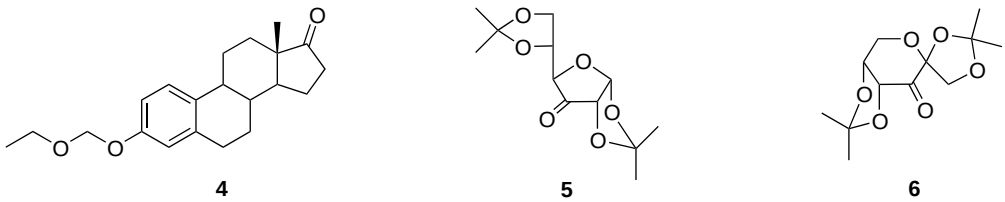


Figure 1.

aqueous hydrochloric acid when CO_2 was used as electrophile), to the expected functionalised steroids **3** (Scheme 1 and Table 1). The common stereochemistry for compounds **1** and **3** was assigned not only by NMR experiments, but also by X-ray analysis of compound **3d**[11] (Table 1, entry 4), in which the stereochemistry of C-(17) contains oxygen in a β-situation. Concerning the possible asymmetric induction with a prochiral electrophile, a ca. 1:1 diastereomeric mixture was isolated when benzaldehyde was used as the electrophile (Table 1, entry 3 and footnote d), whilst in contrast dimer **3f** with C_2 symmetry was obtained when ketone **4** was used as the electrophile because attack of the organolithium intermediate takes place exclusively from the less hindered face of the ketone (Table 1, entry 6 and Fig. 2). When ketones **5** and **6**, which derive from D-glucose and D-fructose, respectively, were used as electrophiles, sugar–steroid hybrids **3g** and **3h** were obtained, respectively (Table 1, entries 7 and 8 and Fig. 2). The stereochemistry of these compounds again corresponds to attack of the organolithium intermediate **2** on the less hindered upper faces of the ketones **5** and **6**.

Compound **1** was prepared from estrone **7** by first ethoxymethyl ether formation to give ketone **4**, followed by epoxidation with trimethylsulfonium iodide and sodium hydride in DMSO at room temperature (Scheme 2). These reaction conditions led exclusively to

Table 1. Preparation of compounds **3** and **10**

Entry	Starting epoxide	Intermediate	Electrophile	Product[a]		
				No.	E	Yield (%)[b]
1	**1**	**2**	H_2O	**3a**	H	>99
2	**1**	**2**	D_2O	**3b**	D	>99[c]
3	**1**	**2**	PhCHO	**3c**	PhCHOH	55[d]
4	**1**	**2**	Me_2CO	**3d**	Me_2COH	60
5	**1**	**2**	$(CH_2)_5CO$	**3e**	$(CH_2)_5COH$	27
6	**1**	**2**	**4**[e]	**3f**[f]	–	26
7	**1**	**2**	**5**[e]	**3g**[f]	–	16
8	**1**	**2**	**6**[e]	**3h**[f]	–	10
9	**1**	**2**	CO_2	**3i**	CO_2H	31
10	**8**	**9**	H_2O	**10a**	H	>99
11	**8**	**9**	D_2O	**10b**	D	>99[g]
12	**8**	**9**	PhCHO	**10c**	PhCHOH	25[d]
13	**8**	**9**	Et_2CO	**10d**	Et_2COH	20
14	**8**	**9**	$(CH_2)_5CO$	**10e**	$(CH_2)_5CO$	30

[a] All compounds **3** or **10** were >95% pure (300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS).

[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting epoxide **1** or **8**.

[c] A ca. 90% deuterium incorporation was obtained (MS).

[d] As a ca. 1:1 diastereomeric mixture.

[e] See Fig. 1.

[f] See Fig. 2.

[g] A ca. 60% deuterium incorporation was obtained (^{13}C NMR).

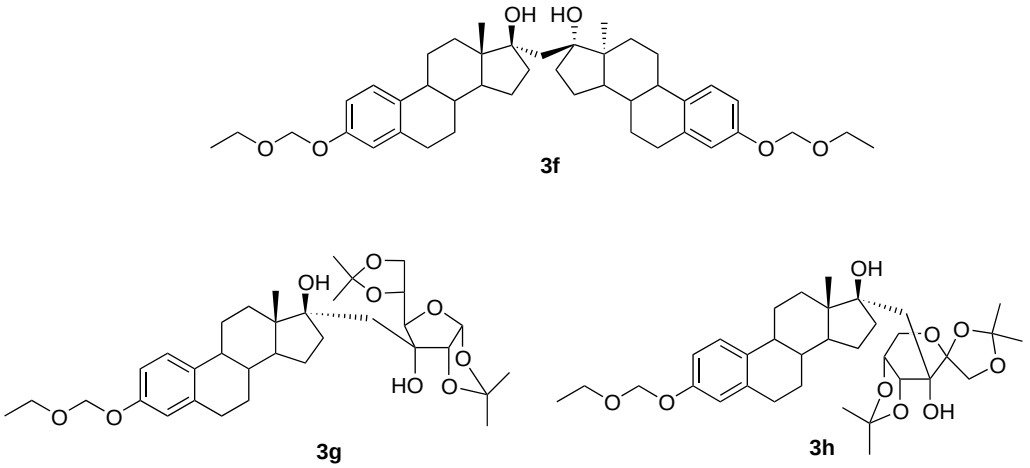
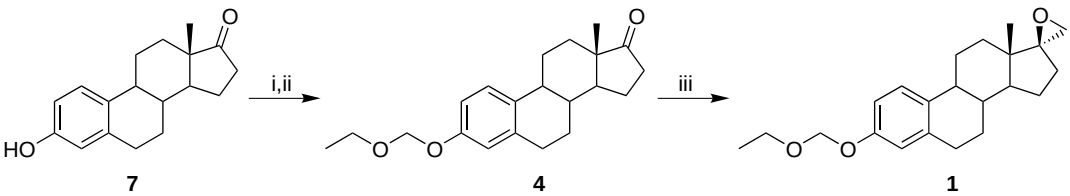


Figure 2.



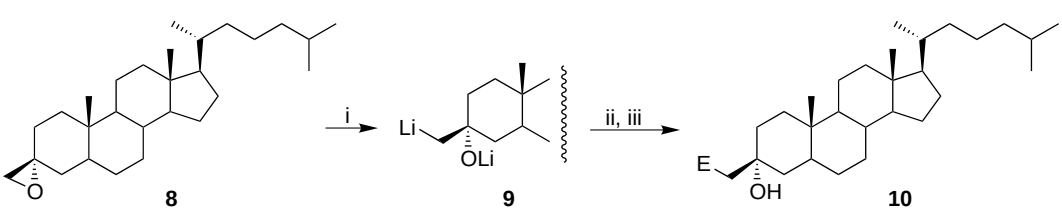
Scheme 2. *Reagents and conditions*: (i) Bu^{n}Li (1.2 equiv.), THF, −78°C; (ii) $EtOCH_2Cl$, THF, −78°C; (iii) NaH (5 equiv.), Me_3SI (2 equiv.), DMSO, 25°C.

the epoxy steroid **1**, while the use of trimethylsulfoxonium iodide and potassium *tert*-butoxide in *tert*-butanol gave a 4:1 diastereomeric mixture of **1** and its C_{17} epimeric epoxide, respectively. Ketone **5** was prepared from commercially available 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose, which was oxidised with pyridinium chlorochromate in dichloromethane, and finally, ketone **6** was prepared starting from D-fructose by successive formation of the corresponding 1,2;5,6-di-*O*-*iso*-propylidene derivative and oxidation.[10d]

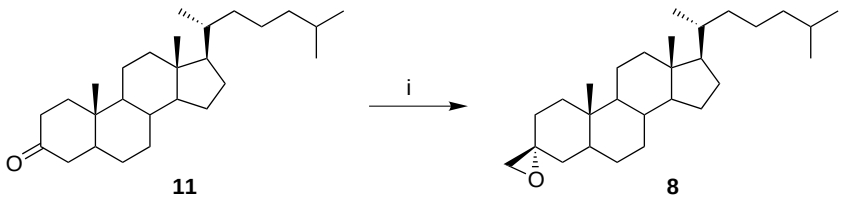
The above described procedure was applied to epoxide **8** derived from cholestanone. Thus, intermediate **9** was formed and reacted with several electrophiles [H_2O, D_2O, PhCHO, Et_2CO, $(CH_2)_5CO$] to yield, after final hydrolysis, the expected products **10** (Scheme 3 and Table 1). In this case, the new stereochemistry at C-(3) in compounds **8** and **10** was assigned by comparison of physical data for compound **10a** with those described in the literature.[12] When benzaldehyde was used as electrophile a ca. 1:1 diastereomeric mixture of diols **10c** was isolated after hydrolysis, proof that asymmetric induction was not occurring in the process (Table 1, entry 12 and footnote d).

Starting epoxy steroid **8** was prepared in a single step by a known methodology from commercially available cholestanone **11** by treatment with trimethylsulfoxonium iodide and potassium *tert*-butoxide in *tert*-butanol (Scheme 4).

In the last part of this study we used a different approach to prepare structurally modified steroids, which consisted of adding functionalised organolithium compounds to estrone derivative **4** (Fig. 1) and cholestanone **11** (Scheme 4). Dianions **13a** and **13b**, easily available by reductive opening of phthalan **12a**[13] and isochroman **12b**[14] with lithium and a catalytic amount of DTBB, were used as organolithium components. The reaction of these anions with estrone derivative **4** afforded, after hydrolysis, the expected compounds **14**, from exclusive nucleophilic attack of the organolithium intermediate **13** on the less hindered face



Scheme 3. *Reagents and conditions*: (i) Li, DTBB (7 mol%), THF, −78°C, 2 h; (ii) $E^+ = H_2O$, D_2O, PhCHO, Et_2CO, $(CH_2)_5CO$, −78°C, 10 min; (iii) H_2O, −78 to 20°C.



Scheme 4. *Reagents and conditions*: (i) KOBu^t (1 equiv.), MeSOI (1 equiv.), Bu^{t}OH, 50°C, 2.5 h.

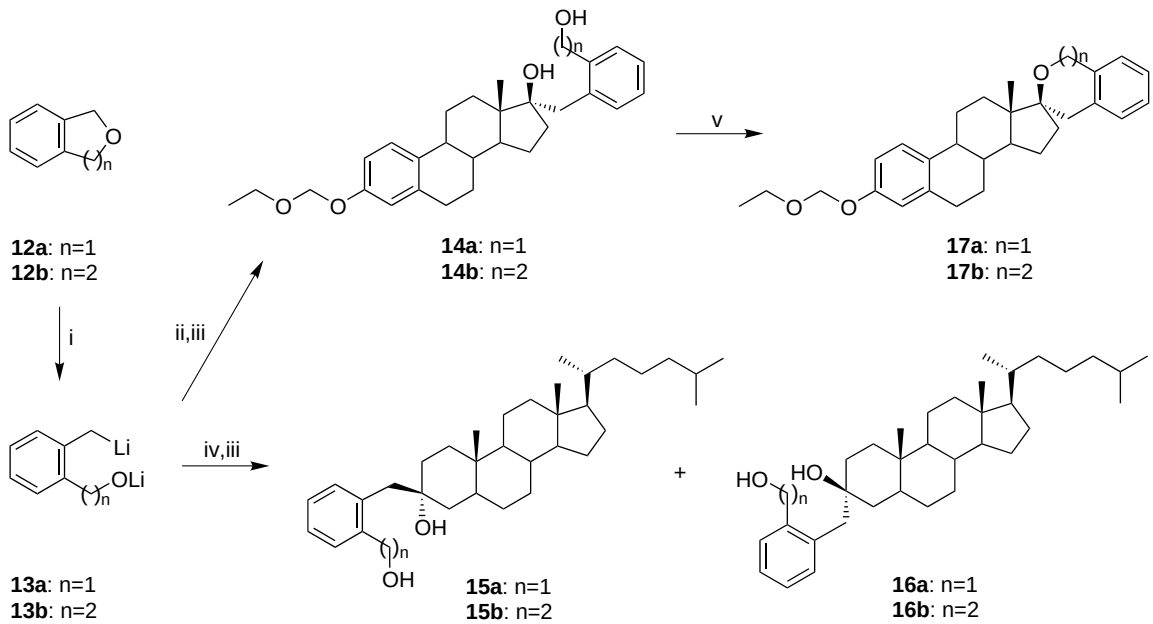
of the carbonyl group. However, in the case of cholestanone, the same reaction yielded an almost 1:1 mixture of epimeric diols **15** and **16**, with nucleophilic attack occurring indiscriminately to both faces of the carbonyl group. Assignment of the stereochemistry of diols **15** and **16** was made on the basis of the study of their NMR spectra and by correlation with other similar compounds (e.g. **10a**) of known stereochemistry. Finally, diols **14** were cyclised under Mitsunobu reaction conditions to yield heterocycles **17** (Scheme 5).

In conclusion, we have reported here a novel means of preparing structurally modified steroids involving reactions between functionalised organolithium compounds derived from steroids with ketones. Yields are in some cases modest due to partial decomposition of the reaction products during purification by column chromatography. In all cases, structurally modified molecules with potential biological activity are prepared.

3. Experimental

3.1. General

Melting points were obtained with a Reichert Thermovar apparatus. FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer, NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) using CDCl as solvent and TMS as internal standard; chemical shifts are given in (ppm) and coupling constants (J) are given in hertz. ^{13}C NMR assignments were made on the basis of DEPT experiments. Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP-5000 spectrometer, fragment ions in m/z with relative intensities (%) in parentheses. Elemental analyses were performed by the Microanalyses Service at the University of Alicante. High resolution mass spectra were performed by the corresponding service at the University of Alicante using a Finnigan MAT 95 S apparatus. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett-Packard HP-5890 instrument equipped with a flame ionisation detector and a 12 m capillary column (0.2 mm diam., 0.33 mm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{\text{injector}} = 275$°C, $T_{\text{column}} =$ 60°C (3 min) and 60–270°C (15°C/min). Thin-layer chromatography (TLC) was carried out on Schleicher & Schuell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel; R_f values are given under these conditions. Column chromatography was performed using silica gel 60 of 35–70 mesh. All starting materials



Scheme 5. *Reagents and conditions*: (i) Li, DTBB (2.5 mol%), THF, −78 to 20°C, 30 min; (ii) **4**, −78°C, 10 min; (iii) H_2O, −78 to 20°C; (iv) **11**, −78°C, 10 min; (v) PPh_3, DIAD, PhH reflux, 3 h.

were commercially available (Acros, Aldrich, Fluka) of the best grade and were used without further purification. THF was dried over benzophenone ketyl under a nitrogen atmosphere and distilled before use.

3.2. Preparation of compound 4

To a THF solution (40 mL) of estrone **7** (0.54 g, 2.0 mmol) at −78°C under nitrogen was added dropwise *n*-butyllithium in hexane solution (1.6 M, 1.62 mL, 2.4 mmol). After 5 min at the same temperature, chloromethyl ethyl ether (0.83 mL, 4.88 mmol) was added and the reaction mixture was allowed to rise to 25°C overnight and then hydrolysed with water (20 mL) and extracted with ethyl acetate (3×20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel, hexane:ethyl acetate) to give 3-*O*-ethoxymethylestrone **4**: (95% yield) R_f 0.42 (hexane:ethyl acetate, 4:1); *v* (film) 3039, 3008 (ArH), 1736 (C=O), 1613, 1502 (ArC), 1008 cm^{-1} (CO); δ_H 0.90 (3H, s, CH_3), 1.23 (3H, t, $J=7.0$, CH_3CH_2), 1.28–1.66 (6H, m), 1.93–2.54 (7H, m), 2.87–2.90 (2H, m), 3.72 (2H, q, $J=7.3$, CH_3CH_2), 5.19 (2H, s, OCH_2O), 6.79 (1H, s, ArH), 6.83 (1H, d, $J=8.5$, ArH), 7.19 (1H, d, $J=8.5$, ArH); δ_C 13.8, 15.0 (CH_3), 21.5, 25.8, 26.5, 29.5, 31.5, 35.8 (CH_2), 38.2, 44.0 (CH), 47.9 (CCH_3), 50.3 (CH), 64.0 (CH_3CH_2O), 93.1 (OCH_2O), 113.8, 116.2, 126.2, (ArCH), 133.1, 137.7, 155.4 (ArC), 220.8 (C=O); *m*/*z* 328 (M^+, 13%), 59 (100), 41 (15) [found: M^+, 328.2029; $C_{21}H_{28}O_3$ requires: M, 328.2038]; $[\alpha]_D^{20}=+124.7$ [$c=0.9$ (CH_2Cl_2)].

3.3. Preparation of epoxide 1

To a suspension of sodium hydride (95%, 0.63 g, 25.0 mmol) and trimethylsulfonium iodide (2.1 g, 10.0 mmol) in DMSO (30 mL) was added dropwise a solution of ketone **4** (1.64 g, 5.0 mmol) in a mixture of THF/DMSO (5/10 mL) at 25°C. The reaction mixture was stirred at the same temperature for 12 h, hydrolysed with water (40 mL) and extracted with ethyl acetate (4×30 mL). The organic layer was washed with water (5×20 mL), dried over anhydrous sodium sulfate filtered and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel, hexane:ethyl acetate) to give 17,17′-anhydro-3-*O*-ethoxymethyl-17α-hydroxymethyl-17β-estradiol **1**: (86% yield) R_f 0.35 (hexane:ethyl acetate, 10:1); *v* (film) 3036 (ArH), 1619, 1502 (ArC), 1013 cm^{-1} (CO); δ_H 0.91 (3H, s, CH_3), 1.22 (3H, t, $J=7.0$, CH_3CH_2), 1.34–1.54 (6H, m), 1.83–2.07 (5H, m), 2.22–2.34 (2H, m), 2.62 (1H, d, $J=5.2$, CC*H*HO), 2.84–2.89 (2H, m), 2.94 (1H, d, $J=5.2$, CCH*H*O), 3.71 (2H, q, $J=7.3$, CH_3CH_2), 5.18 (2H, s, OCH_2O), 6.77 (1H, s, ArH), 6.28 (1H, d, $J=8.5$, ArH), 7.18 (1H, d, $J=8.5$, ArH); δ_C 14.2, 15.0 (CH_3), 23.2, 25.9, 27.1, 29.0, 29.6, 33.9 (CH_2), 38.8 (CH), 40.3 (CCH_3), 43.8, 51.8 (CH), 53.5 (OCH_2O), 64.0 (CH_2CH_3), 70.4 (CCH_2O), 93.1 (OCH_2O), 113.6, 116.1, 126.2 (ArCH), 133.4, 137.8, 155.3 (ArC); *m*/*z* 342 (M^+, 9.5%), 59 (100), 41 (17) [found: M^+, 342.2187; $C_{22}H_{30}O_3$ requires: M, 342.2195]; $[\alpha]_D^{20}=+51.4$ [$c=1.1$ (CH_2Cl_2)].

3.4. Preparation of epoxide 8

To a solution of trimethylsulfoxonium iodide (0.693 g, 3.0 mmol) in *tert*-butanol (10 mL) was added a solution of potassium *tert*-butoxide (0.37 g, 3.0 mmol) in *tert*-butanol (10 mL) at 50°C under nitrogen. The mixture was stirred for 30 min at this temperature, a solution of cholestanone **11** (0.773 g, 2.0 mmol) in *tert*-butanol (10 mL) was added and the mixture stirred for a further 3 h. The resulting mixture was evaporated (15 mmHg), the residue hydrolysed with water (30 mL) and extracted with ethyl acetate (3×40 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated (15 mmHg). The crude product was purified by column chromatography (silica gel, hexane:ethyl acetate) to give 3,3′-anhydro-3β-hydroxymethyl-5α-cholestan-3α-ol **8**: (85% yield) R_f 0.49 (hexane:ethyl acetate, 10:1); mp 124–125°C (dichloromethane/pentane); *v* (KBr) 1030 cm^{-1} (CO); δ_H 0.63–2.03 (46H, m), 2.59 (2H, m, CH_2O); δ_C 11.25, 12.1, 18.6 (CH_3), 21.0 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 27.9 (CH), 28.2, 28.6, 29.2, 31.8 (CH_2), 35.4 (CCH_3), 35.5, 35.8 (CH), 35.85, 36.0 (CH_2), 36.2, 39.5, 40.0 (CH_2), 42.5 (CCH_3), 43.7 (CH), 53.4 (CH_2), 54.0 (CH), 56.2, 56.5 (CH), 58.6 ($OCCH_2$); *m*/*z* 400 (M^+, 13%), 246 (33), 245 (35), 177 (37), 149 (13), 123 (11), 122 (11), 121 (19), 108 (35), 107 (33), 105 (24), 95 (32), 93 (35), 91 (21), 83 (22), 81 (40), 79 (29), 71 (20), 69 (26), 68 (17), 67 (43), 57 (60), 55 (85), 43 (100), 41 (70), 40 (35). Anal. calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 83.59; H, 11.93%. $[\alpha]_D^{20}=+40.5$ [$c=1.0$ (CH_2Cl_2)].

3.5. DTBB-catalysed lithiation of epoxides 1 and 8, and reaction with electrophiles. Isolation of compounds 3 and 10. General procedure

To a cooled (−78°C) blue suspension of powdered lithium (0.10 g, 14.0 mmol) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (0.04 g, 0.15 mmol) in THF (5 mL) was added the corresponding epoxide (1.0 mmol) under nitrogen and the mixture was stirred at the same temperature for 2 h. The corresponding electrophile (1.2 mmol; 0.5 mL in the case of water and deuterium oxide; CO_2 was bubbled for 30 min) was added at −78°C and after 10 min the mixture was hydrolysed with water (20 mL) and the temperature allowed to rise to 20°C overnight. The reaction mixture was extracted with ethyl acetate (3×20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel, hexane:ethyl acetate) and/or recrystallised to yield pure products **3** and **10**. Yields are included in Table 1. Physical, spectroscopic and analytical data follow.

3.5.1. 3-*O*-Ethoxymethyl-17α-methyl-17β-estradiol 3a. R_f 0.42 (hexane:ethyl acetate, 2:1); *v* (film) 3661–3133 (OH), 3036 (ArH), 1605, 1501 (ArC), 1153, 1099, 1012 cm^{-1} (CO); δ_H 0.89 (3H, s, CH_3), 1.23 (3H, t, $J=7.0$, CH_3CH_2), 1.27 (3H, s, $COHCH_3$), 1.30–1.90 (12H, m), 2.16 (1H, br s, OH), 2.29–2.33 (1H, m), 2.83–2.86 (2H, m), 3.72 (2H, q, $J=7.0$, CH_3CH_2), 5.19 (2H, s,

OCH_2O), 6.78 (1H, s, ArH), 6.83 (1H, dd, $J=8.5$, 2.7, ArH), 7.20 (1H, d, $J=8.5$, ArH); δ_C 13.8, 15.1 (CH_3), 22.9 (CH_2), 25.8 ($COHCH_3$), 26.2, 27.4, 29.75, 31.7 (CH_2), 39.0 (CH_2), 39.5, 43.9 (CH), 45.7 (CCH_3), 49.7 (CH), 60.0 (CH_2CH_3), 81.6 (COH), 93.2 (OCH_2O), 113.65, 116.2, 126.2 (ArCH), 133.8, 138.0, 155.2 (ArC); m/z 344 (M^+, 21.5%), 241 (11), 159 (10), 59 (100); 44 (15), 43 (32), 41 (22), 40 (16) [found: M^+, 344.2360; $C_{22}H_{32}O_3$ requires: M, 344.2351]; $[\alpha]_D^{20}=+38.2$ [$c=1.5$ (CH_2Cl_2)].

3.5.2. 17α-Deuteriomethyl-3-*O*-ethoxymethyl-17β-estradiol 3b. Mp 70–71°C (dichloromethane/pentane); R_f 0.42 (hexane:ethyl acetate, 2:1); ν (KBr) 3678–3099 (OH), 3030 (ArH), 1609, 1500 (ArC), 1151, 1105, 1025 cm^{-1} (CO); δ_H 0.89 (3H, s, CH_3), 1.23 (3H, t, $J=7.0$, CH_3CH_2), 1.26 (2H, s, CH_2D), 1.28–1.91 (12H, m), 2.17 (1H, br s, OH), 2.29–2.33 (1H, m), 2.83–2.88 (2H, m), 3.72 (2H, q, $J=7.0$, CH_3CH_2), 5.19 (2H, s, OCH_2O), 6.77 (1H, d, $J=2.4$, ArH), 6.83 (1H, dd, $J=8.5$, 2.4, ArH), 7.20 (1H, d, $J=8.5$, ArH); δ_C 13.8, 15.1 (CH_3), 22.9 (CH_2), 25.5 (t, $J_{CD}=20.75$, CH_2D), 26.2, 27.4, 29.8, 31.7, 39.0 (CH_2), 39.6, 43.9 (CH), 45.7 (CCH_2D), 49.7 (CH), 64.1 (CH_2CH_3), 81.6 (COH), 93.2 (OCH_2O), 113.7, 116.2, 126.3 (ArCH), 133.8, 138.0, 155.2 (ArC); m/z 345 (M^+, 9.5%), 59 (100), 44 (53), 43 (13), 41 (20). Anal. calcd for $C_{22}H_{31}DO_3$: C, 76.48; H, 9.63. Found: C, 76.52; H, 9.23%. $[\alpha]_D^{20}=+40.7$ [$c=0.9$ (CH_2Cl_2)].

3.5.3. 3-*O*-Ethoxymethyl-17α-(2-hydroxy-2-phenylethyl)-17β-estradiol 3c (diastereomeric mixture). R_f 0.31 (hexane:ethyl acetate, 2:1); ν (film) 3667–3202 (OH), 3152 (ArH), 1591, 1441 (ArC), 1109, 1042 cm^{-1} (CO); δ_H 0.93, 0.94 (3H, 2s, CCH_3), 1.21, 1.22 (3H, 2t, $J=7.3$, CH_2CH_3), 1.25–2.34 (17H, m, OH), 2.81–2.84 (2H, m, $PhCH_2$), 3.71, 3.72 (2H, 2q, $J=6.9$, CH_2CH_3), 5.13–5.19 (3H, m, CH, OCH_2O), 6.76–6.84 (2H, m, ArH), 7.13–7.43 (6H, m, ArH); δ_C 13.7, 14.1, 15.0 (CH_3), 22.9, 23.4, 26.1, 26.3, 27.3, 27.4, 29.7, 31.3, 32.9, 34.9 (CH_2), 39.5, 39.6, 43.6, 43.7 (CH), 47.0 (CCH_3), 49.1, 49.5 (CH), 64.0 (CH_2CH_3), 72.0, 72.3 (CH), 84.0, 84.6 (COH), 93.1 (OCH_2O), 113.7, 116.2, 125.7, 125.8, 126.3, 127.4, 128.4, 128.5 (ArCH), 133.6, 137.9, 138.0, 145.1, 145.4, 155.3 (ArC); m/z 450 (M^+, 4%), 107 (22), 104 (15), 79 (37), 77 (25), 59 (100), 41 (11) [found: M^+, 450.2775; $C_{29}H_{38}O_4$ requires: M, 450.2770]; $[\alpha]_D^{20}=+6.7$ [$c=1.0$ (CH_2Cl_2)].

3.5.4. 3-*O*-Ethoxymethyl-17α-(2-hydroxy-2-methylpropyl)-17β-estradiol 3d. Mp 119–120°C (dichloromethane/pentane); R_f 0.30 (hexane:ethyl acetate, 2:1); ν (KBr) 3680–3045 (OH), 3011 (ArH), 1605, 1503 (ArC), 1152, 1027, 1004 cm^{-1} (CO); δ_H 0.89 (3H, s, CH_3), 1.23 (3H, t, $J=7.0$, CH_3CH_2), 1.30 (3H, s, $COHCH_3$), 1.46 (3H, s, $COHCH_3$), 1.34–1.71 (10H, m), 1.87–1.91 (1H, m), 2.04–2.20 (2H, m), 2.32–2.42 (2H, m), 2.82–2.85 (2H, m), 3.07 (2H, br s, OH), 3.71 (2H, q, $J=7.0$, CH_3CH_2), 5.19 (2H, s, OCH_2O), 6.77 (1H, d, $J=2.1$, ArH), 6.83 (1H, dd, $J=8.5$, 2.1, ArH), 7.20 (1H, d, $J=8.5$, ArH); δ_C 13.8, 15.1 (CH_3), 23.8, 26.4, 27.4, 29.8 (CH_2), 30.0 (CH_3), 31.8 (CH_2), 33.4 (CH_3), 37.2 (CH_2), 39.8, 43.7 (CH), 44.9 (CH_2), 47.9 (CCH_3), 49.0 (CH), 64.1 (OCH_2CH_3), 72.1 ($COHCH_3$), 84.3 ($COHCH_2$), 93.2 (OCH_2O), 113.7, 116.2, 126.3 (ArCH), 133.7, 138.0, 155.3 (ArC); m/z 402 (M^+, 0.5%), 387 (11), 354 (16), 255 (31), 99 (16), 81 (29), 59 (100), 55 (17). Anal. calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 75.59; H, 9.51%. $[\alpha]_D^{20}=+31.2$ [$c=1.65$ (CH_2Cl_2)].

3.5.5. 3-*O*-Ethoxymethyl-17α-[(1-hydroxycyclohexyl)-methyl]-17β-estradiol 3e. R_f 0.46 (hexane:ethyl acetate, 2:1); ν (film) 3665–3112 (OH), 3010 (ArH), 1605, 1503 (ArC), 1015 cm^{-1} (CO); δ_H 0.89 (3H, s, CH_3), 1.10–2.33 (30H, m), 2.84 (2H, m), 3.72 (2H, q, $J=7.0$, CH_3CH_2), 5.19 (2H, s, OCH_2O), 6.77 (1H, s, ArH), 6.83 (1H, d, $J=8.5$, ArH), 7.20 (1H, d, $J=8.5$, ArH); δ_C 13.8, 15.1 (CH_3), 21.7, 22.9, 25.8, 26.2, 27.4, 29.8, 30.7, 31.3, 31.7, 39.00 (CH_2), 39.55, 43.9 (CH), 45.7 (CCH_3), 49.7 (CH), 64.0 (CH_2CH_3), 73.0, 81.6 (COH), 93.2 (OCH_2O), 113.65, 116.2, 126.2 (ArCH), 133.8, 138.0, 155.2 (ArC); m/z 442 (M^+, 1%), 99 (12), 81 (25), 59 (100), 55 (17), 43 (12), 41 (17) [found: M^+, 442.3081; $C_{28}H_{42}O_4$ requires: M, 442.3083]; $[\alpha]_D^{20}=+77.3$ [$c=1.3$ (CH_2Cl_2)].

3.5.6. Compound 3f. R_f 0.25 (hexane:ethyl acetate, 1:1); ν (film) 3644–3110 (OH), 3020 (ArH), 1661, 1499 (ArC), 1014 cm^{-1} (CO); δ_H 0.93 (6H, s, 2×CH_3), 1.22 (6H, t, $J=7.1$, 2×CH_2CH_3), 1.29–2.32 (28H, m), 2.83–2.85 (4H, m), 3.47 (1H, d, $J=11.0$, $COHCHHCOH$), 3.72 (4H, q, $J=7.1$, 2×OCH_2CH_3), 3.81 (1H, d, $J=11.0$, $COHCHHCOH$), 5.19 (4H, s, 2×OCH_2O), 6.77 (2H, s, ArH), 8.43 (2H, d, $J=8.5$ ArH), 7.18 (2H, d, $J=8.5$, ArH); δ_C 14.1, 15.1 (CH_3), 23.2, 26.2, 27.4, 29.7, 32.4, 33.9 (CH_2), 39.35, 43.8 (CH), 45.6 (CCH_3), 50.25 (CH), 64.1, 67.0 (CH_2), 83.4 (COH), 93.2 (OCH_2O), 113.7, 116.2, 126.25 (ArCH), 133.6, 138.0, 155.3 (ArC); m/z 655 (M^+–OH, 6%), 604 (10), 580 (14), 563 (18), 554 (19), 500 (14), 454 (18), 393 (23), 381 (19), 374 (23), 360 (42), 352 (26), 344 (30), 339 (42), 327 855), 311 (100), 293 (89), 284 (64), 271 (46), 252 842), 241 (40), 231 (52), 220 (30), 213 (68), 187 (38), 161 (87), 147 (52), 119 (75) [found: M^+–(2EtOH+H_2O), 562.3453; $C_{39}H_{46}O_3$ requires: M, 562.3447]; $[\alpha]_D^{20}=+34.7$ [$c=0.9$ (CH_2Cl_2)].

3.5.7. Compound 3g. Mp 209–210°C (dichloromethane/pentane); R_f 0.33 (hexane:ethyl acetate, 2:1); ν (KBr) 3631–3145 (OH), 3020 (ArH), 1615, 1497 (ArC), 1218, 1082, 1005 cm^{-1} (CO); δ_H 0.90 (3H, s, CH_3), 1.23 (2H, t, $J=7.0$, CH_3CH_2O), 1.37, 1.38, 1.46, 1.59 (12H, 4s, 4×CH_3), 1.30–1.74 (10H, m), 1.87–2.00 (3H, m), 2.17–2.32 (2H, m), 2.80–2.85 (4H, m), 3.72 (2H, q, $J=7.0$, CH_3CH_2O), 3.82 (1H, d, $J=7.7$, $COHCHCHCH_2$), 3.91–3.95 (1H, m, $CHCHH$), 4.10–4.22 (2H, m, $CHCHH$), 5.06 (1H, d, $J=3.3$, $CHCHO_2$), 5.19 (2H, s, OCH_2O), 5.72 (1H, d, $J=3.3$, OCHO), 6.78 (1H, s, ArH), 6.83 (1H, d, $J=8.5$, ArH), 7.20 (1H, d, $J=8.5$, ArH); δ_C 13.8, 15.1 (CH_3), 23.5 (CH_2), 25.5 (CH_3), 26.2 (CH_2), 26.5, 26.6, 26.7 (4×CH_3), 27.3, 29.8, 31.2, 35.2, 37.4 (CH_2), 39.7, 43.7 (CH), 47.65 (C), 48.8 (CH), 64.05, 67.9 (CH_2), 73.1 (CH), 79.8 (C), 81.9, 82.9 (CH), 83.1 (COH), 93.2 (OCH_2), 103.8 (OCHO), 109.6, 112.4 [$O_2C(CH_3)_2$], 113.7, 116.2, 126.2 (ArCH), 133.5, 138.0, 155.3 (ArC); m/z 602 (M^+, 11%), 569 (16), 544 (48), 529

(19), 502 (23), 485 (50), 467 (29), 393 (51), 311 (64), 255 (50), 219 (100), 181 (83), 160 (51), 119 (88), 69 (95) [found: M^+, 602.3459; $C_{34}H_{50}O_9$ requires: M, 602.3455]. Anal. calcd for $C_{34}H_{50}O_9$: C, 67.74; H, 8.37. Found: C, 67.81; H,8.43%. $[\alpha]_D^{20}=+31.4$ [$c=0.9$ (CH_2Cl_2)].

3.5.8. Compound 3h. R_f 0.37 (hexane:ethyl acetate, 2:1); ν (film) 3625–3120 (OH), 3032 (ArH), 1610, 1501 (ArC), 1198 cm^{-1} (CO); δ_H 0.92 (3H, s, CH_3), 1.23 (3H, t, $J=7.0$, CH_3CH_2), 1.35 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.51–1.92 (13H, m), 1.99–2.07 (1H, m), 2.32 (2H, s, OH), 2.37–2.51 (1H, m), 2.87 (2H, m), 3.72 (2H, q, $J=7.0$, CH_2CH_3), 3.99 (1H, d, $J=9.8$, CCHHO), 4.07–4.18 (3H, m, $CHCH_2$), 4.26 (1H, d, $J=4.9$, $CHCHCH_2$), 4.33 (1H, d, $J=9.8$, CCHHO), 5.20 (2H, s, OCH_2O), 6.80 (1H, br s, ArH), 6.87 (1H, d, $J=8.5$, ArH), 7.44 (1H, d, $J=8.5$, ArH); δ_C 13.4, 15.1 (CH_3), 20.7, 23.1 (CH_2), 25.4, 25.7, 25.75, 26.2 (CH_3), 29.7, 29.8 (CH_2), 31.95 (C), 32.2 (CH), 32.3 (CH_2), 40.2 (C), 41.8, 44.7 (CH), 47.7, 53.8, 60.0 (CH_2), 64.2 (OCH_2), 71.4 (CH), 71.8 (CH_2), 72.7 (C), 74.8 (CH), 93.0 (OCH_2O), 106.6 (C), 109.3, 112.45 [$O_2C(CH_3)_2$], 114.4, 116.4, 126.4 (ArCH), 135.35, 138.35, 156.7 (ArC); m/z 602 (M^+, 2%), 555 (12), 455 (17), 354 (15), 324 (19), 285 (18), 267 (32), 231 (31), 195 (22), 181 (54), 155 (21), 133 (48), 105 824), 69 (100) [found: M^+, 602.3460; $C_{34}H_{50}O_9$ requires: 602.3455]; $[\alpha]_D^{20}=-25.3$ [$c=1.1$ (CH_2Cl_2)].

3.5.9. 17α-Carboxymethyl-3-*O*-ethoxymethyl-17β-estradiol 3i. R_f 0.20 (hexane:ethyl acetate, 2:1); ν (film) 3695–2611 (COOH), 3062 (ArH), 1734 (C=O), 1610, 1516 (ArC), 1233, 1014 cm^{-1} (CO); δ_H 0.75 (3H, s, CH_3), 1.25 (3H, t, $J=7.3$, CH_3CH_2), 1.30–2.33 (13H, m), 2.57 (1H, d, $J=16.2$, $CHHCO_2H$), 2.74 (1H, d, $J=16.2$, $CHHCO_2H$), 2.81–2.83 (3H, m, $PhCH_2$, OH), 3.72 (2H, q, $J=7.1$, CH_3CH_2), 5.19 (2H, s, OCH_2O), 6.77 (1H, s, ArH), 6.82 (1H, d, $J=8.5$, ArH), 7.17 (1H, d, $J=8.5$, ArH), 8.06 (1H, br s, CO_2H); δ_C 13.8, 15.1 (CH_3), 21.6, 25.8, 26.5 (CH_2), 29.6 (CH), 31.6, 35.9 (CH_2), 38.3 (CH_2CO_2H), 43.6 (CCH_3), 44.0 (CH_2), 48.0, 50.4 (CH), 64.1 (CH_2CH_3), 82.1 (COH), 93.2 (OCH_2O), 113.8, 116.2, 126.3 (ArCH), 133.1, 137.8, 155.4 (ArC), 176.9 (CO_2H); m/z 388 (M^+, 0.1%), 59 (100), 41 (15) [found: M^+, 388.2230; $C_{23}H_{32}O_5$ requires: M, 388.2249]; $[\alpha]_D^{20}=+114.0$ [$c=1.2$ (CH_2Cl_2)].

3.5.10. 3β-Methyl-5α-cholestan-3α-ol 10a.[12] Mp 123–124°C (dichloromethane/pentane); R_f 0.24 (hexane:ethyl acetate, 10:1); ν (KBr) 3545–3102 (OH), 1102 cm^{-1} (CO); δ_H 0.65 (3H, s, CH_3), 0.74 (3H, s, CH_3), 0.85 (6H, d, $J=6.7$, 2×CHCH_3), 0.90 (3H, d, $J=6.7$, CHCH_3), 1.19 (3H, s, COHCH_3), 0.64–1.98 (32H, m); δ_C 11.2, 12.1, 18.7 (CH_3), 21.0 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 28.0 (CH), 28.2, 28.5 (CH_2), 31.6 (CH_3), 32.0, 34.1, 34.9 (CH_2), 35.5, 35.8 (CH), 36.2, 39.5, 40.1 (CH_2), 41.15 (CH), 41.8 (CH_2), 42.6, 46.7 (C), 54.2, 56.3, 56.5 (CH), 69.8 (COH); m/z 402 (M^+, 24%), 369 (33), 262 (10), 248 (24), 244 (14), 232 (15), 231 (42), 230 (28), 229 (100), 215 (15), 179 (16), 163 (14), 162 (14), 161 (27), 159 (13), 149 (21), 147 (14), 135 (26), 122 (25), 109 (21), 107 (24), 105 (25), 97 (23), 95 (40), 93 (31), 91 (21), 81 (39), 79 (29), 71 (34), 69 (25), 67 (21), 57 (34), 55 (37), 43 (63), 41 (21) [found: M^+, 402.3853; $C_{28}H_{50}O$ requires: M, 402.3862]; $[\alpha]_D^{20}=+36.2$ [$c=0.9$ (CH_2Cl_2)].

3.5.11. 3β-Deuteriomethyl-5α-cholestan-3α-ol 10b. Mp 124–125°C (dichloromethane/pentane); R_f 0.24 (hexane:ethyl acetate, 10:1); ν (KBr) 3615–3028 (OH), 1472, 1444 [$CH(CH_3)_2$], 1382 cm^{-1} (CO); δ_H 0.58–1.97 (37 H), 0.57 (3H, s, CH_3), 0.67 (3H, s, CH_3), 0.79 (6H, d, $J=6.7$, 2×CHCH_3), 0.84 (3H, d, $J=6.7$, CHCH_3); δ_C 11.2, 12.1, 18.7 (CH_3), 21.0 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 28.0 (CH), 28.2, 28.5 (CH_2), 31.2 (CH_2D, t, $J_{CD}=18.9$), 32.0, 34.0, 34.9 (CH_2), 35.5, 35.8 (CH), 36.2, 39.5 (CH_2), 40.1 (CH_2), 41.15 (CH), 41.8 (CH_2), 42.6 (CCH_3), 54.2, 56.3, 56.5 (CH), 69.8 (CCH_3), 76.6 (COH); m/z 403 (M^+, 16%), 402 (12), 369 (31), 248 (21), 245 (16), 231 (38), 229 (100), 215 (16), 161 (29), 135 (23), 122 (25), 95 (42), 93 (28), 91 (20), 81 (40), 79 (31), 71 (34), 69 (25), 67 (16), 57 (32), 55 (38), 43 (53). Anal. calcd for $C_{28}H_{49}DO$: C, 83.30; H, 12.73. Found: C, 83.23; H,12.64%. $[\alpha]_D^{20}=+35.8$ [$c=0.8$ (CH_2Cl_2)].

3.5.12. 3β-[(2-Hydroxy-2-phenyl)ethyl]-5α-cholestan-3α-ol 10c (diastereomeric mixture). Mp 195–196°C (dichloromethane/pentane); R_f 0.42 (hexane:ethyl acetate, 3:1); ν (KBr) 3703–3120 (OH), 3058, 3024 (ArH), 1062 cm^{-1} (CO); δ_H 0.65, 0.75 (6H, 2s, 2×CH_3), 0.86 (6H, d, $J=6.4$, 2×CHCH_3), 0.91 (3H, d, $J=6.2$, CHCH_3), 1.00–2.03 (33H, m), 3.05 (1H, br s, OH), 3.91 (1H; br s, OH), 5.10 (1H, d, $J=10.5$, CHOH), 7.24–7.32 (5H, m, ArCH); δ_C 11.2, 11.3, 12.1, 18.7 (CH_3), 21.0 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 28.0 (CH), 28.2, 28.4, 28.7, 32.0, 32.05, 33.8 (CH_2), 35.5, 35.8 (CH), 35.9 (CCH_3), 36.2, 38.4, 39.5, 40.0 (CH_2), 40.5 (CH), 42.5 (CH_2), 42.6 (CCH_3), 51.5 (CH_2), 54.2, 56.2, 56.5 (CH), 71.3 (CHOH), 72.6, 72.65 (COH), 125.6, 127.4, 128.4 (ArCH), 144.9 (ArC); m/z 508 (M^+, 2%), 490 (10), 417 (21), 369 (33), 245 (63), 229 (21), 169 (31), 95 (42), 93 (28), 91 (100), 81 (42), 71 (36), 69 (26), 57 (35), 55 (31). Anal. calcd for $C_{35}H_{56}O_2$: C, 82.61; H, 11.10. Found: C, 82.75; H,11.07%. $[\alpha]_D^{20}=+46.9$ [$c=0.8$ (CH_2Cl_2)].

3.5.13. 3β-(2-Hydroxy-2-ethylbutyl)-5α-cholestan-3α-ol 10d. R_f 0.16 (hexane:ethyl acetate, 2:1); ν (film) 3578–3032 (OH), 1236, 1052 cm^{-1} (CO); δ_H 0.65 (3H, s, CH_3), 0.75 (3H, s, CH_3), 0.84–2.06 (52H, m), 2.24 (2H, br s, 2×OH); δ_C 7.8, 11.2, 12.1, 18.6 (CH_3), 21.0 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 28.0 (CH), 28.2, 28.5, 29.8, 30.9, 31.4, 32.0, 33.3 (CH_2), 35.5, 35.8 (CH), 36.1 (CCH_3), 36.2, 36.7, 39.5, 40.0 (CH_2), 40.5 (CH), 42.6 (CCH_3), 54.2, 56.2, 56.5 (CH), 71.9 (2×COH); m/z 471 [M^+–(OH), 0.05%], 387 (37), 107 (11), 91 (25), 81 (16), 79 (15), 71 (24), 70 (11), 69 (26), 67 (14), 57 (54), 56 (18), 55 (43), 45 (10), 43 (100), 42 (11), 41 (47) [found: M^+–(OH), 471.4556; $C_{33}H_{58}O$ requires: 471.4566]; $[\alpha]_D^{20}=+25.4$ [$c=0.85$ (CH_2Cl_2)].

3.5.14. 3β-[(1-Hydroxycyclohexyl)methyl]-5α-cholestan-3α-ol 10e. Mp 183–184°C (dichloromethane/pentane); R_f 0.15 (hexane:ethyl acetate, 10/1); ν (KBr) 3637–3051 (OH), 1113, 1014 cm^{-1} (CO); δ_H 0.64–1.82 (57H), 1.94–

1.97 (2H, m, CH_2C), 3.17 (1H, br s, OH); δ_C 11.2, 12.1, 18.7 (CH_3), 21.0, 22.3 (CH_2), 22.6, 22.8 (CH_3), 23.8, 24.2, 25.6 (CH_2), 28.0 (CH), 28.2, 28.5, 28.6, 32.1, 33.8 (CH_2), 34.0 (CCH_3), 34.9 (CH_2), 35.4 (CCH_3), 35.5 (CH), 35.6 (CH_2), 35.8 (CH), 36.2, 39.5, 40.0, 40.1 (CH_2), 40.7 (CH), 41.15 (COH), 41.9, 42.6 (CH_2), 54.2, 56.3, 56.5 (CH), 73.3 (COH); m/z 500 (M^+, 0.12%), 99 (58), 81 (47), 79 (14), 71 (17), 70 (11), 69 (21), 67 (15), 57 (30), 56 (18), 55 (58), 54 (11), 43 (100), 42 (18), 41 (35). Anal. calcd for $C_{34}H_{60}O_2$: C, 81.54; H, 12.07. Found: C, 81.63; H, 11.89%. $[\alpha]_D^{20}=+21.5$ [$c=0.85$ (CH_2Cl_2)].

3.6. Reaction of intermediates 13 with ketones 4 and 11. Isolation of compounds 14, 15 and 16. General procedure

To a cooled (0°C) blue suspension of powdered lithium (0.10 g, 14.0 mmol) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (0.04 g, 0.15 mmol) in THF (6 mL) under nitrogen was added phthalan **12a** or isochroman **12b** (1.0 mmol) and the mixture allowed to warm to 25°C over 30 min. The mixture was cooled to −78°C and a THF solution (0.5 mL) of ketones **4** or **11** (1.0 mmol) was added dropwise. Stirring was continued at the same temperature for 10 min, the mixture was hydrolysed with water (30 mL) and extracted with ethyl acetate (3×20 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel, hexane:ethyl acetate) and/or recrystallised to yield pure products **14**, **15** and **16**. Yields (based on the starting materials **12**), physical, spectroscopic and analytical data follow.

3.6.1. 3-*O*-Ethoxymethyl-17α-[2-(hydroxymethyl)phenylmethyl]-17β-estradiol 14a. Mp 110–111°C (dichloromethane/pentane) (25% yield); R_f 0.25 (hexane:ethyl acetate, 2:1); ν (KBr) 3675–3102 (OH), 3055, 3014 (ArH), 1604, 1498 (ArC), 1141, 1106, 1077, 1012 cm^{-1} (CO); δ_H 0.97 (3H, s, CH_3), 1.23 (3H, t, $J=7.0$, CH_3CH_2), 1.28–2.41 (15H, m), 2.72 (1H, d, $J=13.7$, COHCHHPh), 2.88–2.89 (2H, m), 3.22 (1H, d, $J=13.7$, COHCHHPh), 3.73 (2H, q, $J=7.3$, CH_3CH_2), 4.46 (1H, d, $J=11.6$, PhCHHOH), 4.81 (1H, d, $J=11.6$, PhCHHOH), 5.19 (2H, s, OCH_2O), 6.80 (1H, s, ArH), 6.85 (1H, d, $J=8.5$, ArH), 7.21–7.41 (5H, m, ArH); δ_C 14.1, 15.0 (CH_3), 22.9, 26.2, 27.4, 29.7, 31.0, 33.4, 37.9 (CH_2), 39.7, 43.9 (CH), 47.2 (CCH_3), 49.3 (CH), 63.2, 64.0 (CH_2O), 83.1 (COH), 93.1 (OCH_2O), 113.7, 116.2, 126.2, 126.7, 127.5, 130.5, 132.5 (ArCH), 133.6, 137.0, 137.9, 140.5, 155.2 (ArC); m/z 450 (M^+, 14%), 432 [$M^+-(H_2O)$, 22%], 386 (12), 329 (15), 328 (26), 311 (22), 298 (11), 284 (11), 283 (10), 271 (23), 213 (15), 160 (12), 159 (42), 157 (10), 145 (10), 133 (15), 105 (23), 104 (100), 77 (23), 59 (96), 41 (14). Anal. calcd for $C_{29}H_{38}O_4$: C, 77.30; H, 8.50. Found: C, 77.04; H, 8.43%. $[\alpha]_D^{20}=+55.2$ [$c=1.1$ (CH_2Cl_2)].

3.6.2. 3-*O*-Ethoxymethyl-17α-[2-(2-hydroxyethyl)phenylmethyl]-17β-estradiol 14b. Mp 53–54°C (dichloromethane/pentane) (30% yield); R_f 0.21 (hexane:ethyl acetate, 2:1); ν (KBr) 3674–3088 (OH), 3065, 3024 (ArH), 1607, 1503 (ArC), 1241, 1149, 1108, 1015 cm^{-1} (CO); δ_H 0.97 (3H, s, CH_3), 1.23 (3H, t, $J=7.0$, CH_3CH_2), 1.28–1.97 (13H, m), 2.23–2.40 (2H, m), 2.81 (1H, d, $J=14.0$, COHCHHPh), 2.86–2.89 (2H, m), 2.93–3.08 (3H, m, COHCHHPh, CH_2CH_2Ph), 3.73 (2H, q, $J=7.3$, CH_3CH_2), 3.88–3.92 (2H, m, CH_2OH), 5.2 (2H, s, OCH_2O), 6.79–6.87 (2H, m, ArH), 7.20–7.32 (5H, m, ArH); δ_C 14.4, 15.0 (CH_3), 23.2, 26.2, 27.4, 29.7, 31.1, 33.6, 35.4, 38.1 (CH_2), 39.6, 43.8 (CH), 47.0 (CCH_3), 49.4 (CH), 63.3, 64.0 (CH_2O), 83.6 (COH), 93.1 (OCH_2O), 113.6, 116.1, 125.9, 126.2, 126.5, 129.5, 132.3 (ArCH), 133.7, 137.1, 137.9, 138.4, 155.2 (ArC); m/z 464 (M^+, 4%), 329 (35), 328 (55), 311 (10), 298 (13), 283 (16), 159 (12), 133 (12), 128 (10), 118 (14), 117 (21), 115 (17), 106 (13), 105 (30), 91 (19), 79 (10), 59 (100), 41 (12). Anal. calcd for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found: C, 77.12; H, 8.91%. $[\alpha]_D^{20}=+50.2$ [$c=1.35$ (CH_2Cl_2)].

3.6.3. 3β-[2-(Hydroxymethyl)phenylmethyl]-5α-cholestan-3α-ol 15a. Mp 189–190°C (dichloromethane/pentane) (15% yield); R_f 0.46 (hexane:ethyl acetate, 2:1); ν (KBr) 3664–3051 (OH), 3029 (ArH), 1612, 1470 (ArC), 1114, 1016 cm^{-1} (CO); δ_H 0.58–1.91 (48H, m), 2.78 (2H, s, CH_2COH), 4.52 (2H, s, CH_2OH), 7.09–7.29 (4H, m, ArCH); δ_C 11.3, 12.1, 18.65 (CH_3), 21.0 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 28.0 (CH), 28.2, 28.5, 32.0, 33.8, 33.9 (CH_2), 35.5 (CH), 35.75 (CCH_3), 35.8 (CH), 36.2, 39.5, 40.0, 40.6 (CH_2), 41.1 (CH), 42.6 (CCH_3), 46.1 (CH_2COH), 54.2, 56.2, 56.5 (CH), 63.4 (CH_2OH), 71.6 (COH), 126.9, 127.5, 130.6, 132.2 (ArCH), 135.7, 140.3 (ArC); m/z 508 (M^+, 0.2%), 490 (3), 104 (100), 43 (15). Anal. calcd for $C_{35}H_{56}O_2$: C, 82.62; H, 11.09. Found: C, 82.71; H, 10.91%. $[\alpha]_D^{20}=+28.6$ [$c=0.65$ (CH_2Cl_2)].

3.6.4. 3β-[2-(2-Hydroxyethyl)phenylmethyl]-5α-cholestan-3α-ol 15b. Mp 125–126°C (dichloromethane/pentane) (10% yield); R_f 0.14 (hexane:ethyl acetate, 2:1); ν (KBr) 3640–3114 (OH), 3055 (ArH), 1274 cm^{-1} (CO); δ_H 0.65–2.04 (47H, m), 2.34 (3H, s, CH_2COH), 2.98 (2H, t, $J=6.7$, CH_2CH_2OH), 3.84 (2H, t, $J=6.7$, CH_2CH_2OH), 7.12–7.15 (4H, m, ArCH); δ_C 12.1, 12.3, 18.7 (CH_3), 21.3 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 28.0 (CH), 28.2, 28.7, 31.5, 32.1 (CH_2), 35.4 (CCH_3), 35.5, 35.8 (CH), 36.2, 36.4, 37.0, 38.2, 39.5, 40.0 (CH_2), 42.6 (CCH_3), 44.9, 54.4, 56.3, 56.5 (CH), 62.6 (CH_2OH), 71.4 (COH), 126.0, 126.6, 129.6, 130.4 (ArCH), 136.4, 136.5 (ArC); m/z 504 [$M^+-(H_2O)$, 0.6%], 388 (29), 387 (100), 369 (15), 136 (44), 118 (41), 117 (39), 105 (38), 95 (19), 93 (25), 91 (25), 81 (30), 79 (20), 71 (13), 69 (11), 57 (15), 55 (22). Anal. calcd for $C_{36}H_{58}O_2$: C, 82.70; H, 11.18. Found: C, 82.33; H, 11.58%. $[\alpha]_D^{20}=+26.7$ [$c=0.9$ (CH_2Cl_2)].

3.6.5. 3α-[2-(Hydroxymethyl)phenylmethyl]-5α-cholestan-3β-ol 16a. Mp 167–168°C (dichloromethane/pentane) (15% yield); R_f 0.26 (hexane:ethyl acetate, 2:1); ν (KBr) 3603–3109 (OH), 3071, 3022 (ArH), 1035, 1014 cm^{-1} (CO); δ_H 0.58–1.91 (48H, m), 2.89 (2H, s, CH_2COH), 4.50 (2H, s, CH_2OH), 6.99–7.27 (4H, m, ArCH); δ_C 12.1, 12.3, 18.65 (CH_3), 21.3 (CH_2), 22.5, 22.8 (CH_3), 23.8, 24.2 (CH_2), 28.0 (CH), 28.2, 28.5,

32.1, 34.6 (CH_2), 35.6, 35.8 (CH), 36.1 (C), 36.15, 36.3, 39.0, 39.5, 40.0 (CH_2), 41.5 (CH_2COH), 42.6 (C), 44.0, 54.6, 56.3, 56.5 (CH), 63.3 (CH_2OH), 72.8 (COH), 126.8, 127.6, 130.7, 131.5 (ArCH), 136.3, 140.6 (ArC); m/z 508 (M^+, 0.3%), 490 (1), 104 (100), 43 (12). Anal. calcd for $C_{35}H_{56}O_2$: C, 82.62, H, 11.09. Found: C, 82.66, H, 11.02%. $[\alpha]_D^{20}=+27.6$ [$c=0.95$ (CH_2Cl_2)].

3.6.6. 3α-[2-(2-Hydroxyethyl)phenylmethyl]-5α-cholestan-3β-ol 16b. Mp 163–164°C (dichloromethane/pentane) (20% yield); R_f 0.26 (hexane:ethyl acetate, 2:1); ν (KBr) 3570–3100 (OH), 3063, 3026 (ArH), 1047 cm^{-1} (CO); δ_H 0.64–1.97 (47H, m), 2.05 (OH), 2.81 (2H, s, CH_2COH), 3.01 (2H, t, $J=6.7$, CH_2CH_2OH), 3.84 (2H, t, $J=6.7$, CH_2CH_2OH), 7.13–7.26 (4H, m, ArCH); δ_C 11.3, 12.0, 18.6 (CH_3), 20.9 (CH_2), 22.5, 22.7 (CH_3), 23.8, 24.1 (CH_2), 27.9 (CH), 28.2, 28.5, 32.0, 33.6, 33.7 (CH_2), 35.5 (CH), 35.7 (CCH_3), 35.75 (CH), 36.1, 39.4, 40.0, 40.5 (CH_2), 40.7 (CH), 42.5 (CCH_3), 46.1 (CH_2), 54.1, 56.2, 56.4 (CH), 60.3, 63.4 (CH_2), 72.1 (COH), 125.8, 126.7, 129.7, 132.1 (ArCH), 135.8, 138.2 (ArC); m/z 504 [$M^+-(H_2O)$, 0.4%], 489 (2), 388 (27), 387 (100), 369 (16), 136 (40), 135 (13), 121 (10), 119 (15), 118 (43), 117 (46), 109 (11), 107 (21), 106 (20), 105 (46), 104 (15), 95 (21), 93 (25), 91 (25), 81 (30), 79 (24), 71 (17), 69 (21), 67 (15), 57 (35), 55 (42), 43 (86), 41 (43). Anal. calcd for $C_{36}H_{58}O_2$: C, 82.70; H, 11.18. Found: C, 82.91; H, 11.12%. $[\alpha]_D^{20}=+24.8$ [$c=0.75$ (CH_2Cl_2)].

3.7. Cyclisation of compounds 14. Isolation of compounds 17. General procedure

To a benzene solution (5 mL) of diols **14** (0.25 mmol) and triphenylphosphine (0.16 g, 0.6 mmol) in the presence of 4 Å molecular sieves (0.5 g) under nitrogen was added dropwise di-*iso*-propyl azodicarboxylate (0.12 mL, 0.6 mmol) at 25°C. The reaction mixture was heated at 80°C for 3 h. Then the resulting mixture was evaporated (15 mmHg), the residue hydrolysed with water (10 mL) and extracted with ethyl acetate (3×20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated (15 mmHg). The crude product was purified by column chromatography (silica gel, hexane:ethyl acetate) to give compounds **17**. Yields (based on the starting materials **14**), physical, spectroscopic and analytical data follow.

3.7.1. Compound 17a. (47% yield) R_f 0.43 (hexane:ethyl acetate, 10:1); ν (film) 3070, 3021 (ArH), 1609, 1497 (ArC), 1085, 1018 cm^{-1} (CO); δ_H 0.98 (3H, s, CH_3), 1.22 (3H, t, $J=7.0$, CH_3CH_2), 1.38–1.87 (9H, m), 1.91–2.05 (2H, m), 2.19–2.26 (2H, m), 2.64 (1H, d, $J=15.9$, CHHPh), 2.83–2.86 (2H, m), 3.10 (1H, d, $J=15.9$, CHHPh), 3.71 (2H, q, $J=6.7$, 7.3, 6.7, CH_3CH_2), 4.80 (1H, d, $J=15.9$, OCHHPh), 4.87 (1H, d, $J=15.9$, OCHHPh), 5.17 (2H, s, OCH_2O), 6.77–6.84 (2H, m, ArH), 6.95–6.98 (1H, m, ArH), 7.07–7.22 (4H, m, ArH); δ_C 13.7, 15.1 (2×CH_3), 23.0, 26.3, 27.4, 29.75, 32.5, 33.0, 35.0 (CH_2), 39.3, 43.8 (CH), 46.5 (CCH_3), 49.9 (CH), 64.0, 64.85 (2×CH_2O), 83.95 (CO), 93.2 (OCH_2O), 113.65, 116.2, 123.6, 125.65, 126.1, 126.2, 129.1 (ArCH), 133.5, 133.7, 134.7, 137.9, 155.2 (ArC); m/z 432 (M^+, 100%), 311 (37), 286 (49), 271 (65), 159 (64), 131 (38), 104 (62), 59 (88) [found: M^+, 432.2667; $C_{29}H_{36}O_3$ requires: 432.2664]; $[\alpha]_D^{20}=+21.1$ [$c=1.15$ (CH_2Cl_2)].

3.7.2. Compound 17b. (15% yield) R_f 0.48 (hexane:ethyl acetate, 10:1); ν (film) 3063, 3021 (ArH), 1614, 1496 (ArC), 1008 cm^{-1} (CO); δ_H 0.94 (3H, s, CH_3), 1.23 (3H, t, $J=7.1$, CH_3CH_2), 1.25–1.92 (11H, m), 2.20–2.34 (2H, m), 2.63–2.65 (1H, m, PhCHHCH$_2$), 2.72 (1H, d, $J=14.3$, PhCHHC), 2.84–2.87 (2H, m), 3.20–3.23 (1H, m, $PhCH_2CHH$), 3.28 (1H, d, $J=14.3$, PhCHHC), 3.58 (1H, m, PhCHHCH$_2$), 3.74 (2H, q, $J=7.1$, OCH_2CH_3), 3.95–4.01 (1H, m, $PhCH_2CHH$), 5.19 (2H, s, OCH_2O), 6.78–6.86 (2H, m, ArH), 7.05–7.33 (5H, m, ArH); δ_C 14.5, 15.1 (2×CH_3), 23.2, 26.3, 27.6, 29.3, 29.7, 29.8 (CH_2), 38.9 (CH_2), 39.4 (CH), 44.0 (CH), 44.5 (CH_2), 47.9 (CCH_3), 49.3 (CH), 64.1, 64.8 (CH_2), 85.9 (CO), 93.2 (OCH_2O), 113.7, 116.2, 126.16, 126.2, 126.3, 128.7, 130.7 (ArH), 133.9, 138.0, 139.4, 141.6, 155.2 (ArC); m/z 446 (M^+, 10%), 148 (27), 117 (30), 91 (100), 75 (21) [found: M^+, 446.2831; $C_{30}H_{38}O_3$ requires: 446.2821]; $[\alpha]_D^{20}=+14.5$ [$c=0.7$ (CH_2Cl_2)].

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