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Synthesis of Oxygen-Bridged Antigestagens

Arwed Cleve*, Eckhard Ottow, Günter Neef and Rudolf Wiechert

Research Laboratories of Schering AG, D-1000 Berlin, Germany

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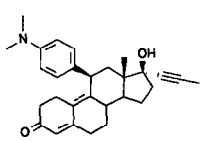
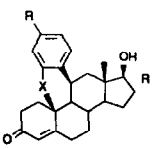
Abstract *A synthetic access to 10,11β-(oxy-1,2-phenylene)-steroids 13 is described Key steps are the S_Ni2' type introduction of suitably ortho substituted arenes into vinyl epoxide 4, and ring closure by an acid catalysed intramolecular epoxide opening with the corresponding phenol The resulting oxygen bridged steroids 13 are transformed into pharmacologically relevant progesterone antagonists 19a-c and 20*

INTRODUCTION

Within the last decade, progesterone antagonists have become an objective of intense chemical and pharmacological research [1a-c] Among the structural variations of lead compound mifepristone (**1**) (figure 1) known so far, one of the most intriguing changes was the introduction of a methylene bridge between C-10 of the steroid skeleton and the 11β-aryl residue [2] The resulting compounds **2a** proved equally or even more potent and selective antigestagens[3] depending upon substituents R and R' Consequently, another promising synthetic goal was replacement of the methylene bridge in **2a** by hetero atoms The corresponding thia analogues **2b** have been prepared[4] following the synthetic scheme (vide infra) which had led to compounds **2a** In this paper we wish to report a new cyclisation route leading to oxygen bridged 11β-aryl steroids (general formula **3**)



1
RU 38 486
mifepristone



2a X = CH_2
b X = S

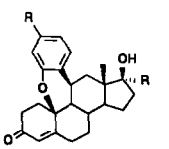


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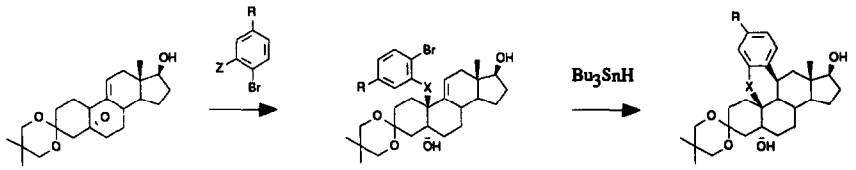
Fig 1

The protocol leading to methylene or thia bridged compounds involved S_N2 opening of α-epoxide **4** by a benzyl Grignard reagent[2,5a] or a thiophenolate[4] (scheme 1) followed by regiospecific 6-*endo-trig* intramolecular radical cyclisation

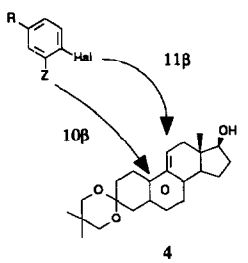


4 **5a** X = CH_2 **b** X = S **6a** X = CH_2 **b** X = S

Z = CH_2MgBr, S^-

Scheme 1

Pursuing an analogous strategy to synthesise oxygen-bridged steroids would have implied an intermolecular epoxide opening by the weaker nucleophile phenolate / phenol, which was not expected to be a favoured process Indeed, neither base nor Lewis acid mediated attempts to open epoxide **4** were successful Based on its latent allyl cation reactivity,[5a-c] vinyl epoxide **4** offers a second synthetic strategy (figure 2) By installing an *ortho* oxygen substituted aryl residue at C-11 first, the desired O - C-10 bond formation would be turned into an entropically favoured intramolecular process Therefore, the 10β-nucleophile introduction - 11β-cyclisation sequence was reversed into an 11β-phenyl addition followed by ring closure at C-10



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Z = CH_2MgBr, S^- ⇒ 1 10β-attack, 2 11β-cyclisation

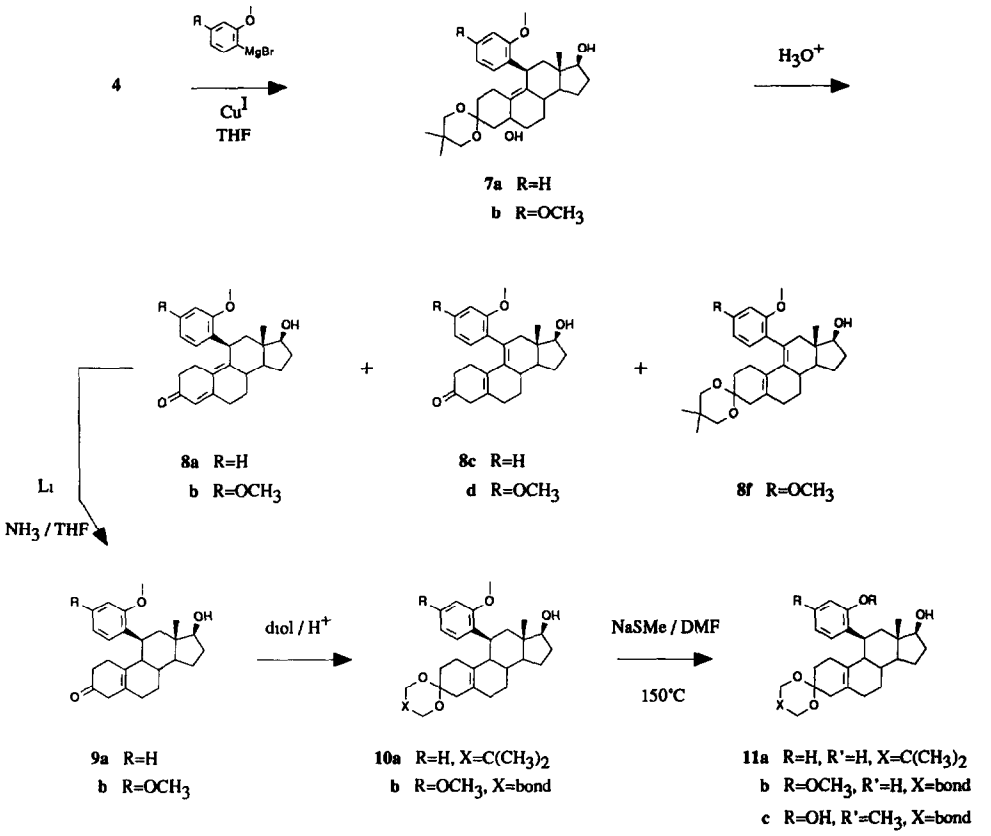
Z = OH ⇒ 1 11β-attack, 2 10β-cyclisation

Fig 2 - retrosynthetic approaches

RESULTS AND DISCUSSION

The S_N2' type opening of α-epoxide **4** according to the procedure presented by G Teutsch et al [5b] succeeded with arenes bearing an *ortho*-methoxy group (scheme 2) as well as with *ortho* unsubstituted arenes Regardless of steric congestion, products **7** were obtained in good yields (78 - 89%) The cyclisation step was envisaged to be a 6-*exo-trig* or 6-*exo-tet* process providing the oxygen bridge plus a chemical equivalent

of a 4(5)-double bond A $\Delta^{5(10)}$-compound appeared to be a reasonable precursor for the cyclisation step, that conceivably might be effected by oxypalladation,[6a,b] iodocyclisation,[7] or epoxidation and subsequent oxirane cleavage Thus compounds **7** were transformed into the $\Delta^{5(10)}$-derivatives **10** by deketalisation, Birch type reduction and ketalisation



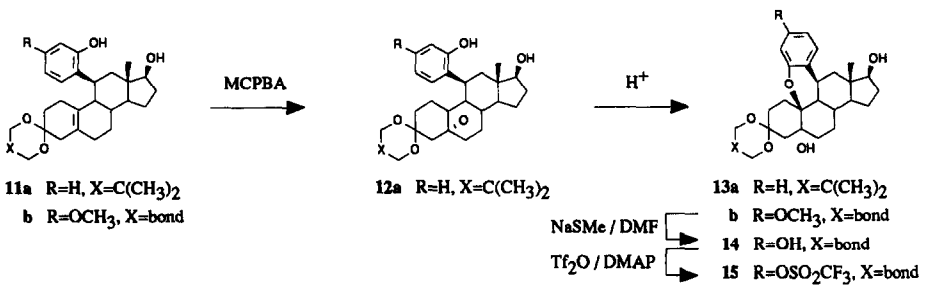
Scheme 2

Unexpectedly, concomitant ketal hydrolysis and dehydration (**7** → **8**) were accompanied by vinylogous 5,11-dehydration giving deconjugated dienones in an undesired side reaction This is not observed to that extent in the *ortho* unsubstituted aryl series Reaction of **7a** in 70% HOAc (room temperature / 6 h) yielded a mixture of **8a** and **8c** (7 3, respectively), whereas **7b** afforded **8b / 8d / 8f** in a ratio of 2 1 3 Under essentially milder conditions (pyridinium *p*-toluenesulfonate / EtOH / 0°C / 45 min) **7b** produced **8b / 8d / 8f** in a ratio of 12 3 5 A sterical factor may account for the unusual hydrolytic behaviour of the *ortho*-methoxyaryl series The *ortho* substituted 11β-aryl residue forces the steroid skeleton into a conformation in which 5α-OH and 11α-H are syn-periplanar, resulting in favourable orbital overlap for *syn* elimination Moreover, the occurrence of diene ketal **8f** which is only observed in the dimethoxyphenyl case,

suggests a competition between dehydration and deketalisation. With increasing aryl electron richness the vinylogous elimination is enhanced These observations indicate that in the *ortho*-methoxyaryl series $\Delta^{5(10),9(11)}$-3-ketones are thermodynamically more stable than the corresponding $\Delta^{4,9}$-3-ketones.

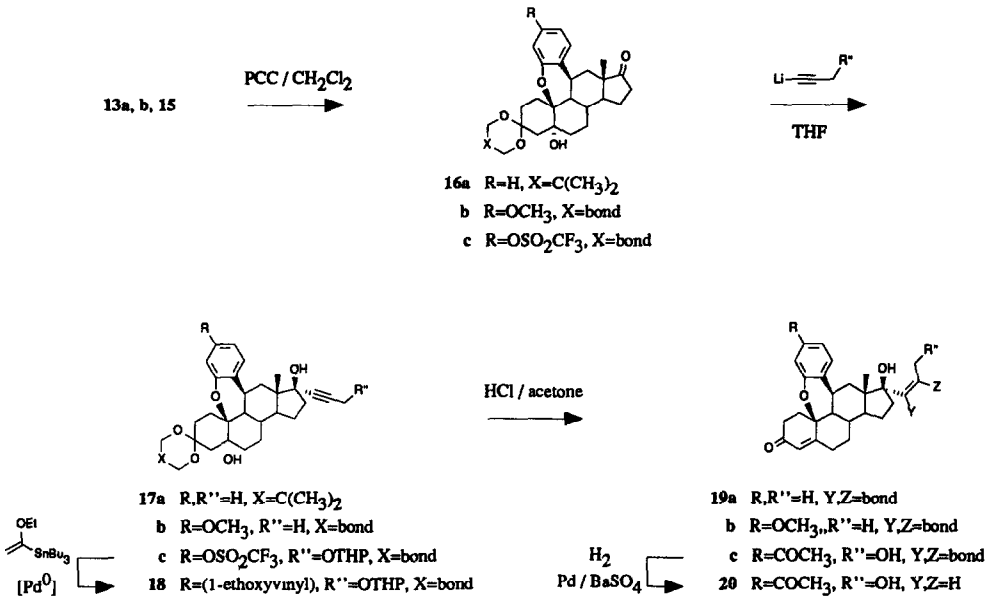
Monomethyl ether **10a** was readily cleaved by reaction with sodium methanethiolate in *N,N*-dimethylformamide (DMF)[8] yielding phenol **11a**, whereas the same conditions applied to bismethyl ether **10b** afforded a mixture of regioisomeric monomethyl ethers **11b** and **11c** in a ratio of 3 · 2. Due to the electron richness of the resulting phenols (**11b / 11c**) any further reaction even with an excess of nucleophilic sodium methanethiolate was inhibited Thus no resorcinol was isolated

Under various oxypalladation conditions no reaction with **11a** was accomplished Presumably due to sterical congestion of $\Delta^{5(10)}$, formation of the requisite palladium complex was disfavoured. An attempted iodocyclisation (I_2 / sat $NaHCO_3$ / CH_2Cl_2) with **11a** yielded only 13% of the expected 5α-iodo oxygen bridged product As that compound turned out to be rather unstable, no optimisation of the reaction was undertaken Epoxidation of compound **11a** with *m*-chloroperbenzoic acid (MCPBA) in the presence of sodium bicarbonate (scheme 3) gave rise to α-epoxide **12a**, and as a less polar by-product, cyclised material **13a** Attempts to effect cyclisation of **12a** under mild basic conditions failed. However, **12a** was smoothly cyclised in a *trans* diaxial manner to **13a** upon treatment with dilute acetic acid In accordance with these experiments, MCPBA epoxidation of **11a** without sodium bicarbonate directly led to **13a** in 58% yield. Under the same conditions resorcinol monomethyl ether **11b** was converted to cyclic ether **13b** As a side reaction, in this case traces of aryl oxidation products were observed Methyl ether cleavage of compound **13b** with sodium methanethiolate followed by reaction with triflic anhydride (Tf_2O) in the presence of 4-(dimethylamino)pyridine (DMAP) gave aryl triflate **15**, a versatile intermediate for palladium-catalysed cross-coupling reactions [9a-c]



Scheme 3

Next, compounds **13a**, **13b**, and **15** were oxidised with pyridinium chlorochromate (PCC) to the corresponding 17-ketones (scheme 4) which, in turn, were allowed to react with either 1-propynyllithium or 3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propynyllithium From 17α-propynyl-compounds **17a** and **17b** the corresponding Δ^4-3-ketones **19a** and **19b** were obtained by deketalisation and dehydration with aqueous HCl in acetone The triflate group of **17c**, so far having served as an unusual phenol protecting group was then cross-coupled in a palladium-catalysed reaction with tributyl(1-ethoxyethenyl)stannane Without purification, the resulting enol ether **18** was submitted to acidic removal of all protecting groups Finally, acetylene **19c** was hydrogenated with Pd / $BaSO_4$ in THF / pyridine to yield *Z*-olefin **20**



Scheme 4

EXPERIMENTAL

NMR General Electric QE 300 and Bruker AC 300 spectrometers, δ in ppm rel to TMS as internal standard IR. Perkin Elmer PE 621 spectrometer. MS: Finnigan TSQ 700 spectrometer Combustion analyses were carried out by Schering analytical department Optical rotations: Perkin Elmer polarimeter mod. 141 Melting points are uncorrected TLC analyses were performed on Merck 60 F_{254} silica gel plates. Column chromatography was performed on Merck silica gel 60, 70-230 mesh, using ethyl acetate / hexane as eluent. The starting α-epoxide 4 was prepared from 3-methoxyestra-1,3,5(10)-trien-17β-ol according to the known procedure [10] All reactions were run under positive argon pressure Solvents were reagent grade and dried prior to use

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-11β-(2-methoxyphenyl)-5α-estr-9-ene-5,17β-diol (7a): A Grignard solution prepared from 1-bromo-2-methoxybenzene (99 9 ml, 802 mmol, 6 equiv) with magnesium turnings (19 5 mg, 802 mmol, 6 equiv) in THF (1500 ml) was cooled to 5°C and CuCl (3.3 g, 33.5 mmol, 0 25 equiv) was added After 15 min a solution of α-epoxide 4 (50 g, 133 5 mmol) in THF (500 ml) was added and the reaction mixture was allowed to warm to room temperature overnight. At 0°C saturated NH_4Cl solution was added carefully and the organic layer was separated The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated The residue was purified by column chromatography to give **7a** (50 3 g, 78%): **mp** 196-198°C (ethyl acetate), $[\alpha]_D^{22}$= +16 0° (c=0 485, $CHCl_3$), **IR** (KBr, cm^{-1})· 3520; **^{1}H NMR** (300 MHz, $CDCl_3$). δ 7 12 (dd, J = 8 Hz and 8.5 Hz, 1H, aryl), 7 05 (d, J = 8 Hz, 1H, aryl), 6 81 (d, J = 8.5 Hz, 1H, aryl), 6.80 (dd, J = 8 Hz and 8 Hz, 1H, aryl), 4 40 (d, J = 9 Hz, 1H, H-11), 4 39 (s, 1H, 5α-OH), 3 86 (s, 3H, OMe), 3.59 (dd, J = 9 Hz and 7 Hz, 1H, H-17), 1 03 (s, 3H, ketal), 0.83 (s, 3H, ketal), 0 52 (s, 3H, H-18), **$C_{30}H_{42}O_5$** (482 7) calcd C 74 66, H 8 77, found C 75 12, H 8 64%

11β-(2,4-Dimethoxyphenyl)-3,3-[2,2-dimethyl-1,3-propanediylbis(oxy)]-5α-estr-9-ene-5,17β-diol (7b): Reaction of α-epoxide 4 (21.6 g, 57 7 mmol) with 3,4-dimethoxyphenylmagnesium bromide, generated from 1-bromo-2,4-dimethoxybenzene (37 5 g, 173 mmol, 3 equiv) and magnesium turnings (4.2 g, 173 mmol,

3 equiv), and CuCl (1 43 g, 14 3 mmol, 0 25 equiv) in THF (450 ml) in the manner described above afforded **7b** (26 3 g, 89%) as a colourless foam: **IR** (KBr, cm^{-1}) 3500, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6 90 (d, J = 9 Hz, 1H, aryl), 6 40 (d, J = 2 Hz, 1H, aryl), 6 32 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 4.30 (d, J = 7.5 Hz, 1H, H-11), 4 38 (s, 1H, 5α-OH), 3 82 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3 57 (m, 1H, H-17), 1.03 (s, 3H, ketal), 0 84 (s, 3H, ketal), 0 52 (s, 3H, H-18), **$C_{31}H_{44}O_6$** (512.7) calcd C 72 63, H 8 65, found C 72.56, H 8 48%.

17β-Hydroxy-11β-(2-methoxyphenyl)estra-4,9-dien-3-one (8a): A solution of **7a** (48 g, 99.4 mmol) in aqueous acetic acid (70%, 480 ml) was stirred at ambient temperature for 6 h After neutralisation with saturated $NaHCO_3$ solution and extraction of the aqueous portion with ethyl acetate, the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated Column chromatography gave isomer 17β-hydroxy-11-(2-methoxyphenyl)estra-5(10),9(11)-dien-3-one **8c** (9 5 g, 25%) {colourless foam **IR** (KBr, cm^{-1}) 3500, 1705 (C=O), **^{1}H NMR** (300 MHz, $CDCl_3$)· δ 7 21 (dd, J = 8 Hz and 8 Hz, 1H, aryl), 6 90-6 80 (m, 3H, aryl), 3 83 (s, 3H, OMe), 3 76 (dd, J = 9 Hz and 8 Hz, 1H, H-17), 2.77 (s, 2H, H-4), 0 93 (s, 3H, H-18), **$C_{25}H_{30}O_3$** (378 5) calcd C 79 33, H 7 99, found C 78 97, H 7 91%} and the desired compound **8a** (23 3 g, 62%) as a colourless foam **IR** (KBr, cm^{-1}) 3430, 1660 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 17 (dd, J = 8 Hz and 8 Hz, 1H, aryl), 6 98 (d, J = 8 Hz, 1H, aryl), 6.85 (d, J = 8 Hz, 1H, aryl), 6 81 (dd, J = 8 Hz and 8 Hz, 1H, aryl), 5 71 (s, 3H, H-4), 4 54 (d, J = 8 5 Hz, 1H, H-11), 3.87 (s, 3H, OMe), 3 64 (m, 1H, H-17), 0 58 (s, 3H, H-18), **$C_{25}H_{30}O_3$** (378 5) calcd C 79 33; H 7.99, found C 79 21, H 7.96%.

11β-(2,4-Dimethoxyphenyl)-17β-hydroxyestra-4,9-dien-3-one (8b): Pyridinium *p*-toluenesulfonate (1 42 g, 5 66 mmol, 0 1 equiv) in ethanol (20 ml) was added to a solution of **7b** (29 g, 56.6 mmol) in ethanol (380 ml) and water (4 ml) at 0°C After 45 min the solvent was evaporated in vacuo, the residue was partitioned between ethyl acetate and half concentrated NaCl solution, the aqueous phase was extracted twice with ethyl acetate, the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Column chromatography yielded the elimination product 11-(2,4-dimethoxyphenyl)-3,3-[2,2-dimethyl-1,3-propanediylbis(oxy)]estra-5(10),9(11)-dien-17β-ol **8f** (5.5 g, 25%) {colourless foam: **IR** (KBr, cm^{-1}): 3490, **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6 83 (d, J = 9 Hz, 1H, aryl), 6 42 (d, J = 2 Hz, 1H, aryl), 6 36 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 3 80 (s, 3H, OMe), 3 79 (s, 3H, OMe), 3 62 (m, 1H, H-17), 1.06 (s, 3H, ketal), 0 89 (s, 3H, ketal), 0 75 (s, 3H, H-18), **$C_{31}H_{42}O_5$** (494 7) calcd. C 75.27, H 8 56, found C 75 09; H 8 5%}, the isomeric ketone 11β-(2,4-dimethoxyphenyl)-17β-hydroxyestra-5(10),9(11)-dien-3-one **8d** (3 37 g, 15%) {yellowish foam. **IR** (KBr, cm^{-1}) 3480, 1710 (C=O), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6 77 (d, J = 9 Hz, 1H, aryl), 6 43 (d, J = 2 Hz, 1H, aryl), 6 36 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 3 80 (s, 6H, OMe), 3.77 (m, 1H, H-17), 2 78 (m, 2H, H-4), 0 92 (s, 3H, H-18); **$C_{26}H_{32}O_4$** (408 5) calcd C 76 44, H 7 99, found C 76 97; H 7 89%}, and the desired dienone **8b** (13.36 g, 58%) as a colourless foam **IR** (KBr, cm^{-1}) 3420, 1660 (C=O), **^{1}H NMR** (300 MHz, $CDCl_3$). δ 6.84 (d, J = 9 Hz, 1H, aryl), 6.43 (d, J = 2 Hz, 1H, aryl), 6 33 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 5.70 (s, 3H, H-4), 4.44 (d, J = 8 Hz, 1H, H-11), 3 85 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.63 (dd, J = 8.5 Hz and 8.0 Hz, 1H, H-17), 0.59 (s, 3H, H-18), **MS** (70 eV, *m/z*) 408 (67%, M^+), 151 (95%), 138 (100%); **$C_{26}H_{32}O_4$** (408 5) calcd C 76 44, H 7 99, found C 76 30, H 7 92%

17β-Hydroxy-11β-(2-methoxyphenyl)estr-5(10)-en-3-one (9a): To a solution of **8a** (5 0 g, 13.2 mmol) in THF (90 ml) and *tert*-butanol (5 ml) liquid ammonia was added at -78°C followed by lithium wire (500 mg, 72 mmol, 5 5 equiv) in small pieces After 1 h at -78°C the mixture was treated with solid NH_4Cl (8 g), the ammonia was evaporated, the residue was treated with water, and the aqueous layer was extracted with ethyl acetate The combined organic layers were dried over Na_2SO_4, filtered, and evaporated Column chromatography afforded **9a** (3 13 g, 62%) **mp** 97-99°C (diisopropyl ether / hexane), $[\alpha]_D^{22}$= +75.3° (c=1 000, $CHCl_3$), **IR** (KBr, cm^{-1}) 3440, 1718 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$). δ 7 38 (d, J = 7 5 Hz, 1H, aryl), 7 12 (dd, J = 8 Hz and 7 5 Hz, 1H, aryl), 6.82 (d, J = 8 Hz, 1H, aryl), 6 75 (dd, J = 7 5 Hz and 7.5 Hz, 1H, aryl), 3 68 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 3 82 (s, 3H, OMe), 3 64 (m, 1H, H-17), 2 78 (d, J = 20 5 Hz, 1H, H-4), 2 76 (d, J = 20 5 Hz, 1H, H-4), 0 42 (s, 3H, H-18), **$C_{25}H_{32}O_3$** (380 5) calcd C 78.91; H 8 48, found C 78.86, H 8 44%

11β-(2,4-Dimethoxyphenyl)-17β-hydroxyestr-5(10)-en-3-one (9b): Reduction of **8b** (13 3 g, 32 6 mmol) in THF (250 ml), *tert*-butanol (3 ml) and liquid ammonia (300 ml) with lithium (904 mg, 130 mmol, 4 equiv) as described above gave **9b** (9.1 g, 68%) as white crystals mp 161°C (diisopropyl ether), $[\alpha]_D^{22}$= +62 4° (c=0 500, $CHCl_3$), **IR** (KBr, cm^{-1}) 3440, 1718 (C=O), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 24 (d, J = 9 Hz, 1H, aryl), 6 40 (d, J = 2 Hz, 1H, aryl), 6 29 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 3 80 (s, 3H, OMe), 3 78 (s, 3H, OMe), 3.63 (m, 1H, H-17), 3 58 (dd, J = 6 5 Hz and J = 5 5 Hz, 1H, H-11), 2 77 (s, 2H, H-4), 0 44 (s, 3H, H-18), **$C_{26}H_{34}O_4$** (410 6) calcd C 76 06, H 8 35, found C 75 99, H 8 33%.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-11β-(2-methoxyphenyl)estr-5(10)-en-17β-ol (10a): **9a** (1 65 g, 4 34 mmol) was stirred for 4 h with 2,2-dimethyl-1,3-propanediol (1 17 g, 11 3 mmol, 2 6 equiv), trimethyl orthoformate (0 57 ml, 5 2 mmol, 1 2 equiv) and a catalytic amount of *p*-toluenesulfonic acid in di-

chloromethane (20 ml) The reaction mixture was poured into saturated $NaHCO_3$ solution, the aqueous layer was extracted with dichloromethane, the organic portions were combined, dried over Na_2SO_4, filtered, and evaporated. The residue was dissolved in methanol (40 ml) and dichloromethane (5 ml) and heated at 60 °C with K_2CO_3 (1 2 g) for 45 min to cleave traces of 17-formate formed in the ketalisation reaction The solvents were evaporated in vacuo, the residue was taken up in dichloromethane and washed with half concentrated NaCl solution The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Column chromatography afforded **10a** (1.62 g, 80%). **mp** 210-212°C (dichloromethane / diisopropyl ether), $[\alpha]_D^{22}$= +82 6° (c=0 500, $CHCl_3$), **IR** (KBr, cm^{-1})· 3460, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 7 10 (ddd, J = 8 Hz and 8 Hz and 1 Hz, 1H, aryl), 6 79 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 6.76 (ddd, J = 8 Hz and 8 Hz and 1 Hz, 1H, aryl), 3 82 (s, 3H, OMe), 3 62 (m, 1H, H-17), 3.58 (m, 1H, H-11), 1 03 (s, 3H, ketal), 0 77 (s, 3H, ketal), 0 38 (s, 3H, H-18), $C_{30}H_{42}O_4$ (466 7) calcd. C 77.21; H 9 07, found C 77.18, H 9 00%

11β-(2,4-Dimethoxyphenyl)-3,3-[1,2-ethanediylbis(oxy)]estr-5(10)-en-17β-ol (10b): Ketalisation of **9b** (7 5 g, 18 3 mmol) with 1,2-ethanediol (2 65 ml, 47.5 mmol, 2.6 equiv), trimethyl orthoformate (2 4 ml, 21.9 mmol, 1 2 equiv), and a catalytic amount of *p*-toluenesulfonic acid in dichloromethane (90 ml), followed by formate cleavage with K_2CO_3 (5 05 g) in methanol (70 ml) in the manner described above yielded **10b** (7 24 g, 87%)· **mp** 188-189°C (diisopropyl ether), $[\alpha]_D^{22}$= +54 4° (c=0 500, $CHCl_3$), **IR** (KBr, cm^{-1}) 3480; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 30 (d, J = 9 Hz, 1H, aryl), 6 40 (d, J = 2 Hz, 1H, aryl), 6 33 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 3 80 (s, 3H, OMe), 3 78 (s, 3H, OMe), 3 61 (m, 1H, H-17), 3 50 (dd, J = 5 5 Hz and 4.5 Hz, 1H, H-11), 2.24 (d, J = 16 Hz, 1H, H-4), 2 18 (d, J = 16 Hz, 1H, H-4), 0.40 (s, 3H, H-18), $C_{28}H_{38}O_5$ (512 7) calcd. C 73 98, H 8 43, found C 74 00, H 8 29%

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-11β-(2-hydroxyphenyl)estr-5(10)-en-17β-ol (11a): Methyl ether **10a** (1 88 g, 4 03 mmol) was heated at 160°C with sodium methanethiolate (1 13 g, 16.1 mmol, 4 equiv) in freshly distilled DMF (20 ml) for 3 h The reaction mixture was poured into ice / $NaHCO_3$ solution, the aqueous layer was extracted with ethyl acetate The organic portions were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated The residue was purified by column chromatography to give phenol **11a** (1 65 g, 90%)· **IR** (KBr, cm^{-1}) 3410, **^{1}H NMR** (300 MHz, $CDCl_3$). δ 7 41 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 6 99 (ddd, J = 8 Hz and 7 5 Hz and 1 Hz, 1H, aryl), 6 73 (ddd, J = 8 Hz and 7 5 Hz and 1 Hz, 1H, aryl), 6 66 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 5 19 (s, 1H, OH), 3 67 (dd, J= 9 Hz and 6.5 Hz, 1H, H-17), 3 55 (m, 1H, H-11), 1 04 (s, 3H, ketal), 0 77 (s, 3H, ketal), 0 42 (s, 3H, H-18), $C_{29}H_{40}O_4$ (452 6) calcd C 76 95, H 8 91, found C 76 88, H 8 79%

3,3-[1,2-Ethanediylbis(oxy)]-11β-(2-hydroxy-4-methoxyphenyl)estr-5(10)-en-17β-ol (11b) and 3,3-[1,2-ethanediylbis(oxy)]-11β-(4-hydroxy-2-methoxyphenyl)estr-5(10)-en-17β-ol (11c): As described above, demethylation of **10b** (5 2 g, 11 4 mmol) was effected by reaction with sodium methanethiolate (3 2 g, 45 8 mmol, 4 equiv) in DMF (60 ml) Column chromatography gave a mixture of regioisomers **11b** and **11c** (4 9 g, 97%, about 3 2) The isomers were separated by fractional crystallisation from chloroform to yield pure 2-hydroxy derivative **11b** (3 16 g, 63%) **mp** > 115°C dec, $[\alpha]_D^{22}$= +46 2° (c=0 500, MeOH), **IR** (KBr, cm^{-1}) 3420, 3250, **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 29 (d, J = 9 Hz, 1H, aryl), 6 35 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6 29 (d, J = 2 Hz, 1H, aryl), 4 80 (s, 1H, OH), 3 74 (s, 3H, OMe), 3 64 (m, 1H, H-17), 3.48 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 0 44 (s, 3H, H-18), $C_{27}H_{36}O_5$ (440 6) calcd C 73 61; H 8 24, found C 73 43; H 8 33%, and pure 4-hydroxy derivative **11c** (905 mg, 18%) **mp** > 143°C dec, $[\alpha]_D^{22}$= +62 4° (c=0 500, MeOH), **IR** (KBr, cm^{-1}) 3370, **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 23 (d, J = 9 Hz, 1H, aryl), 6.37 (d, J = 2 Hz, 1H, aryl), 6 24 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 4 64 (s, 1H, OH), 3 79 (s, 3H, OMe), 3.63 (m, 1H, H-17), 3 49 (m, 1H, H-11), 0 40 (s, 3H, H-18), $C_{27}H_{36}O_5$ (440 6) calcd C 73 61, H 8.24, found C 73 39, H 8 21%

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-11β-(2-hydroxyphenyl)-5,10α-epoxy-5α-estran-17β-ol (12a) and 3,3-[2,2-dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro[1]benzopyrano[2',3',4':10,9,11]-5α-estrane-5,17β-diol (13a): Phenol **11a** (100 mg, 0 22 mmol) was stirred with 50% MCPBA (76 mg, 0 22 mmol, 1 0 equiv) and saturated $NaHCO_3$ solution (0 66 ml) in dichloromethane (3 ml) for 2 h The reaction mixture was treated with 1 M NaOH (5 ml) The organic layer was separated, washed with water, dried over Na_2SO_4, filtered, and evaporated. Column chromatography afforded α-epoxide **12a** (43 mg, 42%) **IR** (KBr, cm^{-1}) 3460, **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 36 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 7 13 (ddd, J = 8 Hz and 8 Hz and 1 Hz, 1H, aryl), 6 78 (ddd, J = 8 Hz and 8 Hz and 1 Hz, 1H, aryl), 6 70 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 5 24 (s, 1H, OH), 3 66 (m, 1H, H-17), 3 59 (m, 1H, H-11), 1 06 (s, 3H, ketal), 0 66 (s, 3H, ketal), 0 35 (s, 3H, H-18), $C_{29}H_{40}O_5$ (468 6) calcd C 74 33, H 8 60, found C 73 98, H 8 40%, along with cyclised product **13a** (10 mg, 10%) **mp** 213-215°C (ethyl acetate / hexane), $[\alpha]_D^{22}$= +2 2° (c=1 000, $CHCl_3$), **IR** (KBr, cm^{-1}) 3480, **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 33 (d, J = 7 5 Hz, 1H, aryl), 7 09 (dd, J = 8 Hz and 7 5 Hz, 1H, aryl), 6 88 (ddd, J = 7 5 Hz and 7 5 Hz and 1 Hz, 1H, aryl), 6 82 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 4 47 (s, 1H, 5α-OH), 3 66 (dd, J= 8 5 Hz and 7 5 Hz, 1H, H-17), 3 10 (dd, J = 6 Hz and 4 Hz, 1H, H-11), 1 00 (s, 3H,

ketal), 0 92 (s, 3H, ketal), 0.28 (s, 3H, H-18), MS (70 eV, *m/z*) 468 (100%, $M^{+\cdot}$), 325 (41%); $C_{29}H_{40}O_5$ (468 6) calcd C 74 33, H 8 60, found C 74 26, H 8 59%

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro[1]benzopyrano[2',3',4':10,9,11]-5α-estrane-5,17β-diol (13a): Phenol **11a** (890 mg, 1.97 mmol) was stirred with 50% MCPBA (679 mg, 1 97 mmol, 1 0 equiv) in dichloromethane (25 ml) for 45 min. The reaction mixture was treated with 1 M NaOH (25 ml) The organic layer was separated, washed with water, dried over Na_2SO_4, filtered, and evaporated. Column chromatography afforded cyclised product **13a** (534 mg, 58%) (see above), along with deketalisation products (234 mg).

3,3-[1,2-Ethanediylbis(oxy)]-9,11α-dihydro-7'-methoxy[1]benzopyrano[2',3',4':10,9,11]-5α-estrane-5,17β-diol (13b): In like fashion, phenol **11b** (3 3 g, 7 5 mmol) was oxidised with 50% MCPBA (3.1 g, 9.0 mmol, 1 2 equiv) in dichloromethane (150 ml) to give cyclised material **13b** (1 56 g, 46%)· **mp** 137°C (diisopropyl ether), $[\alpha]_D^{22}$= +8 6° (c=0.500, $CHCl_3$); **IR** (KBr, cm^{-1}): 3520; ^{1}**H NMR** (300 MHz, $CDCl_3$). δ 7 19 (d, J = 9 Hz, 1H, aryl), 6.49 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6.37 (d, J = 2 Hz, 1H, aryl), 4.38 (d, J = 1 Hz, 1H, 5α-OH), 3 77 (s, 3H, OMe), 3.66 (d, J = 9 Hz and 7 Hz, 1H, H-17), 3.15 (dd, J = 5.5 Hz and 5 Hz, 1H, H-11), 0 32 (s, 3H, H-18); $C_{27}H_{36}O_6$ (456.6) calcd C 71 03, H 7 95, found C 70.91; H 7.69%, and a complex mixture of deketalisation and aryl oxidation products (1 22 g)

3,3-[1,2-Ethanediylbis(oxy)]-9,11α-dihydro-7'-hydroxy[1]benzopyrano[2',3',4':10,9,11]-5α-estrane-5,17β-diol (14): The procedure used was the same as for compound **11a**. From methyl ether **13b** (1.5 g, 3 3 mmol), sodium methanethiolate (921 mg, 13 1 mmol, 4 equiv), and DMF (15 ml), phenol **14** (716 mg, 49%) was obtained. **mp** > 295°C dec (ethyl acetate), $[\alpha]_D^{22}$= +2 2° (c=0.500, MeOH), **IR** (KBr, cm^{-1}) 3540, 3360, ^{1}**H NMR** (300 MHz, pyridine-d_5)· δ 11 28 (s, 1H, phenol), 7 30 (d, J = 9 Hz, 1H, aryl), 6 86 (d, J = 2 Hz, 1H, aryl), 6 82 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 5 96 (s, 1H, 17β-OH), 4 67 (s, 1H, 5α-OH), 3.90 (m, 1H, H-17), 3 19 (dd, J = 5 5 Hz and 5 Hz, 1H, H-11), 0 74 (s, 3H, H-18); $C_{26}H_{34}O_6$ (442.6) calcd. C 70.56, H 7 74, found C 70 69; H 7 65%

3,3-[1,2-Ethanediylbis(oxy)]-9,11α-dihydro-7'-[[(trifluoromethyl)sulfonyl]oxy][1]benzopyrano-[2',3',4':10,9,11]-5α-estrane-5,17β-diol (15): Phenol **14** (690 mg, 1 6 mmol) and 4-(dimethylamino)pyridine (952 mg, 7 8 mmol, 5 equiv) were dissolved in dichloromethane (26 ml), treated with triflic anhydride (0 333 ml, 2 0 mmol, 1.3 equiv) in dichloromethane (3 ml) at -78°C, and stirred for 50 min at that temperature. The reaction mixture was poured into saturated $NaHCO_3$ solution, the aqueous layer was extracted with dichloromethane, the organic portions were combined, washed with water, dried over Na_2SO_4, filtered, and evaporated. Column chromatography afforded triflate **15** (625 mg, 68%)· **mp** 200-201°C (diisopropyl ether), $[\alpha]_D^{22}$= +11 8° (c=0 500, $CHCl_3$); **IR** (KBr, cm^{-1}): 3500, 1420 (SO_2-O); ^{1}**H NMR** (300 MHz, $CDCl_3$). δ 7 38 (d, J = 9 Hz, 1H, aryl), 6.80 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6 78 (d, J = 2 Hz, 1H, aryl), 4.42 (s, 1H, 5α-OH), 3 67 (d, J = 8 5 Hz and 7 Hz, 1H, H-17), 3.20 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 0.27 (s, 3H, H-18), MS (70 eV, *m/z*). 574 (11%, M^+), 441 (67%), 99 (100%), $C_{27}H_{33}F_3O_8S$ (574 6) calcd C 56 44, H 5 79, found C 56 14; H 5 72%

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-5-hydroxy[1]benzopyrano-[2',3',4':10,9,11]-5α-estran-17-one (16a): 17β-Alcohol **13a** (420 mg, 0.90 mmol) was treated with PCC (290 mg, 1 34 mmol, 1 5 equiv) in dichloromethane (25 ml) at ambient temperature. After 2 h the slurry was filtered over silica gel and evaporated The residue was recrystallised from ethyl acetate / hexane to give ketone **16a** (385 mg, 92%) as colourless crystals. **mp** 286-288°C, $[\alpha]_D^{22}$= +17.4° (c=0.500, $CHCl_3$); **IR** (KBr, cm^{-1}): 3500, 1735 (C=O); ^{1}**H NMR** (300 MHz, $CDCl_3$)· δ 7 33 (d, J = 8 Hz, 1H, aryl), 7 09 (dd, J = 8 Hz and 7 5 Hz, 1H, aryl), 6 89 (ddd, J = 7.5 Hz and 7 5 Hz and 1 Hz, 1H, aryl), 6 82 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 4.49 (s, 1H, 5α-OH), 3.27 (dd, J = 6 Hz and 4 Hz, 1H, H-11), 1.02 (s, 3H, ketal), 0 92 (s, 3H, ketal), 0 40 (s, 3H, H-18), $C_{29}H_{38}O_5$ (466 6) calcd. C 74 65, H 8.21, found C 74 55, H 8 18%

3,3-[1,2-Ethanediylbis(oxy)]-9,11α-dihydro-5-hydroxy-7'-methoxy[1]benzopyrano-[2',3',4':10,9,11]-5α-estran-17-one (16b): 17β-Alcohol **13b** (398 mg, 0.87 mmol) was treated with PCC (282 mg, 1.31 mmol, 1 5 equiv) in dichloromethane (25 ml) at ambient temperature. After 2 h the slurry was filtered over silica gel and evaporated The residue was recrystallised from ethyl acetate to give ketone **16b** (375 mg, 95%) as colourless needles **mp** 223°C; $[\alpha]_D^{22}$= +20 4° (c=0 500, $CHCl_3$), **IR** (KBr, cm^{-1}) 3490, 1738 (C=O), ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7 20 (d, J = 9 Hz, 1H, aryl), 6 49 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6 37 (d, J = 2 Hz, 1H, aryl), 4 39 (s, 1H, 5α-OH), 3 77 (s, 3H, OMe), 3.22 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 0 44 (s, 3H, H-18), $C_{27}H_{34}O_6$ (454.6) calcd C 71 34, H 7 54, found C 70 47, H 7 53%

3,3-[1,2-Ethanediylbis(oxy)]-9,11α-dihydro-5-hydroxy-7'-[[(trifluoromethyl)sulfonyl]oxy][1]benzopyrano[2',3',4':10,9,11]-5α-estran -17-one (16c): 17β-Alcohol **15** (460 mg, 0.80 mmol) was treated with PCC (259 mg, 1 20 mmol, 1 5 equiv) in dichloromethane (30 ml) at ambient temperature. After 4 h the slurry was filtered over silica gel and evaporated. The residue was purified by column chromatography to yield ketone **16c** (415 mg, 91%). **mp** 104-105°C (hexane), $[\alpha]_D^{22}$= +20.4° (c=0.500, $CHCl_3$); **IR** (KBr, cm^{-1}). 3500, 1740 (C=O), 1422 (SO_2-O), **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40 (d, J = 9 Hz, 1H, aryl), 6.82 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6.79 (d, J = 2 Hz, 1H, aryl), 4 45 (s, 1H, 5α-OH), 3.28 (dd, J = 5.5 Hz and 5 Hz, 1H, H-11), 0 39 (s, 3H, H-18); $C_{27}H_{31}F_3O_8S$ (572 6) calcd C 56 64; H 5 46, found C 55 99, H 5.36%

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-17α-(1-propynyl)[1]benzopyrano-[2',3',4':10,9,11]-5α-estrane-5,17β-diol (17a): Freshly distilled THF (20 ml) was saturated with 1-propyne at 0°C Butyl lithium (1.6 M in hexane, 3 05 ml, 6 equiv) was added and the solution was stirred for 1 h before a solution of ketone **16a** (380 mg, 0 81 mmol) in THF (10 ml) was added slowly The reaction mixture was allowed to warm to room temperature over a period of 2 h, poured into saturated NH_4Cl solution, and the organic layer was separated The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography to give **17a** (290 mg, 71%). **IR** (KBr, cm^{-1}) 3480, 2220 (C≡C), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 32 (d, J = 8 Hz, 1H, aryl), 7.08 (dd, J = 7.5 Hz and 7 5 Hz, 1H, aryl), 6 88 (ddd, J = 8 Hz and 7 5 Hz and 1 Hz, 1H, aryl), 6.81 (dd, J = 7 5 Hz and 1 Hz, 1H, aryl), 4 51 (s, 1H, 5α-OH), 3 27 (dd, J = 6 Hz and 4 Hz, 1H, H-11), 1 89 (s, 3H, H-17(3)), 1.02 (s, 3H, ketal), 0 92 (s, 3H, ketal), 0 38 (s, 3H, H-18), $C_{32}H_{42}O_5$ (506 7) calcd C 75.86, H 8 36, found C 75.69, H 8 30%

3,3-[1,2-Ethanediylbis(oxy)]-9,11α-dihydro-7'-methoxy-17α-(1-propynyl)[1]benzopyrano-[2',3',4':10,9,11]-5α-estrane-5,17β-diol (17b): As described above, 1-propynyl lithium was generated from 1-propyne in THF (20 ml) with butyl lithium (1 6 M in hexane, 3 09 ml, 6 equiv) and reacted with **16b** (375 mg, 0 82 mmol) in THF (10 ml) to afford **17b** (330 mg, 81%) **IR** (KBr, cm^{-1})· 3490, 2220 (C≡C), **^{1}H NMR** (300 MHz, $CDCl_3$). δ 7.19 (d, J = 9 Hz, 1H, aryl), 6.49 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6.37 (d, J = 2 Hz, 1H, aryl), 4.42 (d, J = 1 Hz, 1H, 5α-OH), 3.77 (s, 3H, OMe), 3 21 (dd, J = 5.5 Hz and 5 Hz, 1H, H-11), 1.90 (s, 3H, H-17(3)), 0 41 (s, 3H, H-18), $C_{30}H_{38}O_6$ (494 6) calcd C 72 85, H 7 74, found C 72 18; H 7 65%

3,3-[1,2-Ethanediylbis(oxy)]-9,11α-dihydro-17α-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propynyl]-7'-[[(trifluoromethyl)sulfonyl]oxy][1]benzopyrano[2',3',4':10,9,11]-5α-estrane-5,17β-diol (17c): To a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (1 ml, 7 07 mmol, 10 equiv) in THF (15 ml) was added butyl lithium (1 6 M in hexane, 4 40 ml, 10 equiv) at 0°C After 0 5 h, at that temperature ketone **16c** (405 mg, 0 71 mmol) was added, the reaction mixture was stirred for 3 h at 0°C and poured into saturated NH_4Cl solution, and the organic layer was separated The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography to afford **17c** (405 mg, 80%) **IR** (KBr, cm^{-1}) 3480, 1425 (SO_2-O), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (d, J = 9 Hz, 1H, aryl), 6 81 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6 78 (d, J = 2 Hz, 1H, aryl), 4.84 (m, 1H, THP), 4 43 (s, 1H, 5α-OH), 4 37 (m, 2H, H-17(3)), 3 89 (m, 1H, THP), 3 57 (m, 1H, THP), 3 27 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 0 38 (s, 3H, H-18); **MS** (70 eV, *m/z*) 712 (2%, M^+), 610 (19%), 477 (22%), 85 (100%), $C_{35}H_{43}F_3O_{10}S$ (712 8) calcd C 58 98; H 6 08, found C 58 09; H 5 95%

9,11α-Dihydro-17β-hydroxy-17α-(1-propynyl)[1]benzopyrano[2',3',4':10,9,11]estr-4-en-3-one (19a): **17a** (280 mg, 0 55 mmol) in acetone (10 ml) was treated with aqueous HCl (4 M, 3 ml) for 18 h The reaction mixture was poured into saturated $NaHCO_3$ solution, the aqueous layer was extracted with ethyl acetate, the organic portions were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated The residue was purified by column chromatography to give Δ^4-3-ketone **19a** (160 mg, 72%). **mp** 257-258°C (ethyl acetate / hexane), $[\alpha]_D^{22}$= +8 5° (c=1 000, $CHCl_3$), **IR** (KBr, cm^{-1}) 3460, 2235 (C≡C), 1672 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7 37 (d, J = 8 Hz, 1H, aryl), 7 12 (dd, J = 8 Hz and 7 5 Hz, 1H, aryl), 6 92 (ddd, J = 8 Hz and 7 5 Hz and 1 Hz, 1H, aryl), 6 85 (dd, J = 8 Hz and 1 Hz, 1H, aryl), 5.96 (s, 1H, H-4), 3 44 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 1 90 (s, 3H, H-17(3)), 0 42 (s, 3H, H-18), **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200 0 (C-3), 161 0 (C-8a'), 153 0 (C-5), 128 7 (C-4), 128 1, 127 6, 124.9 (C-4a'), 121 6, 118 6, 83 2 (C-17(1)), 83 2 (C-17(2)), 81 0 (C-17), 74 2 (C-10), 50 0, 49 3, 47 6 (C-13), 40 0, 35.4, 34 5, 33 9, 32 7, 30 8, 30 7, 30 0, 23 5, 15 7 (C-18), 4 5 (C-17(3)), **MS** (70 eV, *m/z*) 402 (72%, M^+), 320 (45%), 210 (100%), **HRMS** (70 eV) calcd for $C_{27}H_{30}O_3$ 402 2195, obsd 402 2195, $C_{27}H_{30}O_3$ (402 5) calcd C 80 56, H 7 51, found C 80 48, H 7 50%

9,11α-Dihydro-17β-hydroxy-7'-methoxy-17α-(1-propynyl)[1]benzopyrano[2',3',4':10,9,11]estr-4-en-3-one (19b): **17b** (250 mg, 0 51 mmol) was deketalised and dehydrated in the same manner with aqueous HCl (4 M, 3 ml) in acetone (10 ml) to produce Δ^4-3-ketone **19b** (197 mg, 79%)· **mp** 246°C dec (diisopropyl

ether), $[\alpha]_D^{22}$= +33 0° (c=0 500, $CHCl_3$); **IR** (KBr, cm^{-1})· 3460, 2240 (C≡C), 1678 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$). δ 7 23 (d, J = 9 Hz, 1H, aryl), 6.53 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 6.41 (d, J = 2 Hz, 1H, aryl), 5 96 (s, 1H, H-4), 3.78 (s, 3H, OMe), 3.38 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 1.90 (s, 3H, H-17(3)), 0.46 (s, 3H, H-18); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.3 (C-3), 160.2 (C-8a'), 159.0 (C-7'), 153.0 (C-5), 128 7 (C-4), 126 9 (C-5'), 116 3 (C-4a'), 108.1, 102 1, 82 5 (C-17(1)), 82.5 (C-17(2)), 80.3 (C-17), 73.8 (C-10), 55.2 (OMe), 49 2, 48 7, 46 8 (C-13), 39.0, 34.7, 33.7, 33.2, 32.0, 30.1, 29 5, 29 3, 22.8, 15.0 (C-18), 3.8 (C-17(3)); **MS** (70 eV, *m/z*)· 432 (100%, M^+), 137 (47%), **HRMS** (70 eV): calcd. for $C_{28}H_{32}O_4$ 432 2301, obsd 432 2310, $C_{28}H_{32}O_4$ (432.6) calcd C 77.75, H 7.46, found C 76.98; H 7 44%.

7'-Acetyl-9,11α-dihydro-17β-hydroxy-17α-(3-hydroxy-1-propynyl)[1]benzopyrano-[2',3',4':10,9,11]estr-4-en-3-one (19c): Triflate **17c** (400 mg, 0.56 mmol) in dioxane (5 ml) was heated at reflux with tributyl(1-ethoxyethenyl)stannane (0.25 ml, 0.74 mmol, 1.3 equiv), lithium chloride (48 mg, 1.13 mmol, 2 equiv), and tetrakis(triphenylphosphine)palladium(0) (33 mg, 29 µmol, 0.05 equiv) for 2 h. The reaction mixture was filtered over Celite®, the solid was rinsed with ethyl acetate, and the filtrate was evaporated in vacuo to give enol ether **18** The raw material was instantly hydrolysed with aqueous HCl (4 M, 3 ml) in acetone (10 ml) according to the above procedure to yield **19c** (153 mg, 59%) **IR** (KBr, cm^{-1}): 3450, 1670 (C=O), **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 7.46 (d, J = 9 Hz, 1H, aryl), 7 46 (d, J = 2 Hz, 1H, aryl), 5 99 (s, 1H, H-4), 4 38 (m, 2H, H-17(3)), 3.48 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 2 58 (s, 3H, Ac), 0 42 (s, 3H, H-18), $C_{29}H_{32}O_5$ (460 6) calcd C 75 63, H 7.00, found C 75.49; H 6.98%

(Z)-7'-Acetyl-9,11α-dihydro-17β-hydroxy-17α-(3-hydroxy-1-propenyl)[1]benzopyrano-[2',3',4':10,9,11]estr-4-en-3-one (20): Propargyl alcohol **19c** (150 mg, 0.33 mmol) in THF (3 ml) and pyridine (0 3 ml) was hydrogenated over Pd / $BaSO_4$ (10%, 33 mg) until one equivalent of H_2 was consumed. The slurry was filtered over Celite®, and the filtrate was evaporated in vacuo. Column chromatography afforded **20** (100 mg, 66%). **mp** 185-186°C (dichloromethane / diisopropyl ether); $[\alpha]_D^{22}$= +68.8° (c=0.500, $CHCl_3$), **IR** (KBr, cm^{-1}) 3420, 1682 (C=O), 1670 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.53 (dd, J = 9 Hz and 2 Hz, 1H, aryl), 7 47 (d, J = 9 Hz, 1H, aryl), 7 46 (d, J = 2 Hz, 1H, aryl), 5 99 (s, 1H, H-4), 5 75 (ddd, J = 12.5 Hz and 6 Hz and 6 Hz, 1H, H-17(2)), 5.66 (d, J = 12 5 Hz, 1H, H-17(1)), 4.34 (m, 2H, H-17(3)), 3 42 (dd, J = 6 Hz and 5 Hz, 1H, H-11), 2 58 (s, 3H, Ac), 0 49 (s, 3H, H-18), **MS** (70 eV, *m/z*): 462 (3%, $M^{+\cdot}$), 444 (52%, $M^+ - H_2O$), 95 (92%), $C_{29}H_{34}O_5$ (462 6) calcd C 75 30, H 7 41, found C 75 11, H 7 34%

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