Synthesis of 16-[carbamoyl(bromomethyl)alkyl]estradiol: a potential dual-action inhibitor designed to blockade estrogen action and biosynthesis

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The target compound 1, *N*-butyl-*N*-methyl-7-bromomethyl-9-[3′,17′β-dihydroxyestra-1′,3′,5′(10′)-trien-16′α-yl]nonanamide, possesses a bifunctionalized side chain at the 16α position of the steroidal D-ring, and is synthesized from commercially available estrone using a sequence of 13 steps. Two α-alkylations of lithium enolates are performed, yielding a general template that leads to the expected bifunctionalized compound. First, alkylation at position 16 of protected estrone requires an activated electrophile and produces mainly the desired 16α-isomer. Optimal conditions for the second α-alkylation of the resultant ester enolate are established to give mainly the monoalkylated ester. Finally, various functional group transformations can be carried out to generate interesting estradiol derivatives for structure–activity relationship studies.

Introduction

During the past decade, breast cancer has been recognized to be the most prevalent cancer in women throughout the world.[1] It is well established that estrogens act as important endocrine growth factors for at least a third of breast cancers.[2] Endocrine therapy provides a relatively specific, non-toxic approach for the treatment of breast cancer, and drugs that interfere with hormone action have been developed. Among them, estrogen antagonists bearing specifically functionalized side chains at the 7α or 11β positions are now used experimentally *in vivo* for the treatment of breast cancer.[3–6] Such compounds compete with estrogens by binding to the intracellular receptor without provoking mitogenic effects on breast tumour cells.

Although estrogen antagonists represent an important approach to endocrine therapy against breast cancer, the cellular levels of active estrogens are not significantly influenced by these drugs. Active hormonal steroids are now known to be synthesized mainly in peripheral tissues, *e.g.* breast, from a circulating precursor dehydroepiandrosterone through a complex enzymatic pathway.[7] The final step of estradiol biosynthesis is catalysed by 17β-hydroxysteroid dehydrogenase (17β-HSD), which reversibly converts the less active estrogen, estrone, into its potent reduced form, estradiol. Because production of extraovarian estrogens could be blocked by 17β-HSD inhibitors, this enzyme is a logical target for drugs designed to treat estrogen-dependent diseases such as breast cancer.

In our efforts to develop molecules that could inhibit estrogen formation *via* 17β-HSD and estrogen action *via* the intracellular receptor, we proposed the bifunctionalized compound **1** (Fig. 1). The chemical structure of the target compound **1** should possess substituents that retain affinities for the estrogen receptor as well as for the steroidogenic enzymes like 17β-HSD. Earlier reports by our group[8,9] and others[10–12] established that inhibition of 17β-HSD could be achieved by an electrophilic site on the D-ring of estradiol derivatives. Systematic studies have found that side-chain lengths of 3 or 4 carbons at position 16α are optimal for the inhibitory effect of the 16-(bromoalkyl)estradiols.[13] On the other hand, the presence of a bulky basic side chain is an important feature of the above-mentioned estrogen antagonists. The tertiary amide group provides the best separation of agonist–antagonist activity, and substituents on the amide nitrogen are restricted to methyl and butyl.[14] Consequently, the primary bromide was placed in an attempt to introduce an alkylating property that could inactivate 17β-HSD, and the amide moiety should interact with the estrogen receptor to block its activation. This could lead to the development of a single molecule that displays two therapeutic actions and might also contribute to the understanding of the mode of action of the existing molecules.

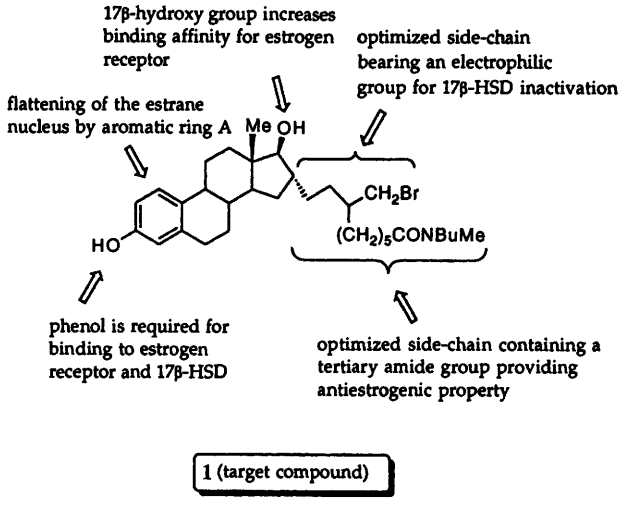
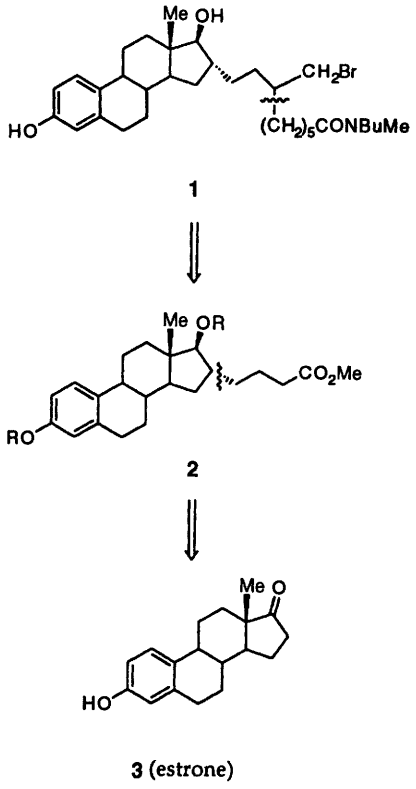


Fig. 1 Design concept leading to dual-action inhibitor

Results and discussion

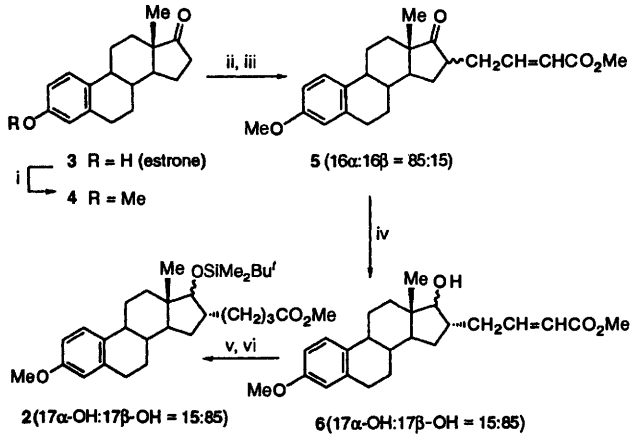
Previous studies by our group[8,13] and others[15–20] have demonstrated that direct α-alkylation at the steroidal 17-ketone requires relatively small and activated electrophiles. A strategy for alkylation at position 16 of activated estrone with unactivated electrophiles was developed by our group.[21] However, this methodology gives mainly the 16β-isomer and consequently could not be used in this case. Thus, a one step introduction of a partially or entirely functionalized electrophile was not suitable for the synthesis of compound **1**. Taking into account this chemical limitation, retrosynthetic analysis of the target compound led us to consider the formation of an intermediate with an ester that could be α-alkylated (Scheme 1). The ester would



Scheme 1 Retrosynthetic analysis of the bifunctionalized target molecule

then be converted to a bromide, whereas the alkylated side chain would be functionalized as an amide.

The key intermediate **2** was prepared in five steps, starting from estrone (**3**), as illustrated in Scheme 2. Alkylation of the

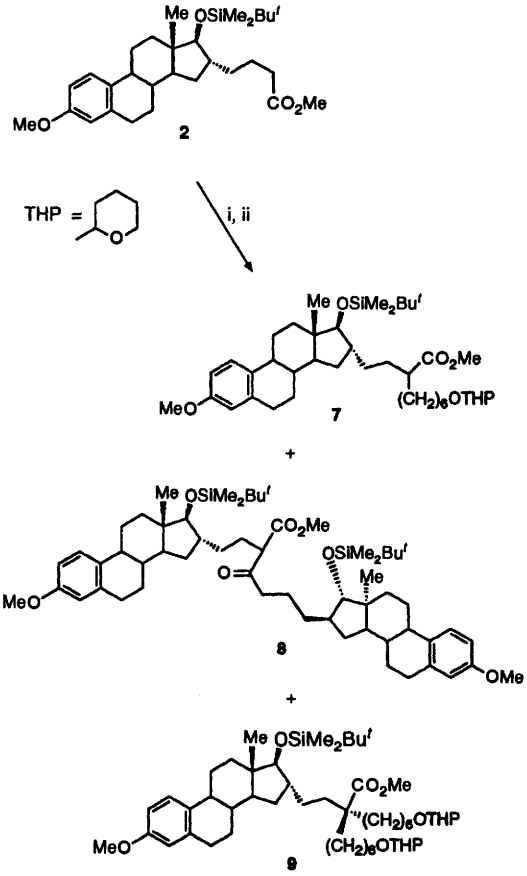


Scheme 2 *Reagents and conditions:* i, MeI, K_2CO_3, DMF, heat, 98%; ii, LDA, HMPA; iii, $BrCH_2CH{=}CHCO_2Me$, 20–50%; iv, $LiAlH_4$, THF, −78 °C, 80%; v, H_2, Pd/C; vi, Bu^tMe_2SiCl, imidazole, DMF, 96% (two steps)

methoxy-protected estrone **4** with methyl 4-bromocrotonate resulted in the formation of **5** as two isomers in proportions varying from 7:3[13] to 9:1. The less hindered α-face of the lithium enolate is known to attack the alkylating agent.[15,16] The ratio of 16α:16β was evaluated by ^1H NMR spectroscopy. The signal of the 18-CH_3 was at δ 0.96 for the 16α-isomer, whereas the same signal appeared at δ 0.91 for the 16β-isomer. The yield of ester **5** was moderate (20–50%) but this can be explained by the recovery of starting ketone **4** (40%). Indeed, literature data indicates that α-alkylation at the C16 position of a steroid occurs with modest yield for some alkylating agents subject to decomposition.[15] Since position 16 of estradiol is not easily accessible, a convergent synthesis involving coupling of the steroidal nucleus with the entirely functionalized side chain should be avoided.

The presence of two enolizable functional groups in compound **5** made it unsuitable for subsequent steps of the synthesis. Therefore, chemoselective reduction of the 17-ketone of **5** was achieved using lithium aluminum hydride. At this stage, the minor 16β-isomer of **6** could be eliminated by standard silica gel chromatography. The reduction was performed at a low temperature (−78 °C) to facilitate an attack by the nucleophilic hydride from the α-face. Unfortunately, the presence of the side chain on the α-face seemed to interfere with the normal induction exerted by the 18-CH_3 and a mixture of two unresolved epimers of **6** was obtained. (Similar results were obtained using sodium borohydride as the reductive agent, and when reduction of the 17-ketone was attempted using the much more hindered lithium tri-*tert*-butoxyaluminohydride, the expected alcohol was obtained in only very low yield.) Hydrogenation of double bond and subsequent protection of the 17-hydroxy group led to key intermediate **2**.

The most important step of the synthesis was realized with the α-alkylation of the lithium ester enolate of **2** with an unactivated electrophile to give the bifunctionalized compound **7** (Scheme 3). Although α-alkylations of simple ester enolates



Scheme 3 *Reagents:* i, LDA, HMPA, THF; ii, $I(CH_2)_6OTHP$

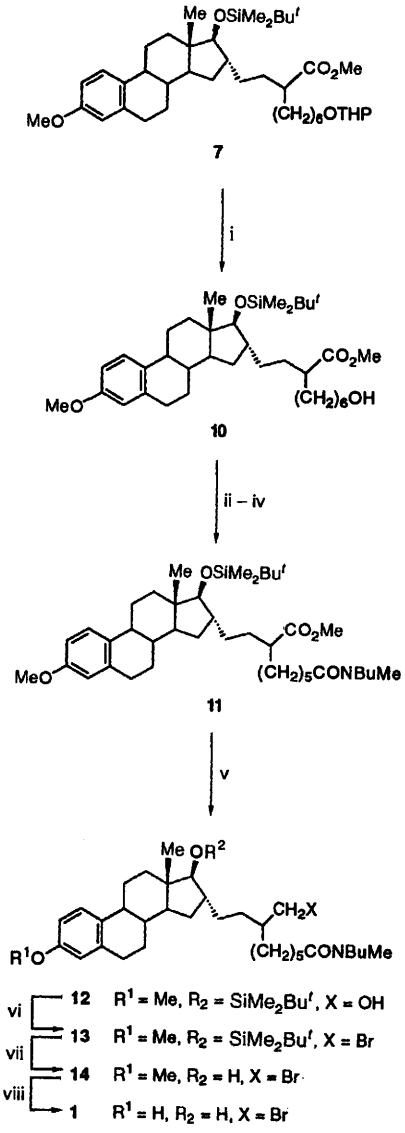
with small electrophiles are well documented,[22] the reactivity of unactivated electrophiles toward substituted and complex ester enolates needs to be investigated more fully. The presence of iodide as the leaving group generally led to a better yield than the presence of either bromide or tosylate.[23] Other functional groups on the electrophile might dramatically decrease its reactivity. In fact, α-alkylation of ester **2** with the entirely functionalized $I(CH_2)_5CONBuMe$ was unsuccessful, and only the starting material was recovered. Enolization of the amide moiety on the electrophile under the reaction conditions might be responsible for this lack of reactivity. Consequently, introduction of a side chain that could easily lead to the amide, such as $I(CH_2)_6OTHP$, proved necessary.

We then focused on conditions that would favour the form-

ation of **7** from alkylation of the lithium ester enolate of **2**. The temperature and concentration of LDA were two crucial parameters. At low temperature (−78 to −25 °C), no alkylated product was observed. When the temperature was increased to 0 °C, self-condensation (to give **8**) occurred predominantly when 1 equiv. of LDA was used. Similar results have been reported by other groups using less reactive electrophiles as alkylating agents for simple ester enolates.[24] Because the lithium ester enolate of **2** could not be fully generated at low temperatures with an equimolar quantity of LDA, an excess of this base (3.5 equiv.) was considered. Dialkylation (to give **9**) was partially avoided by controlling the concentration of electrophile (1 equiv.) and by keeping the reaction temperature below 0 °C immediately after the addition of the electrophile. Similar procedures have already been used to alkylate sterically hindered esters with relatively short electrophiles without self-condensation occurring.[25] Our results show that this methodology is also suitable for the α-alkylation of moderately hindered and complex carboxylic esters with long unactivated electrophiles. At this step of the synthesis, the protected 17β-hydroxy-16α-alkylated product **7** was recovered after purification by silica gel chromatography in 62% yield. This stereochemical feature has been thoroughly studied by our group[13,21] and others.[15,26] The 17α-proton signal, observed at δ 3.3 (J 7.0 Hz) in the ^{1}H NMR spectrum, and the C17 signal, at δ 87.78 in the ^{13}C NMR spectrum, confirmed the proposed C16/C17 stereochemistry of compound **7**.

The next challenge of this synthesis was to determine the order of events during the functionalization of the 16α-side chain. Previous studies by our group[9] together with unpublished observations led us to synthesize the amide moiety before conversion of the ester into the expected primary bromide (Scheme 4). Consequently, hydrolysis of the THP group of compound **7** was performed by weakly acidic MeOH to give mainly alcohol **10**, with a small amount of its 17β-OH analogue. The primary alcohol of **10** was oxidized according to Jones' procedure to yield the carboxylic acid. Without purification, the latter was converted to the *N*-methyl-*N*-butylamide **11** *via* an anhydride-promoted coupling reaction.[9]

It has been observed in our laboratory that a carboxylic ester at position 16 of an estradiol derivative could be reduced with $LiAlH_4$ at −40 °C in THF without any transformation of a tertiary amide present at position 7α of the same molecule. However, attempts to reduce selectively the ester of **11** using this reagent and its less reactive analogue, DIBAL-H, were unsuccessful. In fact, the formation of very polar products occurred under these conditions, suggesting that the amide function was reduced. Fortunately, this amide was inert toward the soft and hindered $LiAl(OBu^t)_3H$; thus, chemoselective reduction of ester **11** gave alcohol **12** in good yield. Bromination of primary alcohol **12** was performed using CBr_4 and PPh_3 to give the bifunctionalized compound **13**. Finally, the hydroxy groups at positions 17 and 3 were regenerated by standard procedures [MeOH–HCl, 2% (v/v) and BBr_3, respectively] to yield target compound **1**. The structure of **1** was confirmed by IR, ^{1}H NMR, ^{13}C NMR and high resolution mass spectral techniques. It should be noted that normal-phase high-performance liquid chromatography revealed, as expected, the presence of two isomers, equally distributed, corresponding to (*R*)-**1** and (*S*)-**1**.



Scheme 4 *Reagents and conditions:* i, PTSA, MeOH, 65–75%; ii, Jones; iii, NBu_3; iv, Bu^tOCOCl, HNBuMe, 70% (two steps); v, $LiAl(OBu^t)_3H$, THF–toluene (2:1), heat, 77%; vi, CBr_4, PPh_3, 72%; vii, HCl 2% (p/v), MeOH, 95%; viii, BBr_3, CH_2Cl_2, 0 °C, 61%

Conclusion

We have synthesized the bifunctionalized estradiol derivative **1** in order to afford a dual-site blocker. A sequence of 13 chemical steps gave the compound **1** from commercially available estrone with an overall yield of 2%. α-Alkylation of the lithium ester enolate of **2** was the key step in this sequence. This reaction was performed by minimizing the occurrence of self-condensation and dialkylation side-products. Apparently, condensation of the newly formed lithium enolate with the starting ester occurs at a rate comparable to that of the alkylation steps using a less reactive electrophile, such as $I(CH_2)_6OTHP$. Consequently, the ester must have been rapidly converted to its corresponding anion to avoid self-condensation. This was realized by using an excess of LDA together with HMPA as the enolization promoter. From this compound, several other bifunctionalized estradiol derivatives can be synthesized and used for a structure–activity relationship study. For these reasons, the reported synthesis of **1** involving an α-alkylation of ester enolate as a key step offers an interesting degree of versatility.

The potency of bifunctionalized target compound **1** to inhibit 17β-HSD type 1[13] and also its intrinsic estrogenic activity[9] were evaluated *in vitro*. A concentration of 4.5 μM is needed to inhibit fifty percent (IC_{50}) of the formation of the most potent estrogen, estradiol, catalysed by 17β-HSD type 1. By way of comparison, the bromobutyl analogue without the alkylamide residue has an IC_{50} of 2.1 μM using the same enzymatic conditions.[13] Afterward, the proliferative and antiproliferative assays were performed on the estrogen-sensitive ZR-75-1 cells. A concentration of 1 μM of **1** caused only 25% stimulation of cellular growth, whereas the same concentration inhibited by 45% the 0.1 nM estradiol-stimulation growth of ZR-75-1 cells. In this assay, estradiol or the bromoalkyl analogue without

alkylamide residue caused a 100% stimulation of cells.[27] Thus, compound **1** is a partial estrogen antagonist which could moderately inhibit estradiol biosynthesis by its action on 17β-HSD type 1.

Experimental

Chemical reagents were purchased from the Aldrich Chemical Company (Milwaukee, WI) and estrone was purchased from Steraloids (Wilton, NH). Solvents were obtained from Fisher Scientific (Montréal, Canada). Tetrahydrofuran (THF) used in anhydrous conditions was distilled from sodium benzophenone ketyl; other dry solvents were stored under argon. Glassware used in anhydrous conditions was baked for 1 h at 80 °C, assembled hot and filled with argon before use. Standard inert-atmosphere techniques were used for solvent transfers by syringe. Thin-layer chromatography (TLC) was performed on 0.20 mm silica gel 60 F_{254} plates, and 230–400 mesh ASTM silica gel 60 (E. Merck, Darmstadt, GE) was used for flash-column chromatography.

Infrared spectra (IR) were recorded on a Perkin-Elmer series 1600 FT-IR spectrometer and are reported in cm^{-1}. The NMR spectra were recorded at 300 MHz for ^1H and 75.5 MHz for ^{13}C on a Bruker AC/F300 spectrometer. The chemical shifts (δ in ppm) were referenced to $CDCl_3$ (δ 7.26 or 77.00, respectively, for ^1H and ^{13}C). In ^1H NMR, only specific signals were reported from upfield to downfield. In ^{13}C NMR, all signals were listed but only safe assignments were given. Several signals are duplicated for the compounds bearing an amide group on the side chain[28] and an asymmetric centre at C-7.[9] For some intermediates and target compound **1**, the carbon assignments were established using 1D and 2D NMR experiments [distortionless enhancement by polarization transfer (DEPT), homonuclear correlated spectroscopy (COSY), heteronuclear shift correlation (HSC) and heteronuclear shift correlation *via* long-range couplings (COLOC)].[29] High-resolution mass spectra (HRMS) obtained from electron impact (EI) or fast atom bombardment (FAB) were provided by the Centre Régional de Spectrométrie de Masse (Université de Montréal, Montréal, Canada). Microanalyses were performed by Galbraith Laboratories Inc. (Knoxville, TN).

Synthesis of the key intermediate 2

3-Methoxyestra-1,3,5(10)-trien-17-one 4. Protection of the phenolic group of estrone **3** with a methoxy group was achieved following the standard procedure and all data were in agreement with the literature.[9]

Methyl 4-[3′-methoxy-17′-oxoestra-1′,3′,5′(10′)-trien-16′α/β-yl]but-2-enoate 5. To lithium diisopropylamide (LDA) prepared from freshly distilled diisopropylamine (0.94 ml, 6.6 mmol) and butyllithium (1.6 M solution in hexanes; 3.8 ml, 6.0 mmol) in 10 ml of dry THF was added ketone **4** (0.86 g, 3.0 mmol) in 10 ml of dry THF and dry hexamethylphosphoramide (HMPA) (0.53 ml, 3.0 mmol), keeping the temperature at −78 °C. The mixture was allowed to stir for 1 h at 0 °C before cooling at −78 °C. Then freshly distilled methyl 4-bromocrotonate (0.8 ml, 6.6 mmol) was slowly added to the solution, which was allowed to stir for 4 h from −78 °C to room temperature. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography (hexane–EtOAc, 9:1) to give 411 mg of recovered ketone **4** (48%), followed by 574 mg (50%) of the desired conjugated ester **5**, as a mixture of two diastereoisomers; white solid; ν_{max}(KBr)/cm^{-1} 1720 and 1732 (C=O, ketone and conjugated ester); δ_H($CDCl_3$) 0.91 and 0.96 (2s, 3H, CH_3-18′ of isomers 16′β:16′α, 15:85), 2.89 (m, 2H, CH_2-6′), 3.68 and 3.74 (2s, 3H, CO_2CH_3), 3.78 (s, 3H, CH_3OAr), 5.88 (d, *J* 15.5, 1H, CH=C*H*CO_2CH_3), 6.64 (d, *J* 2.7, 1H, CH-4′), 6.72 (dd, J_1 2.7, J_2 8.6, 1H, CH-2′), 6.94 (m, 1H, CH_2CH=CH), 7.20 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) [only the major isomer (16′α) is reported] 14.46 (C-18′), 25.76, 26.41, 26.90, 29.56, 31.62, 33.45, 38.24, 43.49, 43.94, 47.94, 48.54 (C-14′), 51.45 ($COOCH_3$), 55.16 (CH_3OAr), 111.58 (C-2′), 113.88 (C-4′), 122.50 (C-3), 126.25 (C-1′), 131.85 (C-10′), 137.65 (C-5′), 146.97 (C-2), 157.61 (C-3′), 166.65 (C-1), 219.91 (C-17′) [HRMS(EI): calc. for $C_{24}H_{30}O_4$, 382.2144. Found: M^+, 382.2138. Calc. for $C_{24}H_{30}O_4$: C, 75.4; H, 7.9. Found: C, 75.3; H, 8.0%].

Methyl 4-[3′-methoxy-17′α/β-hydroxyestra-1′,3′,5′(10′)-trien-16′α-yl]but-2-enoate 6. To a solution of ε-keto esters **5** (5.3 g, 13.9 mmol) in 200 ml of dry THF, lithium aluminium hydride was slowly added under argon at −78 °C. After 15 min, the reaction was quenched by the addition of EtOAc at −78 °C and water at room temperature. The slurry was then diluted with water and extracted with EtOAc. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 7:3) to afford 4.25 g (80%) of alcohol **6** as an unresolved mixture of two diastereoisomers (17′β-OH and 17′α-OH) of the 16′α-configured product (the minor reduced 16′β-configured isomer was not recovered); white solid; ν_{max}(KBr)/cm^{-1} 3400 (OH, alcohol), 1728 (C=O, conjugated ester); δ_H($CDCl_3$) 0.77 and 0.81 [2s, 3H, CH_3-18′ of isomers 17′α(OH):17′β(OH), 15:85], 2.85 (m, 2H, CH_2-6′), 3.32 and 3.48 (2d, *J* 7.8, *ca.* 6, 1H, CH-17′α and CH-17′β respectively), 3.69 and 3.74 (2s, 3H, CO_2CH_3), 3.78 (s, 3H, CH_3OAr), 5.89 (d, *J* 15.7, 1H, CH=C*H*CO_2CH_3), 6.63 (d, *J* 2.6, 1H, CH-4′), 6.72 (dd, J_1 2.7, J_2 8.6, 1H, CH-2′), 7.02 (m, 1H, CH_2CH=CH), 7.19 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) [only the major isomer (17′β-OH) is reported] 11.75 (C-18′), 26.11, 27.16, 29.49, 29.70, 36.61, 37.74, 38.48, 42.65, 43.88, 43.99, 48.27 (C-14′), 51.42 (CO_2CH_3), 55.14 (CH_3OAr), 87.25 (C-17′), 111.42 (C-2′), 113.75 (C-4′), 121.74 (C-3), 126.22 (C-1′), 132.44 (C-10′), 137.87 (C-5′), 148.39 (C-2), 157.39 (C-3′), 167.01 (C-1) [HRMS(EI): calc. for $C_{24}H_{32}O_4$, 384.2301. Found: M^+, 384.2322].

Methyl 4-[3′-methoxy-17′α/β-*tert*-butyldimethylsilyloxyestra-1′,3′,5′(10′)-trien-16′α-yl]butanoate 2. A suspension of the conjugated ester **6** (4.2 g, 10.9 mmol) and 10% Pd–C (100 mg) in MeOH (200 ml) was hydrogenated at 1 atm for 21 h. After filtration through Celite, the solvent was removed under reduced pressure. ^1H NMR analysis of the crude product revealed the disappearance of the alkenic proton signals. Without further purification, the crude alcohol was stirred with imidazole (7.5 g, 110 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (8.3 g, 55 mmol) in dry DMF (100 ml) overnight at room temperature. The mixture was then poured into diethyl ether, and the organic phase was washed with water and dried over $MgSO_4$; the solvent was then removed under reduced pressure. Purification by flash chromatography (hexane–EtOAc, 9:1) gave 5.25 g (96% for two steps) of the expected key intermediate **2** as a colourless oil; ν_{max}(film)/cm^{-1} 1740 (C=O, ester); δ_H($CDCl_3$) 0.05 and 0.06 [2s, 6H, Si(CH_3)$_2$], 0.76 and 0.78 [2s, 3H, CH_3-18′ of isomers 17′α(OTBDMS):17′β(OTBDMS), 15:85], 0.91 [s, 9H, SiC(CH_3)$_3$], 2.85 (m, 2H, CH_2-6′), 3.23 and 3.48 (2d, *J* 7.3, *ca.* 6, 1H, CH-17′α and CH-17′β respectively), 3.68 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CH_3OAr), 6.63 (d, *J* 2.3, 1H, CH-4′), 6.72 (dd, J_1 2.7, J_2 8.6, 1H, CH-2′), 7.21 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) [only the major isomer (17′β-OTBDMS) is reported] −4.09 and −3.95 [Si(CH_3)$_2$], 12.19 (C-18′), 18.12 [SiC(CH_3)$_3$], 23.88, 25.94 [SiC(CH_3)$_3$], 26.36, 27.19, 29.27, 29.86, 34.24 (2×), 37.38, 38.70, 43.54, 43.97, 44.24, 48.20 (C-14′), 51.46 (CO_2CH_3), 55.17 (CH_3OAr), 87.82 (C-17′), 111.43 (C-2′), 113.77 (C-4′), 126.27 (C-1′), 132.76 (C-10′), 138.02 (C-5′), 157.39 (C-3′), 174.18 (C-1) [HRMS(EI): calc. for $C_{30}H_{48}O_4{}^{28}Si$, 499.3244. Found: M^+, 499.3207. Calc. for $C_{30}H_{48}O_4Si$: C, 71.9; H, 9.7. Found: C, 72.0; H, 9.7%].

Synthesis of the bifunctionalized target compound 1

Methyl 4-[3′-methoxy-17′β-*tert*-butyldimethylsilyloxyestra-1′,3′,5′(10′)-trien-16′α-yl]-2-[6″-(tetrahydro-2‴*H*-pyran-2‴-yloxy)hexyl]butanoate 7. A solution of diisopropylamine (0.15 ml, 1.1 mmol) in dry THF was stirred under argon at −78 °C, and butyllithium (2.5 M in hexanes; 40 ml, 0.9 mmol) was added dropwise. The LDA solution was allowed to stir for 30 min at 0 °C before cooling at −78 °C. Ester **2** (0.15 g, 0.3 mmol) dissolved in dry THF (10 ml) and dry HMPA (0.26 ml, 1.5 mmol) was added to the LDA solution, which was stirred at 0 °C for 2 h. The mixture was cooled again to −78 °C and $I(CH_2)_6OTHP$[13] (0.19 ml, 0.6 mmol) was added dropwise. The reaction was allowed to warm slowly from −78 °C to room temperature. After 6–8 h, the addition of water quenched the reaction, and the crude product was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography (hexane–EtOAc, 8:2) afforded 0.13 g (62%) of the expected alkylated product **7**; colourless oil; ν_{max}(film)/cm^{-1} 1736 (C=O, ester); δ_H($CDCl_3$) 0.036, 0.039, 0.051 and 0.070 [4s, 6H, $Si(CH_3)_2$], 0.76 (s, 3H, CH_3-18′), 0.893 and 0.896 [2s, 9H, $SiC(CH_3)_3$], 2.83 (m, 2H, CH_2-6′), 3.20 (d, *J* 7.2, 1H, CH-17′α), 3.38, 3.50, 3.72 and 3.87 (4m, 4H, OCH_2), 3.67 and 3.68 (2s, 3H, CO_2CH_3), 3.77 (s, 3H, CH_3OAr), 4.57 (t, *J ca.* 2, 1H, CH of THP group), 6.62 (d, *J* 2.4, 1H, CH-4′), 6.71 (dd, J_1 2.5, J_2 8.6, 1H, CH-2′), 7.20 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) −4.12 and −4.00 [$Si(CH_3)_2$], 12.13 (C-18′), 18.06 [$SiC(CH_3)_3$], 19.67 (CH_2 of THP group), 25.45, 25.90 [$SiC(CH_3)_3$], 26.05, 26.32, 27.16, 27.38, 29.14, 29.27, 29.37, 29.64, 29.80, 30.73, 31.21, 31.37, 32.25, 32.40, 32.45, 37.32, 38.66, 43.76, 43.93, 44.18, 45.58, 45.94, 48.13 (C-14′), 51.29 (CO_2CH_3), 55.11 (CH_3OAr), 62.29 (OCH_2 of THP group), 67.54 (CH_2O of side chain), 87.78 (C-17′), 98.81 (CH of THP group), 111.38 (C-2′), 113.72 (C-4′), 126.22 (C-1′), 132.71 (C-10′), 137.95 (C-5′), 157.34 (C-3′), 176.80 (CO_2CH_3) [HRMS(FAB): calc. for $C_{41}H_{67}O_6{}^{28}Si$, 683.4707. Found: M − H$^+$, 683.4684. Calc. for $C_{41}H_{68}O_6Si$: C, 71.9; H, 10.0; Si, 4.1. Found: C, 71.4; H, 9.7; Si, 3.8%].

Small amounts of self-condensed product **8** and alkylated product **9** were also isolated from the reaction.

Methyl 6-[3′-*methoxy*-17′β-tert-*butyldimethylsilyloxyestra*-1′,3′,5′(10′)-*trien*-16′α-*yl*]-2-{2″-[3‴-*methoxy*-17‴β-tert-*butyldimethylsilyloxyestra*-1‴,3‴,5‴(10‴)-*trien*-16‴α-*yl*]*ethyl*}-3-*oxohexanoate* **8**.—White amorphous solid; ν_{max}(film)/cm^{-1} 1745 (C=O, ester) and 1715 (C=O, ketone); δ_H($CDCl_3$) 0.032, 0.050, 0.054 and 0.059 [4s, 12H, 2 × $Si(CH_3)_2$], 0.77 (s, 6H, CH_3-18′ and -18‴), 0.90 [s, 18H, 2 × $SiC(CH_3)_3$], 2.83 (m, 4H, CH_2-6′ and -6‴), 3.21 (d, *J* 7.2, 2H, CH-17′α and -17‴α), 3.44 (t, *J* 10, 1H, $CHCO_2CH_3$), 3.73 and 3.74 (2s, 3H, CO_2CH_3), 3.78 (s, 6H, 2 × CH_3OAr), 6.63 (d, *J* 2.6, 2H, CH-4′ and -4‴), 6.71 (dd, J_1 2.6, J_2 8.5, 2H, CH-2′ and -2‴), 7.19 (d, *J* 8.5, 2H, CH-1′ and -1‴); δ_C($CDCl_3$) −4.09 and −3.99 [$Si(CH_3)_2$], 12.13 (C-18′ and -18‴), 18.05 [$SiC(CH_3)_3$], 22.26, 25.89 [$SiC(CH_3)_3$], 26.30, 27.15, 29.00, 29.17, 29.77, 32.36, 32.50, 34.06, 37.31, 38.64, 41.94, 42.19, 43.58, 43.77, 43.89, 44.19, 48.13 (C-14′ and -14‴), 52.24 (CO_2CH_3), 55.09 (CH_3OAr), 58.92 and 59.18 ($CHCO_2CH_3$), 87.65 and 87.77 (C-17′ and -17‴), 111.39 (C-2′ and -2‴), 113.70 (C-4′ and -4‴), 126.19 (C-1′ and -1‴), 132.61 (C-10′ and -10‴), 137.91 (C-5′ and -5‴), 157.36 (C-3′ and -3‴), 170.22 and 170.31 (CO_2CH_3), 205.09 (C=O) [HRMS(FAB): calc. for $C_{59}H_{91}O_7{}^{28}Si_2$, 967.6303. Found: (M − H$^+$), 967.6285. Calc. for $C_{59}H_{92}O_7Si_2$: C, 73.1; H, 9.6. Found: C, 73.1; H, 9.0%].

Methyl 4-[3′-*methoxy*-17′β-tert-*butyldimethylsilyloxyestra*-1′,3′,5′(10′)-*trien*-16′α-*yl*]-2,2-*bis*[6″-(*tetrahydro*-2‴H-*pyran*-2‴-*yloxy*)*hexyl*]*butanoate* **9**.—Colourless oil; ν_{max}(film)/cm^{-1} 1730 (C=O, ester); δ_H($CDCl_3$) 0.03 and 0.05 [2s, 6H, $Si(CH_3)_2$], 0.76 (s, 3H, CH_3-18′), 0.89 [s, 9H, $SiC(CH_3)_3$], 2.82 (m, 2H, CH_2-6′), 3.19 (d, *J* 7.0, 1H, CH-17′α), 3.37, 3.48, 3.71 and 3.86 (4m, 8H, 2 × OCH_2 of side chain and 2 × OCH_2 of THP group), 3.64 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CH_3OAr), 4.56 (t, *J ca.* 2, 2H, 2 × CH of THP group), 6.61 (d, *J* 2.5, 1H, CH-4′), 6.69 (dd, J_1 2.5, J_2 8.6, 1H, CH-2′), 7.18 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) −4.15 and −4.00 [$Si(CH_3)_2$], 12.12 (C-18′), 18.03 [$SiC(CH_3)_3$], 19.62 (CH_2 of THP group), 23.29, 24.04, 25.45, 25.87 [$SiC(CH_3)_3$], 26.17, 26.31, 27.12, 29.12, 29.52, 29.71, 30.02, 30.72, 33.51, 34.33, 34.73, 37.34 (C-12′), 38.66 (C-8′), 43.90, 44.17, 44.35, 48.10 (C-14′), 49.02, 51.31 (CO_2CH_3), 55.10 (CH_3OAr), 62.23 (OCH_2 of THP group), 67.53 (CH_2O of side chain), 87.94 (C-17′), 98.75 (CH of THP group), 111.36 (C-2′), 113.74 (C-4′), 126.17 (C-1′), 132.74 (C-10′), 137.93 (C-5′), 157.36 (C-3′), 177.75 (CO_2CH_3) [HRMS(FAB): calc. for $C_{52}H_{87}O_8{}^{28}Si$, 867.6170. Found: (M − H$^+$), 867.6125].

Methyl 8-hydroxy-2-{2′-[3″-methoxy-17″β-*tert*-butyldimethylsilyloxyestra-1″,3″,5″(10″)-trien-16″α-yl]ethyl}octanoate 10. The tetrahydropyranyl derivative **7** (0.155 g, 0.23 mmol) was dissolved in MeOH (30 ml) with a catalytic amount of toluene-*p*-sulfonic acid (10 mg, 0.05 mmol), and the resulting solution was stirred for 30 min at 0 °C and for 3 h at room temperature. Then water was added and the MeOH was removed *in vacuo*. The residue was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude material was purified by chromatography (hexane–EtOAc, 8:2) to give 102 mg (75%) of the expected alcohol **10** as an amorphous solid; ν_{max}(film)/cm^{-1} 3370 (OH, alcohol) and 1735 (C=O, ester); δ_H($CDCl_3$) 0.05 and 0.06 [2s, 6H, $Si(CH_3)_2$], 0.77 (s, 3H, CH_3-18″), 0.90 [s, 9H, $SiC(CH_3)_3$], 2.83 (m, 2H, CH_2-6″), 3.20 (d, *J* 7.3, 1H, CH-17″α), 3.63 (t, *J* 6.6, 2H, CH_2OH), 3.67 and 3.68 (2s, 3H, CO_2CH_3), 3.77 (s, 3H, CH_3OAr), 6.63 (d, *J* 2.6, 1H, CH-4″), 6.71 (dd, J_1 2.7, J_2 8.5, 1H, CH-2″), 7.20 (d, *J* 8.6, 1H, CH-1″); δ_C($CDCl_3$) −4.14 and −4.02 [$Si(CH_3)_2$], 12.11 (C-18″), 18.04 [$SiC(CH_3)_3$], 25.50, 25.87 [$SiC(CH_3)_3$], 26.28, 27.13, 27.34, 29.10, 29.24, 29.77, 31.21, 31.37, 32.16, 32.32, 32.42, 32.58, 37.29 (C-12″), 38.63 (C-8″), 43.27 and 43.89 (C-9″ and C-16″), 44.15 (C-13″), 45.55, 45.91, 48.10 (C-14″), 51.29 (CO_2CH_3), 55.10 (CH_3OAr), 62.81 (COH), 87.75 (C-17″), 111.35 (C-2″), 113.69 (C-4″), 126.18 (C-1″), 132.70 (C-10″), 137.93 (C-5″), 157.30 (C-3″), 176.82 (CO_2CH_3) [HRMS(FAB): calc. for $C_{36}H_{59}O_5{}^{28}Si$, 599.4132. Found: (M − H$^+$), 599.4112].

Methyl 7-(*N*-butyl-*N*-methylcarbamoyl)-2-{2′-[3″-methoxy-17″β-*tert*-butyldimethylsilyloxyestra-1″,3″,5″(10″)-trien-16″α-yl]ethyl}heptanoate 11. To a stirred solution of the alcohol **10** (338 mg, 0.56 mmol) in acetone (100 ml), Jones' reagent (2.7 M chromic acid solution) was added dropwise at 0 °C. After 15 min, the reaction was completed, propan-2-ol and water were added, and acetone was removed *in vacuo*. The remaining aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the corresponding carboxylic acid. The crude compound was used for the next step without further purification. To a solution of the carboxylic acid in dry CH_2Cl_2 (40 ml), tributylamine (0.83 mmol) and isobutyl chloroformate (0.72 mmol) were added at −10 °C under argon, and the resulting mixture was allowed to stir for 45 min. Then *N*-butylmethylamine (2.77 mmol) was added, and the reaction was stirred at room temperature. After 1.5 h, CH_2Cl_2 was added and the organic phase was washed twice with water and once with brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatography (hexane–EtOAc, 7:3) to give 272 mg of the expected amide **11** (70% yield, two steps) as a colourless oil; ν_{max}(film)/cm^{-1} 1735 (C=O, ester) and 1649 (C=O, amide); δ_H($CDCl_3$) 0.03 and 0.05 [2s, 6H, $Si(CH_3)_2$], 0.76 (s, 3H, CH_3-18″), 0.89 [s, 9H, $SiC(CH_3)_3$], 0.92 and 0.95 (2t, *J* 7.2, 3H, CH_3 of NBu), 2.83 (m, 2H, CH_2-6″), 2.90 and 2.96 (2s, 3H, CH_3N), 3.20 (d, *J* 7.3, 1H, CH-17″α), 3.25 and 3.35 (t, *J* 7.5, 2H, CH_2N), 3.66 and 3.67 (2s, 3H, CO_2CH_3), 3.77 (s, 3H, CH_3OAr), 6.62 (d, *J* 2.6, 1H, CH-4″), 6.70 (dd, J_1 2.6, J_2 8.5,

1H, CH-2″), 7.19 (d, *J* 8.6, 1H, CH-1″); δ_C($CDCl_3$) −4.10 and −4.00 [Si(CH_3)$_2$], 12.15 (C-18″), 13.85 (CH_3 of NBu), 18.08 [Si*C*(CH_3)$_3$], 19.94 and 20.06 (*C*H_2CH$_3$), 24.91, 25.29, 25.91 [SiC(*C*H_3)$_3$], 26.34, 27.18 (C-7″), 27.30, 29.14–29.82, 30.61, 31.26, 31.45, 32.20, 32.35, 32.52, 32.85, 33.33, 33.51 and 35.28 (CH_3N), 37.34 (C-12″), 38.68 (C-8″), 43.74, 43.81, 43.94, 44.21, 45.60, 46.00, 47.39 and 49.74 (CH_2N), 48.15 (C-14″), 51.33 (CO_2CH_3), 55.16 (*C*H_3OAr), 87.79 (C-17″), 111.41 (C-2″), 113.75 (C-4″), 126.25 (C-1″), 132.77 (C-10″), 138.02 (C-5″), 157.36 (C-3″), 172.65 (172.77) [C(O)N], 176.79 (*C*O_2CH_3) [HRMS(FAB): calc. for $C_{41}H_{70}O_5N^{28}Si$, 684.5023. Found: M + H$^+$, 684.4996. Calc. for $C_{41}H_{69}O_5NSi$: C, 72.0; H, 10.2. Found: C, 72.0; H, 10.0%].

***N*-Butyl-*N*-methyl-7-hydroxymethyl-9-[3′-methoxy-17′β-*tert*-butyldimethylsilyloxyestra-1′,3′,5′(10′)-trien-16′α-yl]nonanamide 12.** To a reaction flask containing ester **11** (95 mg, 0.14 mmol), lithium tri-*tert*-butoxyaluminohydride (0.70 mmol) and dry THF (10 ml) were added. Dry toluene (5 ml) was introduced to avoid caking of the residue and to serve as a heat-transfer medium. The flask was connected to a condenser under argon and heated on an oil bath to 100 °C. After 5 h, lithium tri-*tert*-butoxyaluminohydride (1.40 mmol) was added to the cooled mixture, and the reaction was allowed to heat for 3 h at 100 °C. The reducing agent (0.70 mmol) was added again to complete the conversion of ester, and the mixture was stirred overnight at 100 °C. The reaction was quenched by the addition of water and saturated NH_4Cl; the residue was extracted twice with EtOAc and once with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Purification by flash chromatography (hexane–EtOAc, 5:5) gave 70 mg (77% yield) of the expected alcohol **12** as a colourless oil; ν_{max}(film)/cm^{-1} 3430 (OH, alcohol) and 1630 (C=O, amide); δ_H($CDCl_3$) 0.05 and 0.06 [2s, 6H, Si(CH_3)$_2$], 0.76 (s, 3H, CH_3-18′), 0.90 [s, 9H, SiC(CH_3)$_3$], 0.92 and 0.95 (2t, *J* 7.6, 3H, CH_3 of Bu), 2.83 (m, 2H, CH_2-6′), 2.90 and 2.96 (2s, 3H, CH_3N), 3.22 (d, *J* 7.1, 1H, CH-17′α), 3.25 and 3.35 (2t, *J* 7.5, 2H, CH_2N), 3.53 (br d, *J* 5.2, 2H, *C*H_2OH), 3.76 (s, 3H, *C*H_3OAr), 6.62 (d, *J* 2.6, 1H, CH-4′), 6.70 (dd, J_1 2.6, J_2 8.6, 1H, CH-2′), 7.19 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) −4.06 and −3.97 [Si(CH_3)$_2$], 12.17 (C-18′), 13.82 (CH_3 of Bu), 18.11 [Si*C*(CH_3)$_3$], 19.94 and 20.02 (*C*H_2CH$_3$), 24.98, 25.37, 25.93 [SiC(*C*H_3)$_3$], 26.35, 26.63, 27.20 (C-7′), 29.35, 29.66, 29.82 (C-6′), 30.62, 30.83, 31.71, 32.04, 32.90, 33.33, 33.56 and 35.28 (CH_3N), 37.40 (C-12′), 38.72 (C-8′), 40.67 (C-7), 43.96 and 44.12 (C-9′ and C-16′), 44.19 (C-13′), 47.41 and 49.74 (CH_2N), 48.20 (C-14′), 55.14 (*C*H_3OAr), 65.45 and 65.69 (CH_2OH), 87.93 and 87.99 (C-17′), 111.41 (C-2′), 113.75 (C-4′), 126.22 (C-1′), 132.80 (C-10′), 138.01 (C-5′), 157.37 (C-3′), 172.71 (C-1) [HRMS-(FAB): calc. for $C_{40}H_{70}O_4N^{28}Si$, 656.5074. Found: M + H$^+$, 656.5044].

***N*-Butyl-*N*-methyl-7-bromomethyl-9-[3′-methoxy-17′β-*tert*-butyldimethylsilyloxyestra-1′,3′,5′(10′)-trien-16′α-yl]-nonanamide 13.** A mixture of alcohol **12** (68 mg, 0.10 mmol), PPh_3 (0.21 mmol) and CBr_4 (0.21 mmol) in dry CH_2Cl_2 was stirred under argon at room temperature. After 3 h, the crude mixture was preabsorbed on silica gel and chromatography was performed with hexane–EtOAc (8:2) as eluent to give 54 mg (72% yield) of the expected bromide **13** as a colourless oil; ν_{max}(film)/cm^{-1} 1650 (C=O, amide); δ_H($CDCl_3$) 0.06 [s, 6H, Si(CH_3)$_2$], 0.77 (s, 3H, CH_3-18′), 0.90 [s, 9H, SiC(CH_3)$_3$], 0.93 and 0.96 (2t, *J* 7.4, 3H, CH_3 of Bu), 2.84 (m, 2H, CH_2-6′), 2.91 and 2.97 (2s, 3H, CH_3N), 3.23 (d, *J* 7.2, 1H, CH-17′α), 3.25 and 3.35 (2t, *J* 7.4, 2H, CH_2N), 3.45 (t, *J* 4.0, 2H, CH_2Br), 3.77 (s, 3H, C*H*$_3$OAr), 6.62 (d, *J* 2.7, 1H, CH-4′), 6.72 (dd, J_1 2.6, J_2 8.6, 1H, CH-2′), 7.20 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) −4.04 and −3.94 [Si(CH_3)$_2$], 12.17 (C-18′), 13.83 (CH_3 of Bu), 18.11 [Si*C*(CH_3)$_3$], 19.96 (*C*H_2CH$_3$), 25.00, 25.37, 25.93 [SiC(*C*H_3)$_3$], 26.35, 26.46, 27.19 (C-7′), 29.28, 29.42, 29.62, 29.82, 30.63, 31.28, 31.49, 32.32, 32.64, 32.85, 33.50, 33.33 and 35.28 (CH_3N), 37.39 (C-12′), 38.72 (C-8′), 39.26–39.75 (*C*H*C*H_2Br), 43.84 and 43.96 (C-9′ and C-16′), 44.22 (C-13′), 47.41 and 49.74 (CH_2N), 48.21 (C-14′), 55.16 (*C*H_3OAr), 87.91 (C-17′), 111.42 (C-2′), 113.76 (C-4′), 126.22 (C-1′), 132.77 (C-10′), 138.01 (C-5′), 157.39 (C-3′), 172.67 (C-1) [HRMS(FAB): calc. for $C_{40}H_{69}O_3N^{79}Br^{28}Si$, 718.4230. Found: M + H$^+$, 718.4279].

***N*-Butyl-*N*-methyl-7-bromomethyl-9-[3′-methoxy-17′β-hydroxyestra-1′,3′,5′(10′)-trien-16′α-yl]nonanamide 14.** The silylated compound **13** (50 mg, 0.07 mmol) was dissolved in 10 ml of MeOH containing 2% (v/v) of HCl. After 1.5 h at room temperature, water was added and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography (hexane–EtOAc, 5:5) gave 40 mg (95% yield) of the expected 17′β-OH derivative **14** as a colourless oil; ν_{max}(film)/cm^{-1} 3410 (OH, alcohol) and 1630 (C=O, amide); δ_H($CDCl_3$) 0.80 (s, 3H, CH_3-18′), 0.92 and 0.95 (2t, *J* 7.5, 3H, CH_3 of Bu), 2.84 (m, 2H, CH_2-6′), 2.91 and 2.96 (2s, 3H, CH_3-N), 3.27 (d, *J* 7.3, 1H, CH-17′α), 3.25 and 3.35 (2t, *J* 7.3, 2H, CH_2N), 3.46 (m, 2H, CH_2Br), 3.77 (s, 3H, C*H*$_3$OAr), 6.62 (d, *J* 2.5, 1H, CH-4′), 6.70 (dd, J_1 2.6, J_2 8.6, 1H, CH-2′), 7.20 (d, *J* 8.6, 1H, CH-1′); δ_C($CDCl_3$) 11.87 (C-18′), 13.84 (CH_3 of Bu), 19.99 (*C*H_2CH$_3$), 24.94, 25.22, 26.20, 26.29, 26.35, 27.22 (C-7′), 29.40, 29.48, 29.76 (C-6′), 30.08, 30.62, 31.11, 31.23, 32.20, 32.44, 32.58, 32.80, 33.40 and 35.30 (CH_3N), 36.78 (C-12′), 38.61 (C-8′), 39.38–39.53 (*C*H*C*H_2Br), 43.69 and 43.96 (C-9′ and C-16′), 44.12 (C-13′), 47.47 and 49.76 (CH_2N), 48.37 (C-14′), 55.17 (*C*H_3OAr), 88.00 (C-17′), 111.43 (C-2′), 113.79 (C-4′), 126.24 (C-1′), 132.65 (C-10′), 137.95 (C-5′), 157.41 (C-3′), 172.79 (C-1) [HRMS(FAB): calc. for $C_{34}H_{55}O_3N^{79}Br$, 604.3366. Found: M + H$^+$, 604.3326].

***N*-Butyl-*N*-methyl-7-bromomethyl-9-[3′,17′β-dihydroxyestra-1′,3′,5′(10′)-trien-16′α-yl]nonanamide 1.** To a solution of the methoxy derivative **14** (40 mg, 0.07 mmol) in dry CH_2Cl_2, 1.0 M solution to BBr_3 in CH_2Cl_2 (0.20 mmol) was added under argon at 0 °C. After 3 h, water and saturated $NaHCO_3$ were added to the mixture, and extraction of the residue was performed using CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (hexane–EtOAc, 4:6) to give 24 mg (61% yield) of the target bifunctionalized compound **1** as a white amorphous solid; ν_{max}(film)/cm^{-1} 3320 (OH, alcohol and phenol) and 1620 (C=O, amide); δ_H($CDCl_3$) 0.80 (s, 3H, CH_3-18′), 0.92 and 0.94 (2t, *J* 7.5, 3H, CH_3 of Bu), 2.79 (m, 2H, CH_2-6′), 2.92 and 2.97 (2s, 3H, CH_3N), 3.27 (d, *J* 7.3, 1H, CH-17′α), 3.26 and 3.36 (2t, *J* 7.3, 2H, CH_2N), 3.45 (m, 2H, CH_2Br), 6.58 (d, *J* 2.6, 1H, CH-4′), 6.64 (dd, J_1 2.6, J_2 8.4, 1H, CH-2′), 7.13 (d, *J* 8.4, 1H, CH-1′); δ_C($CDCl_3$) 11.90 (C-18′), 13.83 (CH_3 of Bu), 19.93 and 20.02 (*C*H_2CH$_3$), 24.87, 24.94, 25.23, 25.31, 26.21 (C-11′), 27.21 (C-7′), 29.42 and 30.58 (NCH_2*C*H_2), 29.48, 29.60 (C-6′), 30.06, 30.18, 31.12, 31.22, 32.17, 32.39, 32.52, 32.83, 33.55 and 35.42 (CH_3N), 36.76 (C-12′), 38.62 (C-8′), 39.42 (C-7), 39.51 (CH_2Br), 43.83 (C-16′), 43.95 (C-9′), 44.08 (C-13′), 47.60 and 49.88 (CH_2N), 48.33 (C-14′), 88.04 (C-17′), 112.81 (C-2′), 115.33 (C-4′), 126.23 (C-1′), 131.87 (C-10′), 137.92 (C-5′), 154.15 (C-3′), 173.1 and 173.25 (C-1) [HRMS(FAB): calc. for $C_{33}H_{53}O_3N^{79}Br$, 590.3209. Found: M + H$^+$, 590.3242. Calc. for $C_{33}H_{52}O_3NBr$: C, 67.1; H, 8.9; N, 2.4; Br, 13.5. Found: C, 66.9; H, 9.2; N, 2.4; Br, 13.8%]. HPLC analysis (Radial Pak silyl 8 mm × 100 mm, hexane–EtOAc, 3:7) revealed two peaks with retention times of 7.9 (49.4%) and 9.6 min (50.6%), corresponding to both isomers at C-7.

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