Synthesis of 16α-fluoro ICI 182,780 derivatives: powerful antiestrogens to image estrogen receptor densities in breast cancer by positron emission tomography

Yann Seimbille, François Bénard and Johan E. van Lier *

Department of nuclear medicine and radiobiology, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, Québec, Canada J1H 5N4. E-mail: jvanlier@courrier.usherb.ca

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We prepared a new series of 7α-substituted derivatives of 16α-fluoroestradiol, based on the very potent antiestrogen 7α-{9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl}-estra-1,3,5(10)-triene-3,17β-diol (ICI 182,780; Faslodex™). The latter consist of estradiol functionalized with a side chain at the 7α-position, conferring interesting pharmaceutical properties for endocrine therapy of estrogen receptor (ER) positive breast cancer. The considerable advantages of ICI 182,780 over other selective ER-modulators (SERMs) already used in hormonal therapy, lead us to develop three new 16α-fluoro derivatives with potential use in positron emission tomography (PET), for the imaging of ER densities in breast tumors. Introduction of the long side chain at the 7α-position was accomplished by Cu(I)-promoted conjugate addition of a Grignard reagent to 6-dehydro-19-nortestosterone. Subsequent oxidation of the 17-hydoxy group and A-ring aromatization gave a 7α-substituted estrone derivative. Further addition to complete the side chain gave the ICI 182,780 mimics that were converted to the reactive 16β,17β-cyclic sulfates, *i.e.* the key intermediates for the ^{18}F-labeling reaction. Opening of the cyclic sulfates *via* nucleophilic fluorination with Me_4NF, followed by rapid hydrolysis in acidic ethanol of the protecting ether and sulfate groups, yielded the desired 16α-fluoro PET derivatives of ICI 182,780. The latter procedure is readily adapted for radiolabeling with ^{18}F by substituting Me_4NF for $^{18}F^-$ in acetonitrile.

I Introduction

Knowledge of estrogen receptor (ER) and progestin receptor (PR) levels in breast tumors is important for prognosis and therapy of the disease.[1] The hormonal dependence of breast carcinomas is considered to be indicative of the potential responsiveness of a tumor to hormonal agents.[2–5] Currently, the most widely used drug for hormonal treatment of breast carcinoma is the partial-antiestrogen tamoxifen.[6,7] However, tamoxifen-based endocrine therapy is effective in only 50 to 60% of ER(+) breast cancer patients, thus underlining the limitations of partial-antiestrogens in this indication.[8] The combined agonist and antagonist activity of these drugs is responsible for some of the undesirable side effects. Thus treatment with tamoxifen may increase endometrial proliferation, induce a slightly increased risk of endometrial carcinoma, tumor flare and tumor-resistance to the drug. A new generation of steroidal estrogen-based antagonists devoid of estrogen agonist activity was developed.[9–13] The most promising pure antiestrogen ICI 182,780 (Faslodex™), bearing a pentafluoropentylsulfinyl group at the 7α-position, is undergoing clinical trials. The compound shows increased efficacy at various levels including: a more rapid and complete tumor inhibition, an increased time to relapse, a decreased potential for tumor flare and induction of endometrial cancer, and an activity against tamoxifen-resistant ER-positive tumors.[14–18]

Efficacy of these therapeutic agents is directly dependent on their ability to bind with high affinity and selectivity to the ER. Therefore, once labeled with a gamma or positron emitter, they could serve as radiopharmaceuticals to visualize *in vivo* the ER concentration in breast tumors.[19–22] Non-invasive imaging and quantification of ER, using either single photon emission tomography (SPECT) or positron emission tomography (PET), can avoid many disadvantages of *in vitro* analysis of biopsy samples. This approach also may yield tracers for the non-invasive diagnosis of breast cancer response to hormonal therapy.[23–25]

In this paper, we report the preparation of three new steroidal antiestrogens dedicated to PET-scanning of ER(+) breast tumors. The new compounds are substituted at the 7α-position, well-known for the ER tolerance of bulky substituents, with a long side chain identical to that of ICI 182,780, or corresponding to different oxidation states of the sulfur atom within the chain, such as sulfide and sulfone. The fluorine-18 labeling was first considered by an exchange of one of the existing fluorine atoms on the 7α-substituent, but the specific activities obtained would be low, and would not obey to the systemic constraint on minimum specific activity, *i.e.* 1000 Ci mmol^{-1}, required for steroid receptors imaging. In addition, the time required to complete this reaction is incompatible with the short half life of ^{18}F (110 min). Instead, the three derivatives were labeled at the 16α-position with fluorine to obtain PET mimics of ICI 182,780.

II Results and discussion

Our first attempts to synthesize a fluoro derivative of ICI 182,780 consisted of α-alkylation with alkyl halides of the protected 6-ketoepiestriol, according to a method described by Tedesco *et al.*[26,27] This procedure allows for introduction of a methyl or ethyl group stereoselectively, as well as the long undecyl carboxyamide chain of ICI 164,384.[12] However, all our attempts to perform alkylation of the enolate, even if the latter was stabilized by BEt_3, failed.[28] We concluded that the different alkyl halides used in our reactions were not sufficiently functionalized to allow for a high-yield reaction with the C7-nucleophile.

Introduction of the 7α-side chain was thus accomplished by a less direct but versatile synthetic pathway *via* Cu(I)-promoted

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conjugate-addition of 9-(dimethyl-*tert*-butylsilyloxy)nonylmagnesium bromide to 17β-hydroxyestra-4,6-dien-3-one (**1**).[29,12] This approach is however non-stereoselective, leading to a mixture of 7α–β- epimers that were separated by flash chromatography (the 7α-isomer **2** is the major and less polar compound and the 7β-isomer is the minor and more polar product).[12,14] Another disadvantage of this approach is the requirement of the A-ring aromatization step, which is accomplished after protecting the side-chain terminus as an acetate. Prior to these modifications, the 17β-hydroxy compound **2** was oxidized with pyridinium chlorochromate in CH_2Cl_2 at 0 °C to give the corresponding 17-keto derivative **3**. Treatment of **3**, under acidic conditions, resulted in hydrolysis of the TBDMS ether to yield **4**. The primary alcohol was acetylated with acetyl chloride in dichloromethane at 0 °C in the presence of *N*,*N*-diisopropylethylamine to give **5** in 93% yield.[30] A-ring aromatization was then performed by treatment of **5** with $CuBr_2$–LiBr in refluxing acetonitrile to yield the estrone derivative **6** in 68% yield.[31] The presence of the three characteristic aromatic protons in the ^{1}H NMR spectrum confirmed the assigned structure of compound **6**. The latter was converted to the 3,17-enol diacetates **7** with isopropenyl acetate in the presence of acid catalyst. Then, **7** was treated with lead tetraacetate in acetic acid resulting in the rearrangement of the 17-enol acetate to give exclusively the 3,16β-diacetate estrone derivative **8**. The stereochemistry of **8** was confirmed by the characteristic signal of the 16α-H in the ^{1}H NMR spectrum, *i.e.* a triplet at about 5 ppm *vs*. a deshielded broad doublet for the 16β-H.[32] Reduction of the 17-keto compound **8** with lithium tri-*tert*-butoxyaluminium hydride provided the 17β-OH derivative **9**, which was hydrolyzed under basic conditions to give the 16β, 17β-diol **10**. The *cis* configuration of the 16- and 17-hydroxy groups was confirmed by the characteristic coupling constant (*J*) observed between 16α-H and 17α-H in the ^{1}H NMR spectrum. After protecting the 3-OH group as a methoxymethyl (MOM) ether, *i.e.* compound **11**, the primary alcohol was selectively tosylated with toluene-*p*-sulfonyl chloride in dichloromethane in the presence of 4-dimethylaminopyridine (DMAP).[33] The use of DMAP instead of pyridine as a base resulted in a high yield of 62% of tosylate **12**, together with a trace of polytosylates, and 28% of recovered triol **11**. Tosylate **12** was then treated with potassium thioacetate in ethanol to give **13** quantitatively. A basic condensation reaction between **13** and 5-iodo-1,1,1,2,2-pentafluoropentane (readily prepared from 4,4,5,5,5-pentafluoropentanol in one step, see Experimental section) afforded the sulfide **14** in 72% yield.[9] The presence of two triplets at about 2.5 ppm in the ^{1}H NMR spectrum, corresponding to the two protons of CH_2S, confirmed the stucture of **14**. As described in the literature, one of the most widely-used and best methods for the conversion of thioethers to sulfoxides is the oxidation with cold sodium metaperiodate. However, this method could not be applied to obtain **15b** from **14**, due to the ability of $NaIO_4$ to cleave the diols.[34,14] Our first approach was therefore to protect the 16β,17β-diol prior to the oxidation step as a cyclic carbonate, obtained by treatment with an aqueous solution of $NaIO_4$ in acetonitrile, followed by a base mediated hydrolysis to provide compound **15b**.[35,36] However a more elegant synthetic pathway involves oxidation of **14** with one equivalent of 3-chloroperoxybenzoic acid in dichloromethane at −20 °C to yield the sulfoxide **15b**. Increasing the reaction temperature to 0 °C in the presence of an excess of the oxidation agent gave the corresponding sulfone **15c**.[36–38] The vicinal diols **15a**–**c** were transformed efficiently to the corresponding cyclic sulfates **16a**–**c**, *via* treatment with NaH and sulfonyldiimidazole. Cyclic sulfates are more reactive toward nucleophiles than epoxides and are usually quite unstable under mild acidic conditions, thus providing excellent intermediates for the introduction of a 16α-fluoro substituent.[39] Formation of the 16β,17β-*O*-cyclic sulfate further confirmed the *cis* configuration of the 16- and 17-hydroxy groups of **15a**–**c**. These reactive intermediates were stereoselectively opened *via* a nucleophilic fluorination, under anhydrous conditions, with Me_4NF to yield the 16α-fluoro derivatives **17a**–**c**.[40,41,32] The protecting ether and sulfate groups were hydrolyzed under acidic conditions in EtOH to give the 7α-substituted 16α-fluoroestradiols **18a**–**c**. The stereochemistry of products **18a**–**c** was confirmed by their characteristic signals in the ^{1}H NMR spectra, *i.e.* a double doublet at 3.8 ppm (17α-H) and a double multiplet at 4.9 ppm (16β-H).[32] This same procedure was subsequently adapted for the preparation of the analogous [16α-^{18}F]-**18a**–**c**.

In conclusion, three new 16α-fluoro derivatives of the potent antiestrogen ICI 182,780 were prepared as potential radiopharmaceuticals for PET imaging of ER-densities in breast cancer patients. Assuming a minor effect of a 16α-fluoro substituent on receptor binding properties of ICI 182,780, the 16α-^{18}F analog could be a useful radiopharmaceutical to study SERM action mechanisms during hormonal therapy.[42,43] Studies on the receptor binding properties of these new fluorosteroids have been planned and micro-PET studies to evaluate their capacity to visualize ER in a small rodent model are in progress.

Experimental

Analytical thin layer chromatography (TLC) was performed on Aldrich aluminium oxide on polyester plates or Macherey–Nagel silica gel pre-coated plastic sheets, both with fluorescent indicator (UV 254). Visualization was achieved with short-wave ultraviolet light and/or color response upon spraying with H_2SO_4–EtOH and heating at 120 °C. Column chromatography was performed using silica gel (60–200 mesh) or florisil (60–100 mesh). HPLC was performed with a Waters 600 system, using a 6 μm preparative silica gel column (3.9 mm × 300 mm, Waters, Nova-Pak HR Silica 6 μm). HPLC eluents were monitored for UV absorbency at 280 nm.

^{1}H NMR spectra were taken in chloroform-d or dimethylsulfoxide-d_6, on a Bruker AC-300 spectrometer (at 300.13 MHz) using Me_4Si as an internal standard and selected proton resonances are reported. Chemical shifts are expressed in ppm (δ) relative to the standard and coupling constants (*J*) in Hz. Mass spectra were obtained on a Micromass Model ZAB-1F high-resolution mass spectrometer (HRMS). The relative intensity of the salient fragment ions to the base peak (100) is given in parentheses. Chemicals were obtained from the following sources and were used as received, unless otherwise noted: Aldrich, Alfa Aesar, Sigma or Fisher.

Preparation of 9-(dimethyl-*tert*-butylsilyloxy)nonyl bromide

A solution of dimethyl-*tert*-butylsilyl chloride (14.1 g, 93 mmol) in THF (15 mL) was added to a solution of 9-bromononanol (16.7g, 75 mmol) and imidazole (10.8 g, 0.16 mmol) in 40 mL of THF and the mixture was kept at laboratory temperature for 2 hours, then diluted with ether (100 mL) and filtered. The filtrate was evaporated to dryness and the residue purified by chromatography on silica gel using a 4 : 1 v/v mixture of petroleum ether and toluene as eluent to yield 9-(dimethyl-*tert*-butylsilyloxy)nonyl bromide (24.1 g, 95%) as an oil.^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H, CH_3–Si), 0.88 (s, 9H, Si–Bu^t), 3.40 (t, 2H, J = 6.9 Hz, CH_2–Br), 3.59 (t, 2H, J = 6.5 Hz, CH_2–OSi(Me)$_2$Bu^t); MS *m*/*z* (relative intensity) 337 (M^+, 1), 281 ($M^+ - C_4H_9$, 7), 279 ($M^+ - C_4H_9$, 5), 207 (3), 169 (20), 167 (18); HRMS calcd for $C_{15}H_{33}OSiBr - C_4H_9$, 279.0780, found 279.0784.

17β-Hydroxy-7-(9-dimethyl-*tert*-butylsilyloxynonyl)estr-4-en-3-one (2)

A solution of 9-(dimethyl-*tert*-butylsilyloxy)nonyl bromide (24.1 g, 71 mmol) in THF (75 mL) was added over 2 hours to

a stirred suspension of magnesium turnings (1.8 g, 74 mmol) in THF (7.5 mL) under normal conditions for preparation of a Grignard reagent, and the mixture was heated under reflux for 2 hours, diluted with 30 mL of THF and cooled to −30 °C. Cuprous iodide (7.1 g, 37 mmol) was added, the mixture was vigorously stirred for 10 min and a solution of 6-dehydro-19-nortestosterone (5.0 g, 18.4 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 40 min, acetic acid (4.5 mL) was added and the mixture was evaporated to dryness. Water (150 mL) was added to the residue, and the mixture extracted three times with ethyl acetate. The combined extracts were washed with water, dried and evaporated to dryness, and the residue was subjected to chromatography (CH_2Cl_2–EtOAc 10 : 0 to 19 : 1, silica gel) to give the less polar 7α-isomer (**2**) (3.6 g, 37%) and the more polar 7β-isomer (2.3 g, 24%).

2: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H, CH_3–Si), 0.79 (s, 3H, 18-CH_3), 0.88 (s, 9H, Si–Bu^t), 3.58 (t, 2H, J = 6.6 Hz, CH_2–OSi(Me)$_2$Bu^t), 3.66 (t, 1H, J = 8.4 Hz, 17-H), 5.82 (s, 1H, C4-H); MS *m*/*z* (relative intensity) 530 (M^+, 1), 515 (2), 473 ($M^+ - C_4H_9$, 100), 273 (13); HRMS calcd for $C_{33}H_{58}O_3Si$, 530.4155, found 530.4139.

7α-(9-Dimethyl-*tert*-butylsilyloxynonyl)estr-4-ene-3,17-dione (3)

Pyridinium chlorochromate (2 g, 9.3 mmol) was added within 15 min to an ice-cooled solution of **2** (6.8 mmol) in 20 mL of CH_2Cl_2. The solution was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for another 1.5 h. The mixture was diluted with ether (20 mL) and filtered through a short column of florisil, eluted with a 1 : 1 v/v mixture of hexane–EtOAc. The residue was submitted to flash-chromatography (hexane–EtOAc 10 : 0 to 9 : 1, silica gel) to yield **3** (2.91 g, 81%).

3: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H, CH_3–Si), 0.88 (s, 9H, Si–Bu^t), 0.92 (s, 3H, 18-CH_3), 3.58 (t, 2H, J = 6.6 Hz, CH_2–OSi(Me)$_2$Bu^t), 5.84 (s, 1H, C4-H); MS *m*/*z* (relative intensity) 527 ($M^+ - H$, 1), 513 ($M^+ - CH_3$, 2), 471 ($M^+ - C_4H_9$, 100); HRMS calcd for $C_{33}H_{56}O_3Si - H$, 527.3920, found 527.3928.

7α-(9-Hydroxynonyl)estr-4-ene-3,17-dione (4)

A mixture of **3** (5.5 mmol), acetic acid (16.5 mL), water (8.5 mL) and THF (15 mL) was stirred at 50 °C overnight. The solvent was evaporated, the residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ (3 × 150 mL), then dried over anhydrous Na_2SO_4 and evaporated to dryness to yield **4**.

4: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-CH_3), 3.61 (t, 2H, J = 6.6 Hz, CH_2–OH), 5.84 (s, 1H, C4-H); MS *m*/*z* (relative intensity) 414 (M^+, 15), 384 (84), 271 (100); HRMS calcd for $C_{27}H_{42}O_3$, 414.3134, found 414.3127.

7α-(9-Acetoxynonyl)estr-4-ene-3,17-dione (5)

Compound **4** (5.4 mmol) was dissolved in CH_2Cl_2 (10 mL), and cooled to 0 °C in an ice bath. To the chilled solution was added *N*,*N*-diisopropylethylamine (2 eq., 1.8 mL) and the mixture was stirred at 0 °C for 10 min before addition of acetyl chloride (1.2 eq., 0.47 mL). The mixture was stirred at 0 °C for 30 min. Then the solvent was removed under reduced pressure, the residue poured into water and extracted with EtOAc. Evaporation of the dried (Na_2SO_4) extract yielded a yellow oil which was submitted to flash-chromatography (CH_2Cl_2–EtOAc 10 : 0 to 19 : 1, silica gel) to give **5** (2.28 g, 93%).

5: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H, 18-CH_3), 2.03 (s, 3H, –OCOCH_3), 4.03 (t, 2H, J = 6.8 Hz, –CH_2OAc), 5.84 (s, 1H, C4-H); MS *m*/*z* (relative intensity) 456 (M^+, 15), 413 ($M^+ - CH_3CO$, 5), 369 (2), 271 (100); HRMS calcd for $C_{29}H_{44}O_4$, 456.3239, found 456.3250.

3-Hydroxy-7α-(9-acetoxynonyl)estra-1,3,5(10)-trien-17-one (6)

To a solution of **5** (5 mmol) in anhydrous acetonitrile (75 mL) under argon atmosphere was added $CuBr_2$ (2.1 eq., 2.35 g) and LiBr (1.1 eq., 0.48 g) which was refluxed for 30 min. Then, the mixture was cooled and the solvent was evaporated under reduced pressure. The residue was poured into saturated aqueous $NaHCO_3$ and extracted four times with EtOAc. The combined extracts were washed with water, dried and evaporated to dryness, and the crude product was purified by chromatography on a silica gel column using a 10 : 0 to 19 : 1 v/v mixture of CH_2Cl_2 and EtOAc as eluant, to give pure **6** (1.54 g, 68%).

6: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-CH_3), 2.05 (s, 3H, –OCOCH_3), 4.05 (t, 2H, J = 6.8 Hz, –CH_2OAc), 6.57 (d, 1H, J = 2.7 Hz, C4-H), 6.64 (dd, 1H, J = 2.7, 8.4 Hz, C2-H), 7.14 (d, 1H, J = 8.5 Hz, C1-H); MS *m*/*z* (relative intensity) 454 (M^+, 100), 394 (8), 342 (8); HRMS calcd for $C_{29}H_{42}O_4$, 454.3083, found 454.3090.

3,17-Diacetoxy-7α-(9-acetoxynonyl)estra-1,3,5(10),16-tetraene (7)

A mixture of (3.4 mmol) **6**, isopropenyl acetate (9 mL) and catalyst solution (0.4 mL), prepared by mixing isopropenyl acetate (4 mL) and H_2SO_4 (0.1 mL), was refluxed for 2 h. Approximately one third of the solvent was slowly distilled over a period of 1 h. An additional 5 mL of isopropenyl acetate and 0.25 mL of catalyst were added and the solution was concentrated to half the volume by slow distillation for 1 h. The solution was chilled and EtOAc was added. The EtOAc solution was washed with ice-chilled sodium bicarbonate (5%) in water and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified on a column of florisil (hexane–EtOAc, 10 : 0 to 19 : 1) to yield **7** (1.2 g, 66%) as a colorless oil.

7: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-CH_3), 2.04 (s, 3H, –OCOCH_3), 2.18 (s, 3H, 3-OCOCH_3), 2.28 (s, 3H, 17-OCOCH_3), 4.04 (t, 2H, J = 6.8 Hz, –CH_2OAc), 5.51 (m, 1H, 16-H), 6.78 (d, 1H, J = 2.5 Hz, C4-H), 6.84 (dd, 1H, J = 2.5, 8.5 Hz, C2-H), 7.26 (d, 1H, J = 8.5 Hz, C1-H); MS *m*/*z* (relative intensity) 556 (MNH_4^+, 91), 495 (36), 479 (100), 454 (42), 394 (21); HRMS calcd for $C_{33}H_{46}O_6 + NH_4^+$, 556.3638, found 556.3650.

3,16β-Diacetoxy-7α-(9-acetoxynonyl)estra-1,3,5(10)-trien-17-one (8)

A mixture of **7** (2.2 mmol), lead tetraacetate (1.2eq., 1.2 g) and AcOH (10 mL) was stirred for 2.5 h. Then 0.15 g of $Pb(OAc)_4$ was added and the mixture was stirred for another 1 h. The reaction mixture was diluted with $CHCl_3$ (100 mL), washed (2 × 50 mL aqueous 5% sodium thiosulfate; 4 × 150 mL saturated aqueous $NaHCO_3$), then dried over anhydrous Na_2SO_4 and distilled to dryness. The crude product was subjected to chromatography (hexane–EtOAc 10 : 0 to 9 : 1, florisil) to give **8** (1 g, 81%).

8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H, 18-CH_3), 2.04 (s, 3H, –OCOCH_3), 2.13 (s, 3H, 3-OCOCH_3), 2.28 (s, 3H, 16-OCOCH_3), 4.04 (t, 2H, J = 6.7 Hz, –CH_2OAc), 5.07 (t, 1H, J = 8.4 Hz, 16α-H), 6.80 (d, 1H, J = 2.4 Hz, C4-H), 6.86 (dd, 1H, J = 2.4, 8.4 Hz, C2-H), 7.27 (d, 1H, J = 7.5 Hz, C1-H); MS *m*/*z* (relative intensity) 554 (M^+, 2), 512 (12), 476 (23), 452 (100), 434 (25); HRMS calcd for $C_{33}H_{46}O_7$, 554.3243, found 554.3248.

3,16β-Diacetoxy-7α-(9-acetoxynonyl)estra-1,3,5(10)-trien-17β-ol (9)

A solution of **8** (1.8 mmol), lithium tri-*tert*-butoxyaluminium hydride (1.5 g, 5.9 mmol), and THF (35 mL) was stirred for 1 h and then poured with stirring into a mixture of ice (100 g), H_2O (100 mL), and AcOH (15 mL). The mixture was extracted with

$CHCl_3$, washed (3 × 200 mL saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and distilled to dryness to afford **9**.

9: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H, 18-CH_3), 2.05 (s, 3H, –OCOCH_3), 2.10 (s, 3H, 3-OCOCH_3), 2.28 (s, 3H, 16-OCOCH_3), 3.67 (m, 1H, 17-H), 4.04 (t, 2H, J = 6.7 Hz, –CH_2OAc), 5.12 (m, 1H, 16α-H), 6.50–7.00 (m, 3H, aromatic-H); MS *m*/*z* (relative intensity) 556 (M^+, 4), 514 (75), 472 (17), 454 (94), 437 (88); HRMS calcd for $C_{33}H_{48}O_7$, 556.3400, found 556.3412.

7α-(9-Hydroxynonyl)estra-1,3,5(10)-triene-3,16β,17β-triol (10)

The crude compound **9** thus obtained was dissolved in MeOH (15 mL), treated with 15 mL of an aqueous solution of potassium carbonate (100 mg mL^{-1}), and stirred at room temperature for 2 h under N_2. The solution was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to yield a yellow oil which was submitted to chromatography (toluene–acetone 4 : 0 to 3 : 1, silica gel) to give **10** (0.64 g) as a pale yellow solid.

10: ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.71 (s, 3H, 18-CH_3), 3.24 (d, 1H, J = 7.3 Hz, 17-H), 3.33 (m, 2H, –CH_2OH), 3.96 (m, 1H, 16α-H), 6.40 (d, 1H, J = 2.3 Hz, C4-H), 6.48 (dd, 1H, J = 2.4, 8.4 Hz, C2-H), 7.03 (d, 1H, J = 8.5 Hz, C1-H); MS *m*/*z* (relative intensity) 430 (M^+, 90), 414 (35), 355 (10), 300 (25), 157 (100); HRMS calcd for $C_{27}H_{42}O_4$, 430.3083, found 430.3093.

7α-(9-Hydroxynonyl)-3-*O*-methoxymethylestra-1,3,5(10)-triene-3,16β,17β-triol (11)

10 (1.5 mmol), THF (anhydrous, 5 mL) and a magnetic stirrer were placed in a bulb. After adding NaH (60% suspension in mineral oil, 1.6 mmol, 64 mg), the suspension was stirred and a solution of methoxymethyl chloride (0.18 mL, 2.4 mmol) in THF (0.3 mL) was added dropwise. After the suspension had been stirred for 1 h, EtOH (abs., 5 mL) was added. The solvent was removed in vacuo, and the residue extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. Chromatography (CH_2Cl_2–acetone 4 : 0 to 3 : 1, SiO_2) afforded **11** (0.64 g, 91%).

11: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H, 18-CH_3), 3.48 (m, 1H, 17-H), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 3.63 (t, 2H, J = 6.6 Hz, –CH_2OH), 4.23 (m, 1H, 16α-H), 5.15 (s, 2H, 3-OCH_2–), 6.75 (d, 1H, J = 2.6 Hz, C4-H), 6.83 (dd, 1H, J = 2.7, 8.6 Hz, C2-H), 7.20 (d, 1H, J = 8.5 Hz, C1-H); MS *m*/*z* (relative intensity) 474 (M^+, 5), 442 (100), 412 (45), 285 (8); HRMS calcd for $C_{29}H_{46}O_5$, 474.3345, found 474.3356.

7α-[9-(4-Methylbenzylsulfonyloxy)nonyl]-3-*O*-methoxymethylestra-1,3,5(10)-triene-3,16β,17β-triol (12)

To a pre-cooled solution (0 °C) of **11** (1.35 mmol) and DMAP (1.1 eq., 182 mg) in dry CH_2Cl_2 (10 mL) was added tosyl chloride (1.4 eq., 360 mg). The solution was stirred at 0 °C for 1 h, and then it was allowed to warm to room temperature and was stirred for another 14 h. It was then filtered through a column of silica gel, eluted with a 4 : 0 to 3 : 1 v/v mixture of hexane and EtOAc to give **12** (0.53 g, 62%) and unreacted starting material (0.18 g, 28%).

12: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H, 18-CH_3), 2.44 (s, 3H, –O_3Sϕ-CH_3), 3.48 (m, 1H, 17-H), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.01 (t, 2H, J = 6.5 Hz, –CH_2OTs), 4.24 (m, 1H, 16α-H), 5.14 (s, 2H, 3-OCH_2–), 6.75 (d, 1H, J = 2.7 Hz, C4-H), 6.83 (dd, 1H, J = 2.6, 8.6 Hz, C2-H), 7.19 (d, 1H, J = 8.6 Hz, C1-H), 7.34 (d, 2H, J = 8.1 Hz, –O_3S–C_6H_4–), 7.78 (d, 2H, J = 8.3 Hz, –O_3S–C_6H_4–); MS *m*/*z* (relative intensity) 628 (M^+, 10), 596 (62), 536 (14), 492 (52), 460 (48), 442 (27), 424 (100); HRMS calcd for $C_{36}H_{52}O_7S$, 628.3433, found 628.3419.

7α-[9-(Acetylthio)nonyl]-3-*O*-methoxymethylestra-1,3,5(10)-triene-3,16β,17β-triol (13)

A mixture of **12** (0.84 mmol), potassium thioacetate (2 eq., 193 mg) and ethanol (6 mL) was stirred at 50 °C for 2.5 h. The resulting solution was evaporated and the residue was taken up in ethyl acetate. Work-up and chromatography was performed on a silica gel column (hexane–EtOAc, 5 : 0 to 4 : 1, v/v) gave **13** (0.41 g, 91%).

13: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H, 18-CH_3), 2.32 (s, 3H, CH_3–C(O)–), 2.85 (t, 2H, J = 7.4 Hz, –CH_2S–), 3.48 (m, 1H, 17-H), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.24 (m, 1H, 16α-H), 5.15 (s, 2H, 3-OCH_2–), 6.75 (d, 1H, J = 2.6 Hz, C4-H), 6.83 (dd, 1H, J = 2.7, 8.6 Hz, C2-H), 7.19 (d, 1H, J = 8.6 Hz, C1-H); MS *m*/*z* (relative intensity) 532 (M^+, 10), 487 (49), 458 (100), 424 (58); HRMS calcd for $C_{31}H_{48}O_5S$, 532.3222, found 532.3210.

7α-{9-[(4,4,5,5,5-Pentafluoropentyl)thio]nonyl}-3-*O*-methoxymethylestra-1,3,5(10)-triene-3,16β,17β-triol (14)

Preparation of 5-iodo-1,1,1,2,2-pentafluoropentane. Iodine (1 eq., 292 mg) was added while stirring to an ice-cooled solution of triphenylphosphine (1 eq., 302 mg) and imidazole (1 eq., 78 mg) in CH_2Cl_2 (2 mL). After 5 min 4,4,5,5,5-pentafluoropentanol (205 mg, 1.15 mmol) was added dropwise. The ice bath was removed after 2.5 h and the formed crystals were removed by filtration.

Condensation. The above crude solution of the iodopentafluoro derivative (1.15 mmol) was added, under an argon atmosphere, to a solution of thioacetate (**13**) (0.77 mmol) in methanol (4 mL), followed by 10 M aqueous sodium hydroxide (0.16 mL). After heating to 50 °C for 1 h, the mixture was acidified with 2 M hydrochloric acid and the product was extracted with ethyl acetate. Usual work-up and chromatography (hexane–EtOAc 5 : 0 to 4 : 1, SiO_2) afforded **14** (0.36 mg, 72%).

14: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H, 18-CH_3), 2.50 (t, 2H, J = 7.4 Hz, –CH_2S–), 2.58 (t, 2H, J = 7.0 Hz, –CH_2S–), 3.48 (m, 1H, 17-H), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.24 (m, 1H, 16α-H), 5.15 (s, 2H, 3-OCH_2–), 6.75 (d, 1H, J = 2.6 Hz, C4-H), 6.83 (dd, 1H, J = 2.6, 8.6 Hz, C2-H), 7.19 (d, 1H, J = 8.6 Hz, C1-H); MS *m*/*z* (relative intensity) 650 (M^+, 47), 605 (100), 569 (23), 424 (82); HRMS calcd for $C_{34}H_{51}O_4SF_5$, 650.3428, found 650.3419.

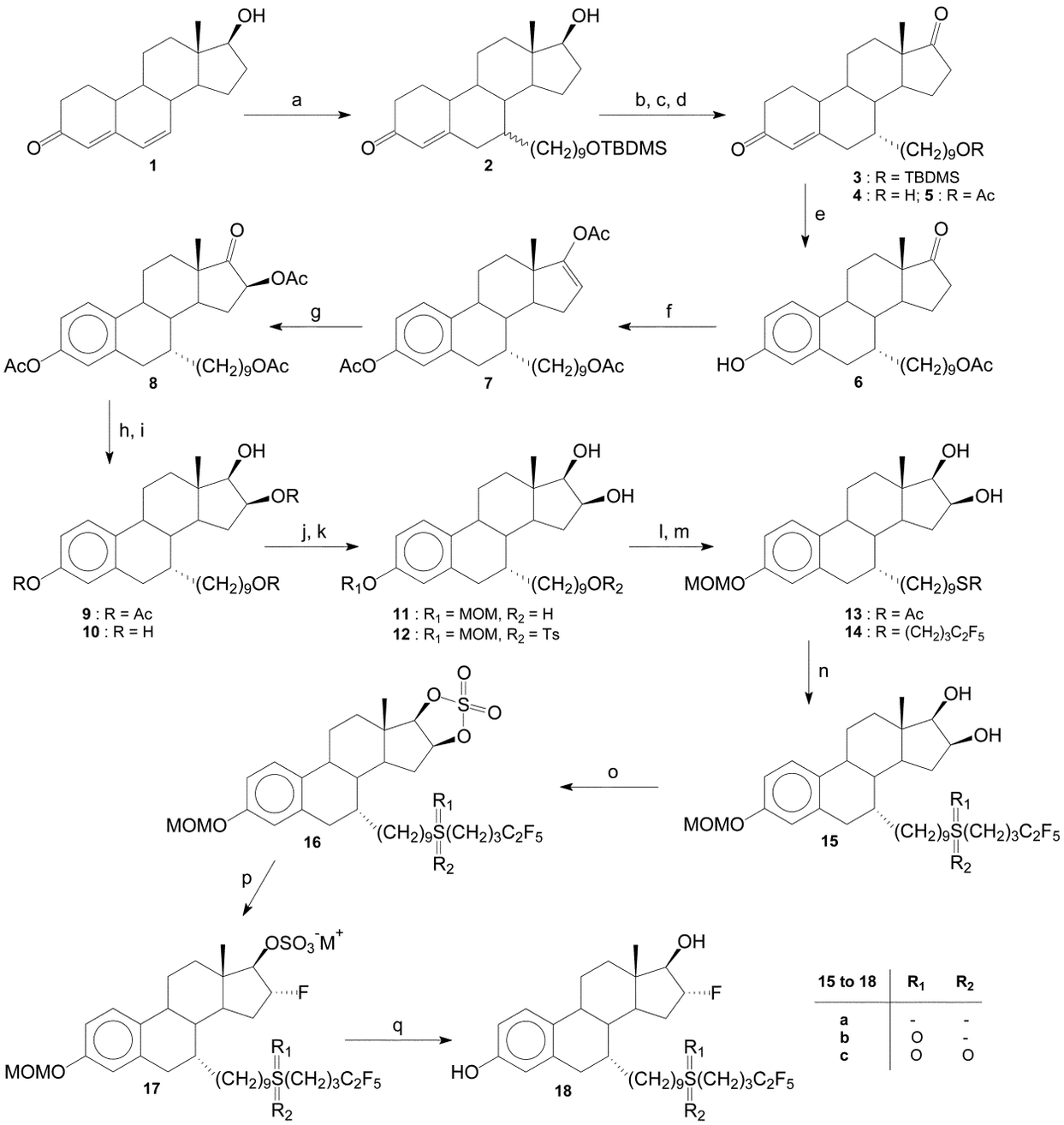
7α-{9-[(4,4,5,5,5-Pentafluoropentyl)sulfinyl]nonyl}-3-*O*-methoxymethylestra-1,3,5(10)-triene-3,16β,17β-triol (15b)

m-Chloroperbenzoic acid (containing 77% peracid) (1 eq., 41 mg) was added to a cooled solution (−20 °C) of sulfide **14** (120 mg, 0.18 mmol) in CH_2Cl_2 (3 mL). After 20 min, the mixture was diluted with methylene chloride and washed with aqueous 5% sodium thiosulfate (75 mL) and saturated aqueous $NaHCO_3$ (75 mL). The crude product was purified by chromatography (benzene–acetone–MeOH 10 : 0 : 0 to 48 : 1 : 1, silica gel) to yield pure **15b** (114 mg, 93%).

15b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H, 18-CH_3), 2.74 (m, 4H, 2CH_2SO), 3.48 (m, 1H, 17-H), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.23 (m, 1H, 16α-H), 5.14 (s, 2H, 3-OCH_2–), 6.75 (d, 1H, J = 2.6 Hz, C4-H), 6.83 (dd, 1H, J = 2.7, 8.6 Hz, C2-H), 7.19 (d, 1H, J = 8.6 Hz, C1-H); MS *m*/*z* (relative intensity) 667 (MH^+, 10), 635 (24), 621 (44), 604 (18), 585 (19), 456 (100); HRMS calcd for $C_{34}H_{51}O_5SF_5$ + H, 667.3455, found 667.3469.

7α-{9-[(4,4,5,5,5-Pentafluoropentyl)sulfonyl]nonyl}-3-*O*-methoxymethylestra-1,3,5(10)-triene-3,16β,17β-triol (15c)

m-Chloroperbenzoic acid (containing 77% peracid) (2,4 eq., 99 mg) was added to an ice-cooled solution of sulfide **14** (120 mg, 0.18 mmol) in CH_2Cl_2. After 1 h, the mixture was diluted with methylene chloride and washed with aqueous 5%



Scheme 1 a) $MgBr(CH_2)_9OTBDMS$, CuI, THF; b) PCC, CH_2Cl_2, 0 °C; c) AcOH, H_2O–THF, 50 °C; d) *N*,*N*-diisopropylethylamine, CH_2Cl_2 then AcCl; e) $CuBr_2$, LiBr, CH_3CN, reflux; f) $CH_3CO_2C(CH_3)=CH_2$, H_2SO_4 cat; g) $Pb(OAc)_4$, AcOH; h) $Li(t\text{-}BuO)_3AlH$, THF; i) K_2CO_3, MeOH–H_2O; j) NaH, THF then MOMCl; k) DMAP, CH_2Cl_2 then TsCl; l) KSAc, EtOH, 50 °C; m) $C_2F_5(CH_2)_3I$, NaOH, MeOH, 50 °C; n) m-CPBA, CH_2Cl_2; o) NaH, THF then sulfonyldiimidazole; p) Me_4NF, CH_3CN, reflux; q) EtOH–H_2SO_4.

sodium thiosulfate (150 mL) and saturated aqueous $NaHCO_3$ (150 mL). The crude product was purified by chromatography (benzene–acetone–MeOH 10 : 0 : 0 to 48 : 1 : 1, silica gel) to yield pure **15c** (120 mg, 95%).

15c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H, 18-CH_3), 3.00 (m, 4H, $2CH_2SO_2$), 3.48 (m, 1H, 17-H), 3.48 (s, 3H, 3-OCH_2–OCH_3), 4.23 (m, 1H, 16α-H), 5.14 (s, 2H, 3-OCH_2–), 6.75 (d, 1H, J = 2.6 Hz, C4-H), 6.83 (dd, 1H, J = 2.7, 8.6 Hz, C2-H), 7.19 (d, 1H, J = 8.6 Hz, C1-H); MS *m*/*z* (relative intensity) 682 (M^+, 100), 650 (60), 619(30), 601 (28), 507 (28); HRMS calcd for $C_{34}H_{51}O_6SF_5$, 682.3326, found 682.3318.

7α-{9-[(4,4,5,5,5-Pentafluoropentyl)thio]nonyl}-3-*O*-methoxymethyl-16β,17β-*O*-sulfurylestra-1,3,5(10)-triene-3,16β,17β-triol (16a) or 7α-{9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl}-3-*O*-methoxymethyl-16β,17β-*O*-sulfurylestra-1,3,5(10)-triene-3,16β,17β-triol (16b) or 7α-{9-[(4,4,5,5,5-pentafluoropentyl)-sulfonyl]nonyl}-3-*O*-methoxymethyl-16β,17β-*O*-sulfurylestra-1,3,5(10)-triene-3,16β,17β-triol (16c)

In a bulb fitted with a magnetic stirrer, **15a** (or **15b** or **15c**) (0.17 mmol) was dissolved in anhydrous THF (3 mL) and NaH (60% suspension in mineral oil, 2.5 eq., 17 mg) was added while stirring. After 10 min a solution of sulfonyldiimidazole (1.05 eq., 36 mg) in anhydrous THF (1 mL) was added dropwise and stirring was continued. After 1 h the solution was filtered and evaporated. The residue was extracted with EtOAc, washed with water, brine and dried (Na_2SO_4). Upon evaporation of the solvent, **16a** (117 mg, 97%), **16b** (122 mg, 93%) or **16c** (116 mg, 95%) were respectively obtained as oils.

16a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H, 18-CH_3), 2.50 (t, 2H, J = 7.3 Hz, –CH_2S–), 2.58 (t, 2H, J = 7.0 Hz, –CH_2S–), 3.48 (s, 3H, 3-OCH_2–OCH_3), 4.60 (d, 1H, J = 7.5 Hz, 17α-H), 5.15 (s, 2H, 3-OCH_2–), 5.17 (m, 1H, 16α-H), 6.76 (d, 1H, J = 2.6 Hz, C4-H), 6.85 (dd, 1H, J = 2.6, 8.6 Hz, C2-H), 7.17 (d, 1H,

J = 8.6 Hz, C1-H); MS *m*/*z* (relative intensity) 712 (M^+, 17), 680 (40), 667 (100), 587 (12), 569 (8); HRMS calcd for $C_{34}H_{49}O_6S_2F_5$, 712.2890, found 712.2883.

16b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H, 18-CH_3), 2.72 (m, 4H, 2CH_2SO), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.60 (d, 1H, J = 7.5 Hz, 17α-H), 5.15 (s, 2H, 3-OCH_2–), 5.18 (m, 1H, 16α-H), 6.76 (d, 1H, J = 2.6 Hz, C4-H), 6.84 (dd, 1H, J = 2.7, 8.6 Hz, C2-H), 7.17 (d, 1H, J = 8.6 Hz, C1-H); MS *m*/*z* (relative intensity) 728 (M^+, 2), 712 (4), 683 (100), 667 (31), 603 (29); HRMS calcd for $C_{34}H_{49}O_7S_2F_5$, 728.2840, found 728.2827.

16c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H, 18-CH_3), 3.00 (m, 4H, 2CH_2SO_2), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.60 (m, 1H, J = 7.5 Hz, 17α-H), 5.15 (s, 2H, 3-OCH_2–), 5.18 (m, 1H, 16α-H), 6.76 (d, 1H, J = 2.6 Hz, C4-H), 6.84 (dd, 1H, J = 2.7, 8.5 Hz, C2-H), 7.17 (d, 1H, J = 8.6 Hz, C1-H); MS *m*/*z* (relative intensity) 744 (M^+, 68), 699 (37), 664 (40), 646 (21), 620 (37); HRMS calcd for $C_{34}H_{49}O_8S_2F_5$, 744.2789, found 744.2798.

Tetramethylammonium 16α-fluoro-7α-{9-[(4,4,5,5,5-pentafluoropentyl)thio]nonyl}-3-*O*-methoxymethyl-3-hydroxyestra-1,3,5(10)-trien-17β-yl sulfate (17a) or tetramethylammonium 16α-fluoro-7α-{9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl}-3-*O*-methoxymethyl-3-hydroxyestra-1,3,5(10)-trien-17β-yl sulfate (17b) or tetramethylammonium 16α-fluoro-7α-{9-[(4,4,5,5,5-pentafluoropentyl)sulfonyl]nonyl}-3-*O*-methoxymethyl-3-hydroxyestra-1,3,5(10)-trien-17β-yl sulfate (17c)

Tetramethyl ammonium fluoride tetrahydrate (11 mg) was carefully dried by azeotropic distillation of acetonitile (3 × 3 mL). A solution of compound **16a** (or **16b** or **16c**) (40 mg) in absolute MeCN (4 mL) was added and refluxed under dry nitrogen for 15 min. The solvent was removed under reduced pressure to yield **17a**, **17b** or **17c** as Me_4N^+ salts.

17a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H, 18-CH_3), 2.49 (t, 2H, J = 7.4 Hz, –CH_2S–), 2.58 (t, 2H, J = 7.0 Hz, –CH_2S–), 3.33 (s, 12H, (CH_3)$_4$–N^+), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.50 (dd, 1H, J = 30.0, 4.0 Hz, 17α-H), 5.14 (s, 2H, 3-OCH_2–), 5.18 (dm, 1H, J = 54 Hz, 16β-H), 6.70–7.20 (m, 3H, aromatic-H).

17b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H, 18-CH_3), 2.72 (m, 4H, 2CH_2SO), 3.33 (s, 12H, (CH_3)$_4$–N^+), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.50 (dd, 1H, J = 30.0, 4.0 Hz, 17α-H), 5.14 (s, 2H, 3-OCH_2–), 5.18 (dm, 1H, J = 54 Hz, 16β-H), 6.70–7.20 (m, 3H, aromatic-H).

17c: ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 0.83 (s, 3H, 18-CH_3), 3.08 (t, 2H, J = 7.9 Hz, –CH_2SO_2–), 3.19 (t, 2H, J = 7.7 Hz, –CH_2SO_2–), 3.33 (s, 12H, (CH_3)$_4$–N^+), 3.48 (s, 3H, 3-OCH$_2$–OCH_3), 4.50 (dd, 1H, J = 30.0, 4.0 Hz, 17α-H), 5.14 (s, 2H, 3-OCH_2–), 5.18 (dm, 1H, J = 54 Hz, 16β-H), 6.70–7.20 (m, 3H, aromatic-H).

16α-Fluoro-7α-{9-[(4,4,5,5,5-pentafluoropentyl)thio]nonyl}estra-1,3,5(10)-triene-3,17β-diol (18a) or 16α-fluoro-7α-{9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl}estra-1,3,5(10)-triene-3,17β-diol (18b) or 16α-fluoro-7α-{9-[(4,4,5,5,5-pentafluoropentyl)sulfonyl]-nonyl}estra-1,3,5(10)-triene-3,17β-diol (18c)

The crude product **17a** (or **17b** or **17c**) thus obtained was dissolved in a mixture of EtOH (10 mL) and concentrated sulfuric acid (50 μL). The solution was heated to 110 °C for 5 min, solvent was removed under reduced pressure, the residue extracted with ethyl acetate, washed with water, dried (Na_2SO_4), and evaporated to dryness. Chromatography (silica gel; hexane–EtOAc, 5 : 0 to 4 : 1, or benzene–acetone–MeOH 10 : 0 : 0 to 48 : 1 : 1, or hexane–EtOAc, 4 : 0 to 3 : 1) afforded respectively **18a** (65% from **16a**, 22 mg), **18b** (64 % from **16b**, 22 mg) or **18c** (73% from **16c**, 25 mg) as oils. Purification by HPLC (Waters Nova-Pak HR Silica 6-μm, 15% EtOAc in hexane; 1 mL min^{-1}) provides analytical samples of **18a** (t_R = 14 min), or **18c** (t_R = 17 min) by using 25% EtOAc in hexane or **18b** (t_R = 16 min) when performed with 50% EtOAc in hexane.

18a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 3H, 18-CH_3), 2.49 (t, 2H, J = 7.4 Hz, –CH_2S–), 2.58 (t, 2H, J = 7.0 Hz, –CH_2S–), 3.87 (dd, 1H, J = 4.6, 28.5 Hz, 17α-H), 4.95 (dm, 1H, J = 54 Hz, 16β-H), 6.54 (d, 1H, J = 2.7 Hz, C4-H), 6.63 (dd, 1H, J = 2.7, 8.4 Hz, C2-H), 7.14 (d, 1H, J = 8.4 Hz, C1-H); MS *m*/*z* (relative intensity) 608 (M^+, 42), 570 (27), 530 (10), 475 (9); HRMS calcd for $C_{32}H_{46}O_2SF_6$, 608.3123, found 608.3117.

18b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H, 18-CH_3), 2.73 (m, 4H, 2CH_2SO), 3.86 (dd, 1H, J = 4.7, 28.5 Hz, 17α-H), 4.93 (dm, 1H, J = 54 Hz, 16β-H), 6.56 (d, 1H, J = 2.6 Hz, C4-H), 6.63 (dd, 1H, J = 2.8, 8.4 Hz, C2-H), 7.12 (d, 1H, J = 8.5 Hz, C1-H); MS *m*/*z* (relative intensity) 624 (M^+, 88), 448 (46), 414 (100); HRMS calcd for $C_{32}H_{46}O_3SF_6$, 624.3072, found 624.3082.

18c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 3H, 18-CH_3), 3.00 (m, 4H, 2CH_2SO_2), 3.86 (dd, 1H, J = 4.7, 28.5 Hz, 17α-H), 4.94 (dm, 1H, J = 54 Hz, 16β-H), 6.55 (d, 1H, J = 2.7 Hz, C4-H), 6.63 (dd, 1H, J = 2.7, 8.5 Hz, C2-H), 7.14 (d, 1H, J = 8.5 Hz, C1-H); MS *m*/*z* (relative intensity) 640 (M^+, 100), 570 (15), 289 (19); HRMS calcd for $C_{32}H_{46}O_4SF_6$, 640.3021, found 640.3014.

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