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Original article

Chemical synthesis and evaluation of 17α-alkylated derivatives of estradiol as inhibitors of steroid sulfatase

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ABSTRACT

Steroid sulfatase (STS) controls the levels of 3-hydroxysteroids available from circulating steroid sulfates in several normal and malignant tissues. This and the known involvement of active estrogens and androgens in diseases such as breast and prostate cancers thus make STS an interesting therapeutic target. Here we describe the chemical synthesis and characterization of an extended series of 17α-derivatives of estradiol (E2) using different strategies. A variant of the samarium-Barbier reaction with stoichiometric samarium metal and catalytic Kagan reagent formation was used for introducing low reactive benzyl substrates in position 17 of estrone (E1) whereas heterocyclic substrates were metalated and reacted with either the carbonyl or the 17-oxirane of E1. *In vitro* evaluation of the inhibitory potency of the new compounds against STS identified new inhibitors and allowed a more complete structure–activity relationship study of this family of 17α-derivatives of E2.

1. Introduction

Steroid sulfatase (STS) catalyzes the hydrolysis of steroid-3-*O*-sulfates into 3-hydroxysteroids. Since the major part of systemic circulating precursors for estrogenic and androgenic active steroid hormones are sulfates such as dehydroepiandrosterone sulfate (DHEAS) and estrone sulfate (E1S) (Fig. 1), STS plays a major role in regulating levels of estrogens and androgens. Thus, inhibition of STS could have important applications mainly against hormone-dependent breast and prostate cancers, but also against other hormone-dependent diseases such as acne and alopecia and other diseases related to less known biological properties of DHEA and DHEAS such as Alzheimer's disease and arthritis [1–6].

Among the most efficient STS inhibitors are sulfamates, with the first, estrone sulfamate (compound **1**), reported by Potter and Reed in 1994 [7]. Arylsulfamates are irreversible type inhibitors of STS [1–6], but sulfamates have many other biological properties such as anti-convulsant, antimicrobial, anti-tumor agent, antiviral, antibiotic and inhibitor of carbonic anhydrases [8–11]. Such interesting biological properties have prompted our group to design the sulfamate linker for solid phase synthesis [12–14]. This linker can be cleaved in two ways, one acid to yield sulfamates and one nucleophilic to yield phenols, two families of compounds with numerous interesting biological properties [15–18].

Although less potent than arylsulfamates, phenolic steroids such as 17α-benzyl derivatives of estradiol (E2), compounds **2a**–**d**, are also inhibitors of STS [19–21]. Results showed that hydrophobic substituents on the 17α-benzyl group of E2 can modulate the inhibitory activity by interacting with a hypothetic hydrophobic pocket in the D-ring area. Thereafter, the published crystal structure of STS [22,23] showed a hydrophobic tunnel and three phenylalanines which could have a π-π interaction with the 17α-benzyl group. We thus considered two likely ways to increase the potency of these inhibitors: 1) introducing highly hydrophobic groups in meta or para position of the benzyl moiety and 2) introducing a cyclopropyl or a heteroaromatic moiety with various electronic distributions in 17α-position of E2 in order to maximize a hypothetic π–π interaction between inhibitor and enzyme. This resulted in the preparation of two series of compounds (Figs. 2 and 3), each targeted for one of the two hypotheses. The first series (phenols **9**–**13**, **17**–**22**) is rather straightforward and uses *t*-butyl, benzyloxy, trifluoromethyl and the lower period, non-electronegative halogens (Br and I). The choices for the second series (phenols **14**–**16**, **23**–**25**, **27** and **29**) were somewhat complicated by the fact that π-π interactions are rarely exploited in structure–activity relationship (SAR) studies in

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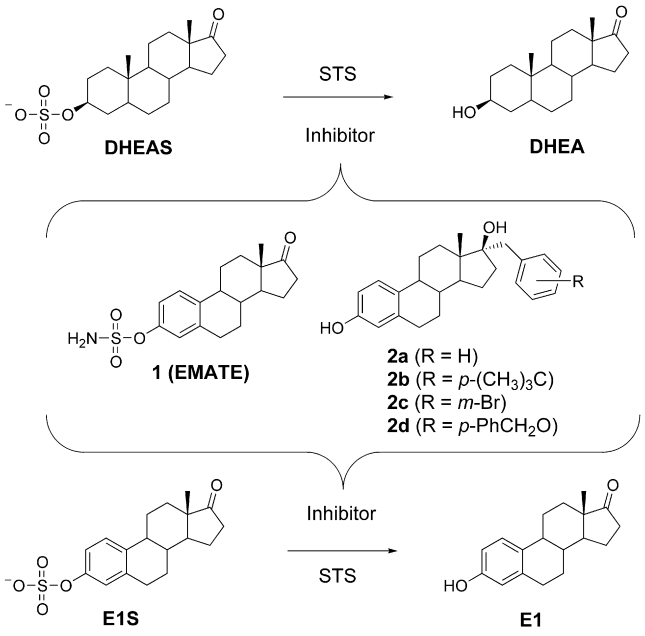


Fig. 1. Natural substrates (DHEAS and E1S) and products (DHEA and E1) of key steroidogenic enzyme STS (steroid sulfatase) and two families of inhibitors represented by sulfamate **1** (EMATE) and phenols **2a-d** (estradiol derivatives).

the context of enzyme–inhibitor interactions. However, it could be hypothesized that interactions could be maximized if the electron density is minimal in the aromatic system so that electronic repulsion is minimized. Aromatic and non-aromatic systems were thus selected with different sizes and electronic distribution, some electron-rich and some electron-deficient. The cyclohexylmethyl group (compound **16**) was chosen as a negative control for aromaticity whereas compounds **2a**–**d** represent our lead compounds. Here we present the chemical synthesis of eighteen new E2 derivatives and their potency as inhibitors of STS.

2. Results and discussion

2.1. Chemical synthesis

The side-chains needed and not commercially available for the synthesis of the E2 derivatives were prepared as reported in Scheme 1. They were next introduced in the 17α-position of E2 using three different strategies (Schemes 2 and 3). In the first strategy (**A**), the benzyl bromides were submitted to metal-halogen exchange using either magnesium metal or samarium metal and subsequently added to the ketone of the *t*-butyldimethylsilyl (TBS) ether of E1 (TBS-E1). In the second strategy (**B**), compound **23** was prepared using lithium metalation of 3-picoline and addition to E1. In the third strategy (**C**), the 17β-oxirane generated from E1 was opened using metalated heteroaromatic substituents. Finally, the preparation of the cyclopropyl compounds is described in Scheme 4.

2.1.1. Synthesis of halogenated side-chains (Scheme 1)

The side-chains **3c**, **4c**, **5b**, **6b** and **8c** were synthesized from available carboxylic acids and aldehydes using standard reduction procedures followed by bromide substitution of the resulting alcohol. In the case of the 3-*tert*-butyl-benzyl bromide (**7d**), formation of the triflate **7a** followed by palladium-catalyzed carbon monoxide insertion yielded the methyl ester which was then submitted to the reduction and bromination procedures.

2.1.2. Synthesis of E2 derivatives via strategy A (Scheme 2)

A series of side-chains were introduced in the 17α-position of E2 to generate **9**–**22** from TBS-E1. In all cases, an attempt was first made at forming the Grignard reagent with powdered magnesium and the halogenated side-chain. No other methods were attempted when success was achieved with the above mentioned method. High excess (8 equiv.) of Grignard reagent (tested using Michler's reagent) was used in all cases because the ketone at position 17 of E1 is known to react poorly with nucleophiles [24]. As many substrates contained halide substituents on the aromatic ring, formation of the Grignard reagent using metal-halogen exchange from a preformed organomagnesium reagent was not thought

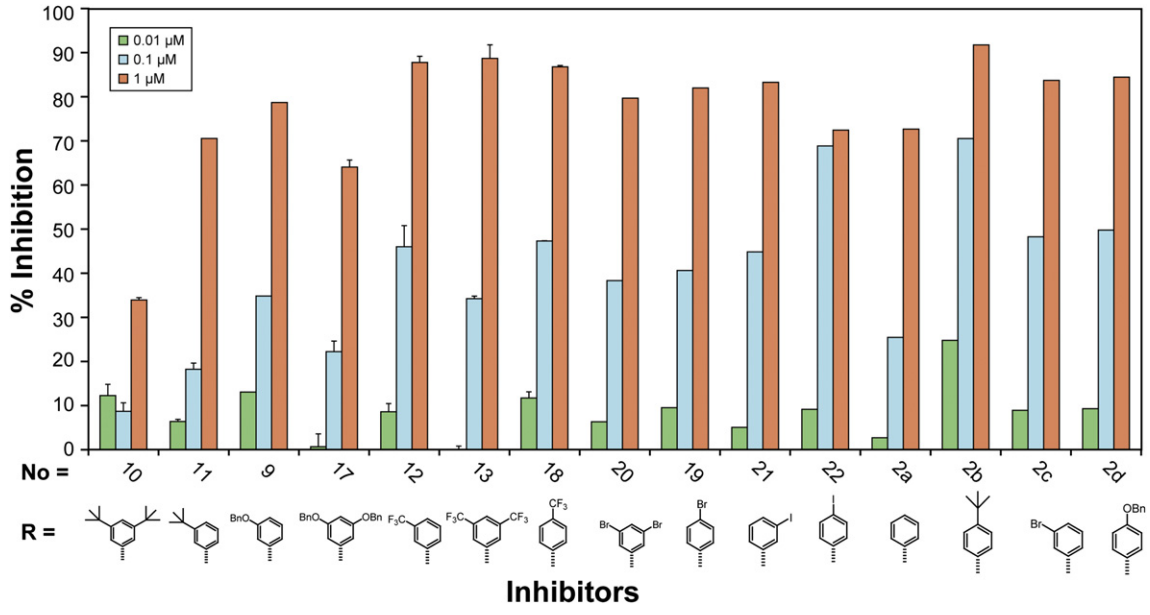


Fig. 2. % inhibition of steroid sulfatase (E1S into E1) by series 1 inhibitors.

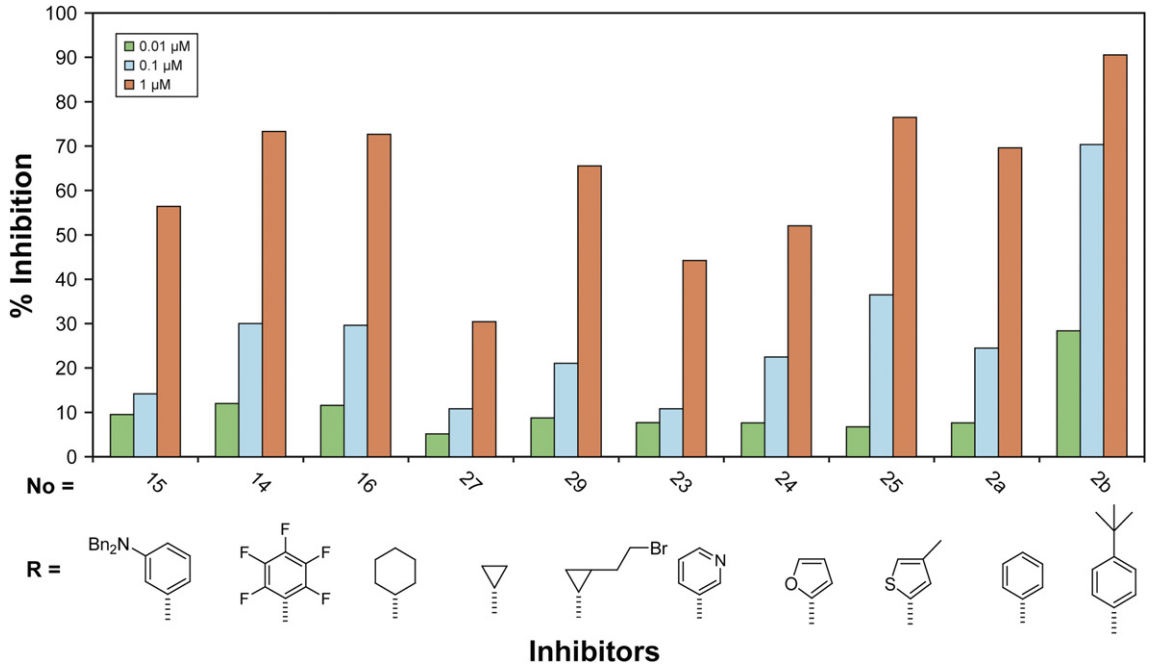
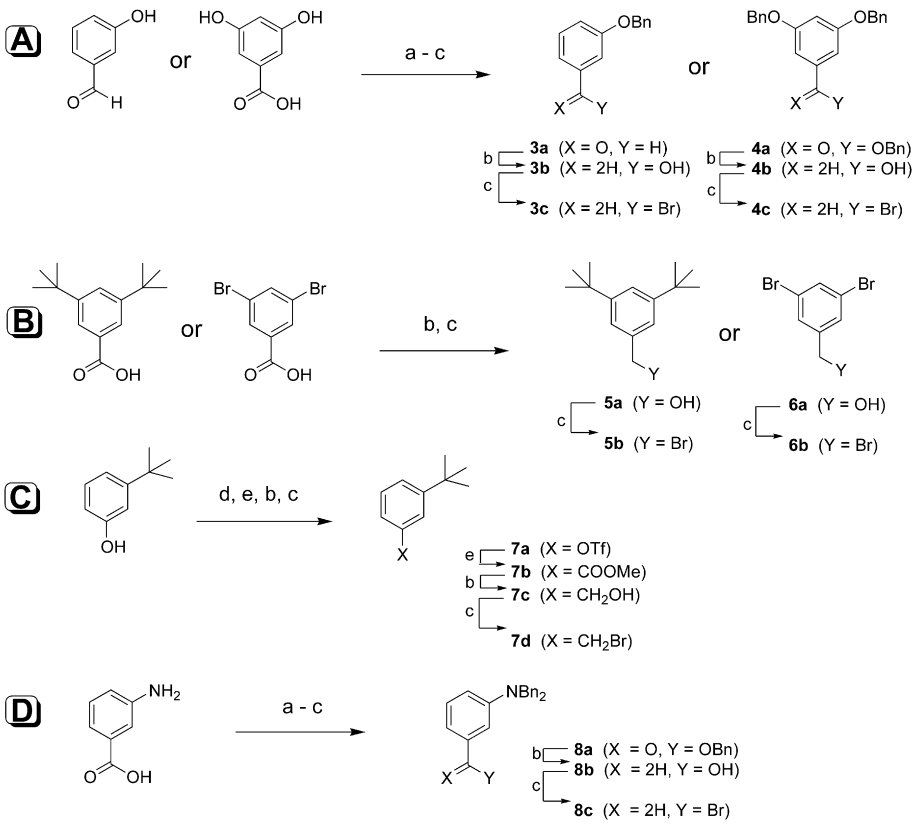
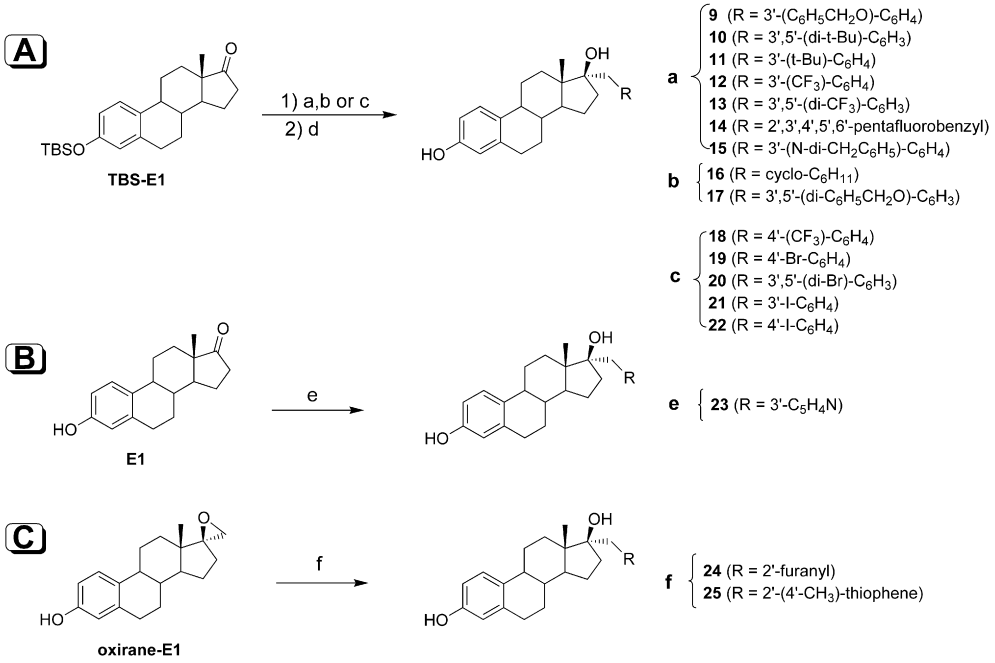


Fig. 3. % inhibition of steroid sulfatase (E1S into E1) by series 2 inhibitors.

possible. In some cases, yield could however be improved using low temperature reaction conditions with dry cerium chloride as an activator of the ketone [24,25]. Of course, as previously observed [26–28], only the product of nucleophilic attack on the α-face of the steroid was formed, with unreacted TBS-E1 and the product of carbonyl reduction as the only other detectable materials. Compounds **9**–**15** were thus obtained using the Grignard reaction with yields varying from 21 to 83%, the lower yields being observed



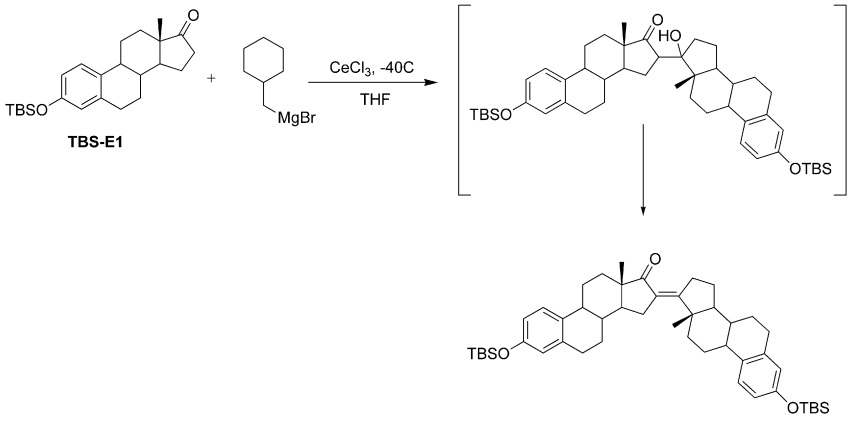
Scheme 1. Synthesis of halogenated side-chains. Reagents: (a) BnBr, Cs_2CO_3, CH_3CN, reflux; (b) $LiAlH_4$, THF; (c) PPh_3, CBr_4, CH_2Cl_2; (d) $(CF_3SO_2)_2O$, 2,6-lutidine, CH_2Cl_2; (e) Et_3N, $Pd(OAc)_2$, dppp, CO(g), DMF, MeOH.



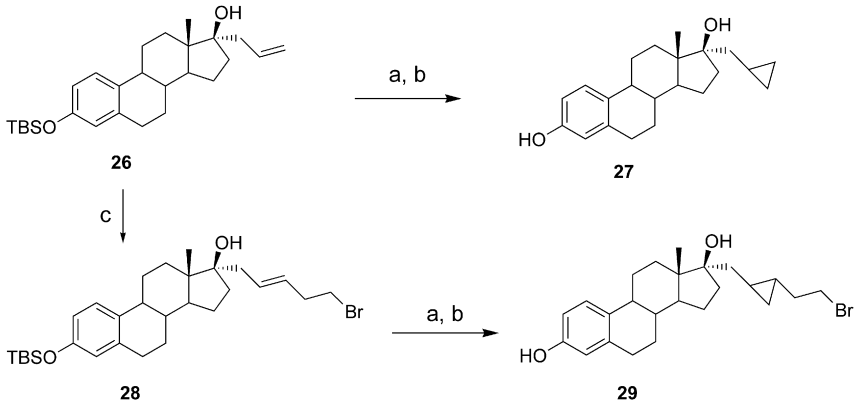
Scheme 2. Synthesis of 17α-derivatives of estradiol by three different strategies (A–C). Reagents: (a) Mg, RCH_2Br, Et_2O, THF; (b) SmI_2, RCH_2Br, THF; (c) Sm, $HgCl_2$, RCH_2Br, THF; (d) TBAF, THF; (e) 3-picoline, *n*-BuLi, HMPA, THF; (f) furan or 4-methylthiophene, *n*-BuLi, THF.

for the three fluorinated compounds. These yields, even in the presence of an excess of Grignard reagent, are expected for a sterically hindered system such as the ketone of TBS-E1 [24].

For the cyclohexylmethyl side-chain, the Grignard reaction using standard conditions or $CeCl_3$ ketone activation failed to yield the desired product **16**, even though the formation of the Grignard reagent appeared successful from the Michler's reagent test. In the case of the $CeCl_3$-assisted Grignard reaction, only an aldol condensation-dehydration steroid-dimer product was isolated in 35% yield (Scheme 3). To obtain the desired product **16**, a reductive alkylation using samarium iodide (the Kagan reagent) was thus attempted [29]. This reaction has the advantage of high regioselectivity of alkyl halides versus aryl halides, increased reactivity for sterically hindered ketones, and very low basicity, which allow tolerance for a wider selection of functional groups [30]. Samarium iodide was generated using purified 1,2-diiodoethane and powdered samarium metal in anhydrous degassed THF. It is notable that the reagent was formed more easily using bottled anhydrous THF (either from Aldrich or EM Science) than using home-distilled anhydrous THF over sodium-benzophenone, even if that is the method being used for distillation of the former. That could be due to the presence of a small amount (25–250 ppm) of 2,6-dimethyl-4-*t*-butylphenol (butylated hydroxytoluene, BHT), an anti-oxidant used as a stabilizer against peroxide formation in the bottled THF. It is known that anti-oxidants help in the formation of SmI_2, but higher concentrations (250 ppm) of BHT seemed to slow down the formation of the Kagan reagent [30]. In the case of compound **16**, this method yielded none of the desired products but only a small amount of E2 (both 17α and 17β-OH). Addition of hexamethylphosphoramide (HMPA), which is known to increase the reducing power of SmI_2 [31,32], and running the reaction in refluxing THF yielded 35% of the desired product **16**. The Kagan reagent used in samarium-Barbier conditions (preformation of SmI_2 followed by addition of both ketone and halide at the same time) yielded compound **17** in 76% yield, which is excellent in view of the hindered ketone and low excess (1.5 equiv.) of di-benzyloxybenzyl-halide side-chain used.



Scheme 3. Formation of unexpected steroid dimer in $CeCl_3$-assisted Grignard reaction.



Scheme 4. Synthesis of cyclopropyl derivatives **27** and **29**. Reagents: (a) $CF_3COOZnEtI$, CH_2Cl_2; (b) TBAF, THF; (c) 4-bromo-1-butene, Grubb's catalyst, CH_2Cl_2.

In the case of compounds **18**–**22**, the desired product was not obtained using the above mentioned conditions. In fact, small amount of TBS-E2 and both reduced benzyl and dibenzyl coupling products were isolated, showing that the Kagan reagent was formed. Addition of HMPA did not yield better results. Both the samarium-Barbier and the samarium-Grignard (addition of the halide and then addition of the ketone) conditions were attempted without success. Another method was then tested following a publication of Gao et al. [33] on the specific reaction of allyl and benzyl halides with ketones. This method uses stoichiometric or excess Sm metal and catalytic $HgCl_2$ in the samarium-Barbier reaction conditions. An alternative method using catalytic iodine instead of $HgCl_2$ also worked in a similar way. Compounds **18**–**22** were obtained using these catalytic samarium-Barbier conditions in 11–58% yields. The successful synthesis of compounds **18**–**22** with these reaction conditions could be explained by the lower concentration of benzyl radical afforded by the catalytic amount of Sm halide in solution, which would reduce the speed of reaction between two benzyl radicals, and thus allow reaction of the benzyl radical with the ketone.

From the results of strategy A, it can be seen that the use of the Kagan reagent allows the tolerance of a greater range of substituents, increases reactivity towards hindered ketones while reducing the excess of halide needed for reaction. For benzyl halides however, except in very specific cases such as the 3,5-dibenzyloxybenzyl side-chain used to generate compound **17**, halide reduction and coupling of benzyl radicals happen at a faster rate than reaction with ketone. In these cases, the preferred reaction method should be the catalytic samarium-Barbier conditions described by Gao et al. [33].

2.1.3. Synthesis via strategy B (Scheme 2)

In the case of the pyridine derivative **23**, the simple strategy of employing the 3-picoline anion generated from 3-picoline and lithium diisopropylamide (LDA) saved us from the necessity to synthesize the *m*-pyridylmethyl bromide. The reaction worked only in presence of HMPA as a disaggregation agent and provided **23** in 14% yield although using an excess of 3-picoline anion.

2.1.4. Synthesis using strategy C (Scheme 2)

For the synthesis of furan and 4-methylthiophene derivatives **24** and **25**, the synthesis of the appropriate brominated side-chains proved to be difficult due to the lack of commercially available precursors, or simply to their instability. It was then decided to proceed through the readily available 17β-oxirane of E1, which is made in one step from estrone using dimethylsulfonium methylide [34]. The oxirane was opened using the lithium reagents obtained from reacting the heterocycles (furan and 4-methylthiophen) with butyllithium. The tertiary alcohols **24** and **25** were thus obtained in low yields but with the right 17β-OH stereochemistry.

2.1.5. Other synthesis methods (Scheme 4)

The cyclopropylmethyl derivative **27** was afforded through cyclopropanation of 17α-allyl-E2 (**26**) using *in situ* generated $CF_3COOZnEtI$ [35]. The completion of the reaction was observed using NMR since the product showed the same R_f on thin-layer chromatography as the starting alkene. For the synthesis of **29**, the intermediate alkene **28** was afforded through Grubb's metathesis of **26** with 4-bromo-1-butene. In a second step, the cyclopropyl **29** was obtained after cyclopropanation of **28** using the aforementioned method and the final removal of the TBS protecting group.

2.2. Inhibitory activity of new E2 derivatives on STS

The enzymatic assay was performed using a homogenate of HEK-293 cells transfected with STS as the source of enzyme. The transformation of [^{3}H]-E1S into [^{3}H]-E1 was measured using scintillation counting of labeled E1S and E1 in the aqueous and organic phases, respectively. The best inhibitors from our previous study [21], compounds **2a**–**d**, were used as positive controls for STS inhibition. Some general tendencies can be deduced when observing the STS inhibition with compounds of series 1 (Fig. 2) and the previously synthesized controls. For most substituting groups that is *t*-butyl (**2b**, **10** and **11**), benzyloxy (**2d**, **9** and **17**), and trifluoromethyl (**12**, **13** and **18**), potency of the *m*-disubstituted benzyl derivatives is lower than both the single substituted meta or para derivatives. The only exception seems to be substitution by bromine (**2c**, **19** and **20**), which happens to be the smallest substituting group of this series. In that case they have roughly the same inhibitory activity. From these observations we can imagine that the hydrophobic pocket in that portion of the active site is deep and narrow. When comparing substitution in meta of the benzyl group, it can be observed that iodine **21**, bromine **2c**, benzyloxy **9** and trifluoromethyl **12** all have similar potency at 0.1 μM whereas *t*-butyl substituted product **11** has lower potency close to that of the benzyl derivative **2a**. The comparison of the different substituting groups when in para position points to a preference for more highly hydrophobic groups with *t*-butyl **2b** and iodine **22** superior to bromine **19** and benzyloxy **2d**.

Series 2 compounds (Fig. 3) were synthesized to explore the influence of different electronic distributions on the aromatic ring and the necessity of aromaticity in the substituting group. The first thing that can be observed is that the cyclohexylmethyl **16** has a similar potency to the benzyl **2a**, which seems to indicate that

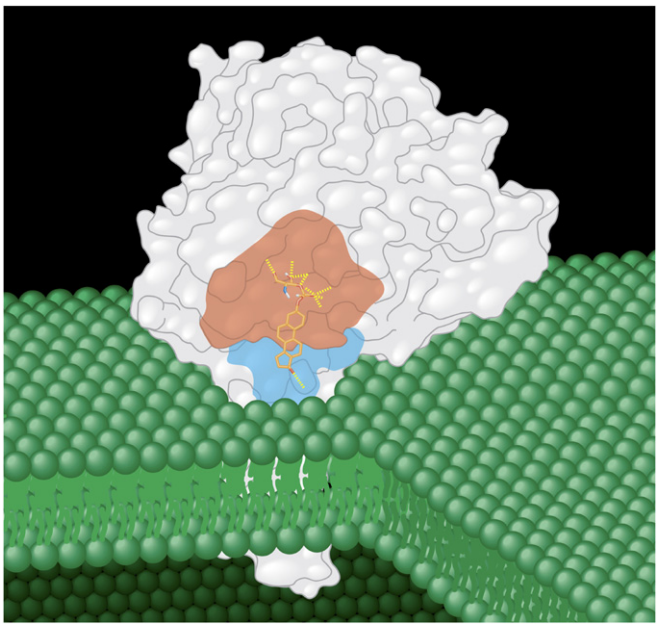


Fig. 4. Schematic representation of the two hypothetic proximate binding sites of STS. In red, the active site containing the manually docked substrate E1S. In blue, the hypothetic access tunnel buried in the bilayer membrane. Figure adapted from [23] (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

aromaticity is not necessary for high potency. Similarly, the inhibitory potency of the pentafluorobenzyl derivative **14** is also the same as that of the benzyl **2a**, suggesting that the interaction involved is not of the π-π type. When comparing different cycles and sizes, cyclopropyl **27** was lower than cyclohexyl **16**, benzyl **2a**, pentafluorobenzyl **14** and 5-bromo-2,3-cyclopropane **29**, which seems to indicate a hydrophobic-driven affinity as stated in the first hypothesis. Increased polarity of the aromatic substituent(s) seems to be detrimental as shown by dibenzylamino **15**, which is less potent than the benzyl **2a**. Similarly, introduction of polarity in the cycle seems detrimental, as seen with low potencies of the *m*-pyridine **23** derivative, and when comparing the furan **24** with the thiophene **25**. In light of the above observations, the hypothetic π-π interaction between 17α-benzyl groups and the phenylalanine residues of the active site seems unlikely, since in that case the cyclohexylmethyl derivative **16** would have shown marked lower potency. Furthermore, higher potency would be expected for the pentafluorobenzyl **14**, given its known favorable interaction with benzyl groups [36]. Previous results showed that benzyl substituents were generally better than flexible alkyl chains, simple phenyl and phenethyl substituents [21]. This is not unexpected since flexible ligands have high entropic energy punishment upon binding due to loss of degrees of freedom, when compared to rigid ligands. It thus seems that inhibitor/enzyme interaction is best with a relatively rigid 17α-moiety separated from the steroid E_2 (a rigid group itself) by one rotatable bond and that, as aforementioned, the hydrophobic cavity is long and narrow, which make 4-*t*-butylbenzyl **2b** and 4-iodobenzyl **22** the best interacting inhibitors in our study.

3. Conclusion

From this work, we have seen that the synthesis of 17α-benzyl derivatives of E2 can be achieved using the catalytic samarium-Barbier method, which tolerates a greater range of functional groups while increasing the reactivity toward sterically hindered ketones compared to the classic Grignard reaction. We obtained only one inhibitor, 17α-(4-iodobenzyl)-E2 (**22**), in the same potency range as our previous 17α-(4-*t*-butylbenzyl)-E2 (**2b**). We however obtained several candidates with higher potency against STS than the starting 17α-benzyl-E2 (**2a**), which could be rendered yet more potent after a sulfamoylation of the phenol. Furthermore, it is known that the *t*-butyl group is oxidized *in vivo* which limits the application of inhibitor **2b** in breast cancer therapy, thus the need to find an inhibitor which has equal or superior potency and more stability *in vivo*.

We did not get a marked increase in inhibitory potency compared with the previously synthesized compounds. As observed in our previous work [21], inhibitory potency tends to increase with hydrophobicity of 17α substituting groups. However, size and position of benzyl substituting group(s) seems to be restricted as seen with 17α-(di-meta-*t*-butyl)-E2 (**10**), which has lower inhibitory potency than the starting 17α-benzyl-E2 (**2a**). The hypothetical π−π interaction does not seem to be important in our inhibitor design as seen with our negative control, 17α-cyclohexylmethyl-E2 (**16**) which showed similar potency to the starting 17α-benzyl-E2 (**2a**). In the previous studies, it was hypothesized that there was a hydrophobic pocket neighboring the D cycle of the enzyme substrate. The x-ray structure of STS confirmed the presence of this hydrophobic pocket in the form of an access tunnel to the active site. Moreover, it has been recently reported that inhibition of STS by E1 and 17α-benzyl-E2 has a non-competitive behavior [37], which is suggestive of an allosteric binding site. Thus, there may be two proximate binding sites on the enzyme (Fig. 4), one of which would allow the product of the reaction, E1, to bind and act as a non-competitive inhibitor to the reaction. Our inhibitors seem to interact mostly with this allosteric site or partially with both binding sites. If the second alternative is true, it may be possible to increase inhibitory potency of the STS inhibitors by maximizing interactions with both sites.

4. Experimental

4.1. Chemistry

4.1.1. General

Reagents and the starting steroid (estrone) were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA) whereas solvents were obtained from VWR (Ville Mont-Royal, Quebec, Canada). Thin-layer chromatography (TLC) was performed on 250 μm silica gel 60 F_{254} plates (E. Merck, Darmstadt, Germany), and compounds were visualized with a solution of ammonium molybdate/sulfuric acid/water with heating. 1,2-Diiodoethane was purified by dissolving in CH_2Cl_2, washing with as saturated solution of sodium sulfite, drying over magnesium sulfate, filtration and evaporation. Purification of final compounds was performed by flash-column chromatography using 230–400 mesh ASTM silica gel 60 (Silicycle, Quebec, Canada). Infrared spectra (IR) were obtained with a Perkin–Elmer 1600 spectrophotometer and data expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded either with a Bruker (AC/F) 300 spectrometer (when mentioned), or with a Bruker AVANCE 400 spectrometer (Billerica, MA, USA). The chemical shifts (δ) were expressed in ppm and referenced to chloroform (7.26 and 77.0 ppm for ^1H and ^{13}C, respectively) or acetone (29.0 ppm for ^{13}C NMR). Low-resolution mass spectra (LRMS) were recorded with an LCQ Finnigan apparatus (San Jose, CA, USA) equipped with an atmospheric pressure chemical ionization (APCI) source.

4.1.2. Synthesis of non-commercially available substrates (building blocks) for alkylation

*4.1.2.1. 3-Benzyloxybenzyl bromide (**3c**) [38].* 3-Hydroxybenzaldehyde (5.00 g, 0.041 mol) was dissolved in anhydrous acetonitrile

(130 mL) under argon atmosphere. Cesium carbonate (20.01 g, 0.061 mol) was added and the suspension stirred for 5 min. Benzyl bromide (11.69 mL, 0.102 mol) was then added and the solution heated at reflux for 16 h. The solution was concentrated on rotary evaporator, water was added and the mixture was extracted with EtOAc. The organic phase was washed twice with water, once with brine, dried over $MgSO_4$, filtered and concentrated. Water was added and the mixture was extracted with CH_2Cl_2. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (80/20) to yield **3a** as a white solid (8.59 g). ^{1}H NMR δ ($CDCl_3$) 5.13 (s, 2H, Ph*CH*$_2$O), 5.33 (s, 2H, COO*CH*$_2$Ph), 7.35–7.50 (m, 9H, 2-CH, 4-CH, 5-CH, 6-CH and *Ph*CH_2O), 10.00 (s, 1H, Ph*CHO*). The aldehyde **3a** was dissolved in anhydrous THF (200 mL) under argon and cooled to 0 °C. Lithium aluminum hydride (1.55 g, 0.041 mol) was added in small portions and the solution stirred at room temperature for 2 h. The reaction was then quenched using water (0.8 mL), a 10% wt aqueous NaOH solution (1.15 mL) and water again (1.9 mL) and left to settle. The suspension was then filtered and concentrated. Water was added and the mixture extracted with EtOAc, the organic phase dried over $MgSO_4$, filtered and concentrated to yield 7.07 g crude alcohol **3b**. ^{1}H NMR δ ($CDCl_3$) 4.68 (s, 2H, Ph*CH*$_2$OH), 5.08 (s, 2H, Ph*CH*$_2$O), 6.90–7.46 (m, 9H, 2-CH, 4-CH, 5-CH, 6-CH and *Ph*CH_2O). Crude alcohol **3b** (7.06 g) was dissolved in anhydrous CH_2Cl_2 (330 mL) and the solution cooled to 0 °C. Triphenylphosphine (17.28 g, 0.066 mol) and carbon tetrabromide (21.85 g, 0.066 mol) were then added and the solution stirred at room temperature for 2 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography on silica gel with hexanes/EtOAc (9/1) to yield 5.85 g (64%) of bromide **3c**. ^{1}H NMR δ ($CDCl_3$) 4.47 (s, 2H, Ph*CH*$_2$Br), 5.07 (s, 2H, Ph*CH*$_2$O), 6.90–7.46 (m, 9H, 2-CH, 4-CH, 5-CH, 6-CH and *Ph*CH_2O); ^{13}C NMR (75 MHz) δ (acetone-d_6) 32.5, 69.4, 114.3, 114.8, 121.0, 127.0 (2×), 127.2, 127.8, 128.0, 129.3, 136.1, 138.6, 158.3.

*4.1.2.2. 3,5-Dibenzyloxybenzyl bromide (**4c**) [39].* 3,5-Dihydroxybenzoic acid (3.70 g, 0.024 mol) was submitted to the same reaction sequence as described for the synthesis of **3c**, except that cesium carbonate and benzyl bromide quantities were tripled in the first step to get the tribenzyl derivative **4a**. The bromide **4c** (1.58 g) was obtained as final product. ^{1}H NMR δ ($CDCl_3$) 4.42 (s, 2H, CH_2Br), 5.03 (s, 4H, 2× Ph*CH*$_2$O), 6.56 (t, 1H, J = 2.2 Hz, 4-CH), 6.65 (d, 2H, J = 2.2 Hz, 2-CH and 6-CH), 7.41 (m, 10H, 2 × Ph*CH*$_2$O); ^{13}C NMR (75 MHz) δ (acetone-d_6) 33.5, 69.7 (2×), 101.8, 108.3 (2×), 127.6 (4×), 127.8 (2×), 128.4 (4×), 137.2 (2×), 140.2, 160.1 (2×).

*4.1.2.3. 3,5-Di-tert-butylbenzyl bromide (**5b**) [40].* 3,5-Di-*t*-butylbenzoic acid (5.00 g, 0.021 mol) was dissolved in anhydrous THF (250 mL) under argon atmosphere and the solution cooled to 0 °C. Lithium aluminum hydride (1.62 g, 0.043 mol) was added in small portions and the solution stirred at room temperature overnight. The reaction was quenched with water, Et_2O (100 mL) was added and the mixture acidified with concentrated HCl solution until the solid residue was dissolved. The medium was extracted with Et_2O and the organic phase dried over $MgSO_4$, filtered and concentrated to yield 4.31g of **5a**. ^{1}H NMR δ ($CDCl_3$) 1.34 (s, 18H, di-*t*-butyl), 4.70 (s, 2H, Ph*CH*$_2$OH), 7.23 (d, 2H, J = 1.8 Hz, 2-CH and 6-CH), 7.38 (t, 1H, J = 1.8 Hz, 4-CH). Crude alcohol **5a** (4.25 g) was dissolved in anhydrous CH_2Cl_2 (500 mL) and cooled at 0 °C. Triphenylphosphine (10.23 g, 0.039 mol) and carbon tetrabromide (12.93 g, 0.039 mol) were added and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography on silica gel with hexanes to yield 4.62 g (86%) of bromide **5b**. ^{1}H NMR δ ($CDCl_3$) 1.33 (s, 18H, di-*t*-butyl), 4.52 (s, 2H, Ph*CH*$_2$Br), 7.23 (d, 2H, J = 1.8 Hz, 2-CH and 6-CH), 7.37 (t, 1H, J = 1.8 Hz, 4-CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 31.4 (6×), 34.8 (2×), 34.9, 122.7, 123.3 (2×), 136.8, 151.3 (2×).

*4.1.2.4. 3,5-Di-bromobenzyl bromide (**6b**) [41].* 3,5-Di-bromobenzoic acid (2.53 g, 9.00 mmol) was submitted to the same reaction sequence as described for the synthesis of **5b** to yield 2.5 g of bromide **6b**. ^{1}H NMR δ ($CDCl_3$) 4.37 (s, 3H, Ph*CH*$_2$Br), 7.48 (s, 2H, 2-CH and 6-CH), 7.60 (s, 1H, 4-CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 30.7, 123.0 (2×), 130.8 (2×), 134.0, 141.3.

*4.1.2.5. 3-tert-Butylbenzyl bromide (**7d**) [42].* 3-*t*-Butylphenol (1.00 g, 6.66 mmol) was dissolved in anhydrous CH_2Cl_2 (130 mL) and cooled to 0 °C in an ice bath. 2,6-Lutidine (1.7 mL, 14.64 mmol) and triflic anhydride (2.2 mL, 13.31 mmol) were added successively. The mixture was stirred overnight at room temperature, quenched with water and extracted with CH_2Cl_2. The organic phase was washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$, filtered and evaporated to yield 1.109 g (59%) of **7a**. ^{1}H NMR δ ($CDCl_3$) 1.33 (s, 9H, *t*-butyl), 7.09 (ddd, 1H, J_1 = 1.4 Hz, J_2 = 2.2 Hz, J_3 = 7.8 Hz 4-CH), 7.25 (t, 1H, J_1 = 2.0 Hz, 2-CH), 7.40 (m, 2H, 5-CH and 6-CH). The triflic ester **7a** (1.11 g, 3.93 mmol) was dissolved in anhydrous DMF (150 mL) and anhydrous MeOH (50 mL). Et_3N (1.6 mL, 11.76 mmol), $Pd(OAc)_2$ (265 mg, 1.18 mmol) and 1,3-bis(diphenylphosphino) propane (486 mg, 1.18 mmol) were added. Gaseous CO was bubbled for 1 h through the mixture while it was heated to 90 °C. The reaction mixture was then stirred overnight at room temperature under a CO atmosphere, after which it was poured into brine and extracted with Et_2O. The organic phase was washed with water, brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel using hexanes/EtOAc (95/5) to yield 554 mg (73%) of **7b**. ^{1}H NMR δ ($CDCl_3$) 1.35 (s, 9H, *t*-butyl), 3.92 (s, 3H, $COOCH_3$), 7.37 (t, 1H, J = 7.8 Hz, 5-CH), 7.60 (dq, 1H, J_1 = 1.2 Hz, J_2 = 7.9 Hz, 4-CH), 7.86 (dt, 1H, J_1 = 1.3 Hz, J_2 = 7.7 Hz, 6-CH), 8.08 (t, 1H, J = 1.8 Hz, 2-CH). The ester **7b** (554 mg, 2.88 mmol) was dissolved in anhydrous THF (30 mL) and cooled to 0 °C. Lithium aluminum hydride (219 mg, 5.76 mmol) was added in small portions and the mixture stirred 2 h under argon at room temperature. Water was then added, concentrated HCl added to acidify the solution and the mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated to achieve quantitatively **7c**. ^{1}H NMR δ ($CDCl_3$) 1.34 (s, 9H, *t*-butyl), 4.70 (s, 2H, Ph*CH*$_2$OH), 7.19 (d, 1H, J_1 = 6.9 Hz, 6-CH), 7.33 (m, 2H, 4-CH and 5-CH), 7.40 (s, 1H, 2-CH). The alcohol **7c** (700 mg, 4.26 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) and cooled at 0 °C. Triphenylphosphine (2.235 g, 8.52 mmol) and carbon tetrabromide (2.827 g, 8.52 mmol) were added. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography on silica gel with hexanes to yield 903 mg (93%) of bromide **7d**. ^{1}H NMR δ ($CDCl_3$) 1.33 (s, 9H, *t*-butyl), 4.51 (s, 2H, Ph*CH*$_2$Br), 7.22 (d, J = 7.6 Hz, 1H, 6-CH), 7.30 (t, 1H, J = 7.4 Hz, 5-CH), 7.33 (d, 1H, J = 7.9 Hz, 4-CH), 7.40 (s, 1H, 2-CH).

*4.1.2.6. 3-Dibenzylaminobenzyl bromide (**8c**).* 3-Aminobenzoic acid (1.00 g, 7.29 mmol) was submitted to the same reaction sequence as described for the synthesis of **3c**. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (90/10) to yield 917 mg (89%) of bromide **8c**. ^{1}H NMR δ ($CDCl_3$) 4.38 (s, 2H, Ph*CH*$_2$Br), 4.65 (s, 4H, (Ph*CH*$_2$)$_2$N), 7.14 (t, 1H, J = 8.2 Hz, 5-CH), 7.34 (m, 13H, 2-CH, 4-CH, 6-CH and (*Ph*CH_2)$_2$N); ^{13}C NMR (75 MHz)

δ (acetone-d_6) 34.5, 54.2 (2×), 112.7, 113.3, 117.4, 126.8 (4×), 128.6 (5×), 129.4 (2×), 138.9 (3×), 149.3.

*4.1.3. Procedure for the Grignard reaction (synthesis of compounds **9**–**15**)*

Powdered magnesium (705 mg, 28.99 mmol) was flame activated under argon in a dry tri-necked flask and left to cool down to room temperature. Dry Et_2O (5.6 mL) was added to the activated Mg powder and a small portion (0.1 mL) of bromide solution (2.26 g of **3c** in 4.0 mL of Et_2O) was added and the reaction started with the heat from the hand or with a few drops of MeI (gas evolution and cloudy solution with heat). The rest of the bromide was then added slowly taking care not to boil off the solvent. The mixture was stirred at room temperature for 2 h. A small amount of the solution was used for a test with Michler's reagent [43]. A blue-green coloration indicated that the Grignard's reagent was formed. The Grignard reagent solution was added slowly at room temperature to a solution of 3-*t*-butyldimethylsilyl-*O*-estrone (TBS-E1) [44] (400 mg, 0.96 mmol) in anhydrous THF (24 mL) and the mixture was stirred overnight at room temperature under argon atmosphere. The mixture was poured in a saturated aqueous NH_4Cl solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. Since the R_f of starting TBS-E1 and the final product were very similar, the remaining starting product was reduced to TBS-E2 by dissolving the crude product in anhydrous MeOH (5 mL) and adding excess (4–5 eq.) of $NaBH_4$. After 1 h at room temperature, water was added, and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel with hexanes/EtOAc (9/1) yielded 364 mg (65%) of 3-TBS-**9** and 3-TBS-E_2, which was not recovered. Only the alkylated compound (3-TBS-**9**) was submitted to the deprotection procedure. The TBS ether of **9** (364 mg, 0.677 mmol) was dissolved in anhydrous THF (7 mL) under argon and cooled to 0 °C. Tetrabutylammonium fluoride (TBAF) in THF (0.81 mL, 0.81 mmol) was added dropwise and the solution stirred at room temperature for 35 min. The reaction was quenched with water, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. The residue was purified with flash chromatography on silica gel using hexanes/EtOAc (85/15) to yield 118 mg (83%) of **9**. The same procedure was used for the synthesis of 3-TBS-**10** (65%), 3-TBS-**11** (44%), 3-TBS-**12** (21%), 3-TBS-**13** (37%), 3-TBS-**14** (27%) and 3-TBS-**15** (65%), which after hydrolysis of the TBS group afforded **10**–**15** (83–87%).

*4.1.3.1. (17β)-17-(3-Benzyloxybenzyl)-estra-1(10),2,4-triene-3,17-diol (**9**).* White powder, IR υ, (film on NaCl) 3330 (OH); ^{1}H NMR δ ($CDCl_3$) 0.97 (s, 3H,18–CH_3), 2.65 and 2.91(2d, 2H, J = 13.3 Hz, 17α-CH_2), 2.85 (m, 2H, 6–CH_2), 4.57 (s, 1H, OH), 5.08 (s, 2H, PhO*CH*$_2$Ph), 6.58 (d, 1H, J = 2.6 Hz, 4-CH), 6.64 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 2-CH), 6.89 (dd, 2H, J_1 = 2.5 Hz, J_2 = 8.1 Hz, 4′-CH and 6′-CH), 6.95 (d, 1H, J = 1.9 Hz, 2′-CH), 7.18 (d, 1H, J = 8.4 Hz, 1-CH), 7.23 (d, 1H, J = 7.9 Hz, 5′-CH), 7.39 (m, 4H, OCH$_2$*Ph*); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.47, 23.30, 26.33, 27.47, 29.64, 31.57, 33.77, 39.63, 42.51, 43.84, 46.84, 49.49, 69.91, 83.13, 112.65, 112.75, 115.23, 117.64, 123.68, 126.51, 127.50 (2×), 127.90, 128.54 (2×), 129.08, 132.70, 137.06, 138.28, 139.97, 153.32, 158.62; LRMS for [M–H_2O+H]$^+$ 451.2 *m/z*.

*4.1.3.2. (17β)-17-[3,5-Bis(tert-butyl)benzyl]-estra-1(10),2,4-triene-3,17-diol (**10**).* White powder; IR υ, (film on NaCl) 3318 (OH); ^{1}H NMR δ ($CDCl_3$) 0.99 (s, 3H, 18-CH_3), 1.34 (s, 18H, di-*t*-butyl), 2.68 and 2.92 (2d, 2H, J = 13.1 Hz, 17α-CH_2), 2.85 (m, 2H, 6–CH_2), ~4.6 (broad s, 1H, OH), 6.58 (d, 1H, J = 2.7 Hz, 4–CH), 6.64 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.11 (d, 2H, J = 1.8 Hz, 2′–CH and 6′–CH), 7.19 (d, 1H, J = 8.4 Hz, 1–CH), 7.33 (t, 1H, J = 1.7 Hz, 4′–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.58, 23.42, 26.36, 27.48, 29.69, 31.50, 33.73, 34.74 (6×), 39.61, 42.72, 43.84, 46.65, 49.46, 62.41 (2×), 82.78, 112.65, 115.23, 120.30, 125.28 (2×), 126.52, 132.70, 136.88, 138.28, 150.59 (2×), 153.34; LRMS for [M + NH_4]$^+$ 492.4 *m/z*.

*4.1.3.3. (17β)-17-(3-tert-Butylbenzyl)-estra-1(10),2,4-triene-3,17-diol (**11**).* White powder; IR υ, (film on NaCl) 3342 (OH); ^{1}H NMR δ ($CDCl_3$) 0.98 (s, 3H, 18-CH_3), 1.34 (s, 9H, *t*-butyl), 2.69 and 2.94 (2d, 2H, J = 13.4 Hz, 17α-CH_2), 2.85 (m, 2H, 6–CH_2), 6.58 (d, 1H, J = 2.2 Hz, 4–CH), 6.64 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.4 Hz, 2–CH), 7.11 (d, 2H, J = 6.8 Hz, 2′-CH), 7.19 (d, 1H, J = 8.4 Hz, 1–CH), 7.28 (m, 3H, 4′-CH, 5′-CH and 6′-CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.54, 23.37, 26.34, 27.48, 29.67, 31.40 (3×), 31.45, 33.70, 34.57, 39.61, 42.55, 43.84, 46.73, 49.47, 83.00, 112.65, 115.23, 123.26, 126.52, 127.65, 128.14 (2×), 132.62, 137.65, 138.25, 151.03, 153.37; LRMS for [M–H_2O+H]$^+$ 401.1 *m/z*.

*4.1.3.4. (17β)-17-(3-Trifluoromethylbenzyl)-estra-1(10),2,4-triene-3,17-diol (**12**).* White powder; IR υ, (film on NaCl) 3330 (OH); ^{1}H NMR δ ($CDCl_3$) 0.97 (s, 3H, 18-CH_3), 2.72 and 3.01 (2d, 2H, J = 13.3 Hz, 17α-CH_2), 2.85 (m, 2H, 6–CH_2), 6.58 (d, 1H, J = 2.6 Hz, 4–CH), 6.65 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.19 (d, 1H, J = 8.0 Hz, 1–CH), 7.43 (m, 1H, 6′-CH), 7.51 (d, 2H, J = 8.0 Hz, 4′-CH and 5′-CH), 7.59 (s, 1H, 2′-CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.39, 23.26, 26.32, 27.45, 29.62, 31.33, 33.94, 39.68, 42.13, 43.84, 46.97, 49.48, 83.31, 112.65, 115.25, 123.06, 125.64, 126.50, 127.69, 128.28, 130.22 (q, J = 31.9 Hz), 132.53, 134.46, 138.25, 139.53, 153.38; LRMS for [M + NH_4]$^+$ 448.2 *m/z*.

*4.1.3.5. (17β)-17-[3,5-Bis(trifluoromethyl)benzyl]-estra-1(10),2,4-triene-3,17-diol (**13**).* White powder; IR υ, (film on NaCl) 3389 (OH); ^{1}H NMR δ ($CDCl_3$) 0.97 (s, 3H, 18-CH_3), 2.76 and 3.08 (2d, 2H, J = 13.7 Hz, 17α-CH_2), 2.85 (m, 2H, 6–CH_2), 4.60 (s, 1H, OH), 6.58 (d, 1H, J = 2.8 Hz, 4–CH), 6.65 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.6 Hz, 2–CH), 7.19 (d, 1H, J = 8.6 Hz, 1–CH), 7.76 (s, 1H 4′-CH), 7.82 (s, 2H, 2′-CH and 6′-CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.28, 23.24, 26.27, 27.42, 29.60, 31.32, 34.25, 39.70, 41.91, 43.83, 47.06, 49.45, 83.39, 112.71, 115.27, 120.18, 123.52 (q, J = 272.7 Hz) (2×), 126.50, 130.88 (q, J = 33.0 Hz) (2×), 131.18 (2×), 132.41, 138.23, 141.30, 153.38; LRMS for [M + NH_4]$^+$ 516.3 *m/z*.

*4.1.3.6. (17β)-17-(2,3,4,5,6-Pentafluorobenzyl)-estra-1(10),2,4-triene-3,17-diol (**14**).* White powder; IR υ, (film on NaCl) 3307 (OH); ^{1}H NMR δ ($CDCl_3$) 0.96 (s, 3H, 18-CH_3), 2.85 (m, 2H, 6–CH_2), 2.94 (s, 2H, penta-FPh*CH*$_2$), 4.56 (s, 1H, OH-phenol), 6.58 (d, 1H, J = 2.8 Hz, 4–CH), 6.65 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.6 Hz, 2–CH), 7.18 (d, 1H, J = 8.6 Hz, 1–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.37, 22.85, 26.28, 27.38, 29.58, 30.15, 31.33, 33.72, 39.73, 43.77, 47.34, 49.76, 84.02, 112.16, 112.67, 115.67, 126.45, 132.33, 138.24, 153.45, CF signals are not visible due to multiple F couplings; LRMS [M–H_2O+H]$^+$ 435.1 *m/z*.

*4.1.3.7. (17β)-17-[3-(Dibenzylamino)benzyl]-estra-1(10),2,4-triene-3,17-diol (**15**).* White powder; IR υ, (film on NaCl) 3325 (OH); ^{1}H NMR δ ($CDCl_3$) 0.91 (s, 3H, 18–CH_3), 2.53 and 2.79 (2d, 2H, J = 13.1 Hz, 17α-CH_2), 2.84 (m, 2H, 6–CH_2), 4.66 (br s, 4H, N(*CH*$_2$Ph)$_2$), 4.78 (s, 1H, OH), 6.57 (d, 1H, J = 2.6 Hz, 4–CH), 6.63 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.3 Hz, 2–CH), 7.12 (d, 1H, J = 7.6 Hz, 4′–CH), 7.16 (d, 1H, J = 8.3 Hz, 1–CH), 7.29 (m, 13H 2′-CH, 5′-CH, 6′-CH and N(CH$_2$*Ph*)$_2$); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.45, 23.20, 26.31, 27.41, 29.65, 31.36, 33.59, 39.56, 42.81, 43.77, 46.67, 49.30, 54.31(2×), 82.89, 110.77, 112.60, 115.18, 119.41, 126.50, 126.71, 126.88 (2×), 128.12 (4×), 128.61 (4×), 129.03, 132.78, 138.29, 138.61 (2×), 139.17, 149.07, 153.26; LRMS [M + H]$^+$ 558.3 *m/z*.

*4.1.4. Procedure for classic samarium–Barbier reaction (synthesis of compounds **16** and **17**)*

In a dry flask, 40 mesh samarium powder (68 mg, 0.45 mmol) and ICH_2CH_2I (85 mg, 0.33 mmol) were weighed under a nitrogen

atmosphere. The flask was purged with argon and anhydrous degassed THF (5 mL) was added with vigorous stirring. After 2 h of stirring, a dark blue SmI_2 solution was obtained. Anhydrous degassed hexamethylphosphoramide (HMPA) (0.21 mL, 1.20 mmol) was then added, turning the blue solution to deep violet. A solution of TBS-E1 [44] (50 mg, 0.12 mmol) and cyclohexylmethyl bromide (33 μL, 0.24 mmol) in anhydrous degassed THF (5 mL) was then added with a cannula to the SmI_2/HMPA solution. The mixture was refluxed overnight, quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (93/7) to yield 22 mg (35%) of TBS-**16**. This TBS ether was treated with a solution of TBAF (1.0 M) in THF as reported above to yield 14 mg (88%) of **16**.

*4.1.4.1. (17β)-17-(Cyclohexylmethyl)-estra-1(10),2,4-triene-3,17-diol (**16**).* White powder; IR υ, (film on NaCl) 3306 (OH); ^{1}H NMR δ ($CDCl_3$) 0.88 (s, 3H, 18-CH_3), 2.82 (m, 2H, 6-CH_2), 6.56 (d, 1H, J = 2.6 Hz, 4-CH), 6.63 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2-CH), 7.15 (d, 1H, J = 8.4 Hz, 1-CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.17, 23.33, 26.31 (2×), 26.57, 26.64, 27.39, 29.63, 31.24, 33.95, 34.32, 35.69, 36.15, 39.64, 43.74, 43.92, 46.90, 49.35, 84.35, 112.56, 115.17, 126.49, 132.77, 138.30, 153.24; LRMS for $[M + H]^+$ 369.1 *m/z*.

*4.1.4.2. (17β)-17-[3,5-Bis(benzyloxy)benzyl]-estra-1(10),2,4-triene-3,17-diol (**17**).* TBS-E1 (200 mg, 0.48 mmol) and **4c** (370 mg, 0.96 mmol) were submitted to the same reaction sequence as described for the synthesis of **16**, except that there was no addition of HMPA and the reaction was run at room temperature to yield 262 mg (76%) of 3-TBS-**17** which was treated with TBAF (1.0 M) as reported above for giving **17** in quantitative yield. White powder; IR υ, (film on NaCl) 3342 (OH); ^{1}H NMR δ ($CDCl_3$) 0.96 (s, 3H, 18-CH_3), 2.61 and 2.88 (2d, 2H, J = 13.2 Hz, 17α-CH_2), 2.84 (m, 2H, 6-CH_2), 5.04 (s, 4H, 2 × PhCH_2O), 6.57 (m, 3H, 4-CH, 2′-CH and 6′-CH), 6.64 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.4 Hz, 2-CH), 7.17 (d, 1H, J = 8.4 Hz, 1-CH), 7.37 (m, 11H, 4′-CH and 2 × *Ph*CH_2O); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.48, 23.28, 26.30, 27.45, 29.63, 31.34, 33.76, 39.59, 42.80, 43.81, 46.83, 49.44, 70.00 (2×), 83.19, 100.18, 110.19 (2×), 112.65, 115.23, 126.49, 127.55 (4×), 127.95 (2×), 128.54 (4×), 132.61, 136.88, 138.24, 140.67 (2×), 153.36, 159.65 (2×); LRMS for $[M + H]^+$ 575.3 *m/z*.

*4.1.5. Procedure for $HgCl_2$-catalyzed samarium-Barbier reaction (synthesis of compounds **18**–**21**)*

In a dry flask, 40 mesh samarium powder (108 mg, 0.72 mmol), TBS-E1 [44] (200 mg, 0.48 mmol) and 4-trifluoromethylbenzyl bromide (172 mg, 0.72 mmol) were weighed under a nitrogen atmosphere. The flask was purged with argon, anhydrous degassed THF (1.5 mL) was added and the solution cooled to 0 °C. $HgCl_2$ (29 mg, 0.107 mmol) was dissolved in anhydrous degassed THF (0.2 mL) and added to the cool mixture. The mixture was stirred under argon at 0 °C for 2 h, at room temperature for 2 h, then filtered on celite and evaporated to give the crude TBS-**18**, which was submitted to the deprotection procedure (TBS hydrolysis with TBAF) as reported above to yield **18** (14%, two steps). The same procedure was used for the synthesis of 3-TBS-**19** (57%), 3-TBS-**20**, 3-TBS-**21** (49%) and TBS-**22** (58%) which after hydrolysis of the TBS group afforded **20** (11%, two steps), **19**, **21** and **22** (91–94%).

*4.1.5.1. (17β)-17-(4-trifluoromethylbenzyl)-estra-1(10),2,4-triene-3,17-diol (**18**).* White powder; IR υ (film on NaCl) 3330 (OH); ^{1}H NMR δ ($CDCl_3$) 0.97 (s, 3H, 18–CH_3), 2.73 and 3.00 (2d, 2H, J = 13.3 Hz, 17α-CH_2), 2.84 (m, 2H, 6–CH_2), 6.59 (d, 1H, J = 2.6 Hz, 4–CH), 6.65 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.18 (d, 1H, J = 8.5 Hz, 1–CH), 7.44 (d, 2H, J = 8.0 Hz, 2′–CH and 6′–CH), 7.57 (d, 2H, J = 8.0 Hz, 3′–CH and 5′–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.39, 23.22, 26.28, 27.45, 29.60, 31.31, 33.86, 39.64, 42.19, 43.81, 46.99, 49.47, 83.41, 112.68, 115.25, 124.80 (2×), 125.74, 126.48, 128.54 (q, J = 32.2 Hz), 131.33 (2×), 132.43, 138.21, 142.79, 153.40; LRMS for $[M–H]^-$ 429.5 *m/z*.

*4.1.5.2. (17β)-17-(4-Bromobenzyl)-estra-1(10),2,4-triene-3,17-diol (**19**).* White powder; IR υ, (film on NaCl) 3342 (OH); ^{1}H NMR δ ($CDCl_3$) 0.96 (s, 3H, 18–CH_3), 2.62 and 2.89 (2d, 2H, J = 13.4 Hz, 17α-CH_2), 2.84 (m, 2H, 6–CH_2), 6.58 (d, 1H, J = 2.6 Hz, 4–CH), 6.64 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.18 (d, 1H, J = 7.5 Hz, 1–CH), 7.19 (d, 2H, J = 8.3 Hz, 2′–CH and 6′–CH), 7.44 (d, 2H, J = 8.3 Hz, 3′–CH and 5′–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.82, 23.68, 26.75, 27.89, 30.04, 31.79, 34.33, 40.11, 42.25, 44.28, 47.34, 49.98, 83.56, 113.10, 115.66, 120.73, 126.90, 131.49 (2×), 133.07, 133.15 (2×), 137.92, 138.67, 153.75; LRMS for $[M–H]^-$ 441.3 and 439.3 *m/z*.

*4.1.5.3. (17β)-17-(3,5-Dibromobenzyl)-estra-1(10),2,4-triene-3,17-diol (**20**).* White powder; IR υ, (film on NaCl) 3378 (OH); ^{1}H NMR δ ($CDCl_3$) 0.95 (s, 3H, 18–CH_3), 2.57 and 2.89 (2d, 2H, J = 13.4 Hz, 17α-CH_2), 2.84 (m, 2H, 6–CH_2), 6.58 (d, 1H, J = 2.6 Hz, 4–CH), 6.64 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.17 (d, 1H, J = 8.4 Hz, 1–CH), 7.44 (d, 2H, J = 1.7 Hz, 2′–CH and 6′–CH), 7.55 (t, 1H, J = 1.7 Hz, 4′–CH); ^{13}C NMR (75 MHz) δ ($CHCl_3$) 14.33, 23.23, 26.25, 27.42, 29.60, 31.24, 34.05, 39.64, 41.79, 43.80, 47.02, 49.44, 83.37, 112.68, 115.23, 122.32 (2×), 126.49, 131.81, 132.44, 132.74 (2×), 138.22, 142.79, 153.33; LRMS for $[M–H]^-$ 519.1 *m/z*.

*4.1.5.4. (17β)-17-(3-Iodobenzyl)-estra-1(10),2,4-triene-3,17-diol (**21**).* White powder; IR υ, (film on NaCl) 3388 (OH); ^{1}H NMR δ ($CDCl_3$) 0.96 (s, 3H, 18–CH_3), 2.60 and 2.88 (2d, 2H, J = 12.6 Hz, 17α-CH_2), 2.86 (m, 2H, 6–CH_2), 6.58 (d, 1H, J = 2.6 Hz, 4–CH), 6.64 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.05 (t, 1H, J = 7.8 Hz, 5′–CH), 7.18 (d, 1H, J = 8.4 Hz, 1–CH), 7.29 (d, 1H, J = 7.8 Hz, 6′–CH), 7.59 (d, 1H, J = 7.9 Hz, 4′–CH), 7.70 (s, 1H, 2′–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.42, 23.28, 26.30, 27.46, 29.63, 31.33, 33.89, 39.65, 41.95, 43.83, 46.94, 49.48, 83.22, 94.18, 112.67, 115.24, 126.50, 129.70, 130.31, 132.58, 135.31, 138.26, 139.88, 141.03, 153.35; LRMS for $[M\text{-}H_2O+H]^+$ 471.0 *m/z*; $[M–H]^-$ 487.3 *m/z*.

*4.1.5.5. (17β)-17-(4-Iodobenzyl)-estra-1(10),2,4-triene-3,17-diol (**22**).* White powder; IR υ, (film on NaCl) 3346 (OH); ^{1}H NMR δ ($CDCl_3$) 0.96 (s, 3H, 18–CH_3), 2.61 and 2.88 (2d, 2H, J = 13.4 Hz, 17α-CH_2), 2.85 (m, 2H, 6–CH_2), 6.58 (d, 1H, J = 2.6 Hz, 4–CH), 6.64 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.07 (d, 2H, J = 8.2 Hz, 2′–CH and 6′–CH), 7.18 (d, 1H, J = 8.4 Hz, 1–CH), 7.64 (d, 2H, J = 8.2 Hz, 3′–CH, 5′–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.44, 23.27, 26.32, 27.48, 29.64, 31.35, 33.84, 39.66, 41.91, 43.85, 46.92, 49.51, 83.24, 91.76, 112.70, 115.26, 126.51, 132.55, 133.14 (2×), 137.08 (2×), 138.14, 138.25, 153.41; LRMS for $[M–H_2O+H]^+$ 471.1 *m/z*; $[M\text{-}H]^-$ 487.8 *m/z*.

*4.1.6. Synthesis of pyridin-3-ylmethyl derivative **23***

An LDA solution was prepared by dissolving diisopropylamine (662 μL, 4.72 mmol) in anhydrous THF (6 mL) cooling the solution to 0 °C, adding a solution of *n*-BuLi (2.1 mL, 4.72 mmol) in hexanes and stirring the mixture at 0 °C for 30 min. Anhydrous HMPA (821 μL, 4.72 mmol) was added and the mixture stirred an additional 15 min at 0 °C. 3-Picoline (454 μL, 4.72 mmol) was dissolved in anhydrous THF (6 mL) and added dropwise to the LDA/HMPA solution and the resulting solution stirred for 30 min at 0 °C. Estrone (319 mg, 1.18 mmol) was dissolved in anhydrous THF (3 mL) and added dropwise to the 3-picoline anion solution. The mixture was stirred 1 h at room temperature, then quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash

chromatography on silica gel with hexanes/EtOAc (60/40 to 70/30) to yield 58 mg (14%) of **23**.

*4.1.6.1. (17β)-17-(Pyridin-3-ylmethyl)-estra-1(10),2,4-triene-3,17-diol (**23**).* White powder; IR υ, (film on NaCl) 3440 (OH); ^{1}H NMR δ (DMSO-d_6) 0.84 (s, 3H, 18–CH_3), 2.55 and 2.85 (2d, 2H, J = 13.6 Hz, 17α-CH_2), 2.70 (m, 2H, 6–CH_2), 6.48 (d, 1H, J = 2.6 Hz, 4–CH), 6.55 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.02 (d, 1H, J = 8.4 Hz, 1–CH), 7.17 (dd, 1H, J_1 = 4.9 Hz, J_2 = 7.7 Hz, 5′–CH), 7.66 (d, 1H, J = 7.8 Hz, 6′–CH), 8.37 (dd, J_1 = 4.9 Hz, J_2 = 1.6 Hz, 4′–CH), 8.47 (d, 1H, J = 1.7 Hz, 2′–CH); ^{13}C NMR (75 MHz) δ (DMSO-d_6) 14.72, 22.90, 26.18, 27.20, 29.20, 31.04, 32.06, 39.66, 43.34, 46.82 (2×), 48.82, 82.00, 112.72, 114.93, 122.63, 126.05, 130.46, 134.95, 137.20, 138.42, 146.75, 151.75, 154.92; LRMS for $[M + H]^+$ 364.3 m/z.

*4.1.7. Procedure for oxirane opening (synthesis of compounds **24** and **25**)*

A 2-furyllithium solution was prepared by cooling a solution of n-BuLi (1.76 mL) in hexanes solution to −20 °C, adding a solution of furan (143 μL, 1.96 mmol) in anhydrous Et_2O (4 mL) and refluxing the solution for 4 h. Oxirane-E1 [34] (60 mg, 0.196 mmol) was dissolved in anhydrous THF (4.4 mL) and added to the furyllithium solution at −78 °C. The mixture was stirred overnight, letting it reach room temperature. It was then quenched with water, extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel with hexanes/EtOAc (80/20) to yield 25 mg (36%) of **24**.

*4.1.7.1. (17β)-17-(2-Furylmethyl)-estra-1(10),2,4-triene-3,17-diol (**24**).* White powder; IR υ, (film on NaCl) 3301 (OH); ^{1}H NMR δ ($CDCl_3$) 0.96 (s, 3H, 18–CH_3), 2.84 and 2.94 (2d, 2H, J = 14.7 Hz, 17α-CH_2), 2.83 (m, 2H, 6–CH_2), 6.18 (d, 1H, J = 3.0 Hz, 5′–CH), 6.35 (dd, 1H, J_1 = 2.0 Hz, J_2 = 3.0 Hz, 3′–CH), 6.56 (d, 1H, J = 2.6 Hz, 4–CH), 6.63 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.17 (d, 1H, J = 8.4 Hz, 1–CH), 7.38 (d, 1H, J = 1.2 Hz, 3′–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.29, 23.41, 26.24, 27.42, 29.62, 31.52, 34.72, 35.94, 39.48, 43.78, 46.52, 49.56, 82.79, 108.26, 110.38, 112.62, 115.20, 126.49, 132.59, 138.25, 141.70, 153.24, 153.30; LRMS for $[M–H_2O+H]^+$ 335.1 m/z.

*4.1.7.2. (17β)-17-(4-Methyl-2-thienyl)-estra-1(10),2,4-triene-3,17-diol (**25**).* This compound was obtained as described above for **24**, but using 4-methylthiophene instead of furan. White powder (22% yield); IR υ, (film on NaCl) 3340 (OH); ^{1}H NMR δ ($CDCl_3$) 0.97 (s, 3H, 18–CH_3), 2.24 (d, 3H, J = 0.7 Hz, 6′–CH), 2.83 (m, 2H, 6–CH_2), 2.91 and 3.05 (2d, 2H, J = 14.4 Hz, 17α-CH_2), 6.58 (d, 1H, J = 2.6 Hz, 4–CH), 6.64 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 6.75 (d, 2H, J = 14.6 Hz, 3′–CH and 5′–CH), 7.17 (d, 1H, J = 8.4 Hz, 1–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 14.51, 15.72, 23.47, 26.30, 27.45, 29.64, 31.50, 34.45, 37.75, 39.61, 43.81, 46.70, 49.81, 82.76, 112.65, 115.23, 119.86, 126.52, 129.91, 132.64, 137.16, 138.28, 140.01, 153.33; LRMS for $[M–H_2O+H]^+$ 365.1 m/z.

*4.1.8. Synthesis of cyclopropyl derivatives **27** and **29***

An Et_2Zn solution in toluene (0.67 mL, 0.74 mmol) was added to anhydrous CH_2Cl_2 (0.75 mL) and cooled to 0 °C. A trifluoroacetic acid solution (0.37 mL, 0.74 mmol) in CH_2Cl_2 was added dropwise and the solution was stirred 20 min at 0 °C. A CH_2I_2 solution in CH_2Cl_2 (0.37 mL, 0.74 mmol) was then added and the solution stirred a further 20 min at 0 °C. Allyl derivative **26** [32] (170 mg, 0.372 mmol) was dissolved in anhydrous CH_2Cl_2 (0.4 mL) and added to the $CF_3CO_2ZnCH_2I$ solution. The mixture was stirred 30 min at room temperature, quenched with a saturated aqueous NH_4Cl solution, extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated to yield 141 mg (80%) of 3-TBS-**26** which was treated with TBAF (1.0M) as reported above to yield 94 mg (93%) of **27**.

*4.1.8.1. (17β)-17-(Cyclopropylmethyl)-estra-1(10),2,4-triene-3,17-diol (**27**).* White powder; IR υ, (film on NaCl) 3320 (OH); ^{1}H NMR δ ($CDCl_3$) 0.13 and 0.55 (2m, 4H, 2′–CH_2 and 3′–CH_2), 0.88 (t, 1H, J = 6.6 Hz, 2′–CH), 0.92 (s, 3H, 18–CH_3), 1.48 (d, 2H, J = 6.0 Hz, 17α-CH_2), 2.81 (m, 2H, 6–CH_2), 6.56 (d, 1H, J = 2.6 Hz, 4–CH), 6.63 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.14 (d, 1H, J = 8.4 Hz, 1–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 4.28, 4.66, 5.81, 14.15, 23.32, 26.28, 27.42, 29.64, 31.60, 34.73, 39.50, 41.68, 43.79, 46.34, 49.38, 84.11, 112.58, 115.18, 126.48, 132.72, 138.29, 153.28; LRMS for $[M–H_2O+H]^+$ 309.1 m/z and $[M + H]^+$ 327.1 m/z.

*4.1.8.2. (17β)-17-{[2-(2-Bromoethyl)cyclopropyl]methyl}estra-1(10),2,4-triene-3,17-diol (**29**).* Allyl derivative **26** [45] (200 mg, 0.44 mmol) was dissolved in anhydrous CH_2Cl_2 (8 mL). 4-Bromobutene (0.44 mL, 4.37 mmol) and 2nd generation Grubb's catalyst ([1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(phenylmethylene)(tricyclohexylphosphine) ruthenium) (37 mg, 0.04 mmol) were added, the mixture refluxed overnight and then concentrated on a rotary evaporator. The crude product was purified using a silica gel 25 + M column on a Biotage chromatographer eluted and hexanes/EtOAc (97.5/2.5 to 85/15) as eluent to yield 166 mg (71%) of **28**. This latter was submitted to cyclopropanation and TBS hydrolysis as described above for compound **27** to yield **29.** White powder; IR υ, (film on NaCl) 3305 (OH); ^{1}H NMR δ ($CDCl_3$) 0.39 (t, 4H, J = 6.5 Hz, CH_2 of cyclopropyl), 0.88 (m, 2H, 1′-CH and 2′-CH), 0.91 (s, 3H, 18–CH_3), 1.47 and 1.50 (2d, J = 8.8 Hz, 17α-CH_2), 2.81 (m, 2H, 6–CH_2), 3.48 (m, 2H, CH_2CH_2Br), 6.56 (d, 1H, J = 2.6 Hz, 4–CH), 6.63 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.4 Hz, 2–CH), 7.14 (d, 1H, J = 8.4 Hz, 1–CH); ^{13}C NMR (75 MHz) δ ($CDCl_3$) 11.23, 13.54, 14.15, 17.82, 23.38, 26.27, 27.41, 29.64, 31.57, 33.25, 34.64, 37.50, 39.51, 40.98, 43.77, 46.41, 49.41, 83.98, 112.60, 115.19, 126.48, 132.70, 138.30, 153.29; LRMS for $[M–H_2O+H]^+$ 415.1 and 417.1 m/z and $[M + H]^+$ 433.1 and 435.1 m/z.

4.2. Enzymatic assay

As described in the previous study [21], the steroid sulfatase (STS) assay was performed using a human embryonic kidney (HEK)-293 cell transiently transfected with a sulfatase expression vector (pCMV-sulfa) as the source of enzyme. The cells were prepared by performing 5 freezing (−80 °C) and thawing cycles and homogenization using a Dounce homogenizer. The reaction was carried out using 100 μM of estrone sulfate (E1S) (0.5% of which were [^{3}H]-E1S) in 1.0 mL of tris-acetate buffer (pH 7.4) containing 5 mM ethylenediaminetetraacetic acid (EDTA), 10% glycerol and an ethanolic solution of test compound. Only ethanol was used for the control. After 2 h of incubation at 37 °C, the reaction was stopped by adding 1.0 mL of xylene. The tubes were vortexed and centrifugated at 3500 g for 20 min to separate organic and aqueous phases. A 400 μL aliquot of each phase was used for radioactivity measurement using a Wallac 1400 scintillation counter (Ramsey, MN, USA). The results were expressed as the percent of estrone (E1) produced (100% for control without inhibitor) and the percent of inhibition then determined for three inhibitor concentrations (0.01, 0.1 and 1 μM).

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