From Suzuki-Miyaura cross coupling reactions of 2-/4-haloestranes to fluorinated benzofuranoestranes

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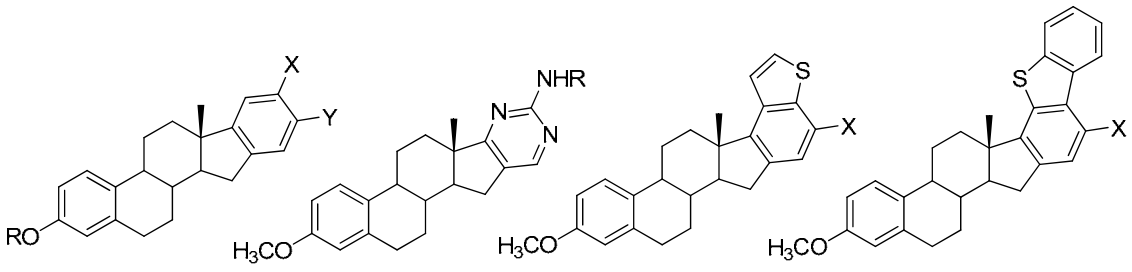
Abstract: 4-Bromoestrone, 2-bromoestrone, 2,4-diodoestrone and the corresponding estradiol derivatives were converted to 2-fluoroaryl- and 4-fluoroarylestrones and estradiols by Suzuki-Miyaura cross-coupling. The coupling products were subjected to an intramolecular aromatic *ipso* S_N reaction to furnish benzofuranoestrones and estradiols. Suzuki-Miyaura cross-coupling reactions were also carried out with other arylboronic acids, using 4-bromoestrone, 2-bromoestrone and 2,4-dibromoestrone as substrates.

Keywords: Suzuki-Miyaura reaction, estrane, benzofuran, ring annelation, fluoro-substituted steroid

Introduction



1

1a: X = H, R = CH_3, Y = H [Ref. 1]
1b: X = CO_2CH_3, R = CH_3, Y = H [Ref. 2]

2

2a: R = H
2b: R = peptide [Ref. 4]

3

3a: X = H
3b: X = $COCH_3$ [Ref. 3]

4

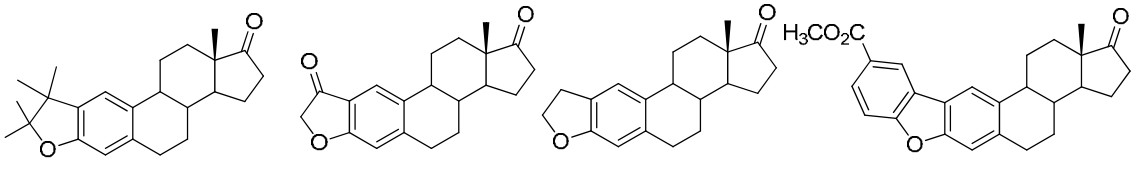
4a: X = H
4b: X = $COCH_3$ [Ref. 3]

Figure 1

In our interest in ring-expanded estrane derivatives, and their interaction with the estrogen receptor, we have prepared previously D-ring areno and hetareno annelated

steroid derived compounds, such as **1** – **4** (Fig. 1). Of these, compound **1a** showed favorable distribution in estrogen receptor – rich tissue in *in-vivo* experiments, although the experiments indicated that the concentration of the compound in those tissues might not have been estrogen-receptor modulated.

Next, our interest turned to ring annelation of the A ring of estradiol and estrone derivatives, which led to the experimentation described below. Previous examples of furano-A-ring annelated estrane derivatives exist, with the compounds **5** – **8** (Figure 2), described by other groups,[5-8] and of which **5** had been tested as an estrogen.



5 Jefferson and Scheinmann [ref. 5]

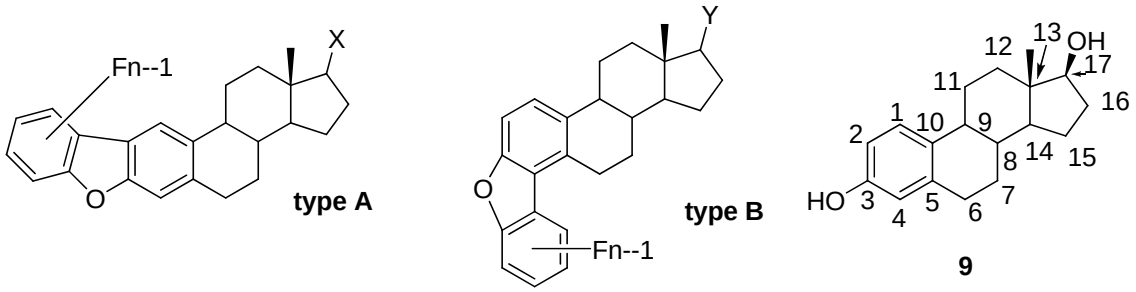
6 Omar et al. [ref. 6]

7 Lehmann [ref. 7]

8 Xiao et al. [ref. 8]

Figure 2

In the following, A-ring fluorobenzofurano annelated estrane derivatives of types A and B (Fig. 3) were chosen as target compounds. Here it was envisaged to couple a fluorinated aryl group at position C4 or position C2 of an estradiol or estrone frame and to use the 3-hydroxy group of the steroid to complete a heterocyclization to a benzofuran (ie., to type A and type B).



type A

Y: =O (keto); -OH (hydroxy)

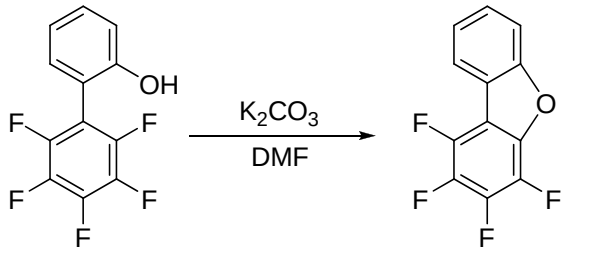
type B

Y: =O (keto); -OH (hydroxy)

9 estradiol with atom-numbering scheme

Figure 3

Indeed, there was precedence of an intermolecular replacement of a fluoro substituent by a phenoxy function in the base-catalysed cyclization of an o'-fluoro-o-hydroxybiphenyl such as **10** to a dibenzofuran such as **11** (Scheme 1).[9]



10 **11** [ref. 9]

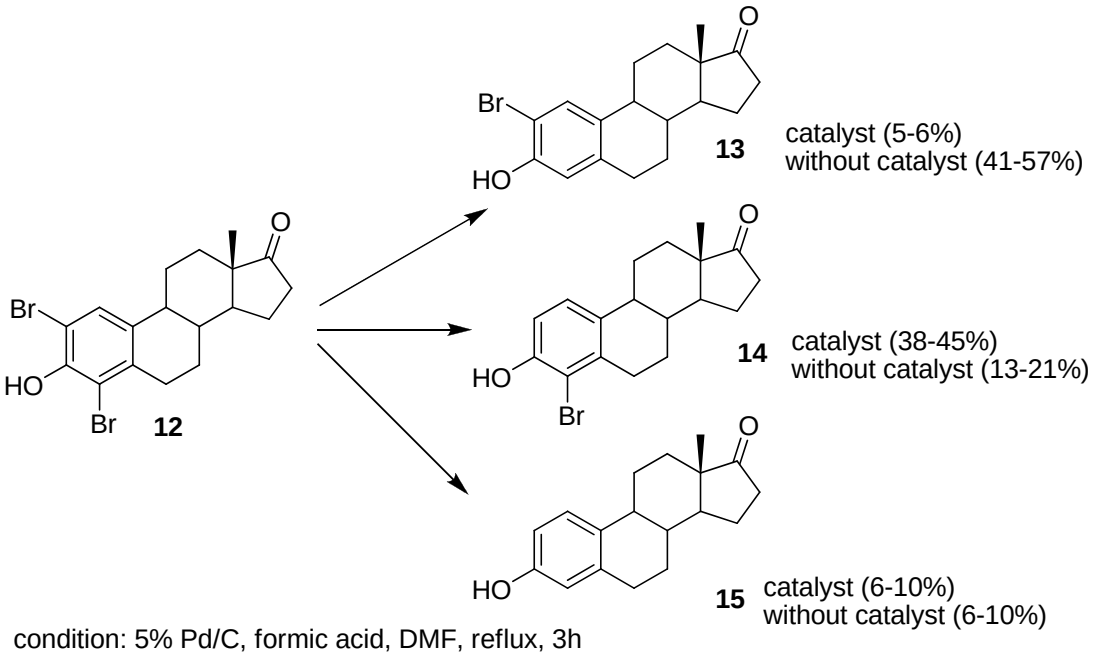
Scheme 1

Results and Discussion

4-Bromoestrone (**14**), 2,4-dibromoestrone (**12**) were prepared from estrone (**15**) by reaction with NBS in dry DMF according to a known procedure by Zhao et al (Scheme 5).[10] While it was not possible to brominate estrone (**15**) at C4 selectively, it was possible to separate out 4-bromoestrone (**14**) without difficulty. The 2,4-dibromoestrone (**12**) could be obtained in good purity by crystallization from ether. Numazawa et al. have developed a reductive dehalogenation of 2,4-dihaloestrone and 2,4-dihaloestradiol to the 4-halogenated derivatives that can be obtained in moderate yield when Pd/C, HCO_2H is used as reductive system.[11] The authors have tried dehalogenative hydrogenolysis over Pd/C under various conditions[12-14] to obtain **14** from **12**, however, without success, where either 2,4-dihaloestrone (eg., **12**) was re-isolated or the molecule was dehalogenated completely to give estrone (**15**) itself (Scheme 3). Also, the iodination of estradiol was reinvestigated in our laboratory. With a slightly more than a double amount of iodine, 2,4-diiodoestrone could be prepared (I_2, aq NH_3, MeOH, THF) and isolated with ease by crystallization after column chromatographic separation. In all cases, where mono-iodination of estradiol was attempted, a mixture of 2-iodoestradiol and 4-estradiol was obtained. Reports on the selective iodination of estradiol in 2-position were not carried out due to the necessity of using toxic thallium and mercury salts. As 2-iodo- and 4-iodoestradiol were difficult to separate, in the case of estradiol, subsequent reactions were carried out with the corresponding 2-bromo- and 4-bromoestradiols. As it turned out later, in the case of the benzofurano[3',2':2,3]estrane series, also 2,4-diodoestrone could be utilized in the cross-coupling reactions.

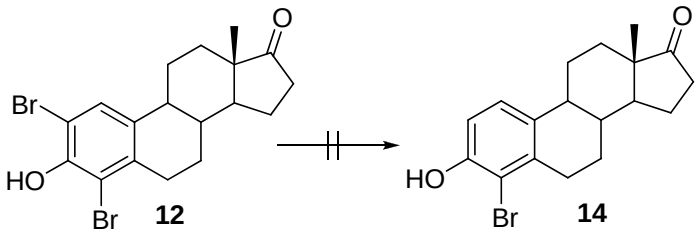
After having the halogenated estranes in hand, a number of Suzuki-Miyaura cross coupling reactions were carried out with differently substituted arylboronic acids. Here, it could be seen that the 2-halo position in the steroid was more accessible to be exchanged than the 4-halo position. This can be seen in the reaction of 2,4-dibromoestrone with 2-methoxyphenylboronic acid as an example. The reactions

were run in a biphasic system (DME, aq. Na_2CO_3), with $Pd(PPh_3)_2Cl_2$ as pro-catalyst but with additional, free PPh_3 as potentially extra ligand. The reactions resulted in mixtures of 2,4-diarylated estranes (eg., **16a**) and 2-aryl-4-bromoestranes (eg., **16b**) (Scheme 4).



Scheme 2

(see also: Numazawa, 1985, ref. 11)

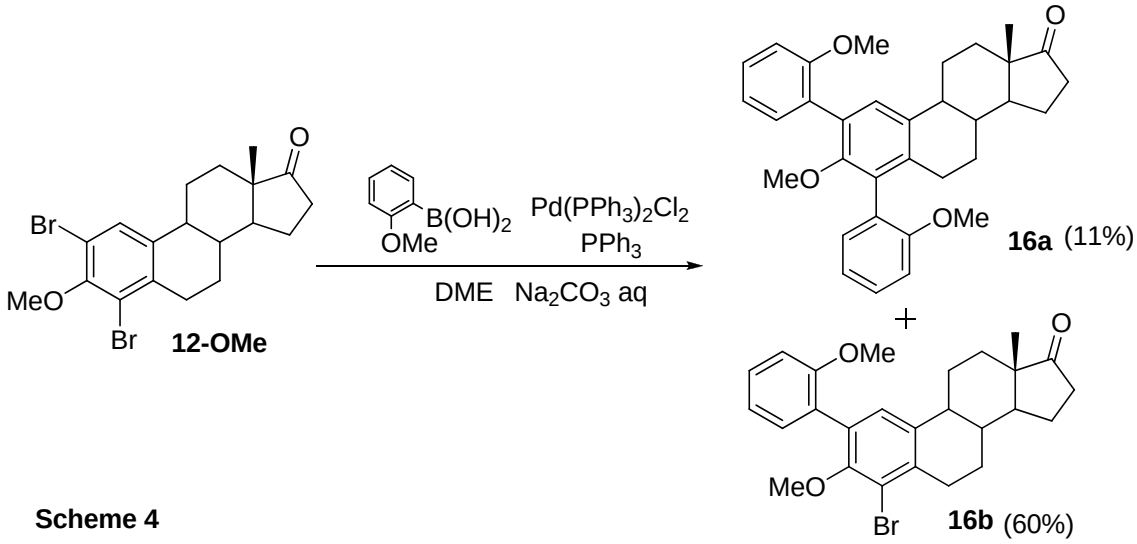


Scheme 3

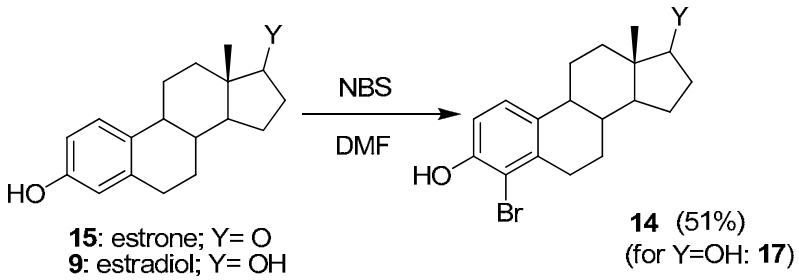
Analogous Suzuki reactions with potassium aryltrifluoroborates under Molander conditions[15] do not work out, most likely due to the acidity of the bromoestranes **12** – **14**.

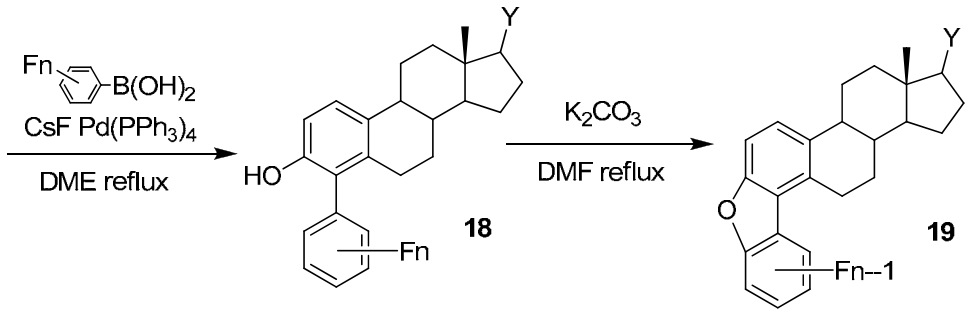
Ultimately, a procedure could be developed with the isolation of the monobrominated 4-bromoestrone and 4-bromoestradiol from the bromination reactions of the steroids

with NBS in DMF. Suzuki-Miyaura cross-coupling of the monobrominated steroids with fluoroarylboronic acids in DME with $Pd(PPh_3)_4$ as catalyst and CsF as base provided the 4-monoarylated estranes **18** (Scheme 5), albeit in low yields. An intramolecular aromatic *ipso* S_N reaction of the 4-(fluorophenyl)estranes **18** (K_2CO_3, DMF, reflux) then furnished benzofuranoestrones **19** (Scheme 5).



Scheme 4

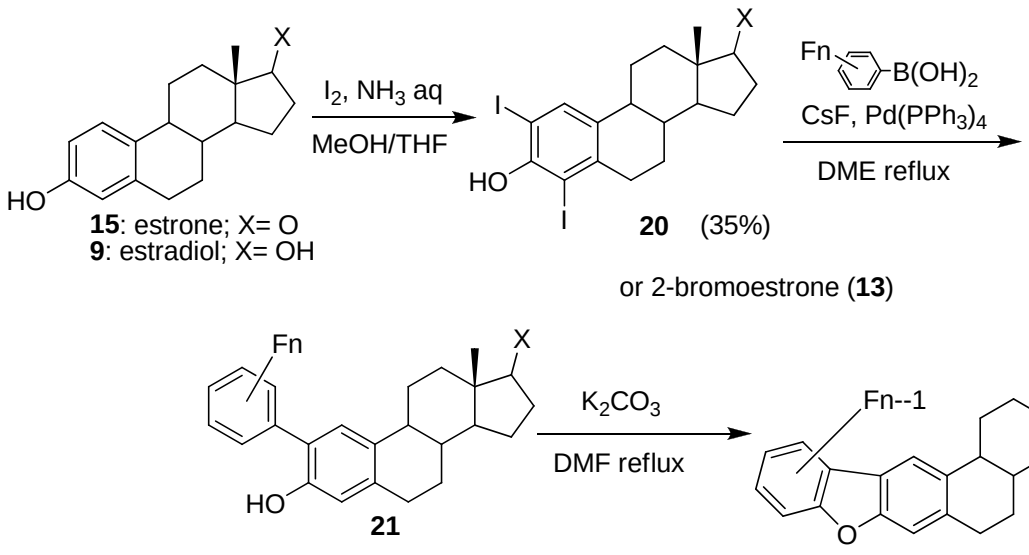




No.	X	Fn
18a	O	2,5-F (21%)
18b	O	2,3-F (3%)
18c	OH	2,4-F

No.	X	Fn--1
19a	O	5-F (9%)
19b	O	3-F (84%)
19c	OH	4-F (16%)

Scheme 5



No.	X	Fn	
21a	O	2,3-F	(64%)
21b	OH	2,4-F	(75%)
21c	OH	2-F	(49%)
21d	OH	4-F	(77%)
21e	OH	4-CF_3	(63%)
21f	OH	4-OMe	(66%)

No.	X	Fn--1	
22a	O	3-F	(35%)
22b	OH	4-F	(80%)

Scheme 6

Equally, the Suzuki reaction, under the same conditions, could be carried out with 2-bromoestrone **13**, prepared according to Numazawa.[11] Lastly, with **20** in hand, it was possible to arylate at C2 with concomitant reduction of the iodo function at C3, obtaining the arylated compounds in yields similar to those when using **13**. Reaction of the compounds **21a** and **21b** in refluxing DMF, in the presence of K_2CO_3, provided fluorobenzofurano[3',2':2,3]estranes **22a** and **22b** (Scheme 6).

Conclusions. In the endeavor to synthesize fluorobenzofurano[3',2':2,3]estranes and fluorobenzofurano[2',3':3,4]estranes, estrone and estradiol were halogenated in ring A. While it was possible to prepare the 4-bromo derivatives with relative ease, the 2-halo derivatives were much more difficult to obtain. The 4-bromo derivatives were used as starting materials for the fluorobenzofurano[2',3':3,4]estranes by Suzuki-Miyaura coupling of the requisite arylbornoic acids, carrying a 2-fluoro substituent, and subsequent intramolecular aromatic *ipso* S_N reaction of that fluoro substituent by the phenoxy function. In the case of the fluorobenzofurano[3',2':2,3]estranes,

2-bromoestrone could be utilized as substrate. Equally, 2,4-diiodoestrone could be used as starting material, where in the Suzuki reaction the arylation occurred selectively at C2 with a concomitant reduction of the iodo substituent at C4. Again, an intramolecular aromatic *ipso* S_N reaction of the *o*-fluoro substituent of the aryl group introduced at C2, by the phenoxy function, provides the desired benzofuranoestranes.

Experimental

General. - IR spectra were measured with JASCO IR-700 and Nippon Denshi JIR-AQ2OM machines. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-270 spectrometer (^{1}H at 270 MHz and ^{13}C at 67.8 MHz) and a (^{1}H at 400 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer [electron impact mode (EI), 70 eV or fast atom bombardment (FAB)]. Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. Column chromatography was carried out on Wakogel C-300.

Procedures – selected examples:

General Procedure of Suzuki-Miyaura cross coupling with 2,4-dibromoestrone. - 2,4-Bis(2-methoxyphenyl)-3-methoxyestra-1,3,5(10)-trien-17-one (**16a**) and 4-bromo-2-(2-methoxyphenyl)-3-methoxyestra-1,3,5(10)-trien-17-one (**16b**). - A mixture of 2,4-dibromo-3*O*-methylestrone (**12a-OMe**, 1.43 g, 3.23 mmol), 2-methoxyphenylboronic acid (2.01 g, 13.2 mmol), $Pd(PPh_3)_2Cl_2$ (80 mg,) and PPh_3 (80 mg, 0.31 mmol) in a mixture of DME (15 mL) and aq. Na_2CO_3 (10 mL, 2.3 M) was kept at 70 ^{o}C for 36h. The cooled reaction mixture was poured into water (60 mL) and extracted with chloroform (2 X 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the crude residue on silica gel (hexane/$CHCl_3$/ether 3:1:1) gave **16a** (184 mg, 11%) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, s, CH_3), 3.11 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.95 – 7.34 (9H, m, ArH); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 497 (23) (MH^+), 496 (29) (M^+). HRMS Found: 496.2612. Calcd. for $C_{33}H_{36}O_4$: 496.2614,

and **16b** (907 mg, 60%) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.00 (3H, s, CH_3), 3.45 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.97 – 7.34 (5H, m, ArH); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 470 (44) ([^{81}Br]M^+), 468 (39) ([^{79}Br]M^+). HRMS Found: 468.1302. Calcd. for $C_{26}H_{29}O_3{}^{79}Br$: 468.1300.

General procedure for the Suzuki-Miyaura cross coupling with 2-bromoestradiol (**13**) and with 4-bromoestradiol (**14**). – A solution of bromoestradiol (35 mg, 0.1 mmol), boronic acid (0.11 mmol), 3 eq. Cs_2CO_3 and 3 mol% $Pd(dppe)Cl_2$ were heated in dry dioxane (1 mL) for 12h at 80 ^oC. The mixture was diluted with ethyl acetate (20 mL) and extracted with water (2 X 20 mL). The aqueous phase was extracted with ethyl acetate (10 mL), and the combined phases were dried and evaporated *in vacuo*. The crude product was either purified by crystallization or column chromatography on silica.

Example: 2-(4'-Methoxyphenyl)estradiol ([not shown in a scheme, 25 mg, 66%) as a colorless solid; ^1H NMR (270 MHz, $CDCl_3$) δ 0.79 (3H, s, CH_3), 1.0 – 3.0 (15H, m), 3.73 (1H, dd, ^3J 8.4 Hz, ^3J 8.4 Hz), 6.70 (1H, s), 7.00 (2H, d, ^3J 8.5 Hz), 7.14 (1H, s), 7.39 (2H, d, ^3J 8.5 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.9, 23.0, 26.3, 27.1, 29.3, 30.5, 36.6, 38.8, 43.2, 43.9, 50.0, 55.3, 81.9, 114.7, 115.6, 125.4, 127.3, 129.8, 130.4, 132.8, 137.7, 150.4, 159.3; MS (EI, 70 eV) m/z (%) 378 (100) (M^+), 350 (16), 319 (4), 278 (9), 252 (9), 239 (6), 211 (8). HRMS Found: 378.2194. Calcd. for $C_{25}H_{30}O_3$: 378.2195.

2-(2'-Fluorophenyl)estradiol (**21c**, 16.5 mg, 49%) as a colorless solid; ^1H NMR (270 MHz, $CDCl_3$) δ 0.78 (3H, s, CH_3), 1.0 – 3.0 (15H, m), 3.73 (1H, dd, ^3J 8.3 Hz, ^3J 8.3 Hz), 4.97 (1H, s), 6.73 (1H, s), 7.16 – 7.41 (4H, m); MS (EI, 70 eV) m/z (%) 366 (86) (M^+), 266 (17), 253 (16), 240 (19), 227 (14). HRMS Found: 366.1989. Calcd. for $C_{24}H_{27}O_2F$: 366.1995.

2-(4'-Fluorophenyl)estradiol (**21d**, 28 mg, 77%) as a colorless solid; ^1H NMR (270 MHz, $CDCl_3$) δ 0.79 (3H, s, CH_3), 1.0 – 3.0 (15H, m), 3.73 (1H, dd, ^3J 8.4 Hz, ^3J 8.4 Hz), 4.97 (1H, s), 6.70 (1H, s), 7.10 – 7.50 (5H, m). MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 366 (10) (M^+), 349 (3). HRMS Found: 366.1988. Calcd. for $C_{24}H_{27}O_2F$: 366.1995 (M^+, FAB, 3-nitrobenzyl alcohol).

2-(2',4'-Difluorophenyl)estradiol (**21b**, 75%) as a colorless solid; ^1H NMR (270 MHz, $CDCl_3$) δ (3H, s, CH_3), 1.0 – 3.0 (15H, m), 3.73 (1H, dd, 3J 8.4 Hz, 3J 8.4 Hz), 4.99 (1H, s), 6.70 (1H, s), 6.80 – 7.00 (2H, m), 7.11 (1H, s), 7.27 – 7.40 (1H, m); MS (EI, 70 eV) *m/z* (%) 384 (100) (M^+), 350 (14), 325 (17), 298 (9), 272 (20), 258 (21), 219 (9). HRMS Found: 384.1904. Calcd. for $C_{24}H_{26}O_2F_2$: 384.1901.

6'-Fluorobenzofurano[3',2':2,3]estra-1,3,5(10)-trien-17β-ol (**22b**). – A mixture of **21b**

(30 mg, $7.8 \cdot 10^{-2}$ mmol) and K_2CO_3 (54 mg, 0.39 mmol) in DMF (2 mL) was kept at 100 ^oC for 2h. Work-up as described above yielded **22b** (22.7 mg, 80%) as a colorless solid; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (3H, s, CH_3), 1.0 – 3.0 (15H, m), 3.77 (1H, dd, ^3J 8.1 Hz, ^3J 8.1 Hz), 7.05 (1H, ddd, *J* 9.5 Hz, *J* 8.5 Hz, *J* 2.3 Hz), 7.23 (1H, dd, *J* 9.3 Hz, *J* 2.3 Hz), 7.26 (1H, s), 7.80 (1H, dd, *J* 8.4 Hz, *J* 5.4 Hz), 7.82 (1H, s); MS (EI, 70 eV) *m/z* (%) 364 (6) (M^+), 347 (3). HRMS Found: 364.1847. Calcd. for $C_{24}H_{25}FO_2$: 364.1839.

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