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Synthesis, Functionalization and Biological Activity of Arylated Derivatives of (+)-Estrone

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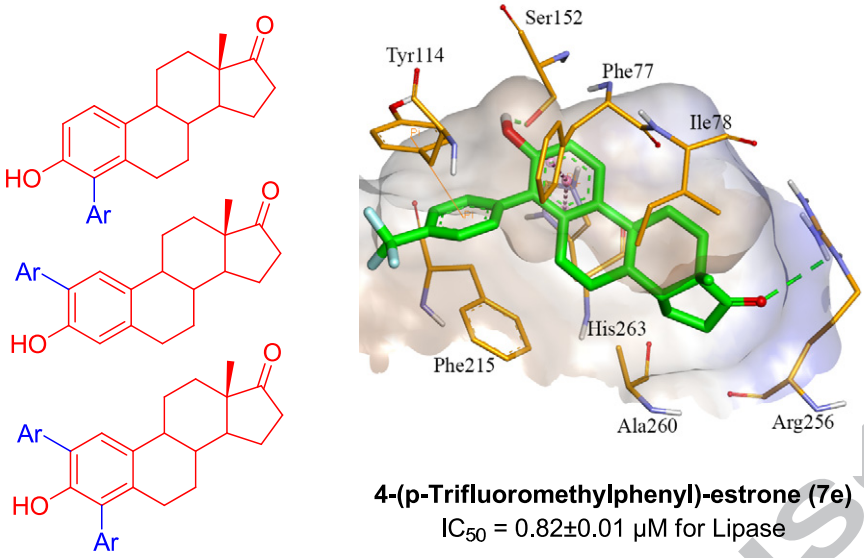
Abstract.

Various novel arylated estrone derivatives, such as 2-aryl-, 4-aryl- and 2,4-diaryl-estrones, by Suzuki-Miyaura reactions. While the synthesis of 4-arylestrones could be carried out under standard conditions, the synthesis of 2-arylestrones and 2,4-diarylestrones required a thorough optimization of the conditions and it proved to be important to use sterically encumbered biaryl ligands. The best results were obtained by the use of RuPhos. Combination of developed Suzuki coupling reactions with subsequent cyclization reactions afforded more complex hybrid structures, containing dibenzofuran, benzocoumarin and steroid moieties. These derivatives were tested as pancreatic lipase inhibitors and it was found that most of the compounds exhibited inhibition of pancreatic lipase but the maximum inhibitory potential was shown by 4-arylestrones. All of the synthesized derivatives showed inhibitory values in the range of 0.82±0.01 to 59.7±3.12 μM. The biological activity was also rationalized on the bases of docking studies.

Graphical abstract

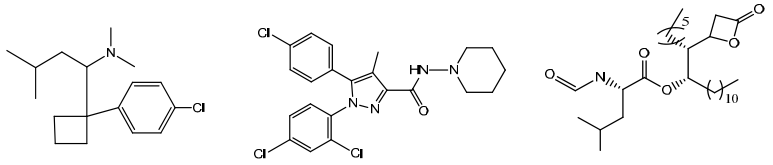


4-(p-Trifluoromethylphenyl)-estrone (7e)
IC_{50} = 0.82±0.01 μM for Lipase

Introduction

Obesity is the fifth leading cause of death in the world and has gained much attention because of its role in different types of cancers, including breast (postmenopausal), pancreatic, gallbladder and liver cancer.[1a] The exact biological mechanisms relating obesity and cancer are complex and still not clearly defined. However, these mechanism may include obesity-related hormones especially estrogen, growth factors, modulation of energy balance and calorie restriction affecting the cancer cell promotion and growth.[1b] Therefore, control of obesity can minimize the risk of cancer. Within the human body lipid metabolism is controlled by the group of enzymes known as lipases.[2] This group of enzymes includes pancreatic and gastric lipases, which are responsible for the hydrolysis of triacylglycerols into free fatty acids.[3] In muscles, these free fatty acids act as a source of energy, whereas in adipose tissue they undergo re-esterification and are ultimately stored. In comparison to gastric lipase, pancreatic lipase is mainly involved in the digestion of dietary fats up to 50-70%.[4] Thus, dietary fat is an important factor that contributes to hyperlipidemia and associated to a variety of diseases including obesity, hypertension, diabetes and cardiovascular problems.[5] It means the inhibition of lipases can help in limiting the hydrolysis of dietary fats which will in turn help to control the obesity.[6a] As a result, further complications arising from obesity can also be prevented.

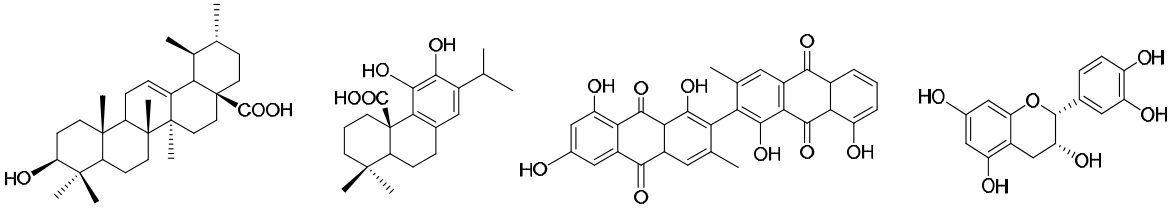
Different synthetic derivatives including phenethylamine (sibutramine),[6b] carboxamide (rimonabant) [6c] and lipstatin (orlistat) [6c] are avialable on the market and are being used as anti-obesity drugs. Sibutramine is a centrally acting drug which causes the inhibition of reuptake of nor-adrenaline, serotonin and dopamine.[6b] Whilst, rimonabant acts through the inhibition of cannabinoid-1 receptors. Although being effective antiobesity drugs, both of these drugs are associated with several side effects including insomnia, headache, hypertension, palpitation, dizziness, constipation and anxiety disorders.[6b,c]



1 2 3

Figure 1: Currently avvailable anti-obesity drug (1) Sibutramine (2) rimonabant (3) orlistat.[6b-c]

Among above mentioned derivatives, only orlistat is considered to be acting directly through inhibition of pancreatic lipase and is able to prevent absorption of approximately 30% of dietary fat.[7a] Apart from its antiobesity activity, it can also modestly decrease blood pressure, prohibit the onset of diabetes type-2 and improve oral glucose tolerance. The mechanism of lipase inhibition by orlistat is via its covalent bonding to the serine which is present in the active site of the lipase.[7b] Despite the promising results of orlistat for obesity treatment, it is associated with certain unpleasant gastrointestinal side effects. The most important adverse effects are diarrhea, liquid stools, fecal urgency, flatulence, oily spotting and abdominal cramping.[8] Due to the adverse effects of orlistat, it may not be well tolerated. Many derivative of alkaloids,[9a] glycosides,[9b] carotinoids,[9c] saponins,[9d] terpenes[9e] and polyphenoles[9f] have also been isolated from plants and reported as pancreatic lipase inhibitors (Figure 2). Hence, it is crucial to identify different compounds (from natural and synthetic source) to overcome obesity and its associated complications. Therefore more researches have been focused on the identification of newer pancreatic lipase inhibitors with less unpleasant adverse effects.



(IC_{50} = 15.83±1.10 µM) **1** (IC_{50} = 12 µg/mL) **2** (IC_{50} = 41.8 µM) **3** (IC_{50} >20 µM) **4**

Figure 2: Previously reported pancreatic lipase inhibitors (**1**) ursolic acid (**2**) carnosic acid (**3**) cassiamin A (**4**) (-)-epicatechin.[9e,f]

Within the human body many steroidal molecules are playing specific physiological functions. For example, cholesterol is an essential structural component of all animal cell membranes, whereas steroid hormones are important part of a signal system within the organisms.[10] Among the steroidal hormones, female primary sex hormones (estrogens) promote the development of female secondary sexual characteristics and regulate the menstrual cycle.[11a] (+)-Estrone (**1**) in Figure 3, is an interesting example of such steroidal molecules. [11b] Different derivatives of estrones have been reported as anticancer agents and used as component of oral contraceptive pills.[12] Moreover, different studies have been reported on 2- and 4-substituted estrones e.g. 1-adamantyl compound ZYC-26 (**2**) as neuroprotective molecule against

cerebralischemia/reperfusion injury[13a,b] and 2- and 4-substituted estrones (**3**) derivatives as steroid sulfatase (STS) inhibitors (Figure 3).[14a-c] There are, however, no studies concerning the effects of the presence of aryl groups located at positions 2 and/or 4 on the bioactivity of steroids.

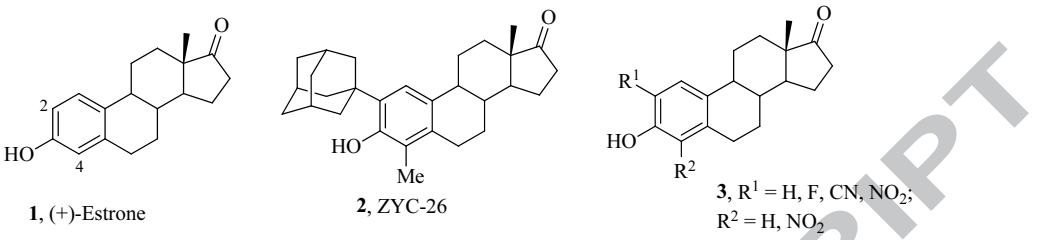
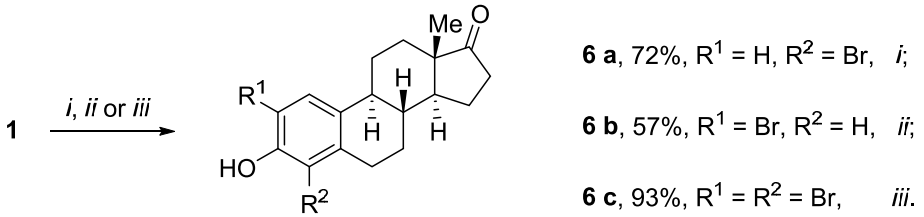


Figure 3. Estrone and its biologically active derivatives[12-14]

As mentioned before, 2- and/or 4-aryl-substituted estrones have only been scarcely studied and there are only a few preparative methods towards these compounds in the literature focusing on transition metal catalyzed CH-activation.[15a, 11b] However, these methods suffer from either moderate yields, requirement of a directing group or the restriction of special nucleophiles. Moreover, non-selective arylation by stoichiometric organo-bismuth derivatives are known to give access to the target products in low yields.[16a,b] Thus, we decided to investigate the scope and limitations of the synthesis of arylated estrone derivatives. On the basis of previous studies,[9e,f] it was observed that steroid derivatives isolated from plants inhibited the pancreatic lipase, therefore, we tested our compounds as lipase inhibitors.

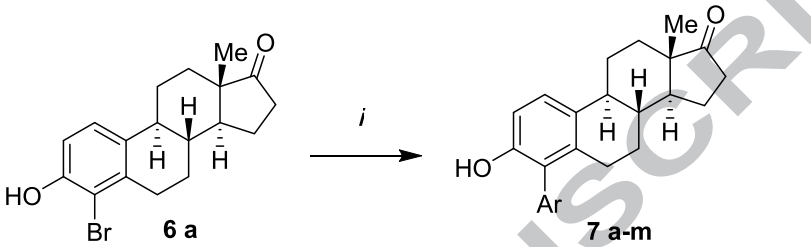
Results and Discussions

The Suzuki-Miyaura cross-coupling reaction is a convenient and powerful tool for diaryl synthesis and the reaction is characterized by a good functional group tolerance. Therefore, we decided to apply this reaction using 2- and 4-bromoestrone and 2,4-dibromoestrone as starting materials. All substrates were easily synthesized by simple bromination[17] using either *N*-bromosuccinimide or 1,3-dibromo-5,5-dimethylhydantoin starting from estrone (Scheme 1).



Scheme 1. Synthesis of substrates **6 a-c**. *Conditions: i*, **1** (1.0 equiv.), *N*-bromosuccinimide (1.1 equiv.), CCl_4, reflux, 3h; *ii*, **1** (1.0 equiv.), *N*-bromosuccinimide (1.1 equiv.), DCM, 20°C, 1h; *iii*, **1** (1.0 equiv.), 1,3-dibromo-5,5-dimethylhydantoin (1.1 equiv.), DCM, 20 °C, 1h.

4-Arylestrones. As a first step we decided to study the Suzuki-Miyaura reaction of 4-bromoestrone. To our delight, application of standard reaction conditions, using 5 mol% of Pd $(PPh_3)_4$, gave the desired 4-arylestrones **7 a-m** in good to excellent yields (Scheme 2, Table 1). The application of boronic acids containing electron-donating as well as electron-withdrawing groups gave equally good results, while more sterically hindered *o*-substituted boronic acids (**7 k-m**) resulted in lower yields. Reduction of the amount of catalyst to 2.5 mol% resulted in a slightly reduced yield. Using DMF instead of dioxane resulted in a dramatically decreased yield.



Scheme 2. Synthesis of 4-arylestrones **7 a-m**. *Conditions*: *i*, **6 a** (1.0 equiv.), boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (2.0 equiv.), dioxane, 101°C, 8 h

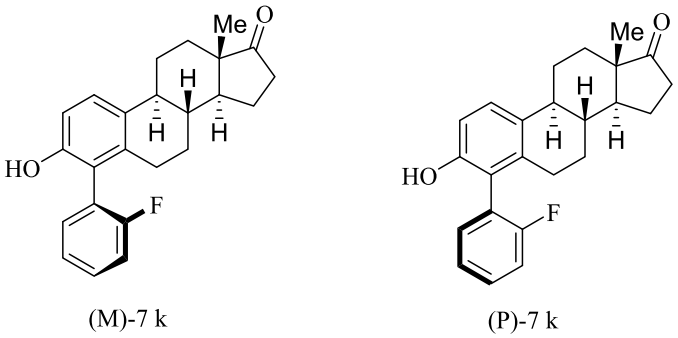
Table 1. Synthesis of 4-arylestrones **7 a-m**.

7	Ar	**7** [%][a]
A	C_6H_5	88
B	4-MeC_6H_4	98
C	4-*t*-BuC_6H_4	90
D	4-$(MeO)C_6H_4$	99
E	4-$(F_3C)C_6H_4$	91
F	4-$(F_3CO)C_6H_4$	96
G	3-FC_6H_4	92
H	3,5-$(MeO)_2C_6H_3$	97
I	4-EtC_6H_4	99
J	4-ClC_6H_4	87
K	2-FC_6H_4	94
L	2,3,4-$(MeO)_3C_6H_2$	67
M	2-$(EtO)C_6H_4$	79

[a] Isolated yields.

It is worth to be noted that, in case of *o*-substituted products **7 k-m** new atropisomers are formed due to hindered rotation, thus forming a mixture of two diastereomers. This was proven by the observation of two sets of NMR signals. Interestingly, even small atoms, such as Fluor, were sufficient for the

occurrence of the described effect (Figure 4). The structure of **7 c** was independently confirmed by X-ray analysis (Figure 5).



(M)-7 k (P)-7 k

Figure 4. M- and P-Atropisomers of **7 k**.

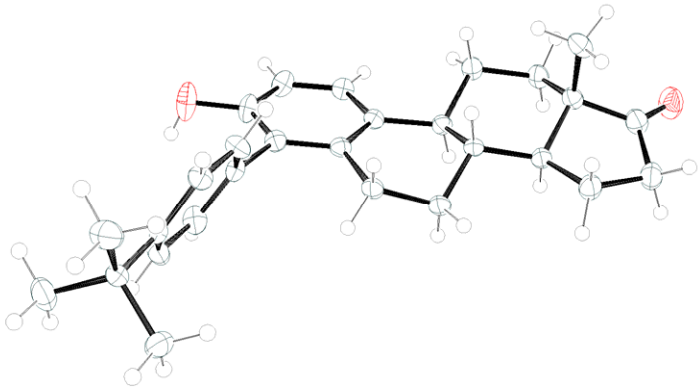
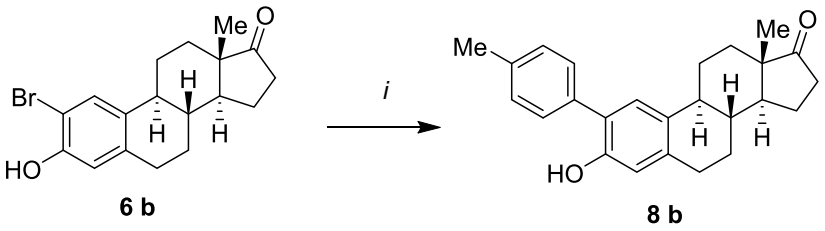


Figure 5. Molecular structure of **7c** (Ortep plot showing thermal ellipsoids at the 50% probability level).

2-Arylestrones. The reaction of 2-bromoestrone (**6 b**) with *p*-tolylboronic acid was next studied (Table 2). We first tested the application of the same conditions as applied for 4-bromoestrone. However, the reactions were unsuccessful and resulted in the formation of complex mixtures. Afterwards, we applied different catalysts, ligands, bases and solvents to find appropriate conditions. Thus, we found that the use of Buchwald's ligands RuPhos and SPhos were crucial to obtain desired arylated product. The use of RuPhos gave the best yields (Table 2). The requirement of such sophisticated catalytic systems was somehow surprising as transition metal catalysts exclusively gave 2-arylated instead of 4-arylated products in CH-activation reactions. [15a, 11b] In particular, Bedford et al. described CH-arylation of carbamate protected estrones with aryliodides which were mainly governed by steric effects. However, in our case the cross-coupling reaction might be effected primarily by electronic effects as the sterically less hindered position 2 is only addressed by a sophisticated catalyst system.

Table 2. Optimization of the Suzuki reaction for 2-tolylestrone **8 b**.



Conditions: **6 b** (1.0 equiv.), *p*-tolylboronic acid (1.5 equiv.), catalyst (5.0 mol%), ligand (5.0 mol%), base (2.0 equiv.), solvent.

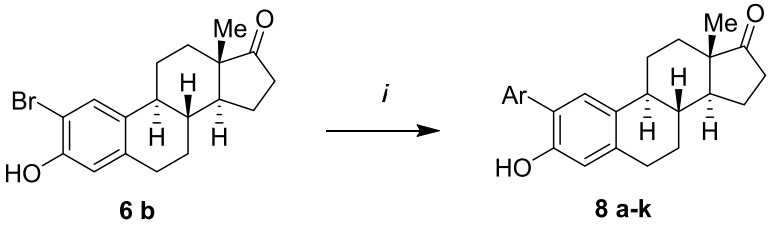
Entry	Catalyst	Ligand	Base	Solvent	T [°C]	Time [h]	Yield [%]
1	$Pd(PPh_3)_4$	-	K_3PO_4	dioxane	101	20	-[b]
2	$Pd(PPh_3)_4$	-	Cs_2CO_3	dioxane	101	18	-[b]
3	$Pd(PPh_3)_4$	-	K_3PO_4	DMF	130	20	-[b]
4	$Pd(PPh_3)_4$	BINAP	K_2CO_3	DMF	130	20	-[b]
5	$Pd(PPh_3)_4$	SPhos	K_2CO_3	dioxane	101	22	66[a]
6	$Pd(PPh_3)_4$	XPhos	K_2CO_3	dioxane	101	22	-[b]
7	$Pd(PPh_3)_4$	RuPhos	K_2CO_3	dioxane	101	22	75[a]
8	$Pd(PPh_3)_4$	$PCy_3{\cdot}HBF_4$	K_2CO_3	dioxane	101	22	35[a]
9	$Pd(PPh_3)_4$	RuPhos	K_3PO_4	dioxane	101	28	69[a]
10	$Pd(PPh_3)_4$	RuPhos	Cs_2CO_3	dioxane	101	28	40[a]
11	$Pd(PPh_3)_4$	RuPhos	KF	dioxane	101	28	63[a]
12	$Pd(PPh_3)_4$	RuPhos	K_2CO_3	toluene	105	20	73[a]
13	$Pd(PPh_3)_4$	RuPhos	K_2CO_3	DMF	105	20	-[c]
14	$Pd(OAc)_2$[d]	$PCy_3{\cdot}HBF_4$	K_2CO_3	dioxane	101	20	-[b]
15	$PdCl_2(PPh_3)_2$	-	K_2CO_3	dioxane	101	20	-[b]

[a] Isolated yields. [b] Low conversion of starting material. [c] Inseparable mixture. [d] 10 mol%.

With this knowledge in hand, we obtained 2-arylestrones **8 a-h** in good yields. As expected, all yields were significantly lower in comparison with the corresponding yields of 4-arylestrones, due to the lower reactivity of this position (Table 3). Electronic properties of the substituents were not affecting the yield. Application of *o*-sustituted arylboronic acids as well as *p*-chlorophenylboronic acid was unsuccessful. The latter can be explained by the occurrence of the competing cross-coupling reaction between two

molecules of arylboronic acids. The structures of **8 c** and **8 e** were independently confirmed by X-ray crystal structure analyses (Figures 6 and 7).

Table 3. Synthesis of 2-arylestrones **8 a-k**.



6 b **8 a-k**

Conditions: *i*, **6 b** (1.0 equiv.), boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (5 mol%), RuPhos (5 mol%), K_2CO_3 (2.0 equiv.), dioxane, 101°C, 16 h.

8	Ar	**8 [%]**[a]
A	C_6H_5	75
B	4-MeC_6H_4	75
C	4-*t*-BuC_6H_4	82
D	4-$(MeO)C_6H_4$	80
E	4-$(F_3C)C_6H_4$	72
F	4-$(F_3CO)C_6H_4$	77
G	3-FC_6H_4	79
H	3,5-$(MeO)_2C_6H_3$	84
I	2-FC_6H_4	-[b]
J	2,3,4-$(MeO)_3C_6H_2$	-[b]
K	4-ClC_6H_4	-[b]

[a] Isolated yields. [b] Inseparable mixture.

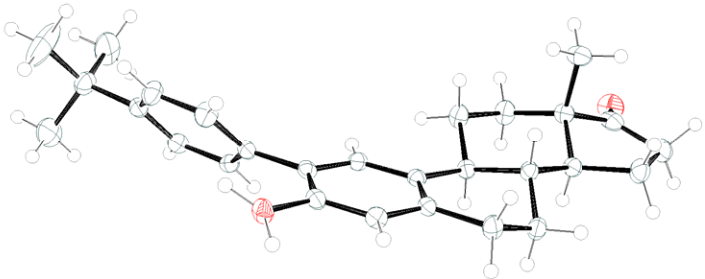


Figure 6. Molecular structure of **8** (Ortep plot showing thermal ellipsoids at the 50% probability level). A solvent molecule (methanol) has been omitted for clarity.

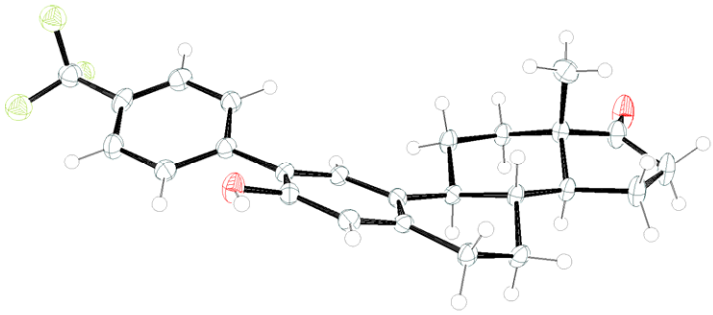
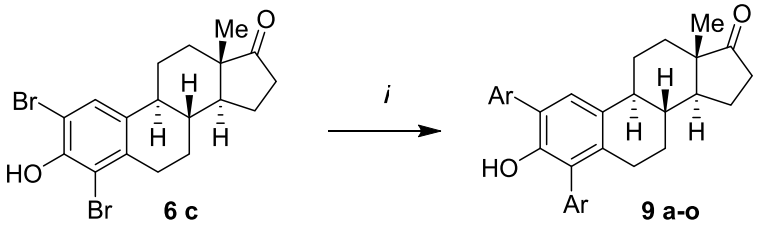


Figure 7. Molecular structure of **8 e** (Ortep plot showing thermal ellipsoids at the 50% probability level).

The disordered atoms of the CF_3 group have been omitted for clarity.**2,4-Diarylestrones.** The conditions used for the synthesis of 2-bromoestrone (**6 b**) were successfully applied to 2,4-dibromoestrone (**6 c**). In contrast, the application of milder conditions used for 4-bromoestrone (**6 a**) resulted in the formation of an inseparable mixture of starting material, di- and mono-substituted products. To exclude formation of the latter we prolonged the reaction time (40 h), applied higher temperature (110 °C) and, hence, used toluene as the solvent. The reactions provided the pure disubstituted products **9 a-o** in excellent yields (Table 4). The electronic properties of the arylboronic acids did not affect the yields, while sterically hindered *o*-arylboronic acids surprisingly gave the corresponding products in good yields. In general, in comparison with the 2-arylestrones, the products were obtained in higher yields. That fact makes us assume that position 2 is strongly affected by the presence of either a bromine atom or an arylring located at position 4, which influences the reactivity of this position and facilitates the reaction. The application of only one equivalent of arylboronic acid gave an inseparable mixture of starting material, mono- and di-arylated products, which underlines the higher reactivity of **6 c** or an 4-arylated intermediated compared to **6 b**. Similar to 4-arylestrones, *ortho*-substituted products **9 j**, **9 m** and **9 n** exist as a mixture of two diastereomers. Interestingly, the presence of *ortho*-substituted aryl groups at position 2 did not result in formation of an additional stereogenic axis, which can be observed by NMR spectroscopy.

Table 4. Synthesis of 2,4-arylestrones **9 a-o**.

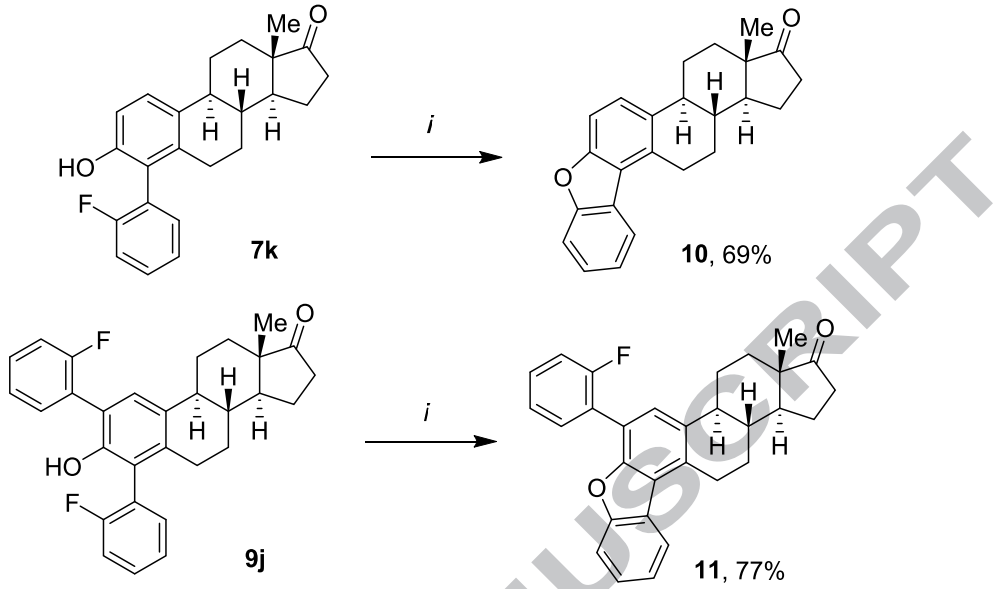


Conditions: *i*, **6 c** (1.0 equiv.), boronic acid (3 equiv.), $Pd(PPh_3)_4$ (5 mol%), RuPhos (5 mol%), K_2CO_3 (4.0 equiv.), toluene, 110 °C, 40 h.

9	Ar	**9 [%]**[a]
A	C_6H_5	99
B	4-MeC_6H_4	91
C	4-*t*-BuC_6H_4	85
D	4-$(MeO)C_6H_4$	99
E	4-$(F_3C)C_6H_4$	89
F	4-$(F_3CO)C_6H_4$	79
G	3-FC_6H_4	85
H	3,5-$(MeO)_2C_6H_3$	70
I	4-EtC_6H_4	99
J	2-FC_6H_4	97[b]
K	3,5-$Me_2C_6H_3$	99
L	4-ClC_6H_4	24
M	2,3,4-$(MeO)_3C_6H_2$	36[b]
N	2-$(EtO)C_6H_4$	72
O	4-FC_6H_4	74

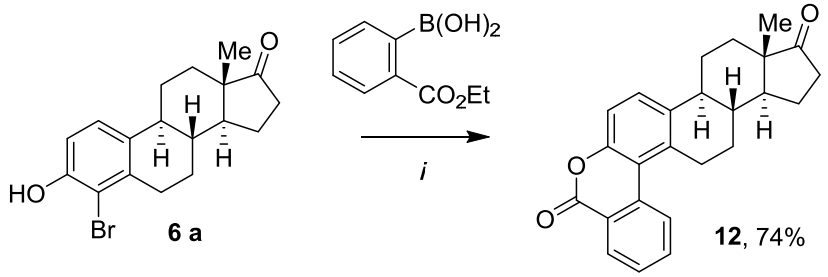
[a] Isolated yields. [b] Reaction time: 72 h.

Further functionalization. We next synthesized, based on the Suzuki reactions described above, novel polycyclic ring structures which contain a steroid and a dibenzofuran moiety. Treatment of **7 k** with K_2CO_3 in DMF at 150 °C afforded the desired product **10** in 69% yield (Scheme 3). Likewise, product **11** was synthesized starting with **9 j**. Fortunately, cyclized product **11** was obtained as the only product and no other isomer, which might derive from cyclization of the 2-fluorophenyl moiety was observed. The structure of 11 was unambiguously confirmed by NMR spectroscopy. During the optimization, we modified a protocol mentioned in a patent[18] for a related transformation and used DMF instead of *N*-methylpyrrolidone and applied a lower temperature than that reported. We also tried to prepare **10** and **11** directly from **6 a** and **6 c** by a one-pot protocol (Suzuki coupling and subsequent base mediated cyclization). In this case, products **10** and **11** were isolated in 34% and 65% overall yields. Thus, the stepwise procedure is better in terms of the yield.



Scheme 3. Synthesis of cyclized products **10** and **11**. *Conditions*: *i*, **7 k** or **9 j** (1.0 equiv.), K_2CO_3 (2.0 equiv.), DMF, 150 °C, 4 h.

In a similar manner, we planned to perform a synthesis of lactone **12**. Unfortunately, we did not achieve to prepare the required *o*-carboxyphenyl derivative of any of the three substrates as an inseparable mixture of starting material, product and side-products was obtained in all cases. However, the harsh conditions used for the arylation of 2,4-bromoestrone, applied for 4-bromoestrone, resulted in a direct one-pot formation of the desired lactone in good yield (Scheme 4). The structure of **12** was independently confirmed by X-ray crystal structure analysis (Figure 8).



Scheme 4. Synthesis of lactone **12**. Conditions: *i*, **6 a** (1.0 equiv.), *ortho*-ethoxycarbonylphenylboronic acid (3 equiv.), $Pd(PPh_3)_4$ (5 mol%), RuPhos (5 mol%), K_2CO_3 (4.0 equiv.), toluene, 110 °C, 72 h.

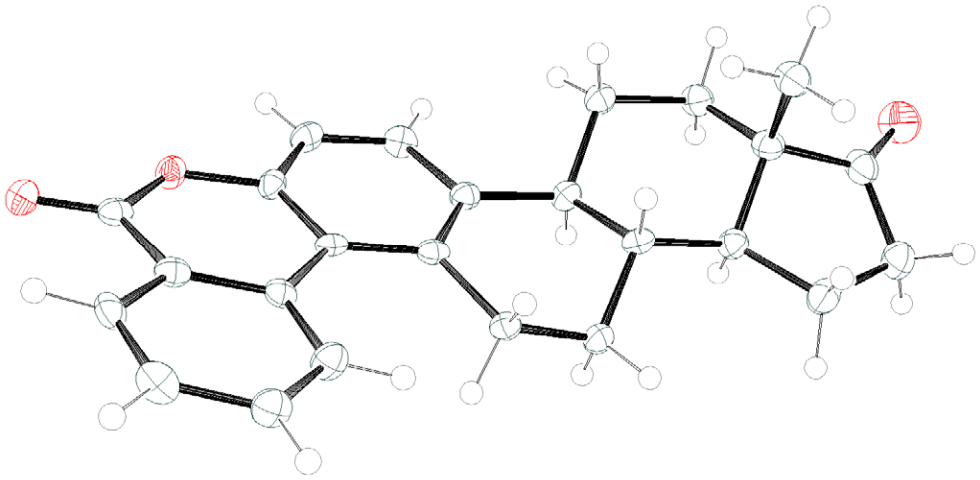


Figure 8. Molecular structure of **12** (Ortep plot showing thermal ellipsoids at the 50% probability level).

Lipase Inhibition Studies and SAR:

Different derivatives of 4-arylestrones, 2-arylestrones and 2,4-diarylestrones were synthesized and tested for their inhibitory potential against lipase. Initial screening was performed at the final concentration of 100 µM. Most of the derivatives were found as potent inhibitors of lipase. It was observed that 4-arylestrones exhibited a higher inhibition of lipase as compared to 2-arylestrones and 2,4-diarylestrones derivatives. Among the 4-arylestrone derivatives, compound **7 e** were found as the most potent inhibitor having the inhibitory value of IC_{50}±SEM = 0.82±0.01 µM. The inhibitory potential of **7 e** (4-arylestrone) was higher than **8 e** (the corresponding 2-arylestrone derivative) and **9 e** (the corresponding 2,4-diarylestrone derivative) having the same substituent located at the benzene ring. Table 5 shows, that substitution of the phenyl ring has substantial effects on the activity. Especially the introduction of fluorine containing groups (particularly compounds **7 e** and **7 g**) improved the activity. Interestingly, compound **7 c** (IC_{50}±SEM = 1.78±0.05 µM) with donating *t*Bu-group exhibited good inhibitory activity, too. Except compound **7 h** (IC_{50}±SEM = 59.7±3.12 µM) and **7 i** (IC_{50}±SEM = 13.6±0.99 µM), the inhibitory activities (IC_{50}±SEM) were in the range of 0.82±0.01 to 6.42±0.44 µM. Similarly in case of 2-arylestrones and 2,4-diarylestrones inhibitory activity was substantially effected by the substitution pattern. 2-Arylestrones were less active compared to their regioisomers 7, except 2-tolylestrone **8 b** which showed good activity (IC_{50}±SEM = 1.21±0.02µM). Regarding diarylestrones, compound **9 o** showed very high activity (IC_{50}±SEM = 0.82±0.02µM), containing again a fluorine substituent in *para*-position of the arylrings. Remarkably, benzofuran derivative **11** performed very well in the studies (IC_{50}±SEM = 0.93±0.04µM), while **9 j** with the same substituent in position 2 showed very low activity.

Table 5. Porcine Pancreatic lipase inhibition in the presence of the synthesized compounds.

Compound	Antilipase acivity	Compound	Antilipase acivity	Compound	Antilipase acivity
		IC_{50} (µM)±SEM/% inhibition			
7a	1.54±0.11	**8c**	5.66±0.76	**9i**	41%
7b	38%	**8d**	12.3±0.78	**9j**	43%
7c	1.78±0.05	**8e**	16.3±1.09	**9k**	24.1±1.21
7d	42%	**8f**	2.54±0.11	**9l**	1.75±0.07
7e	0.82±0.01	**8g**	16.3±1.11	**9m**	37%
7f	6.42±0.44	**8h**	16.4±1.23	**9o**	0.82±0.02
7g	1.34±0.11	**9a**	25.6±1.67	**10**	32%
7h	59.7±3.12	**9b**	39%	**11**	0.93±0.04
7i	13.6±0.99	**9c**	8.29±0.66	**12**	1.36±0.02
7j	45%	**9d**	5.28±0.66	**Orlistat**	0.31±0.02
7l	43%	**9e**	42%		
8a	39%	**9f**	1.21±0.03		
8b	1.21±0.02	**9g**	7.19±0.32		

The experiment was carried out in triplicate at final conc. of 100 µM and IC_{50} values are expressed as mean ± SEM . IC_{50} is the concentration at which 50% of the enzyme activity is inhibited.

Conclusion

In the present study, we have developed conditions for the arylation of bromoestrones by Suzuki-Miyaura reactions. This method allows the preparation of 2-aryl-, 4-aryl- and 2,4-diaryl-estrones in good to excellent yields. Further transformations gave access to hybrids of dibenzofuran and benzocoumarin. Their biological activity studies showed that the synthesized compounds inhibited porcine pancreas lipase enzyme in up to sub-micromolar concentrations. 4-Arylestrone **7 e** and 2,4-diarylestrone **9 o** showed the highest inhibitory activity with an IC_{50}=0.82±0.01 µM, followed by bezofuran-derivative **11** with IC_{50}±SEM = 0.93±0.04µM.

Experimental section

Chemistry

If not otherwise stated NMR data were recorded at room temperature on a **Bruker AVANCE 250 MHz, 300 MHz or 500 MHz.** Chemical shifts in ppm of ^{1}H and ^{13}C NMR spectra were referenced to residual protons of deuterated solvents $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm) or DMSO-*d*6 (^{1}H, 2,50 ppm; ^{13}C, 39.52 ppm). Peak characterization: s = singlet, brs = broad singlet, d = doublet, t = triplet, m = multiplet,

dd = doublet of doublets. Infrared spectra were recorded on a Nicolet 550 FT - IR spectrometer with ATR sampling technique. Gas-chromatography-mass-analysis was carried out on an Agilent HP-5890 instrument with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column using helium carrier gas. ESI HRMS measurements were performed on an Agilent 1969A TOF mass spectrometer. For High Resolution MS (HRMS) Finnigan MAT 95 XP was used. X-Ray single crystal structure analysis was performed on a Bruker**-Nonius** Apex X8 CCD-diffractometer. Data of X-Ray crystal structure analyses were deposited at the CCDC.[19] Melting points were determined on a Micro-Hot-Stage GalenTM III Cambridge Instruments. The melting points are not corrected.

4-Phenyl-3-hydroxyestra-1,3,5(10)-trien-17-one (7 a):[16] 4-Bromoestrone (**6 a**) (100 mg, 0.286 mmol), boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (17.0 mg, 0.05 equiv.), K_3PO_4 (121.5 mg, 2.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred at 101 °C overnight. The solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc = 1:5). **7 a** was isolated as a light yellow solid (87 mg, 88%), mp = 89 – 90 °C, $[\alpha]_D$ = +86.4° (c 1.00, $CHCl_3$) (lit. $[\alpha]_D$ = +83.1° (c 1.77, EtOH)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.31 – 1.39 (m, 1H, aliphatic), 1.45 – 1.65 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.26 – 2.33 (m, 1H, aliphatic), 2.42 – 2.58 (m, 4H, aliphatic), 4.62 (br.s, 1H, OH), 6.86 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, CH_{Ar}), 7.24 – 7.30 (m, 3H, CH_{Ar} + $CDCl_3$), 7.40 – 7.45 (m, 1H, CH_{Ar}), 7.48 – 7.455 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.5 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 112.6 (CH), 125.9 (CH), 127.5 (C), 128.2 (CH), 129.5 (2CH), 130.1 (CH), 130.5 (CH), 132.0 (C), 135.41 (C), 135.45 (C), 150.9 (C), 2.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3363 (w), 2924 (m), 1733 (s), 1587 (w), 1472 (m), 1166 (m), 762 (m), 701 (s). MS (EI, 70 eV): m/z (%) = 346 (100) [M^+], 347 (27), 261 (28), 248 (14), 235 (10), 222 (28), 221 (12), 207 (10), 202 (14), 189 (10), 181 (14), 178 (10), 165 (15), 55 (11), 41 (15). HRMS (EI, 70 eV): calcd. for $C_{24}H_{26}O_2$ [M^+] 346.19273; found 346.19267.

4-(*p*-Tolyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 b): light yellow solid (102 mg, 99%), mp = 104 – 105 °C, $[\alpha]_D$ = +78.4° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.28 – 1.39 (m, 1H, aliphatic), 1.49 – 1.63 (m, 5H, aliphatic), 1.86 – 2.18 (m, 4H, aliphatic), 2.26 – 2.34 (m, 1H, aliphatic), 2.49 (s, 3H, CH_3), 2.49 – 2.53 (m, 4H, aliphatic), 4.68 (br.s, 1H, OH), 6.84 (d, $^3J_{H\text{-}H}$ = 8.54 Hz, 1H, CH_{Ar}), 7.13-7.19 (m, 2H, CH_{Ar}), 7.23 – 7.26 – (m, 1H, CH_{Ar} + $CDCl_3$), 7.30 – 7.34 (m, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.3 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.5 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.5 (CH_{Ar}), 125.8 (CH_{Ar}), 127.4 (C_{Ar}), 129.9 (CH_{Ar}), 130.23 (CH_{Ar}), 130.26 (CH_{Ar}), 130.3 (CH_{Ar}), 131.9 (C_{Ar}), 132.1 (C_{Ar}), 135.5 (C_{Ar}), 137.9 (C_{Ar}), 151.0 (C_{Ar}), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3370 (w), 2923 (m), 2861 (w), 1734 (s), 1588 (w), 1473 (s), 1258 (m), 1165 (m), 1054 (m), 1008 (m), 816 (s). MS (EI, 70 eV): m/z (%) = 360

(100) [M^+], 361 (27), 275 (30), 262 (12), 236 (22), 195 (13). HRMS (EI, 70 eV): calcd. for $C_{25}H_{28}O_2$ [M^+] 360.20838; found 360.20841.

4-(*p*-*tert*-Butylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 c): light yellow solid (104 mg, 90%), mp = 150 – 151 °C, $[\alpha]_D$ = +71.5° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.32 – 1.38 (m, 1H, aliphatic), 1.38 (s, 9H, $C(CH_3)_3$), 1.49 – 1.61 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.27 – 2.33 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 4.67 (br.s, 1H, OH), 6.86 (d, $^3J_{H-H}$ = 8.5 Hz, 1H, CH_{Ar}), 7.18 – 7.26 (m, 3H, CH_{Ar} + $CDCl_3$), 7.50 – 7.53 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.4 ($C(CH_3)_3$), 31.6 (CH_2), 34.7 ($C(CH_3)_3$), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 112.5 (CH_{Ar}), 125.7 (CH_{Ar}), 126.42 (CH_{Ar}), 126.47 (CH_{Ar}), 127.4 (C_{Ar}), 129.6 (CH_{Ar}), 130.1 (CH_{Ar}), 131.9 (C_{Ar}), 132.1 (C_{Ar}), 135.7 (C_{Ar}), 151.05 (C_{Ar}), 151.10 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (w), 2954 (m), 1718 (s), 1585 (w), 1288 (s), 1201 (m), 1056 (m), 819 (s). MS (EI, 70 eV): m/z (%) = 402 (100) [M^+], 403 (31), 387 (26), 317 (15), 278 (10), 57 (20), 55 (10), 41 (17). HRMS (EI, 70 eV): calcd. for $C_{28}H_{34}O_2$ [M^+] 402.25533; found 402.25473.

4-(*p*-Methoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 d): yellow solid (107 mg, 99%), mp = 97 – 98 °C, $[\alpha]_D$ = +60.0° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.31 – 1.39 (m, 1H, aliphatic), 1.49 – 1.62 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.25 – 2.32 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 3.87 (s, 3H, OCH_3), 4.69 (br.s, 1H, OH), 6.85 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, CH_{Ar}), 7.01 – 7.06 (m, 2H, CH_{Ar}), 7.16 – 7.26 (m, 3H, CH_{Ar} + $CDCl_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 28.5 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 55.3 (OCH_3), 112.4 (CH_{Ar}), 114.9 (CH_{Ar}), 115.0 (CH_{Ar}), 125.8 (CH_{Ar}), 127.1 ($2C_{Ar}$), 131.2 (CH_{Ar}), 131.6 (CH_{Ar}), 131.9 (C_{Ar}), 135.8 (C_{Ar}), 151.2 (C_{Ar}), 159.4 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3391 (w), 2924 (m), 1733 (s), 1512 (s), 1472 (s), 1282 (m), 1242 (s), 1174 (s), 1031 (s), 830 (s), 809 (s). MS (EI, 70 eV): m/z (%) = 376 (100) [M^+], 377 (27), 291 (17), 252 (18). HRMS (EI, 70 eV): calcd. for $C_{25}H_{28}O_3$ [M^+] 376.20330; found 376.20304.

4-(*p*-Trifluoromethylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 e): light brown solid (108 mg, 91%), mp = 104 – 105 °C, $[\alpha]_D$ = +85.3° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.33 – 1.40 (m, 1H, aliphatic), 1.53 – 1.59 (m, 5H, aliphatic), 1.89 – 2.16 (m, 4H, aliphatic), 2.26 – 2.37 (m, 1H, aliphatic), 2.44 – 2.54 (m, 4H, aliphatic), 4.59 (br.s, 1H, OH), 6.84 (d, $^3J_{H-H}$ = 8.5 Hz, 1H, CH_{Ar}), 7.26 – 7.29 (m, 1H, CH_{Ar} + $CDCl_3$), 7.39 – 7.44 (m, 2H, CH_{Ar}), 7.75 – 7.78 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.4 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 113.1 (CH_{Ar}), 124.1 (q, $^1J_{C-F}$ = 271.7 Hz, CF_3), 126.2 (m, ^3J not given, $2CH_{Ar}$), 126.40 (C_{Ar}), 126.44 (CH_{Ar}), 130.2 (q, $^2J_{C-F}$ = 32.5 Hz, C_{Ar}-CF_3), 130.6 (CH_{Ar}), 130.9 (CH_{Ar}), 132.4 (C_{Ar}), 135.3 (C_{Ar}), 140.0 (C_{Ar}, 150.6 (C_{Ar}), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 62.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3318 (w), 2926 (m), 1716 (m), 1616 (w) 1321

(s), 1159 (s), 1117 (s), 1065 (s), 835 (m). MS (EI, 70 eV): m/z (%) = 414 (100) [M^+], 415 (27), 357 (12), 330 (12), 329 (25), 316 (18), 304 (12), 303 (13), 301 (10), 291 (10), 290 (27), 289 (10), 55 (12), 41 (14). HRMS (EI, 70 eV): calcd. for $C_{25}H_{25}O_2F_3$ [M^+] 414.18012; found 414.17903.

4-(*p*-Trifluoromethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 f): light yellow solid (118 mg, 96%), mp = 94 – 95 °C, $[\alpha]_D$ = +83.3° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.33 – 1.39 (m, 1H, aliphatic), 1.49 – 1.63 (m, 5H, aliphatic), 1.88 – 2.16 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.42 – 2.54 (m, 4H, aliphatic), 4.57 (br.s, 1H, OH), 6.85 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, CH_{Ar}), 7.25 – 7.38 (m, 5H, CH_{Ar} + $CDCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.9 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.9 (CH_{Ar}), 120.5 (q, $^1J_{C\text{-}F}$ = 257.1 Hz, CF_3), 121.8 (2CH_{Ar}), 126.2 (C_{Ar}), 126.3 (CH_{Ar}), 131.7 (CH_{Ar}), 132.0 (CH_{Ar}), 132.3 (C_{Ar}), 134.4 (C_{Ar}), 135.5 (C_{Ar}), 149.0 (q, $^3J_{C\text{-}F}$ = 1.9 Hz, C_{Ar}-OCF_3), 150.8 (C_{Ar}), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 57.7 (CF_3). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3350 (w), 2928 (w), 1723 (m), 1587 (w), 1475 (m), 1251 (s), 1154 (s), 1009 (m), 812 (m). MS (EI, 70 eV): m/z (%) = 430 (100) [M^+], 431 (26), 346 (12), 345 (30), 332 (15), 320 (10), 319 (11), 306 (23), 69 (15), 55 (10), 41 (11). HRMS (EI, 70 eV): calcd. for $C_{25}H_{25}O_3F_3$ [M^+] 430.17503; found 430.17490.

4-(*m*-Fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 g): light yellow solid (96 mg, 92%), mp = 98 – 99 °C, $[\alpha]_D$ = +112.5° (c 1.00, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 and 0.93 (s, 3H, CH_3), 1.33 – 1.40 (m, 1H, aliphatic), 1.45 – 1.64 (m, 5H, aliphatic), 1.88 – 2.16 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.41 – 2.54 (m, 4H, aliphatic), 4.63 (br.s, 1H, OH), 6.85 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, CH_{Ar}), 6.97 – 7.16 (m, 3H, CH_{Ar}), 7.18 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, CH_{Ar}), 7.43 – 7.53 (m, 1H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.13 and 26.15 (CH_2), 26.5 (CH_2), 28.4 and 28.5 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.78 and 37.80 (CH), 44.28 and 44.34 (CH), 48.0 (C), 50.4 (CH), 112.9 (CH_{Ar}), 115.0 and 115.3 (CH_{Ar}), 117.24 (d, $^2J_{C\text{-}F}$ = 26.6 Hz) and 117.52 (d, $^2J_{C\text{-}F}$ = 26.6 Hz) (CH_{Ar}), 125.90 (d, $^2J_{C\text{-}F}$ = 30.4 Hz) and 125.94 (d, $^2J_{C\text{-}F}$ = 30.6 Hz) (CH_{Ar}), 126.25 and 126.29 (CH_{Ar}), 126.41 (C_{Ar}), 131.03 (d, $^3J_{C\text{-}F}$ = 8.5 Hz) and 131.05 (d, $^3J_{C\text{-}F}$ = 8.7 Hz) (CH_{Ar}), 132.17 (C_{Ar}), 135.30 and 135.33 (C_{Ar}), 137.95 (d, $^3J_{C\text{-}F}$ = 7.4 Hz) and 137.97 (d, $^3J_{C\text{-}F}$ = 7.5 Hz) (C_{Ar}), 150.7 (C_{Ar}), 163.33 (d, $^1J_{C\text{-}F}$ = 248.3 Hz) and 163.40 (d, $^1J_{C\text{-}F}$ = 248.1 Hz) (C_{Ar}-F), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.45 and -111.53 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3340 (w), 2925 (m), 1723 (s), 1580 (s), 1472 (s), 1261 (m), 1152 (m), 1055 (m), 785 (s). MS (EI, 70 eV): m/z (%) = 364 (100) [M^+], 365 (27), 307 (10), 280 (10), 279 (27), 266 (16), 253 (11), 240 (26), 239 (11), 220 (14), 199 (11), 183 (12), 55 (10), 41 (14). HRMS (EI, 70 eV): calcd. for $C_{24}H_{25}O_2F$ [M^+] 364.18331; found 364.18327.

4-(3,5-Dimethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 h): light yellow solid (102 mg, 88%), mp = 95 – 96 °C, $[\alpha]_D$ = +90.9° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.33 – 1.40 (m, 1H, aliphatic), 1.49 – 1.65 (m, 5H, aliphatic), 1.88 – 2.16 (m, 4H, aliphatic), 2.25 – 2.34 (m, 1H, aliphatic), 2.41 – 2.60 (m, 4H, aliphatic), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.78 (br.s,

1H, OH), 6.40 – 6.43 (m, 2H, CH_{Ar}), 6.50 – 6.52 (m, 1H, CH_{Ar}), 6.85 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, CH_{Ar}), 7.23 – 7.26 (m, 1H, CH_{Ar} + $CDCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 55.4 ($2OCH_3$), 100.3 (CH_{Ar}), 107.5 (CH_{Ar}), 108.0 (CH_{Ar}), 112.6 (CH_{Ar}), 126.0 (CH_{Ar}), 127.5 (C_{Ar}), 131.9 (C_{Ar}), 135.2 (C_{Ar}), 137.3 (C_{Ar}), 150.7 (C_{Ar}), 161.7 (C_{Ar}), 161.8 (C_{Ar}), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3400 (w), 2927 (w), 1733 (m), 1587 (s), 1452 (m), 1343 (m), 1202 (s), 1150 (s), 1060 (m), 817 (m). MS (EI, 70 eV): m/z (%) = 406 (100) [M^+], 407 (27), 321 (17), 282 (12), 281 (10), 55 (11), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{26}H_{30}O_4$ [M^+] 406.21386; found 406.21368.

4-(*p*-Ethylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 i): yellow solid (106 mg, 99%), mp = 110 – 111 °C, $[\alpha]_D$ = +78.5° (c 1.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.31 (t, $^3J_{H-H}$ = 7.6 Hz, 3H, CH_2CH_3), 1.28 – 1.35 (m, 1H, aliphatic), 1.49 – 1.61 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.26 – 2.34 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 2.73 (q, $^3J_{H-H}$ = 7.6 Hz, 2H, CH_2CH_3), 4.59 (br.s, 1H, OH), 6.85 (d, $^3J_{H-H}$ = 8.5 Hz, 1H, CH_{Ar}), 7.16 – 7.21 (m, 2H, CH_{Ar}), 7.23 – 7.26 (m, 1H, CH_{Ar} + $CDCl_3$), 7.32 – 7.36 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 15.4 (CH_2CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.5 (CH_2), 28.6 (CH_2CH_3), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.5 (CH_{Ar}), 125.7 (CH_{Ar}), 127.5 (C_{Ar}), 129.0 (CH_{Ar}), 129.03 (CH_{Ar}), 129.9 (CH_{Ar}), 130.4 (CH_{Ar}), 131.9 (C_{Ar}), 132.4 (C_{Ar}), 135.6 (C_{Ar}), 144.2 (C_{Ar}), 151.0 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3369 (w), 2926 (m), 1734 (s), 1587 (m), 1472 (s), 1259 (s), 1165 (m), 830 (s). MS (EI, 70 eV): m/z (%) = 374 (100) [M^+], 375 (30), 289 (22), 276 (11), 250 (20). HRMS (EI, 70 eV): calcd. for $C_{26}H_{30}O_2$ [M^+] 374.22403; found 374.22323.

4-(*p*-Chlorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 j): light yellow solid (95 mg, 87%), mp = 109 – 110 °C, $[\alpha]_D$ = +71.8° (c 1.01, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.31 – 1.39 (m, 1H, aliphatic), 1.49 – 1.61 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.25 – 2.31 (m, 1H, aliphatic), 2.41 – 2.54 (m, 4H, aliphatic), 4.57 (br.s, 1H, OH), 6.84 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, CH_{Ar}), 7.18 – 7.27 (m, 3H, CH_{Ar} + $CDCl_3$), 7.46 – 7.51 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.8 (CH_{Ar}), 126.2 (CH_{Ar}), 126.4 (C_{Ar}), 129.7 ($2CH_{Ar}$), 131.5 (CH_{Ar}), 131.9 (CH_{Ar}), 132.2 (C_{Ar}), 134.1 (C_{Ar}), 134.2 (C_{Ar}), 135.4 (C_{Ar}), 150.8 (C_{Ar}), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3344 (w), 2926 (m), 1723 (s), 1586 (m), 1473 (s), 1285 (m), 1166 (m), 1088 (s), 1014 (m), 820 (s). MS (EI, 70 eV): m/z (%) = 380 (100) [M^+], 382 (37), 381 (26), 297 (11), 296 (10), 295 (28), 282 (18), 270 (10), 269 (12), 256 (26), 215 (13), 202 (13), 189 (11), 178 (10), 165 (11), 67 (10), 55 (16), 41 (17), 39 (10), 29 (10). HRMS (EI, 70 eV): calcd. for $C_{24}H_{25}O_2Cl$ [M^+] 380.15376; found 380.15281; calcd. for $C_{24}H_{25}O_2{}^{37}Cl$ [M^+] 382.15081; found 382.15141.

4-(*o*-Fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 k): brown solid (98 mg, 94%), mp = 95 – 96 °C, $[\alpha]_D$ = +82.1° (c 1.44, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ =

0.92 and 0.93 (2s, 3H, CH_3), 1.33 – 1.42 (m, 1H, aliphatic), 1.50 – 1.66 (m, 5H, aliphatic), 1.88 – 2.28 (m, 4H, aliphatic), 2.25 – 2.35 (m, 1H, aliphatic), 2.40 – 2.63 (m, 4H, aliphatic), 4.60 (br.s, 1H, OH), 6.85 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, CH_{Ar}), 7.19 – 7.29 (m, 4H, CH_{Ar} + $CDCl_3$), 7.40 – 7.47 (m, 1H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 and 13.9 (CH_3), 21.6 (CH_2), 26.0 and 26.1 (CH_2), 26.5 (CH_2), 27.62 and 28.2 (CH_2), 31.64 and 31.66 (CH_2), 35.9 (CH_2), 37.73 and 37.83 (CH), 44.21 and 44.35 (CH), 48.00 and 48.03 (C), 50.44 and 50.48 (CH), 112.85 and 112.87 (CH_{Ar}), 116.48 (d, $^2J_{C\text{-}F}$ = 22.2) and 116.57 (d, $^2J_{C\text{-}F}$ = 22.3) (CH_{Ar}), 121.24 and 121.31 (C_{Ar}), 122.95 (d, $^2J_{C\text{-}F}$ = 17.8 Hz) and 122.98 (d, $^2J_{C\text{-}F}$ = 17.6 Hz) (C_{Ar}), 124.95 – 125.02 (several signals, CH_{Ar}, C_{Ar}), 126.6 (CH_{Ar}), 130.39 (d, $^3J_{C\text{-}F}$ = 8.0 Hz) and 130.41 (d, $^3J_{C\text{-}F}$ = 8.1 Hz) (CH_{Ar}), 132.1 – 132.4 (several signals, CH_{Ar}), 136.21 and 136.37 (C_{Ar}), 151.06 and 151.16 (C_{Ar}), 160.1 (d, $^1J_{C\text{-}F}$ = 246.6 Hz) and 160.4 (2d, $^1J_{C\text{-}F}$ = 246.9 Hz) (C_{Ar}-F), 220.97 and 221.01 (C=O). ^{19}F NMR (75 MHz, $CDCl_3$): δ = -112.8 and -112.5 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3342 (w), 2925 (m), 1721 (s), 1588 (w), 1451 (m), 1214 (m), 1056 (m), 755 (s). MS (EI, 70 eV): m/z (%) = 364 (100) [M^+], 365 (29), 280 (11), 279 (30), 266 (16), 254 (10), 253 (14), 240 (32), 239 (14), 55 (10), 41 (11). HRMS (EI, 70 eV): calcd. for $C_{24}H_{25}O_2F$ [M^+] 364.18331; found 364.18433.

4-(2,3,4-Trimethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 l): light yellow solid (84 mg, 67%), mp = 121 – 122 °C, $[\alpha]_D$ = +82.5° (c 1.00, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 and 0.89 (2s, 3H, CH_3), 1.39 – 1.69 (m, 6H, aliphatic), 1.81 – 1.99 (m, 3H, aliphatic), 2.05 – 2.13 (m, 1H, aliphatic), 2.24 – 2.29 (m, 1H, aliphatic), 2.34 – 2.52 (m, 4H, aliphatic), 3.58 and 3.60 (2s, 3H, OCH_3), 3.81 and 3.82 (2s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.68 – 6.76 (m, 2H, CH_{Ar}), 6.83 – 6.88 (m, 1H, CH_{Ar}), 7.14 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, CH_{Ar}), 8.800 and 8.803 (2s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 and 13.9 (CH_3), 21.5 (CH_2), 25.9 and 26.1 (CH_2), 26.5 and 26.6 (CH_2), 27.5 and 28.4 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 and 37.9 (CH), 44.3 (CH), 48.0 (C), 50.45 and 50.53 (CH), 56.0 (OCH_3), 61.1 (OCH_3), 61.2 (OCH_3), 108.1 and 108.2 (CH_{Ar}), 112.3 and 112.6 (CH_{Ar}), 121.25 and 121.33 (C_{Ar}), 123.8 and 123.9 (C_{Ar}), 125.6 and 125.9 (CH_{Ar}), 125.90 and 125.93 (CH_{Ar}), 131.9 and 132.1 (C_{Ar}), 136.3 and 136.6 (C_{Ar}), 142.9 and 143.1 (C_{Ar}), 151.1 and 151.2 (C_{Ar}), 152.0 (C_{Ar}), 154.0 (C_{Ar}), C=O not given. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3415 (w), 2923 (m), 1725 (s), 1588 (w), 1461 (s), 1408 (m), 1271 (s), 1093 (s), 1008 (s), 795 (m). MS (EI, 70 eV): m/z (%) = 436 (100) [M^+], 437 (27). HRMS (EI, 70 eV): calcd. for $C_{27}H_{32}O_5$[M^+] 436.22443; found 436.22402.

4-(*o*-Ethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (7 m): light yellow solid (88 mg, 79%), mp = 144 – 145 °C, $[\alpha]_D$ = +77.7° (c 2.31, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 and 0.93 (2s, 3H, CH_3), 1.26 and 1.27 (2t, $^3J_{H\text{-}H}$ = 7.0 Hz, 3H, $2CH_2CH_3$), 1.32 – 1.40 (m, 1H, aliphatic), 1.47 – 1.61 (m, 5H, aliphatic), 1.86 – 2.16 (m, 4H, aliphatic), 2.25 – 2.37 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 4.05 (q, $^3J_{H\text{-}H}$ = 7.0 Hz, 3H, $2CH_2CH_3$), 4.67 and 4.72 (2br.s, 1H, OH), 6.84 and 6.85 (2d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, CH_{Ar}), 7.00 – 7.09 (m, 2H, CH_{Ar}), 7.14 – 7.18 (m, 1H, CH_{Ar}), 7.22 – 7.26 (m, 1H, CH_{Ar} + $CDCl_3$), 7.36 – 7.42 (m, 1H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.84 and 13.87 (CH_3), 14.6 and 14.7 (CH_3), 21.55 and 21.57 (CH_2), 25.9 and 26.1 (CH_2), 26.5 and 26.6

(CH_2), 27.2 and 28.3 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 37.8 and 37.9 (CH), 44.2 and 44.4 (CH), 47.99 and 48.01 (C), 50.5 and 50.6 (CH), 63.8 and 64.0 (CH_2CH_3), 112.3 and 112.6 (CH_{Ar}), 112.99 and 113.07 (CH_{Ar}), 121.3 and 121.4 (CH_{Ar}), 124.1 and 124.2 (C_{Ar}), 124.2 and 124.4 (C_{Ar}), 125.5 and 125.7 (CH_{Ar}), 129.78 and 129.83 (CH_{Ar}), 131.6 and 131.8 (C_{Ar}), 132.0 and 132.3 (CH_{Ar}), 136.0 and 136.3 (C_{Ar}), 150.9 and 151.1 (C_{Ar}), 156.3 and 156.9 (C_{Ar}), 220.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3397 (w), 2925 (w), 1733 (s), 1590 (w), 1447 (s), 1341 (m), 1228 (s), 1040 (s), 922 (m), 753 (s). MS (EI, 70 eV): m/z (%) = 390 (100) [M^+], 391 (28), 305 (17), 266 (12), 29 (25). HRMS (ESI, 70 eV): calcd. for $C_{26}H_{30}O_3$ [M^+] 390.21895; found 390.21851.

2-Phenyl-3-hydroxyestra-1,3,5(10)-trien-17-one (8 a):[11b] 2-Bromoestrone (**6 b**) (100 mg, 0.286 mmol), boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (17.0 mg, 0.05 equiv.), RuPhos (6.7 mg, 0.05 equiv.), K_2CO_3 (79.1 mg, 2.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred 16 h at 101°C. The solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc = 1:5). **8a** was isolated as a white solid (74 mg, 75%), mp = 197 – 198 °C (lit. 169 °C), $[\alpha]_D$ = +161.1° (c 1.00, $CHCl_3$) (lit. $[\alpha]_D$ = +112.0° (c 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.42 – 1.70 (m, 6H, aliphatic), 1.93 – 2.20 (m, 4H, aliphatic), 2.25 – 2.35 (m, 1H, aliphatic), 2.37 – 2.57 (m, 2H, aliphatic), 2.91 – 2.96 (m, 2H, aliphatic), 5.17 (br.s, 1H, OH), 6.75 (s, 1H, CH_{Ar}), 7.17 (s, 1H, CH_{Ar}), 7.34 – 7.41 (m, 1H, CH_{Ar}), 7.46 – 7.48 (m, 4H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.4 (CH), 44.0 (CH), 48.0 (C), 50.4 (CH), 115.7 (CH_{Ar}), 125.8 (C_{Ar}), 127.2 (CH_{Ar}), 127.6 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 129.2 ($2CH_{Ar}$), 132.2 (C_{Ar}), 137.4 (C_{Ar}), 137.7 (C_{Ar}), 150.4 (C_{Ar}), 221.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3329 (w), 2928 (m), 1723 (s), 1614 (w), 1409 (s), 1200 (m), 893 (m), 769 (s), 698 (s). MS (EI, 70 eV): m/z (%) = 346 (100) [M^+], 347 (23), 261 (25), 248 (13), 222 (23), 221 (11), 202 (13), 178 (11), 165 (12), 55 (10), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{24}H_{26}O_2$ [M^+] 346.19273; found 346.19267.

2-(*p*-Tolyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (8 b):[11b] white solid (77 mg, 75%), mp = 201 – 202 °C, $[\alpha]_D$ = +160.5° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.47 – 1.65 (m, 6H, aliphatic), 1.93 – 2.19 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.38 – 2.56 (m, 2H, aliphatic), 2.41 (s, 3H, CH_3), 2.91 – 2.95 (m, 2H, aliphatic), 5.26 (br.s, 1H, OH), 6.74 (s, 1H, CH_{Ar}), 7.16 (s, 1H, CH_{Ar}), 7.26 – 7.30 (m, 2H, CH_{Ar} + $CDCl_3$), 7.36 (d, $^3J_{H\text{-}H}$ = 7.9 Hz, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.2 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.6 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.4 (CH), 44.0 (C), 48.0 (CH), 50.4 (CH), 115.6 (CH_{Ar}), 125.8 (C_{Ar}), 127.2 (CH_{Ar}), 128.9 ($2CH_{Ar}$), 129.9 ($2CH_{Ar}$), 132.1 (C_{Ar}), 134.4 (C_{Ar}), 137.4 (C_{Ar}), 137.5 (C_{Ar}), 150.5 (C_{Ar}), 221.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3342 (w), 2925 (m), 1723 (s), 1491 (s), 1237 (s), 1051 (m), 822 (s). MS (EI, 70 eV): m/z (%) = 360 (100) [M^+], 361 (26), 275 (19), 236 (18). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{28}O_2$ [M^+] 360.20838; found 360.20759.

2-(*p*-*tert*-Butylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (8 c): white solid (94 mg, 82%), mp = 229 – 230 °C, $[\alpha]_D$ = +129.6° (c 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.37 (s, 9H, $C(CH_3)_3$), 1.47 – 1.66 (m, 6H, aliphatic), 1.92 – 2.19 (m, 4H, aliphatic), 2.24 – 2.34 (m, 1H, aliphatic), 2.34 – 2.57 (m, 2H, aliphatic), 2.90 – 2.95 (m, 2H, aliphatic), 5.17 (br.s, 1H, OH), 6.74 (s, 1H, CH_{Ar}), 7.17 (s, 1H, CH_{Ar}), 7.37 – 7.41 (m, 2H, CH_{Ar}), 7.48 – 7.52 (m, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.6 (CH_2), 29.3 (CH_2), 31.3 ($C(\mathit{C}H_3)_3$), 31.6 (CH_2), 34.6 ($\mathit{C}(CH_3)_3$), 35.9 (CH_2), 38.4 (CH), 44.0 (CH), 48.0 (C), 50.4 (CH), 115.6 (CH_{Ar}), 125.7 (C_{Ar}), 126.2 ($2CH_{Ar}$), 127.2 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 132.1 (C_{Ar}), 134.3 (C_{Ar}), 137.5 (C_{Ar}), 150.5 (C_{Ar}), 150.7 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3347 (w), 2920 (m), 1723 (s), 1613 (w), 1500 (m), 1395 (m), 1257 (m), 1193 (s), 896 (m), 828 (s), 752 (s). MS (EI, 70 eV): m/z (%) = 402 (100) [M^+], 403 (32), 388 (26), 287 (86), 57 (14), 41 (14). HRMS (ESI, 70 eV): calcd. for $C_{28}H_{34}O_2$ [M^+] 402.25533; found 402.25513.

2-(*p*-Methoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (8 d): light yellow solid (86 mg, 80%), mp = 183 – 184 °C, $[\alpha]_D$ = +137.0° (c 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.47 – 1.64 (m, 6H, aliphatic), 1.92 – 2.19 (m, 4H, aliphatic), 2.22 – 2.32 (m, 1H, aliphatic), 2.37 – 2.57 (m, 2H, aliphatic), 2.89 – 2.94 (m, 2H, aliphatic), 3.85 (s, 3H, OCH_3), 5.15 (br.s, 1H, OH), 6.73 (s, 1H, CH_{Ar}), 6.97 – 7.03 (m, 2H, CH_{Ar}), 7.14 (s, 1H, CH_{Ar}), 7.35 – 7.41 (m, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.4 (CH), 44.0 (CH), 48.0 (C), 50.4 (CH), 55.4 (OCH_3), 114.6 ($2CH_{Ar}$), 115.6 (CH_{Ar}), 125.5 (C_{Ar}), 127.2 (CH_{Ar}), 129.5 (C_{Ar}), 130.2 ($2CH_{Ar}$), 132.1 (C_{Ar}), 137.3 (C_{Ar}), 150.5 (C_{Ar}), 159.2 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3350 (w), 2925 (m), 1720 (s), 1609 (m), 1501 (s), 1242 (s), 1177 (s), 1033 (s), 828 (s). MS (EI, 70 eV): m/z (%) = 376 (100) [M^+], 377 (28), 291 (11), 252 (11). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{28}O_3$ [M^+] 376.20330; found 376.20276.

2-(*p*-Trifluoromethylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (8 e): white solid (85 mg, 72%), mp = 250 – 251 °C, $[\alpha]_D$ = +123.6° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.48 – 1.65 (m, 6H, aliphatic), 1.94 – 2.19 (m, 4H, aliphatic), 2.27 – 2.34 (m, 1H, aliphatic), 2.39 – 2.57 (m, 2H, aliphatic), 2.91 – 2.94 (m, 2H, aliphatic), 5.18 (br.s, 1H, OH), 6.73 (s, 1H, CH_{Ar}), 7.18 (s, 1H, CH_{Ar}), 7.62 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, CH_{Ar}), 7.70 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.3 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 116.2 (CH_{Ar}), 124.6 (C_{Ar}), 124.2 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, CF_3), 125.7 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, $2CH_{Ar}$), 127.4 (CH_{Ar}), 129.41 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C_{Ar}-CF_3), 129.48 ($2CH_{Ar}$), 132.7 (C_{Ar}), 138.5 (C_{Ar}), 141.6 (C_{Ar}), 150.4 (C_{Ar}), 221.2 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.5 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3365 (w), 2937 (w), 1722 (s), 1612 (m), 1324 (s), 1109 (s), 1067 (s), 1013 (m), 840 (s). MS (EI, 70 eV): m/z (%) = 414 (100) [M^+], 415 (28), 357 (12), 330 (10), 329 (23), 316 (17), 304 (11), 303 (14), 301 (12), 290 (22), 289 (12), 55 (12), 41 (13). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{25}O_2F_3$ [M^+] 414.18012; found 414.17980.

2-(*p*-Trifluoromethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (8 f): white solid (95 mg, 77%), mp = 109 – 110 °C, $[\alpha]_D$ = +122.2° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.47 – 1.64 (m, 6H, aliphatic), 1.93 – 2.19 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.38 – 2.56 (m, 2H, aliphatic), 2.90 – 2.94 (m, 2H, aliphatic), 5.06 (br.s, 1H, OH), 6.72 (s, 1H, CH_{Ar}), 7.15 (s, 1H, CH_{Ar}), 7.30 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, CH_{Ar}), 7.48 – 7.53 (m, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.3 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 116.0 (CH_{Ar}), 120.5 (q, $^1J_{C\text{-}F}$ = 257.5 Hz, CF_3), 121.4 ($2CH_{Ar}$), 124.6 (C_{Ar}), 127.4 (CH_{Ar}), 130.6 ($2CH_{Ar}$), 132.5 (C_{Ar}), 136.4 (C_{Ar}), 138.1 (C_{Ar}), 148.5 (q, $^3J_{C\text{-}F}$ = 2.3 Hz, C_{Ar}-OCF_3), 150.3 (C_{Ar}), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -57.8 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3334 (w), 2924 (m), 1721 (s), 1615 (w), 1499 (m), 1249 (s), 1202 (s), 1155 (s). MS (EI, 70 eV): m/z (%) = 430 (100) [M^+], 431 (24), 346 (10), 345 (21), 332 (14), 319 (10), 306 (19), 69 (19), 55 (10). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{25}O_3F_3$ [M^+] 430.17503; found 430.17478.

2-(*m*-Fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (8 g): light yellow solid (82 mg, 79%), mp = 132 – 133 °C, $[\alpha]_D$ = +129.8° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.48 – 1.64 (m, 6H, aliphatic), 1.94 – 2.19 (m, 4H, aliphatic), 2.25 – 2.39 (m, 1H, aliphatic), 2.39 – 2.56 (m, 2H, aliphatic), 2.90 – 2.94 (m, 2H, aliphatic), 5.20 (br.s, 1H, OH), 6.73 (s, 1H, CH_{Ar}), 7.03 – 7.09 (m, 1H, CH_{Ar}), 7.16 – 7.27 (m, 3H, CH_{Ar} + $CDCl_3$), 7.38 – 7.46 (m, 1H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.3 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 114.4 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, CH_{Ar}), 116.0 (CH_{Ar}), 116.2 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, CH_{Ar}), 124.65 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, CH_{Ar}), 124.7 (d, $^4J_{C\text{-}F}$ = 2.0 Hz, C_{Ar}), 127.2 (CH_{Ar}), 130.5 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, CH_{Ar}), 132.4 (C_{Ar}), 138.2 (C_{Ar}), 139.9 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, C_{Ar}), 150.3 (C_{Ar}), 163.1 (d, $^1J_{C\text{-}F}$ = 247.0 Hz, C_{Ar}-F), 221.2 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.1 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3348 (w), 2921 (m), 1721 (s), 1612 (m), 1579 (m), 1402 (s), 1254 (s), 1012 (m), 874 (s), 782 (s). MS (EI, 70 eV): m/z (%) = 364 (100) [M^+], 365 (25), 279 (22), 266 (17), 253 (12), 251 (12), 240 (19), 239 (11), 220 (10), 55 (11), 41 (14). HRMS (ESI, 70 eV): calcd. for $C_{24}H_{25}O_2F$ [M^+] 364.18331; found 364.18303.

2-(3,5-Dimethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (8 h): light yellow solid (116 mg, 84%), mp = 115 – 116 °C, $[\alpha]_D$ = +161.6° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.47 – 1.64 (m, 6H, aliphatic), 1.93 – 2.18 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.37 – 2.56 (m, 2H, aliphatic), 2.90 – 2.94 (m, 2H, aliphatic), 3.82 (s, 6H, $2OCH_3$), 5.32 (br.s, 1H, OH), 6.48 (pt, $^4J_{H\text{-}H}$ = 2.3 Hz, 1H, CH_{Ar}), 6.57 (d, $^4J_{H\text{-}H}$ = 2.3 Hz, 2H, CH_{Ar}), 6.74 (s, 1H, CH_{Ar}), 7.17 (s, 1H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.3 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.4 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 55.4 ($2OCH_3$), 99.7 (CH_{Ar}), 106.9 ($2CH_{Ar}$), 115.6 (CH_{Ar}), 125.6 (C_{Ar}), 126.8 (CH_{Ar}), 132.1 (C_{Ar}), 137.9 (C_{Ar}), 139.3 (C_{Ar}), 150.3 (C_{Ar}), 161.5 ($2C_{Ar}$), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3369 (w), 2924 (m), 1720 (s), 1591 (s), 1453 (m), 1399 (s), 1341 (m), 1192 (s), 1149 (s), 1057 (s), 833 (s). MS (EI, 70 eV): m/z (%) = 406 (100) [M^+], 407 (28), 321 (11), 282 (10). HRMS (ESI, 70 eV): calcd. for $C_{26}H_{30}O_4$ [M^+] 406.21386; found 406.21387.

2,4-Diphenyl-3-hydroxyestra-1,3,5(10)-trien-17-one (9 a): 2,4-Dibromoestrone (**6 c**) (100 mg, 0.234 mmol), boronic acid (3 equiv.), $Pd(PPh_3)_4$ (13.5 mg, 0.05 equiv.), RuPhos (5.5 mg, 0.05 equiv.), K_2CO_3 (129.4 mg, 4.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred 40 h (or 72 h, see Table 4) at 101 °C. The solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc = 1:4). **9a** was isolated as a light yellow solid (98 mg, 99%), mp = 110 – 111 °C (lit.[8] 118 °C), $[\alpha]_D$ = +81.3° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.38 – 1.67 (m, 6H, aliphatic), 1.91 – 2.20 (m, 4H, aliphatic), 2.33 – 2.41 (m, 1H, aliphatic), 2.46 – 2.57 (m, 4H, aliphatic), 4.84 (s, 1H, OH), 7.31 – 7.37 (m, 4H, CH_{Ar}), 7.42 – 7.47 (m, 3H, CH_{Ar}), 7.50 – 7.60 (m, 4H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 125.8 (C_{Ar}), 127.0 (CH_{Ar}), 127.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.2 (C_{Ar}), 128.5 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 129.4 ($2CH_{Ar}$), 130.1 (CH_{Ar}), 130.4 (CH_{Ar}), 132.1 (C_{Ar}), 135.1 (C_{Ar}), 135.9 (C_{Ar}), 138.2 (C_{Ar}), 147.7 (C_{Ar}), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3530 (w), 2922 (m), 1734 (s), 1601 (w), 1461 (m), 1438 (m), 1410 (m), 1230 (m), 1145 (m), 755 (m), 699 (s) . MS (EI, 70 eV): m/z (%) = 422 (100) [M^+], 423 (40), 337 (14), 298 (13), 265 (13), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{30}H_{30}O_2$ [M^+] 422.22403; found 422.22350.

2,4-Di-(*p*-tolyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 b): light yellow solid (96 mg, 91%), mp = 134 – 135 °C, $[\alpha]_D$ = +72.2° (c 1.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.46 – 1.64 (m, 5H, aliphatic), 1.91 – 2.17 (m, 4H, aliphatic), 2.40 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.27 – 2.57 (m, 6H, aliphatic), 4.87 (s, 1H, OH), 7.19 – 7.34 (m, 7H, CH_{Ar} + $CDCl_3$), 7.47 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 125.6 (C_{Ar}), 126.8 (CH), 128.0 (C), 129.1 (2CH), 129.2 (2CH), 129.9 (CH), 130.09 (CH), 130.10 (CH), 130.2 (CH), 131.9 (C_{Ar}), 132.7 (C_{Ar}), 135.0 (C_{Ar}), 135.3 (C_{Ar}), 136.8 (C_{Ar}), 137.7 (C_{Ar}), 147.9 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3526 (w), 2921 (m), 2860 (m), 1737 (s), 1512 (m), 1454 (s), 1256 (m), 1232 (m), 1145 (m), 818 (s). MS (EI, 70 eV): m/z (%) = 450 (100) [M^+], 451 (38), 365 (9), 326 (9), 285 (8). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{34}O_2$ [M^+] 450.25533; found 450.25665.

2,4-Di-(*p*-*tert*-butylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 c): yellow solid (106 mg, 85%), mp = 141 – 142 °C, $[\alpha]_D$ = +66.1° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.36 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.50 – 1.64 (m, 6H, aliphatic), 1.95 – 2.16 (m, 4H, aliphatic), 2.33 – 2.39 (m, 1H, aliphatic), 2.45 – 2.54 (m, 4H, aliphatic), 4.91 (s, 1H, OH), 7.23 – 7.25 (m, 2H, CH_{Ar} + $CDCl_3$), 7.31 (s, 1H, CH_{Ar}), 7.43 – 7.53 (m, 6H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.4 ($2C(CH_3)_3$), 31.6 (CH_2), 34.5 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50,4 (CH), 114.7 (CH_{Ar}), 125.4 (CH_{Ar}), 125.5 (C_{Ar}), 126.25 (CH_{Ar}), 126.30 (CH_{Ar}), 126.35 (CH_{Ar}), 126.8 (CH_{Ar}), 128.0 (C_{Ar}), 128.9

(CH_{Ar}), 129.6 (CH_{Ar}), 130.0 (CH_{Ar}), 131.9 (C_{Ar}), 132.6 (C_{Ar}), 135.0 (C_{Ar}), 135.3 (C_{Ar}), 148.0 (C_{Ar}), 149.9 (C_{Ar}), 150.9 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3530 (w), 2953 (m), 1738 (s), 1610 (w), 1515 (w), 1456 (s), 1259 (s), 1149 (m), 1017 (m), 830 (s). MS (EI, 70 eV): m/z (%) = 534 (100) [M^+], 535 (43), 520 (15), 519 (38), 57 (31), 41 (11). HRMS (ESI, 70 eV): calcd. for $C_{38}H_{46}O_2$ [M^+] 534.34923; found 534.34874.

2,4-Di-(*p*-methoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 d): light yellow solid (112 mg, 99%), mp = 117 – 118 °C, $[\alpha]_D$ = +84.2° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.46 – 1.64 (m, 6H, aliphatic), 1.91 – 2.17 (m, 4H, aliphatic), 2.32 – 2.39 (m, 1H, aliphatic), 2.46 – 2.54 (m, 4H, aliphatic), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.87 (s, 1H, OH), 6.97 (d, $^3J_{H-H}$ = 8.7 Hz, 2H, CH_{Ar}), 7.05 (d, $^3J_{H-H}$ = 8.2 Hz, 2H, CH_{Ar}), 7.21 – 7.28 (m, 3H, CH_{Ar}), 7.51 (d, $^3J_{H-H}$ = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 55.29 (OCH_3), 55.30 (OCH_3), 113.9 ($2CH_{Ar}$), 114.8 (CH_{Ar}), 114.9 (CH_{Ar}), 125.3 (C_{Ar}), 126.7 (CH_{Ar}), 127.6 (C_{Ar}), 127.7 (C_{Ar}), 130.3 ($2CH_{Ar}$), 130.6 (C_{Ar}), 131.2 (CH_{Ar}), 131.6 (CH_{Ar}), 131.9 (C_{Ar}), 135.0 (C_{Ar}), 148.1 (C_{Ar}), 158.8 (C_{Ar}), 159.3 (C_{Ar}), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3521 (w), 2925 (m), 1734 (s), 1607 (m), 1510 (s), 1456 (s), 1241 (s), 1174 (s), 1031 (s), 829 (s). MS (EI, 70 eV): m/z (%) = 482 (100) [M^+], 483 (33), 397 (3), 358 (5), 317 (5). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{34}O_4$ [M^+] 482.24516; found 482.24510.

2,4-Di-(*p*-trifluoromethylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 e): yellow solid (116 mg, 89%), mp = 127 – 128 °C, $[\alpha]_D$ = +52.1° (c 1.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.37 – 1.64 (m, 6H, aliphatic), 1.97 – 2.17 (m, 4H, aliphatic), 2.36 – 2.48 (m, 5H, aliphatic), 4.73 (s, 1H, OH), 7.33 (s, 1H, CH_{Ar}), 7.45 – 7.49 (m, 2H, CH_{Ar}), 7.69 (m, 4H, CH_{Ar}), 7.79 – 7.81 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.2 (CH), 47.9 (C), 50.4 (CH), 124.3 (q, $^1J_{C-F}$ = 272.2 Hz, CF_3), 124.8 (C_{Ar}), 125.4 (q, $^3J_{C-F}$ = 3.7 Hz, $2CH_{Ar}$), 125.6 (q, $^1J_{C-F}$ = 272.4 Hz, CF_3), 126.36 (CH_{Ar}), 126.39 (CH_{Ar}), 127.2 (C_{Ar}), 127.5 (CH_{Ar}), 129.3 (q, $^2J_{C-F}$ = 32.4 Hz, C_{Ar}), 129.6 ($2CH_{Ar}$), 130.5 (q, $^2J_{C-F}$ = 32.6 Hz, C_{Ar}), 130.7 (CH_{Ar}), 130.9 (CH_{Ar}), 132.9 (C_{Ar}), 135.8 (C_{Ar}), 139.8 (C_{Ar}), 141.7 (C_{Ar}), 147.5 (C_{Ar}), 220.6 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.6 (CF_3), -62.5 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3275 (w), 2928 (w), 1725 (m), 1615 (m), 1461 (m), 1398 (m), 1319 (s), 1160 (s), 1105 (s), 1064 (s), 1016 (s), 838 (m). MS (EI, 70 eV): m/z (%) = 558 (100) [M^+], 559 (34), 539 (11), 473 (15), 460 (12), 434 (17), 12 (55). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{28}O_2F_6$ [M^+] 558.19880; found 558.19935.

2,4-Di-(*p*-trifluormethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 f): light yellow solid (109 mg, 79%), mp = 97 – 98 °C, $[\alpha]_D$ = +73.1° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.39 – 1.64 (m, 6H, aliphatic), 1.97 – 2.17 (m, 4H, aliphatic), 2.32 – 2.39 (m, 1H, aliphatic), 2.46 – 2.55 (m, 4H, aliphatic), 4.69 (s, 1H, OH), 7.26 – 7.29 (m, 3H, CH_{Ar} + $CDCl_3$), 7.36 – 7.37 (m, 4H, CH_{Ar}), 7.58 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2

(CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 47.9 (C), 50.4 (CH), 120.49 (q, $^1J_{C\text{-}F}$ = 257.7 Hz, OCF_3), 120.52 (q, $^1J_{C\text{-}F}$ = 257.0 Hz, OCF_3), 120.9 ($2CH_{Ar}$), 121.8 ($2CH_{Ar}$), 124.6 (C_{Ar}), 127.0 (C_{Ar}), 127.3 (CH_{Ar}), 130.7 ($2CH_{Ar}$), 131.7 (CH_{Ar}), 132.0 (CH_{Ar}), 132.6 (C_{Ar}), 134.3 (C_{Ar}), 135.6 (C_{Ar}), 136.7 (C_{Ar}), 147.6 (C_{Ar}), 148.4 (C_{Ar}), 149.1 (C_{Ar}), 220.7 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 57.8 (CF_3), -57.7 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3545 (w), 2928 (w), 1732 (m), 1507 (m), 1460 (m), 1250 (s), 1203 (s), 1153 (s), 1019 (m), 831 (m). MS (EI, 70 eV): m/z (%) = 590 (100) [M^+], 591 (33), 505 (19), 466 (14), 69 (18), 55 (12). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{28}O_4F_6$ [M^+] 590.18863; found 590.18736.

2,4-Di-(*m*-fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 g): light yellow solid (91 mg, 85%), mp = 111 – 112 °C, $[\alpha]_D$ = +108.0° (c 1.00, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.939 and 0.943 (2s, 3H, CH_3), 1.37 – 1.65 (m, 6H, aliphatic), 1.92 – 2.20 (m, 4H, aliphatic), 2.31 – 2.39 (m, 1H, aliphatic), 2.46 – 2.55 (m, 4H, aliphatic), 4.80 and 4.81 (s, 1H, OH), 7.00 – 7.17 (m, 4H, CH_{Ar}), 7.27 – 7.43 (m, 4H, CH_{Ar}), 7.46 – 7.54 (m, 1H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.4 and 28.5 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.2 and 44.3 (CH), 47.9 (C), 50.4 (CH), 114.1 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, CH_{Ar}), 115.2 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, CH_{Ar}), 116.1 and 116.5 (CH_{Ar}), 117.2 (d, $^2J_{C\text{-}F}$ = 20.9 Hz) and 117.5 (d, $^2J_{C\text{-}F}$ = 21.0 Hz) (CH_{Ar}), 124.66 – 124.72 (several signals, C_{Ar}), 124.8 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, CH_{Ar}), 125.85 (d, $^2J_{C\text{-}F}$ = 20.5 Hz) and 125.90 (d, $^2J_{C\text{-}F}$ = 20.4 Hz) (CH_{Ar}), 127.16 (C_{Ar}), 127.18 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, CH_{Ar}), 129.9 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, CH_{Ar}), 131.0 (d, $^3J_{C\text{-}F}$ = 8.4 Hz) and 131.1 (d, $^3J_{C\text{-}F}$ = 8.6 Hz) (CH_{Ar}), 132.5 (C_{Ar}), 135.47 and 135.50 (C_{Ar}), 137.9 and 138.0 (C_{Ar}), 140.2 and 140.3 (C_{Ar}), 147.5 (C_{Ar}), 162.8 (d, $^1J_{C\text{-}F}$ = 245.8 Hz, C_{Ar}-F), 163.3 (d, $^1J_{C\text{-}F}$ = 248.3 Hz) and 163.4 (d, $^1J_{C\text{-}F}$ = 248.3 Hz) (C_{Ar}-F), 220.7 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$): δ = -113.10 and -113.07 (CF), -111.45 and -111.40 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3539 (w), 2924 (m), 1733 (s), 1581 (s), 1458 (m), 1403 (m), 1260 (s), 1194 (s), 873 (m), 785 (s). MS (EI, 70 eV): m/z (%) = 458 (100) [M^+], 459 (28), 373 (17), 360 (11), 334 (12), 55 (15), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{30}H_{28}O_2F_2$ [M^+] 458.20519; found 458.20528.

2,4-Di-(3,5-dimethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 h): light yellow solid (89 mg, 70%), mp = 114 – 115 °C, $[\alpha]_D$ = +52.4° (c 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.32 – 1.41 (m, 1H, aliphatic), 1.51–1.63 (m, 5H, aliphatic), 1.92 – 2.17 (m, 4H, aliphatic), 2.31 – 2.39 (m, 1H, aliphatic), 2.45 – 2.61 (m, 4H, aliphatic), 3.81 (br.s, 12H, $4OCH_3$), 5.07 (s, 1H, OH), 6.45 – 6.47 (m, 3H, CH_{Ar}), 6.51 – 6.53 (m, 1H, CH_{Ar}), 6.71 (d, $^4J_{H\text{-}H}$ = 2.3 Hz, 2H, CH_{Ar}), 7.31 (br.s, 1H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 55.4 ($4OCH_3$), 99.5 (CH), 100.1 (CH), 107.3 ($2CH_{Ar}$), 107.5 (CH_{Ar}), 108.0 (CH_{Ar}), 125.6 (C_{Ar}), 126.7 (CH_{Ar}), 128.2 (C_{Ar}), 132.0 (C_{Ar}), 135.2 (C_{Ar}), 137.8 (C_{Ar}), 140.1 (C_{Ar}), 147.6 (C_{Ar}), 160.8 ($2C_{Ar}$), 161.55 (C_{Ar}) 161.58 (C_{Ar}), 220.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3508 (w), 2926 (m), 1733 (s), 1589 (s), 1453 (m), 1336 (m), 1201 (s), 1150 (s), 1058

(s), 830 (s). MS (EI, 70 eV): m/z (%) = 542 (100), 544 (9), 543 (49), 271 (18). HRMS (EI, 70 eV): calcd. for $C_{34}H_{38}O_6$ [M^+] 542.26629; found 542.26555.

2,4-Di-(*p*-ethylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 i): light yellow solid (111 mg, 99%), mp = 113 – 114 °C, $[\alpha]_D$ = +74.0° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.25 – 1.33 (m, 7 H, $2CH_2CH_3$ + aliphatic), 1.50–1.63 (m, 5H, aliphatic), 1.89 – 2.19 (m, 4H, aliphatic), 2.31 – 2.39 (m, 1H, aliphatic), 2.45 – 2.57 (m, 4H, aliphatic), 2.65 – 2.77 (m, 4H, $2CH_2CH_3$), 4.88 (s, 1H, OH), 7.21 – 7.29 (m, 5H, CH_{Ar} + $CDCl_3$), 7.33 – 7.35 (m, 2H, CH_{Ar}), 7.47 – 7.50 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 15.3 (CH_3), 15.5 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.54 (CH_2), 28.56 (CH_2), 28.61 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 125.6 (C_{Ar}), 126.8 (CH_{Ar}), 128.0 ($2CH_{Ar}$), 128.1 (C_{Ar}), 128.82 (CH_{Ar}), 128.84 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 129.9 (CH_{Ar}), 130.3 (CH_{Ar}), 131.9 (C_{Ar}), 132.9 (C_{Ar}), 135.0 (C_{Ar}), 135.5 (C_{Ar}), 143.1 (C_{Ar}), 144.0 (C_{Ar}), 147.9 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3527 (w), 2927 (m), 1737 (s), 1511 (m), 1455 (s), 1399 (m), 1257 (m), 1145 (m), 829 (s). MS (EI, 70 eV): m/z (%) = 478 (100) [M^+], 479 (55), 152 (12), 151 (13), 133 (19), 57 (10), 55 (12), 41 (12), 36 (10). HRMS (ESI, 70 eV): calcd. for $C_{34}H_{38}O_2$ [M+H] 479.29446; found 479.29408.

2,4-Di-(*o*-fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 j): light yellow solid (104 mg, 97%), mp = 118 – 119 °C, $[\alpha]_D$ = +92.2° (c 1.00, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 and 0.94 (2s, 3H, CH_3), 1.34 – 1.42 (m, 1H, aliphatic), 1.50 – 1.64 (m, 5H, aliphatic), 1.95 – 2.17 (m, 4H, aliphatic), 2.36 – 2.54 (m, 5H, aliphatic), 4.69 and 4.71 (2s, 1H, OH), 7.14 – 7.36 (m, 7H, CH_{Ar} + $CDCl_3$), 7.39 – 7.46 (m, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 and 13.9 (CH_3), 21.5 (CH_2), 26.0 and 26.1 (CH_2), 26.4 (CH_2), 27.6 and 28.3 (CH_2), 31.55 and 31.58 (CH_2), 35.8 (CH_2), 37.71 and 37.77 (CH), 44.1 and 44.2 (CH), 47.9 and 48.0 (C), 50.39 and 50.43 (CH), 115.72 and 115.76 (CH_{Ar}), 116.1 – 116.2 (several signals, CH_{Ar}), 116.5 and 116.6 (CH_{Ar}), 120.1 (C_{Ar}), 121.9 and 122.0 (C_{Ar}), 123.19 (d, $^2J_{C\text{-}F}$ = 17.7 Hz) and 123.28 (d, $^2J_{C\text{-}F}$ = 17.4 Hz) (C_{Ar}), 124.2 – 124.3 (several signals, CH_{Ar}), 124.8 – 124.9 (several signals, CH_{Ar}), 125.29 (d, $^2J_{C\text{-}F}$ = 15.8 Hz) and 125.39 (d, $^2J_{C\text{-}F}$ = 16.0 Hz) (C_{Ar}), 128.2 (CH_{Ar}), 129.4 (d, $^3J_{C\text{-}F}$ = 8.2 Hz) and 129.5 (d, $^3J_{C\text{-}F}$ = 7.9 Hz) (CH_{Ar}), 130.20 (d, $^3J_{C\text{-}F}$ = 7.9 Hz) and 130.24 (d, $^3J_{C\text{-}F}$ = 8.1 Hz) (CH_{Ar}), 131.9 – 132.3 (several signals, $2CH_{Ar}$ + $2C_{Ar}$), 136.6 and 136.7 (C_{Ar}), 148.3 and 148.4 (C_{Ar}), 160.0 (d, $^1J_{C\text{-}F}$ = 246.8 Hz, $2C_{Ar}$-F), 220.9 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$): δ = -112.7 and -112.9 (CF), -114.016 and -114.024 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3550 (w), 2925 (w), 1731 (m), 1576 (w), 1444 (m), 1414 (m), 1206 (m), 755 (s). MS (EI, 70 eV): m/z (%) = 458 (100) [M^+], 459 (31), 373 (20), 360 (11), 334 (24), 55(11). HRMS (EI, 70 eV): calcd. for $C_{30}H_{28}O_2F_2$: 458.20519; found 458.20501.

2,4-Di-(3,5-dimethylphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 k): light yellow solid (111 mg, 99%), mp = 111 – 112 °C, $[\alpha]_D$ = +104.1° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.36 – 1.64 (m, 6H, aliphatic), 1.90 – 2.17 (m, 4H, aliphatic), 2.36 – 2.37 (m, 13H, $4CH_3$ +

aliphatic), 2.46 – 2.59 (m, 4H, aliphatic), 4.94 (br.s, 1H, OH), 6.92 (s, 1H, CH_{Ar}), 6.94 (s, 1H, CH_{Ar}), 6.98 (s, 1H, CH_{Ar}), 7.05 (s, 1H, CH_{Ar}), 7.17 (m, 2H, CH_{Ar}), 7.26 (s, 1H, CH_{Ar} + $CDCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.39 ($2CH_3$), 21.41 ($2CH_3$), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.5 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 38.0 (CH), 44.4 (CH), 48.0 (C), 50.5 (CH), 125.8 (C_{Ar}), 126.6 (CH_{Ar}), 127.0 ($2CH_{Ar}$), 127.6 (CH_{Ar}), 128.0 (CH_{Ar}), 128.3 (C_{Ar}), 128.9 (CH_{Ar}), 129.6 (CH_{Ar}), 131.8 (C_{Ar}), 134.8 (C_{Ar}), 135.9 (C_{Ar}), 138.0 ($2C_{Ar}$), 138.2 (C_{Ar}), 138.86 (C_{Ar}), 138.88 (C_{Ar}), 147.7 (C_{Ar}), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3525 (w), 2917 (s), 1737 (s), 1599 (s), 1453 (s), 1203 (m), 1035 (m), 847 (s), 706 (s). MS (EI, 70 eV): m/z (%) = 478 (100) [M^+], 479 (38). HRMS (ESI, 70 eV): calcd. for $C_{34}H_{38}O_2$ [M^+] 478.28663; found 478.28554.

2,4-Di-(*p*-chlorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 l): dark yellow solid (28 mg, 24%), mp = 119 – 120 °C, $[\alpha]_D$ = +58.2° (c 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (m, 3H, CH_3), 1.32 – 1.36 (m, 1H, ailiphatic), 1.55–1.62 (m, 5H, aliphatic), 1.96 – 2.17 (m, 4H, aliphatic), 2.29 – 2.37 (m, 1H, aliphatic), 2.44 – 2.55 (m, 4H, aliphatic), 4.71 (s, 1H, OH), 7.25 – 7.30 (m, 3H, CH_{Ar} + $CDCl_3$), 7.38 – 7.41 (m, 2H, CH_{Ar}), 7.46 – 7.54 (m, 4H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.2 (CH), 47.9 (C), 50.4 (CH_{Ar}), 124.7 (C_{Ar}), 127.1 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 129.7 ($2CH_{Ar}$), 130.6 ($2CH_{Ar}$), 130.59 (C_{Ar}), 131.5 (CH_{Ar}), 131.8 (CH_{Ar}), 132.5 (C_{Ar}), 133.2 (C_{Ar}), 134.1 (C_{Ar}), 134.3 (C_{Ar}), 135.4 (C_{Ar}), 136.5 (C_{Ar}), 147.54 (C_{Ar}), 220.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3533 (w), 2922 (m), 1731 (s), 1490 (s), 1455 (s), 1230 (m), 1087 (s), 1014 (s), 819 (s), 802 (s), 732 (m), 720 (m), 693 (m), 665 (m), 640 (m), 581 (m). MS (EI, 70 eV): m/z (%) = 490 (100) [M^+], 494 (14), 493 (21), 492 (69), 491 (34). HRMS (EI, 70 eV): calcd. for $C_{30}H_{28}O_2Cl_2$ [M+] 490.14609; found 490.14496; calcd. for $C_{30}H_{28}O_2Cl^{37}Cl$ [M+] 492.14314; found 492.14362.

2,4-Di-(2,3,4-trimethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 m): light yellow solid (52 mg, 37%), mp = 105 – 106 °C, $[\alpha]_D$ = +43.4° (c 1.00, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 and 0.95 (2s, 3H, CH_3), 1.54 – 1.62 (m, 6H, aliphatic), 1.91 – 2.17 (m, 4H, aliphatic), 2.30 – 2.37 (m, 1H, aliphatic), 2.45 – 2.54 (m, 4H, aliphatic), 3.68 – 3.75 (m, 6H, $2OCH_3$), 3.89 – 3.93 (m, 12H, $4OCH_3$), 6.40 and 6.42 (2s, 1H, OH), 6.76 – 6.89 (m, 3H, CH_{Ar}), 7.06 – 7.09 (m, 1H, CH_{Ar}), 7.22 – 7.26 (d, $^3J_{H\text{-}H}$ = 4.5 Hz, 1H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.86 and 13.93 (CH_3), 21.5 (CH_2), 26.0 and 26.2 (CH_2), 26.6 and 27.4 (CH_2), 28.3 and 29.7 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.7 and 37.9 (CH), 44.3 (CH), 48.0 (C), 50.5 and 50.6 (CH), 55.9 and 56.1 ($2OCH_3$), 60.8 – 61.1 (several signals, $3OCH_3$), 61.50 and 61.53 (OCH_3), 107.54 and 107.59 (CH_{Ar}), 108.5 (CH_{Ar}), 122.8 and 123.0 (C_{Ar}), 124.0 (C_{Ar}), 125.30 and 125.33 (CH_{Ar}), 125.52 and 125.56 (C_{Ar}), 126.06 and 126.12 (C_{Ar}), 126.2 (CH_{Ar}), 127.2 and 127.4 (CH_{Ar}), 131.9 and 132.1 (C_{Ar}), 136.3 and 136.5 (C_{Ar}), 142.2 (C_{Ar}), 148.9 and 149.0 (C_{Ar}), 150.34 and 150.36 (C_{Ar}), 151.5 (C_{Ar}), 152.0 (C_{Ar}), 153.05 and 153.14 (C_{Ar}), 153.2 (C_{Ar}), C=O not given. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924 (w), 1734 (m), 1596 (w), 1494 (m), 1455 (s), 1405 (s), 1289

(s), 1212 (m), 1093 (s), 1006 (s), 797 (m). MS (EI, 70 eV): m/z (%) = 602 (100) [M^+], 604 (12), 603 (56), 43 (13). HRMS (EI, 70 eV): calcd. for $C_{36}H_{42}O_8$ [M+] 602.28742; found 602.28714.

2,4-Di-(*o*-ethoxyphenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 n): dark yellow solid (86 mg, 72%), mp = 94 – 95 °C, $[\alpha]_D$ = +52.4° (c 1.00, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.94 and 0.95 (2s, 3H, CH_3), 1.21 – 1.28 (m, 4H, CH_2CH_3 + aliphatic), 1.31 – 1.38 (m, 3H, CH_2CH_3), 1.49 – 1.64 (m, 5H, aliphatic), 1.89 – 2.17 (m, 4H, aliphatic), 2.31 – 2.59 (m, 5H, aliphatic), 4.00 – 4.14 (m, 4H, $2CH_2CH_3$), 6.06 and 6.07 (2s, 1H, OH), 6.99 – 7.20 (m, 5H, CH_{Ar}), 7.24 – 7.26 (m, 1H, CH_{Ar} + $CDCl_3$), 7.29 – 7.44 (m, 3H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.87 and 13.92 (CH_3), 14.7 (CH_2CH_3), 14.8 and 14.9 (CH_2CH_3), 21.6 (CH_2), 25.95 and 26.09 (CH_2), 26.6 and 26.7 (CH_2), 27.1 and 28.0 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.58 and 50.62 (CH), 64.04 and 64.2 (CH_2CH_3), 64.98 (CH_2CH_3), 113.12 (CH_{Ar}), 113.2 and 113.4 (CH_{Ar}), 120.92 and 120.96 (CH_{Ar}), 121.93 and 121.96 (CH_{Ar}), 123.50 and 123.56 (C_{Ar}), 126.45 and 126.48 (C_{Ar}), 127.2 and 127.33 (C_{Ar}), 127.34 and 127.43 (CH_{Ar}), 128.63 – 128.72 (several signals, $2CH_{Ar}$ + C_{Ar}), 131.59 – 131.69 (several signals, CH_{Ar} + C_{Ar}), 132.5 (CH_{Ar}), 136.0 and 136.2 (C_{Ar}), 148.97 and 149.10 (C_{Ar}), 155.01 and 155.05 (C_{Ar}), 156.16 and 156.55 (C_{Ar}), 221.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3371 (w), 2924 (w), 1736 (m), 1596 (w), 1579 (w), 1439 (m), 1227 (m), 1116 (m), 1084 (m), 1038 (m), 750 (s). MS (EI, 70 eV): m/z (%) = 510 (100) [M^+], 511 (36), 317 (9), 271 (7), 107 (8), 29 (9). HRMS (EI, 70 eV): calcd. for $C_{34}H_{38}O_4$: 510.27646; found 510.27613.

2,4-Di-(*p*-fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one (9 o): yellow solid (89 mg, 75%), mp = 126 – 127 °C, $[\alpha]_D$ = +50.3° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.50–1.63 (m, 6H, aliphatic), 1.96 – 2.19 (m, 4H, aliphatic), 2.36 (m, 1H, aliphatic), 2.46 – 2.55 (m, 4H, aliphatic), 4.70 (s, 1H, OH), 7.09 – 7.14 (m, 2H, CH_{Ar}), 7.21 – 7.27 (m, 5H, CH_{Ar} + $CDCl_3$), 7.50 – 7.54 (m, 2H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 47.9 (C), 50.4 (CH), 115.3 ($^2J_{C\text{-}F}$=21.3 Hz, $2CH_{Ar}$), 116.5 ($^2J_{C\text{-}F}$=21.4 Hz, $2CH_{Ar}$), 124.8 (C_{Ar}), 127.1 (CH_{Ar}), 127.2 (C_{Ar}), 130.9 ($^3J_{C\text{-}F}$=7.9 Hz, $2CH_{Ar}$), 131.4 ($^4J_{C\text{-}F}$ = 3.0 Hz, C_{Ar}), 131.6 ($^3J_{C\text{-}F}$=8.1 Hz, CH_{Ar}), 132.1 ($^3J_{C\text{-}F}$=8.0 Hz, CH_{Ar}), 132.3 (C_{Ar}), 134.0 ($^4J_{C\text{-}F}$ = 3.1 Hz, C_{Ar}), 135.3 (C_{Ar}), 147.7 (C_{Ar}), 162.1 ($^1J_{C\text{-}F}$ = 245.7 Hz, CF_{Ar}), 162.5 ($^1J_{C\text{-}F}$ = 248.1 Hz, C_{ar}-F), 221.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3540 (w), 2924 (m), 1732 (s), 1599 (w), 1507 (s), 1457 (m), 1217 (s), 1156 (m), 831 (s). MS (EI, 70 eV): m/z (%) = 458 (100), 459 (28), 373 (10). HRMS (EI, 70 eV): calcd. for $C_{30}H_{28}O_2F_2$: 458.20519; found 458.20512.

General procedure for the synthesis of compounds 10 and 11: 4-(*o*-fluorophenyl)-estrone (**7 k**) or 2,4-di-(*o*-fluorophenyl)-estrone (**9 j**) (0.274 mmol), K_2CO_3 (75.9 mg, 2.0 equiv.) and DMF were added in

a round-bottom 50 ml flask and stirred 4 h at 150 °C. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, heptane/EtOAc = 3:1).

Benzofuro[2',3';3,4]estra-1,3,5(10)-trien-17-one (10): according to the general procedure compound **10** was isolated as a white solid (65 mg, 69%), mp = 268 – 269 °C, $[\alpha]_D$ = +97.6° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.58 – 1.73 (m, 6H, aliphatic), 1.99 – 2.04 (m, 1H, aliphatic), 2.12 – 2.29 (m, 3H, aliphatic), 2.44 – 2.58 (m, 3H, aliphatic), 3.25 – 3.37 (m, 1H, aliphatic), 3.46 – 3.55 (m, 1H, aliphatic), 7.32 – 7.48 (m, 4H, CH_{Ar}), 7.58 (d, $^3J_{H-H}$ = 8.0 Hz, 1H, CH_{Ar}), 8.01 (d, $^3J_{H-H}$ = 7.7 Hz, 1H, CH_{Ar}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.9 (CH_3), 20.6 (CH_2), 25.3 (CH_2), 25.5 (CH_2), 26.8 (CH_2), 30.7 (CH_2) 34.9 (CH_2), 37.0 (CH), 43.4 (CH), 46.9 (C), 49.4 (CH), 107.7 (CH_{Ar}), 110.5 (CH_{Ar}), 121.3 (C_{Ar}), 121.5 (CH_{Ar}), 121.7 (CH_{Ar}), 123.6 (CH_{Ar}), 123.9 (C_{Ar}), 125.4 (CH_{Ar}), 131.3 (C_{Ar}), 133.0 (C_{Ar}), 153.4 (C_{Ar}), 155.4 (C_{Ar}), C=O not given. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 1733 (w), 1258 (s), 1208 (w), 1012 (s), 799 (s), 746 (s). MS (EI, 70 eV): m/z (%) = 344 (100) [M^+], 345 (27), 287 (10), 259 (22), 246 (15), 234 (10), 233 (15), 232 (10), 231 (15), 220 (28), 219 (26), 218 (23), 207 (13), 205 (22), 189 (12), 181 (15). HRMS (EI, 70 eV): calcd. for $C_{24}H_{24}O_2$[M^+] 344.17708; found 344.17727.

2-(*o*-Fluorophenyl)-benzofuro[2',3';3,4]estra-1,3,5(10)-trien-17-one (11): according to the general procedure compound **11** was isolated as a light yellow solid (74 mg, 77%), mp = 256 – 257 °C, $[\alpha]_D$ = +96.3° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3), 1.60 – 1.81 (m, 6H, aliphatic), 2.05 – 2.32 (m, 4H, aliphatic), 2.51 – 2.60 (m, 3H, aliphatic), 3.30 – 3.42 (m, 1H, aliphatic), 3.52 – 3.60 (m, 1H, aliphatic), 7.29 – 7.47 (m, 5H, CH_{Ar}), 7.53 – 7.58 (m, 2H, CH_{Ar}), 7.63 – 7.69 (m, 1H, CH_{Ar}), 8.03 – 8.06 (m, 1H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.7 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 27.8 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 38.0 (CH), 44.4 (CH), 47.9 (C), 50.4 (CH), 111.7 (CH_{Ar}), 116.9 (d, $^2J_{C-F}$ = 22.4 Hz, CH_{Ar}), 117.3 (C_{Ar}), 122.60 (CH_{Ar}), 122.64 (C_{Ar}), 122.70 (CH_{Ar}), 124.1 (d, $^4J_{C-F}$ = 3.4 Hz, CH_{Ar}), 124.5 (d, $^2J_{C-F}$ = 15.0 Hz, C_{Ar}), 124.9 (C_{Ar}), 126.0 (d, $^4J_{C-F}$ = 2.5 Hz, CH_{Ar}), 126.5 (CH_{Ar}), 129.5 (d, $^3J_{C-F}$ = 8.3 Hz, CH_{Ar}), 131.8 (d, $^3J_{C-F}$ = 3.3 Hz, CH_{Ar}), 132.2 (C_{Ar}), 134.2 (C_{Ar}), 151.8 (C_{Ar}), 156.4 (C_{Ar}), 156.8 (d, $^1J_{C-F}$ = 245.2 Hz, C_{Ar}-F), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -114.6 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (m), 1730 (s), 1445 (m), 1254 (m) 1212 (s), 1010 (m), 749 (s). GC/MS (EI, 70 eV): m/z (%) = 438 (100) [M^+], 439 (28), 353 (12), 327 (9), 314 (21), 313 (16), 312 (11), 299 (15), 275 (22). HRMS (EI, 70 eV): calcd. for $C_{30}H_{27}O_2F$ [M+] 438.19896; found 438.19875.

Isocoumarino[3',4';3,4]estra-1,3,5(10)-trien-17-one (12): 4-Bromoestrone (**6 a**) (200 mg, 0.574 mmol), *o*-ethoxycarbonylphenyl boronic acid (340 mg, 3.0 equiv.), $Pd(PPh_3)_4$ (33.2 mg, 0.05 equiv.), RuPhos (13.4 mg, 0.05 equiv.), K_2CO_3 (318.0 mg, 4.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred at 110 °C 72 h. The solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc = 2:1). **12** was isolated as a pale pink solid (158 mg, 74%), mp = 235 – 236 °C, $[\alpha]_D$ = +131.4° (c 1.00, $CHCl_3$). ^{1}H NMR (300

MHz, $CDCl_3$): δ = 0.97 (s, 3H, CH_3), 1.36 – 1.46 (m, 1H, aliphatic), 1.55 – 1.74 (m, 5H, aliphatic), 1.98 – 2.23 (m, 4H, aliphatic), 2.37 – 2.44 (m, 2H, aliphatic), 2.49 – 2.58 (m, 1H, aliphatic), 3.28 – 3.36 (m, 1H, aliphatic), 3.41 – 3.52 (m, 1H, aliphatic), 7.21 (d, $^3J_{H\text{-}H}$ = 8.7 Hz, 1H, CH_{Ar}), 7.46 (d, $^3J_{H\text{-}H}$ = 8.7 Hz, 1H, CH_{Ar}), 7.53 – 7.59 (m, 1H, CH_{Ar}), 7.75 – 7.81 (m, 1H, CH_{Ar}), 8.35 (d, $^3J_{H\text{-}H}$ = 8.4 Hz, 1H, CH_{Ar}), 8.46 (dd, $^4J_{H\text{-}H}$ = 1.5 Hz, $^3J_{H\text{-}H}$ = 7.8 Hz, 1H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.5 (CH_2), 26.68 (CH_2), 26.75 (CH_2), 31.8 (CH_2), 32.5 (CH_2), 35.9 (CH_2), 37.6 (CH), 45.6 (CH), 48.0 (C), 50.3 (CH), 115.7 (CH_{Ar}), 117.3 (C_{Ar}), 122.6 (C_{Ar}), 127.2 (CH_{Ar}), 127.92 (CH_{Ar}), 127.95 (CH_{Ar}), 130.8 (CH_{Ar}), 133.8 (CH_{Ar}), 135.7 (C_{Ar}), 135.9 (C_{Ar}), 136.9 (C_{Ar}), 150.3 (C_{Ar}), 161.4 (C_{Ar}), 220.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2935 (w), 2922 (w), 1714 (s), 1487 (m), 1401 (w), 1256 (s), 1002 (m), 958 (m), 782 (s), 691 (s). GC/MS (EI, 70 eV): m/z (%) = 372 (100) [M^+], 373 (28), 248 (14), 202 (12), 189 (12), 165 (10). HRMS (EI, 70 eV): calcd. for $C_{25}H_{24}O_3$ [M+] 372.17200; found 372.17175.

Protocol of Lipase Assay

The lipase inhibitory activity of synthesized derivatives was carried out with the slight modifications in previously reported method.[20] Initially, all of the derivatives were tested at the a concentration of 0.1 mM. The assay buffer was composed of 100 mM Tris-HC1 (pH 7.0) and 5 mM $CaCl_2$. The enzyme buffer was prepared by adding 10 mM MOPS (morpholinepropanesulphonic acid) and 1 mM EDTA and the pH of buffer was adjusted to 6.8. Total assay volume of 200 µL, contained 160 µL assay buffer, 20 µL of test compound and 10 µL of the pancreatic lipase enzyme (0.5 µg per well). The reaction mixture was allowed to incubate for 10 min at 37 ^oC. Then the absorbance was measured as pre-read at 405 nm by using micro-plate reader (BioTek™ ELx800, Instruments, Inc. USA). After that the reaction was initiated by the addition of 10 µL of *p*-NPB (*p*-nitrophenylbutyrate) as substrate solution and the absorbance was measured after 20 min of incubation. Orlistat was used as a positive control. The compounds with percentage inhibition of above 50 were further dilluted to different concentrations for the determination of IC_{50} values. All the experiments were performed in triplicate. IC_{50} values were calculated by non-linear regression analysis of program PRISM 5.0 (GraphPad, San Diego, California, USA).

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