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Chemoselective Suzuki-Miyaura reactions of 4-bromo-3-*O*-triflyl-estrone. Synthesis and atropisomerism of arylated estrones

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ABSTRACT

4-Bromo-3-*O*-triflyl-estrone has been synthesized in 2 steps from estrone and was successfully employed in chemoselective palladium catalysed Suzuki-Miyaura reactions. Mono- and bis-arylations were carried out selectively by variation of ligands and solvents. Overall 19 derivatives of mono- and bis-arylated estrones were synthesized under optimized conditions in high yields. Various products showed atropisomerism which was studied in detail by NMR spectroscopy.

1. Introduction

Steroids are wide-spread in nature and play a major role in the regulation of many processes of the human body. Cholesterol, for example, is an important structural component of the cell membrane.[1] Cortisol has various functions in the lipometabolism and in the metabolism of carbohydrates and furthermore suppresses the immune system.[2] Androgenic and estrogenic steroids function as sex hormones of human males and females. Estrone, estradiol and estriol are the three major estrogens[3] and their functionalized derivatives have found many applications in pharmaceutical research.[4] These derivatives are widely applied as inhibitors of the estrogenic receptor as well as imaging agents in the treatment of breast cancer.[5]

We have previously shown that 3-alkynylestrones[6] and 4-arylestrones[7] are potent phosphatase and lipase inhibitors, respectively. As part of our ongoing interest in the application of palladium catalysed reactions on estrones[8] we thus decided to work on 4-bromo-3-*O*-triflyl-estrone as an interesting new starting material in such reactions. Our main interest in this work was to investigate the chemoselectivity of the coupling reaction. In fact, to the best of our knowledge, chemoselective palladium catalysed Suzuki-Miyaura reactions have not been reported on estrones so far.

2. Results and discussion

Estrone **1** was converted into 4-bromoestrone **2** by a known procedure in a moderate yield of 44%.[9] A major side-product of this reaction is 2,4-dibromoestrone, which can be isolated in a yield of 27%. 4-Bromoestrone **2** was then converted into its corresponding triflate **3** in 95% yield (Scheme 1). The structure of **3** was independently confirmed by X-ray crystal structure analysis (Fig. 1).

With starting material **3** in hand, we studied the chemoselective arylation by palladium catalysed Suzuki-Miyaura reactions (Table 1). To our delight the initial test reaction using $Pd(PPh_3)_4$ as catalyst gave the mono-arylated product **4a** in very good yield (89%), even though 3 equivalents of arylboronic acid were used. Only 10% of bis-arylated product **5a** was formed under these conditions. The analysis of the products by ^{19}F NMR proved that the bromine atom is substituted first and the triflate group second. We obtained even higher yields of 92 and 98% changing the catalyst to

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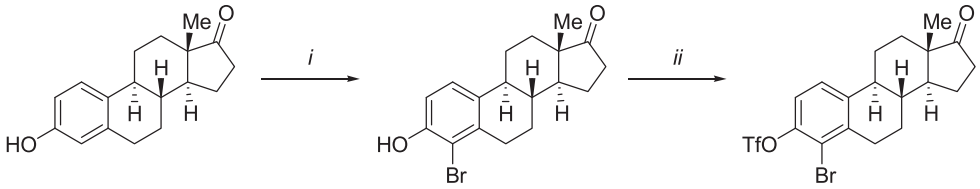


Scheme 1. Synthesis of the starting material **3**; *i*: **1** (3.6 mmol), *N*-bromoacetamide (3.6 mmol), ethanol (50 mL), r.t., 24 h; *ii*: **2** (3.0 mmol), DMAP (0.6 mmol), 2,6-lutidine (5.7 mmol), DCM (30 mL), 0 °C, then Tf_2O (3.6 mmol), r.t., 4 h.

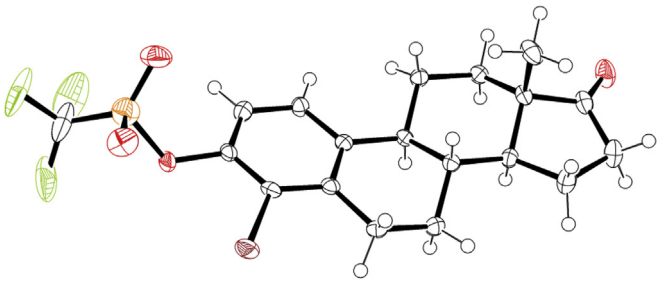


Fig. 1. ORTEP of starting material **3** (disordered atoms of the triflate group have been omitted for clarity).[10]

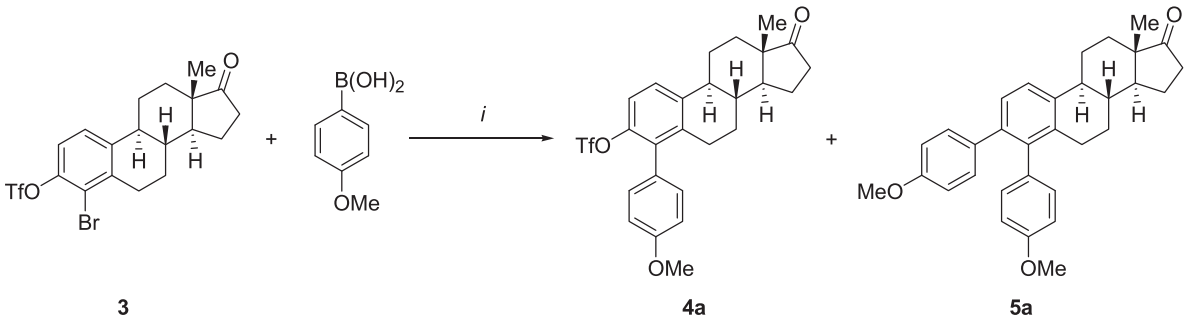
$Pd(OAc)_2$ and using $P(Cy)_3$ or cataCXium® A as ligands, respectively. On the other hand, SPhos proved to be the ligand of choice for bis-arylation, achieving product **5a** in a high yield of 88% using toluene as the solvent. Furthermore, a change of the solvent to dioxane gave a nearly quantitative yield of **5a** (99%). The different reactivity of cataCXium® A and SPhos might result from steric effects and interactions between ligand and substrate. While cataCXium® A might be too sterically encumbered for a second substitution, the aromatic moiety of SPhos is able to rotate out of plane and can furthermore interact with the phenyl-ring of the mono-substituted substrate.

With our optimized conditions in hand, we analysed the scope of the mono-fold Suzuki-Miyaura reaction (Table 2). First, we investigated the impact of steric hindrance. *para*-Methoxy substituted product **4a** was obtained in a high yield of 98%, while the *meta*-product **4b** showed a slightly diminished yield of 84% and was isolated as a mixture of atropisomers (*vide infra*). The *ortho*-product **4c**, however, was not formed at all. In general, all products were isolated in high yields of 84–99%, including those containing electron-donating and electron-withdrawing groups, like OMe, *t*Bu and CF_3, as well as the heterocyclic thienyl group. Only the strongly electron-withdrawing cyano group led to a low yield of 35% for product **4g**. A vinyl-group was tolerated without the occurrence of a potential Heck reaction as a side reaction, leading to product **4h** in 96% yield. All reactions showed a high selectivity towards the mono-arylated products **4a-i**. No formation of bis-arylated products was observed, however, a common side-product is the dehalogenated starting material **3**, which was detected in small amounts in some reactions. For all products **4a-h** a rotational hindrance was observed by ^1H and ^{13}C NMR (*vide infra*).

As the next step, we compared the results of the mono-arylation with the synthesis of bis-arylated products **5a-h** (Table 3). The twofold Suzuki-Miyaura reaction of our starting material **3** works generally in very high yields. All products, independant from the type of functional group used, were isolated in high yields (91–99%). The only exception in our tests was the cyano group as product **5f** was not formed, although the mono-arylated product **4g** could be isolated in 34% yield.

Similar to the other products, *meta*-substituted product **5b** was isolated as a mixture of atropisomers. In fact, a rotational hindrance was observed for all products (**5a-g**) in both ^1H and ^{13}C NMR. While the aryl ring in position 3 rotates freely, rotation of the aromatic

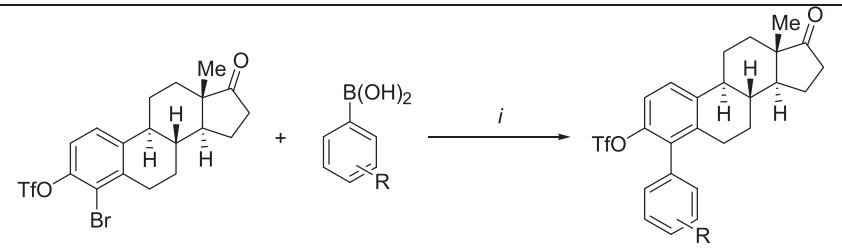
Table 1
Optimization of the chemoselective Suzuki-Miyaura reaction.[a]



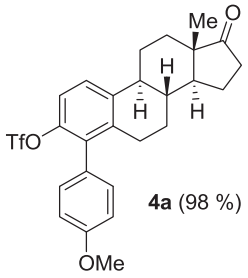
Catalyst [mol%]	Ligand [mol%]	Equivalents boronic acid	Solvent	Yield 4a [%]	Yield 5a [%]
$Pd(PPh_3)_4$ [5]	–	3.0	toluene	89	10
$Pd(OAc)_2$ [5]	$P(Cy)_3$ [10]	3.0	toluene	92	0
$Pd(OAc)_2$ [5]	cataCXium® A [10]	3.0	toluene	98	0
$Pd(OAc)_2$ [5]	cataCXium® A [10]	1.5	toluene	98	0
$Pd(OAc)_2$ [5]	SPhos [10]	3.0	toluene	12	88
$Pd(OAc)_2$ [5]	SPhos [10]	3.0	dioxane	0	99

[a] Reaction conditions *i*: **3** (0.21 mmol), 4-methoxyphenylboronic acid, K_3PO_4 (0.63 mmol), Pd-catalyst, ligand, solvent (4 mL), 100 °C, 20 h; isolated yields.

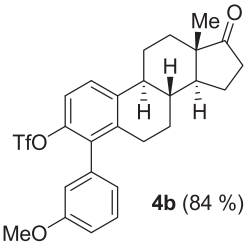
Table 2
Synthesis of compounds **4a-i**.[a]



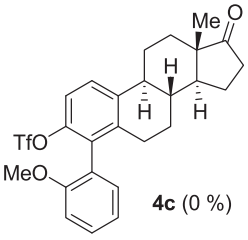
3 **4a-i**



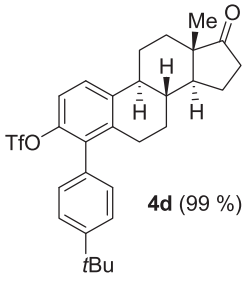
4a (98 %)



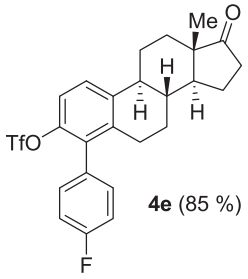
4b (84 %)



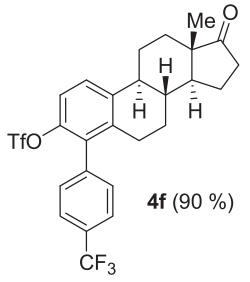
4c (0 %)



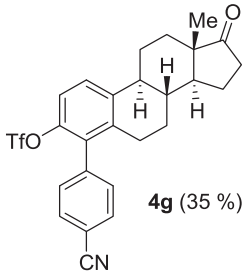
4d (99 %)



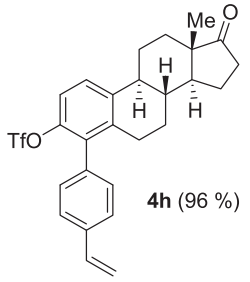
4e (85 %)



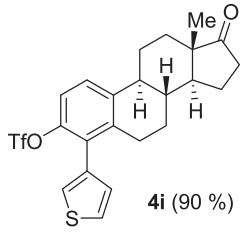
4f (90 %)



4g (35 %)



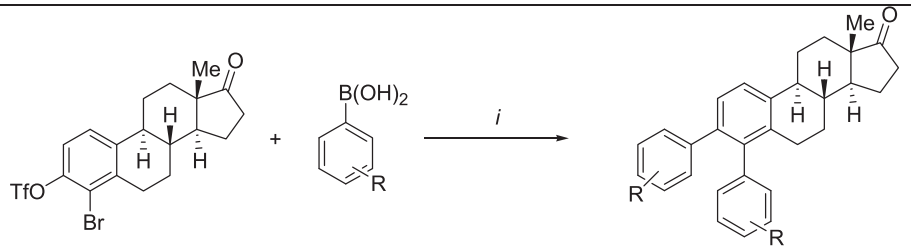
4h (96 %)



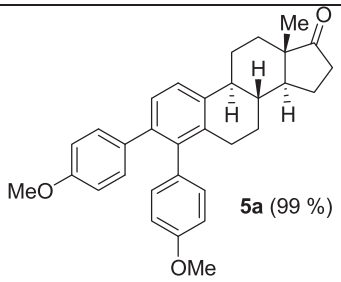
4i (90 %)

[a] Reaction conditions *i*: **3** (0.21 mmol), arylboronic acid (0.32 mmol), K_3PO_4 (0.63 mmol), $Pd(OAc)_2$ (5 mol%), cataCXium® A (10 mol%), toluene (4 mL), 100 °C, 20 h; isolated yields.

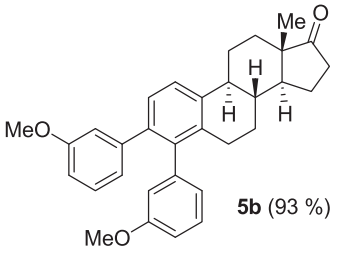
Table 3
Synthesis of compounds **5a-h**.[a]



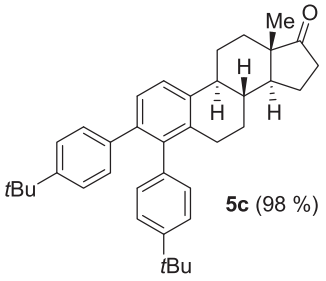
3 **5a-h**



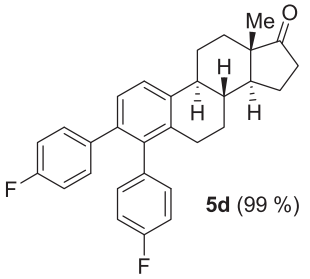
5a (99 %)



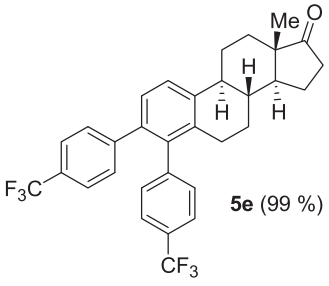
5b (93 %)



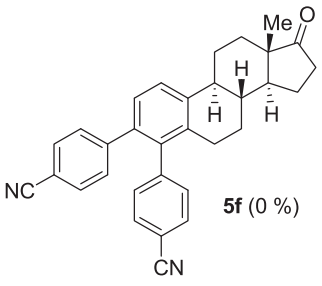
5c (98 %)



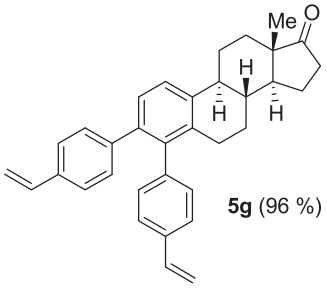
5d (99 %)



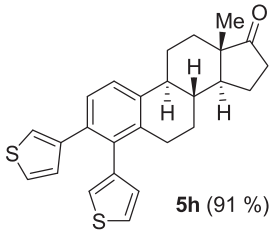
5e (99 %)



5f (0 %)



5g (96 %)



5h (91 %)

[a] Reaction conditions *i*: **3** (0.21 mmol), arylboronic acid (0.63 mmol), K_3PO_4 (0.63 mmol), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), dioxane (4 mL), 100 °C, 20 h; isolated yields.

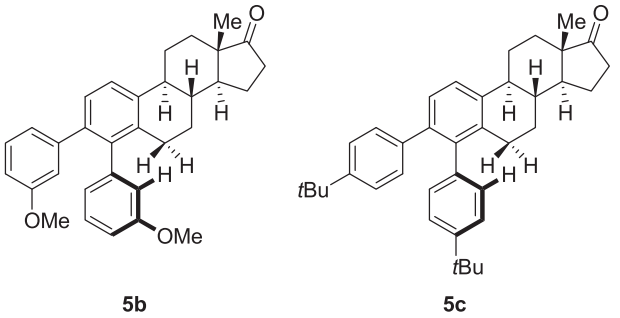


Fig. 2. Sterical hindrance through interaction of the CH_2-group in position 6 and the *ortho*-protons of the aromatic ring.

ring in position 4 is hampered by the corresponding B-ring protons in position 6 of the steroid scaffold (Fig. 2). The same effect was observed for compounds **4a-h**. Hence, we investigated this effect by ^{1}H NMR studies in DMF-*d*7 for compound **5c** at elevated temperatures (Figs. 3 and 4). Interestingly, rotational hindrance was not completely overcome even at 130 °C. However, the transition from magnetically inequivalent protons of the aromatic ring in position 4 into magnetically equivalent protons at higher temperatures is obvious. Furthermore product **5b** has been investigated by ^{1}H NMR at elevated temperatures in DMSO-d_6 and by HPLC. The atropisomerism was overcome at 80 °C for this compound (see Supporting Information). The HPLC measurement showed one peak, most likely due to the high similarity of both isomers.

The structure of **5c** was also independently confirmed by X-ray crystal structure analysis (Fig. 5). The structure shows that the phenyl ring in position 4 is twisted in an angle of 90° from the aromatic A-ring of the estrone, while the phenyl ring in position 3 shows an angle of around 45°.

Finally, we investigated the synthesis of 3,4-bis-arylated estrones containing two different aryl groups (Table 4). We used mono-arylated product **4d** as starting material, as this product could be easily obtained in a 500 mg scale, maintaining a high yield of 99%. **4d** was coupled with four electronically different arylboronic acids, containing a CF_3, OMe and vinyl group as well as a thienyl ring. In comparison to the direct bis-arylation, the mixed secondary arylation of **4d** showed lower yields of 70–97%. However, mixed bis-arylated products containing electronically different substituents, such as **6a** containing a *tert*-butyl and a CF_3 group, are readily available through this type of reaction. This paves the way to a broad number of potential products.

We furthermore applied compound **4d** in a Sonogashira reaction, using a procedure of our previous work on estrones (Scheme 2).[6] Product **7** has been synthesized in 58%. The sterical hindrance of the phenyl ring located at position 4 most likely is responsible for the only moderate yield of 58%.

3. Conclusion

In conclusion, 4-bromo-3-trifyl-estrone **3** has been successfully employed in chemoselective palladium catalysed Suzuki-Miyaura reactions for the first time. The synthesis of mono- and bis-

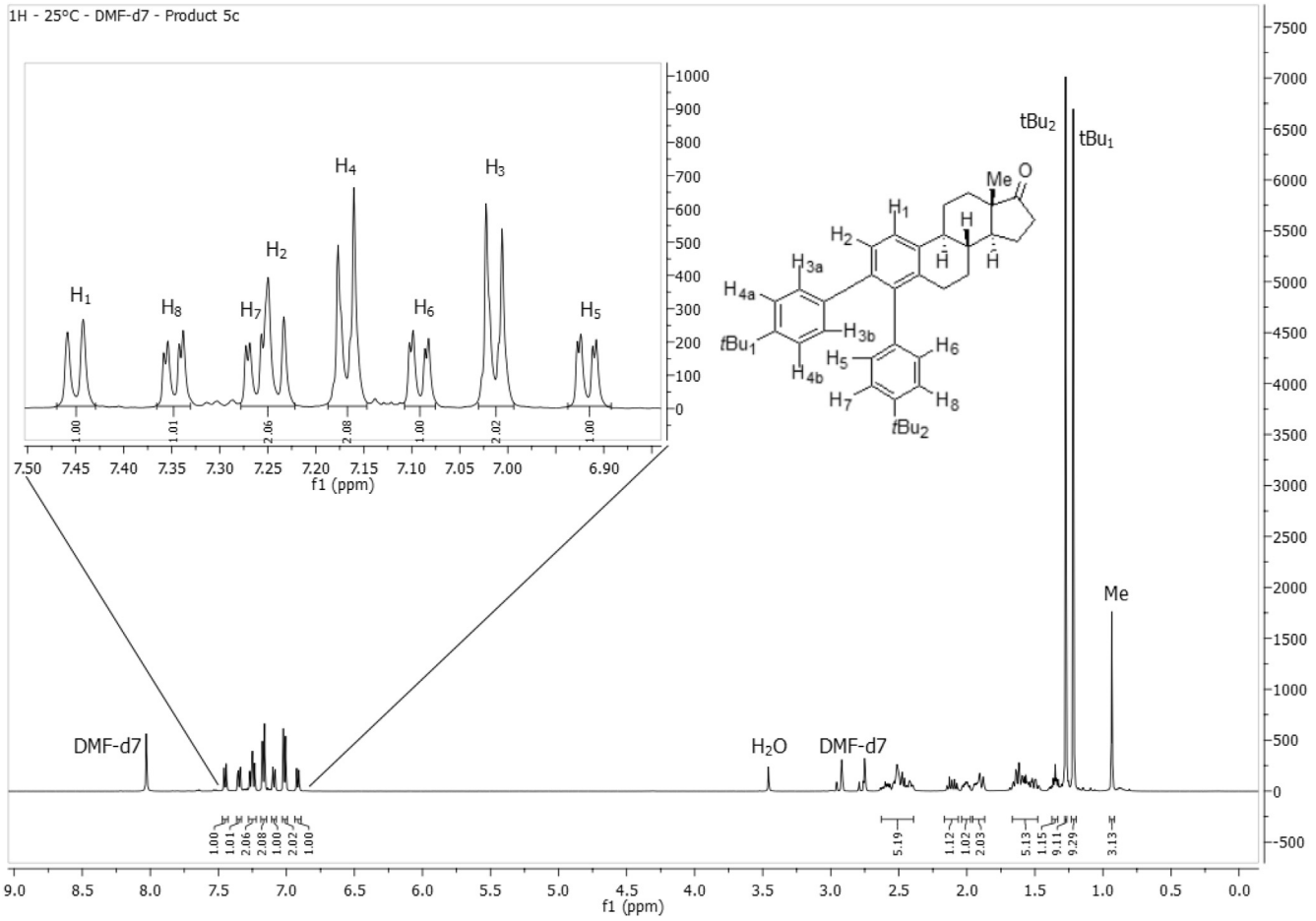


Fig. 3. 1H NMR of product **5c** in DMF-*d*7 at 25 °C, the positions of the aromatic protons were determined via COSY, NOESY, HSQC- and HMBC-2D-NMR.

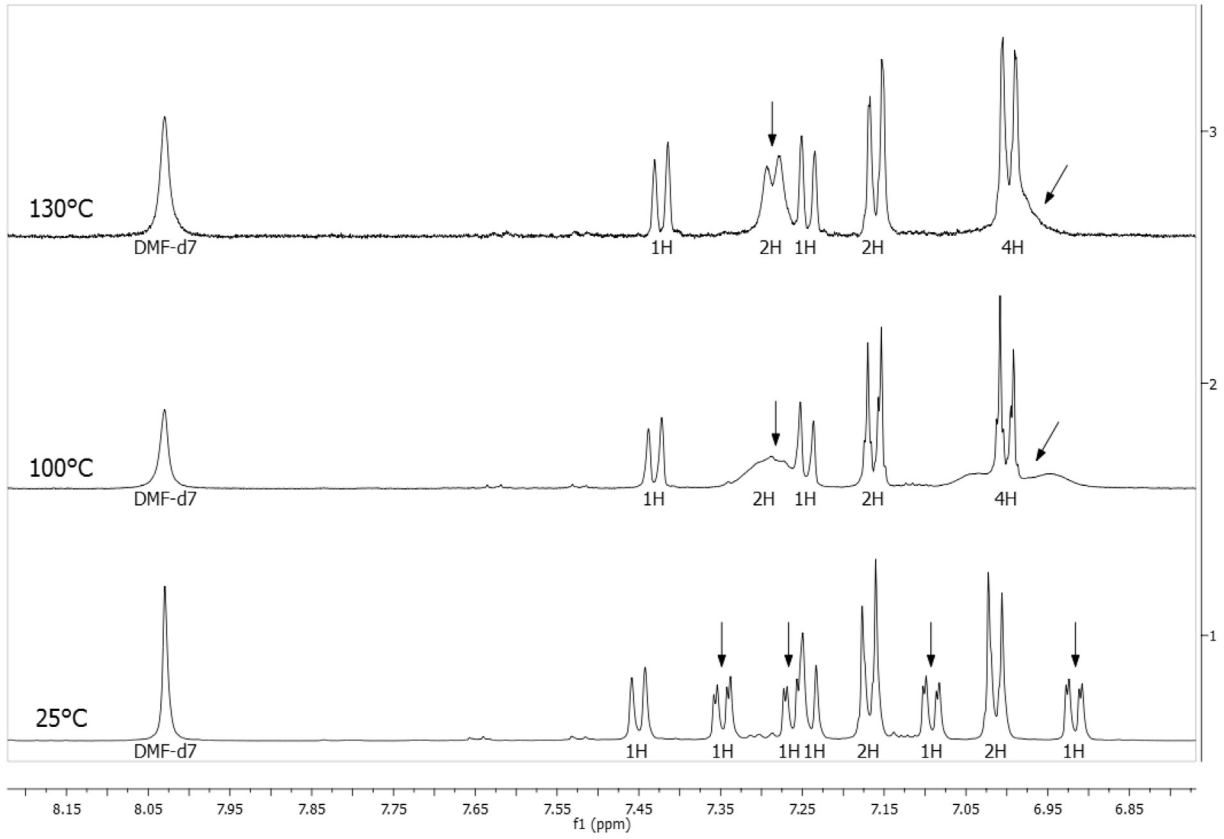


Fig. 4. 1H NMR of product **5c** in DMF-*d*7 at 25 °C, 100 °C and 130 °C.

arylated products is selectively controllable by the choice of ligand. The reaction is generally applicable for many types of electron-rich, electron-withdrawing and heterocyclic groups in very high yields. Overall 19 new examples of mono-, bis-, and mixed bis-arylated products have been synthesized with our optimized conditions, with one further example showing a mixed Suzuki and Songashira product, paving the way for a high number of different estrogenic compounds with potential biological activity.

4. Experimental section

4.1. General

For NMR spectra the substrates were dissolved in $CDCl_3$ or DMSO-d_6 and the spectra were recorded on a Bruker AVANCE 300 III, 250 II or 500. The IR spectra were measured as ATR experiments with a Nicolet 6700 FT-IR spectrometer and a Nicolet 550 FT-IR spectrometer. MS and HRMS were measured by an Agilent 6890 N/5973 GC-MS and an Agilent 1200/6210 Time-of-Flight LC-MS. Melting points were determined by a Micro-Hot-Stage GalenTM III Cambridge Instruments.

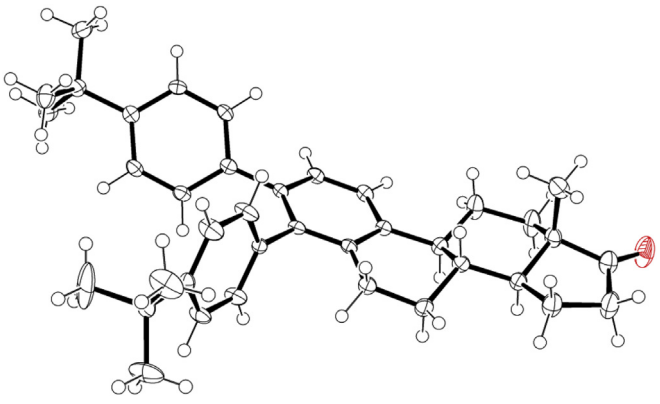
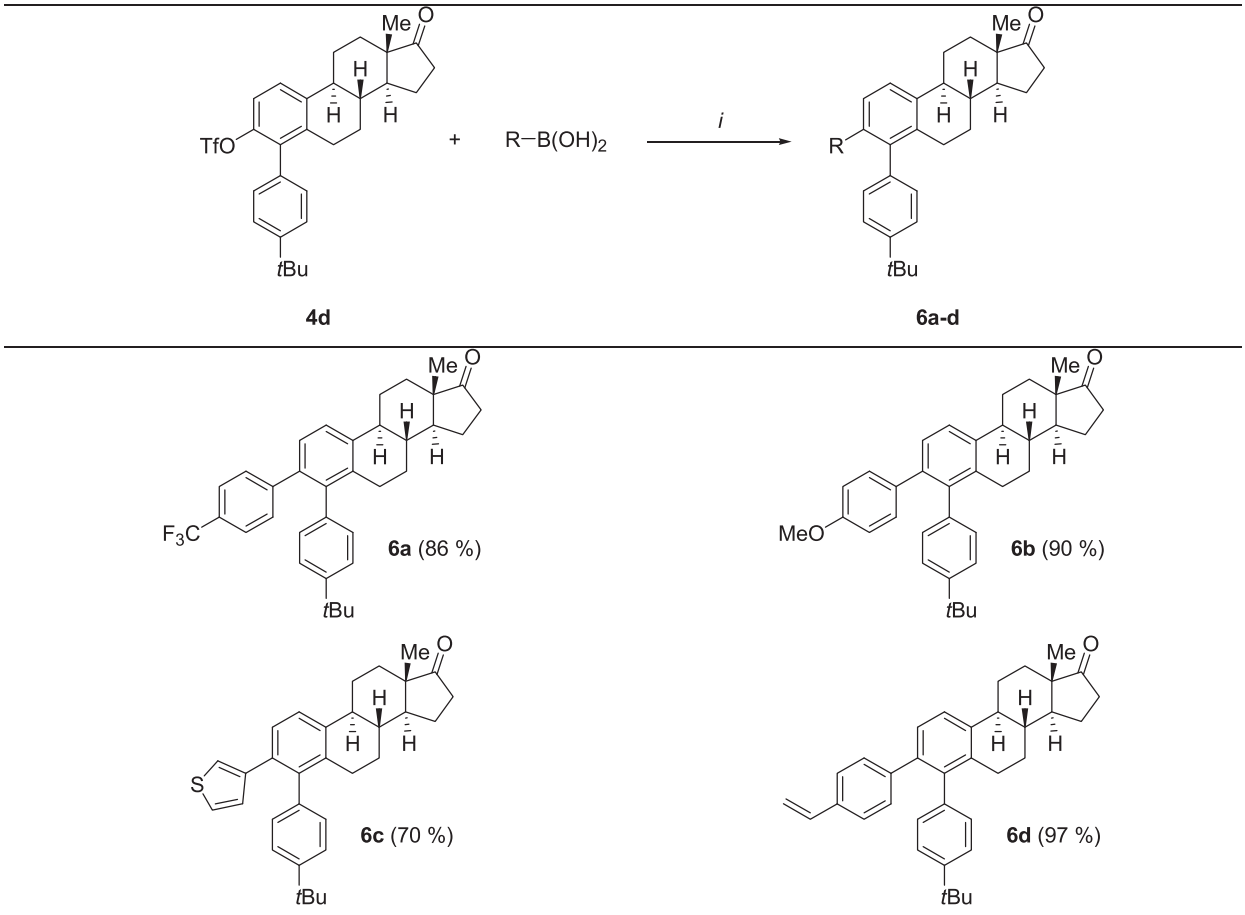


Fig. 5. ORTEP of bis-arylated product **5c** (the disordered atoms of the *tert*-butyl groups have been omitted for clarity).[10]

4.1.1. 4-Bromo-3-hydroxy-13β-estra-1,3,5(10)-trien-17-one [2]

Estrone **1** (3.6 mmol, 973 mg) and *N*-bromoacetamide (3.6 mmol, 497 mg) were dissolved in ethanol (50 mL) and stirred at room temperature for 24 h. The precipitate was filtrated and dried to yield **2** as a white solid (548 mg, 44%). 2,4-Dibromo-3-hydroxy-13β-estra-1,3,5(10)-trien-17-one (421 mg, 27%) can be isolated as side-product from the filtrate by column chromatography (heptane/ethyl acetate 5:1). **mp.** 263–265 °C. **^{1}H NMR** (300 MHz, DMSO-d_6): $\delta = 0.80$ (s, 3H, CH_3); 1.27–1.58 (m, 6H, CH_{Alkyl}); 1.71–1.75 (m, 1H, CH_{Alkyl}); 1.91–2.17 (m, 4H, CH_{Alkyl}); 2.29–2.44 (m, 2H, CH_{Alkyl}); 2.56–2.66 (m, 1H, CH_{Alkyl}); 2.82–2.90 (m, 1H, CH_{Alkyl}); 6.75 (d, $^3J = 8.47$ Hz, 1H, CH_{Ar}); 7.10 (d, $^3J = 8.48$ Hz, 1H, CH_{Ar}); 9.84 (s, 1H, OH). **^{13}C NMR** (75 MHz, DMSO-d_6): $\delta = 13.4$ (CH_3); 21.1, 25.7, 26.2, 30.7, 31.3, 35.4 (CH_2); 37.0, 43.5 (CH); 47.2 (C); 49.4 (CH); 112.5 (C_{Ar}); 113.2, 124.9 (CH_{Ar}); 132.2, 136.3, 151.9 (C_{Ar}); 219.6 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu} = 3417$ (m), 2917 (m), 1728 (s), 1594 (w), 1475 (s), 1407 (m), 1162 (s), 819 (m), 534 (s). **MS** (EI, 70 eV): *m/z* (%) = 351 (21), 350 (M^+, ^{81}Br, 100), 349 (19), 348 (M^+, ^{79}Br, 98), 291 (30), 250 (34), 238 (30), 237 (31), 226 (31), 224 (39), 158 (50), 157 (54), 145 (51), 144 (72), 132 (45), 131 (51), 128 (57), 127 (39), 115 (97), 97 (39), 91 (42), 79 (33), 77 (45), 67 (48), 55 (61), 41 (67). **HRMS** (EI, 70 eV): Calculated for $C_{18}H_{21}BrO_2$ (^{79}Br, M^+), 348.07194; measured 348.07133. Calculated for $C_{18}H_{21}BrO_2$ (^{81}Br, M^+), 350.06990; measured 350.06966.

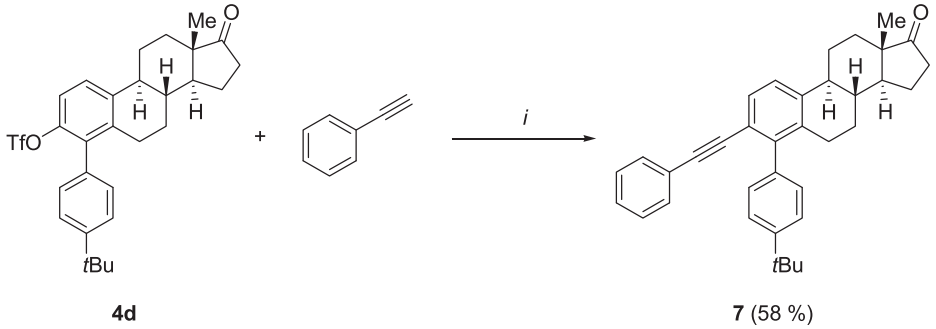
Table 4
Synthesis of compounds **6a-d**.[a]



[a] Reaction conditions *i*: **4d** (0.187 mmol), arylboronic acid (0.281 mmol), K_3PO_4 (0.561 mmol), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), dioxane (4 mL), 100 °C, 20 h; isolated yields.

4.1.2. 4-Bromo-3-(trifluoromethylsulfonyloxy)-13β-estra-1,3,5(10)-trien-17-one [3]

2 (3.0 mmol, 1.048 g), 4-dimethylaminopyridine (DMAP, 0.6 mmol, 0.073 g) and 2,6-lutidine (5.7 mmol, 0.611 g) were dissolved in dichloromethane (30 mL) and cooled to 0 °C. Tf_2O (3.6 mmol, 1.016 g) was added dropwise and the reaction was stirred for 4 h, while warming up to room temperature. 1 M HCl (30 mL) was added. The organic phase was washed with brine, dried with Na_2SO_4 and filtrated. The crude product was purified by column chromatography (heptane/ethyl acetate 5:1) to yield **3** as white solid (1.372 g, 95%). **mp.** 170–171 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): $\delta = 0.91$ (s, 3H, CH_3); 1.43–1.65 (m, 6H, CH_{Alkyl}); 1.96–2.23



Scheme 2. Sonogashira reaction of **4d**; *i*: **4d** (0.42 mmol), phenylacetylene (0.50 mmol), diisopropylamine (1.26 mmol), $Pd(PPh_3)_4$ (10 mol%), CuI (10 mol%), DMF (6 mL), 100 °C, 20 h; isolated yield.

(m, 4H, CH_{Alkyl}); 2.33–2.58 (m, 3H, CH_{Alkyl}); 2.79–2.86 (m, 1H, CH_{Alkyl}); 3.01–3.11 (m, 1H, CH_{Alkyl}); 7.14 (d, $^3J = 8.71$ Hz, 1H, CH_{Ar}); 7.34 (d, $^3J = 8.72$ Hz, 1H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): $\delta = 13.7$ (CH_3); 21.5, 25.9, 26.3, 31.2, 31.4, 35.8 (CH_2); 37.0, 44.4 (CH); 47.7 (C); 50.3 (CH); 118.6 (q, $^1J = 320.6$ Hz, CF_3); 119.0 (C_{Ar}); 119.3, 125.6 (CH_{Ar}); 139.2, 142.1, 145.2 (C_{Ar}); 220.1 (C=O). **^{19}F NMR** (235 MHz, $CDCl_3$): $\delta = -73.48$. **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2934$ (w), 1733 (m), 1592 (w), 1403 (m), 1200 (s), 1135 (s), 936 (m), 810 (s), 704 (m), 673 (m), 583 (m). **MS** (EI, 70 eV): *m/z* (%) = 482 (M^+, ^{81}Br, 100), 481 (16), 480 (M^+, ^{79}Br, 96), 438 (30), 436 (29), 425 (17), 423 (23), 331 (40), 329 (39), 305 (34), 303 (28), 293 (47), 291 (51), 268 (47), 237 (24), 226 (21), 212 (17), 211 (30), 141 (16), 129 (22), 128 (34), 115 (44), 97 (29), 77 (18), 69 (65), 55 (20). **HRMS** (EI, 70 eV): Calculated for $C_{19}H_{20}BrF_3O_4S$ (^{79}Br, M^+), 480.02123; measured 480.02060. Calculated for $C_{19}H_{20}BrF_3O_4S$ (^{81}Br, M^+), 482.01918; measured 482.01909.

4.2. General procedure A for the onefold Suzuki-Miyaura reaction of 3

3 (0.21 mmol, 100 mg), boronic acid (0.32 mmol), K_3PO_4 (0.63 mmol, 132 mg), $Pd(OAc)_2$ (5 mol%, 2.3 mg), cataCXium® A (10 mol%, 7.4 mg) and toluene (4 mL) were heated in a pressure tube under argon atmosphere at 100 °C for 20 h. The reaction was quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried with Na_2SO_4 and filtrated. The crude product was purified by column chromatography (heptane/ethyl acetate) to yield **4a-i**.

4.3. General procedure B for the twofold Suzuki-Miyaura reaction of 3

3 (0.21 mmol, 100 mg), boronic acid (0.63 mmol), K_3PO_4 (0.63 mmol, 132 mg), $Pd(OAc)_2$ (5 mol%, 2.3 mg), SPhos (10 mol%, 8.5 mg) and dioxane (4 mL) were heated in a pressure tube under argon atmosphere at 100 °C for 20 h. The reaction was quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried with Na_2SO_4 and filtrated. The crude product was purified by column chromatography (heptane/ethyl acetate) to yield **5a-h**.

4.4. General procedure C for the Suzuki-Miyaura reaction of 4d

4d (0.187 mmol, 100 mg), boronic acid (0.281 mmol), K_3PO_4 (0.561 mmol, 119 mg), $Pd(OAc)_2$ (5 mol%, 2.1 mg), SPhos (10 mol%, 7.7 mg) and dioxane (4 mL) were heated in a pressure tube under argon atmosphere at 100 °C for 20 h. The reaction was quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried with Na_2SO_4 and filtrated. The crude product was purified by column chromatography (heptane/ethyl acetate) to yield **6a-d**.

4.4.1. 3-(Trifluoromethylsulfonyloxy)-4-(4-methoxyphenyl)-13β-estra-1,3,5(10)-trien-17-one [4a]

4a was synthesized according to general procedure A using 4-methoxyphenylboronic acid (0.32 mmol, 48 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow oil (104 mg, 98%). **^{1}H NMR** (250 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H, CH_3); 1.50–1.65 (m, 6H, CH_{Alkyl}); 1.90–2.17 (m, 4H, CH_{Alkyl}); 2.31–2.57 (m, 5H, CH_{Alkyl}); 3.85 (s, 3H, OCH_3); 6.94–7.01 (m, 2H, CH_{Ar}); 7.09–7.17 (m, 3H, CH_{Ar}); 7.37 (d, $^3J = 8.71$ Hz, 1H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 25.9, 26.2, 28.6, 31.5, 35.8 (CH_2); 37.3, 44.5 (CH); 47.8 (C); 50.4 (CH); 55.2 (OCH_3); 113.7, 118.2 (CH_{Ar}); 118.3 (q, $^1J = 320.3$ Hz, CF_3); 126.0 (CH_{Ar}); 126.5 (C_{Ar}); 130.8, 130.9 (CH_{Ar}); 134.7, 138.5, 140.5, 145.8, 159.3 (C_{Ar}); 220.4 (C=O). **^{19}F NMR** (235 MHz, $CDCl_3$): $\delta = -74.39$. **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2928$ (w), 1737 (m), 1515 (m), 1465 (m), 1247 (s), 1202 (s), 1138 (s), 1109 (m), 1031 (m), 920 (s), 935 (s), 787 (m), 733 (m), 601 (s). **MS** (EI, 70 eV): *m/z* (%) = 509 (14), 508 (M^+, 58), 375 (25), 212 (16), 211 (100). **HRMS** (EI, 70 eV): Calculated for $C_{26}H_{27}F_3O_5S$ (M^+), 508.15258; measured 508.15245.

4.4.2. 3-(Trifluoromethylsulfonyloxy)-4-(3-methoxyphenyl)-13β-estra-1,3,5(10)-trien-17-one [4b]

4b was synthesized according to general procedure A using 3-methoxyphenylboronic acid (0.32 mmol, 48 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow oil (88 mg, 84%). **^{1}H NMR** (300 MHz, $CDCl_3$): $\delta = 0.93$ (s, 6H, CH_3); 1.49–1.65 (m, 12H, CH_{Alkyl}); 1.91–2.17 (m, 8H, CH_{Alkyl}); 2.35–2.60 (m, 10H, CH_{Alkyl}); 3.82 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 6.74–6.82 (m, 4H, CH_{Ar}); 6.93–6.97 (m, 2H, CH_{Ar}); 7.16 (d, $^3J = 8.74$ Hz, 2H, CH_{Ar}); 7.32–7.40 (m, 4H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 25.9, 26.1, 28.3, 31.5, 35.8 (CH_2); 37.2, 44.5 (CH); 47.8 (C); 50.4 (CH); 55.3, 55.3 (OCH_3); 113.6, 113.8, 115.0, 115.3, 118.2 (CH_{Ar}); 118.3 (q, $^1J = 320.1$ Hz, CF_3); 121.8, 122.0, 126.1, 129.5, 129.6 (CH_{Ar}); 134.8, 135.7, 138.0, 138.1, 140.5, 145.3, 159.6, 159.6 (C_{Ar}); 220.4 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): $\delta = -74.36$, -74.37. **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2929$ (w), 1737 (m), 1580 (w), 1417 (s), 1289 (m), 1204 (s), 1138 (s), 1012 (m), 923 (s), 909 (m), 794 (m), 505 (m). **MS** (EI, 70 eV): *m/z* (%) = 509 (24), 508 (M^+, 85), 375 (22), 212 (15), 211 (100), 165 (11). **HRMS** (EI, 70 eV): Calculated for $C_{26}H_{27}F_3O_5S$ (M^+), 508.15258; measured 508.15203.

4.4.3. 3-(Trifluoromethylsulfonyloxy)-4-(4-tert-butylphenyl)-13β-estra-1,3,5(10)-trien-17-one [4d]

4d was synthesized according to general procedure A using 4-*tert*-butylphenylboronic acid (0.32 mmol, 55 mg) and was purified via column chromatography (heptane/ethyl acetate 10:1) to yield a yellow solid (112 mg, >99%). **mp.** 73–74 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H, CH_3); 1.36 (s, 9H, $CH_{3,tBu}$); 1.47–1.64 (m, 6H, CH_{Alkyl}); 1.91–2.17 (m, 4H, CH_{Alkyl}); 2.33–2.60 (m, 5H, CH_{Alkyl}); 7.11–7.17 (m, 3H, CH_{Ar}); 7.37 (d, $^3J = 8.38$ Hz, 1H, CH_{Ar}); 7.43–7.47 (m, 2H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 25.9, 26.2, 28.6 (CH_2); 31.3 ($CH_{3,tBu}$); 31.5 (CH_2); 34.6 (C_{tBu}); 35.8 (CH_2); 37.3, 44.5 (CH); 47.8 (C); 50.4 (CH); 118.2 (CH_{Ar}); 118.3 (q, $^1J = 320.3$ Hz, CF_3); 125.2, 125.3, 125.9, 129.2, 129.3 (CH_{Ar}); 131.3, 135.0, 138.3, 140.4, 145.6, 151.0 (C_{Ar}); 220.5 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): $\delta = -74.49$. **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2957$ (w), 1739 (m), 1515 (w), 1465 (m), 1418 (s), 1202 (s), 1185 (s), 1138 (s), 1022 (s), 936 (m), 922 (s), 837 (s), 664 (m), 599 (s). **MS** (EI, 70 eV): *m/z* (%) = 534 (M^+, 11), 519 (23), 57 (100). **HRMS** (EI, 70 eV): Calculated for $C_{29}H_{33}F_3O_4S$ (M^+), 534.20462; measured 534.20471.

4.4.4. 3-(Trifluoromethylsulfonyloxy)-4-(4-fluorophenyl)-13β-estra-1,3,5(10)-trien-17-one [4e]

4e was synthesized according to general procedure A using 4-fluorophenylboronic acid (0.32 mmol, 47 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow solid (88 mg, 85%). **mp.** 121–122 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H, CH_3); 1.32–1.62 (m, 6H, CH_{Alkyl}); 1.92–2.16 (m, 4H, CH_{Alkyl}); 2.32–2.55 (m, 5H, CH_{Alkyl}); 7.13–7.20 (m, 5H, CH_{Ar}); 7.40 (d, $^3J = 8.68$ Hz, 1H, CH_{Ar}). **^{13}C NMR** (125 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 25.9, 26.1, 28.5, 31.5, 35.8 (CH_2); 37.3, 44.5 (CH); 47.8 (C); 50.4 (CH); 115.5 (d, $^2J = 21.6$ Hz, CH_{Ar}); 115.6 (d, $^2J = 21.5$ Hz, CH_{Ar}); 118.3 (CH_{Ar}); 118.3 (q, $^1J = 320.1$ Hz, CF_3); 126.4 (CH_{Ar}); 130.3 (d, $^4J = 3.48$ Hz, C_{Ar}); 131.4 (d, $^3J = 8.25$ Hz, CH_{Ar}); 131.5 (d, $^3J = 8.29$ Hz, CH_{Ar}); 134.0, 138.2, 140.7, 145.4 (C_{Ar}); 162.5 (d, $^1J = 247.5$ Hz, *C*-F); 220.3 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): $\delta = -74.37$ (CF_3), -113.70 (*C*-F). **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2873$ (w), 1732 (m), 1512 (m), 1466 (m), 1414 (s), 1202 (s), 1159 (m), 1139 (s), 1057

(m), 925 (s), 823 (s), 621 (m), 506 (m). **MS** (EI, 70 eV): *m/z* (%) = 496 (M^+, 20), 251 (17), 225 (21), 200 (15), 199 (100), 109 (14), 69 (14). **HRMS** (ESI): Calculated for $C_{25}H_{25}F_4O_4S$ (M + H^+), 497.14042; measured 497.14048.

4.4.5. 3-(Trifluoromethylsulfonyloxy)-4-(4-trifluoromethylphenyl)-13β-estra-1,3,5(10)-trien-17-one [4f]

4f was synthesized according to general procedure A using 4-trifluoromethylphenylboronic acid (0.32 mmol, 61 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow oil (103 mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3); 1.53–1.67 (m, 6H, CH_{Alkyl}); 1.95–2.09 (m, 4H, CH_{Alkyl}); 2.34–2.57 (m, 5H, CH_{Alkyl}); 7.22 (d, ^3J = 8.76 Hz, 1H, CH_{Ar}); 7.34–7.40 (m, 2H, CH_{Ar}); 7.45 (d, ^3J = 8.71 Hz, 1H, CH_{Ar}); 7.71–7.76 (m, 2H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 25.9, 26.0, 28.5, 31.5, 35.7 (CH_2); 37.2, 44.5 (CH); 47.8 (C); 50.3 (CH); 118.2 (q, ^1J = 320.4 Hz, CF_3); 118.5 (CH_{Ar}); 124.0 (q, ^1J = 272.3 Hz, *C*–CF_3); 125.4 (m, CH_{Ar}); 126.8 (CH_{Ar}); 129.9 (q, ^2J = 32.6 Hz, *C*-CF_3); 130.2, 130.3 (CH_{Ar}); 133.5, 137.7 (C_{Ar}); 138.4 (q, ^5J = 1.29 Hz, C_{Ar}); 140.8, 144.9 (C_{Ar}); 220.3 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −62.66 (CF_3), −74.37 (CF_3). **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2931 (w), 1737 (m), 1618 (w), 1419 (m), 1322 (s), 1207 (s), 1124 (s), 1064 (m), 921 (m), 844 (m), 734 (w), 607 (m). **MS** (EI, 70 eV): *m/z* (%) = 547 (27), 546 (M^+, 94), 502 (32), 489 (19), 395 (43), 393 (16), 303 (17), 301 (46), 299 (18), 289 (17), 287 (19), 275 (47), 250 (15), 249 (100), 233 (18), 97 (19), 69 (33), 55 (17). **HRMS** (EI, 70 eV): Calculated for $C_{26}H_{24}F_6O_4S$ (M^+), 546.12940; measured 546.12963.

4.4.6. 3-(Trifluoromethylsulfonyloxy)-4-(4-cyanophenyl)-13β-estra-1,3,5(10)-trien-17-one [4g]

4g was synthesized according to general procedure A using 4-cyanophenylboronic acid (0.32 mmol, 45 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a white solid (36 mg, 35%). **mp.** 168–169 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3); 1.47–1.65 (m, 5H, CH_{Alkyl}); 1.92–2.28 (m, 5H, CH_{Alkyl}); 2.33–2.55 (m, 5H, CH_{Alkyl}); 7.20 (d, ^3J = 8.77 Hz, 1H, CH_{Ar}); 7.33–7.39 (m, 2H, CH_{Ar}); 7.45 (d, ^3J = 8.71 Hz, 1H, CH_{Ar}); 7.73–7.79 (m, 2H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 25.9, 26.0, 28.5, 31.5, 35.7 (CH_2); 37.2, 44.4 (CH); 47.8 (C); 50.3 (CH); 112.2 (CN); 118.2 (q, ^1J = 320.2 Hz, CF_3); 118.5 (C_{Ar}); 118.6, 127.2, 130.7, 130.8, 132.2, 132.4 (CH_{Ar}); 133.1, 137.5, 139.6, 141.0, 144.7 (C_{Ar}); 220.2 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −74.21. **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2860 (w), 2228 (m), 1735 (m), 1512 (w), 1417 (s), 1205 (s), 1138 (s), 1010 (m), 923 (s), 842 (s), 620 (m), 599 (s). **MS** (EI, 70 eV): *m/z* (%) = 504 (24), 503 (M^+, 100), 459 (30), 446 (16), 352 (29), 258 (23), 206 (34). **HRMS** (EI, 70 eV): Calculated for $C_{26}H_{24}F_3NO_4S$ (M^+), 503.13727; measured 503.13700.

4.4.7. 3-(Trifluoromethylsulfonyloxy)-4-(4-vinylphenyl)-13β-estra-1,3,5(10)-trien-17-one [4h]

4h was synthesized according to general procedure A using 4-vinylphenylboronic acid (0.32 mmol, 47 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow oil (102 mg, 96%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3); 1.48–1.71 (m, 6H, CH_{Alkyl}); 1.91–2.24 (m, 4H, CH_{Alkyl}); 2.36–2.61 (m, 5H, CH_{Alkyl}); 5.32 (dd, ^2J = 0.72 Hz, ^3J = 10.90 Hz, 1H, CH=C$H_{2,cis}$); 5.83 (dd, ^2J = 0.78 Hz, ^3J = 17.61 Hz, 1H, CH=C$H_{2,trans}$); 6.78 (dd, ^3J = 17.62 Hz, ^3J = 10.92 Hz, 1H, *C*H=CH_2); 7.16–7.22 (m, 3H, CH_{Ar}); 7.40 (d, ^3J = 8.91 Hz, 1H, CH_{Ar}); 7.48–7.56 (m, 2H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 25.9, 26.1, 28.5, 31.5, 35.8 (CH_2); 37.2, 44.5 (CH); 47.8 (C); 50.4 (CH); 114.4 ($CH_{2,Vinyl}$); 118.2 (CH_{Ar}); 118.3 (q, ^1J = 320.3 Hz, CF_3); 126.1, 126.2, 126.3, 129.8, 129.9 (CH_{Ar}); 133.9, 134.6 (C_{Ar}); 136.4 (CH_{Vinyl}); 137.2, 138.1, 140.5, 145.4 (C_{Ar}); 220.3 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −74.31. **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2931 (w), 1737 (m), 1710 (s), 1417 (m), 1359 (m), 1205 (s), 1139 (s), 921 (m), 842 (m), 603 (m). **MS** (EI, 70 eV): *m/z* (%) = 504 (M^+, 25), 259 (10), 233 (10), 208 (17), 207 (100), 69 (13), 55 (10). **HRMS** (EI, 70 eV): Calculated for $C_{27}H_{27}F_3O_4S$ (M^+), 504.15767; measured 504.15756.

4.4.8. 3-(Trifluoromethylsulfonyloxy)-4-(3-thienyl)-13β-estra-1,3,5(10)-trien-17-one [4i]

4i was synthesized according to general procedure A using 3-thienylboronic acid (0.32 mmol, 47 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow oil (90 mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3); 1.47–1.73 (m, 6H, CH_{Alkyl}); 1.94–2.17 (m, 4H, CH_{Alkyl}); 2.33–2.63 (m, 5H, CH_{Alkyl}); 6.99 (dd, ^3J = 4.93 Hz, ^4J = 1.25 Hz, 1H, CH_{HetAr}); 7.15 (d, ^3J = 8.76 Hz, 1H, CH_{HetAr}); 7.21 (dd, ^4J = 2.94 Hz, ^4J = 1.25 Hz, 1H, CH_{HetAr}); 7.38 (d, ^3J = 8.73 Hz, 1H, CH_{HetAr}); 7.43 (dd, ^3J = 4.95 Hz, ^4J = 2.95 Hz, 1H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 13.7 (CH_3); 21.5, 25.9, 26.1, 28.4, 31.5, 35.8 (CH_2); 37.2, 44.5 (CH); 47.8 (C); 50.4 (CH); 118.3 (CH_{Ar}); 118.3 (q, ^1J = 320.3 Hz, CF_3); 124.9, 125.7, 126.3, 128.7 (CH_{Ar}); 130.3, 133.7, 138.9, 140.5, 145.8 (C_{Ar}); 220.3 (C=O). **^{19}F NMR** (235 MHz, $CDCl_3$): δ = −74.23. **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2860 (w), 1737 (m), 1418 (s), 1250 (m), 1204 (s), 1138 (s), 1013 (m), 922 (s), 829 (m), 605 (m). **MS** (EI, 70 eV): *m/z* (%) = 485 (20), 484 (M^+, 75), 351 (100), 187 (40). **HRMS** (EI, 70 eV): Calculated for $C_{23}H_{23}F_3O_4S_2$ (M^+), 484.09844; measured 484.09770.

4.4.9. 3,4-Bis-(4-methoxyphenyl)-13β-estra-1,3,5(10)-trien-17-one [5a]

5a was synthesized according to general procedure B using 4-methoxyphenylboronic acid (0.63 mmol, 96 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a brown solid (99 mg, >99%). **mp.** 168–169 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3); 1.53–1.69 (m, 6H, CH_{Alkyl}); 1.92–2.18 (m, 4H, CH_{Alkyl}); 2.42–2.64 (m, 5H, CH_{Alkyl}); 3.73 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 6.68 (d, ^3J = 8.61 Hz, 2H, CH_{Ar}); 6.72–6.77 (m, 1H, CH_{Ar}); 6.79–6.89 (m, 2H, CH_{Ar}); 6.98 (d, ^3J = 8.60 Hz, 2H, CH_{Ar}); 7.04 (dd, ^3J = 8.32 Hz, ^4J = 1.97 Hz, 1H, CH_{Ar}); 7.24 (d, ^3J = 8.02 Hz, 1H, CH_{Ar}); 7.39 (d, ^3J = 8.13 Hz, 1H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 26.0, 26.6, 29.0, 31.7, 35.8 (CH_2); 37.5, 44.8 (CH); 47.9 (C); 50.6 (CH); 55.0, 55.0 (OCH_3); 112.9 (2xCH_{Ar}); 113.2, 113.3, 124.4, 127.4 (CH_{Ar}); 130.7 (2xCH_{Ar}); 131.2, 131.3 (CH_{Ar}); 132.7, 134.3, 135.3, 138.8, 139.1, 140.0, 157.7, 157.9 (C_{Ar}); 220.8 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2924 (m), 1737 (s), 1608 (m), 1510 (m), 1241 (s), 1107 (m), 1028 (s), 819 (s), 583 (m). **MS** (EI, 70 eV): *m/z* (%) = 468 (21), 467 (89), 466 (M^+, 100), 464 (9), 356 (5), 355 (5), 342 (8), 303 (6), 301 (7), 287 (5), 121 (7). **HRMS** (EI, 70 eV): Calculated for $C_{32}H_{34}O_3$ (M^+), 466.25025; measured 466.25053.

4.4.10. 3,4-Bis-(3-methoxyphenyl)-13β-estra-1,3,5(10)-trien-17-one [5b]

5b was synthesized according to general procedure B using 3-methoxyphenylboronic acid (0.63 mmol, 96 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow oil (91 mg, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.96 (s, 6H, 2xCH_3); 1.51–1.71 (m, 14H, CH_{Alkyl}); 1.93–2.24 (m, 8H, CH_{Alkyl}); 2.44–2.66 (m, 8H, CH_{Alkyl}); 3.60 (s, 3H, OCH_3); 3.61 (s, 3H, OCH_3); 3.63 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 6.53–6.54 (m, 1H, CH_{Ar}); 6.60–6.63 (m, 3H, CH_{Ar}); 6.65–6.69 (m, 2H, CH_{Ar}); 6.71–6.80 (m, 6H, CH_{Ar}); 7.04–7.22 (m, 4H,CH_{Ar}); 7.30 (d, ^3J = 8.10 Hz, 2H, CH_{Ar}); 7.43 (d, ^3J = 8.20 Hz, 2H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 26.0, 26.6, 28.8, 31.7, 35.8 (CH_2); 37.6, 44.8, 44.9 (CH); 47.9 (C); 50.6 (CH); 55.0, 55.1, 55.1, 55.3 (OCH_3); 111.9, 112.2, 122.3, 112.4, 114.9, 115.7, 116.0, 122.1, 122.2, 122.8, 122.9, 124.6, 127.3, 128.3, 128.4, 128.6, 128.9 (CH_{Ar}); 134.9, 134.9, 139.0, 139.0, 139.3, 140.1, 140.1, 141.7, 141.7, 143.1, 143.1, 158.6, 159.1, 159.2 (C_{Ar}); 220.7 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (m), 1735 (s), 1577 (m), 1465 (m), 1207 (s),

1039 (s), 908 (m), 777 (s), 729 (s). **MS** (EI, 70 eV): *m/z* (%) = 467 (31), 466 (M^+, 100), 271 (11), 67 (11), 55 (13). **HRMS** (EI, 70 eV): Calculated for $C_{32}H_{34}O_3$ (M^+), 466.25025; measured 466.24979.

4.4.11. 3,4-Bis-(4-tert-butylphenyl)-13β-estra-1,3,5(10)-trien-17-one [5c]

5c was synthesized according to general procedure B using 4-*tert*-butylphenylboronic acid (0.63 mmol, 112 mg) and was purified via column chromatography (heptane/ethyl acetate 10:1) to yield a white solid (107 mg, 98%). **mp.** 226–227 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3); 1.24 (s, 9H, $CH_{3,tBu}$); 1.28 (s, 9H, $CH_{3,tBu}$); 1.53–1.71 (m, 6H, CH_{Alkyl}); 1.94–2.18 (m, 4H, CH_{Alkyl}); 2.40–2.56 (m, 3H, CH_{Alkyl}); 2.64–2.70 (m, 2H, CH_{Alkyl}); 6.85 (dd, ^3J = 8.04 Hz, ^4J = 1.86 Hz, 1H, CH_{Ar}); 6.94 (d, ^3J = 8.34 Hz, 2H, CH_{Ar}); 7.04 (dd, ^3J = 8.02 Hz, ^4J = 1.84 Hz, 1H, CH_{Ar}); 7.10 (d, ^3J = 8.38 Hz, 2H, CH_{Ar}); 7.17 (dd, ^3J = 8.06 Hz, ^4J = 2.04 Hz, 1H, CH_{Ar}); 7.24 (dd, ^3J = 8.11 Hz, ^4J = 2.04 Hz, 1H, CH_{Ar}); 7.30 (d, ^3J = 8.08 Hz, 1H, CH_{Ar}); 7.41 (d, ^3J = 8.15 Hz, 1H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 13.9 (CH_3); 21.5, 26.0, 26.7, 29.0 (CH_2); 31.2, 31.3 ($CH_{3,tBu}$); 31.7 (CH_2); 34.2, 34.4 (C_{tBu}); 35.9 (CH_2); 37.6, 44.9 (CH); 48.0 (C); 50.6 (CH); 124.1 (2xCH_{Ar}); 124.3, 124.4, 124.5, 127.2 (CH_{Ar}); 129.4, 130.0 (2xCH_{Ar}); 135.0, 137.3, 138.8, 138.9, 139.6, 140.6, 148.5, 149.0 (C_{Ar}); 220.9 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2865 (m), 1745 (s), 1467 (m), 1391 (m), 1267 (m), 1114 (m), 837 (m), 598 (m). **MS** (EI, 70 eV): *m/z* (%) = 519 (16), 518 (M^+, 53), 503 (23), 207 (10), 73 (10), 67 (11), 57 (100), 55 (23), 41 (25), 29 (13). **HRMS** (EI, 70 eV): Calculated for $C_{38}H_{46}O$ (M^+), 518.35432; measured 518.35407.

4.4.12. 3,4-Bis-(4-fluorophenyl)-13β-estra-1,3,5(10)-trien-17-one [5d]

5d was synthesized according to general procedure B using 4-fluorophenylboronic acid (0.63 mmol, 88 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a white solid (92 mg, >99%). **mp.** 55–56 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3); 1.54–1.69 (m, 6H, CH_{Alkyl}); 1.92–2.18 (m, 4H, CH_{Alkyl}); 2.41–2.61 (m, 5H, CH_{Alkyl}); 6.79–6.85 (m, 2H, CH_{Ar}); 6.88–6.92 (m, 2H, CH_{Ar}); 6.95–7.00 (m, 3H, CH_{Ar}); 7.04–7.09 (m, 1H, CH_{Ar}); 7.23 (d, ^3J = 8.10 Hz, 1H, CH_{Ar}); 7.42 (d, ^3J = 8.09 Hz, 1H, CH_{Ar}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 26.0, 26.6, 29.0, 31.7, 35.8 (CH_2); 37.5, 44.8 (CH); 47.9 (C); 50.6 (CH); 114.4 (d, ^2J = 21.2 Hz, 2xCH_{Ar}); 114.8 (d, ^2J = 21.5 Hz, CH_{Ar}); 115.0 (d, ^2J = 21.5 Hz, CH_{Ar}); 124.8, 127.3 (CH_{Ar}); 131.2 (d, ^3J = 7.9 Hz, 2xCH_{Ar}); 131.8 (d, ^3J = 7.8 Hz, 2xCH_{Ar}); 135.2 (C_{Ar}); 136.0 (d, ^4J = 3.4 Hz, C_{Ar}); 137.6 (d, ^4J = 3.4 Hz, C_{Ar}); 138.5, 139.4, 139.5 (C_{Ar}); 161.4 (d, ^1J = 245.5 Hz, *C*-F); 161.5 (d, ^1J = 245.8 Hz, *C*-F); 220.6 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −116.66, −115.94. **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (m), 1735 (s), 1602 (m), 1508 (s), 1467 (m), 1218 (s), 1157 (s), 1006 (m), 819 (s), 592 (m). **MS** (EI, 70 eV): *m/z* (%) = 443 (45), 442 (M^+, 100), 277 (8). **HRMS** (EI, 70 eV): Calculated for $C_{30}H_{28}OF_2$ (M^+), 442.21027; measured 442.21000.

4.4.13. 3,4-Bis-(4-trifluoromethylphenyl)-13β-estra-1,3,5(10)-trien-17-one [5e]

5e was synthesized according to general procedure B using 4-trifluoromethylphenylboronic acid (0.63 mmol, 119 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a yellow oil (114 mg, >99%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.97 (s, 3H, CH_3); 1.55–1.71 (m, 6H, CH_{Alkyl}); 1.96–2.19 (m, 4H, CH_{Alkyl}); 2.44–2.60 (m, 5H, CH_{Alkyl}); 7.10 (d, ^3J = 8.06 Hz, 1H, CH_{Ar}); 7.14 (d, ^3J = 7.99 Hz, 2H, CH_{Ar}); 7.27 (dd, ^3J = 7.94 Hz, ^4J = 3.41 Hz, 2H, CH_{Ar}); 7.40 (d, ^3J = 8.11 Hz, 2H, CH_{Ar}); 7.49 (d, ^3J = 8.08 Hz, 2H, CH_{Ar}); 7.55 (d, ^3J = 8.01 Hz, 1H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 26.0, 26.5, 28.9, 31.6, 35.8 (CH_2); 37.5, 44.8 (CH); 47.9 (C); 50.5 (CH); 124.1 (q, ^1J = 272.0 Hz, CF_3); 124.1 (q, ^1J = 272.1 Hz, CF_3); 124.6 (q, ^3J = 3.70 Hz, 2xCH_{Ar}); 124.9 (q, ^3J = 3.79 Hz, CH_{Ar}); 125.1 (q, ^3J = 3.83 Hz, CH_{Ar}); 125.4, 127.4 (CH_{Ar}); 128.5 (q, ^2J = 32.4 Hz, *C*-CF_3); 128.9 (q, ^2J = 32.5 Hz, *C*-CF_3); 129.9 (2xCH_{Ar}); 130.5, 130.6 (CH_{Ar}); 134.9, 137.7, 138.8, 140.2 (C_{Ar}); 143.8 (q, ^5J = 1.18 Hz, C_{Ar}); 145.0 (q, ^5J = 1.17 Hz, C_{Ar}); 220.6 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −62.47. **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2930 (m), 1736 (m), 1616 (m), 1320 (s), 1119 (s), 1063 (s), 1017 (m), 821 (m), 731 (m). **MS** (EI, 70 eV): *m/z* (%) = 543 (45), 542 (M^+, 100), 498 (31), 485 (24), 432 (18), 429 (24), 377 (22), 359 (15), 270 (19), 79 (18), 69 (18), 68 (15), 67 (16), 55 (43), 43 (19), 41 (23). **HRMS** (EI, 70 eV): Calculated for $C_{32}H_{28}OF_6$ (M^+), 542.20389; measured 542.20447.

4.4.14. 3,4-Bis-(4-vinylphenyl)-13β-estra-1,3,5(10)-trien-17-one [5g]

5g was synthesized according to general procedure B using 4-vinylphenylboronic acid (0.63 mmol, 93 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a white solid (92 mg, 96%). **mp.** 72–73 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.97 (s, 3H, CH_3); 1.51–1.71 (m, 6H, CH_{Alkyl}); 1.92–2.22 (m, 4H, CH_{Alkyl}); 2.39–2.65 (m, 5H, CH_{Alkyl}); 5.17–5.25 (m, 2H, CH_{Vinyl}); 5.65–5.75 (m, 2H, CH_{Vinyl}); 6.59–6.74 (m, 2H, CH_{Vinyl}); 6.95 (dd, ^3J = 7.87 Hz, ^4J = 1.71 Hz, 1H, CH_{Ar}); 7.04 (d, ^3J = 8.28 Hz, 2H, CH_{Ar}); 7.13 (dd, ^3J = 7.80 Hz, ^4J = 1.53 Hz, 1H, CH_{Ar}); 7.20 (d, ^3J = 8.19 Hz, 2H, CH_{Ar}); 7.26–7.29 (m, 2H, CH_{Ar}); 7.34 (dd, ^3J = 7.91 Hz, ^4J = 1.79 Hz, 1H, CH_{Ar}); 7.44 (d, ^3J = 8.09 Hz, 1H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 26.0, 26.6, 28.9, 31.7, 35.8 (CH_2); 37.5, 44.9 (CH); 47.9 (C); 50.6 (CH); 113.3, 113.4 ($CH_{2,Vinyl}$); 124.7 (CH_{Ar}); 125.4 (2xCH_{Ar}); 125.7, 125.9, 127.5 (CH_{Ar}); 129.9 (2xCH_{Ar}); 130.4, 130.5 (CH_{Ar}); 135.1, 135.2, 135.5 (C_{Ar}); 136.5, 136.6 (CH_{Vinyl}); 138.8, 139.2, 139.9, 140.0, 141.3 (C_{Ar}); 220.8 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (m), 1735 (s), 1627 (w), 1467 (m), 1255 (m), 1006 (m), 987 (m), 848 (m), 821 (s). **MS** (EI, 70 eV): *m/z* (%) = 459 (40), 458 (M^+, 100), 291 (11), 55 (12). **HRMS** (EI, 70 eV): Calculated for $C_{34}H_{34}O$ (M^+), 458.26042; measured 458.26005.

4.4.15. 3,4-Bis-(3-thienyl)-13β-estra-1,3,5(10)-trien-17-one [5h]

5h was synthesized according to general procedure B using 3-thienylboronic acid (0.63 mmol, 93 mg) and was purified via column chromatography (heptane/ethyl acetate 5:1) to yield a brown solid (80 mg, 91%). **mp.** 195–196 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3); 1.53–1.67 (m, 6H, CH_{Alkyl}); 1.95–2.19 (m, 4H, CH_{Alkyl}); 2.35–2.57 (m, 3H, CH_{Alkyl}); 2.64–2.69 (m, 2H, CH_{Alkyl}); 6.72 (dd, ^3J = 4.97 Hz, ^4J = 1.19 Hz, 1H, CH_{Ar}); 6.85–6.90 (m, 3H, CH_{Ar}); 7.08 (dd, ^3J = 4.97 Hz, ^4J = 2.99 Hz, 1H, CH_{Ar}); 7.29 (dd, ^3J = 4.86 Hz, ^4J = 2.95 Hz, 1H, CH_{Ar}); 7.36–7.38 (m, 2H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 13.8 (CH_3); 21.5, 26.0, 26.6, 28.7, 31.6, 35.8 (CH_2); 37.6, 44.8 (CH); 47.9 (C); 50.5 (CH); 122.4, 123.2, 124.0, 124.9, 126.9, 128.7, 129.5 (CH_{Ar}); 134.5, 135.2, 136.0, 139.3, 140.3, 142.0 (C_{Ar}); 220.7 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu}$ = 2929 (m), 1729 (s), 1471 (w), 1259 (m), 1076 (m), 1010 (m), 850 (m), 788 (s), 765 (s), 678 (m). **MS** (EI, 70 eV): *m/z* (%) = 419 (22), 418 (M^+, 100), 260 (16), 259 (16), 258 (19), 254 (16), 247 (23), 222 (15), 221 (25), 79 (36), 77 (17), 67 (35), 55 (67), 45 (21), 43 (15), 41 (50), 39 (19), 29 (35). **HRMS** (EI, 70 eV): Calculated for $C_{26}H_{26}OS_2$ (M^+), 418.14196; measured 418.14117.

4.4.16. 3-(4-Trifluoromethylphenyl)-4-(4-tert-butylphenyl)-13β-estra-1,3,5(10)-trien-17-one [6a]

6a was synthesized according to general procedure C using 4-trifluoromethylphenylboronic acid (0.281 mmol, 53 mg) and was purified via column chromatography (heptane/ethyl acetate 10:1) to yield a white solid (85 mg, 86%). **mp.** 176–177 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3); 1.29 (s, 9H, $CH_{3,tBu}$); 1.50–1.71 (m, 6H, CH_{Alkyl}); 1.94–2.18 (m, 4H, CH_{Alkyl}); 2.43–2.68 (m, 5H, CH_{Alkyl}); 6.84 (dd, ^3J = 8.03 Hz, ^4J = 1.73 Hz, 1H, CH_{Ar}); 7.04 (dd, ^3J = 8.02 Hz, ^4J = 1.69 Hz, 1H, CH_{Ar}); 7.14 (d, ^3J = 8.00 Hz, 2H,

CH_{Ar}); 7.20 (dd, $^3J = 8.06$ Hz, $^4J = 1.89$ Hz, 1H, CH_{Ar}); 7.24–7.29 (m, 2H, CH_{Ar}); 7.35 (d, $^3J = 8.11$ Hz, 2H, CH_{Ar}); 7.44 (d, $^3J = 8.04$ Hz, 1H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 26.0, 26.6, 28.9 (CH_2); 31.3 ($CH_{3,tBu}$); 31.7 (CH_2); 34.4 (C_{tBu}); 35.8 (CH_2); 38.0, 44.9 (CH); 47.9 (C); 50.6 (CH); 124.2 (q, $^3J = 3.70$ Hz, 2xCH_{Ar}); 124.3 (q, $^1J = 271.9$ Hz, CF_3); 124.6, 124.7, 124.9, 127.1 (CH_{Ar}); 127.9 (q, $^2J = 32.2$ Hz, *C*-CF_3); 129.8, 129.9 (CH_{Ar}); 130.0 (2xCH_{Ar}); 135.5, 136.6, 138.1, 140.0, 140.4 (C_{Ar}); 145.7 (q, $^5J = 1.21$ Hz, C_{Ar}); 149.8 (C_{Ar}); 220.7 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): $\delta = -62.43$. **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2951$ (w), 1739 (s), 1454 (w), 1322 (s), 1159 (s), 1107 (s), 1063 (m), 815 (m), 618 (m). **MS** (EI, 70 eV): *m/z* (%) = 531 (37), 530 (M^+, 100), 516 (36), 515 (100), 57 (21). **HRMS** (EI, 70 eV): Calculated for $C_{35}H_{37}F_3O$ (M^+), 530.27910; measured 530.27937.

4.4.17. 3-(4-Methoxyphenyl)-4-(4-tert-butylphenyl)-13β-estra-1,3,5(10)-trien-17-one [6b]

6b was synthesized according to general procedure C using 4-methoxyphenylboronic acid (0.281 mmol, 43 mg) and was purified via column chromatography (heptane/ethyl acetate 10:1) to yield a white solid (82 mg, 90%). **mp.** 164–165 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H, CH_3); 1.30 (s, 9H, $CH_{3,tBu}$); 1.54–1.68 (m, 6H, CH_{Alkyl}); 1.91–2.18 (m, 4H, CH_{Alkyl}); 2.43–2.66 (m, 5H, CH_{Alkyl}); 3.73 (s, 3H, OCH_3); 6.65 (d, $^3J = 8.84$ Hz, 2H, CH_{Ar}); 6.87 (dd, $^3J = 8.01$ Hz, $^4J = 1.70$ Hz, 1H, CH_{Ar}); 6.96 (d, $^3J = 8.84$ Hz, 2H, CH_{Ar}); 7.05 (dd, $^3J = 8.00$ Hz, $^4J = 1.65$ Hz, 1H, CH_{Ar}); 7.21 (dd, $^3J = 8.02$ Hz, $^4J = 1.87$ Hz, 1H, CH_{Ar}); 7.25–7.30 (m, 2H, CH_{Ar}); 7.40 (d, $^3J = 8.31$ Hz, 1H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 26.0, 26.7, 29.0 (CH_2); 31.4 ($CH_{3,tBu}$); 31.7 (CH_2); 34.4 (C_{tBu}); 35.9 (CH_2); 38.0, 44.9 (CH); 47.9 (C); 50.6 (CH); 55.1 (OCH_3); 112.8 (2xCH_{Ar}); 124.4, 124.5, 124.7, 127.4, 129.8, 130.0 (CH_{Ar}); 130.8 (2xCH_{Ar}); 134.3, 135.2, 137.3, 138.8, 138.9, 140.4, 149.1, 157.7 (C_{Ar}); 220.9 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2933$ (m), 1736 (s), 1608 (m), 1515 (m), 1465 (m), 1244 (s), 1178 (m), 926 (m), 819 (s), 597 (s). **MS** (EI, 70 eV): *m/z* (%) = 493 (39), 492 (M^+, 100), 57 (12). **HRMS** (EI, 70 eV): Calculated for $C_{35}H_{40}O_2$ (M^+), 492.30228; measured 492.30225.

4.4.18. 3-(3-Thienyl)-4-(4-tert-butylphenyl)-13β-estra-1,3,5(10)-trien-17-one [6c]

6c was synthesized according to general procedure C using 3-thienylboronic acid (0.281 mmol, 36 mg) and was purified via column chromatography (heptane/ethyl acetate 10:1) to yield a yellow solid (61 mg, 70%). **mp.** 76–77 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): $\delta = 0.94$ (s, 3H, CH_3); 1.33 (s, 9H, $CH_{3,tBu}$); 1.53–1.63 (m, 6H, CH_{Alkyl}); 1.93–2.18 (m, 4H, CH_{Alkyl}); 2.46–2.61 (m, 5H, CH_{Alkyl}); 6.69 (dd, $^3J = 4.97$ Hz, $^4J = 1.12$ Hz, 1H, CH_{Ar}); 6.76 (dd, $^4J = 2.87$ Hz, $^4J = 1.12$ Hz, 1H, CH_{Ar}); 6.95 (dd, $^3J = 7.92$ Hz, $^4J = 1.75$ Hz, 1H, CH_{Ar}); 7.01 (dd, $^3J = 4.94$ Hz, $^4J = 3.03$ Hz, 1H, CH_{Ar}); 7.07 (dd, $^3J = 7.89$ Hz, $^4J = 1.86$ Hz, 1H, CH_{Ar}); 7.30–7.34 (m, 2H, CH_{Ar}); 7.37–7.38 (m, 2H, CH_{Ar}). **^{13}C NMR** (63 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 26.0, 26.6, 29.0 (CH_2); 31.4 ($CH_{3,tBu}$); 31.7 (CH_2); 34.5 (C_{tBu}); 35.8 (CH_2); 38.0, 44.8 (CH); 47.9 (C); 50.6 (CH); 122.7, 123.6, 124.5, 124.8, 125.0, 126.9, 129.1, 129.4, 129.5 (CH_{Ar}); 133.9, 135.4, 137.5, 139.2, 140.2, 142.9, 149.5 (C_{Ar}); 220.8 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2925$ (m), 1737 (s), 1511 (w), 1463 (m), 1361 (m), 1257 (m), 1006 (m), 829 (s), 790 (s), 649 (m). **MS** (EI, 70 eV): *m/z* (%) = 469 (35), 468 (M^+, 100), 453 (22), 247 (19), 57 (20). **HRMS** (EI, 70 eV): Calculated for $C_{32}H_{36}OS$ (M^+), 468.24814; measured 468.24721.

4.4.19. 3-(4-Vinylphenyl)-4-(4-tert-butylphenyl)-13β-estra-1,3,5(10)-trien-17-one [6d]

6c was synthesized according to general procedure C using 4-vinylphenylborinic acid (0.281 mmol, 42 mg) and was purified via column chromatography (heptane/ethyl acetate 10:1) to yield a colourless oil (88 mg, 97%). **^{1}H NMR** (300 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H, CH_3); 1.29 (s, 9H, $CH_{3,tBu}$); 1.52–1.70 (m, 6H, CH_{Alkyl}); 1.92–2.18 (m, 5H, CH_{Alkyl}); 2.43–2.66 (m, 4H, CH_{Alkyl}); 5.17 (dd, $^3J = 10.90$ Hz, $^2J = 0.74$ Hz, 1H, CH=C$H_{2,cis}$); 5.66 (dd, $^3J = 17.61$ Hz, $^2J = 0.81$ Hz, 1H, CH=C$H_{2,trans}$); 6.63 (dd, $^3J = 17.62$ Hz, $^3J = 10.90$ Hz, 1H, *CH*=CH_2); 6.88 (dd, $^3J = 8.03$ Hz, $^4J = 1.89$ Hz, 1H, CH_{Ar}); 7.01 (d, $^3J = 8.26$ Hz, 2H, CH_{Ar}); 7.06 (dd, $^3J = 8.05$ Hz, $^4J = 1.87$ Hz, 1H, CH_{Ar}); 7.14–7.22 (m, 3H, CH_{Ar}); 7.27 (d, $^3J = 8.70$ Hz, 2H, CH_{Ar}); 7.42 (d, $^3J = 8.20$ Hz, 1H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 26.0, 26.7, 29.0 (CH_2); 31.4 ($CH_{3,tBu}$); 31.7 (CH_2); 34.4 (C_{tBu}); 35.8 (CH_2); 38.0, 44.9 (CH); 47.9 (C); 50.6 (CH); 113.2 ($CH_{2,Vinyl}$); 124.5, 124.5, 124.8 (CH_{Ar}); 125.2 (2xCH_{Ar}); 127.4, 129.8 (CH_{Ar}); 129.9 (2xCH_{Ar}); 135.0, 135.3 (C_{Ar}); 136.6 (CH_{Vinyl}); 137.1138.9, 139.2, 140.3, 141.5, 149.2 (C_{Ar}); 220.8 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2940$ (m), 1737 (s), 1511 (w), 1464 (m), 1257 (m), 1006 (m), 905 (m), 820 (s). **MS** (EI, 70 eV): *m/z* (%) = 489 (38), 488 (M^+, 100), 474 (10), 473 (27), 57 (11). **HRMS** (EI, 70 eV): Calculated for $C_{36}H_{40}O$ (M^+), 488.30737; measured 488.30708.

4.4.20. 3-(Phenylethynyl)-4-(4-tert-butylphenyl)-13β-estra-1,3,5(10)-trien-17-one [7]

4d (0.42 mmol, 225 mg), phenylacetylene (0.50 mmol, 51 mg), diisopropylamine (1.26 mmol, 127 mg), $Pd(PPh_3)_4$ (10 mol%, 48 mg), CuI (10 mol%, 8 mg) and DMF (6 mL) were heated in a pressure tube under argon atmosphere at 100 °C for 20 h. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with Na_2SO_4 and filtrated. The crude product was purified by column chromatography (heptane/ethyl acetate 10:1) to yield a yellow solid (119 mg, 58%). **mp.** 186–187 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H, CH_3); 1.43 (s, 9H, $CH_{3,tBu}$); 1.52–1.64 (m, 6H, CH_{Alkyl}); 1.92–2.21 (m, 4H, CH_{Alkyl}); 2.39–2.67 (m, 5H, CH_{Alkyl}); 6.97–7.01 (m, 2H, CH_{Ar}); 7.17–7.34 (m, 6H, CH_{Ar}); 7.42–7.52 (m, 3H, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3); 21.5, 25.9, 26.4, 28.6 (CH_2); 31.5 ($CH_{3,tBu}$); 31.6 (CH_2); 34.6 (C_{tBu}); 35.8 (CH_2); 37.5, 44.9 (CH); 47.9 (C); 50.6 (CH); 89.9, 92.5 (C≡C); 121.1, 123.6 (C_{Ar}); 124.2, 124.8, 124.9, 127.6 (CH_{Ar}); 127.9 (2xCH_{Ar}); 128.4, 129.0, 129.3 (CH_{Ar}); 131.2 (2xCH_{Ar}); 134.9, 137.6140.5, 144.7, 149.6 (C_{Ar}); 220.7 (C=O). **IR** (ATR, cm^{-1}): $\tilde{\nu} = 2939$ (m), 1738 (s), 1493 (w), 1257 (w), 1112 (w), 1007 (m), 834 (m), 757 (s), 691 (s). **MS** (EI, 70 eV): *m/z* (%) = 487 (16), 485 (M^+, 39), 430 (100), 429 (66), 307 (10), 303 (12), 291 (12), 289 (13), 266 (22), 265 (58), 57 (24). **HRMS** (EI, 70 eV): Calculated for $C_{36}H_{38}O$ (M^+), 486.29172; measured 486.29159.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.02.015.

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10. CCDC 1815969 and 1815970 contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.