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

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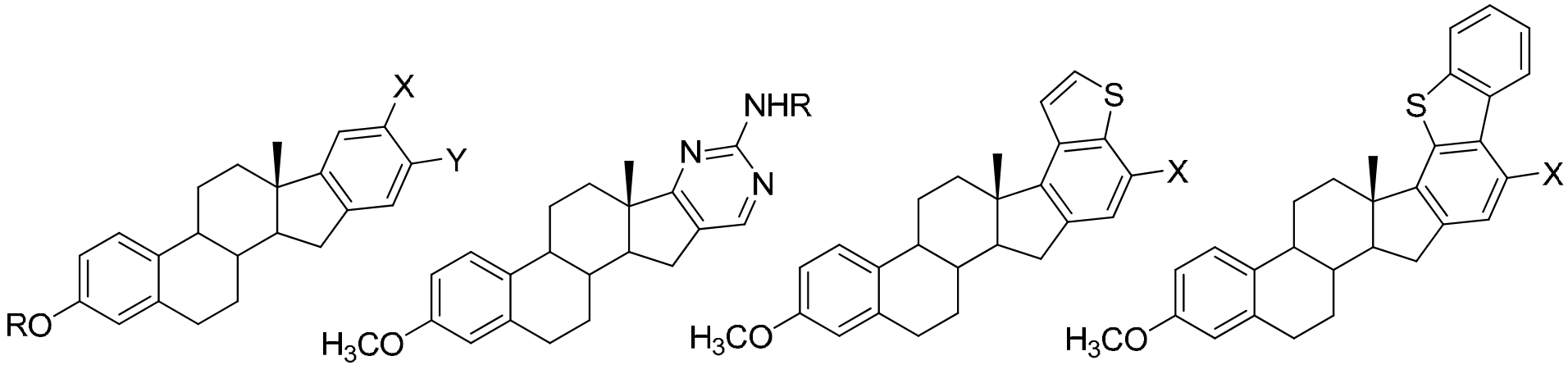



**1**

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

**2**

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

**3**

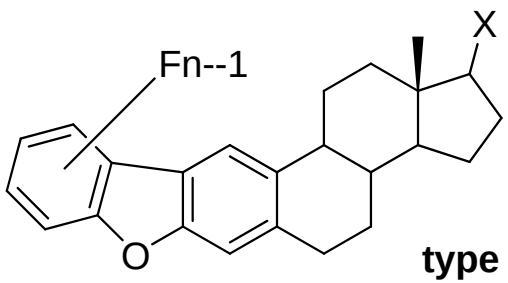
**3a**: X = H
**3b**: X = $COCH_3$ [Ref. 3]

**4**

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

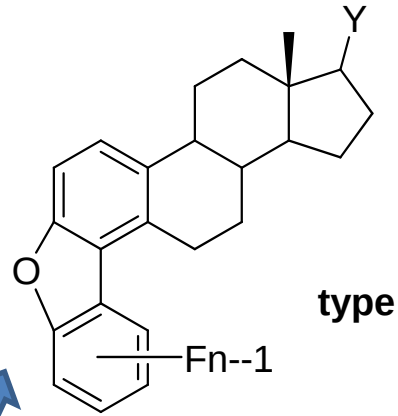
**Figure 1**

16,17-areno annelated estrane derivatives, previously prepared by the group.
Applications are found as ligands to the estrogen receptor and as chiral dopants in organic materials .



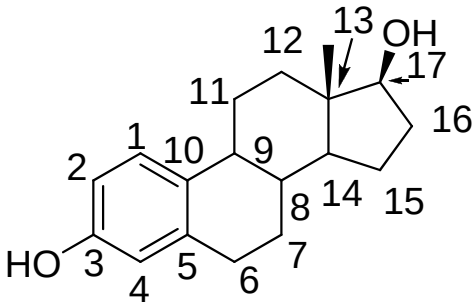

**type A**

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




**type B**

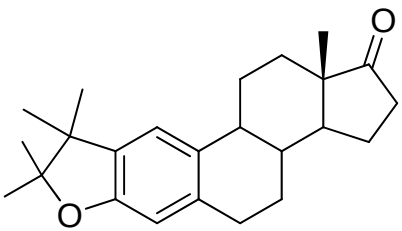
Y: =O (keto); -OH (hydroxy)




**9**

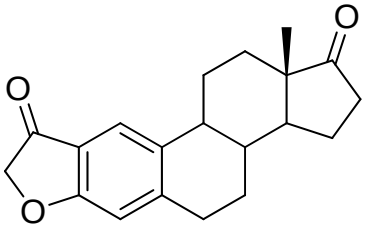
estradiol with atom-numbering scheme

**Figure 2** Target structures of this work



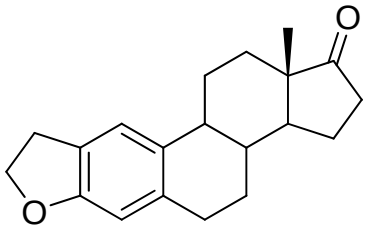

**5**

Jefferson and Scheinmann [ref. 5]



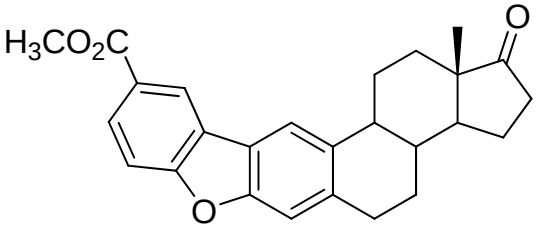

**6**

Omar et al. [ref. 6]




**7**

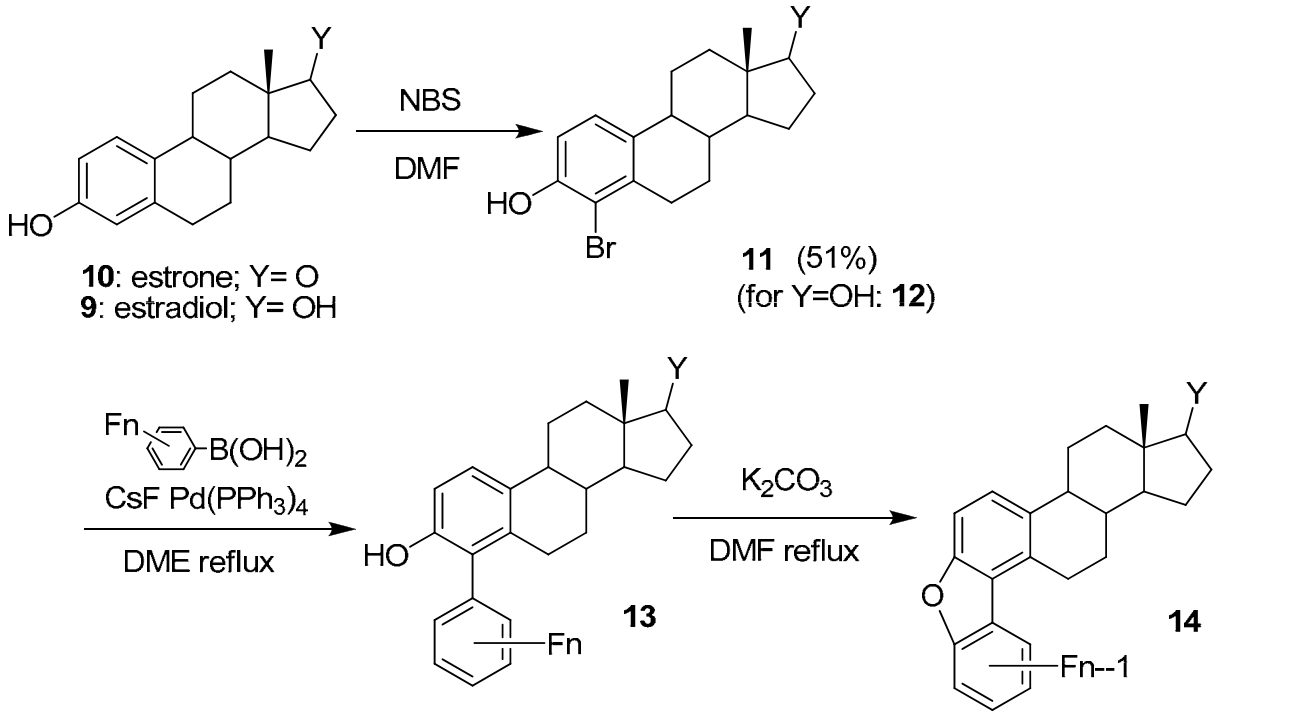
Lehmann [ref. 7]




**8**

Xiao et al. [ref. 8]

**Figure 3** A-ring furano-annelated estranes, published by other groups




**10**: estrone; Y= O
**9**: estradiol; Y= OH

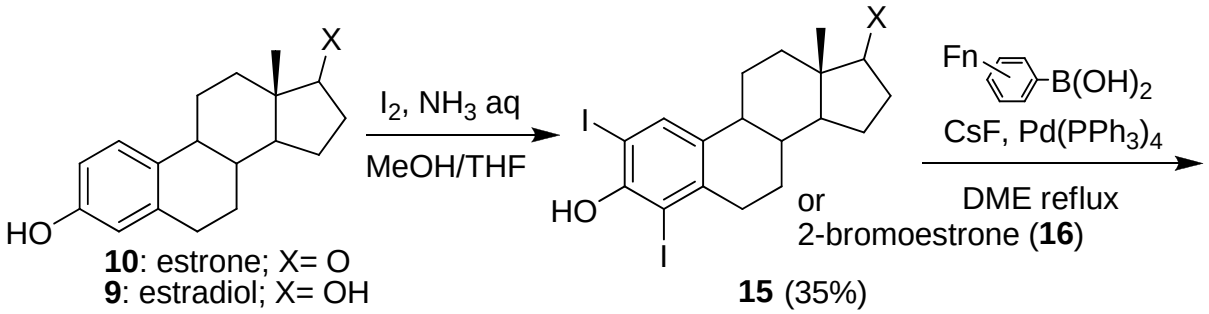
**11** (51%)
(for Y=OH: **12**)

| No. | X | Fn |
|---|---|---|
| **13a** | O | 2,5-F (21%) |
| **13b** | O | 2,3-F (3%) |
| **13c** | OH | 2,4-F |

| No. | X | Fn--1 |
|---|---|---|
| **14a** | O | 5-F (9%) |
| **14b** | O | 3-F (84%) |
| **14c** | OH | 4-F (16%) |

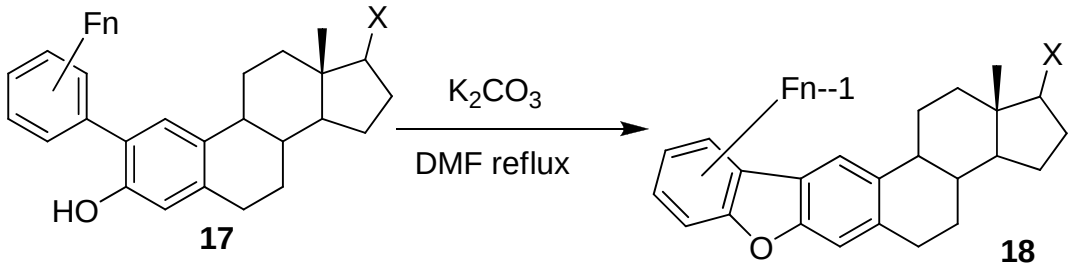
**Scheme 1**

Selective bromination of the estradiol derivative at C4 with NBS, DMF is followed by an arylation through a Suzuki-Miyaura reaction utilizing arylboronic acids bearing a 2-fluoro substituent. Subsequent i*pso*-substitution of the 2-fluoro substituent by the phenoxy group gives the benzofuranoestranes **14**.




**10**: estrone; X= O
**9**: estradiol; X= OH

**15** (35%)




**17**

**18**

| No. | X | Fn | |
|---|---|---|---|
| **17a** | O | 2,3-F | (64%) |
| **17b** | OH | 2,4-F | (75%) |
| **17c** | OH | 2-F | (49%) |
| **17d** | OH | 4-F | (77%) |
| **17e** | OH | 4-$CF_3$ | (63%) |
| **17f** | OH | 4-OMe | (66%) |

| No. | X | Fn--1 | |
|---|---|---|---|
| **18a** | O | 3-F | (35%) |
| **18b** | OH | 4-F | (80%) |

**Scheme 2**

The authors were not able to carry out iodination selectively at C2 or C4. Rather, iodination of 3-OH non-protected estranes led to double iodination at C2 and at C4, such as found in **15**. The Suzuki coupling, however, could be performed with **15** selectively at C2. At the same time, deiodination occurred at C4 to give compounds **17**. These could also be produced by reaction with 2-bromoestrone/estradiol. Cyclization led to benzofuranoestranes **18**.

## Literature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