Regiospecific Synthesis of 2-Fluoro-3-*O*-methylestrone using Caesium Fluorosulfate

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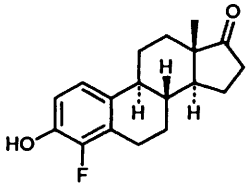
The regiospecific synthesis of an *A*-ring fluorinated estrone is described. Treatment of the η^6-arenetricarbonylchromium(0) complex **4**, derived from 3-*O*-methylestrone, with butyllithium followed by transmetallation to the arylboronic acid was found to give a single regioisomer. This could be elaborated further to give 2-fluoro-3-*O*-methylestrone in 27% yield using caesium fluoroxysulfate. The fluorination step was found to be sufficiently rapid to be of potential use in PETT applications with the ^{18}F radioisotope.

The synthesis of *A*-ring fluorinated estrones (such as **1**) has been much investigated over the last three decades,[1] originally because they were used as chemotherapy reagents. More recently, this interest has been due to their role as radiolabelled, diagnostic tools in the non-invasive technique of Positron Emission Transaxial Tomography ('PETT scanning') using the unstable ^{18}F nucleus.[2]



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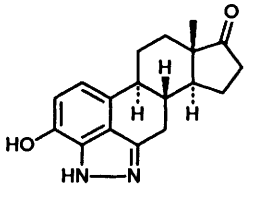

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The electron-rich nature of the aromatic *A*-ring does not lend itself to the currently popular nucleophilic substitution processes,[3] therefore other approaches are necessary. The earliest methods for the synthesis of *A*-ring fluorinated estrones were based on the fluorodeamination reaction using aryldiazonium tetrafluoroborate salts as substrates. Yields of up to 35% of fluoroestrones were obtained.[4] This approach suffered from the drawback that the initial introduction of the amino functionality (generally *via* nitration and subsequent reduction) gave 1:1 mixtures of 2- and 4-substituted regioisomers which required separation before the fluorination step.

The acid-catalysed decomposition of *N,N*-dialkyltriazenes was originally reported to be a suitable method for the synthesis of 3-*O*-methyl-4-fluoroestrone[5] but a later report claimed that the major product was the benzpyrazole **2** in 36% yield which resulted from *in situ* trapping of the intermediate diazonium cation.[6]

More recently, electrophilic fluorinating agents have been used for the direct fluorination of estrone systems. *N*-Fluoro-3,5-dichloropyridinium triflate was shown to react with estrone to give a 1:1 mixture of 2-fluoro- and 4-fluoro-estrones in a total of 52% yield.[7] A 1:1 product mixture (60% yield) was also found in the reaction of estradiol with the same fluorinating agent.[8] Page has reported[9] that the reaction of estrone with the parent *N*-fluoropyridinium triflate gives a mixture of 2-fluoro- and 4-fluoro-estrone (in a ratio of 2.5:1) in 78% yield. These fluorinated isomers could only be separated after further elaboration and the problem of isomeric mixtures is common to all conventional electrophilic fluorinations of estrone.

We have recently demonstrated that arylboronic acids and certain of their derivatives are readily converted into the corresponding fluoroaromatics by treatment with the inorganic reagent, caesium fluoroxysulfate (CFS) in acetonitrile.[10] This electrophilic fluorinating agent is an easily handled, crystalline solid which can be readily prepared from dilute molecular fluorine and aqueous caesium sulfate. It has been used to introduce fluorine into a wide variety of organic substrates.[11]

It therefore appeared likely that if a single arylboronic acid could be prepared from an estrone derivative, then this would provide a regiospecific route to *A*-ring fluorinated estrones *via* the fluorodeboronation process. As a further criterion, the fluorination step should be sufficiently rapid to allow its use in radiolabelling applications with ^{18}F. For this to be so, the time for this final step should be of the order of $\leqslant$4 h or 2 half-lives of this isotope ($t_{\frac{1}{2}}$ 110.9 min).

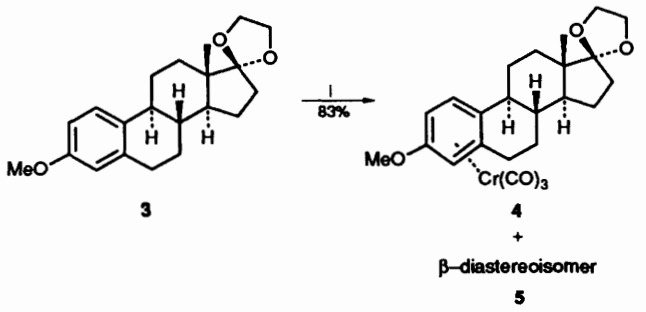
Results and Discussion

The directed metallation reaction has been applied to the synthesis of a number of arylboronic acids for use in the palladium-catalysed coupling reaction with aryl bromides.[12] It was considered that the methoxy group of 3-*O*-methylestrone would provide a directing group for *ortho*-metallation[13] after suitable protection of the C_{17} ketone.

3-*O*-Methylestrone was readily protected as the ketal **3** under standard conditions [catalytic toluene-*p*-sulfonic acid (PTSA), toluene, reflux] in 97% yield. However **3** proved to be inert to a variety of conditions (BuLi, BuLi/TMEDA or Bu^{s}Li/−78 °C/THF), and only reclaimed starting material was isolated (>95%) after quenching the reaction mixture with chlorotrimethylsilane.

Treatment of the ketal **3** under the Snieckus conditions[14] (Bu^{s}Li/TMEDA/−78 °C/THF) followed by chlorotrimethylsilane (TMSCl) quench gave only the deprotected 3-*O*-methylestrone in 82% yield. The chlorosilane was not necessary since comparable yields were obtained in its absence. Presumably deprotonation of a ketal α-hydrogen is followed by ring opening in a similar manner to the well known reaction of THF with strong bases.[15]

In order to overcome this problem, the acidities of the aromatic protons were increased by formation of the estrone-tricarbonylchromium(0) complex. Complexation was also expected to lead to an enhancement in the directing ability of the methoxy group.[16]

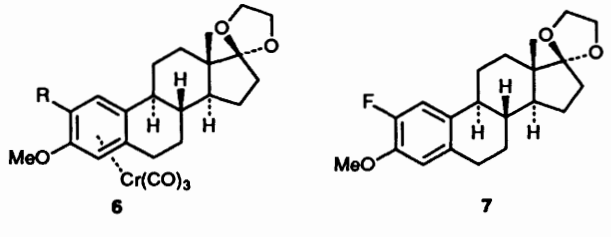


Scheme 1 *Reagents and conditions:* i, $Cr(CO)_6$, Bu_2O/THF, 130–140 °C

Formation of the complex was achieved by treatment of **3** with hexacarbonylchromium at 130–140 °C in Bu_2O/THF under strictly anaerobic conditions. This gave an 83% yield of the bright yellow, air-stable complex as a 1.6:1 mixture of the α- and β-diastereoisomers **4**, **5** which were readily separated by chromatography. The stereochemistry of these diastereoisomers was assigned by comparison of the NMR spectra with published 500 MHz NMR data for the related estradiol complexes the absolute stereochemistry of which had been determined by X-ray analysis.[17]

The favoured site for metallation of **4** was established by generating the aryllithium (with BuLi in THF at −78 °C) and trapping this with TMSCl. The crude reaction mixture was decomplexed (by exposure of a dichloromethane solution to air and sunlight) and after chromatography, 2-trimethylsilyl-3-*O*-methylestrone **6** (R = $SiMe_3$) was obtained in 88% yield. The 4-silylated isomer was not observable by 270 MHz NMR spectroscopic analysis of the crude reaction mixture. This substrate was not a suitable candidate for the fluorination procedure since it had been previously demonstrated that arylsilanes were not sufficiently reactive to undergo preferential *ipso* fluorination. Conventional electrophilic substitution occurred at a competitive rate to fluorodesilylation to give mixed products.[10]

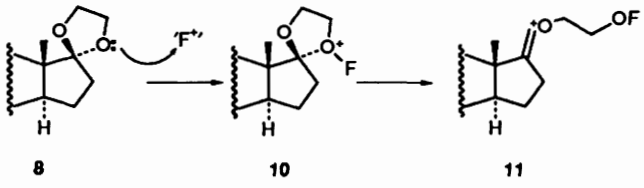
The arylboronic acid **6** [R = $B(OH)_2$], derived from **4**, was formed from the aryllithium *via* transmetallation with $B(OPr^i)_3$ as a highly insoluble, air-stable complex in 78% yield. The insolubility of **6** [R = $B(OH)_2$] proved to be problematic but it was found that the addition of CFS to a suspension of **6** [R = $B(OH)_2$] in methanol induced rapid decomplexation and gave a homogeneous solution. It was hoped to carry out fluorination directly on this solution to give the fluorinated ketal **7**. On carrying out this reaction at either room temperature or 0 °C, however, no aromatic compounds could be isolated although products were detected at early stages of the reaction (by TLC).



It was known that CFS would only oxidise Cr^{II} as far as Cr^{III} [18] and this should also be expected for the Cr^0 liberated on treatment of the complex **6** [R = $B(OH)_2$] with CFS. The effect of the resulting Cr^{III} species on either the free ligand **8** or the fluorination product was not known. Decomplexation of the complex **6** [R = $B(OH)_2$] was therefore necessary but did not occur on exposing a suspension of the complexed boronic acid **6** [R = $B(OH)_2$] in dichloromethane to air and sunlight. It was later found that **6** [R = $B(OH)_2$] dissolved in pyridine, probably *via* adduct formation, and exposure of this solution to air and sunlight gave the free ligand **8** in 84% yield. The latter could be formed in an improved, overall yield of 82% from the starting complex **4** by carrying through the synthesis without any isolation of the intermediate boronic acid complex **6** [R = $B(OH)_2$].

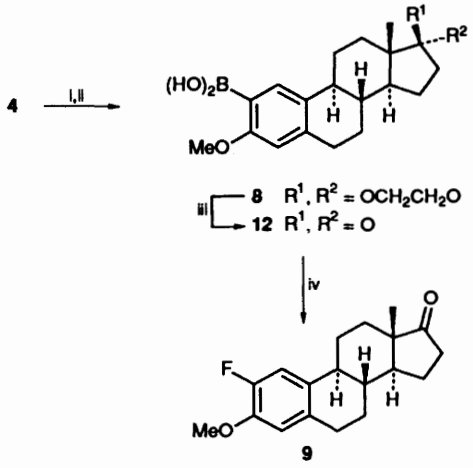
The reaction of the ketal boronic acid **8** with CFS in an acetonitrile–dichloromethane system led to the isolation of the 2-fluorinated ketal **7** in 14% yield after 2 h. As a minor product, the deprotected 2-fluorinated ketone **9** was also formed in 5% yield. Leaving the reaction for longer periods of time or adding further CFS to the reaction mixture caused product decomposition.

A likely pathway for the deketalisation process (Scheme 2) involves attack of a ketal oxygen on CFS giving an *O*-fluoro-oxonium ion **10** which should undergo ring-opening. The fluoroxy reagent **11** thus generated could then follow a number of pathways (*e.g.* loss of HF, reaction as an F^+ source). Such attack of an 'F^+' species on a ketal oxygen has been postulated in reactions of molecular fluorine,[19] as well as in the bromination of ketals.[20]



Scheme 2

The presence of the ketal was therefore undesirable and deprotection to give 2-dihydroxyboryl-3-*O*-methylestrone **12** was necessary. Treatment of **8** with the mild acid pyridinium toluene-*p*-sulfonate (PPTS) in acetone caused only protolysis of the C–B bond to give the free arene ketal **3** in 63% yield. It is probable that the presence of the pyridine enhances the leaving group ability of the dihydroxyboryl group by tetra-coordination of the boron. A similar increase in the leaving group ability of arylboronic acids, on adduct formation with amines, was also noted in fluorination reactions with CFS in acetonitrile.[10]



Scheme 3 *Reagents:* i, BuLi, THF, −78 °C then $B(OPr^i)_3$ (78%); ii, pyridine, air, sunlight (84%); iii, PTSA, acetone (96%); iv, CFS, MeCN/dichloromethane (27%)

A change of acid to PTSA in acetone caused deketalisation of **4** to give the ketone boronic acid **12** in 96% yield (Scheme 3). Treatment of **12** with CFS in an acetonitrile–dichloromethane

mixture gave the *ipso*-fluorination product **9** in 27% yield after only 65 min reaction time. This compares directly to the BF_3-catalysed reaction of estradiol with CFS which required 24 h to give a 40% yield of 2-fluoro- and 4-fluoro-estradiol as a 1:1 mixture.[21]

It is thus apparent that the presence of the ring bonded boron causes a significant increase in both the rate of aromatic fluorination and the regioselectivity observed. The high yields of the earlier steps to give the fluorination precursor and the speed of the final reaction makes it a suitable pathway to [^{18}F]-2-fluoro-3-*O*-methylestrone and should also be applicable to other *A*-ring fluorinated estrogens.

Experimental

M.p.s were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1700 FT spectrometer. ^{1}H NMR spectra were recorded on a Bruker WM250 (250 MHz), a JEOL GSX270 (270 MHz) and a Bruker AM500 (500 MHz) using residual undeuteriated solvent as reference. *J* Values are given in Hz. ^{19}F NMR spectra were recorded on a JEOL FX90Q (84 MHz) with $CFCl_3$ as reference. Elemental analyses and mass spectra were recorded at Imperial College, some accurate masses were recorded at the SERC facility at University College, Swansea. Tetrahydrofuran (THF) and diethyl ether were distilled immediately before use from sodium benzophenone ketyl, dichloromethane and acetonitrile were distilled from calcium hydride. Light petroleum refers to that fraction boiling in the range 40–60 °C. Caesium fluoroxysulfate was prepared according to the method of Zupan.[22] Other materials were purified according to literature procedures.[23]

η^6-α- *and* β-[17,17-*Ethylenedioxy*-3-*methoxyestra*-1,3,5(10)-*triene*]*tricarbonylchromium*(0), **4**, **5**.—A solution of 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-triene[24] (2.100 g, 6.37 mmol) and hexacarbonylchromium (1.936 g, 8.8 mmol, 1.38 equiv.) in a mixture of dibutyl ether–THF (9:1; 60 cm^3) was degassed and then heated at 130–140 °C under a purified nitrogen atmosphere using a modified Strohmeier apparatus.[25] After 28 h, the reaction mixture was allowed to cool to room temperature then filtered through a 2 cm silica pad which was flushed with ether to collect all of the complex. The solution was evaporated and the residue subjected to flash chromatography (SiO_2, 10% ether in light petroleum) to yield initially η^6-β-(17,17-*ethylenedioxy*-3-*methoxyestra*-1,3,5(10)-*triene*)*tricarbonylchromium*(0) **5** as a light yellow solid (0.932 g, 33%); m.p. 162–164 °C; ν_{max}(Nujol)/cm^{-1} 1955, 1882, 1866 (C≡O), 1547, 1280 (C–O) and 1257 (C–O); δ_H(250 MHz; $CDCl_3$) 5.78 (1 H, d, *J* 7.13, 1-H), 5.11 (1 H, dd, *J* 7.04, 2.44, 2-H), 4.97 (1 H, d, *J* 2.48, 4-H), 3.95–3.84 (4 H, m, ketal OCH_2), 3.66 (3 H, s, OCH_3), 2.86–2.78 (2 H, m, 6-H_α, 6-H_β), 2.14–1.25 (13 H, m, skeletal protons) and 0.85 (3 H, s, 18-CH_3); *m/z* (CI, NH_3) 465 (MH^+, 100%), 329, 267 and 99 (Found: *m/z* 465.1369. $C_{24}H_{29}CrO_6$ requires *M*, 465.1369) (Found: C, 62.3; H, 5.9. $C_{24}H_{28}CrO_6$ requires C, 62.06; H, 6.08%).

Further elution gave η^6-α-[17,17-*ethylenedioxy*-3-*methoxyestra*-1,3,5(10)-*triene*]*tricarbonylchromium*(0) **4** as a bright yellow, crystalline solid (1.475 g, 50%); m.p. 164–165 °C; ν_{max}(Nujol)/cm^{-1} 1956, 1881, 1861 (C≡O), 1546, 1281 (C–O) and 1251 (C–O); δ_H(250 MHz; $CDCl_3$) 5.65 (1 H, d, *J* 7.08, 1-H), 4.99 (1 H, d, *J* 2.38, 4-H), 4.92 (1 H, dd, *J* 7.04, 2.44, 2-H), 3.96–3.86 (4 H, m, ketal OCH_2), 3.71 (3 H, s, OCH_3), 3.02 (1 H, m, 6-H_β), 2.71–2.64 (1 H, dd, *J* 16.37, 7.07, 6-H_α), 2.08–1.18 (13 H, m, skeletal protons) and 0.93 (3 H, s, 18-CH_3); *m/z* (CI, NH_3) 465 (MH^+, 100%), 397, 329, 267 and 99 (Found, *m/z* 465.1369. $C_{24}H_{29}CrO_6$ requires *M*, 465.1369) (Found: C, 62.4; H, 6.1. $C_{24}H_{28}CrO_6$ requires C, 62.1; H, 6.1%).

17,17-*Ethylenedioxy*-3-*methoxy*-2-*trimethylsilylestra*-1,3,5-(10)-*triene* **6** (R = $SiMe_3$).—A solution of η^6-α-[17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)triene]tricarbonylchromium-(0) **4** (140.5 mg, 0.30 mmol) in dry THF (5 cm^3) was degassed under a nitrogen atmosphere and cooled to −78 °C. Butyllithium (0.35 cm^3 of 1.5 mol dm^{-3} solution, 0.525 mmol, 1.6 equiv.) was added dropwise *via* a syringe over 2 min and the reaction mixture was stirred at −78 °C for 1.5 h. Neat chlorotrimethylsilane (0.2 cm^3) was added to the solution and stirring continued for 4 h before allowing it to warm to room temperature. Aqueous 2 mol dm^{-3} ammonium chloride (10 cm^3) was added and the layers separated. The aqueous layer was extracted with ether (2 × 20 cm^3) and the combined ether phases were washed with saturated, aqueous brine (1 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. This was dissolved in dichloromethane (5 cm^3) and exposed to air and sunlight for 24 h and then filtered and evaporated. The residue was subjected to flash chromatography (SiO_2; light petroleum–ether, 4:1) to give the *title compound* **6** (R = $SiMe_3$) as a white crystalline solid (105.7 mg, 88%); m.p. 179–181 °C; ν_{max}(Nujol)/cm^{-1} 1598, 1255 (C–O), 1232 (C–O), 1046 and 950; δ_H($CDCl_3$; 270 MHz) 7.31 (1 H, s, 1-H), 6.55 (1 H, s, 4-H), 3.97–3.87 (4 H, m, ketal OCH_2), 3.77 (3 H, s, OCH_3), 2.89–2.82 (1 H, m, 6-H_α), 2.41–2.19 (1 H, m, 6-H_β), 2.07–1.25 (13 H, m, skeletal protons), 0.87 (3 H, s, 18-CH_3) and 0.24 (9 H, s, Si-CH_3); *m/z* (CI, NH_3) 401 (MH^+, 100%), 357, 339 and 329 (Found: *m/z* 400.2434. $C_{24}H_{26}O_3Si$ requires *M*, 400.2433).

η^6-α-[2-*Dihydroxyboryl*-17,17-*ethylenedioxy*-3-*methoxyestra*-1,3,5(10)-*triene*]*tricarbonylchromium*(0) **6** [R = $B(OH)_2$].—η^6-α-(17,17-Ethylenedioxy-3-methoxyestra-1,3,5(10)-triene)tricarbonylchromium(0) **4** (544.4 mg, 1.17 mmol) in dry THF (20 cm^3) was degassed and cooled to −78 °C under a nitrogen atmosphere. A solution of butyllithium (1.09 cm^3; 1.4 mol dm^{-3} in hexane, 1.521 mmol, 1.3 equiv.) was added dropwise *via* a syringe over a period of 12 min. After 2 h, a cold (−78 °C) solution of triisopropyl borate (500 mm^3, 2.101 mmol, 1.8 equiv.) in THF (5 cm^3) was transferred to the orange–brown reaction mixture *via* a cannula over a period of 2 min. The solution was stirred at −78 °C for 1 h and then allowed to warm to room temperature over 2 h and stirred for a further 1 h. The mixture was then partitioned between 2 mol dm^{-3} aqueous HCl (10 cm^3) and ether (50 cm^3) and the solid which separated was collected by filtration and washed repeatedly with ether (5 × 5 cm^3) to yield the *title compound* **6** [R = $B(OH)_2$] as a bright yellow solid (462 mg, 78%); m.p. >300 °C; ν_{max}(Nujol)/cm^{-1} 3359 (BO-H), 1936, 1888, 1853 (C≡O), 1284 and 1236 (C–O); δ_H(500 MHz; [$^2H_6$]-DMSO) 7.64 (2 H, s, BOH), 6.12, (1 H, s, 1-H), 5.52 (1 H, s, 4-H), 3.86–3.77 (4 H, m, ketal OCH_2), 3.73 (3 H, s, OCH_3), 2.84–2.81 (2 H, br d), 2.15–1.19 (13 H, m, skeletal protons) and 0.79 (3 H, s, 18-CH_3); *m/z* (EI) 508 (M^+), 480, 464, 424, 408, 380, 336, 284, 111, 97, 83, 69, 55 and 43 (100%) (Found: *m/z* 508.4484. $C_{24}H_{29}BCrO_8$ requires 508.136 05).

2-*Dihydroxyboryl*-17,17-*ethylenedioxy*-3-*methoxyestra*-1,3,5-(10)-*triene* **8**.—A solution of η^6-α-[2-dihydroxyboryl-17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-triene]tricarbonylchromium(0) **6** [R = $B(OH)_2$] (119.2 mg, 234 μmol) in pyridine (2 cm^3) was exposed to direct sunlight and air for 4 h with occasional swirling. The solution was diluted with ether (20 cm^3) and partitioned between 2 mol dm^{-3} aqueous HCl (20 cm^3) and ether (30 cm^3). The layers were separated and the organic phase was dried ($MgSO_4$) and evaporated to yield the *title compound* **8** as a foam (73.5 mg, 84%); m.p. >300 °C; ν_{max}(Nujol)/cm^{-1} 3392 (BO-H), 1559, 1457, 1378 and 1255 (C–O); δ_H($CDCl_3$; 270 MHz) 7.74 (1 H, s, 1-H), 6.63 (1 H, s, 4-H), 5.64 (2 H, s, BO–H), 3.96–3.85 (4 H, m, ketal OCH_2),

3.87 (3 H, s, OCH_3), 2.90–2.86 (2 H, m, 6-H_α, 6-H_β), 2.03–1.18 (13 H, m, skeletal protons) and 0.88 (3 H, s, 18-CH_3). The mass spectrum was complicated by an intermolecular ethylenedioxy-transfer reaction which occurred in the probe. The high mass products were the 2-(1,3,2-dioxaborolanyl)-17,17-ethylenedioxy-3-methoxyestran-1,3,5(10)-triene, *m/z* (EI) 398 (Found: M^+, 398.2357. $C_{23}H_{31}BO_5$ requires *M*, 398.2264); and 2-(1,3,2-dioxaborolanyl)-3-methoxyestrone, *m/z* 354 (Found: M^+, 354.197 85. $C_{21}H_{27}BO_4$ requires *M*, 354.2002).

Compound **8** could be prepared from η^6-α-[2-dihydroxyboryl-17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-triene]tricarbonylchromium(0) **6** [R = $B(OH)_2$] in a yield of 82% for the two steps by not isolating the intermediate boronic acid chromium tricarbonyl species.

Fluorination of 2-Dihydroxyboryl-17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-triene **8**.—A solution of 2-dihydroxyboryl-3-methoxy-17,17-ethylenedioxyestra-1,3,5(10)-triene **8** (26.2 mg, 70 μmol) in acetonitrile–dichloromethane (1.5 cm^3, 2:1) was stirred at room temperature under a nitrogen atmosphere and solid caesium fluoroxysulfate (17.1 mg, 68.9 μmol) was added in one portion. After being stirred for 2 h, the reaction mixture was diluted with dichloromethane (10 cm^3) and filtered to remove insoluble products. The filtrate was washed with water (1 × 5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, light petroleum–ether, 4:1) to give initially 17,17-*ethylenedioxy*-2-*fluoro*-3-*methoxyestra*-1,3,5(10)-*triene* **7** as a white solid (3.4 mg, 14%); m.p. 102–103 °C; ν_{max}(Nujol)/cm^{-1} 1610, 1576, 1501, 1305, 1280 (C–O), 1254 (C–O), 1179 and 1104; δ_H($CDCl_3$; 270 MHz) 6.98 (1 H, d, J_{H-F} 13.15, 1-H), 6.64 (1 H, d, J_{H-F} 8.81, 4-H), 3.98–3.88 (4 H, m, ketal OCH_2), 3.84 (3 H, s, OCH_3), 2.92–2.79 (2 H, m, 6-H_α, 6-H_β), 2.26–1.08 (13 H, m, skeletal protons) and 0.82 (3 H, s, 18-CH_3); δ_F (84 MHz; $CDCl_3$) −139; *m/z* (EI) 346 (M^+), 302, 287, 160, 115 and 44 (100%) (Found: *m/z* 346.1944. $C_{21}H_{27}FO_3$ requires *M*, 346.1944).

Further elution gave a 2-*fluoro*-3-O-*methylestrone* **9** as a white solid (1.1 mg, 5%); m.p. 127–128 °C (lit.,[4] m.p. 125–128 °C); ν_{max}(Nujol)/cm^{-1} 1738, 1608, 1504, 1316 and 1246 (C–O); δ_H(270 MHz; $CDCl_3$) 6.99 (1 H, d, J_{H-F} 13.19, 1-H), 6.67 (1 H, d, J_{H-F} 8.79, 4-H), 3.85 (3 H, s, OCH_3), 2.88–2.84 (2 H, m, 6-H_α, 6-H_β), 2.49–1.45 (13 H, m, skeletal protons) and 0.91 (3 H, s, 18-CH_3); δ_F(84 MHz; $CDCl_3$) −139; *m/z* (EI) 302 (M^+), 160, 115 and 44 (100%) (Found: C, 75.2; H, 7.9. $C_{19}H_{23}FO_2$ requires: C, 75.5; H, 7.7%).

2-*Dihydroxyboryl*-3-O-*methylestrone* **12**.—A solution of 2-dihydroxyboryl-17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-triene (450.6 mg, 1.21 mmol) and toluene-*p*-sulfonic acid hydrate (48 mg, 20 mol%) in acetone (15 cm^3) was stirred under a nitrogen atmosphere for 20 h. Saturated, aqueous sodium hydrogen carbonate (2 cm^3) was added and the solution was diluted with water to *ca.* 50 cm^3. A white solid was deposited which was collected by filtration, washed with water (2 × 5 cm^3) and dried on the sinter to give the *title compound* **12** which was recrystallised from dichloromethane–light petroleum as a white crystalline solid (381 mg, 96%); m.p. >300 °C; ν_{max}(Nujol)/cm^{-1} 3390 (BO–H), 1727, 1496, 1413, 1338, 1247 (C–O) and 1050; δ_H($CDCl_3$; 270 MHz) 7.76 (1 H, s, 1-H), 6.64 (1 H, s, 4-H), 5.76 (2 H, s, BOH), 3.88 (3 H, s, OCH_3), 2.96–2.91 (2 H, m, 6-H_α, 6-H_β), 2.56–1.45 (13 H, m, skeletal protons) and 0.91 (3 H, s, 18-CH_3); *m/z* (EI) 328 (M^+), 284, 160, 144, 115, 97, 83, 69, 55 and 44 (100%) (Found: C, 69.3; H, 7.8%. $C_{19}H_{25}BO_4$ requires C, 69.5; H, 7.7%).

2-*Fluoro*-3-O-*methylestrone* **9**.—A solution of 2-dihydroxyboryl-3-*O*-methylestrone **12** (92.0 mg, 280 μmol) in acetonitrile–dichloromethane (3 cm^3, 2:1) was stirred at room temperature and solid caesium fluoroxysulfate (78.9 mg, 318 μmol) was added in one portion. After being stirred for 65 min, the reaction mixture was diluted with dichloromethane (15 cm^3) and then filtered to remove insoluble products. The filtrate was washed with water (1 × 5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, light petroleum–ether, 4:1) to give 2-*fluoro*-3-O-*methylestrone* **9** as a white crystalline solid (22.6 mg, 27%); m.p. 127–128 °C (lit.,[4] m.p. 125–128 °C); ν_{max}(Nujol)/cm^{-1} 1738, 1608, 1504, 1316 and 1246 (C–O); δ_H(270 MHz; $CDCl_3$) 6.99 (1 H, d, J_{H-F} 13.19, 1-H), 6.67 (1 H, d, J_{H-F} 8.79, 4-H), 3.85 (3 H, s, OCH_3), 2.88–2.84 (2 H, m, 6-H_α, 6-H_β), 2.49–1.45 (13 H, m, skeletal protons) and 0.91 (3 H, s, 18-CH_3); δ_F(84 MHz; $CDCl_3$) − 139; *m/z* (EI) 302 (M^+), 160, 115 and 44 (100%) (Found: C, 75.2; H, 7.9. $C_{19}H_{23}FO_2$ requires C, 75.5; H, 7.7%).

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