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# REGIOSELECTIVE SYNTHESIS OF A-RING HALOGENATED DERIVATIVES OF 17α-ETHYNYLOESTRADIOL

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*Abstract:* C-2 and C-4 fluorinated and brominated derivatives of 17α-ethynyl-oestradiol have been efficiently prepared *via* the corresponding halo-oestrones

## Introduction

A-ring halogenated steroidal oestrogens have a variety of medical and experimental uses, for example as diagnostic radio-imaging agents,[1] as inhibitors of steroid metabolising enzymes,[2] and as metabolic probes of the mechanisms of oestrogen carcinogenesis.[3,4]

17α-Ethynyloestradiol ($EE_2$) is the usual oestrogenic component of combined oral contraceptives. It undergoes extensive metabolism *in vitro* [5,6] and *in vivo* [7-10] in a number of species including man.[11] Hydroxylation at C-2 is the predominant reaction both *in vitro* [12] and *in vivo*.[5] Formation of 2-hydroxy-17α-ethynyl oestradiol *in vivo* has toxicological implications since it has been demonstrated *in vitro* that this compound is oxidised to reactive intermediates (quinones or semiquinones), which bind irreversibly to microsomal and soluble protein.[6,13]

Fluorination at the C-2 position of 17β-oestradiol has been shown to reduce the carcinogenicity of the oestrogen while at the same time retaining the oestrogenicity.[3] In order to determine the utility of A-ring halogenated oestrogens as metabolic probes of the mechanisms of oestrogen carcinogenesis we have studied the metabolism of 2-fluoro-oestradiol *in vivo*.[14] Such studies necessitate the use of radiolabelled compounds and hence efficient syntheses; we have previously prepared 2-fluoro-oestradiol and other functionalized oestrogens in two principal steps from oestrone.[15] Further investigation required an efficient synthesis of A-ring halogenated ethynyl oestradiols.

Although general procedures for A-ring functionalization of the natural oestrogens, oestrone ($E_1$) and 17β-oestradiol ($E_2$), are available,[15-25] few methods for the regioselective production of A-ring halogenated derivatives of 17α-ethynyloestradiol,

the principal synthetic pharmaceutical oestrogen, have been described. The existing approach [26] to the synthesis of 2- and 4- bromo-17α-ethynyloestradiol was not satisfactory for our purposes: the method involves the reaction between 17α-ethynyloestradiol, *N*-chlorosuccinimide, and sodium bromide, yielding a mixture of 2- and 4- bromo-$EE_2$ and 2,4-dibromo-$EE_2$ together with some starting material; the yields of each product are not indicated.

We are now pleased to report new, convenient, and regioselective syntheses of C2- and C4- fluorinated and brominated derivatives of 17α-ethynyloestradiol.

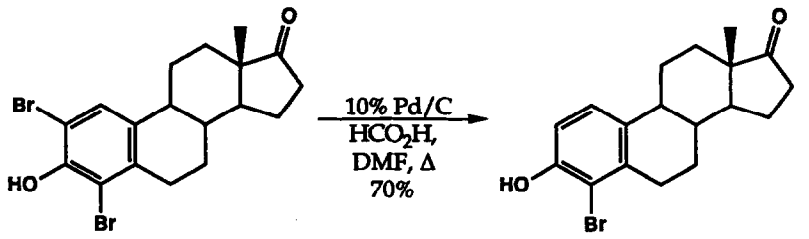
**Results and Discussion**

Previously we have prepared 2,4-dibromo-$EE_2$, by a variation of the methods of Woodward[16] and Utne,[19] in 90% yield by the action of *N*-bromoacetamide upon ethynyl oestradiol in ethanolic solution at ambient temperature.[27] Selective reductive debromination of 2,4-dibromo-oestrone with formic acid, potassium iodide, or ascorbic acid has been reported to yield mixtures of 2- and 4- bromo-oestrones, the major product depending upon the reaction conditions employed.[28] In our hands selective reductive debromination of 2,4-dibromo-$EE_2$ is partially successful, but the rate of reduction of the ethynyl group to vinyl is more rapid than debromination, giving 4-bromo-17α-vinyl oestradiol as the major product in a complex mixture. We therefore chose to synthesise 2- and 4- bromo-oestrones and subsequently to carry out stereoselective ethynylation of the D-rings.

Halo-oestrones have been prepared by a number of groups;[17,18] but the oestrone brominations previously reported commonly either lead to an isomeric mixture of 2- and 4- bromo-oestrones in roughly equal quantities or describe reaction conditions and yields which do not seem to be readily reproducible.[19] However, we have recently developed regioselective syntheses of 2-bromo- and 2- and 4- fluoro-oestrones, and these compounds were therefore already available to us.[15] 2- and 4-Fluoro-oestrones were prepared in good overall yield by direct fluorination of oestrone using *N*-fluoropyridinium triflate. The regioisomers were separated by column chromatography of the corresponding 2- and 4- fluoro-oestrone acetates. 2-Bromo-oestrone was prepared *via* the oestrone acetate–thallium (III) bis(trifluoroacetate) complex by treatment with copper (II) bromide in dioxane solution, giving 2-substituted oestrone acetate, which upon de-acetylation afforded 2-bromo-oestrone in excellent yield. We have found that similar thalliation of $EE_2$ followed by addition of copper (II) bromide leads to a complex mixture of products, making impracticable this potentially very direct route to 2- halo-$EE_2$.

2,4-Dibromo-oestrone (2) was prepared in near-quantitative yield by the reaction of *N*-bromosuccinimide (2.5 equiv) with oestrone in ethanolic solution over 16 hours at ambient temperature, and was used to prepare 4-bromo-oestrone (3) through the selective reductive debromination method. After some adjustment of reaction conditions (Table I), we have found the optimum yield of 4-bromo-oestrone (70%) to

be obtained when a mixture of 2,4-dibromo-oestrone, 10% palladium-on-carbon catalyst, and formic acid is refluxed in DMF solution (*ca.* 153 °C) for 1.75 hours (Scheme 1); under these conditions the only other product formed is oestrone (1). When this reaction was carried out at 100 °C for 12 hours a mixture of 2-bromo-oestrone (4) and 4-bromo-oestrone, together with some 2,4-dibromo-oestrone, was obtained; similar results were observed when the reaction was carried out at 100 °C for 4 and for 8 hours.



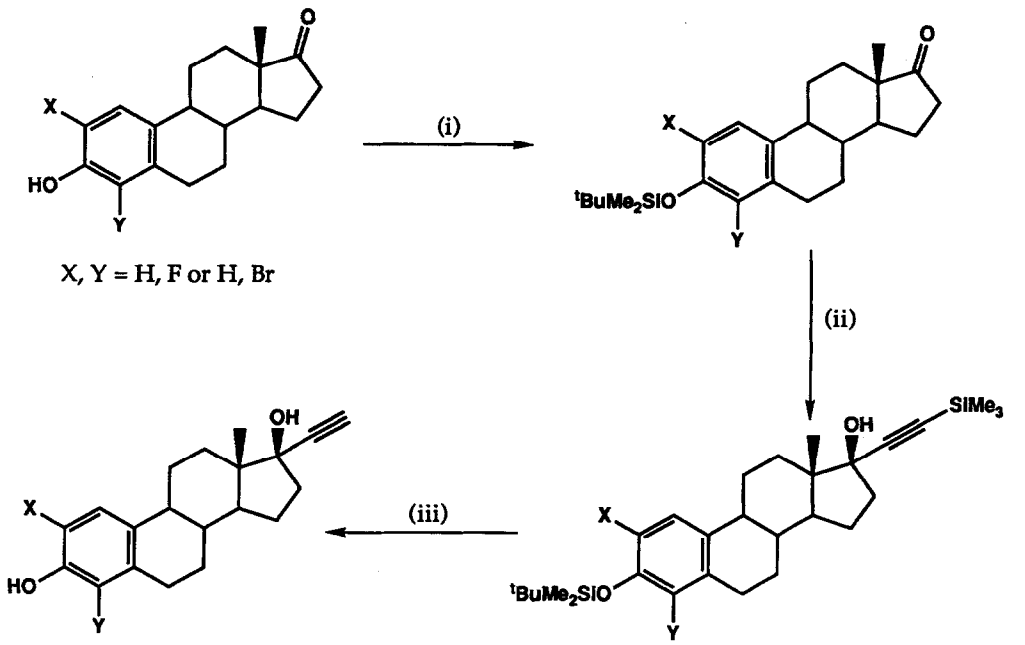

(2) (3)

Scheme 1

**Table 1 Debromination of 2,4-dibromo-oestrone with formic acid in the presence of 10% palladium-on-carbon**

| Entry | Temperature/°C | Time/h | Yields of products (1) : (2) : (3) : (4) |
|---|---|---|---|
| a | 100 | 4 | 3 : 63 : 27 : 6 |
| b | 100 | 8 | 4 : 30 : 62 : 4 |
| c | 100 | 12 | 5 : 19 : 70 : 6 |
| d | reflux | 1.75 | 20 : 0 : 70 : 0 |
| e | reflux | 3 | 73 : <1 : 26 : 0 |

Conversion of 2- and 4- halo-oestrones into the corresponding halo-17α-ethynyloestradiols was readily achieved in three steps. The phenolic hydroxyl group of each halo-oestrone was first protected as its *tert*-butyldimethylsilyl ether under standard conditions; subsequent addition of the anion derived from trimethylsilyl acetylene (1.1 equiv.) (formed by deprotonation of trimethylsilyl acetylene with butyl lithium in THF at −78 °C) was followed by protiodesilylation with commercial tetrabutyl ammonium fluoride (non-anhydrous solution in thf) to give the halo(ethynyl)oestradiols in a one-pot process and excellent overall yields after column chromatography and recrystallization (Scheme 2). As expected, ethynylation took place from the α face of the steroid molecule due to steric hindrance at the β face caused by the C-18 methyl group.




*Reagents*: (i) $^tBuMe_2SiCl$, imidazole,$CH_2Cl_2$, rt, 3 h;
(ii) $Me_3SiCCLi$, THF, –78 — rt, 24 h;
(iii) $Bu_4NF$, THF, rt, 30 min

Scheme 2

**Acknowledgment**

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## Experimental

### General Experimental Details

Light petroleum (b.p. 40-60 °C and b.p. 60-80 °C) was distilled prior to use. Dichloromethane was dried by distillation from calcium hydride. Tetrahydrofuran was dried by distillation from the sodium–benzophenone ketyl radical. Dimethylformamide (DMF) was distilled from calcium hydride; the distillate was flash distilled from alumina activated by heating to 150 °C overnight; the dried DMF was stored over 4 Å molecular sieve. Pyridine was dried by storage over potassium hydroxide pellets and distilled before use. Commercially available reagents were

used as supplied unless otherwise stated. Copper halide salts were purified by washing with thf (2 x 10ml), and dried at 0.5 mmHg. Commercial solutions of butyllithium were fitted with septum caps and stored at -20 °C. The reagent was dispensed by syringe under argon and standardized by the method of Gilman or by use of diphenylacetic acid.

Infrared spectra were recorded in the range 4000—600 $cm^{-1}$ using Perkin-Elmer 298, 1320, or 1720FT spectrophotometers, and were calibrated against the 1602 $cm^{-1}$ absorption of polystyrene. Solid samples were run as Nujol mulls or potassium bromide discs, and liquids as thin films. $^1H$ Nuclear magnetic resonance spectra were recorded using Bruker WM250 (250 MHz), Bruker AC200 (200 MHz), Perkin-Elmer R34 (220 MHz), or Jeol PMX60 (60 MHz) spectrometers. All spectra were recorded in deuteriochloroform solution with tetramethylsilane as internal standard. Electron impact (EI) and FAB mass spectra were recorded on VG Micromass 7070E or VG Tritech TS250 instruments.

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were carried out by the Department of Chemistry microanalytical service.

**2,4-Dibromo-oestrone**

Oestrone (2 g, 7.4 mmol) was dissolved in ethanol (100 ml), *N*-bromosuccinimide (3.95 g, 22 mmol) added, and the resulting mixture stirred at room temperature for 24 hours. The solvent was removed under reduced pressure to give a purple solid which was purified by flash-column chromatography on silica gel (Merck 9385). Elution with light petroleum (b.p 60-80 °C)/ethyl acetate (80:20) gave 2,4-dibromo-oestrone as a white solid (2.98g, 94%), m.p. 235–236 °C; $\nu_{max}$ 3370, 1730, 1580, and 1455 $cm^{-1}$; δ 0.9 (3H,s), 1.0–3.0 (15H, m), and 7.5 (1H, s); m/z 428 ($M^+$), 385, 371, 331, 319, 304, and 291. Found: C, 50.38; H, 4.69; $C_{18}H_{20}Br_2O_2$ requires C, 50.49; H, 4.71%.

**4-Bromo-oestrone**

2,4-Dibromo-oestrone (1.5g, 3.5 mmol) was dissolved in dimethylformamide (50 ml) and 10% palladium-on-carbon (0.5g) was added. Formic acid (1.35 ml, 1.61g, 35 mmol) was added to the solution and the mixture heated under reflux for 1.45 hours. Following completion of the reaction (TLC analysis) the mixture was cooled and the catalyst removed by filtration and washed with ethyl acetate (2x20 ml). The combined organic solutions were washed with aqueous sodium bicarbonate and water, and dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue purified by flash-column chromatography on silica gel (Merck 9385) using light petroleum (b.p. 60-80 °C)/ethyl acetate (80:20) as eluent to afford 4-bromo-oestrone as white solid (0.87 g, 70%), m.p. 281–282 °C; $\nu_{max}$ 3382, 1718, 1384, and 886 $cm^{-1}$; δ 0.95 (3H, s), 1.36–3.00 (15H, m), 6.85 (1H, d, *J* 8 Hz), and 7.20 (1H, d, *J* 8 Hz); m/z 348:350 (1:1) ($M^+$), 348, 291, 270, and 238. Found: C,

61.56; H, 6.03; $C_{18}H_{21}BrO_2$ requires C, 61.90; H, 6.06%.

**General method for the preparation of 2- or 4- halo-3-(O-*tert*-butyldimethylsilyl) oestrones**

2- Or 4- halo-oestrone (1.0 mmol) was dissolved in dry dichloromethane (20ml), and *tert*-butyldimethyl chlorosilane (241 mg, 1.6 mmol) and imidazole (177 mg, 2.6 mmol) added. The solution was stirred under a nitrogen atmosphere at room temperature for three hours and then diluted to a volume of 50 ml by addition of dichloromethane. The solution was washed with brine (3 x 50 ml) and saturated aqueous copper sulphate (3 x 50 ml), and dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue recrystallized from light petroleum (b.p. 40–60 °C)/ethyl acetate (80:20).

**2-Fluoro-3-(O-*tert*-butyldimethylsilyl) oestrone**

2-Fluoro-oestrone (300 mg, 1.0 mmol) was treated as described above. Following work- up the product was recrystallized to give a colourless solid (400 mg, 95%), m.p. 198–199 °C; $\nu_{max}$ 1740, 1388, and 882 $cm^{-1}$; δ 0.22( 6H, s), 0.95 (3H, s), 1.05( 9H, s),1.20–2.90 (15H, m), 6.75 (1H, d, *J* 9 Hz), and 7.10 (1H, d, *J* 13 Hz); m/z 402 ($M^+$), 384, 345, 327, and 231.

**4-Fluoro-3-(O-*tert*-butyldimethylsilyl)-oestrone**

4-Fluoro-oestrone (300 mg, 1.00 mmol) was treated as described above. Following work-up the product was recrystallized to give a colourless solid (390 mg, 93%), m.p. 201–202 °C; $\nu_{max}$ 1745, 1375, and 880 $cm^{-1}$; δ 0.20 (6H, s), 0.92 (3H, s), 1.10 (9H, s), 1.15–2.95 (15H, m), 6.90–7.00 (1H, m), and 7.14 (1H, d, *J* 9 Hz); m/z 402 ($M^+$), 384, 345, 327, and 231.

**2-Bromo-3-(O-*tert*-butyldimethylsilyl)-oestrone**

2-Bromo-oestrone (510 mg, 1.50 mmol) was treated as described above. Following work-up the product was recrystallized to give a colourless solid (660 mg, 97%), m.p 189–191 °C; $\nu_{max}$ 1742, 1381 and 883 $cm^{-1}$; δ 0.2 (6H, s), 0.95 (3H,s), 1.05 (9H, s), 1.10–2.95 (15H, m), 6.55 (1H, s), and 7.35 (1H, s); m/z 405:407 (1:1) ($M^+$–$C(CH_3)_3$).

**4-Bromo-3-(O-*tert*-butyldimethylsilyl)-oestrone**

4-Bromo-oestrone (450 mg, 1.3 mmol) was treated as described above. Following work-up, the product was recrystallized to yield a colourless solid (560 mg, 94%), m.p 193–195 °C; $\nu_{max}$ 1730, 1376, and 880 $cm^{-1}$; δ 0.20 (6H, s), 0.95 (3H, s), 1.05 (9H, s), 1.10–2.95 (15H, m), 6.65 (1H, d, *J* 8 Hz), and 7.05 (1H, d, J 8 Hz); m/z 462:464 (1:1) ($M^+$), 405:407 (1:1) ($M^+$–$C(CH_3)_3$).

**General method for the preparation of 2- and 4-halo-17α-ethynyloestradiols**

Trimethylsilyl acetylene (147 mg, 1.5 mmol) was dissolved in dry tetrahydrofuran (10 ml) and the solution cooled to –78 °C under a nitrogen atmosphere. Butyl lithium (1.4 mmol) was introduced *via* a syringe and the resulting mixture was stirred for a further

hour at –78 °C. A solution of 2- or 4- halo-3-(O-*tert*-butyldimethylsilyl)-oestrone (1.2 mmol) in dry THF was added, and the mixture stirred at –78 °C for one hour and gradually allowed to warm to room temperature overnight. A solution of tetrabutyl ammonium fluoride in thf (3 equiv.) was added to the yellow-orange solution and the mixture stirred for 30 min at room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography using dichloromethane/ethyl acetate (98:2) as eluent and recrystallization from light petroleum (b.p. 60–80 °C)/ethyl acetate (3:2).

**2-Fluoro-17α-ethynyloestradiol**

2-Fluoro-3-(O-*tert*-butyldimethylsilyl)-oestrone (300 mg, 0.75 mmol) was treated as described above. Following work-up, the crude product was recrystallized to give a colourless solid (180 mg, 75%), m.p. 265–266 °C; $\nu_{max}$ 3520, 3350, 3300, and 2100 $cm^{-1}$; δ 0.88 (3H, s), 1.23–2.40 (13H, m) 2.60 (1H, s) 2.80–2.92 (2H, m), 6.72 (1H, d, *J* 9 Hz), and 7.00 (1H, d, *J* 13 Hz); m/z 314 ($M^+$), 296, 288, 246, and 231. Found: C, 76.46, H, 7.40. $C_{20}H_{23}FO_2$ requires C, 76.41; H, 7.37%.

**4-Fluoro-17α-ethynyloestradiol**

4-Fluoro-3-(O-*tert*-butyldimethylsilyl)-oestrone (300 mg, 0.75 mmol) was treated as described above. Following work-up the crude product was recrystallized to give a colourless solid (160 mg, 68%) m.p 258–259 °C; $\nu_{max}$ 3520, 3350, 3300, and 2100 $cm^{-1}$; δ 0.83 (3H, s), 1.22–2.38 (13H, m) 2.58 (1H, s) 2.78–2.90 (2H, m), 6.90–7.02 (1H, m), and 7.15 (1H, d, *J* 9 Hz); m/z 314 ($M^+$), 296, 288, and 246. Found: C, 76.39, H, 7.33. $C_{20}H_{23}FO_2$ requires C, 76.41; H, 7.37%.

**2-Bromo-17α-ethynyloestradiol**

2-Bromo-3-(O-*tert*-butyldimethylsilyl)-oestrone (650 mg, 1.4 mmol) was treated as described above. Following work-up the crude product was recrystallized to give a colourless solid (390 mg, 75%), m.p. 219–221 °C; $\nu_{max}$ 3524, 3350, 3305, and 2105 $cm^{-1}$; δ 0.95 (3H, s),1.00–2.40 (13H, m), 2.60 (1H, s), 2.68–2.95 (2H, m), 6.75 (1H, s), and 7.35 (1H, s); m/z 374:376 (1:1) ($M^+$), 306:308 (1:1), and 291:293 (1:1). Found: C, 64.09; H, 6.28. $C_{20}H_{23}BrO_2$ requires C, 64.01; H, 6.18%.

**4-Bromo-17α-ethynyloestradiol**

4-Bromo-3-(O-*tert*-butyldimethylsilyl)-oestrone (550 mg, 1.2 mmol) was treated as described above. Following work-up the crude product was recrystallized to give a colourless solid (330 mg, 70%), m.p. 177–178 °C; $\nu_{max}$ 3537, 3503, 3290, and 2100 $cm^{-1}$; δ 0.95 (3H, s), 1.00–2.42 (13H, m), 2.60 (1H, s), 2.68–2.98 (2H, m), 6.85 (1H, d, *J* 8 Hz), and 7.20 (1H, d, *J* 8 Hz); m/z 374:376 (1:1) ($M^+$), 306:308 (1:1), and 291:293 (1:1). Found: C, 64.14; H, 6.33. $C_{20}H_{23}BrO_2$ requires C, 64.01; H, 6.18%.

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