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Improved synthesis of mestranol and ethinyl estradiol (EE) related degradation products as authentic references

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ABSTRACT

Preparative chemical methods for the synthesis of 10 degradation or photodecomposition products of mestranol and ethinyl estradiol (EE) are described. The synthesized compounds are useful as reference materials and standards for pharmaceutical analysis of mestranol and EE as bulk chemical or in formulated product. New synthetic methods were presented and the known synthetic procedures were improved. Detailed structural characterization of the degradation or photodecomposition products of mestranol and EE and related compounds was reported.

1. Introduction

Mestranol and ethinyl estradiol (EE) are common components of widely used hormone regulation and therapy medications, e.g. the estrogen components of the combined oral contraceptive agents. Numerous steroid–protein conjugates have been synthesized and used as antigens for the production of specific antisera required for radioimmunoassay [1–5]. Estradiol derivatives were also found recently to act as multitargeted antitumor agents [6–17]. Mestranol and EE have both been proved to be stable in air. Nevertheless, stability samples of formulated drug products containing mestranol and EE stored for years under ambient laboratory conditions were observed by HPLC to contain several oxidative transformation products of the parent compound which were not present at the beginning of the study. It was also found that decomposition of mestranol and EE in the solid state could be accelerated at elevated temperature in the presence of air, as a result of auto-oxidation. On the other hand, although it is mentioned in the monographs in pharmacopoeias that estrogenic steroids have to be protected from light, little is known about the photochemical decomposition of these compounds.

The main degradation or photodecomposition products of mestranol and EE are shown in Fig. 1. Though the chemical synthesis and structural characterization of these compounds are important in view of providing authentic samples for further studies, only several papers described the preparation and characterization of these steroid compounds [1,18–21]. Cotter et al. reported the synthesis of compounds **1–8** (Fig. 1)

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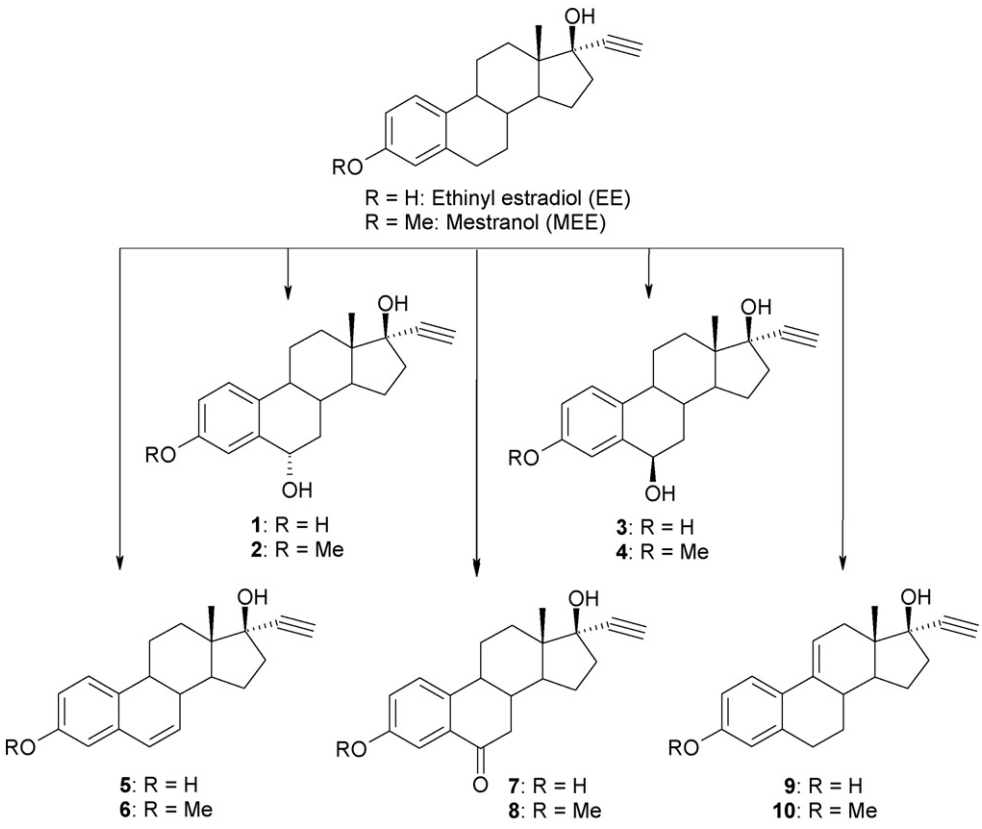


Fig. 1 – Degradation or photodecomposition products of EE and MEE.

but no details was presented in the letter [18]. Rao mentioned preparation of steroids **1**,**2**,**7**, and **8** by a tedious synthetic sequence [1]. Synthesis of compound **9** and **10** appeared only in paper [19] and [20], respectively. In this paper, systematic studies on the main degradation or photodecomposition products of mestranol and EE (compounds **1**–**10**) and related compounds including their efficient synthesis, isolation, and detailed structural characterization are presented.

2. Experimental

2.1. General procedures

All chemical reagents were purchased from commercial sources and used as received unless other statements. Melting points were determined on a WRS-2A capillary melting apparatus and the quoted temperatures were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer. $CDCl_3$ was used as solvent and chemical shifts recorded were internally referenced to Me_4Si (0 ppm). IR spectra were obtained on a Thermo Electron Corporation Nicolet 380 FT-IR spectrophotometer. Mass spectra were recorded on a Finnigan-MAT-8430 instrument using electron ionization (EI) at 70 eV. X-ray crystal structure was measured on a Bruker Smart CCD diffractometer by using Mo Kα radiation at 293 K.

2.2. Synthesis of compounds

2.2.1. Synthesis of 3,17β-dihydroxy-19-norpregna-1,3,5(10)-triene-20-yne-6-one (7)

Norethindrone (**11**) was used as purchased from Zhejiang Xianju Junye Pharmaceutical Co. Ltd., mp 207.8–208.6 °C. ^{1}H NMR ($CDCl_3$) δ 5.81 (s, 1H), 2.57 (s, 1H), 2.40–2.50 (m, 2H), 2.23–2.33 (m), 1.68–2.10 (m), 1.51–1.65 (m), 1.23–1.40 (m), 1.04–1.14 (m), 0.92 (s, 3H).

Norethindrone (17.9 g, 60 mmol) and anhydrous potassium acetate (9.5 g, 96 mmol) in dry dimethylformamide (DMF, 120 mL) was heated to 120 °C and stirred for 20 h while oxygen or air was bubbled through the solution. The reaction mixture was poured onto ice water (100 mL) containing methylene chloride (300 mL). Hydrochloric acid (1N, 150 mL) was added then the organic layer was separated. The aqueous phase was extracted with methylene chloride (150 mL 3×). The organic phases were combined and washed with 150 mL each of 1N hydrochloric acid, water, and brine then dried over $MgSO_4$. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with 20% ethyl acetate in petroleum ether (bp 60–90 °C) to afford **7** (11.4 g, 61%) as pale yellow solid, mp 228.6–229.5 °C (Ref. [19] value: 229–230 °C), R_f 0.25 (petroleum ether/ethyl acetate, 2:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 2.9 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.07 (dd, J = 8.5 and 2.9 Hz, 1H), 5.24 (s, 1H), 2.74 (dd, J = 16.9 and 3.3 Hz, 1H), 2.64 (s, 1H), 2.22–2.55 (m), 1.74–2.08 (m),

1.57–1.66 (m), 1.24–1.43 (m), 0.90 (s, 3H). IR (KBr pellet) ν 3563, 3388, 3277, 2965, 2945, 2891, 2865, 1664, 1607, 1498, 1385, 1311, 1259, 1215, 1178, 1133, 1045 cm^{-1}.

2.2.2. *Synthesis of 19-norpregna-1,3,5(10)-triene-20-yne-3,6α,17β-triol (1) and 19-norpregna-1,3,5(10)-triene-20-yne-3,6β,17β-triol (3)*

Compound **7** (4.97 g, 16 mmol) was dissolved in methanol (70 mL). The solution was cooled in ice-water bath and sodium borohydride (0.73 g, 19.3 mmol) was added in portions. After the mixture was stirred for 12 h at room temperature the excess sodium borohydride was destroyed by the addition of acetone. The reaction mixture was concentrated at reduced pressure then ethyl acetate (120 mL) and dilute hydrochloric acid (1N, 60 mL) were added to the residue. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (40 mL 3×). The organic phases were combined and washed with water and brine then dried over $MgSO_4$. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:1, v/v) to afford **1** (3.20 g, 64%) as pale yellow powder, mp 160–161 °C (Ref. [18] value: 158–161 °C), R_f 0.29 (petroleum ether/ethyl acetate, 1:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.17 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 2.5 Hz, 1H), 6.72 (dd, J = 8.5 and 2.7 Hz, 1H), 4.80 (s, 1H), 4.10 (t, J = 7.1 Hz, 1H), 2.60 (s, 1H), 2.23–2.40 (m), 1.68–2.05 (m), 1.21–1.53 (m), 0.90 (s, 3H). IR (KBr pellet) ν 3289, 2935, 2870, 1612, 1499, 1448, 1377, 1290, 1255, 1066, 1047, 1018 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) 312 (M^+, 25), 295 (17), 294 (70), 237 (10), 229 (35), 227 (13), 226 (36), 224 (25), 213 (13), 212 (19), 211 (100), 209 (17), 208 (11), 207 (16), 198 (10), 197 (23), 195 (12), 185 (10), 184 (12), 183 (19), 182 (10), 181 (12), 174 (13), 173 (11), 171 (18), 170 (20), 167 (15), 165 (13), 161 (11), 160 (10), 159 (31), 158 (51), 157 (68), 153 (10), 149 (11), 147 (15), 145 (18), 144 (20), 137 (14), 135 (10), 133 (15), 132 (10), 131 (19), 129 (11), 128 (15), 127 (12), 125 (10), 124 (19), 123 (12), 121 (11), 119 (10), 115 (15), 111 (15), 107 (20), 105 (17), 98 (23), 97 (24), 96 (10), 95 (22), 91 (22), 85 (15), 83 (24), 82 (11), 81 (21), 79 (14), 77 (20), 71 (20), 70 (11), 69 (26), 67 (16), 57 (27), 55 (32), 53 (13), 44 (27), 43 (41), 41 (21).

Compound **3** (1.01 g, 20%) was obtained as pale yellow solid as the minor product, mp 119–120 °C (Ref. [18] value: 120 °C), R_f 0.44 (petroleum ether/ethyl acetate, 1:1, v/v).

2.2.3. *Synthesis of 3,17β-dihydroxy-19-norpregna-1,3,5(10),6-tetraene-20-yne (5)*

A mixture consisting of **1** and **3** (1.72 g, 5.5 mmol) was heated to 230 °C then was allowed to cool to room temperature. The residue was dissolved in ethyl acetate and the solution was dried over $MgSO_4$. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (3:1, v/v) as eluent to give **5** (0.99 g, 61%) as pale yellow solid, mp 181.8–183.7 °C, R_f 0.64 (petroleum ether/ethyl acetate, 2:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.05 (d, J = 7.8 Hz, 1H), 6.66 (dd, J = 8.2 and 2.6 Hz, 1H), 6.51 (d, J = 2.7 Hz, 1H), 6.35 (dd, J = 9.5 and 2.8 Hz, 1H), 5.91 (dd, J = 9.6 and 1.6 Hz, 1H), 2.54 (s, 1H), 0.82 (s, 3H). IR (KBr pellet) ν 3268, 2923, 2855, 1631, 1606, 1574, 1449, 1381, 1328, 1263, 1191, 1136, 1051, 1015, 798 cm^{-1}.

2.2.4. *Synthesis of 17α-ethinyl-17-hydroxy-3-methoxyestra-1,3,5(10)-triene-6-one (8)*

A mixture consisting of **7** (4.34 g, 14 mmol), anhydrous potassium carbonate (6.36 g, 46 mmol), methyl iodide (6 mL, 13.7 g, 97 mmol), and acetone (40 mL) was stirred at room temperature for 36 h then refluxed for 6 h. The reaction mixture was allowed to cool to room temperature and poured into water (150 mL). The mixture was extracted with ethyl acetate (80 mL 4×) and the combined organic phase was dried over Na_2SO_4. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1, v/v) as eluent or by recrystallization from methylene dichloride/hexane to give **8** (4.3 g, 95%) as pale yellow needles, mp 161.8–162.5 °C (Ref. [1] value: 162–163 °C from ether), R_f 0.57 (petroleum ether/ethyl acetate, 2:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 2.9 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 8.6 and 2.9 Hz, 1H), 3.85 (s, 3H), 2.75 (dd, J = 16.9 and 3.3 Hz, 1H), 2.63 (s, 1H), 2.23–2.57 (m), 1.72–2.05 (m), 1.56–1.66 (m), 1.26–1.49 (m), 0.90 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8 (C=O), 158.2 (3-C), 139.5 (10-C), 133.4 (5-C), 126.6 (1-C), 121.6 (2-C), 109.7 (4-C), 87.2 (21-C), 79.6 (17-C), 74.4 (22-C), 55.5 (OCH_3), 49.3 (13-C), 46.9 (14-C), 44.0 (9-C), 42.6 (7-C), 40.7 (8-C), 38.9 (16-C), 32.4 (12-C), 25.7 (11-C), 22.5 (15-C), 12.5 (CH_3). IR (KBr pellet) ν 3523, 3275, 2946, 1674, 1605, 1493, 1327, 1286, 1246, 1224, 1038 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) 324 (M^+, 77), 256 (50), 241 (68), 227 (12), 214 (15), 200 (60), 188 (100), 174 (19), 161 (23), 145 (10), 128 (12), 115 (18), 103 (11), 91 (11), 77 (13).

2.2.5. *Synthesis of 17α-ethinyl-3-methoxyestra-1,3,5(10)-triene-6α,17β-diol (2)*

Treatment of **8** with sodium borohydride in a manner similar to reduction of **7** gave compound **5** as white solid, yield 95%, mp 144.2–145.6 °C (Ref. [18] value: 144–146 °C), R_f 0.38 (petroleum ether/ethyl acetate, 2:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 6.80 (dd, J = 8.6 and 2.8 Hz, 1H), 4.84 (t, 1H), 3.83 (s, 3H), 2.60 (s, 1H), 2.25–2.38 (m), 1.99–2.08 (m), 1.89–1.93 (m), 1.71–1.85(m), 1.51–1.58 (m), 1.32–1.48 (m), 1.24–1.28 (m), 0.90 (s, 3H). IR (KBr pellet) ν 3412, 2931, 2870, 1610, 1497, 1465, 1383, 1280, 1237, 1090, 1067, 1038 cm^{-1}.

2.2.6. *Synthesis of 6β,17β-dihydroxy-19-norpregna-1,3,5(10)-triene-20-yne 6-(4-nitrobenzoate) (12)*

A solution of diethyl azodicarboxylate (DEAD, 2.40 g, 13.8 mmol) in dry tetrahydrofuran (THF, 10 mL) was added dropwise to a stirred solution containing **2** (1.80 g, 5.5 mmol), triphenylphosphine (1.45 g, 5.5 mmol), and 4-nitrobenzoic acid (2.30 g, 13.8 mmol) in dry THF (30 mL) maintained in ice-water bath under nitrogen atmosphere. The mixture was stirred at room temperature overnight. After evaporation under reduced pressure the residue was chromatographed on a silica gel column. Upon elution with 50% petroleum ether in dichloromethane, a fore running yellow coloration was removed. Further elution with 10% petroleum ether in dichloromethane gave the desired 4-nitrobenzoate derivative **12** (2.5 g, 95%) as pale yellow solid, mp 86.5–88.0 °C, R_f 0.67 (petroleum ether/ethyl acetate, 2:1, v/v). ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 8.6 Hz, 2H), 8.11 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.3 Hz,

1H), 6.84 (s, 1H), 6.82 (s, 1H), 6.20 (s, 1H), 3.69 (s, 3H), 2.55 (s, 1H), 2.07–2.26 (m), 1.89–1.97 (m), 1.55–1.77 (m), 1.18–1.27 (m), 0.86 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 166.6 (C=O), 160.3 (3-C), 152.9 (4′-C), 138.4 (5- or 1′-C), 136.6 (1′- or 5-C), 135.8 (10-C), 133.2 (2′-C), 129.0 (1-C), 125.9 (3′-C), 117.4 (2- and 4-C), 89.7 (21-C), 82.0 (17-C), 76.6 (22-C), 74.0 (6-C), 57.7 (OCH_3), 51.1 (12-C), 49.5 (13-C), 45.8 (9-C), 41.2 (15-C), 37.1 (7-C), 36.3 (8-C), 35.0 (11-C), 28.3 (10-C), 25.1 (14-C), 15.1 (CH_3). IR (KBr pellet) ν 3450, 2940, 1717, 1611, 1528, 1502, 1344, 1272, 1105, 1038, 1009, 853, 720 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 475 (M^+, 12), 308 (57), 240 (29), 226 (20), 225 (100), 184 (28), 173 (21), 172 (67), 171 (89), 159 (23), 158 (32), 124 (43), 121 (20), 115 (21), 108 (20), 104 (17), 65 (22), 55 (14).

2.2.7. *Synthesis of 17α-ethinyl-3-methoxyestra-1,3,5(10)-triene-6β,17β-diol* (**4**)

To a flask containing **12** (2.38 g, 5.0 mmol) were added methanol (20 mL) and THF (20 mL) followed by $LiOH{\cdot}H_2O$ (0.67 g, 16.0 mmol). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and to the residue was added ethyl acetate (65 mL), saturated ammonium chloride solution (22 mL), and 1.0N hydrochloric acid (18 mL). The organic layer was separated and the aqueous phase was further extracted with ethyl acetate (15 mL 3×). The combined organic extract was dried with anhydrous $MgSO_4$ and evaporated to a solid residue. Chromatography on a silica gel column eluted with 20% ethyl acetate in petroleum ether gave the desired 6β-alcohol **4** (1.1 g, 67%) as pale yellow solid, mp 198.5–199.5 °C (Ref. [18] value: 199–200 °C), R_f 0.36 (petroleum ether/ethyl acetate, 2:1, v/v).

2.2.8. *Synthesis of 17α-ethinyl-3-methoxyestra-1,3,5(10),6-tetraene-17-ol* (**6**)

A flask containing **2** (0.76 g, 2.33 mmol) was heated to 230 °C then was allowed to cool to room temperature. The formed brown solid was dissolved in ethyl acetate and the solution was dried over $MgSO_4$. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (4:1, v/v) to give **6** (0.66 g, 92%) as pale yellow solid, mp 124.4–125.3 °C, R_f 0.58 (petroleum ether/ethyl acetate, 4:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.17 (d, J = 8.3 Hz, 1H), 6.74 (dd, J = 8.3 and 2.5 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 9.6 and 2.5 Hz, 1H), 5.97 (d, J = 9.6 Hz, 1H), 3.80 (s, 3H), 2.60 (s, 1H), 2.25–2.40 (m), 2.03–2.14 (m), 1.87–1.95 (m), 1.69–1.77 (m), 1.43–1.57 (m), 1.26 (t), 0.89 (s, 3H). IR (KBr pellet) ν 3386, 3273, 3026, 2934, 2867, 2830, 1604, 1568, 1485, 1279, 1257, 1148, 1060, 1035, 1011 cm^{-1}.

2.2.9. *Synthesis of 3,17β-dihydroxy-19-norpregna-1,3,5(10),9(11)-tetraene-20-yne* (**9**)

Compound **9** was synthesized as reported in Ref. [19] and was obtained as pale yellow solid, mp 181.1–181.9 °C (Ref. [19] value: 180–182 °C), R_f 0.53 (petroleum ether/ethyl acetate, 2:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 1H), 6.57 (brs, 1H), 6.65 (dd, J = 7.5 Hz, 1H), 6.15 (brs, 1H), 3.77–2.85 (m), 2.59 (s, 1H), 2.32–2.36 (m), 1.83–2.07 (m), 1.25–1.63 (m), 0.89 (s, 3H). IR (KBr pellet) ν 3387, 3286, 2927, 2927, 1629, 1607, 1459, 1384, 1294, 1232 cm^{-1}.

2.2.10. *Synthesis of 17α-ethinyl-3-methoxyestra-1,3,5(10),9(11)-tetraene-17-ol* (**10**)

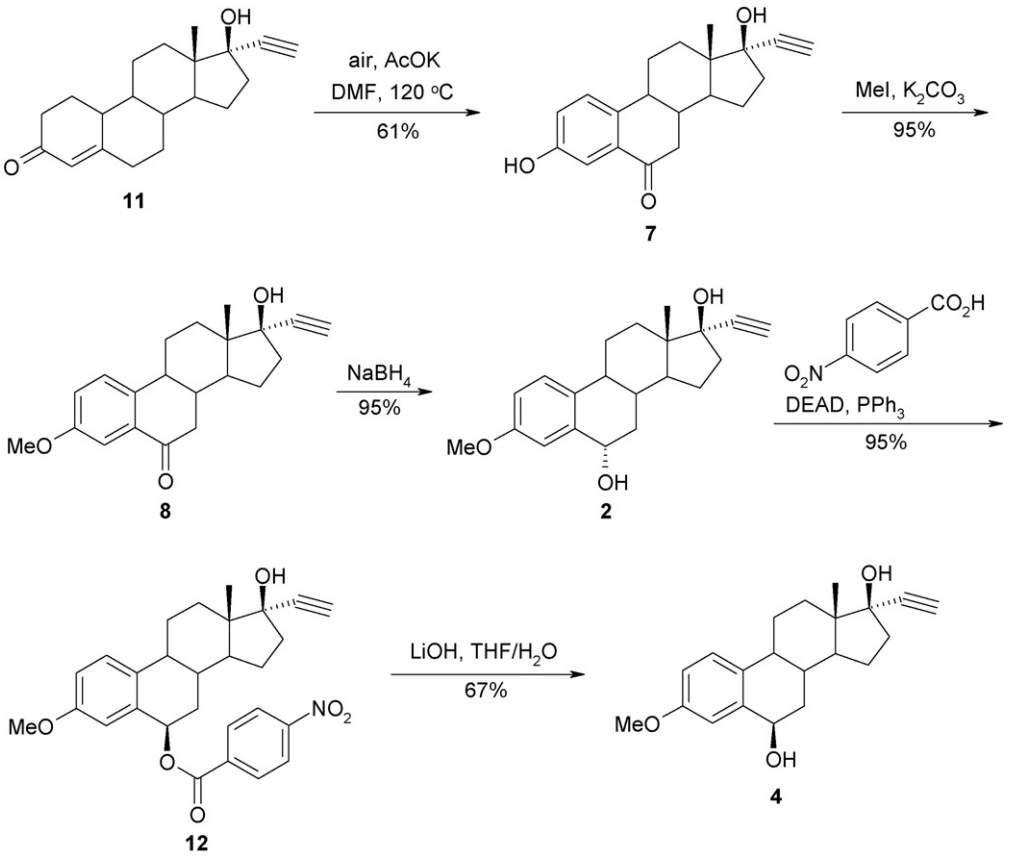
A mixture containing **9** (0.50 g, 1.7 mmol), anhydrous potassium carbonate (0.76 g, 5.5 mmol), methyl iodide (0.7 mL, 1.6 g, 11.3 mmol), and acetone (10 mL) was stirred at room temperature for 45 h then was allowed to cool to room temperature. After water (20 mL) was added the reaction mixture was extracted with ethyl acetate (20 mL 3×) and the combined organic phase was dried over Na_2SO_4. After evaporation to remove solvent, the crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (3:1, v/v) to give **10** (0.45 g, 86%) as pale yellow needles, mp 144.7–145.9 °C, R_f 0.60 (petroleum ether/ethyl acetate, 3:1, v/v). ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1H), 6.60 (brs, 1H), 6.72 (dd, J = 8.0 and 2.5 Hz, 1H), 6.17 (t, 1H), 3.83 (s, 3H), 2.87 (m, 2H), 2.78 (m, 1H), 2.60 (s, 1H), 2.36 (m, 1H), 2.01–2.09 (m, 4H), 1.93 (m, 1H), 1.85 (m, 1H), 1.48 (m, 1H), 1.40 (m, 1H), 0.91 (s, 3H). IR (KBr pellet) ν 3463, 3254, 2972, 2927, 2890, 2874, 2833, 1606, 1499, 1295, 1230, 1111, 1057, 1032 cm^{-1}.

3. Results and discussion

The thermal (178 °C) degradation products **1**, **3**, **5**, and **7** were synthesized starting from norethindrone (**11**). It was first reported by Wiechert and co-workers that norethidrone could be oxidized to 6-keto EE (**7**) by oxygen in DMF containing potassium acetate at 120 °C [21]. This procedure was followed and the yield of compound **7** was about 40% [18,19]. We found that the yield of **7** could be improved up to 61% by prolonging the reaction time from 12 h to 18 h. And the oxidation procedure could be simplified by replacing oxygen with air without substantial decrease in yields (Scheme 1). Reduction of **7** with sodium borohydride in methanol afforded a mixture of the 6α-hydroxy isomer (**1**) and the 6β-hydroxy isomer (**3**) by a similar procedure as reported [18]. The conversion was about 84% and the produced mixture was separated by column chromatography to give **1** and **3** in a yield of 64% and 20%, respectively. Heating a mixture of **1** and **3** at 230 °C resulted elimination of the secondary alcohols to afford **5** in 61% yield.

Methylation of compound **7** with methyl iodide in the presence of potassium carbonate afforded **8**, the minor degradation product of mestranol, in high yield (95%). Reduction of **8** with sodium borohydride showed high stereoselectivity, contrary to the reduction of **7**. The 6α-hydroxy isomer (**2**) was obtained in over 95% yield after chromatography and no 6β-hydroxy isomer (**4**) was isolated. The later could be prepared by transconfiguration of **2** through an esterification/hydrolysis process as shown in Scheme 1. Mitsunobu reaction between compound **2** and 4-nitrobenzoic acid in the presence of DEAD and triphenyl phosphine produced the 4-nitrobenzoate **12** in 95% yield. Hydrolysis of **12** in the presence of lithium hydroxide in THF/H_2O afforded the 6β-hydroxy isomer **4** in about 67% yield, thus providing a practical and scalable preparation method for the 6β-hydroxy isomer **4**.

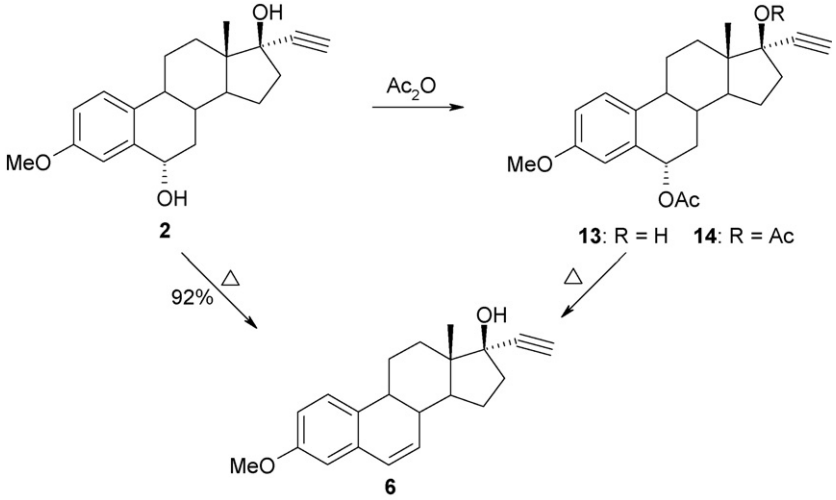
Compound **6** was synthesized as shown in Scheme 2. Cotter et al. reported an indirect synthesis of **6** without its physical data [18]. Compound **2** was first transformed by acetylation



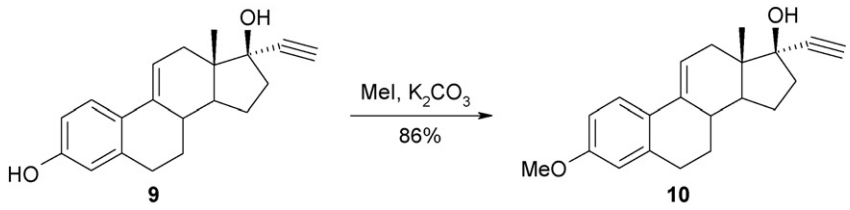
Scheme 1

with acetic anhydride to its monoacetate **13** and diacetate **14**, which could be separated by chromatography. When **13** was heated at 230 °C, the C-6 secondary acetate was eliminated to yield **6** as an oil after chromatographic separation. We improved the preparative procedure of **6** by direct heating of compound **2** at 230 °C, to afford **6** as a pale yellow solid in 92% yield after purification with column chromatography. The chemical structure of **6** was fully characterized by ^{1}H NMR, IR spectrum, and melting point measurements.

Compound **9**, a major oxidative transformation product of EE, was synthesized starting from commercially available estrone by a three-step sequence as reported by Hurley and co-workers [19]. Methylation of **9** with methyl iodide and potassium carbonate at room temperature produced **10** in 86% yield as shown in Scheme 3, providing a practical synthetic method of compound **10**, a photodecomposition product of mestranol [22] for the first time. Single crystals suitable for X-ray crystal diffraction of **10** were obtained by recrystallization



Scheme 2



Scheme 3

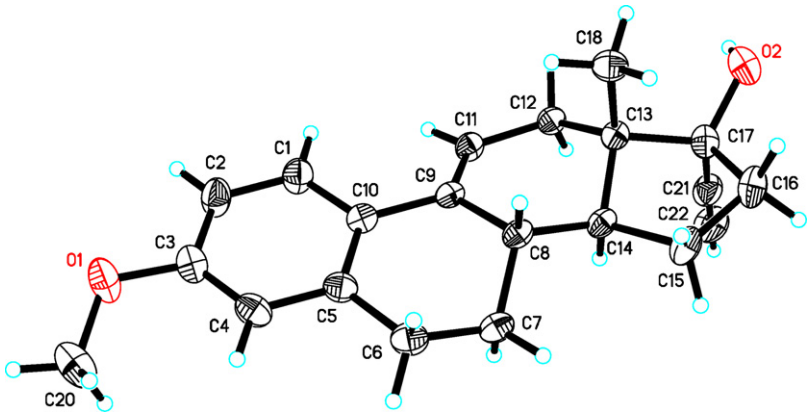


Fig. 2 – Crystal structure of compound 10.

from ethyl acetate. The crystal structure which was shown in Fig. 2 undoubtedly identified the stereochemistry of **10**.

In summary, synthetic procedures of ten degradation or photodecomposition products of mestranol and ethinyl estradiol were detailed. A practical method for scalable preparation of 17α-ethinyl-3-methoxyestra-1,3,5(10)-triene-6β,17β-diol (**4**) by Mitsunobu reaction was described. The preparative procedure of 17α-ethinyl-3-methoxyestra-1,3,5(10),6-tetraene-17-ol (**6**) was simplified. A four-step synthetic protocol for 17α-ethinyl-3-methoxyestra-1,3,5(10),9(11)-tetraene-17-ol (**10**) was also presented. Synthesis of other degradation or photodecomposition products of mestranol and ethinyl estradiol was optimized and their structures were fully characterized.

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