

80. Synthesis of 11-Oxaestrogens *via* Dye-Sensitized Photo-oxygenation of a 9,11-Didehydroestrone Derivative

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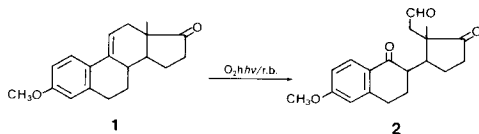
The 3-methoxy-11-oxaestrone (**13**) has been synthesized from estrone (**3**) following an approach that involves the ring-C fragmentation of the estrogenic skeleton by dye-sensitized photo-oxygenation of the properly C(17)-protected 9,11-didehydroestrone derivative **6** as the key step. The C(13)-side-chain degradation of the 9-oxo-9,11-seco-aldehyde **7** followed by reduction to the 9 β ,12-diol **10** and further cyclization yields the 11-oxaestrogenic skeleton. By this procedure, **13** is obtained in 9 steps from **3** with a non-optimized overall yield of *ca.* 15%.

Introduction. – There are a number of studies on the synthesis and physiological activity of heterosteroids. Among them, *Engel et al.* [1] have pointed out, in view of the physiological significance of the 11-oxygen function in adrenocortical hormones, the special interest of those heterosteroids in which the CH₂ group in the 11-position is replaced by a heteroatom. The same authors have synthesized some 11-oxa- and 11-azasteroid analogs describing an interesting separation of activities as compared with natural hormones [2]. For example, 11-oxaprogesterone showed little progestational activity, but it had enhanced ovulation inhibitory activity, the ratio of both being *ca.* 8–9 times more favourable than in the case of progesterone [3].

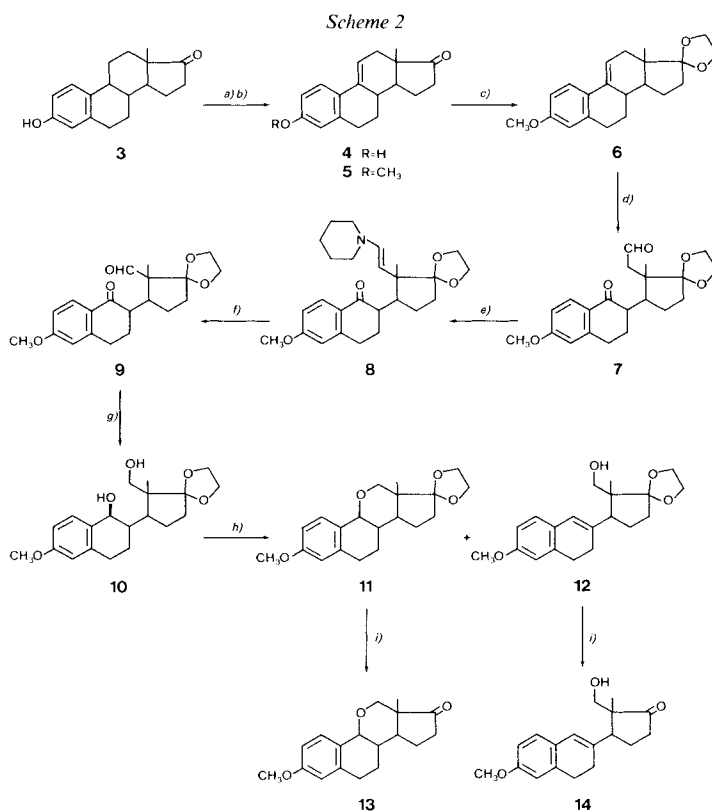
The 11-oxasteroidal framework has been built by two different strategies, both of them applied to pregnane derivatives: acid cyclization of a 11-nor-9,11-seco-9,12-diol as first reported by *Engel* and coworkers [2] and, more recently, by reductive cyclization of a iodo formate after photolysis of hypiodites derived by HgO/I₂ treatment of a C-homo-lactol as described by *Suginome et al.* [4].

Little attention has been paid to 11-oxa analogs of estrogenic hormones in spite of the positive preliminary biological results reported by *Engel et al.* [3] suggesting potential inhibition of ovulation and low estrogenic character. To our knowledge, no transformation of natural estrone to 11-oxaestrogens has been described. This subject attracted our interest in order to develop a new synthesis based on the ring-C fragmentation by dye-sensitized photo-oxygenation of 3-methoxy-9,11-didehydroestrone (**1**) yielding **2** previously described by us [5] (*Scheme 1*). Besides the easy ring-C opening, this reaction affords the appropriate functionalization at C(11) to replace one C-atom by an O-atom.

Scheme 1



Results. – The planned synthesis involves four main steps [6] (*Scheme 2*): *i*) dye-sensitized photo-oxygenation of a 9,11-didehydroestrone derivative properly protected at C(17), *ii*) degradation of the C(13) side chain of the 9,11-seco-steroid **7** to the 11-nor compound **9**, *iii*) reduction of both carbonyl groups to the 9 β ,12-diol **10**, and *iv*) cyclization of **10** to the 11-oxaestrogenic skeleton.



a) DDQ/MeOH, r.t. (80%); *b)* Me₂SO₄/OH[−] (92%); *c)* (CH₂OH)₂/TsOH/C₆H₆ (98%); *d)* O₂/hv/r.b./MeOH (70%); *e)* C₅H₁₀NH/C₆H₆ (100%); *f)* O₃/CH₂Cl₂, −78°; *g)* NaBH₄/MeOH/CH₂Cl₂ (*f* + *g*, 30%); *h)* Δ 40–50° or TsCl/py (85% **11**); *i)* TsOH/acetone, reflux (95% **13**).

Thus, 3-methoxy-9,11-didehydroestrone ethylene acetal (**6**) was prepared from estrone (**3**) in 72% yield as described by Collins and Sjövall [7] (**3**→**4**→**5**→**6**). Photo-oxygenation of **6** in MeOH solution using rose bengal (r.b.) as sensitizer gave the expected fragmentation product **7**. The proper experimental conditions were chosen according to the previous kinetic study [5], avoiding large excess of sensitizer. After chromatographic separation, the 9,11-secoaldehyde **7** was isolated in 70% yield. This higher value with regard to that obtained for **2** (50%) may be due to the greater stability of **7** (one protected carbonyl group) during the purification process. The free aldehyde in the C(13)-side chain allows to apply the enamine/ozonolysis degradation to remove one C-atom in two steps. Ozonolysis of the (*E*)-enamine **8** (configuration assigned by ¹H-NMR) in CH₂Cl₂ solution

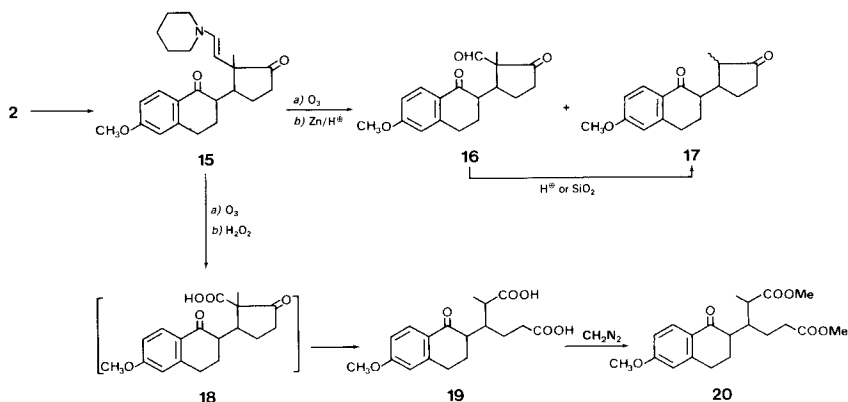
at -78° for a few min yielded the 11-nor-9,11-seco-aldehyde **9**. The enamine fragmentation by means of singlet oxygen ($O_2/r.b. h\nu$ in MeOH) [8] was also tried but, in this case, the reaction was very slow and yielded mainly the aldehyde **7** by slow hydrolysis of the enamine in the alcoholic medium. $NaBH_4$ reduction of **9** afforded a mixture from which the diol **10** was isolated as the major compound. The 9β -OH configuration is tentatively assigned on the basis of its 1H -NMR spectrum ($H-C(9)$ as *d* at 4.56 ppm, $J = 7.2$ Hz).

Cyclization to the 11-oxaestrogenic skeleton was performed by Engel's method [1] [2] or by simple heating in an organic solvent. Thus, treatment of the diol **10** with tosyl chloride in pyridine solution (Engel's method) gave a mixture of 3-methoxy-11-oxaestrone ethylene acetal (**11**) and the unsaturated alcohol **12** (after SiO_2 chromatography, ratio 6:1). The same result was achieved on heating **10** in $CHCl_3/AcOEt$ to $40-50^\circ$. Although the major compound was the desired **11**, the easy elimination of the benzylic $OH-C(9)$ of **10** to give **12** could not be avoided.

A first attempt to deprotect the 17-carbonyl group of **11/12** with TsOH in acetone gave **13**, **14**, and some starting material **11**. While the unsaturated alcohol **14** was easily separated, the isolation of pure **13** proved to be more difficult. In another experiment, longer treatment of pure **11** with TsOH in acetone solution yielded the target 3-methoxy-11-oxaestrone (**13**), identified on the basis of its analytical and spectral data. By this procedure, estrone (**3**) was converted into **13** in 9 steps with a non-optimized overall yield of ca. 15%.

The synthetic scheme developed requires the C(17) carbonyl function to be protected before the ring-C opening step. When the same procedure was tried with the 9,11-seco-aldehyde **2** (free C(17)=O group), undesired reactions took place (Scheme 3). Although

Scheme 3



the enamine could be selectively formed at the C(11)=O group (**2**→**15**), its ozonolysis followed by either reduction ($Zn/AcOH$) or oxidation (H_2O_2) led to the scission of the thus formed 1,3-dicarbonyl system, *i.e.* decarbonylation (**16**→**17**), or to ring-D opening (**18**→**19**), respectively. In the first case ($Zn/AcOH$), **17** was the major product (40% yield) and proved to arise from **16** which was obtained in only 5% yield. When allowed to stand in mild acidic medium ($AcOH$ or SiO_2 in column chromatography), **16** was quantitatively

transformed into the 11,12-dinor compound **17**. In the second case (H_2O_2), the intermediate β -keto acid **18** is assumed to be unstable; the final product **19** was identified as its dimethyl ester **20**.

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Experimental Part

General. See [5].

3-Methoxy-1,3,5(10),9(11)-estratetraen-17-one (5) was synthesized from 3-hydroxy-1,3,5(10)-estratrien-17-one (**3**) according to [7]. DDQ oxidation of **3** in MeOH soln. afforded 3-hydroxy-1,3,5(10),9(11)-estratetraen-17-one (**4**, 80%), and further treatment with dimethyl sulfate in basic medium ($\text{KOH}/\text{H}_2\text{O}/\text{MeOH}$) gave **5** (92%).

3-Methoxy-1,3,5(10),9(11)-estratetraen-17-one Ethylene Acetal (6). A soln. of 6 g of **5**, 12 ml of ethylene glycol, and 180 mg of TsOH in 200 ml of dry benzene was subjected to azeotropic distillation in a *Dean-Stark* apparatus for 6 h. The crude product was poured into ice containing solid NaHCO_3 . Usual workup yielded 6.78 g (98%) of **6**. M.p. 145–146°. UV (EtOH): 204 (17800), 213 (16200), 264 (16000). IR (KBr): 1630, 1610, 1570, 1500, 1260, 1175, 1160, 1050, 1040, 960. $^1\text{H-NMR}$ (CDCl_3): 7.50 (*d*, $J = 9$, $\text{H-C}(1)$); 6.72 (*dd*, $J = 9, 2.7$, $\text{H-C}(2)$); 6.61 (*d*, $J = 2.7$, $\text{H-C}(4)$); 6.10 (*m*, $\text{H-C}(11)$); 3.94 (*m*, $w_{\text{H}} = 13$, $\text{OCH}_2\text{CH}_2\text{O}$); 3.79 (*s*, CH_3O); 2.83 (*m*, 2 $\text{H-C}(6)$); 0.90 (*s*, $\text{CH}_3(18)$). MS: 326 (77, M^+), 311 (20), 267 (15), 266 (58), 265 (100), 264 (29), 227 (15), 226 (10), 225 (34), 224 (20), 223 (12), 211 (11), 99 (49). Anal. calc. for $\text{C}_{21}\text{H}_{26}\text{O}_3$ (326.44): C 77.27, H 8.08; found: C 77.03, H 8.10.

17,17-(Ethylenedioxy)-3-methoxy-9-oxo-9,11-seco-1,3,5(10)-estratrien-11-al (7). For 3 h, 902 mg of **6** and 70 mg of rose bengal in 300 ml of dry MeOH were photo-oxygenated in a tubular photoreactor fitted with a halogen lamp (*Sylvania* 500 W) while bubbling dry O_2 . After evaporation under vacuum at r.t., the red crude mixture was chromatographed on a SiO_2 column with benzene/AcOEt 20:1 to yield 669 mg (70%) of **7**. UV (MeOH): 206 (16100), 224 (11400), 275 (14500). IR: 2750, 1710, 1670, 1600, 1570, 1495, 1270, 1070, 1025, 960. $^1\text{H-NMR}$ (CDCl_3): 9.37 (*dd*, $J = 4, 2.5$, $\text{C}(11)\text{HO}$); 7.89 (*d*, $J = 8.7$, $\text{H-C}(1)$); 6.81 (*dd*, $J = 8.7, 2.5$, $\text{H-C}(2)$); 6.66 (*d*, $J = 2.5$, $\text{H-C}(4)$); 3.84 (*br. s.*, $\text{OCH}_2\text{CH}_2\text{O}$); 3.79 (*s*, CH_3O); 2.95 (*m*, 2 $\text{H-C}(6)$); 2.70 (*m*, 2 $\text{H-C}(12)$); 1.24 (*s*, $\text{CH}_3(18)$). MS: 358 (5, M^+), 315 (3), 183 (100), 182 (38), 177 (15), 176 (85), 175 (16), 139 (30), 115 (24), 113 (31), 112 (59), 77 (21).

The 2,4-dinitrophenylhydrazone of **7** was prepared by dissolving 25 mg (0.07 mmol) of **7** in a soln. of 75 mg (0.38 mmol) of 2,4-(NO_2) $_2\text{C}_6\text{H}_3\text{NH}_2\text{NH}_2$ and 10 drops of conc. HCl in 10 ml of MeOH. Crystallization of the orange precipitate from $\text{CH}_2\text{Cl}_2/(\text{i-Pr})_2\text{O}$ gave some crystals of the 12,17-bis(dinitrophenylhydrazone) of **2**, identical by its spectral data with authentic material [5].

(E)-17,17-(Ethylenedioxy)-3-methoxy-11-(1'-piperidinyl)-9,11-seco-1,3,5(10),11-estratetraen-9-one (8). Azeotropic distillation of a mixture of 960 mg (2.68 mmol) of **7**, 3 ml (30 mmol) of piperidine (freshly distilled over NaOH), and 70 ml of dry benzene for 30 min afforded one single product (IR monitoring, absorbance decrease at 1710 cm^{-1}). Solvent distillation and drying under high vacuum for 12 h yielded 1.14 g (100%) of **8**. UV (MeOH): 205 (20900), 223 (16200), 274 (14100). IR: 1670, 1645, 1600, 1495, 1250, 1115, 1050, 950. $^1\text{H-NMR}$ (CDCl_3): 7.75 (*d*, $J = 8$, $\text{H-C}(1)$); 6.65 (*dd*, $J = 8, 2.5$, $\text{H-C}(2)$); 6.55 (*d*, $J = 2.5$, $\text{H-C}(4)$); 5.55 (*d*, $J = 15$, $\text{H-C}(11)$); 3.90 (*d*, $J = 15$, $\text{H-C}(12)$); 3.80 (*br. s.*, $\text{OCH}_2\text{CH}_2\text{O}$, CH_3O); 2.85–1.7 (*m*, $\text{CH}_2(2')$, $\text{CH}_2(6')$, CH and CH_2 of skeleton); 1.45 (*br.*, $\text{CH}_2(3')$, $\text{CH}_2(4')$, $\text{CH}_2(5')$); 1.10 (*s*, $\text{CH}_3(18)$). MS: 425 (11, M^+), 177 (54), 176 (22), 164 (65), 151 (67), 150 (31), 138 (35), 136 (100), 122 (20), 99 (37), 98 (30).

17,17-(Ethylenedioxy)-3-methoxy-9-oxo-11-nor-9,11-seco-1,3,5(10)-estratrien-12-al (9). Ozonolysis of 1.1 g of **8** in 60 ml of CH_2Cl_2 (previously distilled over CaH_2) at -78° for 20 min gave a blue soln. from where the remaining O_3 was purged by bubbling dry N_2 . The crude mixture, allowed to warm up to r.t., was directly used in the next step (NaBH_4 reduction). A sample of it was purified by column chromatography on SiO_2 (cyclohexane/acetone 4:1) to afford pure **9**. UV (cyclohexane): 211, 221, 228, 269. IR: 2730, 1715, 1670, 1600, 1495, 1250, 1060, 945. $^1\text{H-NMR}$ (cyclohexane/ CDCl_3): 9.65 (*s*, $\text{C}(12)\text{HO}$); 7.93 (*d*, $J = 8.8$, $\text{H-C}(1)$); 6.79 (*dd*, $J = 8.8, 2.4$, $\text{H-C}(2)$); 6.67 (*d*, $J = 2.4$, $\text{H-C}(4)$); 3.84 (*br. s.*, $\text{OCH}_2\text{CH}_2\text{O}$); 3.79 (*s*, CH_3O); 2.95 (*m*, 2 $\text{H-C}(6)$). MS: 344 (5, M^+), 176 (100).

17,17-(Ethylenedioxy)-3-methoxy-11-nor-9,11-seco-1,3,5(10)-estratriene-9 β ,12-diol (10). The crude mixture from enamine ozonolysis containing **9** was diluted with 10 ml of MeOH and treated with 900 mg of NaBH_4 at r.t.

for 5 h. The mixture was poured into ice and extracted with CHCl_3 . After washing of the org. layer till neutrality with 5% HCl soln., solvent evaporation afforded a mixture of two major compounds which were separated by SiO_2 column chromatography: 255 mg (30% from **8**) of **10**. UV (MeOH): 209, 227 (8200), 276 (2200), 284 (2000). IR: 3420, 1610, 1580, 1500, 1260, 1040, 950. $^1\text{H-NMR}$ (CDCl_3): 7.47 (*d*, $J = 8.6$, $\text{H-C}(1)$); 6.75 (*dd*, $J = 8.6$, 2.8, $\text{H-C}(2)$); 6.59 (*d*, $J = 2.8$, $\text{H-C}(4)$); 4.56 (*dd*, $J = 7.2$, $J(\text{H, OH}) < 1$, $\text{H-C}(9)$); $\rightarrow d$, $J = 7.2$, on shaking with D_2O ; 3.94 (*s*, $\text{OCH}_2\text{CH}_2\text{O}$); 3.77 (*s*, CH_3O); 3.51 (*m*, 2 $\text{H-C}(12)$, OH; on shaking with D_2O , 3.65 (*d*, $J = 12$, $\text{H}_A\text{-C}(12)$), 3.35 (*d*, $J = 12$, $\text{H}_B\text{-C}(12)$), and integral decrease of 1 H (OH)); 2.72 (*m*, 2 $\text{H-C}(6)$); 0.84 (*s*, $\text{CH}_3(18)$). MS: no M^+ , 330 (5.5), 160 (100), 149 (14), 100 (11), 99 (39).

Cyclization of 10 by Engel's Method. A soln. of 40 mg (0.12 mmol) of **10** and 200 mg (1.05 mmol) of TsCl in 10 ml of pyridine was heated at 80° under N_2 . After 3 h, addition of ice and usual CHCl_3 extraction afforded 38 mg of oily **11/12**. A sample was separated (see below, thermal cyclization) yielding **11** and **12** in a 6:1 ratio.

Deacetalization of 11/12. The remaining crude **11/12** (see above) was treated with 7.3 mg of TsOH in acetone soln. (5 ml) under reflux for 20 min. Ice and solid NaHCO_3 were added, and the mixture was extracted with CHCl_3 . Solvent evaporation after drying (MgSO_4) afforded 38 mg of a yellowish oil which was chromatographed on SiO_2 with CHCl_3 yielding **11/13** (26 mg) identified by comparison with pure **11** and **13** (see below) and **14** (4 mg).

Data for 11/13: UV (MeOH): 207, 228, 277, 285 (rel. absorbance 1:0.51:0.15:0.14). IR: 1740, 1610, 1580, 1500, 1260, 1100, 1040, 960, 830. $^1\text{H-NMR}$ (CDCl_3): 7.45 (*d*, $J = 8.5$, $\text{H-C}(1)$); 6.75 (*dd*, $J = 8.5$, 2.6, $\text{H-C}(2)$); 6.58 (*d*, $J = 2.6$, $\text{H-C}(4)$); 4.90 (*2d*, $J = 5.3$, 5.3, $\text{H-C}(9)$, **11/13**); 3.76 (*br. s*, CH_3O , $\text{OCH}_2\text{CH}_2\text{O}$ of **11**); 3.50 (*m*, 2 $\text{H-C}(12)$); 2.70 (*m*, 2 $\text{H-C}(6)$); 1.14 (*s*, $\text{CH}_3(18)$, **13**); 1.08 (*s*, $\text{CH}_3(18)$, **11**). MS: 330 (2.3, M^+ (**11**)), 287 (2.1), 286 (10.4, M^+ (**13**)), 229 (9.2), 176 (4), 160 (100), 159 (12.5), 115 (18).

12-Hydroxy-3-methoxy-11-nor-9,11-seco-1,3,5(10),8-estratetraen-17-one (14): UV (MeOH): 213 (18200), 273 (13000). IR: 3460, 1740, 1610, 1575, 1505, 1255, 1045. $^1\text{H-NMR}$ (CDCl_3): 6.95 (*d*, $J = 9$, $\text{H-C}(1)$); 6.70 (*m*, $\text{H-C}(2)$, $\text{H-C}(4)$); 6.28 (*s*, $\text{H-C}(9)$); 3.80 (*dd*, $J = 11.1$, 1.2, $\text{H}_A\text{-C}(12)$); 3.77 (*s*, CH_3O); 3.53 (*d*, $J = 11.1$, $\text{H}_B\text{-C}(12)$); 2.71 (*br. d*, $J = 7.2$, 2 $\text{H-C}(6)$); 0.81 (*s*, $\text{CH}_3(18)$). MS: 286 (22, M^+), 255 (13), 211 (12), 199 (48), 186 (39), 184 (36), 171 (32), 167 (39), 165 (22), 160 (25), 149 (60), 128 (41), 115 (60).

3-Methoxy-11-oxa-1,3,5(10)-estratrien-17-one Ethylene Acetal (11) by Thermal Cyclization. A soln. of 200 mg of **10** in $\text{CHCl}_3/\text{AcOEt}$ was heated at $40\text{--}50^\circ$ while solvent slowly distilled at reduced pressure. The oily residue was chromatographed on a SiO_2 column with CHCl_3 yielding **11** (165 mg) and **12** (27 mg).

Data of 11: white solid. UV (MeOH): 207 (19100), 228 (9400). IR: 1610, 1580, 1500, 1260, 1100, 1040, 980, 950, 930. $^1\text{H-NMR}$ (CDCl_3): 7.46 (*d*, $J = 8.6$, $\text{H-C}(1)$); 6.76 (*dd*, $J = 8.6$, 2.8, $\text{H-C}(2)$); 6.58 (*d*, $J = 2.8$, $\text{H-C}(4)$); 4.89 (*d*, $J = 5.3$, $\text{H-C}(9)$); 3.78 (*s*, CH_3O); 3.72 (*m*, $\text{OCH}_2\text{CH}_2\text{O}$); 3.48 (*d*, $J = 10.2$, $\text{H}_A\text{-C}(12)$); 3.32 (*d*, $J = 10.2$, $\text{H}_B\text{-C}(12)$); 2.69 (*m*, 2 $\text{H-C}(6)$); 1.09 (*s*, $\text{CH}_3(18)$). MS: 330 (11, M^+), 229 (35), 176 (10), 161 (26), 160 (100), 159 (18), 154 (18), 99 (49). Anal. calc. for $\text{C}_{20}\text{H}_{26}\text{O}_4$ (330.43): C 72.70, H 7.93; found: C 73.07, H 8.02.

12-Hydroxy-3-methoxy-11-nor-9,11-seco-1,3,5(10),8-estratetraen-17-one Ethylene Acetal (12): IR: 3540, 1610, 1575, 1500, 1255, 1155, 1130, 1045, 950, 930. By deacetalization, **12** was shown to be the precursor of **14**.

3-Methoxy-11-oxa-1,3,5(10)-estratrien-17-one (13). When a soln. of pure **11** and TsOH in acetone was heated under reflux for 2 h, a white solid was obtained. Purification by column chromatography on SiO_2 with benzene/ AcOEt 20:1 yielded **13** (95% yield). M.p. $140\text{--}140.5^\circ$. UV (EtOH): 229 (8700), 278 (1900), 286 (1900). IR: 1740, 1615, 1580, 1500, 1460, 1255, 1165, 945. $^1\text{H-NMR}$ (CDCl_3): 7.46 (*d*, $J = 8.6$, $\text{H-C}(1)$); 6.78 (*dd*, $J = 8.6$, 2.6, $\text{H-C}(2)$); 6.60 (*d*, $J = 2.6$, $\text{H-C}(4)$); 4.96 (*d*, $J = 5.3$, $\text{H-C}(9)$); 3.78 (*s*, CH_3O); 3.61 (*d*, $J = 11$, $\text{H}_A\text{-C}(12)$); 3.33 (*d*, $J = 11$, $\text{H}_B\text{-C}(12)$); 1.16 (*s*, $\text{CH}_3(18)$). MS: 286 (34, M^+), 255 (11), 177 (11), 160 (100), 145 (18), 115 (20), 109 (30). Anal. calc. for $\text{C}_{18}\text{H}_{22}\text{O}_3$ (286.37): C 75.49, H 7.74; found: C 75.24, H 7.85.

(E)-3-Methoxy-11-(1'-piperidinyl)-9,11-seco-1,3,5(10),11-estratetraene-9,17-dione (15). As described above for **8**, **2** [5] (2.68 g, 8.5 mmol) and piperidine (3 ml, 30 mmol) in 150 ml of dry benzene afforded 3.3 g (100%) of **15**, after azeotropic distillation for 15–20 min. UV (MeOH): 204 (19500), 224 (14400), 274 (15500). IR: 1735, 1670, 1635, 1600, 1495, 1250, 1120. $^1\text{H-NMR}$ (CDCl_3): 7.95 (*d*, $J = 8.6$, $\text{H-C}(1)$); 6.79 (*dd*, $J = 8.6$, 2, $\text{H-C}(2)$); 6.67 (*d*, $J = 2$, $\text{H-C}(4)$); 5.83 (*d*, $J = 14$, $\text{H-C}(11)$); 4.10 (*d*, $J = 14$, $\text{H-C}(12)$); 3.84 (*s*, CH_3O); 2.90 (*m*, 2 $\text{H-C}(6)$); 2.74 (*br.*, $\text{CH}_2(2')$, $\text{CH}_2(6')$); 1.50 (*br.*, $\text{CH}_2(3')$, $\text{CH}_2(4')$, $\text{CH}_2(5')$); 1.13 (*s*, $\text{CH}_3(18)$). MS: 381 (39, M^+), 325 (18), 206 (80), 177 (68), 151 (100), 148 (22), 136 (73), 91 (28), 84 (42), 77 (24).

Ozonolysis of 15 Followed by Reductive Treatment. O_3 was bubbled through a stirred soln. of 3.3 g of **15** in 180 ml of CH_2Cl_2 (freshly distilled over CaH_2) at -78° for 20 min. After allowing to warm to r.t., 10 g of Zn powder and 30 ml of AcOH were added and the mixture stirred for 1 h. Solid removal, washing with aq. NaHCO_3 soln. till neutrality and solvent evaporation afforded 2.69 g of an oil. Chromatographic separation on SiO_2 (benzene/ AcOEt 16:1) gave **17** (40%) and **16** (5%).

3-Methoxy-11,12-dinor-9,11-seco-13 ζ -1,3,5(10)-estratriene-9,17-dione (17): UV (EtOH): 201 (17600), 223 (11400), 273 (14000). IR: 1740, 1670, 1600, 1495, 1250, 1030. $^1\text{H-NMR}$ (CDCl_3): 7.65 (*d*, $J = 8$, $\text{H-C}(1)$); 6.50 (*dd*,

$J = 8, 2, \text{H-C}(2))$; 6.40 ($d, J = 2, \text{H-C}(4))$; 3.70 ($s, \text{CH}_3\text{O}$); 2.9 ($m, 2 \text{H-C}(6))$; 1.0 ($d, J = 6.5, \text{CH}_3(18)$). MS: 272 (2.5, M^+), 215 (20), 176 (100), 175 (20), 161 (21), 115 (19), 91 (23), 77 (17).

3-Methoxy-9,17-dioxo-11-nor-9,11-seco-1,3,5(10)-estratrien-12-al (16): UV (EtOH): 203 (18900), 223 (12100), 275 (14800). IR: 1745, 1710, 1665, 1600, 1490, 1260, 1025. $^1\text{H-NMR}$ (CDCl_3): 9.65 ($s, \text{C}(12)\text{HO}$); 8.0 ($d, J = 8, \text{H-C}(1)$); 6.90 ($dd, J = 8, 2, \text{H-C}(2)$); 6.8 ($d, J = 2, \text{H-C}(4)$); 3.85 ($s, \text{CH}_3\text{O}$); 3.0 ($m, 2 \text{H-C}(6)$); 1.25 ($s, \text{CH}_3(18)$). MS: 300 (1.5, M^+), 215 (21), 176 (100), 175 (14), 161 (12), 148 (10), 91 (10).

When a soln. of **16** in AcOH or in an org. solvent in the presence of SiO_2 was allowed to stand at r.t. for a long time, it was quantitatively transformed into **17**.

Ozonolysis of 15 Followed by Oxidative Treatment. To the crude mixture obtained by O_3 oxidation of **15** as above (768 mg of **15** in 50 ml CH_2Cl_2 at -78° for 10 min), 4 ml of 30% H_2O_2 soln. were added. The soln. was stirred at r.t. for 12 h, followed by addition of an aq. $\text{Na}_2\text{S}_2\text{O}_5$ soln. to reduce the excess of peroxide. Solvent evaporation gave an oil which was difficult to purify by the standard crystallization and chromatographic methods. It was identified as 2-methyl-3-(1',2',3',4'-tetrahydro-6'-methoxy-1'-oxonaphthalen-2'-yl)hexanedioic acid (**19**) by preparing and identifying its dimethyl ester **20** (see below). Data of crude mixture containing **19**: IR: 3500–3000, 1740, 1715, 1675, 1605, 1560, 1500, 1260, 1035. $^1\text{H-NMR}$ (CDCl_3): 7.8 ($d, J = 8, \text{H-C}(8')$); 7.7–7.3 (br., COOH , disappears on shaking with D_2O); 6.7 ($dd, J = 8, 2, \text{H-C}(7')$); 6.55 ($d, J = 2, \text{H-C}(5')$); 3.75 ($s, \text{CH}_3\text{O}$); 2.85 ($m, 2 \text{H-C}(4')$); 1.2 ($d, \text{CH}_3\text{-C}(2)$).

Dimethyl 2-Methyl-3-(1',2',3',4'-tetrahydro-6'-methoxy-1'-oxonaphthalen-2'-yl)hexanedioate (20). The above reaction mixture from H_2O_2 oxidation was dissolved in MeOH/ Et_2O and allowed to react with diazomethane (prepared from 3 g *Diazal*[®] in 90 ml of Et_2O and 1.2 g of KOH in 15 ml of MeOH by distillation at 60°) at 0° . Column chromatography after solvent evaporation ($\rightarrow 659$ mg) with CHCl_3 gave 375 mg (52% from **15**) of **20**. IR: 1740, 1675, 1605, 1560, 1500, 1460, 1260, 1030. $^1\text{H-NMR}$ (CDCl_3): 7.98 ($d, J = 8.6, \text{H-C}(8')$); 6.80 ($dd, J = 8.6, 2, \text{H-C}(7')$); 6.68 ($d, J = 2, \text{H-C}(5')$); 3.85 ($s, \text{CH}_3\text{O-C}(6')$); 3.66 (s, COOCH_3); 3.63 (s, COOCH_3); 1.22 ($d, J = 6.5, \text{CH}_3\text{-C}(2)$). MS: no M^+ , 177 (12), 176 (100), 175 (12), 161 (12), 148 (14), 120 (12), 91 (13).

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