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

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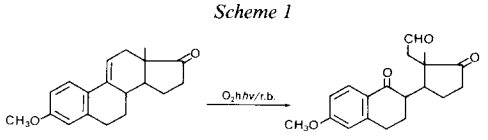
The 3-methoxy-11-oxaestrone (**13**) has been synthetized from estrone (**3**) following an approach that involves the ring-C fragmentation of the estrogenic skeleton by dye-sensitized photo-oxygenation of the properly C(17)-protected 9,11-didehydroestrone derivative **6** as the key step. The C(13)-side-chain degradation of the 9-oxo-9,11-seco-aldehyde **7** followed by reduction to the 9β,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 CH_2 group in the 11-position is replaced by a heteroatom. The same autors have synthetized 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 hypoiodites derived by HgO/I_2 treatment of a *C*-homolactol 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.

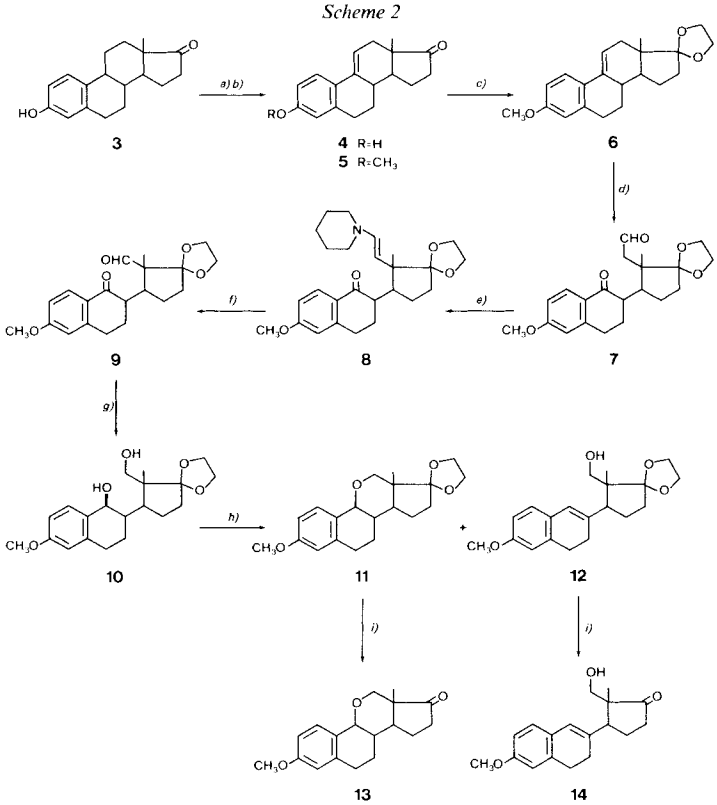
Scheme 1



1 **2**

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 9β,12-diol **10**, and *iv)* cyclization of **10** to the 11-oxaestrogenic skeleton.

Scheme 2



a) DDQ/MeOH, r.t. (80%); *b)* Me_2SO_4/OH^- (92%); *c)* $(CH_2OH)_2/TsOH/C_6H_6$ (98%); *d)* $O_2/h\nu$/r.b./MeOH (70%); *e)* $C_5H_{10}NH/C_6H_6$ (100%); *f)* O_3/CH_2Cl_2, −78°; *g)* $NaBH_4/MeOH/CH_2Cl_2$ (*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**). Photooxygenation 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 ^{1}H-NMR) in CH_2Cl_2 solution

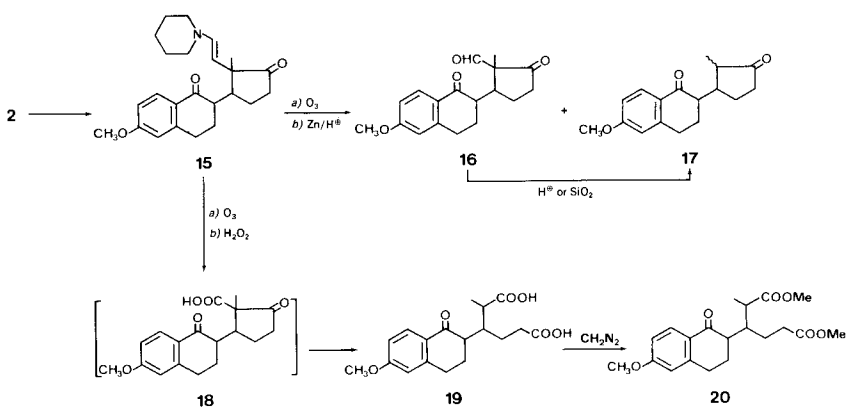
at −78° for a few min yielded the 11-nor-9,11-seco-aldehyde **9**. The enamine fragmentation by means of singlet oxygen (O_2/r.b. *hv* in MeOH) [8] was also tried but, in this case, the reaction was very slow and yielded mainly the aldehyde **7** by slow hydrolysis of the enamine in the alcoholic medium. $NaBH_4$ 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 ^{1}H-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°. 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 synthetized 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 (KOH/H_2O/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}H-NMR ($CDCl_3$): 7.50 (*d*, $J = 9$, H–C(1)); 6.72 (*dd*, $J = 9$, 2.7, H–C(2)); 6.61 (*d*, $J = 2.7$, H–C(4)); 6.10 (*m*, H–C(11)); 3.94 (*m*, $w_{1/2} = 13$, OCH_2CH_2O); 3.79 (*s*, CH_3O); 2.83 (*m*, 2 H–C(6)); 0.90 (*s*, 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 $C_{21}H_{26}O_3$ (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 (*Silvania* 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}H-NMR ($CDCl_3$): 9.37 (*dd*, $J = 4$, 2.5, C(11)HO); 7.89 (*d*, $J = 8.7$, H–C(1)); 6.81 (*dd*, $J = 8.7$, 2.5, H–C(2)); 6.66 (*d*, $J = 2.5$, H–C(4)); 3.84 (br. *s*, OCH_2CH_2O); 3.79 (*s*, CH_3O); 2.95 (*m*, 2 H–C(6)); 2.70 (*m*, 2 H–C(12)); 1.24 (*s*, 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-$(NO_2)_2C_6H_3NH_2NH_2$ and 10 drops of conc. HCl in 10 ml of MeOH. Crystallization of the orange precipitate from CH_2Cl_2/(i-Pr)$_2$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}H-NMR ($CDCl_3$): 7.75 (*d*, $J = 8$, H–C(1)); 6.65 (*dd*, $J = 8$, 2.5, H–C(2)); 6.55 (*d*, $J = 2.5$, H–C(4)); 5.55 (*d*, $J = 15$, H–C(11)); 3.90 (*d*, $J = 15$, H–C(12)); 3.80 (br. *s*, OCH_2CH_2O, CH_3O); 2.85–1.7 (*m*, CH_2(2'), CH_2(6'), CH and CH_2 of skeleton); 1.45 (br., CH_2(3'), CH_2(4'), CH_2(5')); 1.10 (*s*, 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}H-NMR (cyclohexane/$CDCl_3$): 9.65 (*s*, C(12)HO); 7.93 (*d*, $J = 8.8$, H–C(1)); 6.79 (*dd*, $J = 8.8$, 2.4, H–C(2)); 6.67 (*d*, $J = 2.4$, H–C(4)); 3.84 (br. *s*, OCH_2CH_2O); 3.79 (*s*, CH_3O); 2.95 (*m*, 2 H–C(6)). MS: 344 (5, M^+), 176 (100).

17,17-(Ethylenedioxy)-3-methoxy-11-nor-9,11-seco-1,3,5(10)-estratriene-9β,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}H-NMR ($CDCl_3$): 7.47 (*d*, *J* = 8.6, H–C(1)); 6.75 (*dd*, *J* = 8.6, 2.8, H–C(2)); 6.59 (*d*, *J* = 2.8, H–C(4)); 4.56 (*dd*, *J* = 7.2, *J*(H, OH) < 1, H–C(9); →*d*, *J* = 7.2, on shaking with D_2O); 3.94 (*s*, OCH_2CH_2O); 3.77 (*s*, CH_3O); 3.51 (*m*, 2 H–C(12), OH; on shaking with D_2O, 3.65 (*d*, *J* = 12, H_A–C(12)), 3.35 (*d*, *J* = 12, H_B–C(12)), and integral decrease of 1 H (OH)); 2.72 (*m*, 2 H–C(6)); 0.84 (*s*, 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}H-NMR ($CDCl_3$): 7.45 (*d*, *J* = 8.5, H–C(1)); 6.75 (*dd*, *J* = 8.5, 2.6, H–C(2)); 6.58 (*d*, *J* = 2.6, H–C(4)); 4.90 (2*d*, *J* = 5.3, 5.3, H–C(9), **11**/**13**); 3.76 (br. *s*, CH_3O, OCH_2CH_2O of **11**); 3.50 (*m*, 2 H–C(12)); 2.70 (*m*, 2 H–C(6)); 1.14 (*s*, CH_3(18), **13**); 1.08 (*s*, 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}H-NMR ($CDCl_3$): 6.95 (*d*, *J* = 9, H–C(1)); 6.70 (*m*, H–C(2), H–C(4)); 6.28 (*s*, H–C(9)); 3.80 (*dd*, *J* = 11.1, 1.2, H_A–C(12)); 3.77 (*s*, CH_3O); 3.53 (*d*, *J* = 11.1, H_B–C(12)); 2.71 (br. *d*, *J* = 7.2, 2 H–C(6)); 0.81 (*s*, 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 $CHCl_3$/AcOEt was heated at 40–50° 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}H-NMR ($CDCl_3$): 7.46 (*d*, *J* = 8.6, H–C(1)); 6.76 (*dd*, *J* = 8.6, 2.8, H–C(2)); 6.58 (*d*, *J* = 2.8, H–C(4)); 4.89 (*d*, *J* = 5.3, H–C(9)); 3.78 (*s*, CH_3O); 3.72 (*m*, OCH_2CH_2O); 3.48 (*d*, *J* = 10.2, H_A–C(12)); 3.32 (*d*, *J* = 10.2, H_B–C(12)); 2.69 (*m*, 2 H–C(6)); 1.09 (*s*, CH_3(18)). MS: 330 (11, M^+), 229 (35), 176 (10), 161 (26), 160 (100), 159 (18), 154 (18), 99 (49). Anal. calc. for $C_{20}H_{26}O_4$ (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)-estratien-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. 140–140.5°. UV (EtOH): 229 (8700), 278 (1900), 286 (1900). IR: 1740, 1615, 1580, 1500, 1460, 1255, 1165, 945. ^{1}H-NMR ($CDCl_3$): 7.46 (*d*, *J* = 8.6, H–C(1)); 6.78 (*dd*, *J* = 8.6, 2.6, H–C(2)); 6.60 (*d*, *J* = 2.6, H–C(4)); 4.96 (*d*, *J* = 5.3, H–C(9)); 3.78 (*s*, CH_3O); 3.61 (*d*, *J* = 11, H_A–C(12)); 3.33 (*d*, *J* = 11, H_B–C(12)); 1.16 (*s*, CH_3(18)). MS: 286 (34, M^+), 255 (11), 177 (11), 160 (100), 145 (18), 115 (20), 109 (30). Anal. calc. for $C_{18}H_{22}O_3$ (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}H-NMR ($CDCl_3$): 7.95 (*d*, *J* = 8.6, H–C(1)); 6.79 (*dd*, *J* = 8.6, 2, H–C(2)); 6.67 (*d*, *J* = 2, H–C(4)); 5.83 (*d*, *J* = 14, H–C(11)); 4.10 (*d*, *J* = 14, H–C(12)); 3.84 (*s*, CH_3O); 2.90 (*m*, 2 H–C(6)); 2.74 (br., CH_2(2′), CH_2(6′)); 1.50 (br., CH_2(3′), CH_2(4′), CH_2(5′)); 1.13 (*s*, 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-13ς-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}H-NMR ($CDCl_3$): 7.65 (*d*, *J* = 8, H–C(1)); 6.50 (*dd*,

J = 8, 2, H–C(2)); 6.40 (*d*, J = 2, H–C(4)); 3.70 (*s*, CH_3O); 2.9 (*m*, 2 H–C(6)); 1.0 (*d*, J = 6.5, 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}H-NMR ($CDCl_3$): 9.65 (*s*, C(12)HO); 8.0 (*d*, J = 8, H–C(1)); 6.90 (*dd*, J = 8, 2, H–C(2)); 6.8 (*d*, J = 2, H–C(4)); 3.85 (*s*, CH_3O); 3.0 (*m*, 2 H–C(6)); 1.25 (*s*, 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. $Na_2S_2O_7$ 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}H-NMR ($CDCl_3$): 7.8 (*d*, J = 8, H–C(8′)); 7.7–7.3 (br., COOH, disappears on shaking with D_2O); 6.7 (*dd*, J = 8, 2, H–C(7′)); 6.55 (*d*, J = 2, H–C(5′)); 3.75 (*s*, CH_3O); 2.85 (*m*, 2 H–C(4′)); 1.2 (*d*, CH_3–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 (→659 mg) with $CHCl_3$ gave 375 mg (52% from **15**) of **20**. IR: 1740, 1675, 1605, 1560, 1500, 1460, 1260, 1030. ^{1}H-NMR ($CDCl_3$): 7.98 (*d*, J = 8.6, H–C(8′)); 6.80 (*dd*, J = 8.6, 2, H–C(7′)); 6.68 (*d*, J = 2, H–C(5′)); 3.85 (*s*, CH_3O–C(6′)); 3.66 (*s*, $COOCH_3$); 3.63 (*s*, $COOCH_3$); 1.22 (*d*, J = 6.5, CH_3–C(2)). MS: no M^+, 177 (12), 176 (100), 175 (12), 161 (12), 148 (14), 120 (12), 91 (13).

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