[Chem. Pharm. Bull. 35(2) 585—592 (1987)]

Total Synthesis of 12α- and 12β-Carboxylated Estrogens *via* the Thermal Elimination of β-Ketosulfoxide[1)]

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(Received August 11, 1986)

The thermal elimination of β-ketosulfoxide (**2**) afforded the α,β-unsaturated γ-ketoester (**3**) as a Michael acceptor (analogous to the key intermediate in Smith's estrone synthesis), which was condensed with 2-methylcyclopentane-1,3-dione to give the adduct (**4**) having all carbon units of the aromatic steroidal skeleton. The Michael adduct was then cyclized in the presence of methanesulfonic acid to yield the novel estrapentaene (**6**) with a methoxycarbonyl group at the C-12 position. The estrapentaene (**6**) was converted to 12β- and 12α-methoxycarbonylestrones (**25** and **26**) and their estradiol derivatives (**27** and **28**) by selective reductions followed by demethylation.

Keywords——β-ketosulfoxide; thermal elimination; total synthesis; Michael reaction; carbonyl intramolecular reduction; 12α-methoxycarbonylestrone; 12β-methoxycarbonylestrone; 12α-methoxycarbonylestradiol diacetate; 12β-methoxycarbonylestradiol diacetate

Modified estrogens having a substituent group in ring C are not only expected to be useful as haptens for the preparation of specific antisera in radioimmunoassay of estrogenic hormones,[2)] but also are of interest in connection with studies of the interaction between estrogens and their receptors.[3)] However, it is difficult to introduce a substituent group into ring C of natural estrogens. Total synthetic approaches, therefore, have been attempted by the use of a biomimetic polyene cyclization[4)] and the Torgov method.[5)] The Smith method[6)] (an efficient synthesis of estrone) has not been yet applied to substituted estrone derivatives because of difficulty in the preparation of an effective intermediate. As a part of our studies on the synthetic application of β-ketosulfoxides,[7)] we wish to report here the total synthesis of 12α- and 12β-carboxyestrone and estradiol derivatives by means of the thermal elimination of a substituted β-ketosulfoxide.

The β-ketosulfoxide (**1**), prepared from methyl 4-(3-methoxyphenyl) butyrate,[7)] was

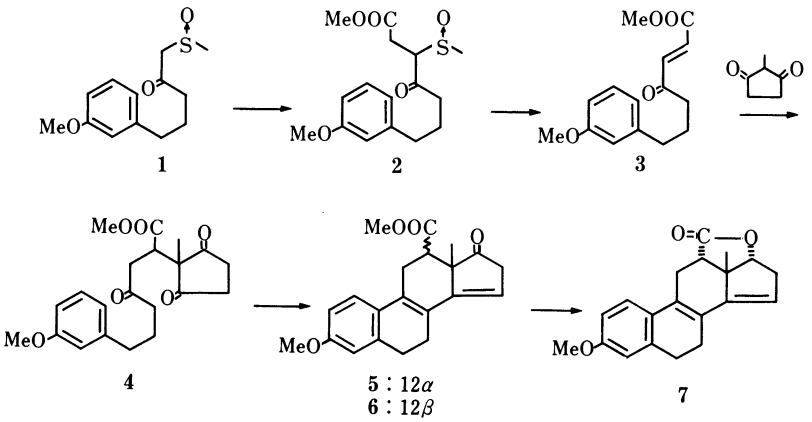

Chart 1

treated with methyl bromoacetate in the presence of potassium hydride to give the α-substituted β-ketosulfoxide (**2**) as an enone precursor in high yield. The nuclear magnetic resonance (NMR) spectrum showed that **2** was a diastereomeric mixture (attributable to the two asymmetric centers, methine and S). The thermal elimination of **2** by heating in dioxane gave the α,β-unsaturated γ-ketoester (**3**) as an acceptor for Michael condensation. Its NMR spectrum showed two doublet signals at 6.60 and 7.05 ppm ($J=14$ Hz) due to the *trans*-oriented olefinic protons. The Michael reaction of **3** with 2-methylcyclopentane-1,3-dione was readily achieved in the presence of catalytic amounts of triethylamine to afford the triketone (**4**). The acid-catalyzed cyclization of the triketone (**4**) was carried out with methanesulfonic acid at 0 °C to give a mixture of 12α- and 12β-methoxycarbonylestrapentaene (**5** and **6**) in the ratio of 1 : 20. In the NMR spectrum of **5**, the signal at 3.55 ppm of the methyl ester group indicated that the α-oriented (axial) ester group is strongly shielded by the double bonds, whereas the other compound (**6**) showed the signal of the β-oriented (equatorial) group at 3.80 ppm. The result of the above NMR analysis was further confirmed by the following chemical reaction. Although the 12β-ester (**6**) gave the 17β-alcohol (**8**) on treatment with sodium borohydride owing to the steric hindrance of the C-18 methyl group, the 12α-epimer (**5**) afforded the lactone (**7**). The formation of the lactone (**7**) could be explained as follows: the C-17 carbonyl group of **5** is initially reduced to a 17α-hydroxy group owing to the steric hindrance of the 12α-ester group to hydride attack from the β-side of the molecule, and the 17α-alcohol is subsequently lactonized with the 12α-substituent. This finding of the α-oriented ester group in **5** is consistent with the reported result of configurational analysis of the 12α-hydroxy group in ethiocholanoic acid.[8] The 12β-carboxylated pentaene (**6**) was hydrogenated with a catalytic amount of palladium on charcoal to give the 14α-estratetraene (**9**) accompanied with a small amount of the 14β-isomer (**10**). The ultraviolet (UV) spectrum of **9** showed an absorption maximum at 280 nm, suggesting the desired C/D-*trans* juncture because of the small bathochromic shift of the absorption maximum compared with that of the *cis* isomer (**10**) at 275 nm.[6,9] The structures of these compounds (**9** and **10**) were also

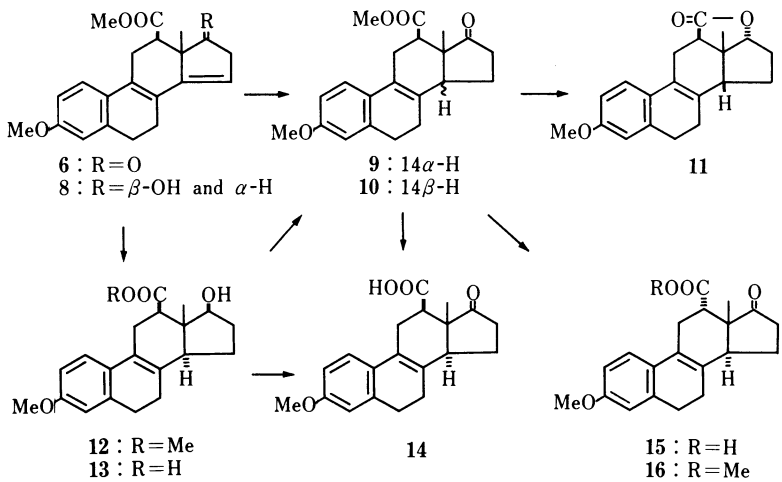

Chart 2

supported by the reported observations and following chemical reaction. Ruffer *et al.*[10] reported that the 14β-isomer (C/D-*cis*) of estrone derivatives gave a 17α-hydroxy compound on reduction with sodium borohydride owing to steric hindrance from the deflection of ring D to the α-side. Actually, the 14β-isomer (**10**) was reduced to give the lactone (**11**), indicating the formation of a 17α-alcohol. In order to avoid the formation of the undesired 14β-isomer,[11]

the 17β-hydroxyestrapentaene (**8**) was hydrogenated to give the 14α-estratetraene (**12**) in high yield (99%). The structure of **12** was defined by its transformation into the 14α-estratetraen-17-one (**9**). The two estratetraene esters (**9** and **12**) were hydrolyzed in order to prevent an unfavorable reaction prior to the following double bond reduction. The 17-hydroxy compound (**12**) was treated with potassium hydroxide in methanol to give the 12β-carboxyestratetraen-17-ol (**13**), which was converted into the 12β-carboxyestratetraen-17-one (**14**) by chromic oxidation. The hydrolysis of the 17-oxo compound (**9**) under the same conditions gave, interestingly, the epimeric 12α-carboxyestratetraen-17-one (**15**) accompanied with a small amount of the 12β-isomer (**14**). The orientation of the 12α-carboxy group in **15** was defined by NMR spectral analysis after conversion to the methyl ester (**16**). The ester (**16**) showed a signal at 3.63 ppm which suggested an α-oriented substituent because of the shielding effect of the unsaturated rings A and B compared with that of 12β-isomer (**9**) at 3.80 ppm. The 17β-hydroxy-tetraene (**13**) was then reduced with sodium in liquid ammonia to give the 12β-carboxyestratrien-17-ol (**17**) and the 17-oxo carboxylic acids (**14** and **15**) also gave the corresponding estratrienes (**18** and **19**). The 12β-carboxy methyl ester (**18**) was converted into the 12β-carboxyestratriene (**20**) by acid-catalyzed hydrolysis since basic hydrolysis gave an epimeric 12α-carboxyestratriene (**21**) as a major product,[12] which was also derived from **19** by using methanolic potassium hydroxide. The 12β-carboxyestratriene (**20**) was additionally prepared by the oxidation of the 17-hydroxy compound (**17**) with chromic

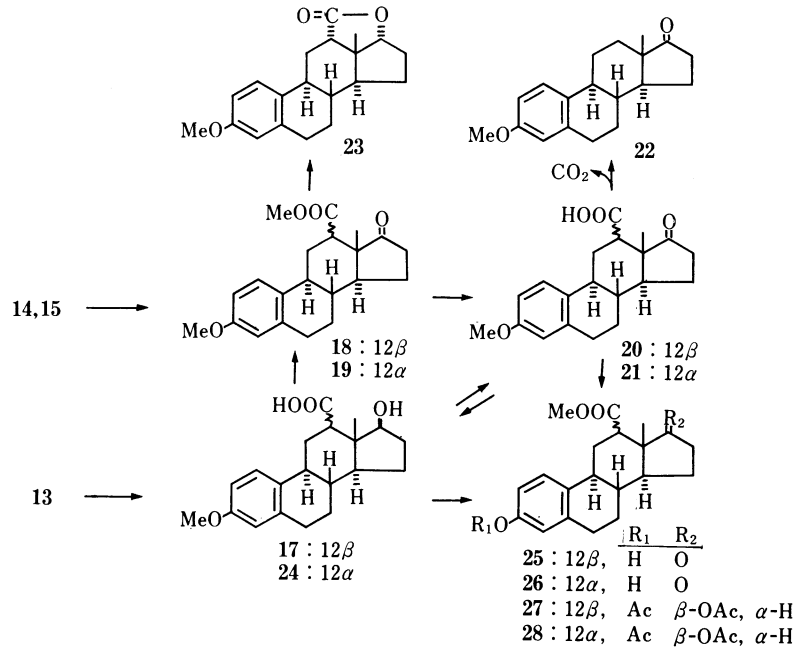

Chart 3

acid. The structures of these trienes (**20** and **21**) were determined by conversion into estrone methyl ether (**22**) using the decarboxylation method.[13] The reduction of the 12α-ester (**19**) with sodium borohydride gave the lactone (**23**) after initial formation of the 17α-ol because of the presence of a 12α-ester group as described above. On the other hand, the 12α-carboxylic acid (**21**) gave the 17β-alcohol (**24**) on reduction with sodium borohydride in dioxane. The β-orientation of the 17-hydroxy group in **24** was deduced from the NMR spectrum, which showed the triplet-like signal of the 17α-proton at 4.60 ppm ($J=9$ Hz) in pyridine.[14] The

difference between the ester (**19**) and the carboxylic acid (**21**) in the reduction with sodium borohydride can be explained as follows. Brown and Subba Rao[15] reported that sodium borohydride forms a complex with carboxylic acids, and the complex has been used as a reducing agent.[16] The 12α-carboxylic acid (**21**), presumably formed such a complex with sodium borohydride on the α-side of the molecule through the α-oriented carboxyl group and then the intramolecular reduction of the 17-carbonyl group occurred to give the 17β-alcohol (**24**). Finally, 12-carboxyestrone methyl ethers (**20** and **21**) were demethylated with chlorotrimethylsilane and sodium iodide[17] to give 12β-methoxycarbonylestrone (**25**) and 12α-methoxycarbonylestrone (**26**) after esterification. The 17-hydroxy compounds (**17** and **24**) were also converted into 12-methoxycarbonylestradiol derivatives (**27** and **28**), which were isolated after esterifications.

These compounds were utilized as new haptens conjugated at the C-12 position with bovine serum albumin for immunoassay of estradiol; details of the investigation on these haptens were reported in this journal.[18] These 12-carboxylated compounds are also expected to be useful as new estrogenic hormones for studies of the interaction between estrogens and their receptors.

Experimental

All melting points were taken on a micro hot stage apparatus and are uncorrected. UV spectra were measured on a Shimadzu UV-200 spectrometer. Infrared (IR) spectra were obtained on a JASCO IR A-102 spectrometer. NMR spectra were recorded on a Hitachi R-40 spectrometer and a JEOL 90-Q spectrometer at 90 MHz using tetramethylsilane as an internal standard. (s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet). Mass spectral (MS) measurements were run on a Shimadzu LKB 9000 spectrometer with the ionizing voltage at 20 eV. For column chromatography, silica gel (70—230 mesh) was used.

Methyl 7-(3-Methoxyphenyl)-3-methylsulfinyl-4-oxoheptanoate (2)——5-(3-Methoxyphenyl)-1-methylsulfinylpentan-2-one[7] (**1**, 7.62 g) in tetrahydrofuran (THF) (20 ml) was added to a stirred solution of KH (1.2 g) in THF (30 ml) at 0 °C under an Ar atmosphere. The stirring was continued for 30 min and $BrCH_2COOMe$ (4.8 g) was added dropwise. After 20 min, the reaction mixture was poured into ice-water and extracted three times with $CHCl_3$. The combined extracts were washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (AcOEt : *n*-hexane = 2 : 1) to yield **2** as a colorless oil (9.2 g, 94%).[19] IR ν_{max}^{neat} cm^{-1}: 1740 (COOMe), 1710 (CO), 1050 (SO). NMR ($CDCl_3$) δ: 2.0 (2H, s), 2.42 and 2.45 (1.4 and 1.6H, respectively, s, CH_3), 3.68 (3H, s, $COOCH_3$), 3.79 (3H, s, OCH_3), 4.02 and 4.24 (0.47 and 0.53H, respectively, t, J = 10 Hz, methine).

Methyl 7-(3-Methoxyphenyl)-4-oxo-2-heptenoate (3)——A solution of **2** (3.62 g) in dioxane (10 ml) was refluxed for 15 min. The reaction mixture was evaporated and the residue was purified by column chromatography (*n*-hexane : AcOEt = 9 : 1) to yield 2.31 g (88%) of **3** as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1730 (COOMe), 1700 (CO), 1660 (C=C). NMR ($CDCl_3$) δ: 2.0 (2H, m), 2.65 (4H, t, J = 6 Hz), 3.80 (6H, s, $COOCH_3$ and OCH_3), 6.60 (1H, d, J = 14 Hz olefinic), 7.05 (1H, d, J = 14 Hz, olefinic). MS m/z (%): 262 (M^+, 4), 230 (6), 134 (100), 121 (33).

2-[6-(3-Methoxyphenyl)-1-methoxycarbonyl-3-oxohexyl]-2-methylcyclopentane-1,3-dione (4)——A solution of **3** (2.62 g) and 2-methylcyclopentane-1,3-dione (1.46 g) in 5% triethylamine–AcOEt (10 ml) was refluxed for 4.5 h. The reaction mixture was evaporated and the residue was recrystallized from MeOH to yield **4** as colorless needles (3.3 g, 88%). mp 123—123.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 1760 (cyclic ketone), 1740 (COOMe), 1720 (CO), 1600, 1580. NMR ($CDCl_3$) δ: 0.98 (3H, s, CH_3), 1.7—2.1 (2H), 2.48 (4H, br s, cyclic methylene), 3.55 (3H, s, $COOCH_3$), 3.77 (3H, s, OCH_3), 3.83 (1H, t, J = 6 Hz, methine). *Anal.* Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.40; H, 7.00.

(±)-12α-Methoxycarbonyl-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (5) and (±)-12β-Methoxycarbonyl-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (6)——Methanesulfonic acid (2 ml) was added to a stirred solution of **4** (3.74 g) in CH_2Cl_2 (15 ml) at 0 °C. The mixture was stirred for 20 min and then poured into ice-water. After extraction with CH_2Cl_2, the extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was recrystallized from MeOH to give colorless plates of **6** (3.05 g, 90%). mp 139—140.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 1745 (CO), 1720 (COOMe). 1560. UV λ_{max}^{EtOH} nm (ε): 314 (41000). NMR ($CDCl_3$) δ: 1.30 (3H, s, CH_3), 3.80 (3H, s, $COOCH_3$), 3.82 (3H, s, OCH_3), 5.93 (1H, t, J = 3 Hz, olefinic). MS m/z (%): 338 (M^+, 80), 317 (82), 310 (36), 261 (31), 251 (100). *Anal.* Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.51; H, 6.51. The mother liquor was subjected to column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **5** (148 mg, 4%) as colorless prisms from MeOH. mp 175.5—177 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1730, 1560. UV λ_{max}^{EtOH} nm (ε): 314 (32000). NMR ($CDCl_3$) δ: 1.15 (3H, s, CH_3), 3.55 (3H, s, $COOCH_3$), 3.82 (3H, s, OCH_3), 6.02 (1H, t, J = 3 Hz, olefinic). MS m/z (%): 338 (M^+, 100), 320 (28), 299 (70), 263 (40), 251 (90). *Anal.* Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.53; H, 6.57.

(±)-3-Methoxyestra-1,3,5(10),8,14-pentaene-12α,17α-carbolactone (7)——A mixture of **5** (70 mg) and $NaBH_4$ (25 mg) in EtOH (30 ml) was stirred for 4 h at room temperature. The reaction mixture was evaporated and the residue was heated in 2 N HCl (5ml) for 30 min. The mixture was then cooled to room temperature and the precipitate was recrystallized from MeOH to give **7** (44 mg) as colorless prisms. mp 146—148.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 1770 (lactone), 1560. NMR ($CDCl_3$) δ: 1.21 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 4.61 (1H, d, J=3 Hz, 17β-H), 5.52 (1H, t, J=3 Hz, olefinic). MS m/z (%): 308 (M^+, 100), 263 (7), 248 (24). *Anal.* Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.63; H, 6.50.

(±)-12β-Methoxycarbonyl-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (8)——A solution of **6** (520 mg) and $NaBH_4$ (18 mg) in benzene (5 ml) and MeOH (20 ml) was stirred for 15 min at 0 °C. The reaction mixture was concentrated and the residue was extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was recrystallized from MeOH to give **8** (497 mg, 95%) as colorless prisms. mp 138—142 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380 (OH), 1720 (COOMe), 1610, 1570. NMR ($CDCl_3$) δ: 0.96 (3H, s, CH_3), 3.75 (6H, s, $COOCH_3$ and OCH_3), 3.85 (1H, br s, 12α-H), 4.30 (1H, m, 17α-H), 5.55 (1H, t, J=3 Hz, olefinic). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.54; H, 6.55. Found: C, 74.52; H, 6.49.

(±)-12β-Methoxycarbonyl-3-methoxy-14α-estra-1,3,5(10),8-tetraen-17-one (9) and (±)-12β-Methoxycarbonyl-3-methoxy-14β-estra-1,3,5(10),8-tetraen-17-one (10)——(a) A mixture of **6** (170 mg) and 10% Pd/C (20 ml) in benzene (10 ml) was hydrogenated under H_2. After removal of the catalyst by filtration, the solvent was removed *in vacuo*. The residue was recrystallized from MeOH to give **9** (136 mg, 80%) as colorless crystals. mp 122.5—123 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740 (CO and COOMe), 1600, 1570. UV λ_{max}^{EtOH} nm (ε): 280 (19600). NMR ($CDCl_3$) δ: 1.10 (3H, s, CH_3), 3.80 (6H, s, $COOCH_3$ and OCH_3). MS m/z (%): 340 (M^+, 100), 325 (5), 280 (15), 224 (38), 223 (35). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.10; H, 7.11. The mother liquor was subjected to column chromatography (*n*-hexane : AcOEt = 6 : 1) to yield **10** (4 mg) as colorless needles from MeOH. mp 186.5—190 °C. IR ν_{max}^{Nujol} cm^{-1}: 1725, 1600, 1570. UV λ_{max}^{EtOH} nm (ε): 275 (17000). NMR ($CDCl_3$) δ: 1.10 (3H, s, CH_3), 3.65 (3H, s, $COOCH_3$), 3.80 (3H, s, OCH_3). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.18; H, 7.08.

(b) A solution of **12** (230 mg) and CrO_3 (380 mg) in pyridine (8 ml) was stirred for 3 h at 50 °C and diluted with AcOEt (25 ml). The resulting suspension was filtered with Al_2O_3 on a sintered glass filter funnel and the filtrate was evaporated. The residue was recrystallized from MeOH to give colorless crystals of **9** (205 mg, 89%). mp 123—124.5 °C.

(±)-3-Methoxy-14β-estra-1,3,5(10),8-tetraen-12β,17α-carbolactone (11)——A solution of **10** (70 mg) and $NaBH_4$ (40 mg) in EtOH was stirred for 2 h at room temperature and evaporated. The oily residue was heated with 2 N HCl (5 ml) for 20 min and cooled to give a precipitate. The precipitate was recrystallized from MeOH to give **11** (42 mg) as pale yellow needles. mp 147—148 °C. IR ν_{max}^{Nujol} cm^{-1}: 1765 (lactone), 1600. NMR ($CDCl_3$) δ: 1.27 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 4.55 (1H, br s, 17β-H). MS m/z (%): 310 (M^+, 100), 308 (6), 265 (7), 223 (5). *Anal.* Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.30; H, 7.22.

(±)-12β-Methoxycarbonyl-3-methoxyestra-1,3,5(10),8-tetraen-17β-ol (12)——A mixture of **8** (340 mg) and 10% Pd/C (50 mg) in benzene (20 ml) was hydrogenated under H_2. Filtration and evaporation gave a crude product which was recrystallized from MeOH to yield **12** (338 mg, 99%) as colorless prisms. mp 121—121.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 3480 (OH), 1710 (COOMe), 1570. NMR ($CDCl_3$) δ: 0.78 (3H, s, CH_3), 3.75 (6H, s, $COOCH_3$ and OCH_3), 3.90 (1H, br s, 12α-H), 4.10 (1H, m, 17α-H). MS m/z (%): 342 (M^+, 100), 309 (16), 265 (33), 223 (32). *Anal.* Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.51; H, 7.61.

(±)-12β-Carboxy-3-methoxyestra-1,3,5(10),8-tetraen-17β-ol (13)——A solution of **12** (342 mg) in 2 N KOH–MeOH (30 ml) was refluxed for 2 h and then concentrated *in vacuo*. The residue was dissolved in H_2O and acidified with 2 N HCl to give a precipitate, which was recrystallized from MeOH to give **13** (325 mg, 99%) as colorless needles. mp 227—229 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH), 2700 (COOH), 1705 (COOH). NMR (pyridine-d_5) δ: 1.07 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.36 (1H, dd, J=7 and 10 Hz, 17α-H). *Anal.* Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.11; H, 7.38.

(±)-12β-Carboxy-3-methoxyestra-1,3,5(10),8-tetraen-17-one (14) and (±)-12α-Carboxy-3-methoxyestra-1,3,5-(10),8-tetraen-17-one (15)——(a) A solution of **9** (340 mg) in 2 N KOH–MeOH (20 ml) was refluxed for 2 h. The reaction mixture was concentrated and acidified with 2 N HCl. Then the mixture was extracted with CH_2Cl_2 twice and the combined extracts were washed with saturated NaCl, dried ($MgSO_4$) and evaporated. The residue was subjected to column chromatography ($CHCl_3$: iso-PrOH = 40 : 1) to afford two fractions. The first fraction gave **14** (7 mg, 2%) as colorless plates from MeOH. mp 205—207 °C. IR ν_{max}^{Nujol} cm^{-1}: 2700 (COOH), 1740 (CO), 1700 (COOH). NMR ($CDCl_3$) δ: 1.00 (3H, s, CH_3), 3.80 (3H, s, OCH_3). MS m/z (%): 326 (M^+, 100), 311 (28), 280 (13), 263 (10), 237 (9), 224 (20). *Anal.* Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.52; H, 6.82. The second fraction gave **15** (293 mg, 90%) as colorless prisms from MeOH. mp 187—189 °C. IR ν_{max}^{Nujol} cm^{-1}: 2700 (COOH), 1750 (CO), 1695 (COOH). NMR ($CDCl_3$) δ: 0.90 (3H, s, CH_3), 3.80 (3H, s, OCH_3). MS m/z (%): 326 (M^+, 30), 311 (28), 280 (20), 263 (55), 237 (27), 233 (100). *Anal.* Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.59; H, 6.80.

(b) A solution of **9** (170 mg) in EtOH (2 ml) and 10% H_2SO_4 (2 ml) was heated under reflux for 4 h. The reaction mixture was extracted with CH_2Cl_2. The extract was washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was recrystallized from MeOH to give **14** (152 mg, 93%) as colorless plates. mp 206—207 °C.

(±)-12α-Methoxycarbonyl-3-methoxyestra-1,3,5(10),8-tetraen-17-one (16)——A solution of **15** (98 mg) in MeOH (5 ml) was treated with diazomethane in ether and then evaporated. The residue was recrystallized from MeOH to give **16** (89 mg) as colorless prisms. mp 167—170 °C. IR ν_{max}^{Nujol} cm^{-1}: 1750 (CO), 1700 (COOMe), 1600, 1570. NMR ($CDCl_3$) δ: 0.87 (3H, s, CH_3), 3.63 (3H, s, $COOCH_3$), 3.76 (3H, s, OCH_3). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.00; H, 7.22.

(±)-12β-Carboxyestradiol 3-Methyl Ether (17)——Sodium (100 mg) was added to stirred liquid NH_3 (70 ml) at −50 °C. After 5 min, **13** (328 mg) in THF (25 ml) and aniline (2 ml) were added to the above solution and stirring was continued for 20 min. After the addition of solid NH_4Cl (5 g), the NH_3 was evaporated off. The residue was dissolved in H_2O, and acidified with 2 N HCl to give a white precipitate, which was recrystallized from MeOH to give **17** (298 mg, 90%) as colorless prisms. mp 212—213 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350, (OH), 1690 (COOH). NMR (pyridine-d_5) δ: 1.02 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.25 (1H, t, J=9 Hz, 17α-H), 6.6—6.9 (2H, m, 2,4-H), 7.25 (1H, d, J=9 Hz, 1-H). *Anal.* Calcd for $C_{20}H_{26}O_4$: C, 66.28; H, 7.23. Found: C, 66.25; H, 7.22.

(±)-12β-Methoxycarbonylestrone Methyl Ether (18)——Sodium (100 mg) was added to stirred liquid NH_3 (60 ml) at −40 °C. After 5 min, a mixture of **14** (300 mg) and aniline (2 ml) in THF (25 ml) was added to the above solution. After 20 min, further sodium (100 mg) was added and the reaction mixture was stirred for an additional 20 min. Solid NH_4Cl (5 g) was added to the mixture and the NH_3 was evaporated off. The residue was dissolved in 27% HCl–MeOH (10 ml) and allowed to stand for 1 h at room temperature. The mixture was concentrated and the residue was extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to give an oily residue, which was oxidized with 8 N H_2CrO_4 in acetone at 0 °C. After usual work-up, the crude product was subjected to column chromatography (*n*-hexane : AcOEt = 3 : 1) to give **18** (201 mg, 67%) as colorless prisms. mp 144.5—145.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740 (CO), 1730 (COOMe), 1600. NMR ($CDCl_3$) δ: 1.13 (3H, s, CH_3), 3.75 (6H, s, $COOCH_3$ and OCH_3), 6.6—6.8 (2H, m, 2, 4-H), 7.15 (1H, d, J=9 Hz, 1-H). MS *m/z* (%): 342 (M^+, 100), 282 (40), 267 (21), 225 (27). *Anal.* Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.52; H, 7.68.

(±)-12α-Methoxycarbonylestrone Methyl Ether (19)——Sodium (200 mg) was added to stirred liquid NH_3 (60 ml) at −40 °C. After 5 min, a mixture of **15** (330 mg) and aniline (2 ml) in THF (10 ml) was added to the above solution. Stirring was continued for 40 min and then NH_4Cl (5 g) was added. After evaporation of the NH_3, the same work-up as used in the preparation of **18** yielded **19** (261 mg, 79%) as colorless needles from MeOH. mp 167.5—170 °C. IR ν_{max}^{Nujol} cm^{-1}: 1745 (CO), 1730 (COOMe). NMR ($CDCl_3$) δ: 1.05 (3H, s, CH_3), 3.71 (3H, s, $COOCH_3$), 3.74 (3H, s, OCH_3), 6.6—6.75 (2H, m, 2, 4-H), 7.00 (1H, d, J=9 Hz, 1-H). MS *m/z* (%): 342 (M^+, 20), 282 (100), 225 (41), 211 (24). *Anal.* Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.48; H, 7.67.

(±)-12β-Carboxyestrone Methyl Ether (20)——(a) A solution of **18** (170 mg) in EtOH (4 ml) and 10% H_2SO_4 (4 ml) was refluxed for 4 h. The reaction mixture was poured into ice-water and the precipitate was recrystallized from MeOH to give **20** (141 mg, 86%) as colorless prisms. mp 182—184 °C. IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO), 1695 (COOH), 1600. NMR (pyridine-d_5) δ: 1.30 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 6.7—6.8 (2H, m, 2, 4-H), 7.20 (1H, d, J=9 Hz, 1-H). *Anal.* Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.14; H, 7.39.

(b) An 8 N H_2CrO_4 solution (1 ml) was added to a stirred solution of **17** (80 mg) in acetone (3 ml) and CH_2Cl_2 (1 ml) at 0 °C. The reaction mixture was stirred for 25 min and extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was recrystallized from MeOH to give **20** (74 mg, 93%) as colorless prisms. mp 180—183 °C.

(±)-12α-Carboxyestrone Methyl Ether (21)——A solution of **19** (171 mg) in 2 N KOH–MeOH (10 ml) was refluxed for 30 min and the reaction mixture was concentrated. The residue was dissolved in H_2O and acidified with 2 N HCl to give a precipitate, which was recrystallized from MeOH to afford **21** (147 mg, 90%) as colorless prisms. mp 227—231 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740 (CO), 1700 (COOH), 1605. NMR (pyridine-d_5) δ: 1.04 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 6.7—6.9 (2H, m, 2, 4-H), 7.10 (1H, d, J=9 Hz, 1-H). *Anal.* Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.08; H, 7.33.

Decarboxylation of 20 and 21——A solution of the carboxylic acid (**20** or **21**, 40 mg) and $SOCl_2$ (200 mg) in $CHCl_3$ (5 ml) was refluxed for 1 h and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in *p*-cymene (5 ml) and pyridine (5 ml). A solution of *tert*-BuOOH (190 mg) in *p*-cymene (2 ml) was added dropwise to the above acid chloride solution with stirring at 0 °C, and stirring was continued for 1 h. The reaction mixture was poured into ice-water and the separated organic layer was dried ($MgSO_4$). The organic layer was then heated to 140 °C for 1 h and evaporated. The oily residue was subjected to column chromatography (*n*-hexane : AcOEt = 10 : 1) to give estrone methyl ether (**22**). The 12β-carboxylic acid (**20**) gave **22** (14 mg, 140—142 °C from MeOH) and the 12α-isomer (**21**) gave **22** (18 mg, mp 141—142.5 °C from MeOH, lit.[6] mp 142—143 °C). The spectral data of both were identical with that of authentic *dl*-estrone methyl ether.

(±)-3-Methoxyestra-1,3,5(10)-triene-12α,17α-carbolactone (23)——A solution of **19** (34 mg) and $NaBH_4$ (15 mg) in EtOH (10 ml) was heated at 60 °C for 1 h. The reaction mixture was acidified with 4 N HCl (5 ml), heated for 10 min, diluted with H_2O and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography (*n*-hexane : AcOEt = 6 : 1) to give **23** (21 mg, 68%) as colorless prisms from MeOH. mp 178—179.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 1760 (lactone), 1600. *Anal.* Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.83; H, 7.72.

(±)-12α-Carboxyestradiol 3-Methyl Ether (24)——A solution of **21** (328 mg) and $NaBH_4$ (40 mg) in dioxane (20 ml) was stirred for 10 min at 4 °C. Stirring was continued for 30 min at room temperature and then the mixture was refluxed for 30 min. The mixture was concentrated and acidified with 2 N HCl, and the precipitate was recrystallized from MeOH to yield **24** (301 mg, 91%) as colorless prisms. mp 188—190.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 2700 (COOH), 1710 (COOH). NMR (pyridine-d_5) δ: 1.20 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.60 (1H, t, J= 10 Hz, 17α-H), 6.8—7.0 (2H, m, 2, 4-H), 7.15 (1H, d, J=9 Hz, 1-H). *Anal.* Calcd for $C_{20}H_{26}O_4$: C, 66.28; H, 7.23. Found: C, 66.21; H, 7.22.

(±)-12β-Methoxycarbonylestrone (25)——A solution of **20** (110 mg), chlorotrimethylsilane (280 mg) and NaI (350 mg) in CH_3CN (6 ml) was heated at 60 °C for 4 h with stirring under N_2. The reaction mixture was diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, 5% $Na_2S_2O_3$ dried (Na_2SO_4) and evaporated. The residue was dissolved in 10% HCl–MeOH (5 ml) and then this solution was heated at 60 °C for 10 min. The mixture was evaporated and the residue was recrystallized from $CHCl_3$–isopropyl ether to yield **25** (96 mg, 87%) as colorless needles. mp 231—235 °C. IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1740 (CO), 1720 (COOMe), 1605. NMR (DMSO-d_6) δ: 0.72 (3H, s, CH_3), 3.70 (3H, s, $COOCH_3$), 6.4—6.6 (2H, m, 2, 4-H), 7.00 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.11; H, 7.62.

(±)-12α-Methoxycarbonylestrone (26)——A solution of **21** (164 mg), chlorotrimethylsilane (540 mg) and NaI (1 g) in CH_3CN (8 ml) was heated at 60 °C with stirring under N_2 for 4 h. After the same work-up as described above, **26** (134 mg) was obtained as colorless prisms, mp 254—257 °C. IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1730 (CO), 1725 (COOMe), 1605. NMR (DMSO-d_6) δ: 1.01 (3H, s, CH_3), 3.66 (3H, s, $COOCH_3$), 6.5—6.7 (2H, m, 2, 4-H), 6.80 (1H, d, J=9 Hz, 1-H). *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.10; H, 7.70.

(±)-12β-Methoxycarbonylestradiol Diacetate (27)——A solution of **17** (100 mg), chlorotrimethylsilane (190 mg) and NaI (220 mg) in CH_3CN (15 ml) was heated at 40 °C for 6 h with stirring under N_2. After the same work-up as described above, the oily residue was dissolved in Ac_2O (1 ml) and pyridine (2 ml). The mixture was kept at room temperature for 24 h, poured into ice-water and extracted with ether. The extract was washed with 2 N HCl and 5% $NaHCO_3$, then dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to yield **27** (94 mg, 75%) as colorless prisms from MeOH. mp 162.5—163.5 °C. NMR ($CDCl_3$) δ: 0.90 (3H, s, CH_3), 2.00 and 2.23 (each 3H, s, OAc), 3.63 (3H, s, $COOCH_3$), 4.81 (1H, dd, J=8 and 9 Hz, 17α-H), 6.7—6.8 (2H, m, 2, 4-H), 7.2 (1H, d, J=9 Hz, 1-H). MS *m/z* (%): 414 (M^+, 48), 372 (100), 312 (7), 269 (5), 253 (10). *Anal.* Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.51; H, 7.30.

(±)-12α-Methoxycarbonylestradiol Diacetate (28)——A solution of **24** (170 mg), chlorotrimethylsilane (280 mg) and NaI (300 mg) in CH_3CN (8 ml) was heated at 40 °C for 6 h with stirring under N_2. After the same work-up as described above, **28** (94 mg, 44%) was obtained as colorless crystals. mp 194—195.5 °C. NMR ($CDCl_3$) δ: 1.02 (3H, s, CH_3), 2.01 and 2.23 (each 3H, s, OAc), 3.65 (3H, s, $COOCH_3$), 4.81 (1H, t, J=9 Hz, 17α-H), 6.7—6.8 (2H, m, 2, 4-H), 7.07 (1H, d, J=9 Hz, 1-H). MS *m/z* (%): 414 (M^+, 4), 354 (61), 312 (100), 294 (22), 252 (57). *Anal.* Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.70; H, 7.44.

Acknowledgements The authors are grateful to Professor O. Yonemitsu and the late Dr. Y. Oikawa of Hokkaido University for helpful discussions. Thanks are also due to the staff of the Analytical Center of Hokkaido University for elemental analyses.

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