Asymmetric Total Synthesis of Estradiol by an Intramolecular Cycloaddition of Benzocyclobutene Derivative

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Abstract: A new type of asymmetric total synthesis of estradiol (**8**) has been described. The key step is an intramolecular cycloaddition of *o*-quinodimethane **4**, derived from optically active 1-*tert*-butoxy-3-ethenyl-2-[2-(4-methoxybenzocyclobutenyl)-ethyl]-2-methylcyclopentane (**2**), to form stereoselectively 17-*O*-*tert*-butyl-3-*O*-methylestradiol (**6**).

Estradiol (**8**) is a nice target compound for synthetic organic chemists[1] since this substance has a perhydrophenanthrene ring with five asymmetric carbons, and also shows a pharmaceutically interesting activity as a sex hormone. On the base of these interests, there are many papers on a stereocontrolled synthesis of this and related compounds,[2,3] and in the last decade attention has been focused on developing asymmetric syntheses of the above type of compounds.[4-6] Recently, Cohen[7] and Eder[8] have reported an asymmetric synthesis of estradiol and related compounds.

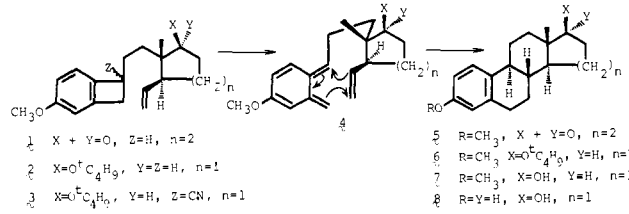
We[9] have previously shown that heating the racemic form of the olefinic benzocyclobutene **1** gave stereoselectively *O*-methyl-D-homoestrone (**5**) in 95% yield by an intramolecular cycloaddition[10,11] through *o*-quinodimethane **4** (n = 2) as shown and the stereoselectivity is controlled by the stereochemistry of substituents on the cyclohexane ring.[11] Vollhardt[12] and Oppolzer[13] have synthesized stereoselectively the 1,3,5(10)-tridehydroestrane system by the same type of cycloaddition reaction.

As a continuation of our work aimed at a total synthesis of natural products by a cycloaddition of *o*-quinodimethane, we have investigated a total synthesis of the optically active steroidal hormone. In this paper, we wish to report a new synthesis of the optically active estradiol by an asymmetric induction based on the chiral cyclopentane derivative, in which the BC ring of the steroidal system is formed in one step by an intramolecular cycloaddition reaction.

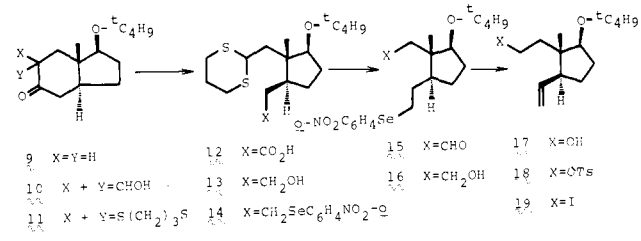
Results and Discussion

The key intermediate, optically active 2-benzocyclobutenylethylcyclopentane (**2**), was prepared from (1*S*,3a*S*,7a*S*)-1-*tert*-butoxy-3a,4,7,7a-tetrahydro-7a-methyl-5(6*H*)-indanone (**9**) [$(\alpha)^{25}_D$ +82.2° ($CHCl_3$)][6] as follows. Treatment of this indanone with ethyl formate in the presence of sodium hydride gave the 2-formyl ketone **10**, which, without purification, was converted into the ketone thioketal **11** ($[\alpha]_D$ +38.5°)[14] in 86.2% yield by the reaction with propane-1,3-dithiol di-*p*-toluenesulfonate and potassium acetate as usual.[15] Hydrolysis of this product was carried out with potassium hydroxide in *tert*-butyl alcohol at 60 °C,[15] affording the carboxylic acid **12** ($[\alpha]_D$ +24.29°),[14] in 90.4% yield, which was reduced with lithium aluminum hydride in tetrahydrofuran at room temperature to furnish the alcohol **13** ($[\alpha]_D$ +22.12°)[14] in 93.4% yield. Treatment of this alcohol with *o*-nitrophenylselenyl cyanide and tri-*n*-butylphosphine in tetrahydrofuran at room temperature[16] gave, in 79.7% yield, the selenide **14** ($[\alpha]_D$ −12.73°)[14] which was converted into the aldehyde **15** ($[\alpha]_D$ −11.92°)[14] by a hydrolysis with methyl iodide in the presence of sodium carbonate in aqueous acetone in 94.56% yield. Sodium borohydride reduction of aldehyde **15** in methanol at 0 °C afforded the alcohol **16** in 93.3% yield ($[\alpha]_D$ −9.5°),[14] whose oxidative deselenation was carried out with 30% hydrogen peroxide in tetrahydrofuran at room temperature for 3 h to form the olefinic alcohol **17** ($[\alpha]_D$ +49.72°)[14] in 75.9% yield. Tosylation of this with *p*-toluenesulfonyl chloride and pyridine, followed by a treatment of the product **18** ($[\alpha]_D$ +16.5°)[14] with sodium iodide in boiling acetone,[9] gave 1β-*tert*-butoxy-3β-ethenyl-2α-(2-iodoethyl)-cyclopentane (**19**) ($[\alpha]_D$ +30.8°)[14] in 51.9% yield.

Scheme I



Scheme II



Condensation of 1-cyano-4-methoxybenzocyclobutene[17] with the iodide **19** in the presence of sodium hydride in dimethylformamide at 40 °C for 45 min furnished 1,1-disubstituted benzocyclobutene **3** in 48.7% yield which was treated with sodium in liquid ammonia in the presence of ethanol[9] to afford the decyanation product, 1-cyclopentylethylbenzocyclobutene (**2**) [*m/e* 342 (M^+)], in 85.2% yield, showing typical vinyl protons at δ 4.70–6.10 in the NMR spectrum. Heating[9] the benzocyclobutene **2** in *o*-dichlorobenzene at 180 °C for 3 h in a current of nitrogen gave, in 83.8% yield, 17-*O*-*tert*-butyl-3-*O*-methylestradiol (**6**) (mp 79–80 °C, $[\alpha]_D$ +41°),[14,18] which showed methyl groups at 0.75 (C_{13}-Me), 1.13 (CMe_3), and 3.75 (OMe), benzylic protons at 2.65–3.0, and C_{17} proton at 3.20–3.60. It is well known that an intramolecular cycloaddition of the benzocyclobutenes carrying on C-1 a chain of six atoms with a terminal olefinic system proceeds stereo- and regioselectively to form the 1,3,5(10)-tridehydroestrane system having a trans-anti-trans BCD ring via *o*-quinodimethane under the steric influence of chiral centers by the configuration of substituents already present in the bridge.[9-11] Since we used the optically active starting material whose array on the cyclopentane ring is the same as that of natural estradiol, the absolute configuration of our product **6** should be identical with that of the natural one. This was proved by the conversion

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of our product into 3-*O*-methylestradiol (**7**) and estradiol (**8**) as follows. Thus, treatment of **6** with 5 N hydrochloric acid in dioxane under reflux for 7 h afforded 3-*O*-methylestradiol (**7**), mp 96–98 °C (lit.[19] mp 98 °C), in 84% yield, which is identical with the authentic sample, prepared from natural estradiol by the known method,[19] in all aspects except the value of optical rotation ($[\alpha]_D$ +69.24°).[14] This indicated the optical purity of our product to be 96.8%, i.e., *l*:*d* = 98.4:1.6. Finally, demethylation of 3-*O*-methylestradiol (**7**) with pyridine hydrochloride at 210 °C for 0.5 h gave, in 80.9% yield, estradiol (**8**), mp 178–179 °C, not differentiated from natural estradiol in IR (KBr) and NMR spectra. Thus, we have accomplished an asymmetric total synthesis of estradiol.

Our synthetic method described above provides a general route for an asymmetric synthesis of a wide range of steroidal substances.

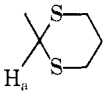
Experimental Section

General. All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-3 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-PMX-60 spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane (Me_4Si). Mass spectra were taken on a Hitachi RMU-7 spectrometer. All optical rotations were obtained on a JASCO-PIP-SL polarimeter at 20 °C using a 1-dm cell in chloroform.

(+)-(1*S*,3a*S*,7a*S*)-1-*tert*-Butoxy-3a,4,7,7a-tetrahydro-[6,6-(propane-1,3-dithio)]-7a-methyl-5-indanone (11). To a solution of 2.91 g (13 mmol) of (+)-(1*S*,3a*S*,7a*S*)-1-*tert*-butoxy-3a,4,7,7a-tetrahydro-7a-methyl-5(6*H*)-indanone (**9**)[6] and 0.36 g (15 mmol) of sodium hydride in 50 mL of anhydrous benzene was added a solution of 0.962 g (13 mmol) of ethyl formate in 10 mL of anhydrous benzene at room temperature. After the solution was stirred at room temperature for 6 h, 50 mL of H_2O was added. The resulting aqueous layer was acidified with 10% H_2SO_4 and extracted four times with 50-mL portions of ether. The combined organic extracts were washed with saturated NaCl solution and were dried over anhydrous sodium sulfate. After removal of the solvent, 3.2 g of crude formyl derivative **10** was obtained and used for the next reaction without further purification. Thus, a solution of 3.2 g of crude **10**, 15 g (36 mmol) of propane-1,3-dithiol di-*p*-toluenesulfonate, and 42 g (428 mmol) of potassium acetate in 150 mL of absolute ethanol was refluxed for 21 h. After removal of the solvent, 50 mL of H_2O was added and extracted three times with 50-mL portions of ether. The combined organic extracts were washed with saturated NaCl solution and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 16 g of crude product, which was chromatographed on 100 g of silica gel using benzene–hexane (3:1) for elution to give, after recrystallization from ethanol, 4.26 g (86.23%) of thioketal ketone **11** as colorless needles: mp 111–113 °C, $[\alpha]_D$ +38.5° (*c* 1); IR ($CHCl_3$) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, s, CH_3), 1.13 (9 H, s, $OC(CH_3)_3$); mass *m/e* 328 (M^+).

Anal. ($C_{17}H_{28}O_2S_2$) C, H.

(+)-(1*S*,2*S*,3*S*)-3-*tert*-Butoxy-2-methyl-2-[2,2-(propane-1,3-dithio)ethyl]cyclopent-1-ylacetic Acid (12). To a stirred solution of 50 mg (0.153 mmol) of thioketal ketone **11** in 5 mL of *t*-BuOH was added 30 mg (0.536 mmol) of powdered potassium hydroxide. The reaction mixture was heated at 60 °C for 3 h. After removal of the solvent, 10 mL of H_2O was added and the aqueous layer was extracted with 20 mL of ether and acidified with 10% HCl. The acidic product was extracted three times with 30-mL portions of ether. The combined organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 55 mg of crude product, which was chromatographed on 1 g of silica gel using hexane–ether (1:1) for elution to give 48 mg (90.48%) of thioacetal acid **12** as a colorless oil: $[\alpha]_D$ +24.29° (*c* 0.7); IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s, CH_3), 1.17 (9 H, s, $OC(CH_3)_3$), 4.20 (1 H, t, *J* = 6 Hz, Ha); mass *m/e* 346 (M^+).



Anal. ($C_{17}H_{30}O_3S_2 \cdot 1/10H_2O$) C, H.

(+)-(1*S*,2*S*,3*S*)-1-*tert*-Butoxy-2-[2,2-(propane-1,3-dithio)ethyl]-3-(2-hydroxyethyl)-2-methylcyclopentane (13). To a stirred suspension of 480 mg (12.6 mmol) of lithium aluminum hydride in 25 mL of anhydrous tetrahydrofuran was added at room temperature a solution of 1.1 g (3.18 mmol) of thioacetal acid **12** in 20 mL of anhydrous tetrahydrofuran. After the solution was stirred for 2 h at room temperature, 20 mL of 10% NaOH was added and the organic layer was separated. The aqueous layer was extracted three times with 30-mL portions of ether. The combined organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. After removal of the solvent, the resulting crude product was chromatographed on 10 g of silica gel using hexane–ether (1:1) for elution to give 980 mg (93.42%) of thioacetal alcohol **13** as a colorless oil: $[\alpha]_D$ +22.12° (*c* 1.56); IR ($CHCl_3$) 3490 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (3 H, s, CH_3), 1.18 (9 H, s, $OC(CH_3)_3$), 3.40–3.81 (2 H, m, $HOCH_2$), 4.19 (1 H, t, *J* = 6 Hz, H_a); mass *m/e* 332 (M^+).

Anal. ($C_{17}H_{32}O_2S_2$) C, H.

(−)-(1*S*,2*S*,3*S*)-1-*tert*-Butoxy-2-[2,2-(propane-1,3-dithio)ethyl]-2-methyl-3-[2-(2-nitrophenylselenyl)ethyl]cyclopentane (14). To a solution of 1.9 g (5.72 mmol) of thioacetal alcohol **13** in 40 mL of anhydrous tetrahydrofuran containing 1.95 g (8.55 mmol) of *o*-nitrophenylselenocyanate was added 1.7 g (8.4 mmol) of tri-*n*-butylphosphine at room temperature under nitrogen. After the solution was stirred at room temperature for 3 h, the solvent was removed in vacuo. Chromatography of the residue on 20 g of silica gel using hexane–ether (4:1) for elution gave 2.35 g (79.7%) of thioacetal *o*-nitrophenylselenide **14** as a yellow oil: $[\alpha]_D$ −12.73° (*c* 1.1); NMR ($CDCl_3$) δ 0.75 (3 H, s, CH_3), 1.15 (9 H, s, $OC(CH_3)_3$), 2.81–3.15 (6 H, m, $SCH_2CH_2CH_2S$ and $SeCH_2CH_2$), 4.15 (1 H, t, *J* = 6 Hz, H_a), 7.10–7.65 (3 H, m, aromatic protons), 8.26 (1 H, d, *J* = 8 Hz, aromatic proton); mass *m/e* 515 (M^+), 517 ($M^+ + 2$).

Anal. ($C_{23}H_{35}O_3NSeS_2$) C, H, N.

(−)-(1*S*,2*S*,3*S*)-1-*tert*-Butoxy-2-methyl-3-[2-(2-nitrophenylselenyl)ethyl]cyclopent-2-ylacetaldehyde (15). A solution of 200 mg (0.39 mmol) of thioacetal *o*-nitrophenylselenide **14**, 400 mg (2.8 mmol) of methyl iodide, and 40 mg (0.38 mmol) of sodium carbonate in 1.5 mL of H_2O and 6 mL of acetone was refluxed for 13 h. After evaporation of acetone, 10 mL of H_2O was added. The aqueous layer was extracted three times with 30-mL portions of ether. The combined organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. After removal of the solvent, the resulting crude product was chromatographed on 5 g of silica gel using hexane–ether (1:1) for elution to afford 156 mg (94.6%) of *o*-nitrophenylselenyl aldehyde **15** as a yellow oil: $[\alpha]_D$ −11.92° (*c* 1.3); IR ($CHCl_3$) 1710 cm^{-1}; NMR (CCl_4) δ 0.87 (3 H, s, CH_3), 1.15 (9 H, s, $OC(CH_3)_3$), 7.10–7.60 (3 H, m, aromatic protons), 8.25 (1 H, d, *J* = 8 Hz, aromatic proton), 9.79 (1 H, t, *J* = 4 Hz, CHO); mass *m/e* 425 (M^+), 427 ($M^+ + 2$).

Anal. ($C_{20}H_{29}NO_4Se$) C, H, N.

(−)-(1*S*,2*S*,3*S*)-1-*tert*-Butoxy-2-methyl-3-[2-(2-nitrophenylselenyl)ethyl]-2-(2-hydroxyethyl)cyclopentane (16). To a solution of 150 mg (0.35 mmol) of *o*-nitrophenylselenyl aldehyde **15** in 20 mL of methanol was added in small portions 60 mg (1.58 mmol) of sodium borohydride at 0 °C. After the solution was stirred for 2 h at room temperature, the solvent was removed in vacuo and 20 mL of H_2O was added to the resulting residue. The aqueous layer was extracted three times with 20-mL portions of ether. The combined organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the crude product, which was chromatographed on 3 g of silica gel using hexane–ether (3:1) for elution to afford 140 mg (93.3%) of *o*-nitrophenylselenyl alcohol **16** as a yellow oil: $[\alpha]_D$ −9.5° (*c* 1); IR ($CHCl_3$) 3490 cm^{-1}; NMR (CCl_4) δ 0.71 (3 H, s, CH_3), 1.20 (9 H, s, $OC(CH_3)_3$), 3.40–3.83 (3 H, m, $HOCH_2$ and C_2H), 7.16–7.56 (3 H, m, aromatic protons), 8.28 (1 H, d, *J* = 8 Hz, aromatic proton); mass *m/e* 427 (M^+), 429 ($M^+ + 2$).

Anal. ($C_{20}H_{31}NO_4Se$) C, H, N.

(+)-(1*S*,2*S*,3*S*)-1-*tert*-Butoxy-3-ethenyl-2-methyl-2-[2-(*p*-toluenesulfonyloxy)ethyl]cyclopentane (18). To a solution of 700 mg (1.64 mmol) of *o*-nitrophenylselenyl alcohol **16** in 20 mL of tetrahydrofuran was added dropwise 2 mL of 30% H_2O_2 at 0 °C and stirring was continued for 3 h at room temperature. The mixture was diluted with 50 mL of H_2O and extracted four times with 50-mL portions of ether. The combined organic layer was washed with 5% sodium carbonate solution and saturated NaCl solution and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on 20 g of silica gel using hexane–ether (4:1) for elution to give 280

mg (75.9%) of olefinic alcohol **17** as a colorless oil: $[\alpha]_D$ +49.72° (*c* 0.9); IR ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (3 H, s, CH_3), 1.21 (9 H, s, $OC(CH_3)_3$), 3.42-3.90 (3 H, m, $HOCH_2$ and C_2H), 4.80-5.70 (3 H, m, $CH{=}CH_2$); mass *m/e* 169 ($M^+ - 57$).

The mixture of 210 mg (0.93 mmol) of olefinic alcohol **17**, 300 mg (1.57 mmol) of *p*-toluenesulfonyl chloride, and 10 mL of pyridine was stirred for 4 h at 0 °C and then the reaction mixture was diluted with 50 mL of H_2O and extracted three times with 50-mL portions of ether. The combined organic layer was washed with 10% HCl solution and saturated NaCl solution and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on 6 g of silica gel using hexane-benzene (4:1) to give, after recrystallization from ether-hexane, 270 mg (76.5%) of olefinic tosylate **18** as colorless needles: mp 69-71 °C; $[\alpha]_D$ +16.5° (*c* 0.9); IR ($CHCl_3$) 1640 cm^{-1}; NMR (CCl_4) δ 0.69 (3 H, s, CH_3), 1.10 (9 H, s, $OC(CH_3)_3$), 3.90-4.33 (3 H, m, CH_2OTs and C_2H), 7.28 (2 H, d, J = 9 Hz, aromatic protons), 7.83 (2 H, d, J = 9 Hz, aromatic protons); mass *m/e* 323 ($M^+ - 57$).

(+)-(1*S*,2*S*,3*S*)-1-*tert*-Butoxy-3-ethenyl-2-(2-iodoethyl)-2-methylcyclopentane (19). The mixture of 135 mg (0.36 mmol) of olefinic tosylate **18**, 640 mg (4.27 mmol) of sodium iodide, and 50 mL of acetone was refluxed for 18 h. After removal of the solvent, 50 mL of H_2O was added. The aqueous layer was extracted three times with 50-mL portions of ether. The combined organic layer was washed with 5% $Na_2S_2O_3$ solution and saturated NaCl solution and dried over anhydrous sodium sulfate. The crude product obtained by evaporation of solvent was chromatographed on 10 g of silica gel using hexane for elution to give 95 mg (79.8%) of iodide **19** as a colorless oil: $[\alpha]_D$ +30.8° (*c* 1); IR ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.65 (3 H, s, CH_3), 1.10 (9 H, s, $OC(CH_3)_3$), 3.0-3.68 (3 H, m, ICH_2CH_2 and C_2H), 4.70-5.95 (3 H, m, $CH{=}CH_2$); mass *m/e* 280 ($M^+ - 56$).

Anal. ($C_{14}H_{25}OI$) C, H.

1-*tert*-Butoxy-3-ethenyl-2-[2-(1-cyano-4-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentane (3). To a suspension of 264 mg (11 mmol) of sodium hydride in 2 mL of anhydrous dimethylformamide was added a solution of 468 mg (2.94 mmol) of 1-cyano-4-methoxybenzocyclobutene[17] in 4.5 mL of anhydrous dimethylformamide at room temperature. After the solution was stirred for 10 min at room temperature, a solution of 485 mg (1.28 mmol) of iodide **19** in 4.5 mL of anhydrous dimethylformamide was added dropwise at room temperature and stirring was continued for 45 min at 40 °C. At this end, the reaction mixture was diluted with 20 mL of H_2O and extracted three times with 50 mL of ether. The combined organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on 5 g of silica gel using hexane-benzene (9:1) for elution to give 258 mg (48.7%) of olefinic benzocyclobutene **3** as a colorless oil: IR ($CHCl_3$) 2230 cm^{-1}; NMR (CCl_4) δ 0.73 (3 H, s, CH_3), 1.15 (9 H, s, $OC(CH_3)_3$), 3.10 (1 H, d, J = 14 Hz, $ArCHH$), 3.63 (1 H, d, J = 14 Hz, $ArCHH$), 3.75 (3 H, s, OCH_3), 4.70-6.03 (3 H, m, $CH{=}CH_2$), 6.63-6.81 (2 H, m, C_3H and C_5H), 7.16 (1 H, d, J = 8 Hz, C_6H); mass *m/e* 367 (M^+).

Anal. ($C_{24}H_{33}NO_2$) C, H.

1-*tert*-Butoxy-3-ethenyl-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentane (2). Sodium (11 mg, 0.48 mmol) was added to a solution of 173 mg (0.47 mmol) of **3** in 30 mL of anhydrous ammonia, 10 mL of anhydrous tetrahydrofuran, and a few drops of absolute ethanol at −78 °C. Stirring was continued for 1 h at −78 °C and then 20 mg of NH_4Cl was added to the reaction mixture. After evaporation of ammonia, the residue was diluted with 50 mL of H_2O and extracted three times with 50-mL portions of ether. The combined organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. Removal of the solvent left a yellow oil, which was chromatographed on 2 g of silica gel using hexane-benzene (9:1) for elution to give 115 mg (85.2%) of decyanated olefinic benzocyclobutene **2** as a colorless oil: NMR (CCl_4) δ 0.75 (3 H, s, CH_3), 1.12 (9 H, s, $OC(CH_3)_3$), 3.74 (3 H, s, OCH_3), 4.70-6.10 (3 H, m, $CH{=}CH_2$), 6.55-6.71 (2 H, m, C_3H and C_5H), 6.91 (1 H, d, J = 9 Hz, C_6H); mass *m/e* 342 (M^+).

Anal. ($C_{23}H_{34}O_2$) C, H.

17-*O*-*tert*-Butyl-3-*O*-methylestradiol (6). A solution of 80 mg (0.23 mmol) of olefinic benzocyclobutene **2** in 5 mL of *o*-dichlorobenzene was stirred for 3 h at 180 °C under nitrogen. After removal of the solvent, the residue was chromatographed on 1 g of silica gel using hexane-benzene (9:1) to afford, after recrystallization from methanol, 67 mg (83.8%) of 17-*O*-*tert*-butyl-3-*O*-methylestradiol (**6**) as colorless needles: mp 79-80 °C; $[\alpha]_D$ +41° (*c* 1); NMR (CCl_4) δ 0.75 (3 H, s, CH_3), 1.13 (9 H, s, $OC(CH_3)_3$), 2.65-3.0 (2 H, m, $ArCH_2$), 3.20-3.60 (1 H, m, $C_{17}H$), 3.75 (3 H, s, OCH_3), 6.42-6.75 (2 H, m, aromatic protons), 7.12 (1 H, d, J = 9 Hz, C_1H); mass *m/e* 342 (M^+).

3-*O*-Methylestradiol (7). A solution of 30 mg of **6** in 20 mL of dioxane containing 2 mL of 5 N HCl was refluxed for 7 h. After removal of the solvent, the residue was extracted with 50 mL of ether. The ethereal solution was washed with saturated NaCl solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave, after recrystallization from methanol, 21 mg (84%) of 3-*O*-methylestradiol (**7**) as colorless prisms, mp 96-98 °C, $[\alpha]_D$ +69.24° (*c* 0.26), which was identical with the authentic sample, $[\alpha]_D$ +72.30° (*c* 0.26), prepared from natural estradiol, in its IR (KBr) and NMR spectra. IR ($CHCl_3$) 3400 cm^{-1}; NMR (CCl_4) δ 0.78 (3 H, s, CH_3), 3.72 (3 H, s, OCH_3), 6.50-7.25 (3 H, m, aromatic protons); mass *m/e* 286 (M^+).

Anal. ($C_{19}H_{26}O_2 \cdot {}^1/_4H_2O$) C, H.

Estradiol (8). The mixture of 40 mg of 3-*O*-methylestradiol (**7**) and 200 mg of freshly prepared pyridine hydrochloride was heated at 240 °C for 45 min. At this end, 5 mL of 10% HCl was added and the aqueous solution was extracted with 50 mL of ether. The organic layer was washed with H_2O and saturated NaCl solution and dried over anhydrous sodium sulfate. Removal of the solvent gave crystalline estradiol. Recrystallization from 80% ethanol afforded 31 mg (80.9%) of estradiol (**8**) as colorless prisms, mp 178-179 °C, which was identical with natural estradiol in its IR (KBr) and NMR (Me_2SO-d_6) spectra.

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References and Notes

(1) A.A. Akhrem and Y. A. Titov, "Total Steroid Synthesis", Plenum Press, New York, N.Y., 1970.
(2) P. A. Bartlett and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 7501 (1973).
(3) S. Danishefsky, P. Cain, and A. Nagel, *J. Am. Chem. Soc.*, **97**, 380 (1975).
(4) J. W. Scott, R. Borer, and G. Saucy, *J. Org. Chem.*, **37**, 1659 (1972).
(5) S. Danishefsky and P. Cain, *J. Am. Chem. Soc.*, **98**, 4975 (1976).
(6) R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, and P. A. Werhrli, *J. Org. Chem.*, **40**, 675 (1975).
(7) N. Cohen, B. L. Banner, W. F. Eichel, D. R. Parrish, and G. Saucy, *J. Org. Chem.*, **40**, 681 (1975).
(8) U. Eder, H. Gibian, G. Haffer, G. Neef, G. Sauer, and R. Wiechert, *Chem. Ber.*, **109**, 2948 (1976).
(9) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, and K. Fukumoto, *J. Am. Chem. Soc.*, **98**, 3378 (1976); T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, H. Matsumoto, and K. Fukumoto, *ibid.*, **99**, 3461 (1977).
(10) T. Kametani and K. Fukumoto, *Heterocycles*, **7**, 465 (1977).
(11) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977).
(12) R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **99**, 5483 (1977).
(13) W. Oppolzer, M. Petrzilka, and K. Bätlig, *Helv. Chim. Acta*, **60**, 2964 (1977).
(14) Rotations were determined in chloroform at 20 °C.
(15) J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, **39**, 1814 (1974).
(16) P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **41**, 1485 (1976).
(17) T. Kametani, Y. Kato, T. Honda, and K. Fukumoto, *J. Am. Chem. Soc.*, **98**, 8185 (1976).
(18) Although a formation of diastereomer(s) in this stage is conceivable, we could not succeed in isolating any diastereomer(s) and the product (**6**) was chromatographically homogeneous.
(19) T. Miki, K. Hiraga, and T. Asako, *Proc. Chem. Soc., London*, 139 (1963).