Total Synthesis of Aromatic Steroids

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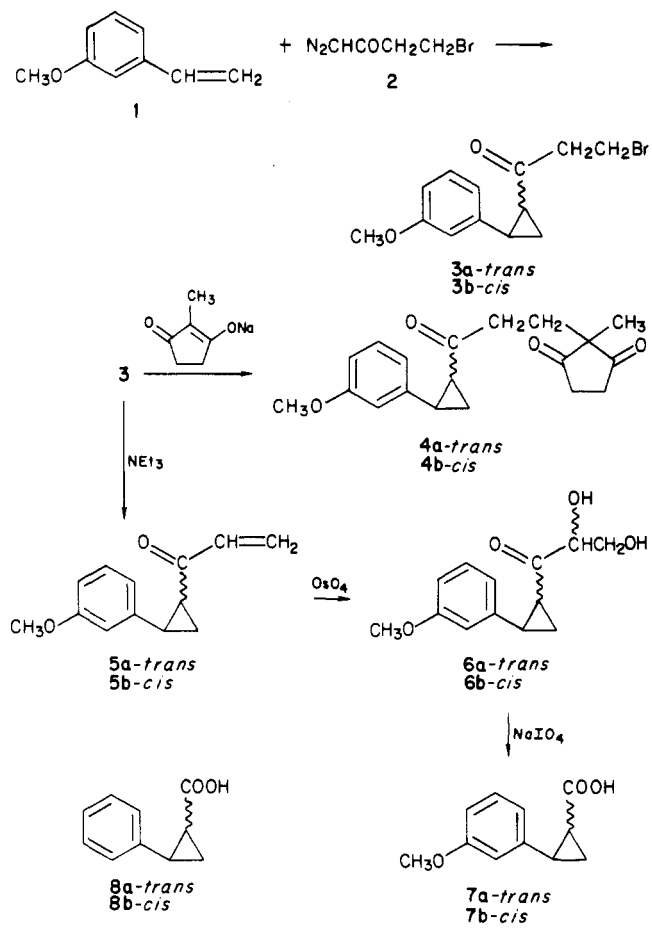
The coupling reaction of *m*-methoxystyrene (1) and 4-bromo-1-diazo-2-butanone (2) over $Pd(OAc)_2$ gave trans and cis (ratio 7:1) cyclopropane derivatives **3a** and **3b**, which were used for the alkylation of 2-methylcyclopentane-1,3-dione to afford triketones **4a** and **4b**, respectively. When copper tartarate was used as a catalyst for the coupling reaction, the optically active triketone **4a** (ee 46%) was obtained, which was then transformed into optically active (ee 10.4%) 14-dehydroequilenin (**14**) and 3-methoxy-1,3,5(10),8,14-estrapentaen-17-one (**18**).

Equilenin and estrone may be used as starting materials for the synthesis of other very important anabolic or contraceptive drugs, but there are not very many chiral total syntheses of these compounds in which the chirality was introduced with a catalyst. The best known chiral syntheses of aromatic steroids were described by the Hoffmann-La Roche and Schering research groups,[1] in which L-proline was used as a catalyst for asymmetric intramolecular aldol condensation.

We would like to present a new approach leading to aromatic steroids. It was known from the literature[2] that ethyl diazoacetate when added to styrene over a chiral catalyst gave the cyclopropane derivative in good optical and chemical yield. However, utilization of a similar coupling reaction to achieve a chiral synthesis of aromatic steroids gave disappointingly low optical yields (vide infra). We first carried out a racemic synthesis of aromatic steroids by this method as shown in Scheme I. The coupling reaction between *m*-methoxystyrene (1) and 4-bromo-1-diazo-2-butanone (2) was carried out in the presence of $Pd(AcO)_2$ as a catalyst giving a mixture of trans and cis bromides **3a** and **3b** in the ratio 7:1. The bromides **3a** and **3b** could be used directly for the alkylation of the sodium salt of 2-methylcyclopentane-1,3-dione giving the triones **4a** and **4b** or may be dehydrobrominated with triethylamine to the vinylic ketones **5a** and **5b**. These, when subjected to Michael reaction with 2-methylcyclopentane-1,3-dione gave the same triones **4a** and **4b**. The overall yield of 4 based on diazo ketone **2** was 65%. The stereochemistry of the bromides **3a** and **3b** was determined by the chemical transformation of **5a** and **5b** into the acids **7a** and **7b**. The bromides **3a** and **3b** were separated by column chromatography and then dehydrobrominated to **5a** and **5b**, which were hydroxylated with OsO_4 to give the diols **6a** and **6b**. Oxidation of the diols with $NaIO_4$ afforded acids **7a** and **7b**. The NMR spectra of **7a** and **7b** were compared with the spectra of the acids **8a** and **8b** described in the literature;[2b] this indicated that the predominant product **3a** had the trans configuration. With triketone 4 easily accessible, its reactions with various reagents were studied and shown in Scheme II.

Reaction of **4a** and **4b** with pyridine hydrogen iodide in acetonitrile gave the known[3] compound **9** in 60% yield; the same reaction in acetic acid containing a catalytic amount

Scheme I



of sodium iodide gave additionally a mixture of the diastereomeric acetates **10**. Use of $TiCl_4$ with **4a** or **4b** in methylene chloride gave a mixture of diastereomers **11** in 85% yield. The same chloro derivatives **11** were obtained by reaction of **4a** and **4b** with trimethylchlorosilane in the presence of Zn powder. Trimethylchlorosilane alone did not react with **4**. The action of trimethylsilyl iodide on **4a** or **4b** for a short period of time (5 min, room temperature) gave a very unstable compound which was reduced with Zn to give known[4] trione **13**. When **4a** was treated with an excess of trimethyliodosilane for a longer period (3 h), a mixture of **12**, **14**, and **15** was obtained. Treatment of **4a** with $SnCl_4$ in methylene chloride at room temperature gave crystalline **16** in 81% yield as a pure diastereoisomer according to its NMR spectrum.

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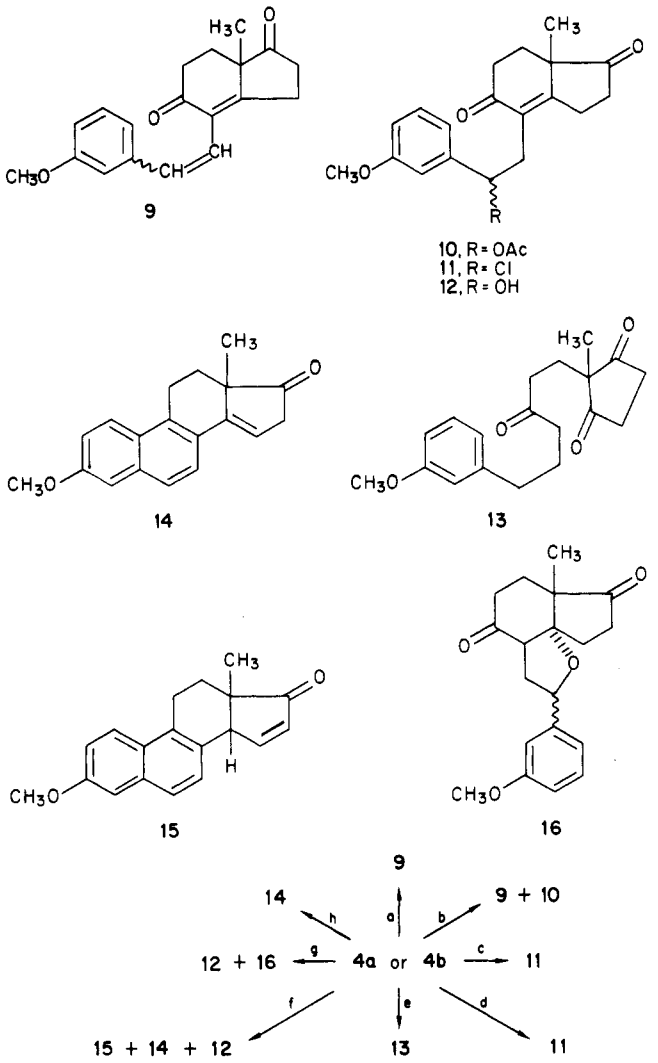
Scheme II[a]

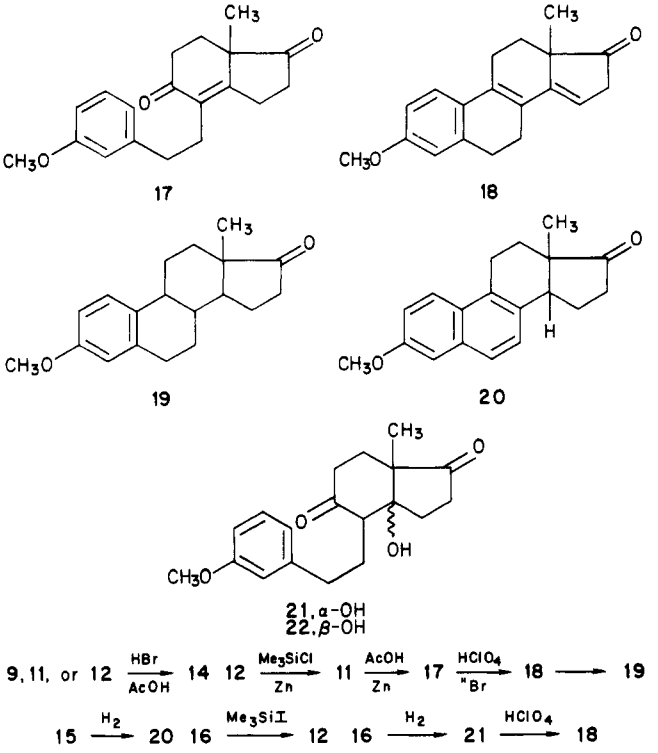


[a] a, Py·HI in CH_3CN; b, AcOH + NaI; c, $TiCl_4$, d, Me_3SiCl + Zn; e, Me_3SiI and Zn; f, Me_3SiI excess; g, $SnCl_4$; h, AcOH + HBr_g.

In order to prove the structures of **15** and **16** as well as to transform **9**, **10**, and **11** into derivatives of interest, we carried out the additional reactions shown in Scheme III.

Compounds **4**, **9**, **10**, and **11** when treated with HBr in acetic acid gave 14-dehydroequilenin 3-methyl ether (**14**), which can be hydrogenated to equilenin.[5] The hydroxy derivative **12** was transformed into **11** with trimethylchlorosilane and zinc. We find that this reaction is very useful for an almost quantitative transformation of benzylic alcohols into the corresponding chlorides. Reduction of **11** with Zn gave the known[3] compound **17**, which was also obtained from **4a** or **4b** as well as from **12** in a one-pot reaction by treatment with trimethylchlorosilane and zinc followed by addition of acetic acid to the reaction mixture. Product **17** can be cyclized to Torgov's pentaene **18** in 64% yield with a mixture of perchloric acid and HBr in acetic acid. The above reaction sequence gave **18** in 29.12% overall yield starting from **1** and **2**. According to the literature,[6] the pentaene **18** can be easily transformed into estrone or other useful derivatives.

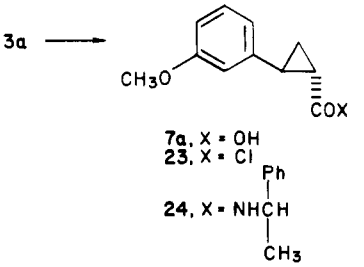
Scheme III



9, 11, or 12 $\xrightarrow[AcOH]{HBr}$ 14 12 $\xrightarrow[Zn]{Me_3SiCl}$ 11 $\xrightarrow[Zn]{AcOH}$ 17 $\xrightarrow[{}^nBr]{HClO_4}$ 18 ⟶ 19

15 $\xrightarrow{H_2}$ 20 16 $\xrightarrow{Me_3SiI}$ 12 16 $\xrightarrow{H_2}$ 21 $\xrightarrow{HClO_4}$ 18

Scheme IV



The known[5,7] 14-isoequilenin (**20**) was obtained by hydrogenation of **15** thus confirming the structure of the latter. Treatment of **16** with trimethyliodosilane gave only one diastereoisomer of **12**. Hydrogenation of **16** under atmospheric pressure over Pd/C in ethanol at 60 °C gave **21**, whose NMR spectrum differ from the spectrum of known[8] **22** in the chemical shift of the signal of the angular methyl group (**21**, singlet of **21** at 1.1 ppm, singlet of **22** at 1.3 ppm) which confirmed the trans C/D ring junction. Cyclization of **21** in acetic acid containing some perchloric acid gave the pentaene **18** in 75% yield.

To obtain optically active compounds we carried out the coupling reaction between *m*-methoxystyrene (**1**) and diazo ketone **2** over bis[(−)-camphoroquinone-α-dioximato]cobalt(II) according to the literature[2] but the yield of **3** was only about 5%. The same reaction carried out over copper tartarate[9] in benzene solution gave bromides **3a** and **3b** (**3a**:**3b** = 12:1) in 30% yield, which were used for the alkylation of the sodium salt of 2-methylcyclopentane-1,3-dione giving the optically active triones **4a** and **4b**. The optical rotation of **4a** and **4b** were $[\alpha]^{20}_D$ 2.2° (*c* 1.2), $[\alpha]^{20}_D$ 0.135° (*c* 0.8), respectively. Compound **4b** was isomerized[10]

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with $PdCl_2$·2PhCN to **4a**, $[\alpha]^{20}_D$ 0.416° (*c* 1.3). The optical purity of **3a** was determined by chemical transformations shown in Scheme IV.

The bromide **3a** was converted to acid **7a** which was transformed to the diastereoisomeric mixture of amides **24** through acid chloride **23** by using optically pure α-methylbenzylamine. Quantitative separation (HPLC) of the amides gae a 2.7:1 ratio for the diastereomers, which means that the optical purity of **3a** was about 46%. Optically active **3a** was used as a substrate for synthesis of **4a** whose reactions with several reagents were studied in order to check the optical induction during cyclization. Cyclization of optically active **4a** in acetic acid with HBr gave racemic 14-dehydroequilenin. Treatment of **4a** with $SnCl_4$ in methylene chloride gave **16**, which was transformed into pentaene **18** through **21**, but unfortunately **16**, **21**, as well as **18** were optically inactive. The cyclopropane ring opening with simultaneous cyclization of optically active **4a** with $TiCl_4$ gave **11**, which was then cyclized to equilenin **14**. The optical rotation of **14** was $[\alpha]^{20}_D$ −4.26°, which means that the optical purity was 10.4% (lit.[11] $[\alpha]^{20}_D$ −41°). Compound **11** was reduced with Zn to **17** $[\alpha]^{20}_D$ 18.5°, 10.22% (lit.[12] $[\alpha]^{20}_D$ 181°)), which was cyclized to the pentaene **18** ($[\alpha]^{20}_D$ 10.72°, 10.4% (lit.[13] $[\alpha]^{20}_D$ 103°)). The optical induction during the cyclopropane ring opening and cyclization process **4a** → **11** → **18** was about 22%. The reaction of optically active **4a** with trimethylchlorosilane and Zn gave **17** with 1.2% optical induction. Reaction of optically active **4a** with trimethyliodosilane gave **12**, which was transformed into **11** with trimethylchlorosilane and zinc. The later compound was reduced to known **17**, whose optical rotation $[\alpha]^{20}_D$ 2.3° indicated 2.76% optical induction.

Experimental Section

Melting points were measured on a microhot plate and are not corrected. NMR spectra were recorded on Jeol 100-MHz spectrometer in $CDCl_3$ solution, with Me_4Si as an internal standard. UV spectra were determined in ethanol solution by Unicam SP-700, MS spectra by LKB-9000S apparatus. IR spectra were recorded on Unicam SP-200 spectrometer. The solvents were purified according to "A Text-Book of Practical Organic Chemistry" by A. I. Vogel, 3rd ed., 1956. The reactions were monitored by TLC. *m*-Methoxystyrene was prepared from *m*-methoxyacetophenone[14] and 1,1-diazo-4-bromobutenone (**2**) from 3-bromopropionic acid.[15] Trimethyliodosilane was prepared in an acetonitrile solution from sodium iodide and trimethylchlorosilane under argon.

***trans*- and *cis*-1-(*m*-Methoxyphenyl)-2-(β-bromopropionyl)cyclopropane (3a and 3b).** To the solution of **1** (7.0 g, 52 mmol) and palladium acetate (359 mg, 1.56 mmol) in benzene (50 mL) was added dropwise the solution of **2** (6.22 g, 36.0 mmol) in dry benzene (20 mL) for 4 h at 25–28 °C. The mixture was stirred for 1 h and then charcoal (0.5 g) and hexane (20 mL) were added. After filtration through Celite and evaporation of solvent the crude mixture of bromides **3a** and **3b** were obtained as light yellow oil, which was used for the next reaction. In order to identify these bromides, the mixture was separated on column chromatography with a hexane/ethyl acetate mixture (20:1) as an eluent. The NMR and IR spectra of **3a** and **3b** were very similar, and the bromides decomposed on standing at room temperature. Compound **3a**: NMR δ 1.25–2.80 (m, 4 H, cyclopropane protons), 3.08–3.25 (m, 2 H, O=CCH_2), 3.55 (t, 2 H, CH_2Br), 3.80 (s, 3 H, OCH_3), 6.54–6.70 (m, 3 H, at C-2, C-4, and C-10), 7.10 (t, 1 H, at C-1, *J* = 9 Hz); IR (film) 1700 cm^{-1}.

***trans*- and *cis*-1-(*m*-Methoxyphenyl)-2-acryloylcyclopropane (5a and 5b).** To the solution of bromides **3a** and **3b** (6.20 g, 22 mmol) in benzene (40 mL) was added triethylamine (5 mL). After 0.5 h the precipitated hydrogen bromide of triethylamine was filtered off and the filtrate was evaporated under reduced pressure. The residue was used for the reaction with 2-methylcyclopentane-1,3-dione. For identification, the crude mixture of **5a** and **5b** was separated on silica gel with hexane and ethyl acetate as an eluent (20:1). The compounds **5a** and **5b** were isolated as oils and were decomposing on standing. Compound **5a**: NMR δ 3.70 (s, 3 H, OCH_3), 5.5–6.4 (m, 3 H, CH=CH_2), 6.6–7.3 (m, 4 H, aromatic protons); IR 1665 cm^{-1}. Compound **5b**: NMR δ 3.70 (s, 3 H, OCH_3), 5.5–6.4 (m, 3 H, CH=CH_2), 6.6–7.4 (m, 4 H, aromatic protons); IR 1670 cm^{-1}.

***trans*- and *cis*-1-(*m*-Methoxyphenyl)-2-[β-(2-methyl-1,3-dioxocyclopent-2-yl)propionyl]cyclopropane (4a and 4b). Method A.** To the solution of compounds **5a** and **5b** (4.1 g, 20 mmol) in dry acetonitrile (20 mL) was added 2-methylcyclopentane-1,3-dione (3.5 g, 31 mmol) and its sodium salt (0.5 g, 3.7 mmol). The mixture was refluxed for 3 h and then acetonitrile was evaporated to dryness. The residue was extracted with benzene (3 × 35 mL) and the extract was evaporated and chromatographed on silica gel with a hexane/ethyl acetate mixture (10:1) as an eluent. This gave **4a**, 4.71 g (74%), and **4b**, 0.67 g (10.5%). **4a**: oil; NMR δ 1.05 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 6.55–6.70 (m, 3 H, at C-2, C-4, C-10), 7.10 (t, 1 H, at C-1, *J* = 7.5 Hz); IR 1740, 1700 cm^{-1}; MS, *m/e* 314. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.13; H, 7.13. **4b**: oil; NMR δ 0.95 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 6.6–6.85 (m, 3 H, at C-2, C-4, C-10), 7.16 (t, 1 H, at C-1, *J* = 7.5 Hz); IR 1730, 1700 cm^{-1}; MS, *m/e* 314. **Method B.** To the solution of bromides **3a** and **3b** (6.2 g, 22 mmol) in acetonitrile (50 mL) was added the sodium salt of 2-methylcyclopentane-1,3-dione (3.6 g, 26.8 mmol). The mixture was left at room temperature overnight. The acetonitrile was evaporated to dryness and the residue was extracted with benzene (3 × 20 mL). Evaporation of the solvent and chromatography on silica gel gave **4a** (5.23 g, 76.4%) and **4b** (0.75 g, 10.9%).

***trans*-1-(*m*-Methoxyphenyl)-2-(α,β-dihydroxypropionyl)cyclopropane (6a).** To the solution of unsaturated ketone **5a** (0.72 g, 3.56 mmol) in pyridine (30 mL) was added OsO_4 (0.9 g, 3.56 mmol) in pyridine (20 mL). The mixture was stirred for 0.5 h at room temperature and then THF (150 mL) and sodium hydrogen sulfite (40 mL, 40% aqueous solution) were added. After 0.5 h of stirring, the reaction mixture was separated and the organic layer was concentrated under reduced pressure. The residue was poured into water (50 mL) and extracted with chloroform (4 × 20 mL). The extract after drying was concentrated and crude diol **6a** was crystallized from ether affording 0.796 g (94%) of **6a**: mp 94–96 °C; NMR δ 3.80 (s, 3 H, OCH_3), 4.02 (d, 2 H, CH_2OH), 4.45 (t, 1 H, O=CCHOH), 6.7–7.3 (m, 4 H, aromatic protons); IR (KBr) 3520, 1680 cm^{-1}; MS, *m/e* 236. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.02; H, 6.85.

***cis*-1-(*m*-Methoxyphenyl)-2-(α,β-dihydroxypropionyl)cyclopropane (6b).** Compound **6b** was obtained in the same manner as **6a**: yield 95%; mp 96–97 °C (from ether); NMR δ 3.80 (s, 3 H, OCH_3), 3.92 (d, 2 H, CH_2OH, *J* = 6 Hz), 4.25 (t, 1 H, O=CCHOH, *J* = 6 Hz); IR 3500, 1680 cm^{-1}; MS, *m/e* 236. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.91; H, 6.92.

***trans*-2-(*m*-Methoxyphenyl)cyclopropanecarboxylic Acid (7a).** To the solution of diol **6a** (0.40 g, 1.7 mmol) in acetone (50 mL) was added a solution of $NaIO_4$ (0.75 g, 3.5 mmol) in water (15 mL). The temperature of the mixture was raised to 60 °C and after 10 min TLC showed the end of that reaction. Water (25 mL) was added to the reaction mixture, which was then extracted with chloroform (4 × 25 mL). The extract after drying with Na_2SO_4 was concentrated and crude **7a** (0.30 g, 91%) was recrystallized from acetone. **7a**: mp 98–99 °C; NMR δ 3.82 (s, 3 H, OCH_3), 6.7–7.35 (m, 4 H, aromatic protons), 13.5 (b s, 1 H, COOH); IR (KBr) 1705 cm^{-1}; MS, *m/e* 192. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.58; H, 6.29.

***cis*-2-(*m*-Methoxyphenyl)cyclopropanecarboxylic Acid (7b).** Compound **7b** was obtained in the same manner as **7a**. Yield 90%; mp 101–103 °C; NMR δ 3.80 (s, 3 H, OCH_3), 6.80–7.35 (m, 4 H, aromatic protons), 13.25 (b s, 1 H, COOH); IR (KBr)

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1700 cm^{-1}; MS, m/e 192. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.60; H, 6.34.

3-Methoxy-9,10-secoestra-1,3,5(10),6,8(14)-pentaene-9,17-dione (9). Method A. The solution of compound **4a** or **4b** (0.20 g, 0.63 mmol) and pyridine hydrogen iodide (0.60 g, 2.8 mmol) in acetonitrile (10 mL) was refluxed under argon for 20 h. The mixture was concentrated; the residue was treated with water (20 mL) and extracted with benzene (3 × 20 mL). The extract was washed with aqueous hydrogen sulfite and, after drying with Na_2SO_4, was concentrated. The residue was chromatographed on silica gel with a hexane/ethyl acetate mixture (9:1). This gave **9** (0.113 g, 60%): mp 89–91 °C (lit.[3] mp 93–94 °C); NMR (CCl_4) δ 1.49 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 6.7–7.32 (m, 6 H, aromatic and olefinic protons); IR (KBr) 1740, 1670, 1630 cm^{-1}; UV λ_{max} 318 (ϵ 9500), 271 (ϵ 13250), 218 nm (ϵ 20350); MS, m/e 296. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.85; H, 6.69. **Method B.** The mixture of **4a** or **4b** (0.63 g, 2.0 mmol), sodium iodide (0.030 g, 0.2 mmol), and acetic acid (20 mL) was refluxed under argon for 3 h. After cooling the mixture was neutralized with an aqueous solution of $NaHCO_3$ and extracted with benzene (3 × 25 mL). The extract was dried with Na_2SO_4 and concentrated and the residue chromatographed on silica gel. Collection of proper fractions gave **9** (0.23 g, 39%) and **10** (0.195 g, 27.3%). Compound **10**: NMR δ 1.18 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3CO), 3.84 (s, 3 H, OCH_3), 5.75 (t, 1 H, at C-6, J = 7.5 Hz), 6.75–6.98 (m, 4 H, aromatic protons); IR (film) 1750, 1670 cm^{-1}; MS, m/e 356. Compound **10** was obtained also by acetylation of **12** with acetic anhydride in pyridine by using a standard procedure.

3-Methoxy-6ξ-chloro-9,10-secoestra-1,3,5(10),8(14)-tetraene-9,17-dione (11). Method A. To the solution of **4a** or **4b** (0.628 g, 2 mmol) in methylene chloride (15 mL) at −10 °C was added the solution of $TiCl_4$ (0.25 mL, 2.3 mmol) in methylene chloride (5 mL). The mixture was stirred at room temperature for 5 h and then poured into water (20 mL). The organic layer was separated and the water layer was extracted with methylene chloride. The combined extracts after washing with brine and drying with Na_2SO_4 were concentrated, giving a brown oil (0.557 g, 85%) of **11**, which usually was used for the next reaction. The analytical sample was obtained by purification on a silica gel column with a hexane/ethyl acetate mixture (10:1) as an eluent. Compound **11** obtained from **4a**: NMR δ 1.1 and 1.3 ratio 0.638 (2 s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 4.95–5.12 (m, 1 H, at C-6), 6.80–7.35 (m, 4 H, aromatic protons); MS, m/e 332; IR (film) 1740, 1660 cm^{-1}. **Method B.** To the solution of compound **12** (0.62 g, 2.0 mmol) in dry methylene chloride (10 mL) was added trimethylchlorosilane (0.53 mL, 4.2 mmol) and zinc powder (0.070 g, 1.1 mmol). The reaction mixture was stirred at room temperature for 1 h, then filtered, and concentrated. The residue was chromatographed on silica gel with a hexane/ethyl acetate mixture (9:1) as an eluent giving **11** (0.554 g, 84%).

3-Methoxy-6ξ-hydroxy-9,10-secoestra-1,3,5(10),8(14)-tetraene-9,17-dione (12). To the solution of **11** (0.150 g, 0.45 mmol) in methanol (10 mL) was added an aqueous solution of $NaHCO_3$ (10%, 2 mL) and the mixture was left overnight at room temperature. Methanol was evaporated under reduced pressure and water (5 mL) was added to the residue. The mixture was extracted with chloroform (3 × 10 mL) and the extract, after drying with Na_2SO_4 and concentration, was chromatographed on silica with a hexane/ethyl acetate mixture (4:1) as an eluent. Compound **12** (0.13 g, 92%) was obtained as a mixture of two diastereoisomers (ratio 1.57 according to NMR spectrum). Compound **12**: NMR δ 1.17 and 1.3 (2 s, 3 H, CH_3, ratio 1.57), 3.80 (s, 3 H, OCH_3), 4.60–4.82 (m, 1 H, at C-6), 6.68–7.25 (m, 4 H, aromatic protons); IR (film) 3500, 1740, 1660 cm^{-1}; MS, m/e 314.

3-Methoxy-9,10-secoestra-1,3,5(10),8(14)-tetraene-9,17-dione (17). Method A. To the solution of **11** (0.450 g, 1.36 mmol) in ether (50 mL) was added zinc powder (0.30 g, 4.6 mmol) and acidic acid (0.5 mL). The mixture was stirred at room temperature for 3.5 h and filtered. The filtrate was washed with water (10 mL) and after drying with Na_2SO_4 was concentrated. The crude compound **17** was purified by chromatography with a hexane/ethyl acetate mixture (4:1) as an eluent. The yield of **17** was 310 mg (76%). The spectral data of **17** were in good agreement with data described in literature.[3] Compound **17**: oil; NMR δ 1.20 (s, 3 H, CH_3), 3.80 (s, 3 $HOCH_3$), 6.50–7.25 (m, 4 H, aromatic protons); IR (film) 1740, 1660 cm^{-1}; MS, m/e 298. **Method B.** To the solution of **4a** or **4b** (0.160 g, 0.5 mmol) and trichlorosilane (0.1 mL, 0.8 mmol) in methylene chloride (10 mL) was added zinc powder (35 mg, 0.53 mmol). The mixture was stirred at room temperature under argon until the substrate disappeared (TLC) and then another portion of zinc (70 mg, 1.1 mmol) and acetic acid (0.1 mL) was added. The reaction mixture was stirred for an additional 2 h and then filtered, washed with water, and dried with Na_2SO_4. Filtration and evaporation of solvents, followed by chromatography gave **17** (115 mg, 70%). **Method C.** To the solution of **12** (0.157 g, 0.5 mmol) in dry methylene chloride (5 mL) was added trimethylchlorosilane (0.14 mL, 1.1 mmol) and zinc powder (65 mg, 1 mmol). The reaction mixture was stirred for 1 h at room temperature under argon until the disappearance of the substrate **12**. Acetic acid (0.1 mL) and zinc (70 mg, 1.08 mmol) were added to the reaction mixture and stirring was continued for an additional 2 h. After the same workup and chromatography as described above compound **17** (120 mg, 73%) was obtained.

6-(*m*-Methoxyphenyl)-1-(2-methyl-1,3-dioxocyclopent-2-yl)hexan-3-one (13). To the solution of **4a** (0.32 g, 1.02 mmol) in methylene chloride (15 mL) was added under argon trimethyliodosilane prepared in situ from sodium iodide (0.15 g, 1.0 mmol) and trimethylchlorosilane in acetonitrile. The mixture was stirred at room temperature for 5 min, poured into water (20 mL), and extracted with methylene chloride (2 × 15 mL). The extract was washed with 10% aqueous sodium sulfite, dried with Na_2SO_4, and concentrated to half volume. Ether (15 mL), acetic acid (0.5 mL), and zinc powder (0.20 g, 3.08 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The excess of zinc powder was filtered off and the filtrate was washed with water (2 × 5 mL), dried with Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column with a hexane/ethyl acetate mixture (10:1) as an eluent, giving compound **13** (0.1. g, 60%) which showed to be identical with **13** obtained by a different route described in the literature.[4]

Reaction of 4a with Excess Trimethyliodosilane. To the solution of **4a** (0.25 g, 0.8 mmol) in methylene chloride was added trimethyliodosilane obtained in situ from sodium iodide (0.45 g, 3 mmol) and trimethylchlorosilane (0.326 g, 3 mmol) in acetonitrile (10 mL). The mixture was stirred for 3 h at room temperature then poured into water (20 mL) and extracted with methylene chloride (3 × 10 mL). The extract was washed with an aqueous solution of sodium sulfite and water and, after drying with Na_2SO_4, was concentrated under reduced pressure. The residue was chromatographed on silica gel column with a hexane/ethyl acetate (20:1 and 10:1) mixture as an eluent. The collection of proper fractions gave compound **12** (105 mg, 42%), **14** (25 mg, 11%), and **15** (20 mg, 9%). The hydrogenation of **15** over palladium catalyst gave known isoequilenin (**20**), mp 127–129 °C (lit.[5] mp 128–130 °C, lit.[7] mp 125–127 °C). Compound 15 was characterized only with NMR: δ 1.28 (s, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 6.18 (dd, 1 H, C-16, J = 6 Hz, J = 1.5 Hz), 7.1–7.7 (m, 5 H, C-2, C-4, C-6, C-7, C-15), 7.95 (d, 1 H, C-1, J = 9 Hz).

4-[2′-(*m*-Methoxyphenyl)ethyl]-7a-methyl-4a,2′-oxyindan-3,7-dione (16). To the solution of **4a** or **4b** (0.63 g, 2.0 mmol) in methylene chloride (20 mL) was added the solution of $SnCl_4$ (1.045 g, 4.0 mmol) in methylene chloride (4 mL). The reaction mixture was left overnight at room temperature and then poured into water (20 mL). Extraction with methylene chloride (3 × 10 mL), followed by drying with Na_2SO_4, filtration, and evaporation of solvent gave a mixture of compounds **16** and **12**, which was separated by column chromatography. Compound **16**: 510 mg (81%); mp 127–127.5 °C (from ether/chloroform mixture); NMR δ 1.2 (s, 3 H, CH_3), 3.9 (s, 3 H, OCH_3), 4.9–5.05 (m, 1 H, PhCHO), 6.88–7.42 (m, 4 H, aromatic protons); IR (nujol) 1740, 1710 cm^{-1}; UV λ_{max} 280 (ϵ 2000), 274 (ϵ 2200), 236 nm (ϵ 8600); MS, m/e 314. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.45; H, 7.13.

3-Methoxy-1,3,5(10),6,8,14-estrahexaen-17-one (14). To the solution of **4a**, **4b**, **9**, **11**, or **12** (2 mmol) in acetic acid (10 mL) was added a solution of HBr in acetic acid (40%, 2 mL) at room temperature. In the case of cyclization of **4a** or **4b** the reaction mixture was poured into water (20 mL) after 3 h but in the case of compounds **9**, **11**, or **12** after 24 h. The mixture was extracted with chloroform (3 × 15 mL), washed with aqueous $NaHCO_3$, and dried with Na_2SO_4. After filtration the filtrate was concentrated

and the residue was chromatographed on a silica gel column and recrystallized from methanol giving **14** (mp 158–160 °C) in 70% yield when **4a** or **4b** was used as a substrate and about 40% yield in the case of **9**, **11**, and **12**. Compound **14**: NMR δ 1.22 (s, 3 H, CH_3), 4.0 (s, 3 H, OCH_3), 6.34 (b s, 1 H, at C-15), 7.2–7.4 (m, 4 H, at C-2, C-4, C-6, C-7), 8.0 (d, 1 H, at C-1, J = 9.0 Hz); IR (KBr) 1740 cm^{-1}; UV λ_{max} 333 (ϵ 1700), 304 (ϵ 11 700), 293 (ϵ 13 200), 283 (ϵ 10 500), 259 (ϵ 39 000), 251 (ϵ 41 400), 238 nm (ϵ 32 700).

3-Methoxy-1,3,5(10),8,14-estrapentaen-17-one (18). To the solution of **17** (0.30 g, 1.0 mmol) in acetic acid (5 mL) was added 40% HBr in acetic acid (0.5 mL) and 70% $HClO_4$ (0.5 mL). The mixture was left overnight at room temperature, poured into water (50 mL), and extracted with benzene (3 × 10 mL). The extract was washed with aqueous $NaHCO_3$ and after drying with Na_2SO_4, filtration, and concentration, the residue was chromatographed on silica gel affording 180 mg (64%) of **18** identical with authentic sample.

The Reaction of 16 with Trimethyliodosilane. To the solution of sodium iodide (0.15 g, 1.0 mmol) in acetonitrile (5 mL) was added trimethylchlorosilane (0.108 g, 1.0 mmol). The reaction mixture was stirred under argon for 15 min, a solution of **16** (160 mg, 0.5 mmol) in methylene chloride (5 mL) was added, and stirring was continued for 2 h. Water (5 mL) was added to the reaction mixture and after 15 min of stirring the mixture was extracted with methylene chloride (3 × 10 mL). The extract was washed with an aqueous solution of sodium sulfite followed by water and dried with Na_2SO_4. Evaporation of solvent and chromatography on silica gel afforded **12** (120 mg, 75%), whose NMR spectrum indicated that compound **12** was the pure epimer at C-6 carbon atom: NMR δ 1.17 (s, 3 H, CH_3), 3.8 (s, 3 H, OCH_3), 4.65–4.85 (m, 1 H, at C-6), 6.7–7.35 (m, 4 H, aromatic protons).

Hydrogenation of 16. The solution of **16** (0.314 g, 1.0 mmol) in ethanol (25 mL) was hydrogenated over 10% Pd/C (0.5 g), at 60 °C under atmospheric pressure for 2 h. After filtration and evaporation of solvent the residue was purified by column chromatography affording **21** (237 mg, 75%) as a amorphous foam: NMR δ 1.12 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 6.8–6.95 (m, 3 H, C-2, C-4, C-10), 7.27 (t, 1 H, C-1, J = 7 Hz); IR ($CHCl_3$) 3600, 3470, 1740, 1720 cm^{-1}; MS, m/e 316.

Cyclization of 21. The compound **21** (0.1 g, 0.316 mmol) was cyclized in acetic acid (3 mL) with 70% $HClO_4$ (0.1 mL) at room temperature for 2 h. Water (5 mL) was added to the reaction mixture which was then extracted with chloroform (5 × 5 mL). The residue was chromatographed on silica gel giving **18** (55 mg, 58%), whose spectra were the same as described in literature.[6]

Synthesis of Optically Active 3. To the stirred slurry of styrene **1** (2.5 g, 18.6 mmol), benzene (50 mL), and copper tartarate (1.9 g, 7.6 mmol) was added dropwise the solution of diazo ketone **2** (2.5 g, 14.1 mmol) in benzene (15 mL) for 3 h at 45–59 °C. The mixture was stirred at this temperature until the evolution of nitrogen ceased. The workup was the same as in the racemic case. The yield of **3a** and **3b** was 1.20 g (30%) in a ratio of 12:1.

Determination of Optical Purity of 3a. The compound **3a** was isolated by chromatography and transformed into acid **7a** as it was described in the racemic series. Acid **7a** was transformed into amide **24** in the following way. The mixture of acid **7a** (385 mg, 2.0 mmol), benzene (20 mL), and thionyl chloride (0.8 mL) was heated to 50 °C for 1 h and then was concentrated. The residue was dissolved in dry benzene (10 mL) and added to the solution of (+)-α-phenylethylamine $[\alpha]^{20}_D$ 39° (0.4 mL in 5 mL of benzene). After 5 min the mixture was washed with 5% hydrochloric acid and then with water. The benzene solution of amides **24** was dried with Na_2SO_4 and after filtration it was concentrated. This gave 540 mg of **24** (90%). The two diastereoisomeric amides were separated by HPLC, and the ratio between them was 2.7:1, which means that the optical purity of the starting bromide **3a** was about 46%. The same amides **24** were obtained starting from racemic **3a** and they were separated by column chromatography. This gave **24a**: mp 169–170 °C (from hexane/ether mixture); $[\alpha]^{20}_D$ 209° (c 1.2 in $CHCl_3$); NMR δ 1.55 (d, 3 H, CH_3), 5.14–5.3 (q, 1 H, CH, J = 7.5 Hz), 6.7–7.48 (m, 9 H, aromatic protons); IR ($CHCl_3$) 3450, 1665 cm^{-1}; MS, m/e 295. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.98; H, 7.13; N, 4.55.

24b: mp 172, 173 °C (from hexane/ether); $[\alpha]^{20}_D$ 158° (c 0.85 in $CHCl_3$); NMR δ 1.55 (d, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 5.25 (q, 1 H, CH, J = 7.5 Hz), 6.7–7.48 (m, 9 H, aromatic protons); IR ($CHCl_3$) 3430, 1665 cm^{-1}; MS, m/e 295. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.13; H, 7.20; N, 4.62.

Synthesis of Optically Active 4a and 4b. To the solution of optically active **3a** and **3b** (1.55 g, 5.47 mmol) in acetonitrile (50 mL) was added the sodium salt of 2-methylcyclopentane-1,3-dione (1.0 g, 7.46 mmol) and the reaction mixture was stirred overnight at room temperature. After workup and chromatography according to the procedure described for the racemic compound, this gave **4a** (1.45 g, 84.3%): $[\alpha]^{20}_D$ 2.2° (c 2.0 in EtOH). **4b** (0.12 g, 6.98%): $[\alpha]^{20}_D$ −0.135° (c 1.3 in EtOH).

Isomerization of 4b into 4a. The solution of **4b** ($[\alpha]^{20}_D$ −0.135° (70 mg) and $PdCl_2$·PhCN (50 mg) in chloroform (10 mL) was maintained at 35 °C for 4 h. The evaporation of solvent and chromatography on silica gel gave **4a** ($[\alpha]^{20}_D$ 0.416°, 64 mg, 91%).

Transformations of Optically Active 4a. The best optical induction was achieved when the optically active **4a** ($[\alpha]^{20}_D$ 2.2°) was transformed into chloro compound **11** with $TiCl_4$ in methylene chloride. The compound **11** was then converted into dione **17**, Torgov's pentaene **18**, and 14-dehydroequilenin (**14**) according to the procedures described for the racemic compounds. The obtained **17** had optical rotation $[\alpha]^{20}_D$ 18.5° (c 2.2 in benzene, 10.22%) (lit.[12] $[\alpha]^{20}_D$ 181°), **18**: $[\alpha]^{20}_D$ 10.72° (c 1.2 in $CHCl_3$, 10.4%) (lit.[13] $[\alpha]^{20}_D$ 103°), **14**: $[\alpha]^{20}_D$ −4.26° (1.1 in $CHCl_3$, 10.4%) (lit.[11] $[\alpha]^{20}_D$ 41°). This means that optical induction during the cyclization process was about 22%. The same **4a** treated with trimethylchlorosilane and zinc gave **11**, which after zinc reduction afforded **17** ($[\alpha]^{20}_D$ −1.0°), which means that optical purity was 0.5% and optical induction 1.2%. The reaction of optically active **4a** with trimethyliodosilane gave **12**, which was then transformed into **17** according to the procedure described above for the racemic compound. The optical rotation of the latter compound was $[\alpha]^{20}_D$ 2.3° (c 3.5 in benzene). The other reactions of optically active **4a** with HBr in acetic acid or with $SnCl_4$ in methylene chloride gave compounds **14** and **16**, respectively, which were optically inactive.

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Registry No. **1**, 626-20-0; **2**, 59813-11-5; (±)-**3a**, 96728-31-3; (±)-**3b**, 96728-32-4; (±)-**4a**, 96728-33-5; (+)-**4a**, 83177-86-0; (±)-**4b**, 96728-34-6; (−)-**4b**, 83177-87-1; (±)-**5a**, 96728-35-7; (±)-**5b**, 96728-36-8; (±)-**6a**, 96728-37-9; (±)-**6b**, 96789-70-7; (±)-**7a**, 96728-38-0; (±)-**7b**, 96728-39-1; (±)-**9**, 38680-42-1; (±)-**10** (isomer 1), 96728-40-4; (±)-**10** (isomer 2), 40903-70-6; (±)-**11** (isomer 1), 96728-41-5; (±)-**11** (isomer 2), 96728-42-6; (±)-**12** (isomer 1), 96789-71-8; (±)-**12** (isomer 2), 40901-62-0; **13**, 4209-95-4; (±)-**14**, 96728-43-7; (−)-**14**, 96789-72-9; (±)-**15**, 96789-73-0; **16**, 96728-44-8; (±)-**17**, 18300-15-7; (+)-**17**, 15375-09-4; (±)-**18**, 1456-50-4; (+)-**18**, 966-47-2; (±)-**20**, 4820-49-9; (±)-**21**, 96789-74-1; (±)-**23**, 96728-45-9; **24** (isomer 1), 83214-16-8; **24** (isomer 2), 83177-89-3; 2-methylcyclopentane-1,3-dione, 765-69-5; 2-methylcyclopentane-1,3-dione sodium salt, 51467-21-1; (+)-2-phenylethylamine, 3886-69-9; (benzonitrile)dichloropalladium, 42531-12-4.