copper with DIBAH to enedione **3** and simultaneous generation of the diisobutylaluminum enolate, which is trapped by electrophiles. In the present studies bromine was used for trapping of the aluminum enolate **4**, and crystalline bromodione **5** was obtained in a 57% yield (Scheme II). Reduction of **5** with lithium (tri-*tert*-butoxyalumino)hydride led to bromo diol **6**, which was transformed into epoxy alcohol **7** after treatment with potassium hydride in HMPA. Oxidation of compound **7** with PDC afforded epoxy ketone **8**, which was reacted with ethyltriphenylphosphonium iodide and potassium *tert*-butoxide in THF to yield epoxy olefin **9**. Treatment of **9** with LAH in THF heated at reflux afforded synthon **1**. Multiplication of given yields results in a 22% overall yield. Synthon **1** and the material reported by Uskokovic[4] have almost identical spectra.

Experimental Section

THF, HMPA, and CuI were anhydrous. All reactions were carried out under argon. The reaction were monitored by TLC. The IR spectra were taken on Beckman 4240 spectrophotometer, and the NMR spectra on a Bruker WP 100 FY spectrometer in $CDCl_3$ unless otherwise noted. The MS spectra were determined with a LKB-9000S apparatus. The starting enedione **3** had optical rotation $[\alpha]_D$ +364° (1.0 in benzene), ee 99%.

(3a*R*,4*S*,7a*S*)-4-Bromooctahydro-7a-methyl-1*H*-indene-1,5-dione (5). *tert*-Butyllithium (2.6 mL, 3.66 mmol, 1.4 M in pentane) was added dropwise to a stirred slurry of CuI (0.58 g, 3.04 mmol) in THF (30 mL) at −40 °C. The reaction mixture was stirred at that temperature for an additional 15 min, and then HMPA (12 mL, 68.9 mmol) was added at −40 °C. The reaction mixture was cooled to −78 °C, and the solution of enedione **3** (1.0 g, 6.1 mmol) in THF (5 mL) was added. To this mixture was added a solution of DIBAH (1.3 mL, 7.3 mmol) in THF (5 mL) and in HMPA (5 mL) slowly during 15 min at −78 °C. The reaction mixture was stirred at −78 °C for an additional 15 min, and the temperature was allowed to raise to −40 °C. Bromine (0.4 mL, 1.27 g, 7.93 mmol) was added to this mixture at −78 °C, and stirring was continued for 5 min. Then an aqueous solution of $CuSO_4$ (100 mL, 10%) was added, and the mixture was extracted with ether (4 × 60 mL). The extract was dried with $MgSO_4$ and chromatographed on a silica gel column with a hexane–ethyl acetate (2:1) mixture as an eluent. Collection of the proper fraction afforded bromo dione **5**, which was crystallized from an ethyl acetate–ether mixture to yield **5** (0.852 g, 57%): mp 133–154 °C; $[\alpha]_D$ +113.9° (1.0, $CHCl_3$); IR (KBr) 1740, 1715 cm^{-1}; ^1H NMR δ 1.19 (s, 3 H, CH_3), 4.71 (d, 1 H, CHBr, J = 12.5 Hz); MS (70 eV), m/e 244, 246. Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.34. Found: C, 49.12; H, 5.45.

(1*S*,3a*R*,4*S*,5*S*,7a*S*)-4-Bromooctahydro-7a-methyl-1*H*-indene-1,5-diol (6). Lithium (tri-*tert*-butoxyalumino)hydride (4.57 g, 18.0 mmol) was added in six portions to a solution of bromo dione **5** (2.0 g, 8.16 mmol) in THF (60 mL) at room temperature during 1 h, whereupon the reaction mixture was heated at reflux for 10 min. After the mixture was cooled to 0 °C, acetic acid (4.3 mL, 72 mmol) was added, and the reaction mixture was filtered through a silica gel layer (2 cm), which was then washed with ethyl acetate (60 mL). After evaporation of the solvent from the filtrate, the residue was crystallized from ethyl acetate to yield bromo diol **6** (1.77 g, 84%): mp 226–227 °C; $[\alpha]_D$ −32.7° (1.0, CH_3OH); IR (KBr) 3240, 3340 cm^{-1}; ^1H NMR (CD_3OD) δ 0.81 (s, 3 H, CH_3), 3.3–4.09 (m, 3 H); MS (70 eV), m/e 248, 250. Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.20; H, 6.88. Found: C, 48.28; H, 6.84.

(1*S*,3a*R*,4*R*,5*S*,7a*S*)-4,5-Epoxyoctahydro-7a-methyl-1*H*-inden-1-ol (7). Potassium hydride (20% suspension in oil, 0.6 g, 3.0 mmol) was added in four portions to a stirred solution of compound **6** (0.30 g, 1.2 mmol) in dry HMPA (6 mL) under argon at 10–15 °C during 1 h. Then the reaction mixture was neutralized with acetic acid (0.3 mL), and an aqueous solution of $CuSO_4$ (40 mL, 10%) was added. The mixture was extracted with ethyl ether (2 × 30 mL). The organic phase was dried with $MgSO_4$ and concentrated, whereupon it was chromatographed on a silica gel column with a hexane–ethyl acetate mixture as an eluent. Compound **7** (0.18 g, 89%) was obtained as an oil: $[\alpha]_D$ +24.8° (1.4, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^1H NMR δ 0.87 (s, 3 H, CH_3), 2.95–3.2 (m, 2 H, C_4 and C_5H), 3.57 (t, 1 H, C_1H, J = 8.0 Hz); MS (70 eV), m/e 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.45; H, 9.65.

(3a,*R*,4*R*,5*S*,7a*S*)-4,5-Epoxyoctahydro-7a-methyl-1*H*-inden-1-one (8). PDC (1.34 g, 3.56 mmol) was added to a stirred solution of **7** (0.15 g, 0.89 mmol) in methylene chloride (30 mL), and stirring was continued at room temperature for 1 h. The mixture was filtered through a silica gel layer (2 cm) and washed with methylene chloride (50 mL). The filtrate was concentrated and chromatographed on a silica gel column with a hexane–ethyl acetate mixture as an eluent, to afford 96 mg of **8** (65%) as a volatile liquid: $[\alpha]_D$ + 42.7° (1.0, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR δ 1.07 (s, 3 H, CH_3), 3.1-3.2 (m, 1 H, C_5H), 3.3 (d, 1 H, C_4H, J = 4.0 Hz); MS (70 eV), m/e 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.52.

(3a*R*,4*R*,5*S*,7a*S*)-(*Z*)-4,5-Epoxy-7a-methyl-1-ethylideneoctahydro-1*H*-indene (9). Compound **8** (0.2 g, 1.2 mmol) was added to a stirred mixture of ethyltriphenylphosphonium iodide (2.0 g, 4.8 mmol) and potassium *tert*-butoxide (0.564 g, 5.04 mmol) in THF (10 mL) at room temperature. The mixture was stirred at this temperature for 20 h, and then another portion of ethyltriphenylphosphonium iodide (1.0 g, 2.4 mmol) and of potassium *tert*-butoxide (282 mg, 2.52 mmol) was added, and stirring was continued for 30 h. Acetic acid (0.4 mL) in water (20 mL) was added to the reaction mixture, which was then extracted with hexane (2 × 10 mL). After drying with $MgSO_4$ and concentration, the residue was purified by chromatography on a silica gel column, with a pentane–ethyl ether mixture as an eluent. Compound **9** was obtained (196 mg, 92%) as a volatile liquid: $[\alpha]_D$ −58.2° (0.7, $CHCl_3$); IR (neat) vw 1680 cm^{-1}; ^1H NMR δ 1.06 (s, 3 H, CH_3), 1.63 (d, 3 H, CH_3, J = 6 Hz), 2.97–3.38 (m, 2 H, C_4 and C_5H), 5.10 (qt, 1 H, CH=, J = 8 and 2 Hz); MS (70 eV), m/e 178. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.80; H, 10.23.

(3a*R*,4*S*,7a*S*)-(*Z*)-1-Ethylideneoctahydro-7a-methyl-1*H*-4-indenol (1). Lithium aluminum hydride (42.6 mg, 1.12 mmol) was added to a solution of **9** (0.1 g, 0.56 mmol) in THF (15 mL), and the mixture was heated at reflux for 45 min. Water-saturated ethyl ether and subsequently aqueous sodium hydroxide (20%) were added until a white precipitate formed. After filtration, the filtrate was evaporated to dryness on a rotary evaporator; the residue was dissolved in hexane; and the solution was filtered through a silica gel layer (1 cm). The product **1** (88.2 mg, 87%) was obtained as an oil: $[\alpha]_D$ −19.7° (1.0, $CHCl_3$); IR (neat) 3430 and vw 1686 cm^{-1} (lit.[4] Raman IR 1688 cm^{-1}); ^1H NMR δ 1.14 (s, 3 H, CH_3), 1.65 (dm, 3 H, CH_3, J = 8.0 Hz), 4.14 (m, 1 H, CHOH), 5.06 (qt, 1 H, CH=, J = 8 and 2 Hz) (Chemical shifts and coupling constants are consistent with the literature[4] values); MS (70 eV), m/e 180; HRMS calcd 180.1520, found 180.1524.

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Registry No. **1**, 93489-58-8; **3**, 17553-86-5; **5**, 113726-26-4; **6**, 115340-15-3; **7**, 115340-16-4; **8**, 115340-17-5; **9**, 115340-18-6; vitamin D, 1406-16-2.

A Facile Total Synthesis of Estrogens

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Although the total syntheses of estrogens have been relatively well described,[1] there is still a chance of either improving them or devising some better ones. In consequence of the discovery of an efficient chiral synthesis of

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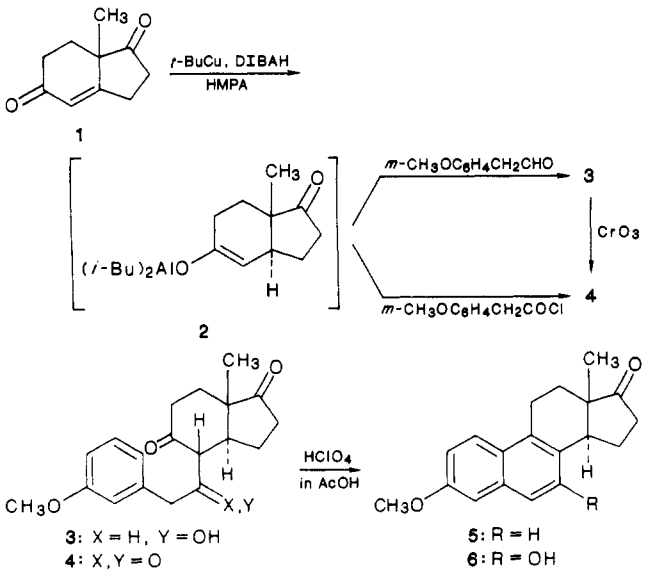
0022-3263/88/1953-5535$01.50/0

Scheme I

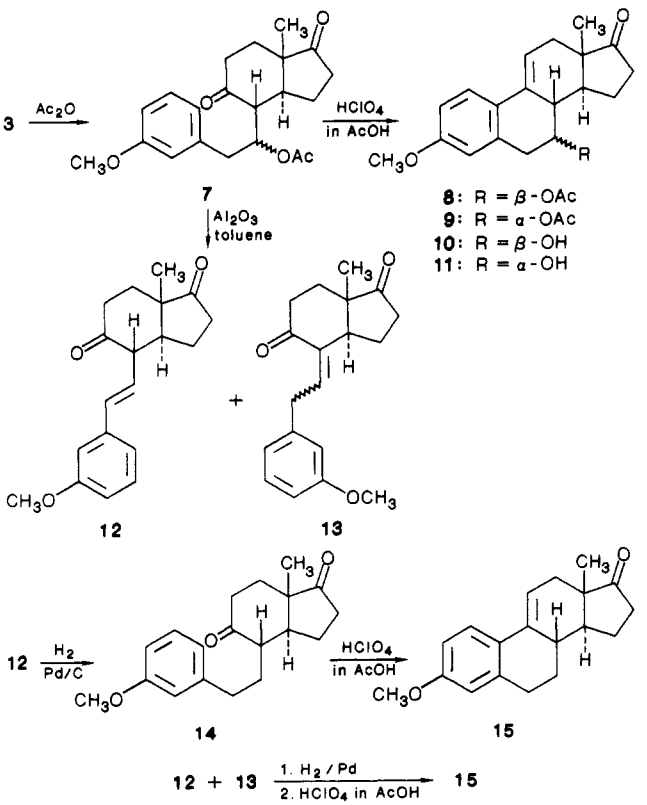


5,6,7,7a-tetrahydro-7a-methyl-1,5-indandione (1) by Eder, Sauer, and Wiechert[2] from Schering A. G., and by Hajos and Parrish[3] from Hoffmann-La Roche Inc., compound 1 has become an attractive substrate for the synthesis of steroids and other natural compounds.

Recently we have reported that compound 1 could be stereoselectively reduced[4] to *trans*-hydrindandione by diisobutylaluminum hydride, as mediated by *tert*-butylcopper, and later we have shown that intermediate diisobutylaluminum enolate **2** can be trapped by an aldehyde.[5] Now we present our recent results on utilization of this reaction for the synthesis of estrogens (Scheme I).

Compounds **3** (an epimeric mixture in a 1:1 ratio at C_7) and **4** were obtained[5] by condensation of enolate **2** with *m*-methoxyphenylacetaldehyde or with *m*-methoxyphenylacetyl chloride in 72% and 20% yield, respectively. The trione **4** was also obtained in a better yield (62%) by oxidation of **3** with CrO_3. These two seco compounds **3** and **4** were cyclized with perchloric acid in acetic acid to yield the methyl ether of equilenin (**5**) and 7-hydroxyequilenin 3-methyl ether (**6**) in 80.7% and 74.1% yield, respectively. The structures of **5** and **6** were consistent with their spectral and analytical data (see Experimental Section). Moreover, the seco compound **3** served as a starting material for the synthesis of 7β- and 7α-hydroxy-9(11)-dehydroestrone 3-methyl ether (**10**, **11**) as well as 9(11)-dehydroestrone 3-methyl ether (**15**), which can be transformed into estrone[6] and other important derivatives (Scheme II). Acetylation of **3** with acetic anhydride in pyridine produced an epimeric mixture of acetates **7** (ratio 1:1), which were cyclized in acetic acid (containing some perchloric acid) to the tetracyclic acetates **8** and **9**. The pure 7β-acetoxy-9(11)-dehydroestrone 3-methyl ether (**8**) (4.83–5.22 ppm, dt, J = 5.5 Hz, J = 10.2 Hz, CHOAc) crystallized from this mixture. Since chromatographic resolution of acetates **8** and **9** is difficult, this mixture was hydrolyzed to hydroxy derivatives **10** and **11**, which were easily separated by column chromatography. The pure 7α-acetoxy-9(11)-dehydroestrone 3-methyl ether

Scheme II



(**9**) (5.35–5.57 ppm, m, CHOAc) was obtained by acetylation of **11**. In order to synthesize estrone, we refluxed an epimeric mixture of acetates **7** in toluene over basic alumina, affording a mixture of **12** and **13** (ratio 5:1) in 85% yield. The trans configuration of the double bond in **12** was confirmed by the coupling constant (16 Hz) between olefinic protons at C_6 and C_7. The pure olefins **13** as well as **12** were equilibrated by refluxing in toluene over basic alumina, yielding in both cases a mixture of **12** and **13** at a 5:1 ratio. The olefin **12** was hydrogenated over Pd/C, affording the 9,10-seco compound **14**, which was cyclized in acetic acid (containing perchloric acid) to known[7] 9-(11)-dehydroestrone 3-methyl ether (**15**) in 86.4% yield. The same overall yield of compound **15** was obtained when we started from a mixture of olefins **12** and **13**, although hydrogenation of **13** should afford the 8α derivative of **14**. This was in agreement with the findings of Eder et al.[8] that acidic cyclization of the 8α derivative of **14** has led to a derivative of 9(11)-dehydroestrone.

Experimental Section

All reactions were monitored by TLC plates developed with a hexane–ethyl acetate mixture. Melting points were measured on a micro hot plate and were not corrected. The IR spectra were taken with a Beckman 4240 spectrophotometer and the NMR spectra with a Bruker WP 100 FY spectrometer in $CDCl_3$ unless otherwise specified. The MS spectra were recorded on a LKB 9000 spectrometer at 70 eV and the UV spectra on a Beckman Acta M VI spectrophotometer. The starting enedione 1 ($[\alpha]^{20}_D$ +360° (*c* 1.0, benzene), 98% ee) was synthesized according to Hajos and Parrish.[3]

3-Methoxy-9,10-secoestra-1,3,5(10)-triene-7,9,17-trione (4). To a stirred solution of compounds **3** as a 1:1 mixture of isomers[5] (204 mg, 0.64 mmol) in acetone (10 mL) was added Jones reagent[9]

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(10 mL) dropwise at room temperature until the compound **3** disappeared. 2-Propanol (0.5 mL) was added, and the liquid part of the reaction mixture was decanted. The acetone solution was neutralized with saturated aqueous potassium bicarbonate, whereupon acetone was evaporated, and the residue was chromatographed on a silica gel column using a hexane–ethyl acetate (2:1) mixture as an eluent, affording compound **4** (172 mg, 86%) mp 88–89 °C (from ether) (lit.[5] mp 88–89 °C; ^{1}H NMR δ 1.01 (s, 3 H, CH_3), 3.69 (d, 1 H, C_8H, J = 13 Hz), 3.8 (s, 5 H, CH_3O and $PhCH_2CO$), 6.6–7.5 (m, 4 H, aromatic H); IR (Nujol) 1745, 1727, 1710 cm^{-1}), being identical with the substance previously described by us.[5]

Equilenin 3-Methyl Ether (5). To a solution of compounds **3** (232 mg, 0.73 mmol) in acetic acid (6 mL) was added perchloric acid (200 μL, 70%), and the reaction mixture was left standing for 4 h at room temperature. Toluene (10 mL) was added, and the reaction mixture was washed with water and saturated aqueous potassium bicarbonate. The toluene solution was dried over $MgSO_4$ and evaporated, and the residue was chromatographed on a silica gel column using a hexane–ethyl acetate solvent system as an eluent, affording **5** (166 mg, 80.7%): mp 186–192 °C (from 2-propanol) (lit.[10a] mp 194–196 °C, lit.[10b] mp 191–193 °C); UV (dioxane) λ_{max} 267.5 (ϵ 4700), 278 (5000), 289 (3400), 323 (2100), 337.5 nm (2750) (lit.[10b] (MeOH) λ_{max} 267.5 (ϵ 5000), 278 (5460), 289 (3800), 322.5 (2100), 337.5 nm (2540)); $[\alpha]^{20}_D$ +73.6° (*c* 1.0, $CHCl_3$) (lit.[10a] $[\alpha]^{20}_D$ +74.0° (*c* 0.7, $CHCl_3$)); ^{1}H NMR δ 0.81 (s, 3 H, CH_3), 1.75–2.9 (m, 6 H), 3.05–3.40 (m, 3 H), 3.92 (s, 3 H, CH_3O), 7.13 (s, 1 H, C_4H), 7.2 (d, 1 H, J = 8.5 Hz), 7.64 (d, 1 H, J = 8.5 Hz), 7.8 (d, 1 H, J = 10 Hz), 7.88 (d, 1 H, J = 10 Hz).

7-Hydroxyequilenin 3-Methyl Ether (6). To a solution of triketone **4** (146 mg, 0.46 mmol) in acetic acid (4.0 mL) was added perchloric acid (70%, 130 μL), and the mixture was left standing for 4 h at room temperature. Toluene (10 mL) was added, and the mixture was washed with water and saturated aqueous potassium bicarbonate. The toluene solution was dried over $MgSO_4$ and evaporated, and the residue was chromatographed on a silica gel column using a hexane–ethyl acetate (3:1) solvent system as an eluent, affording compound **6** (102 mg, 74.1%): mp 220–223 °C (from toluene); $[\alpha]^{20}_D$ +5.6° (*c* 0.55, EtOH), $[\alpha]^{20}_{436}$ +41.3°, $[\alpha]^{20}_{365}$ +123.3°; IR (KBr) 3450, 1720, 1620 cm^{-1}; UV (dioxane) λ_{max} 241 (ϵ 67400), 287 (4300), 297 (4400), 304 (4000), 317 (3600), 332 nm (4800); ^{1}H NMR (CD_3OD) δ 0.88 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3O), 6.85 (s, 1 H), 6.94 (s, 1 H), 7.13 (d, 1 H, J = 9.0 Hz), 7.78 (d, 1 H, J = 9.0 Hz); MS, m/e = 296 (100), 253 (34), 240 (30), 227 (23). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.25; H, 7.00.

7ξ-Acetoxy-3-methoxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (7). A mixture of **3** (600 mg, 1.90 mmol), pyridine (10 mL), and acetic anhydride (3.0 mL) was left standing for 20 h at room temperature. The mixture was neutralized with aqueous potassium bicarbonate, and the product was extracted with toluene (3 × 10 mL). The extract was dried over $MgSO_4$, and after evaporation of solvent under reduced pressure, it was chromatographed on a silica gel column (hexane–ethyl acetate mixture, 3:1), affording compound **7** (640 mg, 94%) as an oil: IR (neat) 1740, 1730, 1713 cm^{-1}; ^{1}H NMR δ 1.05, 1.09 (2 s, 3 H, CH_3), 1.97, 2.01 (2 s, 3 H, CH_3CO), 3.79 (s, 3 H, CH_3O), 5.35–5.73 (m, 1 H, CHOAc), 6.67–6.87 (m, 3 H), 7.08–7.27 (m, 1 H); MS, m/e 358 (4), 298 (40), 173 (63), 83 (100).

7β-Acetoxy-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (8). Cyclization of 7. A mixture of **7** (2.3 g, 6.42 mmol), acetic acid (50 mL), and perchloric acid (70%, 2 mL) was left standing for 4 h at room temperature. Toluene (100 mL) was added, and the mixture was washed with water followed by saturated aqueous potassium bicarbonate. The toluene solution of products **8** and **9** was dried over $MgSO_4$, and after evaporation of solvent, it was chromatographed on a silica gel column using a hexane–ethyl acetate (4:1) solvent system as an eluent, affording a mixture of **8** and **9** (2.05 g, 93.8%). Crystallization of this mixture from ethyl acetate furnished compound **8** (0.8 g, 36.6%): mp 170–194 °C; $[\alpha]^{20}_D$ +285.1° (*c* 1.0, $CHCl_3$); IR (KBr) 1740, 1720 (sh) cm^{-1}; ^{1}H NMR δ 0.96 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3CO), 3.78 (s, 3 H, CH_3O), 4.83–5.22 (dt, 1 H, J = 5.5 Hz, J = 10.2 Hz, CHOAc), 6.12–6.30 (m, 1 H, $C_{11}H$), 6.55 (d, 1 H, J = 2.0 Hz, C_4H), 6.75 (dd, 1 H, J = 2.0 Hz, J = 9.0 Hz, C_2H), 7.45 (d, 1 H, J = 9.0 Hz, C_1H); HRMS calcd for $C_{21}H_{24}O_4$ 340.1675, found 340.1675.

7α-Acetoxy-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (9). A mixture of compound **11** (50 mg, 0.17 mmol), pyridine (3 mL), acetic anhydride (100 μL), and DMAP (10 mg) was refluxed for 30 min. After cooling, water (1.0 mL) and then ether (50 mL) were added. The mixture was washed with hydrochloric acid (5%, 10 mL), followed by aqueous potassium bicarbonate. The ether solution of product **9** was evaporated, and the residue was crystallized from ether, affording compound **9** (48 mg, 82%): mp 165–179 °C; $[\alpha]^{20}_D$ +147.4° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; ^{1}H NMR δ 0.94 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3CO), 3.01–3.17 (m, 2 H), 3.79 (s, 3 H, CH_3O), 5.36–5.47 (m, 1 H, CHOAc), 6.17–6.41 (m, 1 H, $C_{11}H$), 6.56 (d, 1 H, J = 2.0 Hz, C_4H), 6.74 (dd, 1 H, J = 2.0 Hz, J = 9.0 Hz, C_2H), 7.56 (d, 1 H, J = 9.0 Hz, C_1H); HRMS calcd for $C_{21}H_{24}O_4$ 340.1675, found 340.1677.

7β-Hydroxy-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (10) and 7α-Hydroxy-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (11). A mixture (1:1) of acetates **8** and **9** (1.0 g, 2.94 mmol) in methanol (50 mL) and aqueous potassium hydroxide (10 mL, 20%) was refluxed for 15 min. After cooling, the mixture was neutralized with acetic acid, and then water (100 mL) was added. The mixture was extracted with chloroform (3 × 30 mL), and the chloroform extract was, after drying ($MgSO_4$), filtration, and evaporation, chromatographed by using a hexane–ethyl acetate mixture (3:1) as an eluent, affording compound **10** (395 mg) and compound **11** (390 mg). Compound **10**: mp 173–174 °C (from chloroform–ether); $[\alpha]^{20}_D$ +258.6° (*c* 1.0, $CHCl_3$); IR (KBr) 3520, 1730 cm^{-1}; ^{1}H NMR δ 0.96 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3O), 3.80–4.10 (m, 1 H, CHOH), 6.13–6.28 (m, 1 H, $C_{11}H$), 6.61 (d, 1 H, J = 2.0 Hz, C_4H), 6.75 (dd, 1 H, J = 2.0 Hz, J = 9.0 Hz, C_2H), 7.48 (d, 1 H, J = 9.0 Hz, C_1H); UV (dioxane) λ_{max}263 (ϵ 19000), 297 nm (3300); MS, m/e 298 (100), 283 (33), 222 (31), 209 (25). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.36; H, 7.31.

Compound **11**: mp 140–142 °C (from chloroform–ether); $[\alpha]^{20}_D$ +220.6° (*c* 1.0, $CHCl_3$); IR (KBr) 3520, 1720 cm^{-1}; ^{1}H NMR δ 0.94 (s, 3 H, CH_3), 3.03–3.14 (m, 2 H), 3.80 (s, 3 H, CH_3O), 4.15–4.34 (m, 1 H, CHOH), 6.30–6.46 (m, 1 H, $C_{11}H$), 6.63 (d, 1 H, J = 2.0 Hz, C_4H), 6.76 (dd, 1 H, J = 2.0 Hz, J = 9.0 Hz, C_2H), 7.58 (d, 1 H, J = 9.0 Hz, C_1H); UV (dioxane) λ_{max} 264 (ϵ 18500), 297 nm (3100); MS, m/e 298 (100), 283 (12), 265 (53), 222 (16). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.58; H, 7.49.

(*E*)-3-Methoxy-9,10-secoestra-1,3,5(10),6-tetraene-9,17-dione (12) and 3-Methoxy-9,10-secoestra-1,3,5(10),7(8)-tetraene-9,17-dione (13). A mixture of acetates **7** (400 mg, 1.12 mmol) with basic alumina (4.0 g) in toluene (20 mL) was refluxed with stirring for 20 min. After cooling and filtration, the solvent was evaporated and the residue was chromatographed on a silica gel column using hexane–ethyl acetate (3:1) as an eluent, affording compound **12** (236 mg, 70.9%) and compound **13** (47.16 mg, 14.1%) as oils. Compound **12**: $[\alpha]^{20}_D$ +92.1° (*c* 0.9, $CHCl_3$); IR (neat) 1745, 1715 cm^{-1}; ^{1}H NMR δ 1.23 (s, 3 H, CH_3), 3.12–3.31 (dd, 1 H, J = 7.8 Hz, J = 12.5 Hz, C_8H), 3.82 (s, 3 H, CH_3O), 6.03–6.28 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz, C_7H), 6.40 (d, 1 H, J = 16.0 Hz, C_6H), 6.72–7.42 (m, 4 H, aromatic H); UV (EtOH) λ_{max} 254 (ϵ 10000), 293 nm (2500); MS, m/e 298 (11), 173 (15), 152 (23), 135 (38), 119 (99), 117 (100). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.36; H, 7.31.

Compound **13**: $[\alpha]^{20}_D$ +73.0° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 1735, 1705 cm^{-1}; ^{1}H NMR δ 0.91 (s, 3 H, CH_3), 3.72 (s, 3 H, CH_3O), 5.46–5.83 (m, 1 H, C_7H), 6.48–7.38 (m, 4 H, aromatic H); UV (dioxane) λ_{max} 242 (ϵ 6800), 274 (3500), 281 nm (3200); MS, m/e 298 (73), 173 (100), 159 (28), 121 (40).

3-Methoxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (14). Hydrogenation of **12** (100 mg, 0.33 mmol) was carried out in methanol (10 mL) over 19% Pd/C (20 mg) for 1 h at room temperature, at atmospheric pressure. Removal of the catalyst by filtration and evaporation of methanol afforded compound **14** (98.7 mg, 98%) as an oil: $[\alpha]^{20}_D$ +79.8° (*c* 1.0, $CHCl_3$); IR (neat) 1745, 1715 cm^{-1}; ^{1}H NMR δ 1.14 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3O), 6.65–6.85 (m, 3 H, aromatic H), 7.08–7.25 (m, 1 H, aromatic H);

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MS, *m/e* 300 (11), 134 (100), 121 (15).

3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one (15). A mixture of compound **14** (80 mg, 0.27 mmol), acetic acid (3.0 mL), and perchloric acid 70% (80 μL) was left standing at room temperature for 4 h. Water (15 mL) was added, and the mixture was extracted with ether (3 × 10 mL). The extract was washed with saturated aqueous potassium bicarbonate and dried ($MgSO_4$); after filtration followed by evaporation of solvent, it was chromatographed on a silica gel column using a hexane–ethyl acetate (5:1) mixture as an eluent, affording compound **15** (65 mg, 86%): mp 144–147 °C; $[\alpha]^{20}_D$ +287° (*c* 0.5, $CHCl_3$); IR (KBr) 1737 cm^{-1}; ^1H NMR δ 0.94 (s, 3 H, CH_3), 2.80–3.0 (m, 2 H), 6.07–6.22 (m, 1 H, $C_{11}H$), 6.63 (d, 1 H, *J* = 2.8 Hz, C_4H), 6.74 (dd, 1 H, *J* = 8.8 Hz, *J* = 2.8 Hz, C_2H), 7.53 (d, 1 H, *J* = 8.8 Hz, C_1H); UV (EtOH) λ_{max} 264 (ε 18 300), 298 (3200), 310 nm (2300); MS, *m/e* 282. Literature:[7] mp 142.5–144 °C; $[\alpha]_D$ +290.92° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR δ 0.92 (s, 3 H, CH_3), 3.76 (s, 3 H, CH_3O), 6.13 (m, 1 H, $C_{11}H$), 6.68 (m, 2 H, aromatic H), 7.52 (d, 1 H, aromatic H); UV (95% EtOH) λ_{max} 263 (ε 19 300), 297 (3400), 310 nm (2220).

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Registry No. **1**, 17553-86-5; **3** (isomer 1), 113726-22-0; **3** (isomer 2), 113726-23-1; **4**, 113726-27-5; **5**, 3907-67-3; **6**, 116503-14-1; **7** (isomer 1), 116503-15-2; **7** (isomer 2), 116503-16-3; **8**, 116503-17-4; **9**, 116503-18-5; **10**, 116503-19-6; **11**, 116503-20-9; **12**, 116503-21-0; **13**, 116503-22-1; **14**, 968-98-9; **15**, 1670-49-1; *m*-$CH_3OC_6H_4CH_2CHO$, 65292-99-1; *m*-$CH_3OC_6H_4CH_2COCl$, 6834-42-0.

Synthesis and Reactions of Cyanovinyl-Substituted Benzenediazonium Salts for Nonlinear Optics

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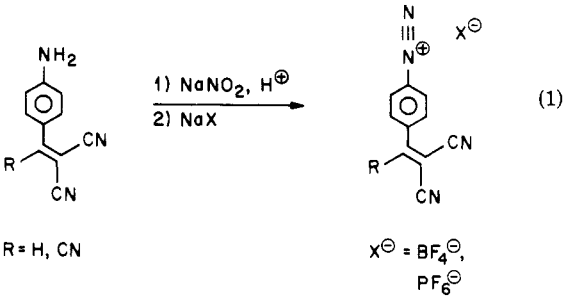
A renewed interest in azo dyes has been sparked by recent efforts to find organic second-order nonlinear optical (NLO) materials suitable for applications such as harmonic generation and optical switching.[1,2] The active components in these materials typically consist of conjugated electron systems connecting terminal electron donor and electron acceptor moieties. By incorporating different end groups and changing the effective length and type of conjugating group, the nonlinear optical activity (molecular susceptibility) of a particular system can be adjusted with some degree of predictability.[3] Azo dyes are of particular interest because they can be fairly readily prepared with a wide range of donor and acceptor groups, and the π system provides excellent conjugation[4] that is necessary for high molecular susceptibilities.[1,2]

We have determined the hyperpolarizabilities of a number of azo dyes, including some with better electron acceptor groups than the nitro group (e.g., di- and tricyanovinyl).[3] These strong electron withdrawing groups conjugated to an amino donor via a diphenylazo linkage provide compounds with some of the largest molecular susceptibilities reported to date. Because the typical synthesis of these compounds may require several steps, which involve severe reaction conditions,[5-7] we have investigated new synthetic methods that will simplify the preparation of such azo dyes and allow the preparation of materials that are otherwise inaccessible (e.g. polymeric dyes). We have isolated benzenediazonium salts derived from (dicyanovinyl)- and (tricyanovinyl)anilines and successfully coupled them to N,N-disubstituted anilines to give azo dyes of interest for NLO studies.

Results

Diazotization Reactions. The benzenediazonium salts are isolated by following the general procedure described by Roe[8] for simple benzene derivatives. This involves diazotization of the aniline in HCl/H_2O with sodium nitrite followed by precipitation of the fluoroborate salt by addition of sodium tetrafluoroborate (eq 1). Due to the low



(1)

solubility of di- and (tricyanovinyl)aniline in $HCl/H_2O/NaNO_2$, we find that HCl/HOAc is a better reaction medium for (tricyanovinyl)aniline. The dicyanovinyl derivative requires H_2SO_4/HOAc for complete dissolution. While the diazonium salts can be formed and isolated in HCl/H_2O, the yield and activity of the salt is greatly improved if the aniline is completely dissolved after addition of the nitrite. It is also important to control the rate of nitrite addition in order to maintain the solution temperature below ~10 °C to minimize side reactions. During the formation of the (dicyanovinyl)benzenediazonium salts, a second product is formed if reaction conditions are not carefully controlled. We have isolated a red solid whose spectral characteristics (NMR, MS) are consistent with [[(dicyanovinyl)phenyl]azo]malononitrile. We believe this side product may be formed by electrophilic attack of the diazonium ion on the dicyanovinyl group of the starting aniline, followed by hydrolytic loss of the aniline moiety.

Via a similar procedure, we have also prepared hexafluorophosphate salts. In a comparison of tetrafluoroborate versus hexafluorophosphate as the counter ion, we find the PF_6^- diazonium salts to be less soluble in the reaction mixture than the corresponding BF_4^- salts, making their isolation easier. Therefore we have usually isolated the PF_6^- salts, keeping the amount of solvent to a minimum. The salts are not purified after isolation since recrystallization is difficult due to low decomposition temperatures and because of the similar solubilities of the salts and other components. However, the activity of the

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