An Efficient Synthetic Route to a Lactone Model for the Gibberellin A Ring[1]

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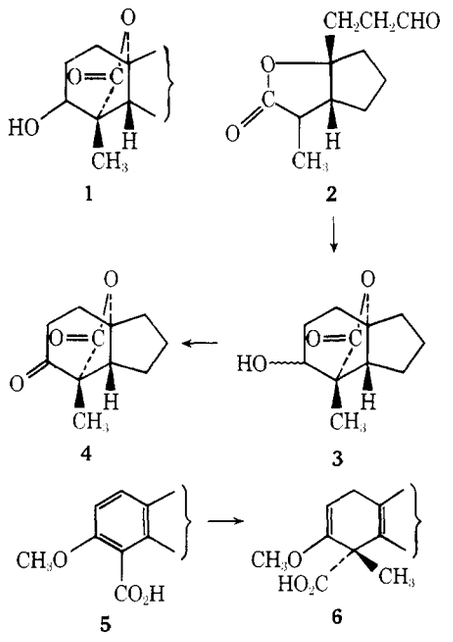
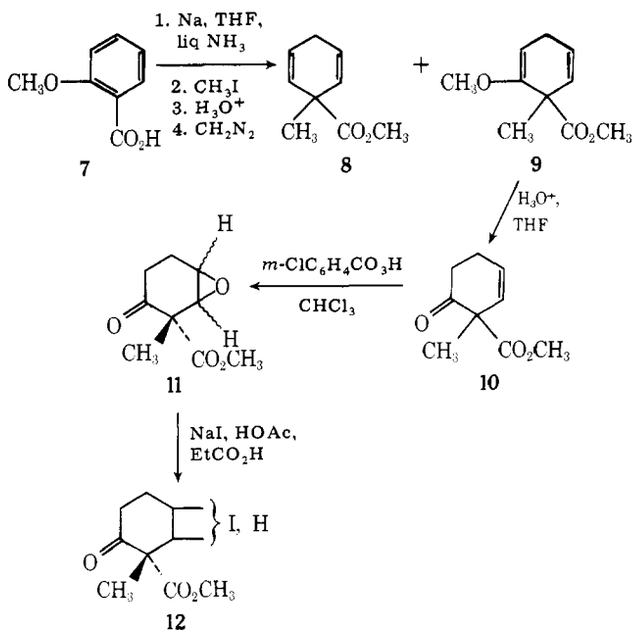
Several reaction sequences have been explored[2] as synthetic routes to the lactone system 1 (Scheme I) present in the A ring of the natural gibberellins. Certain of the synthetic routes were directed toward gibberellins (e.g., gibberellins A_1, A_2, A_4, and A_9) with a saturated A ring (cf. structure 1), while other syntheses offered the possibility of producing gibberellins (e.g., gibberellic acid and gibberellin A_7) in which the A ring contained an additional carbon–carbon double bond. These routes include the acid-catalyzed cyclization of appropriate cyclohexenecarboxylic acid derivatives,[2a–d] the reaction of the unsaturated acids with a peracid,[2e,f] the iodolactonization of the unsaturated acids,[2c,f] and an aldol condensation of the aldehyde lactone 2 to the hydroxy lactones 3, followed by oxidation to the keto lactone 4.[2g] We were particularly interested in developing a route to the lactone system 1 from the cyclohexadiene intermediate 6 because of our finding[3] that this cyclohexadiene system 6 with the correct stereochemistry could be formed by application of the Lowenthal reduction–methylation procedure[2c] to an aromatic acid 5 with an appropriately located carboxyl function in ring B.

We initially examined the possible formation of a lactone from the keto ester 10, derived from the aromatic acid 7 via the cyclohexadiene derivative 9 (Scheme II). Treatment of the keto ester 10 with aqueous mineral acid resulted either in no reaction or in hydrolysis of the ester and subsequent decarboxylation with no evidence for lactone formation. Reaction with *m*-chloroperbenzoic acid converted the keto ester 10 to a separable mixture of comparable amounts of the two stereoisomeric epoxides 11. Each of the epoxides 11 reacted with iodide ion in acidic solution to form a single iodohydrin 12 of uncertain structure. However, we were unsuccessful in finding conditions that would convert either epoxide 11 or iodohydrin 12 to a lactone. Consequently, we turned our attention to halolactonization reactions with unsaturated acids.

Scheme I



Scheme II

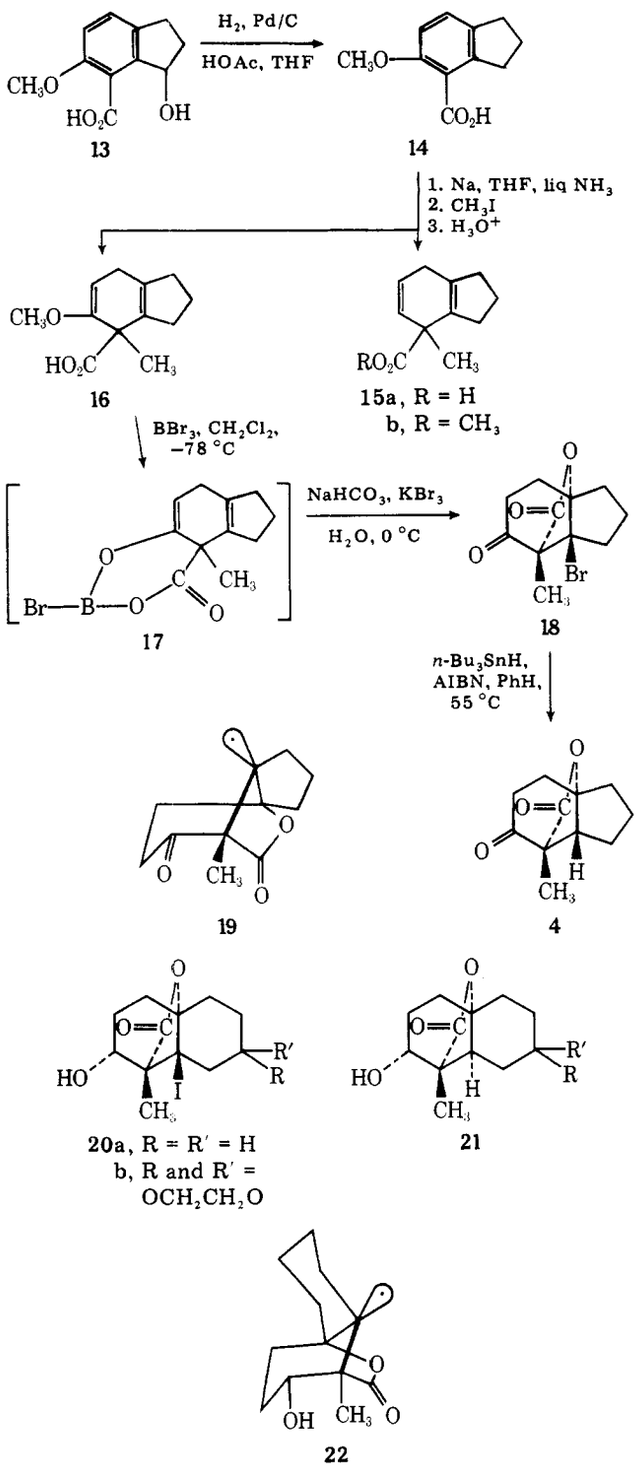


For this study, we employed the unsaturated acid 16 that was prepared from the aromatic acid 14, as indicated in Scheme III. As noted previously,[3] the yield of the demethoxylated by-product 15 was increased when the reduction–methylation sequence was performed with Li rather than Na as the reducing agent. Our attempts to hydrolyze the enol ether acid 16 to the corresponding β-keto acid with aqueous acid were complicated by the fact that the temperature required to hydrolyze the enol ether function in 16 was sufficient to cause decarboxylation of the β-keto acid product. This problem was overcome by reaction of the enol ether 16 with 2–3 molar equiv of BBr_3 in CH_2Cl_2 at −78 °C. The initial product (presumably an enol borate such as 17) was stable under these conditions and could be dissolved in cold aqueous $NaHCO_3$ and KBr_3 to form the salt of the β-keto acid and effect its bromolactonization to the keto lactone 18. Reduction of this bromo keto lactone 18 with *n*-Bu_3SnH yielded the same keto lactone 4 that had been prepared previously.[2g,4]

The reduction of the bromide 18 to form a single stereoisomer of the lactone 4 would at first appear surprising, since a free-radical intermediate (e.g., 19) is involved in this reduction.[5] However, examination of molecular models revealed that the indicated conformation 19 of the free-radical intermediate (the precursor for lactone 4) with the two five-membered rings cis fused is clearly more stable than the alternative conformation with the five-membered rings trans fused. By contrast, in an earlier study[2c] of reduction of the iodolactones 20 by methods [Cr(II) + EtSH, *n*-Bu_3SnH] involving a free-radical intermediate (e.g., 22) either a mixture of stereoisomeric lactones (21 and its epimer) or the lactone 21 with the undesired cis fusion of the two carbocyclic rings was obtained. Examination of molecular models of the radical intermediate in this case (which does not involve two fused five-membered rings) revealed little difference between conformer 22 (the precursor of lactone 21) and the related conformer that would yield a trans-fused decalin system.

As a result of these studies and the related study of the reduction–methylation stereochemistry,[3] we believe that sequence reduction–methylation (e.g., 14 → 16), cleavage and bromolactonization (16 → 17 → 18), and *n*-Bu_3SnH reduction (18 → 4) offers a viable synthetic pathway from a precursor with an aromatic A ring to a product with the functionality and stereochemistry present in the A ring of certain of the natural gibberellins.

Scheme III



13 14 16 15a, R = H b, R = CH_3 17 18 19 4

20a, R = R′ = H
b, R and R′ = OCH_2CH_2O

21 22

Experimental Section[6]

Preparation of the Keto Ester 10. Following a previously described[3] procedure, a solution of 30.9 g (0.204 mol) of acid **7** in 125 mL of THF was added to 900 mL of cold (ca. −78 °C) liquid NH_3. The resulting suspension was allowed to warm to −33 °C and 14.7 g (0.64 g-atom) of Na was added, portionwise and with stirring. While the resulting blue solution was maintained at −33 °C, 92 g (0.64 mol) of MeI was added, dropwise with stirring and cooling, causing the reaction solution to change from blue to red to colorless. After the NH_3 had been allowed to evaporate, the residue was diluted with 200 mL of H_2O, concentrated under reduced pressure, treated with 250 mL of CH_2Cl_2, and acidified by addition, with cooling and stirring, of cold aqueous 1 M HCl. The combined CH_2Cl_2 layer and the CH_2Cl_2 extract of the aqueous phase were washed with aqueous NaCl, dried, concentrated, and esterified with excess ethereal diazomethane. After the resulting product had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was dried, concentrated, and distilled through a 25-cm Vigreux column. After separation of the lowest boiling fraction containing (GLC, LAC-728 on Chromosorb P) 7.14 g (23%) of the crude ester **8** (retention time 5.8 min), bp 80–86 °C (13 mm), n^{25}_D 1.4715 [lit.[3] bp 85–86 °C (18 mm), n^{25}_D 1.4732], the next fraction, 4.17 g of colorless liquid, bp 86–110 °C (13 mm), n^{25}_D 1.4750, contained (GLC) a mixture of esters **8** (5.8 min) and **9** (16.2 min). Subsequent fractions contained (GLC) 15.1 g (41%) of practically pure ester **9**, bp 95–113 °C (5–13 mm), n^{25}_D 1.4833–1.4852 [lit.[3] bp 113–116 °C (16 mm), n^{25}_D 1.4829].

A cold (0 °C) solution of 5.29 g (29.0 mmol) of the ester **9** in 30 mL of THF was treated with 4 mL (48 mmol) of aqueous 12 M HCl, and the mixture was stirred for 1 h while it was allowed to warm to 25 °C. After the mixture had been diluted with H_2O and concentrated under reduced pressure, it was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with aqueous NaCl, dried, and concentrated to leave 4.95 g of the crude keto ester **10** as a pale yellow liquid. Chromatography on silica gel with anEt_2O–hexane eluent (1:9 v/v) afforded 3.89 g (80%) of the keto ester **10** as a colorless liquid, n^{25}_D 1.4707, that exhibited a single peak (retention time 15.5 min) on GLC analysis (LAC-728 on Chromosorb P). A collected (GLC) sample of the keto ester **10**, n^{25}_D 1.4724, was used for characterization: IR (CCl_4), 1745 (ester C=O), 1720 (C=O), 1655 cm^{-1} (weak, C=C); UV (95% EtOH), end absorption (ϵ 1100 at 210 nm) with a maximum at 287 nm (ϵ 34); NMR (CCl_4), δ 5.5–6.1 (2 H, m, vinyl CH), 3.67 (3 H, s, OCH_3), 2.2–2.9 (4 H, m, allylic CH_2 and CH_2CO), 1.32 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 168 (M^+ 39), 140 (36), 126 (100), 125 (40), 112 (34), 111 (60), 109 (71), 108 (27), 96 (44), 95 (53), 81 (65), 79 (33), 67 (56), 53 (39), 43 (23), 41 (61), 39 (54).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.30; H, 7.20.

Preparation of the Epoxides 11 and the Iodohydrins 12. A solution of 2.84 g (16.9 mmol) of the keto ester **10** and 3.70 g of a reagent containing 18.2 mmol of *m*-chloroperbenzoic acid in 50 mL of $CHCl_3$ (EtOH free) was refluxed for 5 h and then allowed to stand for 9 h at 25 °C. After the mixture had been partitioned between CH_2Cl_2 and aqueous Na_2SO_3, the organic layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl, and then dried and concentrated. The residual yellow liquid (4.0 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:3 v/v). The early chromatography fractions contained 1.708 g (55%) of the epoxide **11** (isomer A) as a colorless liquid, n^{25}_D 1.4710. Short-path distillation (0.3 mm with an 85 °C bath) afforded the pure epoxide **11** (isomer A): n^{25}_D 1.4703; IR (CCl_4), 1760 (ester C=O), 1720 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 283 nm (ϵ 36); NMR (CCl_4), δ 3.73 (3 H, s, OCH_3), 3.1–3.5 (2 H, m, epoxide CHO), 2.0–2.6 (4 H, m, CH_2), 1.42 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 184 (m^+, 1), 128 (32), 125 (32), 124 (28), 97 (84), 84 (30), 82 (30), 69 (71), 68 (30), 59 (46), 56 (50), 55 (65), 43 (33), 41 (100), 39 (79).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.70; H, 6.59.

The later chromatography fractions contained 930 mg (30%) of the epoxide **11** (isomer B) as a colorless liquid, n^{25}_D 1.4751. Short-path distillation (0.3 mm with an 85 °C bath) afforded the pure epoxide **11** (isomer B): n^{25}_D 1.4752; IR (CCl_4), 1745 (ester C=O), 1720 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 285 nm (ϵ 25); NMR (CCl_4), δ 3.75 (3 H, s, OCH_3), 3.0–3.5 (2 H, m, epoxide CHO), 1.9–2.8 (4 H, m, CH_2), 1.38 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 184 (M^+, 1), 128 (25), 125 (28), 124 (23), 110 (28), 101 (29), 97 (78), 85 (32), 69 (55), 68 (25), 59 (41), 58 (24), 56 (43), 55 (54), 43 (32), 41 (100), 39 (61).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.84; H, 6.61.

Following a general procedure described previously,[7] a solution of 216 mg (1.17 mmol) of the epoxide **11** (isomer A), 445 mg (2.97 mmol) of NaI, 123 mg (1.5 mmol) of NaOAc, and 1.0 mL of HOAc in 2.0 mL of propionic acid was stirred at 25 °C for 2.5 h. After the mixture had been partitioned between Et_2O and an aqueous solution of $NaCHO_3$ and $NaHSO_3$, the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual liquid (331 mg) crystallized from a CCl_4–hexane mixture as 279 mg of colorless solid, mp 93–94 °C. Recrystallization separated 233 mg (65%) of the iodohydrin **12** (isomer A) as colorless prisms, mp 96–97 °C. Further recrystallization gave the iodohydrin **12** (isomer A): mp 97–99 °C; IR ($CHCl_3$), 3570, 3410 (OH), 1740 (ester C=O), 1712 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 260 nm (ϵ 620); NMR ($CDCl_3$), δ 4.2–4.7 (2 H, m, CHO, CHI), 3.78 (3 H, s, OCH_3), 2.9–3.1 (1 H, m, OH, exchanged with D_2O), 1.9–2.9 (4 H, m, CH_2), 1.43 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 312 (M^+, <1), 185 (41), 153 (36), 125 (30), 107 (45), 97 (32), 83 (55), 79 (40), 71 (32), 69 (32), 59 (45), 56 (28), 55 (99), 54 (25), 42 (30), 41 (100), 39 (64).

Anal. Calcd for $C_9H_{13}IO_4$: C, 34.64; H, 4.20; I, 40.66. Found: C, 34.58; H, 4.26; I, 40.71.

The same procedure was employed with 142 mg (0.77 mmol) of the epoxide **11** (isomer B), 239 mg (1.59 mmol) of NaI, 48 mg (0.59 mmol) of NaOAc, 0.6 mL of HOAc, and 1.0 mL of propionic acid with a reaction time of 3 h at 25 °C. The crude neutral product (199 mg of colorless solid, mp 79–95 °C) was triturated with pentane and recrystallized from a PhH–hexane mixture to separate 121 mg (50%) of the iodohydrin **12** (isomer B) as colorless prisms: mp 106–107 °C; IR ($CHCl_3$), 3500 (br, OH), 1735 (sh, ester C=O), 1718 (shoulder), 1708 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 261 nm (ϵ 640); NMR ($CDCl_3$), δ 4.4–4.9 (1 H, m, CHO or CHI), 3.75 (3 H, s, OCH_3), 3.59 (1 H, OH, exchanged with D_2O), 3.47 (1 H, d, J = 11 Hz, CHO or CH-I), 2.1–2.9 (4 H, m, CH_2), 1.53 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 294 (4), 185 (44), 153 (31), 147 (28), 127 (28), 125 (30), 97 (29), 85 (62), 83 (60), 71 (30), 69 (30), 59 (45), 56 (29), 55 (94), 43 (68), 41 (100), 39 (60).

Anal. Calcd for $C_9H_{13}IO_4$: C, 34.64; H, 4.20; I, 40.66. Found: C, 34.69; H, 4.24; I, 40.69.

Preparation of the Acid 14. Several modifications in the previously described[8] procedure for the hydroxy acid **13** were found desirable. Thus, reduction of 6-methoxyindan-1-one (23.7 g or 146 mmol) with $LiAlH_4$ (2.6 g or 68 mmol) in 250 mL of THF gave 22.8 g (95%) of 6-methoxyindan-1-ol, mp 45.5–46 °C (lit.[8] mp 46–47.5 °C). Reaction of a suspension of 12.3 g (75 mmol) of this alcohol with 194 mmol of *n*-BuLi in 460 mL of hexane at 25 °C for 12 h yielded a red solution of the lithium reagent. This solution was cooled to −78 °C and stirred under an atmosphere of CO_2 for 45 min. The usual isolation procedure[8] yielded 14.7 g (94%) of the hydroxy acid **13**, mp 155–157 °C dec (lit.[8] mp 150–151 to 160–161 °C dec).

A suspension of 3.82 g (18.4 mmol) of the acid **13** in 40 mL of THF and 10 mL of HOAc containing 0.4 mL of aqueous 70% $HClO_4$ was hydrogenated at 25 °C and 1 atm over 300 mg of 5% Pd/C catalyst. After 2 h the H_2 uptake (21.4 mmol) was complete and the reaction mixture was filtered and concentrated. A solution of the residual material in CH_2Cl_2 was washed with H_2O, dried, and concentrated to leave 3.40 g of the solid acid **14**, mp 135–138 °C. Recrystallization from a hexane–CH_2Cl_2 mixture afforded 3.14 g (89%) of crops of the acid **14** as colorless prisms, melting within the range 135–139 °C. Another recrystallization gave the pure acid **14**: mp 138–139 °C; IR ($CHCl_3$), 3250 (carboxyl OH), 1735 (shoulder), and 1725 cm^{-1} (carboxyl C=O); UV λ_{max} (95% EtOH), 294 nm (ϵ 2700) with intense end absorption (ϵ 18 000 at 210 nm); NMR ($CDCl_3$), δ 7.31 (1 H, d, J = 8.5 Hz, aryl CH), 6.82 (1 H, d, J = 8.5 Hz, aryl CH), 3.96 (3 H, s, OCH_3), 3.31 (2 H, t, J = 7.5 Hz, benzylic CH_2), 2.86 (2 H, t, J = 7.5 Hz, benzylic CH_2), 1.7–2.4 (2 H, m, CH_2); mass spectrum, *m/e* (rel intensity), 192 (M^+, 62), 174 (100), 159 (25), 117 (30), 116 (73), 115 (53), 103 (30), 77 (35), 51 (25).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.87; H, 6.30.

Preparation of the Acid 16. A solution of 1.51 g (7.87 mmol) of the acid **14** in 10 mL of THF was added, dropwise and with stirring, to a refluxing solution of 530 mg (23 mg-atom) of Na in 250 mL of liquid NH_3. After the resulting blue solution had been stirred at −33 °C for 15 min, it was cooled in a dry ice–acetone bath and treated with 4.5 g (32 mmol) of CH_3I. The NH_3 was allowed to evaporate from the resulting colorless solution and the residue was acidified with dilute aqueous HCl, the aqueous phase was saturated with NaCl, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and concentrated to leave 1.54 g of pale yellow solid that contained (NMR analysis) ca. 75% of the acid **16** and ca. 25% of the acid **15a**. Recrystallization from an EtOAc–hexane mixture separated 748 mg (46%) of the acid **16**, mp 125–128 °C dec. An additional recrystallization gave the pure acid **16** as colorless plates: mp 126–129 °C dec; IR ($CHCl_3$), 2800–3200 (associated OH), 1708, 1695 (carboxyl C=O), 1658 cm^{-1} (C=C); UV (95% EtOH), end absorption with ϵ 3700 at 210 nm; NMR ($CDCl_3$), δ 11.5 (1 H, s, OH), 4.83 (1 H, t, J = 3.5 Hz, vinyl CH), 3.57 (3 H, s, OCH_3), 1.6–2.9 (8 H, m, CH_2), 1.41 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 164 (48), 149 (21), 91 (22), 44 (100).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.24; H, 7.76.

In a similar experiment a solution of 841 mg (4.38 mmol) of the acid **14** in 20 mL of THF was added to a cold (−33 °C) solution of 113 mg (19 mg-atom) of Li in 100 mL of NH_3. After the resulting mixture had been stirred at −33 °C for 15 min, it was cooled in a dry ice bath and 9.1 g (64 mmol) of MeI was added. The mixture was allowed to warm to −33 °C with stirring, the NH_3 was allowed to evaporate, and the previously described isolation procedure was followed to separate 800 mg of crude acidic product containing (NMR analysis) ca. 45% of the acid **16** and ca. 55% of the acid **15a**. A solution of this mixture in 10 mL of THF and 2 mL of aqueous 6 M HCl was stirred at 25 °C for 30 min to hydrolyze the enol ether **16** and decarboxylate the corresponding keto acid. The resulting mixture was partitioned between aqueous $NaHCO_3$ and Et_2O, and the resulting aqueous phase was acidified (HCl) and extracted with Et_2O. After this extract had been dried and concentrated, the crude residual acid **15a** (418 mg) was esterified with excess ethereal CH_2N_2. The resulting Et_2O solution was washed with aqueous $NaHCO_3$, dried, and concentrated to leave 398 mg of a pale yellow liquid containing (GLC, silicone DC-710 on Chromosorb P) the ester **15b** (retention time 7.0 min) and several minor unidentified impurities (3.0, 8.4 min). A collected (GLC) sample of the ester **15b** was obtained as a colorless liquid: $n^{25}D$ 1.5000; IR (CCl_4), 1735 (C=O), 1645 cm^{-1} (C=C); UV (95% EtOH), end absorption (ϵ 2400 at 210 nm) with inflections at 235 (ϵ 1100) and 270 nm (ϵ 295); NMR (CCl_4), δ 5.4–5.9 (2 H, m, vinyl CH), 3.61 (3 H, s, OCH_3), 1.7–2.9 (8 H, m, aliphatic CH), 1.28 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 192 (M^+, 10), 134 (23), 133 (100), 117 (34), 115 (19), 105 (70), 91 (21).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.00; H, 8.40.

Preparation of the Lactone 4. To a cold (−78 °C) suspension of 528 mg (2.54 mmol) of the acid **16** in 6 mL of CH_2Cl_2 was added, dropwise and with stirring, 1.4 mL of a CH_2Cl_2 solution containing 2.8 mmol of BBr_3. The resulting mixture, which rapidly changed to a clear yellow solution, was stirred at −78 °C for about 1 min and then added to a cold (0 °C) mixture of 7 mL of saturated aqueous $NaCHO_3$ and 7 mL of aqueous 0.8 M KBr_3 (KBr + Br_2). After the resulting two-phase mixture had been stirred at 0 °C for 10 min, sufficient $Na_2S_2O_3$ was added to consume the excess Br_2, and the mixture was partitioned between Et_2O and aqueous $NaHCO_3$. After the ethereal solution had been dried and concentrated, the crude bromo lactone **18** remained as 675 mg of colorless liquid which contained (TLC, silica gel coating with an EtOAc–hexane eluent, 1:4 v/v) the bromo lactone **18** (R_f 0.38) and a minor unidentified impurity (R_f 0.30). The crude bromo lactone **18** from a comparable experiment was partially purified by preparative TLC to obtain the bromo lactone as a colorless semisolid: IR ($CHCl_3$), 1785 (γ-lactone C=O), 1725 cm^{-1} (C=O); NMR ($CDCl_3$), δ 1.8–3.0 (10 H, m, aliphatic CH), 1.35 (3H, s, CH_3). Since samples of the crude bromo lactone **18** rapidly turned blue on standing, our efforts to effect further purification were unsuccessful.

A solution of the crude bromo lactone **18** (675 mg), 1.33 g (4.5 mmol) of *n*-Bu_3SnH, and 5 mg of azobis(isobutyronitrile) in 2 mL of PhH was heated to 55 °C with stirring under an N_2 atmosphere for 1 h and then stirred for an additional 1 h at 25 °C. The crude product contained (TLC) the lactone **4** (R_f 0.19) and several minor components with higher R_f values, but none of the starting bromo lactone **18** was detected. The reaction mixture was concentrated and then chromatographed on silica gel with an EtOAc–hexane eluent (1:4 v/v). The crude lactone **4** obtained (364 mg, contaminated with tin compounds) was chromatographed a second time to separate 322 mg (65% based on the acid **16**) of the lactone **4** as a colorless liquid that solidified on standing, mp 48–50 °C. Recrystallization from Et_2O–pentane afforded 282 mg (57% based on acid **16**) of the pure lactone **4** as colorless prisms: mp 51–52 °C (lit.[2g] mp 45–47 °C); IR (CCl_4), 1786 (γ-lactone C=O), 1725 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 299 nm (ϵ 53); NMR ($CDCl_3$), δ 1.6–3.0 (11 H, m, aliphatic CH), 1.25 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 194 (M^+, 26), 151 (23), 111 (100), 108 (20), 95 (20), 55 (22), 41 (20). Our sample was identified with the previously described product[4] by comparison of IR and NMR spectra.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.09; H, 7.30.

Registry No.—**4**, 10258-34-1; **8**, 59034-54-7; **9**, 21173-69-3; **10**, 63548-79-8; **11**, 63548-80-1; **12**, 63548-85-6; **13**, 33521-61-8; **14**, 60346-39-6; **15a**, 63548-81-2; **15b**, 63548-82-3; **16**, 63548-83-4; **18**, 63548-84-5; 6-methoxyindan-1-one, 13623-25-1; 6-methoxyindan-1-ol, 3469-09-8.

References and Notes

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(4) We are grateful to Professor L. J. Dolby for providing us with the IR and NMR spectra of his product.
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(6) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
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Photocyclization of 2-Methoxy-4,5-dimethylstilbene

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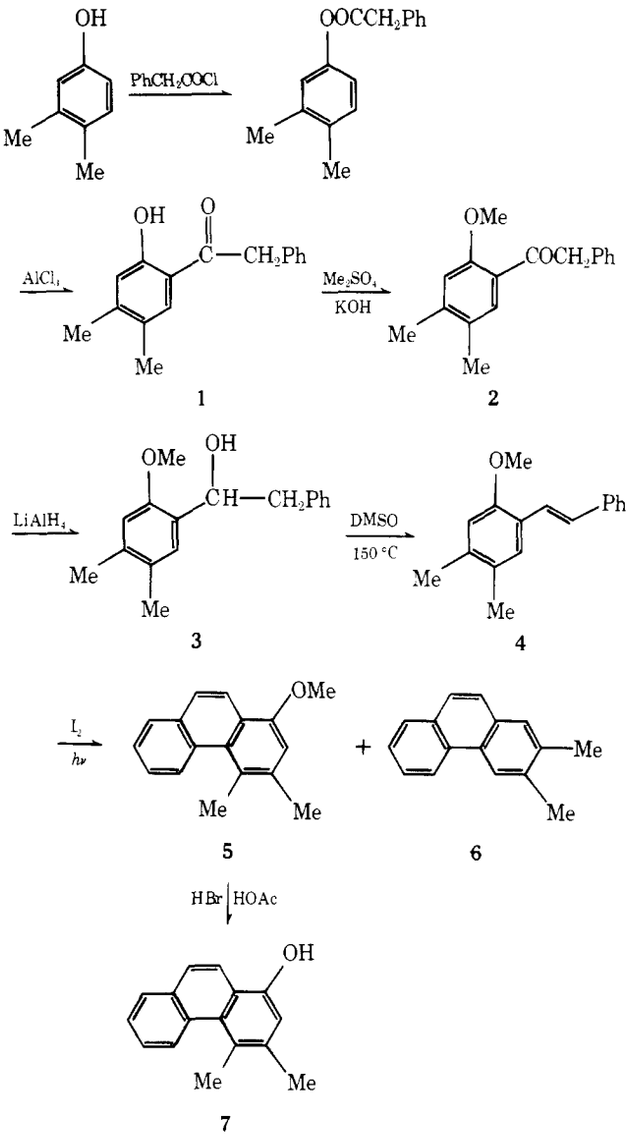
Synthesis of small quantities of substituted phenanthrenes by photocyclization of stilbenes in the presence of an oxidant is the method of choice.[1] Since the procedure does not lead to rearrangement of the substituents, this route is also recommended for the preparation of authentic samples of known structure. Having a need for a comparison sample of 1-hydroxy-3,4-dimethylphenanthrene some years ago we turned to this approach. The results were unsatisfactory in that the sole phenanthrene ring containing compound obtained was 2,3-dimethylphenanthrene. This was one of the earliest reports of the loss of an ortho substituent in this photocyclization.[2] More recently we returned to this reaction and can now report that 1-methoxy-3,4-dimethylphenanthrene can indeed be obtained from the reaction, albeit in low yield. The problems associated with separation of pure products from the reaction mixture and the low yields obtained limit the value of this approach for synthesis of 1-hydroxy-3,4-dimethylphenanthrene in sizable amounts.

Preparation of 2-methoxy-4,5-dimethylstilbene was carried out from 3,4-dimethylphenol in about 40% overall yield in five steps as illustrated in Scheme I. Each step proceeds in good yield and the procedure is nicely adapted to the preparation of large amounts. The stilbene was irradiated with a medium-pressure ultraviolet lamp in cyclohexane solution in the presence of iodine. The photo reaction was not clean; some amorphous yellow powder was always produced along with considerable material which would not migrate on thin-layer chromatograms. The brown oil obtained from the irradiation was readily separated by preparative layer chromatography into two fractions, that with the higher R_f value being 2,3-dimethylphenanthrene. The slower moving band had the same R_f value as the stilbene, and it was a mixture (two OMe bands in the NMR). Repeated development of this band eventually permitted isolation of the desired 1-methoxy-3,4-dimethylphenanthrene. Though it appeared that at least part of the separation problem arose because stilbene remained in the irradiation product, longer irradiation gave intractable black oils. In one case a high melting product (mp 205–207 °C) was isolated in low yield. This was assumed to be a dimer but was not investigated further.

Scheme I



Perhaps the most interesting point, i.e., the relative amounts of 2,3-dimethylphenanthrene and 1-methoxy-3,4-dimethylphenanthrene formed in the photolysis, was not possible to determine with any degree of certainty because of the difficulty of separating the ether from the reaction mixture. However, since the crude separation on thin-layer plates gave about a 2.5 to 1 ratio of the bands from which the ether and the hydrocarbon respectively were isolated, and since the pure compounds were obtained in ca. 1.5 to 1.0 ratio, an estimate of 2 to 1 is probably quite reasonable. In this case then reaction at the substituted ortho position and loss of methanol occurs about half as often as reaction at the unsubstituted position followed by loss of hydrogen. This ratio might be expected to be dependent on the iodine concentration, but though no careful test of this point was made, no dramatic effect was observed by altering the ratio of stilbene to iodine by a factor of fivefold.

Loss of methanol has been observed in a number of examples,[3] and when the irradiation was carried out under conditions similar to those used in our work, the ratio of loss of hydrogen to loss of methanol varied from about two to three. When nonoxidative conditions were employed only methanol loss was observed.[4] It is also interesting that the ratio of loss