Spiro[cyclopentane-1,1′(3′*H*)-isobenzofuran] (6g): bp 58–60 °C (0.05 mmHg); 80% yield; IR (film) ν_{max} 1620 (C=C), 755 (C–H bend of Ph) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.61–2.22 (8 H, m, cyclopentane H), 5.02 (2 H, s, 3′-H), 7.06–7.39 (4 H, m, C_6H_4); UV (ethanol) λ_{max} 265, 272 nm (ϵ_{max} 1155, 1222). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.53; H, 7.99.

Spiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (7g): bp 64–66 °C (0.06 mm); 82% yield; IR (film) ν_{max} 1617 (C=C), 755 (C–H bend of Ph) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.5–1.94 (10 H, m, cyclohexane H), 5.05 (2 H, s, 3′-H), 7.02–7.33 (4 H, m, C_6H_4); UV (ethanol) λ_{max} 265, 272 nm (ϵ_{max} 1000, 1056). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.12; H, 8.46.

3′a,7′a-*cis*-3′a,4′,5′,6′,7′,7′a-Hexahydrospiro[cyclopentane-1,1′(3′*H*)-isobenzofuran] (6i): bp 60–62 °C (0.05 mmHg); 88% yield; NMR (90 MHz, $CDCl_3$) δ 1.0–2.1 (17 H, m, cycloalkane H), 2.33–2.78 (1 H, br m, 3′a-H), 3.46–3.87 (2 H, complex m, 3′-H). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.18; H, 11.03.

3′a,7′a-*cis*-3′a,4′,5′,6′,7′,7′a-Hexahydrospiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (7i): bp 78–80 °C (0.1 mmHg); 71% yield; NMR (90 MHz, $CDCl_3$) δ 1.0–2.0 (19 H, very complex m, cyclohexane H), 2.44–2.89 (1 H, br m, 3′a-H), 3.58–3.91 (2 H, complex m, 3′-H). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.44; H, 11.23.

3′a,7′a-*trans*-3′a,4′,5′,6′,7′,7′a-Hexahydrospiro[cyclopentane-1,1′(3′*H*)-isobenzofuran] (6j): bp 70–72 °C (0.3 mmHg); 83% yield; NMR (90 MHz, $CDCl_3$) δ 0.89–2.22 (18 H, very complex m, cycloalkane H), 3.16–3.42 (1 H, q, AMX, $J_{AX} \simeq 9.5$ Hz, $J_{AM} \simeq 7$ Hz, 3′-H_A), 3.78–4.00 (1 H, t, AMX, $J_{AM} \simeq J_{MX} \simeq 7$ Hz, 3′-H_M). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.12; H, 11.25.

3′a,7′a-*trans*-3′a,4′,5′,6′,7′,7′a-Hexahydrospiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (7j): bp 76–78 °C (0.2 mmHg); 76% yield; NMR (90 MHz, $CDCl_3$) δ 0.89–2.28 (20 H, very complex m, cyclohexane H), 3.18–3.38 (1 H, q, AMX, $J_{AX} \simeq 9.5$ Hz, $J_{AM} \simeq 7$ Hz, 3′-H_A), 3.79–4.00 (1 H, t, AMX, $J_{AM} \simeq J_{MX} \simeq 7$ Hz, 3′-H_{11}). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.61; H, 11.41.

Acknowledgment. We thank the National Research Council of Canada, le Ministre de l'éducation du Gouvernement du Québec, for support of this work and Professor R. H. Burnell for helpful discussions.

Registry No. 1a, 57-57-8; **1b**, 96-48-0; **1c**, 108-29-2; *cis*-**1d**, 24405-07-0; *trans*-**1d**, 24405-08-1; **1e**, 542-28-9; **1f**, 502-44-3; **1g**, 87-41-2; **1h**, 5732-81-0; **1i**, 6939-71-5; **1j**, 7702-72-9; **2a**, 73089-93-7; **2b**, 73057-71-3; **2c**, 73061-24-2; **2d**, isomer 1, 73089-94-8; **2d**, isomer 2, 73104-79-7; **2e**, 52318-90-8; **2f**, 73089-95-9; **2g**, 73061-25-3; **2h**, 73089-96-0; **2i**, 73089-97-1; **2j**, 73089-98-2; **2k**, 73089-99-3; **3a**, 40894-17-5; **3b**, 6963-45-7; **3c**, 73061-26-4; **3d**, isomer 1, 73090-00-3; **3d**, isomer 2, 73090-01-4; **3e**, 57740-07-5; **3f**, 73090-02-5; **3g**, 58931-26-3; **3h**, 73090-03-6; **3i**, 73090-04-7; **3j**, 73090-05-8; **4b**, 33448-80-5; **4e**, 20127-07-5; **4g**, 73090-06-9; **4i**, 73090-07-0; **4j**, 73090-08-1; **5b**, 699-61-6; **5e**, 4481-78-1; **5g**, 5651-49-0; **5i**, 73090-09-2; **5j**, 73090-10-5; **6b**, 176-10-3; **6e**, 177-21-9; **6g**, 73090-11-6; **6i**, 73104-80-0; **6j**, 73090-12-7; **7b**, 176-91-0; **7e**, 180-79-0; **7g**, 171-80-2; **7i**, 73090-13-8; **7j**, 73090-14-9; **8**, 17057-95-3; 1,5-dibromopentane, 111-24-0; 1,4-dibromobutane, 110-52-1; 2-allyl-2-methylmalonic acid, 5281-63-0; 2-methylpent-4-enoic acid, 1575-74-2; *cis*-cyclohexane-1,2-dicarboxylic anhydride, 13149-00-3; *trans*-cyclohexane-1,2-dicarboxylic anhydride, 14166-21-3.

Regiocontrolled Synthesis of Hydroxyphthalides. Synthesis of (±)-Isoochracinic Acid and a Zealeranone Intermediate

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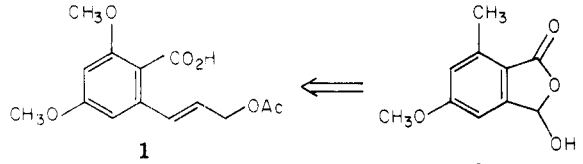
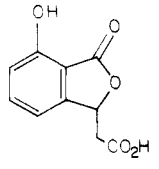
Metalation of 3-methoxy- and 3,5-dimethoxybenzyl alcohol followed by quenching with CO_2 provided the phthalides. Bromination and solvolysis generated 7-methoxy- and 5,7-dimethoxyphthalaldehydic acid in a fully regiocontrolled reaction. The former served as an intermediate in the synthesis of isoochracinic acid, a toxic metabolite from a parasite responsible for black spot disease of Japanese pears, in 44% overall yield from 3-methoxybenzyl alcohol. The latter served as an intermediate for the aromatic portion of zealeranone in a projected synthesis of this macrolide. A chemoselective reduction of an ester using an ate complex of DIBAL and *n*-butyllithium and the effect of tetra-*n*-hexylammonium bromide on the Wadsworth–Horner reaction are also reported.

In pursuing the synthesis of zealeranone[1] via organopalladium chemistry, we required **1** for the aromatic portion of the molecule. A suitable precursor was envisioned to be the lactol **2**. However, the obtainment of **2** from the corresponding phthalic anhydride proceeded in only 16% yield on a preparative scale.[2] The general importance of such intermediates in natural products encouraged us to seek a high-yield alternative route. In this paper, we wish to report such a sequence, (1) its application to the synthesis of **1**, (2) its application to a total synthesis of a toxin, isoochracinic acid (**3**), which arises from a parasite responsible for black spot disease of Japanese pears,[3] (3) a novel use of lithium trialkylaluminum hydride



1

2



3

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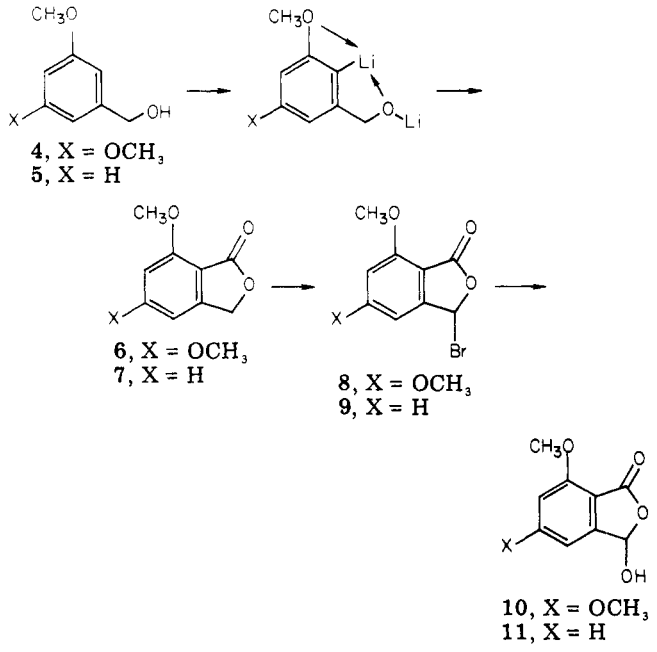
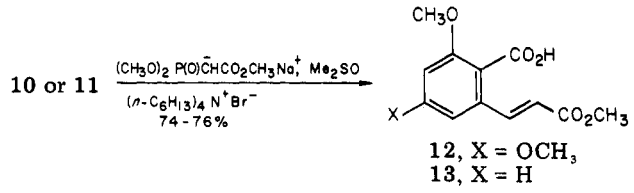
Scheme I. Regiocontrolled Synthesis of Hydroxyphthalides



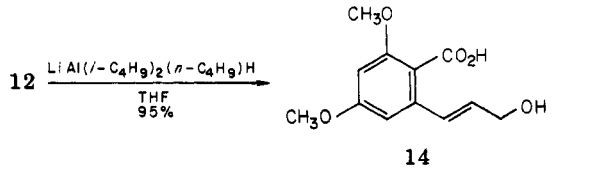
reagents for chemoselective reductions,[4] and (4) the beneficial effect of tetraalkylammonium salts in the Emmons–Wadsworth–Horner[5] reaction of lactols.

Selective synthesis of the phthalide **6** was accomplished in virtually quantitative yield (based upon recovered alcohol) by metallation of 3,5-dimethoxybenzyl alcohol (**4**) with *n*-butyllithium in hexane at 0 °C and quenching with carbon dioxide (see Scheme I).[6] Free-radical bromination with NBS proceeded quantitatively to give **8** as an unstable solid which was used directly in the next step.[7] The bromide proved to be surprisingly resistant to solvolysis and was recovered mostly unchanged by heating in water[8] and only partially converted to hydroxyphthalide by using aqueous sodium bicarbonate. Refluxing with approximately 1 M aqueous potassium hydroxide smoothly converted the bromide **8** to **10**, whose properties were identical with those reported for this important zealeranone intermediate.[2] This three-step synthesis proceeded in 86% overall yield, which compares very favorably to the earlier six-step synthesis which proceeded in 9% overall yield. The same sequence applied to 3-methoxybenzyl alcohol[5] gave, via intermediates **7** and **9**, the hydroxyphthalide **11** in 76% overall yield.

Attempts to subject the phthalides to the Emmons–Wadsworth–Horner reaction led to nonreproducible results and frequently to low yields. On the other hand, addition of 1 mol % or less of tetrahexylammonium bromide to the phosphonate anion in Me_2SO gave excellent yields of the *E* olefins (J = 16 Hz in the proton NMR) **12** and **13**. To

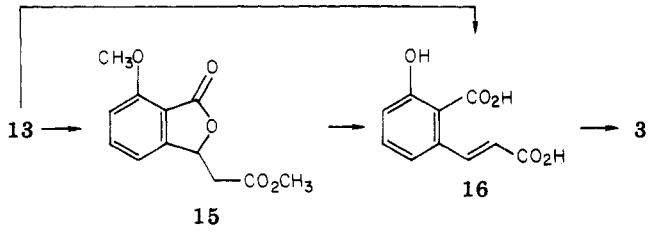


complete the synthesis of the zealeranone intermediate **1**, we required chemoselective reduction of the ester. Most metal hydride reducing agents do not allow employment of a stoichiometric amount of hydride ion. LAH, DIBAL-H, Vitride, etc. proved unsatisfactory. We found that use of 3 equiv (1 equiv to neutralize the acid and 2 equiv to effect reduction) of the ate complex formed between *n*-butyllithium and diisobutylaluminum hydride[4] which has only one active hydride and therefore only one type of active hydride is superb to achieve selective formation of allylic alcohol **14**. Formation of the allylic acetate **1**



was performed with acetic anhydride in pyridine followed by treatment with diethylamine to cleave selectively the small amount of mixed anhydride that formed.

For isoochracinic acid (**3**), **13** was easily cyclized to lactone **15**. Demethylation proved troublesome with



mercaptide ion[9] and the standard silyl iodide methods.[10] Use of the silyl iodide in hot quinoline proved highly satisfactory;[11] however, elimination back to the cinnamate system, i.e., **16**, accompanied demethylation. Alternatively, treatment of **13** with Me_3SiI in hot quinoline led directly to **16** in 80% yield. Cyclization of **16** with Dabco in warm acetonitrile completed the sequence. The isoochracinic acid, whose properties were identical with those reported, was available in 74% yield from **13** or 44% overall yield from 3-methoxybenzyl alcohol. This regiocontrolled synthesis compares quite favorably with an alternative approach based upon use of [[(benzyloxy)carbonyl]-methylene]triphenylphosphorane with 3-methoxyphthalic anhydride in which the Wittig reagent attacked the wrong carbonyl group of the anhydride predominately to give the desired intermediate for isoochracinic acid in only 38% yield.

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Experimental Section

General Methods. All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were determined on a Perkin-Elmer 267 or Beckman Acculab 7 spectrophotometer and are reported in cm^{-1}. Proton NMR spectra were determined in the indicated solvent on a Jeolco MH-100 instrument, and chemical shifts are reported in δ units downfield from internal Me_4Si. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained at an ionizing current of 98 mA and an ionizing voltage of 70 eV. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes or on a hot stage and are uncorrected. TLC and PLC plates were made of E. Merck AG, Darmstadt, silica gel PF-254 or Brinkmann silica gel P/UV-254 no. 66 and activated by drying at 140 °C for 2 h. In experiments requiring dry solvents, THF was distilled from sodium benzophenone ketyl; DMF, quinoline, and acetonitrile were distilled from calcium hydride.

Synthesis of Phthalides. 5,7-Dimethoxyphthalide (6). A suspension of 20.0 g (0.119 mol) of 3,5-dimethoxybenzyl alcohol in 250 mL of dry hexane was cooled to 0 to −5 °C (ice–salt bath) and treated with 189 mL (0.248 mol) of a 1.31 M solution of *n*-butyllithium in hexane at such a rate as to keep the temperature at <0 °C. After completion of the addition, the mixture was vigorously stirred for 1.5 h and the resultant orange solution poured onto excess dry ice covered with 100 mL of hexane which was cooled to −18 °C. The mixture was allowed to warm to 0 °C, and 250 mL of water was added. The aqueous phase was extracted with ether (4 × 50 mL). The combined organic layers were dried and evaporated to give 7.46 g (37%) of recovered alcohol. The aqueous layer was acidified to pH 1 with 5% aqueous hydrochloric acid and the solution stored in a refrigerator overnight. Continuous extraction of this aqueous mixture with ether, drying of the ether layer, and evaporation gave 14.5 g (65%, quantitative based upon recovered starting material) of **6** which was recrystallized from acetone–ether: mp 146–148 °C (lit.[13] mp 151–153 °C); IR ($CDCl_3$) 2850, 1760, 1608, 1497 cm^{-1}; NMR ($CDCl_3$) δ 6.50 (s, 1 H), 6.44 (s, 1 H), 5.16 (s, 2 H), 3.96 (s, 3 H), 3.89 (s, 3 H).

7-Methoxyphthalide 7. As above, 4.09 g (35.5 mmol) of 3-methoxybenzyl alcohol in 100 mL of hexane and 47.5 mL (72.5 mmol) of a 1.54 M solution of *n*-butyllithium gave 3.5 g (71%) of recovered alcohol and 1.38 g (83% based upon recovered starting material) of recrystallized (1:1 ether–pentane) phthalide **7**, mp 103.5–105 °C (lit.[14] mp 107–109 °C). Alternatively, metalating 10.29 g (74.6 mmol) of alcohol with 110 mL (165 mmol) of a 1.5 M solution of *n*-butyllithium for 2 h at room temperature led to 5.14 g (47%) of recovered alcohol and 4.89 g (78% based upon recovered starting material) of phthalide: IR ($CHCl_3$) 1755, 1602, 1500 cm^{-1}; NMR ($CDCl_3$) δ 7.62 (t, J = 8 Hz, 1 H), 7.01 (d, J = 8 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), 5.23 (s, 2 Hz), 4.01 (s, 3 H).

Preparation of Hydroxyphthalides.[8] 5,7-Dimethoxyphthalaldehydic Acid (10). A suspension of 1.006 g (5.19 mmol) of phthalide **6** and 0.954 g (5.30 mmol) of NBS in 75 mL of carbon tetrachloride was refluxed for 30 min while being irradiated with a sunlamp. When the mixture was cooled and filtered through glass wool, a clear solution resulted. Evaporation in vacuo gave 1.417 g (quantitative) of bromide **8** in high purity which was used directly in the next step: IR ($CHCl_3$) 1775, 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 1 H), 6.55 (d, J = 1.5 Hz, 1 H), 6.43 (d, J = 1.5 Hz, 1 H), 3.95 (s, 3 H), 3.90 (s, 3 H).

To a suspension of 5.14 g (18.8 mmol) of **8** in 40 mL of water was added 2.11 g (37.6 mmol) of potassium hydroxide, and the mixture was refluxed 30 min. The mixture was cooled, acidified with potassium hydrogen sulfate (5.2 g), and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give 3.40 g (86%) of hydroxyphthalide **10** which was recrystallized from ethyl acetate–hexane; mp 183–189 °C (lit.[2] mp 184–189; 193–196 °C). Anal. Calcd for $C_{10}H_{10}O_5$: mol wt 210.0527. Found: mol wt 210.0529.

7-Methoxyphthalaldehydic Acid (11). As above, 4.90 g (29.9 mmol) of **7** and 5.37 g (29.9 mmol) of NBS in 300 mL of carbon tetrachloride for 50 min gave 7.26 g (quantitative) of bromide **9**. The crude bromide was solvolyzed in 100 mL of water with 2.10 g of potassium hydroxide at reflux with additional portions of potassium hydroxide to maintain the pH at >10. Adjustment of the pH to 3 with potassium hydrogen sulfate and allowing the mixture to stand in an ice bath precipitated the hydroxyphthalide **11**. Filtration and vacuum drying over P_2O_5 gave 4.93 g (92%) of **11** (mp 152–153 °C) upon recrystallization from ethyl acetate–hexane. Rotoevaporation of the aqueous layer and extraction of the residue with hot methylene chloride gave 0.35 g of a mixture of **7** and **11**. Preparative TLC (5% acetone in methylene chloride) of this fraction gave 70 mg of starting material and 90 mg of additional product for a total of 5.02 g (95% overall yield based upon recovered starting material): IR ($CHCl_3$) 3200–3600, 1760–, 1605, 1485 cm^{-1}; NMR ($CDCl_3$ and Me_2SO) δ 7.67 (t, J = 8 Hz, 1 H), 7.15 (d, J = 8 Hz, 1 H), 7.06 (d, J = 8 Hz, 1 H), 6.51 (s, 1 H), 3.88 (s, 3 H), 3.29 (br s, 1 H); NMR ($CDCl_3$, Me_2SO, and H_2O) δ 7.43 (t, J = 7 Hz, 1 H), 6.95 (d, J = 7 Hz, 1 H), 6.82 (d, J = 8 Hz, 1 H), 6.93 (s, 1 H), 6.87 (s, 3 H). Anal. Calcd for $C_9H_8O_4$: mol wt 180.0420. Found: mol wt 180.0417.

Emmons–Wadsworth–Horner Reactions. Synthesis of Methyl 2-Carboxy-3,5-dimethoxy-(*E*)-cinnamate (12). A suspension of 0.346 g (14.4 mmol) of sodium hydride, washed free of mineral oil with hexane, in 50 mL of dry Me_2SO was prepared. A mixture of 1.21 g (5.76 mmol) of **10** and 0.157 g (0.361 mmol) of tetrahexylammonium bromide was dried by dissolving it in toluene and distilling the toluene–water azeotrope. The residue, after removal of all the toluene, and 2.10 g (11.5 mmol) of trimethyl phosphonoacetate dissolved in 50 mL of dry Me_2SO were added dropwise to the sodium hydride mixture at room temperature. After 2.5 h, it was cooled to 0 °C and quenched by addition of 50 mL of brine and 50 mL of water. The solution was washed with chloroform (3 × 50 mL) and the organic layer set aside. The aqueous solution was added dropwise to 100 mL of chloroform and 100 mL of aqueous hydrochloric acid cooled to 0 °C. The aqueous portion was washed with chloroform (4 × 40 mL). The combined chloroform layers were dried ($MgSO_4$) and evaporated. The residue was taken up in 75 mL of ethyl acetate and the ethyl acetate solution washed with water. The aqueous wash was extracted with ethyl acetate (3 × 50 mL). The combined ethyl acetate layers were dried ($MgSO_4$) and evaporated in vacuo to give 1.13 g (74%) of **12**: mp 147–152 °C, after recrystallization from chloroform–hexane; IR ($CDCl_3$) 2400–3600, 1700, 1635, 1597, 1480 cm^{-1}; NMR ($CDCl_3$) δ 7.92 (d, J = 16 Hz, 1 H), 6.74 (d, J = 1.5 Hz, 1 H), 6.55 (d, J = 1.5 Hz, 1 H), 6.38 (d, J = 16 Hz, 1 H), 3.89 (s, 9 H). Anal. Calcd for $C_{13}H_{14}O_6$: mol wt 266.0630. Found: mol wt 266.0790.

Synthesis of Methyl 2-Carboxy-3-methoxy-(*E*)-cinnamate (13). As above, a mixture of 450 mg (2.5 mmol) of phthalaldehydic acid **11**, 59 mg (0.136 mmol) of tetrahexylammonium bromide, and 910 mg (5.0 mmol) of trimethyl phosphonoacetate in 40 mL of Me_2SO was added to 263 mg (6.25 mmol) of sodium hydride suspended in 30 mL of Me_2SO to give, after the same workup, 520 mg (88%) of **13**, mp 142–145 °C (chloroform–hexane). When 4.93 g (27.4 mmol) of **11**, 0.60 g (1.4 mmol) of ammonium salt, 10.0 g (55.6 mmol) of phosphonate, and 3.30 g (68.8 mmol) of sodium hydride were used, 4.88 g (76%) of product was obtained: IR (KBr) 1720, 1670, 1628, 1565, 1465 cm^{-1}; NMR (CD_3CN–Me_2SO-d_6) δ 7.6–8.3 (vbr, 1 H), 7.52 (d, J = 16 Hz, 1 H), 7.24 (m, 2 H), 6.96 (dd, J = 7, 1.5 Hz, 1 H), 6.40 (d, J = 16 Hz, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H). Anal. Calcd for $C_{12}H_{12}O_5$: mol wt. 236.0684. Found: mol wt 236.0688.

Chemoselective Reduction of 12. Preparation of 2-Carboxy-3,5-dimethoxy-(*E*)-cinnamyl Acetate (1). A solution of the ate complex was prepared by adding 34.72 mL (1.54 M, 53.46 mmol) of *n*-butyllithium in hexane to 60.75 mL (0.58 M, 53.46 mmol) of DIBAL-H in toluene at −5 °C and then adding 200 mL of dry THF. A solution of 4.74 g (17.82 mmol) of acid ester **12**, previously dried by dissolving in toluene and distilling off all the toluene, in 200 mL of dry THF was added dropwise at −70 °C and then stored at −20 °C for 2 h. The solution was recooled to −70 °C and quenched by addition of 12 g of sodium sulfate decahydrate. It was then poured into 500 mL of 0.5 M aqueous potassium bisulfate and 300 mL of chloroform, and the resultant mixture was stirred until all the salts dissolved (~1 h). The aqueous layer was extracted with chloroform (3 × 100 mL),

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and the combined chloroform extracts were dried ($MgSO_4$) and evaporated in vacuo to give 4.01 g (95%) of alcohol **14**. It was further purified by being passed through a short column (10 cm × 1.2 cm) of Florisil, eluted with chloroform, and recrystallized from ethyl acetate–hexane to give crystals: mp 135–137 °C; IR (Nujol) 2500–3500, 1710, 1600, 1570 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (d, J = 16 Hz, 1 H), 6.70 (d, J = 1.5 Hz, 1 H), 6.50 (d, J = 1.5 Hz, 1 H), 6.30 (dt, J = 16, 5 Hz, 1 H), 5.00 (s, 1 H), 4.40 (d, J = 5 Hz, 2 H), 3.98 (s, 3 H), 3.90 (s, 3 H).

A solution of 390 mg (1.64 mmol) of the above **14** in 1.7 mL of dry pyridine at 0 °C was treated with 334 mg (3.28 mmol) of acetic anhydride for 1.5 h. After dilution with ether, the organic layer was washed with 5% aqueous hydrochloric acid (2 × 20 mL) and water (3 × 20 mL). After the organic layer was dried ($MgSO_4$) and evaporated to dryness in vacuo, 480 mg of a crude solid remained which was a mixture of the desired acetate **1** and its mixed anhydride with acetic acid. To a solution of this mixture at 0 °C in 25 mL of methylene chloride was added 120 mg (1.64 mmol) of diethylamine. After being stirred 30 min, the solution was washed with 5% aqueous hydrochloric acid (2 × 20 mL) and water (3 × 20 mL). After the organic layer was dried ($MgSO_4$) and evaporated, 420 mg (92%) of pure product was obtained: mp 123–125 °C (chloroform–hexane); IR ($CHCl_3$) 2500–3600, 1725, 1600, 1580, 1460 cm^{-1}; NMR ($CDCl_3$) δ 7.05 (d, J = 16 Hz, 1 H), 6.60 (d, J = 2 Hz, 1 H), 6.40 (d, J = 2 Hz, 1 H), 6.20 (dt, J = 16, 6 Hz, 1 H), 4.70 (d, J = 6 Hz, 2 H), 3.90 (s, 3 H), 3.85 (s, 3 H). Anal. Calcd for $C_{14}H_{16}O_6$: mol wt 280.1517. Found: mol wt 280.0947.

Preparation of 2-Carboxy-3-hydroxy-(*E*)-cinnamic Acid (16). Method A: via 15. A solution of 400 mg (1.70 mmol) of **13** and 9.5 mg (0.085 mmol) of Dabco in 6 mL of acetonitrile was heated at 60–70 °C for 22 h. The resulting mixture was diluted with 50 mL of chloroform and washed with aqueous ammonium chloride. The organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give 400 mg (quantitative) of pure product **15**, mp 95–96 °C (toluene–hexane). Repetition of this procedure with 4.50 g (19.1 mmol) of **13** and 120 mg (1.07 mmol) of Dabco in 60 mL of acetonitrile for 19 h gave 4.18 g (92%) of **15**: IR ($CHCl_3$) 1765, 1720, 1605, 1485 cm^{-1}; NMR (CD_3CN) δ 7.61 (t, J = 8 Hz, 1 H), 7.03 (d, J = 8 Hz, 1 H), 7.00 (d, J = 8 Hz, 1 H), 5.70 (dd, J = 8, 5 Hz, 1 H), 3.91 (s, 3 H), 3.67 (s, 3 H), 3.04 (dd, J = 15, 5 Hz, 1 H), 2.74 (dd, J = 15, 8 Hz, 1 H).

A solution of 150.7 mg (0.639 mmol) of phthalide **15** and 562 mg (2.81 mmol) of Me_3SiI in 1 mL of dry quinoline was immersed into a preheated oil bath set at 175 °C for 2 min. The flask was cooled by being immersed in a water bath, and the solution was diluted with 50 mL of ethyl acetate and 30 mL of 5% aqueous hydrochloric acid. After the mixture was stirred 5 min, the aqueous phase was extracted with ethyl acetate. All of the organic extracts were combined, dried ($MgSO_4$), decolorized with Norite, filtered through Celite, and evaporated in vacuo. The residue was dissolved in 50 mL of toluene and evaporated to give 150 mg (quantitative) of acid **16**. Recrystallization of 120 mg of this product from ethyl acetate–water–hexane gave 99.4 mg (83%) of white powder: mp 155–156 °C; IR (KBr) 2400–3600, 1690, 1640, 1588, 1495 cm^{-1}; NMR (CD_3CN–Me_2SO-d_6) δ 8.5 (br, 3 H), 8.14 (d, J = 16 Hz, 1 H), 7.39 (t, J = 7 Hz, 1 H), 7.13 (d, J = 7 Hz, 1 H), 7.01 (d, J = 7 Hz, 1 H), 6.08 (d, J = 16 Hz, 1 H). Anal. Calcd for $C_{10}H_8O_5$: mol wt 208.0369. Found: mol wt 208.0358.

Method B. A solution of 524 mg (2.22 mmol) of **13** and 1.97 g (9.84 mmol) of Me_3SiI in 3.5 mL of dry quinoline was reacted and worked up as in method A. In addition, the product was dissolved in 50 mL of aqueous sodium bicarbonate and the bicarbonate layer washed with ethyl acetate. After acidification of the water layer to pH 2 with potassium bisulfate, the product was extracted with ethyl acetate and then worked up as above to give 374 mg (80%) of pure **16**.

Preparation of Isoochracinic Acid. A solution of 374 mg (1.80 mmol) of **16** in 75 mL of acetonitrile containing 45 mg of Dabco was refluxed 16 h, during which time the white suspension became a colorless solution. After the mixture cooled, 5 g of Dowex 50-8X in the acid form was added, and the mixture was stirred 10 min and filtered. The resin was washed with acetone, and the combined organic extracts were evaporated in vacuo to give 392 mg of a foam that still contained some Dabco (~6 mol %). This residue was dissolved in 75 mL of ethyl acetate and washed with 4 mL of saturated aqueous ammonium chloride containing 0.1 mL of concentrated hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($CaCl_2$) and evaporated in vacuo to give 347 mg (93%) of pure product [mp 166 °C[15] (lit.[3] mp 162 °C)] after recrystallization from ether–pentane.

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Registry No. **1**, 73274-83-6; **3**, 66820-34-6; **4**, 705-76-0; **5**, 6971-51-3; **6**, 3465-69-8; **7**, 28281-58-5; **8**, 73274-84-7; **9**, 73274-85-8; **10**, 73274-86-9; **11**, 73274-87-0; **12**, 73274-88-1; **13**, 73274-89-2; **14**, 73274-90-5; **15**, 73274-91-6; **16**, 73274-92-7; tetrahexylammonium bromide, 4328-13-6; trimethyl phosphonoacetate, 5927-18-4; lithium hydridobis(2-methylpropyl)butylaluminate, 62779-58-2; acetic (*E*)-2-[3-(acetyloxy)-1-propenyl]-4,6-dimethoxybenzoic anhydride, 73274-93-8.

(15) Melting point taken on a hot stage.