Synthesis of (±)-Puraquinonic Acid: An Inducer of Cell Differentiation

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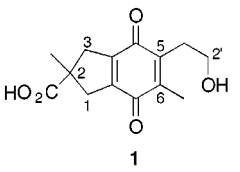
Puraquinonic acid (**1**) was synthesized from 2,5-dimethoxybenzoic acid by way of isochroman **2** and the indanone derivative **3**, a Nazarov cyclization being used to construct the five-membered ring.

We report the synthesis of racemic puraquinonic acid (**1**).[1,2] The optically active[3] substance, which is a fungal metabolite produced by cultures of *Mycena pura*,[1] induces differentiation of HL-60 cells (human promyelocytic leukemia) and may therefore[4] be a lead compound in the design of drugs to treat leukemia. No synthetic work on puraquinonic acid has been described before.



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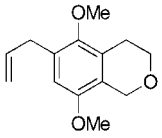

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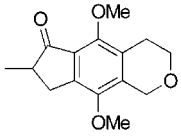

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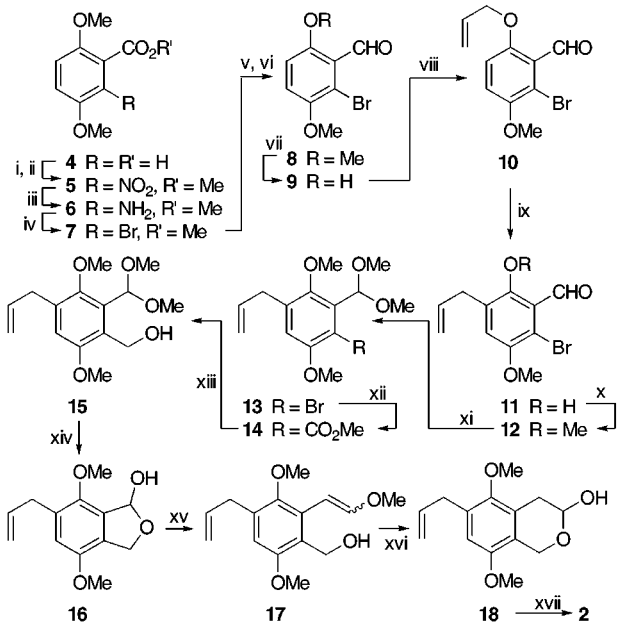
Our route proceeds by way of the isochroman **2** and the derived indanone **3**. The first key intermediate (**2**) was obtained as summarized in Scheme 1. Nitration of commercial 2,5-dimethoxybenzoic acid (**4**) (concentrated HNO_3[5]) and esterification (Me_2SO_4, K_2CO_3) gave **5**[6] as the major product, which could be isolated free of its 3- or 4-nitro isomers in 82% overall yield. Classical nitro group reduction (**5** → **6**,[7] Pd−C, H_2, 97%) and Sandmeyer reaction[8] (**6** → **7**, $NaNO_2$, HBr, CuBr, 100 °C, 81%) gave the expected bromo ester, which was then converted into the corresponding aldehyde (**7** → **8**[9]) by hydride reduction to the alcohol (DIBAL-H, 99%) and oxidation (PCC, 95%). Regioselective[10] demethylation, directed by the aldehyde

Scheme 1[a]



[a] Key: (i) HNO_3, 0 °C, 3 h, 100%; (ii) K_2CO_3, acetone, Me_2SO_4, 12 h, 82% from **4**; (iii) H_2 (50 psi), Pd−C, EtOH, 97%; (iv) $NaNO_2$, HBr, water, 0 °C; then add mixture over 1 h to CuBr, water, 100 °C, then 10 min, 100 °C, 81%; (v) DIBAL-H, PhMe, −78 °C for 2 h, then warm to room temperature, 99%; (vi) PCC, CH_2Cl_2, 10 h, 95%; (vii) BCl_3, CH_2Cl_2, −78 °C to room temperature, 10 h, 96%; (viii) NaH, DMF, allyl bromide, 0 °C to room temperature, 4 h, 83% (9% of **9** is also recovered); (ix) degassed *trans*-decalin, 200 °C, 6.5 h, 74%; (x) K_2CO_3, MeI, DMF, 70 °C, 10 h, 97%; (xi) $CH(OMe)_3$, $TsOH·H_2O$ (catalytic), MeOH, 70 °C, 3.5 h, 96%; (xii) BuLi, THF, −78 °C, MeOC(O)CN, 20 min, 88%; (xiii) DIBAL-H, hexanes−PhMe, added in two equal portions at the start and after 1 h, −78 °C, 2 h in all, 93%; (xiv) 0.1 N HCl, dioxane, 12 h, 71% plus 24% of the corresponding methyl acetal (OMe instead of OH in **16**); the methyl acetal can be hydrolyzed to **16** (0.1 N HCl, dioxane, 12 h, 68%); (xv) Ph_3PCH_2OMeBr, $(Me_3Si)_2NK$ in PhMe, −78 °C, 2 h, then 10 h at room temperature, 93% as a *Z*,*E* isomer mixture; (xvi) 0.1 N HCl, dioxane, 60 °C, 3 h, 86%; (xvii) Et_3SiH (freshly distilled), $BF_3·Et_2O$ (freshly distilled), −78 °C, 3 h, 93%.

(1) Becker, U.; Erkel, G.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 229−236.

(2) Related compounds: Clericuzio, M.; Han, F.; Pan, F.; Pang, Z.; Sterner, O. *Acta Chem. Scand.* **1998**, *52*, 1333−1337.

(3) Natural puraquinonic acid has $[\alpha]^{22}_D$ +1° (*c* 1.0 $CHCl_3$) (ref 1).

(4) (a) Degos, L. *Leukemia Res.* **1990**, *14*, 717−719. (b) Suh, N.; Luyengi, L.; Fong, H. H. S.; Kinghorn, A. D.; Pezzuto, J. M. *Anticancer Res.* **1995**, *15*, 233−240. (c) Mason, M. D. In *Molecular Biology for Oncologists*; Yarnold, J. R., Stratton, M. R., McMillan, T. J., Eds.; Chapman and Hall: London, 1996; pp 112−121.

(5) Ōki, M.; Tanaka, Y.; Yamamoto, G.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 302−305.

(6) Cf. Banerjee, P. K.; Chaudhury, D. N. *J. Indian. Chem. Soc.* **1962**, *39*, 243−246.

(7) (a) Cf. Mehta, L. K.; Parrick, J.; Payne, F. *J. Chem. Res. Synop.* **1998**, 190−191. (b) For the corresponding acid, see: Heaney, H.; Hollinshead, J. H.; Kirby, G. W.; Ley, S. V.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1840−1843.

(8) Cf. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Harlow, 1989.

(9) Cf. Sardessai, M. S.; Abramson, H. N. *Org. Prep. Proc. Int.* **1991**, *23*, 419−424.

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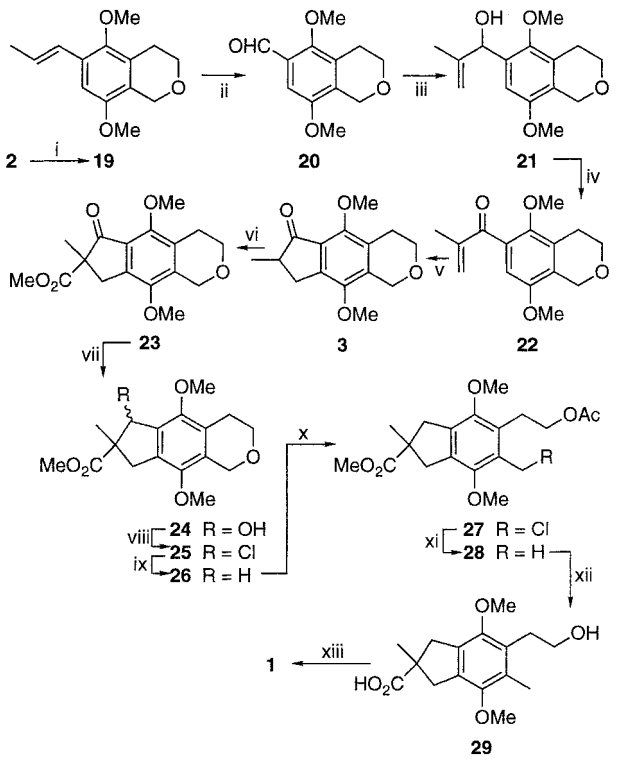
group[11] (**8** → **9**, BCl_3, 96%), allylation (**9** → **10**, NaH, allyl bromide, 83%), and thermal Claisen rearrangement (decalin, 200 °C, 74%), then gave phenol **11**. This was methylated (**11** → **12**, MeI, K_2CO_3, 97%), and the aldehyde group was protected [**12** → **13**, $CH(OMe)_3$, MeOH, $TsOH·H_2O$, 96%]. Use of a *dimethyl* instead of a *cyclic* acetal and the indicated order of the last four steps—allylation, rearrangement, O-methylation, and acetalization—was the best of several possibilities that we examined. At this point, halogen−metal exchange, and treatment with Mander's reagent,[12] gave ester **14** (88%). Of course, quenching of the intermediate anion with MeI rather than MeOC(O)CN would seem to be a more logical step, but such an approach eventually incurred complications, as described below. The ester group of **14**, which—after modification—eventually serves the essential purpose of protecting the C(2′) oxygen (see **1** for numbering), was reduced with DIBAL-H (93%), and then acid hydrolysis of the intermediate hydroxy acetal (0.1 N HCl, 71%) afforded lactol **16**. During the hydrolysis, some (24%) of the lactol methyl ether corresponding to **16** is also formed (OMe instead of OH in **16**), but can be hydrolyzed to the lactol (68%), raising the yield for conversion of **15** into **16** to 87%. The second carbon of the hydroxyethyl chain of puraquinonic acid was now introduced by Wittig reaction [**16** → **17**, Ph_3PCH_2OMeBr, $(Me_3Si)_2NK$,[13] 93%], and mild acid hydrolysis of the resulting enol ethers (*Z*:*E* = 1:2) gave lactol **18** (86%). Finally, deoxygenation, using Et_3SiH and $BF_3·Et_2O$[14]—both freshly distilled—brought the route to the key intermediate **2** (93%).

At this stage, the required five-membered ring was constructed by the method summarized in Scheme 2. Movement of the double bond of **2** into conjugation with the aromatic ring (**2** → **19**, $RhCl_3·3H_2O$, 5:1 PhMe−MeOH,[15] 97%) and treatment with $NaIO_4$ in the presence of a catalytic amount of OsO_4 gave aldehyde **20** (97%).[16] This reacted[17] with isopropenylmagnesium bromide (86%), and the resulting alcohol was oxidized (Dess−Martin reagent, 96%) to enone **22**. On storage in concentrated H_2SO_4 (0 °C, 5 h), the enone underwent efficient Nazarov cyclization[18] to the indanone derivative **3** (83%), which was then deprotonated (LDA) and acylated with Mander's reagent (**3** → **23**, 59% or 82% corrected for recovered **3**).

Scheme 2[a]



[a] Key: (i) $RhCl_3·3H_2O$, 5:1 PhMe−MeOH, 70 °C, 3 h, 97%; (ii) $NaIO_4$, OsO_4 (catalytic), 2:1:1 *t*-BuOH, CCl_4, water, 1.5 h, 97%; (iii) isopropenylmagnesium bromide, Et_2O, 0 °C, 30 min, then remove ice bath, 30 min, 86%; (iv) Dess−Martin, CH_2Cl_2, 1 h, 96%; (v) concd H_2SO_4, 0 °C, 5 h, 83%; (vi) LDA, THF, −78 °C, 30 min, MeOC(O)CN, 30 min, 59%, or 82% corrected for recovered **3**; (vii) $NaBH_4$, MeOH, 0 °C, 1−2 h, 99%; (viii) $SOCl_2$, Et_3N, CH_2Cl_2, 12 h, 54% or 93%, after correction for recovered starting material; (ix) Bu_3SnH, PhMe, AIBN, reflux, 3 h, 95%; (x) AcCl, $ZnCl_2$ (catalytic), CH_2Cl_2, reflux, 4 h, 88%; (xi) Bu_3SnH, PhMe, AIBN, reflux, 3 h, 87%; (xii) LiOH, 1:1 dioxane−water, 12 h, 90%; (xiii) $Ce(NH_4)_2(NO_3)_6$, 2:3 water−MeCN, 2,6-pyridinedicarboxylic acid *N*-oxide, 77%.

At this point, it was necessary to deoxygenate the ketone and open the heterocyclic ring. We had planned to effect both steps by sequential hydride reduction and hydrogenolysis,[19] but this approach was unsuccessful. Instead, the deoxygenation was achieved by successive treatment with $NaBH_4$ (**23** → **24**, 99%), $SOCl_2$−Et_3N (**24** → **25**, 54% or 93%, after correction for recovered alcohol), and Bu_3SnH−AIBN (**25** → **26**, 95%), and the heterocyclic ring was then opened by heating with AcCl in the presence of $ZnCl_2$[20] (**26** → **27**, 88%). The resulting chloride was reduced with Bu_3SnH (**27** → **28**, 87%). Finally, basic hydrolysis (LiOH, aqueous dioxane, 90%) released hydroxy acid **29**, and oxidation (77%) with $Ce(NH_4)_2(NO_3)_6$ in the presence of 2,6-pyridinedicarboxylic acid *N*-oxide[21]

(10) An attempt to demethylate ester **7** with boron *tribromide* resulted in extensive demethylation of both ether groups. We subsequently found that **7** can be demethylated regioselectively with boron *trichloride*, but demethylation at that stage makes no substantive difference to the overall synthesis.

(11) (a) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, 4153−4159. (b) Review on ether cleavage: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249−282. (c) Lal, K.; Ghosh, S.; Salomon, R. G. *J. Org. Chem.* **1987**, *52*, 1072−1078.

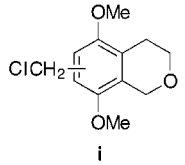
(12) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.

(13) Cf. Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791−5799.

(14) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417−2419.

(15) Clive, D. L. J.; Joussef, A. C. *J. Org. Chem.* **1990**, *55*, 1096−1098.

(16) In principle, compound **i**, available in low yield and of unestablished regiochemistry (Retamal, J. I.; Ruiz, V. M.; Tapia, R. A.; Valderrama, J. A.; Vega, J. C. *Synth. Commun.* **1982**, *12*, 279−285), could be converted into **20** or its regioisomer (aromatic H and CHO interchanged), but we have not investigated this approach.



i

(17) An excess of Grignard reagent must be avoided; otherwise, O-demethylation occurs.

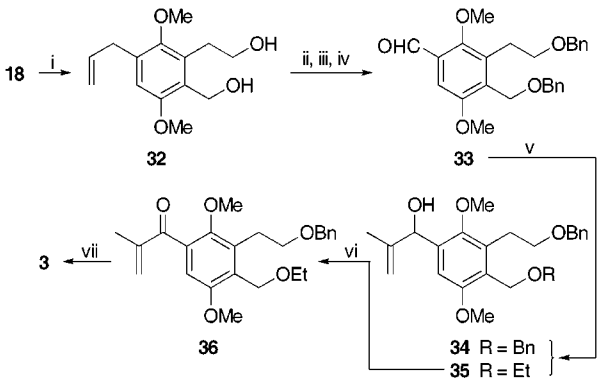
(18) Carter, R. H.; Garson, M. J.; Hill, R. A.; Staunton, J.; Sunter, D. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 471−479.

(19) Cf. Meyer, A. L.; Turner, R. B. *Tetrahedron* **1971**, *27*, 2609−2615.

(20) Hayler, J. D.; Howie, S. L. B.; Giles, R. G.; Negus, A.; Oxley, P. W.; Walsgrove, T. C.; Walsh, S. E.; Dagger, R. E.; Fortunak, J. M.; Mastrocola, A. *J. Heterocycl. Chem.* **1995**, *32*, 875−882.

(21) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521−522.

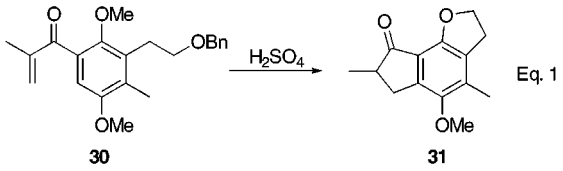
Scheme 3[a]



[a] Key: (i) $NaBH_4$, MeOH, 0 °C, 90%. (ii) NaH, BnBr, THF, 0 °C, 3 h, 68%; (iii) $RhCl_3 \cdot 3H_2O$, 5:1 PhMe−MeOH, reflux, 3 h, 89%; (iv) O_3, CH_2Cl_2, −78 °C; Ph_3P, 2 h, 76%; (v) isopropenylmagnesium bromide, THF, −10 °C, 2 h, 44% of **35** and 18% of **34**; (vi) PCC, 4 Å molecular sieves, CH_2Cl_2, 1 h, 89%; (vii) H_2SO_4, 6 h, 86%.

completed the synthesis of (±)-puraquinonic acid (**1**), which was identified by comparison of its spectral properties with the published[1] values.

As mentioned above, trapping of the carbanion derived from **13** with Mander's reagent (Scheme 1), rather than with MeI, was an unusual but essential step. When we used MeI, and elaborated the product into **30**, application of the Nazarov cyclization led to **31** (eq 1), which we were unable to incorporate into a route to puraquinonic acid because attempts to open the heterocycle (BBr_3 or Me_3SiI) gave unidentifiable products. By using Mander's reagent, however, it was possible to avoid formation of the dihydrofuran system.



We also prepared key intermediate **3** by a slightly different route (Scheme 3). During our studies, we reduced lactol **18** ($NaBH_4$) and protected the resulting diol (**32**) as its bis-benzyl ether. The double bond in the side chain was moved into conjugation with the aromatic ring, as before, and then cleaved to afford aldehyde **33**. When this material was treated with isopropenylmagnesium bromide in a THF-Et_2O mixture, the main product (44%) was the ethyl ether **35**, while the expected product (**34**) was isolated in only 18% yield. Alcohol **35** was oxidized to ketone **36**, and when this was subjected to conditions for the Nazarov cyclization, indanone derivative **3** was again formed in good yield (86%).

Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst[22] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and EtOAc used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Cannula transfers were done under slight pressure (Ar), not by suction.

Commercial thin-layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid[23] or *p*-anisaldehyde,[24] followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230−400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from sodium and benzophenone ketyl.

FTIR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively.

Methyl 3,6-Dimethoxy-2-nitrobenzoate (5). (a) 3,6-Dimethoxy-2-nitrobenzoic Acid. The literature method[5] was modified slightly. Concentrated HNO_3 (100 mL) was placed in a three-necked flask fitted with a low temperature thermometer and cooled to 0 °C. 2,5-Dimethoxybenzoic acid (10.0 g, 54.9 mmol) was added in small portions over 30 min with stirring (the temperature was not allowed to rise above 0 °C). The resulting yellow solution was stirred at 0 °C for another 3 h and then poured onto cracked ice (300 mL). A yellow precipitate formed immediately. It was filtered off, air-dried overnight, and dried further under oil-pump vacuum for 4 h to yield a 5:1 mixture (12.4 g, 100%) of 3,6-dimethoxy-2-nitrobenzoic acid and an isomer. The isomer ratio was determined from the isolated yields of the easily separable methyl esters described in the following paragraph.

(b) Methyl 3,6-Dimethoxy-2-nitrobenzoate (5). K_2CO_3 (40.00 g, 290.0 mmol), dry acetone (250 mL), and Me_2SO_4 (13.3 mL, 18.4 g, 145 mmol) were added successively to the crude acid (26.40 g, 116.2 mmol) obtained from the previous step, and the resulting orange solution was stirred for 12 h. The solvent was evaporated and the residue was kept under oil-pump vacuum for 12 h. The resulting yellow solid was dissolved in a small amount of EtOAc and purified by flash chromatography over silica gel (4 × 27 cm), using 15:85 EtOAc−hexane, to give ester **5** (23.0 g, 82%) and an isomer (4.4 g, 16%). Major isomer (**5**): mp 118−119 °C (lit.[6] mp 122 °C); FTIR (CH_2Cl_2 cast) 1742, 1530, 1271 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.86 (s, 3 H), 3.88 (s, 3 H), 3.94 (s, 3 H), 7.09 (AB q, $\Delta\nu_{AB}$ = 5.4 Hz, J = 9.3 Hz, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 53.1 (q′), 57.0 (q′), 57.2 (q′), 115.7 (d′), 116.1 (d′), 118.1 (s′), 145.3 (s′), 150.6 (s′), 163.4 (s′), 165.1 (s′); exact mass *m*/*z* calcd for $C_{10}H_{11}O_6N$ 241.05860, found 241.05902.

Minor isomer (presumably methyl 2,5-dimethoxy-4-nitrobenzoate[25]): mp 102.5−103.5 °C; FTIR (CH_2Cl_2 cast) 1706, 1517, 1251 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.92 (s, 3 H), 3.96 (s, 3 H), 3.98 (s, 3 H), 7.45 (s, 1 H), 7.55 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 52.7 (q′), 56.9 (q′), 57.2 (q′), 109.5 (d′), 117.1 (d′), 125.1 (s′), 141.5 (s′), 146.2 (s′), 152.2 (s′), 165.1 (s′); exact mass *m*/*z* calcd for $C_{10}H_{11}O_6N$ 241.0586, found 241.05892.

Methyl 2-Amino-3,6-dimethoxybenzoate (6). Pd−C (10%, 25.0 mg) was added to a solution of ester **5** (1.50 g, 6.22 mmol) in EtOH (95%, 100 mL), and the mixture was shaken in a Parr bottle under H_2 (50 psi) until all the starting material was consumed (ca. 12 h, TLC control, silica, 1:4 EtOAc−hexane).

(22) Supplied by Chemical Dynamics Corp., South Plainfield, NJ.

(23) Phosphomolybdic acid (15 g) and $(NH_4)_2Ce(NO_3)_6$ (2.5 g) dissolved in a mixture of water (485 mL) and concentrated H_2SO_4 (15 mL).

(24) *p*-Anisaldehyde (15 drops) was added to concentrated H_2SO_4 (6 mL) and EtOH (94 mL).

(25) ^1H NMR data for methyl 2,5-dimethoxy-3-nitrobenzoate have been reported: Goris, A.; Frigot, P.; Molho, D.; Aknin, J.; Muller, P.; Cibault, M. *Phytochemistry* **1971**, *10*, 679−682.

(The apparatus was opened periodically for examination by TLC.) The mixture was filtered through a pad (4 × 3 cm) of silica gel, using EtOAc (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 × 15 cm), using 3:2 EtOAc−hexane, gave amine **6**[7] (1.266 g, 97%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 3489, 3379 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3 H), 3.82 (s, 3 H), 3.92 (s, 3 H), 5.35 (broad s, 2 H), 6.15 (d, J = 8.8 Hz, 1 H), 6.75 (d, J = 8.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 51.9 (q′), 56.4 (q′), 56.5 (q′), 98.4 (d′), 105.0 (s′), 113.1 (d′), 140.7 (s′), 141.8 (s′), 154.1 (s′), 168.8 (s′); exact mass (HR electrospray) m/z calcd for $C_{10}H_{13}NNaO_4$ (M + Na) 234.07423, found 234.07467. Anal. Calcd for $C_{10}H_{13}N$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.71; H, 6.31; N, 6.61.

Methyl 2-Bromo-3,6-dimethoxybenzoate (7). HBr (48% in water, 17.0 mL) was added to amine **6** (9.232 g, 43.75 mmol), and the mixture was stirred vigorously with a mechanical stirrer. The resulting white solid was broken up with a glass rod from time to time to allow reaction of the remaining amine. The slurry was further diluted with HBr (48% in water, 7.0 mL) and cooled (0 °C). A cooled (0 °C) solution of $NaNO_2$ (3.169 g, 45.94 mmol) in water (8.5 mL) was added dropwise by Pasteur pipet, maintaining the temperature below 5 °C. The resulting brownish red solution was stored in an ice bath and was added dropwise, using a Pasteur pipet, to a refluxing solution (100 °C) of CuBr (4.14 g, 0.66 equiv) in HBr (48% in water, 5.0 mL). The color of the reaction mixture changed from deep purple to black and later to brown. Upon completion of the addition, heating was continued for 10 min. The reaction mixture was cooled to room temperature and diluted with boiling Et_2O (10 mL). The aqueous layer was extracted with Et_2O (5 × 100 mL) until extraction was complete (TLC control, silica, 15:85 EtOAc−hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The black, crude material was dissolved in hot 4:1 EtOH-acetone, and applied directly to a column of flash chromatography silica gel (5 × 20 cm). The column was developed using 15:85 EtOAc−hexane, to give **7** (9.698 g, 81%) as a white solid: mp 97 °C; FTIR (CH_2Cl_2 cast) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3 H), 3.82 (s, 3 H), 3.92 (s, 3 H), 6.83 (AB q, $\Delta\nu_{AB}$ = 16.0 Hz, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.8 (q′), 56.6 (q′), 57.0 (q′), 109.9 (s′), 110.9 (d′), 113.1 (d′), 127.5 (s′), 150.3 (s′), 150.8 (s′), 166.5 (s′); exact mass (HR electrospray) m/z calcd for $C_{10}H_{11}{}^{79}BrNaO_4$ (M + Na) 296.97384, found 296.97328. Anal. Calcd for $C_{10}H_{11}BrO_4$: C, 43.66; H, 4.03. Found: C, 43.59; H, 3.85.

2-Bromo-3,6-dimethoxybenzaldehyde (8). (a) (2-Bromo-3,6-dimethoxyphenyl)methanol. DIBAL (1.0 M in hexanes, 70.7 mL, 71 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of ester **7** (9.692 g, 35.37 mmol) in dry PhMe (250 mL). The mixture was stirred at −78 °C for 2 h and then stirred for 1 h at 0 °C (ice bath). Stirring was continued for another 6 h without recharging the ice bath. The solution was recooled (−78 °C), and MeOH (10 mL), $Na_2SO_4{\cdot}10H_2O$ (4 g), Celite (6.0 g), and water (2 mL) were added successively. The cold bath was removed, and stirring was continued for 30 min. The slurry was filtered through a sintered disk funnel and washed with EtOAc. The filtrate was concentrated, and the residue was dissolved in a small amount of EtOAc and purified by flash chromatography over silica gel (5 × 20 cm), using 1:4 EtOAc−hexane, to give (2-bromo-3,6-dimethoxyphenyl)methanol (8.78 g, 99%) as a white solid: mp 127−128 °C; FTIR (CH_2Cl_2 cast) 3489 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2 .44 (t, J = 7 Hz, 1 H), 3.82 (s, 6 H), 4.83 (d, J = 7 Hz, 2 H), 6.85 (s, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 56.6 (q′), 57.1 (q′), 60.6 (t′), 110.6 (d′), 112.0 (d′), 115.2 (s′), 130.5 (s′), 150.7 (s′), 153.0 (s′); exact mass (HR electrospray) m/z calcd for $C_9H_{11}{}^{79}BrNaO_3$ (M + Na) 268.97892, found 268.97943. Anal. Calcd for $C_9H_{11}BrO_3$: C, 43.75; H, 4.49. Found: C, 43.68; H, 4.32.

(b) 2-Bromo-3,6-dimethoxybenzaldehyde (8). A mixture of PCC (9.795 g, 45.52 mmol) and powdered 4 Å molecular sieves (3.0 g) was added to a stirred solution of (2-bromo-3,6-dimethoxyphenyl)methanol (8.012 g, 32.52 mmol) in dry CH_2Cl_2 (200 mL). Stirring was continued for 10 h, by which time oxidation was complete. The solvent was evaporated to approximately 50 mL, and the slurry was filtered through a pad (5 × 3 cm) of silica gel which was washed with 1:1 EtOAc−hexane (400 mL, TLC control, silica, 1:1 EtOAc−hexane). The filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (15 mL) and purified by flash chromatography over silica gel (5 × 15 cm), using 2:3 EtOAc−hexane, to give aldehyde **8**[9] (7.530 g, 95%) as a white solid: mp 99.5 °C (lit.[9] mp 102−103 °C); FTIR (CH_2Cl_2 cast) 1695 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.82 (s, 3 H), 3.84 (s, 3 H), 7.00 (AB q, $\Delta\nu_{AB}$ = 49.5 Hz, J = 9.1 Hz, 2 H), 7.11 (d, J = 9.1 Hz, 1 H) 10.41 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 56.6 (q′), 57.2 (q′), 111.4 (d′), 114.8 (s′), 117.1 (d′), 124.8 (s′), 150.4 (s′), 155.4 (s′), 190.8 (d′); exact mass (HR electrospray) m/z calcd for $C_9H_9{}^{79}BrNaO_3$ (M + Na) 266.96327, found 266.96351. Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 43.94; H, 3.26.

2-Bromo-6-hydroxy-3-methoxybenzaldehyde (9). BCl_3 (1.0 M in hexanes, 59 mL, 59 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of aldehyde **8** (4.805 g, 19.69 mmol) in dry CH_2Cl_2 (200 mL). The resulting bright red solution was stirred for 10 h without recharging the cold bath. The solution was recooled to 0 °C, and ice−water (100 mL) was added slowly. The resulting deep yellow solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The yellow residue was dissolved in CH_2Cl_2 (5 mL) and purified by flash chromatography over silica gel (4 × 20 cm), using 15:85 EtOAc−hexane, to give aldehyde **9** (4.317 g, 96%) as a yellow solid: mp 89 °C; FTIR (CH_2Cl_2 cast) 1645 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.89 (s, 3 H), 6.95 (d, J = 9.1 Hz, 1 H), 7.21 (d, J = 9.1 Hz, 1 H), 10.41 (s, 1 H), 11.51 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 57.8 (q′), 116.4 (s′), 117.8 (d′), 118.3 (s′), 122.7 (d′), 149.7 (s′), 158.2 (s′), 198.6 (d′); exact mass m/z calcd for $C_8H_8{}^{79}BrO_3$ (M + H) 230.96568, found 230.96632. Anal. Calcd for $C_8H_7BrO_3$: C, 41.59; H, 3.05. Found: C, 41.67; H, 2.72.

2-Bromo-3-methoxy-6-(2-propenyloxy)benzaldehyde (10). Aldehyde **9** (6.14 g, 26.59 mmol) in DMF (5 mL) was added dropwise to a stirred and cooled (0 °C) slurry of NaH (772.5 mg, 30.58 mmol) in dry DMF (30 mL).[26] The cold bath was removed, and the resulting bright yellow slurry was stirred for 1 h. The solution was recooled to 0 °C, and allyl bromide (4.60 mL, 53.2 mmol) was added dropwise. The cold bath was removed, and stirring was continued for 4 h. The mixture was poured into brine (50 mL) and extracted with Et_2O. The combined organic extracts were washed with aqueous KOH (10%, 20 mL) and brine, dried ($MgSO_4$), and evaporated. The pale yellow crude residue was dissolved in CH_2Cl_2 (5 mL) and purified by flash chromatography over silica gel (4 × 20 cm), using 1:4 EtOAc−hexane, to give allyl ether **10** (6.01 g, 83%) as a white, crystalline solid: mp 77 °C; FTIR (CH_2Cl_2 cast), 1696 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.87 (s, 3 H), 4.57 (d, J = 6 Hz, 2 H), 5.29 (d, J = 12 Hz, 1 H), 5.43 (d, J = 18 Hz, 1 H), 6.00−6.09 (m, 1 H), 7.02 (AB q, $\Delta\nu_{AB}$ = 44.5 Hz, J = 9.1 Hz, 2 H), 7.07 (d, J = 9 Hz, 1 H), 10.38 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 57.4 (q′), 70.8 (t′), 113.6 (d′), 113.7 (s′), 117.3 (d′), 118.0 (t′), 125.8 (s′), 133.0 (d′), 151.1 (s′), 154.8 (s′), 190.7 (d′); exact mass (HR electrospray) m/z calcd for $C_{11}H_{11}{}^{79}BrO_3Na$ (M + Na) 292.97892, found 292.97870.

2-Bromo-6-hydroxy-3-methoxy-5-(2-propenyl)benzaldehyde (11). *trans*-Decalin was degassed by several freeze−thaw cycles (liquid N_2/oil-pump vacuum). A solution of aldehyde **10** (810.0 mg, 3.011 mmol) in degassed decalin (3 mL) was refluxed under Ar for 6.5 h and then cooled to room temperature. Flash chromatography of the mixture (without evaporation of the solvent) over silica gel (2 × 15 cm), using 1:12 EtOAc−hexane, gave phenol **11** (602.8 mg, 74%) as a yellow oil: FTIR (CH_2Cl_2 cast) 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.40 (d, J = 6 Hz, 2 H), 3.87 (s, 3 H), 5.05−5.20 (m, 2 H), 5.85−6.07 (m, 1 H), 7.06 (s, 1 H), 10.40 (s, 1 H), 11.90 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 33.5 (t′), 57.9 (q′),

(26) Cf. Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513.

113.7 (s′), 116.8 (t′), 117.6 (s′), 123.2 (d′), 129.6 (s′), 135.6 (d′), 149.2 (s′), 156.3 (s′), 198.8 (d′); exact mass (HR electrospray) *m*/*z* calcd for $C_{11}H_{11}{}^{79}BrNaO_3$ (M + Na) 292.97892, found 292.97870.

2-Bromo-3,6-dimethoxy-5-(2-propenyl)benzaldehyde (12). MeI (4.74 g, 2.08 mL, 33.4 mmol) was added dropwise to a stirred mixture of phenol **11** (1.808 g, 6.696 mmol) and K_2CO_3 (4.587 g, 33.37 mmol) in dry DMF (20 mL). The mixture was warmed to 70 °C, and stirring was continued for 10 h at this temperature. The solids were filtered off, and the filtrate was poured into brine (20 mL) and extracted with Et_2O. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 × 20 cm), using 1:4 EtOAc−hexane, gave aldehyde **12** (1.857 g, 97%) as a yellowish-white solid: mp 50 °C; FTIR (CH_2Cl_2 cast) 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.43 (dt, J = 6.5, 1.3 Hz, 2 H), 3.80 (s, 3 H), 3.90 (s, 3 H), 5.08−5.16 (m, 2 H), 5.90−6.00 (m, 1 H), 6.95 (s, 1 H), 10.38 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 33.7 (t′), 57.2 (q′), 63.9 (q′), 111.6 (s′), 116.9 (t′), 118.1 (d′), 129.7 (s′), 135.1 (s′), 136.4 (d′), 153.0 (s′), 153.6 (s′), 191.4 (d′); exact mass *m*/*z* calcd for $C_{12}H_{13}{}^{81}BrO_3$ 286.00275, found 286.00154.

1-Bromo-2-(dimethoxymethyl)-3,6-dimethoxy-4-(2-propenyl)benzene (13). $CH(OMe)_3$ (3.0 mL, 27.4 mmol) was added dropwise to a stirred solution of aldehyde **12** (1.211 g, 4.248 mmol) in dry MeOH (3 mL) containing $TsOH\cdot H_2O$ (5.0 mg). The mixture was warmed to 70 °C and stirring was continued for 3.5 h at this temperature. The mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3 × 18 cm), using 1:4 EtOAc−hexane, gave ketal **13** (1.345 g, 96%) as a colorless oil: ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.37 (d, J = 6.3 Hz, 2 H), 3.43 (s, 6 H), 3.71 (s, 3 H), 3.83 (s, 3 H), 5.07−5.16 (m, 2 H), 5.68 (s, 1 H), 5.90−6.04 (m, 1 H), 6.77 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.1 (t′), 56.0 (two overlapping q′), 57.0 (q′), 63.1 (q′), 105.4 (d′), 110.5 (s′), 114.0 (d′), 116.5 (t′), 132.1 (s′), 134.1 (s′), 137.0 (d′), 151.0 (s′), 152.9 (s′); exact mass *m*/*z* calcd for $C_{14}H_{19}{}^{79}BrO_4$ 330.0467138, found 284.00485 (M − C_2H_6O).

Methyl 3,6-Dimethoxy-2-(dimethoxymethyl)-4-(2-propenyl)benzoate (14). BuLi (1.6 M in hexanes, 3.7 mL, 9.2 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of bromide **13** (2.024 g, 6.116 mmol) in dry THF (50 mL), and the resultant pale brown solution was stirred at −78 °C for 25 min. MeOC(O)CN (0.85 mL, 10.7 mmol) in THF (0.85 mL) was then added dropwise over 5 min. Stirring was continued at −78 °C for 20 min, and the cold bath was removed. The mixture was allowed to warm to 0 °C (ca. 10 min) and was then diluted with water (20 mL) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the pale yellow residue over silica gel (3 × 22 cm), using 1:3 EtOAc−hexane, gave ester **14** (1.673 g, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1737 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.34 (s, 6 H), 3.44 (d, J = 6 Hz, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 5.09−5.15 (m, 2 H), 5.47 (s, 1 H), 5.91−6.02 (m, 1 H), 6.82 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.1 (t′), 52.1 (q′), 55.2 (q′), 56.7 (q′), 62.6 (q′), 101.6 (d′), 113.9 (d′), 116.6 (t′), 121.9 (s′), 130.4 (s′), 135.6 (s′), 136.9 (d′), 150.5 (s′), 152.7 (s′), 168.0 (s′); exact mass *m*/*z* calcd for $C_{16}H_{22}O_6$ 310.14163, found 310.14154.

[2-(Dimethoxymethyl)-3,6-dimethoxy-4-(2-propenyl)-phenyl]methanol (15). DIBAL (1.0 M in hexanes, 3.9 mL, 3.9 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of ester **14** (596.8 mg, 1.925 mmol) in dry PhMe (20 mL). The mixture was stirred at −78 °C for 1 h and then DIBAL (1.0 M in hexanes, 1.9 mL, 1.9 mmol) was added, and stirring was continued for 1 h (TLC control, silica, 1:4 EtOAc−hexane). MeOH (3 mL), $Na_2SO_4\cdot 10H_2O$ (2.0 g), Celite (1.0 g) and water (1 mL) were added successively. The cold bath was removed and stirring was continued for 30 min. The slurry was filtered through a short pad of Celite on a sintered disk and the pad was washed with EtOAc. The filtrate was evaporated and the residue was dissolved in a small amount of EtOAc and purified by flash chromatography over silica gel (2 × 20 cm), using 1:4 EtOAc−hexane, to give **15** (504.9 mg, 93%) as a white solid: FTIR (CH_2Cl_2 cast) 3430 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.97 (t, J = 6 Hz, 1 H), 3.44 (d, J = 6.5 Hz, 2 H), 3.48 (s, 6 H), 3.67 (s, 3 H), 3.81 (s, 3 H), 4.81 (d, J = 6 Hz, 2 H), 5.08−5.10 (m, 1 H), 5.11−5.13 (m, 1 H), 5.61 (s, 1 H), 5.93−6.04 (m, 1 H), 6.76 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.3 (t′), 55.5 (t′), 56.4 (q′), 56.6 (q′), 62.9 (two q′), 103.9 (d′), 114.0 (d′), 116.2 (t′), 128.2 (s′), 131.7 (s′), 133.3 (s′), 137.3 (d′), 150.4 (s′), 155.0 (s′); exact mass *m*/*z* calcd for $C_{15}H_{22}O_5$, 282.14671, found 282.14673.

1,3-Dihydro-4,7-dimethoxy-6-(2-propenyl)isobenzofuran-1-ol (16) and 1,3-Dihydro-1,4,7-trimethoxy-6-(2-propenyl)isobenzofuran. Dilute hydrochloric acid (0.1 M, 10 mL) was added dropwise to a stirred solution of acetal **15** (1.304 g, 4.624 mmol) in dioxane (10 mL). Stirring was continued for 12 h, by which time all the starting material had been consumed (TLC control, silica, 2:3 EtOAc−hexane). The mixture was neutralized with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 18 cm), using 1:4 EtOAc−hexane, gave lactol **16** (778.1 mg, 71%) as a white solid and the corresponding methyl ether [1,3-dihydro-1,4,7-trimethoxy-6-(2-propenyl)isobenzofuran] (276.7 mg, 24%) as a colorless oil. Lactol **16** had: mp 157.5 °C; FTIR (CH_2Cl_2 cast) 3335 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.31−3.45 (m, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 4.88 (d, J = 12 Hz, 2 H), 5.01−5.18 (m, 2 H), 5.88−6.09 (m, 1 H), 6.59 (dd, J = 6, 1.8 Hz, 1 H), 6.7 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.4 (t′), 56.0 (q′), 61.4 (q′), 70.6 (t′), 101.0 (d′), 113.7 (d′), 115.7 (t′), 127.7 (s′), 132.3 (s′), 133.5 (s′), 137.6 (d′), 147.4 (s′), 149.7 (s′); exact mass (HR electrospray) *m*/*z* calcd for $C_{13}H_{16}NaO_4$ (M + Na) 259.09463, found 259.09467.

1,3-Dihydro-1,4,7-trimethoxy-6-(2-propenyl)isobenzofuran: ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.41 (s, 3 H), 3.42 (m, 2 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 4.82−5.15 (m, 4 H), 5.85−6.12 (m, 1 H), 6.25 (d, J = 3 Hz, 1 H), 6.68 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 35.9 (t′), 55.8 (q′), 57.5 (q′), 62.7 (q′), 72.3 (t′), 108.5 (d′), 115.2 (d′), 117.3 (t′), 129.8 (s′), 132.1 (s′), 134.7 (s′), 139.3 (d′), 149.0 (s′), 151.1 (s′); exact mass (HR electrospray) *m*/*z* calcd for $C_{14}H_{18}NaO_4$ (M + Na) 273.11028, found 273.10998.

The 1,3-dihydro-1,4,7-trimethoxy-6-(2-propenyl)isobenzofuran was hydrolyzed to lactol **16**, as follows. Dilute hydrochloric acid (0.1 M, 12 mL) was added dropwise to a stirred solution of the lactol methyl ether (1.146 g, 4.58 mmol) in dioxane (10 mL). Stirring was continued for 12 h, by which time all the starting material had been consumed (TLC control, silica, 2:3 EtOAc−hexane). The mixture was neutralized with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 18 cm), using 1:4 EtOAc−hexane, gave lactol **16** (737 mg, 68%).

***(E)*- and *(Z)*-[3,6-Dimethoxy-2-(2-methoxyethenyl)-4-(2-propenyl)phenyl]methanol (17).** (Methoxymethyl)triphenylphosphonium bromide (511.3, 1.483 mmol) was placed in a long-necked flask and dry THF (2 mL) was added. The white slurry was stirred and cooled to −78 °C, and $(Me_3Si)_2NK$ (0.5 M solution in PhMe, 1.7 mL, 0.85 mmol) was added dropwise over 5 min. The resulting red slurry was stirred at −78 °C for 2 h, and a solution of lactol **16** (100.0 mg, 0.424 mmol) in dry THF (1 mL plus 1 mL as a rinse) was added dropwise over ca. 5 min. The resulting pale orange solution was stirred for 10 h without recharging the cold bath. The resulting white slurry was filtered off using a sintered disk, and washed with EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 × 15 cm), using 1:4 EtOAc−hexane, gave the isomeric enol ethers (*E*)-**17** (70.8 mg, 63%) and (*Z*)-**17** (33.5 mg, 30%) as colorless oils. Compound (*E*)-**17**: FTIR (CH_2Cl_2 cast) 3462 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.16 (t, J = 6.9 Hz, 1 H), 3.40 (dt, J = 1.4, 6.6 Hz, 2 H), 3.62 (s, 3 H), 3.71 (s, 3 H), 3.84 (s, 3 H), 4.65 (d, J = 6.9 Hz, 2 H), 5.05−5.14 (m, 2 H), 5.85 (d, J = 15 Hz, 1 H), 5.92−6.05 (m, 1 H), 6.61 (s, 1 H), 6.99 (d, J = 15 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5

MHz) δ 34.7 (t′), 56.1 (q′), 56.7 (q′), 58.0 (t′), 60.4 (q′), 98.0 (d′), 110.1 (d′), 115.9 (t′), 126.0 (s′), 130.8 (s′), 133.4 (s′), 137.7 (d′), 150.1 (s′), 153.1 (d′), 154.9 (s′); exact mass (HR electrospray) *m/z* calcd for $C_{15}H_{20}NaO_4$ (M + Na) 287.12593, found 287.12595.

Compound (*Z*)-**17**: FTIR (CH_2Cl_2 cast) 3462 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.78 (t, *J* = 6.9 Hz, 1 H), 3.40 (dt, *J* = 1.4, 6.6 Hz, 2 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.82 (s, 3 H), 4.54 (d, *J* = 6.9 Hz, 2 H), 5.05−5.14 (m, 2 H), 5.41 (d, *J* = 6.8 Hz, 1 H), 5.93−6.23 (m, 1 H), 6.25 (d, *J* = 6.8 Hz, 1 H), 6.67 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.5 (t′), 56.1 (q′), 59.2 (t′), 60.3 (q′), 61.0 (q′), 100.8 (d′), 111.3 (d′), 116.0 (t′), 127.7 (s′), 129.1 (s′), 133.0 (s′), 137.7 (d′), 148.4 (d′), 150.2 (s′), 154.8 (s′); exact mass (HR electrospray) *m/z* calcd for $C_{15}H_{20}NaO_4$ (M + Na) 287.12593, found 287.12572.

5,8-Dimethoxy-6-(2-propenyl)isochroman-3-ol (18). Dilute hydrochloric acid (0.1 M, 21.9 mL), was added dropwise to a stirred solution of enol ethers **17** (1.822 g, 6.90 mmol) in dioxane (70 mL), and the mixture was then heated at 60 °C for 3 h, by which point all the starting material had reacted (TLC control, silica, 2:3 EtOAc−hexane). The mixture was cooled to room temperature and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 20 cm), using 1:2 EtOAc−hexane, gave lactol **18** (1.500 g, 86%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3404 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.71 (dd, *J* = 11.5, 5.2 Hz, 1 H), 3.00 (dd, *J* = 16.6, 3.6 Hz, 1 H), 3.08 (d, *J* = 4.5 Hz, 1 H), 3.39 (d, *J* = 6.6 Hz, 2 H), 3.65 (s, 3 H), 3.76 (s, 3 H), 4.66 (d, *J* = 16 Hz, 1 H), 4.85 (d, *J* = 16 Hz, 1 H), 5.05−5.14 (m, 2 H), 5.22−5.29 (m, 1 H), 5.93−6.03 (m, 1 H), 6.54 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 30.0 (t′), 34.4 (t′), 55.7 (q′), 60.7 (t′), 61.0 (q′), 92.4 (d′), 109.4 (d′), 115.8 (t′), 121.7 (s′), 126.2 (s′), 131.5 (s′), 137.8 (d′), 150.0 (s′), 151.6 (s′); exact mass *m/z* calcd for $C_{14}H_{18}O_4$ 250.12051, found 250.11985.

5,8-Dimethoxy-6-(2-propenyl)isochroman (2). Freshly distilled $BF_3{\cdot}Et_2O$ (270 μL, 2.12 mmol) was added dropwise to a stirred and cooled (−78 °C) mixture of Et_3SiH[14] (freshly distilled, 462 μL, 2.90 mmol) and lactol **18** (482 mg, 1.93 mmol) in dry CH_2Cl_2 (15 mL). After 2 h the cold bath was removed, stirring was continued for 18 h, and the mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The resulting mixture was extracted with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 2:3 EtOAc−hexanes, gave isochroman **2** (423 mg, 93%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.82 (t, *J* = 5.6 Hz, 2 H), 3.42 (d, *J* = 6.5 Hz, 2 H), 3.70 (s, 3 H), 3.77 (s, 3 H), 3.91 (t, *J* = 5.6 Hz, 2 H), 4.70 (s, 2 H), 5.08−5.13 (m, 2 H), 5.94−6.04 (m, 1 H), 6.51 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.5 (t′), 34.1 (t′), 55.3 (q′), 60.7 (q′), 64.3 (t′), 64.5 (t′), 108.7 (d′), 115.8 (t′), 122.7 (s′), 128.1 (s′), 130.4 (s′), 137.3 (d′), 149.4 (s′), 151.6 (s′); exact mass *m/z* calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1249.

(*E*)-5,8-Dimethoxy-6-(1-propenyl)isochroman (19). $RhCl_3{\cdot}3H_2O$ (22.9 mg, 5 mol %) was added to a stirred solution of olefin **2** (406 mg, 1.73 mmol) in dry 5:1 PhMe-MeOH (28.8 mL). The mixture was refluxed for 16 h, cooled, and evaporated. Flash chromatography of the residue over silica, using 1:3 EtOAc−hexanes, gave olefin **19** (393 mg, 97%) as a white crystalline solid: mp 60−65 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.93 (dd, *J* = 6.6, 1.6 Hz, 3 H), 2.80 (t, *J* = 5.6 Hz, 2 H), 3.69 (s, 3 H), 3.80 (s, 3 H), 3.91 (t, *J* = 5.6 Hz, 2 H), 4.70 (s, 2 H), 6.23 (dq, *J* = 15.8, 6.6 Hz, 1 H), 6.66 (dd, *J* = 15.9, 1.7 Hz, 1 H), 6.75 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.8 (q′), 23.3 (t′), 55.3 (q′), 60.9 (q′), 64.3 (t′), 64.6 (t′), 104.2 (d′), 123.6 (s′), 125.6 (d′), 126.3 (d′), 128.2 (s′), 128.7 (s′), 148.6 (s′), 151.8 (s′); exact mass *m/z* calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1254.

5,8-Dimethoxyisochroman-6-carbaldehyde (20). OsO_4 (7.0 mg, 5 mol %) was added to a stirred solution of olefins **19** (129 mg, 0.551 mmol) in 5:2:2 CCl_4-water-*t*-BuOH (13.5 mL) (the starting material was dissolved in CCl_4-*t*-BuOH, and the water was added last). The mixture was stirred and, after 15 min, $NaIO_4$ (300 mg, 1.38 mmol) was added in one portion. After a further 1.5 h the suspension was diluted with water (5 mL) and extracted with Et_2O. The organic extracts were washed with 10% aqueous $NaHSO_3$ and water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.8 × 20 cm), using 1:4 EtOAc−hexanes, gave aldehyde **20** (117 mg, 97%) as a brown solid: mp 144−149 °C; FTIR ($CDCl_3$ cast) 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.85 (t, *J* = 5.6 Hz, 2 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.93 (t, *J* = 5.6 Hz, 2 H), 4.74 (s, 2 H), 7.12 (s, 1 H), 10.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.9 (t′), 55.6 (q′), 63.6 (q′), 64.1 (t′), 64.5 (t′), 104.5 (d′), 126.9 (s′), 129.4 (s′), 132.9 (s′), 152.1 (s′), 155.9 (s′), 189.6 (d′); exact mass *m/z* calcd for $C_{12}H_{14}O_4$ 222.0892, found 222.0893.

(5,8-Dimethoxyisochroman-6-yl)-2-methyl-2-propen-1-ol (21). Isopropenylmagnesium bromide (0.5 M in hexanes, 6.22 mL, 3.89 mmol) was added dropwise to a stirred and cooled (0 °C) solution of aldehyde **20** (576 mg, 2.59 mmol) in dry Et_2O (50 mL). After 30 min, the cold bath was removed and stirring was continued for 1 h. The mixture was recooled (0 °C), quenched with saturated aqueous NH_4Cl (10 mL), and taken up in Et_2O (50 mL). The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 EtOAc−hexanes, gave alcohol **21** (590 mg, 86%) as a colorless oil: FTIR ($CDCl_3$ cast) 3417 cm^{-1} (br); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.69 (s, 3 H), 2.40 (br s, 1 H), 2.81 (t, *J* = 5.5 Hz, 2 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 3.84−3.96 (m, 2 H), 4.64−4.72 (m, 2 H), 5.01−5.03 (m, 1 H), 5.21 (s, 1 H), 5.41 (s, 1 H), 6.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.5 (q′), 23.5 (d′), 55.4 (q′), 61.2 (q′), 64.3 (t′), 64.4 (t′), 72.3 (d′), 105.9 (d′), 110.9 (t′), 124.5 (s′), 128.3 (s′), 132.4 (s′), 146.8 (s′), 149.4 (s′), 151.8 (s′); exact mass *m/z* calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1360.

(5,8-Dimethoxyisochroman-6-yl)-2-methyl-2-propen-1-one (22). Dess−Martin periodinane (80 mg, 0.19 mmol) was added to a stirred solution of allylic alcohol **21** (32.6 mg, 0.126 mmol) in dry CH_2Cl_2 (2.5 mL). After 1 h, the mixture was diluted with EtOAc (5 mL) and then stirred for 5 min with saturated aqueous $NaHCO_3$ (2.5 mL) containing $Na_2S_2O_3$ (250 mg). More water (10 mL) was added, and the aqueous layer was extracted with EtOAc. The combined extracts were evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 EtOAc−hexanes, gave enone **22** (32.0 mg, 96%) as a white crystalline solid: mp 90−92 °C; FTIR ($CDCl_3$ cast) 1662 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 3 H), 2.80 (t, *J* = 5.5 Hz, 2 H), 3.65 (s, 3 H), 3.77 (s, 3 H), 3.92 (t, *J* = 5.6 Hz, 2 H), 4.71 (s, 2 H), 5.69 (s, 1 H), 5.96 (t, *J* = 1.2 Hz, 1 H), 6.57 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.3 (q′), 23.3 (t′), 55.5 (q′), 62.0 (q′), 64.2 (t′), 64.3 (t′), 107.1 (d′), 127.1 (s′), 128.7 (s′), 129.4 (s′), 130.6 (s′), 144.9 (s′), 149.0 (s′), 151.0 (s′), 198.4 (s′); exact mass *m/z* calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1203.

2,3,7,8-Tetrahydro-5*H*-4,9-dimethoxy-2-methyl-6-oxacyclopenta[*b*]naphthalen-1-one (3). Cold (0 °C) concentrated H_2SO_4 (0.1 mL) was added to stirred enone **22**. The resulting brown solution was stirred for 5 h at 0 °C, diluted with ice-cold water (10 mL) and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:3 EtOAc−hexanes, gave indanone **3** (26.6 mg, 83%) as a white crystalline solid: mp 123 °C; FTIR (CH_2Cl_2 cast) 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, *J* = 7.2 Hz, 3 H), 2.60−2.71 (m, 2 H), 2.81 (t, *J* = 5.7 Hz, 2 H), 3.38 (q, *J* = 8.8 Hz, 1 H), 3.80 (s, 3 H), 3.86 (t, *J* = 5.8 Hz, 2 H), 3.87 (s, 3 H), 4.81 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.5 (q′), 22.9 (t′), 31.7 (t′), 42.4 (d′), 59.8 (q′), 61.4 (q′), 64.6 (d′), 64.7 (d′), 126.8 (s′), 127.4 (s′), 136.3 (s′), 142.2 (s′), 148.4 (s′), 152.0 (s′), 206.0 (s′); exact mass (HR electrospray) *m/z* calcd for $C_{15}H_{18}NaO_4$ (M + Na) 285.11028, found 285.10978.

Methyl 2,3,7,8-Tetrahydro-5*H*-4,9-dimethoxy-2-methyl-1-oxo-6-oxacyclopenta[*b*]naphthalene-2-carboxylate (23). BuLi (2.5 M in hexanes, 0.74 mL, 1.85 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (278 μL, 1.98 mmol) in THF (5 mL). Stirring was continued for 30 min, and the resulting LDA solution was added dropwise

by cannula over ca. 10 min to a stirred and cooled (−78 °C) solution of indanone **3** (371 mg, 1.42 mmol) in THF (15 mL). Stirring was continued for 40 min and the resulting lithium enolate was quenched with neat Mander's reagent [MeOC(O)-CN (184 μL, 1.98 mmol)]. After 20 min, the mixture was transferred to a cold bath at 0 °C, and stirring was continued for 10 min. The mixture was recooled to −78 °C, and saturated aqueous NH_4Cl (5 mL) was added. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:4 EtOAc−hexanes, gave ester **23** [269 mg, 59% or 82% after correction for recovered starting material (103 mg)] as a colorless liquid: FTIR ($CDCl_3$ cast) 1745, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.59 (s, 3 H), 2.82 (t, J = 5.7 Hz, 2 H), 2.95 (d, J = 17 Hz, 1 H), 3.66 (d, J = 17 Hz, 1 H), 3.69 (s, 3 H), 3.83 (s, 3 H), 3.92 (t, J = 5.8 Hz, 2 H), 3.94 (s, 3 H), 4.81 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.3 (q′), 22.9 (t′), 36.7 (t′), 52.8 (q′), 56.4 (s′), 60.0 (q′), 61.7 (q′), 64.60 (t′), 64.63 (t′), 125.1 (s′), 128.0 (s′), 137.3 (s′), 141.1 (s′), 148.3 (s′), 152.8 (s′), 172.5 (s′), 200.0 (s′); exact mass m/z calcd for $C_{17}H_{20}O_6$ 320.1260, found 320.1253.

Methyl 2,3,7,8-Tetrahydro-1-hydroxy-5*H*-4,9-dimethoxy-2-methyl-6-oxacyclopenta[*b*]naphthalene-2-carboxylate (24). $NaBH_4$ (95 mg, 2.52 mmol) was added in several portions over 40 min to a stirred and cooled (0 °C) solution of ketone **23** (269 mg, 0.84 mmol) in dry MeOH (20 mL). After 1 h at 0 °C, water (2 mL) was added, and the resulting cooled solution was stirred for 30 min, and then extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:24:75 MeOH−EtOAc−hexanes, gave alcohols **24** (268 mg, 99%) as a colorless oil: FTIR ($CHCl_3$ cast) 3430, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (mixture of diastereoisomers) δ 1.25 (s, 0.71), 1.35 (s, 2.4 H), 1.59 (s, 0.91 H), 2.60 (d, J = 7.8 Hz, 0.69 H), 2.68−2.86 (m, 2 H), 2.92 (d, J = 15.8 Hz, 0.8 H), 3.37 (d, J = 15.8 Hz, 0.8 H), 3.73−3.96 (m including three s, 10.5 H in all), 4.73 (s, 2 H), 5.09 (d, J = 4.5 Hz, 0.16 H); ^{13}C NMR ($CDCl_3$, 106 MHz) (mixture of diastereoisomers) δ 18.3 (q′), 23.2 (t′), 23.3 (t′), 23.4 (q′), 37.2 (t′), 38.7 (t′), 52.3 (q′), 52.4 (q′), 55.2 (t′), 55.4 (t′), 59.8 (q′), 60.6 (q′), 61.4 (q′), 64.6 (t′), 64.7 (t′), 77.8 (d′), 79.3 (d′), 126.7 (s′), 126.9 (s′), 129.0 (s′), 129.5 (s′), 129.7 (s′), 131.2 (s′), 132.3 (s′), 133.0 (s′), 148.4 (s′), 150.7 (s′), 151.3 (s′), 176.9 (s′); exact mass m/z calcd for $C_{17}H_{22}O_6$ 322.1416, found 322.1413.

Methyl 1-Chloro-2,3,7,8-tetrahydro-5*H*-4,9-dimethoxy-2-methyl-6-oxacyclopenta[*b*]naphthalene-2-carboxylate (25). $SOCl_2$ (121 μL, 1.66 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohols **24** (268 mg, 0.832 mmol) and Et_3N (232 μL, 1.66 mmol) in dry CH_2Cl_2 (5 mL). After 30 min the cold bath was removed, and the mixture was refluxed for 4 h. The mixture was cooled and poured into water (10 mL). The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:5 EtOAc−hexanes, gave chlorides **25** [153 mg, 54% or 93% after correction for recovered starting material (114 mg)] as a colorless liquid: FTIR ($CHCl_3$ cast) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (mixture of diastereoisomers) δ 1.31 (s, 1.4 H), 1.61 (s, 2.0 H), 2.69−2.90 [m including d (J = 20.6 Hz) at δ 2.85, 2.46 H in all], 2.96 (d, J = 15.6 Hz, 0.59 H), 3.60−3.65 [m including s and d (J = 20.6 Hz), 2.3 H in all], 3.75−4.00 [m including singlets at δ 3.78, 3.81, 3.83, 3.89, 3.90 and d at δ 3.82 (J = 15.6 Hz), 9.4 H in all], 4.68−4.79 (m, 2 H), 5.27 (s, 0.38 H), 5.86 (s, 0.46 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (mixture of diastereoisomers) δ 21.2 (q′), 23.3 (t′), 23.8 (q′), 36.7 (t′), 37.9 (t′), 52.3 (q′), 52.8 (q′), 56.9 (t′), 57.4 (t′), 59.8 (q′), 59.9 (q′), 60.8 (q′), 60.9 (q′), 64.58 (t′), 64.61 (t′), 65.9 (d′), 66.0 (d′), 127.1 (s′), 127.2 (s′), 130.1 (s′), 130.2 (s′), 130.4 (s′), 131.1 (s′), 132.2 (s′), 133.8 (s′), 147.9 (s′), 149.0 (s′), 149.8 (s′), 150.4 (s′), 173.7 (s′), 175.4 (s′); exact mass m/z calcd for $C_{17}H_{21}{}^{35}ClO_5$ 340.1078, found 340.1080.

Methyl 2,3,7,8-Tetrahydro-5*H*-4,9-dimethoxy-2-methyl-6-oxacyclopenta[*b*]naphthalene-2-carboxylate (26). A mixture of chloride **25** (138 mg, 0.405 mmol), Bu_3SnH (220 μL, 0.810 mmol) and AIBN (10 mg, 0.061 mmol) in dry PhMe (5 mL) was refluxed for 3 h. The mixture was cooled and applied to a column of silica gel (1 × 20 cm), which was developed successively with hexanes, 1:20 EtOAc−hexanes, 1:10 EtOAc−hexanes and 1:5 EtOAc−hexanes, to give **26** as a colorless oil contaminated with tin residues. Flash chromatography over silica gel, using 1:5 EtOAc−hexanes, gave ester **26** (118 mg, 95%) as a colorless oil: FTIR ($CHCl_3$ cast) 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.36 (3 H), 2.76 (t, J = 5.6 Hz, 2 H), 2.87 (d, J = 15.7 Hz, 2 H), 3.46 (dd, J = 15.8, 3.0 Hz, 2 H), 3.73−3.74 (overlapping singlets at δ 3.73, 3.735, 3.74, 9 H in all), 3.83−3.94 (m, 2 H), 4.74 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.2 (t′), 25.0 (q′), 41.0 (t′), 41.2 (t′), 50.1 (t′), 52.2 (q′), 59.6 (q′), 59.7 (q′), 64.5 (t′), 64.7 (t′), 125.8 (s′), 126.9 (s′), 130.7 (s′), 131.9 (s′), 148.3 (s′), 150.0 (s′), 177.7 (s′); exact mass m/z calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1464.

Methyl 6-[2-(Acetyloxy)ethyl]-5-chloromethyl-4,7-dimethoxy-2-methylindan-2-carboxylate (27). $ZnCl_2$ (5.5 mg, 10 mol %) and AcCl (82 μL, 1.16 mmol) were added to a stirred solution of isochroman **26** (118 mg, 0.39 mmol) in dry CH_2Cl_2 (6 mL), and the mixture was refluxed (Ar atmosphere) for 6 h. The solvent was then evaporated, and flash chromatography of the residue over silica gel (1.8 × 20 cm), using 1:4 EtOAc−hexanes, gave acetate **27** (131 mg, 88%) as a colorless oil: FTIR ($CDCl_3$ cast) 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.36 (s, 3 H), 2.05 (s, 3 H), 2.89 (dd, J = 16.1, 2.8 Hz, 2 H), 3.05 (t, J = 7.2 Hz, 2 H), 3.47 (d, J = 10.3 Hz, 1 H), 3.51 (d, J = 10.5 Hz, 1 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 4.21 (t, J = 7.6 Hz, 2 H), 4.76 (AB q, $\Delta\nu_{AB}$ = 25.5 Hz, J = 10.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.0 (q′), 25.0 (q′), 26.1 (t′), 38.2 (t′), 41.2 (t′), 41.6 (t′), 50.1 (t′), 52.2 (q′), 60.2 (q′), 60.9 (q′), 64.1 (t′), 128.9 (s′), 133.5 (s′), 135.2 (s′), 151.2 (s′), 151.6 (s′), 170.9 (s′), 177.5 (s′) (two signals in this spectrum overlap); exact mass m/z calcd for $C_{19}H_{25}{}^{35}ClO_6$ 384.1340, found 384.1337.

Methyl 6-[2-(Acetyloxy)ethyl]-4,7-dimethoxy-2,5-dimethylindan-2-carboxylate (28). Bu_3SnH (136 μL, 0.51 mmol) and AIBN (7 mg, 15 mol %) were added to a stirred solution of chloride **27** (97.8 mg, 0.25 mmol) in PhMe (6 mL), and the mixture was refluxed for 1.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:9 EtOAc−hexanes, gave acetate **28** contaminated with tin residues. Flash chromatography over silica gel (1.8 × 12 cm), using 1:9 EtOAc−hexanes, gave acetate **28** (77.3 mg, 87%) as a colorless oil: FTIR ($CDCl_3$ cast) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.35 (s, 3 H), 2.05 (s, 3 H), 2.23 (s, 3 H), 2.87 (dd, J = 15.4, 4.0 Hz, 2 H), 2.96 (dt, J = 7.7, 2.2 Hz, 2 H), 3.44 (d, J = 13.0 Hz, 1 H), 3.48 (d, J = 12.9 Hz, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 4.14 (t, J = 7.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 12.1 (q′), 21.1 (q′), 25.2 (q′), 26.6 (t′), 41.1 (t′), 41.6 (t′), 50.1 (t′), 52.2 (q′), 60.0 (q′), 60.2 (q′), 63.8 (t′), 127.9 (s′), 129.3 (s′), 131.1 (s′), 133.3 (s′), 150.9 (s′), 151.5 (s′), 171.1 (s′), 177.8 (s′); exact mass m/z calcd for $C_{19}H_{26}O_6$ 350.1730, found 350.1727.

6-(2-Hydroxyethyl)-4,7-dimethoxy-2,5-dimethylindan-2-carboxylic Acid (29). $LiOH{\cdot}H_2O$ (28.0 mg, 0.66 mmol) was added to a stirred solution of ester **28** (15.3 mg, 0.044 mmol) in 1:1 dioxane-water (4 mL). After 3 h, the mixture was acidified with hydrochloric acid (1.0 M, 4 mL) and then extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 20 cm), using 1:19 MeOH−CH_2Cl_2, gave alcohol **29** (11.6 mg, 90%) as a white solid: FTIR ($CHCl_3$ cast) 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 3 H), 2.09 (s, 1 H), 2.21 (s, 3 H), 3.18−3.27 [m including dd (J = 15.8, 3.6 Hz) at δ 3.2 and t (J = 6.7 Hz) at δ 3.25, 4 H in all), 3.87 (d, J = 11.7 Hz, 1 H), 3.92 (d, J = 11.6 Hz, 1 H), 4.11 (s, 3 H), 3.72−3.80 (m including s at δ 4.17, 5 H in all); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 12.2 (q′), 25.0 (q′), 30.5 (t′), 41.1 (t′), 41.5 (t′), 50.0 (t′), 60.0 (q′), 60.2 (q′), 62.7 (t′), 129.1 (s′), 129.2 (s′), 131.2 (s′), 133.0 (s′), 151.1 (s′), 151.2 (s′), 183.2 (s′); exact mass m/z calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1467.

2,3,4,7-Tetrahydro-5-(2-hydroxyethyl)-2,6-dimethyl-4,7-dioxo-1*H*-indene-2-carboxylic Acid (Puraquinonic Acid) (1). An ice-cold solution of $(NH_4)_2Ce(NO_3)_6$ (277 mg,

0.506 mmol) in 1:1 MeCN−water (0.8 mL) was added slowly to a stirred and cooled (0 °C) solution of alcohol **29** (45.8 mg, 0.156 mmol) in 2:1 MeCN-water (0.9 mL) containing pyridine-2,6-dicarboxylic acid *N*-oxide (92.7 mg, 0.506 mmol). After 40 min, the mixture was diluted with water (5 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography over silica gel (1.8 × 20 cm), using CH_2Cl_2, gave quinone **1** (31.7 mg, 77%) as a brown liquid with ^1H and ^{13}C NMR identical, within experimental error, with the reported[1] values.

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Supporting Information Available: NMR spectra of new compounds for which combustion analytical data were not obtained and experimental procedures for reactions summarized in Scheme 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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