Syntheses of 3,7-Dimethyl-8-hydroxy-6-methoxyisochroman, the 3,7-Dimethyl-6-hydroxy-8-methoxy Isomer, and Their Ester and Ether Derivatives: Plant Growth Regulatory Activity

Horace G. Cutler*

Natural Products Discovery Group, Southern School of Pharmacy, Mercer University, 3001 Mercer University Drive, Atlanta, Georgia 30341

George Majetich,* Xinrong Tian, and Paul Spearing

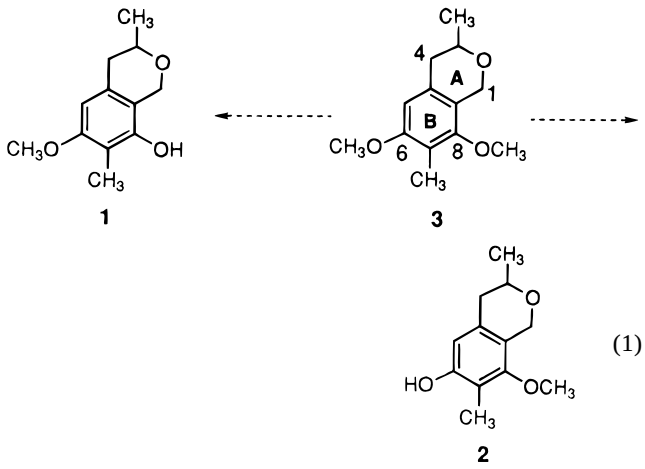
Box 218, Department of Chemistry, The University of Georgia, Athens, Georgia 30602

A systematic invesitgation of ester and ether derivatives of 3,7-dimethyl-8-hydroxy-6-methoxyisochroman and 3,7-dimethyl-6-hydroxy-8-methoxyisochroman has established that all of the derivatives synthesized exhibited activity in the wheat coleoptile assay, with several of the compounds being more active than the parent systems.

Keywords: *Esters and ethers of isochroman; plant growth regulatory activity*

We earlier reported the isolation of 3,7-dimethyl-8-hydroxy-6-methoxyisochroman (**1**) from *Penicillium corylophilum* and demonstrated that it inhibited etiolated wheat coleoptiles at 10^{-3} and 10^{-4} M, as did the acetoxy and methoxy synthetic derivatives (Cutler et al., 1989). The parent compound had originally been isolated from moldy millet hay implicated in the death of cattle (Cox et al., 1979), but the metabolite had not been tested in plants. Because of the results obtained in the wheat coleoptile bioassay, isochroman **1** and two derivatives were assayed on greenhouse-grown bean, corn, and tobacco plants. The methyl ether exhibited the most herbicidal activity in all of the plants treated, while the parent and its acetoxy derivative were only active against corn.

Because it was surprising that the acetoxy and methoxy synthetic derivatives exhibited herbicidal activity, we were curious whether other esters and ether derivatives of **1** and its isomer, 3,7-dimethyl-6-hydroxy-8-methoxyisochroman (**2**), would also exhibit significant plant growth regulatory activity. We reasoned that 3,7-dimethyl-6,8-dimethoxyisochroman (**3**) represents a logical precursor for the systematic preparation of the desired ester and ether analogues of isochromans **1** and **2**. To test this hypothesis, we needed both an efficient synthesis of compound **3** and a practical way to selectively demethylate the C(6) or C(8) ethers (eq 1).



(1)

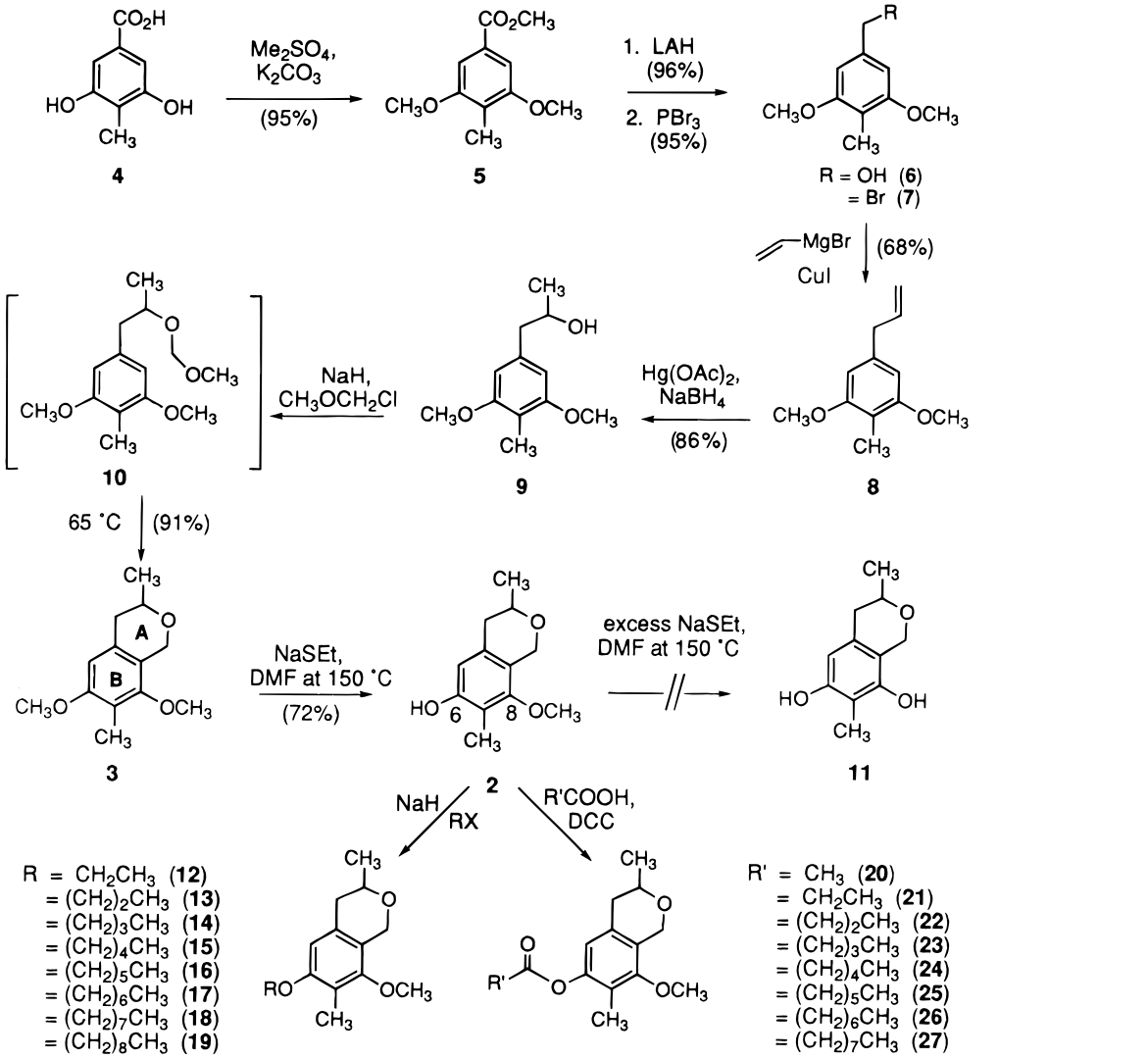
While numerous synthetic routes are known for the preparation of the isochroman skeleton (Macchia et al., 1993; Saeed and Rama, 1995), we instead chose to modify the synthetic strategy reported by Deady and Steyn (Deady et al., 1963; Steyn et al., 1967). Our synthesis of isochroman **3** begins with commerically available 3,5-hydroxy-4-methylbenzoic acid (**4**) (Aldrich), which was exhaustively methylated to provide ester **5** (Scheme 1). Reduction of ester **5** with $LiAlH_4$, followed by bromination of the benzylic alcohol (i.e., **6**) with PBr_3, furnished bromide **7** in 91% overall yield. Subsequent treatment of bromide **7** with vinylmagnesium bromide in the presence of a catalytic amount of copper(I) iodide produced olefin **8** in 68% yield. Oxymercuration–demercuration of **8** gave secondary alcohol **9** in 68% yield, along with some unreacted starting material. Upon treatment with sodium hydride and chloromethyl methyl ether in refluxing tetrahydrofuran, alcohol **9** generated the methoxymethyl ether *in situ* (cf. **10**), which cyclized under these reaction conditions to produce isochroman **3** in 91% yield. While Lewis acid-catalyzed cyclialkylations (Brunson and Kroeger, 1940) have been used to synthesize chroman (Deady et al., 1963) and ochratoxin A37 (Steyn et al., 1967), the cyclization of **10** to **3** occurred under thermal conditions without a Lewis acid catalyst.

With a practical synthesis of isochroman **3** in hand, its demethylation was then attempted. Methyl phenyl ethers can be easily deprotected using strong mineral acid (Greene and Wuts, 1991) or TMS-I (Jung and Lyster, 1977). We were concerned, however, that acidic reagents known to effect demethylation might compromise the "A" ring of the isochroman. This concern led us to employ nucleophilic reagents, such as sodium ethyl thiolate, to effect deprotection (Feutrill and Mirrington, 1970). We were pleased to discover that treatment of **3** with excess NaSEt in hot DMF (150 °C) gave only

* Authors to whom correspondence should be addressed [(H.G.C.) fax (770) 986-3423; cutler_hg@mercer.edu; (G.M.) fax (706) 542-9454; majetich@sunchem.chem.uga.edu].

S0021-8561(96)00618-8 CCC: $14.00

Scheme 1



isochroman **2** in 72% yield in which the less sterically hindered C(6) methoxy group was selectively demethylated. With a practical synthesis of isochroman **2** in hand, we were able to prepare the ether and ester derivatives **12**−**27** without any complications using a DCC-based esterification procedure (Ziegler and Berger, 1979). DCC-based esterifications are simple to conduct but are notorious for having difficult to remove urea byproducts or unreacted carbodiimide. However, we found these difficulties could be avoided during ethereal workup by washing the crude reaction mixture with dilute aqueous acid. Although not used in this study, an improved DCC-based esterification procedure has been developed (Boden and Keck, 1985).

Surprisingly, neither prolonged heating nor a large excess of ethyl thiolate was able to effect the further deprotection of **2** to provide resorcinol derivative **11**. Efforts were therefore made to remove the C(8) protective group *prior* to the cyclialkylation. Toward this end, substrates **28** and **29** were prepared (Figure 1); unfortunately, both compounds failed to cyclize under a variety of conditions, including the use of Lewis acid catalysts.

Aryl phenylthiomethyl ethers are stable to most nucleophiles (Holton and Nelson, 1980). This led us to protect isochroman **2** with a phenylthiomethyl ether (Scheme 2). Treatment of **30** with sodium ethyl thiolate selectively removed the C(8) methyl ether, leaving the

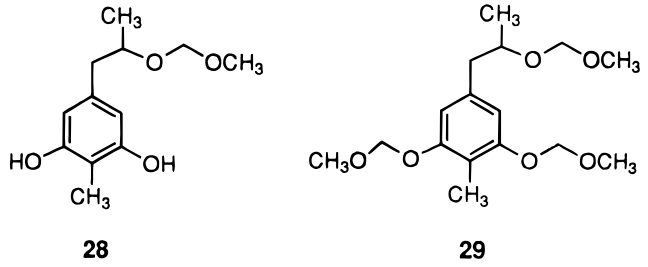
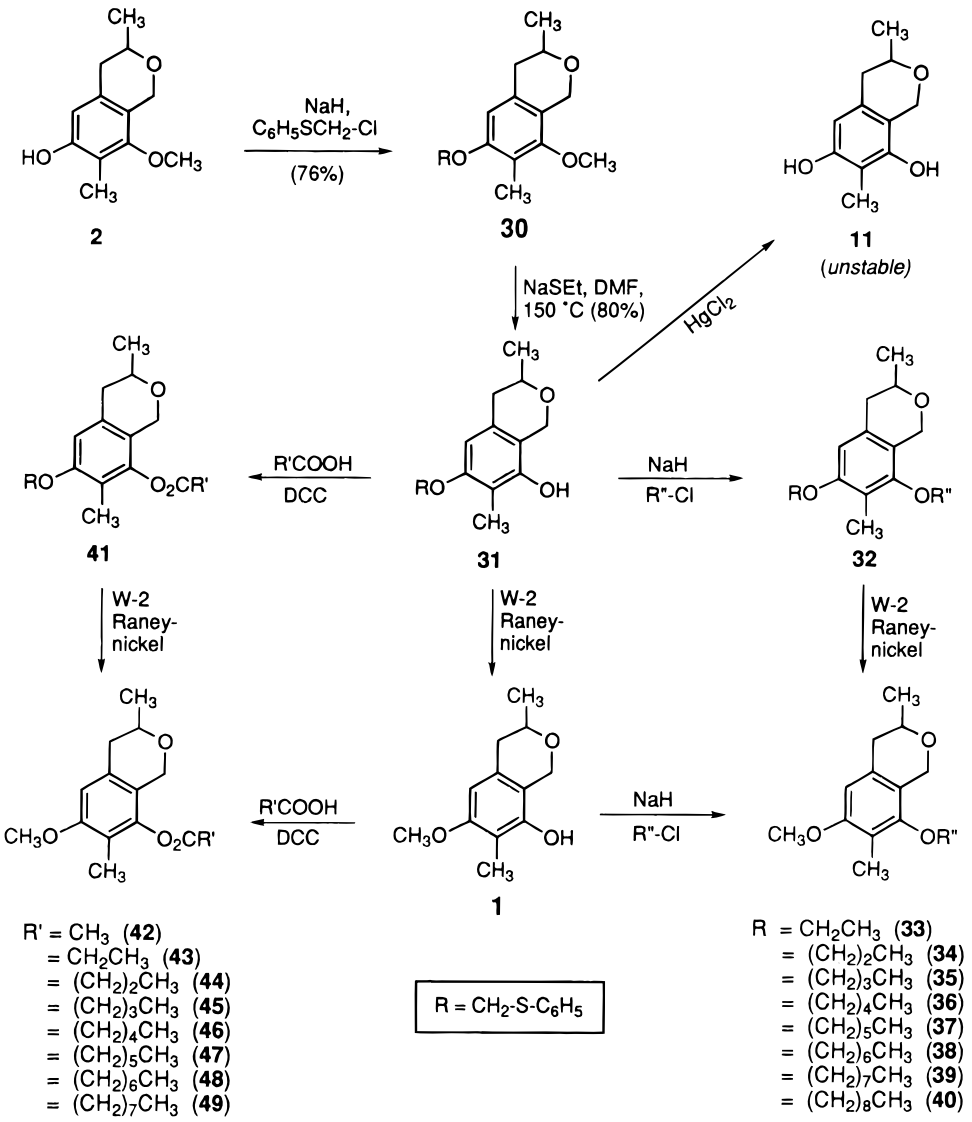


Figure 1.

C(6) phenylthiomethyl ether intact (cf. **31**). Desulfurization of **31** with W-6 Raney nickel (Fieser and Fieser, 1967) converted the phenylthiomethyl ether protecting group into a methoxy ether, thereby furnishing isochroman **1**. While the conversion of **1** into the ethers **32**−**39** could be achieved using standard Williamson ether synthesis conditions, these ethers could be prepared in higher overall yield if isochroman **31** was alkylated prior to desulfurization of the phenylthiomethyl ether group, i.e., **31** → **32** → **33**−**40**. In theory, esters **42**−**49** could be prepared from either **41** or **1** as shown in Scheme 2. In practice, however, the sequence **31** → **1** → **42**−**49** was employed because it required the preparation of fewer intermediates. Finally, hydrolysis of **31** using vigorous conditions (mercuric chloride in refluxing 4:1, acetonitrile/water) generated 6,8-dihydro-

Scheme 2



3,7-dimethylisochroman (**11**), which decomposed under the reaction conditions.

We were delighted to find that all of the synthetic derivatives of isochromans **1** and **2** exhibited activity in the wheat coleoptile assay up to C_8, with some of the compounds being more active than the parent. These results are summarized in Tables 1 and 2.

EXPERIMENTAL PROCEDURES

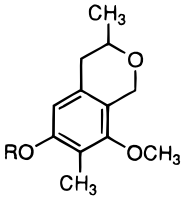
General. All reactions were run under an inert atmosphere of nitrogen and monitored by TLC analysis until the starting material was completely consumed. Unless otherwise indicated, all ethereal workups consisted of the following procedure: The reaction was quenched at room temperature with saturated aqueous ammonium chloride and diluted with ether. The resulting phases were separated, and the aqueous phase was extracted with ether (three times). The combined ethereal phases were washed with brine and dried over anhydrous $MgSO_4$. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 Torr to a constant weight, afforded a crude residue which was purified by flash chromatography using NM silica gel 60 (230−400 mesh ASTM) and distilled reagent grade solvents. All spectra were obtained using $CDCl_3$ as the solvent. Proton NMR spectra were calibrated using trace $CHCl_3$ present (δ 7.26) as an internal reference.

Bioassay. Etiolated wheat coleoptiles were used to determine the biological activity of the compounds. Wheat seed (*Triticum aestivum* L. cv. Wakeland) was germinated on vermiculite at 22 ± 1 °C for 4 days in the dark. The seedling were individually picked and fed into a Van der Weij guillotine, the apical 2 mm was cut and discarded, and the next 4 mm from each coleoptile was saved for bioassay. Ten 4 mm sections were placed in each test tube with phosphate−citrate buffer at pH 5.6 containing 2% sucrose and the compound to be tested, in a dilution series, from 10^{-3} to 10^{-6} M. Ten microliters of acetone was added to each test tube prior to addition of the sucrose buffer to aid in formulating the materials, and controls were treated in the same manner. The test tubes were placed in a roller tube apparatus for 18 h at 22 °C, and then the coleoptiles were removed from the tubes and blotted dry; their images were magnified (×3) and recorded (Cutler, 1984). All data were statistically analzyed (Kurtz et al., 1965), and experiments were duplicated.

Methyl 3,5-Dimethoxy-4-methylbenzoate (5). To a solution of benzoic acid **4** (3.9 g, 22.0 mmol) in acetone (50 mL) was added K_2CO_3 (21.3 g, 155 mmol) and dimethyl sulfate (15.6 mL, 165 mmol). The mixture was refluxed for 18 h and then acidified with 10% aqueous HCl. Standard ethereal workup provided ester **5** as a light brown solid (4.40 g, 95%) which was homogeneous on the basis of TLC analysis (hexanes/ether, 5:1, R_f **5** = 0.44): mp 100.5−102 °C; ^{1}H NMR (250 MHz) δ 2.13 (s, 3 H), 3.88 (s, 6 H), 3.92 (s, 3 H), 7.23 (s, 2 H); ^{13}C NMR (62.5 MHz) 178.1, 157.9, 128.1, 120.2, 104.5, 55.7, 52.0, 8.5 ppm; IR (neat) 1713, 1142 cm^{-1}; ESI-MS, *m/z* 211 (MH^+).

3,5-Dimethoxy-4-methylphenylmethyl Alcohol (6). $LiAlH_4$ (1.0 g, 26.4 mmol) was slowly added to a solution of ester

Table 1. Effects of the Ether and Ester Derivatives of 3,7-Dimethyl-6-hydroxy-8-methoxyisochroman on the Growth of Etiolated Wheat Coleoptiles (*T. aestivum* L. Cv. Wakeland)

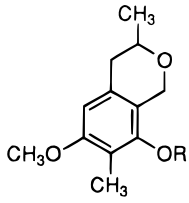


Controls: 17.1 mm (x3)

*Significant Inhibition ($p < 0.01$)
Initial length of Coleoptides: 12.0 mm (x3)

	wheat coleoptile assay (mm ×3)			
R	10^{-3} M	10^{-4} M	10^{-5} M	10^{-6} M
ethyl (**12**)	13.0*	14.5*	17.0	17.1
propyl (**13**)	13.1*	14.5*	17.2	17.2
butyl (**14**)	12.0*	14.1*	17.0	17.1
pentyl (**15**)	12.0*	13.1*	17.1	17.1
hexyl (**16**)	15.1*	15.1*	17.0	17.1
heptyl (**17**)	15.0*	17.0	17.1	17.1
octyl (**18**)	15.9*	17.0	17.1	17.1
nonyl (**19**)	17.1	17.1	17.1	17.1
acetate (**20**)	12.0*	14.5	17.1	17.1
propanoate (**21**)	12.0*	15.1*	17.0	17.2
butanoate (**22**)	12.0*	14.0*	17.1	17.1
pentanoate (**23**)	12.1*	14.0*	17.1	17.1
hexanoate (**24**)	13.2*	14.5*	17.1	17.0
heptanoate (**25**)	13.0*	15.8*	17.1	17.1
octanoate (**26**)	13.1*	13.9*	17.0	17.1
nonanoate (**27**)	17.0	17.0	17.1	17.1

Table 2. Effects of the Ether and Ester Derivatives of 3,7-Dimethyl-8-hydroxy-6-methoxyisochroman on the Growth of Etiolated Wheat Coleoptiles (*T. aestivum* L. Cv. Wakeland)



Controls: 17.1 mm (x3)

*Significant Inhibition ($p < 0.01$)
Initial length of Coleoptides: 12.0 mm (x3)

	wheat coleoptile assay (mm ×3)			
R	10^{-3} M	10^{-4} M	10^{-5} M	10^{-6} M
ethyl (**33**)	12.0*	13.7*	17.0	17.2
propyl (**34**)	12.0*	13.5*	17.1	17.0
butyl (**35**)	12.0*	13.5*	17.0	17.0
pentyl (**36**)	12.0*	15.2*	17.1	17.0
hexyl (**37**)	15.2*	17.0	17.1	17.1
heptyl (**38**)	15.0*	17.0	17.0	17.1
octyl (**39**)	17.1	17.0	17.1	17.1
nonyl (**40**)	14.7*	17.0	17.1	17.1
acetate (**42**)	12.0*	15.1	17.0	17.1
propanoate (**43**)	12.08*	14.3*	17.1	17.0
butanoate (**44**)	12.0*	14.8*	17.1	17.1
pentanoate (**45**)	12.0*	13.2*	17.0	17.1
hexanoate (**46**)	13.0*	14.3*	17.0	17.0
heptanoate (**47**)	17.0	17.0	17.1	17.0
octanoate (**48**)	17.1	17.1	17.1	17.1
nonanoate (**49**)	17.0	17.1	17.1	17.1

5 (4.40 g, 20.8 mmol) in ether (150 mL) at 0 °C. The mixture was stirred for 2 h and then quenched with saturated aqueous NH_4Cl. Standard ethereal workup, followed by chromatography (elution with hexanes/ether, 4:1), gave 3.63 g of alcohol **6** as a white solid (96%), which was homogeneous on the basis of TLC analysis (hexanes/ether, 1:1, R_f **6** = 0.26): mp 67.5−69 °C; ^{1}H NMR (250 MHz) δ 1.77 (t, 1 H, J = 5.9 Hz), 2.09 (s, 3 H), 3.83 (s, 6 H), 4.65 (d, 2 H, J = 5.9 Hz), 6.56 (s, 2 H); ^{13}C NMR (62.5 MHz) 158.3, 139.3, 113.6, 102.1, 65.7, 55.6, 8.0 ppm; IR (neat) 3250−3600, 1590, 1138 cm^{-1}; ESI-MS, m/z 183 (MH^+).

3,5-Dimethoxy-4-methylphenylmethyl Bromide (7). To a solution of alcohol **6** (3.60 g, 19.8 mmol) in ether (60 mL) was added PBr_3 (2.25 mL, 23.7 mmol) at 0 °C. After 2 h, the reaction was quenched with ice. Standard ethereal workup, followed by chromatography of the residue (elution with hexanes/ether, 4:1), gave 4.60 g of benzyl bromide **7** as a white crystalline solid (95%), which was homogeneous on the bais of TLC analysis (hexanes/ether, 2:1, R_f **7** = 0.86): mp 88−90 °C; ^{1}H NMR (250 MHz) δ 2.08 (s, 3 H), 3.84 (s, 6 H), 4.50 (s, 2 H), 6.57 (s, 2 H); ^{13}C NMR (62.5 MHz) 158.2, 135.8, 114.9, 104.1, 55.6, 34.6, 8.1 ppm; IR (neat) 1591, 1142 cm^{-1}; EI-MS, m/z (relative intensity) 246 (10), 244 (10), 165 (100), 150 (10), 120 (11), 105 (8), 91 (22), 77 (20), 51 (15).

1,3-Dimethoxy-2-methyl-5-(2-propenyl)benzene (8). Vinylmagnesium bromide (1.0 M solution in THF, 28.2 mL) was added to a stirred suspension of CuI (0.53 g, 2.8 mmol) in THF (40 mL) at −40 °C and stirred for 10 min. Bromide **7** (2.3 g, 9.4 mmol) was then added, and the mixture was stirred at −25 °C for 2.5 h. Standard ethereal workup, followed by chromatography of the residue (elution with hexanes), gave 1.23 g of adduct **8** as a yellow oil (68%), which was homogeneous on the basis ofTLC analysis (hexanes/ether, 10:1, R_f **8** = 0.82): ^{1}H NMR (250 MHz) δ 2.09 (s, 3 H), 3.38 (d, 2 H, J = 6.7 Hz), 3.83 (s, 6 H), 5.08−5.18 (m, 2 H), 5.91−6.05 (m, 1 H), 6.40 (s, 2 H); ^{13}C NMR (62.5 MHz) 158.2, 138.4, 137.4, 125.5, 115.7, 103.8, 55.6, 30.2, 7.9 ppm; IR (neat) 1588, 1109 cm^{-1}; ESI-MS, m/z 193 (MH^+).

1-(3,5-Dimethoxy-4-methylphenyl)propan-2-ol (9). To a solution of $Hg(OAc)_2$ (2.04 g, 6.4 mmol) in THF (30 mL)/H_2O (15 mL) was added **8** (1.23 g, 6.4 mmol) in THF (10 mL) at room temperature. The mixture was stirred until the yellow color faded (approximatly 20 min) and then cooled to 0 °C. $NaBH_4$ (0.63 g, 16.7 mmol) in THF (10 mL) was added, and after 20 min, the solution was saturated with NaCl. Standard ethereal workup furnished 1.79 g of a crude oil. Chromatography of this residue (elution with hexane/ether, 3:2) gave 0.92 g of alcohol **9** as a white crystalline solid (86% yield, based on recovery of 0.25 g of **8**), which was homogeneous on the basis of TLC analysis (hexanes/ether, 1:1, R_f **9** = 0.31): mp 68−69 °C; ^{1}H NMR (250 MHz) δ 1.26 (d, 3 H, J = 6.0 Hz), 1.76 (s, 1 H), 2.07 (s, 3 H), 2.57−2.81 (m, 2 H), 3.82 (s, 6 H), 3.98−4.08 (m, 1 H), 6.40 (s, 2 H); ^{13}C NMR (62.5 MHz) 158.2, 136.7, 112.4, 104.4, 68.8, 55.6, 46.2, 22.7, 7.9 ppm; IR (neat) 3300−3550, 1587, 1101 cm^{-1}; ESI-MS, m/z 211 (MH^+).

6,8-Dimethoxy-3,7-dimethylisochroman (3). Alcohol **9** (3.89 g, 18.5 mmol) in THF (50 mL) was added to a stirred suspension of NaH (1.85 g, 46.3 mmol of a 60% dispersion in mineral oil) at room temperature and was stirred for 45 min. Chloromethyl methyl ether (3.52 mL, 46.3 mmol) was added, and the solution was heated to 65 °C for 2 h. Standard ethereal workup, followed by chromatography (elution with hexane/ether, 5:1), gave 3.74 g of isochroman **3** as a white crystalline solid (91%), which was homogeneous on the basis of TLC analysis (hexanes/ether, 4:1, R_f **3** = 0.51): mp 52.5−54 °C; ^{1}H NMR (250 MHz) δ 1.35 (d, 3 H, J = 6.0 Hz), 2.12 (s, 3 H), 2.65 (d, 2 H, J = 6.7 Hz), 3.69 (s, 3 H), 3.80 (s, 6 H), 4.70 (d, 1 H, J = 15.1 Hz), 4.93 (d, 1 H, J = 15.1 Hz), 6.39 (s, 1 H); ^{13}C NMR (62.5 MHz) 154.7, 133.8, 132.2, 119.9, 116.9, 106.0, 70.5, 64.5, 60.1, 55.5, 35.8, 21.5, 8.5 ppm; IR (neat) 1608, 1456, 1121 cm^{-1}; ESI-MS, m/z 223 (MH^+).

3,7-Dimethyl-6-hydroxy-8-methoxyisochroman (2). Ethanethiol (21.0 mL, 285 mmol) was added to a stirred suspension of NaH (17.0 g, 425 mmol of a 60% dispersion in mineral oil) in DMF (150 mL) at 0 °C and then stirred for 1 h at room temperature. Isochroman **3** (3.15 g, 14.2 mmol) was added to the reaction mixture, and the resulting mixture was heated to 130 °C for 6 h. The reaction was quenched with saturated aqueous NH_4Cl, acidified with 10% aqueous HCl, saturated with NaCl, and then extracted with ether (5 × 40 mL). The combined organic layers were washed with brine and then stirred vigorously with $CuSO_4$ (50.0 g) for 1 h. The solids were filtered and the filtrate concentrated. The resulting residue was chromatographed (elution with hexanes/ether,

2:1) to yield 2.12 g of phenol **2** as a white crystalline solid (72%), which was homogeneous on the basis of TLC analysis (hexanes/ether, 1:1, R_f **2** = 0.56): mp 149.5−151 °C; ^{1}H NMR (250 MHz) δ 1.34 (d, 3 H, J = 6.0 Hz), 2.07 (s, 3 H), 2.63 (d, 2 H, J = 5.9 Hz), 3.71−3.82 (m, 1 H), 3.79 (s, 3 H), 4.65 (d, 2 H, J = 14.8 Hz), 4.67 (s, 1 H), 4.92 (d, 1 H, J = 14.8 Hz), 6.23 (s, 1 H); ^{13}C NMR (62.5 MHz) 156.4, 149.9, 132.2, 114.1, 108.3, 102.7, 70.4, 64.3, 55.5, 35.8, 21.4, 7.5 ppm; IR (neat) 3150−3500, 1591, 1126 cm^{-1}; ESI-MS, m/z 209 (MH$^+$).

3,7-Dimethyl-6-ethoxy-8-methoxyisochroman (12). Isochroman **2** (80 mg, 0.38 mmol) was added to a stirred suspension of NaH (18 mg, 0.46 mmol of a 60% dispersion in mineral oil) in DMF (0.5 mL) at 0 °C. After 30 min of stirring at room temperature, iodoethane (37 μL, 0.46 mmol) was added and the mixture stirred for 90 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether (3 × 5 mL). The combined ethereal extracts were washed with 10% aqueous $CuSO_4$ and brine, then dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed (elution with hexanes/ether, 5:1) to yield 79 mg of ether **12** (87%) as a white crystalline solid: R_f **12** = 0.80 (hexanes/ether, 1:1); mp 75−76.5 °C; ^{1}H NMR (250 MHz) δ 1.34 (d, 3 H, J = 6.1 Hz), 1.39 (t, 3 H, J = 7.2 Hz), 2.11 (s, 3 H), 2.64 (d, 2 H, J = 6.7 Hz), 3.68−3.85 (m, 3 H), 3.79 (s, 3 H), 4.69 (d, 1 H, J = 15.1 Hz), 4.94 (d, 1 H, J = 15.1 Hz), 6.38 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.0, 153.9, 132.0, 120.1, 117.1, 105.8, 70.5, 68.3, 64.7, 55.4, 35.8, 21.5, 15.6, 8.8 ppm; IR (neat) 1609, 1124 cm^{-1}; ESI-MS, m/z 237 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-propoxyisochroman (13). The alkylation of isochroman **2** with 1-bromopropane (cf. the preparation of **12**) produced ether **13** in 76% yield as a white crystalline solid: R_f **13** = 0.80 (hexanes/ether, 1:1); mp 53−54 °C; ^{1}H NMR (250 MHz) δ 1.05 (t, 3 H, J = 7.4 Hz), 1.34 (d, 3 H, J = 6.4 Hz), 1.79 (sextet, 2 H, J = 7.0 Hz), 2.10 (s, 3 H), 2.65 (d, 2 H, J = 6.8 Hz), 3.69 (t, 2 H, J = 6.6 Hz), 3.69-3.80 (m, 1 H), 3.79 (s, 3 H), 4.69 (d, 1 H, J = 14.9 Hz), 4.95 (d, 1 H, J = 14.9 Hz), 6.38 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.1, 153.9, 132.0, 120.0, 117.1, 105.8, 74.3, 70.5, 64.7, 55.4, 35.8, 23.5, 21.5, 10.5, 8.8 ppm; IR (neat) 1609, 1122 cm^{-1}; ESI-MS, m/z 251 (MH$^+$).

6-Butoxy-3,7-dimethyl-8-methoxyisochroman (14). The alkylation of isochroman **2** with 1-bromobutane (cf. the preparation of **12**) produced ether **14** in 86% yield as a colorless oil: R_f **14** = 0.82 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 1.00 (t, 3 H, J = 7.3 Hz), 1.35 (d, 3 H, J = 6.0 Hz), 1.47−1.56 (m, 2 H), 1.70−1.78 (m, 2 H), 2.11 (s, 3 H), 2.65 (d, 2 H, J = 6.6 Hz), 3.73 (t, 2 H, J = 6.5 Hz), 3.68−3.80 (m, 1 H), 3.79 (s, 3 H), 4.69 (d, 1 H, J = 15.4 Hz), 4.95 (d, 1 H, J = 15.4 Hz), 6.38 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.1, 153.9, 132.0, 120.0, 117.1, 105.8, 72.5, 70.5, 64.7, 55.4, 35.8, 32.3, 21.5, 19.2, 13.9, 8.8 ppm; IR (neat) 1609, 1125 cm^{-1}; ESI-MS, m/z 265 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-pentanoxyisochroman (15). The alkylation of isochroman **2** with 1-bromopentane (cf. the preparation of **12**) produced ether **15** in 89% yield as a colorless oil: R_f **15** = 0.85 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.95 (t, 3 H, J = 7.0 Hz), 1.35 (d, 3 H, J = 6.0 Hz), 1.37−1.45 (m, 4 H), 1.71−1.80 (m, 2 H), 2.11 (s, 3 H), 2.64 (d, 2 H, J = 6.6 Hz), 3.70 (t, 2 H, J = 6.6 Hz), 3.69−3.80 (m, 1 H), 3.79 (s, 3 H), 4.69 (d,1 H, J = 15.0 Hz), 4.95 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.1, 153.9, 132.0, 120.0, 117.1, 105.8, 72.8, 70.5, 64.7, 55.4, 35.8, 29.9, 28.1, 22.5, 21.5, 14.0, 8.8 ppm; IR (neat) 1609, 1465, 1125 cm^{-1}; ESI-MS, m/z 279 (MH$^+$).

3,7-Dimethyl-6-hexanoxy-8-methoxyisochroman (16). The alkylation of isochroman **2** with 1-bromohexane (cf. the preparation of **12**) produced ether **16** in 83% yield as a colorless oil: R_f **16** = 0.85 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.92 (t, 3 H, J = 6.4 Hz), 1.35 (d, 3 H, J = 5.9 Hz), 1.27−1.55 (m, 6 H), 1.69−1.83 (m, 2 H), 2.11 (s, 3 H), 2.65 (d, 2 H, J = 6.6 Hz), 3.72 (t, 2 H, J = 6.6 Hz), 3.68−3.81 (m, 1 H), 3.79 (s, 3 H), 4.69 (d, 1 H, J = 15.0 Hz), 4.94 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.0, 153.9, 132.0, 120.0, 117.1, 105.8, 72.8, 70.5, 64.7, 55.4, 35.8, 31.7, 30.2, 25.7, 22.5, 21.5, 13.9, 8.8 ppm; IR (neat) 1609, 1465, 1125 cm^{-1}; ESI-MS, m/z 293 (MH$^+$).

3,7-Dimethyl-6-heptanoxy-8-methoxyisochroman (17). The alkylation of isochroman **2** with 1-bromoheptane (cf. the preparation of **12**) produced ether **17** in 81% yield as a colorless oil: R_f **17** = 0.87 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.91 (t, 3 H, J = 6.8 Hz), 1.27−1.55 (m, 11 H), 1.71−1.82 (m, 2 H), 2.11 (s, 3 H), 2.65 (d, 2 H, J = 6.6 Hz), 3.72 (t, 2 H, J = 8.1 Hz), 3.68−3.80 (m, 1 H), 3.79 (s, 3 H), 4.70 (d, 1 H, J = 15.1 Hz), 4.95 (d, 1 H, J = 15.1 Hz), 6.38 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.1, 153.9, 132.0, 120.0, 117.1, 105.8, 72.8, 70.5, 64.7, 55.4, 35.8, 31.7, 30.3, 29.1, 22.5, 21.5, 14.0, 8.8 ppm; IR (neat) 1610, 1465, 1125 cm^{-1}; ESI-MS, m/z 307 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-octanoxyisochroman (18). The alkylation of isochroman **2** with 1-bromooctane (cf. the preparation of **12**) produced ether **18** in 89% yield as a colorless oil: R_f **18** = 0.88 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.91 (t, 3 H, J = 6.7 Hz), 1.28−1.53 (m, 13 H), 1.71−1.80 (m, 2 H), 2.11 (s, 3 H), 2.65 (d, 2 H, J = 6.5 Hz), 3.72 (t, 2 H, J = 6.6 Hz), 3.68−3.80 (m, 1 H), 3.80 (s, 3 H), 4.69 (d, 1 H, J = 15.1 Hz), 4.95 (d, 1 H, J = 15.1 Hz), 6.38 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.0, 153.9, 132.0, 120.0, 117.1, 105.8, 72.8, 70.5, 64.7, 55.4, 35.8, 31.7, 30.2, 29.4, 29.2, 26.1, 22.6, 21.5, 14.0, 8.8 ppm; IR (neat) 1610, 1465, 1125 cm^{-1}; ESI-MS, m/z 321 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-nonanoxyisochroman (19). The alkylation of isochroman **2** with 1-bromononane (cf. the preparation of **12**) produced ether **19** in 84% yield as a colorless oil: R_f **19** = 0.90 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.90 (t, 3 H, J = 7.0 Hz), 1.28−1.51 (m, 15 H), 171−1.82 (m, 2 H), 2.11 (s, 3 H), 2.65 (d, 2 H, J = 6.6 Hz), 3.72 (t, 2 H, J = 6.6 Hz), 3.69−3.81 (m, 1 H), 3.79 (s, 3 H), 4.69 (d, 1 H, J = 15.0 Hz), 4.94 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (62.5 MHz) 157.1, 153.9, 132.0, 120.0, 117.1, 105.8, 72.8, 70.5, 64.7, 55.4, 35.8, 31.7, 30.2, 29.4, 29.2, 26.0, 22.6, 21.5, 14.0, 8.8 ppm; IR (neat) 1610, 1465, 1125 cm^{-1}; ESI-MS, m/z 335 (MH$^+$).

6-Acetoxy-3,7-dimethyl-8-methoxyisochroman (20). Isochroman **2** (84 mg, 0.40 mmol) was added to a mixture of DCC (92 mg, 0.45 mmol), DMAP (5 mg, 0.04 mmol), and acetic acid (23 μL, 0.45 mmol) in CH_2Cl_2 (2.0 mL) and stirred at room temperature for 2 h. The solution was filtered and the filtrate washed with 5% aqueous HCl and saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated. (The aqueous acid wash serves to hydrolyze any unreacted DCC.) The residue was chromatographed (elution with hexane/ether, 2:1) to yield 85 mg of acetate **20** as a white crystalline solid (85%), which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f **20** = 0.66): mp 60.5−62 °C; ^{1}H NMR (300 MHz) δ 1.33 (d, 3 H, J = 6.1 Hz), 1.97 (s, 3 H), 2.31 (s, 3 H), 2.65 (d, 2 H, J = 6.7 Hz), 3.69−3.80 (m, 1 H), 3.79 (s, 3 H), 4.52 (d, 1 H, J = 14.9 Hz), 4.70 (d, 1 H, J = 14.9 Hz), 6.49 (s, 1 H); ^{13}C NMR (75.5 MHz) 168.8, 155.9, 145.8, 132.4, 118.9, 116.9, 108.1, 70.5, 63.9, 55.6, 35.6, 21.4, 20.3, 8.8 ppm; IR (neat) 1765, 1622, 1203, 1116 cm^{-1}; ESI-MS, m/z 251 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-propanoyloxyisochroman (21). The condensation of isochroman **2** with propionic acid (cf. the preparation of **20**) produced ester **21** in 75% yield as a white crystalline solid: R_f **21** = 0.67 (hexanes/ether, 1:1); mp 68−70 °C; ^{1}H NMR (300 MHz) δ 1.29 (t, 3 H, J = 5.5 MHz), 1.33 (d, 3 H, J = 6.1 Hz), 1.96 (s, 3 H), 2.59 (q, 2 H, J = 5.5 Hz), 3.69−3.81 (m, 1 H), 3.79 (s, 3 H), 4.52 (d, 1 H, J = 14.8 Hz), 4.68 (d, 1 H, J = 14.8 Hz), 6.48 (s, 1 H); ^{13}C NMR (75.5 MHz) 171.9, 156.7, 145.7, 132.3, 118.9, 116.9, 107.9, 70.4, 64.0, 55.6, 35.6, 27.3, 21.4, 9.4, 8.8 ppm; IR (neat) 1758, 1621, 1261, 1121 cm^{-1}; ESI-MS, m/z 265 (MH$^+$).

6-Butanoyloxy-3,7-dimethyl-8-methoxyisochroman (22). The condensation of isochroman **2** with butanoic acid (cf. the preparation of **20**) produced ester **22** in 83% yield as a white crystalline solid: R_f **22** = 0.72 (hexanes/ether, 1:1); mp 56−58 °C; ^{1}H NMR (300 MHz) δ 1.31−1.40 (m, 8 H), 1.96 (s, 3 H), 2.65 (d, 2 H, J = 6.7 MHz), 2.83 (m, 2 H), 3.69−3.82 (m, 1 H), 3.79 (s, 3 H), 4.51 (d, 1 H, J = 14.6 Hz), 4.69 (d, 1 H, J = 14.6 Hz), 6.48 (s, 1 H); ^{13}C NMR (75.5 MHz) 174.4, 156.7, 145.6, 132.3, 118.9, 116.9, 107.9, 70.5, 64.0, 55.6, 35.6, 34.1, 21.4, 19.1, 8.7 ppm; IR (neat) 1754, 1261, 1115, 1093 cm^{-1}; ESI-MS, m/z 279 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-pentanoyloxyisochroman (23). The condensation of isochroman **2** with pentanoic acid

(cf. the preparation of **20**) produced ester **23** in 86% yield as a colorless oil: R_f **23** = 0.75 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.98 (t, 3 H, J = 7.3 Hz), 1.33 (d, 3 H, J = 6.0 Hz), 1.38−1.50 (m, 2 H), 1.70−1.82 (m, 2 H), 1.96 (s, 3 H), 2.57 (t, 2 H, J = 7.7 Hz), 2.65 (d, 2 H, J = 6.7 Hz), 3.69−3.82 (m, 1 H), 3.79 (s, 3 H), 4.53 (d, 1 H, J = 14.7 Hz), 4.69 (d,1 H, J = 14.7 Hz), 6.48 (s, 1 H); ^{13}C NMR (62.5 MHz) 171.2, 156.6, 145.5, 132.2, 118.9, 116.8, 107.9, 70.4, 64.0, 55.5, 35.5, 33.6, 27.1, 22.3, 21.4, 13.6, 8.8 ppm; IR (neat) 1755, 1261, 1142, 1116, 1093 cm^{-1}; ESI-MS, m/z 293 (MH$^+$).

3,7-Dimethyl-6-hexanoyloxy-8-methoxyisochroman (24). The condensation of isochroman **2** with hexanoic acid (cf. the preparation of **20**) produced ester **24** in 75% yield as a colorless oil: R_f **24** = 0.77 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.94 (t, 3 H, J = 6.7 Hz), 1.33 (d, 3 H, J = 6.0 Hz), 1.35−1.46 (m, 4 H), 1.71−1.97 (m, 2 H), 2.06 (s, 3 H), 2.56 (t, 2 H, J = 7.7 Hz), 2.65 (d, 2 H, J = 6.7 Hz), 3.70−3.81 (m, 1 H), 3.79 (s, 3 H), 4.52 (d, 1 H, J = 14.7 Hz), 4.69 (d, 1 H, J = 14.7 Hz), 6.49 (s, 1 H); ^{13}C NMR (62.5 MHz) 171.2, 156.6, 145.5, 132.2, 118.9, 116.8, 107.9, 70.4, 64.0, 55.5, 35.5, 33.8, 31.2, 24.7, 22.2, 21.4, 13.8, 8.8 ppm; IR (neat) 1757, 1261, 1142, 1116, 1093 cm^{-1}; ESI-MS, m/z 307 (MH$^+$).

3,7-Dimethyl-6-heptanoyloxy-8-methoxyisochroman (25). The condensation of isochroman **2** with heptanoic acid (cf. the preparation of **20**) produced ester **25** in 88% yield as a colorless oil: R_f **25** = 0.79 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.89 (t, 3 H, J = 5.8 Hz), 1.26−1.41 (m, 9 H), 1.71−1.82 (m, 2 H), 1.96 (s, 3 H), 2.56 (t, 2 H, J = 7.6 Hz), 2.65 (d, 2 H, J = 6.7 Hz), 3.71−3.81 (m, 1 H), 3.79 (s, 3 H), 4.52 (d, 1 H, J = 14.7 Hz), 4.69 (d, 1 H, J = 14.7 Hz), 6.48 (s, 1 H); ^{13}C NMR (62.5 MHz) 171.2, 156.6, 145.5, 132.2, 118.9, 116.8, 107.9, 70.4, 64.0, 55.5, 35.5, 33.9, 31.3, 28.8, 24.9, 22.4, 21.4, 13.9, 8.8, 5.1 ppm; IR (neat) 1757, 1261, 1141, 1115, 1094 cm^{-1}; ESI-MS, m/z 321 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-octanoyloxyisochroman (26). The condensation of isochroman **2** with octanoic acid (cf. the preparation of **20**) produced ester **26** in 72% yield as a colorless oil: R_f **26** = 0.83 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.91 (t, 3 H, J = 6.9 Hz), 1.30−1.46 (m, 1 H), 1.71−1.83 (m, 2 H), 2.56 (t, 2 H, J = 7.8 Hz), 2.66 (d, 2 H, J = 6.7 Hz), 3.71−3.82 (m, 1 H), 3.79 (s, 3 H), 4.53 (d, 1 H, J = 14.7 Hz), 4.69 (d,1 H, J = 14.7 Hz), 6.48 (s, 1 H); ^{13}C NMR (62.5 MHz) 171.2, 156.6, 145.5, 132.2, 118.9, 116.8, 107.9, 70.4, 64.0, 55.5, 35.6, 33.9, 31.5, 29.1, 28.8, 25.0, 22.5, 21.4, 13.9, 12.3, 8.8 ppm; IR (neat) 1757, 1261, 1141, 1116, 1094 cm^{-1}; ESI-MS, m/z 335 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-nonanoyloxyisochroman (27). The condensation of isochroman **2** with nonanoic acid (cf. the preparation of **20**) produced ester **27** in 70% yield as a colorless oil: R_f **27** = 0.85 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.90 (t, 3 H, J = 7.0 Hz), 1.29−1.44 (m, 13 H), 1.71−1.81 (m, 2 H), 2.56 (t, 2 H, J = 7.6 Hz), 2.66 (d, 2 H, J = 6.7 Hz), 3.70−3.81 (m, 1 H), 3.79 (s, 3 H), 4.52 (d, 1 H, J = 14.7 Hz), 4.69 (d, 1 H, J = 14.7 Hz), 6.49 (s, 1 H); ^{13}C NMR (62.5 MHz) 171.2, 156.6, 145.5, 132.2, 118.9, 116.8, 107.9, 70.4, 64.0, 55.5, 35.5, 33.9, 31.7, 29.1, 29.0, 25.0, 22.5, 21.4, 13.9, 8.8 ppm; IR (neat) 1757, 1260, 1141, 1117, 1094 cm^{-1}; ESI-MS, m/z 349 (MH$^+$).

3,7-Dimethyl-8-methoxy-6-phenylthiomethoxyisochroman (30). Isochroman **2** (1.14 g, 5.5 mmol) was added to a stirred suspension of NaH (0.33 g, 8.3 mmol of a 60% dispersion in mineral oil) in HMPA (20 mL) at 0 °C. After 30 min, chloromethyl phenyl sulfide (1.5 mL, 11.0 mmol) and NaI (1.0 g, 6.7 mmol) were added, and the resulting mixture was stirred at room temperature for 2 h. Ether (25 mL) and water (15 mL) were then added, and the aqueous layer was saturated with NaCl. Standard ethereal workup afforded a crude residue, which was chromatographed (elution with hexane/ether, 2:1) to yield 1.36 g of ether **30** (76%) as a pale yellow solid: R_f **30** = 0.75 (hexanes/ether, 1:1); mp 102.5−104 °C; ^{1}H NMR (250 MHz) δ 1.32 (d, 3 H, J = 6.0 Hz), 2.09 (s, 3 H), 2.64 (d, 2 H, J = 6.9 Hz), 3.67−3.81 (m, 1 H), 3.79 (s, 3 H), 4.67 (d, 1H, J = 15.2 Hz), 4.93 (d, 1 H, J = 15.2 Hz), 5.29 (s, 2 H), 6.41 (s, 1 H) 7.22−7.36 (m, 3 H), 7.50−7.54 (m, 2 H); ^{13}C NMR (62.5 MHz) 157.2, 152.7, 135.7, 132.4, 129.9, 129.0, 126.9, 120.4, 117.0, 106.8, 77.6, 70.5, 65.2, 55.6, 35.8, 21.6, 9.7 ppm; IR (neat) 1612, 1582, 1116 cm^{-1}; ESI-MS, m/z 331 (MH$^+$).

3,7-Dimethyl-8-hydroxy-6-phenylthiomethoxyisochroman (31). Ethanethiol (7.0 mL, 94.5 mmol) was added to a stirred suspension of 5.7 g of NaH (143 mmol of a 60% dispersion in mineral oil) in DMF (100 mL) at 0 °C. After 1 h, isochroman **30** (1.56 g, 4.7 mmol) was added and the mixture heated to 120 °C for 18 h. The reaction was quenched with saturated aqueous NH_4Cl, acidified with 10% aqueous HCl, saturated with NaCl, and extracted with ether (5 × 40 mL). The combined organic extracts were stirred vigorously with $CuSO_4$ (50.0 g) for 1 h, and the solids were suction filtered. The filtrate was concentrated and the residue chromatographed (elution with hexanes/ether, 2:1) to yield 1.19 g of isochroman **31** (80%) as a white crystalline solid: R_f **31** = 0.55 (hexanes/ether, 1:1); mp 107.5−109 °C; ^{1}H NMR (250 MHz) δ 1.31 (d, 3 H, J = 5.1 Hz), 2.10 (s, 3 H), 2.53 (d, 2 H, J = 5.1 Hz), 3.65−3.76 (m, 1 H), 4.65 (d, 1 H, J = 12.5 Hz), 4.93 (d, 1 H, J = 12.5 Hz), 5.27 (s, 2 H), 5.56 (s, 1 H), 6.31 (s, 1 H), 7.21−7.33 (m, 3 H), 7.49 (d, 2 H, J = 6.1 Hz); ^{13}C NMR (62.5 MHz) 153.6, 152.9, 135.5, 132.5, 129.9, 129.0, 127.0, 120.1, 115.2, 111.2, 77.6, 70.8, 65.1, 35.3, 21.4, 9.6 ppm; IR (neat) 3500−3150, 1614, 1066 cm^{-1}; ESI-MS, m/z 317 (MH$^+$).

3,7-Dimethyl-8-hydroxy-6-methoxyisochroman (1). A solution of **31** (0.83 g, 2.6 mmol) in ethanol (20 mL) was added to W-6 Raney nickel (approximately 1.0 g), and the mixture was refluxed for a 3 h period. The mixture was filtered on a bed of Celite and concentrated to yield 0.50 g of phenol **1** (92%), which was homogeneous by TLC analysis (hexanes/ether, 1:1, R_f **1** = 0.51) as a white crystalline solid: mp 143−145 °C; ^{1}H NMR (250 MHz) δ 1.33 (d, 3 H, J = 6.0 Hz), 2.14 (s, 3 H), 2.59 (d, 2 H, J = 6.6 Hz), 3.68 (s, 3 H), 3.67−3.80 (m, 1 H), 4.68 (d, 1 H, J = 15.1 Hz), 4.93 (d, 1 H, J = 15.1 Hz), 4.94 (s, 1 H), 6.35 (s, 1 H); ^{13}C NMR (62.5 MHz) 154.9, 153.3, 132.5, 119.8, 114.9, 110.4, 70.6, 64.5, 60.1, 35.3, 21.4, 8.4 ppm; IR (neat) 3500−3150, 1614, 1098 cm^{-1}; ESI-MS, m/z 209 (MH$^+$).

3,7-Dimethyl-8-ethoxy-6-methoxyisochroman (33). The alkylation of isochroman **1** with iodoethane (cf. the preparation of **12**) produced ether **33** in 81% yield as a colorless oil: R_f **33** = 0.80 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 1.34 (d, 3 H, J = 6.1 Hz), 1.42 (t, 3 H, J = 7.0 Hz), 2.12 (s, 3 H), 2.63 (d, 2 H, J = 6.2 Hz), 3.69 (s, 3 H), 3.70−3.82 (m, 1 H), 3.98 (q, 2 H, J = 7.0 Hz), 4.69 (d, 1 H, J = 15.2 Hz), 4.93 (d, 1 H, J = 15.2 Hz), 6.37 (s, 1 H); ^{13}C NMR (75.5 MHz) 156.5, 154.8, 132.1, 119.8, 117.3, 107.2, 70.6, 64.5, 63.8, 60.0, 35.8, 21.5, 14.9, 8.6 ppm; IR (neat) 1608, 1261, 1121 cm^{-1}; ESI-MS, m/z 237 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-propoxyisochroman (34). The alkylation of isochroman **1** with 1-bromopropane (cf. the preparation of **12**) produced ether **34** in 63% yield as a colorless oil: R_f **34** = 0.81 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 106 (t, 3 H, J = 7.4 Hz), 1.34 (d, 3 H, J = 6.1 Hz), 1.76−1.87 (m, 2 H), 2.13 (s, 3 H), 2.63 (d, 2 H, J = 6.3 Hz) 3.69 (s, 3 H), 3.70−3.80 (m, 1 H), 3.89 (t, 2 H, J = 6.3 Hz), 4.69 (d, 1 H, J = 15.0 Hz), 4.93 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (75.5 MHz) 156.7, 154.8, 132.1, 119.7, 117.3, 107.1, 70.6, 69.7, 64.6, 50.1, 35.8, 22.6, 21.5, 10.6, 8.6 ppm; IR (neat) 1610, 1262, 1120, cm^{-1}; ESI-MS, m/z 251 (MH$^+$).

8-Butoxy-3,7-dimethyl-6-methoxyisochroman (35). The alkylation of isochroman **1** with 1-bromobutane (cf. the preparation of **12**) produced ether **35** in 66% yield as a colorless oil: R_f **35** = 0.83 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.98 (t, 3 H, J = 7.6 Hz), 1.34 (d, 3 H, J = 6.1 Hz), 1.45−1.57 (m, 2 H), 1.73−1.82 (m, 2 H), 2.12 (s, 3 H), 2.63 (d, 2 H, J = 6.4 Hz), 3.69 (s, 3 H), 3.69−3.80 (m, 1 H), 3.92 (t, 2 H, J = 6.4 Hz), 4.69 (d, 1 H, J = 15.0 Hz), 4.93 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (75.5 MHz) 156.7, 154.9, 132.1, 119.8, 117.7, 107.1, 70.6, 67.9, 64.6, 60.1, 35.8, 31.4, 21.5, 19.3, 13.8, 8.6 ppm; IR (neat) 1609, 1262, 1119, cm^{-1}; ESI-MS, m/z 265 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-pentanoxyisochroman (36). The alkylation of isochroman **1** with 1-bromopentane (cf. the preparation of **12**) produced ether **36** in 75% yield as a colorless oil: R_f **36** = 0.83 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.94 (t, 3 H, J = 7.0 Hz), 1.34 (d, 3 H, J = 6.1 Hz), 1.35−1.50 (m, 4 H), 1.74−1.84 (m, 2 H), 2.12 (s, 3 H), 2.63 (d, 2 H, J = 6.4 Hz), 3.69 (s, 3 H), 3.70−3.79 (m, 1 H), 3.91 (t, 2 H, J = 6.3

Hz), 4.69 (d,1 H, J = 15.0 Hz), 4.93 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (75.5 MHz) 162.9, 156.7, 154.8, 132.1, 119.7, 117.3, 107.1, 70.6, 68.2, 64.6, 60.0, 35.8, 29.0, 28.3, 22.4, 21.5, 14.0, 8.6 ppm; IR (neat) 1609, 1262, 1091 cm^{-1}; ESI-MS, m/z 279 (MH$^+$).

3,7-Dimethyl-8-hexanoxy-6-methoxyisochroman (37). The alkylation of isochroman **1** with 1-bromohexane (cf. the preparation of **12**) produced ether **37** in 71% yield as a colorless oil: R_f **37** = 0.85 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.92 (t, 3 H, J = 6.9 Hz), 1.34 (d, 3 H, J = 6.1 Hz), 1.31−1.54 (m, 6 H), 1.73−1.82 (m, 2 H), 2.12 (s, 3 H), 2.63 (d, 2 H, J = 6.3 Hz), 3.69 (s, 3 H), 3.70−3.79 (m, 1 H), 3.92 (t, 2 H, J = 6.6 Hz), 4.69 (d, 1 H, J = 15.0 Hz), 4.93 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (75.5 MHz) 156.7, 154.8, 132.1, 119.7, 117.3, 107.1, 70.6, 68.2, 64.6, 60.0, 35.8, 31.5, 29.3, 25.8, 22.6, 21.5, 13.9, 8.6 ppm; IR (neat) 1609, 1262, 1118, 1091 cm^{-1}; ESI-MS, m/z 293 (MH$^+$).

3,7-Dimethyl-8-heptanoxy-6-methoxyisochroman (38). The alkylation of isochroman **1** with 1-bromoheptane (cf. the preparation of **12**) produced ether **38** in 70% yield as a colorless oil: R_f **38** = 0.86 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.90 (t, 3 H, J = 6.9 Hz), 1.34 (d, 3 H, J = 6.1 Hz), 1.29−1.51 (m, 8 H), 1.72−1.83 (m, 2 H), 2.12 (s, 3 H), 2.63 (d, 2 H, J = 6.4 Hz), 3.69 (s, 3 H), 3.69−3.79 (m, 1 H), 3.91 (t, 2 H, J = 6.3 Hz), 4.69 (d, 1 H, J = 15.0 Hz), 4.93 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (75.5 MHz) 156.7, 154.8, 132.1, 119.7, 117.3, 107.1, 70.6, 68.2, 64.6, 60.1, 35.8, 31.8, 29.3, 29.0, 26.1, 22.6, 21.5, 14.0, 8.6 ppm; IR (neat) 1609, 1262, 1118, 1092 cm^{-1}; ESI-MS, m/z 307 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-octanoxyisochroman (39). The alkylation of isochroman **1** with 1-bromoctane (cf. the preparation of **12**) produced ether **39** in 72% yield as a colorless oil: R_f **39** = 0.89 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.89 (t, 3 H, J = 6.7 Hz), 1.29−1.51 (m, 13 H), 1.74−1.83 (m, 2 H), 2.12 (s, 3 H), 2.63 (d, 2 H, J = 6.4 Hz), 3.69 (s, 3 H), 3.68−3.79 (m, 1 H), 3.91 (t, 2 H, J = 6.4 Hz), 4.69 (d, 1 H, J = 15.0 Hz), 4.93 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (75.5 MHz) 156.8, 155.2, 132.1, 119.7, 117.6, 107.1, 70.6, 68.2, 64.6, 60.1, 35.8, 31.8, 29.3, 29.2, 26.1, 22.6, 21.6, 14.1, 8.6 ppm; IR (neat) 1610, 1262, 1118, 1092 cm^{-1}; ESI-MS, m/z 321 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-nonanoxyisochroman (40). The alkylation of isochroman **1** with 1-bromononane (cf. the preparation of **12**) produced ether **40** in 62% yield as a colorless oil: R_f **40** = 0.91 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.89 (t, 3 H, J = 6.3 Hz), 1.28−1.51 (m, 15 H), 1.73−1.83 (m, 2 H), 2.12 (s, 3 H), 2.63 (d, 2 H, J = 6.6 Hz), 3.69 (s, 3 H), 3.69−3.80 (m, 1 H), 3.91 (t, 2 H, J = 6.2 Hz), 4.70 (d, 1 H, J = 15.0 Hz), 4.94 (d, 1 H, J = 15.0 Hz), 6.37 (s, 1 H); ^{13}C NMR (62.5 MHz) 156.7, 154.7, 132.0, 119.6, 117.2, 107.0, 70.5, 68.2, 64.5, 60.0, 35.8, 31.8, 29.4, 29.3, 26.0, 22.6, 21.5, 14.0, 8.6 ppm; IR (neat) 1609, 1262, 1118, 1091 cm^{-1}; ESI-MS, m/z 335 (MH$^+$).

8-Acetoxy-3,7-dimethyl-6-methoxyisochroman (42). The condensation of isochroman **1** with acetic acid (cf. the preparation of **20**) produced ester **42** in 72% yield as a white crystalline solid: R_f **42** = 0.61 (hexanes/ether, 1:1); mp 83−84 °C; ^{1}H NMR (250 MHz) δ 1.33 (d, 3 H, J = 6.1 Hz), 2.06 (s, 3 H), 2.31 (s, 3 H), 2.64 (d, 2 H, J = 6.8 Hz), 3.70 (s, 3 H), 3.68−3.80 (m, 1 H), 4.70 (d, 1 H, J = 15.6 Hz), 4.97 (d, 1 H, J = 15.6 Hz), 6.59 (s, 1 H); ^{13}C NMR (62.5 MHz) 169.2, 154.8, 148.4, 132.9, 125.7, 121.0, 117.5, 70.4, 64.5, 60.1, 35.2, 21.4, 20.7, 14.6, 9.1 ppm; IR (neat) 1761, 1206, 1119, 1085 cm^{-1}; ESI-MS, m/z 251 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-propanoyloxyisochroman (43). The condensation of isochroman **1** with propionic acid (cf. the preparation of **20**) produced ester **43** in 74% yield as a white crystalline solid: R_f **43** = 0.64 (hexanes/ether, 1:1); mp 58−59 °C; ^{1}H NMR (300 MHz) δ 1.25−1.34 (m, 6 H), 2.05 (s, 3 H), 2.55−2.65 (m, 4 H), 3.70 (s, 3 H), 3.64−3.78 (m, 1 H), 4.70 (d, 1 H, J = 15.2 Hz), 4.97 (d, 1 H, J = 15.2 Hz), 6.58 (s, 1 H); ^{13}C NMR (75.5 MHz) 172.8, 154.9, 148.5, 132.9, 125.6, 121.1, 117.5, 70.4, 64.6, 60.1, 35.3, 27.5, 21.5, 9.2 ppm; IR (neat) 1758, 1357, 1142, 1088 cm^{-1}; ESI-MS, m/z 265 (MH$^+$).

8-Butanoyloxy-3,7-dimethyl-6-methoxyisochroman (44). The condensation of isochroman **1** with butanoic acid (cf. the preparation of **20**) produced ester **44** in 77% yield as a white crystalline solid: R_f **44** = 0.65 (hexanes/ether, 1:1); mp 59−60 °C; ^{1}H NMR (250 MHz) δ 1.25−1.40 (m, 8 H), 2.05 (s, 3 H), 2.64 (d, 2 H, J = 6.8 Hz), 2.77−2.88 (m, 2 H), 3.69 (s, 3 H), 3.70−3.79 (m, 1 H), 4.70 (d, 1 H, J = 15.5 Hz), 4.97 (d, 1 H, J = 15.5 Hz), 6.56 (s, 1 H); ^{13}C NMR (62.5 MHz) 175.3, 154.7, 148.4, 132.8, 125.4, 121.1, 117.4, 70.4, 64.4, 60.1, 35.2, 34.0, 21.4, 18.9, 9.1 ppm; IR (neat) 1754, 1358, 1120, 1084 cm^{-1}; ESI-MS, m/z 279 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-pentanoyloxyisochroman (45). The condensation of isochroman **1** with pentanoic acid (cf. the preparation of **20**) produced ester **45** in 83% yield as a colorless oil: R_f **45** = 0.70 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.97 (t, 3 H, J = 7.1 Hz), 1.33 (d, 3 H, J = 6.1 Hz), 1.41−1.49 (m, 2 H), 1.71−1.80 (m, 2 H), 2.05 (s, 3 H), 2.57 (t, 2 H, J = 7.4 Hz), 2.64 (d, 2 H, J = 6.7 Hz), 3.70 (s, 3 H), 3.67−3.80 (m, 1 H), 4.70 (d, 1 H, J = 15.6 Hz), 4.97 (d, 1 H, J = 15.6 Hz), 6.57 (s, 1 H); ^{13}C NMR (75.5 MHz) 172.3, 154.8, 148.7, 132.8, 125.7, 121.1, 117.5, 70.4, 64.6, 60.1, 35.3, 33.9, 27.1, 22.3, 21.5, 13.7, 9.2 ppm; IR (neat) 1756, 1358, 1142, 1086 cm^{-1}; ESI-MS, m/z 293 (MH$^+$).

3,7-Dimethyl-8-hexanoyloxy-6-methoxyisochroman (46). The condensation of isochroman **1** with hexanoic acid (cf. the preparation of **20**) produced ester **46** in 79% yield as a colorless oil: R_f **46** = 0.73 (hexanes/ether, 1:1); ^{1}H NMR (250 MHz) δ 0.94 (t, 3 H, J = 6.8 Hz), 1.33 (d, 3 H, J = 6.3 Hz), 1.34−1.43 (m, 4 H), 1.71−1.81 (m, 2 H), 2.05 (s, 3 H), 2.56 (t, 2 H, J = 7.4 Hz), 2.64 (d, 2 H, J = 6.8 Hz), 3.70 (s, 3 H), 3.69−3.81 (m, 1 H), 4.70 (d, 1 H, J = 15.7 Hz), 4.97 (d, 1 H, J = 15.7 Hz), 6.58 (s, 1 H); ^{13}C NMR (62.5 MHz) 172.0, 154.8, 148.4, 132.8, 125.5, 121.0, 117.5, 70.4, 64.5, 60.1, 35.2, 34.1, 31.2, 24.6, 22.2, 21.4, 13.8, 9.2 ppm; IR (neat) 1757, 1357, 1142, 1086 cm^{-1}; ESI-MS, m/z 307 (MH$^+$).

3,7-Dimethyl-8-heptanoyloxy-6-methoxyisochroman (47). The condensation of isochroman **1** with heptanoic acid (cf. the preparation of **20**) produced ester **47** in 74% yield as a colorless oil: R_f **47** = 0.78 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.89 (t, 3 H, J = 6.0 Hz), 1.29−1.52 (m, 9 H), 1.70−1.81 (m, 2 H), 2.05 (s, 3 H), 2.56 (t, 2 H, J = 7.6 Hz), 2.64 (d, 2 H, J = 6.8 Hz), 3.69 (s, 3 H), 3.68−3.80 (m, 1 H), 4.70 (d, 1 H, J = 15.6 Hz), 4.97 (d, 1 H, J = 15.6 Hz), 6.57 (s, 1 H); ^{13}C NMR (75.5 MHz) 172.1, 154.8, 148.5, 132.9, 125.6, 121.1, 117.6, 70.4, 64.6, 60.1, 35.3, 34.2, 31.7, 29.1, 25.0, 22.6, 21.5, 14.1, 9.2 ppm; IR (neat) 1757, 1357, 1140, 1086 cm^{-1}; ESI-MS, m/z 321 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-octanoyloxyisochroman (48). The condensation of isochroman **1** with octanoic acid (cf. the preparation of **20**) produced ester **48** in 80% yield as a colorless oil: R_f **48** = 0.79 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.90 (t, 3 H, J = 6.8 Hz), 1.31−1.51 (m, 11 H), 1.71−1.81 (m, 2 H), 2.05 (s, 3 H), 2.56 (t, 2 H, J = 7.5 Hz), 2.64 (d, 2 H, J = 6.8 Hz), 3.69 (s, 3 H), 3.68−3.80 (m, 1 H), 4.70 (d, 1 H, J = 15.5 Hz), 4.97 (d, 1 H, J = 15.5 Hz), 6.57 (s, 1 H); ^{13}C NMR (75.5 MHz) 172.1, 154.9, 148.3, 133.2, 125.8, 121.1, 117.5, 70.4, 64.6, 60.1, 35.3, 34.2, 31.6, 29.1, 28.9, 25.0, 22.5, 21.5, 14.0, 9.2 ppm; IR (neat) 1757, 1358, 1141, 1086 cm^{-1}; ESI-MS, m/z 335 (MH$^+$).

3,7-Dimethyl-6-methoxy-8-nonanoyloxyisochroman (49). The condensation of isochroman **1** with nonanoic acid (cf. the preparation of **20**) produced ester **49** in 78% yield as a colorless oil: R_f **49** = 0.84 (hexanes/ether, 1:1); ^{1}H NMR (300 MHz) δ 0.90 (t, 3 H, J = 6.8 Hz), 1.28−1.49 (m, 13 H), 1.71−1.81 (m, 2 H), 2.05 (s, 3 H), 2.57 (t, 2 H, J = 7.6 Hz), 2.65 (d, 2 H, J = 6.7 Hz), 3.69 (s, 3 H), 3.68−3.79 (m, 1 H), 4.70 (d, 1 H, J = 15.5 Hz), 4.97 (d, 1 H, J = 15.5 Hz), 6.57 (s, 1 H); ^{13}C NMR (75.5 MHz) 172.1, 154.9, 148.4, 132.9, 125.6, 121.1, 117.5, 70.4, 64.6, 60.1, 35.3, 34.1, 31.4, 28.8, 24.9, 22.4, 21.5, 13.9, 9.2 ppm; IR (neat) 1757, 1358, 1141, 1095 cm^{-1}; ESI-MS, m/z 349 (MH$^+$).

ACKNOWLEDGMENT

This work was supported by a joint USDA/UGA Cooperative Agreement (58-6612-5-018), and a patent application has been filed (08/667,749).

LITERATURE CITED

Boden, E. T.; Keck, G. E. Proton-Transfer Steps in Steglich Esterification: A Very Practical New Method for Macrolactonization. *J. Org. Chem.* **1985**, *50*, 2394.

Brunson, H. A.; Kroeger, J. W. Cycli-Alkylation of Aromatic Compounds by the Friedel and Crafts Reaction. *J. Am. Chem. Soc.* **1940**, *62*, 36.

Cox, R. H.; Hernandez, O.; Dorner, J. W.; Cole, R. J.; Fennel, D. I. A New Isochroman Mycotoxin Isolated from *Penicillium steckii*. *J. Agric. Food Chem.* **1979**, *27*, 999.

Cutler, H. G. *Proceedings of the 11th Annual Meeting*; Plant Growth Regulation Society of America: Boston, MA, 1984; p 1.

Cutler, H. G.; Arrendale, R. F.; Cole, P. D.; Davis, E. E.; Cox, R. H. 3,7-Dimethyl-8-hydroxy-6-methoxyisochroman from *Penicillium corylophilium:* Plant Growth Regulatory Activity. *Agric. Biol. Chem.* **1989**, *53*, 1975.

Deady, L. W.; Topsom, R. D.; Vaughan, J. Preparation of Some Chromans from 1,3-Diaryloxypropanes. *J. Chem. Soc.* **1963**, 2094.

Feutrill, G. I.; Mirrington, R. N. Demethylation of Aryl Methyl Ethers with Thioethoxide Ion in Dimethyl Formamide. *Tetrahedron Lett.* **1970**, 1327.

Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 729.

Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 145.

Holton, R. A.; Nelson, R. V. A New Protecting Group for Phenols: Phenylthiomethyl (PTM) Ethers. *Synth. Commun.* **1980**, *10*, 911.

Jung, M. E.; Lyster, M. A. Quantitative Dealkylation of Alkyl Ethers via Treatment with Trimethylsilyl Iodide. A New Method for Ether Hydrolysis. *J. Org. Chem.* **1977**, *42*, 3761.

Kurtz, T. E.; Link, R. F.; Tukey, J. W.; Wallace, D. L. *Technometrics* **1965**, *7*, 95.

Macchia, B.; Balsamo, A.; Breschi, M. C.; Chiellini, G.; Lapucci, A.; Macchia, M.; Manera, C.; Martinelli, A.; Scatizzi, R.; Barretta, G. U. Conformationally Restrained Analogs of Sympathomimetic Catecholamines. Synthesis, Conformational Analysis, and Adrenergic Activity of Isocroman Derivatives. *J. Med. Chem.* **1993**, *36*, 3077.

Saeed, A.; Rama, N. H. Synthesis of (±)-6,8-Dimethoxy-3-pentadecylisocroman, Its 1-Hydroxy Derivative and (±)-3,4-Dihydro-6,8-Dimethoxy-3-pentacdecylisocourmarin Related to Peniolactol. *Arabian J. Sci. Eng.* **1995**, *20*, 693.

Steyn, P. S.; Holzapfel, C. W. The Synthesis of Ochratoxins A and B Metabolites of *Aspergillus ochraceus* Wilh. *Tetrahedron* **1967**, *23*, 4449.

Ziegler, F. E.; Berger, G. D. A Mild Method for the Esterification of Fatty Acids. *Synth. Commun.* **1979**, *9*, 539.

Received for review August 14, 1996. Revised manuscript received January 16, 1997. Accepted January 27, 1997.[⊗]

JF960618L

[⊗] Abstract published in *Advance ACS Abstracts*, March 1, 1997.