JOC Article

Formal Synthesis of Angiogenesis Inhibitor NM-3

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We report the formal synthesis of angiogenesis inhibitor NM-3 (**1**) in six steps from either of the 2,4-dimethoxyhalobenzenes **13a,b** or 3,5-dimethoxychlorobenzene (**13c**). The first key reaction is the regiospecific alkylation/rearrangement between the aryne derived from **13a**−**c** with sodium diethylmalonate in THF to produce diester **11**, which after hydrolysis and cyclization affords homophthalic anhydride **3**. The second is the reaction of anhydride **3** with either ethyl 2-methylmalonate (**28a**), in the presence of 1,1′-carbonyldiimidazole, or ethyl-2-methylmalonyl chloride (**28b**) under basic conditions to afford key isocoumarin **27**. The conversion of **27** constitutes a formal synthesis of NM-3.

Introduction

The process of angiogenesis, the development and growth of new vasculature, is involved in a variety of normal biological functions, as well as disease states including arthritis, psoriasis, and cancer.[1] For this reason, angiogenesis inhibition has become an active area of pharmaceutical research, and over 40 such agents are currently undergoing clinical trials.[2] The isocoumarin NM-3 (**1**, Figure 1), an analogue of the natural product cytogenin **2**, inhibits the growth of human endothelial cells in culture and tumor angiogenesis in human tumor xenograft models.[3] Significantly, reductions in mean tumor volume were observed in animal models when NM-3 was administered in combination with other chemotherapeutic agents or radiation, beyond those observed with chemotherapy or radiotherapy alone.[4] NM-3 is currently undergoing Phase I clinical trials.

The patented synthesis of NM-3 by Tsuchida and coworkers[5] involves six steps from dimethyl 1,3-acetonedicarboxylate and diketene. Though elegant, this route suffers from a poor yield in the initial step and the undesirable expense associated with the use of 1,1′-carbonyldiimidazole (CDI). A variety of other synthetic strategies for isocoumarins are known. These include ortho-metalation approaches,[6] palladium-catalyzed cyclizations of 2-iodobenzoic acid derivatives,[7] Friedel−Crafts approaches from benzoic acids,[8] and ozonolysis of indanone enol acetates and trifluoroacetates.[9] Unfortunately, these approaches would not resolve significant practical and economic issues for a commercial synthesis of NM-3.

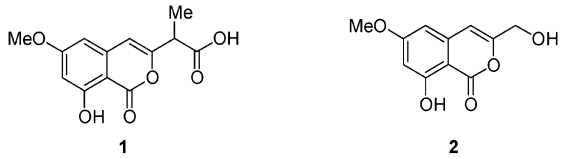

FIGURE 1.

Results and Discussion

As part of our efforts to develop a more efficient process for NM-3, we investigated the reactions of 3,5-dimethoxyhomophthalic anhydride (**3**) with malonate nucleophiles. Our initial preparation of **3** is shown in Scheme 1. Thus 3,5-dimethoxycinnamic acid (**4**) was reduced by transfer hydrogenation to **5** and then cyclized in methanesulfonic acid to give indanone **6**. Acylation of **6** with diethyloxalate

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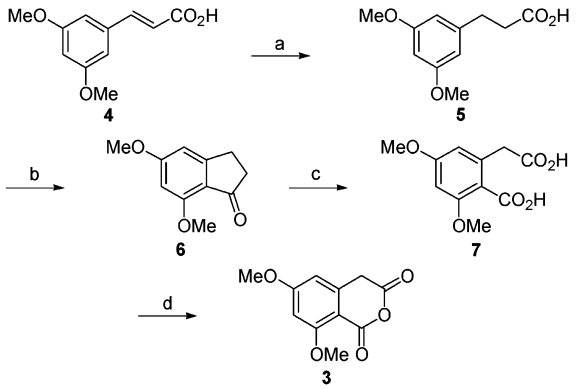
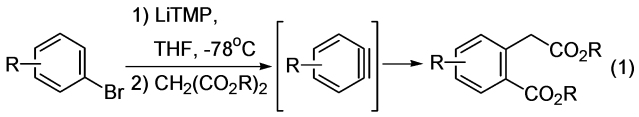
SCHEME 1[a]



[a] (a) HCO_2NH_4, 10% Pd/C, EtOH (95% yield); (b) $MeSO_3H$ (70% yield); (c) (i) $(EtO_2C)_2$, NaOMe, toluene, (ii) 30% H_2O_2, KOH, MeOH (54% yield); (d) Ac_2O, toluene, reflux (97% yield).

and subsequent oxidation with alkaline hydrogen peroxide, according to Bhakta's conditions,[10] afforded 3,5-dimethoxyhomophthalic acid (**7**). Cyclization of **7** to **3** was accomplished with acetic anhydride in hot toluene,[11] and the product was isolated directly from the reaction as a white powder.

The high cost of cinnamic acid **4** and concerns of an uncontrolled exotherm in steps b and c (Scheme 1) led us to explore an alternative approach to homophthalic acid **7**. The addition of malonate anions to arynes and their subsequent rearrangement to homophthalate esters (eq 1), originally reported by Danishefsky,[12] was recently

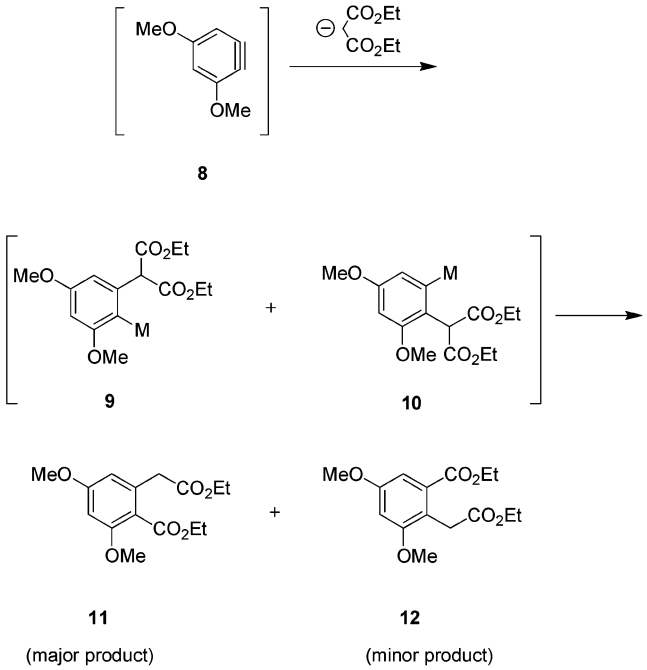


employed by Kita and co-workers in their synthesis of Fredericamycin A.[13] Notably, they found that the addition of dimethyl malonate anion to the aryne derived from 1-bromo-2,3,5-trimethoxybenzene occurred with only modest regioselectivity (3:2).

We reasoned that an aryne of type **8** would react with diethyl malonate anion to afford intermediate **9** preferentially over **10**, owing primarily to the ortho-stabilization of the aryl anion by the methoxy group (Scheme 2).[14] The resulting homophthalic ester rearrangement product **11** would have the desired regiochemistry to prepare anhydride **3**.

Our preliminary experiments, using conditions analogous to those of Kita and Danishefsky (LiTMP, THF, −78 °C), gave the desired ester along with a host of byproducts and dark-colored material that was not fully characterized. We turned to optimizing the reaction conditions using the less expensive base lithium diisopropylamide (LDA). One prominent byproduct, which we observed early on, was the *N*,*N*-diisopropylaniline **14**, resulting from competitive trapping of the aryne intermediate (Scheme 3).[15] We therefore decided on an approach that would keep the effective concentration of LDA low at all times: by using a different base to generate the malonate anion, using only enough LDA as to generate the aryne intermediate, and adding the LDA slowly to the reaction mixture. The most useful base for the generation of the malonate anion was sodium hydride. Sodium amide and lithium hydride were both unsatisfactory owing to low solubility of either the base

SCHEME 2



SCHEME 3

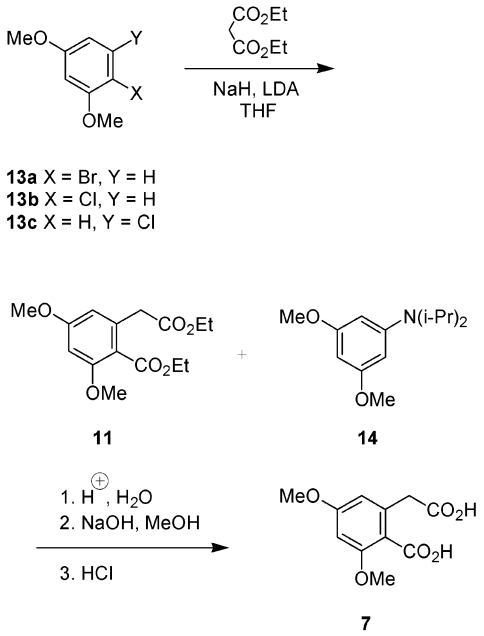


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TABLE 1. Comparison of Reaction Profiles for the Alkylation of 13a−c with Diethyl Malonate

		crude product mixture area % (HPLC)			% yield
entry	substrate	**12**	**11**	**14**	isolated **7**
1	**13a**	0	82.2	7.8	39
2	**13b**	0	70.0	5.0	44
3	**13c**	0	66.4	8.8	36

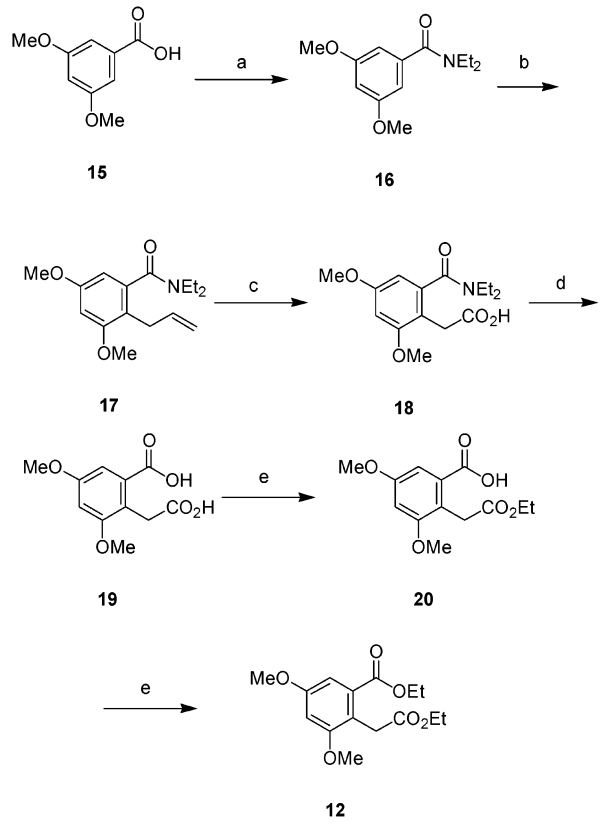
or the resultant malonate, respectively, under our reaction conditions.

As the oily homophthalate ester **11** was difficult to isolate from the excess diethyl malonate, it was convenient to saponify the reaction mixture directly and isolate the corresponding homophthalic acid **7** as a white solid. Authentic samples of **11** and aniline **14** were purified by column chromatography for characterization. Consistent with the aryne mechanism, similar results were observed for the bromoarene **13a** and the isomeric chloroarenes **13b** and **13c** (Table 1). Compound **13b**, conveniently prepared by dimethylation of commercially available 4-chlororesorcinol, was our preferred reagent.

Some specific aspects of our reaction conditions merit additional comment. Extensive experimentation showed that addition of LDA over a period of approximately 1 h to a mixture of the malonate and haloarene at 0−5 °C obviated the formation of complex mixtures observed at lower temperatures. Use of minimal LDA was essential to reducing the quantity of diisopropylaniline byproduct, as was the use of excess malonate. In practice, 1−1.5 equiv of LDA and 4 equiv of diethylmalonate reproducibly gave greater than 95% conversion while keeping the amount of diisopropylaniline **14** to less than 10%. Interestingly, 5.9−6.0 equiv of NaH was required to achieve greater than 95% conversion. The origin of this effect does not appear to be related to the NaH purity, which we tested and found to be consistent with the label claim.

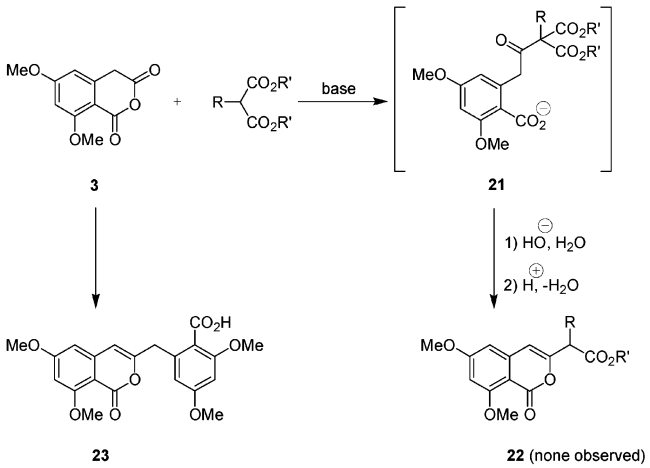
One salient characteristic of these reactions is the absence of the isomeric homophthalate ester **12**. An authentic sample of **12** was prepared by the route shown in Scheme 4. Thus, 3,5-dimethoxybenzoic acid (**15**) was converted to the corresponding diethylamide **16** using CDI and diethylamine[16] in the presence of acetic acid. This reaction fails in the absence of acetic acid, possibly because the more basic amine prevents protonation of imidazole functions. Amide **16** was then ortho-lithiated and allylated in the presence of cuprous bromide dimethyl sulfide complex[17] to give **17**. Oxidative cleavage of the terminal olefin to **18**, and subsequent hydrolysis of the amide afforded homophthalic acid **19**.[18] Conversion of **19** to the diethyl ester could not be achieved solely by treatment with thionyl chloride and ethanol, which gave only the half ester **20**, probably because of in situ formation of the homophthalic anhydride. Esterification of **20** with CDI and ethanol led to the desired homophthalate **12**. The presence of **12** in crude reaction mixtures from **13a−c** and diethylmalonate was not detected by HPLC.

SCHEME 4. Preparation of Authentic Homophthalate Ester 12[a]



[a] (a) CDI, Et_2NH, AcOH, DCE, reflux; (b) (i) s-BuLi, THF, −78 °C, (ii) CuBr·Me_2S, (iii) allyl bromide; (c) $RuCl_3$, $NaIO_4$, CCl_4, H_2O, MeCN; (d) 6 N HCl, heat; (e) $SOCl_2$ then EtOH; (f) CDI, CH_2Cl_2, EtOH.

SCHEME 5. Reaction of Anhydride 3 with a Dialkylmalonates



With an acceptable route to homophthalic anhydride **3**, we anticipated that reaction of this material with an appropriate malonate nucleophile would result in formation of condensation product **21** (Scheme 5), which, after monosaponification and decarboxylation, would cyclize in the presence of acid to the isocoumarin **22**. In practice, we were not able to obtain any isocoumarin product from such reactions. However, when **3** was reacted with ethyl malonate (half ester) in the presence of triethylamine,

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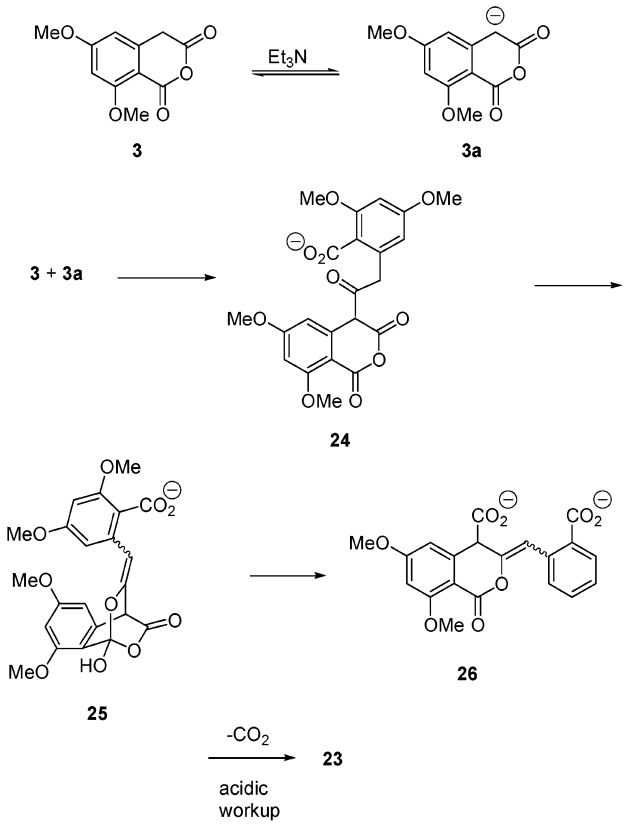
SCHEME 6. Proposed Mechanism for the Formation of Isocoumarin 23



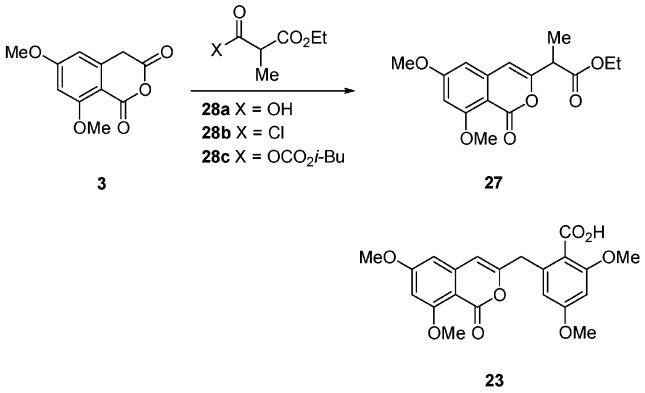
the principal product resulted from a self-condensation reaction between two homophthalic anhydrides. Characterization revealed the structure as isocoumarin **23**. The same product was observed upon reaction of **3** with Horner−Emmons reagents or with potassium carbonate and a phase transfer catalyst in THF.

A possible mechanism for the formation of **23** is shown in Scheme 6. Homophthalic anhydride **3**, in the presence of triethylamine, is assumed to be in equilibrium with its enolate form **3a**. Carbonyl addition by another molecule of **3** leads to **24**, which undergoes transannular *O*-acylation to afford **25**. Base-promoted ring opening of **25** affords **26**. Decarboxylation and olefin isomerization then result in **23**.

Although we were unable to detect the formation of intermediates **24**−**26** by HPLC monitoring of the reaction, evidence for the proposed mechanism comes from the work of Srivastava and co-workers,[19] who have reported that the reaction of homophthalic acids with anhydrides in pyridine led to benzylic aylation products. Isocoumarins were obtained if the reaction was carried out on a steam bath. The similarity of the reactions suggests that the *O*-acylation of intermediate **24** (Scheme 6) and the decarboxylation of intermediate **26** are more facile than in the compounds studied by Srivastava.

The formation of isocoumarin **23** suggested that a suitably activated malonate might be reacted with homophthalic anhydride **3**, under basic conditions, to generate an isocoumarin such as **27**. The results of this

SCHEME 7



study are shown in Scheme 7 and Table 2. Reaction of the acid **28a** with CDI, followed by triethylamine and anhydride **3**, afforded a 66% yield of the desired isocoumarin **27** (entry 1). Significantly, the ratio of desired isocoumarin **27** to **23** was 89:11, indicating that the intermediate acyl imidazole (or ketene) derived from **28a** could compete effectively with the anhydride. When the acid chloride **28b** was reacted under similar conditions, the ratio was almost opposite that of the CDI reaction, in favor of isocoumarin **23** (entry 2). We reasoned that using a stronger base would enolize the anhydride to a greater extent and thus minimize the chances of self-condensation, leading to **23**. Consistent with this proposal, when anhydride **3** was added to a mixture of acid chloride **28b** and DBU in acetonitrile, only a trace of the undesired **23** was observed and **27** was isolated in 78% yield (entry 3). Our initial attempts to use *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) as a base failed because of acylation of the base by the malonyl chloride. The problem was circumvented by adding **3** to a solution of TMG (1 equiv), followed by addition of triethylamine as acid scavenger (1 equiv), and finally the malonyl chloride. By this procedure, there was no detectable **23** formed and **27** was isolated in good yields (entries 4 and 5). Interestingly, the reaction of the mixed anhydride derived from malonic acid **28a** and isobutyl chloroformate (entry 6, **28c**) failed to give any **27**, producing only **23**.

The preparation of **27** constitutes a formal synthesis of NM-3.[5] The final two steps were carried out according to the reported procedures, and the NM-3 thus produced was identical to an authentic sample.

In conclusion, we have developed a new synthesis of NM-3. The regiospecific addition and rearrangement of diethylmalonate to unsymmetrically substituted aryne **8** at unusually high temperature gave rapid access to anhydride **3**. The remarkably facile reaction of **3** with activated malonates **28a,b** to afford isocoumarin **27** in high yield under mild conditions led to an advanced intermediate in the reported synthesis of NM-3.

Experimental Section

3-(3,5-Dimethoxyphenyl)-propionic Acid (5). Cinnamic acid **4** (49.77 g, 239 mmol), 10% Pd/C (2.54 g, 2.39 mmol), and EtOH (375 mL) were combined, and solid HCO_2NH_4 (16.58 g, 263 mmol) was added portionwise over 15 min. The mixture was stirred at ambient temperature for 16 h. The mixture was filtered through Celite, and the flask and solids were rinsed with EtOH. The combined filtrate and washes were reduced

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TABLE 2. Formation of Isocoumarins 27 and 23 from Homophthalic Anhydride 3

entry	malonate	conditions	ratio 27:23	isolated yield, %
1	**28a**	CDI, Et_3N, MeCN, rt 22 h then reflux 2.5 h	89:11	66
2	**28b**	Et_3N, MeCN, rt 22 h then reflux 2.5 h	12:87	11
3	**28b**	DBU, MeCN, rt	99.8:0.2	78
4	**28b**	TMG, NMP, Et_3N, 0 °C	100:0	78
5	**28b**	TMG, MeCN, Et_3N, 0 °C	100:0	86
6	**28c**	Et_3N, MeCN, rt 17 h then 50 °C 2 h	0:100	0

in vacuo. H_2O (250 mL) was added to the residue, and the resulting suspension was cooled to 0 °C and acidified with 12 M HCl until pH <2. The suspension was filtered, and the flask and filter cake were washed with H_2O. The wet solid was dried to give **5** as a white powder (47.54 g, 95%), mp 59−61 °C: ^{1}H NMR ($CDCl_3$) δ 6.38−6.33 (m, 2H), 3.78 (s, 6H), 2.91 (t, 2H, J = 7.7), 2.68 (t, 2H, J = 7.7). The spectrum was in agreement with the reported data.[20]

5,7-Dimethoxyindan-1-one (6). Compound **5** (45.02 g, 214.2 mmol) and methane sulfonic acid (MSA, 150.6 g, 1567 mmol) were combined and heated to 95 °C for 6 h. The mixture was cooled to ambient temperature and poured over crushed ice. NaOH (50%, 125.4 g, 1567 mmol) was added to neutralize the MSA. The mixture was extracted with EtOAc (3 × 670 mL), and each organic portion was washed with 5% $NaHCO_3$. The organic portions were combined, dried ($MgSO_4$), and reduced in vacuo. The residue was triturated with *tert*-butylmethyl ether (TBME, 100 mL), and the resulting suspension was filtered and dried to give **6** as a tan powder (28.6 g, 70%), mp 99−100 °C: ^{1}H NMR ($CDCl_3$) δ 6.47 (br s, 1H), 6.28 (br s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.03−2.98 (m, 2H), 2.66−2.61 (m, 2H). The spectrum was in agreement with the reported data.[20]

2-Carboxymethyl-4,6-dimethoxybenzoic Acid (7). A solution of **6** (36.83 g, 181.8 mmol) and diethyl oxalate (42.03 g, 287.7 mmol) in toluene (400 mL) was added over 45 min to a suspension of NaOMe (20.21 g, 374.1 mmol) in toluene (20 mL) at 0 °C. After addition was complete, the cooling bath was removed, and the mixture was stirred for 1 h at ambient temperature. The solvent was removed in vacuo, and the residue was suspended in MeOH (1000 mL). Solid KOH (85%, 96.24 g, 1458 mmol) was added portionwise over 45 min, keeping the temperature below 50 °C. H_2O_2 (30%, 191 mL, 1870 mmol) was added over 3 h, keeping the temperature below 64 °C. Gas was evolved during H_2O_2 addition. After addition was complete, the mixture was stirred at ambient temperature for 16 h. The mixture was filtered, and the filtrate was partially reduced in vacuo to remove MeOH. The remaining aqueous filtrate was washed with TBME, and the organic layer was discarded. The aqueous layer was acidified with 12 M HCl until pH <2 (~140 mL). The acidic aqueous layer was extracted with EtOAc, and the combined organic portions were dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was triturated with TBME. The resulting suspension was filtered and dried to give **7** as a tan powder (25.33 g, 54%), mp 173−174 °C: ^{1}H NMR (acetone-d_6) δ 6.59−6.55 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.77 (s, 2H); ^{13}C NMR (acetone-d_6) δ 171.7, 168.1, 162.6, 159.9, 137.6, 116.2, 109.3, 97.8, 56.2, 55.6, 39.7. The proton spectrum was in agreement with the reported data.[21]

6,8-Dimethoxy-isochroman-1,3-dione (3). Acetic anhydride (4.00 mL, 41.1 mmol) was added via syringe to a slurry of diacid **7** (8.98 g, 37.4 mmol) in toluene (90 mL), and the mixture was heated at reflux for 1 h. The flask was cooled in an ice bath to ≤2 °C, the solid product was filtered, and the cake was washed with heptane. The solid was collected and dried to afford **3** as light yellow crystals (8.04 g, 96.7%), mp 159−162 °C: ^{1}H NMR ($CDCl_3$) δ 6.44 (d, 1H, J = 2.0), 6.35 (apparent t, 1H, J = 1.0), 3.98 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8, 165.0, 163.8, 156.8, 138.7, 103.8, 103.2, 98.2, 56.2, 55.8, 35.3. The proton spectrum was in agreement with the reported data.[11]

1-Chloro-2,4-dimethoxybenzene (13b). Sodium hydroxide (50%, 10.8 mL, 204.5 mmol) was added to a solution of 4-chlororesorcinol (10.02 g, 69.29 mmol) in H_2O (46 mL) over 6 min, keeping the temperature below 20 °C. Heptane (84 mL) was added, followed by dimethyl sulfate (18.1 mL, 191.3 mmol) over 7 min, keeping the temperature below 39 °C. The mixture was stirred at ambient temperature for 16 h. Stirring was stopped, and the layers were separated. The aqueous layer was discarded, and the organic layer was washed with a 3% NH_4OH solution and then H_2O. The organic layer was vacuum filtered through silica gel (2.15 g), and the filtrate was reduced in vacuo to give **13b** as a colorless oil (10.3 g, 86%): ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 1H, J = 8.7), 6.49 (d, 1H, J = 2.7), 6.41 (dd, 1 H, J = 8.7, 2.7), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.4, 155.5, 130.0, 113.9, 105.0, 99.8, 55.9, 55.4. The spectra were in agreement with the reported data.[22]

2-Ethoxycarbonylmethyl-4,6-dimethoxybenzoic Acid Ethyl Ester (11). Diethyl malonate (65.81 g, 410.8 mmol) was added to a mixture of **13b** (17.73 g, 102.7 mmol), sodium hydride (60%, 24.65 g, 616.3 mmol), and THF (190 mL) over 2.4 h, keeping the temperature below 6 °C. LDA (2.0 M, 52 mL, 104 mmol) was added over 2 h, keeping the temperature below 3 °C. The reaction was quenched into a solution of 12 M HCl (71 mL, 852 mmol) in H_2O (200 mL), keeping the temperature below 21 °C. The layers were separated, and the aqueous layer was extracted with TBME (95 mL). The aqueous layer was acidified and extracted to provide a sample of (3,5-dimethoxyphenyl)-diisopropylamine (**14**) for analysis: ^{1}H NMR ($CDCl_3$) δ 6.07 (d, 2H, J = 2.1), 5.95 (t, 1H, J = 2.1), 3.78 (septet, 2H, J = 6.8), 3.77 (s, 6H), 1.25 (d, 12H, J = 6.8); ^{13}C NMR ($CDCl_3$) δ 160.8, 149.8, 97.0, 89.3, 55.0, 47.5, 21.2; IR (neat, cm^{-1}) 2969, 1612, 1558. Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.41; H, 8.84; N, 5.12. Found: C, 61.28; H, 8.60; N, 5.04. The organic portions were combined, and the solvent was removed in vacuo to give crude **11**. A portion of this material was purified by column chromatography (50% EtOAc/hexanes) to give pure **11** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.40 (s, 2H), 4.34 (q, 2H, J = 7.2), 4.14 (q, 2H, J = 7.2), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 (s, 2H), 1.35 (t, 3H, J = 7.2), 1.24 (t, 3H, J = 7.2); ^{13}C NMR ($CDCl_3$) δ 170.6, 167.1, 161.4, 158.8, 134.8, 116.2, 107.3, 97.7, 60.8, 55.8, 55.2, 39.5, 14.0 The proton spectrum was in agreement with the reported data.[5]

2-Carboxymethyl-4,6-dimethoxybenzoic Acid (7). The residue containing crude **11** was dissolved in MeOH (170 mL), and NaOH (50%, 45 mL, 852.2 mmol) was added over 0.5 h, keeping the temperature below 46 °C. The resulting suspension was stirred for 0.5 h and then filtered. The flask and solids were washed with MeOH. The solid was discarded, and the filtrate was reduced in vacuo. H_2O was added, and the mixture was heated to reflux for 6 h. The mixture was cooled and filtered to remove particulates. The filtrate was washed with TBME, and the organic portion was discarded. After clarifica-

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tion with charcoal (2.5 g), the aqueous portion was acidified with 12 M HCl until pH <2 and then extracted with EtOAc. The organic portion was reduced in vacuo to ~150 mL, cooled to 0 °C, stirred for 0.5 h, filtered, and dried to give **7** as a tan powder (10.93 g, 44%).

***N,N*-Diethyl-3,5-dimethoxybenzamide (16).** CDI (9.79 g, 1.10 mmol) was added in one portion to a solution of acid **15** (10.0 g, 54.9 mmol) in 1,2-dichloroethane (105 mL) **Caution:** CO_2 is evolved. Diethylamine (6.25 mL, 60.4 mmol) was added followed by HOAc (3.3 mL, 60.4 mmol). The reaction was refluxed for 2.25 h. The reaction was cooled to ambient temperature, additional CDI (8.90 g, 54.9 mmol) was added, and the mixture was stirred for 16 h at ambient temperature. An additional amount of diethylamine (5 mL, 48.3 mmol) was added, and the reaction was warmed to 50 °C and stirred for 22 h. Additional small amounts of CDI and diethylamine were added over 2 days at 50 °C until a conversion of >97% was observed by HPLC. The reaction mixture was cooled to ambient temperature, and 50 mL of 1 M HCl was added to quench the reaction. The layers were separated, and the organic layer was washed with 1 M HCl. The combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and then saturated NaCl. The organic layer was dried ($MgSO_4$), and solvent was removed in vacuo to afford a dark peach-colored liquid. The product was purified by silica gel chromatography (50% EtOAc/heptane) to afford amide **16** as a pale yellow oil (13.83 g, 56.55 mmol, 103%): ^{1}H NMR ($CDCl_3$) δ 6.47 (m, 3H), 3.78 (s, 6H), 3.45−3.55 (br, 1.5H), 3.40−3.20 (m, 2.5H), 1.25−1.05 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 170.7, 160.7, 139.0, 110.4, 101.1, 55.3, 43.1, 39.8, 14.1, 12.9; IR (neat, cm^{-1}) 3481, 2971, 1629, 1604. The proton spectrum was in agreement with the reported data.[23] The major contaminate was determined to be diethylacetamide: ^{1}H NMR ($CDCl_3$) δ 3.38 (q, 2H, J = 7.1), 3.30 (q, 2H, J = 7.1), 2.06 (s, 3H), 1.10 (t, 3H, J = 7.1), 1.08 (t, 3H, J = 7.1).

2-Allyl-*N,N*-diethyl-3,5-dimethoxybenzamide (17). 1,10-Phenanthroline (10 mg, used as an indicator) and THF (20 mL) were combined. The mixture was cooled to −70 °C under a nitrogen purge. Freshly titrated *s*-BuLi (0.96 M) was charged dropwise until a purple/brown color persisted, and then the full charge of base (10.5 mL, 10.1 mmol) was added. Amide **16** (2.0 g, 8.43 mmol) was dissolved in THF (10 mL) and slowly added to the *s*-BuLi solution over 30 min. Copper(I) bromide dimethyl sulfide complex (2.53 g, 12.8 mmol) was charged in a single portion. The reaction changed from orange to yellow and was stirred for 5 min. Allyl bromide (0.88 mL, 10.1 mmol) was added over 10 min, and the mixture was stirred an additional 70 min. The reaction was poured into 1 M HCl. The product was extracted with EtOAc, and the organic layers were washed with H_2O. Insoluble copper salts formed and were filtered out. The organic layer was separated, washed with saturated NaCl, and dried ($MgSO_4$), and the solvent was removed in vacuo to give the crude product as a brown oil. Attempted purification by silica gel chromatography (20% EtOAc/heptane) gave crude amide **17** as a light yellow oil (1.00 g, 43%, 88% auc): ^{1}H NMR ($CDCl_3$) δ 6.43 (d, 1H, J = 2.3), 6.30 (d, 1H, J = 2.3), 5.99−5.81 (m, 1H), 5.00 (d, 1H, J = 1.8), 4.90 (dd, 1H, J = 10.1, 2.0), 3.90−3.70 (m, 2H, under other peaks), 3.80 (s, 3H), 3.78 (s, 3H), 3.27 (d, 2H, J = 6.36) 3.09 (m, 2H), 1.24 (t, 3H, J = 7.1), 1.04 (t, 3H, J = 7.1); IR (neat, cm^{-1}) 2974, 1632, 1602, 1462, 1432; HRMS calcd for $C_{16}H_{23}NO_3$ 277.1678, found 277.1680.

(2-Diethylcarbamoyl-4,6-dimethoxyphenyl)acetic Acid (18). Crude allyl benzamide **17** (920 mg, 3.32 mmol) was dissolved in MeCN (19.8 mL), H_2O (12.6 mL), and CCl_4 (12.6 mL). $RuCl_3 \cdot H_2O$ (68.9 mg, 0.332 mmol) was added to the stirring solution. $NaIO_4$ (7.09 g, 33.2 mmol) was charged in three portions over 3.5 h, and the mixture was stirred vigorously for an additional 4 h. The reaction mixture was filtered through Celite, and the cake was rinsed with EtOAc. The phases were separated, the organic layer was washed with H_2O, and the combined aqueous layers were back-extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo to yield crude **18** (0.88 g, 90%). Purification by preparative HPLC (50% H_2O/MeCN) afforded **18** (241 mg, 25%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.49 (d, 1H, J = 2.3), 6.34 (d, 1H, J = 2.3), 3.83 (s, 3H), 3.80 (s, 3H) 3.59 (br m, 1H), 3.31 (q, 3H, J = 7.1), 1.27 (t, 3H, J = 7.1), 1.13 (t, 3H, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 171.6, 159.7, 159.5, 159.4, 137.1, 112.9, 101.8, 99.2, 55.7, 55.4, 43.6, 39.7, 34.4, 14.0, 12.6; IR (neat, cm^{-1}) 2975, 1729, 1601, 1463, 1329; HRMS calcd for $C_{15}H_{21}NO_5$ 295.1420, found 295.1418.

2-Carboxymethyl-3,5-dimethoxybenzoic Acid (19). Benzamide **18** (129.6 mg, 0.439 mmol) was heated in H_2O (2 mL) and 12 M HCl (2 mL) to reflux for 2.5 h. Upon cooling, a solid precipitated out of solution. The solid was dissolved in EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1 M HCl and saturated NaCl and dried ($MgSO_4$), and the solvent was removed in vacuo to give **19** as a tan solid (85.5 mg, 81%): ^{1}H NMR (10% $CD_3OD/CDCl_3$) δ 7.13 (d, 1H, J = 2.5), 6.65 (d, 1H, J = 2.5), 4.03 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (10% $CD_3OD/CDCl_3$) δ 174.8, 169.5, 158.9, 158.8, 131.6, 117.5, 106.0, 102.3, 55.6, 55.2, 31.4; IR (neat, cm^{-1}) 3404, 2924, 2850, 1714, 1604, 1461, 1266, 1204; HRMS calcd for $C_{11}H_{12}O_6$ 240.0634, found 240.0634.

2-Ethoxycarbonylmethyl-3,5-dimethoxybenzoic Acid (20). Diacid **19** (85.5 mg, 0.356) was dissolved in EtOH (anhydrous, 200 proof, 5 mL). DMF (1 drop) was charged to the solution followed by $SOCl_2$ (0.26 mL, 0.356 mmol). The solvent was removed in vacuo. The crude product was not purified prior to conversion into diester **12**.

2-Ethoxycarbonylmethyl-3,5-dimethoxybenzoic Acid Ethyl Ester (12). Crude **20** was dissolved in CH_2Cl_2 (1 mL), CDI (65 mg, 0.40 mmol) was charged in a single portion, and the mixture was stirred for 25 min. EtOH (0.5 mL) was added, and the mixture was stirred overnight. Additional CDI (32.5 mg, 0.20 mmol) was charged, followed by more EtOH (0.5 mL). The reaction was stirred for 2 h. The reaction ceased progressing and was worked up. The solvent was removed, and the residue was dissolved in EtOAc. The organic phase was washed with 1 M HCl and then with saturated NaCl. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by preparative TLC (1/1 EtOAc/Hept + 0.2% AcOH) to give **12** as a tan oil (8.5 mg, 8.1%): ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 1H, J = 2.5), 6.62 (d, 1H, J = 2.5), 4.32 (q, 2H, J = 7.1), 4.14 (q, 2H, J = 7.1), 4.00 (s 2H), 3.84 (s, 3H), 3.80 (s, 3H), 1.36 (t, 3H, J = 7.1), 1.24 (t, 3H, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 172.0, 167.2, 159.0, 158.8, 131.9, 117.5, 105.9, 102.2, 61.0, 60.3, 55.9, 55.4, 31.6, 14.1; IR (neat, cm^{-1}) 2980, 2942, 1722, 1605, 1464, 1064; MS $[M + Na]^+$ 319; HRMS calcd for $C_{15}H_{20}O_6$ 296.1260, found 296.1259.

2-(6,8-Dimethoxy-1-oxo-1*H*-isochromen-3-yl)-propionic Acid Ethyl Ester (27). A solution of anhydride **3** (444.4 mg, 2.00 mmol) in MeCN (12 mL) was added via syringe pump to a solution of TMG (0.28 mL, 2.20 mmol) in MeCN (5 mL) over 36 min, maintaining an internal temperature of ≤0 °C. Triethylamine (0.56 mL, 4.00) was added in one portion. Compound **28b** (527 mg, 3.20 mmol) was added via syringe over 3 min, and the mixture was stirred an additional 18 min. An IPC showed 98.8% conversion by HPLC. The cooling bath was removed, and the reaction was allowed to warm to ambient temperature. The reaction mixture was quenched by addition of 1 M HCl (5 mL). The two phases were separated, and the organic layer was washed with saturated NaCl and then dried (Na_2SO_4) prior to removal of solvent in vacuo to dryness. The residue was taken into EtOAc (0.5 mL), and the product was precipitated by addition of heptanes (1.0 mL). The solid product was filtered and dried to give **27** as a beige solid (528 mg, 86% yield), mp 109−110 °C: ^{1}H NMR ($CDCl_3$) δ 6.45

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(d, 1H, $J = 2.3$), 6.37 (d, 1H, $J = 2.3$), 6.25 (s, 1H), 4.18 (q, 2H, $J = 7.2$), 3.96 (s, 3H), 3.89 (s, 3H), 3.55 (q, 1H, $J = 7.3$), 1.51 (d, 3H, $J = 7.3$), 1.25 (t, 3H, $J = 7.2$); ^{13}C NMR ($CDCl_3$) δ 171.4, 165.3, 163.1, 158.7, 156.1, 141.6, 103.6, 103.1, 100.1, 98.6, 61.3, 56.2, 55.5, 43.6, 15.0, 14.0. The proton spectrum was in agreement with the reported data.[5]

2-(6,8-Dimethoxy-1-oxo-1*H*-isochromen-3-ylmethyl)-4,6-dimethoxybenzoic Acid (23). Refer to Scheme 7 and Table 2 for a discussion of this compound, mp 191−193 °C: ^{1}H NMR ($CDCl_3$) δ 6.56 (d, 1H, $J = 2.2$), 6.44 (d, 1H, $J = 2.3$, 6.36 (d, 1H, $J = 2.2$), 6.26 (d, 1H, $J = 2.3$), 6.10 (s, 1H), 4.09 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.81 (s, 1H); ^{13}C NMR ($CDCl_3$) 167.7, 165.3, 163.0, 162.4, 159.6, 159.5, 156.6, 142.2, 140.3, 112.7, 109.0, 104.6, 104.3, 102.8, 99.8, 98.4, 97.8, 56.4, 56.1, 55.5, 37.8; IR (neat, cm^{-1}) 3060, 2943, 1713, 1602; MS [M − H]$^-$ 399.1; HRMS calcd for $C_{21}H_{20}O_8$ 400.1158, found 400.1155.

Supporting Information Available: General experimental conditions and analytical data for compounds **3**, **5**−**7**, **11**, **12**, **13b**, **14**, **16**−**19**, **25**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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