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Total Synthesis of Psoralidin, an Anticancer Natural Product

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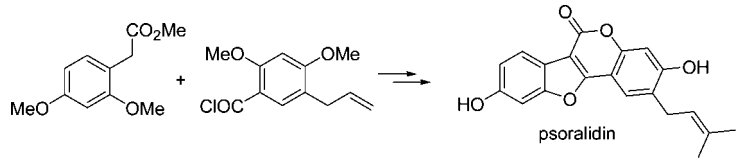
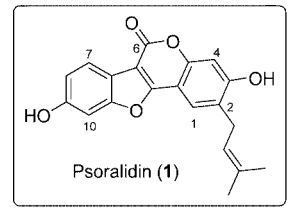
Received November 21, 2008

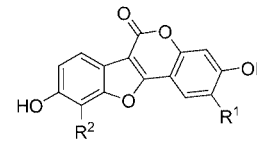


A base-catalyzed condensation of phenyl acetate with acid chloride, followed by intramolecular cyclization and microwave-assisted cross-metathesis reaction, leads to the first total synthesis of psoralidin, a natural product with a broad range of biological activities, in a highly convergent and regioselective manner.

Introduction

Psoralidin (**1**) was first isolated from seeds of *Psoralea corylifolia* Linn in 1948 by Chakravarti et al.,[1] and later its structure was corrected by Khastgir et al. in 1961.[2] It was found to be an active ingredient of many Indian and Chinese traditional herbal medicines.[3] Psoralidin (**1**) exhibits a variety of biological activities like antioxidant,[4] antibacterial,[5] and antidepressant activities.[6,7] It also shows inhibitory activities against protein tyrosine phosphatase 1B, which plays a major role in the negative regulation of insulin signaling.[8] In addition, psoralidin inhibits antigen IgE-induced degranulation in RBL−2H3 cells[9] and acts as a potent antidepressant by strongly inhibiting forskolin-induced corticotrophin releasing factor (CRF) gene transcription.[6,7] Psoralidin also has great potential as an anticancer agent, showing cytotoxic effects on gastric (SNU−1 and SNU−16), colon (HT−29), and breast (MCF−7) cancer cell lines.[10,11] Recently, we reported that **1** inhibits protein kinase Akt phosphorylation, and thus, inhibits the growth of androgen-independent prostate cancer cells both *in vitro* and *in vivo*.[12]





2: R^1 = - $CH_2CH_2CH(Me)_2$, R^2 = H; Dihydropsoralidin
3: R^1 = H, R^2 = - $CH_2CH{=}C(Me)_2$; Phaseol
4: R^1 = H, R^2 = H; Coumesterol

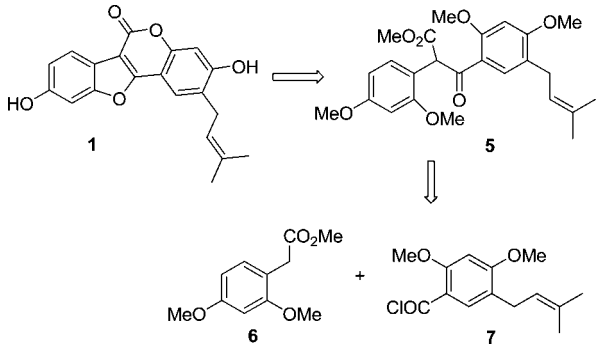
FIGURE 1. Chemical structures of psoralidin and related natural products.

Psoralidin **1** is a member of the coumestane family of natural products having an isopentenyl group at the C−2 position of coumesterol (**4**). In 1961, Nashipuri and Pyne[13] reported the synthesis of dihydropsoralidin (**2**) and confirmed the structure of the natural product. Jain et al.[14] reported the synthesis of some prenylated coumestanes as analogues of psoralidin, and most recently Fürstner et al.[15] synthesized and corrected the proposed structure of phaseol (**3**), a structural isomer of **1**.

(1) Chakravarti, K. K.; Bose, A. K.; Siddiqui, S. *J. Sci. Ind. Res.* **1948**, *7B*, 24–26.
(2) Khastgir, H. N.; Sengupta, P.; Duttagupta, P. C. *Tetrahedron* **1961**, *14*, 275–283.
(3) Ranga, R. S.; Girija, R.; Nur-e-alam, M.; Sathishkumar, S.; Akbarsha, M. A.; Thirugnanam, S.; Rohr, J.; Ahmed, M. M.; Chendil, D. *Cancer Chemother. Pharmacol.* **2004**, *54*, 7–15.
(4) Guo, J. M.; Weng, X. C.; Wu, H.; Li, Q. H.; Bi, K. S. *Food Chem.* **2005**, *91*, 287–292.
(5) Khatune, N. A.; Islam, M. E.; Haque, M. E.; Khondkar, P.; Rahman, M. M. *Fitoterapia* **2004**, *75*, 228–230.
(6) Yi, L. T.; Li, Y. C.; Pan, Y.; Li, H. M.; Xu, Q.; Mo, S. F.; Qiao, C. F.; Jiang, F. X.; Xu, H. X.; Lu, X. B.; Kong, L. D.; Kung, H. F. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2008**, *32*, 510–519.
(7) Chen, Y. C.; Cheung, Y. T.; Kong, L. D.; Ng, T. B.; Qiao, C. F.; Mo, S. F.; Xu, H. X.; Kung, H. F. *Life Sci.* **2008**, *82*, 1117–1121.
(8) Kim, Y. C.; Oh, H.; Kim, B. S.; Kang, T. H.; Ko, E. K.; Han, Y. M.; Kim, B. Y.; Ahn, J. S. *Planta Med.* **2005**, *71*, 87–89.
(9) Matsuda, H.; Sugimoto, S.; Morikawa, T.; Matsuhira, K.; Mizuguchi, E.; Nakamura, S.; Yoshikawa, M. *Chem. Pharm. Bull.* **2007**, *55*, 106–110.
(10) Mar, W.; Je, K. H.; Seo, E. K. *Arch. Pharmacal Res.* **2001**, *24*, 211–213.
(11) Yang, Y. M.; Hyun, J. W.; Sung, M. S.; Chung, H. S.; Kim, B. K.; Paik, W. H.; Kang, S. S.; Park, J. G. *Planta Med.* **1996**, *62*, 353–354.
(12) Kumar, R.; Srinivasan, S.; Koduru, S.; Pahari, P.; Rohr, J.; Kyprianou, N.; Damodaran, C. *Cancer Prev. Res.* **2009**, *2*, in press.
(13) Nasipuri, D.; Pyne, G. *J. Chem. Soc.* **1962**, 3105–3106.
(14) Jain, A. C.; Jain, S. M.; Gupta, S. M.; Singh, K. V. *Indian J. Chem., Sect. B* **1984**, *23*, 1028–1029.
(15) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760–4763.

10.1021/jo8025884 CCC: $40.75
Published on Web 03/02/2009

SCHEME 1. Retrosynthetic Analysis



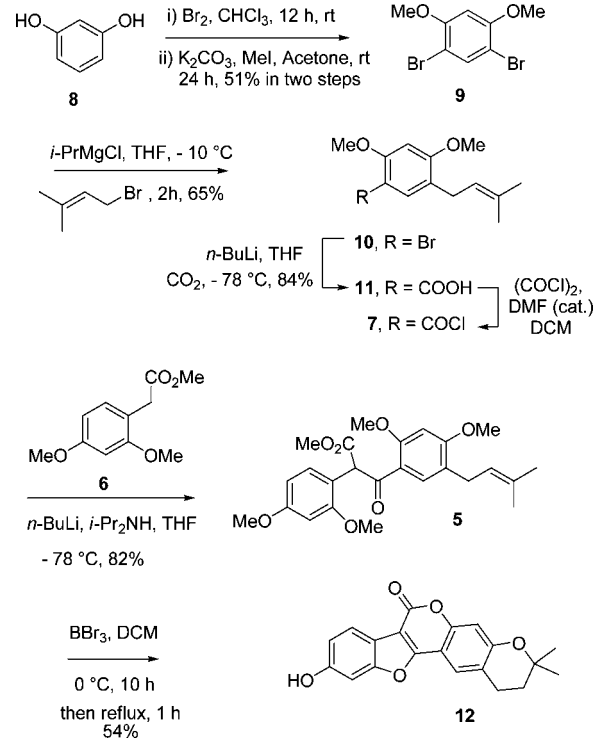
However, there are no reports on the synthesis of **1** so far. In our ongoing work on the investigation of the chemical constituents of *Rasagenthi lehyam*, a complementary and alternative medicine for prostate cancer used as Ayurveda and Siddha medicine in different parts of India, we isolated **1** as the active principle of this mixture of 38 different botanicals, metals, and fats.[12] However, the isolated natural product was found to be insoluble in water and, therefore, less effective for *in vivo* studies. To overcome this problem, we plan to generate a synthetic library of psoralidin analogues that can be utilized to study structure-activity relationships (SAR), which in turn will pave the way for the synthesis of an active analogue or derivative with increased water solubility. Herein, we report an efficient and general synthesis of **1** that can be easily adopted for the synthesis of various analogues.

Many routes to prepare coumestanes can be found in literature, but most of them are complicated and require multistep syntheses.[16−24] Retrosynthetically, **1** can be reduced to **5** through the opening of the lactone and furan rings; in turn, **5** can be obtained from two relatively simple starting materials, namely 2,4-dimethoxy-phenylacetic acid methylester (**6**) and 2,4-dimethoxy-5-prenyl benzoylchloride (**7**) (Scheme 1). This strategy was expected to be flexible enough for the preparation of various analogues, considering the facile preparation of the starting materials. Al-Maharik and Botting[24] used a similar strategy for their synthesis of ^{13}C-labeled **4**.

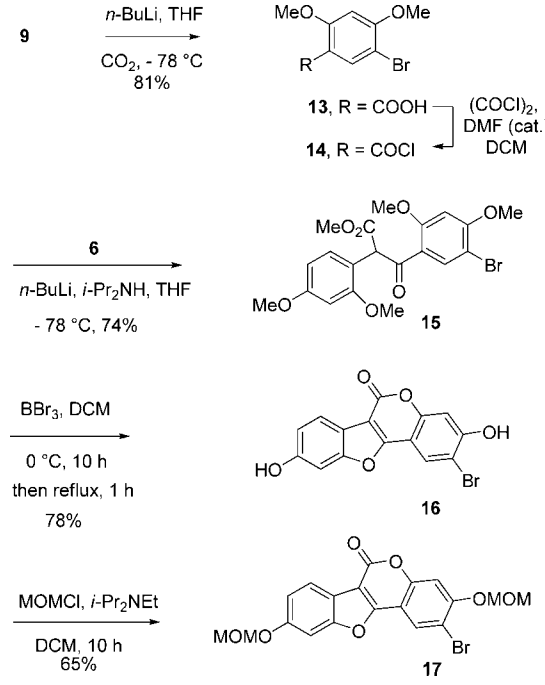
Results and Discussion

We started our synthesis of 1,5-dibromo-2,4-dimethoxybenzene (**9**),[25] which was prepared from resorcinol **8** through bromination with $Br_2/CHCl_3$ and O-methylation of the hydroxyl groups using K_2CO_3/MeI. Br/Mg exchange with *i*-PrMgCl at ∼10 °C and quenching with prenylbromide provided **10** exclusively in 65% yield. The same reaction was carried out

SCHEME 2



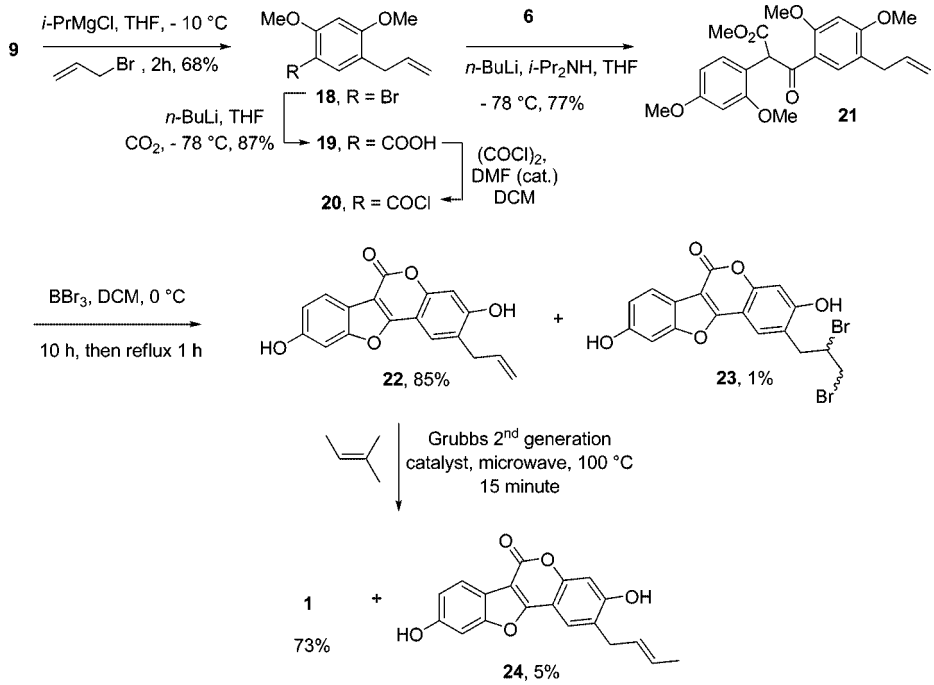
SCHEME 3



using *n*-BuLi and diprenylated and monodebrominated side products were found that were not easy to separate. Acid **11** was obtained by replacing the bromine atom of **10** using *n*-BuLi and CO_2 gas that was bubbled through the reaction mixture. The other starting molecule, compound **6**, was prepared by the condensation of 2,4-dimethoxybenzaldehyde and hippuric acid following a literature procedure.[26] Treatment of acid **11** with oxalyl chloride in the presence of catalytic amounts of DMF produced acid chloride **7** that, without further purification, was reacted with the anion obtained from the treatment of **6** with

(16) Chang, C. F.; Yang, L. Y.; Chang, S. W.; Fang, Y. T.; Lee, Y. J. *Tetrahedron* **2008**, *64*, 3661–3666.
(17) Li, C. C.; Xie, Z. X.; Zhang, Y. D.; Chen, J. H.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 8500–8504.
(18) Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, *149*, 1501–1509.
(19) Yao, T. L.; Yue, D. W.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985–9989.
(20) Hiroya, K.; Suzuki, N.; Yasuhara, A.; Egawa, Y.; Kasano, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4339–4346.
(21) Kraus, G. A.; Zhang, N. *J. Org. Chem.* **2000**, *65*, 5644–5646.
(22) Mali, R. S.; Tilve, S. G. *Synth. Commun.* **1990**, *20*, 1781–1791.
(23) Pandey, G.; Muralikrishna, C.; Bhalerao, U. T. *Tetrahedron* **1989**, *45*, 6867–6874.
(24) Al-Maharik, N.; Botting, N. P. *Tetrahedron* **2004**, *60*, 1637–1642.
(25) Srebnik, M.; Mechoulam, R.; Yona, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1423–1427.

SCHEME 4



LDA and produced the desired compound **5** in an overall 82% yield. The structure of **5** was confirmed by spectroscopic analysis. At this point, it was expected that demethylation followed by intramolecular cyclization would yield **1** in a one pot reaction. The demethylation of the four methoxy groups was carried out with BBr_3 at 0 °C, but the attempted *in situ* cyclization ended up with isopsoralidin (**12**) instead of **1**.[2] The structure of **12** was confirmed by comparison with reported data (Scheme 2).[13,27] The formation of **12** can be explained by the generation of a stable tertiary carbocation produced from the prenyl group in acidic conditions, which is attacked by the *ortho*-hydroxy group to yield the undesired dihydropyran ring. A similar reaction of a prenyl group was reported by Molyneux and Jurd.[27]

To avoid this undesired reaction, we modified our strategy and planned to introduce the prenyl group at the concluding step of the reaction sequence. Thus, we started with acid **13**,[28] which was prepared from **9** by treatment with *n*-BuLi/CO_2 (Scheme 3). The reaction was optimized using less than one equiv of *n*-BuLi and provided a single product **13** in 81% yield. Reaction of the corresponding acid chloride **14** with **6** under similar conditions as above provided **15**, which was demethylated and cyclized into **16** in 78% yield. The structures of compounds **13**−**16** were confirmed by ^{1}H and ^{13}C NMR spectroscopy, as well as HRMS. Protection of the two phenolic OH-groups of **16** as MOM-ethers, using diisopropylethylamine (*i*-Pr_2NEt) and methoxy methyl chloride (MOMCl), gave compound **17** in 65% yield. It was anticipated that Br/Mg or Br/Li exchange of **17** followed by electrophilic addition of prenyl bromide would complete the synthesis. However, all attempts to convert **17** with *i*-PrMgBr/prenyl bromide or *n*-BuLi/prenyl bromide under various reaction conditions ended up with complex product mixtures. A Pd(0)-catalyzed Ullmann type cross-coupling reaction also failed to give any product.

In the search for a specific functional group which could survive the acidic conditions necessary for the cyclization reaction and could be easily transformed to a prenyl group, we considered the olefin cross-metathesis reaction. Recently Hastings et al.[29] used an olefin cross-metathesis reaction in the presence of Grubbs second-generation catalyst to convert an allyl side chain to prenylated compound in very good yields. We hoped that a possible primary or secondary carbocation produced from an allyl group under acidic conditions would not be stable enough to cause an undesired cyclization reaction, like in the case of the tertiary carbocation from the prenyl residue described above. We prepared the allylated compound **18** from **9** using *i*-PrMgBr and allyl bromide. A similar reaction sequence using *n*-BuLi/CO_2 and **6**/LDA as described above provided compounds **19** and **21**, respectively. Demethylation and cyclization produced the expected allylated compound **22** in 85% yield along with very small amounts of the dibrominated side product **23** (1%, Scheme 4). Compounds **18**, **19**,and **21**−**23** were characterized by ^{1}H and ^{13}C NMR spectroscopy, as well as HRMS for structure verification.

Our attempt to perform the alkene cross-metathesis reaction of **22** in the presence of a Grubbs second-generation catalyst and 2-methyl-2-butene initially failed when using identical reaction conditions as described by Hastings et al.[29] Even stirring the reaction at rt for 72 h or refluxing the mixture for 48 h with repeated addition of Grubbs catalyst and 2-methyl-2-butene failed to give any isolable product. To check the feasibility of the reaction, we performed the same reaction on **18** which produced prenylated compound **10** in very good yields. Since compound **22** might require a higher temperature for the cross-metathesis reaction, which was limited in this case by both the chosen solvent and the reagent 2-methyl-2-butene, we decided to carry out the reaction in a sealed tube in a microwave oven to allow higher reaction temperature and to avoid loss of starting material.[30] Thus, the final step of the total synthesis was

(26) Barua, A. K.; Chakrabarty, M.; Datta, P. K.; Ray, S. *Phytochemistry* **1988**, *27*, 3259–3261.
(27) Molyneux, J. R.; Jurd, L. *Tetrahedron* **1970**, *26*, 4743–4751.
(28) Rick, G. P. *J. Am. Chem. Soc.* **1926**, *48*, 3125–3130.
(29) Hastings, J. M.; Hadden, M. K.; Blagg, B. S. J. *J. Org. Chem.* **2008**, *73*, 369–373.

achieved by heating a mixture of **22**, Grubbs second-generation catalyst, and 2-methyl-2-butene in CH_2Cl_2 in a sealed tube microwave reactor at 100 °C for 15 min. The reaction produced **1** in 73% yield along with compound **24** as a minor side product. All spectroscopic data of the synthetic compound matched those of the natural product (Table 1 in Supporting Information) except for the melting point, which was significantly higher for the synthetic compound than reported for the natural product. Since there was no ambiguity about the structure of the synthetic compound, we assumed that the melting point of the natural product was lowered by minor impurities.

Conclusions

In summary, we achieved the first total synthesis of psoralidin **1** in a convergent and highly regioselective manner. The synthetic scheme described here is straightforward and efficient. The longest linear sequence is only five steps starting with commercially available resorcinol. The process is readily adaptable and flexible as substitutions can be introduced in both the phenyl acetate and the allyl benzoyl chloride starter molecules to furnish numerous analogues for SAR studies. Further structural diversification could be achieved on the level of the concluding Grubbs reaction. Biological assays to determine and compare the efficacy of **16**, **22**, and **23** with that of **1**, as well as syntheses of various regioisomers, are in progress.

Experimental Section[31]

Psoralidin 1. Grubbs second-generation catalyst (3 mg, 0.0035 mmol) was added to a degassed solution of **22** (20 mg, 0.06 mmol) in CH_2Cl_2 (10 mL) and 2-methyl-2-butene (2 mL). The solution was heated in a sealed tube at 100 °C for 15 min by a microwave reactor (Biotage Initiator 2.0, standard configuration, temperature control, external IR temperature sensor, fixed hold time). CH_2Cl_2 was removed in vacuum, and the mixture was purified by reverse phase semipreparative HPLC (symmetry ^{18}C, 7 μm, solvent gradient 9:1 CH_3CN:H_2O) to get compound **1** (16 mg, 73%) as a white solid along with a minor amount of side product **24** (1 mg, 5%). R_f = 0.4 (50% ethyl acetate in hexane); mp >400 °C (lit.[1] 315 °C); ν_{max} (film) cm^{-1} 1719, 1629, 1597, 1419, 1370, 1260, 1092. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.68 (d, 1H, J = 8.0 Hz), 7.62 (s, 1H), 7.17 (d, 1H, J = 2.0 Hz), 6.94 (dd, 1H, J = 8.0, 2.0 Hz), 6.93 (s, 1H), 5.35 (t, 1H, J = 7.5 Hz), 3.32 (d, 2H, J = 7.5 Hz), 1.74 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.6 (C), 159.0 (C), 157.8 (C), 157.0 (C), 156.0 (C), 152.9 (C), 132.6 (C), 126.5 (C), 121.8 (CH), 121.0 (CH), 120.6 (CH), 114.7 (C), 114.0 (CH), 103.8 (C), 102.4 (CH), 102.0 (C), 98.8 (CH), 27.6 (CH_2), 25.7 (CH_3), 17.7 (CH_3). HRMS (EI+) m/z 336.1008 ($[M]^+$ $C_{20}H_{16}O_5$, requires 336.0998).

***(E)*-2-(But-2-enyl)-3,9-dihydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (24).** R_f = 0.35 (50% ethyl acetate in hexane); mp >400 °C; ν_{max} (film) cm^{-1} 1718, 1637, 1629, 1267, 1213, 1093. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.68 (d, 1H, J = 8.5 Hz), 7.64 (s, 1H), 7.17 (d, 1H, J = 2.0 Hz), 6.94 (dd, 1H, J = 8.5, 2.0 Hz), 6.90 (s, 1H), 5.70−5.50 (m, 2H), 1.67 (d, 3H, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.6 (C), 157.8 (C), 157.0 (C), 155.9 (C), 153.1 (C), 128.7 (CH), 126.3 (CH), 126.2 (CH), 125.3 (C), 121.3 (C), 120.5 (CH), 118.6 (C), 114.7 (CH), 113.9 (CH), 102.4 (C), 98.7 (CH), 31.9 (CH_2), 17.8 (CH_3). HRMS (EI+) m/z 322.0847 ($[M]^+$ $C_{19}H_{14}O_5$, requires 322.0841).

Methyl-3-[2,4-dimethoxy-5-(3-methyl-but-2-enyl)-phenyl]-2-(2,4-dimethoxy-phenyl)-3-oxo-propionate (5). To a stirred solution of compound **11** (340 mg, 1.36 mmol) in CH_2Cl_2 (8 mL) under N_2 atmosphere, DMF (one drop) and oxalyl chloride (0.18 mL, 2.04 mmol) were added. The mixture was stirred for 3 h at rt, and then the solvent was removed under vacuum to yield acid chloride **7**, which was directly used for the next reaction without further purification.

A solution of compound **6** (430 mg, 2.1 mmol) in THF (5 mL) was added at −78 °C to a solution of LDA, prepared from *n*-BuLi (2.5 M in THF, 1.1 mL, 2.72 mmol) and *i*-Pr_2NH (0.38 mL, 2.72 mmol) in THF (6 mL) at 0 °C under N_2 atmosphere. This produced a yellowish colored anion that was stirred at −78 °C for 45 min, and then a solution of crude acid chloride **7** in THF (10 mL) was added dropwise. The reaction mixture was stirred at the same temperature for another 45 min and then at room temperature for 4 h. The reaction was quenched by the addition of 10% HCl (10 mL), THF was removed in vacuum, and the water layer was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography to yield **5** (495 mg, 82%) as a yellowish oily compound. R_f = 0.3 (50% ethyl acetate in hexane); ν_{max} ($CHCl_3$) cm^{-1} 2359, 2341, 1738, 1666, 1604, 1507, 1463, 1270, 1211, 1029. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (s, 1H), 7.01 (d, 1H, J = 8.0 Hz), 6.41 (s, 1H), 6.40 (d, 1H, J = 8.0 Hz), 6.30 (s, 1H), 5.91 (s, 1H), 5.22 (t, 1H, J = 7.5 Hz), 3.82 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.18 (d, 2H, J = 7.5 Hz), 1.68 (s, 3H), 1.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.0 (C), 171.1 (C), 162.6 (C), 160.3 (C), 159.6 (C), 157.9 (C), 132.7 (CH), 132.3 (CH), 130.3 (CH), 122.6 (C), 122.0 (C), 118.2 (C), 115.9 (C), 104.1 (CH), 98.5 (CH), 94.2 (CH), 57.3 (CH_3), 55.6 (CH_3), 55.5 (CH_3), 55.4 (CH_3), 55.3 (CH_3), 52.2 (CH), 27.6 (CH_2), 25.9 (CH_3), 17.8 (CH_3). HRMS (EI+) m/z 442.1993 ($[M]^+$ $C_{25}H_{30}O_7$, requires 442.1992).

1-Bromo-2,4-dimethoxy-5-(3-methyl-but-2-enyl)-benzene (10). Compound **9** (3.10 g, 10.47 mmol) was added to a solution of *i*-PrMgCl (1 M in THF, 13 mL, 13 mmol) at −10 °C under N_2 atmosphere. After 45 min of stirring, prenyl bromide (1.3 mL, 11.5 mmol) was added dropwise, and the mixture was allowed to stir at the same temperature for 30 min and then at rt for 2 h. The reaction was quenched by the addition of 10% HCl (15 mL). THF was removed in vacuum, and the mixture was extracted with ethyl acetate (2 × 75 mL). The organic layer was washed with water (2 × 30 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting crude compound was purified by column chromatography to yield **10** (1.94 g, 65%) as a colorless liquid along with 550 mg of unreacted starting material **9**. R_f = 0.5 (5% ethyl acetate in hexane); ν_{max} ($CHCl_3$) cm^{-1} 1599, 1500, 1463, 1295, 1208, 1029. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (s, 1H), 6.44 (s, 1H), 5.21 (t, 1H, J = 7.0 Hz), 3.87 (s, 3H), 3.82 (s, 3H), 3.19 (d, 2H, J = 7.0 Hz), 1.72 (s, 3H), 1.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5 (C), 154.8 (C), 133.1 (C), 133.0 (CH), 124.0 (C), 122.2 (CH), 101.6 (C), 96.8 (CH), 56.6 (CH_3), 55.9 (CH_3), 27.6 (CH_2), 26.0 (CH_3), 17.9 (CH_3). HRMS (EI+) m/z 284.0414 ($[M]^+$ $C_{13}H_{17}O_2Br$, requires 284.0412).

2,4-Dimethoxy-5-(3-methyl-but-2-enyl)-benzoic acid (11). *n*-BuLi (2.5 M in THF, 2.1 mL, 5.34 mmol) was added dropwise to a stirred solution of **10** (1.27 g, 4.45 mmol) in THF (15 mL) at −78 °C under N_2 atmosphere. After 30 min, CO_2 gas was passed through the solution for 45 min, and then it was allowed to warm up to rt. THF was removed in vacuum, and the mixture was treated with saturated $NaHCO_3$ solution (30 mL). The water layer was washed with ethyl acetate (2 × 20 mL) and then acidified with conc. HCl. The mixture was extracted with ethyl acetate (2 × 75 mL). The organic layer was washed with water (2 × 30 mL), brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. Recrystallization from ethyl acetate produced **11** (930 mg, 84%) as a white solid. R_f = 0.1 (50% ethyl acetate in hexane); mp: 98−99 °C; ν_{max} (film): cm^{-1} 1719, 1616, 1442, 1278,1168, 1020. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (s, 1H), 6.41 (s, 1H), 5.16 (t, 1H, J = 7.0 Hz), 3.97 (s, 3H), 3.84 (s, 3H), 3.14 (d, 2H, J = 7.0 Hz), 1.64 (s, 3H),

(30) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, *112*, 1125–1132.
(31) For general experimental methods, see Supporting Information.

1.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2 (C), 162.6 (C), 158.5 (C), 133.6 (CH), 132.9 (C), 123.9 (CH), 121.6 (C), 108.9 (C), 94.5 (CH), 56.7 (CH_3), 55.7 (CH_2), 27.6 (CH_3), 25.8 (CH_3), 17.7 (CH_3). HRMS (EI+) *m*/*z* 250.1206 ([M]$^+$ $C_{14}H_{18}O_4$, requires 250.1205).

Methyl-3-(5-bromo-2,4-dimethoxy-phenyl)-2-(2,4-dimethoxy-phenyl)-3-oxo-propionate (15). This compound was prepared as a yellowish oil (320 mg, 74%) from compound **13** and **6**, following an analogous reaction sequence as described above for the synthesis of compound **5** (for the exact procedure, see Supporting Information). R_f = 0.3 (50% ethyl acetate in hexane); mp 136−137 °C; ν_{max} (film): cm^{-1} 1730, 1668, 1613, 1590, 1508, 1465, 1334, 1271, 1213, 1155, 1021. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (s, 1H), 7.00 (d, 1H, J = 9.0 Hz), 6.43 (s, 1H), 6.42 (d, 1H, J = 9.0 Hz), 6.34 (s, 1H), 5.88 (s, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.76 (s, 6H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.1 (C), 170.8 (C), 160.6 (C), 160.5 (C), 160.1 (C), 157.9 (C), 136.0 (CH), 130.4 (CH), 120.2 (C), 115.3 (C), 104.3 (CH), 103.2 (C), 98.7 (CH), 95.8 (CH), 57.3 (CH_3), 56.6 (CH_3), 55.7 (CH_3), 55.6 (CH_3), 55.4 (CH_3), 52.4 (CH). HRMS (EI+) *m*/*z* 452.0477 ([M]$^+$ $C_{20}H_{21}O_7Br$, requires 452.0471).

2-Bromo-3,9-dihydroxy-benzo[4,5]furo[3,2-c]chromen-6-one (16). BBr_3 (1 M in CH_2Cl_2, 1.72 mL, 1.72 mmol) was added at 0 °C to a solution of **15** (130 mg, 0.29 mmol) in CH_2Cl_2 (6 mL) under N_2 atmosphere. The mixture was stirred at the same temperature for 10 h, and water (10 mL) was added. CH_2Cl_2 was removed in vacuum, and the mixture was heated to reflux for 1 h. The water layer was extracted with ethyl acetate (2 × 30 mL), and the organic layer was washed with water (2 × 15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Crude product was purified by column chromatography to get **16** (78 mg, 78%) as a white solid. R_f = 0.3 (50% ethyl acetate in hexane); mp 362−364 °C; ν_{max} (film) cm^{-1} 1719, 1634, 1599, 1418, 1368, 1272, 1085. ^{1}H NMR (DMSO- d_6, 500 MHz) δ 8.08 (s, 1H), 7.68 (d, 1H, J = 8.5 Hz), 7.15 (d, 1H, J = 2.0 Hz), 7.03 (s, 1H), 6.94 (dd, 1H, J = 8.5, 2.0 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 158.2 (C), 157.5 (C), 157.3 (2C, C), 156.1 (C), 153.4 (C), 125.0 (CH), 120.8 (CH), 114.5 (C), 114.2 (CH), 107.0 (C), 105.4 (C), 103.9 (CH), 102.8 (C), 98.7 (CH). HRMS (EI+) *m*/*z* 345.9475 ([M]$^+$ $C_{15}H_7O_5Br$, requires 345.9477).

2-Bromo-3,9-bis-methoxymethoxy-benzo[4,5]furo[3,2-c]chromen-6-one (17). *i*-Pr_2NEt (0.05 mL, 0.29 mmol) was added to a solution of **16** (40 mg, 0.11 mmol) in CH_2Cl_2 (6 mL) at rt. The mixture was stirred for 15 min, and then MOMCl (0.02 mL, 0.25 mmol) was added. The reaction was stirred for 10 h and quenched by the addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the organic layer was washed with water (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography to get **17** (35 mg, 65%) as a white solid. R_f = 0.8 (30% ethyl acetate in hexane); mp 212−214 °C; ν_{max} (film) cm^{-1} 1758, 1629, 1490, 1353, 1257, 1163, 1072, 957. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (s, 1H), 7.94 (d, 1H, J = 8.5 Hz), 7.35 (s, 1H), 7.29 (s, 1H), 7.14 (d, 1H, J = 8.5 Hz), 5.33 (s, 2H), 5.25 (s, 2H), 3.53 (s, 3H), 3.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0 (C), 158.0 (C), 157.2 (C), 156.5 (C), 156.3 (C), 153.9 (C), 125.6 (CH), 122.0 (CH), 117.6 (C), 115.5 (CH), 109.3 (C), 108.2 (C), 104.7 (CH), 102.7 (C), 99.9 (CH), 95.5 (CH_2), 95.2 (CH_2), 56.9 (CH_3), 56.4 (CH_3). HRMS (EI+) *m*/*z* 433.9992 ([M]$^+$ $C_{19}H_{15}O_7Br$, requires 434.0001).

Acknowledgment. This work was supported by a grant from the National Institutes of Health (AT002890) to J.R. Authors are thankful to Professor Gregory I. Elliott for the use of the microwave instrument and also for valuable advice, the NMR core facility and mass spectrometry facility of the University of Kentucky, as well as the Department of Chemistry at the University of Kentucky for letting us use their instruments.

Supporting Information Available: General experimental methods, experimental details, and characterization data for compounds **9**, **12**, **13**, **15**, **18**, **19**, **21**-**23**, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8025884