The Synthesis of Mycophenolic Acid from 2,4-Dihydroxybenzoic Acid[1]

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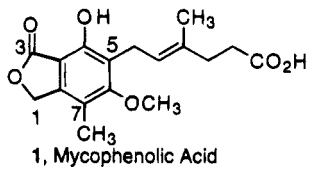
Mycophenolic acid (**1**) has been synthesized from 2,4-dihydroxybenzoic acid by regioselective introduction of the three required carbon substituents. A key transformation in this sequence is the introduction of the methyl substituent at position 5 by a rapid, uncatalyzed replacement of the bromide in **8** at low temperature by methyllithium. The scope and mechanism of this methylation reaction are examined.

Mycophenolic acid (**1**) a metabolite[3] of *Penicillium brevi-compactum*, is currently of medicinal interest[4] because of its immunosuppressant properties. Structurally, mycophenolic acid contains a hexasubstituted benzene ring. The preparation of highly substituted benzenes is one of the classic problems of organic synthesis, and mycophenolic acid has often served as a foil[5] for synthetic methods. With one exception[5h] these literature syntheses of mycophenolic acid use benzene ring constructions which simultaneously introduce five of the six substituents required for mycophenolic acid. This general strategy for synthesis of highly substituted aromatic compounds is now standard practice. The alternate synthetic approach of sequential introduction of substituents requires lengthy linear sequences, and as noted in a review by Bamfield and Gordon,[6] this "tends to negate the advantages of using cheap and readily available starting materials." In spite of these considerations, the fact remains that 2,4-dihydroxybenzoic acid is inexpensive and an intriguing starting material for the synthesis of mycophenolic acid because it contains three of the requisite substituents, including both the hydroxyl groups, which are the most difficult substituents to introduce by aromatic substitution chemistry.



1, Mycophenolic Acid

By using the previously developed method for the conversion of an allyl moiety into the (*E*)-4-methyl-4-hexenoic acid side chain of mycophenolic acid (ozonolysis, reaction with 2-propenylmagnesium bromide and ortho-ester Claisen rearrangement), the allyl-substituted phthalide **33** becomes the key intermediate in this new synthesis of mycophenolic acid. Taking 2,4-dihydroxybenzoic acid as the starting material then reduces the synthesis of mycophenolic acid to the tasks of methylating the hydroxyl group at C-4 and introducing three carbon substituents: an allyl group at C-3, a methyl at C-5, and a hydroxymethyl at C-6. In planning this synthesis, two of these tasks seemed straightforward. First, it was known that alkylation of 2,4-dihydroxybenzoic acid with iodomethane was selective for the 4-hydroxyl. Second, because the carboxylic acid has only one unsubstituted ortho position, an ortho metalation reaction would introduce the hydroxymethyl group regiospecifically at C-6. This analysis then leads to the conclusion that the success of this synthesis of mycophenolic acid depends on selectively differentiating between C-3 and C-5 of 2,4-dihydroxybenzoic acid. Because C-3 and C-5 are very similar electronically (both are ortho or para to two hydroxyl groups and both are meta to the carboxyl group), it seemed unlikely that any electrophilic substitution reaction would show much positional selectivity. The strategy investigated here was to first methylate the 4-hydroxyl group of 2,4-dihydroxybenzoic acid and then alkylate the 2-hydroxyl group with allyl bromide and use the general preference of the thermal Claisen rearrangement to give a preponderance of *o*-allylphenol over the para isomer.[7] With C-3 blocked, electrophilic bromination should go selectively to the activated position (C-5). A methyl group could then be introduced into the resulting protected 5-bromo compound by a halogen–metal exchange, followed by alkylation with iodomethane. Finally, if the carboxyl group had been protected as an amide, ortho metalation could be used to introduce a hydroxymethyl moiety at C-6 to complete the synthesis of **33**.

The chemistry used to selectively alkylate C-3 of a protected 2,4-dihydroxybenzoic acid is illustrated in Scheme 1. Thus, methyl 2-hydroxy-4-methoxybenzoate (**2**), prepared[8] in one step by alkylation of 2,4-dihydroxybenzoic acid with iodomethane/potassium carbonate in acetone, was alkylated with allyl bromide to give the allyl ether **3**. Thermal Claisen rearrangement of this allyl

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(1) Contribution No. 864 from the Syntex Institute of Organic Chemistry.

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(3) For a summary of references to the isolation and structure determination and the first synthesis of mycophenolic acid, see: Birch, A. J.; Wright, J. J. *Aust. J. Chem.* **1969**, *22*, 2635.

(4) Mycophenolate mofitel, the morpholinoethyl ester of mycophenolic acid (Lee, W.A.; Gu, L.; Miksztal, A. R.; Chu, N.; Leung, K.; Nelson, P. N. *Pharm. Res.* **1990**, 7, 161), is under study as a treatment for heart and kidney transplant rejection and rheumatoid arthritis.

(5) (a) Patterson, J. W. *Tetrahedron* **1993**, *49*, 4789. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (c) Kobayashi, K.; Shumizu, H.; Itoh, M.; Suginome, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2435. (d) Kobayashi, K.; Shumizu,H.; Itoh, M.; Suginome, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2435. (e) Watanabe, M.; Tsukayashi, H.; Hamada, Y.; Iwao, M.; Fukukawa, S. *Chem. Pharm. Bull.* **1990**, *44*, 2453. (f) Auricchio, S.; Ricca, A.; de Pava, O. V. *J. Org. Chem.* **1983**, *48*, 602. (g) Colombo, L.; Gennari, C.; Potenza, D.; Scolastice, C. *J. Chem. Soc., Chem. Commun.* **1979**, 1021. (h) Cononica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. *Tetrahedron* **1972**, *28*, 4395.

(6) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, 441.

(7) Wipf, P. In *Comprehensive Organic Synthesis;* Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5, Chapter 7.2, pp 827–873.

(8) Corey, E. J.; Dittiami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256.

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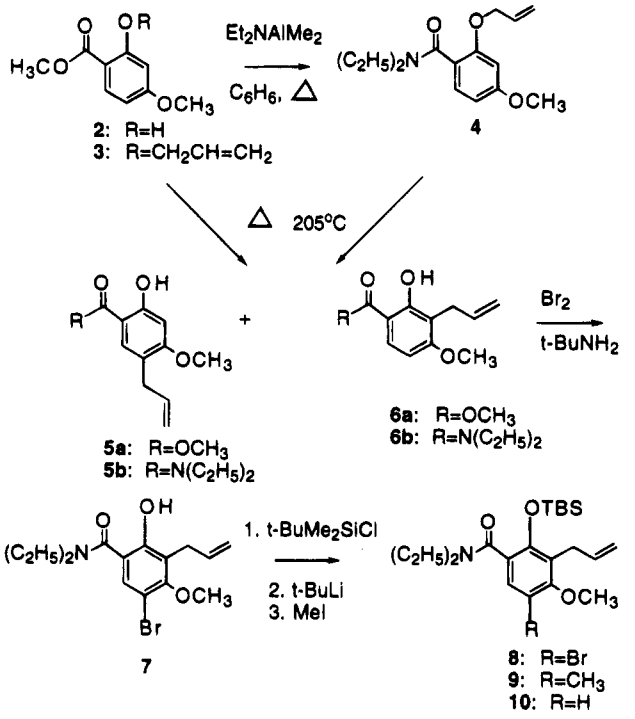
Scheme 1

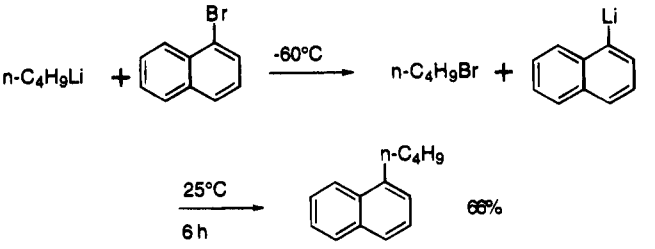


ether in tetramethylbenzene (210 °C) gave a mixture of *o*- and *p*-allylphenols in a 87:13 ratio as shown by examination of the ^{1}H NMR spectrum of the product mixture, and pure **6a** could be easily obtained in 60% yield by crystallization. As mentioned above, the C-6 hydroxymethyl group was to be introduced by ortho metalation of a benzamide. The amidation of ester **3** would yield a second substrate suitable for examining the ratio of C-3 to C-5 alkylation in the Claisen rearrangement. Hence, the methyl ester **3** was converted to the diethyl amide **4** by reaction with 2 equiv of the aluminum amide reagent prepared[9] from diethylamine and trimethylaluminum. It was pleasing to find that heating **4** in tetramethylbenzene (210 °C) induced a Claisen rearrangement, giving the *o*- and *p*-allylphenols **6b** and **5b** in an improved ratio of 96:4.[10]

With both positions ortho to the hydroxyl group in compound **6b** blocked, bromination[11] with bromine/*tert*-butylamine then gave the *p*-bromophenol **7**, which was protected as the *tert*-butyldimethylsilyl ether **8**. Halogen–metal exchange between bromide **8** and *t*-BuLi followed by alkylation of the intermediate aryllithium compound with iodomethane gave **9** (45%) and the nonmethylated amide **10** (14%). A considerable series of experimental variations failed to raise the yield of **9**.

In an attempt to improve the yield for the conversion of **8** to **9**, the reaction of bromide **8** with MeLi under a variety of conditions was investigated. For example, it was previously known[12] that aryl and vinyl halides at low temperatures (−60 to −70 °C) undergo halogen–metal exchange with an alkyllithium to give an aryllithium and an alkyl halide. If the reaction mixture is then warmed to room temperature, the aryllithium reacts with the alkyl halide to give the coupled aryl alkyl compound in good yield as shown in Scheme 2. When bromide **8** in THF was treated at −70 °C with MeLi and the reaction mixture then allowed to warm to room temperature, the product consisted of **8** (18%), **9** (18%), and **10** (22%). What was totally unexpected was that reverse addition, that is addition of **8** to 1.12 equiv of MeLi in THF at −70 °C, gave rapid conversion to **9**. If the reaction was quenched with MeOH at −70 °C, 8 min after the addition was complete, 82% of **9** and 9% of **10** were obtained. The lack of reactivity of the product **9** toward the excess of MeLi present during the course of the reaction is also surprising. As a test, product **9** was added to MeLi at −65 °C under the same conditions used for the conversion of **8** to **9**. There was no evidence of any product being formed, and workup and chromatography recovered 92% of **9**. Although all the MeLi reactions discussed here were performed with low-halide MeLi in ether, MeLi–LiI complex in ether gave essentially the same result.

Scheme 2



From a synthetic point of view, direct displacement of a bromobenzene by MeLi under such mild conditions and in high yield is without precedent. The older literature contains many examples of the methylation of bromobenzenes but under much more vigorous conditions and accompanied by side products. Some initial efforts have been made to determine the mechanism of the reaction of bromide **8** with MeLi. Two mechanisms for the replacement of an aromatic bromine by an alkyllithium which are well-precedented in the literature were considered: (1) halogen–metal exchange followed by alkylation of the aryllithium by bromomethane generated *in situ* and (2) elimination of hydrogen bromide from **8** to form a benzyne which undergoes nucleophilic addition of MeLi to give an *o*-lithio-*m*-methyl amide.

The halogen–metal exchange mechanism (Scheme 3, path a) was eliminated on the basis of the experiments described above on the reaction of **8** with *t*-BuLi followed by addition of iodomethane. Namely, the rate of halogen–metal exchange of the aryl bromide **8** would be expected to be much faster with *t*-BuLi than with MeLi and that the rate of alkylation of the resultant aryllithium with iodomethane would also be expected to be much more rapid than alkylation with bromomethane generated *in situ*. In fact, the reaction of **8** with MeLi is complete at −78 °C as soon as it is added to the MeLi, whereas the *t*-BuLi/methyl iodide reaction after 1.5 h at temperatures up to +10 °C gives only a 45% yield of **9** and leaves 14% as the nonmethylated amide **10**. This very large difference in the rates of these reactions clearly eliminates the halogen–metal exchange product **11** as a possible intermediate in the conversion of **8** to **9** by addition to MeLi.

The involvement of a benzyne intermediate (Scheme 3, path b) in the reaction of **8** with MeLi initially appears

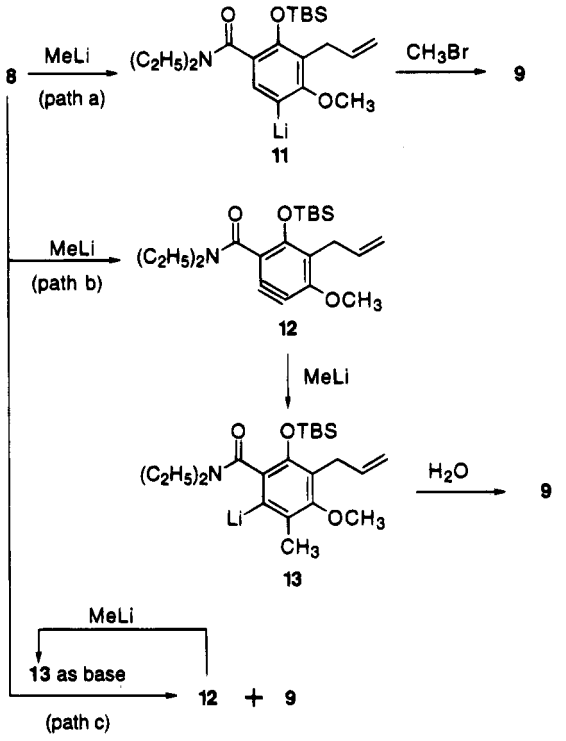
(9) Weinreb, S. *Synth. Commun.* **1982**, 989.

(10) It is well-known that the position and type of substituents influence the ortho/para product ratio; for an extensive review of the Claisen rearrangement, see: Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. The finding that amide **4** gave a higher ortho/para ratio than ester **3** is a simple empirical observation, and no other acid derivatives were studied.

(11) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1977**, *42*, 2359.

(12) (a) Normant, J. F.; Commercon, A.; Cahiez, G.; Villeras, J. *C. R. Acad. Sci., Ser. C* **1974**, *278*, 967. (b) Millon, J.; Lorne, R.; Linsturmello, G. *Synthesis* **1975**, 434.

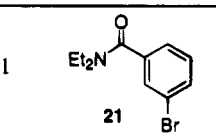
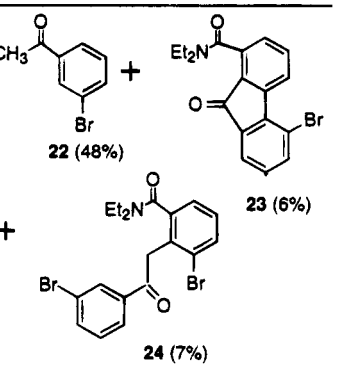
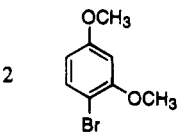
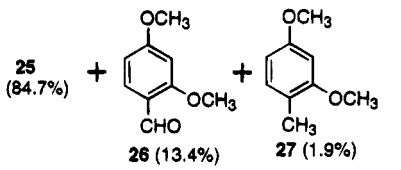
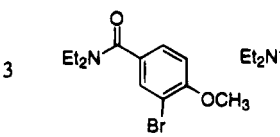
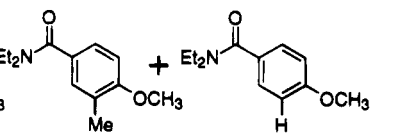
Scheme 3



unlikely on the basis of the stoichiometry of the reaction. Yields of **9** in excess of 80% are obtained with 1.12 equiv of MeLi. However, if MeLi was functioning as the base to convert **8** to the benzyne **12**, a second equivalent of MeLi would need to be added to the benzyne to produce the methylated *o*-lithiobenzamide **13**, which upon quenching with water gives the observed product **9**. Furthermore, if the reaction between **8** and MeLi is quenched with CH_3OD prior to workup, there is no deuterium incorporated into product **9**. On the basis of stoichiometry and the lack of deuterium incorporation, the mechanism shown in path b of Scheme 3 can be eliminated.

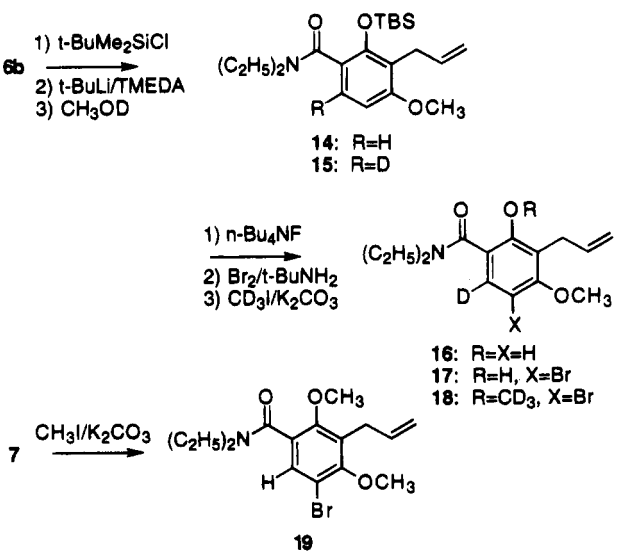
However, there is another possibility for a benzyne mechanism as shown in path c of Scheme 3 wherein the intermediate *o*-lithiobenzamide **13** serves as a base to deprotonate the starting material **8**. This variation of the benzyne mechanism requires only 1 equiv of MeLi, and because **13** is protonated by **8**, there would be no deuterium incorporation with a CH_3OD quench. Although one may argue that the broad utility of *o*-lithiobenzamides as synthetic intermediates is only possible because of the absence of proton exchange during their reactions, there are some obvious experimental differences between the reaction of **8** with MeLi and the usual o-lithiobenzamide synthesis. In particular, *o*-lithiobenzamides are usually generated with *tert*-butyl- or *sec*-butyllithium at −90 to −100 °C. In the case of the conversion of **8** to **9**, MeLi is a much weaker base than *tert*-butyl- or *sec*-butyllithium which makes it more likely that the *o*-lithiobenzamide **13** could compete as a base. In addition, the conversion of **8** to **9** is done at −65 to −60 °C and the rates of proton exchange in a variety of carbanionic reactions are known to increase at higher temperatures. Also, the formation of the fluorenone **23** discussed below (Table 1, entry 1) probably involves the intermediacy of a benzyne. For these reasons, the labeled **18** and unlabeled **19** methoxybenzamides were prepared from intermediate **6b** as shown in Scheme 4 and subjected to the crossover experiment of Scheme 5.

Table 1. The Reaction of Bromobenzenes with MeLi at −65 °C

Entry	Starting Material	Products[a]
1		
2		
3		

[a] Entry 2 was quenched with DMF.

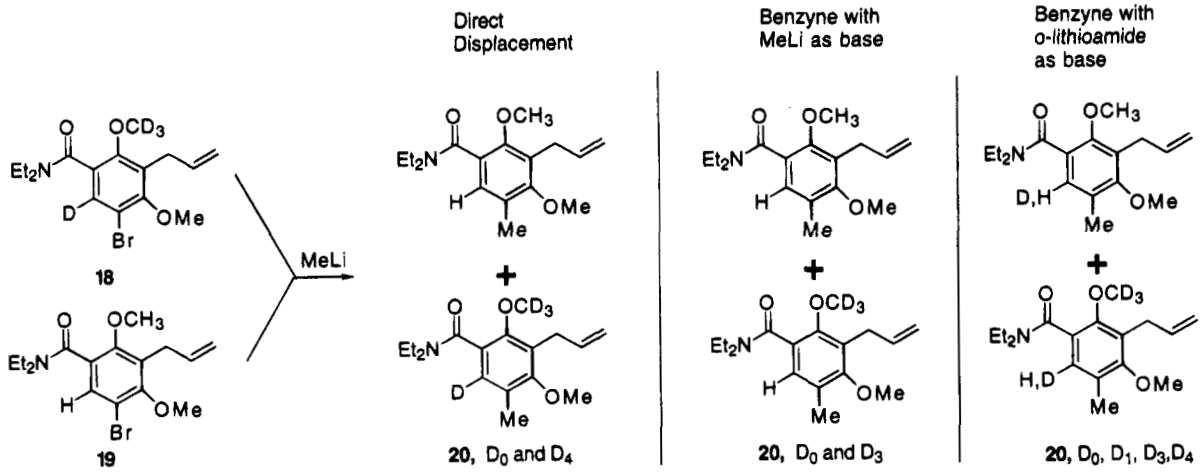
Scheme 4



An equimolar mixture of **18** and the corresponding nondeuterated **19** were added to a slight excess of MeLi. The 5-methylbenzamide products **20** were isolated by flash chromatography and examined by mass spectroscopy and were found to be 49% D_0, 4% D_1, and 47% D_4, showing that there was essentially no deprotonation of the starting bromides **18** and **19** by the hypothetical *o*-lithio amide intermediate, and consequently, by analogy, the mechanism depicted in path c of Scheme 3 is not involved in the transformation of **8** to **9**.

These experiments eliminate both halogen−metal exchange and benzyne formation as mechanisms for the replacement of bromine by methyl in the reaction of **8** with MeLi. Among various other mechanistic possibili-

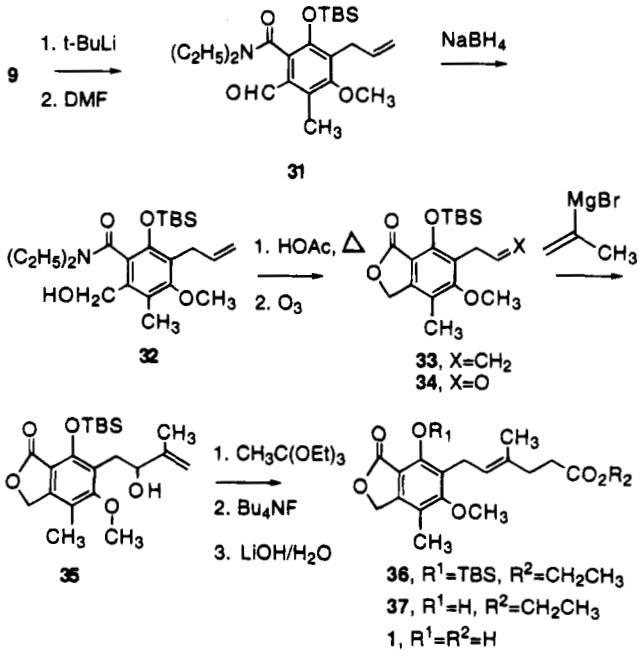
Scheme 5



ties are direct displacement via a four-centered transition state and single electron transfer processes. The exact details of this replacement reaction mechanism await further study. However, because the reverse addition of the bromide to the MeLi maintains a high concentration of MeLi during the course of the reaction, a single electron/radical chain process seems likely.

The vast amount of work devoted to the development of transition metal catalysts[13] for coupling of halobenzenes with organometallic reagents suggests that the simple uncatalyzed coupling of MeLi with this type of bromide is not a general reaction. To determine the minimum structural requirements for this alkylation reaction, *N,N*-diethyl-3-bromobenzamide[14] (**21**), 4-bromo-1,3-dimethoxybenzene (**25**), and *N,N*-diethyl-3-bromo-4-methoxybenzamide (**28**) were reacted with MeLi under the conditions which gave **9**, and the results are shown in Table 1. *N,N*-Diethyl-3-bromobenzamide (**21**) (entry 1) when added to MeLi gave a mixture of 3-bromoacetophenone (**22**), the fluorenone **23**, and the deoxybenzoin **24**. A mechanism for the formation of **24** invloves the deprotonation of **21** at the 2 position by MeLi followed by alkylation with MeBr (generated *in situ* by halogen–metal exchange) to give a 3-bromo-2-methylbenzamide.[15] Deprotonation of the methyl of this 2-bromo-3-methylbenzamide gives a carbanion which condenses on the carbonyl group of a second molecule of **21** to give the observed deoxybenzoin **24**. The most noticeable feature of this reaction is that no products could be found which result from the replacement of the bromide by a methyl group. Entry 2 shows the reaction of 4-bromo-1,3-dimethoxybenzene (**25**) with MeLi. The large amount of recovered starting material indicates that **25** is very much less reactive toward MeLi than is **8**. In a second experiment, after 75 min at −65 °C, 33% of the bromide **25** remained unchanged. The product distribution indicates that halogen–metal exchange is 6 times as rapid as the formation of the 4-methyl product, which is just the opposite of the relative rates of reaction observed for the reaction of bromide **8** with MeLi. *N,N*-Diethyl-3-bromo-4-methoxybenzamide (**28**) was prepared from methyl 3-bromo-4-hydroxybenzoate[16] by methylation of the phenolic hydroxyl and conversion of the ester function to the diethyl amide by reaction with the appropriate aluminum amide reagent.[9] This substrate was found to react with MeLi in the same way as compound **8**, that is to say that, when **28** was added to MeLi at −65 °C, it reacted to give primarily the methylation product **29** (48%) and a smaller amount of halogen–metal exchange product **30**[17] (11%). The reactivity of these three bromobenzenes confirms the conjecture above that this methylation reaction is highly substrate selective, working only on bromides **8**, **28**, and the 2,4-dimethoxybenzamides **18** and **19**.

Scheme 6



Scheme 6 illustrates the sequence of reactions used to introduce the lactone ring and elaborate the side chain to complete the synthesis of mycophenolic acid. The 5-methylbenzamide **9** was lithiated in the 6 position by reaction with *t*-BuLi/TMEDA and the resulting *o*-lithio amide quenched with DMF to give the benzaldehyde **31**.

(13) For an excellent recent review, see: Tamao, K. In *Comprehensive Organic Synthesis*; Pattenden, G., Vol. Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 435–480.

(14) Johnson, H. L.; Skinner, W. A.; Skidmore, D.; Maibach, H. I. *J. Med. Chem.* **1968**, *11*, 1265.

(15) Deprotonation of a benzene at a position ortho to bromine without formation of a benzyne is rare but has precedent: Jung, M. E.; Lowen, G. *Tetrahedron Lett.* **1986**, *27*, 5319.

(16) Kelly, S. M. *Helv. Chim. Acta* **1989**, *72*, 594.

(17) Suryanarayana, M. V. S.; Pandey, K. S.; Prakash, K.; Raghuveeran, C. D.; Dangi, R. S.; Swamy, R. V.; Rao, K. M. *J. Pharm. Sci.* **1991**, *80*, 1055.

Reduction of the aldehyde **31** with sodium borohydride gave the alcohol **32** which cyclized to phthalide **33** in the presence of acetic acid. As described in the Experimental Section, this sequence of nine steps has been scaled up to produce 12.4 g of intermediate **33** in an overall yield of 38% from 2,4-dihydroxybenzoic acid. The previously disclosed[18] elaboration of **33** into mycophenolic acid in five steps was used to prepare 4.6 g of mycophenolic acid (**1**). This is in contrast to the existing syntheses[5] which produce 30–200 mg of mycophenolic acid. Hence, this report demonstrates a convenient laboratory scale synthesis of mycophenolic acid requiring a minimal number of chromatographic separations and having many intermediates which can be purified by distillation or recrystallization.

Experimental Section

General. The MeLi in ether refers to Aldrich 19,734-3 which is 0.05 M in halide and was titrated with 1 M 1-butanol in xylene using 1,10-phenanthroline as an indicator.[19] HPLC analyses were performed using a Chiracel AD column eluted with isopropanol/hexane mixtures as indicated below. Areas of the peaks of UV absorbance curves measured at 214 nm were corrected using standard solutions having known ratios of the constituents. Drying referred to in the workup procedures consists of washing with saturated aqueous NaCl followed by standing over anhydrous $MgSO_4$.

Methyl 4-Methoxy-2-(prop-2-enyloxy)benzoate (3). A mixture of methyl 2-hydroxy-4-methoxybenzoate (**2**) (92.5 g, 0.508 mol), K_2CO_3 (80.0 g, 0.58 mol), and allyl bromide (54 mL, 0.63 mol) in DMF (160 mL) was stirred at room temperature for 16 h. The mixture was poured into ice–water and extracted with ether (3 × 200 mL). The extracts were dried and evaporated *in vacuo*. The resulting residue was distilled (Kugelrohr) to afford **3** (109.1 g, 98%): bp 120 °C/0.15 mm; mp 45.5–48.0 °C (*t*-BuOMe/hexane); IR (KBr) 1689, 1608, 1441, 1275, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 1H, J = 8.6 Hz), 6.5 (m, 2H), 6.05 (m, 1H), 5.6–5.3 (m, 2H), 4.6 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 164.1, 160.3, 133.9, 132.7, 117.4, 112.9, 105.1, 100.5, 69.5, 55.4, 51.6. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.09; H, 6.37.

***N,N*-Diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide (4).** A solution of diethylamine (62.1 mL, 0.60 mol) in toluene (100 mL) was cooled on ice and treated with trimethylaluminum (300 mL, 2 N in toluene) over 50 min. After the mixture was stirred an additional 1 h at 25 °C, **3** (63.86 g, 0.29 mol) in toluene (50 mL) was added over 30 min, and then the reaction mixture was heated for 18 h at 75 °C. The resulting solution was cooled to room temperature and slowly poured into a mixture of concentrated HCl (225 mL), ice (1 L), and ethyl acetate (300 mL). This mixture was extracted with ethyl acetate (3 × 250 mL), dried, and evaporated *in vacuo*. The resulting residue was distilled (Kugelrohr) to afford **4** (74.5 g, 98%): bp 130 °C/0.15 mm; IR (neat) 2974, 1628, 1610, 1427, 1307, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1H, J = 8.3 Hz), 6.51 (dd, 1H, J = 8.3, 2.3 Hz), 6.44 (d, 1H, J = 2.3 Hz), 6.0 (m, 1H), 5.4–5.2 (m, 2H), 4.52 (m, 2H), 3.80 (s, 3H), 3.7–3.3 (m, 2H), 3.17 (q, 2H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz), 1.02 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 161.1, 155.5, 132.9, 128.5, 120.4, 117.2, 105.2, 100.0, 69.1, 55.4, 42.8, 38.9, 14.0, 12.8. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.32; H, 8.07; N, 5.47.

***N,N*-Diethyl-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide (6) and *N,N*-Diethyl-2-hydroxy-4-methoxy-5-(prop-2-enyl)benzamide (5).** A mixture of **4** (71.23 g, 0.27 mol) and tetramethylbenzene (140 mL) was stirred at 210 °C for 6 h. The mixture was cooled and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel eluted with EtOAc/hexane. The fractions containing the main product were evaporated and distilled (Kugelrohr) to give **6** (61.12 g, 86%): bp 130–140 °C/0.07 mm; IR (neat) 2974, 1626, 1593, 1460, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, 1H, J = 8.8 Hz), 6.39 (d, 1H, J = 8.8 Hz), 6.0 (m, 1H), 5.0 (m, 2H), 3.84 (s, 3H), 3.51 (q, 4H, J = 7.1 Hz), 3.43 (d, 2H, J = 6.2 Hz), 1.27 (t, 6H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 160.3, 158.5, 136.4, 126.3, 116.1, 114.3, 110.9, 100.8, 55.6, 42.2, 27.2, 13.4. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.76; H, 8.13; N, 5.50.

Further elution and distillation (Kugelrohr) gave the *p*-allylphenol **5** (3.00 g, 4%): bp 110–115 °C/0.07 mm; IR (neat) 2976, 1618, 1587, 1460, 1205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.47 (s, 1H), 5.9 (m, 1H), 5.0 (m, 2H), 3.81 (s, 3H), 3.49 (q, 4H, J = 7.1 Hz), 3.28 (d, 2H, J = 6.5 Hz), 1.27 (t, 6H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 160.5, 160.4, 136.9, 128.4, 118.6, 115.7, 109.2, 99.8, 55.5, 42.3, 33.1, 13.4. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.80; H, 8.08; N, 5.46.

***N,N*-Diethyl-5-bromo-2-hydroxy-4-methoxy-3-(prop-2-enyl)benzamide (7).** A solution of *tert*-butylamine (23 mL, 0.22 mol) in toluene (300 mL) was cooled to −20 °C and treated with bromine (5.60 mL, 0.11 mol) over 5 min. The reaction mixture was cooled to −60 °C and treated with a solution of phenol **6** (26.3 g, 0.10 mol) in CH_2Cl_2 (20 mL) over 25 min. The solution was allowed to warm to −5 °C over 3 h. The reaction mixture was poured into dilute aqueous $Na_2S_2O_3$, extracted twice with EtOAc, and then washed sequentially with 5% HCl and aqueous $NaHCO_3$. Drying and evaporation gave a residue which was crystallized from hexane to give **7** (16.759 g). The filtrates were chromatographed on silica gel, eluting with EtOAc/hexane, to give an additional 13.312 g of **7** (total: 29.972 g, 88%): mp 56.7–57.1 °C (*t*-BuOMe); IR (KBr) 2974, 1604, 1456, 1417, 1221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.0 (m, 1H), 5.0 (m, 2H), 3.84 (s, 3H), 3.51 (q, 4H, J = 7.1 Hz), 3.48 (m, 2H), 1.28 (t, 6H, J = 7.1 Hz); ^{13}C NMR δ (75 MHz, $CDCl_3$) δ 170.6, 158.1, 158.0, 136.0, 129.3, 124.3, 115.3, 105.5, 85.0, 61.4, 42.3, 18.9, 13.3. Anal. Calcd for $C_{15}H_{20}NBrO_3$: C, 52.64; H, 5.89; N, 4.09. Found: C, 52.67; H, 5.91; N, 4.19.

***N,N*-Diethyl-5-bromo-2-[(*tert*-butyldimethylsilyl)oxy]-4-methoxy-3-(prop-2-enyl)benzamide (8).** A mixture of **7** (29.77 g, 0.087 mol) and imidazole (11.8 g, 0.173 mol) in DMF (100 mL) was treated with *tert*-butyldimethylsilyl chloride (15.76 g, 0.104 mol) and stirred for 2 h at room temperature. The mixture was poured into ice–water and extracted with ether (3 × 150 mL). The extracts were washed with water, dried, and evaporated *in vacuo*. The resulting residue was recrystallized from *t*-BuOMe/hexane to afford **8** (38.25 g, 96%): mp 75.2–75.5 °C (hexane); IR (KBr) 2928, 1630, 1616, 1427, 1221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 5.9 (m, 1H), 4.9 (m, 2H), 3.81 (s, 3H), 3.7–3.0 (m, 4H), 3.44 (m, 2H), 1.24 (t, 3H, J = 7.1 Hz), 1.00 (t, 3H, J = 7.1 Hz), 0.98 (s, 9H), 0.17 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 156.7, 149.3, 136.2, 130.4, 127.7, 127.5, 114.9, 109.9, 61.3, 43.0, 39.7, 29.3, 26.0, 18.6, 14.1, 13.0. Anal. Calcd for $C_{21}H_{34}NBrO_3Si$: C, 55.25; H, 7.57; N, 3.07. Found: C, 55.51; H, 7.51; N, 3.06.

***N,N*-Diethyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-methoxy-5-methyl-3-(prop-2-enyl)benzamide (9) and *N,N*-Diethyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-methoxy-3-(prop-2-enyl)-benzamide (10).** Tetrahydrofuran (200 mL) was cooled to −70 °C and treated with MeLi (75.6 mL, 94 mmol, 1.25 N in ether, 0.05 M halide, Aldrich 19,734-3). A solution of bromide **8** (38.25 g, 83.8 mmol) in THF (70 mL) was then added over 25 min. After stirring for another 8 min at −70 °C, the reaction mixture was poured into ice–water and extracted with EtOAc (3 × 200 mL). These extracts were dried and evaporated *in vacuo*. Chromatography of the resulting residue on silica gel eluted with EtOAc/hexane gave the methylated benzamide **9** (26.92 g, 82%): mp 61.5–62.2 °C (*t*-BuOMe/hexane); IR (KBr) 2936, 1632, 1462, 1441, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.0 (m, 1H), 5.0–4.7 (m, 2H), 3.70 (s, 3H), 3.7–3.1 (m, 6H), 2.23 (s, 3H), 1.24 (t, 3H, J = 7.1

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Hz), 0.98 (m, 12H), 0.16 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 158.3, 152.6, 147.6, 137.1, 128.6, 125.9, 124.9, 114.3, 60.6, 42.9, 39.7, 28.8, 26.1, 18.5, 15.7, 14.1, 13.1. Anal. Calcd for $C_{22}H_{37}NO_3Si$: C, 67.47; H, 9.52; N, 3.57. Found: C, 67.51; H, 9.60; N, 3.82.

Further elution gave benzamide **10** (2.87 g, 9%): bp 130 °C/0.06 mm; IR (neat) 2934, 1635, 1464, 1425, 1286 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 1H, J = 8.5 Hz), 6.59 (d, 1H, J = 8.5 Hz), 5.9 (m, 1H), 4.9 (m, 2H), 3.81 (s, 3H), 3.7–3.0 (m, 6H), 1.24 (t, 3H, J = 7.2 Hz), 0.99 (s, 9H), 0.95 (t, 3H, J = 7.2 Hz), 0.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 159.2, 149.5, 136.6, 127.1, 123.2, 119.9, 114.0, 104.8, 55.7, 42.9, 39.8, 27.9, 26.1, 18.5, 14.1, 13.2. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34; N, 3.71. Found: C, 66.77; H, 9.40; N, 3.90.

MeLi–LiI complex (Aldrich 31,676-8, 7.3 mL, 1 N in ether) was added to THF (17 mL) at −70 °C. A solution of **8** (3.043 g, 6.7 mmol) in THF (6 mL) was added to the reaction mixture over 18 min. After the mixture was stirred for 4 min at −70 °C, the reaction was quenched and worked up as above. Chromatography gave **9** (2.210 g, 85%) and **10** (0.140 g, 6%).

***N,N*-Diethyl-2-[(*tert*-butyldimethylsilyl)oxy]-6-formyl-4-methoxy-5-methyl-3-(prop-2-enyl)benzamide (31).** A solution of TMEDA (13.0 mL, 86 mmol) in THF (105 mL) was cooled to −90 °C and treated with *t*-BuLi (56 mL, 1.7 N in pentane). Amide **9** (26.62 g, 68.0 mmol) in THF (40 mL) was then added dropwise over 20 min, and the resulting mixture was stirred at −90 °C for 40 min. The reaction was then quenched with DMF (12 mL in 5 mL of THF) and then the reaction mixture allowed to warm to −30 °C over 90 min. The resulting solution was poured into ice–water and extracted with EtOAc (2 × 200 mL). The extracts were dried and evaporated *in vacuo*. Chromatography of the resulting residue on silica gel eluted with EtOAc/hexane gave the formylbenzamide **31** (26.74 g, 94%): IR (neat) 2934, 1699, 1636, 1433, 1313 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 6.0 (m, 1H), 5.0–4.7 (m, 2H), 3.95 (m, 2H), 3.70 (s, 3H), 3.48 (m, 1H), 3.25–3.0 (m, 3H), 2.51 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz), 1.05 (t, 3H, J = 7.1 Hz), 0.99 (s, 9H), 0.24 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 166.8, 158.4, 148.3, 135.9, 131.3, 129.5, 127.6, 115.1, 61.1, 43.0, 39.4, 29.3, 26.2, 18.8, 13.8, 12.6, 12.4, −3.0, −3.8. Anal. Calcd for $C_{23}H_{37}NO_4Si$: C, 65.83; H, 8.89; N, 3.34. Found: C, 65.77; H, 8.87; N, 3.47.

***N,N*-Diethyl-2-[(*tert*-butyldimethylsilyl)oxy]-6-(hydroxymethyl)-4-methoxy-5-methyl-3-(prop-2-enyl)-benzamide (32) and 1,3-Dihydro-4-[(*tert*-butyldimethylsilyl)oxy]-6-methoxy-7-methyl-3-oxo-5-(prop-2-enyl)isobenzofuran (33).** A solution of the *o*-formylbenzamide **31** (21.34 g, 50.9 mmol) in EtOH (200 mL) was cooled on ice and treated with $NaBH_4$ (0.65 g, 17.2 mmol). After 30 min at 0 °C, the excess $NaBH_4$ was destroyed by dropwise addition of HOAc (3 mL). The reaction mixture was poured into ice–water and extracted with EtOAc. The extracts were dried (over K_2CO_3) and evaporated to give the (*o*-hydroxymethyl)benzamide **32**: mp 61.8–62.3 °C (*t*-BuOMe/hexane); IR (KBr) 2934, 1636, 1614, 1429, 1148 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.9 (m, 1H), 4.9 (m, 1H), 4.8 (m, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.24 (d, J = 12.2 Hz), 3.84 (m, 1H), 3.69 (s, 3H), 3.42 (m, 2H), 3.29 (m, 2H), 3.06 (m, 1H), 2.32 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H), 0.97 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 147.5, 136.9, 126.4, 124.5, 114.4, 60.9, 60.3, 43.5, 40.2, 28.9, 26.1, 18.6, 14.0, 13.0, 11.7, −3.2, −4.1. Anal. Calcd for $C_{23}H_{39}NO_4Si$: C, 65.51; H, 9.32; N, 3.32. Found: C, 65.74; H, 9.42; N, 3.54.

The unpurified (hydroxymethyl)benzamide **32** was dissolved in EtOAc (100 mL) and HOAc (8 mL) and the solution stirred at 25 °C for 15 h. The reaction mixture was poured into brine and aqueous $NaHCO_3$ and extracted with EtOAc. After the mixture was dried and evaporated, the residue was recrystallized to give **33** (10.24 g): mp 93.2–93.9 °C (*t*-BuOMe/hexane); IR (KBr) 2932, 1755, 1462, 1143 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 1H), 5.08 (s, 2H), 4.95 (m, 2H), 3.79 (s, 3H), 4.46 (dt, J = 6.0, 1.6 Hz, 2H), 2.16 (s, 3H), 1.03 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 163.2, 151.9, 146.4, 136.3, 126.1, 118.0, 115.2, 111.6, 67.7, 61.1, 28.8, 28.1, 18.8, 11.4, −3.4, −3.5. Anal. Calcd for $C_{19}H_{28}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.31; H, 8.10.

The filtrate from the crystallization of **33** (containing some desilylated phenol) was treated with *tert*-butyldimethylsilyl chloride (4 g) and imidazole (4 g) in DMF (25 mL). Following an ether–water workup, the residue was chromatographed on silica gel (EtOAc/hexane) to give **33** (2.245 g). The total yield of **33** was 12.487 g (70% from **31**).

Reaction of *N,N*-Diethyl-3-bromobenzamide (21) with MeLi. THF (40 mL) was cooled to −70 °C and treated with MeLi (12.6 mL, 1.25 M in ether). A solution of bromide **21** (3.586 g, 14 mmol) in THF (10 mL) was added over 11 min at −70 to −63 °C. The reaction mixture was stirred for another 3 min, at which time TLC indicated that the starting material had been consumed. The reaction mixture was poured into ice–water and extracted with EtOAc. The extracts were dried and evaporated, and the residue was chromatographed on silica gel (EtOAc/hexane) to give 3-bromoacetophenone (**22**) (1.337 g, 48%) identical to a commercial sample.

Further elution gave *N,N*-diethyl-5-bromo-2-fluoreneone carboxamide (**23**) (0.138 g, 6%): mp 158.2–159.9 °C (*t*-BuOMe/hexane); IR (KBr) 1716, 1637, 1458, 1290 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.40 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.67 (apparent t, J = 7.7 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 7.30 (apparent t, J = 8 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 3.70 (sextet, J = 7.1 Hz, 1H), 3.36 (sextet, J = 7.1 Hz, 1H), 3.15 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 156.6, 144.0, 141.9, 139.6, 136.5, 135.9, 134.9, 130.4, 129.4, 127.4, 123.6, 123.1, 117.7, 42.7, 39.0, 14.0, 12.5; MS (M^+) 357, 359. Anal. Calcd for $C_{18}H_{16}NO_2Br$: C, 60.34; H, 4.50; N, 3.91. Found: C, 60.19; H, 4.51; N, 3.99.

Further elution gave 3-bromo-2-[2-(3-bromophenyl)-2-oxoethyl]-*N,N*-diethylbenzamide (**24**) (0.232 g, 7%): mp 116.5–117.2 °C (*t*-BuOMe); IR (KBr) 1693, 1618, 1435, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (t, J = 1.8 Hz, 1H), 7.94 (dt, J = 7.9, 1.3 Hz, 1H), 7.72 (m, 1H), 7.62 (m, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.20 (m, 2H), 4.58 (s, 2H), 3.7–3.0 (m, 4H), 1.05 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 169.4, 139.9, 138.3, 136.3, 133.1, 132.1, 131.1, 130.3, 128.5, 127.0, 126.7, 124.5, 123.2, 43.0, 42.9, 38.6, 13.7, 12.4; MS (M^+) 451, 453. Anal. Calcd for $C_{19}H_{19}NO_2Br_2$: C, 50.35; H, 4.23; N, 3.09. Found: C, 50.62; H, 4.27; N, 3.19.

Reaction of 4-Bromo-1,3-dimethoxybenzene (25) with MeLi. THF (60 mL) was cooled to −65 °C and treated with MeLi (22.0 mL, 1.25 M in ether). A solution of bromide **25** (3.45 mL, 24.0 mmol) in THF (14 mL) was then added over 15 min at −65 °C, and the reaction mixture was stirred for 75 min at −65 °C and then the reaction quenched by addition of DMF (3.72 mL, 48 mmol) in THF (4 mL). After a further 15 min at −65 °C, the reaction mixture was poured into ice–water and extracted with EtOAc. HPLC analysis (93:7 hexane:*i*-PrOH) indicated this product to be a mixture of 4-methyl-1,3-dimethoxybenzene (**27**) (33.2%), 4-bromo-1,3-dimethoxybenzene (**25**) (33.3%), 2,4-dimethoxybenzaldehyde (**26**) (31.2%), and 1,3-dimethoxybenzene (2.3%). Compounds **25**–**27** were isolated by flash chromatography (EtOAc/hexane) and identified by comparison of ^{1}H NMR spectra to those of commercial samples. 1,3-Dimethoxybenzene was identified by HPLC retention time but could not be suitably purified by chromatography.

A second experiment was run which was identical to that above except for using one-half the scale and quenching the reaction 5 min after the addition was complete. This gave a product mixture of 4-methyl-1,3-dimethoxybenzene (**27**) (1.9%), 4-bromo-1,3-dimethoxybenzene (**25**) (84.7%), and 2,4-dimethoxybenzaldehyde (**26**) (13.4%).

***N,N*-Diethyl-3-bromo-4-methoxybenzamide (28).** A mixture of methyl 3-bromo-4-hydroxybenzoate (48.3 g, 0.251 mol), K_2CO_3 (48.3 g, 0.35 mol), and MeI (22 mL, 0.35 mol) in DMF (100 mL) was stirred at 25 °C for 2 h. The reaction mixture was poured into ice–water and extracted with 1:1 ether:EtOAc. These extracts were washed with water, dried, and evaporated. The resulting residue was recrystallized from EtOAc/hexane to give the methyl ether (42.516 g, 71%). A solution of Et_2HN (16.5 mL, 0.16 mol) in benzene (80 mL) was treated with Me_3Al (2 N in toluene, 80 mL) over 1 h. The reaction mixture was stirred for 1 h at 25 °C, and then the

methyl benzoate (43.4 g, 0.177 mol) was added as a solid. The reaction mixture was stirred at 75 °C for 40 h. The reaction mixture was cooled and then slowly added to a mixture of HCl (60 mL, concd), water, and EtOAc with ice cooling. After the mixture was stirred for 1 h, the product was extracted with EtOAc, dried, evaporated, and distilled (Kugelrohr) to give **28** (39.08 g, 75%): bp 110–120 °C/0.07 mm; IR (KBr) 1628, 1427, 1290, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 2.1 Hz, 1H), 7.32 (dd, J = 8.4, 2.1 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 3.4 (m, 4H), 1.18 (t, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 156.5, 131.7, 130.7, 127.0, 111.5, 56.3, 43–39, 13.5. Anal. Calcd for $C_{12}H_{16}NO_2Br$: C, 50.30; H, 5.46; N, 4.89. Found: C, 50.36; H, 5.63; N, 4.86.

Reaction of *N,N*-Diethyl-3-bromo-4-methoxybenzamide (28) with MeLi. THF (30 mL) was cooled to −65 °C and treated with MeLi (10.8 mL, 1.25 M in ether). A solution of bromide **28** (3.434 g, 12.0 mmol) in THF (7 mL) was then added over 11 min at −65 °C, and the reaction mixture was stirred for 1 min at −65 °C and then the reaction quenched by addition of MeOH (1.0 mL) in THF (3 mL). The reaction mixture was poured into ice–water and extracted with EtOAc. After the mixture was dried and evaporated, the resulting residue was chromatographed on silica gel (EtOAc/hexane) to give *N,N*-diethyl-4-methoxy-3-methylbenzamide (**29**) (1.295 g, 49%): bp 80–90 °C/0.07mm; IR (neat) 1634, 1425, 1273, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 2H), 6.80 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.4 (m, 4H), 2.22 (s, 3H), 1.17 (t, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 158.5, 129.2, 126.7, 125.4, 109.4, 55.4, 16.2, 13.5.

Further elution gave *N,N*-diethyl-4-methoxybenzamide (**30**)[17] (0.281 g, 11%): bp 80–85 °C/0.07 mm.

***N,N*-Diethyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-methoxy-3-(prop-2-enyl)benzamide (14).** A mixture of **6b** (10.533 g, 0.04 mol) and imidazole (5.44 g, 0.08 mol) in DMF (40 mL) was treated with *tert*-butyldimethylsilyl chloride (7.855 g, 0.05 mol) and stirred 2.5 h at room temperature. A workup as described above for the preparation of **8** gave a residue which was distilled to give **14** (15.012 g, 99%): bp 140 °C/0.25 mm (Kugelrohr); IR (neat) 1637, 1425, 1286, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 5.82 (m, 1H), 4.8 (m, 2H), 3.72 (s, 3H), 3.6–2.9 (m, 6H), 1.15 (t, J = 7.2 Hz, 3H), 0.91 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H), 0.1–0 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 159.1, 149.4, 136.5, 127.0, 123.2, 119.8, 114.0, 104.8, 55.7, 42.9, 39.7, 27.9, 26.1, 18.5, 14.1, 13.2, −3.3, 13.6. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34; N, 3.71. Found: C, 66.77; H, 9.40; N, 3.96.

***N,N*-Diethyl-2-[(*tert*-butyldimethylsilyl)oxy]-6-deutero-4-methoxy-3-(prop-2-enyl)benzamide (15).** A solution of TMEDA (3.77 mL, 0.025 mol) in THF (30 mL) was cooled to −90 °C and treated with *t*-BuLi (14.7 mL, 1.7 N in pentane). A solution of amide **14** (6.797 g, 0.018 mol) in THF (5 mL) was added over 15 min, and the reaction mixture was stirred ar −90 °C for 45 min. The reaction was quenched by addition of MeOD (3mL) in THF (3 mL). Aqueous workup with EtOAc gave a residue which was distilled to give **15** (5.844 g, 86%): bp 120 °C/ 0.07 mm (Kugelrohr); IR (neat) 1636, 1410, 1282, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 1H), 5.9 (m, 1H), 4.9 (m, 2H), 3.81 (s, 3H), 3.6–3.0 (m, 6H), 1.24 (t, J = 7.1 Hz, 3H), 0.99 (s, 9H), 0.95 (t, J = 7.1 Hz, 3H), 0.1 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 159.1, 149.4, 136.5, 123.2, 119.8, 114.0, 104.7, 55.7, 42.9, 39.7, 27.9, 26.1, 18.5, 14.1, 13.2, −3.3, −4.2; MS (M + H) 379. Anal. Calcd for $C_{21}H_{34}DNO_3Si$: C, 66.62; H, 9.31; N, 3.70. Found: C, 67.00; H, 9.46; N, 3.84.

***N,N*-Diethyl-5-bromo-2-hydroxy-6-deutero-4-methoxy-3-(prop-2-enyl)benzamide (17).** A solution of silyl ether **15** (5.60 g, 0.0148 mol) in THF (30 mL) was cooled to 0 °C and treated with *n*-Bu_4NF (17 mL, 1 N in THF). After stirring for 5 min, the reaction mixture was poured into ice–water and extracted with ether, dried, and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL) and added to a mixture of *t*-$BuNH_2$ (4.20 mL, 0.040 mol) and Br_2 (0.92 mL, 0.018 mol) in benzene (50 mL) which was cooled to −45 °C. The reaction mixture was allowed to warm to −10 °C over 1 h and then poured into cold aqueous $Na_2S_2O_3$. Extraction with EtOAc, drying, and evaporation gave a residue which was chromatographed (EtOAc/hexane) to give **17** (4.052 g, 80%): IR (neat) 1637, 1599, 1404, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (m, 1H), 5.0 (m, 2H), 3.85 (s, 3H), 3.49 (q, J = 7.1 Hz, 4H), 1.27 (t, J = 7.1 Hz, 6H); MS (M^+) 342, 344.

***N,N*-Diethyl-5-bromo-6-deutero-2-(methoxy-d_3)-4-methoxy-3-(prop-2-enyl)benzamide (18).** A mixture of bromophenol **17** (2.879 g, 0.00775 mol) and K_2CO_3 (2.08 g, 0.015 mol) in DMF (10 mL) was treated with CD_3I (0.94 mL, 0.015 mol). After stirring for 2 h at room temperature, the reaction mixture was poured into ice–water. Extraction with EtOAc, drying, and evaporation gave a residue which was distilled to give **18** (2.337 g, 84%): bp 135 °C/0.07 mm (Kugelrohr); IR (neat) 1632, 1404, 1288, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (m, 1H), 5.0 (m, 2H), 3.84 (s, 3H), 3.7–3.1 (m, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 156.5, 154.5, 136.5, 129.2, 128.4, 115.3, 111.9, 61.2, 43.0, 39.1, 29.1, 13.8, 12.6. Anal. Calcd for $C_{16}H_{18}BrD_4NO_3$: C, 53.34; H, 6.16; N, 3.89. Found: C, 53.22; H, 6.11; N, 3.81.

***N,N*-Diethyl-5-bromo-2,4-dimethoxy-3-(prop-2-enyl)-benzamide (19).** A mixture of bromophenol **7** (3.422 g, 10 mmol), K_2CO_3 (2.08 g, 15 mmol), and MeI (1.24 mL, 20 mmol) in DMF (10 mL) was heated at 70 °C for 30 min. The reaction mixture was cooled and diluted with ice–water. Workup as described for the preparation of **18** gave **19** (3.287 g, 92%): bp 110–115 °C/0.09 mm; IR (neat) 1632, 1458, 1417, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.0 (m, 1H), 5.0 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.7–3.1 (m, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 156.6, 154.6, 136.6, 129.8, 129.3, 128.6, 115.5, 112.2, 62.2, 61.4, 43.1, 39.1, 29.2, 13.9, 12.7. Anal. Calcd for $C_{16}H_{22}BrNO_3$: C, 53.93; H, 6.23; N, 3.93. Found: C, 53.94; H, 6.64; N, 3.89.

Reaction of 18 and 19 with MeLi. A mixture of **18** (0.714 g, 1.98 mmol) and **19** (0.707 g, 1.98 mmol) in THF (3.5 mL) was added to a solution of MeLi (3.6 mL, 1.25 N in ether) in THF (9.5 mL) at −65 °C over a 12 min period. After an additional 3 min, the reaction was quenched with MeOH (0.5 mL). Workup and chromatography as described for the preparation of **9** gave **20** (0.831 g, 72%) and a small amount of the nonmethylated benzamide (0.086 g, 8%).

Liquid secondary ion mass spectroscopy of **20** produced in this experiment in a *m*-nitrobenzyl alcohol matrix showed it to be 49% D_0, 4% D_1, and 47% D_4 when corrected for natural isotope abundance.

In an identical experiment, pure **18** was reacted with MeLi to give **20**-d_4 with the following spectral properties: ^1H NMR (300 MHz, $CDCl_3$) δ 6.1–5.9 (m, 1H), 5.05–4.9 (m, 2H), 3.73 (s, 3H), 3.8–3.1 (m, 6H), 2.25 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 157.9, 153.1, 137.3, 126.8, 126.7, 126.4, 114.7, 60.6, 42.9, 38.9, 28.5, 15.7, 13.8, 12.7. Anal. Calcd for $C_{17}H_{21}D_4NO_3$: C, 69.12; H, 8.53; N, 4.74. Found: C, 68.73; H, 8.48; N, 4.95.

Supporting Information Available: ^1H and ^{13}C NMR spectra of **29** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any currrent masthead page for ordering information.

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