An Efficient Synthesis of 5,7-Dimethoxy-4-methylphthalide, a Key Intermediate in the Synthesis of Mycophenolic Acid

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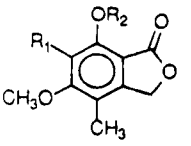
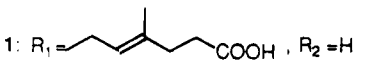
Mycophenolic acid (**1**), a metabolite isolated from *Penicillium brevicompactum*,[1] has been shown to possess significant antineoplastic,[2] antiparasitic,[3] antiviral,[4] and immunosuppressive[5] activity. The compound acts through inhibition of inosine monophosphate dehydrogenase.[6] The compound is also very potent against psoriasis.[7] The original total synthesis of mycophenolic acid by Birch *et al.*[8] used phthalide **2** as a key intermediate. The phthalide was prepared in an 11 step sequence (8% yield) using an Alder–Rickert reaction.[9] This or related phthalide skeleta have been used in several total[10] and formal[11] syntheses except for Danheiser's methodology which involves a thermal combination of heterosubstituted acetylenes and cyclobutenones.[12] However, the latter approach does not enable diverse structural modification of **1**; thus, the preferred synthetic route involves intermediates such as **2** or **3** with subsequent elaboration of the hexenoic acid side chain via stereospecific orthoester Claisen rearrangements.[13] This approach has been limited by low overall yields, over several steps, for the synthesis of the bicyclic phthalide system (the highest[10b] being 16%).





1: R_1 = , R_2 = H

2: R_1 = H, R_2 = H

3: R_1 = H, R_2 = CH_3

As part of our continuing effort to prepare mycophenolic acid derivatives, we have developed an efficient method for the preparation of **3** that involves four simple steps which can be conducted on either small or large scale. The flexible approach permits the introduction of various substituents on the aromatic ring.

Results and Discussion

Our strategy (Scheme 1) was based on the application of two Vilsmeier formylations[14] starting from the commercially available 3,5-dimethoxybenzyl alcohol (**5**, which also can be prepared economically from the corresponding ester). Electrophilic substitution occurred regioselectively para to one of the activating methoxy groups. The alcohol **5** was added to the mixture of $POCl_3$ (excess) and DMF at 25 °C in order to convert the hydroxyl to the chloride to avoid the formation of 5-membered hemiacetal upon formylation.[15] The mixture was then heated to 75 °C to effect formylation.

Selective reduction of the aldehyde **6** to compound **7** was expected to be difficult because halides, and particularly benzylic halides, are also susceptible to reduction under similar conditions. Thus, Pd catalyst in a variety of solvents afforded 3,5-dimethoxy-2-methyltoluene exclusively. However, it is known that platinum and rhodium are relatively ineffective in halogen cleavage and therefore may be the catalyst of choice in hydrogenations when halogen is to be preserved.[16] We found PtO_2 and platinum on carbon to be the most selective, but PtO_2 produced numerous side products. Apolar solvents retarded dehydrohalogenation while traces of acid or base led to complete loss of selectivity and rapid reduction of both substituents. Thus, Pt on carbon in carbon tetrachloride gave crude **7** [87% yield, containing *ca.* 16% 3,5-dimethoxy-2-methyl-toluene (based on ^1H NMR)]. This method was attempted on three different scales [0.05, 0.30, 2.00 g of aldehyde (the maximum that could be carried out with the available apparatus)], giving rise to the same ratio of products. The end of the reactions was indicated by the cease of hydrogen uptake in all cases. A large excess of hydrogen (20–40 equiv) was consumed probably due to concomitant reduction of the carbon tetrachloride. The mixture was not purified at this point because only the benzylic chloride was capable of ring closure to the lactone in the last step. The acidic side product was easily removed by base extraction.

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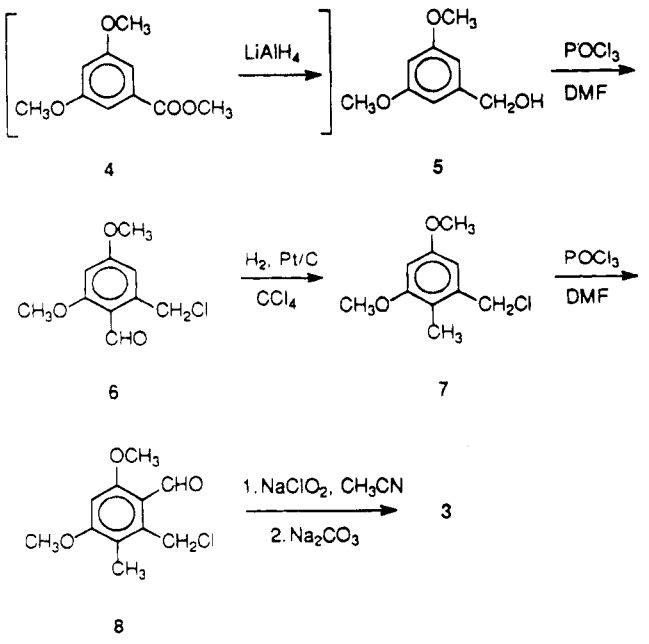
Scheme 1



Vilsmeier formylation of **7** gave aldehyde **8** which was subjected to selective oxidation by sodium chlorite.[17] Subsequent intramolecular attack of the resultant carboxylate on the benzylic chloride under alkaline conditions afforded phthalide **3** in 40% overall yield from **5**.

Experimental Section

Melting points (uncorrected) were determined in an open capillary. IR spectra were determined in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were determined at 300 MHz in $CDCl_3$ solution. Combustion analyses were performed by Atlantic Microlab, Atlanta, GA. All materials and solvents were purchased from Aldrich Chemical Co. except for carbon tetrachloride, diethyl ether, and methanol (Baker Chemical Co.) and were used without further purification. Pt on carbon was purchased from Engelhard Industries, Inc., and Aldrich Chemical Co.

6-(Chloromethyl)-2,4-dimethoxybenzaldehyde (6). Phosphorus oxychloride (3.0 mL, 5.02 g, 32.7 mmol) was added dropwise to DMF (5 mL, 4.72 g, 64.7 mmol) over 15 min under 10 °C. The thick colorless mixture was stirred at room temperature for 20 min. Alcohol **5** (1.5 g, 8.93 mmol) was added in one portion, and the mixture was slowly heated to 75 °C and stirred for 2 h. The orange solution was cooled to 25 °C and was added to water (50 mL) under 10 °C. The ice bath-cooled solution was neutralized with 20% NaOH solution, stirred for 1 h, and filtered. The crystals were washed with water and ice-cold methanol (3 mL) and dried to give **6** (1.745 g, 91%) as a white solid: mp 102 °C; ^{1}H NMR δ 3.89 (6H, s), 5.05 (2H, s), 6.44 (1H, d), 6.75 (1H, d), 10.45 (1H, s); ^{13}C NMR δ 45.44, 56.23, 56.57, 98.20, 108.14, 116.45, 142.92, 165.61, 165.83, 190.48; IR 1669, 1597 cm^{-1}. Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17; Cl, 16.52. Found: C, 55.80; H, 5.22; Cl, 16.38.

3,5-Dimethoxy-2-methylbenzyl Chloride (7). Platinum on carbon (2.9 g, 5%, Engelhard; 3.4 g, 5%, Aldrich) was added to a solution of **6** (2.0 g, 9.32 mmol) in CCl_4 (150 mL) and hydrogenated in a Parr bottle at room temperature around 8 psi for 12 min after a total of 29 psi (38.5 equiv) of hydrogen had been consumed. The catalyst was filtered and washed with CCl_4 (80 mL). The filtrate was concentrated to afford a gray solid (1.623 g, 87%) which was *ca.* 83% pure and used in the next reaction without purification. A small amount of this product was recrystallized from methanol for analysis. The compound had: mp 70–71 °C; ^{1}H NMR δ 2.22 (3H, s), 3.82 (6H, s), 4.59 (2H, s), 6.47 (1H, d), 6.50 (1H, d); ^{13}C NMR δ 11.01, 45.70, 55.94, 56.20, 99.40, 106.17, 118.76, 137.43, 158.95, 159.40; IR 1611 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClO_2$: C, 59.85; H, 6.53; Cl, 17.67. Found: C, 59.96; H, 6.53; Cl, 17.75.

2-(Chloromethyl)-4,6-dimethoxy-3-methylbenzaldehyde (8). Phosphorus oxychloride (6.25 mL, 10.45 g, 68.2 mmol) was added dropwise to DMF (10 mL, 9.44 g, 129.4 mmol) over 30 min under 10 °C. The thick colorless mixture was stirred at room temperature for 20 min. Compound **7** (6.0 g, 29.9 mmol) was added in one portion, and the mixture was slowly heated to 80 °C and stirred for 2 h. The deep red solution was cooled to 25 °C and was added to water (300 mL) under 10 °C. The sticky byproduct was rapidly filtered, and the ice bath-cooled filtrate was neutralized with 20% NaOH solution, stirred for 1.5 h, and filtered. The crystals were washed with water and ice-cold methanol (5 mL) and dried to give **6** (5.45 g, 80%) as a white solid: mp 174–175 °C; ^{1}H NMR δ 2.21 (3H, s), 3.91 (6H, s), 5.15 (2H, s), 6.44 (1H, s), 10.51 (1H, s); ^{13}C NMR δ 10.47, 39.83, 56.31, 56.60, 95.05, 116.01, 120.85, 139.20, 163.75, 164.43, 190.96; IR 1674, 1593 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73; Cl, 15.50. Found: C, 57.70; H, 5.72; Cl, 15.52.

5,7-Dimethoxy-4-methylphthalide (3). A solution of $NaH_2PO_4 \times H_2O$ (280 mg, 2.0 mmol) in water (4 mL) was added to the suspension of **8** (1.0 g, 0.22 mmol) in acetonitrile (36 mL) at 20 °C. Hydrogen peroxide (0.375 mL, 453 mg, 50%, 6.67 mmol) and a solution of $NaClO_2$ (0.75 g, 80%, 6.62 mmol) in water (1.8 mL) was added, and the resulting mixture was stirred at 20 °C for 2.5 h. Na_2SO_3 (0.7 g, 6.62 mmol) was added, and the yellow solution was stirred for 30 min. The pH was adjusted to 1 with HCl solution (5 mL, 5%), the mixture was diluted with ethyl acetate–water (100 mL, 1:1), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (50 mL), and then the combined organic layer was washed with water (100 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in a mixture of dioxane (50 mL) and Na_2CO_3 solution (70 mL, 5%) and heated at reflux for 20 h. The mixture was cooled to room temperature and acidified (pH = 1) with HCl solution. Ethyl acetate (100 mL) and water (50 mL) were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layer was washed with Na_2CO_3 solution (100 mL, 5%) and water (100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to afford **3** (0.577 mg, 63%) as a yellowish solid which was pure according to NMR and could be decolorized by filtering from methanol: mp 200–202 °C (lit.[10a] mp 202 °C); ^{1}H NMR δ 2.01 (3H, s), 3.92 (3H, s), 3.96 (3H, s), 5.08 (2H, s), 6.39 (1H, s); ^{13}C NMR δ 11.01, 56.60, 56.63, 68.62, 94.89, 112.01, 112.19, 149.26, 158.83, 164.29, 170.11; IR 1740, 1623 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.42; H, 5.84.

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