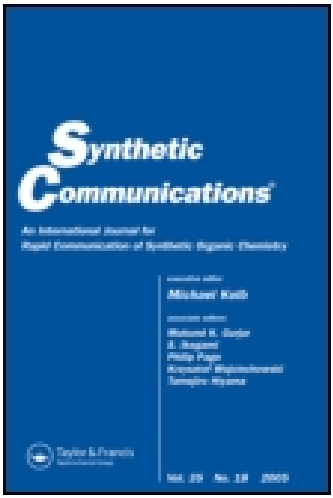

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An Improved Synthesis of 5,7-Dimethoxy-4-methylphthalide, A Key Intermediate in the Synthesis of Mycophenolic Acid

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AN IMPROVED SYNTHESIS OF 5,7-DIMETHOXY-4-METHYL-PHTHALIDE, A KEY INTERMEDIATE IN THE SYNTHESIS OF MYCOPHENOLIC ACID

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Abstract: An efficient synthetic pathway is described for 5,7-dimethoxy-4-methylphthalide, a key intermediate in the synthesis of mycophenolic acid and its analogues. The procedure starts from methyl 3,5-dimethoxybenzoate and involves five simple steps to give phthalide **3** in 55% overall yield.

Mycophenolic acid (MPA, **1**) was first reported in the last century and, since that time, this mold metabolite has assumed a role of central importance as an inhibitor of inosine monophosphate dehydrogenase. A prodrug of MPA, the morpholinoethyl ester, is currently in advanced clinical trial as an

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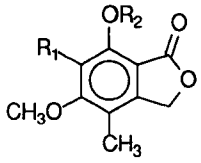
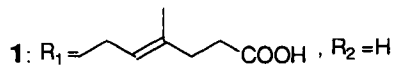
immunosuppressant and MPA has been shown to possess significant antineoplastic[1], antiparasitic[2], and antiviral[3] activity. It is also very active against psoriasis.[4] The compound acts through inhibition of inosine monophosphate dehydrogenase.[5]





2: R_1 =H, R_2 =H

3: R_1 =H, R_2 =CH_3

The original total synthesis of mycophenolic acid by Birch *et al*[6] used phthalide **2** as a key intermediate. The phthalide was prepared in an 11 step sequence (8% yield) using an Alder-Rickert reaction.[7] This or related phthalide skeleta have been subject to several total[8] and formal[9] syntheses because the preferred synthetic route to MPA involves intermediates such as **2** or **3** with subsequent elaboration of the hexenoic acid side chain via stereospecific orthoester Claisen rearrangement.[10] Patterson recently developed a novel approach to assemble the bicyclic system in high yields with regioselective substitutions of the aromatic ring through organolithium species as key steps[9f]. We simultaneously reported a new, very efficient synthesis of **3** starting from the commercially available 3,5-dimethoxybenzylalcohol.[11] The method, however,

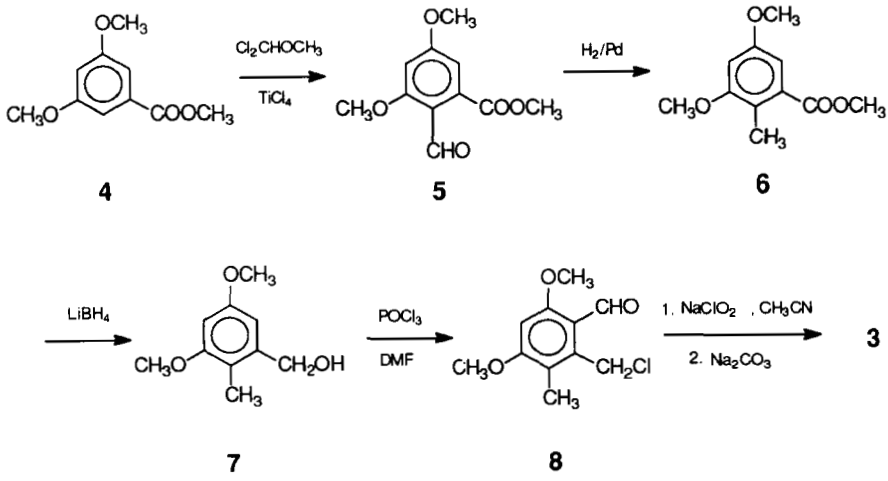
has two problems. The starting benzylic alcohol is very expensive and the selective hydrogenolysis of an aromatic aldehyde in the presence of benzylic chloride moiety could only be carried out in carbon tetrachloride. The problem is that our recent investigations have shown that the yield varies dramatically depending upon the source and quality of the solvent. This reduction can also be effected using TFA/Et_3SiH but the overall yield (40%) was not enhanced significantly.

The above disadvantages led us to devise an alternate pathway to phthalide **3** (Scheme 1). Methyl 3,5 dimethoxy-2-methylbenzoate (**6**) was prepared from methyl 3,5-dimethoxybenzoate (**4**) by formylation with α,α-dichloromethyl-methyl ether/$TiCl_4$ and subsequent hydrogenation of the resultant aldehyde **5** in ethyl acetate (94% overall yield)[12].

The ester was reduced ($LiBH_4$/diethyl ether/THF/MeOH) to alcohol **7** in 92% yield. Conversion of the hydroxyl group to the corresponding chloride and concomitant formylation were effected with $POCl_3$ in DMF. The resulting aldehyde **8** was oxidized with $NaClO_2$ to give the carboxylic acid which underwent ring closure under alkaline conditions to give phthalide **3** in 55% overall yield. This flexible approach permits diverse modification of the bicyclic ring and appears to be superior to our previous method.

Experimental Section

Melting point (uncorrected) was determined in an open capillary. ^1H NMR spectra were determined at 300 MHz in $CDCl_3$ solution. All materials and



Scheme 1

solvents were purchased from Aldrich Chemical Co. except for diethyl ether and methanol (Baker Chemical Co.) and were used without further purification. Pd on carbon was purchased from Engelhard Industries Inc.

3,5-Dimethoxy-2-methylbenzylalcohol (7). $LiBH_4$ (1.09 g, 50.0 mmol) was added to the solution of ester **6** (6.66 g, 31.71 mmol) in THF (29 mL) and diethyl ether (79 mL). The mixture was stirred for 1 h at 40 °C then it was cooled to 5 °C with ice bath. Water (100 mL) was added slowly to destroy the excess hydride and then the mixture was acidified with 10% HCl solution. Diethyl ether (50 mL) was added and the phases were separated. The aqueous layer was extracted with diethyl ether (2x60 mL) and the combined organic layer was washed with brine, dried and concentrated to give **7** (5.31 g, 92%) as a colorless oil[12]. ^{1}H NMR δ 2.12 (3H, s), 3.81 (6H, s), 4.67 (2H, s), 6.42 (1H, d), 6.59 (1H,d).

2-Chloromethyl-4,6-dimethoxy-3-methylbenzaldehyde (8). Phosphorous oxychloride (5.92 mL, 9.89 g, 64.6 mmol) was added dropwise to DMF (9.3 mL, 8.78 g, 120.3 mmol) over 30 min under 10 °C. The thick colorless mixture was stirred at room temperature for 20 min. Alcohol **7** (3.0 g, 16.48 mmol) was added under 40 °C and the mixture was slowly heated to 75 °C and stirred for 2 h. The deep red solution was cooled to 25 °C and added to water (170 mL) under 10 °C. The mixture was neutralized with 20% NaOH solution and stirred for 1.5 h at 10 °C. The precipitate was filtered, washed with water and ice-cold methanol (3 mL), and dried to give **8** (3.40 g, 90%) as a yellow solid[11]. ^{1}H NMR δ 2.21 (3H, s), 3.91 (6H, s), 5.15 (2H, s), 6.44 (1H, s), 10.51 (1H, s).

5,7-Dimethoxy-4-methylphthalide (3). A solution of $NaH_2PO_4xH_2O$ (2.23 g, 15.9 mmol) in water (24 mL) was added to the suspension of **8** (5.88 g, 25.7 mmol) in acetonitrile (210 mL) at 20 °C. Hydrogen peroxide (2.18 mL, 2.63 g, 50%, 38.8 mmol) and a solution of $NaClO_2$ (4.41 g, 80%, 38.9 mmol) in water (11 mL) was added and the resulting mixture was stirred at 20 °C for 2.5 h. Na_2SO_3 (4.12 g, 38.9 mmol) was added and the yellow solution was stirred for 30 min. The pH was adjusted to 1 with HCl-solution and the mixture was diluted with ethyl acetate-water (500 mL, 1:1) and the two phases were separated. The aqueous layer was extracted with ethyl acetate (200 mL) then the combined organic layer was washed with water (500 mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in a mixture of dioxane (165 mL) and Na_2CO_3 solution (470 mL, 6%) and heated at reflux for 2.5 h. The mixture was cooled to room

temperature, acidified (pH=1) with HCl solution and stirred overnight at room temperature. Methylene chloride (300 mL) and water (100 mL) were added, the layers were separated and the aqueous layer was extracted with methylene chloride (150 mL). The combined organic layer was washed with Na_2CO_3 solution (250 mL, 5%), water (250 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to afford **3** (3.73 g, 70%) as a yellowish solid[11] which was pure according to NMR and could be decolorized by filtering from methanol: mp 200-202 °C (lit. 202 °C[8a]); ^{1}H NMR δ 2.01 (3H, s), 3.92 (3H, s), 3.96 (3H, s), 5.08 (2H, s), 6.39 (1H, s).

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