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An Efficient Synthesis of 5,7-Dihydroxy-4-methylisobenzofuran-1(3*H*)-one, a Metabolite of *aspergillus flavus* and a Key Intermediate in the Synthesis of Mycophenolic Acid1)

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Synopsis. An efficient new synthesis of 5,7-dihydroxy-4-methylisobenzofuran-1(3*H*)-one, a metabolite of *aspergillus flavus* and a key intermediate in the synthesis of mycophenolic acid, is reported. The new synthesis involves the preparation of 1,2-dihydro-4,6-dimethoxy-3-methylbenzocyclobuten-1-ol and a regioselective β-scission of alkoxyl radical generated from it with lead tetraacetate as the key steps.

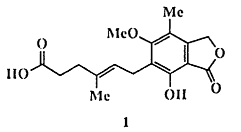
Mycophenolic acid (**1**) has recently attracted much attention because of its significant antiviral and antitumor activities.2) Several excellent methods for synthesizing this metabolite have been reported,3) some of which use 5,7-dihydroxy-4-methylisobenzofuran-1(3*H*)-one (**2**),3b,4) a molecule found in metabolites of *aspergillus flavus*,5) as the key intermediate.

We report here an efficient method to synthesize the phthalide **2** based on a modified procedure of our general synthesis of phthalide derivatives involving β-scission of alkoxyl radicals generated from 1-ethylbenzocyclobutenols.6) A synthetic process is outlined in Scheme 1: thus, bromination of 2,4-dimethoxybenzaldehyde (**3**) followed by a Clemensen reduction of the resulting 5-bromo-2,4-dimethoxybenzaldehyde (**4**) gave 1-bromo-2,4-dimethoxy-5-methylbenzene (**5**). Bromobenzene **5** was then transformed into 4,6-dimethoxy-3-methylbenzocyclobuten-1(2*H*)-one (**6**) according to a procedure reported by Stevens and Bisacchi.8) Benzocyclobutenone **6** was further transformed into the corresponding 1,2-dihydrobenzocyclobutenol **7** by reduction with lithium aluminum hydride and into 1,2-dihydrobenzocyclobutenol **8** by treatment with ethylmagnesium bromide, respectively.

Irradiation of a solution of the hypoiodite of 1,2-dihydrobenzocyclobutenol **8** (prepared in situ with mercury(II) oxide and iodine in benzene) under the conditions reported in previous paper6) gave solely 2-iodomethyl-4,6-dimethoxy-3-methylbenzaldehyde (**9**) (72 %), which arises from a β-scission of the corresponding alkoxyl radical. The reaction of 1,2-dihydrobenzocyclobutenol **7** under the same conditions as the case of 1,2-dihydrobenzocyclobutenol **8** also gave exclusively ethyl 2-iodomethyl-4,6-dimethoxy-3-methylphenyl ketone (**10**) in 74 % yield.

The synthesis of phthalide (**11**) (58 %), however, was achieved by treating 1,2-dihydrobenzocyclobutenol **7** in benzene with 2 equivalents of lead tetraacetate9,10) at room temperature. Phthalide **11** was then demethylated with boron tribromide according to a published procedure3b) to give 5,7-dihydroxy-4-methylisobenzofuran-1(3*H*)-one (**2**). Phthalide **2** can, thus, be synthesized in an overall yield of 15% in 6 steps from commercially available 2,4-dimethyoxybenzaldehyde (**3**).

One of the probable pathways leading to phthalide **9** from cyclobutenol **7** is outlined in Scheme 2: β-scission of the cyclobutenyloxyl radical **A** generates a benzyl radical **B**. An intramolecular combination of radical **B** with the formyl oxygen affords phthalide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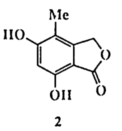
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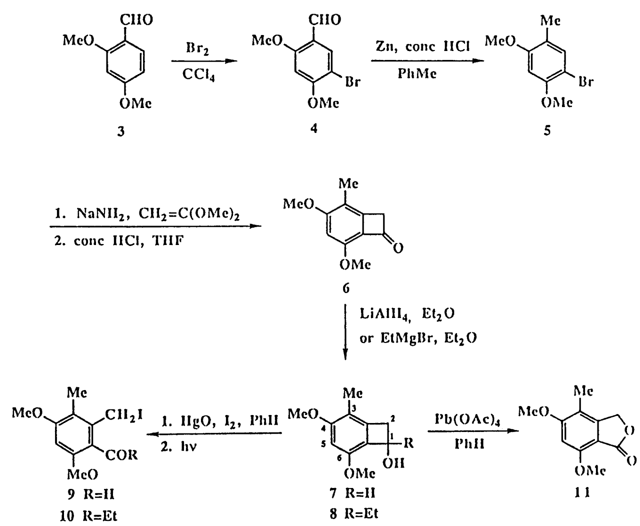
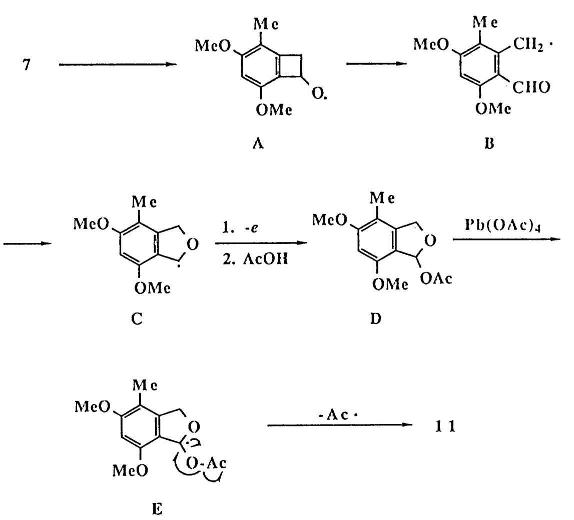


Scheme 1.



Scheme 2.

radical.[6] A one-electron oxidation of the cyclic radical **C** followed by a reaction involving the resulting cation with acetic acid gives intermediate **D**. Phthalide **9** is most probably formed through β-scission of intermediate **E** generated by hydrogen abstraction with lead tetraacetate since hydrogen abstraction from 1-methoxy-1,4-dihydrobenzofuran has been reported to result in the formation of phthalide through β-scission.[11]

It is of interest to note that the trapping of iodine by the benzyl radical **B** is a faster process than intramolecular combination with the formyl oxygen when β-scission of the cyclobutenyloxyl radical **A** is executed by mercury(II) oxide-iodine reagent. Failure of the normally preferred intramolecular reaction[6,12] in this particular case is attributable to the presence of two ortho-substituents (Me and OMe), the steric and electronic effects of which slow down the intramolecular reaction.

Experimental

Melting points were recorded with a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded for Nujol mulls with a Hitachi 285 infrared spectrophotometer. The ^{1}H NMR spectra were recorded with a Hitachi R-90B spectrometer (90 MHz, solvent $CDCl_3$; $SiMe_4$ as an internal standard). TLC was performed with Merck silica gel 60 GF_{254}. The high- and low-resolution mass spectra were determined with a JEOL JMS-300 spectrometer (70 eV, Faculty of Pharmaceutical Sciences of this University). Elemental analyses were carried out by the staff of the analytical laboratory of the Faculty of Pharmaceutical Sciences. All of the solvents used were dried over appropriate drying agents and distilled under nitrogen before use.

5-Bromo-2,4-dimethoxybenzaldehyde (4); To a stirred solution of 2,4-dimethoxybenzaldehyde (1.0 g, 6 mmol) in carbon tetrachloride (15 ml) at 0 °C was added dropwise bromine (1.0 g, 6.4 mmol) over a period of 40 min. The mixture was then stirred for 1 h at room temperature and filtered. The precipitate was dissolved in dichloromethane, washed with 5% aqueous sodium thiosulfate and dried over anhydrous calcium chloride. Removal of the solvent gave a solid residue which could be recrystallized from diethyl ether-hexane to afford **4** (1.2 g, 81%). The filtrate was washed with 2 M (1 M=1 mol dm^{-3}) sodium hydroxide, water and brine and dried over anhydrous calcium chloride. After removing the solvent, the residue was purified by preparative TLC on silica gel (1 : 3 ethyl acetate-hexane, RF 0.25) to give **4**, mp 130—133 °C, (diethyl ether-hexane) (0.15 g, 10%) (lit,[7] mp 134—138 °C); IR (Nujol) 1674 (CHO), and 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.95 (3H, s, OMe), 3.98 (3H,s, OMe), 6.45 (1H, s, 3-H), 8.00 (1H, s, 6-H) 10.70 (1H, s, CHO); MS *m/z* (rel intensity) 246 (98), 244 (M$^+$, 100). Found: C, 43.94; H, 3.68%. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70%.

1-Bromo-2,4-dimethoxy-5-methylbenzene (5). A mixture of zinc (2.35 g, 35.9 mg), mercury(II) chloride (235 mg, 0.87 mmol), water (3.8 ml) and concd hydrochloric acid (0.11 ml) was stirred for 15 min at room temperature. The solvent was decanted. To the residual solid was added successively water (1.52 ml), concd hydrochloric acid (3.4 ml), toluene (3.8 ml) and aldehyde **4** (1.35 g, 5.5 mmol). The mixture was heat under reflux for 2 h and was then cooled to room temperature. After filtering the resulting mixture the filtrate was extracted with diethyl ether. The extract was then washed with water and brine and dried over anhydrous magnesium sulfate. After removing the solvent, the residue was subjected to preparative TLC (1 : 3 ethyl acetate-hexane, R_f 0.63), affording **5**, mp 89—91 °C (hexane), (636 mg, 50%). IR (Nujol) 1600 cm^{-1}; ^{1}H NMR δ=2.12 (3H, s, Me), 3.83 (3H, s, OMe), 3.88 (3H, s, OMe), 6.45 (1H, s, 3-H) 7.25 (1H, s, 6-H); MS *m/z* (rel intensity) 232 (98), 230 (M$^+$, 100). Found: C, 46.78; H, 4.85%. Calcd for $C_{19}H_{11}BrO_2$; C, 46.78; H, 4.80%.

4,6-Dimethoxy-3-methylbenzocyclobuten-1(2*H*)-one (6). A mixture of **5** (630 mg, 2.7 mmol), 1,1-dimethoxyethene (0.48 g, 5.4 mmol) and sodium amide (224 mg, 5.7 mmol) in tetrahydrofuran was heated under reflux in a nitrogen atmosphere for 18 h. Water was then added to the reaction mixture and the organic layer was removed. The aqueous layer was extracted with diethyl ether. The combined extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give a residue which was treated with 20% hydrochloric acid (1 ml) in tetrahydrofuran (3 ml) at room temperature for 16 h. The solvent was removed and the residue extracted with diethyl ether. The extract was washed with water and aqueous sodium hydrogencarbonate and dried over anhydrous magnesium sulfate. After concentration, the resulting residue was purified by preparative TLC on silica gel (1 : 5 ethyl acetate-hexane) to afford cyclobutenone **6** (R_f 0.44, 126 mg, 25%; 87% based on the consumed starting material) and the starting material (455 mg, 72%). **6**: mp 139—141 °C (hexane); IR (Nujol) 1745 cm^{-1} (C=O) ^{1}H NMR δ=1.99 (3H, s, Me), 3.68 (2H, s, 2-CH_2-), 3.76 (3H, s, OMe), 4.02 (3H, s, OMe), 6.20 (1H, s, 5-H); MS *m/z* (rel intensity) 192 (M$^+$, 100). Found: M$^+$, 192.0799. Calcd for $C_{11}H_{12}O_3$: M, 192.0787.

1,2-Dihydro-4,6-dimethoxy-3-methylbenzocyclobuten-1-ol (7). To a stirred suspension of lithium aluminum hydride (50 mg, 1.2 mmol) in diethyl ether (10 ml) at −78 °C was added dropwise an diethyl ether solution (20 ml) of cyclobutenone **6** (115 mg, 0.60 mmol). After 10 min, the reaction was quenched by the addition of several drops of saturated sodium sulfate. The mixture was then dried over anhydrous magnesium sulfate, and filtered through a Celite pad. The solvent was evaporated to give a residue which was purified by preparative TLC on silica gel (1 : 3 ethyl acetate-hexane, R_f 0.25) to afford butenol **7**, mp 124—126 °C (hexane) (110 mg, 95%); IR (Nujol) 3300, 3200 (OH), 1625, 1584 cm^{-1}; ^{1}H NMR (C_6D_6) δ=1.28 (1H, d, *J*=10.1 Hz, OH), 2.10 (3H, s, Me), 2.52 (1H, dd, *J*=14.3 and 1.8 Hz, 2-H), 3.15 (1H, dd, *J*=14.3 and 4.4 Hz, 2-H), 3.33 (3H, s, OMe), 3.79 (3H, s, OMe), 4.90 (1H, ddd, *J*=10.1, 4.4, and 1.8 Hz, 1-H), 6.35 (1H, s, 5-H); MS *m/z* (rel intensity) 194 (M$^+$, 91), 193 [(M-1)$^+$, 100]. Found: M$^+$, 194.0942. Calcd for $C_{11}H_{14}O_3$: M, 194.0942.

1-Ethyl-1,2-dihydro-4,6-dimethoxy-3-methylbenzocyclobuten-1-ol (8). To a stirred solution of cyclobutenone **6** (62 mg, 0.32 mmol) in diethyl ether (5 ml) at 0 °C was added dropwise ethylmagnesium bromide (2 M solution in diethyl ether, 0.4 ml). After 10 min, the reaction mixture was poured into iced water and extracted with diethyl ether. The extract was washed with aqueous ammonium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was subjected to preparative TLC (1 : 3 ethyl acetate-hexane, R_f 0.48) to give butenol **8**, mp 79—80 °C (hexane), (64 mg, 89%). IR (Nujol) 3150, (OH), 1628, 1580 cm^{-1}; ^{1}H NMR (C_6D_6) δ=0.96 (3H, t, *J*=7.25 Hz, $\underline{CH_3}CH_2$), 1.58 (1H, s, OH), 1.6—2.0 (2H, m, $\underline{CH_2}CH_3$), 2.14 (3H, s, Me), 2.59 (1H, d, *J*=13.85 Hz, 2-H), 3.05 (1H, d, *J*=13.85 Hz, 2-H), 3.36 (3H, s, OMe), 3.72 (3H, s, OMe), 6.33 (1H, s, 5-H); MS *m/z* (rel intensity) 222 (M$^+$, 11), 204 [(M-H_2O)$^+$, 16], 1193 [(M-C_2H_5)$^+$, 100]. Found: M$^+$, 222.1267. Calcd for $C_{13}H_{18}O_3$: M, 222.1256.

2-Iodomethyl-4,6-dimethoxy-3-methylbenzaldehyde (9). A benzene solution (15 ml) of butenol **7** (56 mg, 0.29 mmol) containing mercury(II) oxide (187 mg, 0.87 mmol) and iodine (220 mg, 0.87 mmol) was irradiated with a 100-W high-pressure mercury arc through a Pyrex filter under a nitrogen atmosphere for 50 min. After filtering the mixture through a Celite pad, the filtrate was washed with 5% sodium thiosulfate and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to give a residue which was purified by preparative TLC on silica gel (1:3 ethyl acetate-hexane, R_f 0.50) to afford **9**, mp 124—126 °C (diethyl ether-hexane); (69 mg, 74%). IR (Nujol) 2720, 1715 cm^{-1} (CHO); ^{1}H NMR δ=2.14 (3H, s, 3-H), 3.85 (3H, s, OMe), 3.89 (3H, s, OMe), 4.12 (2H, s, CH_2I), 6.44 (1H, s, 5-H), 9.70 (1H, s, CHO); MS m/z (rel intensity) 320 (M$^+$, 100). Found: M$^+$, 319.9928. Calcd for $C_{11}H_{13}IO_3$: M, 319.9911.

Ethyl 2-Iodomethyl-4,6-dimethoxy-3-methylphenyl Ketone (10). A benzene solution (20 ml) of butenol **8** (64 mg, 0.29 mmol) containing mercury(II) oxide (187 mg, 0.87 mmol) and iodine (221 mg, 0.87 mmol) was irradiated (as mentioned above) worked up and purified (as above) to give ketone **10**, mp 96—98 °C, (diethyl ether-hexane); IR (Nujol) 1710 cm^{-1}; ^{1}H NMR δ=1.07 (3H, t, J=7.25 Hz, $CH_2\underline{CH_3}$), 2.10 (3H, s, Me), 2.49 (2H, q, J=7.25 Hz, $\underline{CH_2}CH_3$), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe), 4.09 (2H, s, CH_2I), 6.41 (1H, s, 5-H): MS m/z (rel intensity) 348 (M$^+$, 21), 221 [(M-I)$^+$, 100]. Found: M$^+$, 348.0220. Calcd for $C_{13}H_{17}IO_3$: M, 348.0224.

5,7-Dimethoxy-4-methylisobenzofuran-1(3*H*)-one (11). A mixture of butenol **7** (88 mg, 0.45 mol) and lead tetraacetate (400 mg, 0.90 mmol) in benzene (30 ml) was stirred under a nitrogen atmosphere for 18 h at room temperature. After filtering the mixture, the filtrate was washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a residue which was purified by preparative TLC on silica gel (1:2 ethyl acetate-hexane, R_f 0.24) to give phthalide **11** (34 mg, 34%; 58% based on consumed starting material) along with the starting material **7**, mp 205—207 °C (diethyl ether-hexane) (36 mg, 41%). (lit,[3b)] mp 202—203 °C).

5,7-Dihydroxy-4-methylisobenzofuran-1(3*H*)-one (2). Conversion of **11** to its demethylated derivative **2** was carried out by the reported procedure.[3b)] **2**: Mp 252—255 °C (MeOH-H_2O) (lit,[3b)] mp 252—254 °C).

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