An Efficient Synthesis of Phthalides by Diels–Alder Reaction of Sulfur-Substituted Furanones with Silyloxydienes: A Formal Synthesis of Mycophenolic Acid

Mitsuaki WATANABE,*[a] Masao TSUKAZAKI,[a] Yumiko HAMADA,[a] Masatomo IWAO,*[b] and Sunao FURUKAWA[a]

Faculty of Pharmaceutical Sciences[a] and Faculty of Liberal Arts,[b] Nagasaki University, Nagasaki 852, Japan. *Received April 25, 1989*

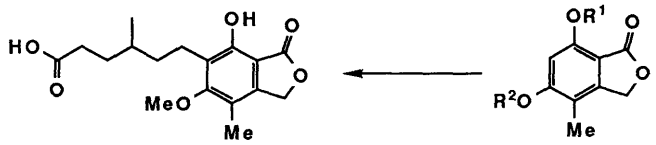
Highly substituted phthalides including a key intermediate in the synthesis of mycophenolic acid were prepared by the Diels–Alder reaction of 3-(phenylthio)- or 3-(phenylsulfinyl)-2(5*H*)-furanones with silyloxydienes.

Keywords 3-(phenylthio)-2(5*H*)-furanone; 3-(phenylsulfinyl)-2(5*H*)-furanone; silyloxydiene; phthalide; mycophenolic acid; Diels–Alder reaction

2(5*H*)-Furanone derivatives[1] are useful intermediates in organic synthesis. Versatile reactions of 2(5*H*)-furanones as Michael acceptors have been developed and successfully used for the syntheses of natural products,[2] and exploitation of 2(5*H*)-furanones as dienophiles in the Diels–Alder reaction have recently been investigated.[3] In this paper, the utility of 3-(phenylthio)- and 3-(phenylsulfinyl)-2(5*H*)-furanones as dienophiles is demonstrated for the general synthesis of highly substituted phthalides including the key intermediate in the synthesis of mycophenolic acid.

In general, substituted phthalides have been prepared using aromatic directed lithiation[4] or thallation[5] and annulation[6] of aliphatic systems. To the best of our knowledge, there is no report concerning the use of 2(5*H*)-furanones as synthons for the phthalide skeleton.

Mycophenolic acid (**1**),[7] one of the highly substituted phthalides, was isolated from *Penicillium brevicompactum*[8] and possesses antiviral and antitumor activities.[9] Total syntheses of mycophenolic acid (**1**) have been reported in 1969 by Birch and Wright,[10] and in 1972 by Canonica *et al.*[11] In these approaches, phthalides such as 7-hydroxy-5-methoxy-4-methylphthalide (**2a**), 5,7-dihydroxy-4-methylphthalide (**2b**), and 5,7-dimethoxy-4-methylphthalide (**3a**) were used as key intermediates for the convergent syntheses (Chart 1). Phthalides **3a** and **2b** were synthesized by Logan and Newbold in 1957,[12] and Ricca *et al.*[13] in 1983 *via* multistep sequences.



mycophenolic acid (**1**)

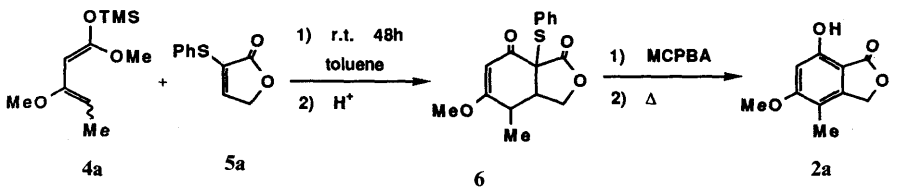
	R^1	R^2
2a	H	Me
2b	H	H
3a	Me	Me

Chart 1

Recently, we developed[14] convenient methods for the syntheses of 3-(phenylthio)-2(5*H*)-furanones and 3-(phenylthio)furans using 3-(phenylthio)propenal as a common starting compound and these methods were successfully applied to the syntheses of the *Quercus* lactones and a 2,5-diarylfuran natural product. To extend the utility of 3-(phenylthio)-2(5*H*)-furanones (**5**), we became interested in testing the Diels–Alder reactivity of **5** with silyloxydienes in order to prepare highly substituted phthalides, especially the key intermediates for mycophenolic acid.

The Diels–Alder reaction of 1,3-dimethoxy-1-trimethylsilyloxy-1,3-pentadiene (**4a**), readily prepared from methyl 3-methoxy-3-ethylacrylate by the standard method,[15] with 3-(phenylthio)-2(5*H*)-furanone (**5a**)[14,16] was initially examined (Chart 2). Treatment of 2.0 eq of **4a** with 1.0 eq of **5a** in dry toluene by stirring at room temperature gave, after standard work-up, the adduct (**6**) in 78% yield. Oxidation with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at 0 °C followed by heating gave **2a** in 75% yield (59% overall yield from **5a**). The structure of **2a** was confirmed by comparison of the melting point and spectroscopic data with those reported.[10,11]

To generalize this reaction, the phenylsulfinyl congeners were next examined as dienophiles. In general, electron-withdrawing groups such as phenylsulfinyl increase the Diels–Alder reactivity of the dienophiles. In addition, the phenylsulfinyl would act as a good leaving group in the resulting Diels–Alder adduct to lead the reaction directly to the desired phthalides in a one-pot procedure. To confirm this idea, the Diels–Alder reactions between silyloxydienes (**4a, b**) and various 3-(phenylsulfinyl)-2(5*H*)-furanones (**7a—e**) were carried out (Chart 3) and the results are summarized in Table I. In these cases, **7a—e** were prepared from the corresponding sulfides (**5**) using MCPBA[16] and, because of their thermal instability, were used without purification in the Diels–Alder reaction. A toluene solution of 1.0 eq of **7a**[16,17] and 2.0 eq of **4a** was stirred at 0 °C (2 h), then at room temperature (2 h), and finally heated at 100 °C



4a **5a** **6** **2a**

Chart 2

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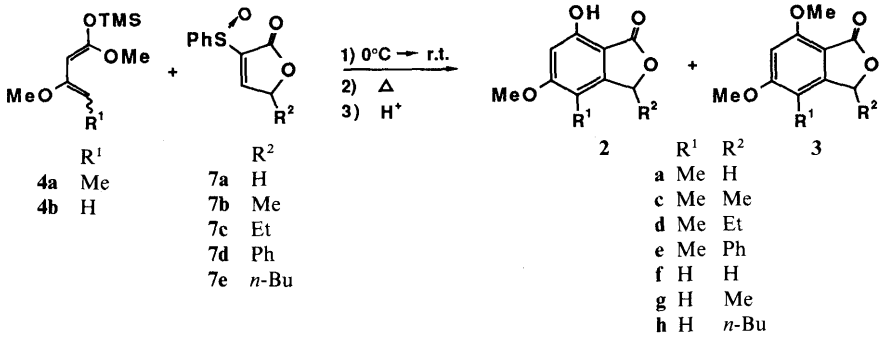

	R^1		R^2
4a	Me	**7a**	H
4b	H	**7b**	Me
		7c	Et
		7d	Ph
		7e	*n*-Bu

	R^1	R^2
a	Me	H
c	Me	Me
d	Me	Et
e	Me	Ph
f	H	H
g	H	Me
h	H	*n*-Bu

Chart 3

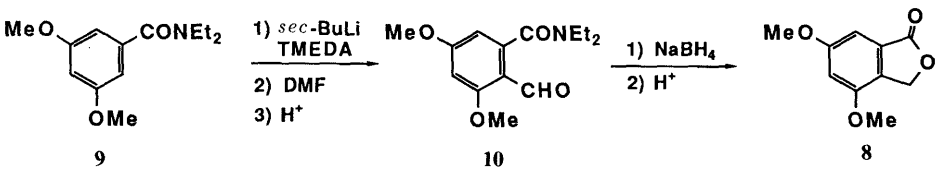

Chart 4

TABLE I. Synthesis of Phthalides (**2**, **3**)

Run	Diene (**4**)	Furanone (**7**)	Phthalide (**2**, **3**) **2**	Yield (%)	**3**	Yield (%)
1	**4a**	**7a**	**2a**	51	**3a**	16
2	**4a**	**7b**	**2c**	51	**3c**	21
3	**4a**	**7c**	**2d**	58	**3d**	33
4	**4a**	**7d**	**2e**	47	**3e**	24
5	**4b**	**7a**	**2f**	45	**3f**	16
6	**4b**	**7b**	**2g**	54	**3g**	18
7	**4b**	**7e**	**2h**	41	**3h**	21

(30 min) to give, after chromatography, **2a** (51%) and **3a** (16%).[11,12] Methylation of **2a** under standard conditions gave **3a** whose physical properties and spectral data were completely in accord with the reported values.[11,12] When 1.0 eq of **7a** was treated with 2.0 eq of 1,3-dimethoxy-1-trimethylsilyloxy-1,3-butadiene (**4b**)[15] under similar reaction conditions, 7-hydroxy-5-methoxyphthalide (**2f**)[10,18] and 5,7-dimethoxyphthalide (**3f**)[10,12,18] were produced in 45% and 16% yields, respectively. Similarly, highly substituted phthalides such as 3,4,5,7-tetrasubstituted phthalides (**2c—e** and **3c—e**) and 3,5,7-trisubstituted phthalides (**2g, h** and **3g, h**) were prepared by the reactions of **7** with **4a** and **4b**, respectively, in a one-pot process. In every case, 7-hydroxyphthalides (**2**) were obtained as major compounds. When triethylamine[19] instead of 10% HCl was employed for the aromatization of the intermediate in the reaction of **4a** with **7a**, the yields of **2a** and **3a** were decreased to 27% and 25%, respectively.

The structures of the synthesized phthalides (**2** and **3**) were established by infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR) and mass spectral (MS) methods. Compound **2a** was demethylated to **2b**[20] using BBr_3.[11] Synthetic **2b** was shown to be identical with an authentic sample[13] on the basis of melting point, and spectroscopic (^{1}H-NMR, IR, and ultraviolet (UV)) and thin layer chromatography (TLC) comparisons. In addition, we have synthesized the regioisomer of **3f**, 4,6-dimethoxyphthalide (**8**), using the directed lithiation strategy (Chart 4).[4] Thus, *N*,*N*-diethyl-3,5-dimethoxybenzamide (**9**) was sequentially *ortho*-lithiated (*sec*-BuLi–*N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA)–tetrahydrofuran (THF)/−78 °C) and treated with dimethylformamide (DMF). After acidic work-up, *N*,*N*-diethyl-2-formyl-3,5-dimethoxybenzamide (**10**) was obtained in 71% yield. Compound **10** was reduced to the corresponding hydroxymethyl compound, which was cyclized by heating in toluene under reflux in the presence of *p*-toluenesulfonic acid to give **8** in 44% overall yield. Characteristic differences between **3f** and **8** were observed in their ^{1}H-NMR spectra. Thus, the absorptions of aromatic protons for these compounds appeared at different chemical shifts (**3f**: δ 6.42 (1H, s) and δ 6.49 (1H, s), **8**: δ 6.67 (1H, d, J = 1.8 Hz) and δ 6.91 (1H, d, J = 1.8 Hz)). The low chemical shifts of aromatic protons of **8** are consistent with the proposed structure.

In conclusion, we have shown that 3-(phenylthio)- and 3-(phenylsulfinyl)-2(5*H*)-furanones (**5** and **7**) are highly reactive dienophiles in the Diels–Alder reaction with silyloxydienes. There have been several reports[3] on the use of 2(5*H*)-furanones as dienophiles, but, in general, high pressure, high temperature, and long reaction times are required for the Diels–Alder reaction. In contrast, the Diels–Alder reactions of **5** and **7** with silyloxydienes are regioselective, rapid, and clean to give, after thermal elimination of phenylsulfenic acid, highly substituted phthalides in moderate to good yields. The key intermediates (**2a, b, 3a**) in the synthesis of mycophenolic acid have been previously prepared in 8% (**2a**),[11] 6% (**2b**),[13] 17.5% (**3a**),[12] and 9.3% (**3a**)[11] overall yields. Our approach yields **2a** in 59% (Chart 2) and in 51% overall yields (Chart 3).

Experimental

All melting points are uncorrected. The IR spectra were obtained in KBr disk using a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% ethanol on a Hitachi 323 spectrophotometer. The ^{1}H-NMR spectra were obtained with JEOL FX 90Q, JEOL JNM-PMX 60, and Hitachi R-600 spectrometers using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference. The MS were determined on a JEOL JMX-DX 303 mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in

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Nagasaki University. All solvents used for lithiation reaction were freshly distilled from sodium benzophenone ketyl before use. Conventional column or flash column chromatography was carried out on Merck Kieselgel 60 (230—400 mesh).

1,3-Dimethoxy-1-trimethylsilyloxy-1,3-pentadiene (4a) A solution of methyl 3-methoxy-3-ethylacrylate (9.1 g, 63 mmol) in THF (10 ml) was added to a solution of lithium *N,N*-diisopropylamide (LDA) (72 mmol; prepared from a 1.25 M solution of *n*-BuLi in hexane, 57.6 ml, and *N,N*-diisopropylamine, 10 ml at 0 °C) in THF (50 ml) at −78 °C under a nitrogen atmosphere. After 15 min, chlorotrimethylsilane (11.4 ml, 90 mmol) was injected. The reaction mixture was allowed to warm to 0 °C, and concentrated *in vacuo*. The residue was treated with dry pentane (100 ml) to precipitate LiCl and filtered. After evaporation, the residue was distilled under high vacuum to give **4a** (9.8 g, 72%, bp 34—36 °C/0.2 mmHg). ^{1}H-NMR δ: 0.23 (9H, s), 1.63 (3H, d, J=6.8 Hz), 3.38 (3H, s), 3.54 (3H, s), 3.97 (1H, s), 4.83 (1H, q, J=6.8 Hz).

Diels–Alder Reaction of 3-(Phenylthio)-2(5*H*)-furanone (5a) with 4a A mixture of **5a** (0.38 g, 2.0 mmol) and **4a** (0.86 g, 4.0 mmol) in dry toluene (15 ml) was stirred for 48 h under a nitrogen atmosphere, and quenched with 10% HCl. The organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was chromatographed using dichloromethane as the eluent to give the adduct (**6**, 0.47 g, 78%). mp 181—182 °C (CH_2Cl_2–*n*-hexane). MS *m/z*: 304 (M^+). IR cm^{-1}: 1655 (C=O), 1790 (C=O). UV nm (log ε): 234 (3.95), 264 (4.19). ^{1}H-NMR δ: 1.12 and 1.52 (3H, d, J=7.0 Hz, ratio 4 : 1), 2.7—3.1 (2H, m), 3.75 and 3.77 (3H, s, ratio 4 : 1), 4.04 (1H, dd, J=8.8, 19.2 Hz), 4.24 (1H, dd, J=8.8, 7.8 Hz), 5.51 (1H, d, J=1.5 Hz), 7.26—7.45 (3H, m), 7.55—7.67 (2H, m). A solution of **6** (0.75 g, 2.5 mmol) in dichloromethane (20 ml) was treated with 70% MCPBA (0.67 g, 2.7 mmol) at 0 °C. After stirring for 1 h, the mixture was successively washed with 5% $NaHCO_3$ and brine. The dichloromethane solution was then refluxed for 1 h and evaporated to give a residue, which was purified by recrystallization (CH_2Cl_2) to give **2a** (0.37 g, 75%). mp 216—218 °C (ethyl acetate) (lit.[11] mp 216—218 °C). MS *m/z*: 194 (M^+). IR cm^{-1}: 1735 (C=O), 3450 (OH). UV nm (log ε): 218 (4.50), 259 (4.13), 297 (3.75). ^{1}H-NMR δ: 2.04 (3H, s), 3.86 (3H, s), 5.16 (2H, s), 6.38 (1H, s), 7.47 (1H, s). *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.81; H, 5.25.

Diels–Alder Reaction of 3-(Phenylsulfinyl)-2(5*H*)-furanones (7a—e) with Silyloxydienes (4a, b). General Procedure The 3-(phenylsulfinyl)-2(5*H*)-furanones (**7**) were prepared from **5** by MCPBA oxidation.[16] Without purification, the furanones (**7**) were used for the following Diels–Alder reaction. Under a nitrogen atmosphere, 3.0 mmol of the silyloxydiene (**4**) was added to a stirred solution of 1.5 mmol of the 3-(phenylsulfinyl)-2(5*H*)-furanone (**7**) in dry toluene (10 ml) at 0 °C. After stirring at 0 °C (2 h), at room temperature (2 h), and at 100 °C (30 min), the reaction mixture was quenched with 10% HCl solution and the organic layer was separated, washed successively with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a mixture of 7-hydroxyphthalides (**2**) and 7-methoxyphthalides (**3**), which were chromatographed on silica gel. In general, the 7-hydroxyphthalides (**2**) were eluted faster than 7-methoxyphthalides (**3**) with chloroform as the eluent. The yield of each compound is shown in Table I. The following phthalides were obtained in this manner. 7-Hydroxy-5-methoxy-4-methylphthalide (**2a**) was also obtained by this method.

5,7-Dimethoxy-4-methylphthalide (3a) mp 201—203 °C (CH_2Cl_2) (lit.[11] mp 202—203 °C; lit.[12] mp 202—203 °C). MS *m/z*: 208 (M^+). IR cm^{-1}: 1750 (C=O). UV nm (log ε): 224 (4.52), 261 (4.16), 298 (3.87). ^{1}H-NMR δ: 2.01 (3H, s), 3.92 (3H, s), 3.95 (3H, s), 5.03 (2H, s), 6.37 (1H, s). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.44; H, 5.82.

7-Hydroxy-5-methoxy-3,4-dimethylphthalide (2c) mp 118 °C (ether). MS *m/z*: 208 (M^+). IR cm^{-1}: 1715 (C=O), 3150 (OH). UV nm (log ε): 218 (4.51), 259 (4.13), 299 (3.81). ^{1}H-NMR δ: 1.62 (3H, d, J=6.0 Hz), 2.04 (3H, s), 3.83 (3H, s), 5.50 (3H, q, J=6.0 Hz), 6.32 (1H, s), 7.28 (1H, br s). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.42; H, 5.85.

5,7-Dimethoxy-3,4-dimethylphthalide (3c) mp 143—145 °C (acetone). MS *m/z*: 222 (M^+). IR cm^{-1}: 1740 (C=O). UV nm (log ε): 224 (4.48), 260 (4.15), 299 (3.89). ^{1}H-NMR δ: 1.56 (3H, d, J=6.6 Hz), 2.07 (3H, s), 3.40 (1H, q, J=6.6 Hz), 3.93 (3H, s), 3.96 (3H, s), 6.37 (1H, s). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.89; H, 6.35. Found: C, 64.72; H, 6.37.

3-Ethyl-7-hydroxy-5-methoxy-4-methylphthalide (2d) mp 142—143 °C (CH_2Cl_2). MS *m/z*: 222 (M^+). IR cm^{-1}: 1710 (C=O), 3220 (OH). UV nm (log ε): 218 (4.49), 259 (4.12), 299 (3.80). ^{1}H-NMR δ: 0.92 (3H, t, J=7.3 Hz), 1.60—2.01 (2H, m), 2.07 (3H, s), 3.87 (3H, s), 5.45 (1H, dd, J=7.0, 7.1 Hz), 6.41 (1H, s). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.64; H, 6.32.

3-Ethyl-5,7-dimethoxy-4-methylphthalide (3d) mp 91—91.5 °C (ether–*n*-hexane). MS *m/z*: 236 (M^+). IR cm^{-1}: 1740 (C=O). UV nm (log ε): 224 (4.50), 261 (4.17), 299 (3.92). ^{1}H-NMR δ: 0.89 (3H, t, J=7.3 Hz), 1.42—1.88 (2H, m), 2.08 (3H, s), 3.93 (3H, s), 3.98 (3H, s), 5.34 (1H, dd, J=6.8, 6.9 Hz), 6.41 (1H, s). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.88; H, 6.83.

7-Hydroxy-5-methoxy-4-methyl-3-phenylphthalide (2e) mp 186—188 °C (CH_2Cl_2). MS *m/z*: 270 (M^+). IR cm^{-1}: 1750 (C=O), 3450 (OH). UV nm (log ε): 219 (4.55), 260 (4.10), 301 (3.82). ^{1}H-NMR δ: 1.72 (3H, s), 3.82 (3H, s), 6.24 (1H, s), 6.44 (1H, s), 7.22—7.35 (5H, m), 7.70 (1H, br s). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.84; H, 5.61.

5,7-Dimethoxy-4-methyl-3-phenylphthalide (3e) mp 196—197 °C (CH_2Cl_2–*n*-hexane). MS *m/z*: 284 (M^+). IR cm^{-1}: 1740 (C=O). UV nm (log ε): 218 (4.55), 262 (4.16), 300 (3.96). ^{1}H-NMR δ: 1.73 (3H, s), 3.90 (3H, s), 4.00 (3H, s), 6.16 (1H, s), 6.47 (1H, s), 7.17—7.40 (5H, m). *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.75; H, 5.76.

7-Hydroxy-5-methoxyphthalide (2f) mp 184—186 °C (MeOH) (lit.[10] mp 183—184 °C; lit.[18] mp 186—188 °C). MS *m/z*: 180 (M^+). IR cm^{-1}: 1740 (C=O), 3260 (OH). UV nm (log ε): 217 (4.54), 256 (4.17), 293 (3.65). ^{1}H-NMR δ: 3.85 (3H, s), 5.24 (2H, s), 6.45 (2H, s), 7.61 (1H, s). *Anal.* Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.70; H, 4.63.

5,7-Dimethoxyphthalide (3f) mp 152—153 °C (MeOH). (lit.[12] mp 151—153 °C; lit.[10] mp 152 °C; lit.[18] mp 151—153 °C). MS *m/z*: 194 (M^+). IR cm^{-1}: 1755 (C=O). UV nm (log ε): 216 (4.52), 257 (4.19), 291 (3.70). ^{1}H-NMR δ: 3.87 (3H, s), 3.93 (3H, s), 5.13 (2H, s), 6.39 (1H, s), 6.42 (1H, s). *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.66; H, 5.15.

7-Hydroxy-5-methoxy-3-methylphthalide (2g) mp 109—110 °C (ether). MS *m/z*: 194 (M^+). IR cm^{-1}: 1740 (C=O), 3200 (OH). UV nm (log ε): 218 (4.57), 257 (4.18), 293 (3.67). ^{1}H-NMR δ: 1.63 (3H, d, J=6.6 Hz), 3.86 (3H, s), 5.48 (1H, q, J=6.6 Hz), 6.43 (2H, s), 7.75 (1H, br s). *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.82; H, 5.23.

5,7-Dimethoxy-3-methylphthalide (3g) mp 94—95 °C (CH_2Cl_2–*n*-hexane). MS *m/z*: 208 (M^+). IR cm^{-1}: 1740 (C=O). UV nm (log ε): 217 (4.56), 257 (4.20), 291 (3.74). ^{1}H-NMR δ: 1.58 (3H, d, J=7.0 Hz), 3.87 (3H, s), 3.94 (3H, s), 5.34 (1H, q, J=7.0 Hz), 6.38 (2H, s). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.26; H, 5.83.

7-Hydroxy-5-methoxy-3-butylphthalide (2h) mp 83—84 °C (ether–*n*-hexane). MS *m/z*: 236 (M^+). IR cm^{-1}: 1720 (C=O), 3240 (OH). UV nm (log ε): 218 (4.57), 257 (4.19), 293 (3.71). ^{1}H-NMR δ: 0.91—2.15 (9H, m), 3.86 (3H, s), 5.40 (1H, dd, J=7.3, 4.4 Hz), 6.42 (2H, s), 7.72 (1H, br s). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.86; H, 6.82.

5,7-Dimethoxy-3-butylphthalide (3h) Oil. MS *m/z*: 250 (M^+). IR cm^{-1}: 1750 (C=O). UV nm (log ε): 217 (4.50), 258 (4.16), 291 (3.69). ^{1}H-NMR δ: 0.90—2.08 (9H, m), 3.89 (3H, s), 3.95 (3H, s), 5.29 (1H, dd, J=4.0, 7.3 Hz), 6.40 (1H, s), 6.41 (1H, s). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.68; H, 7.15.

5,7-Dihydroxy-4-methylphthalide (2b) A solution of **2a** (0.12 g) and BBr_3 (0.2 ml) in CH_2Cl_2 (15 ml) was stirred at room temperature for 8 d. After standard work-up,[11] **2b** was obtained in 80% yield. mp 249—250 °C (ethyl acetate) (lit.[11] mp 252—254 °C; lit.[13] mp 240 °C; lit.[20] mp 242 °C). MS *m/z*: 180 (M^+). IR (Nujol) cm^{-1}: 1625 (C=O). ^{1}H-NMR δ: 2.04 (3H, s), 5.16 (2H, s), 6.34 (1H, s).

4,6-Dimethoxyphthalide (8) A solution of *sec*-BuLi (8.1 ml, 7 mmol) was slowly injected into a stirred solution of *N,N*-diethyl-3,5-dimethoxybenzamide (1.2 g, 5 mmol) and TMEDA (1 ml, 7 mmol) in THF (50 ml) at −78 °C under a nitrogen atmosphere. After stirring of this mixture for 1 h, a solution of DMF (0.6 ml, 8 mmol) in THF (5 ml) was injected. After 1 h, the dry ice–acetone bath was removed and the solution was stirred overnight. The reaction mixture was quenched with 10% HCl, and evaporated under reduced pressure. The residue was extracted with ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated to give *N,N*-diethyl-2-formyl-3,5-dimethoxybenzamide (**10**, 0.91 g, 71%). mp 114—116 °C (CH_2Cl_2–*n*-hexane). MS *m/z*: 265 (M^+). IR cm^{-1}: 1630 (C=O), 1670 (C=O). UV nm (log ε): 237 (4.23), 280 (4.03), 319 (3.99). ^{1}H-NMR δ: 1.03 (3H, t, J=7.0 Hz), 1.33 (3H, t, J=7.0 Hz), 3.06 (2H, q, J=7.0 Hz), 3.56 (2H, q, J=7.0 Hz), 3.87 (3H, s), 3.94 (3H, s), 6.37 (1H, s), 6.44 (1H, s), 10.33 (1H, s). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.02; H, 7.08; N, 5.29.

An EtOH (20 ml) solution of **10** (0.26 g, 1 mmol) and $NaBH_4$ (0.05 g, 1.3 mmol) was stirred at 0 °C for 2 h. The mixture was quenched with 10% HCl, and concentrated. The residue was extracted with dichloromethane and the extract was dried over Na_2SO_4 and evaporated to give an oily residue. A solution of this material and *p*-toluenesulfonic acid (0.5 g) in dry toluene (60 ml) was refluxed for 8 h. The reaction mixture was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated. The residual

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oil was dissolved in ether and the mixture was left overnight. The precipitate was collected by filtration to give 4,6-dimethoxyphthalide (0.12 g, 62%). An analytical sample was obtained by recrystallization from CH_2Cl_2–*n*-hexane as colorless needles, mp 167—168 °C. MS *m/z*: 194 (M^+). IR cm^{-1}: 1755 (C=O). UV nm (log ε): 219 (sh) (4.40), 250 (3.66), 307 (3.59). ^{1}H-NMR δ: 3.86 (3H, s), 3.87 (3H, s), 5.19 (2H, s), 6.67 (1H, d, J=1.8 Hz), 6.91 (1H, d, J=1.8 Hz). *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.73; H, 5.20.

Acknowledgement We are grateful to Dr. A. Ricca, Politecnico di Milano, for providing an authentic sample of 5,7-dihydroxy-4-methylphthalide. We are indebted to the staff of the Center for Instrumental Analysis in Nagasaki University for IR, UV, MS, and NMR measurements and elemental analysis.

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