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Syntheses of Mycophenolic Acid and Its Analogs by Palladium Methodology

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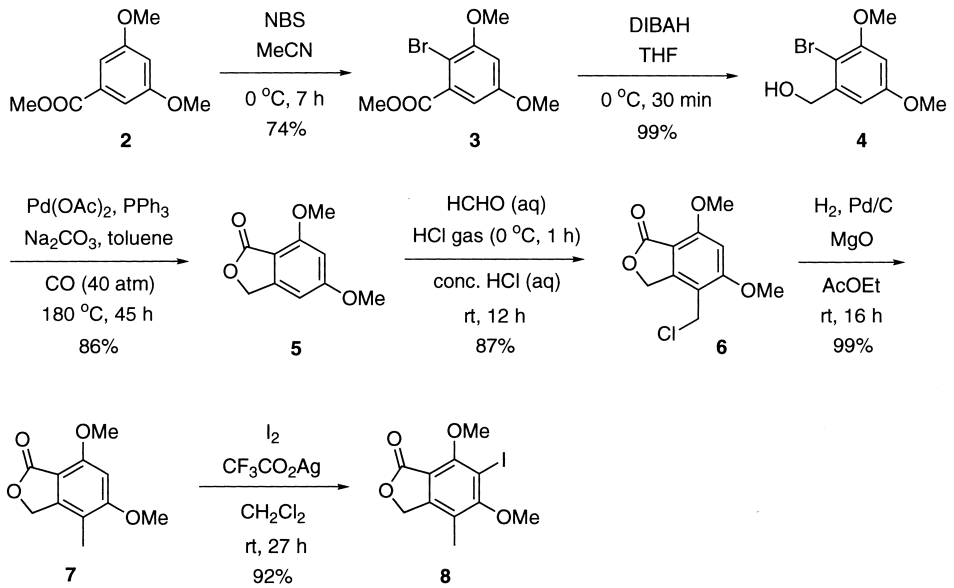
Syntheses of mycophenolic acid (MPA, **1**) and its analogs were carried out using palladium-catalyzed Heck carbonylation and olefination. Thus, the reaction of 2-bromo-3,5-dimethoxybenzyl alcohol (**4**) in toluene under carbon monoxide at 180 °C in the presence of palladium catalyst using sodium carbonate as a base gave 5,7-dimethoxyphthalide (**5**) in 88% yield. The phthalide **7** was converted to 6-iodo-5,7-dimethoxy-4-methylphthalide (**8**). Reaction of aromatic iodide **8** with isoprene and dimethyl malonate in the presence of palladium(0) catalyst gave the three component coupling product **9**, which was converted into **1** in three steps. 4-NorMPA (**16**) and 4-homoMPA (**22**) were synthesized similarly.

Mycophenolic acid (MPA, **1**) is produced by the fermentation of a number of penicillium species.[1] Recently this compound and its analogs have been found to possess several significant biological activities, such as antineoplastic, antiparastic, antiviral, and immunosuppressive activities.[2] The synthesis of **1** was first reported by Birch,[3] and later several other methods were reported. The most common and practical synthetic strategy toward MPA is preparation of the phthalide **7** as the key intermediate and subsequent introduction of an isoprenoid side chain. So far, several examples which follow this strategy have appeared in the literature.[4] However, the known methods both for preparing the phthalide **7** and for introducing the hexenoic acid side chain at C-6 position of **7** are somewhat tedious, and more simple methods have been sought for practical synthesis. We have developed a convenient synthetic method of MPA involving simple preparation of the phthalide and introduction of isoprenoid side chain using palladium catalysts.

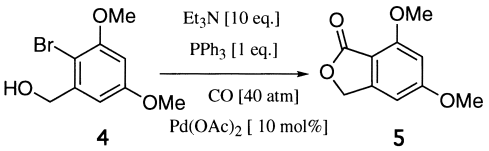
Results and Discussion

Synthesis of Phthalides by Palladium Catalyzed Carbonylation. 3,5-Dihydroxybenzoic acid is considered to be a suitable starting material for the phthalide synthesis. The first problem is how to construct the phthalide skeleton from the benzoic acid. Among various known synthetic methods for phthalides,[5] catalytic carbonylation of aryl halides is supposed to provide the most efficient method, especially for a large-scale preparation. So far, several examples of phthalide synthesis from *o*-halobenzyl alcohols by palladium-catalyzed carbonylation have been reported.[6,7] Although *o*-iodobenzyl alco-



Scheme 1. Synthesis of an intermediate of mycophenolic acid (**1**).

Table 1. Effect of Solvent in Carbonylation



4 5

Entry	Solvent	Temp/°C	Time/h	Yield/%
1	DMF	120	20	47
2	toluene	120	20	20
3	DMF	160	20	57
4	toluene	160	20	73
5	toluene	180	20	84
6[a)]	toluene	180	45	86

a) Na_2CO_3 was used instead of Et_3N.

hols can be carbonylated easily at atmospheric pressure of carbon monoxide, the corresponding reaction with the bromo derivatives did not give satisfactory results.[6] From the practical point of view, carbonylation of bromo derivatives rather than those of iodide are preferable from the economical reason. In the course of our synthetic study for biologically active phthalides and their derivatives, we have found the possibility to apply the palladium-catalyzed carbonylation of the *o*-bromobenzyl alcohol (**4**) to the phthalide **5**.

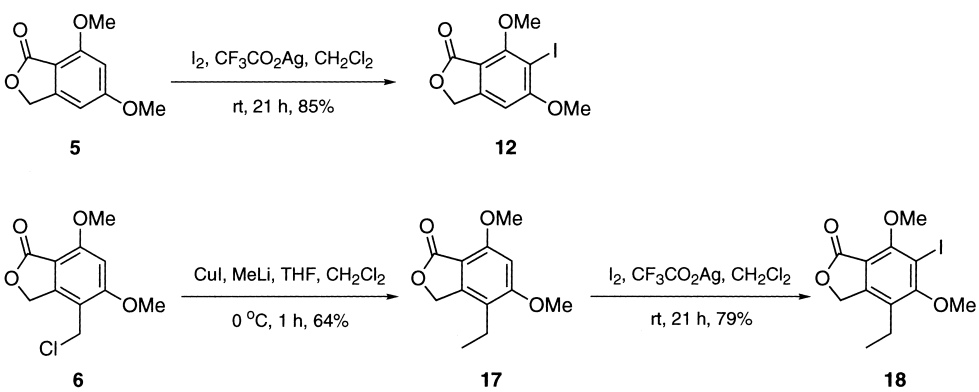
Methyl 3,5-dimethoxybenzoate (**2**) was prepared in a quantitative yield from commercially available 3,5-dihydroxybenzoic acid by esterification with trimethyl orthoacetate and subsequent O-methylation with dimethyl carbonate.[8] Bromination of **2** with *N*-bromosuccinimide (NBS) in acetonitrile at 0 °C gave the bromo ester **3** in 74% yield (Scheme 1). When excess NBS was used at room temperature, dibromination proceeded to give a 2,6-dibrominated compound as a major product. Reduction of the ester **3** was carried out using $LiAlH_4$ in THF at 0 °C to give the alcohol **4** quantitatively. However, it is expected that the use of a large amount of insoluble $LiAlH_4$ powder would cause handling problems in the case of a large-scale synthesis, which urges us to search for other more convenient reducing agents. When the $NaAlH_2(OCH_2OMe)_3$ (SAH) was used as a reducing agent, reductive removal of bromine atom from the aryl bromide took place to afford 3,5-dimethoxybenzyl alcohol in a considerable yield. Eventually the reduction of the bromo ester **3** to 2-bromo-3,5-dimethoxybenzyl alcohol (**4**) was carried out with DIBAH in 86–99% yield.

Carbonylation of **4** to the phthalide **5** may be useful for industrial scale preparations and was examined using palladium catalysts under various reaction conditions. The results are summarized in Table 1. No carbonylation reaction proceeded at 60 °C, a higher temperature was necessary for smooth reaction. The reaction proceeded slowly at 120 °C and satisfactory results were obtained at 160 °C. The reaction proceeded at this temperature with triphenylphosphine as a ligand of palladium catalyst, but tributylphosphine did not give good results. DMF is a better solvent than toluene at 120 °C, but did not give good results at 180 °C probably because DMF decomposed at this temperature to cause poisoning of the catalyst. On the contrary, the reactions in toluene gave good results at 180 °C (Entries 5 and 6).

3,5-Dimethoxyphthalide (**5**) can be converted to the known intermediate of MPA (**1**) in three steps. Thus, the reaction of **5** in aqueous formaldehyde with hydrochloric acid gave a mixture of the chloromethyl compound **6** (87%) and a small amount of 4-hydroxymethyl compound as a by-product. Hydrogenolysis of the chloride **6** using Pd/C catalyst with MgO in ethyl acetate at room temperature gave the 4-methylphthalide **7** in 99% yield. Iodination of the 4-methylphthalide **7** with I_2 in the presence of silver trifluoroacetate in CH_2Cl_2 at room temperature for 16 h gave the iodide **8** in 95% yield.

For the study of the structure-activity relationships of **1** we prepared some other iodide, **12** for an intermediate of 4-normycophenolic acid (**16**) without the methyl group and **18** for 4-homomycophenolic acid (**22**), an ethyl derivative at C-4 position, respectively. Thus, iodination of **5** gave **12** in 85% yield. Reaction of **6** with Me_2CuLi gave the ethyl derivative **17**, which was subjected to the iodination to give **18** in 79% yield (Scheme 2).

Synthesis of Mycophenolic Acid by Palladium-Catalyzed Three Component Coupling Reaction. Not only MPA but also a lot of natural phenols having isoprenoid side chains are known. These compounds have various kinds of important biological activities. The introduction of isoprenoid side chains at α-position of phenols or their protecting forms is an important synthetic problem. We focused on the palladium-catalyzed three component coupling reaction, consisting of aromatic halides, 1,3-dienes, and nulceophiles developed by Heck[9] as shown in Scheme 3. Reaction of **8**, isoprene, and



Scheme 2. Syntheses of an intermediates of 4-NorMPA (**16**) and 4-HomoMPA (**22**).

Table 2. Palladium-Catalyzed Reaction of Iodide **8**, Isoprene, and Dimethyl Malonate (DM)

Entry	Solvent	Base/eq	Temp/°C	Time/h	**9**/%
1	DMF	$NaHCO_3$ (3)	100	4	26
2	dioxane	$NaHCO_3$(3)	100	4	27
3	DM	$NaHCO_3$ (3)	100	4	78
4	DMSO	$NaHCO_3$ (3)	100	4	85[a)]
5	DMSO	$NaHCO_3$ (3)	80	24	76[b)]
6	DMSO	NaOAc (3)	80	4	trace[c)]
7	DMSO	Et_3N (3)	80	4	0[d)]
8	DMSO	K_2CO_3 (5.2)	80	4	0[e)]
9	DMSO	NaH (3)	80	4	22[f)]

a) E/Z = 82/18. b) E/Z = 84/16. c),d) **5** was obtained as a main product. e) Phthalide **7** was obtained in 90% yield. f) Phthalide **7** was obtained as a main product (55%). $[Pd_2(dba)_3CHCl_3]$ (5 mol%) and *n*-Bu_4NCl (1.1eq) were used in all entries.

dimethyl malonate was carried out under various conditions. The results are summarized in Table 2. Among various solvents investigated, the best result was obtained when the reaction was carried out in DMSO at 100 °C to give **9** in 85% as an 82:18 mixture of *E*:*Z* isomers. A small amount of the diene **iii** was also formed as a by-product. The choice of base is important for the three component coupling, thus, $NaHCO_3$ was found to be a suitable base whereas Et_3N, K_2CO_3, and NaH did not give the satisfactory results.

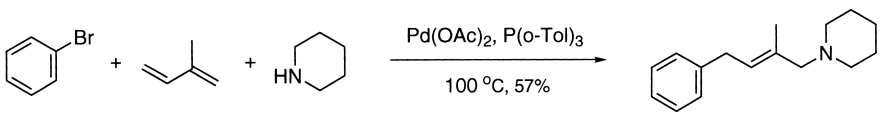
The reaction is explained as shown in Scheme 4. Oxidative addition of the aryl iodide **8** to Pd(0) species gives the aryl palladium complex **i**, which reacts with isoprene to give the π-allylpalladium intermediate **ii** by an insertion reaction at the less hindered double bond of isoprene. Nucleophilic attack of the malonate anion at the terminal carbon of the η^3-allylpalladium intermediate **ii** gives the three components coupling product **9**, and the palladium(0) species is regenerated to carry on the catalytic cycle. When β-elimination reaction from the η^3-allylpalladium intermediate takes place prior to the expected nucleophilic reaction, the undesired diene **iii** is formed.

The coupling product **9** was converted to **1** in three steps. Thus, the removal of one of the ester groups in **9** to give **10** (49%), hydrolysis of the remaining ester of **10** to form **11**(88%), and selective deprotection of one of the methyl groups in **11** gave **1** (70%). Similarly 4-norMPA and 4-homoMPA were synthesized as *E*/*Z* mixtures from the iodides **12** and **18**, respectively (Scheme 5).

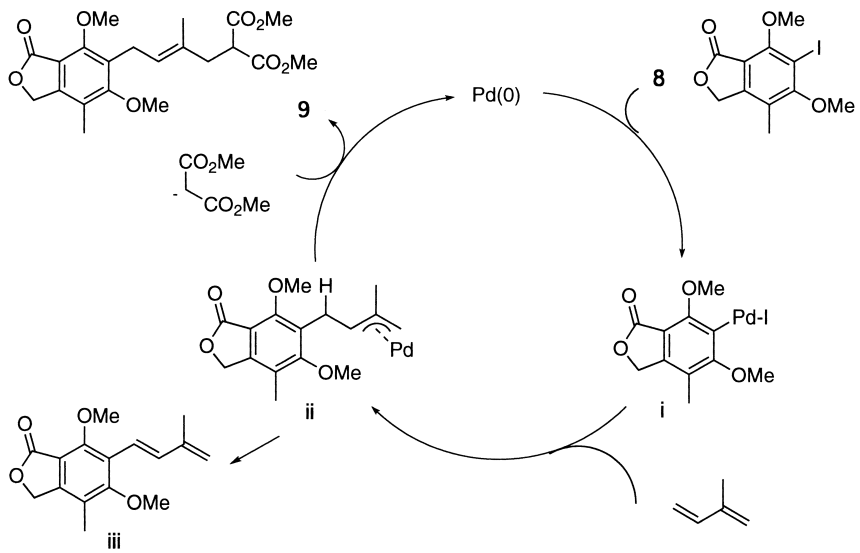
In conclusion, we have prepared the phthalide **5** as a key intermediate of mycophenolic acid and their derivatives from the bromide **4** by the palladium catalyzed carbonylation. Synthesis of mycophenolic acid (**1**) can be achieved using the palladium-catalyzed three component coupling reaction. This method provides a useful means for syntheses of not only mycophenolic acid but also of other related isoprenoid substituted aromatic compounds.

Experimental

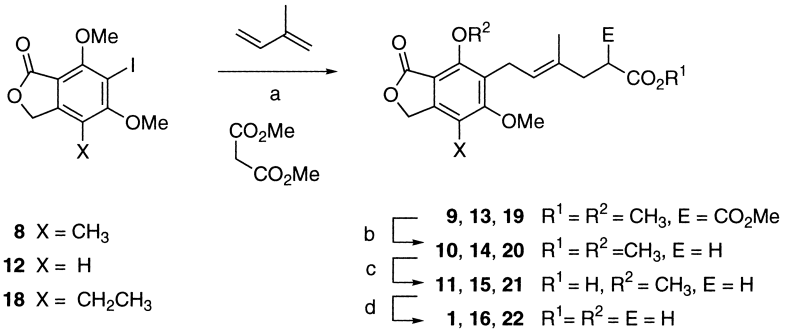
Methyl 2-Bromo-3,5-dimethoxybenzoate (3). *N*-Bromosuccinimide (6.29 g, 35.2 mmol) was added to a solution of **2** (6.92 g, 35.2 mmol) in acetonitrile (53 mL) in one portion at 0 °C; then the mixture was stirred at 0 °C for 7 h. Saturated Na_2SO_3 solution was added to the mixture, and the resulting mixture was extracted with ether. The combined organic layers were washed



Scheme 3. Palladium-catalyzed three component coupling reaction by Heck et al.[9]



Scheme 4. A plausible reaction mechanism of **9** from **8.**



a) $[Pd_2(dba)_3CHCl_3]$ (5 mol%), $NaHCO_3$, n-Bu_4NCl, DMSO, 100 °C, 4 h, **9** = 85%, **13** = 93 %, **19** = 67%
b) NaCl, H_2O, DMSO, **10** = 150 °C, 3 h, 49%, **14** = 140 °C, 3 h, 62%, **20** = 140 °C, 3 h, 42%
c) LiOH, MeOH, H_2O, rt, **11** = 40 h, 88% , **15** = 25 h, 71%, **21** = 31 h, 91%
d) Mg, I_2, Et_2O, Benzene, Pyridine, 90 °C, **1** = 6 h, 70%, **16** = 4 h, 55%, **22** = BCl_3, CH_2Cl_2, rt,1 week, 19%

Scheme 5. Syntheses of MPA (**1**), 4-NorMPA (**16**), and 4-HomoMPA (**22**).

with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 2/8) to give **3** (7.14 g, 74%). mp 55–57 °C, ^{1}H NMR (400 MHz) δ 6.68 (d, 1H, J = 2.9 Hz), 6.46 (d, 1H, J = 2.9 Hz), 3.82 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz) δ 166.8, 159.3, 156.8, 134.5, 105.9, 101.5, 56.2, 55.4, 52.2; IR (cm^{-1}) 1729; MS *m/z* (M^+) 277.

2-Bromo-3,5-dimethoxbenzyl Alcohol (4). To a solution of **3** (0.275 g, 1 mmol) in THF (12 mL) at 0 °C was added dropwise a solution of DIBAH (2.69 mL, 2.5 mmol, 0.93 M in hexane). This mixture was stirred for 30 min. To the reaction mixture was added 1 M potassium tartarate in water (5.3 mL); the resulting mixture was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 3/7)to give **4** (0.246 g, 99%). mp 94–95.2 °C, ^{1}H NMR (400 MHz) δ 6.69 (d, 1H, J = 2.6 Hz), 6.42 (d, 1H, J = 2.6 Hz), 4.71 (d, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 2.23 (t, 1H); ^{13}C NMR (100 MHz) δ 159.9, 156.4, 141.6, 104.6, 102.1, 98.8, 65.2, 56.2, 55.5; IR (cm^{-1}) 3018; MS *m/z* (M^+) 246.

A larger scale preparation was carried out similarly starting with **3** (6.92 g, 25.1 mmol) to give **4** (5.37 g, 86% yield).

Palladium-Catalyzed Synthesis of 5,7-Dimethoxyphthalide (5). A mixture of **4** (3.89 g, 15.6 mmol), Na_2CO_3 (2.48 g, 23.4 mmol), $Pd(OAc)_2$ (0.35 g, 1.56 mmol), and PPh_3 (4.08 g, 15.6 mmol) in dry toluene (50 mL) was heated at 180 °C while stirring in an autoclave under carbon monoxide (40 atm) for 45 h. The reaction mixture was filtered on celite with CH_2Cl_2; then the filtrate was concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 3/7) to give **5** (2.60 g, 86%); mp 148–149.2 °C (Ref. 3. mp 151–153 °C), ^{1}H NMR (400 MHz) δ 6.45 (s, 1H), 6.40 (s, 1H), 5.15 (s, 2H), 3.93 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz) δ 168.7, 166.6, 159.5, 151.5, 106.5, 98.7, 97.5, 68.5, 55.98, 55.93; IR (KBr, cm^{-1}) 1749; MS *m/z* (M^+) 194.

4-Chloromethyl-5,7-dimethoxyphthalide (6). The phthalide **5** (1 g, 5.15 mmol) was suspended in hydrochloric acid (2 mL) and aqueous formaldehyde (35 wt%, 1.2 mL), and the mixture was treated with dry hydrogen chloride at 0 °C for 1 h. The mixture was stirred for an additional 12 h at rt; then the mixture was treated with water and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a silica-gel column to give the chloride **6** (1.09 g, 87%). ^{1}H NMR (400 MHz) δ 6.41 (s, 1H), 5.23 (s, 2H), 4.55 (s, 2H), 3.98 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (100 MHz) δ 168.5, 163.5, 160.2, 150.3, 111.5, 105.9, 94.7, 67.3, 56.5, 56.2, 36.3, MS *m/z* (M^+) 242.

5,7-Dimethoxy-4-methylphthalide (7). A solution of **6** (1.09 g, 4.47 mmol) in dry ethyl acetate (270 mL) was stirred vigorously in the presence of palladium–carbon (10% of palladium on charcoal, 0.055 g) and magnesium oxide (2.18 g) under hydrogen (a pressure of balloon) at rt for 16 h. The reaction mixture was filtered and concentrated in vacuo. The residue was chromatographed on a silica-gel column to give **7** (0.925 g, 99%). ^{1}H NMR (90 MHz) δ 6.38 (s, 1H), 5.04 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz) δ 169.2, 163.4, 157.9, 148.4, 111.3, 104.7, 94.2, 67.8, 55.97, 55.89, 10.33; IR (KBr, cm^{-1}) 1738; MS *m/z* (M^+) 208; mp 200.9–202.7 °C (Ref. 4 mp 202–203 °C; Ref. 5 mp 201–203 °C).

6-Iodo-5,7-dimethoxy-4-methylphthalide (8). To a mixture of **7** (1.37 g, 6.58 mmol) and CF_3CO_2Ag (1.74 g, 7.89 mmol) in CH_2Cl_2 (20 mL) was added slowly I_2 (2.00 g, 7.89 mmol) dissolved in CH_2Cl_2 (10 mL) at rt over 30 min. The reaction mixture was stirred at rt for 27 h and then was filtered. To the filtrate was added 1 M NaOH (aq) and $Na_2S_2O_3$ (aq). The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 3/7) to give **8** (2.02 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.068 (s, 2H), 3.996 (s, 3H), 3.77 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.31, 163.57, 157.77, 149.41, 121.16, 113.14, 91.3, 68.2, 62.5, 60.6, 12.0; IR (neat, cm^{-1}) 1762; MS *m/z* (M^+) 334.

Synthesis of 5,7-Dimethoxy-6-[5,5-bis(methoxycarbonyl)-3-methyl-2-pentenyl]-4-methylphthalide (9) By the palladium-catalyzed three-component coupling reaction. A typical experimental procedure for Table 2 is as follows. A mixture of 8 (98 mg, 0.29 mmol), isoprene (0.09 mL, 0.879 mmol), dimethyl malonate (0.17 mL, 1.46 mmol), $NaHCO_3$ (75.4 mg, 0.879 mmol), $[Pd_2(dba)_3CHCl_3]$ (15.4 mg, 0.051 mmol), and *n*-Bu_4NCl (91.6 mg, 0.33 mmol) in DMSO (1 mL) was stirred at 100 °C for 4 h in a PYREX tube. The reaction mixture was quenched with NH_4Cl(aq). The organic layer was extracted with Et_2O, dried over

$MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 2/8) to give 9 (108 mg, 85%). E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (t, 1 H, J = 6.8 Hz), 5.14 (s, 2 H), 4.04 (s, 3 H), 3.76 (s, 3 H), 3.65 (s, 6 H), 3.56 (t, 1 H, J=7.8 Hz), 3.38 (d, 2 H, J = 7.0 Hz), 2.59 (d, 2 H, J = 7.9 Hz), 2.18 (s, 3 H), 1.80 (s, 2.4 H, E isomer). The ratio of *E*:*Z* isomers was calculated from olefinic protons. *Z* isomer δ 4.84 (t, olefinic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.69, 162.5, 156.5, 146.6, 131.09, 128.3, 125.7, 119.8, 112.3, 68.2, 62.5, 60.9, 52.3, 50.4, 38.4, 23.4, 15.9, 11.5. No signals of Z isomer could be recognized; IR (neat, cm^{-1}) 1758; MS *m*/*z* (M^+) 406.

5,7-Dimethoxy-6-(5-methoxycarbonyl-3-methyl-2-pentenyl)-4-methylphthalide (10). A mixture of **9** (50 mg, 0.123 mmol) and NaCl (14.4 mg, 0.246 mmol) in H_2O/DMSO (5.3 mg, 0.246 mmol/0.14 mL) was stirred at 150 °C for 3 h. To the mixture was added water. The organic layer was extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 2/8) to give **10** (22.1 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, 1 H, J = 6.6 Hz), 5.06 (s, 2 H), 3.97 (s, 3 H), 3.69 (s, 3 H), 3.54 (s, 3 H), 3.33 (d, 2 H, J = 6.8 Hz), 2.34 (t, 2 H, J = 6.8 Hz), 2.24 (m, 2 H), 2.11 (s, 3 H), 1.73 (s, 2.4 H, E isomer); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.7, 168.9, 162.7, 156.8, 146.7, 133.8, 128.9, 123.6, 119.9, 112.5, 68.3, 62.6, 61.0, 51.4, 34.6, 32.8, 23.4, 16.1, 11.5; MS *m*/*z* (M^+) 348.

6-(5-Carboxy-3-methyl-2-pentenyl)-5,7-dimethoxy-4-methylphthalide (11). A mixture of **10** (0.223 g, 0.641 mmol) and LiOH (38 mg, 1.60 mmol) in water/MeOH (0.5 mL/3 mL) was stirred at rt for 40 h. To the mixture was added 1 M HCl and the resulting mixture was stirred for 30 min. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 1/1) to give **11** (0.186 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, 1 H, J = 4.9 Hz), 5.06 (s, 2 H), 4.03 (s, 3 H), 3.96 (s, 3 H), 3.68 (s, 3 H), 3.33 (d, 2 H, J = 6.9 Hz), 2.36 (t, 2 H, J = 7.6 Hz), 2.24 (m, 2 H), 2.10 (s, 3 H), 1.73 (s, 2.4 H, *E* isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 168.8, 162.6, 156.6, 146.6, 133.4, 128.8, 123.7, 119.9, 112.5, 68.3, 62.7, 61.0, 34.2, 32.8, 23.4, 16.2, 11.5.

Mycophenolic Acid (1). To a mixture of Mg (145 mg, 5.98 mmol) and I_2 (0.759 g, 2.99 mmol) were added Et_2O (0.5 mL) and benzene (1 mL). After the resulting mixture was stirred at rt for 30 min, benzene (20 mL), pyridine (0.13 mL, 1.50 mmol) and **11** (0.5 g, 1.50 mmol) were added to the mixture. The reaction mixture was stirred at 90 °C for 6 h. To the resulting mixture was added 1 M HCl. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The residual solid was recrystallized from CH_2Cl_2 to give **1** (76.4 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (brs, 1 H), 5.25 (t, 1 H, J = 6.8 Hz), 5.19 (s, 2 H), 3.75 (s, 3 H), 3.39 (d, 2 H, J = 7.1 Hz), 2.44 (t, 2 H, J = 8.4 Hz), 2.31 (t, 2 H, J = 7.1 Hz), 2.14 (s, 3 H), 1.80 (s, 2.4 H, *E* isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 172.8, 163.5, 153.5, 143.9, 133.8, 122.8, 122.1, 116.6, 106.3, 70.0, 61.0, 34.2, 32.7, 22.6, 16.2, 11.6; IR (neat, cm^{-1}) 3433, 2939.5, 1732.7; MS *m*/*z* (M^+) 320.

6-Iodo-5,7-dimethoxyphthalide (12). To a mixture of **5** (194 mg, 1 mmol) and CF_3CO_2Ag (0.332 g, 1.5 mmol) in CH_2Cl_2 (20 mL) was added slowly I_2 (0.381 g, 1.5 mmol) dissolved in CH_2Cl_2 (10 mL) at rt over 30 min. The reaction mixture was stirred at rt for 21 h and then was filtered. To the filtrate was added 1 M NaOH (aq) and $Na_2S_2O_3$ (aq). The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOA/hexane = 3/7) to give **12** (271 mg, 85%). ^{1}H NMR (300 MHz) δ 6.38 (s, 1H), 4.96 (d, 2H), 4.00 (s, 3H), 3.99 (s, 3H); IR (cm^{-1}) 1744.

5,7-Dimethoxy-6-[5,5-bis(methoxycarbonyl)-3-methyl-2-pentenyl]phthalide (13). A mixture of **12** (300 mg, 0.94 mmol), isoprene (0.84 mL, 2.8 mmol), dimethyl malonate (0.536 mL, 4.7 mmol), $NaHCO_3$ (325.2 mg, 2.8 mmol), $[Pd_2(dba)_3CHCl_3]$ (48.9 mg, 0.047mmol), and *n*-Bu_4NCl (286.7 mg, 1.03 mmol) in DMSO (3 mL) was stirred at 100 °C for 4 h in a PYREX tube. The reaction mixture was quenched with NH_4Cl (aq). The organic layer was extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 2/8) to give **13** (347 mg, 93%). *E* isomer: ^{1}H NMR (300 MHz) δ 6.39 (s, 1 H), 5.08 (t, 1 H), 5.02 (s, 2H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.58 (s, 4.8 H, E isomer), 3.53 (t, 1 H, J = 5.9 Hz), 3.16 (d, 2 H, J = 7.5 Hz), 2.54 (d, 2 H, J = 8.1 Hz), 1.71(s, 2.4 H, *E* isomer). The ratio of *E*:*Z* (7:3) isomers was calculated from protons in olefinic methyl group; ^{13}C NMR (75 MHz) δ 169.31, 163.33, 158.47, 148.68, 131.93, 124.02, 120.37, 114.76, 105, 94.58, 67.74, 56.09, 56.01, 52.45, 50.31, 38.48, 24.30, 15.68. Signals of *Z* isomer could not be recognized; IR (cm^{-1}) 1753, 1731; MS *m*/*z* (M^+) 392.

5,7-Dimethoxy-6-[5-(methoxycarbonyl)-3-methyl-2-pentenyl]phthalide (14). A mixture of **13** (150 mg, 0.38 mmol) and NaCl (44.3 mg, 0.76 mmol) in H_2O(0.03 mL, 0.76mmol) and DMSO (3.2 mL) was stirred at 140 °C for 3 h. To the mixture was added water. The organic layer was extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 2/8) to give **14** (78.7 mg 62%). ^{1}H NMR (400 MHz) δ 6.40 (s, 1 H), 5.10 (t, 1 H), 5.06 (s, 2 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.58 (s, 2.4 H, *E* isomer), 2.38 (t, 2 H, J = 7.6 Hz), 2.29 (t, 3 H, J = 3.2 Hz), 1.71 (s, 2.4 H, *E* isomer); ^{13}C NMR (100 MHz) δ 173.30, 169.08, 163.11, 158.29, 148.39, 134.44, 121.47, 114.92, 105.03, 94.53, 67.71, 56.04, 55.90, 51.33, 34.42, 32.60, 24.19, 15.85; IR (cm^{-1}) 1752; MS *m*/*z* (M^+) 334.

6-(5-Carboxy-3-methyl-2-pentenyl)-5,7-dimethoxy-phthalide (15). A mixture of **14** (65 mg, 0.19 mmol) and LiOH (12.7 mg, 0.53 mmol) in water/MeOH (1 mL/6 mL) was stirred at rt for 25 h. To the mixture was added 1 M HCl and the resulting mixture was stirred for 30 min. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 1/1) to give **15** (43.4 mg, 71%). ^{1}H NMR (400 MHz) δ 6.42 (s, 1 H), 5.13 (t, 1 H, J = 7.6 Hz), 5.07 (s, 2 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.22 (d, 2 H, J = 6.8 Hz), 2.45 (t, 2 H, J = 7.8 Hz), 2.31 (t, 2 H, J = 7.1 Hz), 1.75 (s, 2.4 H, E isomer); ^{13}C NMR (100 MHz) δ 178.74, 169.31, 163.22, 158.43, 148.59, 134.37, 121.72, 115.04, 105.24, 94.65, 67.86, 56.12, 55.98, 34.68, 32.58, 24.30, 15.99; IR (cm^{-1}) 1757, 1709.

6-(5-Carboxy-3-methyl-2-pentenyl)-7-hydroxy-5-methoxyphthalide (4-NorMPA, 16). To a mixture of Mg (12.6 mg, 0.52 mmol) and I_2 (66 mg, 0.26 mmol) were added Et_2O (0.5 mL) and benzene (1 mL). After the resulting mixture was stirred at rt for 30 min, pyridine (0.01 mL, 0.13 mmol) and **15** (42 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) were added to the mixture. The reaction mixture was stirred at 90 °C for 6 h. To the resulting mixture was added 1 M HCl. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The residual solid was recrystallized from CH_2Cl_2 to give **16** (22 mg, 55%). ^{1}H NMR (400 MHz) δ 6.37 (s, 1 H), 5.11 (t, 1 H), 5.09 (s, 2 H), 3.79

(s, 3 H), 3.16 (d, 2 H, J = 6.4 Hz), 2.39 (t, 2 H, J = 7.6 Hz), 2.29 (m, 2 H), 1.67 (s, 2.4 H, *E* isomer); ^{13}C NMR (100 MHz) δ 178.63, 172.52, 164.10, 156.21, 145.68, 134.46, 121.77, 115.64, 103.01, 98.25, 69.87, 56.27, 34.22, 32.51, 24.59, 16.02; IR (cm^{-1}) 1738, 1706. Found: C, 61.36; H, 5.97%. Calcd for $C_{16}H_{18}O_6$: C, 62.7; H, 5.9%.

4-Ethyl-5,7-dimethoxyphthalide (17). To a suspension of MeLi (1.14 M, 4.5 mL) in THF (15 mL) was added CuI and stirred for 1 h at 0 °C. To this resulting mixture **6** (587 mg, 2.42 mmol) in CH_2Cl_2 was added and stirred for 1 h at 0 °C. To the mixture was added NH_4Cl (aq) and the organic layer was extracted with ether and washed with NH_4Cl (aq) and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane) to give **17** (343 mg, 64%). ^{1}H NMR (400 MHz) δ 6.42 (s, 1H), 5.15 (s, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 2.50 (q, 2H), 1.10 (t, 3H); ^{13}C NMR (100 MHz) δ 169.32, 163.43, 158.24, 148.13, 117.96, 105.13, 94.64, 67.76, 56.05, 56.03, 19.17, 13.57; MS *m*/*z* (M^+) 222.

4-Ethyl-6-iodo-5,7-dimethoxyphthalide (18). To a mixture of **17** (114 mg, 0.52 mmol) and CF_3CO_2Ag (136.9 mg, 0.62 mmol) in CH_2Cl_2 (20 mL) was added slowly I_2 (157.3 mg, 0.62 mmol) dissolved in CH_2Cl_2 (5 mL) at rt over 30 min. The reaction mixture was stirred at rt for 21 h and then was filtered. To the filtrate was added 1 M NaOH (aq) and $Na_2S_2O_3$ (aq). The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOA/hexane = 3/7) to **18** (140.8 mg, 79%). ^{1}H NMR (400 MHz) δ 5.12 (s, 2H), 4.00 (s, 3H), 3.81 (s, 3H), 2.59 (q, 2H), 1.13 (t, 3H); ^{13}C NMR (100 MHz) δ 167.28, 163.57, 157.95, 148.94, 127.75, 113.45, 91.65, 67.96, 62.55, 61.58, 20.59, 14.08; IR (cm^{-1}) 1761; MS *m*/*z* (M^+) 348.

4-Ethyl-5,7-dimethoxy-6-[5,5-bis(methoxycarbonyl)-3-methyl-2-pentenyl]phthalide (19). A mixture of **18** (240 mg, 0.69 mmol), isoprene (0.62 mL, 2.07 mmol), dimethyl malonate (0.393 mL, 3.45 mmol), $NaHCO_3$ (173.9 mg, 2.07 mmol), $[Pd_2(dba)_3CHCl_3]$ (35.89 mg, 0.00345 mmol), and *n*-Bu_4NCl (211.2 mg, 0.759 mmol) in DMSO (3.5 mL) was stirred at 100 °C for 4 h in a PYREX tube. The reaction mixture was quenched with NH_4Cl (aq). The organic layer was extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 2/8) to give **19** (193 mg, 67%). *E* isomer: ^{1}H NMR (400 MHz) δ 5.19 (t, 1 H), 5.15 (s, 2 H), 4.01 (s, 3 H), 3.74 (s, 3 H), 3.63 (s, 6 H), 3.51 (t, 1H, J = 7.2 Hz), 3.34 (d, 2 H, J = 7.1 Hz), 2.56 (m, 4 H), 1.77 (s, 3 H), 1.16 (t, 3 H, J = 7.6 Hz). The ratio of *E*:*Z* (7:1) isomers was calculated from olefinic protons. *Z* isomer δ 4.89 (m, olefinic); ^{13}C NMR (100 MHz) δ 169.30, 162.42, 156.83, 146.14, 137.73, 131.20, 128.75, 125.81, 119.48, 112.62, 68.04, 62.58, 61.89, 52.40, 50.50, 38.52, 23.64, 20.00, 16.02, 14.13. No signals of *Z* isomer could be recognized; IR (cm^{-1}) 1756, 1598; MS *m*/*z* (M^+) 420.

4-Ethyl-5,7-dimethoxy-6-[5-(methoxycarbonyl)-3-methyl-2-pentenyl]phthalide (20). A mixture of **19** (100 mg, 0.24 mmol) and NaCl (27.8 mg, 0.476 mmol) in H_2O (0.01 mL, 0.476 mmol) and DMSO (2.1 mL) was stirred at 140 °C for 3 h. To the mixture was added water. The organic layer was extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 2/8) to **20** (36 mg, 42%). ^{1}H NMR (400 MHz) δ 5.20 (t, 1 H), 5.19 (s, 2 H), 4.04 (s, 3 H), 3.78 (s, 3 H), 3.61 (s, 3 H), 3.40 (d, 2 H, J = 6.6 Hz), 2.60 (q, 2 H, J = 7.8 Hz), 2.40 (m, 2 H), 2.31 (m, 2 H), 1.80 (s, 3 H), 1.19 (t, 3 H, J = 7.6 Hz); ^{13}C NMR (100 MHz) δ 174.48, 169.62, 163.29, 157.66, 146.84, 134.46, 129.82, 127.13, 124.22, 113.29, 68.39, 62.91, 62.23, 51.74, 34.76, 33.02, 23.70, 20.11, 16.29, 14.20; IR (cm^{-1}) 1760, 1598; MS *m*/*z* (M^+) 362.

6-(5-Carboxy-3-methyl-2-pentenyl)-4-ethyl-5,7-dimeth-oxyphthalide (21). A mixture of **20** (23 mg, 0.06 mmol) and LiOH (3.95 mg, 0.165 mmol) in water/MeOH (0.4 mL/2.5 mL) was stirred at rt for 31 h. To the mixture was added 1 M HCl and the resulting mixture was stirred for 30 min. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on a silica-gel column (EtOAc/hexane = 1/1) to give **21** (20.2 mg, 91%). ^{1}H NMR (400 MHz) δ 5.13 (t, 1 H), 5.11 (s, 2 H), 3.97 (s, 3 H), 3.72 (s, 3 H), 3.33 (d, 2 H, J = 6.6 Hz), 2.52 (q, 2 H, J = 7.6 Hz), 2.37 (m, 2 H), 2.24 (m, 2 H), 1.73 (s, 3 H), 1.12 (t, 3 H, J = 7.6 Hz); ^{13}C NMR (100 MHz) δ 179.63, 169.67, 163.30, 157.67, 146.89, 134.19, 129.77, 127.16, 124.44, 113.32, 68.44, 62.95, 62.27, 34.40, 32.81, 23.70, 20.12, 16.33, 14.20; IR (cm^{-1}) 1757, 1709.

6-(5-Carboxy-3-methyl-2-pentenyl)-4-ethyl-7-hydroxy-5-methoxyphthalide (4-HomoMPA, 22). BCl_3 (54 mL, 5.4 mmol) was added slowly to a solution of **21** (18.8 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C. The mixture was stirred at rt for one week. To the resulting mixture water was added. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica-gel column (EtOAc/hexane = 1/4) to give **22** (3.5 mg, 19%). ^{1}H NMR (400 MHz) δ 5.19 (t, 1 H), 5.14 (s, 2 H), 3.75 (s, 3 H), 3.33 (s, 2 H), 2.51 (q, 2 H, J = 4.9 Hz), 2.49 (m, 2 H), 2.34 (m, 2 H), 1.97 (s, 3 H), 1.10 (t, 3 H, J = 7.6 Hz); IR (cm^{-1}) 3418, 2927, 1734.

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