Total synthesis of mycophenolic acid

Ricardo A. de la Cruz, Francisco X. Talamás, Alfredo Vázquez, and Joseph M. Muchowski

Abstract: A total synthesis of mycophenolic acid is reported. Diels–Alder reaction of [5-methoxy-3-(1-methoxypropenyl)-4,5-dihydrofuran-2-yloxy]-trimethylsilane with 3-benzenesulfinyl-5*H*-furan-2-one afforded the hexasubstituted nucleus. The side chain was constructed from the unveiled aldehyde.

Key words: mycophenolic acid, Diels–Alder reaction, pentasubstituted diene.

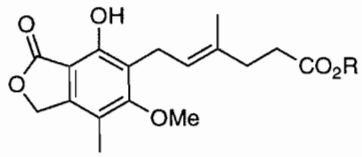
Résumé : On a effectué une synthèse totale de l'acide mycophénolique. Une réaction de Diels–Alder du [5-méthoxy-3-(1-méthoxypropényl)-4,5-dihydrofuran-2-yloxy]-triméthylsilane avec la 3-benzènesulfinyl-5*H*-furan-2-one a permis d'obtenir le noyau hexasubstitué. On a créé la chaîne latérale à partir de l'aldéhyde déprotégé.

Mots clés : acide mycophénoliquie, réaction de Diels–Alder, diène pentasubstitué.

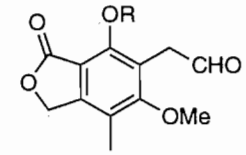
[Traduit par la rédaction]

Introduction

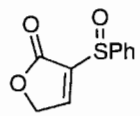
Mycophenolic acid (**1***a*), a metabolite of several Penicillium species (1), has been known as a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) for over 25 years (2). It has recently become of importance in organ transplant rejection due to its immunosuppressive activity and low degree of toxicity (3). As a consequence of the pharmacological activity of **1***a*, much effort has been devoted to the preparation of congeners thereof (4) as well as to its total synthesis (5). The known (5b) phthalide **2***b* was chosen as a synthetic target because it is a useful precursor of mycophenolic acid itself and of several highly active side-chain-modified derivatives (4). This article describes a new synthesis of the phthalides **2***a*-**2***c* and the conversion of **2***c* into mycophenolic acid using the process of Patterson and Huang (5*b*, 6). Like others (5) who have utilized phthalides as precursors of **1***a*, we chose to use a Diels–Alder strategy, as did Watanabe et al. (5*d*), as the first step en route to **2***b*. Of several processes studied, the most successful involved the use of the dienophile **3** and the pentasubstituted diene **4**.



1*a* R = H
1*b* R = Et



2*a* R = H
2*b* R = $SiMe_2t$-Bu
2*c* R = $CH_2O(CH_2)_2OCH_3$



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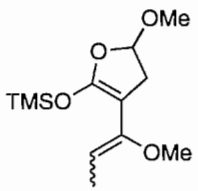

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Results and discussion

Compound **3** was prepared (98% yield) by *m*-chloroperbenzoic acid oxidation from the corresponding (7) sulfide. The starting material for the diene **4** was 5-methoxy-2(3H)-dihydrofuranone **5** (8), which was deprotonated with lithium bis(trimethylsilyl)amide (2.1 equiv.) in anhydrous THF (−78°C) and treated with propionyl chloride (1.1 equiv., −78°C) to give the β-ketolactone **6** (68%). The extra equivalent of base used was required to drive the reaction to completion. When lithium diisopropylamide (LDA) was used as the base in this reaction, the yield decreased considerably. Attempts to transform **6** into the enol ether **7** under different basic conditions (e.g., KH, MeI, HMPA) resulted in complex mixtures. Better results were obtained when acid catalysis was used for this transformation. Reaction of **6** with trimethyl orthoformate (2.0 equiv.), containing a catalytic quantity of concentrated H_2SO_4 (r.t.) (9) gave the enol ether **7** (63% yield after flash chromatography, SiO_2) contaminated by a minor amount (ca 10%) of its geometric isomer (10). This compound was converted into the diene **4** (60% yield after distillation) by lithiation with LDA (THF, −78°C) followed by reaction with chlorotrimethylsilane (TMSCl) (−78°C to r.t.) (11).

The optimum conditions for the [4π + 2π] cycloaddition

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This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

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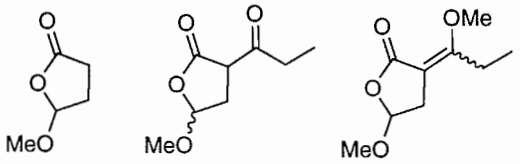

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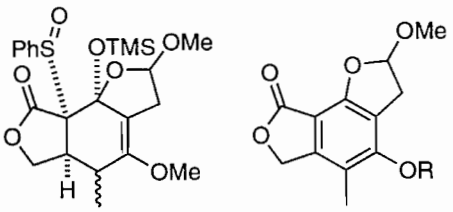
and subsequent aromatization involved reaction of **3** with 2.0 equivalents of the diene **4** in toluene solution under mild conditions (0°C, 1 h; r.t., 1 h) followed by thermolysis of the putative adduct **8** at reflux temperature (30 min). Column chromatography separation (SiO_2) of the reaction mixture provided the expected phthalide derivative **9***a* as well as the phenol **9***b* in 33 and 14% yields, respectively. Since **9***b* is readily and efficiently (89%) methylated (MeI, NaH, DMF), **9***a* is thus obtained in 45% combined yield. When the reaction was carried out under the same reaction conditions but with the sulfoxide **3** as the excess reagent (2.0 equiv.), compound **9***a* was obtained in only 13% yield. To convert **9***a* into the desired phthalide, deprotection with 89% formic acid (r.t., 20 min, quant.) to the phenolic aldehyde **2***a* was carried out. The most notable feature of this process is that a hexasubstituted benzenoid derivative containing all the functionality required for conversion into mycophenolic acid, or side-chain congeners thereof, is produced with a considerable economy in steps and reasonable efficiency.

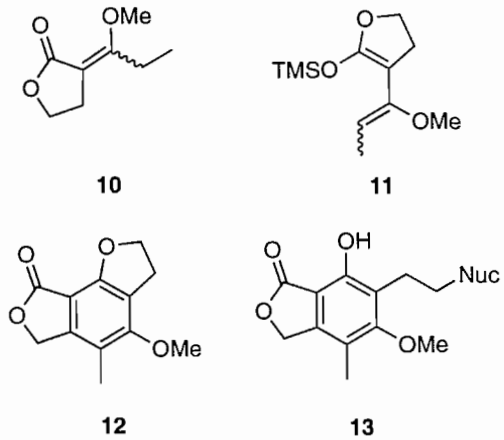


8 **9***a* R = Me
9*b* R = H

Protection of the latent aldehyde protected as an acetal through the synthesis up to this point solved the problem encountered in an early attempt as described in Scheme 1. Thus, 3-propionyldihydrofuran-2-one was converted into the enol ether **10** (10) under acid conditions (H_2SO_4, trimethyl orthoformate). Compound **10** was converted to the diene **11** in 75% yield, using the conditions employed for the transformation of **7** to **4**. Reaction of sulfoxide **3** and diene **11** (2.0 equiv.) in toluene solution (0°C–reflux, 2.5 h) afforded, after column chromatography, the phthalide **12** in 46% yield. Attempts to obtain the phenol **13** by opening of the dihydrofuran moiety on **12** with nucleophiles were unsuccessful. Although transient formation of **13** presumably occurred, closure back to the starting material or loss of the methoxy group was observed. Extensive studies were carried out before it was decided to start with the desired oxidation state on an early intermediate as described above.

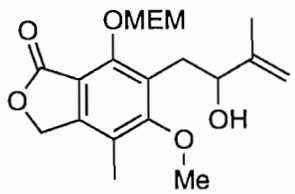
The synthesis was completed as follows. Treatment of compound **2***a* with *tert*-butyldimethylsilyl chloride (TBDMSCl) (imidazole, DMF) (12) afforded the desired aldehyde **2***b* in only 18% yield along with other by-products. Although the aldehyde **2***b* could not be generated with acceptable efficiency under a wide variety of conditions (13), the ether **2***c* was easily

Scheme 1.



10 11 12 13

prepared (86%) from **2***a* and 2-methoxyethoxymethyl chloride (MEMCl) by the procedure of Corey et al. (*i*-Pr_2NEt–CH_2Cl_2) (14). This compound was reacted with prop-2-enyl magnesium bromide (THF, −40°C) and the allylic alcohol **14** so obtained (67%) was subjected to the *ortho*-ester Claisen conditions of Patterson (5*b*, 6). Removal of the MEM group from the product (PPTS, *t*-BuOH, 80°C, 6 h) gave ethyl mycophenolate **1***b* (60% from **14**), which on saponification provided mycophenolic acid (**1***a*) in near quantitative yield.



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The process described herein could without doubt be applied to the synthesis of a wide variety of nucleus- and side-chain-modified analogs of mycophenolic acid.

Experimental

General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled under argon atmosphere from sodium–benzophenone directly before use. Hexamethyldisilazane and diisopropylamine were distilled from CaH_2 before use. Toluene was degassed by bubbling argon and applying ultrasound for 5 min. Reactions and chromatography fractions were monitored by thin-layer chromatography. Chromatography was carried out using Merck 60 (230–400 mesh) silica gel. Melting points are uncorrected. IR spectra were recorded as $CHCl_3$ solution using a Perkin–Elmer 1720-X instrument. ^1H NMR measurements were recorded at 200.0 MHz and ^{13}C NMR measurements were recorded at 50.0 MHz using a Varian Gemini-200 instrument. Spectra are reported in ppm downfield from tetramethylsilane as the internal standard. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution. Low-resolution mass spectra (LRMS) were

recorded on a Finnigan MAT-INCOS XL instrument. Elemental analyses were performed using a Fison EA-1108 instrument or were done at Midwest-Microlab, 7212N Shadeland Ave. Indianapolis, IN 46250, U.S.A.

3-Benzenesulfinyl-5*H*-furan-2-one (3)

Sulfoxide **3** was prepared as reported (*7a*) to obtain an oil, which was crystallized to obtain yellow needles; mp 87–88.5°C (EtOH); IR: 3014, 1766, 1216, 1052 cm^{-1}; ^1H NMR δ: 8.05 (t, J = 1.6 Hz, 1H), 7.89–7.76 (m, 2H), 7.59–7.48 (m, 3H), 5.05 (dd, J = 19.0, 1.7 Hz, 1H), 4.89 (dd, J = 19.0, 1.6 Hz, 1H); ^{13}C NMR δ: 167.2, 151.6, 141.6, 141.3, 132.2, 129.6, 124.9, 71.3; LRMS (EI), *m/z* (relative intensity): 208 (M^+, 14), 51 (100). Anal. calcd. for $C_{10}H_8O_3S$: C 57.67, H 3.87, S 15.39; found: C 57.52, H 3.81, S 15.19.

5-Methoxy-3-propionyl-dihydrofuran-2-one (6)

A 1.38 M solution of *n*-BuLi–hexanes (145.0 ml, 0.2 mol) was added to hexamethyldisilazane (42.3 mL, 0.2 mol) in THF (195.0 ml) at 0°C under argon. The reaction was stirred for 20 min, cooled to −78°C, and **5** (11.1 g, 0.095 mol) was added in THF (27.0 ml). After 30 min, propionyl chloride (9.14 mL, 0.105 mol) was added and the mixture was stirred for 15 min at −78°C and then allowed to reach room temperature. The reaction was quenched with 10% NH_4Cl (50.0 mL), diluted with EtOAc, and the organic phase was washed with 10% NH_4Cl (2 × 50.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue (14.5 g) purified by flash chromatography (SiO_2, hex–EtOAc 85:15) to obtain **6** as an oil (11.1 g, 68%). The NMR spectra show **6** as a 1:1 mixture of two diastereoisomers: IR: 3025, 1774, 1724, 1355, 1110, 932 cm^{-1}; ^1H NMR δ: 5.45 (dd, J = 5.8, 1.7 Hz, 1H), 3.88 (t, J = 8.8 Hz, 0.5H), 3.50 (s, 3H), 3.25–2.82 (m, 2H), 2.81–2.38 (m, 2H), 2.14 (ddd, J = 13.8, 9.0, 1.9 Hz, 0.5 H), 1.10 (t, J = 7.1 Hz, 3H); LRMS (EI), *m/z* (relative intensity): 173 (M^+, 11), 57 (100). Anal. calcd. for $C_8H_{12}O_4$: C 55.80, H 7.03; found: C 55.72, H 7.10.

5-Methoxy-3-(1-methoxypropylidene)-dihydrofuran-2-one (7)

To a solution of the β-keto lactone **6** (11.2 g, 0.065 mol) in trimethyl orthoformate (14.2 mL, 0.13 mol) at 0°C under argon was slowly added concentrated H_2SO_4 (0.18 mL, 3.24 mmol); the mixture was stirred for 15 min at the same temperature and then for 3.5 h at room temperature. The reaction was diluted with CH_2Cl_2, washed with 10% $NaHCO_3$ (2 × 50.0 mL) and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue (12.2 g) was purified by flash chromatography (SiO_2, hex–EtOAc 85:15) to obtain the enol ether **7** as an oil (7.69 g, 63%). IR: 3020, 1738, 1654, 1229, 1074, 1014, 915 cm^{-1}; ^1H NMR δ: 5.32 (dd, J = 6.5, 2.2 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 3H), 3.05–2.80 (m, 3H), 2.71 (dd, J = 16.7, 2.1 Hz, 1H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ: 171.4, 170.3, 101.0, 98.7, 56.1, 54.6, 32.8, 19.0, 12.2; LRMS (EI), *m/z* (relative intensity): 186 (M^+, 28), 57 (100). Anal. calcd. for $C_9H_{14}O_4$: C 58.05, H 7.58; found: C 57.66, H 7.74.

[5-Methoxy-3-(1-methoxypropenyl)-4,5-dihydrofuran-2-yloxy]-trimethylsilane (4)

A 1.38 M solution of *n*-BuLi–hexanes (18.0 mL, 24.9 mmol) was added to diisopropylamine (3.8 mL, 27.1 mmol) in THF (44.0 mL) at 0°C under argon. The reaction was stirred for 20 min, cooled to −78°C, and **7** (4.1 g, 21.9 mmol) was added in THF (22.0 mL). After 30 min, chlorotrimethylsilane (3.4 mL, 27.1 mmol) was added; the mixture was stirred for 15 min at −78°C and then allowed to reach room temperature. The reaction mixture was concentrated until a precipitate formed, then diluted with hexane, filtered through Celite®, and concentrated to dryness to obtain an oil. The crude product was distilled to obtain the diene **4** (3.39 g, 60%) as a colorless liquid; bp 74–76°C (0.37 Torr; 1 Torr = 133.3 Pa); IR: 3014, 2938, 1694, 1255, 855 cm^{-1}; ^1H NMR δ: 5.29 (dd, J = 7.2, 2.4 Hz, 1H), 4.53 (q, J = 7.0 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.99 (dd, J = 15.0, 7.2 Hz, 1H), 2.56 (dd, J = 15.0, 2.2 Hz, 1H), 1.56 (d, J = 6.8 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR δ: 152.3, 150.1, 103.8, 103.1, 93.7, 55.3, 54.5, 37.0, 12.7, 0.24; LRMS (EI), *m/z* (relative intensity): 258 (M^+, 4), 73 (100).

2,4-Dimethoxy-5-methyl-3,6-dihydro-2*H*-1,7-dioxa-*as*-indacen-8-one (9*a*) and 4-hydroxy-2-methoxy-5-methyl-3,6-dihydro-2*H*-1,7-dioxa-*as*-indacen-8-one (9*b*)

To a solution of the sulfoxide **3** (1.24 g, 6.0 mmol) in degassed toluene (10.0 mL) at 0°C under argon was added dropwise the diene **4** (3.27 g, 12.65 mmol). The reaction was stirred for 1 h at 0°C, 1 h at room temperature, and for 30 min at reflux. The solvent was removed and the crude product purified by flash chromatography (SiO_2, CH_2Cl_2–acetone 98:2) to obtain **9*a*** (489 mg, 33%) and **9*b*** (199 mg, 14%). Compound **9*a***, mp 135–137°C (hex–EtOAc), presents the following spectroscopic data: IR: 3023, 1759, 1639, 1615, 951 cm^{-1}; ^1H NMR δ: 5.83 (dd, J = 6.4, 2.1 Hz, 1H), 5.14 (s, 2H), 3.97 (s, 3H), 3.59 (s, 3H), 3.49 (dd, J = 16.3, 6.5 Hz, 1H), 3.25 (dd, J = 16.1, 2.0 Hz 1H), 2.06 (s, 3H); ^{13}C NMR δ: 168.8, 159.7, 155.8, 146.8, 115.1, 114.1, 109.0, 102.8, 69.0, 59.0, 56.3, 35.3, 10.9; LRMS (EI), *m/z* (relative intensity): 250 (M^+, 100). Anal. calcd. for $C_{13}H_{14}O_5$: C 62.39, H 5.64; found: C 62.01, H 5.70. Compound **9*b***, mp 168–170°C (hex–EtOAc), presents the following spectroscopic data: IR: 3588, 3250, 3019, 1757, 1625, 950 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ: 9.08 (s, 1H, D_2O exchange), 5.82 (dd, J = 6.4, 2.3 Hz, 1H), 5.13 (s, 2H), 3.57 (s, 3H), 3.26 (dd, J = 16.5, 6.5 Hz, 1H), 3.07 (dd, J = 16.6, 2.1 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 168.2, 157.2, 154.5, 147.4, 111.8, 110.9, 109.4, 99.3, 68.7, 55.6, 33.4, 10.5; LRMS (EI), *m/z* (relative intensity): 236 (M^+, 57), 43 (100). Anal. calcd. for $C_{12}H_{12}O_5$: C 61.01, H 5.12; found: C 60.83, H 5.14.

Conversion of 9*b* to 9*a*

To a solution of **9*b*** (100 mg, 0.42 mmol) in DMF (5.0 mL) at 0°C under argon was added 60% NaH–oil (20 mg, 0.5 mmol) The reaction was stirred for 15 min and then CH_3I (0.06 mL, 1.05 mmol) was added. The reaction was stirred for 30 min at 0°C and 30 min at room temperature, then poured on water and the product extracted with EtOAc (3×). The organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue purified by flash chromatography (SiO_2, hex–EtOAc 6:4) to obtain **9*a*** (94 mg, 89%).

(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-acetaldehyde (2*a*)

A solution of **9*a*** (73 mg, 0.29 mmol) in 89% formic acid (2.0 mL) was stirred at room temperature for 20 min and con-

centrated to dryness. The residue was azeotroped with toluene (3×) to remove traces of acid. The aldehyde **2***a* (66 mg, quantitative) was obtained as a white solid in pure form. The NMR spectra shows the phenol-aldehyde **2***a* to be in equilibrium with the corresponding cyclic hemiacetal in solution; mp 144–145°C (hex–CH_2Cl_2); IR: 3417, 1755, 1640, 1612 cm^{-1}; ^1H NMR δ: 9.75 (t, J = 1.5 Hz, 0.18H, aldehyde), 7.70 (s, 1H, D_2O exchange), 6.29 (dd, J = 6.5, 2.6 Hz, 0.82H, hemiacetal), 5.24 (s, 0.36H), 5.14 (s, 1.64H), 3.98 (s, 2.46H), 3.80 (d, J = 1.4 Hz, 0.36 H), 3.73 (s, 0.54H), 3.49 (dd, J = 16.0, 6.5 Hz, 0.82H), 3.22 (dd, J = 16.1, 2.5 Hz, 0.82H), 2.17(s, 0.54H), 2.05 (s, 2.46H); LRMS (EI), *m/z* (relative intensity): 236 (M^+, 2), 208 (55), 159 (100). Anal. calcd. for $C_{12}H_{12}O_5$: C 61.01, H 5.12; found: C 61.29, H 5.03.

3-(1-Methoxypropylidene)-dihydrofuran-2-one (10)

To a solution of 3-propionyl-dihydrofuran-2-one (16.8 g, 0.12 mol) in trimethyl orthoformate (19.4 mL, 0.17 mol) at 0°C was added concentrated H_2SO_4 (0.3 mL). The reaction was allowed to reach room temperature and was stirred for 15 h. The solution was concentrated and quinoline (0.8 mL) added. The crude product was distilled to give **10** as the *E* isomer (10) (2.76 g) and *Z* isomer (10.9 g) as colorless liquids in 74% yield. The *E* isomer, bp 68–70°C (3.0 Torr), presents the following spectroscopic data: IR: 1689, 1640 cm^{-1}; ^1H NMR δ: 4.41 (t, J = 9.7 Hz, 2H), 3.71 (s, 3H), 2.89 (tt, J = 9.6, 1.0 Hz, 2H), 2.66 (qt, J = 7.6, 1.0 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H); LRMS (EI), *m/z* (relative intensity): 155 ($M^+ - 1$). The *Z* isomer, bp 120–122°C (3.0 Torr), presents the following spectroscopic data: IR: 1728, 1653 cm^{-1}; ^1H NMR δ: 4.25 (t, J = 7.7 Hz, 2H), 3.82 (s, 3H), 3.03–2.80 (m, 4H), 1.15 (t, J = 7.5 Hz, 3H); LRMS (EI), *m/z* (relative intensity): 156 (M^+).

[3-(1-Methoxypropenyl)-4,5-dihydrofuran-2-yloxy]-trimethylsilane (11)

Enol ether **10** (3.0 g, 19.2 mmol) was converted to the diene **11** (3.28 g) in 75% yield as described for **4**; bp 75–81°C (0.35 Torr); IR: 1691, 860 cm^{-1}; ^1H NMR δ: 4.51 (q, J = 6.7 Hz, 1H), 4.27 (dd, J = 9.1, 8.6 Hz, 2H), 3.46 (s, 3H), 2.75 (t, J = 0.9 Hz, 2H), 1.55 (d, J = 6.9 Hz, 3H), 0.21 (s, 9H); LRMS (EI), *m/z* (relative intensity): 228 (M^+).

4-Methoxy-5-methyl-3,6-dihydro-2*H*-1,7-dioxa-*as*-indacen-8-one (12)

Diels–Alder reaction of **11** (1.21 g, 5.0 mmol) and **3** (0.54 g, 2.6 mmol) as described for **9** afforded compound **12** (0.26 g) in 46% yield; mp 141–142°C (hex–CH_2Cl_2); IR: 1749 cm^{-1}; ^1H NMR δ: 5.13 (s, 2H), 4.78 (t, J = 8.8 Hz, 2H), 3.98 (s, 3H), 3.41 (t, J = 8.8 Hz, 2H), 2.06 (s, 3H); LRMS (EI), *m/z* (relative intensity): 220 (M^+).

[4-(*tert*-Butyldimethylsilanyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl]-acetaldehyde (2*b*)

To a solution of **2***a* (200 mg, 0.85 mmol) and imidazole (116 mg, 1.7 mmol) in DMF (10.0 mL) was added TBDMSCl (153 mg, 1.02 mmol). The reaction was stirred at room temperature overnight, then diluted with water and EtOAc. The organic phase was separated and washed with 10% HCl, 10% $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent the residue was purified by flash chromatography (SiO_2, hex–EtOAc 4:1) to give **2***b* (53 mg, 18%) as a white solid (4*a*). 1H NMR δ: 9.62 (m, 1H), 5.10 (s, 2H), 3.72 (s, 5H), 2.18 (s, 3H), 1.01 (s, 9H), 0.21 (s, 6H); LRMS (EI), *m/z* (relative intensity): 350 (M^+).

[6-Methoxy-4-(2-methoxyethoxymethoxy)-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl]-acetaldehyde (2*c*)

A solution of the phenol **2***a* (1.76 g, 7.45 mmol), *N,N*-diisopropylethylamine (3.24 mL, 18.6 mmol), and 2-methoxyethoxymethyl chloride (1.1 g, 8.9 mmol) in CH_2Cl_2 (50.0 mL) was stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2 and washed with 10% $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue purified by flash chromatography (SiO_2, hex–acetone 7:3) to obtain the MEM ether **2***c* (1.98 g, 86%) as a solid; mp 45–50°C; IR: 3021, 1760, 1724, 1130, 1069, 961 cm^{-1}; ^1H NMR δ: 9.72 (t, J = 1.5 Hz, 1H), 5.44 (s, 2H), 5.17 (s, 2H), 3.92–3.84 (m, 4H), 3.74 (s, 3H), 3.60–3.52 (m, 2H), 3.37 (s, 3H), 2.21 (s, 3H); ^{13}C NMR δ: 199.0, 168.7, 162.9, 154.0, 148.3, 121.1, 120.4, 112.2, 100.2, 71.5, 69.4, 68.3, 60.8, 59.0, 39.7, 11.6; LRMS (EI), *m/z* (relative intensity): 324 (M^+, 1), 59 (100). Anal. calcd. for $C_{16}H_{20}O_7$: C 59.25, H 6.21; found: C 59.42; H, 6.35.

6-(2-Hydroxy-3-methylbut-3-enyl)-5-methoxy-7-(2-methoxyethoxymethoxy)-4-methyl-3*H*-isobenzofuran-2-one (14)

To a solution of the aldehyde **2***c* (1.4 g, 4.3 mmol) in THF (40.0 mL) at −40°C under argon was added freshly prepared prop-2-enyl magnesium bromide (0.58 M in THF, 15 mL) and stirred for 40 min. The reaction was diluted with EtOAc and 50% NH_4Cl and allowed to reach room temperature. The organic phase was washed with 10% NH_4Cl and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography (SiO_2, hex–EtOAc 7:3) to obtain the MEM alcohol **14** (949 mg, 67%) as an oil. IR: 1758, 1604, 1129, 1068 cm^{-1}; ^1H NMR δ: 5.45 (q, J = 6.7 Hz, 2H), 5.14 (s, 2H), 4.99 (br t, J = 0.82 Hz, 1H), 4.84 (br t, J = 1.2 Hz, 1H), 4.32 (dd, J = 8.2, 5.0 Hz, 1H), 4.06–3.86 (m, 2H), 3.82 (s, 3H), 3.59 (t, J = 4.7 Hz, 2H), 3.37 (s, 3H), 3.12–2.92 (m, 2H), 2.20 (s, 3H), 1.86 (s, 3H); ^{13}C NMR δ: 169.0, 163.1, 154.3, 147.7, 147.2, 126.8, 120.5, 112.3, 110.4, 100.4, 75.5, 71.5, 69.4, 68.2, 60.9, 59.0, 31.3, 18.0, 11.7; LRMS (EI), *m/z* (relative intensity): 366 (M^+, 1), 220 (25), 59 (100). Anal. calcd. for $C_{19}H_{26}O_7$: C 62.27, H 7.53; found: C 61.95, H 7.49.

6(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-hex-4-enoic acid ethyl ester (1*b*)

A solution of the allylic alcohol **14** (930 mg, 2.56 mmol), freshly distilled triethyl orthoformate (8.0 mL, 43.6 mmol), and pivalic acid (6 mg, 0.05 mmol) in xylene (45.0 mL) was heated in an oil bath at 135–140°C for 6 h. The solvent was removed, the residue dissolved in *t*-BuOH (70.0 mL), PPTS (700 mg, 2.8 mmol) was added, and the solution stirred at 80°C for 6 h. The reaction was diluted with EtOAc, washed with 10% $NaHCO_3$, and water, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue (1.34 g) was purified by flash chromatography (SiO_2, hex–acetone 85:15) to give the ester **1***b* (516 mg, 60% from **14**); mp 95–96°C (hex–CH_2Cl_2); IR: 3454, 1735, 1628, 1138 cm^{-1};

^{1}H NMR δ: 7.66 (s, 1H, D_2O exchange), 5.24 (t, J = 6.9 Hz, 1H), 5.20 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.38 (d, J = 6.8 Hz, 2H), 2.44–2.22 (m, 4H), 2.14 (s, 3H), 1.80 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ: 173.3, 163.6, 153.6, 143.9, 134.2, 122.6, 122.1, 116.7, 106.3, 70.0, 60.9, 60.1, 34.6, 33.1, 22.5, 16.1, 14.1, 11.5; LRMS (EI), *m/z* (relative intensity): 348 (M^+, 6), 207 (100). Anal. calcd. for $C_{19}H_{24}O_6$: C 65.50, H 6.94; found: C 65.41, H 7.00.

Mycophenolic acid (1*a*)

A solution of the ester **1***b* (100 mg, 0.28 mmol) in methanol (3 mL) was treated with LiOH (34 mg, 0.81 mmol) in water (0.5 mL). The reaction was stirred for 12 h, diluted with EtOAc, and washed with water. The aqueous phase was cooled on ice and 10% HCl was added to pH = 1, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to give **1***a* (119 mg, 98%) as a white solid; mp 140°C (hex–CH_2Cl_2) (5).

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