EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300974

Total Synthesis of Mycophenolic Acid by a Palladium-Catalyzed Decarboxylative Allylation and Biomimetic Aromatization Sequence

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Dedicated to Professor Robert M. Williams on the occasion of his 60th birthday

Keywords: Natural products / Total synthesis / Medicinal chemistry / Biomimetic synthesis / Allylation / Cyclization

This paper describes the total synthesis of the fungal natural product mycophenolic acid through palladium-catalyzed allylation, biomimetic cyclization, and aromatization. Methyl (4*E*)-6-hydroxy-4-methylhex-4-enoate, which was converted in four steps into the key diketo ester dioxinone via two selective *C*-acylation reactions, was transformed into a resorcylate. Subsequent phenol methylation, lactonization, iodoether formation, and halogenation gave a tricyclic intermediate. Palladium-catalyzed cross-coupling with DABCO–$(AlMe_3)_2$ and saponification gave mycophenolic acid. An alternative approach with early stage arene methyl incorporation unexpectedly resulted in the formation of a γ-pyrone.

Introduction

As early as 1893, an astonishing 120 years ago, Italian physician Bartolomeo Gosio extracted, purified, and characterized (with the limited methods of his time) a crystalline material from a *Penicillium* fungal strain. Furthermore, Gosio discovered that this compound, later termed mycophenolic acid (MPA, **1**, Figure 1),[1] inhibited the growth of the anthrax bacillus.[2] MPA therefore constitutes the world's first purified antibiotic natural product. The correct determination of its structure was completed six decades later in the 1950s,[3] and today MPA is known to be produced by several *Penicillium* species.[4] Its biological activity is remarkable; it is, for example, a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH). Furthermore, MPA (in pro-drug form) has been successfully used as an immunosuppressant to prevent rejection in organ transplantation.[5] Several medicinal chemistry campaigns have tried to derive more active compounds from MPA, but no significant improvements on the original natural product have been observed.[1,6]

Aside from its biological activity, MPA attracted the attention of synthetic organic chemists because of its challenging structure. Notably, the central core contains an arene with six different substituents. The first total synthesis of MPA was reported by A. J. Birch in 1969,[7] and since then several other syntheses have been achieved.[8] These syntheses were generally low-yielding and/or had long multistep sequences, so we sought to devise a short and efficient total synthesis of **1** based on our recently developed allylation and biomimetic polyketide aromatization methodology.[9] Our retrosynthetic analysis is outlined in Scheme 1.

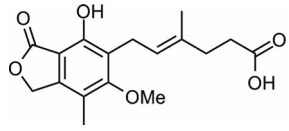

Figure 1. Mycophenolic acid (MPA, **1**).

In the course of this project, we investigated two different strategies to access the hexasubstituted arene **1** by biomimetic aromatization. The direct approach (R = Me) would be to assemble the bicyclic structure of **1** by cyclization and aromatization of diketo dioxinone **2** and subsequent lactonization. The allylic side chain of **2** could be attached by a palladium-catalyzed decarboxylation and alkenylation reaction, starting from allyl ester **3** (R = Me). This diketo ester dioxinone should in turn be available by two subsequent *C*-acylations from dioxinone **4** and acid chlorides **5** (R = Me) and **6**. Ester **5** could be obtained in two steps from Meldrum's acid derivative **7** (R = Me) and alcohol **8**. In this strategy, the arene methyl group is introduced right at the beginning of the synthesis as part of acid chloride **5** via its precursor **7**. In this regard, the second strategy (R = H) is the exact opposite, because the arene is assembled with only five of the six required substituents, and the methyl group is incorporated at a late stage of the synthesis.

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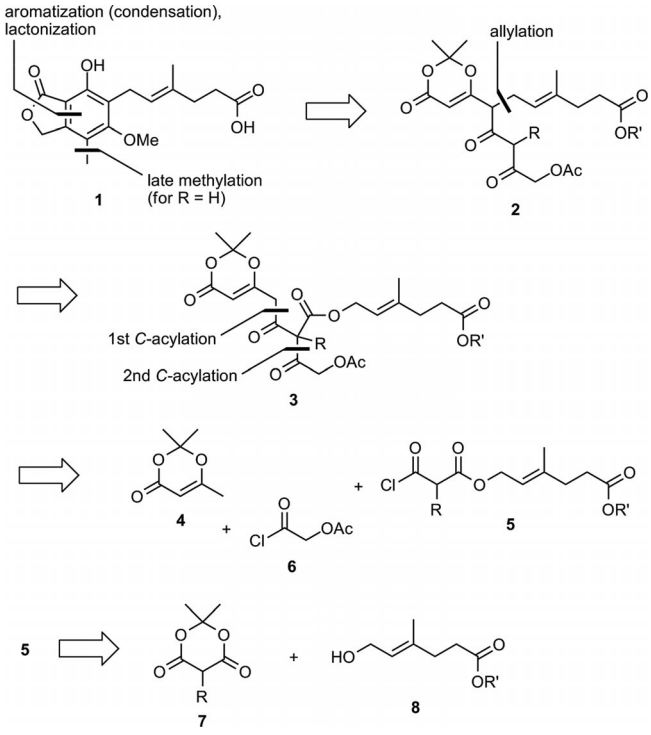
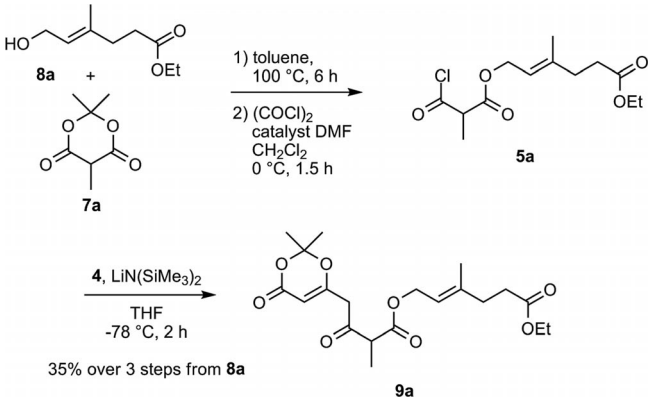
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300974.



Scheme 1. Retrosynthetic analysis of mycophenolic acid (**1**). R = Me for the direct approach and R = H for the late methylation strategy, whereas R′ = Me or Et.

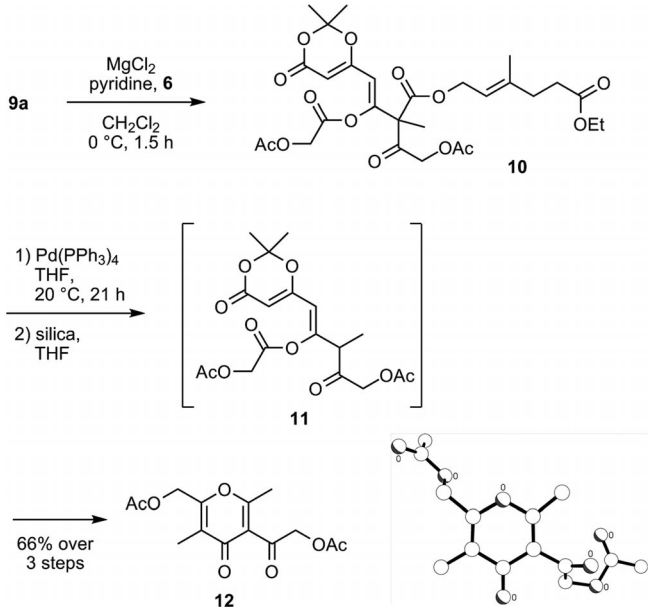
Results and Discussion

Meldrum's acid derivative **7a** (Scheme 2) was heated with allyl alcohol **8a**,[10] and the resultant malonic acid monoester was converted into acid chloride **5a** with oxalyl chloride.[11] The lithium enolate derived from dioxinone **4** was allowed to react with acyl chloride **5a**, to afford keto ester dioxinone **9a** in 35% yield over three steps.

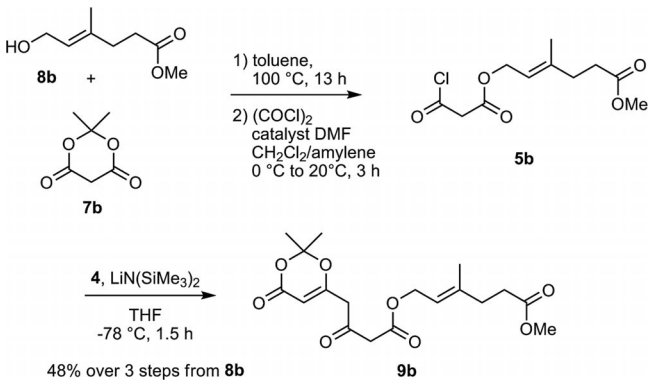


Scheme 2. Synthesis of keto ester dioxinone **9a**.

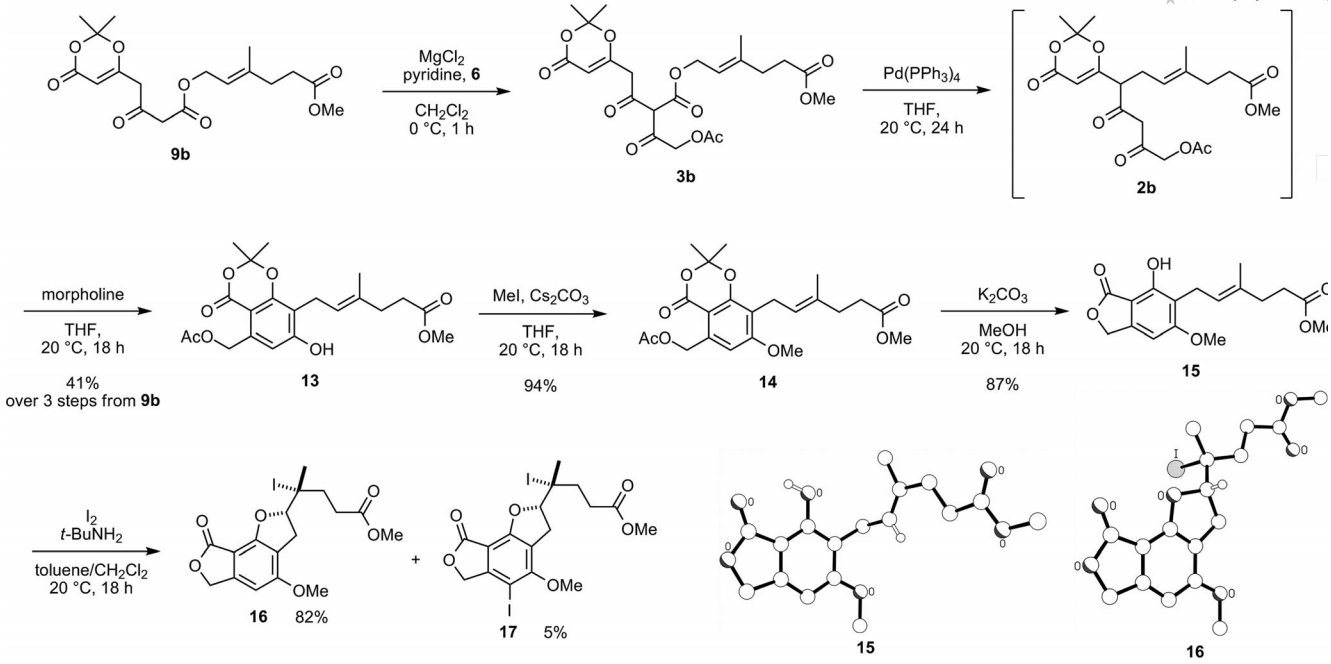
With keto ester dioxinone **9a** to hand, elaboration to MPA was planned as follows: a selective Claisen reaction with acid chloride **6**, decarboxylative alkenylation to attach the allyl side chain, and a biomimetic cyclization and aromatization. Unfortunately, the initial acylation step (**9a**→**3**) proved problematic, which further complicated downstream transformations towards dioxinone **2**. A selective Claisen reaction between a β-keto ester and an acid chloride, mediated by magnesium chloride and pyridine,[12] which had previously proved very reliable with several systems,[9] proved to be incompatible when the α-position was substituted. A side reaction that could not be suppressed led to *O*-acylation of the ketone in addition to the desired *C*-acylation (Scheme 3). Because this could not be prevented, we increased the number of equivalents of acid chloride **6** in the hope of achieving full conversion into the doubly acylated product **10**, which should be able to react as the *O*-acylated analogue of **2**. The subsequent palladium-catalyzed reaction, however, unexpectedly led to the formation of γ-pyrone **12** in 66% yield over three steps. Apparently, the *O*-acylated intermediate **11**, which is formed from **10** by deallylation and decarboxylation, does not undergo a cross-coupling reaction with the thereby formed Pd-allyl species. This distinguishes it from the related, non-*O*-acylated substrates.[9] Instead a rearrangement of the *O*-acyl moiety, loss of acetone, and another decarboxylation occurred, resulting



Scheme 3. Synthesis and X-ray crystal structure of γ-pyrone **12**.[18]



Scheme 4. Synthesis of keto ester dioxinone **9b**.



Scheme 5. Synthesis of iodohydrins **16** and **17** and X-ray crystal structures of lactone **15** and iodo-ether **16**.[18]

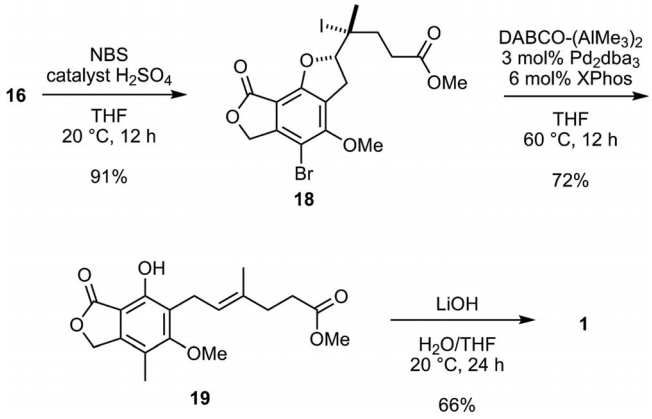
in the formation of pyrone **12**.[13] The structure of pyrone **12** was unambiguously assigned by X-ray crystallography.

The attempted direct synthesis of mycophenolic acid **1** was unsuccessful, although it led to the interesting alternative observation of pyrone ring closure. We therefore turned our attention to late-stage arene methylation, which should circumvent the critical failure of *C*-acylation and decarboxylative allylic rearrangement. The starting point of this route was Meldrum's acid (**7b**, Scheme 4) and alcohol **8b**,[8f] which were converted over three steps via acid chloride **5b** into keto ester dioxinone **9b** in 48% yield.

A selective Claisen reaction between keto ester **9b** and acyl chloride **6** gave diketo ester dioxinone **3b** (Scheme 5). Palladium-catalyzed decarboxylation and alkenylation occurred without any problems and with the anticipated regioselectivity,[9] giving the diketo dioxinone intermediate **2b**. Subsequent morpholine-catalyzed cyclization[14] smoothly provided resorcylate **13** in 41% yield over three steps. Phenol methylation with iodomethane and cesium carbonate gave ether **14** (94%). Potassium-carbonate-mediated transesterification, acetone loss, and lactonization directly gave lactone **15** (87%), a demethylmycophenolate derivative.[15]

It was planned to introduce the arene methyl group through a cross-coupling reaction. However, the required halogenation of arene **15** proved to be troublesome. Treatment with NBS, NIS, bromine, or iodine under various conditions led to intractable mixtures, mainly due to side reactions at the alkene unit. In contrast, treatment with iodine and *tert*-butylamine[16] gave clean conversion to iodo-ether **16** (Scheme 5, 82%) and diiodide **17** (5%). Both iodides **16** and **17** were isolated as single diastereoisomers,[17] X-ray crystal structure determinations of the starting material and both products[18] confirmed their structures unambiguously. Because neither increased amounts of iodine and *tert*-butylamine, nor longer reaction time or elevated temperatures significantly changed the ratio of product **16** to product **17**, we assume that only the free phenol **15** is reactive enough to allow arene iodination under these conditions. The competing formation of iodo-ether **16** thus prevents efficient arene iodination.

Although this method did not provide a compound with the required arene halogen substituent, but instead led to selective formation of an iodo-ether, we sought to use iodo-ether **16** to protect the double bond for more forcing arene electrophilic halogenation reaction conditions. Treatment of iodo-ether **16** with NBS and sulfuric acid gave bromide **18** (91%, Scheme 6).



Scheme 6. Synthesis of mycophenolic acid (**1**).

Cross-coupling of bromide **18** under Suzuki or Stille conditions proved completely unsatisfactory. Treatment with DABCO–$(AlMe_3)_2$ complex[19] in the presence of a palladium catalyst (Pd_2dba_3 and XPhos), however, not only me-

diated the critical cross-coupling reaction, but also conveniently resulted in deprotection of the double bond, thereby providing methyl mycophenolate (**19**) in 72% yield. It is noteworthy that, despite the deprotection of the iodo-ether, both the ester and the lactone functionality were tolerated under these reaction conditions. Furthermore, the deprotection resulted in formation of only one geometric isomer (*E*) for the alkene.[17] Final saponification of the methyl ester gave mycophenolic acid (**1**) in 66% yield. The analytical data for synthetically produced **1** are in full agreement with reported values for the isolated natural product.[7,8,21]

Conclusions

In conclusion, we describe the total synthesis of the fungal natural product mycophenolic acid (**1**) from alcohol **8b** in twelve steps and 6% overall yield. Key steps were a palladium-catalyzed decarboxylation and allylation (**3b**→**2b**) with subsequent biomimetic cyclization and aromatization (**2b**→**13**), and a cross-coupling with DABCO–$(AlMe_3)_2$ for late-stage arene methyl incorporation (**18**→**19**). Attempts to introduce this methyl group at an early stage led to the unexpected formation of γ-pyrone **12** instead of a mycophenolate derivative.

Experimental Section

General Methods: All reactions were carried out in oven-dried glassware under argon, with commercially supplied solvents and reagents unless otherwise stated. THF was redistilled from Na/Ph_2CO. "Hexanes" refers to petroleum spirit (boiling range 40–60 °C). Column chromatography was carried out on silica gel by flash techniques (eluents are given in parentheses). Analytical TLC was performed on pre-coated silica gel F_{254} aluminum plates with visualization under UV light or by staining with acidic vanillin or anisaldehyde spray reagents. Melting points were measured with a hot-stage apparatus. IR spectra were recorded neat. ^{1}H NMR spectra were recorded at 400 or 500 MHz, whereas ^{13}C NMR spectra were recorded at 100 or 125 MHz. Chemical shifts (δ) are quoted in ppm.

Synthesis of γ-Pyrone 12

Ethyl (*E*)-6-[4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2-methyl-3-oxobutanoyloxy]-4-methylhex-4-enoate (9a): 2,2,5-Trimethyl-1,3-dioxane-4,6-dione (**7a**, 1.58 g, 10.0 mmol, 1.0 equiv.) was dissolved in toluene (10 mL), and alcohol **8a**[10] (1.72 g, 10.0 mmol, 1.0 equiv.) was added. The solution was heated at 100 °C for 6 h. After the system had cooled to 20 °C, the solvent was evaporated and the resulting (*E*)-3-(6-ethoxy-3-methyl-6-oxohex-2-enyloxy)-2-methyl-3-oxopropanoic acid (2.72 g, 10.0 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (24 mL) and cooled to 0 °C. Oxalyl chloride (1.1 mL, 13.0 mmol, 1.3 equiv.) and a drop of DMF were added and the reaction mixture was stirred at 0 °C for 1.5 h. The solvents were evaporated, and the resulting oil was dried in vacuo to afford crude acid chloride **5a** as a brown oil. Hexamethyldisilazane (8.1 mL, 39.0 mmol, 3.9 equiv.) was dissolved in THF (150 mL) and the mixture was cooled to 0 °C. *n*BuLi in *n*-hexane (2.5 M, 16.4 mL, 41.0 mmol, 4.1 equiv.) was added dropwise, and the resulting mixture was stirred at 0 °C. After 1 h, it was cooled to –78 °C, whereupon dioxinone **4** (4.8 mL, 36.0 mmol, 3.6 equiv.) was added dropwise with stirring. After 1 h, the crude acid chloride **5a** was dissolved in THF (7 mL) and added dropwise with stirring to the dioxinone enolate at –78 °C. After 2 h, saturated aqueous NH_4Cl (5 mL) was added, the mixture was allowed to warm to 20 °C and diluted with Et_2O (150 mL), and HCl (1 M) was added to adjust the pH to ≈2. The mixture was extracted, the organic layer was separated, and the aqueous layer was reextracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator), and the residue was chromatographed on silica (hexanes/Et_2O 3:1→2:1→1:1→1:2) to afford β-keto ester **9a** (1.37 g, 3.46 mmol, 35% over two steps from alcohol **8a**) as a yellow oil. R_f = 0.21 (hexanes/Et_2O 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 5.32 (tq, *J* = 7.1, 1.3 Hz, 1 H, 5_{Hex}-H), 5.32 (s, 1 H, 5_{dioxin}-H), 4.62 (d, *J* = 7.2 Hz, 2 H, 6_{Hex}-H), 4.08 (q, *J* = 7.3 Hz, 2 H, $CO_2CH_2CH_3$), 3.55 (q, *J* = 7.1 Hz, 1 H, 2_{Bu}-H), 3.50 (d, *J* = 16.8 Hz, 1 H, 4_{Bu}-H^a), 3.42 (d, *J* = 16.8 Hz, 1 H, 4_{Bu}-H^b), 2.41–2.38 (m, 2 H, 2_{Hex}-H), 2.35–2.32 (m, 2 H, 3_{Hex}-H), 1.69 (s, 3 H, 4_{Hex}-Me), 1.67 (s, 6 H, 2_{dioxin}-Me_2), 1.33 (d, *J* = 7.1 Hz, 3 H, 2_{Bu}-Me), 1.21 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 198.6 (C-3_{Bu}), 172.7 (CO_2Et), 169.5 (C-1_{Bu}), 163.9 (C-4_{dioxin}), 160.5 (C-6_{dioxin}), 141.6 (C-4_{Hex}), 118.1 (C-5_{Hex}), 107.2 (C-2_{dioxin}), 96.9 (C-5_{dioxin}), 62.2 (C-6_{Hex}), 60.3 ($CO_2CH_2CH_3$), 52.8 (C-2_{Bu}), 45.5 (C-4_{Bu}), 34.2 (C-3_{Hex}), 32.4 (C-2_{Hex}), 24.9 (2_{dioxin}-Me^a), 24.8 (2_{dioxin}-Me^b), 16.4 (4_{Hex}-Me), 14.1 ($CO_2CH_2CH_3$), 12.4 (2_{Bu}-Me) ppm. IR: $\tilde{\nu}$ = 1720, 1638, 1442, 1452, 1390, 1374, 1334, 1272, 1251, 1200, 1116, 1089, 1013, 963, 932, 901, 855, 807, 636 cm^{-1}. HRMS (ESI) calcd. for $C_{20}H_{29}O_8$ [M + H]$^+$ 397.1862; found 397.1868.

[5-(2-Acetoxyacetyl)-3,6-dimethyl-4-oxo-4*H*-pyran-2-yl]methyl Acetate (12): Pyridine (0.52 mL, 6.40 mmol, 3.0 equiv.) and $MgCl_2$ (203 mg, 2.13 mmol) were added at 0 °C with stirring to β-keto ester **9a** (750 mg, 2.13 mmol, 1.0 equiv.) in CH_2Cl_2 (8.5 mL). After 15 min, acetoxyacetyl chloride (**6**, 0.57 mL, 5.34 mmol, 2.5 equiv.) was added dropwise and the resulting mixture was stirred at 0 °C for 1.5 h. Saturated aqueous NH_4Cl (5 mL) was added, followed by HCl (1 M) to adjust the pH to ≈2. The mixture was extracted, the organic layer was separated, and the aqueous layer was reextracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator), the crude ester **10** was dissolved in THF (11 mL), and the solution was purged with argon through a cannula for 15 min. $Pd(PPh_3)_4$ (96 mg, 0.08 mmol, 0.04 equiv.) was added and the reaction mixture was stirred at 20 °C for 21 h. Silica (3.0 g) was added, and the solvent was evaporated. The crude product was chromatographed on silica (hexanes/Et_2O 1:1) to afford γ-pyrone **12** (415 mg, 1.40 mmol, 66% over three steps from β-keto ester **9a**) as colorless crystals. R_f = 0.47 (hexanes/Et_2O 1:1), m.p. 93–96 °C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 5.10 [s, 2 H, 5-(CO)CH_2], 4.96 (s, 2 H, 2-CH_2), 2.43 (s, 3 H, 6-Me), 2.13 [s, 3 H, 5-(CO)CH_2O(CO)*Me*], 2.11 [s, 3 H, 2-CH_2O(CO)*Me*], 2.00 (s, 3 H, 3-Me) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 194.9 [5-(*C*O)CH_2], 177.2 (C-4), 170.6 [2 C, C-6, 5-(CO)CH_2-O(*C*O)Me], 170.0 [2-CH_2O(*C*O)Me], 156.5 (C-2), 125.0 (C-3), 122.3 (C-5), 70.0 [5-(CO)*C*H$_2$], 60.0 (2-CH_2), 20.4 [2 C, 2 × O(CO)*Me*], 19.4 (6-Me), 9.1 (3-Me) ppm. IR: $\tilde{\nu}$ = 1744, 1736, 1715, 1689, 1660, 1619, 1543, 1425, 1390, 1370, 1361, 1257, 1224, 1208, 1153, 1112, 1075, 1028, 989, 974, 948, 907, 843, 786, 768, 701, 695, 650, 623 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{17}O_7$ [M + H]$^+$ 297.0969; found 297.0976. $C_{14}H_{16}O_7$ (296.27): calcd. C 56.76, H 5.44; found C 56.69, H 5.37.

Analytical data for intermediate **10**: Yellow oil. R_f = 0.36 (hexanes/Et_2O 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 5.97 (s, 1 H, 4_{Bu}-H), 5.39 (s, 1 H, 5_{dioxin}-H), 5.31 (t, *J* = 6.8 Hz, 1 H, 5_{Hex}-H),

4.91 [d, J = 17.3 Hz, 1 H, 2_{Bu}-(CO)CH_2^a], 4.86 [d, J = 17.3 Hz, 1 H, 2_{Bu}-(CO)CH_2^b], 4.72 [d, J = 16.6 Hz, 1 H, 3_{Bu}-O(CO)CH_2^a], 4.67 [d, J = 16.6 Hz, 1 H, 3_{Bu}-O(CO)CH_2^b], 4.66 (dd, J = 15.1, 6.9 Hz, 2 H, 6_{Hex}-H^a), 4.63 (dd, J = 15.1, 6.9 Hz, 2 H, 6_{Hex}-H^b), 4.08 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 2.41–2.37 (m, 2 H, 3_{Hex}-H), 2.34–2.31 (m, 2 H, 2_{Hex}-H), 2.13 [s, 3 H, 2_{Bu}-(CO)CH_2O(CO)*Me*], 2.10 [s, 3 H, 3_{Bu}-O(CO)CH_2O(CO)*Me*], 1.69 (s, 3 H, 4_{Hex}-Me), 1.66 (s, 3 H, 2_{dioxin}-Me_2^a), 1.64 (s, 3 H, 2_{dioxin}-Me_2^b), 1.58 (s, 3 H, 2_{tBu}-Me), 1.20 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 196.8 [2_{Bu}-(*C*O)CH_2], 172.7 (*C*O_2Et), 169.7 [2 C, 2 × O(*C*O)Me], 167.7 (C-1_{Bu}), 164.4 (C-4_{dioxin}), 160.8 (C-6_{dioxin}), 160.2 [3_{Bu}-O(*C*O)CH_2], 148.9 (C-3_{Bu}), 142.5 (C-4_{Hex}), 117.4 (C-5_{Hex}), 113.9 (C-4_{Bu}), 107.2 (C-2_{dioxin}), 98.2 (C-5_{dioxin}), 65.9 [2_{Bu}-(CO)*C*H_2], 63.3 (C-2_{Bu}), 63.2 (C-6_{Hex}), 60.3 ($CO_2CH_2CH_3$), 59.8 [3_{Bu}-O(CO)*C*H_2], 34.1 (C-3_{Hex}), 32.4 (C-2_{Hex}), 24.8 (2_{dioxin}-Me_2^a), 24.4 (2_{dioxin}-Me_2^b), 20.2 [2 C, 2 × O(CO)*Me*], 19.1 (2_{Bu}-Me), 16.4 (4_{Hex}-Me), 14.1 ($CO_2CH_2CH_3$) ppm. Dioxinone **10** was obtained as mainly one diastereoisomer,[17] although the configuration of the $C3_{Bu}$=$C4_{Bu}$ double bond could not be determined.

Total Synthesis of Mycophenolic Acid (1)

Methyl (*E*)-6-[4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoyloxy]-4-methylhex-4-enoate (9b): Alcohol **8b**[8f] (1.64 g, 10.4 mmol, 1.0 equiv.) was added to Meldrum's acid (**7b**, 1.49 g, 10.4 mmol, 1.0 equiv.) in toluene (3 mL), and the mixture was heated at 100 °C for 13 h. After the system had cooled to 20 °C, the solvent was evaporated. The resulting (*E*)-3-(6-methoxy-3-methyl-6-oxohex-2-enyloxy)-3-oxopropanoic acid (2.53 g, 10.4 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (11 mL) and 2-methyl-2-butene (amylene, 11 mL, 104 mmol, 10 equiv.) and cooled to 0 °C. A drop of DMF was added, followed by oxalyl chloride (1.0 mL, 11.4 mmol, 1.1 equiv.), and the mixture was stirred at 0 °C for 30 min and subsequently at 20 °C for 2.5 h. Concentration (rotary evaporator) and further drying in vacuo gave the crude acid chloride **5b** as a brown oil. Under argon, hexamethyldisilazane (6.8 mL, 32.8 mmol, 3.2 equiv.) was dissolved in THF (56 mL) and cooled to 0 °C. *n*BuLi in *n*-hexane (2.5 M, 13.9 mL, 34.8 mmol, 3.4 equiv.) was added dropwise, and the resulting mixture was stirred at 0 °C for 2.5 h and cooled to –78. Dioxinone **4** (4.1 mL, 30.7 mmol, 3.0 equiv.) in dry THF (5 mL) was added dropwise with stirring. After 1 h, the crude acid chloride **5b** was dissolved in THF (5 mL) and added dropwise with stirring to the dioxinone enolate at –78 °C. After 1.5 h, saturated aqueous NH_4Cl (20 mL) was added, and after warming to 20 °C, the solution was diluted with Et_2O (100 mL), and HCl (1 M) was added to adjust the pH to ≈2. The mixture was extracted, the organic layer was separated, and the aqueous layer was further extracted with Et_2O (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed on silica (hexanes/Et_2O 1:1→1:2) to give β-keto ester **9b** (1.82 g, 4.94 mmol, 48% over three steps from alcohol **8b**) as a yellow oil. R_f = 0.33 (hexanes/Et_2O 1:3). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 5.36 (s, 1 H, 5_{dioxin}-H), 5.34 (m_c, 1 H, 5_{Hex}-H), 4.65 (d, J = 7.0 Hz, 2 H, 6_{Hex}-H), 3.66 (s, J = 7.3 Hz, 3 H, CO_2Me), 3.50 (s, 2 H, 2_{Bu}-H), 3.49 (s, 2 H, 4_{Bu}-H), 2.46–2.42 (m, 2 H, 2_{Hex}-H), 2.38–2.34 (m, 2 H, 3_{Hex}-H), 1.72 (s, 3 H, 4_{Hex}-Me), 1.70 (s, 6 H, 2_{dioxin}-Me_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 195.6 (C-3_{Bu}), 173.3 (*C*O_2Me), 166.3 (C-1_{Bu}), 163.5 (C-4_{dioxin}), 160.4 (C-6_{dioxin}), 141.6 (C-4_{Hex}), 118.1 (C-5_{Hex}), 107.3 (C-2_{dioxin}), 97.1 (C-5_{dioxin}), 62.3 (C-6_{Hex}), 51.6 (OMe), 49.0 (C-2_{Bu}), 46.9 (C-4_{Bu}), 34.2 (C-3_{Hex}), 32.3 (C-2_{Hex}), 25.0 (2 C, 2_{dioxin}-Me_2), 16.4 (4_{Hex}-Me) ppm. IR: $\tilde{\nu}$ = 1722, 1638, 1390, 1375, 1271, 1252, 1200, 1158, 1015, 982, 902, 807 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{25}O_8$ [M + H]$^+$ 369.1549; found 369.1541.

Methyl (*E*)-6-[5-(Acetoxymethyl)-7-hydroxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-8-yl]-4-methylhex-4-enoate (13): β-Keto ester **9b** (2.28 g, 6.19 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (60 mL) and cooled to 0 °C. Pyridine (1.0 mL, 12.4 mmol, 2.0 equiv.) and $MgCl_2$ (589 mg, 6.19 mmol, 1.0 equiv.) were added with stirring at 0 °C. After 15 min, acetoxyacetyl chloride (**6**, 1.0 mL, 7.4 mmol, 1.2 equiv.) was added dropwise with stirring at 0 °C. After 1 h, saturated aqueous NH_4Cl (10 mL) was added, followed by HCl (1 M) to adjust the pH to ≈2. The mixture was extracted, the organic layer was separated, and the aqueous layer was reextracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator), and the resulting crude diketo ester dioxinone **3b** was dissolved in THF (18.5 mL), and degassed by purging with argon for 15 min. $Pd(PPh_3)_4$ (215 mg, 0.19 mmol, 0.03 equiv.) was added and the mixture was stirred at 20 °C for 24 h. Morpholine (0.54 mL, 6.2 mmol, 1.0 equiv.) was added, the mixture was stirred at 20 °C for 18 h and diluted with Et_2O (100 mL), and HCl (1 M, 50 mL) was added. The mixture was extracted, the organic layer was separated, and the aqueous layer was further extracted with Et_2O (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed on silica (hexanes/Et_2O 2:1→1:1) to afford resorcylate **13** (1.03 g, 2.54 mmol, 41% over three steps from β-keto ester **9b**) as a yellow oil. R_f = 0.38 (hexanes/Et_2O 1:3). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 8.30 (s, 1 H, OH), 6.67 (s, 1 H, 6_{HetAr}-H), 5.46 (s, 2 H, CH_2OAc), 5.15 (t, J = 7.1 Hz, 1 H, 5_{Hex}-H), 3.59 (s, 3 H, OMe), 3.25 (d, J = 7.1 Hz, 2 H, 6_{Hex}-H), 2.39–2.35 (m, 2 H, 2_{Hex}-H), 2.26–2.23 (m, 2 H, 3_{Hex}-H), 2.08 [s, 3 H, CH_2O(CO)*Me*], 1.72 (s, 3 H, 4_{Hex}-Me), 1.64 (s, 6 H, 2_{HetAr}-Me_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 174.3 (*C*O_2Me), 171.0 [CH_2O(*C*O)Me], 161.0 (C7_{HetAr}), 160.9 (C-4_{HetAr}), 156.3 (C$8a_{HetAr}$), 139.1 (C-5_{HetAr}), 134.0 (C-4_{Hex}), 121.9 (C-5_{Hex}), 115.1 (C8_{HetAr}), 109.7 (C-6_{HetAr}), 105.2 (C-2_{HetAr}), 102.8 (C-$4a_{HetAr}$), 64.1 (*C*H_2OAc), 51.5 (OMe), 34.5 (C-3_{Hex}), 32.3 (C-2_{Hex}), 25.0 (2 C, 2_{HetAr}-Me_2), 21.6 (C-6_{Hex}), 20.7 [CH_2O(CO)*Me*], 15.8 (4_{Hex}-Me) ppm. IR: $\tilde{\nu}$ = 1718, 1598, 1298, 1275, 1209, 1228, 1166, 1030, 906, 726, 648, 614 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{27}O_8$ [M + H]$^+$ 407.1706; found 407.1710.

Methyl (*E*)-6-[5-(Acetoxymethyl)-7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-8-yl]-4-methylhex-4-enoate (14): Cs_2CO_3 (1.68 g, 5.17 mmol, 3.0 equiv.) and MeI (0.32 mL, 5.17 mmol, 3.0 equiv.) were added with stirring at 20 °C to phenol **13** (700 mg, 1.72 mmol, 1.0 equiv.) in THF (17 mL). After 18 h, saturated aqueous NH_4Cl (50 mL) and Et_2O (50 mL) were added. The mixture was extracted, the organic layer was separated, and the aqueous layer was reextracted with Et_2O (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated. The crude product was chromatographed on silica (hexanes/Et_2O 1:1) to afford methyl ether **14** (682 mg, 1.62 mmol, 94%) as a colorless oil. R_f = 0.24 (hexanes/Et_2O 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 6.69 (s, 1 H, 6_{HetAr}-H), 5.55 (s, 2 H, CH_2OAc), 5.08 (t, J = 7.3 Hz, 1 H, 5_{Hex}-H), 3.89 (s, 3 H, ArO*Me*), 3.59 (s, 3 H, CO_2Me), 3.26 (d, J = 7.3 Hz, 2 H, 6_{Hex}-H), 2.39–2.34 (m, 2 H, 2_{Hex}-H), 2.28–2.23 (m, 2 H, 3_{Hex}-H), 2.15 [s, 3 H, CH_2O(CO)*Me*], 1.74 (s, 3 H, 4_{Hex}-Me), 1.67 (s, 6 H, 2_{HetAr}-Me_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 173.7 (*C*O_2Me), 170.4 [CH_2O(*C*O)Me], 162.4 (C7_{HetAr}), 160.2 (C-4_{HetAr}), 155.5 (C$8a_{HetAr}$), 139.9 (C-5_{HetAr}), 133.8 (C-4_{Hex}), 122.0 (C-5_{Hex}), 117.0 (C8_{HetAr}), 105.2 (C-2_{HetAr}), 104.5 (C-6_{HetAr}), 104.2 (C-$4a_{HetAr}$), 64.3 (*C*H_2OAc), 55.7 (ArO*Me*), 51.5 (CO_2*Me*), 34.6 (C-3_{Hex}), 32.8 (C-2_{Hex}), 25.7 (2 C, 2_{HetAr}-Me_2), 21.7 (C-6_{Hex}), 20.9 [CH_2O(CO)*Me*], 15.9 (4_{Hex}-

Me) ppm. IR: ṽ = 1724, 1608, 1580, 1295, 1219, 1206, 1166, 1119, 1030, 987 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{28}O_8Na$ [M + Na]$^+$ 443.1682; found 443.1690.

Methyl (*E*)-6-(4-Hydroxy-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate (15): Ester **14** (392 mg, 0.93 mmol, 1.0 equiv.) was dissolved in dry MeOH (19 mL). K_2CO_3 (387 mg, 2.80 mmol, 3.0 equiv.) was added, and the reaction mixture was stirred at 20 °C for 18 h. The solvent was evaporated and Et_2O (50 mL) was added, followed by HCl (1 M) to adjust the pH to ≈2. The mixture was extracted, the organic layer was removed, and the aqueous layer was reextracted with Et_2O (2× 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator) to leave pure lactone **15** (260 mg, 0.81 mmol, 87%) as a colorless solid. R_f = 0.34 (hexanes/Et_2O 1:3), m.p. 100–102 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.72 (s, 1 H, OH), 6.48 (s, 1 H, 7_{HetAr}-H), 5.23 (s, 2 H, 1_{HetAr}-H), 5.20 (t, J = 7.2 Hz, 1 H, 5_{Hex}-H), 3.89 (s, 3 H, ArO*Me*), 3.60 (s, 3 H, CO_2Me), 3.34 (d, J = 7.2 Hz, 2 H, 6_{Hex}-H), 2.40–2.36 (m, 2 H, 2_{Hex}-H), 2.30–2.25 (m, 2 H, 3_{Hex}-H), 1.77 (s, 3 H, 4_{Hex}-Me) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 173.9 (*C*O_2Me), 172.8 (C-3_{HetAr}), 164.8 (C-6_{HetAr}), 154.5 (C-4_{HetAr}), 146.0 (C$7a_{HetAr}$), 134.1 (C-4_{Hex}), 122.2 (C-5_{Hex}), 116.5 (C-5_{HetAr}), 104.2 (C-$3a_{HetAr}$), 96.0 (C7_{HetAr}), 70.4 (C-1_{HetAr}), 56.1 (ArO*Me*), 51.4 (CO_2*Me*), 34.7 (C-3_{Hex}), 32.9 (C-2_{Hex}), 21.5 (C-6_{Hex}),15.9 (4_{Hex}-Me) ppm. IR: ṽ = 1729, 1615, 1469, 1438, 1345, 1289, 1252, 1202, 1168, 1127, 1077, 1055 cm^{-1}. HRMS (CI) calcd. for $C_{17}H_{24}NO_6Na$ [M + NH_4]$^+$ 338.1604; found 338.1598.

Methyl (*S)-4-Iodo-4-[(*R**)-4-methoxy-8-oxo-2,3,6,8-tetrahydro-1*H*-furo[3,4-*g*]benzofuran-2-yl]pentanoate (16) and Methyl (*S**)-4-Iodo-4-[(*R**)-5-iodo-4-methoxy-8-oxo-2,3,6,8-tetrahydro-1*H*-furo[3,4-*g*]benzofuran-2-yl]pentanoate (17):** I_2 (307 mg, 1.21 mmol, 2.0 equiv.) and *t*$BuNH_2$ (0.25 mL, 2.42 mmol, 4.0 equiv.) in toluene (9 mL) were stirred for 15 min, after which phenol **15** (194 mg, 0.61 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) was added with stirring at 20 °C. After 18 h, CH_2Cl_2 (50 mL), water (20 mL), HCl (1 M, 5 mL), and saturated aqueous $Na_2S_2O_3$ (5 mL) were added. The mixture was extracted, the organic layer was separated, and the aqueous layer was reextracted with CH_2Cl_2 (2× 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed on silica (hexanes/Et_2O 1:3→Et_2O) to afford iodo-ether **16** (221 mg, 0.50 mmol, 82%) and diiodide **17** (19 mg, 0.03 mmol, 5%) as colorless solids.

Analytical data for **16**: R_f = 0.18 (hexanes/Et_2O 1:3), m.p. 122–124 °C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 6.45 (s, 1 H, 5_{HetAr}-H), 5.19 (s, 2 H, 6_{HetAr}-H), 4.80 (pseudo-t J = 8.4 Hz, 1 H, 2_{HetAr}-H), 3.90 (s, 3 H, ArO*Me*), 3.69 (s, 3 H, CO_2Me), 3.36 (dd, J = 16.4, 9.8 Hz, 1 H, 3_{HetAr}-H^a), 3.20 (dd, J = 16.4, 7.3 Hz, 1 H, 3_{HetAr}-H^b), 2.71 (ddd, J = 16.1, 11.1, 5.0 Hz, 1 H, 2_{Pent}-H^a), 2.59 (ddd, J = 16.2, 11.1, 5.2 Hz, 1 H, 2_{Pent}-H^b), 2.29 (ddd, J = 15.6, 11.3, 5.2 Hz, 1 H, 3_{Pent}-H^a), 2.08 (ddd, J = 15.2, 11.1, 5.2 Hz, 1 H, 3_{Pent}-H^b), 1.85 (s, 3 H, 5_{Pent}-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 172.9 (*C*O_2Me), 168.2 (C8_{HetAr}), 161.3 (C-4_{HetAr}), 158.1 (C$8b_{HetAr}$), 150.3 (C-$5a_{HetAr}$), 114.1 (C-$3a_{HetAr}$), 102.1 (C$8a_{HetAr}$), 96.6 (C-5_{HetAr}), 91.9 (C-2_{HetAr}), 69.4 (C-6_{HetAr}), 56.5 (ArO*Me*), 55.9 (C-4_{Pent}), 51.8 (CO_2*Me*), 38.7 (C-3_{Pent}), 32.7 (C-2_{Pent}), 32.5 (C-3_{HetAr}), 27.4 (C-5_{Pent}) ppm. IR: ṽ = 1753, 1633, 1613, 1457, 1355, 1332, 1298, 1226, 1201, 1140, 1089, 1015 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{19}NO_6NaI$ [M + Na]$^+$ 469.0124; found 469.0116.

Analytical data for **17**: R_f = 0.39 (hexanes/Et_2O 1:3), m.p. 124–128 °C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 4.99 (s, 2 H, 6_{HetAr}-H), 4.74 (dd, J = 8.9, 7.4 Hz, 1 H, 2_{HetAr}-H), 4.06 (s, 3 H, ArO*Me*), 3.72 (s, 3 H, CO_2Me), 3.68 (dd, J = 16.2, 9.6 Hz, 1 H, 3_{HetAr}-H^a), 3.49 (dd, J = 16.1, 7.1 Hz, 1 H, 3_{HetAr}-H^b), 2.73 (ddd, J = 16.1, 11.0, 5.0 Hz, 1 H, 2_{Pent}-H^a), 2.61 (ddd, J = 16.3, 11.1, 5.3 Hz, 1 H, 2_{Pent}-H^b), 2.30 (ddd, J = 16.1, 11.0, 5.0 Hz, 1 H, 3_{Pent}-H^a), 2.05 (ddd, J = 15.1, 11.0, 5.3 Hz, 1 H, 3_{Pent}-H^b), 1.89 (s, 3 H, 5_{Pent}-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 172.9 (*C*O_2Me), 167.8 (C8_{HetAr}), 159.9 (C-4_{HetAr}), 159.8 (C$8b_{HetAr}$), 153.1 (C-$5a_{HetAr}$), 116.1 (C-$3a_{HetAr}$), 105.6 (C$8a_{HetAr}$), 91.8 (C-2_{HetAr}), 73.1 (C-5_{HetAr}), 71.8 (C-6_{HetAr}), 59.8 (ArO*Me*), 56.0 (C-4_{Pent}), 52.0 (CO_2*Me*), 38.5 (C-3_{Pent}), 34.2 (C-3_{HetAr}), 32.6 (C-2_{Pent}), 27.8 (C-5_{Pent}) ppm. IR: ṽ = 2923, 1759, 1629, 1437, 1386, 1295, 1253, 1219, 1128, 1065, 1021, 980 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{19}NO_6I_2$ [M + H]$^+$ 572.9271; found 572.9272.

Methyl (*S)-4-Iodo-4-[(*R**)-5-Bromo-4-methoxy-8-oxo-2,3,6,8-tetrahydro-1*H*-furo[3,4-*g*]benzofuran-2-yl]pentanoate (18):** *N*-Bromosuccinimide (26 mg, 0.15 mmol, 1.5 equiv.) and concentrated H_2SO_4 (20 μL) were added sequentially with stirring at 20 °C to arene **16** (51 mg, 0.11 mmol, 1.0 equiv.) in THF (0.6 mL). After 12 h, saturated aqueous $NaHCO_3$ (1 mL) and $Na_2S_2O_3$ (1 mL) were added and the mixture was extracted with EtOAc (3× 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed on silica (hexanes/Et_2O 1:1) to give bromide **18** (54 mg, 0.10 mmol, 91%) as a white crystalline solid. R_f = 0.40 (hexanes/Et_2O 1:3), m.p. 65–68 °C (EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 5.09 (s, 2 H, 6_{HetAr}-H), 4.75 (m_c, 1 H, 2_{HetAr}-H), 4.07 (s, 3 H, ArO*Me*), 3.72 (s, 3 H, CO_2Me), 3.66 (dd, J = 16.2, 9.6 Hz, 1 H, 3_{HetAr}-H^a), 3.48 (dd, J = 16.4, 7.1 Hz, 3_{HetAr}-H^b), 2.73 (ddd, J = 16.1, 10.9, 5.1 Hz, 1 H, 2_{Pent}-H^a), 2.61 (ddd, J = 16.2, 11.1, 5.3 Hz, 1 H, 2_{Pent}-H^b), 2.31 (ddd, J = 15.9, 11.0, 5.1 Hz, 1 H, 3_{Pent}-H^a), 2.06 (ddd, J = 15.1, 11.0, 5.3 Hz, 1 H, 3_{Pent}-H^b), 1.89 (s, 3 H, 5_{Pent}-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 172.8 (*C*O_2Me), 167.4 (C8_{HetAr}), 158.4 (C-4_{HetAr}), 157.8 (C$8b_{HetAr}$), 148.8 (C-$5a_{HetAr}$), 117.7 (C-$3a_{HetAr}$), 104.9 (C$8a_{HetAr}$), 99.1 (C-5_{HetAr}), 91.9 (C-2_{HetAr}), 70.0 (C-6_{HetAr}), 59.9 (ArO*Me*), 56.0 (C-4_{Pent}), 51.9 (CO_2*Me*), 38.6 (C-3_{Pent}), 34.2 (C-3_{HetAr}), 32.6 (C-2_{Pent}), 27.8 (C-5_{Pent}) ppm. IR: ṽ = 2941, 1757, 1738, 1626, 1435, 1390, 1248, 1194, 1133, 961 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{18}BrINaO_6$ [M + Na]$^+$ 546.9229; found 546.9224. $C_{17}H_{18}BrINaO_6$ (523.93): calcd. C 38.88, H 3.45; found C 38.91, H 3.38.

Methyl (*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate (19): Bromide **18** (50 mg, 0.10 mmol, 1.0 equiv.), tris(dibenzylidenacetone)dipalladium [$Pd_2(dba)_3$, 2.6 mg, 2.9 μmol, 0.03 equiv.], and 2-dicyclohexylphosphanyl-2′,4′,6′-triisopropylbiphenyl (XPhos, 2.7 mg, 5.7 μmol, 0.06 equiv.) were suspended in THF (0.8 mL) and stirred for 10 min at 20 °C. Bis(trimethylaluminum)–1,4-diazabicyclo[2.2.2]octane [DABCO–($AlMe_3$)$_2$, 39 mg, 0.15 mmol, 1.5 equiv.] was added in one portion with stirring and the resulting red solution was kept at 60 °C for 12 h. The mixture was cooled to 20 °C and quenched by addition of aqueous HCl (2 M, 2 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), concentrated (rotary evaporator), and chromatographed on silica (hexanes/Et_2O 1:1) to give resorcylate **19** (23 mg, 69 μmol, 72%) as an off-white crystalline solid. R_f = 0.49 (hexanes/Et_2O 1:3), m.p. 98–101 °C (Et_2O), ref.[20] 96–97 °C (MeOH and hexane). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.69 (s, 1 H, OH), 5.26 (t, J = 7.1 Hz, 1 H, 5_{Hex}-H), 5.23 (s, 2 H, 1_{HetAr}-H), 3.79 (s, 3 H, ArO*Me*), 3.65 (s, 3 H, CO_2Me), 3.41 (d, J = 6.9 Hz, 2 H, 6_{Hex}-H), 2.45–2.43 (m, 2 H, 2_{Hex}-H), 2.36–2.33 (m, 2 H, 3_{Hex}-H), 2.18 (s, 3 H, 7_{HetAr}-Me), 1.83 (s, 3 H, 4_{Hex}-Me) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 173.8 (*C*O_2Me), 172.9 (C-3_{HetAr}), 163.7 (C-6_{HetAr}), 153.7 (C-4_{HetAr}),

143.9 ($C7a_{HetAr}$), 134.2 ($C\text{-}4_{Hex}$), 122.7 ($C7_{Hex}$), 122.1 ($C\text{-}5_{Hex}$), 116.7 ($C\text{-}5_{HetAr}$), 106.4 ($C\text{-}3a_{HetAr}$), 70.0 ($C\text{-}1_{HetAr}$), 60.9 (ArO*Me*), 51.5 (CO_2*Me*), 34.6 ($C\text{-}3_{Hex}$), 32.9 ($C\text{-}2_{Hex}$), 22.6 ($C\text{-}6_{Hex}$), 16.1 (4_{Hex}-Me), 11.6 (7_{HetAr}-Me) ppm. IR: $\tilde{\nu}$ = 3438, 2930, 1729, 1625, 1451, 1367, 1165, 1132, 1073, 1027, 969 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{23}O_6$ $[M + H]^+$ 335.1495; found 335.1501. The spectra match the reported data for **19**.[8a,8f,20]

(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic Acid (Mycophenolic Acid, 1): Methyl ester **19** (10 mg, 0.03 mmol, 1.0 equiv.) and LiOH (2.8 mg, 0.12 mmol) were suspended in a mixture of H_2O and THF (1:4, 1.2 mL) and stirred at 20 °C for 24 h. THF (5 mL) was added, and the solution was concentrated to dryness. The resulting residue was treated with aqueous HCl (1 M, 1 mL), H_2O (4 mL), and EtOAc (10 mL). The mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts were washed with brine (2 mL) and dried ($MgSO_4$), and the solvents were evaporated. The crude product was chromatographed on silica (CH_2Cl_2/EtOAc 1:1) and recrystallized (CH_2Cl_2 and pentane) to give acid **1** (6.3 mg, 20 μmol, 66%) as an off-white crystalline solid. R_f = 0.29 (CH_2Cl_2/EtOAc 1:1), m.p. 137–140 °C (CH_2Cl_2 and pentane), ref.[8g] 140 °C (CH_2Cl_2 and hexane). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 5.27 (t, J = 6.6 Hz, 1 H, 5_{Hex}-H), 5.25 (s, 2 H, 1_{HetAr}-H), 3.77 (s, 3 H, ArO*Me*), 3.41 (d, J = 6.8 Hz, 2 H, 6_{Hex}-H), 2.47–2.43 (m, 2 H, 2_{Hex}-H), 2.34–2.30 (m, 2 H, 3_{Hex}-H), 2.16 (s, 3 H, 7_{HetAr}-Me), 1.82 (s, 3 H, 4_{Hex}-Me) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 178.2 (CO_2H), 172.9 ($C\text{-}3_{HetAr}$), 163.7 ($C\text{-}6_{HetAr}$), 153.7 ($C\text{-}4_{HetAr}$), 143.9 ($C7a_{HetAr}$), 133.9 ($C\text{-}4_{Hex}$), 122.9 ($C7_{Hex}$), 122.1 ($C\text{-}5_{Hex}$), 116.7 ($C\text{-}5_{HetAr}$), 106.4 ($C\text{-}3a_{HetAr}$), 70.0 ($C\text{-}1_{HetAr}$), 60.9 (ArO*Me*), 34.2 ($C\text{-}3_{Hex}$), 32.5 ($C\text{-}2_{Hex}$), 22.6 ($C\text{-}6_{Hex}$), 16.1 (4_{Hex}-Me), 11.6 (7_{HetAr}-Me) ppm. IR: $\tilde{\nu}$ = 3418, 2934, 1738, 1701, 1623, 1410, 1328, 1203, 1131, 1073, 1027, 964, 914 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{23}O_6$ $[M - H]^+$ 319.1182; found 319.1172. The spectra match the reported data for **1**.[7,8,21]

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of mycophenolic acid (**1**), keto ester dioxinones **9a**–**b**, intermediate **10**, γ-pyrone **12**, resorcylates **13**–**15** and **19**, and iodo-ethers **16**–**18**, X-ray structural data for γ-pyrone **12**, resorcylate **15**, iodo-ether **16**, and diiodide **17**, and possible mechanism for the formation of **12** from **10**.

Acknowledgments

The authors thank the European Research Council (ERC) for generous grant support, GlaxoSmithKline for the Glaxo endowment, and P. R. Haycock and R. N. Sheppard for high-resolution NMR spectroscopy.

[1] For an excellent and comprehensive review on mycophenolic acid, see: R. Bentley, *Chem. Rev.* **2000**, *100*, 3801–3825.
[2] a) B. Gosio, *G. R. Accad. Med. Torino* **1893**, *61*, 484–487; b) B. Gosio, *Riv. Ig. Sanità Pubbl.* **1896**, *7*, 825–849; c) B. Gosio, *Riv. Ig. Sanità Pubbl.* **1896**, *7*, 869–888.
[3] a) J. H. Birkinshaw, H. Raistrick, D. J. Ross, *Biochem. J.* **1952**, *50*, 630–634; b) W. R. Logan, G. T. Newbold, *J. Chem. Soc.* **1957**, 1946–1951; X-ray crystal structure determination: c) W. Harrison, H. M. M. Shearer, J. Trotter, *J. Chem. Soc. Perkin Trans. 2* **1972**, 1542–1544.
[4] a) N. G. Vinokurova, N. E. Ivanushkina, G. A. Kochkina, M. U. Arinbasarov, S. M. Ozerskaya, *Appl. Biochem. Microbiol.* **2005**, *41*, 83–86; b) J. C. Frisvad, U. Thrane, R. A. Samson, J. I. Pitt, *Adv. Exp. Med. Biol.* **2006**, *571*, 3–31.
[5] a) D. N. Planterose, *J. Gen. Virol.* **1969**, *4*, 629–630; b) A. Mitsui, S. Suzuki, *J. Antibiot.* **1969**, *22*, 358–363; c) A. C. Allison, E. M. Eugui, *Immunol. Rev.* **1993**, *136*, 5–28; d) S. Gabardi, J. Cerio, *Prog. Transplant.* **2004**, *14*, 148–156; e) T. R. Srinivas, J. D. Schold, H.-U. Meier-Kriesche, *Expert Rev. Clin. Immunol.* **2006**, *2*, 495–518.
[6] G. Cholewinski, M. Malachowska-Ugarte, K. Dzierzbicka, *Curr. Med. Chem.* **2010**, *17*, 1926–1941.
[7] a) A. J. Birch, J. J. Wright, *J. Chem. Soc. C* **1969**, 788–789; b) A. J. Birch, J. J. Wright, *Aust. J. Chem.* **1969**, *22*, 2635–2644.
[8] a) L. Canonica, B. Rindone, E. Santaniello, C. Scolastico, *Tetrahedron* **1972**, *28*, 4395–4404; b) R. L. Danheiser, S. K. Gee, J. J. Perez, *J. Am. Chem. Soc.* **1986**, *108*, 806–810; c) J. W. Patterson, G. T. Huang, *J. Chem. Soc., Chem. Commun.* **1991**, 1579–1580; d) J. W. Patterson, *Tetrahedron* **1993**, *49*, 4789–4798; e) J. W. Patterson, *J. Org. Chem.* **1995**, *60*, 4542–4548; f) P. A. Plé, A. Hamon, G. Jones, *Tetrahedron* **1997**, *53*, 3395–3400; g) R. A. de la Cruz, F. X. Talamás, A. Vázquez, J. M. Muchowski, *Can. J. Chem.* **1997**, *75*, 641–645; h) A. Covarrubias-Zúñiga, A. Gonzalez-Lucas, *Tetrahedron Lett.* **1998**, *39*, 2881–2882; i) I. Shimizu, Y. Lee, Y. Fujiwara, *Synlett* **2000**, 1285–1286; j) Y. Lee, Y. Fujiwara, K. Ujita, M. Nagatomo, H. Ohta, I. Shimizu, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1437–1443; k) A. Covarrubias-Zúñiga, A. Gonzalez-Lucas, M. M. Domínguez, *Tetrahedron* **2003**, *59*, 1989–1994.
[9] a) K. Anderson, F. Calo, T. Pfaffeneder, A. J. P. White, A. G. M. Barrett, *Org. Lett.* **2011**, *13*, 5748–5750; b) J. Cordes, F. Calo, K. Anderson, T. Pfaffeneder, S. Laclef, A. J. P. White, A. G. M. Barrett, *J. Org. Chem.* **2012**, *77*, 652–657; c) J. Cordes, S. Laclef, A. J. P. White, A. G. M. Barrett, *J. Org. Chem.* **2012**, *77*, 3524–3530.
[10] A. D. Fischer, A. Barakat, Z. Xin, M. E. Weiss, R. Peters, *Chem. Eur. J.* **2009**, *15*, 8722–8741.
[11] The diketo dioxinones and triketo compounds exist as mixtures of keto–enol tautomers. For simplicity, all are drawn in the all-keto form.
[12] M. W. Rathke, P. J. Cowan, *J. Org. Chem.* **1985**, *50*, 2622–2624.
[13] A detailed discussion of the possible mechanism for the formation of **12** from **10** can be found in the Supporting Information.
[14] J. Cordes, A. G. M. Barrett, *Eur. J. Org. Chem.* **2013**, 1318–1326.
[15] Unfortunately, the arene methyl group is essential for the activity of mycophenolic acid, for details, see ref. 16a.
[16] a) P. H. Nelson, S. F. Carr, B. H. Devens, E. M. Eugui, F. Franco, C. Gonzalez, R. C. Hawley, D. G. Loughhead, D. J. Milan, E. Papp, J. W. Patterson, S. Rouhafza, E. B. Sjogren, D. B. Smith, R. A. Stephenson, F. X. Talamas, A.-M. Waltos, R. J. Weikert, J. C. Wu, *J. Med. Chem.* **1996**, *39*, 4181–4196; b) S. Yonezawa, T. Komurasaki, K. Kawada, T. Tsuri, M. Fuji, A. Kugimiya, N. Haga, S. Mitsumori, M. Inagaki, T. Nakatani, Y. Tamura, S. Takechi, T. Taishi, M. Ohtani, *J. Org. Chem.* **1998**, *63*, 5831–5837.
[17] Determined by ^1H NMR spectroscopy.
[18] For details on the X-ray crystal structure determinations see the Supporting Information. CCDC-945709 (for γ-pyrone **12**), -945710 (for lactone **15**), -945711 (for iodo-ether **16**) and -945712 (for diiodide **17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[19] T. Cooper, A. Novak, L. D. Humphreys, M. D. Walker, S. Woodward, *Adv. Synth. Catal.* **2006**, *348*, 686–690.
[20] D. B. Smith, A. M. Waltos, D. G. Loughhead, R. J. Weikert, D. J. Morgans Jr, J. C. Rohloff, J. O. Link, R. Zhu, *J. Org. Chem.* **1996**, *61*, 2236–2241.
[21] a) Y. Fujimoto, M. Kamiya, H. Tsunoda, K. Ohtsubo, T. Tatsuno, *Chem. Pharm. Bull.* **1980**, *28*, 1062–1066; b) M. Seibold, P. Wolschann, O. Olsen, *Monatsh. Chem.* **2011**, *142*, 1309–1315.

Received: July 1, 2013
Published Online: September 24, 2013

