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THE SYNTHESIS OF MYCOPHENOLIC ACID[1]

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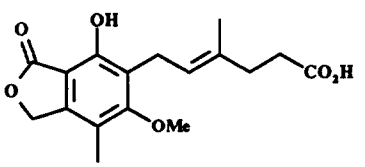
Summary: A new synthesis of mycophenolic acid **1**, has been accomplished using silyloxy-1,3-cyclohexadiene **9** which undergoes cycloaddition to dimethyl acetylenedicarboxylate and subsequent elimination of ethylene (Alder-Rickert reaction) to give the trisubstituted dimethyl phthalate **11**. After conversion of **11** to phthalide **16**, the (E)-4-methyl-4-hexenoic acid side-chain was constructed via an orthoester Claisen rearrangement using allylic alcohol **19** and triethyl orthoacetate.

Mycophenolic acid (**1**), a metabolite of Penicillium brevi-compactum, first isolated nearly 100 years ago[2], has lately become of interest as an immunosuppressant with possible utility in the treatment of organ transplant rejection and rheumatoid arthritis[3]. Mycophenolic acid (**1**) was originally synthesized by Birch and Wright[2] and has been the subject of several total[4,5] and formal[6] syntheses which focus on preparation of the important phthalide intermediate **2**.



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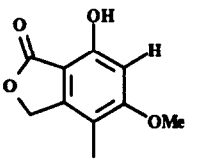

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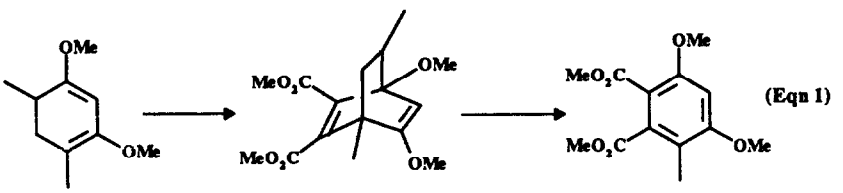
The Birch synthesis of mycophenolic acid employs an Alder-Rickert reaction[7] to construct the pentasubstituted benzene intermediate **5** as shown in Equation 1. The diene **3** was prepared by metal-



(Eqn 1)

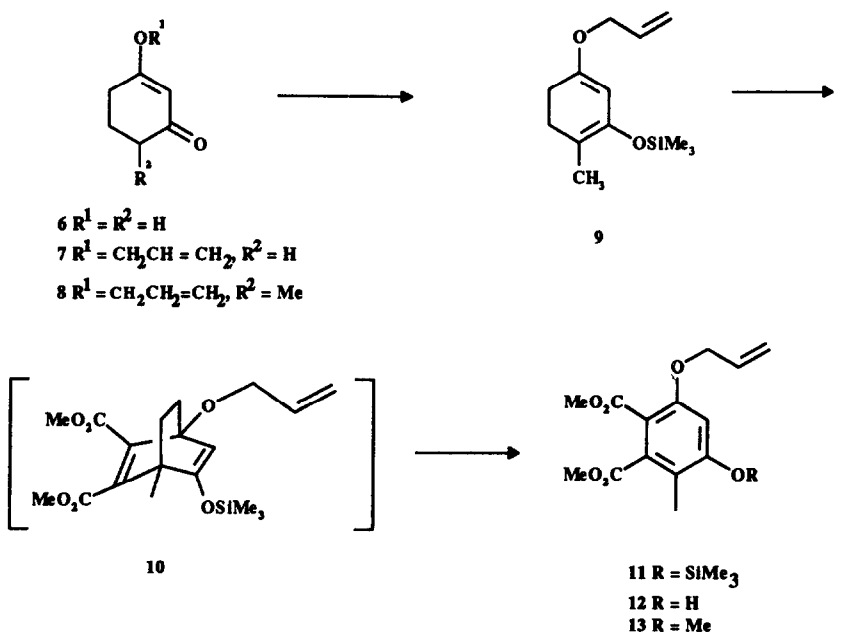
3 **4** **5**

ammonia reduction of 1,3-dimethoxy-4,6-dimethylbenzene followed by base catalyzed isomerization. In the past twenty years much progress has been made in the development of synthetic methods for the conversion of α,β-unsaturated ketones into silyloxy-1,3-dienes and their subsequent use in cycloaddition reactions[8]. The subject of this report is a new synthesis of mycophenolic acid using a 1,3-cyclohexadiene (**9**) prepared from

a 3-alkoxy-2-cyclohexenone (**8**) in an Alder-Rickert reaction to construct a pentasubstituted benzene intermediate **11**[9]. The conclusion of the synthesis demonstrates the application of the orthoester Claisen rearrangement for the stereospecific introduction of the (E)-4-methyl-4-hexenoic side-chain[10].

This approach to the synthesis of mycophenolic acid begins with the preparation of a 1,3-cyclohexadiene **9** and its conversion to a dimethylphthalate derivative **12** as shown in Scheme 1. The 3-alkoxy-2-cyclohexenone chosen as starting material, namely 3-allyloxy-6-methyl-2-cyclohexenone **8**, is readily available[11] from cyclohexane-1,3-dione **6** by the p-toluenesulfonic acid catalyzed reaction with allyl alcohol to give enol ether **7** which was alkylated on the 6-position using the kinetic enolate procedure of Stork and Danheiser[12] to produce enone **8**. This methylated enone was deprotonated in the presence of chlorotrimethylsilane[13] the give the enol ether **9** which undergoes cycloaddition to dimethylacetylene dicarboxylate (DMAD, 25°C) to generate bicyclooctadiene **10**. Without isolation, heating of the crude reaction mixture of **10** at 120°C causes the extrusion of ethylene to yield the trisubstituted dimethyl phthalate **11**. Shaking the crude reaction mixture with aqueous HCl removed the trimethylsilyl ether group producing the hydroxy phthalate **12**. Methylation of **12** with methyl iodide then gave **13** in 43% overall yield from cyclohexane-1,3-dione **6**.

Scheme 1



6 $R^1 = R^2 = H$
7 $R^1 = CH_2CH = CH_2$, $R^2 = H$
8 $R^1 = CH_2CH_2{=}CH_2$, $R^2 = Me$

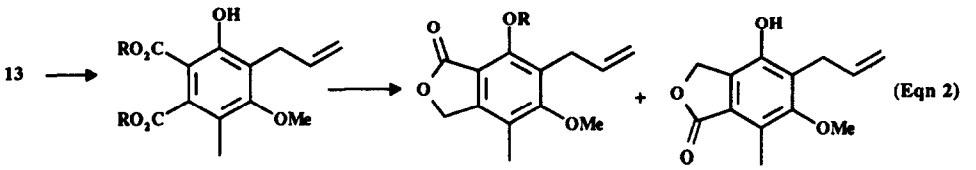
9

10

11 R = $SiMe_3$
12 R = H
13 R = Me

Equation 2 illustrates the Claisen rearrangement of allyl phenyl ether **13** to give the C-allyl phthalate **14**. It should be noted that the choice of allyl as the alkoxy group exploits the fact that the three thermal reactions in this sequence proceed at increasing temperatures: the Diels-Alder addition (25°C), the Alder-Rickert extrusion of ethylene (120°C) and the Claisen rearrangement (205°C). This choice of an allyl ether as a protecting group in intermediates **7** - **13** has produced an apparent economy in the number of steps. The allyl

group is removed by the Claisen rearrangement which introduces the sixth substituent on the benzene ring, and simultaneously generates a free phenol ortho the carboxylic ester which protects it from reduction in the next



14 R = Me
15 R = H

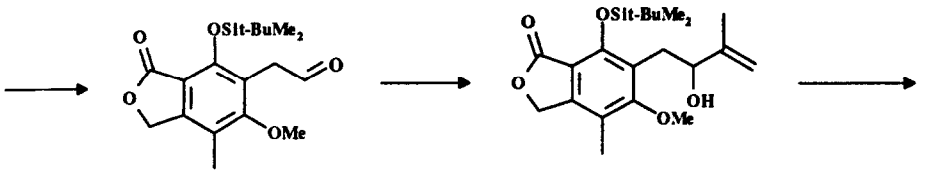
16 R = H
17 R = Sit-BuMe$_2$

16a

sequence. Hydrolysis of **14** with aqueous sodium hydroxide gave the phthalic acid **15**. Because the reduction of 3-hydroxyphthalic anhydrides to 7-hydroxyphthalides reported by Birch was done in aqueous HCl/acetic acid at 100°C, it seems probable that the anhydride is in equilibrium with the phthalic acid. Conversely, if one begins with the phthalic acid under these reaction conditions the same equilibrium mixture with the phthalic anhydride should result and the zinc reduction should proceed. This proved to be the case, as the direct reduction of acid **15** with zinc in aqueous HCl/acetic acid at 75°C gave the phthalide **16** in 56% yield. Whether or not an anhydride is involved as an intermediate, the reduction of the diacid **15** shows high regioselectivity for reduction of the carboxyl distal to the phenol. Examination of minor products from this reduction indicated less than 3% of the isomeric phthalide **16a** was formed. Phthalide **16** was prepared by this sequence in 37% overall yield from **11**.

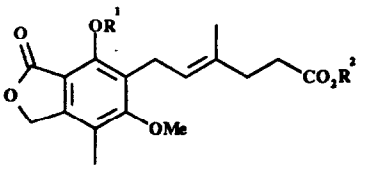
The final sequence[10] in this synthesis of mycophenolic acid is the transformation of the allyl group into the required side-chain (Scheme 2). Hence, the phenolic hydroxyl of **16** is protected[14] as the t-butyldimethylsilyl ether **17** and then the olefin is cleaved by oxidation with excess ozone to give the phenylacetaldehyde **18**. Condensation of **18** with 2-propenylmagnesium bromide gave the allylic alcohol **19** which upon thermolysis with triethyl orthoacetate in the presence of propionic acid gave a mixture of the

Scheme 2



18

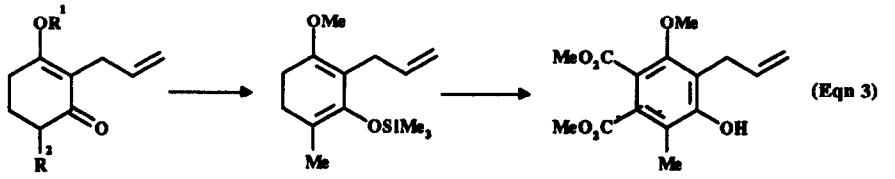
19



20 R^1 = Sit-BuMe$_2$, R^2 = Et
21 R^1 = H, R^2 = Et

E-olefin **20** (46%) and the corresponding phenol **21** (18%). No product corresponding to the Z-isomer of **20** was isolated from this reaction and the ^{1}H NMR spectrum of **20** was devoid of duplicate signals leading to the conclusion that the stereoselectivity of this orthoester Claisen rearrangement was at least 95%. The t-butyldimethylsilyl ether was cleaved with tetrabutylammonium fluoride[14] and the ethyl ester saponified to give mycophenolic acid **1**. By the process of Scheme 2, intermediate **16** is converted to mycophenolic acid **1** in 33% overall yield.

As a final observation about the use of the Alder-Rickert reaction in the construction of polysubstituted benzenes, the direct introduction of all the substituents necessary for mycophenolic acid as shown in Equation 3 was investigated.



(Eqn 3)

22 $R^1 = R^2 = H$
23 $R^1 = Me$, $R^2 = H$
24 $R^1 = R^2 = Me$

25

26

The readily available 2-allylcyclohexane-1,3-dione[15] (**22**) was converted to enol ether **23** and then alkylated with methyl iodide to give enone **24**. In the same manner as with enone **8** above, this dialkylated enone **24** was subjected to the Alder-Rickert sequence by conversion to the silyl enol ether **25**, cycloaddition with DMAD and finally pyrolysis at 120°C. Although this does produce the hexasubstituted intermediate **26** directly, the requirement of methylating the free phenol and demethylating the methoxyl ortho to the ester group would make this a longer route to phthalate **14** than the route discussed above via the Alder-Rickert product **12**.

In conclusion this is a new synthesis of mycophenolic acid based on the Alder-Rickert construction of benzene rings. This synthesis uses enolate chemistry to prepare the requisite cyclohexadiene, a direct reduction of phthalic acid **15** to phthalide **16** and a new synthesis of the side-chain using an orthoester Claisen rearrangement.

EXPERIMENTAL SECTION

All reactions were carried out under nitrogen with magnetic stirring. THF was purified by distillation from Na/benzophenone. Chromatography refers to flash chromatography on 230-400 mesh silica gel. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF-300 spectrometer and listed as ppm downfield from internal Me_4Si. The infrared spectra were recorded on a Pye Unicam 3-200 spectrometer.

3-(2-Propenyloxy)-2-cyclohexenone (7).

A mixture of cyclohexane-1,3-dione (150 g, 1.34 mol), allyl alcohol (200 mL, 2.94 mol), p-toluenesulfonic acid (5 g, 0.026 mol) and benzene (400 mL) was refluxed with a Dean-Stark trap for 90 min. Additional p-toluenesulfonic acid (1.5 g) was added and the reaction mixture was refluxed 30 min further. After cooling the reaction mixture to room temperature it was diluted with ether (300 mL) and washed with aqueous NaOH (200 mL, 1N). The aqueous layer was extracted again with ether and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was removed in vacuo and the residue distilled in a Kugelrohr to give 169.99 g (83%) of **7**: bp 120°C (0.2 mm); IR (film) 2949, 1655, 1604, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.36 (d, J=17 Hz, 1H), 5.35 (s, 1H), 5.30 (d, J=10 Hz, 1H), 4.37 (d, J=5 Hz, 2H), 2.42 (t, J=6 Hz, 2H), 2.34 (t, J=7 Hz, 2H), 1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 177.4, 131.4, 118.9, 103.2, 69.1, 36.7, 29.0, 21.2. Anal. Calcd for $C_9H_{12}O_2$: C, 71.01; H, 7.95. Found: C, 70.68; H, 8.36.

6-Methyl-3-(2-propenyloxy)-2-cyclohexenone (8).

A solution of lithium diisopropylamide (0.22 mol) was prepared by addition of n-BuLi (138 mL, 1.6N) to diisopropylamine (30.8 mL, 0.22 mol) in THF (250 mL) at -30°C. The LDA solution was cooled to -65°C and enone **7** (31.96 g, 0.21 mol in 15 mL of THF) was added over 20 min. After stirring 15 min longer at -65°C MeI (19.92 mL, 0.32 mol) was added over 10 min to the reaction mixture which was then allowed to warm to -40°C over 90 min. Water (30 mL) was added to the reaction mixture and the THF was removed in vacuo. The residue was diluted with water and extracted three times with ether to give, after drying over $MgSO_4$ and evaporation, a residue which upon distillation in a Kugelrohr gave 32.73 g (94%) of **8**: bp 105°C (0.14 mm); IR (film) 1659, 1609, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.36 (d, J=17 Hz, 1H), 5.33 (s, 1H) 5.30 (d, J=10 Hz, 1H), 4.36 (d, J=5 Hz, 2H), 2.45 (m, 2H), 2.30 (m, 1H), 2.06 (m, 1H), 1.70 (m, 1H), 1.14 (d, J=7Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 176.5, 131.5, 118.9, 102.5, 69.1, 40.1, 29.2, 28.4, 15.3. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.00; H, 8.50.

Dimethyl 5-Hydroxy-6-methyl-3-(2-propenyloxy) phthalate (12).

A solution of lithium diisopropylamide (0.090 mol) was prepared by addition of n-BuLi (57 mL, 1.6 N in hexane) to diisopropylanine (12.6 mL, 0.090 mol) in THF (120 mL) at -40°C. This reaction mixture was cooled to -65°C and treated with Me_3SiCl (14.0 mL, 0.11 mol) over 5 min. A solution of enone **8** (14.13 g, 0.085 mol) in 10 mL of THF was added over 20 min and the reaction mixture was stirred for 40 min at -65°C. Et_3N (15 mL, 0.11 mole) was added and the reaction mixture was poured into ice water and hexane. The organic layer was separated, washed with brine and dried over K_2CO_3. Evaporation in vacuo then gave enol ether **9** which was diluted with m-xylene (45 mL), cooled to -40°C and treated with DMAD (14 mL, 0.11 mol). The reaction mixture was stirred at room temperature 2 hr and then heated at 120°C for 110 min. The m-xylene was removed in vacuo and the resulting oil dissolved in 300 mL of ethyl acetate and stirred with 300 mL of water containing 30 mL of concentrated HCl. The product was isolated by extraction with ethyl acetate followed by chromatography on silica gel eluting with 30% EtOAc/hexane to yield 13.99 g (59%) of **12**: mp 100.6-111.4°C; IR (KBr) 3345, 1714, 1688, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.88 (m,

1H) 5.27 (d, J=17 Hz, 1H), 5.20 (d, J=11 Hz, 1H), 3.99 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHx, $CDCl_3$) δ 169.4, 167.4, 158.7, 156.4, 135.8, 132.2, 117.6, 111.0, 101.3, 69.3, 52.7, 52.5, 12.0. Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.71. Found: C, 60.20; H, 5.90.

Dimethyl 5-Methoxy-6-methyl-3-(2-propenyloxy) phthalate (13).

A mixture of the dimethyl phthalate **12** (11.65 g, 41.6 mmol), K_2CO_3 (10.0 g, 72 mmol), methyl iodide (5 mL,, 80 mmol) and 40 mL of DMF was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with ether. The organic extracts were washed with water and brine, dried over $MgSO_4$ and evaporated to give a solid residue which was recrystallized from t-BuOMe to give 11.48 g (94%) of **13**: mp 84.3-85.2°C; IR (KBr) 1732, 1716, 1591, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (s, 1H), 6.03 (m, 1H), 5.44 (d, J=15 Hz, 1H), 5.29 (d, J=10 Hz, 1H), 4.60 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 168.7, 166.6, 160.5, 156.6, 135.4, 132.8, 117.7, 117.5, 112.9, 70.4, 55.8, 52.4, 52.2, 12.1. Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.19; H, 6.17. Found: C, 60.83; H, 6.40.

Dimethyl 3-Hydroxy-5-methoxy-6-methyl-4-(2-propenyl) phthalate (14).

A solution of the allylic ether **13** (4.00 g, 13.6 mmol) in 1,2,3,5-tetramethylbenzene (50 mL, technical, 85% Aldrich) was refluxed 4 h. The reaction mixture was cooled and the tetramethylbenzene was removed on a Kugelrohr (80°C, 2 mm). The resulting residue was chromatographed on silica gel, eluting with 15% EtOAc/hexane to give 2.99 g (75%) of **14**: IR (film) 2953, 1740, 1672, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (m, 1H), 5.0 (m, 2H), 3.92 (s, 6H), 3.76 (s, 3H), 3.48 (d, J=6 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 169.4, 162.3, 159.9, 135.9, 134.5, 122.7, 120.0, 115.1, 105.2, 61.1, 52.9, 52.4, 28.2, 12.5. Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.19; H. 6.17. Found: C, 61.45; H, 6.50.

3-Hydroxy-5-methoxy-6-methyl-4-(2-propenyl)phthalic acid (15).

Dimethyl phthalate **14** (4.71 g, 16.0 mmol) in MeOH (30 mL) was treated with a solution of NaOH (3.84, 96 mmol) in water (50 mL). The reaction mixture was heated at 50°C for 18 h. After cooling the solution was diluted with water and washed with ether. The aqueous phase was cooled on ice, acidified with 10% HCl and extracted with EtOAc. After drying over $MgSO_4$, evaporation of the solvent gave phthalic acid **15** (3.81 g, 89%): mp 156-157°C (t-BuOMe); IR (KBr) 3430, 1705, 1647, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (m, 1H), 5.0 (m, 2H), 3.72 (s, 3H), 3.43 (dt, J = 6, 1 Hz, 2H), 2.21 (s, 3H). ^{13}C (75 MHz, $CDCl_3$) δ 171.8, 171.6. 162.1, 160.3, 136.2, 121.7, 118.9, 114.9, 105.2, 60.9, 28.1, 12.5. Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.89; H, 5.37.

1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-(2-propenyl) isobenzofuran (16).

A solution of phthalic **15** (1.015 g, 3.81 mmol) in acetic acid (4 mL) and concentrated HCl (1 mL) was heated to 75°C and treated with zinc dust (0.8 g) at 1 h intervals for 6 h. The reaction mixture was cooled, diluted with water and extracted with EtOAc. The extracts were washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and chromatographed on silica gel eluting with 30% EtOAc/hexane to give phthalide **16** (0.50 g, 56%):

mp 91-92°C (t-BuOMe/hexane) (lit[2] mp 91-92°C); IR (KBr) 3422, 1736, 1622, 1217, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (m, 1H), 5.22 (s, 2H), 5.06 (m, 1H), 5.01 (m, 1H), 3.80 (s, 3H), 3.46 (dt, J = 6, 2 Hz, 2H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 163.8, 153.7, 144.4, 135.9, 120.6, 116.9, 115.2, 106.4, 70.1, 61.3, 27.7, 11.6. Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.63; H, 6.03. Found: C, 66.97; H, 6.10.

From a similar reduction reaction a small amount (2.6%) of the isomeric phthalide **1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-1-oxo-5-(2-propenyl)isobenzofuran (16a)** was isolated: mp 137.6-138.5°C (t-BuOMe/hexane); IR (KBr) 1725, 1713, 1329 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (m, 1H), 5.30-5.20 (m, 2H), 5.21 (s, 2H), 3.75 (s, 3H), 3.61 (dt, J = 6, 2 Hz), 2.58 (s, 3H). Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 67.00; H, 6.00.

1,3-Dihydro-4-(tert-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-(2-propenyl isobenzofuran (17).

A mixture of the hydroxy phthalide **16** (1.35 g, 5.76 mmol), imidazole (0.75 g, 11 mmol), t-$BuMe_2SiCl$ (1.00 g, 6.6 mmol) and 5 mL of DMF was stirred 90 min at room temperature. The reaction mixture was diluted with water. Extraction with ether, drying over $MgSO_4$ and concentrating gave an oil which was crystallized (t-BuOMe/hexane) to give 1.71 g (85%) of **17**: mp 93.4-94.6°C; IR (KBr) 3441, 1757, 1462, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.10 (s, 2H), 4.97 (m, 2H), 3.79 (s, 3H), 3.47 (d, J=6 Hz, 2H), 2.18 (s, 3H), 1.05 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 163.2, 151.9, 146.4, 136.3, 126.1, 118.0, 115.2, 111.6, 67.7, 61.1, 28.8, 26.1, 18.8, 11.4, -3.4. Anal. Calcd for $C_{19}H_{28}O_4Si$:. C, 65.46; H, 8.10. Found: C, 65.13; H, 7.99.

2-[1,3-Dihydro-4-(tert-butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]acetaldehyde (18).

A solution of olefin **17** (1.602 g, 4.57 mmol) in CH_2Cl_2 (20 mL), CH_3OH (20 mL) and pyridine (0.5 mL) was cooled to -70°C and treated with ozone until the reaction mixture turned blue. Dimethyl sulfide (2 mL) was added and the reaction mixture was stirred at room temperature for 2 h. **CAUTION: The α-methoxy hydroperoxide intermediate is potentially explosive; however, it does give a positive starch/iodide test. The reduction with Me_2S should be continued until the test is negative before working up the reaction. In some cases this required 12 h and addition of more Me_2S.** The reaction mixture was poured into cold 2% HCl. Extraction with CH_2Cl_2, drying and concentrating gave an oil which was crystallized from t-BuOMe/hexane to yield **18** (1.35 g, 84%): mp 91.6-93.3°C; IR (KBr) 1757, 1716, 1471, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (t, J=1.7 Hz, 1H), 5.13 (s, 2H), 3.74 (s, 5 H), 2.20 (s, 3H), 1.04 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 168.8, 163.2, 152.1, 148.0, 119.7, 118.0, 112.0, 67.8, 60.4, 39.7, 26.0, 18.7, 11.5, -3.6. Anal. Calcd for $C_{18}H_{26}O_5Si$: C, 61.66; H, 7.48. Found: C, 61.84; H, 7.62.

(±)-4-[1,3-Dihydro-4-(tert-butyldimethylsilyoxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-3-hydroxy-2-methylbutene (19).

To a mixture of magnesium turnings (3.00 g, 0.12 mol) in THF (20 mL) containing one crystal of I_2 was added a solution of 2-bromopropene (8.9 mL, 0.10 mol) in THF (80 mL) at a rate which maintained reflux. After stirring for an additional hour at 25°C, 20 mL of this Grignard reagent was added over 25 min to a

solution of aldehyde **18** (5.25 g, 15 mmol) in THF (70 mL) at -70°C. The reaction mixture was stirred at -40°C for 15 min and then quenched in saturated aqueous NH_4Cl. Extraction with ether, drying over K_2CO_3, evaporating and crystallization from t-BuOMe/hexane gave **19** (4.03 g). Chromatography of the filtrates eluting with 10% EtOAc/hexane gave 0.623 g for a total yield of 4.65 g (79%) of **19**: mp 133-134°C; IR (KBr) 3557, 1770, 1470, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 2H), 4.96 (m, 1H), 4.81 (m, 1H), 4.24 (m, 1H), 3.80 (s, 3H), 3.95 (m, 2H), 2.25 (d, 1H, hydroxyl), 2.16 (s, 3H), 1.81 (s, 3H), 1.03 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 163.3, 152.2, 147.4, 146.7, 125.0, 118.2, 112.1, 110.9, 75.5, 67.6, 60.8, 31.2, 26.1, 18.6, 17.8, 11.5, -3.3, -3.6. Anal. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.21. Found: C, 64.46; H, 8.14.

Ethyl E-6-[1,3-Dihydro-4-(tert-butyldimethylsiloxy) -6-methoxy-7-methyl-3-oxo-5-isobenzo-furanyl]-4-methyl-4-hexenoate (20).

A solution of allylic alcohol **19** (605 mg, 1.54 mmol) in triethyl orthoacetate (15 mL, 82 mmol) and propionic acid (0.15 mL, 2.0 mmol) was heated at 80°C for 30 min in a three-necked flask while a slow stream of N_2 was passed through. The reaction mixture was then heated at 110°C for 1.5 h while a solution of triethyl orthoacetate (15 mL) and propionic acid (0.15 mL) was added. The reaction mixture was cooled and the excess orthoacetate removed in vacuo. The resulting residue was chromatographed on silica gel, eluting with 25% EtOAc/hexane to give **20** (328 mg, 46%): mp 54-56°C (hexane); IR (KBr) 2934, 1762, 1729, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18 (t, J = 6 Hz, 1H), 5.07 (s, 2H), 4.07 (q, J = 7 Hz, 2H), 3.74 (s, 3H), 3.37 (d, J = 6 Hz, 2H), 2.34 (m, 4H), 2.15 (s, 3H), 1.76 (s, 3H), 1.20 (t, J = 7 Hz, 3H), 1.03 (s, 9H), 0.24 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 169.2, 163.2, 152, 146.0, 133.8, 127.7, 123.5, 117.9, 111.6, 67.7, 60.7, 34.5, 33.1, 26.1, 23.7, 18.8, 16.4, 14.2, 11.4, -3.5. Anal. Calcd. for $C_{25}H_{38}O_6Si$: C, 64.89; H, 8.28. Found: C, 64.55; H, 8.43.

Further elution with EtOAc/hexane gave **21** (94 mg, 18%) which is characterized immediately below.

Ethyl E-6-[1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate (21).

The silylether **20** (450 mg, 0.973 mmol) is dissolved in THF (3 mL) and treated with tetra-n-butylammonium fluoride (1.0 mL, 1N). After 1 h the reaction mixture was diluted with water and extracted twice with EtOAc. After drying over $MgSO_4$, evaporation of the solvent gave the phenol **21** (333 mg, 98%): mp 87-88°C (t-BuOMe/hexane); IR (KBr) 3412, 1732, 1622, 1244, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (t, J = 7 Hz, 1H), 5.21 (s, 2H), 4.08 (q, J = 7 Hz, 2H), 3.77 (s, 3H), 3.39 (d, J = 7 Hz, 2H), 2.37 (m, 4H), 2.16 (s, 3H), 1.81 (s, 3H), 1.22 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 172.9, 163.7, 153.6, 144.0, 134.2, 122.7, 122.2, 116.7, 106.3, 70.1, 61.0, 60.2, 34.6, 33.1, 22.6, 16.1, 14.2, 11.6. Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.13; H, 7.11.

E-6-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoicacid(1).

Ester **21** (132 mg, 0.379 mmol) in MeOH (2 mL) was treated with a solution of LiOH (45 mg, 1.07 mmol) in 0.4 mL of water. The reaction mixture was stirred at 23°C for 5 h and then diluted with water and washed with ether. The aqueous layer was cooled on ice, acidified with 10% HCl and extracted with EtOAc. Drying over $MgSO_4$ and evaporation gave mycophenolic acid **1** (113 mg, 93%): mp 139-141°C (t-BuMe/EtOAc) (lit[2] mp 141°C).

3-Methoxy-2-(2-propenyl)-2-cyclohexenone (23).

A mixture of 2-(2-propenyl)-1,3-cyclohexanedione (40.0 g, 0.263 mol) **22**, methanol (140 mL), trimethylorthoformate (42 mL) and p-toluenesulfonic acid (2g) was heated at 65° for 16 h. The reaction mixture was cooled and the methanol removed in vacuo. This residue was diluted with EtoAc (500 mL) and washed with aqueous $NaHCO_3$ and brine. After drying over K_2CO_3 the solvent was evaporated and distillation in a Kugelrohr gave 35.0 g (80%) of **23**[9b]: bp 100°C (0.09 mm).

3-Methoxy-6-methyl-2-(2-propenyl)-2-cyclohexenone (24).

A procedure identical to that above for the preparation of compound **8** was used to methylate cyclohexone **23** to give **24** (92%): bp 105°C (0.10 mm); IR (film) 1651, 1614, 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1H), 4.4 (m 2H), 3.82 (s, 3H), 3.00 (d, J = 7 Hz, 2H), 2.6 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H), 1.7 (m. 1H), 1.13 (d, J = 8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 171.3, 136.7, 116.3, 113.8, 55.1, 39.4, 28.7, 26.6, 24.6, 15.5.

Dimethyl 4-(2-Propenyl)-5-hydroxy-3-methoxy-6-methylphthalate (26).

Using the procedure described above for the synthesis of phthate **12**, cyclohexenone **24** (6.67 g, 0.037 mol) was converted to silylenol ether **25** which was condensed with DMAD and pyrolysed at 120°C to give the tetrasubstituted phthalate **26** (4.432 g, 41%): oil; IR (film) 1732, 1341, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (m, 1H), 5.2 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 3.51 (dt, J = 6, 2 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.9, 156.2, 155.7, 135.0, 133.2, 120.6, 119.5, 118.1, 117.2, 63.3, 52.5, 28.4, 12.6. Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.16. Found: C, 60.98; H, 6.27.

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