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A Total Synthesis of Mycophenolic Acid

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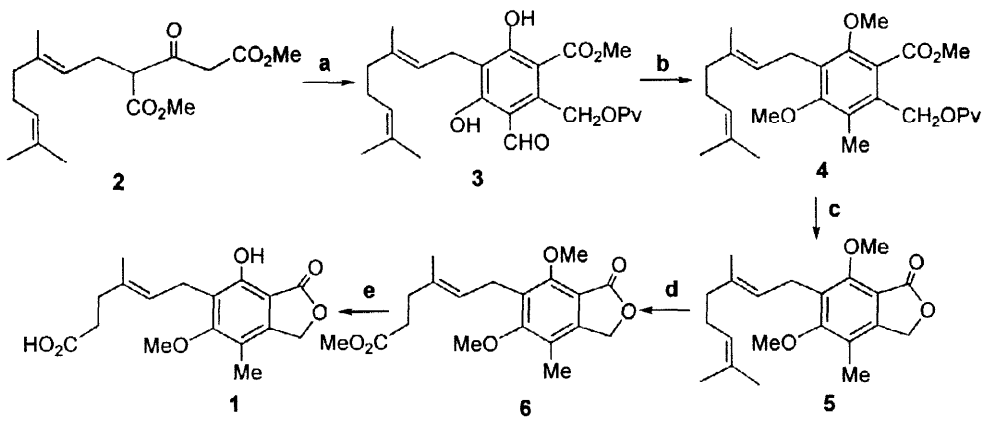
Abstract: A total convergent synthesis of mycophenolic acid **1** from 2-geranyl-dimethyl-1,3-acetonedicarboxylate **2** and 4-pivaloyloxy-2-butynal using a Michael addition-Dieckmann cyclization as key step is described.

Mycophenolic acid **1**, is produced as metabolite of a number of Penicillium spp, notably *brevi compactum*,[1] the synthesis of **1** has been reported,[2] it has many *in vitro* and *in vivo* biological activities, including antifungal,[3] antibacterial,[4] antiviral,[5] an immunosuppressive[6] properties. We describe a novel total synthesis of mycophenolic acid **1** using as key step tandem reactions (Michael-addition and intramolecular regioselective Dieckmann-cyclization) of 2-geranyl-dimethyl-1,3-acetonedicarboxylate[7] anion with 4-pivaloyloxy-2-butynal,[8] which produces the hexasubstituted resorcinol **3** with all substituents already in place with high regiocontrol in one pot (33% yield). The following scheme of reactions shows our synthetic approach.



SCHEME 1

reagents: **a**. NaH, THF, 4-pivaloyloxy-2-butynal, 25°C 2h; **b**. i) NaH, DMF, Me_2SO_4; ii) $NaBH_4$, MeOH, iii) Et_3N, $MeSO_2Cl$, CH_2Cl_2, 1.5h; iv) $NaBH_4$, DMF; **c**. K_2CO_3, MeOH; **d**. i) O_3, CH_2Cl_2, pyridine, Me_2S, -78°C; ii) CrO_3, H^+, acetone, -30°C, iii) , CH_2N_2, AcOEt; **e**. i) BCl_3, CH_2Cl_2, 8d; ii) LiOH, H_2O, H^+.

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Dimethylation of resorcinol **3** with NaH, Me_2SO_4 in dry DMF, gave us the dimethyl ether in 88% yield and the reduction of the formyl group with $NaBH_4$ in dry MeOH gave the alcohol in 89% yield, mesylation of the alcohol with MsCl and Et_3N in CH_2Cl_2 and subsequent reduction of the crude mesylate with $NaBH_4$ in dry DMF produce the compound **4** in 77% yield . The formation of phthalide **5** was effected in quantitative yield on treatment of **4** with a catalytic amount of K_2CO_3 in dry MeOH. Selective ozonolysis of compound **5** followed by Jones oxidation[2c] and esterification with CH_2N_2 produce the methyl O-methyl ester of mycophenolic acid in 28% yield from **6**, the selective demethylation with BCl_3 in CH_2Cl_2 was achieved in 86% yield and finally the hydrolysis of the methyl ester furnished mycophenolic acid as colorless crystals, mp 139-141 (lit.[2c] mp 139-141°C) with identical properties of the natural compound. The structure of the compounds were established spectroscopically[9] (^{1}H NMR, IR, EM).

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9. **3** IR (neat) 3347, 1739, 1676, 1135 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.5 1.54 (s, 3H), 1.60 (s, 3H), 1.90-2.10 (m, 4H), 3.37 (d, 2H, J=6.3), 3.92 (s, 3H), 5.01 (t, 1H, J=6.3), 5.18 (t, 1H, J=7.2), 5.57 (s, 2H), 10.11 (s, 1H), 11.66 (s, 1H), 12.84 (s, 1H). **4** IR (neat) 1731, 1204, 1148 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.54 (s, 3H), 1.61 (s, 3H), 1.75 (s, 3H), 1.90-2.10 (m, 4H), 2.25 (s, 3H), 3.36 (d, 2H, J=6.6), 3.68 (s, 3H), 3.74 (s, 3H), 3.87 (s, 3H), 5.03 (s, 2H), 5.17 (td, 2H, J=6.6). **5** 1761, 1600, 1473, 1128 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (s, 3H), 1.63 (s, 3H), 1.79 (s, 3H), 1.90-2.10 (m, 4H), 2.18 (s, 3H), 5.04 (td, 2H, J=6.9), 3.70 (s, 3H), 4.05 (s, 3H), 5.04 (td, 2H, J=6.6), 5.13 (s, 2H). **6** mp 94-96°C ^{1}H NMR 2.12 (s, 3H), 2.10-2.47 (m, 4H), 3.34 (d, 2H, J=6.6), 3.55 (s, 3H), 3.71 (s, 3H), 3.97 (s, 3H), 5.08 (s, 2H), 5.05-5.15 (m, 1H). MS: 348 (M^+, 93), 275 (32), 243 (43), 221 (100), 44 (53).