Pergamon

Tetrahedron Letters, Vol. 36, No. 43, pp. 7803-7806, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01652-X

Mycophenolate Dianions[1]

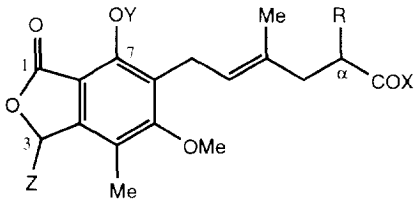
John C. Rohloff,*† John O. Gardner† and R. W. Towne‡

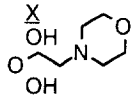
†Institute of Organic Chemistry, ‡Institute of Analytical Research, Syntex Discovery Research
3401 Hillview Ave. R6-201, Palo Alto, CA 94304

Key Words: Mycophenolic acid, dianion, oxazolidinone, immunosuppressant.

Abstract: Dianions derived from simple protected derivatives of mycophenolic acid were utilized to synthesize the highly potent semisynthetic analogue (*S*)-α-methylmycophenolic acid and the natural product 3-hydroxymycophenolic acid.

The mold metabolite mycophenolic acid **1** is a potent inhibitor of *de novo* guanosine nucleotide biosynthesis, causing a suppression of lymphocyte proliferation in humans.[2] The 2-N-morpholinoethyl ester prodrug **2** is currently in Phase III clinical trials as an immunosuppressant for prevention of renal transplant rejection.[3] Preparation of analogs with enhanced potency has been a topic of considerable interest for several years due to the large clinical dosage required (>2 g/day). Unfortunately, nearly all modifications of the natural product skeleton have resulted in reduced, or abolished, activity.[4] It has recently been discovered that

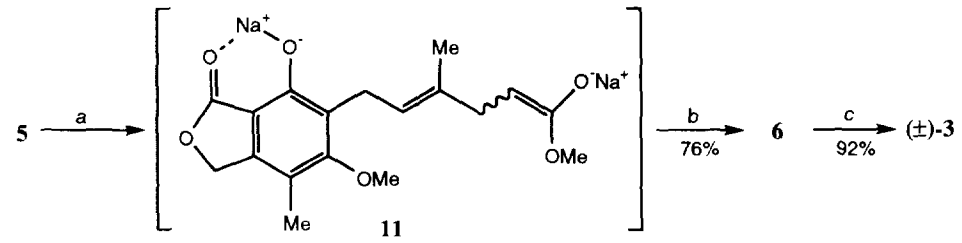


	Z	Y	R	X
1	H	H	H	OH
2	H	H	H	
3	H	H	(*S*)-Me	OH
4	H	H	H	OMe
5	H	TBDMS	H	OMe
6	H	H	Me	OMe
7	H	H	H	Cl
8	OH	H	H	OH
9	H	MEM	H	OH
10	OH	MEM	H	OH

substitution of small alkyl groups at the position α to the carboxylic acid results in enhanced potency. This is exemplified in (*S*)-α-methylmycophenolic acid **3** which is ca. fivefold more active than the parent molecule **1** in IMPDH inhibition *in vitro*.[5] While α-alkyl derivatives of mycophenolic acid are, in principle, available by semi- or total synthesis,[6] it is clearly most economical to simply alkylate the readily-available natural product. This communication describes simple methodology for chemoselective formation and alkylation of the mycophenolate ester enolate.

Initial attempts at formation of the α-enolate were complicated by competing deprotonation of the benzylic positions. For example, alkylation of phenol-protected derivatives such as methyl 7-O-(*tert*-

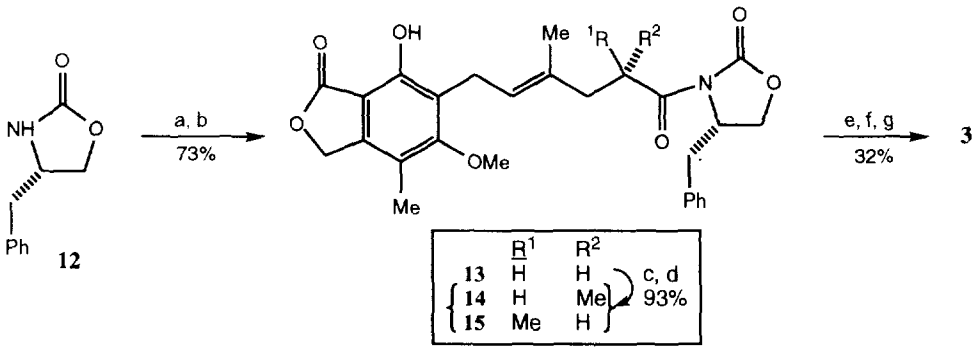
Scheme 1



Reagents and conditions: a) **5**, THF, -70°C to NaHMDS (1 M, 2.2 eq), THF, -70°C, 0.5 h. b) MeI (5 eq), -70°C→0°C, 1 h. c) LiOH (3 eq), aq. THF, 23°C, 12 h; HCl, EtOAc.

butyldimethylsilyl)mycophenolate **5** with amide bases gave complex mixtures. Better results were obtained with the dianion derived from an unprotected phenol. Addition of methyl mycophenolate **4** to sodium hexamethyldisilyazide (NaHMDS, 2.2 eq.) in THF at -70°C formed a soluble species, presumably dianion **11** (Scheme 1), which upon quenching with methyl iodide afforded (±)-methyl α-methylmycophenolate **6** in 76% yield.[7] The partial negative charge on the aromatic ring resulting from phenol deprotonation apparently deactivates the benzylic positions sufficiently to allow selective formation of the ester enolate. No trace of phenolic O-methylation was detected, even on extended stirring with MeI, implying tight chelation of the phenoxide sodium counterion. Saponification of **6** afforded racemic α-methylmycophenolic acid (±)-**3** in 92% yield.

Scheme 2



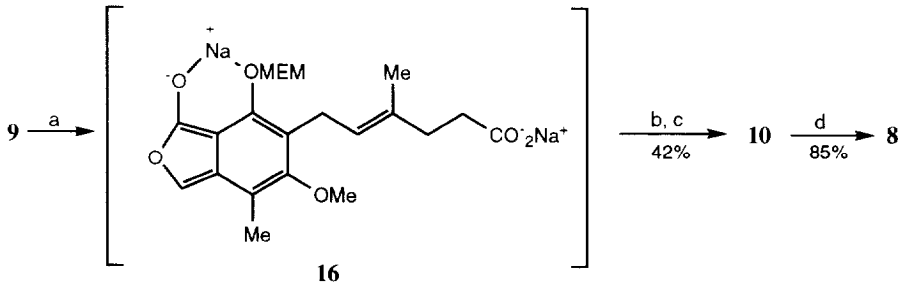
Reagents and conditions: a) *tert*-butanol (1 eq), THF, then n-BuLi (2.5 M, 2 eq), -70°C, 1 h. b) **7**, THF, -70°C, 0.2 h. c) **13**,THF, -70°C to NaHMDS (1 M, 2.2 eq), THF, -70°C, 0.5 h. d) MeI (5 eq), -70°C→0°C, 1 h. e) LiOH (2 eq), 30% aq H_2O_2 (3 eq), aq. THF, 0°C, 0.4 h; Na_2SO_3; HCl. f) (+)-MBA (2.4 eq), acetone (20 parts), stirred, 23°C, 12 h. g) H_2SO_4 (2 M, 2 eq), EtOAc.

The optically pure acid **3** was prepared using Evans' oxazolidinone methodology[8] (Scheme 2). Acylation of the lithium salt of (*S*)-4-benzyl-2-oxazolidinone **12** with mycophenoloyl chloride **7** (1 eq), in the presence of lithium *tert*-butoxide (1 eq.), afforded the crystalline imide **13**[9] in 73% yield. Alkylation of the disodium derivative, as described above, afforded an 88:12 mixture of (S,S):(S,R) diastereomers **14:15** in

93% yield. Cleavage of the auxiliary with lithium hydroperoxide gave crude acid **3** (86% ee) which was crystallized to optical purity as its salt with (+)-α-methylbenzylamine ((+)-MBA), from acetone.[10] The stoichiometry of the salt was 1:1, but efficient crystallization required excess (+)-MBA (2-3 eq.) to be present.[11] After a sulfuric acid wash, the pure acid **3** (>98% ee) was isolated in 32% overall yield from **13**.

A different mycophenolate dianion was utilized to prepare the *Penicillium* oxidation product 3-hydroxy-mycophenolic acid **8**,[12] which was required in gram quantities as an analytical reference standard. Based on the results described above it was hypothesized that initial formation of the carboxylate anion in a phenol-protected carboxylic acid derivative would direct a second deprotonation to the 3-position, adjacent to the aromatic ring. Thus, 7-O-(2-methoxy- ethoxymethyl)mycophenolic acid **9**[13] was added to NaHMDS (2.2 eq.) in THF at -70°C to form the dianion **16**, depicted as its probable dienolate tautomer (Scheme 3). Addition of the dianion to N-bromosuccinimide gave an unstable bromide which upon aqueous workup afforded hydroxylactone **10** in 42% yield. Deprotection gave 3-hydroxymycophenolic acid **8**, which had spectral data in accord with reported literature values.[12,14]

Scheme 3



Reagents and conditions: a) to NaHMDS (1 M, 2.2 eq), THF, TMEDA, -70°C, 0.5 h. b) to N-bromosuccinimide (1.5 eq), -70°C, 1 h. c) aq. NaOH, 40°C, 1 h. d) trifluoroacetic acid, CH_2Cl_2, 23°C, 1.25 h.

These unprecedented reaction conditions for chemoselective C-3 and α-functionalization of mycophenolic acid should facilitate preparation of novel semisynthetic derivatives.[15]

References

1. Contribution #911 from the Institute of Organic Chemistry, Syntex Discovery Research, Palo Alto, CA 94304.
2. Allison, A. C. "Approaches to the Design of Immunosuppressive Agents", *The Molecular Biology of Immunosuppression*, Thomson, A. W. Ed, Molecular Medical Science Series, John Wiley and Sons Ltd. (Chichester **1992**), 181-250 and references cited therein.
3. *Pharmaprojects*; Hutton, I.; Ed. PJB Publications: Richmond, Surrey, UK **1994**; Vol. 15 (15), p. 847a.
4. (a) Nelson, P. H.; Eugui, E.; Wang C. C. *J. Med. Chem.* **1990**, *33*, 833-838. (b) Nelson, P. H.; Carr, S. F.; Devens, B. H.; Eugui, E. M.; Franco, F.; Gonzalez, C.; Hawley, R. C.; Loughhead, D. G.; Milan, D. J.; Papp, E.; Patterson, J. W.; Rouhafza, S.; Sjogren, E. B.; Stephenson, R. A.; Talamas, F. X.; Waltos, A. M.; Weikert, R. J.; Wu, J. C. *J. Med. Chem.*, **1995**, *submitted.*
5. Morgans, D. J., Jr.; Smith, D. B; Talamas, F. X.; *et al J. Med.Chem.* **1995**, *manuscript in preparation.*
6. (a) Patterson, J. W. *Tetrahedron* **1993**, *49*, 4789-4798. (b) Patterson, J. W.; Huang, G. T. *J. Chem. Soc. Chem. Commun.* **1991**, 1579-80, and references cited therein.
7. The yield is base-dependent, under the same conditions LiHMDS, LDA or KHMDS gave a very

complex mixture of products.

8. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525-5540, and references 19 and 30 cited therein.
9. (**13**): mp 112-113° C; $[\alpha]_D$ +31.4° (c 1, CH_2Cl_2); IR (KBr), 1779, 1747, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (s, 1 H, OH), 7.35-7.12 (m, 5 H, C_6H_5), 5.29 (1 H, t, *J* = 7.0 Hz, C=CH), 5.04 (d, 1 H, *J* = 15.2 Hz, C_3H), 4.96 (d, 1 H, *J* = 15.2 Hz, C_3H'), 4.57 (m, 1 H, NCH), 4.13 (m, 2 H, OCH_2), 3.77 (s, 3 H, OCH_3), 3.44 (m, 2 H, $ArCH_2C{=}C$), 3.20-2.30 (m, 6 H), 2.08 (s, 3 H, $ArCH_3$), 1.86 (s, 3 H, $C{=}CCH_3$). Anal. Calcd for $C_{27}H_{29}NO_7$ (479.53): C, 67.63; H, 6.10; N, 2.92. Found: C, 67.48; H, 6.09; N, 3.04.
10. (**3•(+)-MBA**): mp 146-149°C (acetone); $[\alpha]_D$ +13.9° (c 1, MeOH). Anal. Calcd for $C_{26}H_{33}NO_6$ (455.55): C, 68.55; H, 7.30; N, 3.07. Found: C, 68.64; H, 7.15; N, 3.25. Optical purity of was determined by HPLC (Chiral AGP, 0°C, 92% 0.5 M $(NH_4)H_2PO_4$ [pH=5.5]/8% CH_3CN, 225 nm, 1 mL/min): RT(***R*-3**) = 10 min.; RT(***S*-3**) = 7.5 min.; RT(**1**)= 6 min.
11. Carman, R. M. *Aust. J. Chem.* **1978**, *31*, 353-364.
12. Jones, D. F.; Moore, R. H.; Crawley, G. C. *J. Chem. Soc. C* **1970**, 1725.
13. Prepared by saponification of methyl 7-O-(2-methoxyethoxymethyl)mycophenolate; ref. 4.
14. (**8**): mp 139-140°C (EtOAc/hexane/toluene), [lit.[12] 142-144°C]; IR (KBr), 3413, 1713 cm^{-1}; CIMS (NH_3) *m/z* 354 (MNH_4^+), 337 (MH^+); UV (MeOH) λ_{max} (log ε) 217 (4.60), 250 (3.90), 309 (3.70) nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.95 (bs, 1 H, COOH), 9.32 (s, 1 H, ArOH), 7.88 (d, 1 H, *J* = 8.6 Hz, C_3OH), 6.51 (d, 1 H, *J* = 8.6 Hz, C_3H), 5.15 (t, 1 H, *J* = 6.1 Hz, C=CH), 3.69 (s, 3 H, OCH_3), 3.31 (d, 2 H, *J* = 6.0 Hz, $ArCH_2$), 2.30-2.05 (m, 4 H, CH_2CH_2), 2.17 (s, 3 H, $ArCH_3$), 1.74 (s, 3 H, $C{=}CCH_3$). Anal. Calcd for $C_{17}H_{20}O_7$ (336.34): C, 60.71; H, 5.99. Found: C, 61.19; H, 6.11.
15. Smith, D. B.; Waltos, A. M., Loughhead, D. G.; Weikert, R. J.; Morgans, D. J., Jr.; Rohoff, J. C.; Link, J. O.; Zhu, R. *J. Org. Chem.* **1995**, *submitted*.

(*Received in USA* 11 *July* 1995; *accepted* 22 *August* 1995)