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PARTIAL SYNTHESIS OF BOROMYCIN

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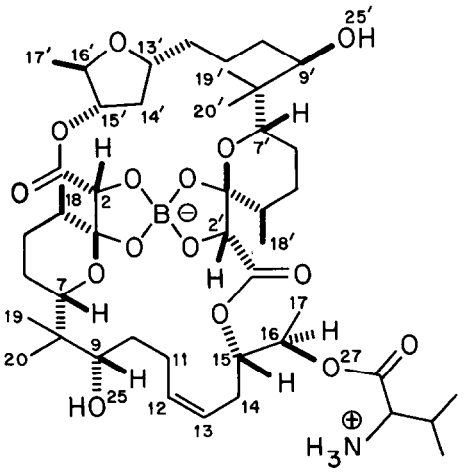
Summary: Desborodesvalinylboromycin has been converted to boromycin via a stereospecific boration, followed by selective acylation with t-Boc-D-valine.

Boromycin, an ionophoric metabolite of Streptomyces antibioticus (Waksman et Woodruff),[2] ha been the subject of extensive structural investigations by Dunitz, Prelog, and coworkers.[3] Careful saponification of boromycin was reported to yield D-valine, together with a macrocyclic triol.[2] An X-ray crystallographic analysis of the rubidium complex of this triol revealed that it possessed structure 2, and boromycin, which thereby became the first natural product known to contain boron,[4] was assigned structure 1. Placement of the valine residue at C16 on the macrolide perimeter was inferred from steric arguments based on the solid state conformation of 2, which precludes acylation at the hindered C9 and C9' alcohols but allows the protonated



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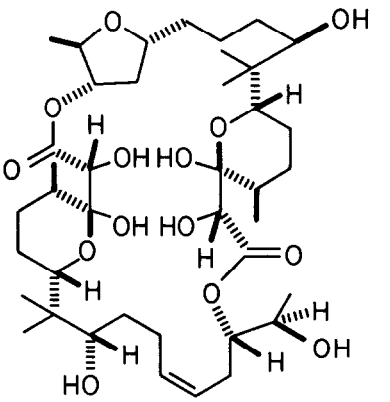

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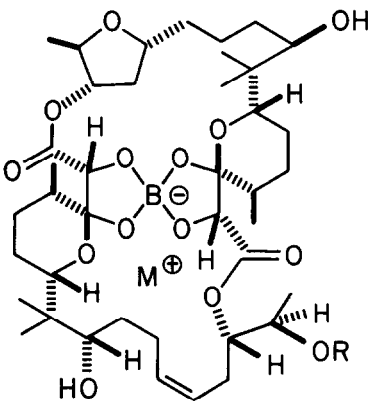
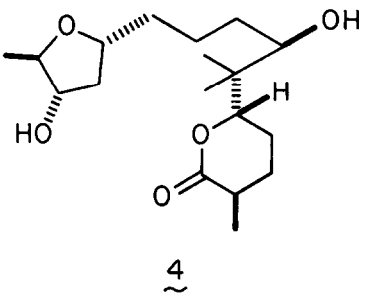
amino group of a D-val residue at C16 to lie within the cleft of boromycin and hence within ionic bonding distance of the borate core.[2]

It has also been demonstrated that exposure of desvalinylboromycin to 6N HCl results in removal of the borate nucleus without disruption of the macrolide framework.[5] An X-ray analysis of the resulting desvalinyldesboro compound 3 shows that it retains essentially the same conformation as 2. Our attempts at further systematic degradation of the boromycin structure has



2. M = Rb, R = H
6. M = R = H
7. M = Na, R = H
8. M = Na, R = OCCHCHMe$_2$ (NHBoc)



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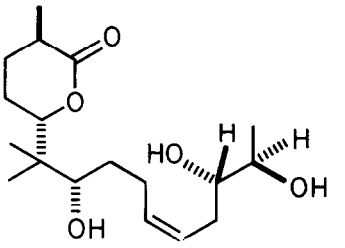

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been frustrated by the surprisingly inert lactone carbonyl groups, and it has not been possible to dissect the molecule into its component halves. However, treatment of boromycin in methanol with 20% aqueous NaOH (2h at reflux followed by 17h at room temp) and then with 5% HCl gave δ-lactones 4 and 5, resulting from a retro-Claisen scission of the glycollate moiety in the "northern" and "southern" halves respectively.

Because the sequence 3 → 2 → 1 is a likely finale in any projected total synthesis of boromycin, and particularly since previous attempts were reported to be unsuccessful,[5] we have investigated the reconstitution of 1 along these lines. First, however, it was necessary to determine whether the conformations observed for boromycin derivatives in the crystalline state are upheld in solution. Proton NMR spectra at 300 MHz of 2,3, and boromycin-Na^+ complex revealed a large number of distinguishable hydrogens which were identified by double irradiation. The data in Table I, show that the strongly anisotropic shielding effects observed for the C9

Table I. ^{1}H NMR Assignments for Boromycin Derivatives (in $CDCl_3$)

Proton	Boromycin-Na^+ Complex	Desvalinyl-boromycin (2)	Desborodesvalinyl-boromycin (3)
2,2'	4.42(s),4.48(s)	4.45(s),4.48(s)	4.32(d,J=12.1),4.33(d,J=10.2)
4,4'	1.88(m),1.91(m)	ca 1.90(m),1.90(m)	2.00(m),2.00(m)
7,7'	3.70(dd,J=11.5,1.5) 3.81(dd,J=10,1.5)	3.81(dd,J=12.0,2.0) 3.92(dd,J=12.0,2.0)	3.71(d,J=11),3.84(dd,J=11)
9,9'	3.08(dd,J=7,10) 4.12(dd,J=9.5,3.5)	3.12(dd,J=6.7,10.5) 4.16(m)	3.10(t,J=10),4.10(dd,J=10.5,3)
11	ca 1.5(m),2.59(q,J=12)	1.58(m),2.73(br q,J=13)	ca 1.6(m),2.84(q,J=12)
12	5.54(t,J=10)	5.51(t,J=10)	5.49(t,J=11)
13	5.28(t,J=10)	5.20(t,J=10)	5.18(t,J=10)
13'	4.19(br t,J=10)	4.16(br t,J=10)	4.20(t,J=10)
14	2.10(br d,J=12),2.88(q,J=12)	2.02(m),2.82(dt,J=14,11)	3.00(dt,J=15,12),ca 2.00
14'α	2.45(ddd,J=14.5,9.0,4.0)	2.51(dd,J=14.0,8.2,4.0)	2.48(ddd,J=14.0,9.0,5.0)
14'β	2.10(m)	1.82(d,J=14.0)	ca 1.66(d,J~15)
15	5.37(d,J=12)	5.11(dt,J=2,12)	5.00(dt,J=2,12)
15'	5.01(d,J=4)	5.01(d,J=4.0)	5.13(d,J=4)
16	4.98(dt,J=6.4,2.0)	4.16(m)	4.06(m)
16'	4.55(q,J=7)	4.85(q,J=7)	4.71(q,J=7)
17CH_3	1.37(d,J=7)	1.20(d,J=7)	1.21(d,J=7)
17'CH_3	1.09(d,J=7)	1.09(d,J=7)	1.10(d,J=7)
18,18'CH_3	0.95(d,J=7),0.98(d,J=7)	0.95(d,J=7),0.97(d,J=7)	0.97(d,J=6.5),0.99(d,J=6.5)
19,19',20,20'CH_3	0.60(s),0.72(s),0.74(s),0.93(s)	0.64(s),0.72(s),0.79(s),0.94(s)	0.78(s),0.79(s),0.80(s),0.93(s)
2,2'OH			5.55(d,J=10.2),6.21(d,J=12.1)
3,3'OH			5.20(d,J=2.0),[b]5.18(d,J=2.0)[b]
25,25'OH	5.01(d,J=7),5.66(s)	5.23(d,J=6.4),7.28(s)	3.76(d,J=9.0),4.6(s) or 5.48(s)
27OH[a]		5.56(d,J=4.3)	5.48(s) or 4.60(s)
H_2O of crystalln.		3.46(s)	4.60(s)

[a]Proton signals due to the D-valine residue appeared at δ 3.41 (1H,d,J=5.0), 1.98 (1H,m), and ca 1.0 (6H). [b]Coupled to 4,4'H

and C9' protons, the nonequivalent C11 methylene hydrogens, and the widely separated methyl signals are common to all three compounds and thus argue strongly for conformational homogeneity in this series. A corollary of this is the expectation that incorporation of boron into 3 should yield a single stereoisomer, with configuration at the tetrahedral borate corresponding to natural boromycin. In fact, treatment of a rigorously dry solution of 3 in MeOH with trimethylborate (reflux, 4h) gave initially 6,[6] which was converted immediately by passage through a column of silica to 7 (70%), identical by ^{1}H NMR, CI mass spectrometry, and TLC with material obtained by saponification of boromycin with NaOH.[3]

Esterification of 7 with t-Boc-D-val was effected in the presence of dicyclohexylcarbodiimide and 4-N,N'-dimethylaminopyridine (CH_2Cl_2, room temp, 48h)[7] to give a single product 8 in 85% yield. Removal of the t-Boc protecting group was accomplished with trifluoroacetic acid (CH_2Cl_2, room temp, 1h) and gave 1, identical with natural boromycin by TLC comparison in three solvents and by ^{1}H NMR and CI mass spectrometry. Although other derivatives of D-val with more readily removable amine-blocking groups (e.g. Fmoc) were tested, steric factors made these systems unreactive towards 2. Nevertheless, these results demonstrate the feasibility of stereospecific incorporation of boron into the Böeseken complex 2 as well as selective acylation at the C16 OH of the latter with D-valine.

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