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REGIOSELECTIVE, INTRAMOLECULAR OXYSELENATION AS A ROUTE TO THE TETRAHYDROFURAN UNITS OF BOROMYCIN AND APLASMOMYCIN

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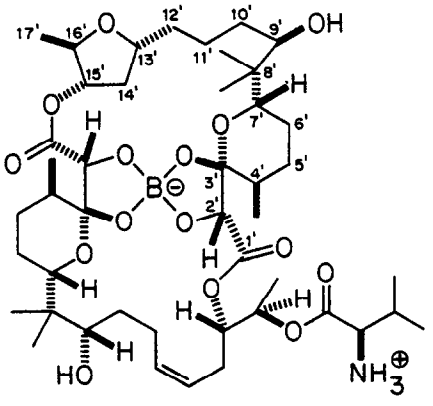
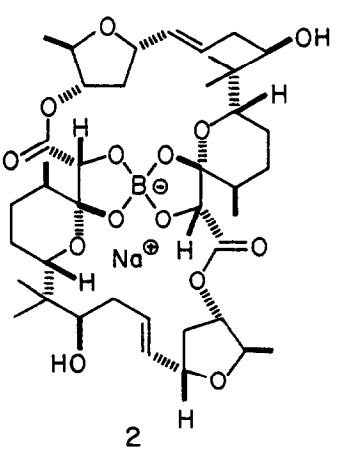
Summary: A substance possessing the functionality and absolute configuration of the C(1')-C(17') half of boromycin has been synthesized, employing an intramolecular oxyselenation for construction of the tetrahydrofuran moiety from an olefinic diol.

We recently reported the synthesis of a substance representing the C(1)-C(17) ("lower") half of the ionophore antibiotic boromycin (1),[1] along with a protocol which permits reconstitution of 1 from its desborodesvalinyl derivative.[2] The "upper", C(1')-C(17') half of 1 contains, in addition to reversed configuration at C(9'), a tetrahydrofuran moiety which distinguishes this substructure from the "lower" half,[3] and which lends it striking similarity to the half structure of aplasmomycin (2).[4] In principle, a common synthetic pathway to the C(1')-C(17') component of 1 and its 11',12'-dehydro version present in 2 is available from an intermediate en route to the "lower" half of 1 via closure of the C(16) oxygen at the C(13) terminus of an olefin.[5]

It appeared that a favorable outcome for this key tetrahydrofuran construction could be anticipated from intramolecular oxyselenation of an intermediate having a trans 12,13-double bond. Accordingly, the 5S,6R propargylic alcohol 3[1] was reduced ($LiAlH_4$, $AlCl_3$, THF, reflux, 3 h)[6] to trans allylic



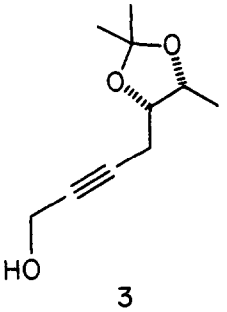
1



2

alcohol 4 (88%) and this was transformed (N-chlorosuccinimide, Me_2S)[7] to the chloride 5 (91%). Alkylation of the enolate of keto sulfone 6[1] (n-BuLi, DMSO, THF) with 5 in the presence of KI, followed by reductive removal (Al/Hg, THF-H_2O (10:1), 75°C, 1 h) of the sulfonyl group, furnished 7 (64% from 6), which was reduced ($NaBH_4$, MeOH, 0°C) to give a mixture of 7R (8) and 7S (9) alcohols in the ratio 3.5:1 (92%). These were conveniently separated as their respective acetates 10 and 11 (Ac_2O, CH_2Cl_2, pyridine, DMAP). The major acetate 10 was cleanly hydrolyzed to ester 14 (p-TsOH, THF-H_2O (4:1), 25°C, 20 h) and the resulting diol was acetylated (Ac_2O, CH_2Cl_2, pyridine, DMAP) to provide 13 (63%). A subsequent, more vigorous hydrolysis (p-TsOH, THF-H_2O (4:1), 56°C, 20 h) afforded diol 14 (95%).

Baldwin's rules[8] lead to the prediction that intramolecular oxyselenation of 14 should take place by attack of the C(14) hydroxyl group at the C(11) terminus of the double bond (5-exo-trig). In the event, exposure of 14 to phenylselenyl chloride (CH_2Cl_2, -78°C, 10 min), followed by oxidation with H_2O_2 (THF, 25°C, 4.5 h),[9] produced a 1:1 mixture of the tetrahydrofuran 15 and its 11R stereoisomer in 71% yield, with no trace of other cyclization products. The



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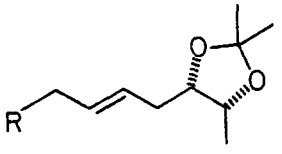
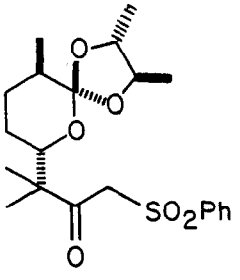


4, R = OH

5, R = Cl



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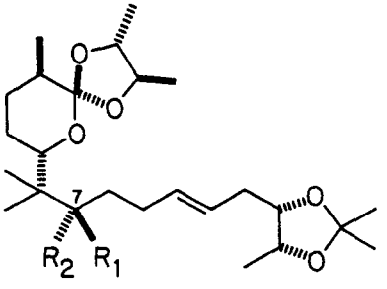


7, R_1, R_2 = O

8, R_1 = OH, R_2 = H

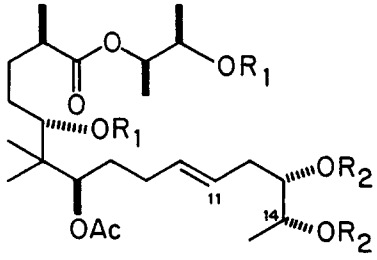
9, R_1 = H, R_2 = OH

10, R_1 = OAc, R_2 = H

11, R_1 = H, R_2 = OAc

desired isomer 15 was separated chromatographically as its tert-butyldimethyl silyl ether 16 (TBS triflate, CH_2Cl_2, lutidine, 0°C, 5 min) and, for the purpose of authenticating configurational assignments, this material was brought into convergence with 18, previously obtained by degradation of boromycin.[3] Thus, cleavage of the silyl ether of 16 ($Bu_4N^+F^-$, THF, 25°C, 1h), followed by saponification (20% aqueous NaOH, THF, MeOH, 25°C for 13 h then 40°C for 1 h) and acidification (5% aqueous HCl, $CHCl_3$, 2 h), furnished δ-lactone 17, which was hydrogenated (10% Pd/C, EtOAc) to give 18 (56% from 16). The latter was spectroscopically identical with one of the δ-lactones derived from boromycin,[10] and its diacetate 19 ($[\alpha]_D^{20}$ +30.8°; Ac_2O, CH_2Cl_2, pyridine, DAMP) also matched the corresponding substance ($[\alpha]_D^{20}$ +31.3°) of natural origin.[11]

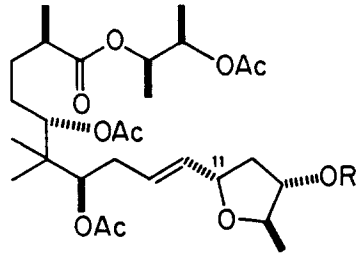
Completion of a substructure comprising the entire C(1')-C(17') half of 1 was achieved along lines similar to those employed earlier for the complemen-



12, R_1=H, R_2,R_2=CMe_2

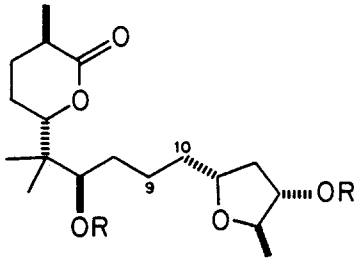
13, R_1=Ac, R_2,R_2=CMe_2

14, R_1=Ac, R_2=H



15, R=H

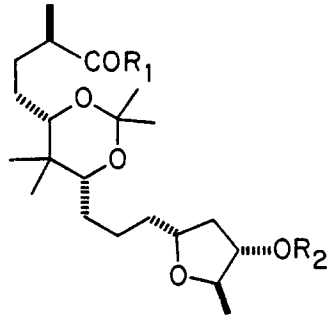
16, R=TBS



17, R=H, $\Delta^{9,10}$

18, R=H

19, R=Ac



20, R_1=OMe, R_2=H

21, R_1=OMe, R_2=TBS

22, R_1=OH, R_2=TBS

23, R_1=  , R_2=TBS

24, R_1=$CHCO_2Me$, $OCMe_2OMe$, R_2=TBS

tary "lower" half.[1] Thus, treatment of 18 with 2,2-dimethoxypropane (p-TsOH, C_6H_6, MeOH, 25°C, 1 h) led to 20 which, with tert-butyldimethylsilyl chloride (DMAP, CH_2Cl_2, 25°C, 42 h), gave 21 (86%). This was saponified (20% aqueous NaOH, MeOH), and the derived carboxylic acid 22 was converted to the acylimidazole 23 (1,1'-carbonyldiimidazole, THF, 25°C, 24 h). Acylation of the enolate of methyl methoxyisopropylglycolate (LDA, THF, -78°C, 12 min) with 23 yielded 24 as a C(2) epimeric mixture (46% from 21). The utility of this approach for a total synthesis of 1 and, by extrapolation from 16, for 2, is under investigation.

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References and Notes

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5. For an account of the elegant work by the Hanessian group in this area, see Hanessian, S.; Delorme, D.; Tyler, P.C.; Demailly, G.; Chapleur, Y. in "Current Trends in Organic Synthesis"; Nozaki, H. Ed.; Pergamon Press: Oxford, U.K., 1983; p. 205.
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7. Corey, E.J.; Kim, C.U.; Takeda, M. Tetrahedron Lett. 1972, 4339.
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10. Lactone 18 was obtained from 1 by (i) saponification of the valine ester (20% aqueous NaOH in MeOH, reflux, 10 min) (ii) acetylation (Ac_2O, pyridine, DMAP, 20 h) (iii) acidification (5% HCl, THF (1:1)) to hydrolyze the borate (iv) oxidative cleavage of the resulting tetraol (H_5IO_6, THF, 25°C, 1 h) (v) saponification of the pair of glyoxylate esters (20% aqueous NaOH, THF, 25°C, 1.5 h) (iv) treatment of the mixture of δ-lactones with $Me_2C(OMe)_2$, MeOH, C_6H_6 (1:4:16) (cat. CSA, 2½ days), and (vii) chromatographic separation of 20 (44% from 16). Hydrolysis of 20 (HOAc, H_2O, Δ) gave 18 quantitatively.
11. A parallel sequence departing from the 11R isomer of 15 produced a diacetate ($[\alpha]_D^{20}$ +27.6°) which was different from 19 in chromatographic behavior and spectral properties.

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