Stereocontrolled Synthesis of the C(1)–C(17) Half of Boromycin

James D. White,* Mitchell A. Avery, Satish C. Choudhry, Om P. Dhingra, Myung-chol Kang, and Alan J. Whittle

Department of Chemistry, Oregon State University Corvallis, Oregon 97331

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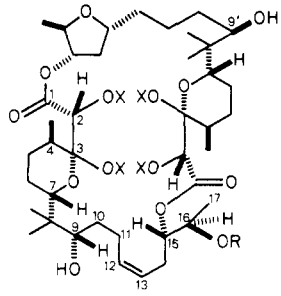
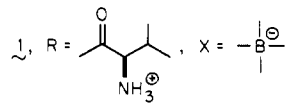
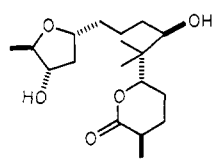
The ionophore boromycin (**1**)[1] consists of two stereochemically related halves linked head to tail to form a diolide, with a borate bridge spanning the macrocycle.[2] We recently described[3] the



1, R = 

2, R = X = H



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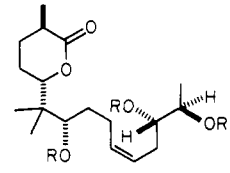
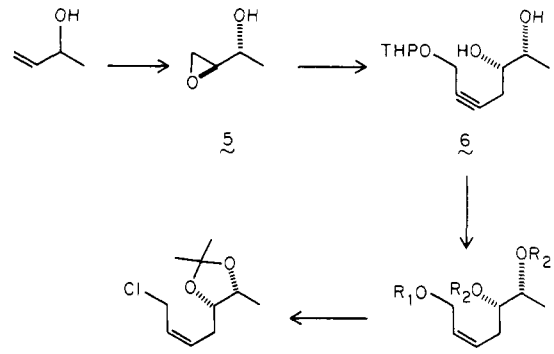


4, R = H

25, R = Ac

reconstitution of **1** from a degradation product **2**,[4] in which the macrodiolide nucleus was first converted to a borate and then selectively esterified with D-valine. In parallel with these efforts, we have pursued syntheses of the two halves of **2**[5] via a route that permits convergence with lactones **3** and **4** derived by further degradation of **2**.[2,3] Hanessian et al.[6] have independently reported chiral syntheses of these lactones, and recently, Corey et al.[7] announced the total synthesis of aplasmomycin,[8] a symmetrical macrocyclic borate structurally allied to **1**.

A synthesis of the chiral C(11)–C(17) segment of **2** was achieved from 3-buten-2-ol via enantioselective epoxidation with *tert*-butyl hydroperoxide in the presence of titanium tetraisopropoxide and diisopropyl D-(−)-tartrate.[9] The resulting epoxide **5**, which possessed the desired (2R,3S) configuration,[10] was alkylated with the tetrahydropyranyl ether of propargyl alcohol (*n*-BuLi, THF, −78 → 25 °C) to give **6** (91%). This acetylene was semihydrogenated (10% $Pd/BaSO_4$, quinoline, MeOH), affording cis olefin **7** (98%), and the latter was converted directly to **8** (91%) with 2,2-dimethoxypropane (*p*-TsOH, MeOH, C_6H_6). In preparation for coupling with the C(3)–C(10) segment, **8** was transformed to allylic chloride **9** (83%) with *N*-chlorosuccinimide and dimethyl sulfide.[11]



5

6

9

7, R_1 = THP, R_2 = H

8, R_1 = H, R_2,R_2 = CMe_2

Synthesis of the C(3)–C(10) moiety began from 3,3-dimethoxy-2,2-dimethylpropanol (**10**),[12] obtained via condensation of isobutyraldehyde with formaldehyde.[13] Oxidation of **10** (PCC) provided the malondialdehyde derivative **11** (66%, bp 55 °C (17 mm)), which was alkylated with the dianion[14] of tiglic acid (2.2 equiv of LDA, THF, −78 → 25 °C, 24 h) to give **12** (95%). This hydroxy acid was hydrogenated (94%, 10% Pd/C, EtOAc) and lactonized (DCC, DMAP) to yield **13** (80%) as a 40:60 mixture of cis/trans isomers.[15] Without separation, this mixture was taken to aldehyde **14** ($TiCl_4$, AcCl, CH_2Cl_2, 0 °C, 0.5 h)[16] and then to carboxylic acid **15** ($RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O; 68% from **13**),[17] which, upon esterification (CH_2N_2), furnished **16** (96%). Treatment of **16** with (2*R*,3*R*)-(−)-butanediol (camphorsulfonic acid, C_6H_6) afforded the ortho ester **17**[18] in 84% yield as a mixture of four diastereomers, in which the trans/cis ratio was 3.7:1.[19] Condensation of this mixture with the *dianion*[20] of methyl phenyl sulfone (1.5 equiv, 3 equiv of *n*-BuLi, THF, 0 °C) gave a mixture of keto sulfones (92%), from which the desired diastereomer **18** (mp 96–98 °C) was obtained (35% from **16**) by HPLC on μPorasil.

Alkylation of the enolate of **18** (1.06 equiv of *n*-BuLi, Me_2SO–THF) with **9** in the presence of KI yielded **19** (97%) as a pair of diastereomers. The sulfonyl group was removed (Al/Hg,

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(5) A portion of this work was communicated previously. See: White, J. D. "Abstracts of Papers", 179th National Meeting of the American Chemical Society, Houston, TX, March 24–28, 1980; American Chemical Society: Washington, DC, 1980; ORGN 48.

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(9) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(10) It was established by an independent synthesis of **5** that epoxidation had taken place in 91% enantiomeric excess. See: White, J. D.; Sheldon, B. G.; Kang, M.-c. *Tetrahedron Lett.*, in press.

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(15) Treatment of this mixture with LDA–THF gave an equilibrium composition of 80:20 in favor of *trans*-**13**.

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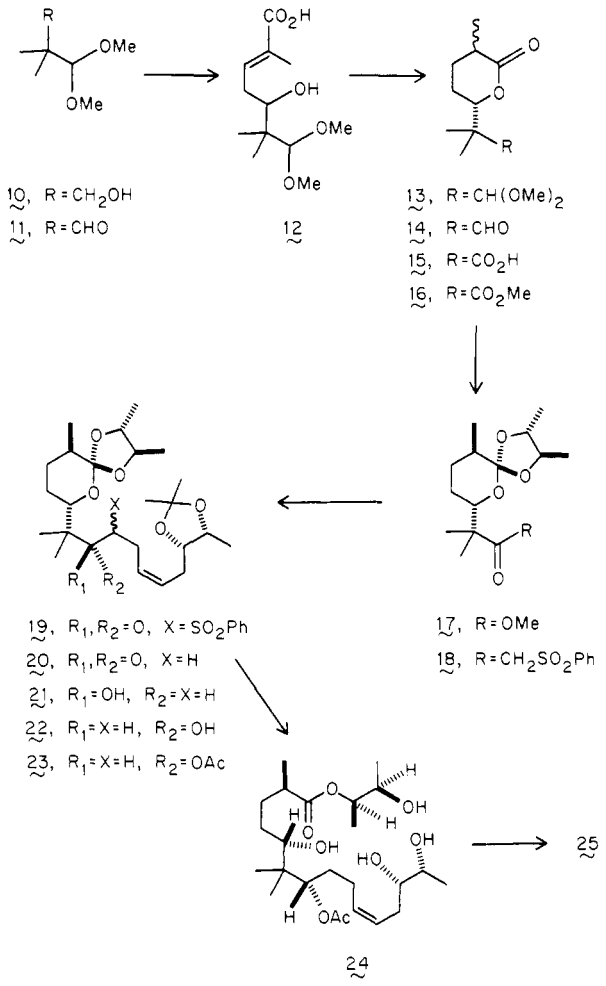
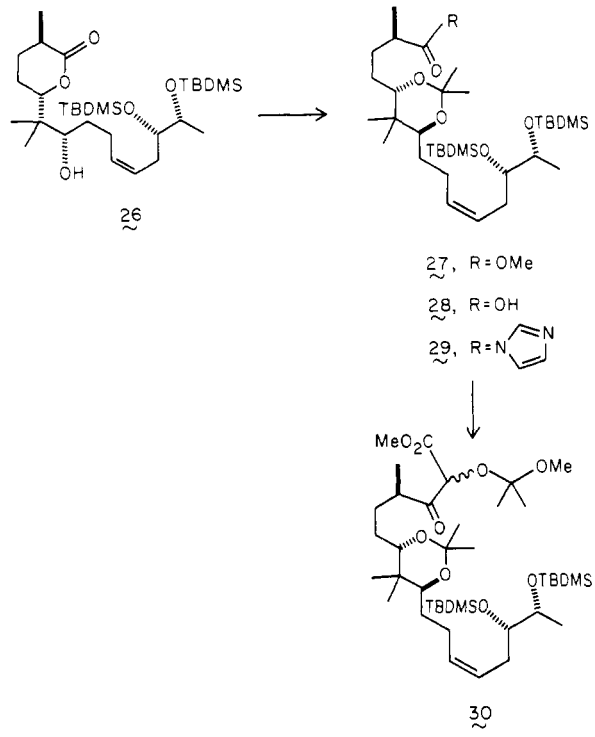
THF-H_2O (10:1), 75 °C, 1 h) to furnish **20** as an oil ($[\alpha]^{23}_D$ +3.5°) in 75% yield from **18**. Reduction of this ketone ($NaBH_4$, MeOH, 25 °C) gave a mixture of **21** and **22** (98%; 2:1 respectively), the acetates of which (Ac_2O, pyridine, DMAP) were easily separated. The 7*S* acetate **23** underwent hydrolysis (*p*-TsOH, THF-H_2O (4:1), 56 °C, 12 h) to **24**, which was saponified (NaOH, THF-H_2O, 25 °C, 3 h) and acidified (5% aqueous HCl) to provide **4** (91% from **23**), identical with the degradation product from boromycin.[3] For a rigorous comparison with naturally derived material, synthetic **4** was converted to triacetate **25** (68%,



$[\alpha]^{20}_D$ +14.2°; Ac_2O, pyridine, DMAP), which was spectroscopically identical with the substance ($[\alpha]^{20}_D$ +17.6°)[6b] obtained from **1**.

With the configuration at the five chiral centers in this segment authenticated, attention was turned to its homologation in order to complete the C(1)-C(17) perimeter of **2**. After protection of **4** as its bis(*tert*-butyldimethylsilyl) ether **26** (excess TBDMSCl, imidazole, DMF, 48 h), the latter was treated with 2,2-dimethoxypropane (*p*-TsOH, C_6H_6-MeOH) to give a quantitative yield of **27**. This ester was saponified (20% aqueous NaOH, MeOH, followed by 2% HCl, 0 °C), and the derived carboxylic acid **28** was converted to **29** (carbonyldiimidazole, THF). Acylation of the enolate of methyl methoxyisopropylglycolate[21] (LDA, THF, -78 °C, 10 min) with **29** afforded **30** as a C(2) epimeric mixture in 35% overall yield from **27**.[22] Stereochemical inhomogeneity at this stage is probably of no consequence, since it has been demonstrated in the synthesis of aplasmomycin that borate formation from the macrocyclic tetraol is accompanied by epimer-



ization at C(2) to the natural *R* configuration.[7]

The synthesis of **30** permits access to a fully functionalized subunit of **2** with rigorously defined stereochemistry and also opens a prospective route to the second half of boromycin.

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(21) Prepared by exposing a mixture of methyl glycolate and 2-methoxypropene to the vapor of $POCl_3$ (**Caution**: exotherm).

(22) For a recent account of the elegant approaches by Hanessian to the two halves of boromycin, 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.

New Mechanism-Based Serine Protease Inhibitors: Inhibition of Human Leukocyte Elastase, Porcine Pancreatic Elastase, Human Leukocyte Cathepsin G, and Chymotrypsin by 3-Chloroisocoumarin and 3,3-Dichlorophthalide

J. Wade Harper, Keiji Hemmi, and James C. Powers*

School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332

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Mechanism-based irreversible inhibitors, which have been reported for porcine pancreatic (PP) elastase and bovine pancreatic chymotrypsin A_α, include halo enol lactones and 6-chloropyrones.[1] Human leukocyte (HL) elastase and cathepsin G are related serine proteases which are involved in the connective tissue destruction that occurs in emphysema and various inflammatory diseases. Both enzymes are inhibited reversibly by heterocyclic structures such as benzoxazinones[2] and benzisothiazolinones,[3] and this

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