Versatile β-Lactam Synthons: Enantiospecific Synthesis of (-)-Polyoxamic Acid[1]

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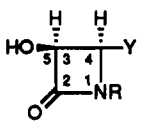
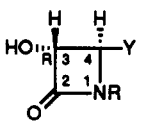
Received October 12, 1992

Summary: An optically pure *cis*-α-hydroxy β-lactam of predictable absolute configuration prepared from readily available D-mannitol has been utilized for the synthesis of the non-natural enantiomer of polyoxamic acid through a series of stereospecific reactions.

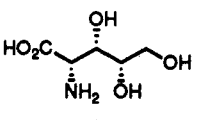
Discovery of penicillins, cephalosporins, and related antibiotics such as nocardicins and monobactams has led to sustained interest in the synthesis of *cis*-α-amino β-lactams. After the discovery of thienamycin, PS-5, PS-6, and related compounds in nature, trans α-alkyl β-lactams have attracted much attention. We[2-5] have been engaged in the synthesis of variously substituted cis and trans α-hydroxy β-lactams **1a** and **1b** as synthons for β-lactam antibiotics[6] as well as other natural products such as amino sugars, alkaloids, and amino acids.



1a



1b



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We wish to illustrate the versatility of optically active and diversely substituted 3-hydroxy-2-azetidinones **1** as synthons by describing the enantiospecific synthesis of a polyhydroxyamino acid. (+)-Polyoxamic acid (**2**)[7] found in nature has been established by chemical correlation studies to be (+)-(2*S*,3*S*,4*S*)-2-amino-3,4,5-trihydroxypentanoic acid.[8] Recently, Palamo[9] described the formation of (±)-amino acid derivatives through the C_2–C_3 bond cleavage of β-lactams. Ojima[10] has studied the N–C_4 bond cleavage of C_4-aryl β-lactams via hydrogenolysis. We describe here the synthesis of **22** which is a non-natural antipode of **2**[11] through the intermediacy of an optically active β-lactam. The key step in our general approach is the formation of a single, optically pure, cis α-(benzyloxy) β-lactam **5** of predictable absolute configuration by the annelation of a Schiff base **4** derived from a homochiral aldose and an achiral amine with a suitable acid chloride **3** (Scheme I).[12] We have indication that the absolute configuration at C-3 and C-4 of the 2-azetidinone **5** depends solely on the absolute configuration of the chiral group adjacent to the imino group.[13]

We have used easily available D-mannitol diacetonides **6** and **9** as the starting point for both antipodes of α-hydroxy β-lactams (Schemes II and III). In a recent publication[1] we have described the rapid[14] preparation using the MORE technique of (3*R*)-3-hydroxy-2-azetidinones **8b** via the Schiff base **7** from D-glyceraldehyde acetonide obtained from the symmetrical diacetonide **6** (Scheme II).

The diacetonide **9**, readily obtained by the selective hydrolysis of D-mannitol triacetonide, was converted by sodium periodate oxidation to D-arabinose diacetonide[15] (**10**) following an earlier publication. Formation of the Schiff base **11** and its reaction with (benzyloxy)acetyl chloride and triethylamine led to a single 3-(benzyloxy)-2-azetidinone **12** in 70% yield. The absolute configuration of this cis β-lactam was assigned on a tentative basis as shown in the stereostructure **12**. Mild hydrolysis with aqueous acetic acid[16] converted **12** into **13** by selective cleavage of the less hindered acetonide group (Scheme III).

The optically active β-lactam **13** has five chiral centers and several functional groups that can be manipulated selectively and in diverse fashion. In particular, two antipodal forms of α-amino acid can be generated by transforming either the C_5 or the C_3 centers in **13** to a carboxyl group while retaining the amino function at C_4. Thus, oxidation at C_5 center affords an L-amino acid[17]

(1) Studies on Lactams 89. For part 88, see: Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, K. J.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 3603. For part 87, see ref 2. Presented at the 204th National meeting of the American Chemical Society, Washington, D.C., Aug 1992; ORGN 437.

(2) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R. *Tetrahedron* **1992**, *48*, 4831.

(3) Wagle, D. R.; Garai, C.; Chiang, J.; Montelone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227.

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(5) Manhas, M. S.; Hegde, V. R.; Wagle, D. R.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2045.

(6) Also see: (a) Sheehan, J. C.; Lo, Y. S.; Loliger, J.; Podowell, C. C. *J. Org. Chem.* **1974**, *39*, 1444. (b) Lo, S. Y.; Sheehan, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 8253. (c) Palomo, C.; Cossio, F. P.; Ontoria, J. M.; Odoriozola, J. M. *Tetrahedron Lett.* **1991**, *32*, 3105.

(7) Polyoxins are antifungal antibiotics[8] which also act as competitive inhibitors of the enzyme chitin synthetase. Chemically they are nucleosides with a carbamoylated peptide side chain attached to the ribose unit. Decarbamoylated polyhydroxy amino acid obtained by the basic hydrolysis of polyoxins is called polyoxamic acid.

(8) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7499.

(9) Cassio, F. P.; Lopez, C.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1988**, *29*, 3130.

(10) Ojima, I.; Qiu, X. *J. Am. Chem. Soc.* **1987**, *109*, 6537.

(11) For synthesis of polyoxamic acid (**2**) see: (a) Savage, I.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 717. (b) Hirama, M.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1988**, *29*, 3125. (c) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979. (d) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Org. Chem.* **1986**, *51*, 5024. (e) Kuzuhara, H.; Kimura, M.; Emoto, S. *Carbohydr. Res.* **1975**, *45*, 245. (f) Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1973**, 5051.

(12) The enantiospecific synthesis of α-azido and α-amino β-lactam from Schiff bases derived from chiral aldehydes and achiral amines was developed independently by two laboratories: (a) Hubschwerlen, C.; Schmidt, G. *Helv. Chim. Acta* **1983**, *66*, 2206. (b) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R.; Hegde, V. R. Third International Symposium on Recent Advances in the Chemistry of β-lactam antibiotics, July 1984, spec. publ. No. 52; The Royal Society of Chemistry: London, 1985; p. 387. (c) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R.; Hegde, V. R.; Krishnan, L. *Tetrahedron Lett.* **1985**, *26*, 33 and later publications.

(13) (a) Bose, A. K.; Womelsdorf, J. F.; Krishnan, L.; Urbanczyk-Lipkowska, Z.; Shelly, D. C.; Manhas, M. S. *Tetrahedron* **1991**, *47*, 5379. (b) Bose, A. K.; Hegde, V. R.; Wagle, D. R.; Bari, S. S.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1986**, 161. Also see ref 12b and 12c.

(14) (a) Microwave-induced organic reaction enhancement (MORE) chemistry techniques[1] were used for the rapid formation of α-(benzyloxy) β-lactam **8a** and the hydrogenolysis of its benzyloxy group. (b) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 741.

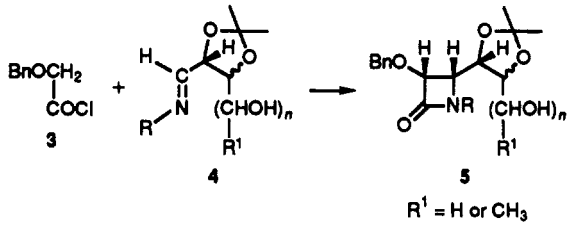
(15) Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126.

(16) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33.

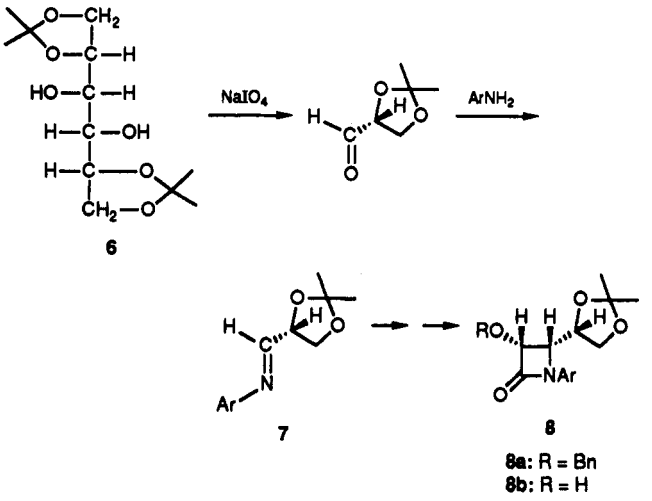
(17) We[3] have oxidized the C_5 substituent in an enantiopure β-lactam to yield a derivative of an L-amino acid.

0022-3263/93/1958-0307$04.00/0

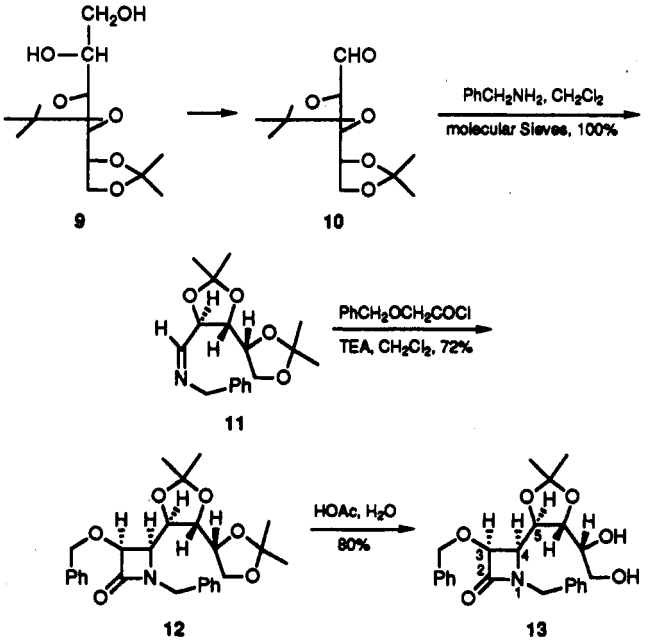
Scheme I



Scheme II



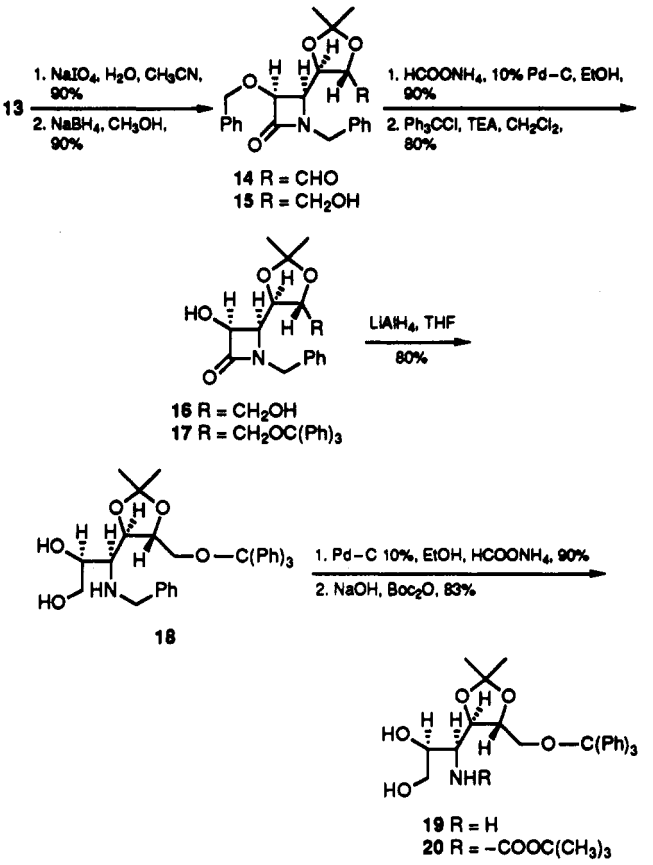
Scheme III



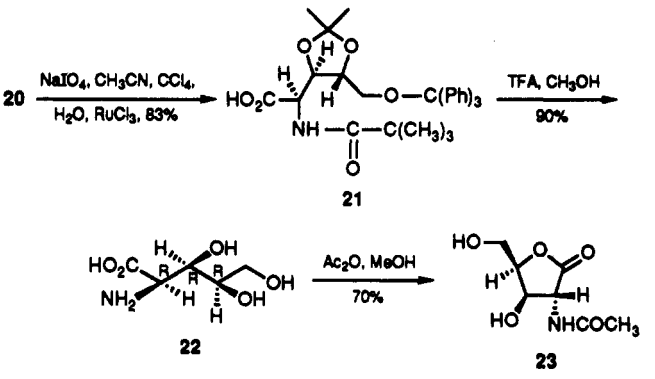
whereas a similar conversion involving the C_3 moiety results in a D-amino acid. We describe here the transformation of 13 to a D-amino acid derivative 21.

Sodium periodate oxidation followed by sodium borohydride reduction converted 13 to the primary alcohol 15 via the aldehyde 14 (Scheme IV). On the basis of our previous experience,[1] it was possible to conduct the hydrogenolysis of the OBn group in preference to the NBn group. Transfer hydrogenation[18] of 15 with ammonium formate in the presence of Pd/C led to 16. Selective protection of the primary hydroxyl group by tritylation was possible and the intermediate 17 with a free secondary hydroxyl group was obtained.

Scheme IV



Scheme V



The diol 18 was prepared by the cleavage of the β-lactam ring of 17 by reduction with lithium aluminum hydride. Catalytic-transfer hydrogenation[18] of 18 removed the *N*-benzyl group. The amino group in 19 was then protected by conversion of the *tert*-butoxycarbonyl derivative 20 (Scheme IV).

Oxidation of the diol side chain in 20 to a carboxylic acid was carried out by periodate oxidation followed by RuO_4 oxidation when 21, the protected form of polyoxamic acid, was formed (Scheme V). Treatment of 21 with trifluoroacetic acid and methanol at room temperature[11d] resulted in the simultaneous removal of the acetonide, trityl, and *tert*-butoxycarbonyl protective groups and gave

(18) (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91 and references cited therein. (b) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968. (c) Also see ref 1 which describes hydrogenation on a few gram scale in 1–5 min with ammonium formate and Pd/C in ethylene glycol as the reaction medium in a domestic microwave oven.

(−)-22. As expected, the product 22[19] proved to be the antipode of natural (+)-polyoxamic acid (2).

(−)-Polyoxamic acid (22) was characterized as its acetylated lactone (23) by treating it with acetic anhydride and methanol, mp 148 °C (lit.[11d] mp 147–150 °C; lit.[8] mp 150–152 °C). The infrared and ^{1}H NMR spectral data of 23 were compatible with the spectra supplied by two groups[11a,d] of earlier workers.

This conversion of the Schiff base 11 to (−)-polyoxamic acid (22) via a series of stereospecific steps validates the absolute configuration assignment made for the β-lactam 12. It should be possible now to start with various homochiral aldoses and assign with confidence the absolute configuration of the resulting α-hydroxy β-lactams. That such β-lactams can serve as efficient synthons for a variety of polyhydroxyamino acids and related compounds in both enantiomeric forms will be demonstrated in future publications.

Acknowledgment. We are grateful to Stevens Institute of Technology and the Howard Hughes Medical Institute (C-BEE grant) for the support of this research. We thank Dr. B. N. Pramanik for high-resolution mass spectral data and Dimple Shah, an undergraduate research participant, for technical assistance. We also thank Dr. A. K. Ganguly of Schering Plough Corporation and Mr. Ian Savage of the University of Oxford for supplying the spectra of their acetylated polyoxamic acid lactone for comparison purposes.

Supplementary Material Available: Experimental procedures and compound characterization data (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) All new compounds reported here gave satisfactory elemental analysis and spectral data. Purification of 22 was achieved by ion-exchange chromatography[11d] using an AG 50W-X8 H^+ column and aqueous ammonia as the eluent. The purified product was obtained as a white amorphous solid, mp 163–171 °C dec; $[\alpha]^{23}_D$ −5.1° (c 1.0, H_2O) [lit.[8] mp 171–173 °C dec; $[\alpha]^{23}_D$ +2.8° (c 1.0, H_2O); lit.[11d] mp 162–188 °C dec; $[\alpha]^{23}_D$ +2.8° (c 1.0, H_2O); lit.[11a] $[\alpha]^{23}_D$ +6.0° (c 1.0, H_2O)]. (−)-Polyoxamic acid (22)[20] which is unstable can be converted easily to a stable *N*-acetyl lactone 23.

(20) Non-natural enantiomers of natural products are of current interest for studies on their physiological activity and their interaction with binding sites.