COMMUNICATIONS

Synthetic approaches to β-lactam antibiotics: a stereocontrolled synthesis of *trans* 3-(*S*)-amino-4-(*S*)-ethyl-2-oxo-1-azetidine[1]

STEPHEN HANESSIAN AND SOUMYA P. SAHOO
Department of Chemistry, Université de Montréal, Montréal, P.Q., Canada H3C 3V1

Received January 30, 1984

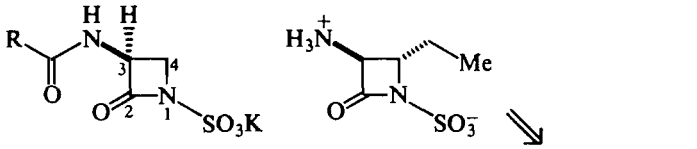
STEPHEN HANESSIAN and SOUMYA P. SAHOO. Can. J. Chem. **62**, 1400 (1984).

A synthesis of the title compound, an immediate precursor of the biologically active 4-ethyl monobactam, from 2-amino-2-deoxy-D-glucose is described. The strategy allows for the synthesis of a variety of β-substituted α-amino acids, which are otherwise difficultly accessible.

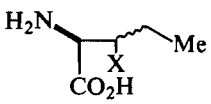
STEPHEN HANESSIAN et SOUMYA P. SAHOO. Can. J. Chem. **62**, 1400 (1984).

La synthèse d'un précurseur de l'antibiotique 4-ethyl monobactame, à partir du 2-amino-2-deoxy-D-glucose est décrite. La stratégie suivie permet la synthèse d'un nombre d'acide α-aminés contenant un substituant sur la position β, et qui sont difficilement accessibles par d'autres voies.

Since the discovery of the monobactams, a family of monocyclic β-lactam antibiotics produced by various gram-negative bacteria (1), extensive studies have been devoted to the synthesis of the parent structure **1** (2) as well as its analogs (3). These intense efforts have been rewarded by the emergence of aztreonam, a *trans* 3-(*S*)-amino-4-(*S*)-methyl-2-oxo-1-azetidinesulfonic acid substituted with a heterocyclic moiety at N-3, as a clinical candidate. Related structures with a *cis*-substitution pattern are also known (4). A noteworthy feature



1 **2**



3, X = OH
4, X = NH_2

of the 4-substituted monobactams is their higher intrinsic antibacterial activity and resistance to β-lactamases as manifested, for example, by the N-acyl derivative of a racemic structure corresponding to expression **2** (3). Since the structures of the naturally-occurring monobactams do not lend themselves to chemical modification at the C-4 position, recourse has been made to totally synthetic and semi-synthetic routes in order to probe into aspects of structure–activity relationships (3, 5). As with any synthetic program with a biological objective, the quest for enantiomerically pure targets becomes a matter of concern.

Compared to the structurally more impressive bicyclic β-lactam antibiotics, the synthesis of the monobactams as exemplified by the optically pure title compound may appear to present a trivial exercise (for some recent syntheses of 4-substituted azetidinones, see for example ref. 6). Indeed, a simple retrosynthetic analysis of the target reveals logical progeny from a 2-amino-3 hydroxy pentanoic acid (L-ethylserine) **3**, or a 2,3-diaminopentanoic acid **4** as potential chirons (7). These, however, are not readily available amino acids in optically pure form, hence the reason why the title compound was prepared and tested as a racemic mixture (3, 5). The prospects of azetidinone formation in the β-hydroxy-α-amino acid series must be dealt with with some caution because of the propensity for elimination, racemization, and intramolecular reactions (see for example, ref. 8). We have recently found an expedient solution to this problem in the facile 3-step transformation of N-[(benzyloxy)carbonyl]-L-serine *p*-methoxyphenylamide into 3-(*S*)-1-amino-2-oxo-1-azetidine, the parent monobactam structure corresponding to **1** (9).

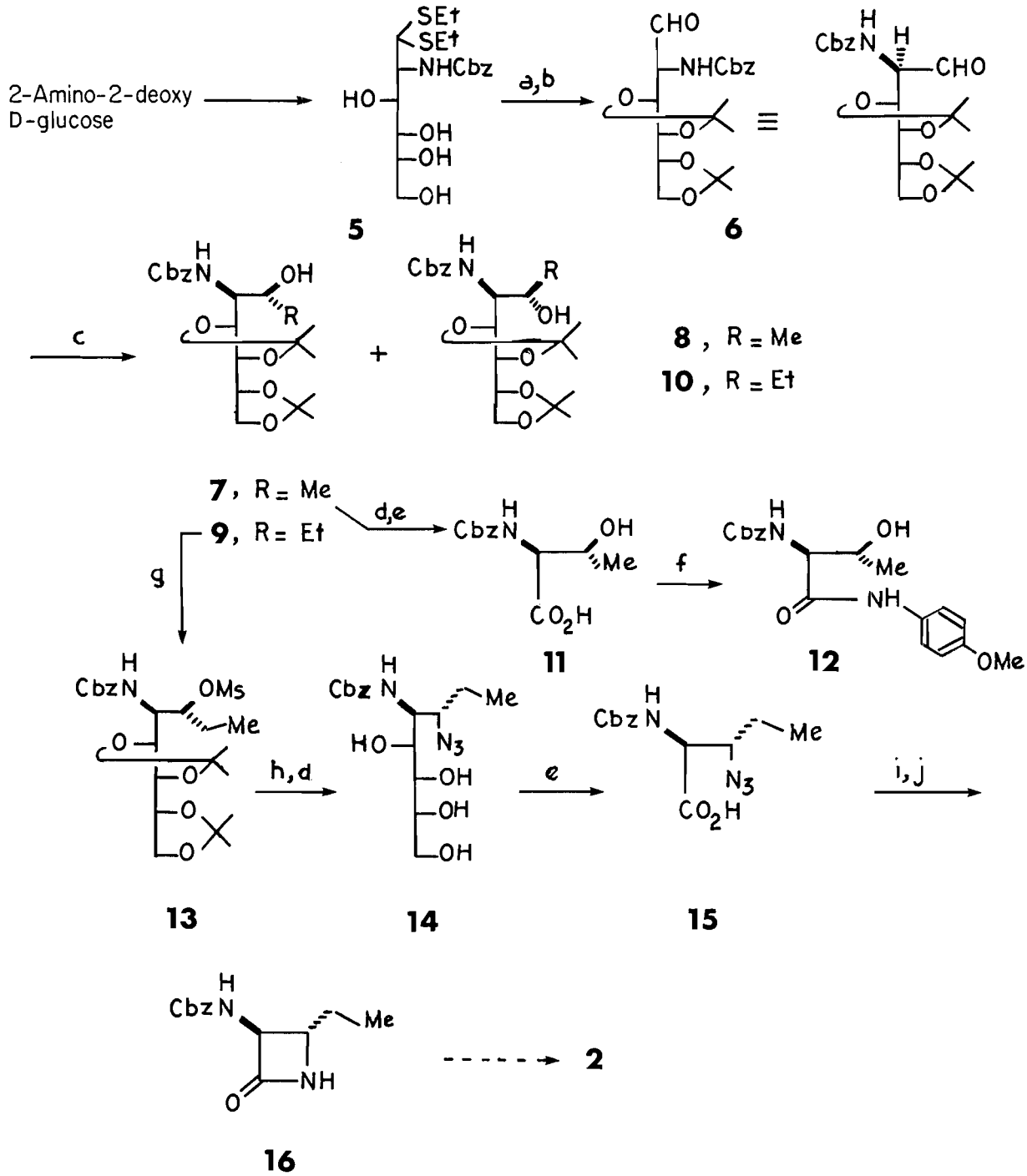
In this paper, we describe a general synthetic protocol for the stereocontrolled access to optically active 2-amino-3-hydroxy acids with a specific application to the total synthesis of the title monobactam precursor **2**. The strategy utilizes 2-amino-2-deoxy-D-glucose as a chiral template in which, quite fortuitously, the sense of chirality of the amine-bearing carbon atom is convergent with C-3 in the target. Stereocontrolled attack by an ethyl Grignard on the aldehyde function of **6** which is readily available from **5** (10) was expected to occur in an anticipated sense to give a high preponderance of the desired material (Scheme 1). Adjustment of functionality and manipulation of expendable appendages would thus lead to the intended target. These chemical events were experimentally realized.

Acetonation of **5** gave the crystalline diacetonide derivative (98%), mp 54–56°C; $[\alpha]_D$ − 28.2° ($CHCl_3$). Conversion to the aldehyde **6** followed by treatment with methylmagnesium chloride led to a nearly quantitative yield of a 4:1 mixture of isomers **7** and **8** which were readily separated by preparative hplc.[2,3] Hydrolysis of the acetal functions in the major isomer **7** (syrup, $[\alpha]_D$ 0 ± 1° ($CHCl_3$), MH^+ 410), followed by oxidative cleavage (11) gave N-Cbz L-threonine **11**, characterized as the crystalline *p*-methoxybenzamide derivative **12**, mp 165–167°C; $[\alpha]_D$ −63.2° ($CHCl_3$), identical with an authentic sample. Thus, nucleophilic attack on the aldehyde took place

[1] Reported in part at the Symposium on Stereocontrolled Elaboration of Organic Molecules, San Miniato, Italy, Sept. 12–16, 1983.

[2] Waters Prep. 500 chromatograph using 20% ethyl acetate in hexanes as eluent.

[3] New compounds reported in this paper were adequately characterized by spectroscopic (nmr, 90, 400 MHz; mass) and analytical data.



SCHEME 1. Abbreviations: a. acetone, camphorsulfonic acid, dimethoxypropane, 3 h (98%); b. aq. acetone, $HgCl_2$, HgO, 2 h, 83%; c. MeMgCl or EtMgBr, THF, 0°C, then r.t., 3–4 h, ~quant.; d. 80% aq. AcOH, 60°C, 18 h, ~quant.; e. $NaIO_4$–$KMnO_4$, aq. acetone, 18 h, (60%); f. *p*-anisidine, ethyl(diethylaminopropyl) carbodiimide hydrochloride, 2–3 h; g. MsCl, Et_3N, CH_2Cl_2, 0°C, then r.t., ~quant.; h. $n\text{-}Bu_4NN_3$, toluene, 80°C, 18 h, 80%; i. Ra-Ni, MeOH, 15 min; j. Ph_3P, dipyridyldisulfide (1.1 equiv. each, MeCN, reflux 18 h, 1 mmol of amine/180 mL solvent); 50% (2 steps).

in the anticipated manner, and it was expected that bulkier Grignard reagents would increase the stereoselectivity even more. Thus, treatment of **6** with ethylmagnesium bromide gave a 9:1 mixture of isomers **9** and **10**, in almost quantitative yield, which were easily separated by flash column chromatography. The major component **9**, $[\alpha]_D$ +9.2° ($CHCl_3$), MH^+ 424, was mesylated to **13** (syrup, ~quant.) and the potential amino group was introduced by an inversion process to give the azide **14** as a syrup (80%); $[\alpha]_D$ +2° ($CHCl_3$). Oxidative cleavage then gave the β-azido acid **15** (syrup, 60%)[4] which was reduced and subjected to a variety of ring closure procedures.[5] We

[4] The corresponding methyl ester showed $[\alpha]_D$ +22.2° ($CHCl_3$); MH^+ 307.

[5] A variety of methods, including various carbodiimide-related cyclizations, led to decomposition or unidentified products. Methods for azetidinone formation of 3,4-disubstituted systems, from the corresponding β-amino acids, are not widely known, see ref. 9.

found a minor modification of the Ohno method (12) to be the most effective, particularly at higher dilutions than originally reported. With this proviso, it was possible to obtain the target β-lactam **16** in 50% yield (2 steps), $[\alpha]_D$ −34.3° (MeOH); ir ($CHCl_3$): 1770 cm^{-1} (β-lactam); 1750 cm^{-1} (Cbz); ^1H nmr (400 MHz, $CDCl_3$), ppm: 4.37, H-3 (dd, $J_{3,4}$ = 1.8 Hz; $J_{3,NH}$ = 8.25 Hz); 3.5, H-4 (ddd, $J_{4,3}$ = 1.8 Hz, $J_{4,4''}$ = 6.5 Hz, $J_{4,4''}$ = 6.7 Hz); etc; MH^+ 249. Compound **16** (racemic form) has been previously transformed into the corresponding N-sulfonic acid and the latter further elaborated into biologically active N-acyl derivatives (3, 5).

The presently described route to optically active β-hydroxy amino acids can nicely converge with the Squibb process (2, 5) or related ones (8) which rely on a Mitsunobu reaction (13) in the β-lactam ring-forming step. Our methodology also provides access to rare amino acids. For example, reaction of **6** with phenylmagnesium bromide gave the corresponding carbinol as the preponderant, if not exclusive, product having the expected stereochemistry. Oxidative degradation would lead to 2-(*R*)-amino-3-(*R*)-hydroxyphenyl propionic acid (phenylserine) which is commercially available in racemic form (for some recent reviews on the asymmetric synthesis of amino acids, see ref. 14).

Finally, it should be noted that even though the C-4—C-6 segment of the original amino sugar is sacrificed en route to the target β-lactam, its inherent functional and stereochemical features have served their intended useful purpose, firstly, to provide the chiral framework that secured the high degree of stereoselection in the Grignard reaction and, secondly, to act as a latent carboxyl group of the target amino acid. In view of the very low cost of this amino sugar and the obvious advantages of the strategy, the planned "burning off" of essentially half the original molecule may be tolerable.

Acknowledgments

We wish to acknowledge generous financial support from NSERCC and Le Ministère de l'éducation du Québec, as well as from Sandoz (Vienna). We also thank Dr. P. M. Tan for high resolution nmr spectra and Mr. M. Evans for mass spectra.

1. R. B. SYKES, C. M. CIMARUSTI, D. P. BONNER, K. BUSH, D. M. FLOYD, N. H. GEOROGOPAPADAKOU, W. KOSTER, W. C. LIU, W. L. PARKER, P. A. PRINCIPE, M. L. RATHUM, W. A. SLUSARCHYK, W. H. TREJO, and J. S. WELL. Nature, **291**, 489 (1981); A. IMADA, K. KITANO, K. KINTAKA, M. MUROI, and M. ASAI. Nature, **289**, 590 (1981); see also C. M. CIMARUSTI and R. B. SYKES. Chem. Br. 302 (1983).
2. W. L. PARKER, W. H. KOSTER, C. M. CIMARUSTI, D. M. FLOYD, W. LIU, and M. L. RATHUM. J. Antibiot. **35**, 189 (1982); W. L. PARKER and M. L. RATHUM. J. Antibiot. **35**, 300 (1982); C. M. CIMARUSTI, H. E. APPLEGATE, H. W. CHANG, D. M. FLOYD, W. H. KOSTER, W. A. SLUSARCHYK, and M. G. YOUNG. J. Org. Chem. **47**, 179 (1982); D. M. FLOYD, A. W. FRITZ, and C. M. CIMARUSTI. J. Org. Chem. **47**, 176 (1982).
3. C. M. CIMARUSTI, D. P. BONNER, H. BREVER, H. W. CHANG, A. W. FRITZ, D. M. FLOYD, T. P. KISSICK, W. H. ROSTER, D. KRONENTHAL, F. MASSA, R. H. MUELLER, J. PLUSCEC, W. A. SLUSARCHYK, R. B. SYKES, M. TAYLOR, and E. R. WEAVER. Tetrahedron, **39**, 2577 (1983).
4. S. KISHIMOTO, M. SENDAI, S. HASHIGUCHI, M. TOMIMOTO, Y. SATOH, T. MATSUO, M. KONDO, and M. OCHIAI. J. Antibiot. **36**, 1421 (1983); C. C. WEI, J. TENGI, and M. WEIGELE. 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, Nevada, Oct. 24, 1983, Abstract 324.
5. R. B. SYKES, W. L. PARKER, C. M. CIMARUSTI, W. H. KOSTER, W. A. SLUSARCHYK, A. W. FRITZ, and D. M. FLOYD. U.K. Patent No. 2,071,650. 1981.
6. G. GEORG and T. DURST. J. Org. Chem. **48**, 2092 (1983); H. MATSUNAGA, T. SAKAMAK, H. NAGAOKA, and Y. YAMADA. Tetrahedron Lett. **24**, 3009 (1983); A. J. BILOSKI, R. D. WOOD, and B. G. GANEM. J. Am. Chem. Soc. **104**, 3233 (1982); and references cited therein, see also ref. 3.
7. S. HANESSIAN. *In* The total synthesis of natural products: the 'chiron' approach. *Edited by* J. E. Baldwin. Pergamon Press, Oxford, England. 1983.
8. M. J. MILLER, P. G. MATTINGIY, M. A. MORRISON, and J. F. KERWIN, JR. J. Am. Chem. Soc. **102**, 7026 (1980); A. K. BOSE, D. P. SAHU, and M. S. MANHAS. J. Org. Chem. **46**, 1229 (1981); C. A. TOWNSEND and L. T. NGUYEN. J. Am. Chem. Soc. **103**, 4582 (1981).
9. S. HANESSIAN, C. COUTURE, and H. WYSS. To be published.
10. M. W. WHITEHOUSE, P. W. KENT, and C. A. PASTERNAK. J. Chem. Soc. 2315 (1954).
11. R. U. LEMIEUX and E. VON RUDOLFF. Can. J. Chem. **33**, 1701 (1955); **33**, 1710 (1955).
12. S. KOBAYASHI, T. IIMORI, T. IZAWA, and M. OHNO. J. Am. Chem. Soc. **103**, 2406 (1981).
13. M. WADA and O. MITSUNOBU. Tetrahedron Lett. 1279 (1972); O. MITSUNOBU. Synthesis, 1 (1981).
14. K. WEINGES and B. STEMMLE. Recent. Dev. Chem. Nat. Carbon Compd. **7**, 89 (1976); K. DRAUZ, A. KLEEMAN, and J. MARTENS. Angew. Chem. Int. Ed. Engl. **21**, 584 (1982); J. W. APSIMON and R. P. SEGUIN. Tetrahedron, **35**, 2797 (1979); I. WAGNER and H. MUSSO. Angew. Chem. Int. Ed. Engl. **22**, 816 (1983).