Stereo- and Enantio-controlled Synthesis of Chiral Intermediates for the Total Synthesis of Thienamycin and Related β -Lactam Antibiotics from 3-Hydroxybutyrates

Gunda I. Georg* and Harpal S. Gill

Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045–2500, U.S.A.

The synthesis of (1'R,3S,4S)- and (1'R,3S,4R)-3-(1'-t-butyldimethylsilyloxyethyl)-4-hydroxymethyl-2-azetidinone from ethyl (S)-3-hydroxybutyrate is reported.

One major difficulty in the synthesis of thienamycin (1) and related β -lactam antibiotics (2) and (3) is the control of the relative and absolute stereochemistry of the three contiguous chiral centres.¹

Since we and Hart first demonstrated² that 3-hydroxybutyrates³ can be used as chiral building blocks for the synthesis of 3-(1'-hydroxyethyl)-2-azetidinones in a one-flask procedure a number of other groups have reported similar findings.⁴ In this paper we now convey the synthesis, from ethyl (S)-3-hydroxybutyrate (Scheme 1), of optically active *trans*- and *cis*-3-(1'-t-butyldimethylsilyloxymethyl)-4-hydroxymethyl-2-azetidinones, intermediates which can be converted into thienamycin and olivanic acids by a known procedure.⁵ We used ethyl (S)-3-hydroxybutyrate with 86% optical purity,





HO HO CO₂Et (4) 77 % C OMe MeO (5) (6) 84 °/• ü HO OMe OMe (8)(3%)(7) iii quant. Bu^tMe₂SiQ Bu^tMe₂SiQ 86 - 97% 'OMe (9) trans (10a) (10b) cis 81-97 % Bu^t Me₂SiQ OH н *trans* (11a) $[\alpha]_{D}^{25} - 14.1^{\circ}$ cis (11b) $[\alpha]_{D}^{25} - 45.6^{\circ}$

Scheme 1. Reagents: i, tetrahydrofuran (THF), 2 LICA (lithium isopropylcyclohexylamine), -20–10 °C; ii, THF, PPh₃, diethyl azodicarboxylate (DEAD), HCO₂H, 0 °C–room temp., 1.5 h; MeOH, HCl, room temp., 15 h; iii, dimethylformamide (DMF), t-butyldimethylsilyl chloride, imidazole, room temp., 15 h; iv, MeCN, ammonium cerium(iv) nitrate, -20 °C, 20 min; v, CH₂Cl₂, O₃, NaBH₄, -78–0 °C.



Scheme 2. Reagents: i, DMF, t-butyldimethylsilyl chloride, imidazole, room temp., 15 h; ii, CH_2Cl_2 , O₃, NaBH₄, -78 to -20 °C; iii, acetone, Jones reagent, -5 °C, 2 h; iv, MeCN, Pb(OAc)₄, Cu(OAc)₂, 70 °C, 0.5 h.

obtained from reduction of ethyl acetoacetate using baker's yeast.³ The dianion imine condensation-cyclisation reaction of ethyl (S)-3-hydroxybutyrate (4) and N-anisylcinnamylidenimine (5) gave a 1:1 mixture of *trans*- and *cis*- β -lactam (6) in 77—100% yield.⁶ Mitsunobu inversion^{2a,7} of (6) followed by acid hydrolysis of the intermediate formyl esters cleanly produced the inverted (R)-hydroxyethyl-2-azetidinones (7) in 84% yield. We also isolated a small amount (3%) of the elimination product (8). After protection of (7) as its t-butyldimethylsilyl ether we were able to separate the trans and cis isomers (9) by flash chromatography. We then subjected them separately to oxidative dearylation⁸ with ammonium cerium(iv) nitrate, to obtain the N-unprotected β-lactam trans (10a) {97% yield, m.p. 85-86 °C (light petroleum–CH₂Cl₂), $[\alpha]_D^{25}$ +40.7° (*c* 0.8555 CHCl₃)} and *cis* (10b) {86% yield, m.p. 80 °C (light petroleum–CH₂Cl₂), $[\alpha]_D^{25}$ -45.9° (c 1.06 CHCl₃). Ozonolysis of (10a) and (10b), followed by reductive work-up9 produced the 4-hydroxymethyl-2-azetidinones trans (11a) { (yield 97%, m.p. 89—90 °C (light petroleum), $[\alpha]_D^{25} - 14.1^\circ$ (*c* 0.595 CHCl₃)} and cis (11b)¹⁰ (yield 81%, m.p. 94 °C (light petroleum), $[\alpha]_{D}^{25} - 45.6^{\circ} (c \ 0.8 \ \text{CHCl}_{3}) \}. \dagger$

The overall yield from ethyl (S)-3-hydroxybutyrate for *trans* (11a) was 30% and 23% for *cis* (11b).¹¹ These yields are comparable to other reported methods for the synthesis of chiral thienamycin precursors.^{8b,11} The optical rotation of (11a) was found to be identical to the literature value for (1'R,3S,4S)-3-(1'-t-butyldimethylsilyloxyethyl)-4-hydroxy-methyl-2-azetidinone.^{11b,c} After we had unequivocally estab-

lished the absolute stereochemistry of the *trans* products, we decided to determine the configuration of the *cis*-azetidinones through *cis*-*trans* isomerization at position 4 (Scheme 2). Reider and Grabowski had previously shown,^{11a} that oxida-tive decarboxylation of 3-(1'-hydroxyethyl)-4-(carboxylic acid)-2-azetidinone results in exclusive introduction of the acetoxy group at C-4 opposite the hydroxyethyl group at C-3.

The *cis-trans* mixture (6) (racemic) was quantitatively converted into the t-butyldimethylsilyl ether (12). Ozonolysis of (12) followed by reductive work-up with NaBH₄ and then oxidation with Jones reagent gave the carboxylic acid (13).

[†] All intermediates showed spectroscopic data in agreement with their structures.

After oxidative decarboxylation with lead tetra-acetate¹² we obtained *trans*- β -lactam (14) as single isomer in an overall yield of 40% (Scheme 2).

Financial assistance from the National Institutes of Health and the University of Kansas is acknowledged. We thank Professor D. L. Boger for interesting discussions and K. S. Furlought and V. Huselsy for their help.

Received, 4th June 1985; Com. 769

References

- For reviews: R. B. Morin and M. Gorman, 'Chemistry and Biology of β-Lactam Antibiotics,' Academic Press, New York, 1982; T. Kametani, *Heterocycles*, 1982, 17, 463; D. Hoppe, *Nachr. Chem. Techn. Lab.*, 1982, 30, 25; R. Labia and C. Motin, J. *Antibiot.*, 1984, 37, 1103.
- 2 (a) G. I. Georg, Tetrahedron Lett., 1984, 25, 3779; (b) D.-C. Ha, D. J. Hart, and T.-K. Yang, J. Am. Chem. Soc., 1984, 106, 4819.
- 3 D. Seebach, M. A. Sutter, R. H. Weber, and M. F. Zueger, Org. Synth., 1984, 63, 1, and references cited therein; D. Seebach and M. Zueger, Helv. Chim. Acta, 1982, 65, 495.
- 4 T. Chiba, N. Nagatsuma, and T. Nakai, *Chem. Lett.*, 1984, 1927;
 G. Cainelli, M. Contento, D. Giacomini, and M. Panunzio, *Tetrahedron Lett.*, 1985, 26, 937; T. Iimori and M. Shibasaki, *ibid.*, 1985, 26, 1523.

- 5 T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and I. A. Bouffard, J. Am. Chem. Soc., 1980, 102, 6161; R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, Tetrahedron Lett., 1980, 21, 31.
- 6 Addition cyclization reactions between enolates and imines: I. Ojima, S. Inaba, and K. Yoshida, *Tetrahedron Lett.*, 1977, 3643;
 C. Gluchowski, L. Cooper, D. E. Bergbreiter, and M. Newcomb, J. Org. Chem., 1980, 45, 3413;
 D. J. Hart, K. Kanai, D. G. Thomas, and T. K. Yank, *ibid.*, 1983, 48, 289;
 E. W. Colvin and D. G. McGarry, J. Chem. Soc., Chem. Commun., 1985, 539.
- 7 D. G. Melillo, T. Liu, K. Ryan, M. Sletzinger, and I. Shinkai, *Tetrahedron Lett.*, 1981, 22, 913; D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, *ibid.*, 1980, 21, 2783.
- 8 (a) D. R. Kronenthal, C. Y. Han, and M. K. Taylor, J. Org. Chem., 1982, 47, 2765; (b) H. Yanagisawa, A. Ando, M. Shiozaki, and T. Hiraoka, Tetrahedron Lett., 1983, 24, 1037.
- 9 G. Georg and T. Durst, J. Org. Chem., 1983, 48, 2092.
- 10 The enantiomer of cis (11b) is a suitable intermediate for the synthesis of cis-olivanic acid (3) [from methyl (R)-3-hydroxybutyrate]. For the synthesis of olivanic acids see; J. H. Bateson, R. I. Hickling, P. M. Roberts, T. C. Smale, and R. Southgate, J. Chem. Soc., Chem. Commun., 1980, 1084; R. J. Ponsford, and R. Southgate, *ibid.*, 1980, 1085.
- (a) P. J. Reider and E. J. Grabowski, *Tetrahedron Lett.*, 1982, 23, 2293; (b) M. Shiozaki, N. Ishida, T. Hiraoka, and H. Yanigasawa, *ibid.*, 1981, 22, 5205; (c) M. Shiozaki, N. Ishida, T. Hiroako, and H. Maruyama, *ibid.*, 1984, 40, 1795.
- 12 J. K. Kochi and J. D. Bacha, J. Org. Chem., 1968, 33, 2746.

1435