Tetrahedron Letters,Vol.26,No.5,pp 587-590,1985
Printed in Great Britain

0040-4039/85 $3.00 + .

SYNTHETIC CARBAPENEM ANTIBIOTICS III.[1] 1-METHYL THIENAMYCIN

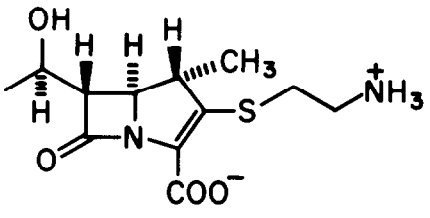
David H. Shih,* Lovji Cama and Burton G. Christensen

Merck Sharp & Dohme Research Laboratories, P. O. Box 2000, Rahway, New Jersey 07065

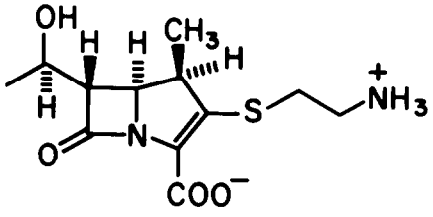
Abstract. Total syntheses of 1α- and 1β-methyl thienamycin are reported. 1β-Methyl thienamycin the antibacterial activity of thienamycin and is highly resistant to hydrolysis by DHP-I enzyme.

Thienamycin[2] is one of the most potent naturally occurring broad spectrum β-lactam antibiot its intrinsic chemical stability is insufficient to allow its development as a clinical drug candidate. synthetic structural modification of thienamycin produced a chemically stable product, imipenem,[3] has the antibacterial activity and potency of the parent, but like other naturally occurring carbape is readily metabolized by renal dehydropeptidase-I (DHP-I), thus necessitating the co-administrai DHP-I inhibitor.[4] Therefore, the design of a metabolically stable and efficacious carbapenem an became a major objective of our program. In the pursuit of this objective, we have engaged in an ex program of conventional side chain modification[5] as well as studies directed toward more fund modification of the nucleus.[6]

Herein we report the total synthesis and stereochemical assignments of 1α-methyl thienamycin 1β-methyl thienamycin (**2**). The biological properties of these two isomers reveal a major breakthr the design of DHP-I resistant carbapenem antibiotics.



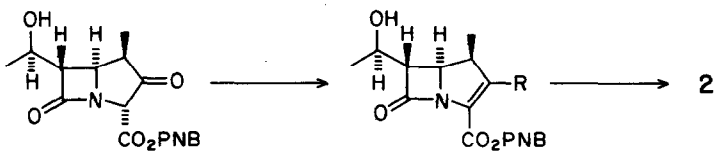
1



2

The key synthetic intermediate, 1β-methyl keto ester **3**, which was reported previously,[1] w to prepare 1β-methyl thienamycin as shown in Scheme I. The cysteamine side chain of 1β- thienamycin was introduced by a displacement reaction of 1β-methyl enol phosphate **4** with N-(p-nitrol oxycarbonyl)aminoethanethiol under conditions similar to those employed previously in the carbapenem (diisopropylethylamine/acetonitrile, r.t.).[7]

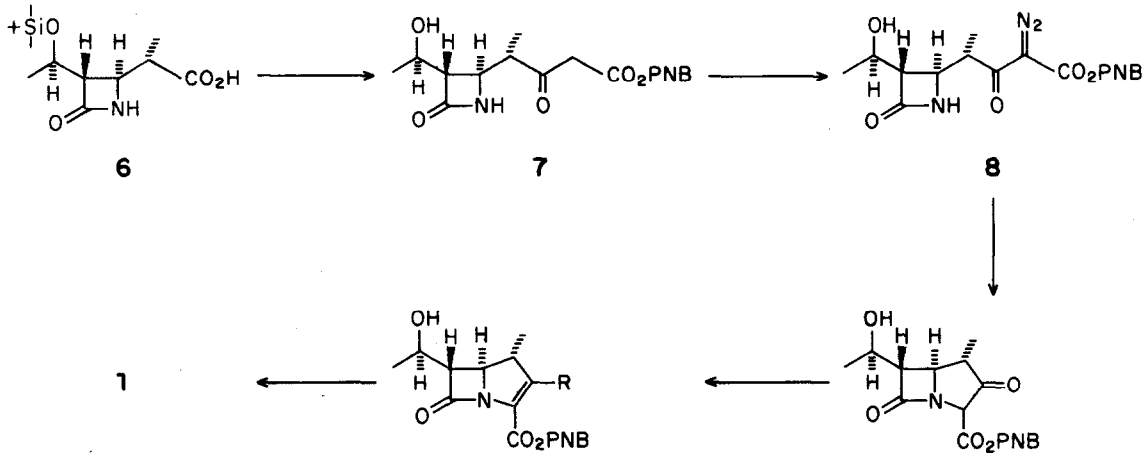
Scheme I



3 4 R=OP(O)(OPh)$_2$ 5 R=SCH$_2$CH$_2$NHCO$_2$PNB

Preparation of 1α-methyl keto ester **9** from **6** was carried out under conditions similar to those used for the preparation of **3** (Scheme II). Treatment of **6** under Masamune's conditions followed by desilylation with 6N hydrochloric acid afforded the chain extended β keto ester **7**, which was diazotized with polymer-SO_2N_3 in acetonitrile in the presence of triethylamine to give diazo intermediate **8**. Treatment of

Scheme II



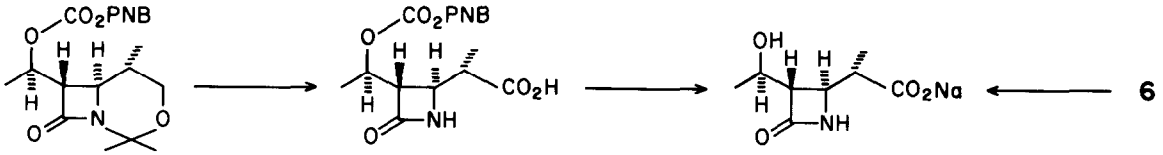
10 R=OSO$_2$CF$_3$
11 R=SCH$_2$CH$_2$NHCO$_2$PNB

8 with rhodium acetate yielded the bicyclic keto ester **9**. However, the formation of 1α-methyl enol phosphate from 1α-methyl keto ester **9** was very sluggish and subsequent displacement of the phosphonate with the same mercaptan was also difficult. Therefore, the preparation of 1α-methyl thienamycin from keto ester **9** required a less hindered and more reactive leaving group. Trifluoromethylsulfonate **10** (trifluoromethanesulfonic anhydride/diisopropylethylamine in acetonitrile, -20°) was sufficiently reactive. Hydrogenolysis of **5** and **11** (40 psi hydrogen, 10% Pd/C in THF/phosphate buffer) followed by Dowex 50x4 (sodium form) purification gave the desired 1β- and 1α-methyl thienamycins, respectively.

The stereochemical assignments of these compounds were based upon the correlation of the key intermediate **6**[1] with an authentic sample synthesized independently by a stereocontrolled route from **12**,[1b] the structure of which was established by X-ray crystallography. These correlations are summarized in Scheme III. Treatment of **12** with two equivalents of Jones reagent (acetone, r.t.) gave azetidinone

carboxylic acid **13**, which upon saponification with sodium hydroxide yielded sodium salt **14**, whose proton NMR spectrum was identical to the product derived from **6** by acidic desilylation (6 N HCl, in methanol/water solution, r.t.) followed by neutralization with sodium hydroxide and lyophilization.

Scheme III



12 **13** **14**

Isomers **1** and **2** proved to be significantly different in both antibacterial activity and DHP-I susceptibility. The 1β-methyl thienamycin is biologically more active than thienamycin and more significantly, it is highly resistant to enzymic hydrolysis by DHP-I. The 1α-methyl isomer is rather resistant to DHP-I hydrolysis but its antibacterial activities are very much decreased. These findings have opened new opportunities to design a variety of metabolically stable carbapenem antibiotics based upon the 1β-methylcarbapenem nucleus.[1,8]

Acknowledgments. The authors thank Dr. C. Shunk and A. Matzuk for large-scale preparation of intermediates; J. S. Kahan, H. Kropp and J. G. Sundelof for the biological evaluations; Drs. J. Heck and T. Salzmann and Ms. J. Garoniak for their helpful discussions in preparing this manuscript.

References

1. (a) For Part 1, see D. H. Shih, F. Baker, L. Cama and B. G. Christensen, Heterocycles, 1984, **21**, 29; (b) For Part II, see D. H. Shih, J. A. Fayter, L. Cama, B. G. Christensen and J. Hirshfield, the preceding paper.
2. (a) H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum, Abstract 228, 16th Intersci. Conf. Antimicrob. Agents and Chemother., Chicago, Ill. 1976; (b) J. Kahan, F. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff and J. Birnbaum, J. Antibiot., 1980, **32**, 1; (c) G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin and B. G. Christensen, J. Amer. Chem. Soc., 1978, **100**, 6491.
3. W. J. Leanza, K. J. Wildonger, T. W. Miller and B. G. Christensen, J. Med. Chem., 1979, **22**, 1435.
4. H. Kropp, J. G. Sundelof, R. Hajdu and F. M. Kahan, Antimicrob. Agents Chemother., 1982, **22**, 62.
5. (a) W. J. Leanza, R. W. Ratcliffe, F. DiNinno, G. Patel, K. J. Wildonger, D. A. Muthard, R. R. Wilkening and B. G. Christensen, Abstract 334, 23rd Intersci. Conf. Antimicrob. Agents and Chemother., Las Vegas, 1983; (b) A. Andrus, F. Baker, F. A. Bouffard, L. D. Cama, B. G. Christensen, R. N. Guthikonda, J. V. Heck, D. B. R. Johnston, W. J. Leanza, R. W. Ratcliffe, T. N. Salzmann, S. M. Schmitt, N. V. Shah, D. H. Shih, K. J. Wildonger and R. R. Wilkening, Symposium on "Recent Advances in the Chemistry of β-Lactam Antibiotics," Cambridge, 1984; (c) W. J. Leanza, K. J. Wildonger, J. Hannah, D. H. Shih, R. W. Ratcliffe, L. Barash, E. Walton, R. A. Firestone, G. F. Patel, F. M. Kahan, J. S. Kahan and B. G. Christensen, ibid., Gregory G. I. (ed.) 240, 1980; (d) D. H. Shih,

J. Hannah and B. G. Christensen, J. Amer. Chem. Soc., 1978, **100**, 8004; (e) D. H. Shih, J. A. Fayter and B. G. Christensen, Tet. Lett., 1984, **25**, 1639; (f) L. Cama, K. J. Wildonger, R. Guthikonda, R. W. Ratcliffe and B. G. Christensen, Tet. Lett., 1983, **39**, 2531.

6. (a) D. H. Shih and R. W. Ratcliffe, J. Med. Chem., 1981, **24**, 639; (b) A. Andrus, B. G. Christensen and J. V. Heck, Tet. Lett., 1984, **25**, 595; (c) A. Andrus, J. V. Heck, B. G. Christensen and B. Partridge, J. Amer. Chem. Soc., 1984, **106**, 1808; (d) T. N. Salzmann, R. W. Ratcliffe and B. G. Christensen, Tet. Lett., 1980, **21**, 1193.

7. (a) D. G. Melillo, I. Shinkai, T. Liu, K. Ryan and M. Sletzinger, Tet. Lett., 1980, **21**, 2783; (b) T. N. Salzmann, R. Ratcliffe, B. G. Christensen and F. A. Bouffard, J. Amer. Chem. Soc., 1980, **102**, 616.

8. (a) D. H. Shih, J. A. Fayter, F. Baker, L. Cama and B. G. Christensen, Abstract 333, 23rd Intersci. Conf. Antimicrob. Agents and Chemother., Las Vegas, 1983; (b) F. Baker, L. D. Cama, B. G. Christensen, W. J. Leanza, D. H. Shih and K. J. Wildonger, Proc. IUPHAR 9th International Congress of Pharmacology, London, 1984.

9. Spectra Data: Proton NMR chemical shifts in ppm (200 MHz NMR in $CDCl_3$, TMS as internal standard unless otherwise specified). **1**: UV $\lambda_{max}^{H_2O}$ 293 nm; NMR (D_2O): 3.12 (d, 3 H, J = 8.0 Hz, 1α-Me), 3.18 (d, 3 H, J = 6.0 Hz, CH_3CHOH), 2.75-2.98 (m), 3.22 (quintet, 1 H, J = 8.0 Hz, H_1), 3.35 (dd, 1 H, J = 3.0 and 6.0 Hz, H_6), 3.70 (dd, 1 H, J = 3.0 and 8.0 Hz, H_5), 4.10 (quintet, 1 H, J = 6.0 Hz, H_6). **2**: UV $\lambda_{max}^{H_2O}$ 294 nm; NMR (D_2O): 1.06 (d, 3 H, J = 7.8 Hz, 1β-Me), 1.14 (d, 3 H, J = 6.4 Hz, CH_3CHOH), 2.70-3.26 (m), 3.32 (dd, 1 H, J = 3.0 and 6.0 Hz, H_6), 4.06 (dd, 1 H, J = 3.0 and 9.5 Hz, H_5) and 4.12 (m, 1 H, H_8). **5**: IR ($CHCl_3$): 1770 and 1724 cm^{-1}; UV λ_{max}^{EtOH} 322 and 285 nm; NMR: 1.26 (d, 3 H, J = 6.4 Hz, 1β-Me), 1.37 (d, 3 H, J = 6.4 Hz, CH_3CHOH), 2.94-3.10 (m, 2 H, SCH_2), 3.28 (dd, 1 H, J = 2.5 and 6.5 Hz, H_6), 3.49 (m, 3 H, NCH_2 and H_1), 4.24 (dd, 1 H, J = 2.5 and 9.0 Hz, H_5), 4.25 (m, 1 H, H_8), 5.21 (s, 2 H, $NHCOOCH_2$), 5.24 (d, 1 H, J = 3.2 Hz, $COOCH_2$), 5.54 (d, 1 H,J = 3.2 Hz, $COOCH_2$), 7.52 (d, 2 H, J = 8.0 Hz, PNB), 7.68 (d, 2 H, J = 8.0 Hz, PNB), 8.23 (d, 4 H, J = 8.0 Hz, PNB). **7**: 300 Hz NMR: 1.26 (d, 3 H, J = 6.8 Hz, 1α-Me), 1.34 (d, 3 H, J = 6.0 Hz, CH_3CHOH), 2.79 (dq, 1 H, J = 6.8 and 8.0 Hz, $CHCH_3$), 2.83 (dd, 1 H, J = 2.0 and 7.0 Hz, H_3), 3.64 (s, 2 H, $CH_2COOPNB$), 3.78 (dd, 1 H, J = 2.0 and 8.0 Hz, H_4), 4.18 (m, 1 H, CH_3CHOH), 5.28 (s, 2 H, benzylic protons), 5.98(s, 1 H, NH), 7.55 (d, 2 H, J = 7.8 Hz, PNB), and 8.28 (d, 2 H, J = 7.8 Hz, PNB). **8**: 1.24 (d, 3 H, J = 6.8 Hz, 1α-Me), 1.36 (d, 3 H, J = 6.5 Hz, CH_3CHOH), 2.93 (dd, 1 H, J = 2.0 and 6.5 Hz, H_3), 3.64 (dq, 1 H, J = 6.8 and 8.1 Hz, CH_3CH), 3.91 (dd, 1 H, J = 2.0 and 8.1 Hz, H_4), 4.19 (m, 1 H, H_5), 5.40 (s, 2 H, $COOCH_2$), 5.90 (s, 1 H, NH), 7.58 (d, 2 H, J = 7.2 Hz, PNB) and 8.31 (d, 2 H, J = 7.2 Hz, PNB). **9**: NMR: 1.29 (d, 3 H, J = 6.8 Hz, 1α-Me), 1.41 (d, 3 H, J = 7.0 Hz,CH_3CHOH), 2.38 (dq, 1 H, J = 6.8 and 8.0 Hz, H_1), 3.25 (dd, 1 H, J = 2.0 and 6.8 Hz, H_6), 3.75 (dd, 1 H, J = 2.0 and 8.0 Hz, H_5), 4.36 (quintet, 1 H, J = 7.0 Hz, H_8), 4.85 (s, 1 H, H_2), 5.28 (d, 1 H, J = 13 Hz, benzylic proton), 5.39 (d, 1 H, J = 13 Hz, benzylic proton), 7.58 (d, 2 H, J = 8.1 Hz, PNB), 8.29 (d, 2 H, J = 8.1 Hz, PNB). **11**: UV λ_{max}^{EtOH} 322 and 285 nm; NMR: 1.35 (d, 3 H, J = 6.4 Hz, 1α-Me), 1.39 (d, 3 H, J = 8.0 Hz, CH_3CHOH), 3.04 (t, 2 H, J = 8.0 Hz, SCH_2), 3.30 (dd, 1 H, J = 3.0 and 6.0 Hz, H_6), 3.40 (m, 3 H, CH_2N and H_1), 3.83 (dd, 1 H, J = 3.0 and 7.0 Hz, H_5),4.27 (m, 1 H, H_9), 5.22 (s, 2 H, $NHCOOCH_2PNB$), 5.30 (d, 1 H, J = 14.5 Hz, $COOCH_2$), 5.52 (d, 1 H, J = 14.5 Hz, $COOCH_2$), 7.54 (d, 2 H, J = 8.0 Hz, PNB), 7.70 (d, 2 H, J = 8.0 Hz, PNB), 8.26 (d, 4 H, J = 8.0 Hz, PNB). **14**: 300 MHz NMR (D_2O): 1.14 (d, 3 H, J = 8.0 Hz, 1α-Me), 1.28 (d, 3 H, J = 6.4 Hz, CH_3CHOH), 2.26 (dq, 1 H, J = 8.0 and 9.0 Hz, CH_3CH), 3.00 (dd, 1 H, J = 5.4 and 2.1 Hz, H_3), 3.70 (dd, 1 H, J = 9.0 and 2.1 Hz, H_4) and 4.19 (quintet, 1 H, J = 6.4 Hz, CH_3CHOH).

(Received in USA 11 September 1984)