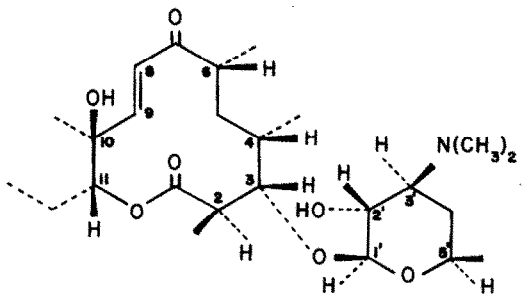
Tetrahedron Letters No. 13, pp. 1029-1032, 1970. Pergamon Press. Printed in Great Britain.

MACROLIDE ANTIBIOTIC STUDIES. XIV.*
THE TOTAL ABSOLUTE CONFIGURATION OF METHYMYCIN

D. G. Manwaring, R. W. Rickards and R. M. Smith
Research School of Chemistry, Australian National University,
Canberra, A.C.T.

(Received in UK 16 January 1970; accepted for publication 12 February 1970)

Assignments of absolute stereochemistry relating to the macrolide antibiotic[1] methymycin[2] from Streptomyces venezuelae have previously been made for the free sugar desosamine, 3,4,6-tridesoxy-3-dimethylamino-D-xylo-hexose[3], and for four centres of asymmetry in the aglycone, namely 2R[4], 3S[4], 4S[5], and 6R[5]. Additional evidence now permits the total absolute configuration of methymycin (I) to be defined as 2R; 3S; 4S; 6R; 8,9-trans; 10S; 11R; 1'S; 2'R; 3'S; 5'R.



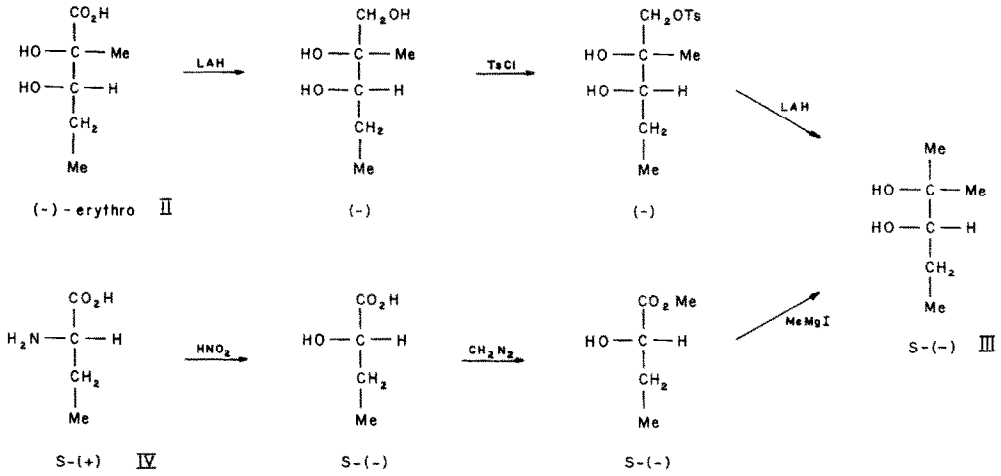
I

The pmr spectrum (in $CDCl_3$) of methymycin shows the olefinic protons H_8 and H_9, τ 3.71 and 3.41 respectively, as trans-coupled doublets with J 16.0 Hz. The H_1' doublet, J 7.3 Hz, at τ 5.55 closely resembles the anomeric proton resonances in other β-D-desosamine glycosides[6,7], and by relation to the adjacent 2'R stereochemistry[3] establishes the β or 1'S configuration at this centre. The same anomeric configuration is indicated by the method[6,7] of molecular rotation difference.

Ozonolysis of methymycin afforded a (+)-2,3-dihydroxy-2-methylpentanoic acid,

* Part XIII, R. W. Rickards and R. M. Smith, preceding paper.

identified as the erythro isomer on comparison of the acid and its methyl ester with authentic (±)-erythro specimens[8]. Resolution[8] of the racemic erythro acid gave the (-)-erythro-2,3-dihydroxy-2-methylpentanoic acid, confirmed by optical rotatory dispersion as the enantiomer of the acid from methymycin. The asymmetry at C-2 in this (-)-acid (II) was destroyed by the sequence (shown in Fischer projections) of reduction with lithium aluminium hydride, selective tosylation of the resulting primary hydroxyl, and cleavage of the tosylate with lithium aluminium hydride to yield (-)-2,3-dihydroxy-2-methylpentane (III), $[\alpha]_D^{28}$ -31.5° (c. 0.58 in ether). The absolute stereochemistry of this diol (III) was established as 3S by synthesis from S-(+)-butyrine (IV). Deamination of the α-amino-acid is known[9] to proceed with retention of configuration, and the resulting (-)-α-hydroxybutyric acid, after esterification, was reacted with methyl magnesium iodide to yield the identical diol (III), $[\alpha]_D^{28}$ -32.6° (c. 1.1 in ether). It follows that the stereochemistry of the synthetic (-)-erythro-2,3-dihydroxy-2-methylpentanoic acid at C-3 is S, and hence that at C-2 is also S. The enantiomeric (+)-acid from methymycin is therefore 2R; 3R.



Translating this stereochemistry to methymycin itself leads to the final aglycone designations 10S; 11R as in structure (I), which are in agreement with the predictions of Celmer's configurational model[7,10] for macrolide antibiotics. Extension of these methymycin

results to similar structural features of closely related macrolides supports the predicted[7,10] assignments 10R; 11S for neomethymycin[11], 12S; 13R for picromycin[12], and 12R; 13R for narbomycin[13], allowance being made[7,10] for the expected retention of configuration[14] during enzymic hydroxylation at C-10 in methymycin and C-12 in picromycin. Such extension of the present results is justified by the absolute configurational correspondence previously demonstrated[4,5] at four other asymmetric centres in the aglycones, and by the production of three of these antibiotics by the same organism[11,15], the exception, narbomycin[13], being structurally a 12-desoxypicromycin[12].

Acknowledgement: We thank Mr. C. Arandjelovic for pmr spectra.

REFERENCES

1. R. B. Woodward, Festschrift Arthur Stoll, p. 524, Birkhauser, Basel (1957), and Angew. Chem. 69, 50 (1957); M. Berry, Q. Rev. chem. Soc. 17, 343 (1963).

2. C. Djerassi and J. A. Zderic, J. Am. chem. Soc. 78, 2907, 6390 (1956); and references therein.

3. C. H. Bolton, A. B. Foster, M. Stacey and J. M. Webber, J. chem. Soc., 4831 (1961); W. Hofheinz and H. Grisebach, Tetrahedron Lett., 377 (1962); P. W. K. Woo, H. W. Dion, L. Durham and H. S. Mosher, Tetrahedron Lett., 735 (1962).

4. R. W. Rickards and R. M. Smith, preceding paper.

5. C. Djerassi and O. Halpern, J. Am. chem. Soc. 79, 3926 (1957); C. Djerassi, O. Halpern, D. I. Wilkinson and E. J. Eisenbraun, Tetrahedron 4, 369 (1958).

6. W. D. Celmer, J. Am. chem. Soc. 87, 1799 (1965).

7. W. D. Celmer, Biogenesis of Antibiotic Substances, p. 99, ed. Z. Vanek and Z. Hostalek, Czechoslovak Academy of Sciences, Prague (1965).

8. L. D. Bergel'son, E. V. Dyatlovitskaya, M. Tichy and V. V. Voronkova, Bull. Acad. Sci. U.S.S.R. Div. chem. Sci., 1612 (1962).

9. P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, Nature, Lond. 166, 179 (1950); cf. F. Bohlmann and G. Grau, Chem. Ber. 98, 2608 (1965).

10. W. D. Celmer, J. Am. chem. Soc. 87, 1801 (1965); Antimicrobial Agents and Chemotherapy 1965, p. 144, ed. G. L. Hobby, Am. Soc. Microbiol., Ann Arbor (1966); J. Am. chem. Soc. 88, 5028 (1966).

11. C. Djerassi and O. Halpern, J. Am. chem. Soc. 79, 2022 (1957), and Tetrahedron 3, 255 (1958).

12. R. W. Rickards, R. M. Smith and J. Majer, Chem. Comm., 1049 (1968); H. Muxfeldt, S. Shrader, P. Hansen and H. Brockmann, J. Am. chem. Soc. 90, 4748 (1968); and references therein.

13. V. Prelog, A. M. Gold, G. Talbot and A. Zamojski, Helv. chim. Acta 45, 4 (1962); and references therein.

14. M. Hayano, Oxygenases, p. 181, ed. O. Hayaishi, Academic Press, New York (1962).

15. S. E. DeVoe, H. B. Renfroe and W. K. Hausmann, Antimicrobial Agents and Chemotherapy 1963, p. 125, ed. J. C. Sylvester, Am. Soc. Microbiol., Ann Arbor (1964).