Tetrahedron Letters No. 1, pp. 33–36, 1970. Pergamon Press. Printed in Great Britain.

LINCOMYCIN. X. THE CHEMICAL SYNTHESIS OF LINCOMYCIN

Barney J. Magerlein

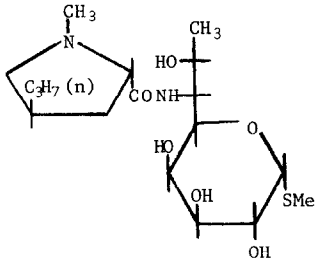
Research Laboratories, The Upjohn Company

Kalamazoo, Michigan 49001

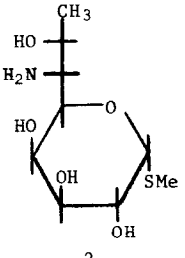
(Received in USA 28 October 1969; received in UK for publication 6 December 1969)

The discovery of the antibiotic lincomycin (1) was announced in 1962 (1), and disclosure of its structure was made shortly thereafter (2). Since that time a number of reports describing chemical modification of lincomycin have appeared (3). We now present the first chemical synthesis of lincomycin.

Previous reports from these laboratories have described the cleavage of lincomycin to form the amino sugar, methyl α-thiolincosaminide (2) (4) and *trans*-1-methyl-4-n-propyl-L-proline (5). The recombination of these fragments as well as the synthesis of the amino acid were reported (5), so that the synthesis of amino sugar (2) was the sole hiatus in a chemical synthesis of lincomycin.

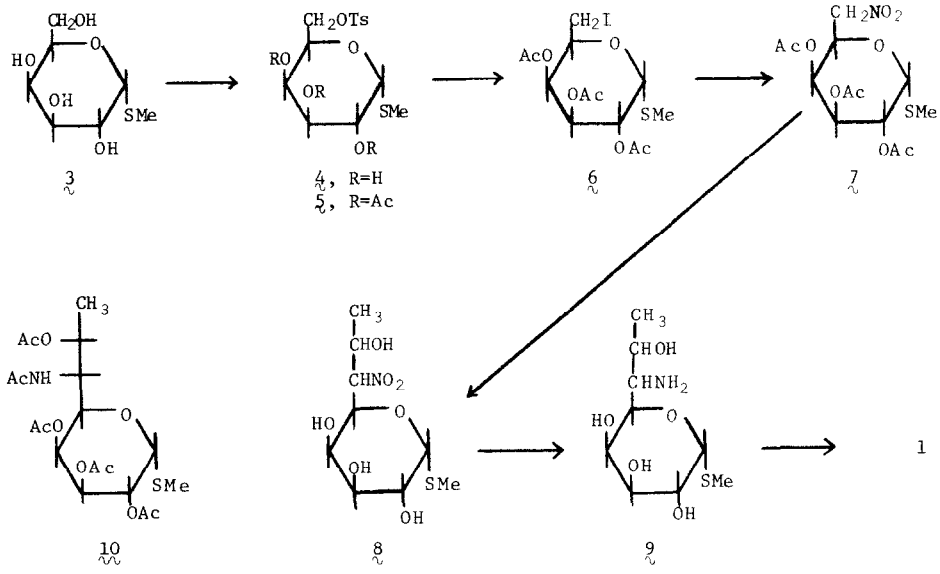


1



2

Several reports of research directed toward the synthesis of methyl α-thiolincosaminide (2) from galactose have recently appeared (6). In each case introduction of the S-methyl group appears to be planned for the later stages of synthesis. We have elected to introduce the S-methyl group into galactose and then to construct the amino-alcohol side chain.



Treatment of D-galactose in hydrochloric acid with methanethiol (7) afforded methyl 1-thio-α-D-galactopyranoside# (3)*(8), $C_7H_{14}O_5S$, mp 104-105°, $[\alpha]_D^{25}$ +296° (H_2O), M^+ m/e 210. Controlled tosylation of 3 in pyridine gave methyl 6-p-toluenesulfonyl-1-thio-α-D-galactopyranoside (4) $C_{14}H_{20}O_7S_2$, mp 155-157°, $[\alpha]_D^{25}$ +183° (pyridine). This material was acylated with acetic anhydride-pyridine. The oily triacetate 5, M^+ m/e 490, was treated with sodium iodide in acetone at 125° to form the 6-iodide 6, M^+ m/e 446. Although this compound showed only one spot on tlc (cyclohexane-acetone: 2:1) after chromatography, it resisted crystallization. Replacement of the 6-iodide by nitro ion using sodium nitrite in DMF (8) was slow, but about 20% yield of methyl 6-deoxy-6-nitro-1-thio-α-D-galactopyranoside (7), $C_{13}H_{19}NO_9S$, mp 172-176°, M^+ m/e 365, was isolated. Repeated additions of acetaldehyde and sodium methoxide to a methanolic solution of 7 gave a 50% yield of nitro alcohols (8), $C_9H_{17}NO_7S$, M^+ m/e 283 as a mixture of isomers which was reduced with LAH in THF to amino sugars 9.

For identification purposes, the crude methyl α-thiolincosaminides (9) were fully acylated. Careful chromatography over silica gel afforded 2,3,4,7-O-6-N-pentaacetyl methyl-α-thiolincos-

---

#The author acknowledges the prior preparation of methyl 1-thio-α-D-galactopyranoside (3) from D-galactose by Dr. B. Bannister using a different method of synthesis.

aminide (10), mp 199-201°, identified by tlc, infrared spectrum and mp with a sample prepared by acylation of methyl α-thiolincosaminide derived from lincomycin (4,10). The slightly less polar 7-epi isomer was found in the fractions preceding 10. It was identified by tlc and mass spectrum (9).

Methyl α-thiolincosaminide (9) was also condensed with 1-methyl-4-n-propyl-L-proline to afford lincomycin (1) which after purification and conversion to the crystalline hydrochloride salt was identified by tlc (chemical visualization and inhibition of *S. lutea*) mass spectrum pattern, infrared absorption (10) and VPC-mass spectrum of its silylated derivative. 7-Epi-lincomycin was identified in the less polar chromatographic fractions by tlc (chemical visualization and inhibition of *S. lutea*) (11).

Acknowledgment. The author expresses his appreciation to Dr. T. E. Eble for his interest and encouragement throughout this project and to R. J. Reid, whose experimentation was invaluable.

REFERENCES

*Acceptable elemental analyses were obtained for compounds where the empirical formula is given. All compounds gave acceptable I.R. and N.M.R. spectra. Mass spectral data was kindly supplied by Dr. M. F. Grostic and R. J. Wnuk.

(1) D. J. Mason, A. Dietz and C. DeBoer, Antimicrobial Agents and Chemotherapy - 1962, p. 554.

(2) H. Hoeksema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp and R. R. Herr, J. Amer. Chem. Soc., 86, 4223 (1964).

(3) See for example B. J. Magerlein, R. D. Birkenmeyer and F. Kagan, Antimicrobial Agents and Chemotherapy - 1966, p. 727. B. J. Magerlein and F. Kagan, J. Med. Chem., 12, 780 (1969).

(4) W. Schroeder, B. Bannister and H. Hoeksema, J. Amer. Chem. Soc., 89, 2448 (1967).

(5) B. J. Magerlein, R. D. Birkenmeyer, R. R. Herr and F. Kagan, ibid., 2459 (1967).

(6) G.B. Howarth, D. G. Lance, W. A. Szarek, and J. K. N. Jones, Can. J. Chem., 47, 75 (1969). D. Horton, M. Nakadate and J. M. J. Tronchet, Carbohydrate Res., 7, 57 (1968). H. Saeki, T. Iwashige, E. Ohki, K. Furuya and M. Shivasaka, Ann. Sankyo Res. Lab., 19, 137 (1967). Personal communication from Dr. Ohki to Dr. H. Hoeksema.

(7) J. Fried and D. E. Walz, J. Amer. Chem. Soc., 71, 140 (1949).

(8) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberrg, E. P. Oliveto, and G. E. Graham, ibid., 78, 1487 (1956). N. Kornblum and J. W. Powers, J. Org. Chem., 22, 455 (1957).

(9) The author is indebted to Dr. B. Bannister for a sample of methyl 7-epi-α-thiolincosaminide.

(10) Attenuated total reflection (ATR) infrared spectra were obtained for these compounds through the courtesy of Dr. T. F. Brodasky.

(11) The author is indebted to R. D. Birkenmeyer for a sample of 7-epilincomycin.