# Synthesis of a Congener of the Cyclohexadepsipeptide Antibiotic Monamycin

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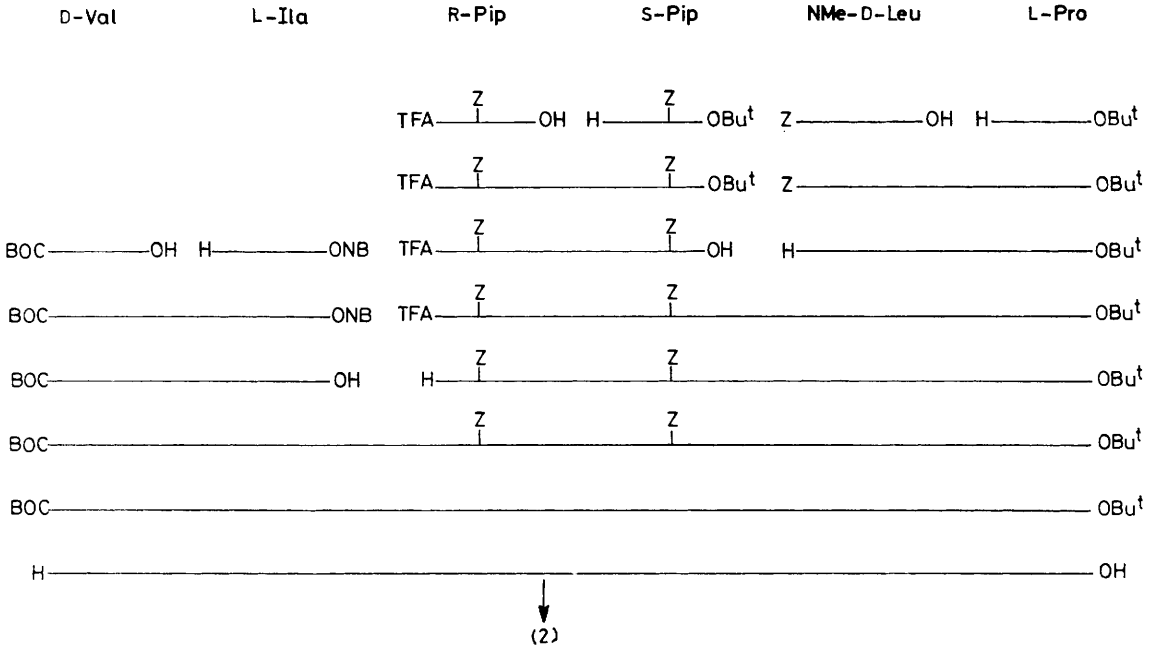
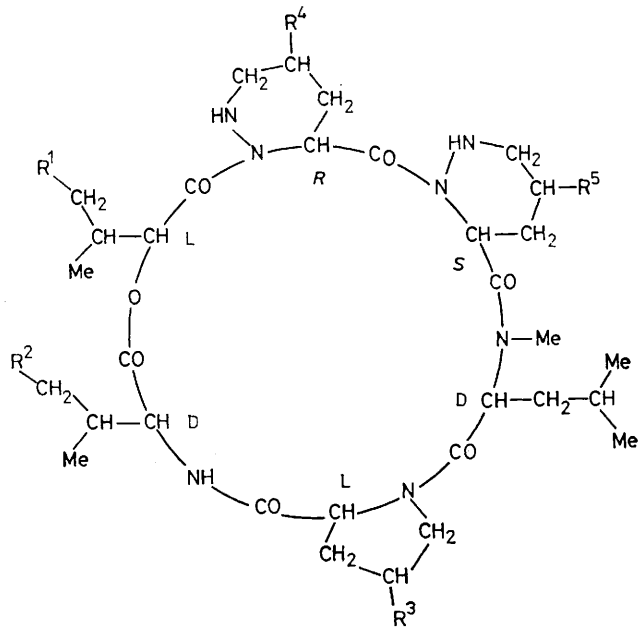
*Summary* A congener of the cyclohexadepsipeptide antibiotic, monamycin, has been synthesised; it contains residues of D-Val, L-isoleucic acid, D-Pip, L-Pip, NMe-D-Leu, and L-Pro and has antibacterial activity.

THE structures (**1**) of the naturally occurring members of the monamycin family of cyclodepsipeptide antibiotics have been determined by degradation and the use of $^1$H n.m.r. and mass spectrometry.[1a,b] We have undertaken to confirm the structure of this cyclodepsipeptide system by synthesis. The availability of this procedure for the preparation of monomycin congeners makes it possible to investigate structure–activity relationships in the series, through the preparation of further analogues including compounds incorporating synthetic (3*S*,5*S*)-hydroxypiperazic acid.[2]

The Scheme, which is outlined for the synthesis of deoxymonamycin-$B_3$, involves the coupling of t-butyloxycarbonyl-D-valyl-L-isoleucic acid (**3**) with the t-butyl ester of the bisbenzyloxycarbonyl-protected tetrapeptide (**4**), followed by removal of protecting groups and cyclisation of the linear hexadepsipeptide (**6**) with *N*-hydroxysuccinimide and dicyclohexylcarbodi-imide. This yielded the crystalline congener, $C_{33}H_{55}N_7O_7$, in 40% yield; it was fully characterised by $^1$H and $^{13}$C n.m.r. spectroscopy, elemental and amino-acid analyses, and mass spectrometry as the cyclodepsipeptide corresponding to the structure (**2**).



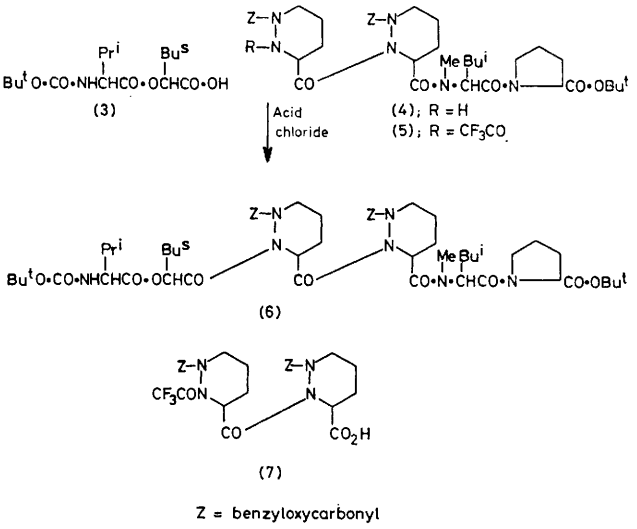

SCHEME. An outline for the synthesis of deoxymonamycin-$B_3$ (**2**). Pip = Hexahydropiperazic acid; Ila = isoleucic acid [Me-$CH_2CH(Me)CH(OH)CO_2H$]; Z = benzyloxycarbonyl-; BOC = t-butyloxycarbonyl-; TFA = trifluoroacetyl-; ONB = 4-nitrobenzyl-.



| | | | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|---|---|
| (1) | Monamycin | A | H | H | Me | H | OH |
| | " | $B_1$ | H | H | Me | H | OH |
| | " | $B_2$ | H | Me | H | H | OH |
| | " | $B_3$ | Me | H | H | H | OH |
| | " | C | Me | H | Me | H | OH |
| | " | $D_1$ | Me | H | Me | H | OH |
| | " | $D_2$ | H | Me | Me | H | OH |
| | " | E | Me | Me | Me | H | OH |
| | " | F | Me | Me | Me | H | OH |
| | " | $G_1$ | H | H | Me | Cl | OH |
| | " | $G_2$ | H | Me | H | Cl | OH |
| | " | $G_3$ | Me | H | H | Cl | OH |
| | " | $H_1$ | Me | H | Me | Cl | OH |
| | " | $H_2$ | H | Me | Me | Cl | OH |
| | " | I | Me | Me | Me | Cl | OH |
| (2) | Deoxymonamycin | $B_3$ | Me | H | H | H | H |

The synthesis of the protected tetrapeptide (**5**) was through coupling the t-butyl ester of *N*-methyl-D-Leu-L-Pro at low temperature with the acid chloride of the dipeptide (**7**); this was prepared from the corresponding derivatives of the respective enantiomers obtained by resolving 2-*N*-benzyloxycarbonyl-(*R*,*S*)-piperazic acid into (*R*)(*D*) and (*S*)(*L*) forms with (+)- and (−)-ephedrine, respectively.[3] Piperazic acid was prepared by the published route;[1a] reaction with benzyl chloroformate yielded the 2-*N*-benzyloxycarbonyl-(*R*,*S*)-piperazic acid exclusively.

The synthetic material (**2**) has antibacterial activity against *Staphylococcus aureus* similar to monamycin I[4] but this is only 25% of the activity of the more active congener, monamycin $D_1$.[5]



(*Received*, 13*th June* 1977; *Com.* 584.)

[1] (a) K. Bevan, J. S. Davies, C. H. Hassall, R. B. Morton, and D. A. S. Phillips, *J. Chem. Soc.* (*C*), 1971, 514; (b) C. H. Hassall, Y. Ogihara, and W. A. Thomas, *ibid.*, p. 522; C. H. Hassall, R. B. Morton, Y. Ogihara, and D. A. S. Phillips, *ibid.*, p. 526.
[2] C. H. Hassall and K. L. Ramachandran, *Heterocycles*, in the press.
[3] K. Oki, K. Suzuki, S. Tuchida, T. Saito, and H. Kotake, *Bull. Chem. Soc. Japan*, 1970, **43**, 2554.
[4] M. J. Hall, personal communication.
[5] M. J. Hall, B. O. Handford, C. H. Hassall, D. A. S. Phillips, and A. V. Rees, *Antimicrob. and Chemother.*, 1973, **3**, 380.