Tetrahedron Letters, Vol. 33, No. 38, pp. 5485-5486, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

SYNTHESIS OF THE LIPOSIDOMYCIN DIAZEPANONE

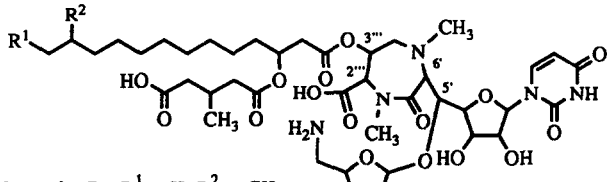
Spencer Knapp*, Santosh Nandan, and Lynn Resnick

Department of Chemistry, Rutgers The State University of New Jersey, New Brunswick, New Jersey 08903 USA

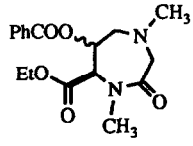
Key words: complex nucleoside, antibiotic, dipeptide, aldol reaction, reductive amination

Abstract: *Acrolein and two sarcosines are combined to give the diazepanone substructure of the liposidomycin nucleoside antibiotics. Conformational analysis of the substituted diazepanone ring is presented.*

The liposidomycins are complex, lipid-bearing nucleoside antibiotics (e. g. **1** and **2**) that selectively inhibit bacterial peptidoglycan synthesis.[1,2] Liposidomycin C (**2**) has been shown to specifically inhibit *in vitro* the phospho-*N*-acetylmuramyl-pentapeptide transferase from *E. coli* Y-10, which catalyzes the first step in the peptidoglycan lipid cycle.[3] Structures were ascribed to **1** and **2** based on degradation studies and NMR and mass spectral evidence, but several stereogenic centers on or near the diazepanone ring (5', 6', 2''', and 3''') remain unassigned.[2] As a step toward elucidating the relative and absolute stereochemistry of **1** and **2**, we report the synthesis of the diazepanone substructure as represented by **3** and **4**, and also the conversion of **3** and **4** to tetrahydrodiazepinone **13**, a substructure of the products of acid and base hydrolysis of **1**.

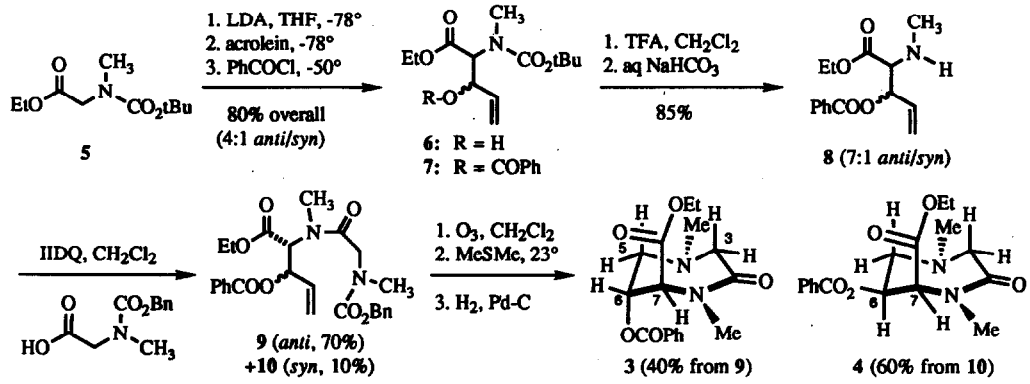


1, liposidomycin B: R^1 = H, R^2 = CH_3
2, liposidomycin C: R^1 = CH_3, R^2 = H

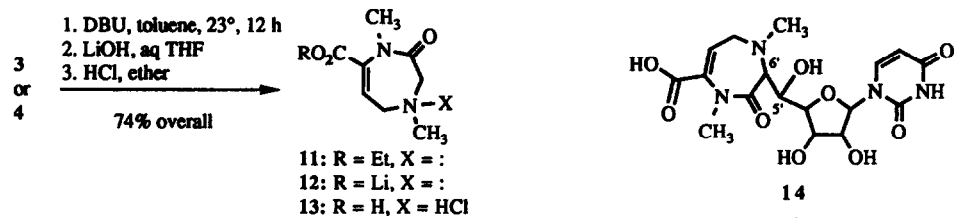


3 (*trans*)
4 (*cis*)

Aldol reaction of the anion of **5** and acrolein gave adduct **6** as a 4:1 *anti/syn* mixture of diastereomers. Because **6** is not stable to chromatography, it was acylated directly and isolated from the crude reaction mixture as the benzoate **7**. Removal of the BOC and neutralization led to a 7:1 mixture of amines **8**; the apparent enrichment in the *anti* diastereomer is the result of selective loss of the *syn* diastereomer by an *O*-to-*N* benzoyl migration. IIDQ-mediated coupling[4] with Z-sarcosine gave the dipeptides **9** and **10**, easily separable at this stage, along with a small amount of the benzoyl migration product. The stereochemistry of the aldol adducts **6** was proven by *in situ* lithium borohydride reduction to a 4:1 mixture of diols, each of which was purified and separately converted to an acetonide with diagnostic proton coupling constants.[5] The predominance of the *anti* aldol product from the lithium anion of **5** is consistent with preferential (and typical[6]) formation of the *E* ester enolate isomer. Ozonolysis of the vinyl group and reductive cyclization gave the *trans* diazepanone **3** from purified *anti* dipeptide **9**, and *cis* diazepanone **4** from purified *syn* dipeptide **10**. Fully decoupled ^1H NMR spectra of **3** and **4** suggest the solution conformations shown. In particular, the H(6)-H(7) coupling constants (J = 5.2 and 2.2, respectively) are consistent with pseudo-axial carbethoxy substituents, which avoid a repulsive interaction with the N(1) methyl group. A five-bond "W" coupling (J = 2) between $H(3_{eq})$ and $H(5_{eq})$ is observed for **3**. These conformations are reproduced as minima by the MacroModel© program (Amber subroutine),[7] which also predicts[8] H(6)-H(7) coupling constants of 5.1 and 1.8, respectively.



The *trans* and *cis* diazepanones **3** and **4** were each converted to the tetrahydrodiazepinone ester **11** under mild conditions by treatment with DBU. Hydrolysis of the ester group gave the carboxylate salt **12**, and protonation led to the ammonium salt **13**. The ability to generate this tetrahydrodiazepinone carboxylate ring system from any of several substituted diazepanone esters should be useful for the synthesis of the liposidomycin degradation[2] product **14**, and thus assignment of the stereochemistry at C(5') and C(6') of **1**.



Acknowledgments. We are grateful to the Charles and Johanna Busch Memorial Fund, Berlex, and Hoffmann-LaRoche for financial support of this work, and Prof. Ronald R. Sauers for helpful discussions.

References and Notes

1. Isono, K.; Uramoto, M.; Kusakabe, H.; Kimura, K.; Izaki, K.; Nelson, C. C.; McCloskey, J. A. *J. Antibiot.* **1985**, *38*, 1617-1621.
2. Ubukata, M.; Isono, K.; Kimura, K.; Nelson, C. C.; McCloskey, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 4416-4417.
3. Kimura, K.; Miyata, N.; Kawanishi, G.; Kamio, Y.; Izaki, K.; Isono, K. *Agric. Biol. Chem.* **1989**, *53*, 1811-1815.
4. Kiso, Y.; Yajima, H. *J. Chem. Soc., Chemical Commun.* **1972**, 942-943.
5. Georg, G. I.; Akgun, E. *Tetrahedron Lett.* **1991**, 32, 5521-5524. Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1783-1784.
6. Heathcock, C. H. The Aldol Addition Reaction. In *Asymmetric Synthesis, Vol. 3, Stereodifferentiating Addition Reactions, Part B*; Morrison, J. D. Ed.; Academic Press: Orlando, 1984; pp 111-212.
7. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Computational Chem.* **1990**, *11*, 440-467.
8. Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783-2792.

(Received in USA 4 May 1992)