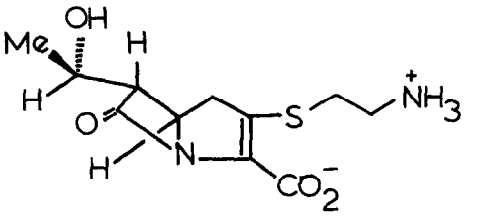
Tetrahedron Letters No. 45, pp 4359 - 4362. 0040-4039/79/1101-4359$02.00/0

Thienamycin. A Solution of the Stereochemical Problem.

Joseph J. Tufariello*, George E. Lee
Pushpananda A. Senaratne and Mohammed Al-Nuri
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214

Abstract - A new nitrone-based synthesis of β-lactams is described which makes provision for the 1-hydroxyethyl moiety in the potent antibiotic thienamycin. Moreover, the relative stereochemical features of the natural product are defined in a step involving the cycloaddition of a nitrone with methyl crotonate.

Recent intense interest has been focused on novel β-lactam antibiotics derived from several strains of Streptomyces which exhibit high antibacterial potency and substantial β-lactamase inhibitory behavior.[1-9] Of particular interest is thienamycin (1) and related antibiotics containing a 1-hydroxyethyl moiety at C-7. Thienamycin provides a special synthetic challenge[4,6,8] which has already been met by one total synthesis.[4] In our

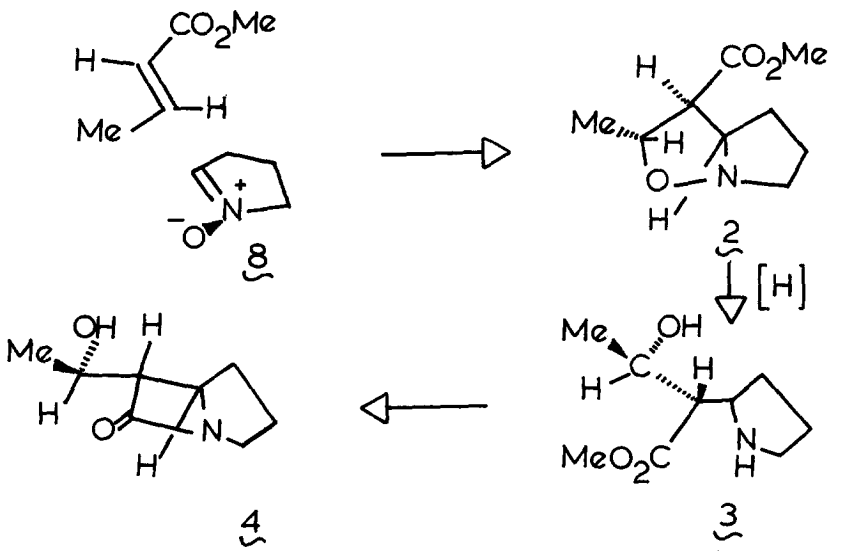


1 thienamycin

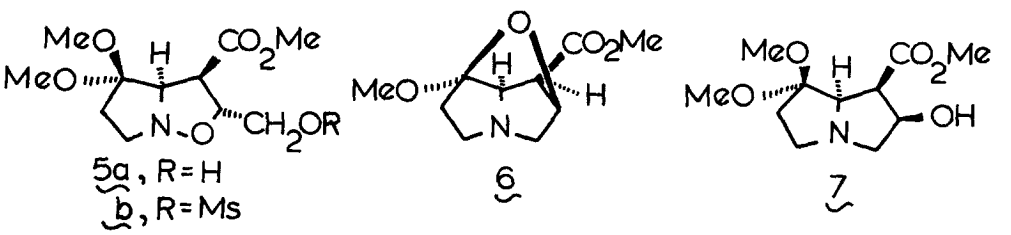
view, this molecule presents at least two major aspects which must be addressed by any successful synthetic approach. Firstly, the relative stereochemistry at C-5, C-6, and C-8 must be confronted and, secondly, the pattern of substitution in the five-membered ring (i.e. at C-2 and C-3) must be accommodated. We report herein a solution to the former challenge.

While monosubstituted alkenes such as methyl acrylate undergo cycloaddition with nitrones to afford 5-substituted isoxazolidines predominantly,[10] 1,2-disubstituted unsaturated esters (e.g., methyl crotonate) exhibit the opposite regiochemical preference (cf. Scheme 1).[11,12] This reversal in regiochemistry to afford β-oxa esters (i.e., 2) rather than α-oxa esters, holds the key to the synthesis of β-lactams. We knew[11] that the isoxazolidine 2 could be cleaved readily under conditions of catalytic hydrogenolysis to give a hydroxyester (i.e., 3, which we anticipated [13] could be cyclized to a β-lactam containing the desired 1-hydroxyethyl grouping.

SCHEME 1



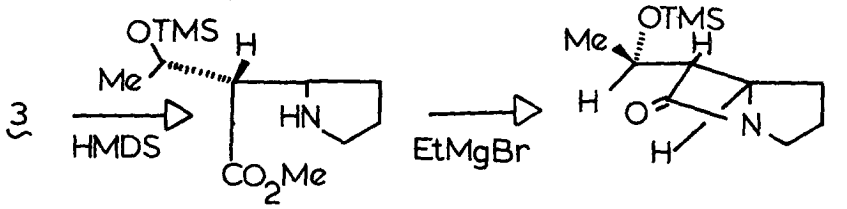
The nitrone-based route offers far more than another approach to β-lactams. A study[12] of the stereochemistry of nitrone-crotonate cycloadditions has demonstrated a significant tendency for secondary orbital effects to be manifest. Indeed we have shown that the isoxazolidine (i.e., 5a) derived from 3,3-dimethoxypyrroline 1-oxide and methyl 3-hydroxy-



crotonate gives, after mesylation (i.e., to afford 5b) and hydrogenolysis (10% Pd/C; H_2: MeOH), the internally bridged ether 6 (80%). The latter (MS: M^+ 213) shows no absorption in the 2.7-3.0 μ region of the infrared and only two methyl singlets at δ 3.68 (s, 3) and 3.30 ppm (s, 3) in the NMR spectrum ($CDCl_3$; 60 MHz). Moreover, this bridged ether can be quantitatively transformed into 7 by treatment with methanolic HCl (reflux; 15 min). These results can only be accommodated by the stereochemical assignment depicted for 5a. This, in turn, is in accord with an important secondary orbital effect controlling the cycloaddition of nitrones with crotonates. These findings and conclusions suggest that the generation of β-lactams

as shown in Scheme 1 should involve high stereoselectivity, producing the β-lactam 4 with the relative stereochemistry necessary for the synthesis of thienamycin (1).

The cycloaddition of 1-pyrroline 1-oxide (8) with methyl crotonate proceeds smoothly (90%) to give isoxazolidine 2 (Scheme 1) as previously described.[11] After hydrogenolysis,[11] the aminoalcohol 3 was selectively blocked[14] with hexamethyldisilazane (MHDS) to give amine

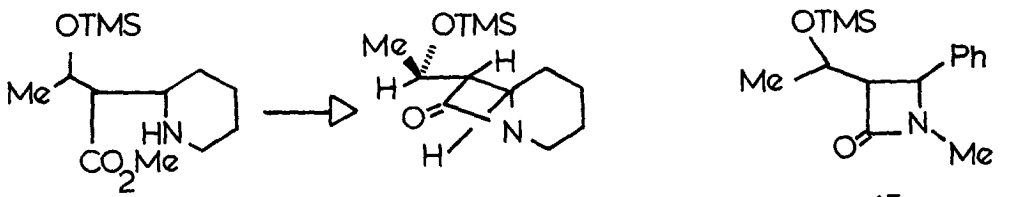


9 10

9 (82%). The latter (IR; neat; 5.82 μ) exhibits the anticipated singlets, at δ 3.54 (s, 3) and 0.00 ppm (s, 9), and a doublet at δ 1.06 ppm (d, 3, J = 6 Hz). Upon treatment with three equivalents of ethylmagnesium bromide,[15] the β-lactam 10 (50%) was isolated upon aqueous work-up. The IR spectrum (neat) shows an absence of absorption in the 2-3 μ region but the presence of an intense carbonyl stretch (5.70 μ).

The NMR spectrum (100 MHz, $CDCl_3$) shows the expected singlet at δ 0.12 (s, 9) and a doublet at δ 1.26 ppm (d, 3, J = 6.5 Hz). In addition, a singlet (H-6) appears at δ 2.72 ppm (dd, 1, J = 2.2, 6.6 Hz) which confirms the trans-relationship of the protons at C-5 and C-6.[16] Finally, the molecular ion (MS) appears at 227. Since we have not been able to confirm the presence of any stereoisomers corresponding to 10, we believe the original nitrone cycloaddition 8 → 2 is highly regioselective. Interestingly, exposure of 10 to methanol (3h, 25°C) provides aminoalcohol 3.[11]

The addition of 3,4,5,6-tetrahydropyridine 1-oxide (11) to methyl crotonate (83%) affords, after hydrogenolysis (82%) and treatment with HMDS (68%), a piperidine 12, which can be converted into the corresponding β-lactam 13 (70%) as before. The latter exhibits a strong carbonyl absorption at 5.70 μ (IR, neat) and displays the H-7 proton at δ 2.70 (dd, 1, J = 6.7, 1.8 Hz), again indicating a trans-relationship of the protons on the β-lactam ring.



12 13 15

Finally, C-phenyl-N-methylnitrone (14) was carried through the same sequence of reactions to give the monocyclic β-lactone 15 (IR, 5.68 μ; MS, M^+ 277). The stereochemical aspects of this series of transformations is under current study.

Acknowledgement - We wish to thank the Institute of General Medical Sciences of the NIH (GM 25303) for financial support. We also thank Mr. Joseph Puglis for help in obtaining the mass spectra.

References and Notes

1. A. G. Brown, D. F. Corbett, A. J. Eglington, T. T. Howarth, J. Chem. Soc., Chem. Commun., 523 (1977).

2. D. F. Corbett, A. J. Eglington, T. T. Howarth, ibid., 953 (1977).

3. F. DiNinno, T. R. Beattie, and G. G. Christensen, J. Org. Chem., 42, 2960 (1977).

4. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, J. Am. Chem. Soc., 100, 315 (1978).

5. G. Albers-Schonberg, et. al., ibid., 100, 6491 (1978).

6. A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgates, J. Chem. Soc. Chem. Commun., 236 (1979).

7. D. Brown, J. R. Evans and R. A. Fletton, ibid., 282 (1979).

8. F. DiNinno, E. V. Linek and B. G. Christensen, J. Am. Chem. Soc., 101, 2210 (1979).

9. H. E. Applegate, C. M. Cimarusti, and W. A. Slusarchyk, Tetrahedron Lett., 1637 (1979) and references cited therein.

10. R. Huisgen, Angew. Chem. Int. Ed., Engl., 2, 565, 633 (1963).

11. J. J. Tufariello and J. P. Tette, J. Org. Chem., 40, 3866 (1975).

12. M. Joucla, F. Tonnard, D. Gree and J. Hamelin, J. Chem. Res. (M), 290 (1978) and references cited therein.

13. For a recent review dealing with synthetic routes to β-lactams, see N. S. Isaacs, Chem. Soc. Rev., 181 (1976).

14. L. Birkofer and A. Ritter, Angew Chem. Int. Ed., Engl., 4, 417 (1965).

15. L. Tantanella and E. Testa, Liebigs Ann. Chem., 625, 95 (1959).

16. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", L. M. Jackman and S. Sternell, Pergamon Press, 2nd ed., p. 287.

(Received in USA 24 July 1979)