Tetrahedron Letters Vol. 21, pp 1193 - 1196 0040-4039/80/0322-1193$02.00/0

TOTAL SYNTHESIS OF (-) HOMOTHIENAMYCIN[1]

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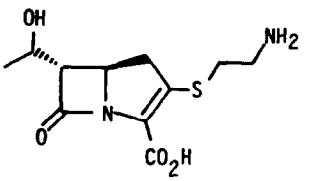
The total synthesis of a ring expanded analog of thienamycin has been developed. The key step utilizes a highly efficient carbene insertion reaction to form the carbacephem ring system.

Thienamycin **1** is a naturally occurring, bicyclic β-lactam antibiotic of exceptional potency and breadth of spectrum.[2] Of special interest is its stability toward bacterial β-lactamases and its unparalleled activity against Pseudomonas sp.



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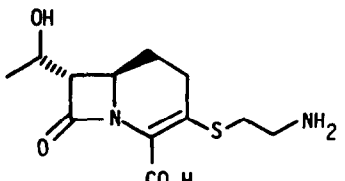

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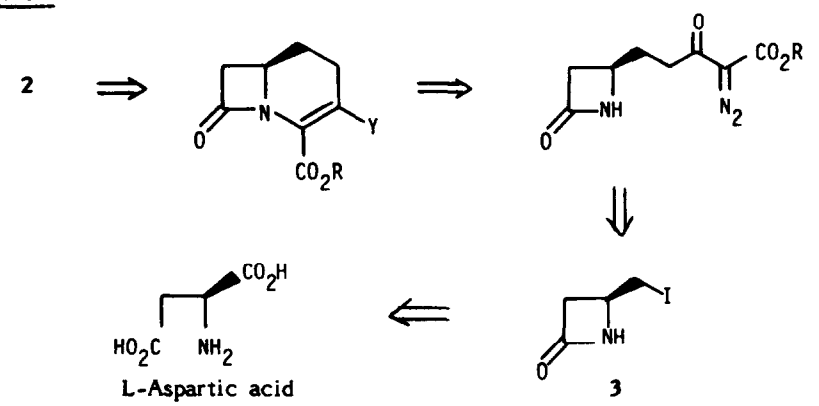
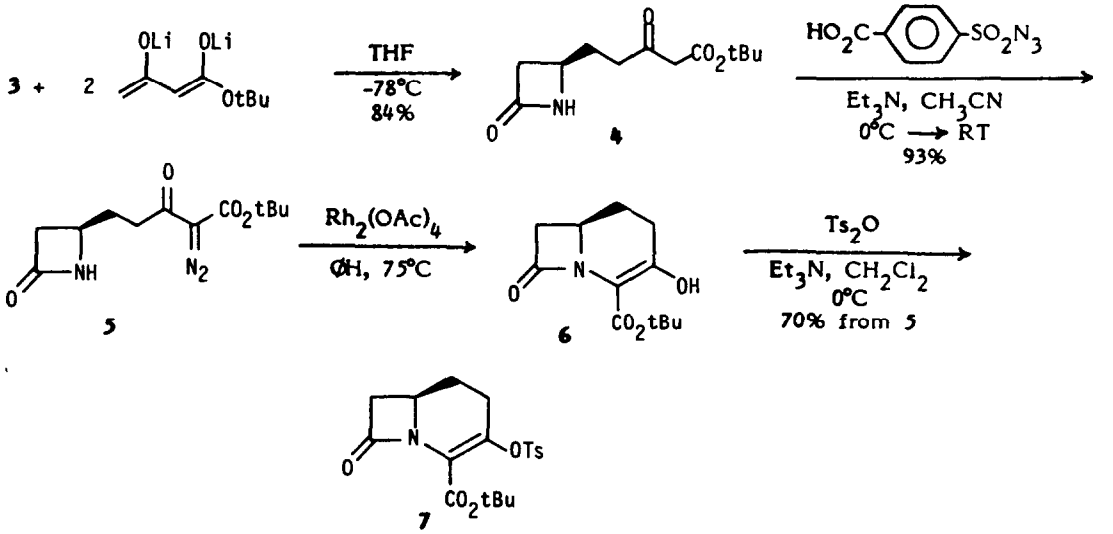
The structure[3] of thienamycin differs from the classical penicillins and cephalosporins, most notably by incorporation of the novel carbapenem nucleus[4] and the unusual hydroxyethyl and cysteamine side chains. In such a structure, the β-lactam amide bond would be expected to be highly reactive due to both ring strain and electronic effects. In fact, stability studies have revealed that thienamycin is relatively unstable in concentrated aqueous solutions suitable for therapeutic use.[2] In order to more fully understand the factors responsible for this instability and in the hope of obtaining a clinically useful antibiotic, we proposed to synthesize an analog which would incorporate all the essential functionality of thienamycin in a less strained ring system, namely homothienamycin **2**.

Several considerations guided our choice of a synthetic approach to homothienamycin. We desired a short and efficient route which would also allow for potential introduction of alternative substituents at positions 3 and 7 (cephalosporin numbering). We also hoped to develop a chiral synthesis from a readily available and inexpensive starting material. With these goals in mind, we formulated the general synthetic strategy shown in retrosynthetic form in Scheme I.

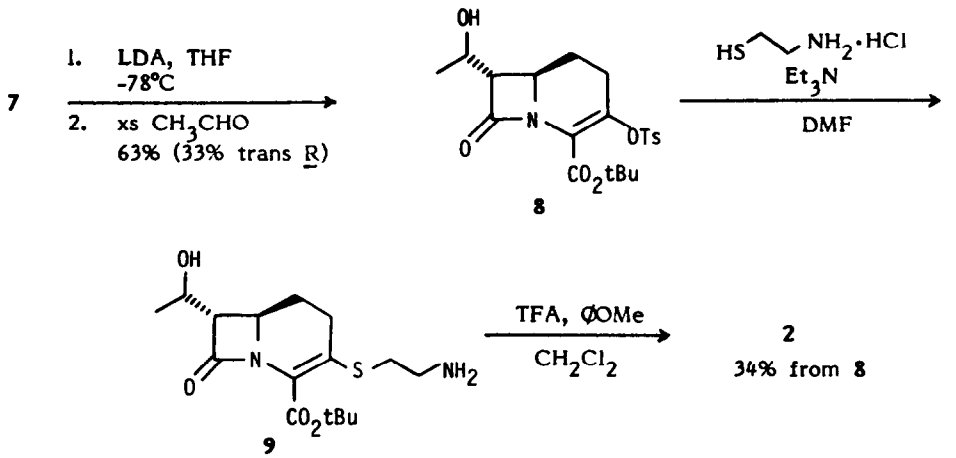
Scheme I



We have previously described[1,5] the conversion of L-aspartic acid to the first key intermediate, iodide **3**. Elaboration of the remaining carbon atoms necessary to construct the bicyclic nucleus was accomplished in one step via the regiospecific alkylation[6] of the dianion derived from t-butyl acetoacetate with **3**. This reaction required the use of two equivalents of the dianion and presumably involves an initial deprotonation of the azetidinone nitrogen of **3** to yield the active alkylating agent.[7] The resulting keto ester **4** was smoothly converted to the diazo derivative **5** by reaction with p-carboxybenzenesulfonyl azide.[9] The crucial ring closure was then effected by heating compound **5** to ca. 75°C in benzene solution containing a catalytic amount of rhodium (II) acetate.[10] Since the resulting bicyclic product existed primarily in the enolic form **6**, purification at this stage was difficult so the crude reaction mixture was treated with p-toluenesulfonic anhydride to effect formation of the stable, crystalline enol tosylate **7**, in 70% overall yield from **5**.



The required hydroxyethyl side chain was introduced by treating compound **7** with LDA followed by quenching the resulting enolate with excess acetaldehyde to yield **8** as a mixture of isomers.[11] The desired trans R isomer was separated chromatographically and treated with cysteamine to provide the t-butylester **9** of homothienamycin. Treatment of **9** with trifluoroacetic acid followed by chromatography on Dowex 50 and lyophilization gave homothienamycin **2** as an off-white powder.



As anticipated, the chemical stability of **2**, both as the lyophilized solid and in concentrated aqueous solution, was vastly superior to that of thienamycin. However, the biological activity of homothienamycin was disappointing. Only very low levels of activity were observed even against highly susceptible bacterial species.[12] Thus, it appears likely that the exceptional biological activity of thienamycin is due mainly to the presence of the highly reactive carbapenem nucleus.[13]

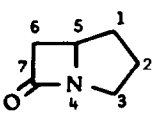
References and Notes

1) Presented in part at the 176th ACS National Meeting, Miami Beach, Florida, September, 1978, Abstract Medi 12.

2) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff and J. Birnbaum, J. Antibiot., **32**, 1 (1978), and references therein.

3) G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin and B. G. Christensen, J. Amer. Chem. Soc., **100**, 6491 (1978).

4) As a convenience for naming the members of this series, we suggest the terms carbapenam and carbapenem for structures **i** and **ii**. This system is in accord with the widely accepted penam and cepham-cephem nomenclature.



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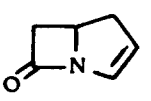

ii

5) Submitted for publication.

6) S. N. Huckin and L. Weiler, J. Amer. Chem. Soc., **96**, 1082 (1974).

7) Base induced cyclization of **3** to provide 1-azabicyclo(2,1,0)pentan-2-one as the alkylating agent was ruled out by the observation that **3** can be N-alkylated by successive treatment with LDA and t-butyl bromoacetate.

8) This and all other new compounds gave satisfactory combustion analysis or high resolution mass spectra. Selected physical properties are given in footnote 14.

9) J. B. Hendrickson and W. A. Wolf, J. Org. Chem., **33**, 3610 (1968).

10) A similar ring closure was previously used in the synthesis of oxabisnorpenicillin, L. D. Cama and B. G. Christensen, Tetrahedron Lett., 4233 (1978).

11) The isomer ratio in this case was trans S:trans R:cis R - 52:33:15. A similar introduction of the hydroxyethyl side chain was previously used in the total synthesis of thienamycin, D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard and B. G. Christensen, J. Amer. Chem. Soc., **100**, 313 (1978). The stereochemical assignment of the epimers of **8** was based on the relative chemical shifts and coupling constants of the C-7 and C-9 protons using previously developed correlations; see F. A. Bouffard, D. B. R. Johnston and B. G. Christensen, J. Org. Chem., in press.

12) We are grateful to Ms. J. S. Kahan for in vitro assays.

13) See for example L. D. Cama and B. G. Christensen, J. Amer. Chem. Soc., **100**, 8006 (1978).

14) Physical data. **4**: mp 63-64°C; $[\alpha]_D$ +2.90° (c = 4.41 in $CHCl_3$); IR ($CHCl_3$) 1750, 1705 cm^{-1}; PMR ($CDCl_3$) δ 6.02 (1H, br s, NH), 3.7 (1H, m, H4), 3.36 (2H, s, $-CCH_2CO_2$, tBu), 3.08 (1H, ddd, J = 15, 5, 2.5, H3α), 2.6 (3H, overlapping m, H3β + $-CH_2CH_2C$), 1.95 (2H, m, $-CH_2CH_2C$), δ 1.50 (9H, s, tBu), mass spectrum m/e 241 (M^+), 185, 168, 126. **5**: mp 92-94°C; IR ($CHCl_3$) 3415, 2118, 1755, 1704, 1649 cm^{-1}; PMR ($CDCl_3$) δ 6.64 (1H, br a, N-H), 3.63 (1H, m, H4), 3.02 (1H, ddd, J = 16, 5, 2, H3α), 2.9 (2H, m, $-CH_2CH_2C$), 2.55 (1H, ddd, J = 16, 2, 1.5, H3β), 1.9 (2H, m, $-CH_2CH_2C-$), 1.55 (9H, s, tBu). **7**: mp 99-100°C; $[\alpha]_D$ = -132.5° (c = 3.57 in $CHCl_3$); IR ($CHCl_3$) 1772, 1725, 1600, 1155 cm^{-1}; PMR ($CDCl_3$) δ 7.61 (4H, AA'BB', aromatic), 3.64 (1H, m, H6), 3.28 (1H, dd, J = 15.2, 5, H7α), 2.64 (1H, dd, J = 15.2, 2.3, H7β), 2.4-2.55 (1H, m, H2a), 2.45 (3H, s, CH_3-Ar), 2.23 (1H, m, H2b), 1.3-1.7 (2H, m, H1a & b), 1.49 (9H, s, tBu); mass spectrum m/e 393 (M^+) 337, 320, 292, 238, 182, 155. **8**: IR ($CHCl_3$) 3480, 1763, 1724; PMR ($CDCl_3$) δ 7.62 (4H, AA'BB', aromatic), 4.20 (1H, dq, J = 6.8, 6.5, H9), 3.62 (1H, ddd, J = 11, 2.1, 2, H6), 2.87 (1H, dd, J = 6.5, 2.1, H7), 2.46 (3H, s, CH_3-Ar), 2.2-2.4 (2H, m, H2a & b), 1.3-1.7 (2H, m, H1a & b), 1.48 (9H, s, tBu), 1.33 (3H, d, J = 6.8, CH_3CHOH); mass spectrum m/e 437 (M^+), 381, 364, 336, 282, 226, 182. **2**: UV (H_2O) 279 nm; PMR (D_2O) δ 4.26 (1H, dq, J = 6.8, 6.5, H9), 3.70 (1H, ddd, J = 11, 2, 2, H6), 3.18 (1H, dd, J = 6.5, 2, H7), 3.0-3.3 (2H, m, H_2NCH_2-), 2.8-3.2 (2H, m, -S-CH_2), 2.3-2.6 (3H, m, H2a & b, H1a), 1.7 (1H, m, H1b), 1.29 (3H, d, J = 6.8, CH_3CHOH); F.D. mass spectrum m/e 287 (M^+ + H); IR (Nujol) 1760, 1600 cm^{-1}; $[\alpha]_D$ -0.33° (c = 1.36 in H_2O).

(Received in USA 10 December 1979)