THE FACILE SYNTHESIS OF AN IMPORTANT KEY INTERMEDIATE FOR THE
SYNTHESIS OF (±)-8S*-THIENAMYCIN — A FORMAL TOTAL SYNTHESIS
OF (±)-8S*-THIENAMYCIN

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Abstract — 8S*-Isomer of the potent antibiotic thienamycin (1) was
formally synthesized in short steps via trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methylisoxazoline (2).

Thienamycin (1) was recently isolated from fermentation broths of the soil microorganism Streptomyces cattleya by a Merck research group.1 It is a novel β-lactam antibiotic of exceptional antibacterial potency and spectrum including activity against Pseudomonas and gram-negative bacteria and β-lactamase producing species.2 It has also been found that descysteaminylthienamycin (2), derived from thienamycin, has antibacterial activity as potent as that of thienamycin.3 (±)-Thienamycin (1)4 and its derivative 55 were totally synthesized through the same intermediate by the Merck group. We now report a short and effective synthesis of the key synthetic intermediate containing all the chiral centers of (±)-8S*-thienamycin. By 1,3-dipolar cycloaddition, the nitrile oxide, derived from 3-nitropropanal dimethyl acetal (3)6 with phenyl isocyanate7, was added to methyl crotonate to give regio- and stereoselectively trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methylisoxazoline (3)8 (53.8%) which was separable from the isomer 99 (21.5%), concomitantly formed, by distillation and column chromatography. Preferential formation of 3 and its trans-stereochemistry were expected from Huisgen's report10 and application of Houk's molecular orbital perturbation treatment.11 Reaction of the isoxazoline 3 in the presence of hydrogen (4.5 atm) and Adams catalyst in acetic acid yielded quantitatively a stereoisomeric mixture of the amino ester 12, which was hydrolyzed with methanolic sodium hydroxide and then treated with dicyclohexylcarbodiimide13 in aqueous dioxane to afford, after alumina column
chromatography, the desired trans-azetidinone $\alpha^{14}$ in 22.5 % yield. A small amount of the epimer $\alpha^{15}$ was formed by the above reactions and isolated in 0.8 % yield by preparative TLC on silica gel. The small coupling constant ($J = 2.0$ Hz) between the protons at $C_5$ and $C_6$ positions and that ($J = 6.0$ Hz) between the protons at $C_6$ and $C_8$ positions of the major azetidinone $\beta$, indicates trans-azetidinone and $8S^*$-configuration.4,16 On the other hand, both coupling constants ($J = 4.5$ and 10.0 Hz) of the minor one $\beta'$, suggest the cis-azetidinone.17 Furthermore, the observation of the signal due to $C_6$-H of $\beta$ at higher field (2.92 ppm) than that of $\beta'$ (3.21 ppm) supports the above stereochemical relationships.17

Treatment of $\alpha$ with p-nitrobenzyl chloroformate in a mixture of pyridine and dioxane gave the acetal $\alpha^{18}$ (85 %). Deacetalization of $\alpha^{10}$ with aqueous acetic acid at 60°C, followed by reduction with sodium borohydride furnished the alcohol $\alpha^{14,19}$ (90 % from $\alpha^{10}$), the 60 MHz NMR spectrum (CDCl$_3$) of which was closely similar to that of the authentic $8R^*$-compound.4

![Chemical Structures](https://example.com/structure.png)
Reaction of the acetal $\text{I}_1$ with excess $N$-$p$-nitrobenzyloxycarbonylcysteamine in dry trifluoroacetic acid$^{20}$ at room temperature yielded the thioacetal $\text{II}_1$ (86%). Since the thioacetal $\text{II}_4$, which had previously been prepared from chlorosulfonyl isocyanate in 10 steps$^4$, had already been converted into (±)-8S*-thienamycin (I)$^4$, the present work accomplished the formal total synthesis of (±)-8S*-thienamycin.$^{22}$

ACKNOWLEDGMENT

We thank Mr. K. Kawamura, Mrs. C. Koyanagi, Miss K. Mushiake, Mrs. R. Kobayashi, and Miss K. Ohtomo for microanalysis, spectral measurements, and manuscript preparation. We are grateful to Dr. B. G. Christensen for his kind gift of the NMR spectrum of the alcohol $\text{III}_1$, and to Dr. M. Furukawa of Daiichi Seiyaku Co., Ltd. for X-ray analysis.

REFERENCES AND NOTES


8. NMR(CCl₄) δ 1.36 (d, 3H, J = 6 Hz, C₅-Me), 2.72 (d, 2H, J = 5.5 Hz, CH-CH₂-C≡N),
3.30 and 3.36 (each s, each 3H, 2xOME), 3.76 (s, 3H, CO₂Me), 4.60 [t, 1H, J = 5.5 Hz, CH(OMe)₂].

9. NMR (CCl₄) δ 1.29 (d, 3H, J = 6 Hz, C₄-Me), 2.42 and 2.73 (each d of d, each 1H, J = 15 and 5.5 Hz, CH₂-CH₂-C=N), 3.33 (s, 6H, 2xOME), 3.77 (s, 3H, CO₂Me), 4.44 (d, 1H, J = 6 Hz, C₅-H), 4.57 [t, 1H, J = 5.5 Hz, CH-(OMe)₂].


12. NMR (CDCl₃) δ 2.83 (br s, 2H, NH₂), 3.33 (s, 6H, 2xOME), 3.70 (s, 3H, CO₂Me), the epimeric mixture of 1 was used in the next reactions without separation.


14. IR (CHCl₃) 3450 (NH), 1758 (C=O); NMR (CDCl₃) δ 1.33 (d, 3H, J = 6.5 Hz, C₉-Me), 1.98 (d of d, 2H, J = 5 and 7 Hz, C₄-H₂), 2.92 (d of d, 1H, J = 6 and 2 Hz, C₆-H), 3.35 (s, 6H, 2xOME), 3.66 (t of d, 1H, J = 7 and 2 Hz, C₅-H), 4.15 (q of d, 1H, J = 6.5 and 7 Hz, C₈-H), 4.51 (t, 1H, J = 5 Hz, C₃-H), 6.90 (br s, 1H, NH). Calcd. for C₁₉H₁₈N₂O₈ (M⁺+1); m/e 204.1235. Found: m/e 204.1213.

15. IR (CHCl₃) 3450 (NH), 1758 (C=O); NMR (CDCl₃) δ 1.47 (d, 3H, J = 6.5 Hz, C₉-Me), 3.21 (d of d, 1H, J = 10 and 4.5 Hz, C₆-H), 3.42 (s, 6H, 2xOME), 6.12 (br s, 1H, NH); MS m/e 204 (M⁺+1).

16. For convenience the carbon atoms have been numbered to correspond to the position they will occupy in thienamycin. ¹


18. IR (CHCl₃) 3450 (NH), 1760 and 1750 (C=O), 1345 (NO₂); NMR (CDCl₃) δ 1.47 (d, 3H, J = 6.5 Hz, C₉-Me), 1.97 (d of d, 2H, J = 5 and 7 Hz, C₄-H₂), 3.18 (d of d, 1H, J = 6 and 2 Hz, C₆-H), 3.36 (s, 6H, 2xOME), 3.67 (t of d, 1H, J = 7 and 2 Hz, C₅-H), 4.50 (t, 1H, J = 5 Hz, C₃-H), 5.04 – 5.53 (m, 1H, C₈-H), 5.33 (s, 2H, CH₂Ar), 6.26 (br s, 1H, NH), 7.66 (d, 2H, J = 9 Hz, 2xArH), 8.34 (d, 2H, J = 9 Hz, 2xArH); Calcd. for C₁₇H₂₃N₂O₈ (M⁺+1); m/e 383.1454. Found: 383.1482.

19. X-ray analysis of the following compound (L) derived from the the acetal (L) confirmed the 8S*-stereochemistry.
20. T. Kametani, S. Yokohama, Y. Shiratori, F. Satoh, M. Ihara, and K. Fukumoto, 
*Heterocycles*, 1979, 12, 669.

21. IR (CHCl₃) 3480 and 3450 (NH), 1760, 1720 (C=O), 1340 (NO₂); NMR (CDCl₃) δ 
1.43 (d, 3H, J = 6.5 Hz, C₉-Me), 2.10 (d of d, 2H, J = 5 and 7 Hz, C₄-H₂), 6.77 
(br s, 1H, NH), 7.59 (d, 6H, J = 9 Hz, 6xArH), 8.27 (d, 6H, J = 9 Hz, 6xArH).

22. Prevention of the undesirable epimerization which occurred during hydrolysis of 
7 or on β-lactam formation (7 + 8), is under investigation in order to assemble the 
same stereochemistry as that of thienamycin.

Received, 21st July, 1979