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

Tetsuji Kametani,* Shyh-Pyng Huang, and Masataka Ihara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

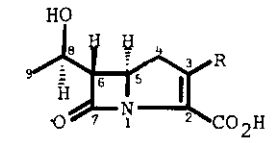
Abstract —— 8S*-Isomer of the potent antibiotic thienamycin (1) was formally synthesized in short steps via trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methylisoxazoline (5)

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 2[5] 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 isocyanate[7], was added to methyl crotonate to give regio- and stereoselectively trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methylisoxazoline (5)[8] (53.8 %) which was separable from the isomer 6[9] (21.5 %), concomitantly formed, by distillation and column chromatography. Preferential formation of 5 and its trans-stereochemistry were expected from Huisgen's report[10] and application of Houk's molecular orbital perturbation treatment.[11]

Reaction of the isoxazoline 5 in the presence of hydrogen (4.5 atm) and Adams catalyst in acetic acid yielded quantitatively a stereoisomeric mixture of the amino ester 7[12], which was hydrolyzed with methanolic sodium hydroxide and then treated with dicyclohexylcarbodiimide[13] in aqueous dioxane to afford, after alumina column

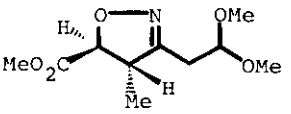
chromatography, the desired trans-azetidinone 8[14] in 22.5 % yield. A small amount of the epimer 9[15] was formed by the above reactions and isolated in 0.8 % yield by preparative TLC on silica gel. The small coupling constant (J = 2.0 Hz) between the protons at C_5 and C_6 positions and that (J = 6.0 Hz) between the protons at C_6 and C_8 positions of the major azetidinone 8, 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 9, suggest the cis-azetidinone.[17] Furthermore, the observation of the signal due to C_6-H of 8 at higher field (2.92 ppm) than that of 9 (3.21 ppm) supports the above stereochemical relationships.[17]

Treatment of 8 with p-nitrobenzyl chloroformate in a mixture of pyridine and dioxane gave the acetal 10[18] (85 %). Deacetalization of 10 with aqueous acetic acid at 60°C, followed by reduction with sodium borohydride furnished the alcohol 11[4,19] (90 % from 10), the 60 MHz NMR spectrum ($CDCl_3$) of which was closely similar to that of the authentic 8R*-compound.[4]



1 R=S–⟨⟩–NH2

2 R=H



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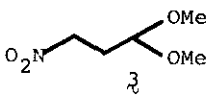

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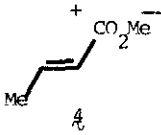

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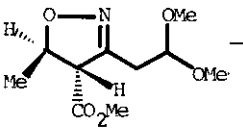

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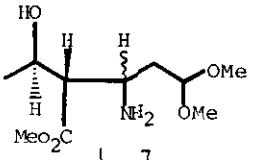

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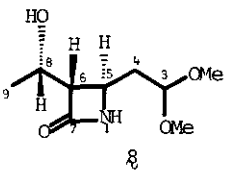

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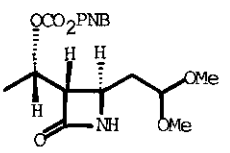

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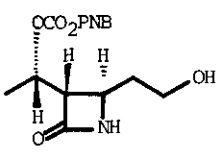
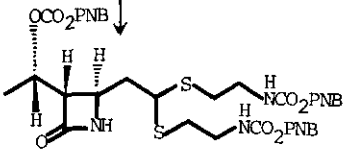


11



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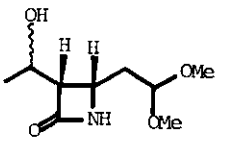

9

Reaction of the acetal 10 with excess N-p-nitrobenzyloxycarbonylcysteamine in dry trifluoroacetic acid[20] at room temperature yielded the thioacetal 12[21] (86 %). Since the thioacetal 12, which had previously been prepared from chlorosulfonyl isocyanate in 10 steps[4], had already been converted into (±)-8S*-thienamycin (1),[4] the present work accomplished the formal total synthesis of (±)-8S*-thienamycin.[22]

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2. The following thienamycin analogues were found in Streptomyces species; MM4550 and 13902 (A. G. Borwn, D. F. Corbett, A. J. Eglington and T. T. Howarth, J. C. S., Chem. Comm., 1977, 523), MM17880 (D. F. Corbett, A. J. Eglington, and T. T. Howarth, J. C. S., Chem. Comm., 1977, 953), MC96-SY2-A (K. Maeda, S. Takahashi, M. Sezaki, K. Iinuma, H. Naganawa, S. Kondo, M. Ohno, and H. Umezawa, J. Antibiotics, 1977, 30, 770) and PS-5 (K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimanouchi, K. Kouno, and T. Ishikura, J. Antibiotics, 1978, 30, 480).

3. D. H. Shih, J. Hannah, and B. G. Christensen, J. Amer. Chem. Soc., 1978, 100, 8004.

4. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, J. Amer. Chem. Soc., 1978, 100, 313; B. G. Christensen, D. B. R. Johnston, and S. M. Schmitt, Japan. Kokai, 65, 892 (1978).

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8. NMR(CCl_4) δ 1.36 (d, 3H, J = 6 Hz, C_5-Me), 2.72 (d, 2H, J = 5.5 Hz, CH-CH_2-C=N),

3.30 and 3.36 (each s, each 3H, 2xOMe), 3.76 (s, 3H, CO_2Me), 4.60 [t, 1H, J = 5.5 Hz, $C\underline{H}(OMe)_2$].

9. NMR (CCl_4) δ 1.29 (d, 3H, J = 6 Hz, C_4-Me), 2.42 and 2.73 (each d of d, each 1H, J = 15 and 5.5 Hz, CH-$C\underline{H}_2$-C=N), 3.33 (s, 6H, 2xOMe), 3.77 (s, 3H, CO_2Me), 4.44 (d, 1H, J = 6 Hz, C_5-H), 4.57 [t, 1H, J = 5.5 Hz, $C\underline{H}$-$(OMe)_2$].

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12. NMR ($CDCl_3$) δ 2.83 (br s, 2H, NH_2), 3.33 (s, 6H, 2xOMe), 3.70 (s, 3H, CO_2Me), the epimeric mixture of 7 was used in the next reactions without separation.

13. J. C. Sheehan and K. R. Henery-Logan, J. Amer. Chem. Soc., 1957, 79, 1262; 1959, 81, 3089.

14. IR ($CHCl_3$) 3450 (NH), 1758 (C=O); NMR ($CDCl_3$) δ 1.33 (d, 3H, J = 6.5 Hz, C_9-Me), 1.98 (d of d, 2H, J = 5 and 7 Hz, C_4-H_2), 2.92 (d of d, 1H, J = 6 and 2 Hz, C_6-H), 3.35 (s, 6H, 2xOMe), 3.66 (t of d, 1H, J = 7 and 2 Hz, C_5-H), 4.15 (q of d, 1H, J = 6.5 and 7 Hz, C_8-H), 4.51 (t, 1H, J = 5 Hz, C_3-H), 6.90 (br s, 1H, NH). Calcd. for $C_9H_{18}NO_4$ (M^++1); m/e 204.1235. Found: m/e 204.1213.

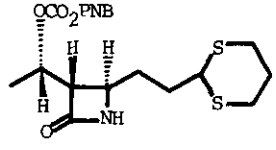
15. IR ($CHCl_3$) 3450 (NH), 1758 (C=O); NMR ($CDCl_3$) δ 1.42 (d, 3H, J = 6.5 Hz, C_9-Me), 3.21 (d of d, 1H, J = 10 and 4.5 Hz, C_6-H), 3.42 (s, 6H, 2xOMe), 6.12 (br s, 1H, NH); MS m/e 204 (M^++1).

16. For convenience the carbon atoms have been numbered to correspond to the position they will occupy in thienamycin.[4]

17. F. DiNinno, T. R. Beattie, and B. G. Christensen, J. Org. Chem., 1977, 42, 2960.

18. IR ($CHCl_3$) 3450 (NH), 1760 and 1750 (C=O), 1345 (NO_2); NMR ($CDCl_3$) δ 1.47 (d, 3H, J = 6.5 Hz, C_9-Me), 1.97 (d of d, 2H, J = 5 and 7 Hz, C_4-H_2), 3.18 (d of d, 1H, J = 6 and 2 Hz, C_6-H), 3.36 (s, 6H, 2xOMe), 3.67 (t of d, 1H, J = 7 and 2 Hz, C_5-H), 4.50 (t, 1H, J = 5 Hz, C_3-H), 5.04 - 5.53 (m, 1H, C_8-H), 5.33 (s, 2H, $C\underline{H}_2$Ar), 6.26 (br s, 1H, NH), 7.66 (d, 2H, J = 9 Hz, 2xArH), 8.34 (d, 2H, J = 9 Hz, 2xArH); Calcd. for $C_{17}H_{23}N_2O_8$ (M^++1): m/e 383.1454. Found: 383.1482.

19. X-ray analysis of the following compound (13) derived from the the acetal (10) confirmed the 8S*-stereochemistry.



(13)

20. T. Kametani, S. Yokohama, Y. Shiratori, F. Satoh, M. Ihara, and K. Fukumoto, Heterocycles, 1979, 12, 669.

21. IR ($CHCl_3$) 3480 and 3450 (NH), 1760, 1720 (C=O), 1340 (NO_2); NMR ($DCDl_3$) δ 1.43 (d, 3H, J = 6.5 Hz, C_9-Me), 2.10 (d of d, 2H, J = 5 and 7 Hz, C_4-H_2), 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.

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