

THE FACILE SYNTHESIS OF AN IMPORTANT KEY INTERMEDIATE FOR THE  
SYNTHESIS OF ( $\pm$ )-8S<sup>\*</sup>-THIENAMYCIN — A FORMAL TOTAL SYNTHESIS  
OF ( $\pm$ )-8S<sup>\*</sup>-THIENAMYCIN

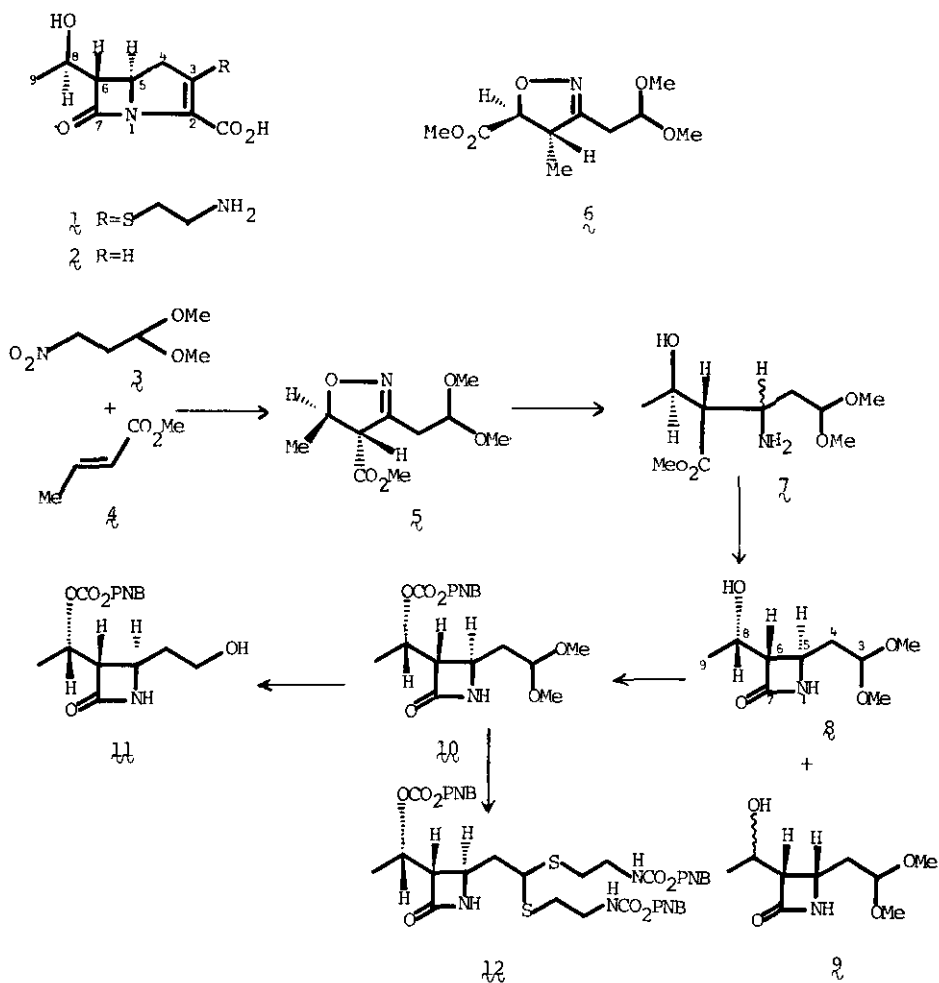
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**Abstract** — 8S<sup>\*</sup>-Isomer of the potent antibiotic thienamycin (1) was formally synthesized in short steps via trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methylisoxazoline (5)

Thienamycin (1) was recently isolated from fermentation broths of the soil microorganism Streptomyces cattleya by a Merck research group.<sup>1</sup> It is a novel  $\beta$ -lactam antibiotic of exceptional antibacterial potency and spectrum including activity against Pseudomonas and gram-negative bacteria and  $\beta$ -lactamase producing species.<sup>2</sup> It has also been found that descysteaminylthienamycin (2), derived from thienamycin, has antibacterial activity as potent as that of thienamycin.<sup>3</sup> ( $\pm$ )-Thienamycin (1)<sup>4</sup> and its derivative 2<sup>5</sup> 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 ( $\pm$ )-8S<sup>\*</sup>-thienamycin. By 1,3-dipolar cycloaddition, the nitrile oxide, derived from 3-nitropropanal dimethyl acetal (3)<sup>6</sup> with phenyl isocyanate<sup>7</sup>, was added to methyl crotonate to give regio- and stereoselectively trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methylisoxazoline (5)<sup>8</sup> (53.8 %) which was separable from the isomer 6<sup>9</sup> (21.5 %), concomitantly formed, by distillation and column chromatography. Preferential formation of 5 and its trans-stereochemistry were expected from Huisgen's report<sup>10</sup> and application of Houk's molecular orbital perturbation treatment.<sup>11</sup> 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<sup>12</sup>, which was hydrolyzed with methanolic sodium hydroxide and then treated with dicyclohexylcarbodiimide<sup>13</sup> in aqueous dioxane to afford, after alumina column

chromatography, the desired trans-azetidinone  $\mathfrak{8}^{14}$  in 22.5 % yield. A small amount of the epimer  $\mathfrak{9}^{15}$  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  $\mathfrak{8}$ , indicates trans-azetidinone and  $8S^*$ -configuration.<sup>4,16</sup> On the other hand, both coupling constants ( $J = 4.5$  and  $10.0$  Hz) of the minor one  $\mathfrak{9}$ , suggest the cis-azetidinone.<sup>17</sup> Furthermore, the observation of the signal due to  $C_6$ -H of  $\mathfrak{8}$  at higher field (2.92 ppm) than that of  $\mathfrak{9}$  (3.21 ppm) supports the above stereochemical relationships.<sup>17</sup>

Treatment of  $\mathfrak{8}$  with *p*-nitrobenzyl chloroformate in a mixture of pyridine and dioxane gave the acetal  $\mathfrak{10}^{18}$  (85 %). Deacetalization of  $\mathfrak{10}$  with aqueous acetic acid at  $60^\circ\text{C}$ , followed by reduction with sodium borohydride furnished the alcohol  $\mathfrak{11}^{4,19}$  (90 % from  $\mathfrak{10}$ ), the 60 MHz NMR spectrum ( $\text{CDCl}_3$ ) of which was closely similar to that of the authentic  $8R^*$ -compound.<sup>4</sup>



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

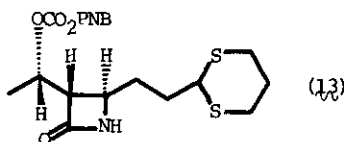
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8. NMR(CCl<sub>4</sub>)  $\delta$  1.36 (d, 3H, J = 6 Hz, C<sub>5</sub>-Me), 2.72 (d, 2H, J = 5.5 Hz, CH-CH<sub>2</sub>-C=N),

- 3.30 and 3.36 (each s, each 3H, 2xOMe), 3.76 (s, 3H, CO<sub>2</sub>Me), 4.60 [t, 1H, J = 5.5 Hz, CH(OMe)<sub>2</sub>].
9. NMR (CCl<sub>4</sub>) δ 1.29 (d, 3H, J = 6 Hz, C<sub>4</sub>-Me), 2.42 and 2.73 (each d of d, each 1H, J = 15 and 5.5 Hz, CH-CH<sub>2</sub>-C=N), 3.33 (s, 6H, 2xOMe), 3.77 (s, 3H, CO<sub>2</sub>Me), 4.44 (d, 1H, J = 6 Hz, C<sub>5</sub>-H), 4.57 [t, 1H, J = 5.5 Hz, CH-(OMe)<sub>2</sub>].
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12. NMR (CDCl<sub>3</sub>) δ 2.83 (br s, 2H, NH<sub>2</sub>), 3.33 (s, 6H, 2xOMe), 3.70 (s, 3H, CO<sub>2</sub>Me), the epimeric mixture of λ 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<sub>3</sub>) 3450 (NH), 1758 (C=O); NMR (CDCl<sub>3</sub>) δ 1.33 (d, 3H, J = 6.5 Hz, C<sub>9</sub>-Me), 1.98 (d of d, 2H, J = 5 and 7 Hz, C<sub>4</sub>-H<sub>2</sub>), 2.92 (d of d, 1H, J = 6 and 2 Hz, C<sub>6</sub>-H), 3.35 (s, 6H, 2xOMe), 3.66 (t of d, 1H, J = 7 and 2 Hz, C<sub>5</sub>-H), 4.15 (q of d, 1H, J = 6.5 and 7 Hz, C<sub>8</sub>-H), 4.51 (t, 1H, J = 5 Hz, C<sub>3</sub>-H), 6.90 (br s, 1H, NH). Calcd. for C<sub>9</sub>H<sub>18</sub>NO<sub>4</sub> (M<sup>+</sup>+1); m/e 204.1235. Found: m/e 204.1213.
15. IR (CHCl<sub>3</sub>) 3450 (NH), 1758 (C=O); NMR (CDCl<sub>3</sub>) δ 1.42 (d, 3H, J = 6.5 Hz, C<sub>9</sub>-Me), 3.21 (d of d, 1H, J = 10 and 4.5 Hz, C<sub>6</sub>-H), 3.42 (s, 6H, 2xOMe), 6.12 (br s, 1H, NH); MS m/e 204 (M<sup>+</sup>+1).
16. For convenience the carbon atoms have been numbered to correspond to the position they will occupy in thienamycin.<sup>4</sup>
17. F. DiNinno, T. R. Beattie, and B. G. Christensen, J. Org. Chem., 1977, 42, 2960.
18. IR (CHCl<sub>3</sub>) 3450 (NH), 1760 and 1750 (C=O), 1345 (NO<sub>2</sub>); NMR (CDCl<sub>3</sub>) δ 1.47 (d, 3H, J = 6.5 Hz, C<sub>9</sub>-Me), 1.97 (d of d, 2H, J = 5 and 7 Hz, C<sub>4</sub>-H<sub>2</sub>), 3.18 (d of d, 1H, J = 6 and 2 Hz, C<sub>6</sub>-H), 3.36 (s, 6H, 2xOMe), 3.67 (t of d, 1H, J = 7 and 2 Hz, C<sub>5</sub>-H), 4.50 (t, 1H, J = 5 Hz, C<sub>3</sub>-H), 5.04 - 5.53 (m, 1H, C<sub>8</sub>-H), 5.33 (s, 2H, CH<sub>2</sub>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<sub>17</sub>H<sub>23</sub>N<sub>2</sub>O<sub>8</sub> (M<sup>+</sup>+1): m/e 383.1454. Found: 383.1482.
19. X-ray analysis of the following compound (λ) derived from the the acetal (λ) confirmed the 8S<sup>\*</sup>-stereochemistry.



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

21. IR (CHCl<sub>3</sub>) 3480 and 3450 (NH), 1760, 1720 (C=O), 1340 (NO<sub>2</sub>); NMR (DCD<sub>3</sub>) δ 1.43 (d, 3H, J = 6.5 Hz, C<sub>9</sub>-Me), 2.10 (d of d, 2H, J = 5 and 7 Hz, C<sub>4</sub>-H<sub>2</sub>), 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  $\lambda$  or on  $\beta$ -lactam formation ( $\lambda \rightarrow \xi$ ), is under investigation in order to assemble the same stereochemistry as that of thienamycin.

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