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A FACILE, STEREOCONTROLLED ENTRY TO KEY INTERMEDIATES FOR THIENAMYCIN SYNTHESIS FROM ETHYL (S)-3-HYDROXYBUTANOATE

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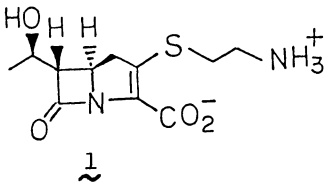
A new synthetic approach to optically active key intermediates for thienamycin synthesis is described which involves the highly stereocontrolled transformation of the 2-azetidinone obtained via the condensation of ethyl (S)-3-hydroxybutanoate with the N-silyl-imine of trimethylsilylpropynal.

Thienamycin (1) is representative of a group of carbapenem antibiotics which have been the focus of current synthetic attention.[1] Recently we have reported a synthetic route to the key thienamycin intermediate (+)-4 from methyl (R)-3-hydroxybutanoate ((-)-2), which involves the enolate-imine condensation followed by the seven-step elaboration including crucial processes for correcting the wrong stereochemistry of the condensation product (-)-3 (Eq. 1).[2] A major problem in this route is that the key elaboration process is not highly stereoselective. Thus, a more efficient alternative route is highly desirable. A recent publication[3] dealing with the synthesis of (+)-4 from (S)-2' prompts us to disclose here the results of our continuing effort. We now report a shorter, fully stereocontrolled entry to another key thienamycin intermediate (+)-5[4] starting from (S)-2' which is more readily accessible than (R)-2 (Eq. 2).



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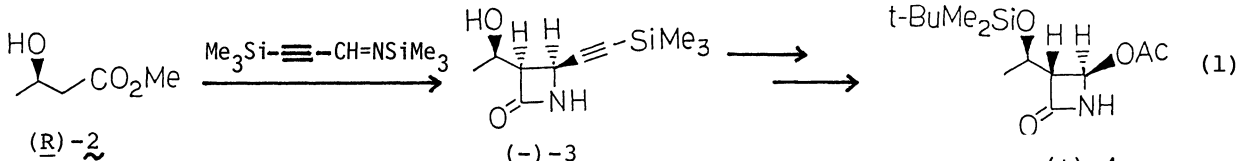
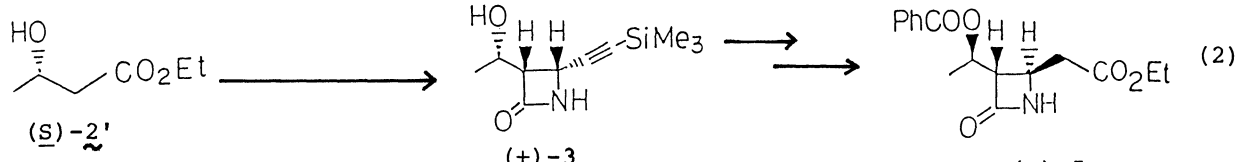


(R)-2 (-)-3 (+)-4 (1)



(S)-2' (+)-3 (+)-5 (2)

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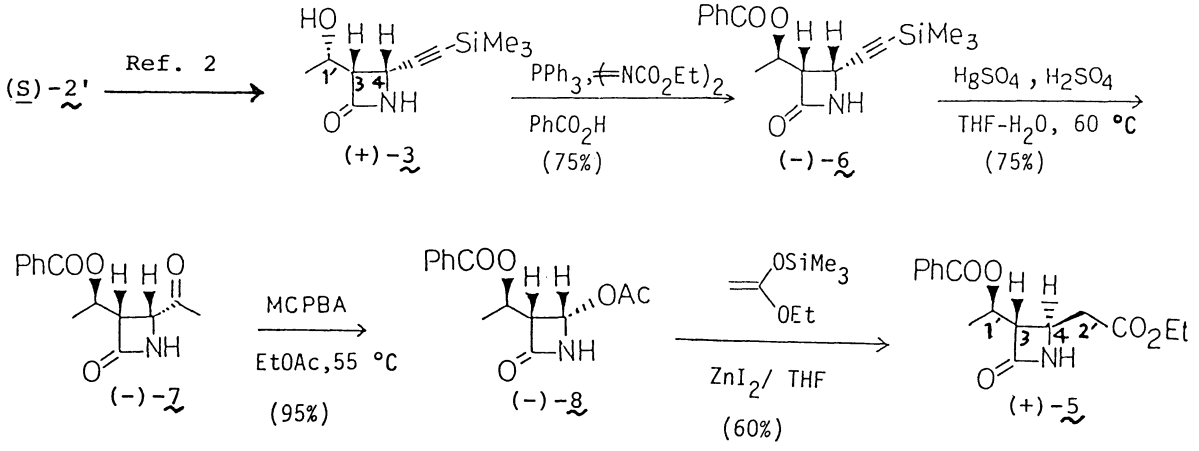
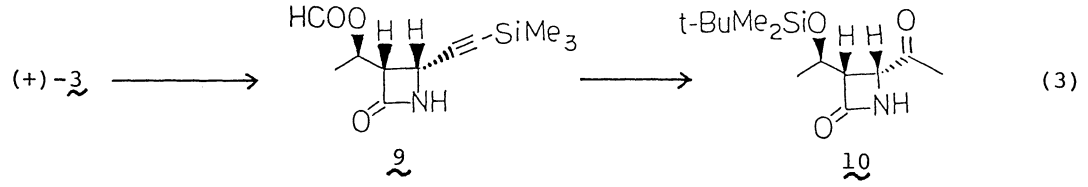
The complete transformation is depicted in Scheme 1. The key starting 2-azetidinone (+)-3 was prepared from (S)-2' (90% ee) obtained via baker's yeast reduction of ethyl acetoacetate according to the procedure described in our previous paper.[2] The crucial epimerization at C-1' was best accomplished by the Mitsunobu reaction[5] using benzoic acid as the nucleophile to afford the benzoate (-)-6 as a single stereoisomer ($[\alpha]_D^{20}$ -72.5° (c 1.26, $CHCl_3$)).[6] The (1',3)-syn configuration of (-)-6 was evidenced by the coupling constant ($J_{1',3}$= 6.0 Hz).[7] Usual hydration of (-)-6 yielded the ketone (-)-7 ($[\alpha]_D^{22}$ -112.9° (c 1.22, $CHCl_3$)).[8] which was then subjected to the Baeyer-Villiger reaction to give the 4-acetoxy-2-azetidinone (-)-8 ($[\alpha]_D^{20}$ -124.9° (c 1.34, $CHCl_3$)).[8] Finally, the reaction of (-)-8 with the ketene silyl acetal derived from ethyl acetate afforded the desired 2-azetidinone (+)-5 ($[\alpha]_D^{20}$ +5.5° (c 1.22, $CHCl_3$)).[9] The (3,4)-trans configuration of (+)-5 was unequivocally assigned on the basis of the coupling constant ($J_{3,4}$= 2.7 Hz), indicating that the reaction proceeds with complete inversion at C-4. Thus, the present sequence establishes the desired stereochemistry over the three chiral centers through the stereochemical corrections at C-1' and C-4. Particularly noteworthy is that the transformation is fully stereocontrolled, thus requiring no separation of stereoisomeric intermediates.



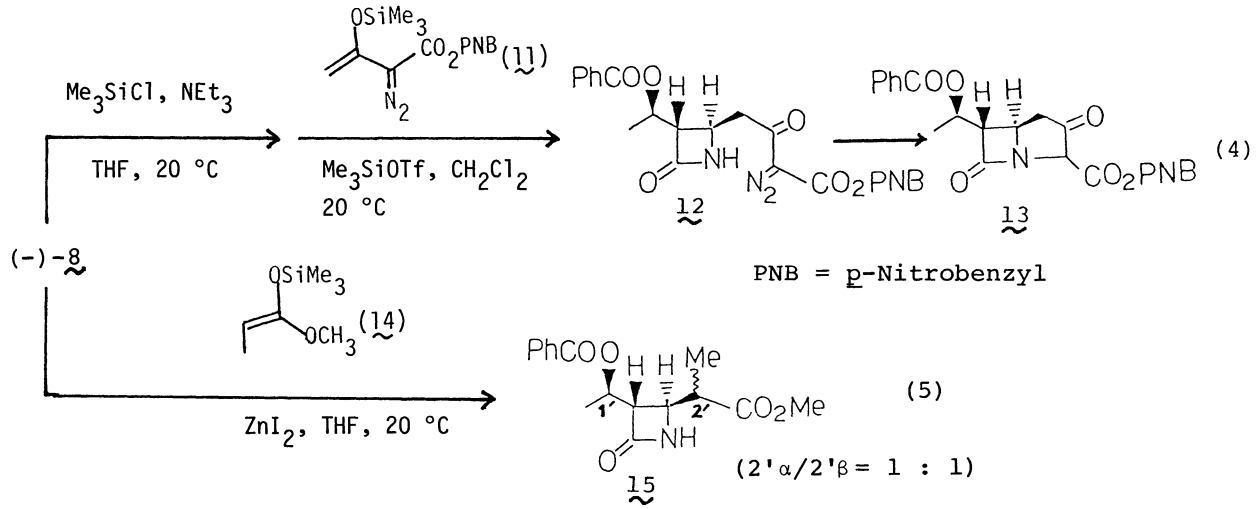
Scheme 1.

The epimerization at C-1' described above deserves special comments.[10] The use of formic acid instead of benzoic acid was found to afford a comparable yield of the corresponding inversion product 9,[11] as recently reported for a related substrate.[3] However, the formate moiety was not tolerable in the subsequent hydration process. Thus, the hydration was carried out after hydrolytic deprotection followed by reprotection by t-butyldimethylsilyl group to give the potentially useful intermediate 10[12] in 30% overall yield (Eq. 3).

Finally, we further studied the reaction of (-)-8 with different silyl enol ethers to clarify the reactivity characteristic of the benzoyl-protected (3,4)-



cis-azetidinone.[13] We found that the reaction of the N-silylated derivative of 8 with the diazo-synthon 11 in the presence of trimethylsilyl triflate afforded in 90% yield the corresponding (3,4)-trans product 12[8] which could be converted, by the known procedure,[14] to the thienamycin skeleton 13 (Eq. 4). Furthermore, the reaction of 8 with the (E)-ketene silyl acetal (14) was found to give a 1 : 1 mixture of the diastereomeric products 15[15] (Eq. 5). The non-stereoselectivity over C-2' and C-4 is in contrast to the α-preference (2'α/2'β = 3.4) reported for a similar reaction of the silyl-protected (3,4)-trans counterpart.[16]



In summary, we have described a new synthetic method for key thienamycin intermediates such as (+)-5 from inexpensive (S)-2'. The newly developed method is more advantageous than our previous route to (+)-4 from (R)-2 in terms of the shorter length of the sequence and the higher level of stereocontrol. Thus, the present method compares quite favorably with the existing methods,[3,4] particularly in terms of the availability of the starting material and the simplicity of the procedures. The improvement of the present method as well as its applications to the synthesis of 1-methylthienamycin are in progress in our laboratory.

References

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2) T. Chiba and T. Nakai, Chem. Lett., 1985, 651.
3) G. Cainelli, M. Contento, D. Giacomini, and M. Panunzio, Tetrahedron Lett., 26, 937 (1985); cf. G. I. Georg, ibid., 25, 3779 (1984).

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5) Review: O. Mitsunobu, Synthesis, 1981, 1.

6) NMR ($CDCl_3$, TMS), δ 1.43 (d, J=6.0 Hz, 1'-CH_3), 3.57 (d,d, J=5.7 and 6.0 Hz, 3-H), and 4.40 (d, J=5.7 Hz, 4-H).

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

8) The IR and NMR spectral data of these compounds are in agreement with the assigned structures.

9) IR (nujol), 3400, 1765, and 1720 cm^{-1}; NMR ($CDCl_3$), δ 1.18 (t, J=7.5 Hz, 3H), 1.45 (d, J=6.6 Hz, 1'-CH_3), 2.53-2.77 (m, 2H), 3.10 (d,d, J=2.4 and 7.5 Hz, 3-H), 3.87-4.27 (m, 3H), 5.33-5.67 (m, 1H), 6.60 (br. s, NH), 7.33-7.67 (m, 3H), and 8.00-8.20 (m, 2H). The spectral data are well correlated with those reported for the O-silylated counterpart.[4]

10) The use of acetic acid in place of benzoic acid was found to afford a much lower yield (ca. 10%) of the corresponding inversion product.

11) NMR ($CDCl_3$), δ 1.53 (d, J=6.0 Hz, 1'-CH_3), 3.57 (d,d, J=5.1 and 7.5 Hz, 3-H), 4.43 (d, J=5.1 Hz, 4-H), and 8.10 (s, CHO).

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