ASYMMETRIC SYNTHESIS OF 4-ACETOXY-3-HYDROXYETHYLAZETIDIN-2-ONE, A KEY INTERMEDIATE FOR THE PREPARATION OF PENEM AND CARBAPENEM ANTIBIOTICS

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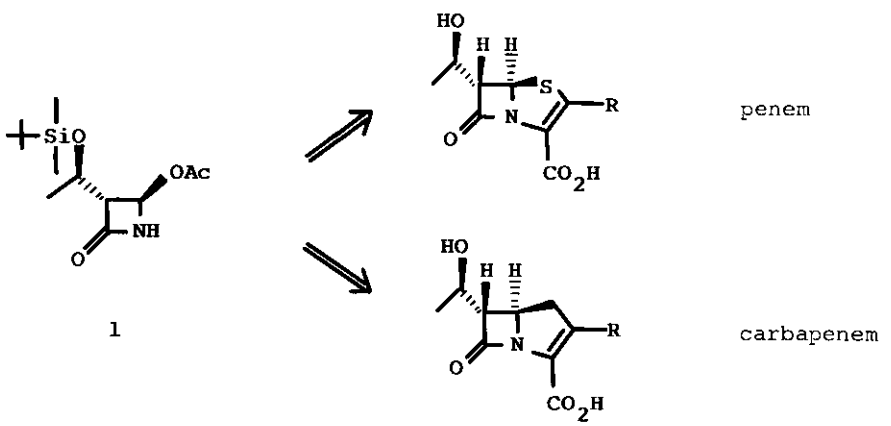
Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.

Abstract —— Asymmetric synthesis of 4-acetoxy-3-hydroxyethyl-azetidin-2-one with desired stereochemistry has been achieved by employing [3+2]dipolar cycloaddition of a chiral nitrone with benzyl crotonate as a key reaction.

4-Acetoxy-3-hydroxyethylazetidin-2-one derivative (1) was recognized to be a versatile starting material in the synthesis of non-classical β-lactam antibiotics because of its successful conversion into penem[1] and carbapenem[2] derivatives, including thienamycin. Therefore a number of enantiospecific synthesis of 1 have appeared by elaboration of a chiral natural source such as 6-aminopenicillanic acid,[3] (+)-aspartic acid,[4] and β-hydroxybutyrate[5] and by an asymmetric [2+2]cyclo-

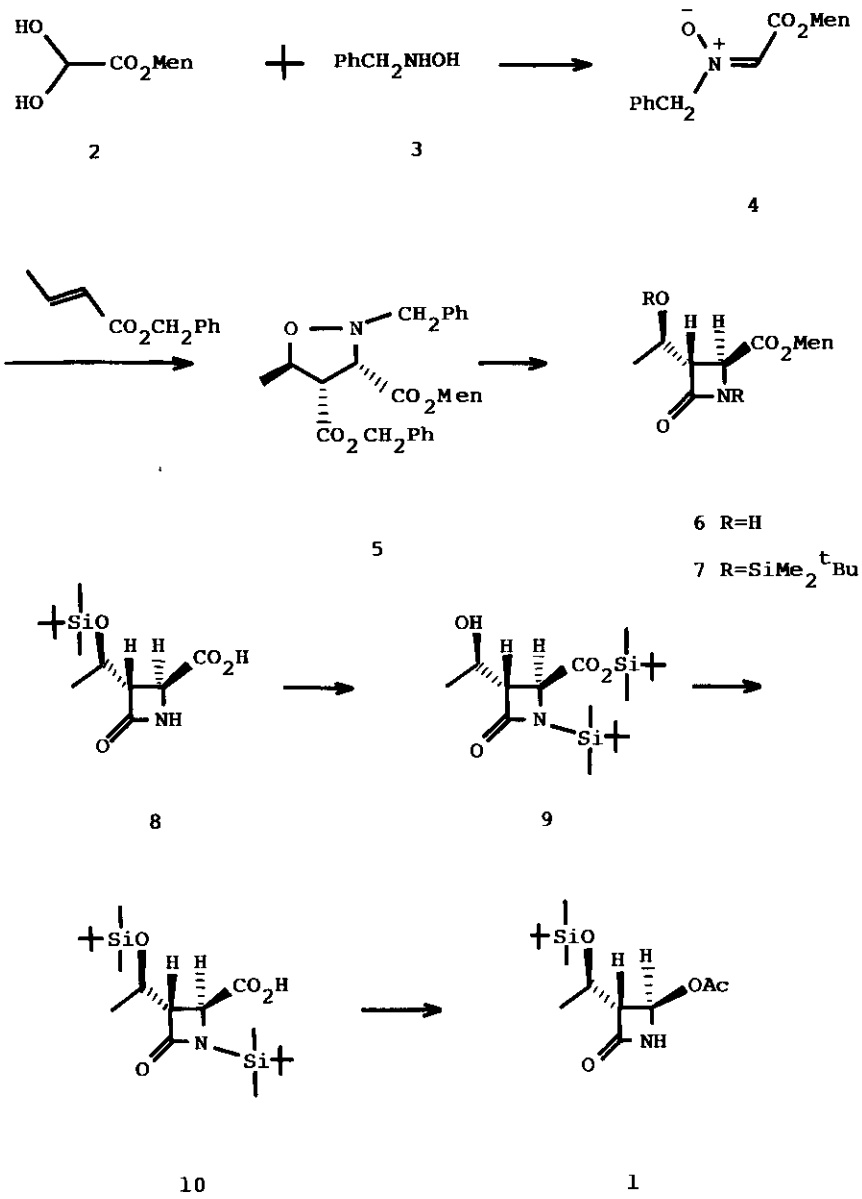


Scheme 1

addition reaction.[6]

We have recently demonstrated[7] the enantioselective synthesis of a carbapenem antibiotic, thienamycin, in which [3+2]dipolar cycloaddition of a chiral nitrone has played a key role to control the stereochemistry with the desired chirality. We here report a novel chiral synthesis of 4-acetoxy-3-hydroxyethylazetidin-2-one derivative (**1**) by further application of the above synthetic strategy employing an asymmetric [3+2]dipolar cycloaddition reaction as a key step. Condensation of L-(-)-menthyl glyoxalate hydrate (**2**)[8] with benzylhydroxylamine (**3**) in refluxing benzene afforded the nitrone (**4**), whose treatment with benzyl crotonate brought about [3+2]cycloaddition reaction to furnish the desired isoxazolidine (**5**)[9] as a major product in 30 % yield, together with the other stereoisomers. Catalytic reduction of **5** over platinum oxide in methanol under a current of hydrogen gave the amino acid, which without purification was treated with N,N-dicyclohexylcarbodiimide in acetonitrile to afford the azetidinone (**6**)[10] in 39 % yield. The stereochemistry of **6** was determined based on its nmr spectrum to have 3,4-trans relationship, though the absolute configuration could not be determined at this stage. After silylation of the hydroxy and amide groups of **6** with tert-butyldimethylchlorosilane, the silyl derivative (**7**) was subjected to hydrolysis with 1N-NaOH to provide the acid (**8**)[11] in 64 % yield from **6**. Treatment of the resulting acid (**8**) with 2 eq. molar amount of tert-butyldimethylchlorosilane in N,N-dimethylformamide in the presence of triethylamine yielded the silyl ester (**9**) in 94 % yield. Obviously the migration of the silyl group occurred during the silylation reaction. The silyl ester (**9**) was interestingly converted into the acid (**10**) by treatment with acetic acid in tetrahydrofuran in 82 % yield. Finally the acid (**10**) was transformed to the desired 4-acetoxy derivative (**1**), mp 105 ℃ (lit.,[3a] 104 - 106 ℃), $[\alpha]_D$ +49.31° (c=0.073, $CHCl_3$) [lit.,[3a] +48.8° ($CHCl_3$)], by oxidative acetoxylation with lead tetraacetate in 70 % yield. Since the physicochemical properties of **1** were identical with those reported, its stereochemistry was determined to have 3R and 4R configuration.

Thus, the chiral synthesis of **1** was achieved by employing [3+2]dipolar cycloaddition of a chiral nitrone with benzyl crotonate as a key step. Furthermore, since the acid (**8**) was already converted[3b] to thienamycin, this synthesis constitutes a formal synthesis of (+)-thienamycin.



2 3 4

5

6 R=H

7 R=$SiMe_2{}^tBu$

8 9

10 1

Scheme 2

REFERENCES

1. T. Miyadera, J. Synth. Org. Chem. (Japan), 1983, **41**, 1168.
2. (a) T. Kametani, K. Fukumoto, and M. Ihara, Heterocycles, 1982, **17**, 463; (b) M. Shibuya, J. Synth. Org. Chem. (Japan), 1983, **41**, 62.
3. (a) A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, Chem. Pharm. Bull., 1981, **29**, 2899; (b) K. Hirai, Y. Iwano, and K. Fujimoto, Tetrahedron Lett., 1982, **23**, 4021, 4025; (c) W. J. Leanza, F. DiNinno, D. A. Muthard, R. R. Wilkening, K. J. Wildoner, R. W. Ratchiffe, and B. G. Christensen, Tetrahedron, 1983, **39**, 2505.
4. P. J. Reider and E. J. J. Grabowski, Tetrahedron Lett., 1982, **23**, 2293.
5. (a) T. Chiba, M. Nagatsuma, and T. Nakai, Chemistry Lett., 1984, 1927; ibid., 1985, 1343; (b) T. Chiba and T. Nakai, Chemistry Lett., 1985, 651; (c) G. Cainelli, M. Contents, D. Giacomini, and M. Panunzio, Tetrahedron Lett., 1985, **26**, 937.
6. (a) Sumitomo Chemical Ind. Co., Ltd., Japan Kokai, Patent No 58-99463 (1983) and No 60-32765 (1985); (b) Kanegafuchi Chemical Co., Ltd., Japan Kokai, Patent No 61-18791 (1986).
7. T. Kametani, T. Nagahara, and T. Honda, J. Org. Chem., 1985, **50**, 2327.
8. J. Jurczak and A. Zamojski, Rocz. Chem., 1970, **44**, 2257.
9. mp 95 ℃; $[\alpha]_D^{25}$ -76.42° (c=1.086, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3H, d, J = 6.1 Hz, 5-Me), 3.16 (1H, dd, J = 8.3 and 8.5 Hz, 4-H), 3.75 (1H, d, J = 8.5 Hz, 3-H), 4.41 (1H, dd, J = 6.1 and 8.3 Hz, 5-H), 5.12 (2H, s, CH_2Ar); MS m/z 493 (M^+).
10. An oil; $[\alpha]_D^{25}$ -55.48° (c=1.77, $CHCl_3$); IR ($CHCl_3$) 3400, 1765, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (3H, d, J = 6.3 Hz, 1'-Me), 2.75 - 3.27 (1H, ddd, J = 1, 2.8 and 5.6 Hz, 3-H), 4.29 (1H, d, J = 2.8 Hz, 4-H); MS m/z 298 ($M^+ + 1$).
11. mp 134 ℃ [lit.,[3b] 134 ℃]; $[\alpha]_D^{25}$ -21.0° (c=0.2, $CHCl_3$); The melting point of this acid was identical with the literature value,[3b] however, its optical rotation was not reported.

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