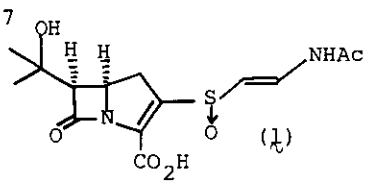
A FORMAL TOTAL SYNTHESIS OF (±)-CARPETIMYCIN A (C-19393 H_2): STEREOSELECTIVE SYNTHESIS OF (±)-*CIS*-4-CARBOXYMETHYL-3-(1-METHYL-1-TRIMETHYLSILYLOXYETHYL)-2-AZETIDINONE *VIA* AN ISOXAZOLINE DERIVATIVE

Masataka Ihara, Fujiko Konno, and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama Sendai 980, Japan
Tetsuji Kametani*
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

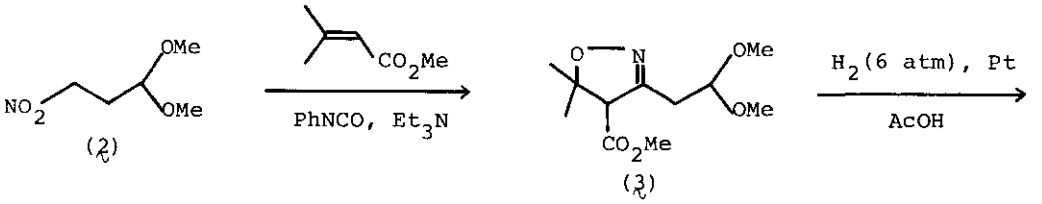
Abstract —— The synthetic intermediate, (±)-*cis*-4-carboxymethyl-3-(1-methyl-1-trimethylsilyloxyethyl)-2-azetidinone (10), of the carbapenem antibiotics, carpetimycin A, was stereoselectively prepared *via* an isoxazoline derivative (3).

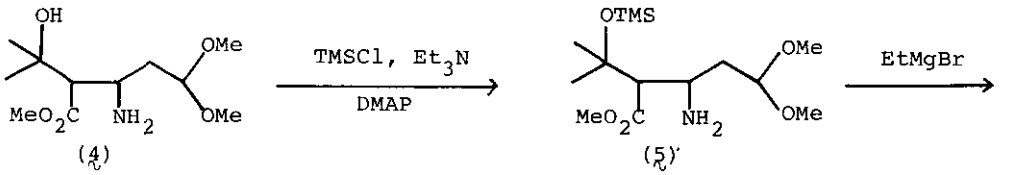
The carbapenem antibiotics carpetimycin A[1] and C-19393 H_2[2] were isolated by two independent groups and assigned to the same structure (1). This *cis*-substituted carbapenem was reported to possess not only a highly potent, broad-spectrum antibacterial activity, but also a strong β-lactamase inhibitory activity. Recently its racemate was synthesized by the Takeda's group[3] while the synthesis of the natural levorotatory form was achieved by Ohno and his coworkers.[4] On the other hand, in the case of our synthesis of thienamycin and its derivatives *via* isoxazoline derivatives,[5] we realized that a *cis*-substituted β-lactam could be preferentially obtained if a less bulky ester of the isoxazoline derivative was used as a synthetic precursor.[6] On the basis of this knowledge, we have planned a stereoselective synthesis of carpetimycin A and its related compounds and here wish to report the successful result.[7]

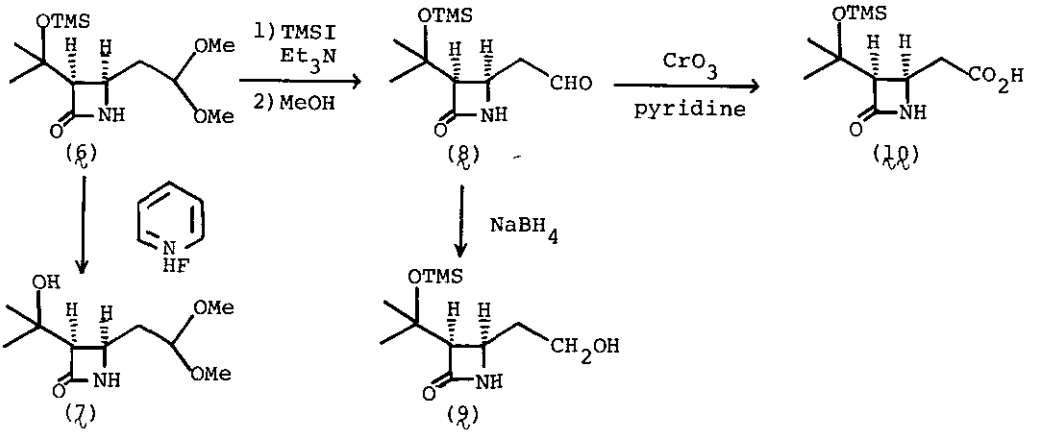


(1)

Heating 3-nitropropanal dimethyl acetal (2) in the presence of two molar equivalents of phenyl isocyanate and catalytic amount of triethylamine[8] in large excess methyl 3,3-dimethylacrylate at 130 - 140°C for 6.5 h followed by chromatography on neutral alumina eluting with hexane - ether (1 : 1 v/v) gave the desired isoxazoline (3) in 56 % yield and no regio-isomer was obtained. Such high regio-selectivity on the 1,3-dipolar cycloaddition between some nitrile oxides and 3,3-dimethylacrylate was observed by Christl and Huisgen.[9] Catalytic hydrogenation of the isoxazoline (3) in the presence of Adams catalyst in acetic acid under a medium pressure of hydrogen (6 atm) at room temperature for 3 days afforded quantitatively the corresponding amino-ester (4). Without purification, the ester (4) was treated







with excess trimethylsilyl chloride and triethylamine in the presence of catalytic amount of 4-N,N-dimethylaminopyridine in benzene at room temperature for 8 h. After filtration to remove a solid formed, evaporation of the filtrate gave an oily residue, whose NMR spectrum indicated the O-monosilylated structure (5). The product was then cyclized by the reaction with ethylmagnesium bromide[10] in tetrahydrofuran at room temperature for 2 days. The cis-substituted β-lactam (6), IR ($CHCl_3$) cm^{-1}: 3450 (NH), 1758 (C=O); NMR ($CDCl_3$) δ: 0.13 (9H, s, TMS), 1.32 (3H, s, Me), 1.52 (3H, s, Me), 3.14 (1H, d, J = 5.5 Hz, C_3-H), 3.32 (6H, s, 2 × OMe); FD-MS m/e 289 (M^+), was obtained in 61 % yield from 3 after purification by silica gel column chromatography eluting with acetone - benzene (1 : 4 v/v). But the trans-isomer formed in less than 12 % yield could not be gained as a pure form. Trimethylsilyl group of 6 was removed by the action of pyridinium hydrofluoride[11] in tetrahydrofuran at room temperature for 12 h to give, in 79 % yield, the alcohol (7), mp 97 - 98°C; IR ($CHCl_3$) cm^{-1}: 3450 (NH), 1758 (C=O); NMR ($CDCl_3$) δ: 1.33 (3H, s, Me), 1.50 (3H, s, Me), 3.33 (6H, s, 2 × OMe), 4.47 [1H, t, J = 6 Hz, $CH(OMe)_2$], 7.66 (1H, br s, NH). However selective deprotection of the acetal group was difficult under the acidic reaction conditions. The conversion of the acetal (6) into the aldehyde (8) was achieved by the reaction using three molar equivalents of trimethylsilyl iodide[12] and four molar equivalents of triethylamine in methylene chloride at room temperature for 30 min. Since N-trimethylsilylation also effectively occurred, the product was successively treated with methanol giving in 83 % yield the aldehyde (8); NMR ($CDCl_3$) δ: 0.11 (9H, s, TMS), 1.30 (3H, s, Me), 1.54 (3H, s, Me), 9.75 (1H, s, CHO); FD-MS m/e 243 (M^+). When the deprotection reaction using trimethylsilyl iodide was carried out without triethylamine, no desired product formed.

Reduction of 8 with sodium borohydride produced the alcohol (9), mp 112 - 115°C, NMR ($CDCl_3$) δ: 0.12 (9H, s, TMS), 1.34 (3H, s, Me), 1.51 (3H, s, Me), 3.17 (1H, d, J = 5.0 Hz, C_3-H) in 88 % yield. Oxidation of 8 with excess chromic anhydride in pyridine at room temperature for 16 h furnished in 71 % yield the corresponding acid (10), mp 135 - 136°C, whose IR ($CHCl_3$) and NMR ($CDCl_3$) spectra were identical with those of the authentic optically active compound.[4] Since the dextrorotatory compound of 10 was transformed into (-)-carpetimycin A (1)[4], a formal total synthesis of the racemate has been accomplished.

ACKNOWLEDGEMENT

We thank Prof. M. Ohno, University of Tokyo, for the generous donation of the authentic sample and its spectra.

REFERENCES AND NOTES

1. M. Nakayama, A. Iwasaki, S. Kimura, T. Mizoguchi, S. Tanabe, A. Murakami, I. Watanabe, M. Okuchi, H. Itoh, Y. Saino, F. Kobayashi, and T. Mori, J. Antibiotics, 1981, 33, 1388; M. Nakayama, S. Kimura, S. Tanabe, T. Mochizuki, I. Watanabe, T. Mori, K. Miyahara, and T. Kawasaki, ibid., 1981, 34, 818.
2. A. Imada, Y. Nozaki, K. Kintaka, K. Okonogi, K. Kitano, and S. Harada, ibid., 1980, 33, 1417; S. Harada, S. Shinagawa, Y. Nozaki, M. Asai, and T. Kishi, ibid., 1980, 33, 1425.
3. H. Natsugari, Y. Matsushita, N. Tamura, K. Yoshioka, and M. Ochiai, J. Chem. Soc., Perkin I, 1983, 403.
4. T. Iimori, Y. Takahashi, T. Izawa, S. Kobayashi, and M. Ohno, J. Am. Chem. Soc., 1983, 105, 1659.
5. T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, J. Am. Chem. Soc., 1980, 102, 2060; T. Kametani, S.-P. Huang, T. Nagahara, S. Yokohoma, and M. Ihara, J. Chem. Soc., Perkin I, 1981, 964; T. Kametani, S.-P. Huang, T. Nagahara, and M. Ihara, ibid., 1981, 2282.
6. T. Kametani, T. Nagahara, Y. Suzuki, S. Yokohama, S.-P. Huang, and M. Ihara, Tetrahedron, 1981, 37, 715.
7. Most of the present work was presented on the 41th Symposium on the Synthetic Organic Chemistry in Tokyo, June 1982.
8. T. Mukaiyama and T. Hoshino, J. Am. Chem. Soc., 1960, 82, 5339.
9. M. Christl and R. Huisgen, Chem. Ber., 1973, 106, 3345.
10. L. Birkofer and J. Schramm, Annalen, 1975, 2195.
11. K. C. Nicolau, S. P. Seitz, M. R. Pavia, and N. A. Petasis, J. Org. Chem., 1979, 44, 4011.
12. M. E. Jung, W. A. Andrus, and P. L. Ornstein, Tetrahedron Lett., 1977, 4175.

Received, 25th July, 1983