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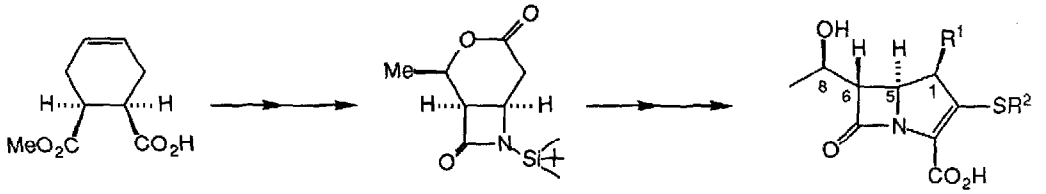
A Stereoselective Route to the Key Intermediate of 1β-Methylcarbapenems by Chemicoenzymatic Approach[1)]

Harumi Kaga[2)], Susumu Kobayashi and Masaji Ohno*
Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: *The key intermediate 15 of 1β-methylcarbapenem antibiotics 4 was synthesized enantioselectively under complete stereochemical control starting from the chiral monoester 1, enzymatically generated.*

We have recently reported the chemicoenzymatic approach to thienamycin **3** starting from the chiral monoester **1**[3a)] through the bicyclic β-lactam **2**.[3c)] The strategy involved the introduction of the chiral center at C-8[4)] by taking advantage of the bicyclic ring system and the epimerization of the stereochemistry at C-6.

Scheme 1



1 **2**

3 Thienamycin
$R^1 = H$, $R^2 = CH_2CH_2NH_2$

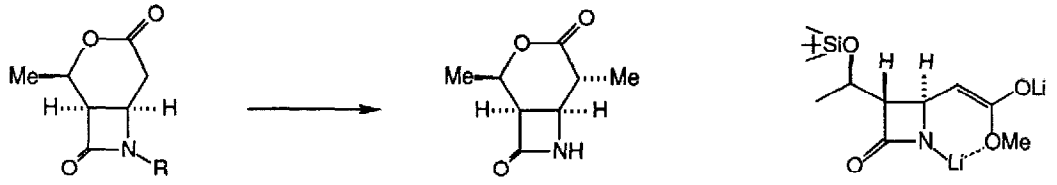
4 $R^1 = Me$, $R^2 = CH_2CH_2NH_2$

In this paper we wish to demonstrate that the bicyclic β-lactam **2** can also serve as a potential intermediate in the synthesis of 1β-methylcarbapenem antibiotics **4** of current medicinal and synthetic interests[5)] in the field of β-lactam antibiotics. The stereochemical control of the contiguous four chiral centers is indeed interesting from a synthetic point of view, and a variety of methods have been devised[6)] since the pioneering molecular design by the Merck group.[5)] Our plan to this solution was rather straightforward, and we tried to introduce the methyl group at α to the lactonic carbonyl in **2**. The methylation would occur from the convex face by considering the structural feature of this bicyclo[4.2.0] ring system.

The bicyclic β-lactam **2**, prepared from **1** in 30% overall yields,[3)] was initially converted to the desilylated β-lactam **5** in quantitative yield (2N HCl / MeOH). Deprotonation of **5** with 2.2 equiv of LDA (lithium diisopropylamide) in THF (tetrahydrofuran) at -78°C for 40 min and the subsequent reaction with methyl iodide (2.2 equiv) at -78°C for 1h afforded the methylation product **6**[7)] in 77%

yield as a single stereoisomer. The structure of **6** was unambigously established by X-ray crystallographic analysis.[8]

Scheme 2



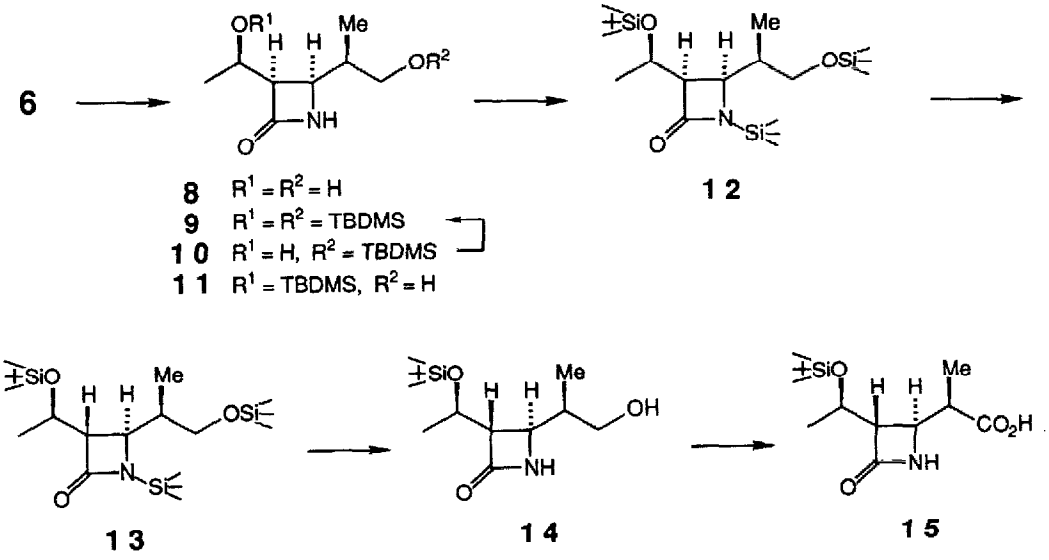
2 R = TBDMS
5 R = H

6

7

It is interesting to compare the different stereochemical course of the methylation in the present bicyclic case and monocyclic β-lactam cases.[5,9] For example, the Merck group has reported that the methylation of the dianion **7**, generated from the corresponding monocyclic β-lactam, gave *ca* 4:1 diastereomeric mixture of methylation products in favor of 1*S*-isomer.[4,5] They explained the predominant formation of 1*S*-isomer by considering the 6-membered ring chelation structure **7**. In both cases, the methylation occurred from α face to result in the formation of different stereoisomers. Our success is attributed to employing the lactone **5** as an intermediate which has a cis-fused ring system of bicyclo[4.2.0]octane.

Scheme 3



8 $R^1 = R^2 = H$
9 $R^1 = R^2 = TBDMS$
10 $R^1 = H$, $R^2 = TBDMS$
11 $R^1 = TBDMS$, $R^2 = H$

12

13

14

15

The bicyclic **6** was reduced with lithium borohydride and methanol[10] in dimethoxyethane at 50°C for 2h to produce the monocyclic β-lactam **8** in 91% yield. The coupling constant of 5.0 Hz for $J_{5,6}$ is typical for a cis relationship in the β-lactam. The diol **8** was initially transformed to the bis-TBDMS (*t*-butyldimethylsilyl) ether **9** in 89% yield[11] (3.0 equiv TBDMSCl, 6.0 equiv imidazole / DMF, 40°C), and **9** was then converted to the mono-TBDMS ether **11** by the selective desilylation at the primary hydroxyl group (1N HCl / MeOH, 0°C, 91%).

We then examined the epimerization at C-6. This was most cleanly achieved by the following stepwise procedure: (1) Trimethylsilylation of the primary hydroxyl and the β-lactam nitrogen with hexamethyldisilazane and TMSCl in pyridine;[12] (2) epimerization with 2.0 equiv trimethylsilyl triflate[13] and 2.1 equiv Et_3N in methylene chloride at 40°C for 24h;[12] (3) detrimethylsilylation with 1N HCl in methanol at 0°C for 10 min to give the desired trans β-lactam **14** [m.p. 88.5~89.5°C, $[\alpha]_D^{20}$ -21.1° (*c* 0.96, $CHCl_3$); lit[6] m.p. 90~91°C, $[\alpha]_D^{20}$ -21.7° (*c* 0.46, $CHCl_3$)] in 58% overall yields from **11**.[14] The trans stereochemistry was suggested by a smaller coupling constant ($J_{5,6}$=2.2Hz) than that of the corresponding cis isomer **11** ($J_{5,6}$=5.1Hz). Furthermore, the structure was unambigously confirmed by comparison of spectral data with those provided by Terashima.[6]

Oxidation of **14** with PDC (pyridinium dichromate) in DMF at room temperature afforded the key intermediate **15** [m.p. 145~146°C (dec.), $[\alpha]_D^{25}$ -34.0° (*c* 0.37, MeOH); lit[6] m.p. 146~147°C (dec.), $[\alpha]_D^{25}$ -34.6° (*c* 0.26, MeOH)] in 92% yield. Since the transformation of **15** to 1β-methylcarbapenems has already been established,[5,6] the present study provides a new entry to 1β-methylcarbapenem antibiotics. It should be noted that all the desired chiral centers were introduced under complete stereochemical control.

Acknowledgment: We are grateful to Professor Y. Iitaka for X-ray crystallographic analysis of **6**. We are also indebted to Dr. S. Terashima, Sagami Chemical Research Center, for providing spectroscopic data of **14**. This work was financially supported in part by Sapporo Bioscience Foundation and Grant-in-Aid (No.63616005) for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan.

References and Notes:

1. Construction of Novel Chiral Synthons with Enzymes and Application to Natural Product Synthesis, Part 26. Part 25; M. Shimada, S. Kobayashi, and M. Ohno, *Tetrahedron Lett.*, in press
2. Visiting scientist from Government Industrial Development Laboratory, Hokkaido.
3. (a) S. Kobayashi, K. Kamiyama, T. Iimori, and M. Ohno, *Tetrahedron Lett.*, **25**, 2557 (1984); (b) M. Kurihara, K. Kamiyama, S. Kobayashi, and M. Ohno, *ibid.*, **26**, 5831 (1985); (c) H. Kaga, S. Kobayashi, and M. Ohno, *ibid.*, **29**, 1057 (1988).
4. The carbon numbers are expressed according to the thienamycin numbering in this paper.
5. (a) D. H. Shih, J. A. Fayter, F. Baker, L. Cama, and B. G. Christensen, Abstract 333, *23rd Interscience Conference on Antimicrobial Agents and Chemotherapy*, Las Vegas, Nevada, 1983; (b) D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles*, **21**, 29 (1984).

6. T. Kawabata, Y. Kimura, Y. Ito, S. Terashima, A. Sasaki, and M. Sunagawa, *Tetrahedron*, **44**, 2149 (1988), and references cited therein.
7. All compounds described herein gave consistent elemental analysis and spectra data (^{1}H-NMR, IR, MS) in accord with the assigned structures. The selected data of the typical intermediates are as follows:
6 m.p. 158.5~159.5°C; $[\alpha]_D^{20}$ +138.4° (*c* 1.11, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.33 (d, *J*=7.7Hz, 3H), 1.62 (d, *J*=6.6Hz, 3H), 3.05 (qd, *J*=7.7, 1.8Hz, 1H), 3.52 (ddd, *J*=5.1, 3.3, 2.2Hz, 1H), 3.92 (dd, *J*=5.1, 1.8Hz, 1H), 4.76 (qd, *J*=6.6, 3.3Hz, 1H), 6.14 (br.s, 1H, NH); Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28%. Found: C, 56.55; H, 6.58; N, 8.32%.
8 $[\alpha]_D^{20}$ -73.0° (*c* 1.00, MeOH); ^{1}H-NMR (400MHz, 10% CD_3OD-$CDCl_3$) δ 1.00 (d, *J*=7.0Hz, 3H), 1.41 (d, *J*=6.7Hz, 3H), 2.35~2.45 (m, 1H), 3.25 (dd, *J*=5.0, 3.5Hz, 1H), 3.5~3.6 (m, 3H), 4.28 (qd, *J*=6.7, 3.5Hz, 1H), 6.54 (br.s, 1H, NH).
11 $[\alpha]_D^{20}$ -46.5° (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400MHz, CD_3OD-$CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.95 (d, *J*=7.0Hz, 3H), 1.41 (d, *J*=6.6Hz, 3H), 2.43~2.54 (m, 1H), 3.28 (dd, *J*=5.1, 2.9Hz, 1H), 3.51~3.61 (m, 3H), 4.41 (qd, *J*=6.6, 2.9Hz, 1H).
14 ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.89 (d, *J*=6.6Hz, 3H), 0.92 (s, 9H), 1.35 (d, *J*=6.2Hz, 3H), 1.81~1.92 (m, 1H), 3.12 (dd, *J*=9.5, 4.0Hz, 1H, OH), 3.17 (ddd, *J*=9.2, 2.2, 1.1Hz, 1H), 3.28 (dd, *J*=9.2, 2.2Hz, 1H), 3.47 (ddd, *J*=11.7, 8.8, 4.0Hz, 1H), 3.58 (ddd, *J*=11.7, 9.5, 4.4Hz, 1H), 4.13 (dq, *J*=9.2, 6.2Hz, 1H), 5.99 (br.s, 1H, NH); Calcd. for $C_{14}H_{29}NO_3Si$: C, 58.49; H, 10.17; N, 4.87%. Found: C, 58.74; H, 10.19; N, 4.80%.
15 ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.068 (s, 3H), 0.074 (s, 3H), 0.87 (s, 9H), 1.20 (d, *J*=6.2Hz, 3H), 1.26 (d, *J*=7.0Hz, 3H), 2.75 (qd, *J*=7.0, 5.1Hz, 1H), 3.03 (dd, *J*=4.4, 2.2Hz, 1H), 3.94 (dd, *J*=5.1, 2.2Hz, 1H), 4.20 (qd, *J*=6.2, 4.4Hz, 1H), 6.29 (br.s, 1H, NH); Calcd. for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65%. Found: C, 55.54; H, 8.99; N, 4.83%.
8. X-ray crystallographic analysis of **6** was done by Professor Y. Iitaka, University of Tokyo.
9. L. G. de Vries and G. Sigmund, *Tetrahedron Lett.*, **26**, 587 (1985).
10. K. Soai, A. Ookawa, and H. Hayashi, *J. Chem. Soc., Chem. Commun.*, **1983**, 668.
11. A small amount of mono-TBDMS ether **10** was also isolated, and this was resilylated to give **9** in the similar manner (1.1 equiv TBDMSCl, 1.5 equiv imidazole / DMF, 40°C, 93%).
12. Purification of the intermediates, **12** and **13**, is possible by the chromatography on florisil (100~200 mesh, Floridin Co.), and **12** and **13** were characterized, respectively.
13. T. Chiba and T. Nakai, *Tetrahedron Lett.*, **26**, 4647 (1985).
14. We have also treated **9** and **11** with TMSOTf and Et_3N in CH_2Cl_2 in a similar manner. However, this *in situ* method resulted in the complex mixture of products, probably due to the use of an excess TMSOTf and Et_3N and/or the presence of a large amount of ammonium triflate. The overall yields were usually lower than 50%. Therefore, we employed the stepwise method.

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