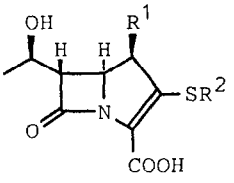
Tetrahedron Letters,Vol.27,No.47,pp 5751-5754,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NOVEL SYNTHESIS OF (3R,4R)-4-ACETOXY-3-[(R)-1-(t-BUTYLDIMETHYLSILYLOXY)ETHYL]-2-AZETIDINONE, THE VERSATILE KEY INTERMEDIATE OF CARBAPENEM SYNTHESIS, FROM (S)-ETHYL LACTATE

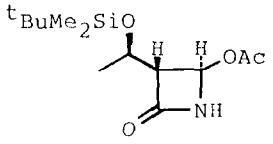
Yoshio Ito, Takeo Kawabata, and Shiro Terashima*
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Abstract: A highly efficient synthesis of the title compound was accomplished employing the addition of diketene to chiral imine as a key stereoselective reaction and using inexpensive (S)-ethyl lactate as a starting material.

The carbapenem β-lactam antibiotics represented by thienamycin (**1**), have been the target of recent synthetic endeavor because of their prominent antibacterial activities and broad spectra.[1] In several syntheses of these novel antibiotics so far reported,[1,2] the title compound, (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone (**2**), hold a pivotal position as one of the most versatile key synthetic intermediates. Thus, various types of carbon chains required to construct the five-membered ring fused with β-lactam, can be readily introduced into **2** by substituting its acetoxy group with nucleophiles.[2] The same synthetic strategy has been also applied for producing the key intermediates of 1β-methylcarbapenems such as **3**,[3] chemically and metabolically stable carbapenem antibiotics showing excellent antibacterial activities.[3a,4] Accordingly, a number of synthetic methods of **2** has hitherto been explored by employing various chiral compounds as starting materials.[2a-d,5]



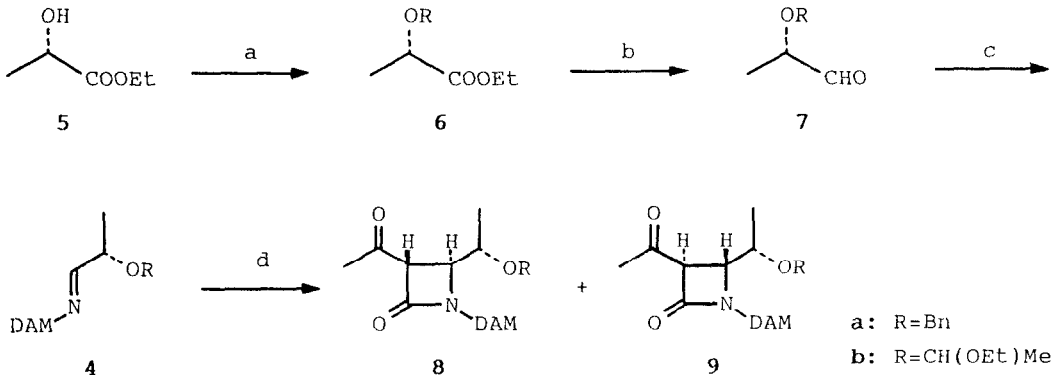
1: R^1=H, R^2=$CH_2CH_2NH_2$
3: R^1=Me, R^2=$CH_2C(NMe_2)$=NH



2

We wish to report here another novel synthesis of **2** in which the highly stereoselective addition of diketene to the optically active imine (**4**) readily obtainable from commercially available inexpensive (S)-ethyl lactate (**5**), plays a key role to construct the chiral 3-acetyl-β-lactam (**8**) bearing the desired absolute stereochemistry.

It was recently uncovered that the addition reactions of diketene to imines derived from aromatic aldehydes[6] or alkyl glyoxylates,[7] can proceed in a highly stereoselective manner to afford 3,4-trans-3-acetyl-β-lactams. However, this novel β-lactam formation which is formally a [2+2] cycloaddition reaction of acetyl ketene presumably produced from diketene, has never been examined with the imines prepared from optically active aliphatic aldehydes carrying a chiral center at the α-position.[8] We have now found that the absolute stereochemistry of 3,4-trans-3-acetyl-β-lactam can be effectively controlled by the adjacent chiral

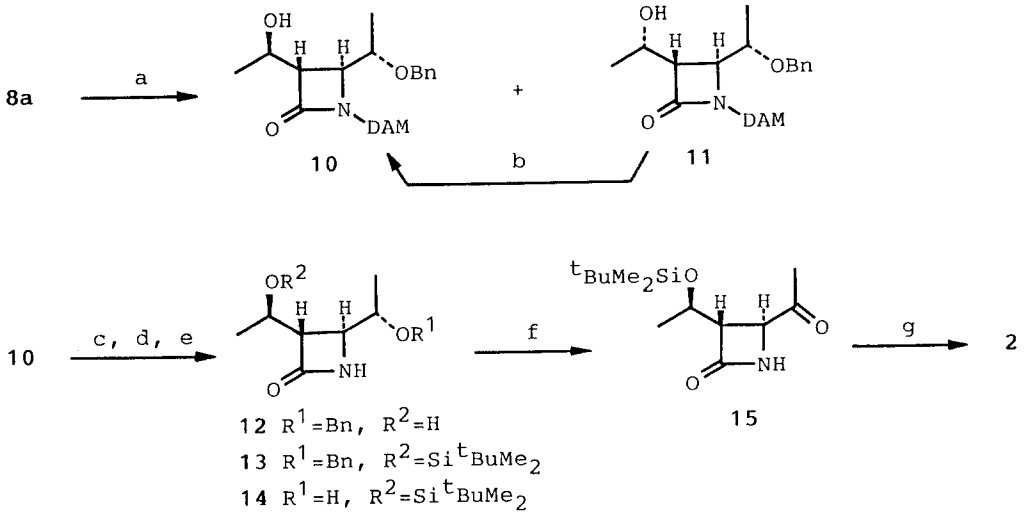


a) $CCl_3C(NH)OCH_2Ph$-TfOH (cat.), 69% or $CH_3CH_2OCHCH_2$-TsOH (cat), 100% b) DIBAL in ether, -78 °C, 82% c) DAM-NH_2-$MgSO_4$ in PhMe d) diketene (4 equiv.)-imidazole (1 equiv.) in THF, -30 °C, 2 days, 72% (from **7a**) or 74% (from **7b**)

center, and that the highly optically active 3-acetyl-β-lactam (**8**) can be readily derived to **2**.

The explored synthetic scheme commences with protection of the hydroxy group of **5**. Thus, after conversion of **5** into the corresponding benzyl ether (**6a**), the ester group of **6a** was reduced with diisobutylaluminium hydride (DIBAL) to afford the aldehyde (**7a**). Treatment of **7a** with di-*p*-anisylmethylamine (DAM-NH_2) in the presence of magnesium sulfate as a dehydrating agent gave rise to the chiral imine (**4a**), which was immediately subjected to the next addition reaction. Addition of diketene to **4a** which constitutes the key stereoselective reaction of our synthesis, was effected in the presence of imidazole, giving a mixture of the 3-acetyl-β-lactams (**8a** and **9a**) in a good yield.[9] The stereoselectivity was determined as **8a**:**9a**=7:1 by integrating the acetyl protons which appeared as two singlets in the ^1H NMR spectrum of the mixture.[10] The major isomer (**8a**) obtained as an oil by subjecting the mixture of **8a** and **9a** to column chromatography (SiO_2, CH_2Cl_2:ether=1:0-9:1), showed $[\alpha]_D^{20}$ -7.3° (c 1.48, $CHCl_3$). The enantiomeric excess of **8a** was estimated to be 96%ee by the ^1H NMR spectrum measured in the presence of chiral shift reagent, Eu(hfc)$_3$. Exchange of the protective group from benzyl to 1-ethoxyethyl resulted in the decrease of stereoselectivity of the addition reaction (**8b**:**9b**=3:1).[11]

With the adduct (**8a**) in hand, preparation of **2** was next attempted. Reduction of the acetyl group of **8a** with potassium tri-*sec*-butylborohydride in the presence of potassium iodide[12] underwent highly stereoselectively, to give a mixture of the two epimeric alcohols (**10** and **11**, **10**:**11**=12:1) with a 4% recovery of **8a**. On the other hand, complete reduction of **8a** was effected with potassium triethylborohydride,[13] yielding a mixture of **10** and **11** in the same stereoselectivity. The two epimeric alcohols (**10** and **11**) separated by TLC (SiO_2, *n*-hexane:ethyl acetate=2:3), showed $[\alpha]_D^{25}$ -5.5° (c 2.02, $CHCl_3$) and $[\alpha]_D^{25}$ +13.8° (c 0.65, $CHCl_3$), respectively. The undesired epimer (**11**) could be converted to **10** in an excellent combined yield by the Mitsunobu reaction.[4] Oxidative removal of the di-*p*-anisylmethyl group of **10** with cerium(IV) ammonium nitrate (CAN)[14] afforded the *N*-unprotected β-lactam (**12**), mp 129-130 °C, $[\alpha]_D^{25}$ +61.5° (c 1.45, $CHCl_3$). After protection of the hydroxy group of **12** in a



a) KB(s-Bu)$_3$H-KI in THF, 0 °C, 92% or KBEt$_3$H in THF, 0 °C, 98% b) i) EtOCON=NCOOEt-PPh$_3$-HCOOH, ii) K_2CO_3 in MeOH, 90% (2 steps) c) CAN in aq. CH_3CN, 0 °C, 86% d) t-BuMe$_2$SiCl-ImH in DMF, 97% e) H_2-Pd/C in AcOEt, 100% f) CrO_3 in pyridine, 89% g) MCPBA in AcOEt, 93%

form of t-butyldimethylsilyl ether, the benzyl ether (**13**), $[\alpha]_D^{25}$ +32.5° (c 2.37, $CHCl_3$), was subjected to hydrogenolysis, giving the alcohol (**14**), $[\alpha]_D^{25}$ -11.5° (c 1.48, $CHCl_3$). Since direct transformation of **14** to **2** by oxidative cleavage of the 1,2-amido alcohol with sodium periodate in the presence of sodium acetate turned out to be fruitless, the following two step procedure was examined. Thus, oxidation of **14** with chromium trioxide gave the ketone (**15**), mp 71-74 °C, $[\alpha]_D^{25}$ -14.3° (c 0.57, $CHCl_3$). On treatment with m-chloroperbenzoic acid (MCPBA), **15** cleanly produced **2**, mp 108-109 °C, $[\alpha]_D^{25}$ +47.8° (c 0.56, $CHCl_3$) [lit.,[2b] mp 101-103 °C, $[\alpha]_D^{25}$ +47.9° (c 1.00, $CHCl_3$); lit.,[5a] mp 104-106 °C, $[\alpha]_D^{25}$ +48.8° (c 0.41, $CHCl_3$); lit.,[5d] mp 107-108 °C, $[\alpha]_D^{20}$ +50° (c 0.5, $CHCl_3$)]. Spectral data (IR, ^{1}H NMR, and MS) of **2**[15] were identical with those reported.[2b,5e]

As disclosed above, we have succeeded in exploring the novel synthetic route to **2** by featuring the addition of diketene to chiral imine as a key stereoselective reaction. Taking into account high stereoselectivity observed for the β-lactam formation and use of commercially available inexpensive (S)-ethyl lactate as a starting material, the overall process may hold promise as one of the most practical methods for preparing **2**.

Acknowledgement: The authors are indebted to Dr. M. Sunagawa, Research Laboratories, Research and Development Division, Sumitomo Pharmaceuticals Co. Ltd., for stimulating discussions and generous supply of di-p-anisylmethylamine.

References and Notes

1) W. Durckheimer, J. Blumback, R. Lattrell, and K. H. Scheunemann, Angew. Chem. Int. Ed. Engl., **24**, 180 (1985); T. Kametani, K. Fukumoto, and M. Ihara, Heterocycles, **17**, 463 (1982); M. Shibuya, Yuki Gosei Kagaku Kyokai Shi, **41**, 62 (1983); T. Nakai and T.

Chiba, Farumashia, **22**, 612 (1986).

2) a) P. J. Reider and E. J. J. Grabowski, Tetrahedron Lett., **23**, 2293 (1982); b) M. Shiozaki, N. Ishida, H. Maruyama, and T. Hiraoka, Tetrahedron, **39**, 2399 (1983); c) H. Maruyama, M. Shiozaki, and T. Hiraoka, Bull. Chem. Soc. Jpn., **58**, 3264 (1985); d) K. Fujimoto, Y. Iwano, and K. Hirai, Bull. Chem. Soc. Jpn., **59**, 1887 (1986); e) Idem., ibid., **59**, 1363 (1986); f) T. Miyadera, Y. Sugiura, T. Hashimoto, T. Tanaka, K. Iino, T. Shibata and S. Sugawara, J. Antibiotis, **36**, 1034 (1983); g) Y. Ueda, G. Roberge, and V. Vinet, Can. J. Chem., **62**, 2936 (1984); h) A. Yoshida, Y. Tajima, N. Takeda, and S. Oida, Tetrahedron Lett., **25**, 2793 (1984).

3) a) T. Shibata, K. Iino, T. Tanaka, T. Hashimoto, Y. Kameyama, and Y. Sugimura, Tetrahedron Lett., **26**, 4739 (1985); b) H. Fliri and C.-P. Mak, J. Org. Chem., **50**, 3438 (1985); c) T. Chiba, M. Nagatsuma, and T. Nakai, Chem. Lett., **1985**, 1343.

4) D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, Heterocycles, **21**, 29 (1984).

5) a) A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, Chem. Pham. Bull., **29**, 2899 (1981); b) T. Chiba and T. Nakai, Chem. Lett., **1985**, 651; c) Idem., Tetrahedron Lett., **26**, 4647 (1985); d) T. Ohashi, K. Suga, I. Sada, T. Miyama, and K. Watanabe, Japan Kokai Tokkyo Koho JP 61-18791 (1986); e) W. J. Leanza, F. DiNinno, D. A. Muthard, R. R. Wilkening, K. J. Wildonger, R. W. Ratcliffe, and B. G. Christensen, Tetrahedron, **39**, 2505 (1983).

6) M. Sato, H. Ogasawara, E. Yoshimizu, and T. Kato, Chem. Pham. Bull., **31**, 1902 (1983).

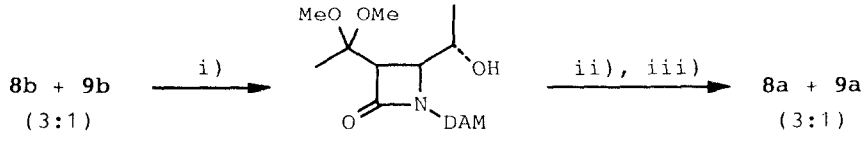
7) M. Sunagawa, K. Goda, M. Enomoto, and A. Sasaki, Japan Kokai Tokkyo Koho JP 59-70663 (1984) and 59-70664 (1984).

8) Recently, [2+2] cycloaddition reactions of ketene derivatives to chiral aliphatic imines were reported: A. K. Bose, U. R. Hegde, D. R. Wagle, S. S. Bari, and M. S. Manhas, J. Chem. Soc. Chem. Commun., **1986**, 161; C. Hubschwerlen and G. Schmid, Helv. Chim. Acta, **66**, 2206 (1983).

9) Byproducts of this addition reaction were N-(di-p-anisylmethyl)acetoacetamide (<20%) and dehydroacetic acid. The latter acid could be easily removed by extracting the reaction mixture with 1N-NaOH.

10) The observed stereochemistry can not be rationalized since it is quite ambiguous whether the true reactant is diketene, acetylketene, or 1-(acetoacetyl)imidazole, and the β-lactam formation is concerted, stepwise, or the mixture of both processes.

11) The stereochemistries of **8b** and **9b** were determined by transforming the mixture into **8a** and **9a** along the following reaction scheme.



i) $HC(OMe)_3$-Camphorsulfonic acid (cat.) in MeOH, rt, 10 min, ii) NaH-BnBr in THF, rt, 1 day, iii) 0.5N-HCl, rt

12) F. A. Bouffard and B. G. Christensen, J. Org. Chem., **46**, 2208 (1981).

13) Y. Ito, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., **26**, 4643 (1985).

14) G. Guanti, L. Banfi, E. Narisano, C. Scolastico, and E. Bosone, Synthesis, **1985**, 609.

15) Satisfactory analytical data were obtained for this compound. Found: C, 54.45; H, 8.88; N, 4.80%. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87%.

(Received in Japan 7 August 1986; accepted 20 September 1986)