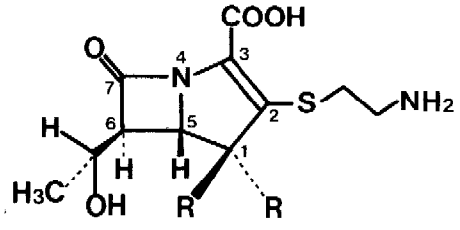
Tetrahedron Letters Vol. 21, pp 4009 - 4012 0040-4039/80/1008-4009$02.00/0

SYNTHESIS OF A 1,1-DIMETHYLCARBAPEN-2-EM DERIVATIVE VIA AN ALDOL-TYPE CYCLIZATION

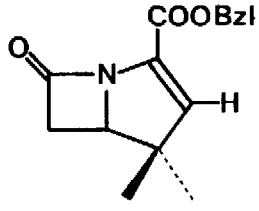
Masayuki Shibuya* and Seiju Kubota
Faculty of Pharmaceutical Sciences, University of Tokushima,
Shomachi, Tokushima, Japan

Summary: The synthesis of 1,1-dimethylcarbapen-2-em derivative 3 is described. The key step in the synthesis is an intramolecular aldol-type condensation reaction.

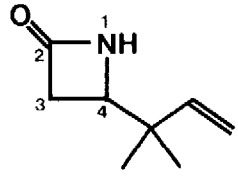
Since the discovery of thienamycin (1),[1] a potent and broad spectrum β-lactam antibiotic, much effort has been directed towards the synthesis of compounds with a carbapen-2-em ring system. Although a number of such compounds have been synthesized,[2] 1,1-disubstituted carbapen-2-em compounds, such as 2, are unknown. Here we describe the first synthesis of 1,1-dimethylcarbapen-2-em derivative 3 and related compounds. The key step in the synthesis is an intramolecular aldol-type condensation reaction.



1 R = H
2 R = CH_3



3



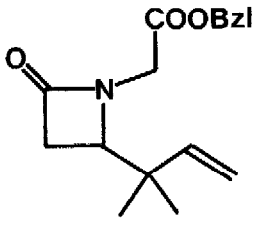
4

The azetidin-2-one 4, which is now readily available through our recent work,[3] seemed to be the most suitable starting material for 3. Reaction of 4 with benzyl bromoacetate[4] [$LiN(TMS)_2$, THF, -78°] provided ester 5[5] (96%), which was oxidized [(i) O_3, MeOH, -20°, (ii) Me_2S, -20° to rt] to aldehyde 6 (82%). No aldol-type ring closure to produce a carbapenam ring system has been reported in the literature, presumably because the reaction would involve competing enolization of the aldehyde group and high strain of the product. Compound 6, having an unenolizable aldehyde group, is suitable as a material to elucidate the problem. Base treatment [$LiN(TMS)_2$, THF, -78°] of 6 followed by quenching with *p*-toluenesulfonic acid gave carbapenam 7[6] (52%). Treatment of the reaction mixture with chlorotrimethylsilane or methanesulfonyl chloride before quenching gave 10 (78%) and 11 (53%),[7] respectively. Similarly, keto ester 8, which was obtained from 6 [(i) C_6H_5-MgBr in ether, CH_2Cl_2, -78° to rt, (ii) aq. NH_4Cl, (iii) Jones reagent, 0°] in 65 % yield, was cyclized in the same manner to carbapenam 9 (41%).[8] Each reaction gave a single isomer and the

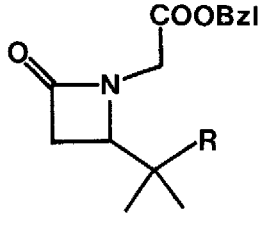
relative stereochemistry[6] of the products was substantiated by the NMR Nuclear Overhauser Effect (N. O. E.) in compounds 7 and 10 (Table 1). The low-field methyl signals in the NMR spectra of 7 and 10 were assigned to the C-1β-methyl protons, since irradiation of the low-field methyl peaks resulted in 14 % increase for C-5H in both compounds. The data in Table 1 also show proximity of the C-1α-methyl protons (high-field) to C-2H, C-3H, and C-6Hα and that both C-2H and C-3H are *anti* to C-5H (*i. e.* 2S*, 3R*, and 5S*). Our stereochemical results are explicable in terms of a chelated transition state[9] depicted in structure 12, which is assumed to be more favorable than other transition states, *e. g.* 13. The stereochemistry of 9 was tentatively assigned on the basis of the above findings and discussion.

Dehydromesylation of 11 (3,3,6,9,9-pentamethyl-2,10-diaza-bicyclo-[4.4.0]-1-decene,[10] CH_2Cl_2, rt) provided carbapenem 3 (82%)[11] which was stable towards silica. Dehydration of 9 to the carbapenem system was found to be surprisingly difficult: attempts to dehydrate 9 with thionyl chloride, methanesulfonyl chloride, or trifluoromethanesulfonic anhydride under various conditions were unsuccessful.

Biological tests indicated that 3 was inactive against gram-negative and gram-positive organisms at a level of 50 μg/ml.

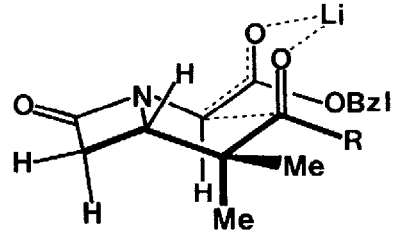


5

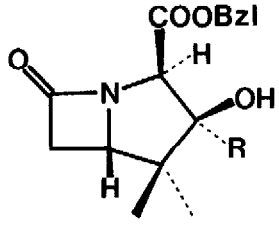


6 R = CHO

8 R = COC_6H_5

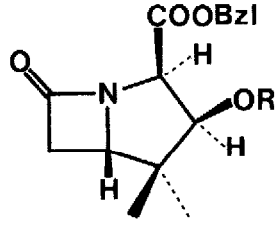


12



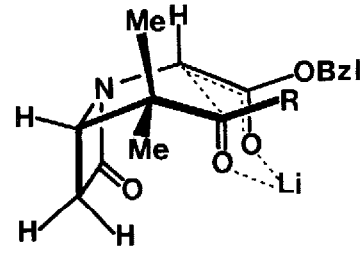
7 R = H

9 R = C_6H_5



10 R = $SiMe_3$

11 R = Ms



13

Table 1 Nuclear Overhauser Effects (N.O.E.) in Compounds 7 and 10

Compound	Protons irradiated (δ, ppm)	Intensity increase, % (±2)[a]				
		C-2H[b]	C-3H[b]	C-5H	C-6Hα[c]	C-6Hβ[c]
7	Low-field methyl (1.16)	0	0	14	0	0
	High-field methyl (0.84)	8	10	0	11	0
10	Low-field methyl (1.11)	0	0	14	0	0
	High-field methyl (0.86)	8	10	0	11	0

(a) All N.O.E. experiments were carried out on argon-sparged solutions (sample concentrations, 12 % w/v) with TMS as an internal lock in $CDCl_3$ using a JEOL PS-100 instrument.

(b) Assignment of C-2H for compound 7 is based on the broadening of the signal due to coupling with a hydroxy proton. C-2H and C-3H of compound 10 were tentatively assigned on the basis of the similarities of their chemical shifts to those of 7.

(c) Assignments of C-6α (*trans*) and C-6β (*cis*) protons are based on the coupling constants between the protons at C-5 and C-6, *i. e.* 2 Hz (C-6Hα) and 5 Hz (C-6Hβ). The reported values for the carbapenam systems[2a,g] are in accord with the above data.

PHYSICAL DATA

5 : ν ($CHCl_3$) 1755, 1740, and 1640 cm^{-1}; δ ($CDCl_3$) 0.97 (s, 3, CH_3), 1.00 (s, 3, CH_3), 2.64 (dd, 1, J = 3 and 15, H3), 2.88 (dd, 1, J = 5 and 15, H3), 3.70 (d, 1, J = 18, NCH_2), 3.73 (dd, 1, J = 3 and 5, H4), 4.28 (d, 1, J = 18, NCH_2), 4.84-5.92 (m, 3, $CH=CH_2$), 5.12 (s, 2, CO_2CH_2), and 7.32 (s, 5, C_6H_5). 6 : mp 59-60°; ν ($CHCl_3$) 1755, 1745, and 1725 cm^{-1}; δ ($CDCl_3$) 1.07 (s, 3, CH_3) 1.12 (s, 3, CH_3), 2.72 (dd, 1, J = 3 and 15, H3), 3.03 (dd, 1, J = 5 and 15, H3), 3.68 (d, 1, J = 18, NCH_2), 4.08 (dd, 1, J = 3 and 5, H4), 4.24 (d, 1, J = 18, NCH_2), 5.13 (s, 2, CO_2CH_2), 7.34 (s, 5, C_6H_5), and 9.44 (s, 1, CHO). 7 : mp 149-150°; ν ($CHCl_3$) 1760 and 1735 (sh) cm^{-1}; δ ($CDCl_3$) 0.84 (s, 3, CH_3), 1.16 (s, 3, CH_3), 2.66 (dd, 1, J = 2 and 15.5, H6), 3.00 (br, 1, OH), 3.05 (dd, 1, J = 5 and 15.5, H6), 3.75 (dd, 1, J = 2 and 5, H5), 4.21 (br d, 1, J = 4.5, H2), 4.48 (d, 1, J = 4.5, H3), 5.16 (s, 2, CO_2CH_2), and 7.32 (s, 5, C_6H_5). 8 : ν ($CHCl_3$) 1750 and 1670 cm^{-1} δ ($CDCl_3$) 1.34 (s, 3, CH_3), 1.41 (s, 3, CH_3), 2.72 (dd, 1, J = 3 and 15, H3), 3.04 (dd, 1, J = 5 and 15, H3), 3.76 (d, 1, J = 18, NCH_2), 4.31 (d, 1, J = 18, NCH_2), 4.41 (dd, 1, J = 3 and 5, H4), 5.14 (s, 2, CO_2CH_2), 7.20-7.80 (m, 5, C_6H_5), and 7.31 (s, 5, C_6H_5). 9 : mp 195-196°; ν ($CHCl_3$) 1760 and 1735 (sh) cm^{-1}; δ ($CDCl_3$) 0.60 (s, 3, CH_3), 1.04 (s, 3, CH_3), 2.72 (dd, 1, J = 2 and 16, H6), 3.13 (dd, 1, J = 5 and 16, H6), 3.21 (s, 1, OH), 4.02 (dd, 1, J = 2 and 5, H5), 5.00 (d, 1, J = 12.5, CO_2CH_2), 5.08 (s, 1, H3), 5.15 (d, 1, J = 12.5, CO_2CH_2), and 6.80-7.60 (m, 10, $2C_6H_5$). 10 : mp 103-104°; ν ($CHCl_3$) 1755 and 1735 (sh) cm^{-1}; δ ($CDCl_3$) 0.10 (s, 9, $SiMe_3$), 0.86 (s, 3, CH_3), 1.11 (s, 3, CH_3), 2.66 (dd, 1, J = 2 and 15.5, H6), 3.06 (dd, 1, J = 5 and 15.5, H6), 3.76 (dd, 1, J = 2 and 5, H5), 4.30 (d, 1, J = 4, H2), 4.47 (d, 1, J = 4, H3), 5.00 (d, 1, J = 12.5, CO_2CH_2), 5.28 (d, 1, J = 12.5, CO_2CH_2), and 7.34 (s, 5, C_6H_5). 11 : ν ($CHCl_3$) 1755 and 1735 (sh) cm^{-1}; δ ($CDCl_3$) 0.97 (s, 3, CH_3), 1.28 (s, 3, CH_3), 2.70 (s, 3, Ms), 2.76 (dd, 1, J = 2 and 16,

H6), 3.16 (dd, 1, J = 5 and 16, H6), 3.78 (dd, 1, J = 2 and 5, H5), 4.65 (d, 1, J = 4.5, H3), 5.07 (d, 1, J = 12, CO_2CH_2), 5.18 (d, 1, J = 4.5, H2), 5.28 (d, 1, J = 12, CO_2CH_2), and 7.36 (s, 5, C_6H_5). 3 : ν ($CHCl_3$) 1778, 1723, and 1610 cm^{-1}; λ (EtOH) 270 nm (ε = 4680); δ ($CDCl_3$) 1.13 (s, 3, CH_3), 1.31 (s, 3, CH_3), 2.99 (dd, 1, J = 3 and 16.5, H6), 3.27 (dd, 1, J = 5.5 and 16.5, H6), 3.84 (dd, 1, J = 3 and 5.5, H5), 5.25 (s, 2, CO_2CH_2), 6.32 (s, 1, H2), and 7.20-7.48 (m, 5, C_6H_5).

REFERENCES AND NOTES

1. G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Amer. Chem. Soc.*, 100, 6491 (1978).
2. (a) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Amer. Chem. Soc.*, 100, 313 (1978); F. A. Bouffard, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 45, 1130 (1980); S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 45, 1135 (1980); S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 45, 1142 (1980); (b) A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. C. S. Chem. Comm.*, 236 (1979); (c) R. J. Ponsford, P. M. Roberts, and R. Southgate, *J. C. S. Chem. Comm.*, 847 (1979); (d) H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Letters*, 3867 (1979); (e) T. Kametani, Shyh-Pyng Huang, and M. Ihara, *Heterocycles*, 12, 1189 (1979); T. Kametani, Shyh-Pyng Huang, S. Yokohama, Y. Suzuki, and M. Ihara, *J. Amer. Chem. Soc.*, 102, 2060 (1980); (f) J. H. Bateson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. C. S. Chem. Comm.*, 185 (1980); (g) R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Letters*, 21, 31 (1980); (h) L. Cama and B. G. Christensen, *Tetrahedron Letters*, 21, 2013 (1980); (i) A. J. G. Baxter, R. J. Ponsford, and R. Southgate, *J. C. S. Chem. Comm.*, 429 (1980).
3. M. Shibuya and S. Kubota, *Heterocycles*, 14, 601 (1980).
4. J. C. Bradley and G. Büchi, *J. Org. Chem.*, 41, 699 (1976).
5. Satisfactory microanalyses for crystalline compounds and accurate high resolution mass data for oily compounds were obtained.
6. The new substances described are *dl*-mixtures, but the enantiomer related to thienamycin is depicted for convenience.
7. Mesylate 11 could also be obtained from 7 (MsCl, NEt_3, CH_2Cl_2, -78° to rt, 65 %).
8. Unreacted oily keto ester 8 (53%) could be separated from crystalline carbapenam 9 by simple recrystallization ($CHCl_3$ and i-Pr_2O) of the product.
9. Recently kinetic stereoselection in aldol condensation of the acyclic system has been extensively investigated, see P. A. Bartlett, *Tetrahedron*, 36, 2 (1980).
10. F. Heinzer, M. Soukup, and A. Eschenmoser, *Helv. Chim. Acta*, 61, 2851 (1978).
11. When 1,5-diazabicyclo-[5.4.0]-undec-5-ene (DBU) was used as a base, the yield was only 33 %.

(Received in Japan 12 July 1980)