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SYNTHESIS OF 1,1-DIMETHYLCARBA-2-PENEM DERIVATIVES VIA A DIECKMANN-TYPE CYCLIZATION

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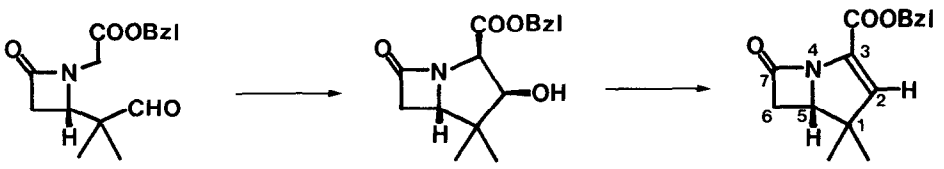
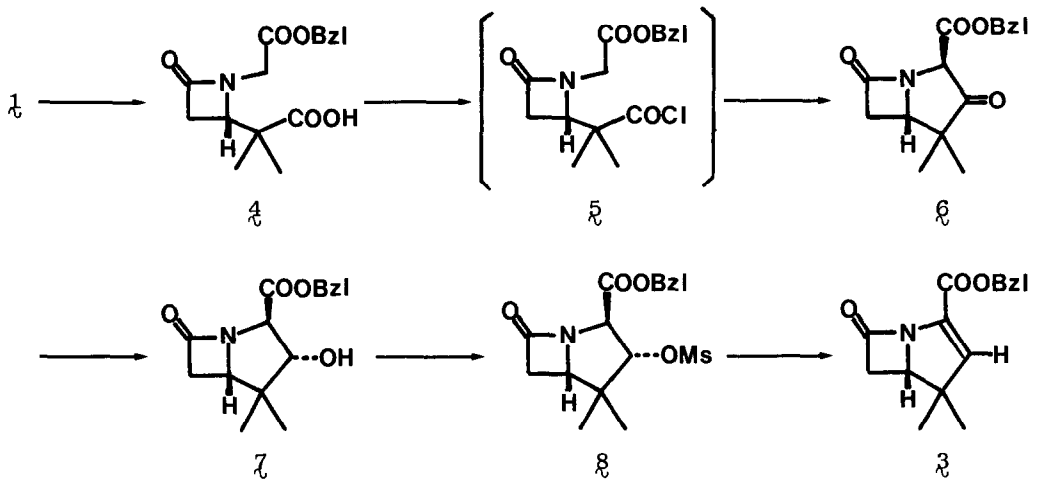
Summary: The synthesis of 1,1-dimethylcarba-2-penem derivatives *via* a Dieckmann-type cyclization and the use of a new method for removing the benzyl protecting group are reported.

The recent discoveries of thienamycin[1] and related antibiotics have led to interest in the synthesis of compounds with a carba-2-penem ring system. The construction of the five membered ring attached to the azetidinone ring is a major problem in the synthesis of the carbapenem derivatives and has attracted considerable attention.[2] Recently, we have applied an aldol-type condensation reaction to the synthesis of 1,1-dimethylcarba-2-penem derivative 3 and related systems.[3] Here we report a novel method for preparation of 1,1-dimethylcarbapenam-2-one ring system by a Dieckmann-type condensation reaction and its application to the synthesis of some 1,1-dimethylcarba-2-penem derivatives.[4,5]

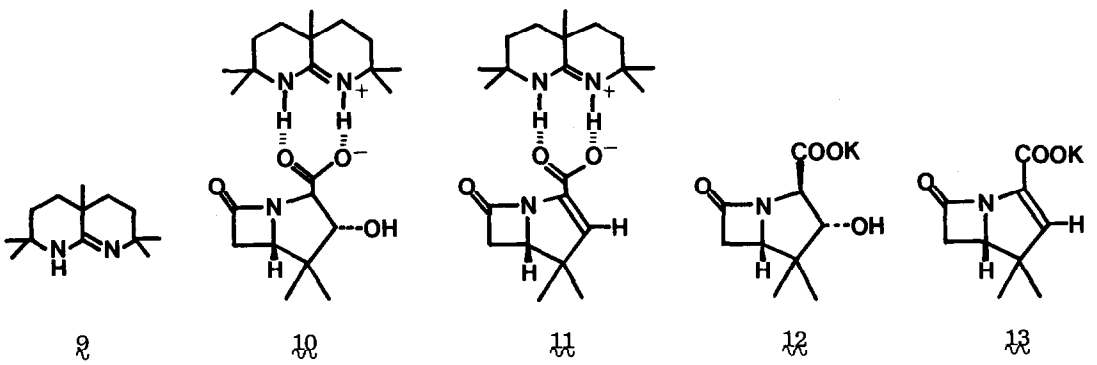


1 2 3

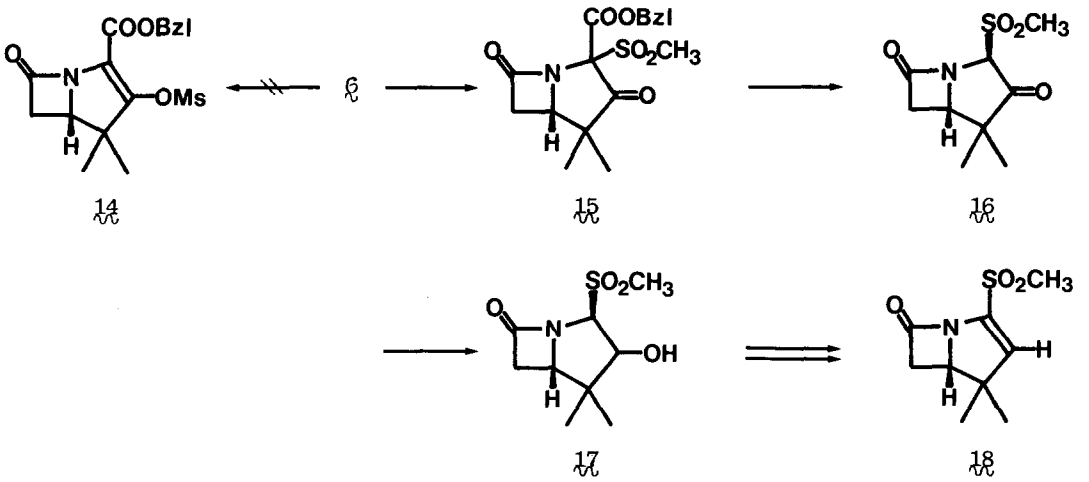
The carboxylic acid 4 was prepared from the corresponding aldehyde 1[3] by oxidation with Jones' reagent (0°) in 92% yield. The acid 4 was converted to the chloride (oxalyl chloride, pyridine, benzene, 0° to rt), and then the product without purification on treatment with base [2 equiv $LiN(TMS)_2$, THF, -78°, 15 min] cyclized to give a single isomer of the bicyclic keto ester 6.[6] After chromatography, overall yield of 6 based on acid 4 was found to be of order of 88∿96% (1∿10 mmol scale). Reduction ($NaBH_4$, THF, EtOH, -60° to -50°) of the keto ester 6 afforded a single alcohol 7 (98%), which was considered to be C-2 isomer of the hydroxy ester 2[3] by comparison of their physical data. Confirmation of the *trans* structure in 7 was obtained by NMR Nuclear Overhauser Effect (NOE) in a similar manner to that reported previously for compound 2 and its derivative.[3] (Table 1) The alcohol 7 was found to be more stable than the isomeric alcohol 2. In the latter case, retroaldol-type ring opening takes place in part, during the following mesylation reaction. Mesylation (MsCl, N,N-diisopropylethylamine, 4-dimethylaminopyridine, CH_2Cl_2, -78° to rt) of the hydroxy ester 7 followed by dehydromesylation[7] (3,3,6,9,9-pentamethyl-2,10-diaza-bicyclo-[4.4.0]-1-decene 9,[8] CH_2Cl_2, rt) provided the carbapenem 3 (91% from 7).



One of the major difficulties encountered in the synthesis of carbapenams or carbapenems was deprotection of the ester moiety of intermediates, because of the instability of the products.[9] We have found a new promising method for the deprotection which was applicable for a non-activated benzyl protecting group. Catalytic hydrogenolysis of the benzyl esters 7 and 3 (10% Pd-C, THF, rt, 1h) in the presence of 1 equiv of the amidine 9[8] afforded the salts 10 (95%) and 11 (71%), respectively. The amidine salts were freely soluble in dichloromethane or water, and were converted easily into the corresponding potassium salts 12 and 13 in quantitative yields when treated with 1 equiv of potassium 2-ethylhexanoate in tetrahydrofuran. Compounds 10~13 were found rather stable in aqueous solution at room temperature and be lyophilized without decomposition.



To obtain the enol mesylate 14, the keto ester 6 was treated with methanesulfonic anhydride (N,N-diisopropylethylamine, 4-dimethylaminopyridine, CH_2Cl_2, rt), but the product was unexpected C-3 sulfonyl compound 15 (81%). The product 15 was a single isomer, but no physical evidence for its stereochemistry was available. Simultaneous deprotection and decarboxylation (10% Pd-C, H_2, AcOEt, rt) of 15 gave the keto sulfone 16 (98%).[10] Sodium borohydride reduction (THF, EtOH, -60°) of 16 yielded a stereoisomeric mixture of two alcohols 17 (93%) in a ratio of 5 : 1, which were separated by chromatography on silica gel. It was found difficult to determine the stereochemistry of these alcohols from their physical data. Mesylation and dehydromesylation of major isomer of 17 was carried out in a similar manner as for the



14 6 15 16 17 18

hydroxyester 7, afforded the conjugated sulfone 18 (66%) which was a new type of carbapenem derivative.

In vitro antibacterial tests revealed that 11 and 13 exhibited considerable activities against a number of Gram positive and Gram negative organisms.

Table 1 Nuclear Overhauser Effects (NOE) in Compound 7

Protons irradiated (δ, ppm)	Intensity increase, % (±2)[a]				
	C-2H[b]	C-3H[b]	C-5H	C-6Hα[c]	C-6Hβ[c]
Low-field methyl (1.10)	17	0	12	0	0
High-field methyl (0.86)	0	12	0	10	0

(a) NOE experiment was carried out on argon-sparged solution (sample concentration, 12% w/v) with TMS as an internal lock in $CDCl_3$ using JEOL PS-100 instrument.

(b) Assignment of C-2H is based on the coupling of the signal with a hydroxy proton.

(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).[3]

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2. T. Aida, R. Legault, D. Dugat, and T. Durst, *Tetrahedron Letters*, 4993 (1979); R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Letters*, 21, 31 (1980); B. Venugopalan, A. B. Hamlet, and T. Durst, *Tetrahedron Letters*, 22, 191 (1981); K. Hirai, K. Fujimoto, Y. Iwano, T. Hiraoka, T. Hara, and C. Tamura, *Tetrahedron Letters*, 22, 1021 (1981).
3. M. Shibuya and S. Kubota, *Tetrahedron Letters*, 21, 4009 (1980).
4. Satisfactory microanalyses for crystalline compounds and accurate high resolution mass data for oily compounds were obtained. All new compounds were homogeneous by TLC and gave NMR,

IR, and mass spectra consistent with the assigned structure. The substances described are *dl*-mixtures, but the enantiomer related to thienamycin is depicted for convenience.

5. Selected data, **4** : mp 95∿96°; ν ($CHCl_3$) 1760 and 1745 cm^{-1}. **6** : ν ($CHCl_3$) 1775(sh), 1768, and 1745 cm^{-1}; δ ($CDCl_3$) 1.06 (3H, s), 1.24 (3H, s), 3.00 (1H, dd, J = 2 and 16), 3.46 (1H, dd, J = 5 and 16), 3.84 (1H, dd, J = 2 and 5), 4.76 (1H, s), 5.21 (2H, s), and 7.37 (5H, s). **7** : mp 83∿84°; ν ($CHCl_3$) 1763 and 1735(sh) cm^{-1}; δ ($CDCl_3$) 0.86 (3H, s), 1.10 (3H, s), 2.80 (1H, dd, J = 2 and 16), 3.08 (1H, d, J = 4.5, OH), 3.09 (1H, dd, J = 5 and 16), 3.42 (1H, dd, J = 2 and 5), 4.04 (1H, d, J = 7.5), 4.16 (1H, dd, J = 4.5 and 7.5), 5.17 (2H, s), and 7.32 (5H, s). **8** : mp 113∿114°; ν ($CHCl_3$) 1770 and 1750(sh) cm^{-1}. **10** : mp 186∿188°; ν ($CHCl_3$) 1755 and 1660 cm^{-1}; δ ($CDCl_3$) 0.88 (3H, s), 1.16 (3H, s), 1.30 (9H, s), 1.37 (6H, s), 1.40∿2.25 (8H, m), 2.72 (1H, dd, J = 2.5 and 16), 3.04 (1H, dd, J = 5 and 16), 3.41 (1H, dd, J = 2.5 and 5), 3.76 (1H, d, J = 9), 3.97 (1H, d, J = 9), and 11.28 (2H, br. s). **11** : mp 168∿170°; ν ($CHCl_3$) 1767 and 1660 cm^{-1}; δ ($CDCl_3$) 1.10 (3H, s), 1.25 (3H, s), 1.28 (3H, s), 1.32 (6H, s), 1.40 (6H, s), 1.40∿2.30 (8H, m), 2.90 (1H, dd, J = 3 and 16), 3.13 (1H, dd, J = 5 and 16), 3.76 (1H, dd, J = 3 and 5), 5.96 (1H, s), and 11.56 (2H, br. s); λ (EtOH) 260 nm (ε = 4870). **12** : mp 245∿247°(dec); ν (KBr) 3220, 1753, and 1615 cm^{-1}; δ (D_2O) 0.97 (3H, s), 1.25 (3H, s), 3.00 (1H, dd, J = 2 and 16), 3.28 (1H, dd, J = 5 and 16), 3.64 (1H, dd, J = 2 and 5), 3.90 (1H, d, J = 8), and 4.20 (1H, d, J = 8). **13** : mp 230∿240°(dec); ν (KBr) 1753 and 1590 cm^{-1}; δ (D_2O) 1.20 (3H, s), 1.40 (3H, s), 3.12 (1H, dd, J = 3 and 17), 3.38 (1H, dd, J = 5 and 17), 3.96 (1H, dd, J = 3 and 5), and 6.23 (1H, s); λ (H_2O) 260 nm (ε = 4850). **15** : mp 111∿112°; ν ($CHCl_3$) 1785, 1775 and 1750 cm^{-1}; δ ($CDCl_3$) 1.08 (3H, s), 1.31 (3H, s), 3.08 (1H, dd, J = 3 and 16), 3.20 (3H, s), 3.45 (1H, dd, J = 5 and 16), 4.01 (1H, dd, J = 3 and 5), 5.16 (1H, d, J = 12), 5.30 (1H, d, J = 12), and 7.33 (5H, s). **16** : mp 135∿136°; ν ($CHCl_3$) 1785 and 1772(sh) cm^{-1}. **17** (major isomer) : mp 158∿159°; ν ($CHCl_3$) 1778 cm^{-1}. **17** (minor isomer) : mp 164∿165°; ν ($CHCl_3$) 1778 cm^{-1}. **18** : ν ($CHCl_3$) 1788 and 1598 cm^{-1}; δ ($CDCl_3$) 1.20 (3H, s), 1.38 (3H, s), 3.08 (1H, dd, J = 3 and 17), 3.20 (3H, s), 3.36 (1H, dd, J = 5.5 and 17), 4.03 (1H, dd, J = 3 and 5.5), and 6.34 (1H, s).
6. The keto ester **6** is predictable to have the thermodynamically preferred *exo* carboxylate orientation as shown. The structure has been confirmed by preparing the same compound **6** from the hydroxyester **2**[3] (Jones' reagent, -10°).
7. The rate was found to be slower than that of dehydromesylation *via* the isomeric alcohol **2** because the reaction of **8** would involve the inversion at C-3 position, followed by a *trans* coplanar elimination of CH_3SO_3H.
8. The amidine **9** was synthesized first by Eschenmoser and has been shown to afford crystalline salts with a wide variety of acids. The resulting salts were shown to exhibit a good solubility in different organic solvents; F. Heinzer, M. Soukup, and A. Eschenmoser, *Helv. Chim. Acta*, 61, 2851 (1978).
9. See for example, L. D. Cama and B. G. Christensen, *J. Amer. Chem. Soc.*, 100, 8006 (1978); H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Letters*, 3867 (1979).
10. The stereochemical structure having the thermodynamically preferred orientation was tentatively assigned to **16**.

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