Tetrahedron Vol. 38, No. 17, pp. 2659 to 2665, 1982
Printed in Great Britain.

0040-4020/82/172659-07$03.00/0

SYNTHESIS OF 6-(1-HYDROXYETHYL)-1,1-DIMETHYL-1-CARBA-2-PENEM DERIVATIVES VIA DIECKMANN-TYPE CYCLIZATION

MASAYUKI SHIBUYA,* MASAHIKO KURETANI and SEIJU KUBOTA
Faculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

(*Received in Japan* 12 *December* 1981)

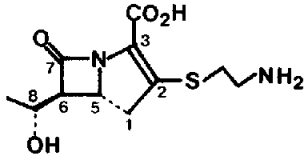
Abstract—Three diastereomers of 4 - (1,1 - dimethyl - 2 - propenyl) - 3 - hydroxyethyl - 2 - azetidinones **2**, **3**, and **11** were obtained by the reaction of acetaldehyde with the enolate of the silyl azetidinone **5** and dilithiated intermediate **10**: The trans isomers **2** and **3** were converted into 6 - (1 - hydroxyethyl) - 1,1 - dimethyl - 1 - carba - 2 - penems **19** and **20** *via* a Dieckmann-type cyclization.

Recently, much attention has been directed at the synthesis of thienamycin **1**[1] and its analogues, potent "non-classical" β-lactam antibiotics with broad-spectrum activities. The construction of a 5-membered ring attached to a 2-azetidinone is a major problem in the synthesis of carbapenem nucleus, the fundamental skeleton of thienamycin. Of the approaches described in the literature, a general ring closure process involves an intramolecular carben insertion[2] and an intramolecular Wittig reaction.[3]

Recently, we developed a new efficient synthesis of 1,1-dimethyl analogues of the 1-carbapenem skeleton (**VI**) *via* an intramolecular aldol-type reaction (**I**→**II**→**III**→**VI**)[4a,5a] and a Dieckmann-type cyclization (**IV**→**V**→**III**→**VI**)[4b,5b] (Scheme 1). Although some of the resultant 1,1-dimethyl-1-carbapenems showed considerable antibacterial activities, different functionalization in the molecule for the enhancement of potency is desirable.

In the thienamycin series, the C-6 hydroxyethyl side chain is considered to be the most important moiety for the antibacterial activity, since it has been indicated that addition of the side chain not only enhances the potency of the carbapenem nucleus considerably, but also increases the stability against β-lactamase.[6]

The present paper describes the preparation of three isomers of 3-(1-hydroxyethyl)-2-azetidinones (**2**, **3** and **11**) and the transformation of 3,4-trans isomers, **2** and **3**, into corresponding 1,1 - dimethyl - 6 - hydroxyethyl - 1 - carba - 2 - penems[7] by the methodology shown in Scheme 1.[8]

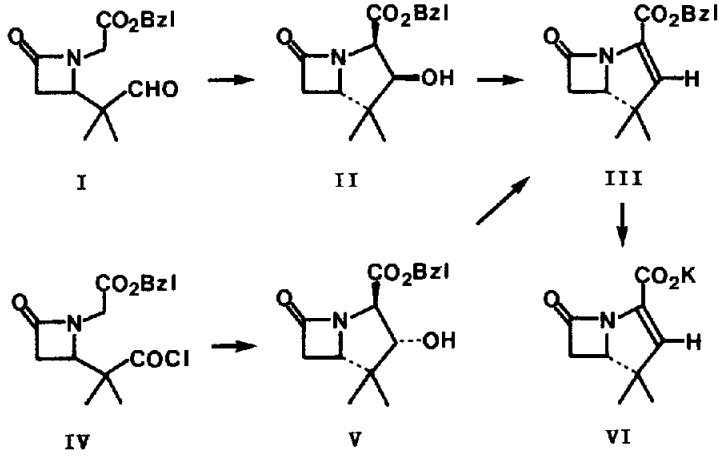


1

Fig. 1.

Synthesis of 3-(1-*hydroxyethyl*)-2-*azetidinones*

The starting N-protected azetidinone **5** was obtained by silylation with t-butylchlorodimethylsilane and triethylamine in dimethylformamide from the azetidinone **4**, which has been prepared recently by us.[9] The introduction of the hydroxyethyl side chain in a non-stereocontrolled manner *via* an aldol reaction was employed to obtain the stereoisomers of the carbapenem for structure-activity studies (Scheme 2). The synthetic utility of



Scheme 1.

mono- and dimetalated azetidinones had been demonstrated by Durst *et al.*[10] Analogously, metalation of the silylated azetidinone **5** with lithium diisopropylamide (LDA) at −78° followed by quenching with excess acetaldehyde gave a mixture of diastereomeric hydroxyethylated products. Simple separation by silica gel chromatography afforded trans isomers **6** (37% yield) and **7** (34% yield), and an inseparable mixture of cis isomer **8** (11% yield). The trans relationship between C_3–H and C_4–H in **6** and **7** is obvious from their smaller proton coupling constants, and NMR Nuclear Overhauser Effects (NOE) of bicyclic derivatives as will be described later.

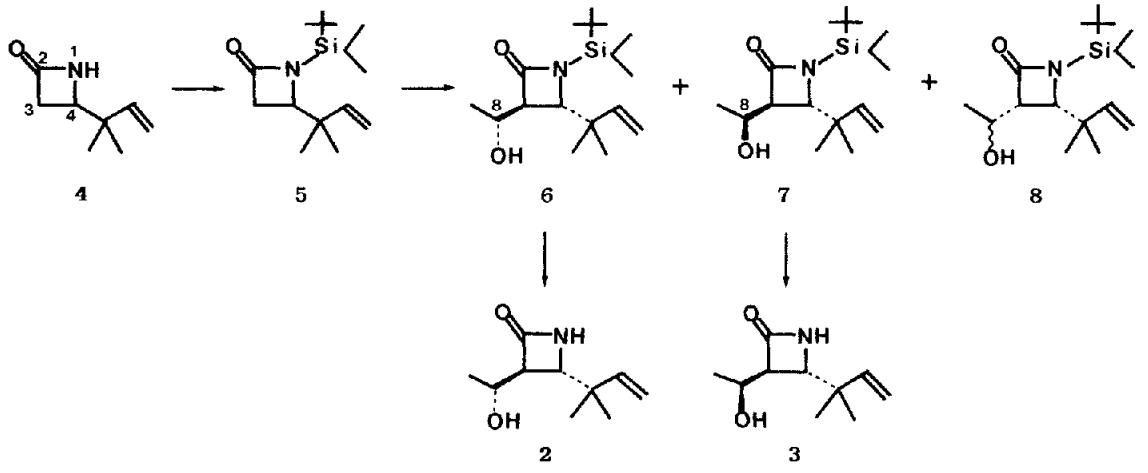
Evidence for the assignment of the side chain stereochemistry in **6** and **7** could be obtained from the results of the complex borohydride reduction of an acetylazetidinone **9** obtained from **6** and **7** (Scheme 3), on the basis of a recent study by Merck group[11] about the correlation between the reduction conditions of analogous acetylazetidinones and the 8R*/8S*[12] product ratio. Thus, the oxidation of 1:1 mixture of **6** and **7** (TFAA-DMSO/Et_3N, CH_2Cl_2, −60°)[13] gave trans acetylazetidinone **9**. The reduction of **9** with 2.4 equiv of K-Selectride in ether at 25° is expected to form the 8R* epimer exclusively *via* direct borohydride attack on a chelated reaction intermediate, and provided the carbinol **6** in 80% yield accompanied by another isomer **7** (1.6% yield, **6**/**7** = 98). On the other hand, reduction of **9** with 1.2 equiv of K-Selectride in ether in the presence of 18-crown-6, which prevents the internal metal ion complexation with the carbonyl groups, provided **6** and **7** in a ratio of 58:42. In conclusion, these results suggest that the 8R* epimer is assigned to **6** and 8S* epimer to **7**.

Deprotection of the carbinols **6** and **7** gave azetidinones **2** (8R*) and **3** (8S*), respectively.

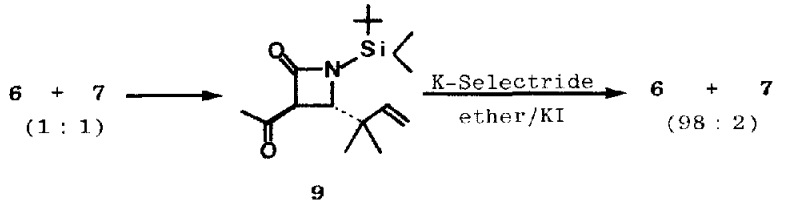
The alternative method for obtaining the hydroxyethylazetidinones was the aldol reaction of the dilithiated intermediate **10** which was obtained from **4** (Scheme 4). After acid treatment of the product to hydrolyze the partly formed N-hydroxyethylated products, the major diastereomers (trans, **2** + **3**, 1:1, 52% yield) and the two minor diastereomers (cis, 13% yield) were separated from the products by silica gel chromatography. The latter was purified by recrystallization to afford a single isomer of **11**.[14] The former was unable to separate at this stage, but after monosilylation of the mixture, it was separated by column chromatography on silica gel to give **6** and **7**.

Synthesis of 1,1 - *dimethyl* - 6 - (1 - *hydroxyethyl*) - 1 - *carba* - 2 - *penems*

The alkylation of azetidinones **2** and **3** with benzyl bromoacetate and lithium hexamethyldisilazide in tetrahydrofuran at −78° to 0° provided esters **12a** (69% yield) and **12b** (81% yield), respectively. The hydroxyl groups of **12a** and **12b** were protected with benzyloxycarbonyl group to give **13a** (83% yield) and **13b** (82% yield). Oxidative cleavage of the terminal double bonds of **13a** and **13b** by ozonolysis at −20° to −30° in methanol followed by oxidation with Jones reagent at 0° afforded the carboxylic acids **14a** (86% yield) and **14b** (88% yield), respectively. The carboxylic acids **14a** and **14b** were converted into the corresponding chlorides by oxalyl chloride and pyridine in dry benzene, and the chlorides were used without purification for the next step. The



Scheme 2.

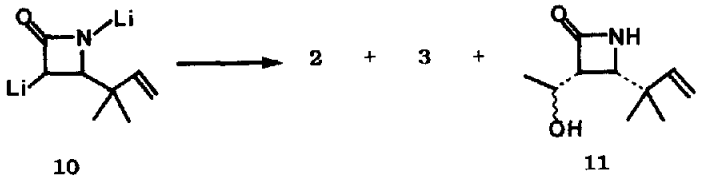


Scheme 3.

cyclization of the chlorides using 2 equiv of lithium hexamethyldisilazide in tetrahydrofuran at −78° provided 2-oxocarbapenams **15a** (83% overall yield) and **15b** (86% overall yield), respectively.

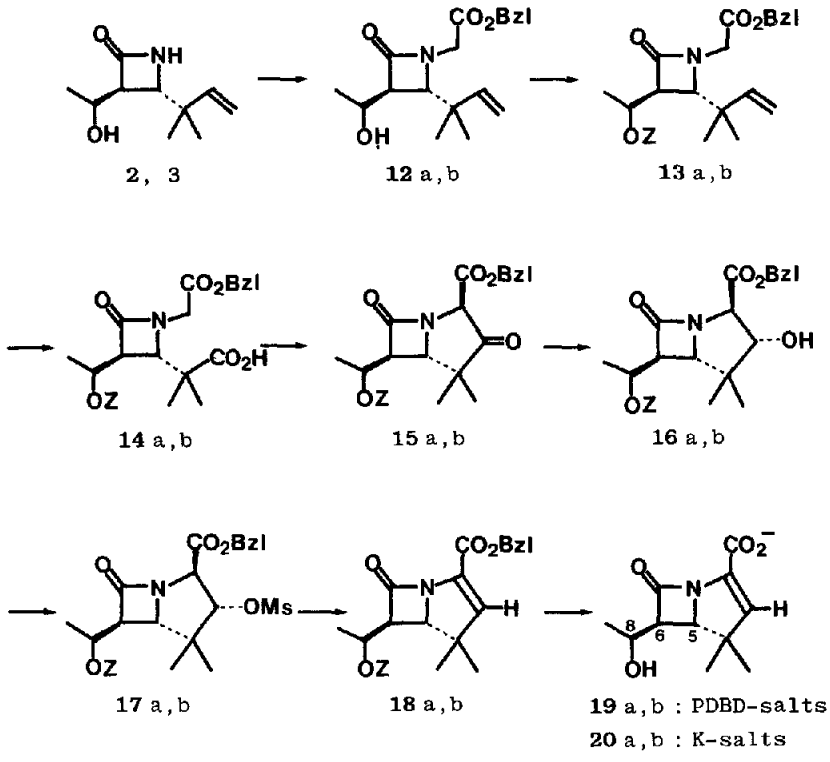
On the reduction of **15a** and **15b** with sodium borohydride in ethanol/tetrahydrofuran (1:1 v/v) at −60°, carbinols **16a** (88% yield) and **16b** (88% yield) were obtained stereoselectively. NMR spectra and tlc of the crude products did not show the presence of isomeric alcohol in each case. The relative stereochemistry at C-2, C-3 and C-5 of **16a** and **16b** was substantiated by NOE experiments as shown in Table 1 in a similar manner to that reported previously for the simple 1,1-dimethyl-1-carbapenams.[4] In addition, the trans relationship of the β-lactam hydrogens is obvious from these NOE data. Mesylation of **16a** and **16b** with methanesulfonic anhydride in dichloromethane at 0° using N,N-diisopropylethylamine and 4-dimethylaminopyridine as bases gave mesylates **17a** (96% yield) and **17b** (86% yield), respectively. Dehydromesylation of **17a** and **17b** by use of 3,3,6,9,9 - pentamethyl - 2,10 - diazabicyclo - [4.4.0] - 1 - decene (PDBD)[15] in dichloromethane at room temperature provided desired carbapenems **18a** (91% yield) and **18b** (94% yield), respectively. Deprotection of **18a** and **18b** was carried out by the similar procedure as we have reported previously for the synthesis of 1,1-dimethylcarbapenems[4b] and 2,2-dimethylcarbapenams.[16] Thus, hydrogenolysis of the carbapenems using 10% Pd-C in the presence of 1 equiv of PDBD under a current of hydrogen in dry tetrahydrofuran provided the respective amidine salts **19a** and **19b** in good yields after purification using silica gel column followed by recrystallization. Treatment of **19a** and **19b** with 1 equiv of potassium 2-ethylhexanoate in ether/tetrahydrofuran (1:1 v/v) gave the potassium salts **20a** and **20b** quantitatively.

In vitro antibacterial test revealed that **19** and **20** showed considerable activities against a number of Gram positive and Gram negative organisms, including Pseudomonas species.



10 11

Scheme 4.



2, 3 **12** a,b **13** a,b

14 a,b **15** a,b **16** a,b

17 a,b **18** a,b **19** a,b : PDBD-salts
20 a,b : K-salts

Z ≙ CO_2Bzl, a : 5SR,6SR,8RS
b : 5SR,6SR,8SR

Scheme 5.

Table 1. Nuclear Overhauser Effects (NOE) in compounds **16a** and **16b**

Compound	Protons irradiated (δ, ppm)	Intensity increase, %			
		C-2H	C-3H	C-5H	C-6H
16a	Low-field methyl (1.02)	12	∿2	12	4
	High-field methyl (0.86)	5	16	∿2	25
16b	Low-field methyl (1.02)	12	∿2	13	3
	High-field methyl (0.86)	6	16	∿2	21

All NOE experiments were carried out in argon-sparged solution (sample concentrations, 5 % w/v) with internal ^{2}H-lock in $CDCl_3$ using JEOL JNM-FX200 instrument at room temp. Measureing conditions: Flip angle, π/6; PD, 30 sec; IRMOD, homo gate decoupling; Spectro width, 2000 Hz, Data points, 16KW; Accumuration time, 8 times; Resonance frequency, 199.6 MHz; RF-intensity, 4.7T .

EXPERIMENTAL

IR spectra were obtained with a JASCO DS-701G spectrometer, NMR spectra were determined with a JEOL JMS-PS100 spectrometer using TMS as an internal reference. Mass spectra were recorded on a JEOL JMS-D 300 mass spectrometer generally at 20 ev using a direct insertion probe. A Hitachi Model 330 spectrophotometer was used for the UV absorption spectra. Mps were determined by the capillary method and are uncorrected.

All experiments were caried out under argon atmosphere unless otherwise specified. Usual work-up refers to addition of a reaction mixture to a mixture of excess ice and AcOEt, phase separation, re-extraction of the aqueous phase, washing of the combined organic layers with brine, drying the organic extracts over $MgSO_4$, filtration, and evaporation of the solvents under reduced pressure at 20–35°. For column chromatography, a 1:1 mixture of Merck 70–230 mesh Kieselgel 60 and Mallinckrodt 100 mesh silicic acid was employed.

1 - *t* - *Butyldimethylsilyl* - 4 - (1,1 - *dimethyl* - 2 - *propenyl*) - 2 - *azetidinone* (**5**). A soln of t-butylchlorodimethylsilane (2.472 g) in DMF (10 ml) was added dropwise to a stirred soln of azetidinone **4** (2.075 g) and Et_3N (2.5 ml) in DMF (10 ml) at 0°. The resulting soln was then stirred for 4 hr at room temp. The usual work-up gave a pale yellow oil which was purified by silica gel chromatography to provide 3.477 g (92% yield) of **5** as a colorless syrup. IR ν_{max} ($CHCl_3$) 1728 (C=O); NMR ($CDCl_3$) δ 0.22 and 0.24 (each 3H, s, $SiMe_2$), 0.97 (9H, s, t-Bu), 1.04 (6H, s, 2xMe), 2.64 (1H, dd, J = 3 and 15.5 Hz, C_3–H), 2.94 (1H, dd, J = 6 and 15.5 Hz, C_3–H), 3.43 (1H, dd, J = 3 and 6 Hz, C_4–H), and 4.88–6.00 (3H, m, $CH=CH_2$); MS *m/e* 253.1843. Calc. for $C_{14}H_{27}NOSi$: 253.1862 (M^+).

1 - *t* - *Butyldimethylsilyl* - 4 - (1,1 - *dimethyl* - 2 - *propenyl*) - 3 - (1 - *hydroxyethyl*) - 2 - *azetidinones* (**6**, **7** and **8**). A soln of **5** (4.194 g) in THF (40 ml) was added dropwise over a period of 5 min at −78° to a freshly prepared soln of LDA made from n-BuLi (11 ml of a 1.66 M soln in n-hexane, 1.1 equiv) and $(i\text{-}Pr)_2NH$ (2.009 g, 1.2 equiv) in THF (40 ml). The resulting enolate soln was kept at −78° for a period of 1 hr and then treated with neat CH_3CHO (2.78 ml, 3 equiv). The reaction was quenched in 10 min by the addition of sat NH_4Cl soln (30 ml). The usual work-up gave 5.2 g of a yellow oil. Single chromatography on silica gel (300 g, eluting with 6–9% acetone/$CHCl_3$) provided 0.541 g (11% yield) of diastereomeric cis carbinols **8**, 1.662 g (34% yield) of trans 8S* carbinol **7**, and 1.798 g (37% yield) of trans 8R* carbinol **6** as colorless oils.

Data for **8** which eluted first: NMR (major isomer) ($CDCl_3$) δ 0.22 and 0.26 (each 3H, s, $SiMe_2$), 0.98 (9H, s, t-Bu), 1.13 (6H, s, 2xMe), 1.20 (3H, d, J = 6 Hz, $CHCH_3$), 3.22 (1H, t, J = 5 Hz, C_3–H), 3.66 (1H, d, J = 5 Hz, C_4–H), 4.34 (1H, m, $CHCH_3$), and 4.92–6.12 (3H, m, $CH=CH_2$).

Data for **7** which eluted second: IR ν_{max} ($CHCl_3$) 3500 (OH) and 1723 (C=O); NMR ($CDCl_3$) δ 0.22 and 0.24 (each 3H, s, $SiMe_2$), 0.97 (9H, s, t-Bu), 1.05 (6H, s, 3xMe), 1.28 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.45 (1H, d, J = 4 Hz, OH), 2.78 (1H, dd, J = 2.5 and 6.5 Hz, C_3–H), 3.24 (1H, d, J = 2.5 Hz, C_4–H), 3.92 (1H, m, $CHCH_3$), and 4.92–6.00 (3H, m, $CH=CH_2$); MS *m/e* 298.2183. Calc. for $C_{16}H_{32}NO_2Si$: 298.2202 ($M^+ + H$).

Data for **6**: IR ν_{max} ($CHCl_3$) 3420 (OH) and 1727 (C=O); NMR ($CDCl_3$) δ 0.24 (6H, s, $SiMe_2$), 0.98 (9H, s, t-Bu), 1.06 (6H, s, 2xMe), 1.26 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.58 (1H, d, J = 5 Hz, OH), 2.82 (1H, dd, J = 2.5 and 5.5 Hz, C_3–H), 3.40 (1H, d, J = 2.5 Hz, C_4–H), 4.04 (1H, m, $CHCH_3$), and 4.90–6.04 (3H, m, $CH=CH_2$); MS *m/e* 298.2205. Calc. for $C_{16}H_{32}NO_2Si$: 298.2202 ($M^+ + H$).

trans - 1 - *t* - *Butyldimethylsilyl* - 4 - (1,1 - *dimethyl* - 2 - *propenyl*) - 3 - (1 - *oxoethyl*) - 2 - *azetidinone* (**9**). A soln of $(CF_3CO)_2O$ (1.35 ml) in CH_2Cl_2 (7 ml) was added dropwise with stirring over 10 min to a soln of DMSO (884 mg) in CH_2Cl_2 (7 ml) at −60°. After stirring for 10 min at the same temp, a soln of a 1 : 1 mixture of **6** and **7** (2.590 g) in CH_2Cl_2 (7 ml) is added dropwise over 10 min. After the mixture was stirred for 30 min at −60°, Et_3N (3.48 ml) was added. The mixture was allowed to warm up to room temp, and then usual work-up gave 2.58 g of an oil, which was purified by silica gel column to provide 2.295 g (89% yield) of **9** as a colorless oil. IR ν_{max} ($CHCl_3$) 1744 and 1712 (C=O); NMR ($CDCl_3$) δ 0.20 and 0.27 (each 3H, s, $SiMe_2$), 0.97 (9H, s, t-Bu), 1.06 (3H, s, 2xMe), 2.27 (3H, s, Ac), 3.88 (2H, s, C_3–H and C_4–H), and 4.92–6.02 (3H, m, $CH=CH_2$); MS *m/e* 295.1967. Calc. for $C_{16}H_{29}NO_2Si$: 295.1948 (M^+).

K-selectride reduction of **9**. *Method A.* A 0.5 M soln of K-Selectride (37.1 ml, 2.4 equiv) in THF and KI (1.411 g, 1.1 equiv) was added to a soln of acetylazetidinone **9** (2.285 g) in ether (50 ml) at 0°. The resulting soln was stirred for 3 hr at 25°, and then quenched by the addition of AcOH (1.4 g). The mixture was diluted with AcOEt (150 ml) and filtered through a filter paper. The filter cake was washed with additional EtOAc. The filtrate was evaporated to give crude mixture of carbinols which was separated by silica gel column to give 1.848 g (80% yield) of **6** and 0.037 g (1.6% yield) of **7**.

Method B. By the same procedure as above, but with addition of 18-crown-6 (248 mg, 1.1 equiv) in place of KI, crude diastereomeric carbinols were obtained from **9** (252 mg) and K-Selectride (2.05 ml, 1.2 equiv). Column chromatography on silica gel provided 96 mg (38% yield) of **6** and 69 mg (27% yield) of **7**.

trans - 4 - (1,1 - *Dimethyl* - 2 - *propenyl*) - 3 - [(1*R**) - 1 - *hydroxyethyl*] - 2 - *azetidinone* **2**. A mixture of **6** (1.785 g) and $(n\text{-}Bu)_4NF$ (1.726 g, 1.1 equiv) in THF (30 ml) was stirred for 30 min under ice cooling. After evaporation of the solvent, the residue was chromatographed on silica gel to give 1.063 g (97% yield) of **2** as a white solid. Recrystallization of **2** from 20% $i\text{-}Pr_2O/CHCl_3$ gave an analytical sample, m.p. 106–107°. IR ν_{max} ($CHCl_3$) 3410 (NH) and 1755 (C=O); NMR ($CDCl_3$) δ 1.04 (6H, s, 2xMe), 1.26 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.66 (1H, br, OH), 2.85 (1H, ddd, J = 1, 2 and 4.5 Hz, C_3–H), 3.48 (1H, d, J = 2 Hz, C_4–H), 4.14 (1H, m, $CHCH_3$), 4.92–6.00 (3H, m, $CH=CH_2$), and 6.34 (1H, br, NH). (Found: C, 65.42; H, 9.64; N, 7.34. $C_{10}H_{17}NO_2$ requires: C, 65.54; H, 9.35; N, 7.64%).

trans - 4 - (1,1 - *Dimethyl* - 2 - *propenyl*) - 3 - [(1*S**) - 1 - *hydroxyethyl*] - 2 - *azetidinone* **3**. The same procedure as that for **2** yielded **3** from **7** (2.244 g) and $(n\text{-}Bu)_4NF$ (2.169 g, 1.1 equiv) as a white solid (1.353 g, 98% yield). Recrystallization of **3** from 30% $i\text{-}Pr_2O/CHCl_3$ gave an analytical sample, m.p. 98–99°. IR ν_{max} ($CHCl_3$) 3410 (NH) and 1752 (C=O); NMR ($CDCl_3$) δ 1.02 (6H, s, 2xMe), 1.30 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.82 (1H, ddd, J = 1, 2 and 6 Hz, C_3–H), 2.84 (1H, d, J = 4.5 Hz, OH), 3.32 (1H, d, J = 2 Hz, C_4–H), 4.00 (1H, m, $CHCH_3$), 4.92–5.96 (3H, m, $CH{=}CH_2$), and 6.46 (1H, br, NH). (Found: C, 65.35; H, 9.46; N, 7.66. $C_{10}H_{17}NO_2$ requires: C, 65.54; H, 9.35; N, 7.64%).

Reaction of dilithiated azetidinone **10** *with acetaldehyde.* To a soln of the azetidinone **4** (3.268 g) in THF (30 ml) at −78°, 29.7 ml (2.1 equiv) of 1.66 M soln of n-BuLi in n-hexane was added over a period of 15 min and then warmed up to 0°. After stirring at 0° for 1 hr, the mixture was cooled again to −78°. Acetaldehyde (7.7 ml, 1.2 equiv) in THF (3 ml) was added and the soln was allowed to stir for a further 15 min at −78°. The reaction was quenched by adding sat NH_4Cl (15 ml). The usual work-up gave the crude product which was dissolved again in the soln of conc HCl (5 ml) in MeOH (50 ml). After stirring at room temp for 1 hr, the solvents were evaporated under reduced pressure to give 3.336 g of pale yellow oil. The column chromatography on silica gel provided, overall, 0.550 g (13% yield) of diastereomeric cis carbinols **11** as a solid and 2.233 g (52% yield) of diastereomeric trans carbinols (**2** + **3**, *ca.* 1 : 1 by NMR analysis) as a colorless oil. The cis isomers (*ca.* 12 : 1 by NMR analysis) was purified by recrystallization from $i\text{-}Pr_2O$ to provide a single isomer of **11** (0.352 g), m.p. 83–84°. IR ν_{max} ($CHCl_3$) 3410 (NH) and 1750 (C=O); NMR ($CDCl_3$) δ 1.12 and 1.14 (each 3H, s, Me), 1.30 (3H, d, J = 6 Hz, $CHCH_3$), 3.00–3.40 (1H, br, OH), 3.18 (1H, ddd, J = 1, 5 and 7 Hz, C_3–H), 3.65 (1H, d, J = 5 Hz, C_4–H), 4.38 (1H, m, $CHCH_3$), 4.96–6.16 (3H, m, $CH{=}CH_2$), and 7.15 (1H, br, NH). (Found: C, 65.70; H, 9.64; N, 7.80. $C_{10}H_{17}NO_2$ requires: C, 65.54; H, 9.35; N, 7.64%).

The trans carbinols (**2** + **3**) was silylated as follows; a mixed soln of **2** + **3** (2.233 g) in THF (20 ml) was added to a stirred suspension of freshly prepared TMS_2NLi which was made from 7.75 ml (1.05 equiv) of 1.65 M soln of n-BuLi in n-hexane and 2.163 g (1.1 equiv) of TMS_2NH in ether (10 ml) at −78°. After stirring for 10 min, a soln of t-butylchlorodimethylsilane (2.020 g, 1.1 equiv) was added. The resulting reaction mixture was warmed slowly up to 0° and then stirred at the same temp for 2 hr. The crude substance obtained by the usual work-up was chromatographed on silica gel giving **6** (1.283 g, 35% yield) and **7** (1.195 g, 33% yield).

Benzyl 4 - (1,1 - *dimethyl* - 2 - *propenyl*) - 3 - (1 - *hydroxyethyl*) - 2 - *oxo* - 1 - *azetidineacetate* **12a** *and* **12b**. A soln of **2** (720 mg) in THF (10 ml) was added dropwise over a period of 5 min at −78° to a stirred suspension of freshly prepared TMS_2NLi made from n-BuLi (2.49 ml of a 1.66 M soln in n-hexane, 1.05 equiv) and TMS_2NH (698 mg, 1.1 equiv) in 3 ml ether. Stirring was continued for 10 min at −78°, benzyl bromoacetate (1.080 g, 1.2 equiv) in THF (10 ml) was then added to the soln. The resulting mixture was warmed up to 0° over a period of 30 min and stirred at 0° for 5 min. The usual work-up gave 1.285 g of an oil which was purified by column chromatography to give 892 mg (69% yield) of **12a** as a colorless oil. IR ν_{max} ($CHCl_3$) 3470 (OH), 1755, and 1740 (C=O); NMR ($CDCl_3$) δ 1.00 and 1.02 (each 3H, s, Me), 1.27 (3H, d, J = 6 Hz, $CHCH_3$), 2.56 (1H, br, OH), 2.89 (1H, dd, J = 2 and 6 Hz, C_3–H), 3.70 (1H, d, J = 2 Hz, C_4–H), 3.70 and 4.30 (each 1H, d, J = 18 Hz, NCH_2), 4.09 (1H, m, $CHCH_3$), 4.88–5.96 (3H, m, $CH{=}CH_2$), 5.12 (2H, s, OCH_2), and 7.35 (5H, s, Ar); MS *m/e* 331.1802. Calc. for $C_{19}H_{25}NO_4$: 331.1783 (M^+).

The same procedure as for **12a** gave **12b** from azetidinone **3** (1.258 g), n-BuLi (4.34 ml of a 1.66 M soln in n-hexane, 1.05 equiv), TMS_2NH (1.219 g, 1.1 equiv), and benzyl bromoacetate (1.887 g, 1.2 equiv) as a colorless oil (1.836 g, 81% yield). IR ν_{max} ($CHCl_3$) 3500 (OH), 1755 and 1740 (C=O); NMR ($CDCl_3$) δ 0.98 and 1.01 (each 3H, s, Me), 1.27 (3H, d, J = 6 Hz, $CHCH_3$), 2.77 (1H, d, J = 4 Hz, OH), 2.87 (1H, dd, J = 2 and 6.5 Hz, C_3–H), 3.56 (1H, d, J = 2 Hz, C_4–H), 3.68 and 4.32 (each 1H, d, J = 18 Hz, NCH_2), 4.00 (1H, m, $CHCH_3$), 4.85–5.90 (3H, m, $CH{=}CH_2$), 5.11 (2H, s, OCH_2), and 7.32 (5H, s, Ar); MS *m/e* 331.1777. Calc. for $C_{19}H_{25}NO_4$: 331.1783 (M^+).

Benzyl 3 - (1 - *benzyloxycarboxyethyl*) - 4 - (1,1 - *dimethyl* - 2 - *propenyl*) - 2 - *oxo* - 1 - *azetidineacetate* **13a** *and* **13b**. Benzyl chloroformate (0.48 ml, 1.5 equiv) was added to a stirred soln of the carbinol **12a** (745 mg), DMAP (412 mg, 1.5 equiv) and $Et(i\text{-}Pr)_2N$ (0.39 ml, 1 equiv) in CH_2Cl_2 (6 ml) at −10°. The cooling bath was removed, and stirring was continued for 1 hr. Immediate column chromatography of the homogeneous reaction mixture provided the carbonate **13a** (865 mg, 83% yield) as a colorless syrup. IR ν_{max} ($CHCl_3$) 1755 (sh) and 1745 (C=O); NMR ($CDCl_3$) δ 0.92 and 0.96 (each 3H, s, Me), 1.42 (3H, d, J = 6.5 Hz, $CHCH_3$), 3.00 (1H, dd, J = 2 and 8.5 Hz, C_3–H), 3.62 (1H, d, J = 2 Hz, C_4–H), 3.66 and 4.28 (each 1H, d, J = 18 Hz, NCH_2), 4.80–5.85 (4H, m, $CH{=}CH_2$ and $CHCH_3$), 5.08 (4H, s, $2xOCH_2$), and 7.29 (10H, s, Ar); MS *m/e* 465.2170. Calc. for $C_{27}H_{31}NO_6$: 465.2151 (M^+).

The same procedure as that for **13a** yielded **13b** from the carbinol **12b** (1.325 g), DMAP (619 mg, 1.5 equiv), $Et(i\text{-}Pr)_2N$ (0.70 ml, 1 equiv), and benzyl chloroformate (0.86 ml, 1.5 equiv) as a colorless syrup (1.523 g, 82% yield). IR ν_{max} ($CHCl_3$) 1755 (sh) and 1745 (C=O); NMR ($CDCl_3$) δ 0.93 and 0.97 (each 3H, s, Me), 1.39 (3H, d, J = 6.5 Hz, $CHCH_3$), 3.21 (1H, dd, J = 2 and 4.5 Hz, C_3–H), 3.65 and 4.33 (each 1H, d, J = 18 Hz, NCH_2), 3.72 (1H, d, J = 2 Hz, C_4–H), 4.75–5.88 (4H, m, $CH{=}CH_2$ and $CHCH_3$), 5.09 and 5.12 (each 2H, s, OCH_2), and 7.32 (10H, s, Ar); MS *m/e* 465.2153. Calc. for $C_{27}H_{31}NO_6$: 465.2151 (M^+).

Benzyl 3-(1-*benzyloxycarboxyethyl*)-4-(1-*carboxy*-1-*methylethyl*) - 2 - *oxo* - 1 - *azetidineacetate* **14a** *and* **14b**. A soln of **13a** (850 mg) in MeOH (20 ml) was treated with O_3 at −20° to −30° for 1 hr. After removal of the excess O_3 with argon, Me_2S (0.5 ml) was added and then stirred for 1 hr at room temp. Evaporation of the soln under reduced pressure and the residue obtained was taken up in acetone (10 ml). To the stirred soln at 0°, Jones reagent was added dropwise until the orange color persisted. The usual work-up gave an oil which was purified by silica gel chromatography to provide the carboxylic acid **14a** (726 mg, 86% yield) as a colorless oil. IR ν_{max} ($CHCl_3$) 1755 (sh), 1745 and 1720 (sh) (C=O); NMR ($CDCl_3$) δ 1.16 (6H, s, 2xMe), 1.42 (3H, d, J = 6 Hz, $CHCH_3$), 3.11 (1H, dd, J = 2 and 8 Hz, C_3–H), 3.68 and 4.30 (each 1H, d, J = 18 Hz, NCH_2), 4.02 (1H, d, J = 2 Hz, C_4–H), 5.05 (1H, m, $CHCH_3$), 5.09 (4H, s, $2xOCH_2$), 7.31 and 7.33 (each 5H, s, Ar) and 8.45 (1H, br, COOH); MS *m/e* 483.1916. Calc. for $C_{26}H_{29}NO_8$: 483.2310 (M^+).

By use of the same procedure as that for **14a**, **14b** was obtained from **13b** (1.490 g) as a colorless oil (1.364 g, 88% yield). IR ν_{max} ($CHCl_3$) 1755 (sh), 1745 and 1720 (sh) (C=O); NMR ($CDCl_3$) δ 1.12 and 1.15 (each 3H, s, Me), 1.38 (3H, d, J = 6.5 Hz, $CHCH_3$), 3.33 (1H, dd, J = 2 and 4 Hz, C_3–H), 3.68 and 4.36 (each 1H, d, J = 18 Hz, NCH_2), 4.12 (1H, d, J = 2 Hz, C_4–H), 5.08 (1H, m, $CHCH_3$), 5.09 and 5.11 (each 2H, s, OCH_2), 7.30 and 7.32 (each 5H, s, Ar), and 10.04 (1H, br, COOH); MS *m/e* 483.1884. Calc. for $C_{26}H_{29}NO_8$: 483.2310 (M^+).

Benzyl 6 - (1 - *benzyloxycarboxyethyl*) - 1,1 - *dimethyl* - 2,7 - *dioxo* - 1 - *carbapenam* - 3 - *carboxylate* **15a** *and* **15b**. A soln of oxalyl chloride (0.26 ml, 2 equiv) in benzene (3 ml) was added dropwise to a stirred soln of **14a** (732 mg) and pyridine (126 mg, 1.05 equiv) in benzene (5 ml) at 0° and the reaction mixture was stirred at 0° for 5 min and then at room temp for 30 min. The precipitate formed was filtered and washed thoroughly with benzene. The combined filtrate and washings were concentrated to give 677 mg of crude chloride, which was used without further purification for the next reaction. A soln of the crude chloride (677 mg) in THF (10 ml) was added dropwise at −78° over 5 min period to a stirred suspension of freshly prepared TMS_2NLi from n-BuLi (1.71 ml of a 1.66 M soln in n-hexane, 2.1 equiv) and TMS_2NH (479 mg, 2.2 equiv) in ether (3 ml). The resulting yellow soln was stirred for further 10 min at −78°. The reaction was quenched with a soln of $TsOH{\cdot}H_2O$ (770 mg) in THF (5 ml) and the usual work-up gave 655 mg of crude **15a**. Chromatography on silica gel provided 584 mg of **15a** (83% overall yield) as a colorless oil. IR ν_{max} ($CHCl_3$) 1770 and 1745 (C=O); NMR ($CDCl_3$) δ 1.00 and 1.12 (each 3H, s, Me), 1.48 (3H, d, J = 6 Hz, $CHCH_3$), 3.33 (1H, dd, J = 2 and 8 Hz, C_6–H), 3.75 (1H, d, J = 2 Hz, C_5–H), 4.72 (1H, s, C_3–H), 5.14 and 5.17 (each 2H, s, OCH_2), 5.15 (1H, m, $CHCH_3$), and 7.35 (10H, s, Ar); MS *m/e* 465.1774. Calc. for $C_{26}H_{27}NO_7$: 465.1787 (M^+).

The conversion of **14b** (1.334 g) into **15b** was performed as

described above. Chromatography of the crude carbapenam on silica gel provided 1.105 g of **15b** (86% overall yield) as an oil. IR ν_{max} ($CHCl_3$) 1770 and 1745 (C=O); NMR ($CDCl_3$) δ 1.00 and 1.13 (each 3H, s, Me), 1.45 (3H, d, J = 6.5 Hz, $CHCH_3$), 3.52 (1H, dd, J = 2 and 5.5 Hz, C_6–H), 3.65 (1H, d, J = 2 Hz, C_5–H), 4.70 (1H, s, C_3–H), 5.10 and 5.13 (each 2H, s, OCH_2), 5.12 (1H, m, $CHCH_3$), 7.31 and 7.34 (each 5H, s, Ar); MS *m/e* 465.1810. Calc. for $C_{26}H_{27}NO_7$: 465.1787 (M^+).

Benzyl 6 - (1 - *benzyloxycarboxyethyl*) - 2 - *hydroxy* - 1,1 - *dimethyl* - 7 - *oxo* - 1 - *carbapenam* - 3 - *carboxylate* **16a** *and* **16b**. To a stirred soln of **15a** (554 mg) in 6 ml of THF/EtOH (1:1 v/v), $NaBH_4$ (23 mg) was added at −60°. After stirring for 1 hr at the same temp, the mixture was quenched with 35 mg of AcOH and then worked up in the usual manner. The oily product obtained was purified by chromatography on silica gel to give **16a** (488 mg, 88% yield) as a white solid. Recrystallization of **16a** from i-Pr_2O gave an analytical sample, m.p. 118–119°. IR ν_{max} ($CHCl_3$) 1765 and 1735 (sh) (C=O); NMR ($CDCl_3$) δ 0.86 and 1.02 (each 3H, s, Me), 1.42 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.58 (1H, d, J = 4 Hz, OH), 3.20 (1H, dd, J = 2 and 8.5 Hz, C_6–H), 3.37 (1H, d, J = 2 Hz, C_5–H), 4.02 (1H, d, J = 7.5 Hz, C_3–H), 4.13 (1H, dd, J = 4 and 7.5 Hz, C_2–H), 5.10 (1H, m, $CHCH_3$), 5.10 and 5.16 (each 2H, s, OCH_2), and 7.33 (10H, s, Ar). (Found: C, 66.59; H, 6.25; N, 2.76. $C_{26}H_{29}NO_7$ requires: C, 66.79; H, 6.25; N, 3.00%).

By use of the same procedure as that for **16a**, **16b** was obtained from **15b** (1.073 g) by reduction with $NaBH_4$ (44 mg) as a colorless oil (944 mg, 88% yield). IR ν_{max} ($CHCl_3$) 1760 and 1735 (sh) (C=O); NMR ($CDCl_3$) δ 0.86 and 1.02 (each 3H, s, Me), 1.39 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.72 (1H, d, J = 4 Hz, OH), 3.25 (1H, d, J = 2 Hz, C_5–H), 3.38 (1H, dd, J = 2 and 5.5 Hz, C_6–H), 4.02 (1H, d, J = 7.5 Hz, C_3–H), 4.13 (1H, dd, J = 4 and 7.5 Hz, C_2–H), 5.06 (1H, m, $CHCH_3$), 5.10 and 5.15 (each 2H, s, OCH_2), 7.31 and 7.33 (each 5H, s, Ar); MS *m/e* 467.1929. Calc. for $C_{26}H_{29}NO_7$: 467.1944 (M^+).

Benzyl 6 - (1 - *benzyloxycarboxyethyl*) - 2 - *methanesulfonyloxy* - 1,1 - *dimethyl* - 7 - *oxo* - 1 - *carbapenam* - 3 - *carboxylate* **17a** *and* **17b**. To a stirred soln of **16a** (330 mg), Et(i-Pr)$_2$N (0.12 ml, 1 equiv), and DMAP (86 mg, 1 equiv) in CH_2Cl_2 (6 ml), Ms_2O (184 mg, 1.5 equiv) was added at 0° and the mixture was stirred for 30 min at the same temp. Direct column chromatography of the resulting soln gave **17a** (368 mg, 96% yield) as a colorless oil. IR ν_{max} ($CHCl_3$) 1775 and 1745 (C=O); NMR ($CDCl_3$) δ 0.93 and 1.05 (each 3H, s, Me), 1.39 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.84 (3H, s, Ms), 3.23 (1H, dd, J = 2 and 8 Hz, C_6–H), 3.45 (1H, d, J = 2 Hz, C_5–H), 4.30 (1H, d, J = 6.5 Hz, C_3–H), 5.02 (1H, d, J = 6.5 Hz, C_2–H), 5.08 (1H, m, $CHCH_3$), 5.08 and 5.13 (each 2H, s, OCH_2), and 7.31 (10H, s, Ar); MS *m/e* 545.1730. Calc. for $C_{27}H_{31}NO_9S$: 545.1719 (M^+).

By use of the same procedure as that for **17a**, **17b** was obtained from **16b** (690 mg) by use of Et(i-Pr)$_2$N (0.15 ml), DMAP (180 mg), and Ms_2O (386 mg) as a colorless oil (695 mg, 86% yield). IR ν_{max} ($CHCl_3$) 1775 and 1745 (C=O); NMR ($CDCl_3$) δ 0.95 and 1.08 (each 3H, s, Me), 1.39 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.88 (3H, s, Ms), 3.35 (1H, d, J = 2.5 Hz, C_5–H), 3.45 (1H, dd, J = 2.5 and 5 Hz, C_6–H), 4.32 (1H, d, J = 6 Hz, C_3–H), 5.04 (1H, d, J = 6 Hz, C_2–H), 5.10 (1H, m, $CHCH_3$), 5.10 and 5.16 (each 2H, s, OCH_2), 7.32 and 7.34 (each 5H, s, Ar); MS *m/e* 545.1715. Calc. for $C_{27}H_{31}NO_9S$: 545.1719 (M^+).

Benzyl 6 - (1 - *benzyloxycarboxyethyl*) - 1,1 - *dimethyl* - 7 - *oxo* - 1 - *carba* - 2 - *penem* - 3 - *carboxylate* **18a** *and* **18b**. A soln of PDBD (155 mg, 1.1 equiv) in 2 ml of CH_2Cl_2 was added slowly to a soln of mesylate **17a** (368 mg) in CH_2Cl_2 (3 ml) at 0°. After stirring for 1 hr at the same temp, the soln was subjected immediately to chromatography on silica gel. Elution with 3% acetone/$CHCl_3$ gave the carbapenem **18a** (277 mg, 91% yield) as a colorless syrup. IR ν_{max} ($CHCl_3$) 1778 and 1738 (C=O); NMR δ 1.08 and 1.21 (each 3H, s, Me), 1.43 (3H, d, J = 6 Hz, $CHCH_3$), 3.35 (1H, dd, J = 3 and 7.5 Hz, C_6–H), 3.81 (1H, d, J = 3 Hz, C_5–H), 5.11 (1H, m, $CHCH_3$), 5.12 (2H, s, OCH_2), 5.16 and 5.25 (each 1H, d, J = 12.5 Hz, OCH_2), 6.23 (1H, s, C_2–H), and 7.33 (10H, s, Ar); MS *m/e* 449.1848. Calc. for $C_{26}H_{27}NO_6$: 449.1838 (M^+).

By use of the same procedure as that for **18a**, **18b** was obtained from mesylate **17b** (665 mg) by use of PDBD (279 mg, 1.1 equiv) as a colorless syrup (513 mg, 94% yield). IR ν_{max} ($CHCl_3$) 1780 and 1738 (C=O); NMR ($CDCl_3$) δ 1.05 and 1.24 (each 3H, s, Me), 1.43 (3H, d, J = 6.5 Hz, $CHCH_3$), 3.57 (1H, dd, J = 3 and 5 Hz, C_6–H), 3.70 (1H, d, J = 3 Hz, C_5–H), 5.08 (1H, m, $CHCH_3$), 5.12 (2H, s, OCH_2), 5.16 and 5.25 (each 1H, d, J = 12 Hz, OCH_2), 6.20 (1H, s, C_2–H), and 7.33 (10H, s, Ar); MS *m/e* 449.1813. Calc. for $C_{26}H_{27}NO_6$: 449.1838 (M^+).

Deprotection of the carbapenems **18a** *and* **18b**. To a soln of **18a** (257 mg) in THF (10 ml), was added 10% Pd/C (257 mg) and PDBD (119 mg, 1 equiv). The suspension was stirred for 15 min under a current of H_2 at room temp. After filtration, the residual catalyst was washed thoroughly with MeOH and the combined filtrate and washings were concentrated under reduced pressure. The crude amidine salt obtained was purified by column chromatography on silica gel. Elution with MeOH/acetone/$CHCl_3$ (7:15:78 v/v) gave a colorless solid of **19a** (245 mg), which was further purified by recrystallization from CH_2Cl_2/i-Pr_2O (1:19 v/v) to give colorless plates of **19a** (183 mg, 74% yield), m.p. 192–193° (decomp). IR ν_{max} ($CHCl_3$) 1760 and 1660 (C=O); NMR ($CDCl_3$) δ 1.10, 1.26, 1.30, 1.32 and 1.40 (total 24H, s, 8xMe), 1.45–2.25 (8H, m, 4xCH_2), 2.75 (1H, br, OH), 3.12 (1H, dd, J = 2.5 and 7 Hz, C_6–H), 3.78 (1H, d, J = 2.5 Hz, C_5–H), 4.21 (1H, m, $CHCH_3$), 5.96 (1H, s, C_2–H) and 11.45 (~2H, D/H exchange with $CDCl_3$ was observed, br, NH); UV λ_{max} (H_2O) 262 nm (ϵ = 5670). (Found: C, 65.36; H, 9.28; N, 9.38. $C_{24}H_{39}N_3O_4 \cdot \frac{1}{2}H_2O$ requires: C, 65.13; H, 9.11; N, 9.50%).

Carbapenem **18b** (500 mg) was treated by the same procedure as that for **18a** to give **19b** (325 mg, 67% yield) as colorless fine plates, m.p. 166–167° (decomp). IR ν_{max} ($CHCl_3$) 1757 and 1662 (C=O); NMR ($CDCl_3$) δ 1.12, 1.24, 1.28, 1.30, 1.33 and 1.40 (total 24H, 8xMe), 1.40–2.20 (8H, m, 4xCH_2), 2.65 (1H, br, OH), 3.18 (1H, dd, J = 3 and 7.5 Hz, C_6–H), 3.58 (1H, d, J = 3 Hz, C_5–H), 4.16 (1H, m, $CHCH_3$), 5.92 (1H, s, C_2–H) and 11.45 (~2H, D/H exchange with $CDCl_3$ was observed, br, NH); UV λ_{max} (H_2O) 262 nm (ϵ = 5760). (Found: C, 65.74; H, 9.09; N, 9.43. $C_{29}H_{39}N_3O_4 \cdot \frac{1}{4}H_2O$ requires: C, 65.80; H, 9.09; N, 9.59%).

Potassium 6 - (1 - *hydroxyethyl*) - 1,1 - *dimethyl* - 7 - *oxo* - 1 - *carba* - 2 - *penem* - 3 - *carboxylate* **20a** *and* **20b**. To a stirred suspension of **19a** (65 mg) in ether (3 ml), a soln of potassium 2-ethylhexanoate (33 mg, 1.2 equiv) in THF (3 ml) was added at room temp. After stirring for 30 min, the resulting precipitate was filtered, washed well with ether/THF (1:1 v/v), and dried to give a spectroscopically pure powder of the potassium salt **20a** (37 mg, 100% yield). Crystallization from H_2O/acetone provided a colorless plates, m.p. 170–175° (decomp). IR ν_{max} (KBr) 1755 and 1590 (C=O); NMR (D_2O) δ 1.20 and 1.40 (each 3H, s, Me), 1.35 (3H, d, J = 6.5 Hz, $CHCH_3$), 3.46 (1H, dd, J = 3 and 6 Hz, C_6–H), 3.91 (1H, d, J = 3 Hz, C_5–H), 4.31 (1H, m, $CHCH_3$) and 6.18 (1H, s, C_2–H); UV λ_{max} (H_2O) 262 nm (ϵ = 5160).

Treatment of **19b** (78 mg) with potassium 2-ethylhexanoate (39 mg, 1.2 equiv) similar to the above manner gave **20b** as a spectroscopically pure powder (43 mg, 97% yield). Crystallization from H_2O/acetone provided a colorless fine plates, m.p. 148–150° (decomp). IR ν_{max} (KBr) 1755 and 1593 (C=O); NMR (D_2O) δ 1.23 and 1.42 (each 3H, s, Me), 1.43 (3H, d, J = 6.5 Hz, $CHCH_3$), 3.54 (1H, dd, J = 2.5 and 5.5 Hz, C_6–H), 3.88 (1H, d, J = 2.5 Hz, C_5–H), 4.30 (1H, m, $CHCH_3$), 6.22 (1H, s, C_2–H); UV λ_{max} (H_2O) 262 nm (ϵ = 5050).

REFERENCES

[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. Am. Chem. Soc.* **100**, 6491 (1978).

[2]A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale and R. Southgate, *J. Chem. Soc. Chem. Commun.* 236 (1979); H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano and W. Nagata, *Tetrahedron Letters* 3867 (1979); R. J. Ponsford, P. M. Roberts and R. Southgate, *J. Chem. Soc. Chem. Commun.* 847 (1979); T. Kametani, S. P. Huang, S. Yokohama, Y. Suzuki and M. Ihara, *J. Am. Chem. Soc.* **102**, 2060 (1980); L. Cama and B. G. Christensen, *Tetrahedron*

Letters **21**, 2013 (1980); A. J. G. Baxter, P. Davis, R. J. Ponsford and R. Southgate, *Ibid.* **21**, 5071 (1980); D. F. Corbett and A. J. Eglington, *J. Chem. Soc. Chem. Commun.* 1083 (1980).

[3]For recent reports, see T. Kametani, S. P. Huang, T. Nagahara, S. Yokohama and M. Ihara, *J. Chem. Soc. Perkin I* 964 (1981); D. G. Melillo, T. Liu, K. Ryan, M. Sletzinger and I. Shinkai, *Tetrahedron Letters* **22**, 913 (1981); D. A. Berges, E. R. Snipes, G. W. Chan, W. D. Kingsbury and C. M. Kinzig, *Ibid.* **22**, 3557 (1981); T. Kametani, T. Honda, A. Nakayama, Y. Sasaki, T. Mochizuki and K. Fukumoto, *J. Chem. Soc. Perkin I* 2228 (1981); T. Kametani, S. P. Huang, T. Nagahara and M. Ihara, *Ibid.* 2282 (1981).

[4a]M. Shibuya and S. Kubota, *Tetrahedron Letters* **21**, 4009 (1980); [b]M. Shibuya and S. Kubota, *Ibid.* **22**, 3611 (1981).

[5]Recently, similar aldol-type and Dieckmann-type condensation reaction have been reported in the synthesis of different carbapenams: [a]M. W. Foxton, R. C. Mearman, C. E. Newall and P. Ward, *Tetrahedron Letters* **22**, 2497 (1981); [b]M. Hatanaka, Y. Yamamoto, H. Nitta and T. Ishimaru, *Ibid.* **22**, 3883 (1981).

[6]B. G. Christensen *et al.*, *Recent Advances in the Chemistry of β-Lactam Antibiotics*, (Edited by G. I. Gregory), p. 240. Second International Symposium, Cambridge, England, The Royal Society of Chemistry.

[7]The numbering of the bicyclic compounds adopted throughout this paper is based on that proposed by Merck group; S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, *J. Org. Chem.* **45**, 1135 (1980).

[8]All compounds described are racemic, but the enantiomer related to thienamycin is depicted for convenience.

[9]M. Shibuya and S. Kubota, *Hererocycles* **14**, 601 (1980).

[10]T. Durst and M. J. LeBelle, *Can. J. Chem.* **50**, 3196 (1972); T. Durst, R. V. D. Elzen and R. Legault, *Ibid.* **52**, 3206 (1974).

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

[12]This numbering system corresponds to that of thienamycin analogues.

[13]S. L. Huang, K. Omura and D. Swern, *Synthesis* 297 (1978).

[14]The relative stereochemistry of **11** has been determined as 5SR, 6RS, 8RS; M. Shibuya, "Nagai Memorial Symposium", Tokushima, Japan, Dec., 1980.

[15]F. Heinzer, M. Soukup and A. Eschenmoser, *Helv. Chim. Acta* **61**, 2851 (1978). This amidine base is abbreviated as PDBD throughout this paper.

[16]M. Shibuya, M. Kuretani and S. Kubota, *Tetrahedron Letters* **22**, 4453 (1981).