SYNTHESIS AND *IN VITRO* ACTIVITY OF NOVEL QUATERNARY AMMONIUM CARBAPENEMS: 2-PYRIDINIOPROPYL AND 1-PYRIDINIOETHYL CARBAPENEMS

YASUTSUGU UEDA† and VIVIANE VINET

Antiinfective Chemistry Department, Pharmaceutical Research Institute,
Bristol-Myers Squibb Company,
Candiac, Quebec, Canada J5R 1J1

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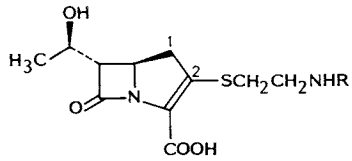
The synthesis of new carbapenems having either a pyridiniopropyl group at the 2-position or a pyridinioethyl group at the 1-position is described, along with the preparation of their corresponding hydroxy and acetoxy analogs. The antibacterial activity, susceptibility to dehydropeptidase-I (DHP-I) enzyme and chemical stability of these new carbapenems are also reported. 2-Pyridiniopropylcarbapenem **4** was found to possess excellent antibacterial activity. It was more stable chemically and less susceptible to the DHP-I enzyme than the thio analog **3**. 1-Pyridinioethylcarbapenem **5** showed significantly reduced antibacterial activity as compared to 2-pyridiniopropylcarbapenem **4**.

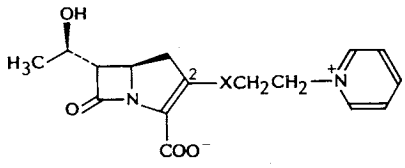
Since the discovery of a potent and broad spectrum β-lactam antibiotic, thienamycin (**1**)[1,2] a number of carbapenem compounds have been isolated from natural sources[2]. Interestingly, like thienamycin, most of these compounds contain a sulfur atom at the 2-position of the carbapenem nucleus. Hence a majority of the synthetic efforts have been focused on 2-thiocarbapenems. Investigation of carbapenems carrying a carbon substituent directly attached to the 2-position of the nucleus have received relatively little attention[3]. However, in recent years, a considerable interest in C-2 carbon-substituted carbapenems has been generated in search for a unique and biologically stable substitute for imipenem (**2**), a chemically stable analog of thienamycin (**1**)[4~7].

During an extensive search for a potent and broad spectrum carbapenem antibiotic which possesses improved chemical and metabolic stability over imipenem (**2**) by chemical modification, two groups of scientists[8,9] discovered that carbapenems linked to a quaternary heterocyclic alkylthio group at the C-2 position had an excellent and broad spectrum of antibacterial activity. In addition, these carbapenems possessed good anti-pseudomonal activity and greater stability than imipenem toward the renal dehydropeptidase-I (DHP-I). Among the many C-2 quaternary heterocyclic alkylthio carbapenems reported, 2-pyridinioethylthiocarbapenem **3** was one of the most promising analogs in terms of antibacterial activity and stability toward the DHP-I enzyme. Consequently our interest focused on the carbon analog of **3**, 2-pyridiniopropylcarbapenem **4**. Here we describe the synthesis of 2-pyridiniopropylcarbapenem **4** together with 1-pyridinioethylcarbapenems **5** which were derived from regio-isomeric by-products formed during the synthesis of **4**. 1-Pyridinioethylcarbapenems **5** are of particular interest because it has been reported that introduction of a 1β-methyl group into the carbapenem ring system has lead to chemically and metabolically stable carbapenems[9,10]. Although a number of 1-oxycarbapenems have been reported in recent years[9,11,12] very few 1-alkyl or 1-substituted alkyl carbapenems[9] have appeared with the exception

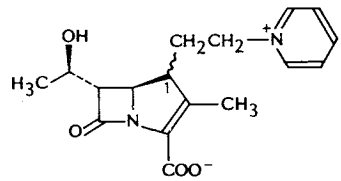
† Present address: Central Chemistry—203, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, P.O. Box 5100, Wallingford, CT 06492-7660, U.S.A.



1 R=H
2 R=CH=NH



3 X=S
4 $X=CH_2$



5a 1α-Substitution
5b 1β-Substitution

of 1-methylcarbapenems.

This paper also describes *in vitro* antibacterial activity, chemical stability and DHP-I susceptibility of the above pyridinioalkylcarbapenems, **4** and **5**, and their corresponding hydroxy (**16**, **24**) and acetoxy (**19**, **26**) analogs.

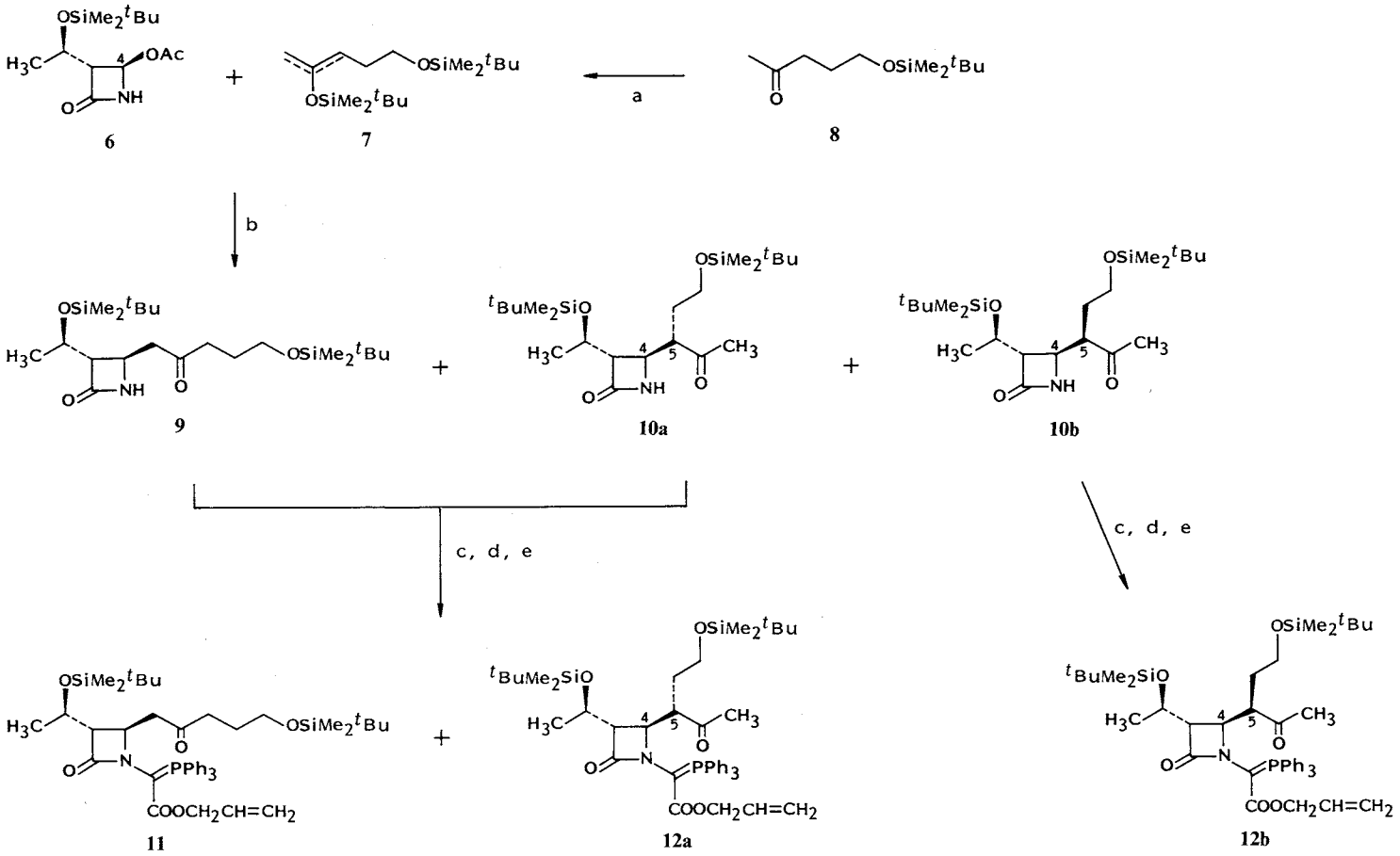
Chemistry

The zinc chloride mediated C-4 alkylation[13] of chiral 4-acetoxyazetidinone **6**[14,15] with a geometrical mixture of silylenol ethers **7**, which was prepared from ketone **8** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine, produced a mixture of three *trans*-azetidinones **9**, **10a** and **10b**. Azetidinone **10b** was separated by column chromatography but azetidinones **9** and **10a** were inseparable at this stage. The mixture of **9** and **10a** was converted to a mixture of phosphoranes **11** and **12a** by a three-step process[16], which involved condensation with allyl glyoxlate[17], chlorination and treatment with triphenylphosphine. These two phosphoranes were successfully separated by column chromatography, giving phosphoranes **11** and **12a** in 25% and 16% overall yield from **6**, respectively. The same treatment on azetidinone **10b** produced phosphorane **12b** in 14% overall yield from **6** (see Scheme 1). The stereochemistry at the C-5 position of phosphoranes **12a** and **12b** was assigned, after conversion to the carbapenem ring system, by comparison of the ^1H NMR data.

The silyl groups of the phosphorane **11** were removed by treatment with a mixture of tetrabutylammonium fluoride (TBAF) and acetic acid[18] to produce phosphorane diol **13** in 75% yield. Intramolecular Wittig cyclization[3] in refluxing toluene gave 2-hydroxypropylcarbapenem **14** in 99% yield. The pyridinio group was introduced by treatment with trifluoromethanesulfonic anhydride in pyridine[19] to furnish pyridiniopropylcarbapenem ester **15** in 38% yield. Deprotection of the allyl group[20] with $Pd(PPh_3)_4$ gave 2-pyridiniopropylcarbapenem **4** in 37% yield (see Scheme 2).

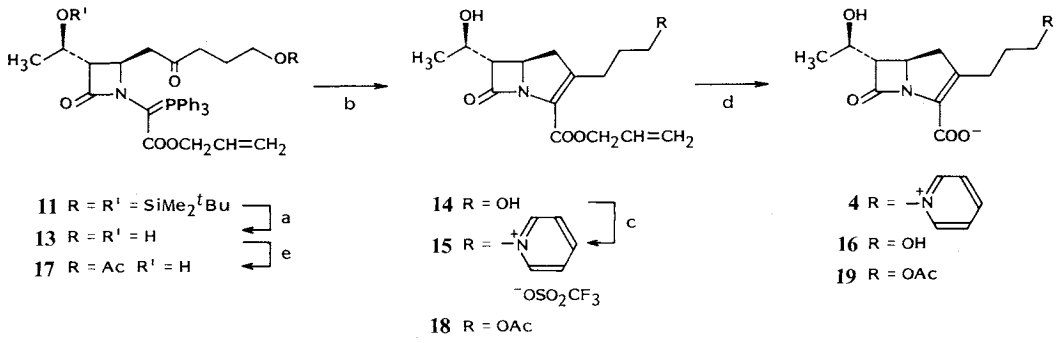
2-Hydroxypropylcarbapenem **16** was prepared from allyl ester **14** in 29% yield as shown in Scheme 2. 2-Acetoxypropylcarbapenem **19** was obtained from phosphorane diol **13** in a three-step process as outlined in Scheme 2. Selective acetylation of **13** with acetyl chloride in pyridine gave phosporane mono-

Scheme 1.



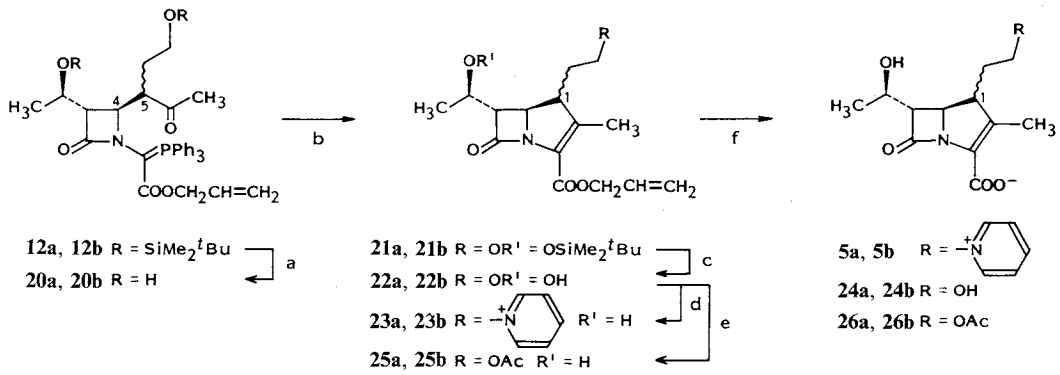
a $^tBuMe_2SiOSO_2CF_3$ - Et_3N - CH_2Cl_2
b $ZnCl_2$ - CH_2Cl_2
c $OHC-CO_2CH_2CH=CH_2$ - Et_3N - THF
d $SOCl_2$ - pyridine - THF
e PPh_3 - 2,6-lutidine - DMF

Scheme 2.



a $(n\text{-Bu})_4$NF - HOAc - THF
b toluene, reflux
c $(CF_3SO_2)_2O$ - pyridine
d $Pd(PPh_3)_4$
e AcCl - pyridine

Scheme 3.*



* The subscripts a and b refer either to the α- and β-isomers of the carbapenems of the undefined stereo centers, respectively, or they refer to the isomers (**12**, **20**) which lead to the α- and β-isomer of the carbapenems.

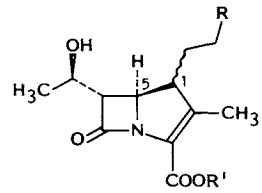
Reaction conditions:

a $(n\text{-Bu})_4$NF - HOAc - THF
b toluene, reflux
c $(n\text{-Bu})_4$NF - THF
d $(CF_3SO_2)_2O$ - pyridine
e AcCl - pyridine
f $Pd(PPh_3)_4$

acetate **17** which was cyclized to 2-acetoxypropylcarbapenem ester **18**. Removal of the allyl group with $Pd(PPh_3)_4$ produced acetoxypropyl carbapenem **19** in overall yield of 27% from **13**.

Similar treatment on each stereoisomeric phosphorane **12a** and **12b** furnished 1α-substituted carbapenems **5a**, **24a**, **26a** and 1β-substituted carbapenems **5b**, **24b**, **26b** as shown in Scheme 3. Although cyclization of dihydroxyphosphoranes **20a** and **20b**, which were obtained by the removal of the silyl groups (TBAF - HOAc), to produce dihydroxycarbapenems **22a** and **22b** was not successful, disiloxyphosphoranes, **12a** and **12b** were smoothly cyclized in refluxing toluene, giving disiloxycarbapenems **21a** and **21b**, respectively in *ca.* 95% yield. It is worth noting that one isomer, phosphorane **12a** cyclized significantly

Table 1. Chemical shifts of C-5 protons[a].



Compounds	R	R'	δ ppm		Δδ ppm
			1α-isomer	1β-isomer	(δβ − δα)
21	$OSiMe_2{}^tBu$	$-CH_2CH=CH_2$	3.77	4.15	0.38
22	OH	$-CH_2CH=CH_2$	3.87	4.19	0.32
23	$C_5H_5N^+$	$-CH_2CH=CH_2$	4.09	4.34	0.25
5	$C_5H_5N^+$	—	3.92	4.22	0.30
1-Methylthienamycin[b]			3.70	4.06	0.36

[a] Measured in CD_3COCD_3 or D_2O; see Experimental section.
[b] Data taken from ref 22.

faster than the other isomer **12b**. The removal of the silyl groups was achieved by treatment of **21a** and **21b** with TBAF in THF to produce hydroxycarbapenems **22a** and **22b** in 72~75% yield. The 1α- and 1β-pyridinioethylcarbapenems **5a** and **5b** were prepared, respectively from **22a** and **23b** by introduction of the pyridinio group to **23a** and **23b**, followed by palladium-catalyzed deprotection of the allyl group. The hydroxyethylcarbapenems **24a** and **24b** were obtained from the corresponding allyl esters **22a** and **22b** by palladium-catalyzed deprotection reaction. Preparation of 1-acetoxyethylcarbapenems **26a** and **26b** was achieved by selective acetylation of dihydroxycarbapenems **22a** and **22b** to acetoxycarbapenems **25a** and **25b**, followed by removal of the allyl group, respectively.

The stereochemical assignment at the 1-position of 1-substituted carbapenems was made by comparison of the chemical shift of the C-5 proton in their NMR spectra. The chemical shifts of the C-5 proton for several 1-substituted carbapenems are listed in Table 1. The C-5 proton of one isomer appeared at higher field than that of the other isomer, the difference being 0.25~0.38 ppm (see Table 1). The isomers having the C-5 proton which resonates at higher field are assigned as 1α-substituted carbapenems based on the fact that the vicinal proton *cis* to the alkyl group are shifted to the higher field than the proton *trans* to the alkyl substituent in a conformationally rigid system due to the steric compression[21]. This assignment is also supported by the fact that the C-5 proton of 1α-methylthienamycin whose stereochemical assignment has already been established[22], appears at higher field ($\Delta\delta = 0.36$ ppm) than that of 1β-methylthienamycin[22] (see Table 1). It is interesting to note that the effect of the steric compression on the bridgehead proton of the bicyclic β-lactams has been observed not only in the 1-substituted carbapenems but also in the 5-substituted 1-azabicyclo[4.2.0]octan-8-one system[23], suggesting potential usefulness in determining stereochemical assignment at the position next to the bridgehead carbon in these ring systems.

In Vitro Antibacterial Activity and Stability

In vitro antibacterial activity of these new carbapenems was tested and the minimum inhibitory concentrations (MICs) against Gram-positive and Gram-negative bacteria are listed in Table 2. The MICs of pyridinioethylthiocarbapenem **3** are also included for comparison. The carbon analog of **3**, pyridiniopropylcarbapenem **4** was found to show good antibacterial activity against both Gram-positive

Table 2. *In vitro* antibacterial activity, DHP-I stability and chemical stability of several new carbapenems.

Organisms[a] (strain No.)	MIC (μg/ml)[a]									
	3	**4**	**16**	**19**	**5a**	**5b**	**24a**	**24b**	**26a**	**26b**
Str. pneumoniae (A9585)	0.002	0.002	0.016	0.13	0.5	0.5	2	1	0.13	0.5
Staph. aureus (A9537)	0.016	0.016	0.06	8	2	2	8	8	1	2
E. coli (A15119)	0.03	0.13	0.13	4	1	1	4	2	2	16
K. pneumoniae (A9664)	0.25	0.25	0.25	16	16	1	8	4	8	32
Pr. mirabilis (A9900)	0.06	0.25	0.25	4	8	1	4	2	2	4
Ps. aeruginosa (A9843A)	2	4	>63	>63	8	8	>63	>63	>63	>63
DHP-I susceptibility (relative rate)[b]	0.37	0.19	—	—	0.37	1.16	3.62	3.62	2.66	4.02
Chemical stability[c] half-lives, hours	14	21	14	13	8	23	15	57	20	81

[a] Determined by 2-fold serial broth dilution method using Mueller-Hinton broth, with incubation at 37°C for 17 hours. *Str.* = *Streptococcus*, *Staph.* = *Staphylococcus*, *E.* = *Escherichia*, *K.* = *Klebsiella*, *Pr.* = *Proteus*, *Ps.* = *Pseudomonas*.

[b] The rates of degradation by hog renal dipeptidase (DHP-I) were measured as described in ref 8, and the relative rates to that of imipenem (= 1.00) are listed here.

[c] Chemical stability was obtained by measuring the rate of hydrolysis in pH 7.4 buffer solution at 37°C according to the method described in ref 24, and expressed by half-lives in hours. First-order kinetics were observed during the first two half-lives for most of the compounds.

and Gram-negative organisms, including *Pseudomonas aeruginosa*. It was almost as potent as the thio analog **3**. The hydroxypropylcarbapenem **16** retained good antibacterial activity except against *Pseudomonas* species. However the acetoxy derivative **19** showed much reduced activity as compared to **4** or **16**. Generally, 1-substituted carbapenems exhibited poor antibacterial activity except 1-pyridinioethyl carbapenems **5a** and **5b** which showed anti-pseudomonal activity. These data seem to further support the previous observation[7~9] that strongly basic substituents or positively charged substituents are required for good anti-pseudomonal activity in the carbapenem series. Among the 1-substituted carbapenems, 1β-pyridinioethyl analog **5b** exhibited weak but the most balanced antibacterial activity.

The DHP-I enzyme susceptibilities of some of new carbapenems are expressed by the relative degradation of imipenem[8]. These are also listed in Table 2. The compound with the number less than 1.0 are more stable than imipenem toward the DHP-I. The pyridiniopropylcarbapenem **4** was found to be more stable toward the DHP-I enzyme than imipenem and it also appeared to be less susceptible to DHP-I than the sulfur analog **3**. In the 1-substituted carbapenem series, 1α-pyridinioethyl analog **5a** was more stable to DHP-I than imipenem and all others, including 1β-pyridinioethyl derivative **5b** were more susceptible to DHP-I than imipenem.

Chemical stability of the carbapenems prepared above was obtained by measuring the rate of hydrolytic degradation in pH 7.4 buffer at 37°C[24] and the half-lives were listed in Table 2. Under these conditions, the carbon analog of pyridiniocarbapenem **4** was found to be slightly more stable than the corresponding sulfur analog **3**. One interesting finding is that the 1β-substituted carbapenems (**5b**, **24b**, **26b**) were three to four times more slowly degraded than the 1α-substituted carbapenems (**5a**, **24a**, **26a**).

In conclusion, although the carbon analog of **3**, pyridiniopropylcarbapenem **4** did not show significant improvement over the sulfur analog **3** in antibacterial potency, it demonstrated overall excellent antibacterial activity, along with good stability toward DHP-I enzyme and good chemical stability. 1-Substituted

carbapenems **5** and **24** showed much reduced antibacterial activity as compared to the corresponding 2-substituted analogs **4** and **16**.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are not corrected. The infrared spectra were recorded on a Perkin-Elmer 267 grating infrared spectrometer. The ^{1}H NMR spectra were taken with a Varian EM-360 (60 MHz), when unspecified, or a Varian CFT-20 (80 MHz) spectrometer. Tetramethylsilane was used as an internal standard and chemical shifts were reported in parts per million (δ) relative to the internal standard. The ultraviolet spectra were recorded on a Unicam SP8-100 spectrophotometer. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Analytical thin layer chromatography (TLC) was conducted on either precoated plates (Silica gel 60F-254, E. Merck) unless specified or reverse-phase silica plates (Analtech) to obtain Rf values. Column chromatography for water-soluble carbapenems was conducted on reverse-phase silica gel, Prep PAK-500/C_{18} (Waters Associate). Column chromatography for others was carried out on Silica gel 60 (70~230 mesh, E. Merck) unless specified. For purifications of acid-sensitive materials, Silica gel 60 pure (70~230 mesh, E. Merck No. 7754) was used. The analyses were performed by Micro-Tech Laboratories, Skokie, Illinois, U.S.A.

A Mixture of 2,5-Di-(*tert*-butyldimethylsiloxy)pent-1- and 2-enes (**7**)

To a stirred solution of 5-(*tert*-butyldimethylsiloxy)-2-pentanone (**8**) (16.3 g, 75.3 mmol) in CH_2Cl_2 (150 ml) was added at −78°C under a nitrogen atmosphere triethylamine (15.0 ml, 107 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (17.35 ml, 75.3 mmol). The mixture was stirred (−78°C, N_2) for 1.25 hours and then diluted with CH_2Cl_2 (100 ml). This was washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (pure SiO_2, No. 7754) eluting with 5% EtOAc-CH_2Cl_2 which was pre-cooled in a dry-ice-acetone bath, to obtain 20.0 g (60.5 mmol, yield 80.3%) of the title compounds **7** as colorless oil: Rf 0.66 (CH_2Cl_2); IR ν_{max}^{neat} cm^{-1} 1675 (w), 1470, 1460, 1255, 1100, 830, and 770; ^{1}H NMR (CCl_4) δ 0.1 (s, $-Si(CH_3)_2$), 0.97 (s, $-Si^tBu$), 1.00 (s, $-Si^tBu$), 1.3~2.3 (m, $-CH_2-$), 3.55 (t, J=7 Hz, $-CH_2OSi-$ of 2,5-disiloxy-2-pentene), 3.63 (t, J=6 Hz, $-CH_2OSi-$ of 2,5-disiloxy-1-pentene), 4.00 (s, vinyl protons of 2,5-disiloxy-1-pentene), and 4.2 (m, vinyl protons of 2,5-disiloxy-2-pentene).

5-(*tert*-Butyldimethylsiloxy)-2-pentanone (**8**)

To a stirred solution of 3-acetylpropanol (10.2 g, 0.10 mol) and *tert*-butyldimethylsilyl chloride (18.1 g, 0.12 mol) in DMF (50 ml) was added at room temperature under a nitrogen atmosphere imidazole (17.0 g, 0.25 mol). The mixture was stirred (room temperature, N_2) for 20 hours, and then diluted with hexane (400 ml), washed with H_2O (×2), brine and dried (Na_2SO_4). Evaporation of the solvent gave crude oil. This was purified by column chromatography eluting with 5% EtOAc-CH_2Cl_2 to obtain 16.3 g (75.3 mmol, yield 75.3%) of the title compound **8** as a colorless oil: BP 116~118°C (21 Torr); IR ν_{max}^{neat} cm^{-1} 1720 (ketone); ^{1}H NMR ($CDCl_3$) δ 0.03 (6H, s, $-Si(CH_3)_2$), 0.90 (9H, s, $-Si^tBu$), 1.5~2.0 (2H, m, $-CH_2-$), 2.15 (3H, s, CH_3CO-), 2.48 (2H, t, J=7 Hz, $-COCH_2-$), and 3.58 (2H, t, J=7 Hz, $-CH_2OSi-$).

Anal Calcd for $C_{11}H_{24}O_2Si$: C 61.05, H 11.18.
Found: C 60.63, H 10.96.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-[5-(*tert*-butyldimethylsiloxy)pentan-2-on-1-yl]-2-azetidinone (**9**) and (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-[(3*S*/*R*)-5-(*tert*-butyldimethylsiloxy)pentan-2-on-3-yl]-2-azetidinones (**10a** and **10b**)

To a stirred solution of (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-2-azetidinone (**6**)[14,15] (8.70 g, 30.3 mmol) in CH_2Cl_2 (125 ml) was added $ZnCl_2$ (2.05 g, 15.1 mmol) at room temperature under a nitrogen atmosphere and the mixture stirred for 45 minutes. To this was added a mixture of silylenolethers **7** (20.0 g, 60.5 mmol). The mixture was stirred at room temperature (N_2) for 1.5 hours and then diluted with EtOAc, washed with saturated $NaHCO_3$ (×3), brine (×1), dried ($MgSO_4$) and

concentrated to yield waxy solid. This was purified by column chromatography eluting with 20% EtOAc-CH_2Cl_2 to obtain 3.05 g (6.87 mmol, yield 22.7%) of (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-[(3*R*)-5-(*tert*-butyldimethylsiloxy)pentan-2-on-3-yl]-2-azetidinone (**10b**) as white solid: MP 137~138°C (hexane); Rf 0.36 (20% EtOAc-CH_2Cl_2); IR ν_{max}^{film} cm^{-1} 3180 (NH), 1755 (β-lactam), and 1715 (ketone); $[\alpha]_D^{21}$ −22.5° (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, CFT-20) δ 0.03 (6H, s, $-Si(CH_3)_2$), 0.05 (6H, s, $-Si(CH_3)_2$), 0.86 (9H, s, $-Si^tBu$), 0.87 (9H, s, $-Si^tBu$), 1.16 (3H, d, J=6.3 Hz, 1′-CH_3), 1.5~2.1 (2H, m, $-CH_2-$), 2.23 (3H, s, CH_3CO-), 2.90 (1H, dd, $J_{3\text{-}1'}$=4.3 Hz, $J_{3\text{-}4}$=2.2 Hz, 3-H), 2.95 (1H, m, −CHCO−), 3.61 (2H, t, J=6 Hz, $-CH_2OSi-$), 3.79 (1H, dd, $J_{4\text{-}1'}$=6.1 Hz, $J_{4\text{-}3}$=2.2 Hz, 4-H), 4.17 (1H, m, 1′-H) and 6.01 (1H, br s, NH).

Anal Calcd for $C_{22}H_{45}NO_4Si_2$: C 59.54, H 10.22, N 3.16.
Found: C 59.65, H 10.21, N 3.13.

and 9.60 g (21.6 mmol, yield 71.5%) of a mixture of *trans*-azetidinones **9** and **10a** as white solid in a ratio of *ca.* 1:1: MP 102~108°C (hexane); Rf 0.27 (20% EtOAc-CH_2Cl_2); IR ν_{max}^{film} cm^{-1} 3160 (NH), 3090 (NH), 1755 (β-lactam), and 1710 (ketone); ^1H NMR ($CDCl_3$, CFT-20) δ 0.03 (6H, s, $-Si(CH_3)_2$), 0.05 (6H, s, $-Si(CH_3)_2$), 0.86 (9H, s, $-Si^tBu$), 0.87 (9H, s, $-Si^tBu$), 1.20 (3H, d, J=6.2 Hz, 1′-CH_3), 1.23 (3H, d, J=6.3 Hz, 1′-CH_3), 1.5~2.0 (4H, m, $-CH_2-$), 2.21 (3H, s, CH_3CO-), 2.4~2.9 (mixture of m, −CHCO−, $-CH_2CO-$, 3-H), 3.5~3.9 (mixture of m, $-CH_2OSi-$, 4-H), 4.1 (2H, m, 1′-H), 5.85 (br s, NH), and 6.02 (br s, NH).

Allyl [(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-[5-(*tert*-butyldimethylsiloxy)pentan-2-on-1-ly]-2-azetidinon-1-yl]triphenylphosphoranylideneacetate (**11**) and Allyl [(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-[(3*S*)-5-(*tert*-butyldimethylsiloxy)pentan-2-on-3-yl]-2-azetidinon-1-yl]-triphenylphosphoranylideneacetate (**12a**)

A solution of allyl glyoxylate[17] (4.02 g, 35.3 mmol) in benzene (150 ml) was heated at reflux with a Dean-Stark trap for 2 hours. The solvent was evaporated *in vacuo* at room temperature, but not to dryness. The residue was dissolved in THF (160 ml). To this solution was added at room temperature under a nitrogen atmosphere a mixture of *trans*-azetidinones **9** and **10a** (9.60 g, 21.6 mmol) and then triethylamine (1.61 ml, 11.6 mmol). This mixture was stirred at room temperature (N_2) for 2 hours, and then the solvent was evaporated. The residue was purified by column chromatography eluting with 20% EtOAc-CH_2Cl_2 to obtain 11.7 g (21.0 mmol, yield 97.1%) of the adducts as an oil: IR ν_{max}^{film} cm^{-1} 3400 (OH), 1760 (br, β-lactam and ester), and 1710 (ketone); ^1H NMR ($CDCl_3$) δ 0.04 (s, $-Si(CH_3)_2$), 0.06 (s, $-Si(CH_3)_2$), 0.86 (s, $-Si^tBu$), 0.88 (s, $-Si^tBu$), 1.15~1.28 (3H, mixture, 1′-CH_3), 1.6~2.0 (2H, m, $-CH_2-$), 2.25 (s, CH_3CO-), 2.4~3.2 (mixture of $-CH_2CO-$ and 3-H), 3.5~3.8 (mixture of $-CH_2OSi$ and 4-H), 4.1 (1H, m, 1′-H), and 4.5~6.2 (5H, m, $-CO_2CH=CH_2$). This crude mixture was used in the subsequent reaction without any purification.

To a stirred solution of a mixture of the glyoxylate adducts obtained above (11.7 g, 21.0 mmol) in THF (230 ml) was added at −20°C under a nitrogen atmosphere pyridine (2.34 ml, 29.0 mmol), followed by thionyl chloride (2.00 ml, 27.4 mmol). The mixture was stirred (−20°C, N_2) for 5 minutes. The white precipitates formed were filtered over Celite, washed with benzene. The filtrate and washings were combined and evaporated *in vacuo* without heat. The residue was re-dissolved in benzene, removing any insoluble materials. Evaporation of the solvent gave 12.0 g (20.8 mmol, yield 99.0%) of the chloro compounds as crude oil: IR ν_{max}^{film} cm^{-1} 1775 (β-lactam), 1750 (ester), and 1715 (ketone). This material was immediately used in the subsequent reaction.

A solution of a mixture of the chloro compounds obtained above (12.0 g, 20.8 mmol) in DMF (115 ml) was treated with triphenylphosphine (6.01 g, 22.9 mmol), followed by 2,6-lutidine (2.41 ml, 20.8 mmol). The mixture was stirred at room temperature under a nitrogen atmosphere for 27 hours, then in a cold room for 20 hours. This was diluted with EtOAc, washed with H_2O (×4), brine-H_2O (1:1), dried ($MgSO_4$) and concentrated to yield a crude oil. This oil was purified by column chromatography (pure SiO_2, No. 7754) eluting with 20% EtOAc-CH_2Cl_2 to obtain 6.11 g (7.62 mmol, yield 36.6%) of phosphorane (**11**) as a yellowish oil: Rf 0.36 (20% EtOAc-CH_2Cl_2): IR ν_{max}^{neat} cm^{-1} 1745 (β-lactam), 1715 (ketone), 1650 (ester), and 1620 (phenyl); $[\alpha]_D^{21}$ −4.73° (*c* 1.0, CH_2Cl_2), and 4.00 g (5.99 mmol, yield 24.0%) of phosphorane (**12a**) as yellowish foam: Rf 0.55 (20% EtOAc-CH_2Cl_2); IR ν_{max}^{neat} cm^{-1} 1745 (β-lactam), 1705 (ketone), 1655 (ester), and 1620 (phenyl); $[\alpha]_D^{21}$ −13.2° (*c* 1.0, CH_2Cl_2).

Allyl [(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-[(3*R*)-5-(*tert*-butyldimethylsiloxy)pentan-2-on-3-yl]-2-azetidinon-1-yl]triphenylphosphoranylideneacetate (**12b**)

The title compound **12b** was prepared in 63% yield from azetidinone **10b** by the three-step process described above for the preparation of **11** and **12a**. The glyoxylate adducts (diastereomeric mixture): Rf 0.78 and 0.68 (20% EtOAc-CH_2Cl_2); IR ν_{max}^{neat} cm^{-1} 3400 (OH), 1750 (br, β-lactam and ester), and 1710 (ketone); ^1H NMR ($CDCl_3$) δ 0.07 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $-Si^tBu$), 1.23 (d, $J=7$ Hz, 1'-CH_3), 1.27 (d, $J=7$ Hz, 1'-CH_3), 1.6~2.1 (m, $-CH_2$), 2.25 (s, $-COCH_3$), 2.30 (s, $-COCH_3$), 3.02 (1H, dd, $J_{4\text{-}1''}=6.5$ Hz, $J_{4\text{-}3}=3$ Hz, 4-H), 3.65 (2H, t, $J=5$ Hz, $-CH_2OSi$), 3.9~4.3 (2H, m, 1'-H, 3-H) and 4.5~6.2 (5H, m, $-CO_2CH_2CH=CH_2$).

The chloro compounds: IR ν_{max}^{neat} cm^{-1} 1780 (β-lactam), 1755 (ester), and 1715 (ketone).

The phosphorane **12b**: white foam; Rf 0.50 (20% EtOAc-CH_2Cl_2); IR ν_{max}^{film} cm^{-1} 1745 (β-lactam), 1715 (ketone), 1660 (ester), and 1625.

Anal Calcd for $C_{45}H_{64}NO_6PSi_2$: C 67.38, H 8.04, N 1.75.
Found: C 66.83, H 7.87, N 1.69.

Allyl [(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-(5-hydroxypentan-2-on-1-yl)-2-azetidinon-1-yl]triphenylphosphoranylideneacetate (**13**)

To a stirred solution of phosphorane **11** (3.06 g, 3.81 mmol) in THF (39 ml) was added a mixture of 1 M tetrabutylammonium fluoride in THF (11.68 ml, 11.68 mmol) and acetic acid 3.97 g (66.1 mmol, glacial) at room temperature under a nitrogen atmosphere. The mixture was stirred for 67 hours and then diluted with EtOAc, washed with aqueous $NaHCO_3$. All aqueous layers were combined, saturated with sodium chloride and re-extracted with EtOAc. All EtOAc extracts were combined, washed with brine, dried ($MgSO_4$) and concentrated, yielding orange foam. This was purified by column chromatography eluting with 50% EtOAc-acetone to obtain 1.645 g (2.87 mmol, yield 75.3%) of the title compound **13** as yellowish foam: Rf 0.25 (50% EtOAc-acetone); IR ν_{max}^{film} cm^{-1} 3420 (OH), 1735 (β-lactam), 1710 (sh, ketone), and 1615 (ester); $[\alpha]_D^{21}$ $-35.5°$ (*c* 1.0, CH_2Cl_2).

This material was redisolved in CH_2Cl_2, washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated to yield the material, free of any acidic impurities, for a subsequent reaction.

Allyl (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-hydroxypropyl)carbapen-2-em-3-carboxylate (**14**)

A solution of dihydroxyphosphorane **13** (300 mg, 0.523 mmol) in toluene (10 ml) was heated at reflux under a nitrogen atmosphere for 35 minutes. Evaporation of the solvent *in vacuo* gave a crude oil which was purified by column chromatography (pure SiO_2, No. 7754), eluting with EtOAc to yield 153 mg (0.518 mmol, yield 99.0%) of the title compound **14** as an oil: Rf 0.15 (EtOAc); IR ν_{max}^{film} cm^{-1} 3360 (OH), 1770 (β-lactam), and 1710 (ester); ^1H NMR (acetone-d_6, CFT-20) δ 1.24 (3H, d, $J=6.2$ Hz, 1'-CH_3), 1.5~1.9 (2H, m, $-CH_2-$), 2.5~3.0 (mixture of m, OH, 1-Hs, 2-CH_2), 3.16 (1H, dd, $J_{6\text{-}1'}=7.0$ Hz, $J_{6\text{-}5}=2.8$ Hz, 6-H), 3.53 (2H, t, $J=5.8$ Hz, $-CH_2OH$), 3.9~4.3 (2H, m, 1'-H, 5-H), 4.66 (2H, m, $-CO_2CH_2-$), and 5.1~6.1 (3H, m, vinyl-Hs). This material was used immediately in the subsequent reaction.

Allyl (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-pyridiniopropyl)carbapen-2-em-3-carboxylate Trifluoromethanesulfonate (**15**)

A solution of dihydroxycarbapenem **14** (208 mg, 0.705 mmol) in anhydrous pyridine (5.3 ml) was treated with trifluoromethanesulfonic anhydride (125 μl, 0.743 mmol; freshly distilled from P_2O_5) at $-10°C$ to $-15°C$ (ice-methanol bath) under a nitrogen atmosphere for 5 minutes. The pyridine was removed *in vacuo* without heat and the residue was directly purified by column chromatography on a reverse-phase silica gel (Waters Assoc. Prep PAK-500/C_{18}) eluting with distilled water to obtain 137 mg (0.270 mmol, yield 38.4%) of the title compound **15** as orange solid: IR ν_{max}^{film} cm^{-1} 3440 (OH), 1775 (β-lactam), 1715 (ester), 1630 (C=C), and 1030 (SO_3); ^1H NMR (acetone-d_6, CFT-20) δ 1.22 (3H, d, $J=6.3$ Hz, 1'-CH_3), 2.40 (2H, q, $J=7.5$ Hz, $-CH_2-CH_2N^+$), 2.6~3.1 (mixture of m, 1'-Hs, 2-CH_2OH), 3.18 (1H, dd, $J_{6\text{-}1'}=6.9$ Hz, $J_{6\text{-}5}=3.0$ Hz, 6-H; partially seen), 3.8~4.3 (2H, m, 1'-H, 6-H), 4.6 (2H, m, $-CO_2CH_2-$), 4.92 (2H, t, $J=7.3$ Hz, $-CH_2N^+$), 5.0~6.1 (3H, m, vinyl-Hs), and 8.0~9.4 (5H, m, Ar-Hs). This material was immediately used in the subsequent reaction.

(5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-pyridiniopropyl)carbapen-2-em-3-carboxylate (**4**)

To a stirred solution of compound **15** (135 mg, 0.267 mmol) in CH_3CN (0.8 ml) were added successively a solution of potassium 2-ethylhexanoate in EtOAc (0.5 M, 0.532 ml, 0.266 mmol), triphenylphosphine (6.2 mg) and tetrakis(triphenylphosphine)palladium (0) (6.2 mg, 0.0054 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature (N_2) for 40 minutes. The solvents were evaporated *in vacuo* without heat and the residue purified by column chromatography on a cold reverse-phase silica gel (Waters Assoc. Prep PAK-500/C_{18}), eluting with distilled water. Lyophilization of the appropriate fractions gave 32 mg (0.10 mmol, yield 37%) of the title compound **4** as orange solid: IR ν_{max}^{KBr} cm^{-1} 3400 (OH), 1750 (β-lactam), 1630 (C=C), and 1585 ($-CO_2^-$); ^1H NMR (D_2O, CFT-20) δ 1.23 (3H, d, J=6.4 Hz, 1'-CH_3), 2.19 (2H, q, J=6.5 Hz, $-CH_2CH_2N^+$), 2.6 (2H, m, 2-CH_2), 2.79 (2H, d, J=9.2 Hz, 1-Hs), 3.22 (1H, dd, $J_{6\text{-}1'}$=6.2 Hz, $J_{6\text{-}5}$=2.7 Hz, 6-H), 4.02 (1H, td, $J_{5\text{-}1}$=9 Hz, $J_{5\text{-}6}$=2.7 Hz, 5-H; partially seen), 4.15 (1H, q, J=6.4 Hz, 1'-H), 4.59 (2H, t, J=6.6 Hz, $-CH_2N^+$), 8.02 (2H, t, J=7 Hz, Ar-Hs), 8.52 (1H, t, J=7.8 Hz, Ar-Hs), and 8.81 (2H, d, J=5.4 Hz, Ar-Hs); UV (H_2O) λ_{max} nm 259 (ε 9,600).

Potassium (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-hydroxypropyl)carbapen-2-em-3-carboxylate (**16**)

Deprotection of the allyl ester **14** (140 mg, 0.474 mmol) and purification as described in the preparation of **4** gave 40 mg (0.14 mmol, yield 29%) of the title compound **16** as white powder: Rf 0.44 (H_2O, reverse-phase plate); IR ν_{max}^{neat} cm^{-1} 3360 (OH), 1750 (β-lactam), and 1580 (CO_2^-); ^1H NMR (D_2O, CFT-20) δ 1.24 (3H, d, J=6.4 Hz, 1'-CH_3), 1.66 (2H, q, J=7 Hz, $-CH_2-$), 2.54 (2H, t, J=7.6 Hz, 2-CH_2), 2.84 (2H, d, J=9.0 Hz, 1-Hs), 3.27 (1H, dd, $J_{6\text{-}1'}$=6.2 Hz, $J_{6\text{-}5}$=2.6 Hz, 6-H), 3.53 (2H, t, J=6.4 Hz, $-CH_2OH$), 4.09 (1H, td, $J_{5\text{-}1}$=9 Hz, $J_{5\text{-}6}$=2.6 Hz, 5-H), and 4.17 (1H, q, J=6.3 Hz, 1'-H); UV (H_2O) λ_{max} nm 267 (ε 5,080).

Allyl [(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-(5-acetoxypentan-2-on-1-yl)-2-azetidinon-1-yl]triphenylphosphoranylideneacetate (**17**)

The stirred solution of phosphorane **13** (300 mg, 0.523 mmol) and pyridine (63 μl, 0.78 mmol) in CH_2Cl_2 (5 ml) was added dropwise at -10°C to -15°C (ice-methanol bath) under a nitrogen atmosphere a solution of acetyl chloride in CH_2Cl_2 (1 M, 0.523 ml, freshly prepared). The mixture was stirred at -10°C to -15°C for 20 minutes and diluted with CH_2Cl_2, washed with H_2O, saturated $NaHCO_3$ and then brine. The organic phase was dried (Na_2SO_4) and concentrated to yield 271 mg of a crude oil which was purified by column chromatography eluting with 50% EtOAc-acetone to obtain 246 mg (0.399 mmol, yield 76.3%) of the title compound **17** as foam: Rf 0.42 (50% EtOAc-acetone); IR ν_{max}^{film} cm^{-1} 3450 (OH), 1635 (br, β-lactam, acetate, ketone), and 1630 (ester); ^1H NMR ($CDCl_2$, CFT-20) δ 1.1 (br, 1'-CH_3), 1.88 (2H, q, J=6.7 Hz, $-CH_2-$), 2.03 (3H, s, $-$OAc), 4.04 (2H, t, J=6.3 Hz, $-CH_2OAc$), and 7.6 (br, Ar-Hs), others are not well resolved.

Allyl (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-acetoxypropyl)carbapen-2-em-3-carboxylate (**18**)

A solution of compound **17** (240 mg, 0.390 mmol) in toluene (10 ml) was heated at reflux for 4.5 hours. Evaporation of the solvent *in vacuo* gave crude oily solid which was purified by column chromatography (pure SiO_2, No. 7754) eluting with EtOAc to give 85 mg (0.23 mmol, yield 58%) of the title compound **18** as an oil: Rf 0.36 (EtOAc); IR ν_{max}^{film} cm^{-1} 3500 (OH), 1775 (β-lactam), 1740 (acetate), 1715 (ester), and 1625 (C=C); ^1H NMR (acetone-d_6, CFT-20) δ 1.24 (3H, d, J=6.2 Hz, 1'-CH_3), 1.82 (2H, q, J=6.5, $-CH_2-$), 1.98 (3H, s, OAc), 2.70 (2H, t, J=7 Hz, 2-CH_2), 2.74 (s, OH), 2.98 (2H, d, J=9.6 Hz, 1-Hs), 3.18 (1H, dd, $J_{6\text{-}1'}$=7.0 Hz, $J_{6\text{-}5}$=2.9 Hz, 6-H), 4.04 (2H, t, J=6.6 Hz, $-CH_2OAc$), 3.9~4.3 (2H, m, 1'-H, 5-H), 4.7 (2H, m, $-CO_2CH_2-$), and 5~6.1 (3H, m, vinyl-Hs).

Potassium (5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-acetoxypropyl)carbapen-2-em-3-carboxylate (**19**)

Deprotection of the allyl ester **18** (85 mg, 0.23 mmol) and purification as described in the preparation of **4** provided 47 mg (0.14 mmol, yield 62%) of the title compound **19** as white powder: Rf 0.45 (H_2O, reverse-phase silica gel plate); IR ν_{max}^{KBr} cm^{-1} 3420 (OH), 1750 (sh, β-lactam), 1730 (acetate), and 1590 (CO_2^-); ^1H NMR (D_2O, CFT-20) δ 1.26 (3H, d, J=6.4 Hz, 1'-CH_3), 1.80 (2H, q, J=6.8 Hz, $-CH_2-$), 2.06 (3H, s, OAc), 2.54 (2H, t, J=7.8 Hz, 3-CH_2), 2.86 (2H, d, J=9.0 Hz, 1-Hs), 3.23 (1H, dd, $J_{6\text{-}1'}$=6.2 Hz, $J_{6\text{-}5}$=2.6 Hz, 6-H), 4.07 (2H, t, J=6.3 Hz, $-CH_2OAc$), and 3.9~4.4 (2H, m, 1'-H, 5-H); UV (H_2O) λ_{max} nm

265 (ε 8,400).

Allyl (1*S*,5*R*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-1-[2-(*tert*-butyldimethylsiloxy)ethyl]-2-methylcarbapen-2-em-3-carboxylate (**21b**)

A solution of phosphorane **12b** (1.00 g, 1.25 mmol) in toluene (25 ml) was heated at reflux under a nitrogen atmosphere for 10 hours. Evaporation of the solvent gave an oily residue which was purified by column chromatography (pure SiO_2, No. 7754) eluting with 5% EtOAc-CH_2Cl_2 to obtain 600 mg (1.15 mmol, yield 92.0%) of the title compound **21b** as an oil: Rf 0.5 (5% EtOAc-CH_2Cl_2); IR ν_{max}^{film} cm^{-1} 1775 (β-lactam), 1720 (ester), and 1630 (C=C); ^1H NMR (acetone-d_6, CFT-20) δ 0.09 (s, $-Si(CH_3)_2$), 0.13 (s, $-Si(CH_3)_2$), 0.91 (18H, s, $-Si^tBu$), 1.28 (3H, d, J=6.0 Hz, 1'-CH_3), 1.5~2 (2H, m, $-CH_2-$), 2.12 (3H, d, J=0.8 Hz, 2-CH_3), 3.12 (1H, td, J=10 and 4.5 Hz, 1-H; partially seen), 3.23 (1H, dd, $J_{6\text{-}1'}$=6.5 Hz, $J_{6\text{-}5}$=3.0 Hz, 6-H), 3.7 (2H, m, $-CH_2OSi$), 4.15 (1H, dd, $J_{5\text{-}1}$=10 Hz, $J_{5\text{-}6}$=3 Hz, 5-H), 4.25 (1H, q, J=6.2 Hz, 1'-H), 4.65 (2H, m, $-CO_2CH_2-$), and 5~6.1 (3H, m, vinyl-Hs).

Allyl (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-(2-hydroxyethyl)-2-methylcarbapen-2-em-3-carboxylate (**22b**)

To a stirred solution of disiloxycarbapenem **21b** (183 mg, 0.349 mmol) in THF (4.0 ml) was added at 0~5°C under a nitrogen atmosphere, 1 M solution of tetrabutylammonium fluoride in THF (1.03 ml, 1.03 mmol). The mixture was stirred at 0~5°C (N_2) for 1 hour, and then diluted with EtOAc (30 ml), washed with brine (20 ml), dried ($MgSO_4$) and concentrated to yield a yellow oil. This was purified immediately by column chromatography (pure SiO_2, No. 7754) eluting first with EtOAc to remove non-polar impurities and then with 40% acetone in EtOAc to obtain 77 mg (0.26 mmol, yield 75%) of the title compound **22b** as an oil: Rf 0.59 (50% acetone-EtOAc); IR ν_{max}^{neat} cm^{-1} 3420 (OH), 1750 (β-lactam), 1705 (ester), and 1625 (C=C); ^1H NMR (acetone-d_6, CFT-20) δ 1.27 (3H, d, J=6.2 Hz, 1'-CH_3), 1.6~2.0 (2H, m, $-CH_2-$), 2.10 (3H, d, J=0.9 Hz, 2-CH_3), 2.79 (s, OH), 3.11 (1H, td, J=10 and 5 Hz, 1-H), 3.27 (1H, dd, $J_{6\text{-}1'}$=7.3 Hz, $J_{6\text{-}5}$=3 Hz, 6-H), 3.69 (2H, t, J=6 Hz, $-CH_2OH$), 3.9~4.3 (1H, m, 1'-H), 4.19 (1H, dd, $J_{5\text{-}6}$=3 Hz, 5-H), 4.7 (2H, m, $-CO_2CH_2-$), and 5~6.2 (3H, m, vinyl-Hs). Because of the instability of the compound, this material was immediately used in the subsequent reaction.

Allyl (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-(2-pyridinioethyl)-2-methylcarbapen-2-em-3-carboxylate Trifluoromethanesulfonate (**23b**)

A solution of allyl ester **22b** (103 mg, 0.349 mmol) in pyridine (2.50 ml) was treated with trifluoromethanesulfonic anhydride (62 μl, 0.369 mmol; freshly distilled over P_2O_5) at −10°C to −15°C (ice-methanol bath) under a nitrogen atmosphere for 45 minutes. The pyridine and any volatile materials were removed *in vacuo* at room temperature and the residue was purified by column chromatography on a reverse-phase silica gel (Waters Assoc. Prep PAK-500/C_{18}) eluting with H_2O (60 ml), 10% CH_3CN-H_2O, 20% CH_3CN-H_2O and then 30% CH_3CN-H_2O. The appropriate fractions, eluted with 20~30% CH_3CN-H_2O, were lyophilized to obtain 70 mg (0.14 mmol, yield 40%) of the title compound **23b** as yellow solid: Rf 0.13 (50% CH_3CN-H_2O, reverse-phase silica gel palte); IR ν_{max}^{film} cm^{-1} 3480 (OH), 1770 (β-lactam), 1715 (ester), 1635 (pyridinium), 1490, and 1030 (SO_3^-); ^1H NMR (acetone-d_6, CFT-20) δ 1.37 (3H, d, J=6.1 Hz, 1'-CH_3), 2.08 (3H, d, J=1.3 Hz, 2-CH_3), 2.2~2.7 (2H, m, $-CH_2-$), 2.78 (s, OH), 3.15 (1H, br t, J=11 Hz, 1-H), 3.60 (1H, dd, $J_{6\text{-}1'}$=9.2 Hz, $J_{6\text{-}5}$=3.6 Hz, 6-H), 4~4.4 (1H, m, 1'-H), 4.34 (1H, dd, $J_{5\text{-}1}$=10.5 Hz, $J_{5\text{-}6}$=3.6 Hz, 5-H), 4.7 (2H, m, $-CO_2CH_2-$), 5.06 (2H, t, J=8 Hz, $-CH_2N^+$), 5.0~6.2 (3H, m, vinyl-Hs), 8.30 (2H, t, J=7 Hz, Ar-Hs), 8.8 (1H, m, Ar-H), and 9.28 (2H, dd, J=6.7 and 1.3 Hz, Ar-Hs); UV (EtOH) λ_{max} nm 259 (ε 8,300).

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-(2-pyridinioethyl)-2-methylcarbapen-2-em-3-carboxylate (**5b**)

The allyl ester **23b** (70 mg, 0.14 mmol) was deprotected as described for the preparation of compound **4** to provide 16.6 mg (0.0525 mmol, yield 38%) of the title compound **5b** as yellowish powder: Rf 0.44 (50% CH_3CN-H_2O, reverse-phase silica gel plate); IR ν_{max}^{KBr} cm^{-1} 3400 (br, OH), 1755 (β-lactam), 1625, 1600 (pyridinium), and 1590 (br, CO_2^-); ^1H NMR (D_2O, CFT-20) δ 1.34 (3H, d, J=6.3 Hz, 1'-CH_3), 1.93 (3H, s, 2-CH_3), 2~2.5 (2H, m, $-CH_2-$), 2.99 (1H, td, J=10 and 4.5 Hz, 1H), 3.41 (1H, dd, $J_{6\text{-}1'}$=7.4 Hz,

$J_{6\text{-}5}=3.0$ Hz, 6-H), 4.22 (1H, dd, $J_{5\text{-}1}=10$ Hz, $J_{5\text{-}6}=3$ Hz, 5-H), 4.25 (1H, q, $J=6.5$ Hz, 1'-H), 4.7 (t, $-CH_2N$, partially seen), 8.06 (3H, t, $J=7$ Hz, Ar-Hs), 8.56 (1H, t, $J=8$ Hz, Ar-H), and 8.85 (2H, d, $J=7$ Hz, Ar-Hs); UV (H_2O) λ_{max} nm 260 (ε 12,800).

Potassium (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-(2-hydroxyethyl)-2-methylcarbapen-2-em-3-carboxylate (**24b**)

Deprotection of the allyl ester **22b** (103 mg, 0.349 mmol) and purification as described in the preparation of **4** gave 53 mg (0.18 mmol, yield 52%) of the title compound **24b** as white powder: Rf 0.75 (H_2O, reverse-phase plate); IR ν_{max}^{KBr} cm^{-1} 3360 (OH), 1735 (β-lactam), and 1590 (CO_2^-); ^1H NMR (D_2O, CFT-20) δ 1.28 (3H, d, $J=6.4$ Hz, 1'-CH_3), 1.5~2 (2H, m, CH_2), 1.96 (3H, s, 2-CH_3), 2.97 (1H, td, $J_{1\text{-}5}=10$ Hz, $J_{1\text{-}1''}=3.5$ Hz, 1-H), 3.31 (1H, dd, $J_{6\text{-}1'}=6.1$ Hz, $J_{6\text{-}5}=2.7$ Hz, 6-H), 3.6 (2H, m, CH_2OH), 4.14 (1H, dd, $J_{5\text{-}1}=10$ Hz, $J_{5\text{-}6}=2.8$ Hz, 5-H), and 4.21 (1H, q, $J=6.4$ Hz, 1'-H); UV (H_2O) λ_{max} nm 269 (ε 7,700).

Allyl (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-(2-acetoxyethyl)-2-methylcarbapen-2-em-3-carboxylate (**25b**)

To a stirred solution of dihydroxy carbapenem **22b** (110 mg, 0.373 mmol) in CH_2Cl_2 (4 ml) were added successively in a methanol-ice bath, under a nitrogen atmosphere, freshly prepared 1 M solution of pyridine in CH_2Cl_2 (0.50 ml, 0.50 mmol) and freshly prepared 1 M solution of acetyl chloride in CH_2Cl_2 (0.42 ml, 0.42 mmol). The mixture was stirred (−10°C to −15°C, N_2) for 1 hour. This was diluted with CH_2Cl_2 (20 ml), washed with H_2O, then brine, dried (Na_2SO_4) and the solvent removed, yielding 121 mg of a crude oil. This was purified by column chromatography (pure SiO_2, No. 7754) eluting with 50% EtOAc in CH_2Cl_2 to obtain 58 mg (0.17 mmol, yield 46%) of the title compound **25b** as a colorless oil: Rf 0.26 (20% EtOAc-CH_2Cl_2); IR ν_{max}^{film} cm^{-1} 3490 (OH), 1770 (β-lactam), 1735 (acetate), 1715 (ester), 1620 (C=C), and 1235 (acetate); $[\alpha]_D^{22}$ +90.5° (*c* 0.62, CH_2Cl_2); ^1H NMR (acetone-d_6, CFT-20) δ 1.30 (3H, d, $J=6.1$ Hz, 1'-CH_3), 1.5~2.2 (2H, m, CH_2), 2.01 (3H, s, OAc), 2.11 (3H, d, $J=1.2$ Hz, 2-CH_3), 2.79 (s, OH), 3.07 (1H, td, $J=10.5$ and 3.7 Hz, 1-H), 3.38 (1H, dd, $J_{6\text{-}1'}=7.3$ Hz, $J_{6\text{-}5}=3.2$ Hz, 6-H), 3.9~4.5 (4H, m, 1'-H, 5-H, CH_2OAc), 4.70 (2H, m, CO_2CH_2), and 5~6.3 (3H, m, vinyl protons). This was used immediately in the subsequent reaction.

Potassium (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-(2-acetoxyethyl)-2-methylcarbapen-2-em-3-carboxylate (**26b**)

Deprotection of the allyl ester **25b** (53 mg, 0.16 mmol) and purification as described in the preparation of **4** provided 37.7 mg (0.11 mmol, yield 70%) of the title compound **26b** as fluffy white powder: Rf 0.25 (H_2O, reverse-phase plate); IR ν_{max}^{KBr} cm^{-1} 3390 (OH), 1740 (C=O), 1630 (sh, C=C), 1590 (CO_2^-), and 1245 (acetate); $[\alpha]_D^{22}=+59.8°$ (*c* 0.51, H_2O); ^1H NMR (D_2O, CFT-20) δ 1.29 (3H, d, $J=6.3$ Hz, 1'-CH_3), 1.97 (3H, d, $J=0.7$ Hz, 1'-CH_3), 2.08 (3H, s, OAc), 3.00 (1H, td, $J=10$ and 3.5 Hz, 1-H), 3.40 (1H, dd, $J_{6\text{-}1}=6.1$ Hz, $J_{6\text{-}5}=2.8$ Hz, 6-H), and 4~4.4 (4H, m, 1'-H, 5-H, CH_2OAc); UV (H_2O) λ_{max} nm 268 (ε 4,870).

The 1α-isomer series, **5a**, **21a**, **22a**, **23a**, **24a**, **25a**, and **26a** were prepared in the same manner as described above for the 1β-isomer series. The physical properties and the spectroscopic data are as follows:

5a: Yield 34%; white powder; Rf 0.35 (15% CH_3CN-H_2O); IR ν_{max}^{KBr} cm^{-1} 3400 (OH), 1755 (β-lactam), 1630 (C=C), and 1575 (CO_2^-); ^1H NMR (D_2O, CFT-20) δ 1.30 (3H, d, $J=6.4$ Hz, 1'-CH_3), 1.88 (3H, d, $J=1.4$ Hz, 2-CH_3), 2.27 (2H, m, $-CH_2-$), 3.1~3.5 (1H, m, 1-H), 3.34 (1H, dd, $J_{6\text{-}1'}=7.2$ Hz, $J_{6\text{-}5}=2.6$ Hz, 6-H), 3.92 (1H, dd, $J_{5\text{-}1}=7.9$ Hz, $J_{5\text{-}6}=2.6$ Hz, 5-H), 4.22 (1H, q, $J=6.7$ Hz, 1'-H), 4.66 (2H, t, $J=8.2$ Hz, $-CH_2N^+$), 8.05 (2H, t, $J=7.5$ Hz, Ar-Hs *meta* to N), 8.55 (1H, t, $J=8$ Hz, Ar-Hs *para* to N), and 8.88 (2H, dd, $J=6.7$ and 1.3 Hz, Ar-Hs *ortho* to N); UV (H_2O) λ_{max} nm 257 (ε 6,440).

21a: Yield 98%; 4 hours reflux; an oil; Rf 0.67 (10% EtOAc-CH_2Cl_2); IR ν_{max}^{neat} cm^{-1} 1780 (β-lactam), 1720 (ester), and 1630 (C=C); ^1H NMR (acetone-d_6, CFT-20) δ 0.08 (6H, s, $-Si(CH_3)_2$), 0.11 (6H, s, $-Si(CH_3)_2$), 0.90 (9H, s, $-Si^tBu$), 0.91 (9H, s, $-Si^tBu$), 1.27 (3H, d, $J=6.3$ Hz, 1'-CH_3), 1.5~2.0 (2H, m, $-CH_2-$), 2.09 (3H, d, $J=1.7$ Hz, 2-CH_3), 3.18 (1H, dd, $J_{6\text{-}1'}=4.7$ Hz, $J_{6\text{-}5}=2.7$ Hz, 6-H), 3.29 (1H, m, 1-H), 3.77 (1H, dd, $J_{5\text{-}1}=5.7$ Hz, $J_{5\text{-}6}=2.7$ Hz, 5-H), 3.8 (2H, m, $-CH_2OSi$), 4.26 (1H, q, $J=5$ Hz, 1'-H), 4.65 (1H, m, $-CO_2CH_5$), and 5~6.2 (3H, m, vinyl-Hs).

22a: Yield 72%; an oil; Rf 0.52 (50% EtOAc-acetone); IR ν_{max}^{neat} cm^{-1} 3400 (OH), 1760 (β-lactam), 1715 (ester), and 1625 (C=C); ^1H NMR (acetone-d_6, CFT-20) δ 1.25 (3H, d, $J=6.2$ Hz, 1'-CH_3), 2.08 (3H,

d, J=1.7 Hz, 2-CH_3), 3.13 (1H, dd, $J_{6\text{-}1'}$=8.0 Hz, $J_{6\text{-}5}$=2.7 Hz, 6-H), 3.2 (1H, m, 1-H), 3.76 (2H, t, J=6.1 Hz, $-CH_2OH$), 3.87 (1H, dd, $J_{5\text{-}1}$=8.3 Hz, J=2.6 Hz, 5-H), 4.05 (1H, m, 1'-H), 4.68 (2H, m, $-CO_2CH_2-$), and 5.0~6.2 (3H, m, vinyl-Hs).

23a: Yield 43%; yellowish powder; Rf 0.14 (50% CH_3CN-H_2O, reverse-phase silica gel plate); IR ν_{max}^{film} cm^{-1} 3470 (OH), 1770 (β-lactam), 1710 (ester), 1635 (C=C), 1495, and 1030 ($-SO_3^-$); ^1H NMR (acetone-d_6, CFT-20) δ 1.32 (3H, d, J=6.2 Hz, 1'-CH_3), 2.07 (3H, d, J=1.2 Hz, 2-CH_3), 2~2.6 (2H, m, $-CH_2-$), 3.25 (1H, dd, $J_{6\text{-}1'}$=8.9 Hz, $J_{6\text{-}5}$=2.7 Hz, 6-H), 2.9~3.7 (1H, m, 1-H), 4.09 (1H, dd, $J_{5\text{-}1}$=8.0 Hz, $J_{5\text{-}6}$=2.7 Hz, 5-H), 3.9~4.5 (1H, m, 1'-H), 4.7 (2H, m, $-CO_2CH_2-$), 5.00 (2H, t, J=8 Hz, $-CH_2N^+$), 4.8~6.2 (3H, m, vinyl-Hs), 8.30 (2H, t, J=6.5 Hz, Ar-Hs), 8.78 (1H, t, J=8 Hz, Ar-H), and 9.35 (2H, dd, J=6.8 and 1.3 Hz, Ar-Hs).

24a: Yield 21%; yellowish powder; Rf 0.69 (H_2O, reverse-phase plate); IR ν_{max}^{KBr} cm^{-1} 3400 (OH), 1740 (β-lactam), and 1585 (CO_2^-); ^1H NMR (D_2O, CFT-20) δ 1.28 (3H, d, J=6.4 Hz, 1'-CH_3), 1.5~2 (2H, m, CH_2), 1.94 (3H, d, J=1.2 Hz, 2-CH_3), 2.3~3.2 (1H, m, 1-H), 3.30 (1H, dd, $J_{6\text{-}1'}$=6 Hz, $J_{6\text{-}5}$=2.1 Hz, 6-H), 3.5~3.9 (3H, m, CH_2OH, 5-H), and 4.2 (1H, m, 1'-H); UV (H_2O) λ_{max} nm 267 (ε 7,800).

25a: Yield 46%; an oil; Rf 0.34 (50% EtOAc-CH_2Cl_2); IR ν_{max}^{film} cm^{-1} 3460 (OH), 1770 (β-lactam), 1740 (acetate), 1715 (ester), 1625 (C=C), and 1240 (acetate); $[\alpha]_D^{22}$ +87.3° (c 0.3, CH_2Cl_2); ^1H NMR (acetone-d_6, CFT-20) δ 1.27 (3H, d, J=6.2 Hz, 1'-CH_3), 1.5~1.3 (2H, m, CH_2), 2.00 (3H, s, OAc), 2.10 (3H, d, J=1.5 Hz, 2-CH_3), 2.78 (s, OH), 3.16 (1H, dd, $J_{6\text{-}1'}$=7.2 Hz, $J_{6\text{-}5}$=2.7 Hz, 6-H), 3~3.3 (1H, m, 1-H), 3.86 (1H, dd, $J_{5\text{-}1}$=8.3 Hz, $J_{5\text{-}6}$=2.6 Hz, 5-H), 4~4.3 (3H, m, 1'-H and CH_2OAc), 4.65 (2H, m, CO_2CH_2), and 5~6.2 (3H, m, vinyl protons).

26a: Yield 52%; white powder; IR ν_{max}^{KBr} cm^{-1} 3400 (OH), 1740 (C=O), 1630 (C=C), 1590 (CO_2^-), and 1250 (acetate); ^1H NMR (D_2O, CFT-20) δ 1.27 (3H, s, J=6.4 Hz, 1'-CH_3), 1.5~2.3 (2H, m, CH_2), 1.94 (3H, d, J=1.5 Hz, 2-CH_3), 2.08 (3H, s, OAc), 3.30 (1H, dd, $J_{6\text{-}1'}$=5.9 Hz, $J_{6\text{-}5}$=2.5 Hz, 6-H), 3.82 (1H, dd, $J_{5\text{-}1}$=8.2 Hz, $J_{5\text{-}6}$=2.5 Hz, 5-H), and 4.4~4 (3H, m, 1'-H and CH_2OAc); UV (H_2O) λ_{max} nm 267 (ε 5,180).

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