THE SYNTHESIS OF 2-(FUNCTIONALIZED METHYL)-1β-METHYLCARBAPENEMS

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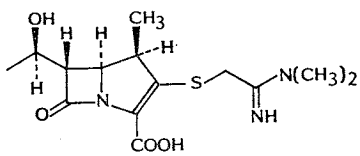
The synthesis of 1β-methylcarbapenems having a $ROCH_2$ substituent at the 2-position is described. Their *in vitro* antibacterial activity and DHP-I susceptibilities are presented.

Due to the increased chemical and metabolic stability and the potent antibacterial activity of (−)-(1*R*,1″*R*,5*S*,6*S*)-2-(2′-*N*,*N*-dimethylamino-2′-iminoethylthio)-6-(1″-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylic acid (**1**)[1], the 1β-methylcarbapenems, in general, are of great interest to us and others. Specifically, our recent synthetic efforts have been directed toward the preparation of 1β-methylcarbapenems having a functionalized methyl group at the 2-position as in **2**. This publication will present the preparation and bioactivity of **2** where X=O and R has been varied as indicated in structures **2a**~**2g**. Cases where XR=SR in structure **2** will be discussed in a paper now in preparation from these laboratories. Similar 2-(functionalized methyl) compounds have been synthesized in the penem and carbapenem series[2~6]. However, in the carbapenem series, it has been reported that hydrogenolytic deblock to give the material analogous to **2a** was unsuccessful and that other *O*-derivatives were unstable in high aqueous concentration[6].

Chemistry

The pyridyl thioester **3a**[7] was converted to the methyl ketone **3b** with MeMgBr (66%), and the silyl group was removed to yield **3c** (0.2 M HCl in aqueous MeOH 84%). Reprotection of the alcohol with allyl chloroformate in the presence of 4-dimethylaminopyridine (DMAP) provided **3d** (80%). Interchange of the protecting groups was deemed necessary since F^--mediated desilylation (in some instances where X=S) had caused partial double bond migration to the exocyclic position. Hydroxylation of the enolate of **3d** was accomplished using MoOPH[8] to give **3e** (58%). Cyclization in refluxing toluene then provided the key 2-hydroxymethyl-1β-methylcarbapenem **4a** (76%) which was deblocked[9] to give **2a** (66%).

A MITSUNOBU reaction[10] on **4a** provided the acetoxymethyl species **4b** (75%) which was deblocked as above to give **2b** (45%). Reaction



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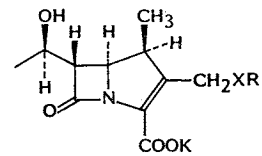
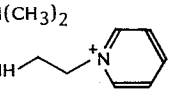
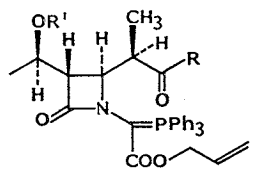
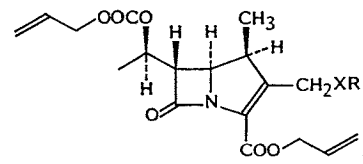


2a XR = OH
2b XR = OAc
2c XR = $OCONH_2$
2d XR = $OCONHCH_3$
2e XR = OCONHPh
2f XR = $OCON(CH_3)_2$
2g XR = OCONH





3a R = S-pyridine R' = Si
3b R = CH_3 R' = Si
3c R = CH_3 R' = H
3d R = CH_3 R' = COO
3e R = CH_2OH R' = COO



4a XR = OH
4b XR = OAc
4c XR = $OCONH_2$
4d XR = $OCONHCH_3$
4e XR = OCONHPh
4f XR = $OCON(CH_3)_2$
4g XR = OCONH
4h XR = OCONH

Table 1. Relative antibacterial potencies[a] and DHP-I susceptibilities of **2a**~**2g**.

Organism	2a	2b	2c	2d	2e	2f	2g
Staphylococcus aureus[b]	0.4	0.7	0.9	0.8	1.2	1.4	0.87
Enterococcus[c]	1.0	2.8	5.7	3.7	2.8	1.2	2.3
Escherichia coli[d]	2.3	4.0	6.1	5.7	0.6	0.6	0.93
Enterobacter[e]	3.7	7.0	23	9.8	0.2	0.8	2.1
Klebsiella[f]	2.0	2.5	7.0	7.0	0.2	0.4	1.1
Serratia[g]	4.3	12	32	16	0.3	1.4	2.1
Proteus[h] (indole+ and −)	3.0	28	15	16	4.9	11	2.5
Pseudomonas aeruginosa[i]	0.2	0.09	0.4	0.2	0.03	0.04	0.33
DHP[j] susceptibility	0.76	0.52	0.39	0.59	1.35	0.29	0.05

[a] Agar diffusion assay: Antibiotic activity is expressed as the geometric mean potency against the genus or species relative to thienamycin=1. Strains, deposited in the Culture Collection of Merck & Co., Inc., are as follows.
[b] MB No. 2985, 2314, 210, 2867.
[c] MB No. 2862, 2863, 2864.
[d] MB No. 2482, 2964, 2884, 2891.
[e] MB No. 2646, 2647, 2828, 2902, 2903, 2906.
[f] MB No. 2888, 2890, 2889, 2921, 2922.
[g] MB No. 2840, 2855.
[h] MB No. 3125, 2830, 2831, 2833, 2834.
[i] MB No. 2835, 3286, 3350, 3286CB.
[j] DHP assay: Activity is expressed relative to thienamycin=1.

of **4a** with trichloroacetyl isocyanate in CCl_4 followed by concentration and methanolysis in the presence of silica gel[11] provided the carbamoyl **4c** (85%) which was deblocked to give **2c** (46%).

The bioactivity of **2c** (Table 1) prompted us to explore the urethane area more completely. Condensation of **4a** with excess methyl and phenyl isocyanate in a sealed tube gave **4d** (79%) and **4e** (54%) which were deblocked to provide **2d** (65%) and **2e** (36%) respectively. The dimethylurethane **4f** (32%) was prepared by treating **4a** with phosgene in toluene in the presence of dimethylaniline followed by dimethylamine in toluene. Deblock then provided **2f** (59%).

The effect of the presence of a cationic site on the urethane side chain was demonstrated by preparing the iodoethylurethane **4g** (74%) by treating **4a** with $I(CH_2)_2NCO$ in toluene in the presence of 1 equivalent pyridine. The iodo was then displaced by heating **4g** at 70°C in pyridine to give the

pyridinium iodide **4h** (52%). Deblock then gave **2g** (29%).

Biological Results and Discussion

The bioactivities and DHP-I susceptibilities[12] of **2a**~**2g** are reported in Table 1. The unsubstituted urethane **2c** is by far the most active compound and except for its DHP-I susceptibility, and reduced *Pseudomonas* Index (retains only 40% of the activity of thienamycin) would warrant further attention. As expected, the cationic side chain present in **2g** did substantially decrease the compound's susceptibility to the DHP-I dipeptidase, but its acitivity, except for *Pseudomonas*, was much reduced relative to **2c**. A report on our further work in the area of 2-(functionalized methyl)-1β-methylcarbapenems is planned.

Experimental

IR spectra were recorded on a Perkin-Elmer 137 grating spectrophotometer. Mass spectra were recorded on a LKB Model 9000 spectrometer. ^{1}H NMR spectra were recorded on Varian XL-200 (200 MHz) and Varian SC-300 (300 MHz) spectrometers. Chemical shifts are expressed in ppm downfield from TMS. In the case of spectra taken in D_2O no internal standard was used; the DOH peak is assigned at 4.80 ppm. UV spectra were recorded on a Perkin-Elmer 552A spectrophotometer. Preparative TLC was performed on 1,000-μm Analtech Silica gel GF plates. Product bands were extracted with EtOAc - CH_2Cl_2 (1 : 1) or MeOH - CH_2Cl_2 (1 : 9). Aqueous preparative TLC was performed on 500 or 1,000-μm Analtech RPS-F plates. Column chromatography was performed on Baker (60~200 mesh) silica gel. Product solutions were concentrated at ambient temperature using a Büchi rotatory evaporator at 15~25 mmHg.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1″*R*)-1″-(methylcarbonyl)ethyl]azetidin-2-one (**3b**)

To a stirred soln of 1.06 g (1.41 mmol) thiopyridyl ester **3a**[7] in 25 ml anhydrous THF at −78°C under N_2 was added dropwise 690 μl 3 M MeMgBr (2.07 mmol) in ether. After 5 minutes an additional 140 μl 3 M MeMgBr (0.42 mmol) was added, and stirring was continued for 10 minutes. The reaction mixture was added to 35 ml satd NH_4Cl soln, H_2O and 40 ml EtOAc. The aq layer was extracted again with EtOAc. The combined organic layers were washed sequentially with 35 ml cold 1 N HCl, 35 ml cold 10% $NaHCO_3$ and 35 ml brine. After drying over $MgSO_4$ the organic layer was concd *in vacuo*, and the resultant foam was chromatographed on silica gel (gradient elution with 0 to 20% EtOAc in CH_2Cl_2) to give 800 mg **3b** (approx 90% pure).

Preparative TLC eluting with EtOAc - hexane (1 : 1) then provided pure **3b** (650 mg, 70%): IR (CH_2Cl_2) cm^{-1} 1750, 1720, 1650, 1625; MS *m/z* 658 (M+1), 600 (M−*tert*-butyl); ^{1}H NMR ($CDCl_3$) δ (selected absorbances) 0.8 ($C(CH_3)_3$), 2.22 (s, CH_3C=O), 6.0 (m, CH=CH_2), 7.4~8.0 (aromatic protons).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1′*R*)-1′-hydroxyethyl]-4-[(1″*R*)-1″-(methylcarbonyl)ethyl]azetidin-2-one (**3c**)

At ambient temperature 38 mg (0.058 mmol) methyl ketone **3b** was stirred under N_2 in 2.4 ml of 0.2 N HCl in MeOH - H_2O (9 : 1) for 6 hours. After the addition of 1.2 ml 1 M K_2HPO_4, 0.7 ml 1 M KH_2PO_4, 5 ml H_2O and extraction with 5 ml EtOAc, the aq phase was again extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concd *in vacuo* to give crude **3c**. Preparative TLC eluting with EtOAc provided **3c** (26 mg, 84%): IR (CH_2Cl_2) cm^{-1} 3550, 1745, 1700, 1640, 1620; MS *m/z* 544 (M+1), 262 (Ph_3P), 185; ^{1}H NMR ($CDCl_3$) δ (selected absorbances) 1.01 (d, CH_3CHOH), 1.53 (d, 1β-CH_3), 2.19 (s, CH_3C=O), 6.0 (m, CH=CH_2), 7.4~8.0 (aromatic protons).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1′*R*)-1′-[[(allyloxy)carbonyl]oxy]ethyl]-4-[(1″*R*)-1″-(methylcarbonyl)ethyl]azetidin-2-one (**3d**)

A stirred soln of 66 mg (0.12 mmol) of **3c** in 0.5 ml CH_2Cl_2 was treated with 19 mg (0.16 mmol)

DMAP and 16 μl (0.15 mmol) allyl chloroformate at 0°C under N_2 for 10 minutes followed by 50 minutes at ambient temperature. Equivalent amounts of the chloroformate and DMAP were then added and stirring continued for 2.5 hours. Equivalent amounts of both reagents were again added followed by an additional 2-hour of reaction time. Dilution of the reaction mixture with CH_2Cl_2 was followed by extraction with 1.5 ml 1 M K_2HPO_4 and 1 ml 1 M KH_2PO_4. The aq layer was again extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concd *in vacuo* to provide crude **3d**. Preparative TLC eluting with EtOAc - hexane (1 : 1) afforded **3d** (61 mg, 80%): IR (CH_2Cl_2) cm^{-1} 1750, 1725, 1650, 1625; MS *m/z* 628 (M+1), 570 (M−O−allyl), 262 (Ph_3P); ^1H NMR ($CDCl_3$) δ (selected absorbances) 1.07 (d, CH_3CHO), 1.38 (d, 1β-CH_3), 5.94 (m, $CH=CH_2$), 7.4~8.0 (aromatic protons).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1′*R*)-1′-[[(allyloxy)carbonyl]oxy]ethyl]-4-[(1″*R*)-1″-(hydroxymethylcarbonyl)ethyl]azetidin-2-one (**3e**)

To a stirred soln of 264 μl (1.9 mmol) diisopropylamine in 9 ml anhydrous THF at 0°C under N_2 was added 1.2 ml of 1.6 M BuLi (1.9 mmol) in hexane. After a few minutes, 6.5 ml of the above LDA soln (1.2 mmol) was added to a soln of 591 mg **3d** (0.94 mmol) in 21 ml THF at −78°C under N_2. After 30 seconds 622 mg (1.43 mmol) MoOPH was added, and the reaction mixture was warmed to −30°C and stirred for 1 hour. The reaction mixture was then poured into 10 ml concd Na_2SO_3, 4.5 ml 1 M KH_2PO_4, 36 ml H_2O and 55 ml EtOAc and stirred for 5 minutes. The layers were separated, and the aq layer was re-extracted with EtOAc. The combined organic layers were extracted with brine, dried ($MgSO_4$) and concd *in vacuo* to give crude **3e**. Preparative TLC eluting with EtOAc - CH_2Cl_2 (1 : 1) afforded **3e** (348 mg, 58%): IR (CH_2Cl_2) cm^{-1} 3590 (br), 1740, 1640, 1620; MS *m/z* 644 (M+1), 262 (Ph_3P); ^1H NMR ($CDCl_3$) δ (selected absorbances) 1.08 (d, CH_3CHO), 1.39 (d, 1β-CH_3), 4.28 (CH_2OH), 5.93 (m, $CH=CH_2$), 7.4~7.9 (aromatic protons).

Allyl (1*S*,5*R*,6*S*)-2-Hydroxymethyl-6-[(1′*R*)-1′-[[(allyloxy)carbonyl]oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (**4a**)

A soln of 338 mg (0.53 mmol) of **3e** in 35 ml toluene was heated at reflux for 1 hour under N_2. After conc *in vacuo* preparative TLC of the crude material eluting with EtOAc - CH_2Cl_2 (1 : 1) provided the bicyclic carbapenem **4a** (145 mg, 76%): IR (CH_2Cl_2) cm^{-1} 3560 (br), 1775, 1740, 1720 (sh); MS *m/z* 366 (M+1); ^1H NMR ($CDCl_3$) δ 1.20 (d, 1β-CH_3), 1.46 (d, CH_3CHO), 3.14 (t, *J*=6 Hz, OH), 3.23 (m, 1-H), 3.42 (dd, *J*=3 and 8 Hz), 4.18 (dd, *J*=3 and 10 Hz, 6-H), 4.37 (dd, *J*=15 and 6 Hz, CH_2OH), 4.50 (dd, *J*=15 and 6 Hz, CH_2OH), 4.62 and 4.77 (center of m's for two $CH_2CH=CH_2$), 5.13 (m, 1′-H), 5.26~5.48 (m, two $CH=CH_2$), 5.94 (m, two $CH=CH_2$).

Potassium (1*S*,5*R*,6*S*)-2-Hydroxymethyl-6-[(1′*R*)-1′-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**2a**)

A mixture of 19 mg (0.052 mmol) of **4a**, 4 mg Ph_3P (0.0153 mmol), 4.8 mg tetrakistriphenylphosphine palladium (0.0042 mmol), 110 μl of 0.5 M potassium 2-ethylhexanoate in EtOAc (0.055 mmol) and 8.8 μl (0.055 mmol) 2-ethylhexanoic acid in 2 ml EtOAc - CH_2Cl_2 (1 : 1) was stirred at ambient temperature for 2 hours. After conc *in vacuo*, the residue was washed with Et_2O (3×1 ml). The resultant white solid was dried *in vacuo*, dissolved in 600 μl 2% EtOH in H_2O and chromatographed on two 500-μm RPS-F plates eluting with 4% EtOH in H_2O in a cold room. The main UV active band was extracted with 30 ml CH_3CN - H_2O (4 : 1), concd *in vacuo* to a volume of approx 6 ml and extracted with hexane (2×2 ml). Lyophilization of the aq soln at 0°C yielded the title compound **2a** (9.6 mg, 66%): UV $\lambda_{max}^{H_2O}$ nm (ε) 268 (4,500) (NH_2OH extinguishable); ^1H NMR (D_2O, DOH at 4.80) δ 1.10 (d, 1β-CH_3), 1.27 (d, CH_3CHO), 3.26 (m, 1-H), 3.40 (dd, *J*=3 and 6 Hz, 6-H), 4.21 (m, 5-H and 1′-H), 4.26 (d, *J*=14 Hz, CH_2OH), 4.64 (d, *J*=14 Hz, CH_2OH).

Allyl (1*S*,5*R*,6*S*)-2-Acetoxymethyl-6-[(1′*R*)-1′-[[(allyloxy)carbonyl]oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (**4b**)

At ambient temperature under N_2 12 μl (0.08 mmol) diethylazodicarboxylate, 4.5 μl HOAc (0.08 mmol) and 21 mg Ph_3P (0.08 mmol) were added to a stirred soln of 25 mg (0.07 mmol) of **4a** in 0.7 ml Et_2O. After 5 minutes 1 ml of 0.5 M pH 7 phosphate buffer and additional Et_2O was added. The

layers were separated, and the aq layer was re-extracted with Et_2O. The combined Et_2O layers were washed with brine, dried ($MgSO_4$) and concd *in vacuo* to give crude **4b**. Preparative TLC eluting with EtOAc - hexane (1 : 1) provided **4b** (22 mg, 75%): IR (CH_2Cl_2) cm^{-1} 1790, 1755; ^1H NMR ($CDCl_3$) δ 1.19 (d, 1β-CH_3), 1.47 (d, CH_3CHO), 2.10 (s, Ac), 3.29 (m, 1-H), 3.45 (dd, J=3 and 8 Hz, 6-H), 4.24 (dd, J=3 and 10 Hz, 5-H), 4.60~4.92 (m's, $COOCH_2$), 4.87 (d, J=15 Hz, CH_2OAc), 5.16 (m, CH_3CHO), 5.26~5.54 (m, CH=CH_2), 5.44 (d, J=15 Hz, CH_2OAc), 5.97 (m, CH=CH_2).

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

Deblocking 22 mg (0.054 mmol) of **4b** as described in the preparation of **2a** provided crude **2b** which was dissolved in 0.8 ml CH_2Cl_2 and chromatographed in the cold on two 500-μm RPS-F plates eluting with 5% EtOH in H_2O. Work-up of the plates and lyophilization as described for **2a** provided the title compound **2b** (7.9 mg, 45%): UV $\lambda_{max}^{H_2O}$ nm (ε) 267 (4,700) (NH_2OH extinguishable); ^1H NMR (D_2O, DOH at 4.80) δ 1.10 (d, 1β-CH_3), 1.25 (d, CH_3CHO), 2.08 (s, Ac), 3.24 (m, 1-H), 3.42 (dd, J=2 and 6 Hz, 6-H), 4.19 (m, 5-H and 1′-H), 4.71 (half of d, other half under DOH, CH_2OAc), 5.30 (d, J=12 Hz, CH_2OAc).

Allyl (1*S*,5*R*,6*S*)-2-[[(Aminocarbonyl)oxy]methyl]-6-[(1′*R*)-1′-[[(allyloxy)carbonyl]oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (**4c**)

A soln of trichloroacetyl isocyanate (0.073 mmol) in 0.5 ml CCl_4 was added to 25 mg (0.068 mmol) of **4a** in 2 ml CCl_4. After stirring under N_2 for 1 hour at ambient temperature, the reaction was concd *in vacuo*. The residue was dissolved in 1.1 ml MeOH and stirred in the presence of 280 mg silica gel at 35°C for 2 hours. The mixture was filtered, and the silica gel was washed well with MeOH - CH_2Cl_2 (1 : 9) (5×2 ml) and then EtOAc - CH_2Cl_2 (1 : 1) (2×5 ml). The combined initial filtrate and washings were concd *in vacuo* and then redissolved in CH_2Cl_2 and dried ($MgSO_4$). Conc *in vacuo* then provided the crude carbamate **4c**. Preparative TLC eluting with EtOAc - CH_2Cl_2 (1 : 5) provided pure **4c** (24 mg, 85%): IR (CH_2Cl_2) cm^{-1} 3650, 3530, 1780, 1740; ^1H NMR ($CDCl_3$) δ 1.20 (d, 1β-CH_3), 1.47 (d, CH_3CHO), 3.30 (m, 1-H), 3.45 (dd, J=3 and 8 Hz, 6-H), 4.23 (dd, J=3 and 10 Hz, 5-H), 4.60~4.94 (m, $COOCH_2$'s), 4.88 (d, J=14 Hz, CH_2O), 5.14 (m, 1′-H), 5.26~5.52 (m, CH=CH_2's), 5.43 (d, J=14 Hz, CH_2O), 5.98 (m, CH=CH_2's).

Potassium (1*S*,5*R*,6*S*)-2-[[(Aminocarbonyl)oxy]methyl]-6-[(1′*R*)-1′-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**2c**)

Deblocking 24 mg (0.058 mmol) of **4c** as described in the preparation of **2a** provided crude **2c** which was dissolved in 600 μl 2.5% EtOH in H_2O and chromatographed in the cold on two 500-μm RPS-F plates eluting with 5% EtOH in H_2O. Work-up of the plates and lyophilization as described for **2a** provided the title compound **2c** (11 mg, 60%): UV $\lambda_{max}^{H_2O}$ nm (ε) 267 (4,600) (NH_2OH extinguishable); ^1H NMR (D_2O, DOH at 4.80) δ 1.13 (d, 1β-CH_3), 1.27 (d, CH_3CHO), 3.26 (m, 1-H), 3.44 (dd, J=3 and 6 Hz, 6-H), 4.24 (m, 5-H and 1′-H), 4.72 (half of d, CH_2O), 5.28 (d, J=14 Hz, CH_2O).

Allyl (1*S*,5*R*,6*S*)-2-[[(Methylaminocarbonyl)oxy]methyl]-6-[(1′*R*)-1′-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**4d**)

A soln of 53 mg (0.15 mmol) of **4a** in 650 μl MeNCO was heated in a sealed tube at 65°C for 24 hours. The reaction mixture was concd *in vacuo* to give the crude carbamate **4d**. Preparative TLC eluting with EtOAc - hexane, 1 : 1 provided **4d** (46 mg, 73%): IR (CH_2Cl_2) cm^{-1} 3570, 1780, 1740 (sh), 1720; ^1H NMR ($CDCl_3$) δ 1.18 (d, 1β-CH_3), 1.45 (d, CH_3CHO), 2.81 (d, NHCH_3), 3.26 (m, 1-H), 3.42 (dd, J=3 and 8 Hz, 6-H), 4.19 (dd, J=3 and 10 Hz, 5-H), 4.58~4.86 (m, $COOCH_2$'s), 4.86 (d, J=14 Hz, CH_2O), 5.12 (m, 1′-H), 5.24~5.50 (m, CH=CH_2's), 5.44 (d, J=14 Hz, CH_2O), 5.95 (m, CH=CH_2's).

Potassium (1*S*,5*R*,6*S*)-2-[[(Methylaminocarbonyl)oxy]methyl]-6-[(1′*R*)-1′-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**2d**)

Deblocking 58 mg (0.14 mmol) of **4d** as described in the preparation of **2a** provided crude **2d** which was dissolved in 1 ml H_2O and chromatographed in the cold on two 1,000-μm RPS-F plates eluting

with 5% EtOH in H_2O. Work-up of the plates and lyophilization as described for **2a** provided the title compound **2d** (30 mg, 64%): UV $\lambda_{max}^{H_2O}$ nm (ε) 267 (6,300) (NH_2OH extinguishable); ^1H NMR (D_2O, DOH at 4.80) δ 1.16 (d, 1β-CH_3), 1.31 (d, CH_3CHO), 2.74 (s, NHCH_3), 3.27 (m, 1-H), 3.46 (dd, J=3 and 6 Hz, 6-H), 4.26 (m, 5-H and 1'-H), 4.74 (half of d, CH_2O), 5.32 (d, J=14 Hz, CH_2O).

Allyl (1*S*,5*R*,6*S*)-2-[[(Phenylaminocarbonyl)oxy]methyl]-6-[(1'*R*)-1'-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**4e**)

A soln of 57 mg (0.16 mmol) of **4a** in 0.3 ml PhNCO and 0.3 ml toluene was heated in a sealed tube at 70°C overnight. After conc *in vacuo*, the residue was purified by preparative TLC eluting with EtOAc - CH_2Cl_2 (1 : 9) to give **4e** (41 mg, 54%): IR (CH_2Cl_2) cm^{-1} 3530, 1780, 1740; ^1H NMR ($CDCl_3$) δ 1.21 (d, 1β-CH_3), 1.46 (d, CH_3CHO), 3.31 (m, 1-H), 3.43 (dd, J=3 and 8 Hz, 6-H), 4.21 (dd, J=3 and 10 Hz, 5-H), 4.54~4.88 (m, COOCH_2's), 4.95 (d, J=14 Hz, CH_2O), 5.12 (m, 1'-H), 5.22~5.40 (m, CH=CH_2's), 5.52 (d, J=14 Hz, CH_2O), 5.93 (m, CH=CH_2's), 6.64 (br s, NH), 7.02~7.40 (m, aromatic protons).

Potassium (1*S*,5*R*,6*S*)-2-[[(Phenylaminocarbonyl)oxy]methyl]-6-[(1'*R*)-1'-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**2e**)

Deblocking 40 mg (0.08 mmol) of **4e** as described in the preparation of **2a** provided crude **2e** which was dissolved in 1 ml CH_2Cl_2 and chromatographed in the cold on two 1,000-μm RPS-F plates eluting with CH_3CN - H_2O (1 : 9). Work-up of the plates and lyophilization as described for **2a** provided the title compound **2e** (12 mg, 36%): UV $\lambda_{max}^{H_2O}$ nm (ε) 233, 267 (7,100) (NH_2OH extinguishable); ^1H NMR (D_2O, DOH at 4.80) δ 1.15 (d, 1β-CH_3), 1.27 (d, CH_3CHO), 3.28 (m, 1-H), 3.44 (dd, J=3 and 6 Hz, 6-H), 4.21 (m, 5-H and 8-H), 4.87 (part of d, CH_2O), 5.39 (d, J=14 Hz, CH_2O), 7.11~7.44 (m, aromatic protons).

Allyl (1*S*,5*R*,6*S*)-2-[[(Dimethylaminocarbonyl)oxy]methyl]-6-[(1'*R*)-1'-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**4f**)

To a soln of 26 mg (0.071 mmol) of **4a** in 1 ml toluene at 0°C under N_2 was added 13.5 μl (0.11 mmol) *N*,*N*-dimethylaniline and 56 μl (0.11 mmol) of 1.93 M phosgene in toluene. After 1 hour 18 μl (0.15 mmol) *N*,*N*-dimethylaniline and 68 μl (0.14 mmol) of 2.1 M dimethylamine in toluene was added, and the reaction was stirred at 0°C for 1 hour. A mixture of EtOAc, 1 ml 1 M K_2HPO_4 and 1 ml 1 M KH_2PO_4 was added, and after phase separation the aq layer was re-extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concd *in vacuo* to provide crude **4f**. Preparative TLC eluting with 30% acetone in hexane provided pure **4f** (14 mg, 45%): IR (CH_2Cl_2) cm^{-1} 1780, 1750, 1700; ^1H NMR ($CDCl_3$) δ 1.19 (d, 1β-CH_3), 1.47 (d, CH_3CHO), 2.90 and 2.92 (2s, NCH_3's), 3.27 (m, 1-H), 3.41 (dd, J=3 and 8 Hz, 6-H), 4.19 (dd, J=3 and 10 Hz, 5-H), 4.56~4.84 (m, $COOCH_2$'s), 4.86 (d, J=14 Hz, CH_2O), 5.12 (m, 1'-H), 5.24~5.50 (m, CH=CH_2's), 5.42 (d, J=14 Hz, CH_2O), 5.95 (m, CH=CH_2's).

Potassium (1*S*,5*R*,6*S*)-2-[[(Dimethylaminocarbonyl)oxy]methyl]-6-[(1'*R*)-1'-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**2f**)

Deblocking 27 mg (0.062 mmol) of **4f** as described in the preparation of **2a** provided crude **2f** which was dissolved in 0.8 ml H_2O and chromatographed in the cold on two 1,000-μm RPS-F gel plates eluting with 12% CH_3CN in H_2O. Work-up of the plates and lyophilization as described for **2a** provided the title compound **2f** (13 mg, 59%): UV $\lambda_{max}^{H_2O}$ nm (ε) 266 (6,200) (NH_2OH extinguishable); ^1H NMR (D_2O, DOH at 4.80) δ 1.15 (d, 1β-CH_3), 1.29 (d, CH_3CHO), 2.92 (s, NCH_3's), 3.27 (m, 1-H), 3.44 (dd, J=3 and 6 Hz, 6-H), 4.21 (m, 5-H and 1-H), 4.72 (half of d, CH_2O), 5.30 (d, J=14 Hz, CH_2O).

Allyl (1*S*,5*R*,6*S*)-2-[[[2'-(Iodoethylamino)carbonyl]oxy]methyl]-6-[(1''*R*)-1''-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**4g**)

A soln of 93 mg (0.25 mmol) of **4a**, 21 μl (0.26 mmol) pyridine, and 62 μl (0.62 mmol) iodoethyl isocyanate in 1 ml toluene was heated at 70°C for 2.5 hours under N_2. After conc *in vacuo* preparative TLC eluting with EtOAc - CH_2Cl_2 (1 : 9) provided **4g** (104 mg, 74%): IR (CH_2Cl_2) cm^{-1} 3520, 1780,

1740 (sh), 1725; MS *m/z* 563 (M+1); ^{1}H NMR 1.19 (d, 1β-CH_3), 1.47 (d, CH_3CHO), 3.27 (m, CH_2I), 3.42 (dd, J=3 and 8 Hz, 6-H), 3.55 (m, NCH_2), 4.20 (dd, J=3 and 10 Hz, 5-H), 4.58~4.86 (m, $COOCH_2$'s), 4.86 (d, J=14 Hz, CH_2O), 5.12 (m, 1″-H), 5.22~5.48 (m, CH=CH_2), 5.43 (d, J=14 Hz, CH_2O), 5.96 (m, CH=CH_2's).

Iodide of Allyl (1*S*,5*R*,6*S*)-2[[[[2′-(Pyridiniumethyl)amino]carbonyl]oxy]methyl]-6-[(1″*R*)-1″-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**4h**)

A soln of 104 mg (0.19 mmol) **4g** in 1 ml pyridine was heated under N_2 at 70°C for 2 hours. After conc *in vacuo* preparative TLC eluting with MeOH - CH_2Cl_2 (1 : 9) provided the pyridinium iodide **4h** (62 mg, 52%): IR (CH_2Cl_2) cm^{-1} 1780, 1750, 1725; MS *m/z* 514 (M−I); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, 1β-CH_3), 1.46 (d, CH_3CHO), 3.33 (m, 1-H), 3.42 (dd, J=3 and 8 Hz, 6-H), 3.93 (m, NHCH_2), 4.20 (dd, J=3 and 10 Hz, 5-H), 4.59 (d, J=14 Hz, CH_2O), 4.66~4.86 (m, $COOCH_2$'s), 5.18 (m, 1″-H), 5.28~5.52 (m, CH_2 pyridine, CH=CH_2's half of CH_2O), 5.96 (m, CH=CH_2's), 6.67 (t, NH), 8.08, 8.52 and 9.28 (t, t, d, aromatic protons).

(1*S*,5*R*,6*S*)-2[[[[2′-(Pyridiniumethyl)amino]carbonyl]oxy]methyl]-6-[(1″*R*)-1″-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**2g**)

Deblocking 62 mg (0.097 mmol) of **4h** as described in the preparation of **2a** using 15 mg Ph_3P (0.057 mmol) and 20 mg $(Ph_3P)_4Pd$ (0.017 mmol) provided crude **2g** which was dissolved in 1 ml THF - H_2O (1 : 9) and chromatographed in the cold on two 1,000-μm RPS-F plates eluting with THF - H_2O (1 : 9). Work-up of the plates and lyophilization as described for **2a** provided the title compound **2g** (11 mg, 29%): UV $\lambda_{max}^{H_2O}$ nm 259, 263 (sh) (partially NH_2OH extinguishable); ^{1}H NMR (D_2O, DOH at 4.80) δ 1.05 (d, 1β-CH_3), 1.27 (d, CH_3CHO), 3.08 (m, 1-H), 3.41 (dd, J=2.5 and 6 Hz, 6-H), 3.72 (m, NHCH_2), 4.14 (dd, J=2.5 and 10 Hz, 5-H), 4.22 (m, 1″-H), 4.54 (d, J=14 Hz, CH_2O), 4.70 (m, CH_2 pyridine), 5.12 (d, J=14 Hz, CH_2O), 8.06, 8.57 and 8.84 (aromatic protons).

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