THE SYNTHESIS, ANTIBACTERIAL, AND β-LACTAMASE INHIBITORY ACTIVITY OF A NOVEL ASPARENOMYCIN ANALOG

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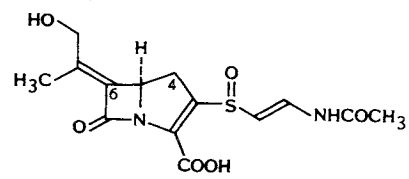
An analog, 6-(2′-hydroxyethylidene)-4β-methyl-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**11**), of the carbapenem β-lactamase inhibitor, asparenomycin A, was synthesized. It possessed a spectrum of antibacterial activity that was comparable to that of asparenomycin A but was less effective as a β-lactamase inhibitor. With ampicillin, it only exhibited a moderate level of synergy against a variety of β-lactamase-producing organisms. Although the presence of a 4β-methyl group in the analog brought about a significant increase in chemical stability relative to that of asparenomycin A, it did not result in an increase in stability to kidney dehydropeptidase enzyme.

The asparenomycins, *e.g.* **1**[1], are carbapenems which are broad spectrum antibacterial agents and potent β-lactamase inhibitors. This aspect of these compounds[2] and some analogs[3~5] has been the subject of several studies. We would like to report the synthesis[6], antibacterial and β-lactamase inhibitor activity of a novel asparenomycin analog **11**. This compound lacks a methyl group in the 6-alkylidene side chain but possesses a methyl group on the β-face at C-4. It was felt that the former modification would result in a sterically less hindered and hence more active β-lactam while the latter modification would bring an improvement[7] in chemical stability and, as has been observed in the case of *N*-formidoylthienamycin, reduced susceptibility to degradation by kidney dehydropeptidase enzyme.

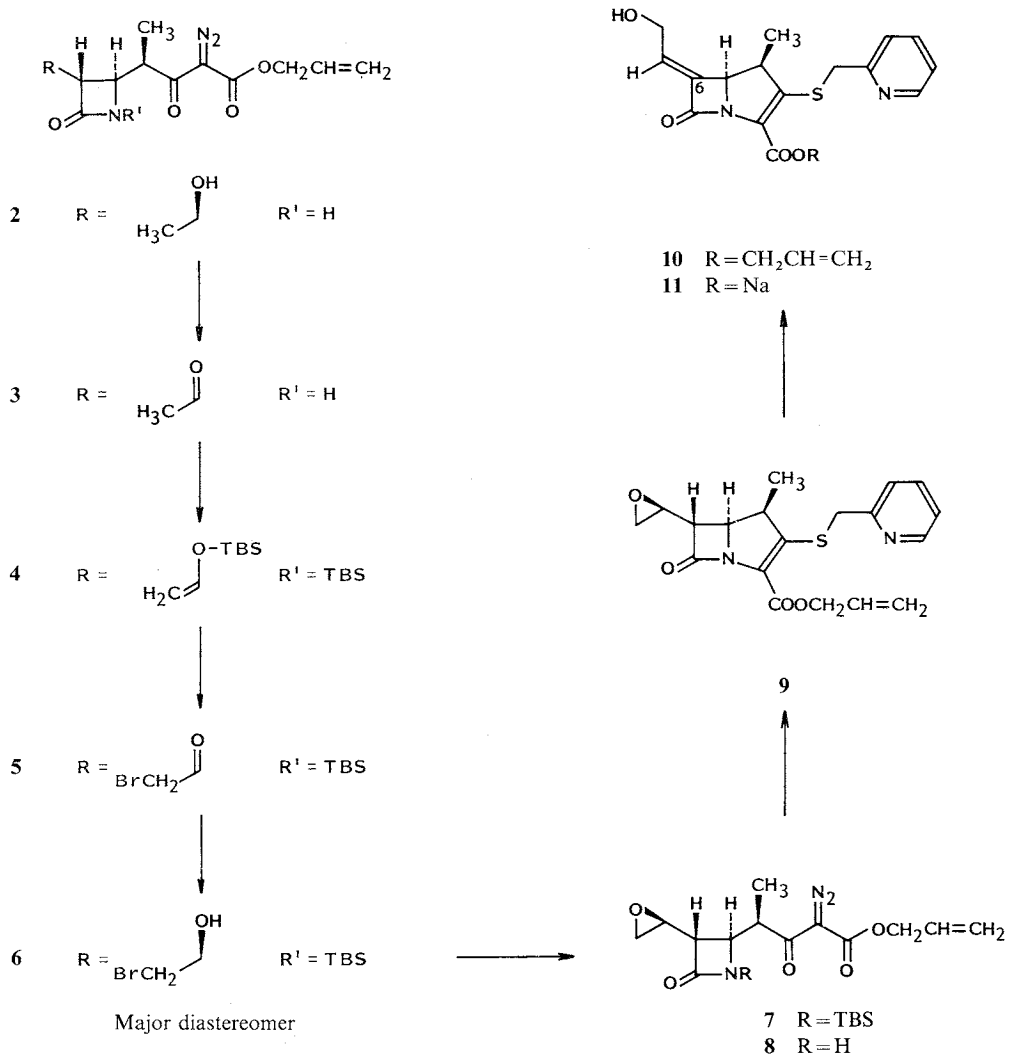
Chemistry

The 3-hydroxyethyl azetidinone (**2**)[8] was oxidized (Scheme 1) with Jones reagent to give the 3-acetyl derivative (**3**). This was converted to the silyl derivative of the kinetic enolate (**4**). Treatment of this derivative with bromine gave the α-bromoketone (**5**). The ketone was reduced with sodium borohydride to give a mixture of alcohol epimers in which the isomer (**6**) with the *S* configuration[6] at the carbon atom bearing the hydroxyl group predominated. This mixture of alcohol isomers was treated with sodium hydride to give a mixture of isomeric epoxides (**7**). Removal of the silyl group followed by chromatography allowed for the isolation of the major epoxide isomer (**8**). This was transformed into the carbapenem (**9**) using the standard procedure[7]. Isomerization of the epoxide (**9**) to the 6-hydroxyethylidene derivative (**10**) was effected with 1,8-diazabicyclo[5.4.0]undec-7-ene in the presence of a catalytic amount of zinc chloride. The asparenomycin analog (**11**) was obtained after the palladium-catalyzed removal of the allyl protecting group. It and asparenomycin A were found to possess half-lives (pH 7.4, 0.07 M phosphate buffer, 37°C)[9] of 225 and 26 hours, respectively.



Asparenomycin A (**1**)

Scheme 1.



Biology

The effect of the analog (**11**), asparenomycin A, and lithium clavulanate on the antibacterial activity of ampicillin against β-lactamase-producing bacteria is shown in Table 1. It was found that **11**, by itself, was active against a broad range of β-lactamase-producing bacteria but not *Pseudomonas aeruginosa*. However, while the combination of lithium clavulanate and ampicillin synergistically inhibited *Staphylococcus aureus*, *Proteus* species, TEM-1-producing *Escherichia coli* and *Klebsiella oxytoca* and the combination with asparenomycin A reduced ampicillin MICs to *S. aureus* and *P. vulgaris*, **11** did not exhibit synergy with ampicillin against the strains of β-lactamase-producing bacteria examined. The inhibitory effect that was observed with this latter combination was almost identical to that exhibited by **11** alone.

The analog (**11**) was comparable to potassium clavulanate in ability to inhibit the *P. vulgaris* and TEM-1 β-lactamases but less effective against the β-lactamase of *S. aureus* (Table 2). It was less effective

Table 1. Activity (MIC μg/ml) of ampicillin alone and in combination with β-lactamase inhibitors.

Organism	Richmond-Sykes Class	**11**	Asparenomycin A	Clavulanate	Ampicillin plus β-lactamase inhibitors[a]			
					None	**11**	Asparenomycin A	Clavulanate
Staphylococcus aureus	—	1	32	16	32	1	1	0.5
Enterobacter cloacae	Ia	>128	32	32	>128	128	32	32
Escherichia coli	Ib	4	8	16	>128	4	8	16
Proteus vulgaris	Ic	2	8	16	>128	2	2	2
Pseudomonas aeruginosa	Id	>128	>128	128	>128	>128	>128	128
Proteus mirabilis	IIa	2	32	64	>128	2	16	4
E. coli (TEM-1)	IIIa	32	4	32	>128	32	4	8
Klebsiella oxytoca	IVa	64	8	32	>128	64	8	8

[a] Inhibitor and ampicillin were tested together at equal concentrations.

Table 2. β-Lactamase inhibitory activity.

Source of β-lactamase[a]	Richmond-Sykes Class	Minimum effective concentration (μg/ml)[b]		
		11	Asparenomycin A	Clavulanate
Staphylococcus aureus	—	32	8	0.25
Proteus vulgaris	Ic	0.25	0.001	0.13
Pseudomonas aeruginosa	Id	8	4	128
Escherichia coli (TEM-1)	IIIa	0.25	0.008	0.25

[a] Concentrations of β-lactamase inhibited were 248 units/ml for *S. aureus*; 9.0 units/ml *P. vulgaris;* 4.5 units/ml *P. aeruginosa*, and 40.1 units/ml *E. coli* (TEM-1).

[b] Inhibitors were preincubated with enzyme at 30°C for 10 minutes prior to adding nitrocefin (50 μg/ml) and the minimum concentration inhibiting color change at 60 minutes was determined.

than asparenomycin A against all β-lactamases tested.

It was found (Table 3) that **11** was about eight fold and four fold more susceptible to degradation by kidney dehydropeptidase enzyme than asparenomycin A and imipenem, respectively.

Table 3. Dehydropeptidase stability.

Compound	Relative stability to DHP[a]
Imipenem	1.00
11	3.88
Asparenomycin A	0.48

[a] Hydrolysis by hog kidney dehydropeptidase (spec. act. = 7.3 units/mg prot.) relative to imipenem set at 1.

Conclusion

The analog (**11**) was found to be a less effective β-lactamase inhibitor than asparenomycin A. Although the presence of a 4β-methyl group did seem to impart significant chemical stability, a corresponding increase in stability to the dehydropeptidase enzyme was not observed. In light of these findings, further work in this area is not planned.

Experimental

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. The UV and IR spectra were recorded respectively on Hewlett-Packard 8451A and Perkin-Elmer 781 spectrophotometers. The ^{1}H NMR spectra were obtained on a Bruker AC 200 instrument using tetramethylsilane or sodium 3-(trimethylsilyl) propionate-2,2,3,3-d_4

as the internal standard. TLC was performed with Merck Art. No. 5719 Kieselgel 60 F_{254} plates. Medium pressure column chromatography employed Merck Art. No. 9385 Kieselgel 60 (230~400 mesh) and used mixtures of ethyl acetate and hexane as eluent. Analytical HPLC of the final product was performed using a Waters C_{18} Bondapak column (10 μm particle size, 3.8 mm × 30 cm) with a Waters 481 LC spectrophotometric detector. Where necessary, solvents were dried and reactions were conducted under an Ar atmosphere.

For the synergy studies, two fold serial dilutions of inhibitor and ampicillin were added in equal volumes and testing was by microbroth dilution using inocula of 5×10^5 cfu/ml. The MIC value was recorded after 18 hours at 35°C.

The β-lactamase enzymes of Gram-negative bacteria were obtained as sonic extracts of the organism and a unit of β-lactamase was defined as that amount of enzyme which hydrolyzes one micromole of nitrocefin per minute. The β-lactamase of *S. aureus* was the extracellular fraction and a unit was that amount of enzyme which hydrolyzes one micromole of nitrocefin per hour.

The dehydropeptidase (DHP) stability studies utilized partially purified hog kidney DHP and were performed spectrophotometrically by monitoring the absorbance maximum and molar extinction coefficient of the substrate.

(3*S*,4*R*)-4-(1′*R*-Methyl-3′-allyloxycarbonyl-2′-oxo-3′-diazopropyl)-3-(1′-oxo-ethyl)-azetidinone (**3**)

Jones reagent (5 ml) was added dropwise to an ice-cooled solution of (3*S*,4*R*)-3-(1′*R*-hydroxyethyl)-4-(1′*R*-methyl-3′-allyloxycarbonyl-2′-oxo-3′-diazopropyl)-azetidin-2-one (**2**) (2.95 g, 10 mmol) in acetone (25 ml). After 15 minutes, the reaction was diluted with ethyl acetate and water. This was stirred and sufficient solid $NaHSO_3$ was added to decolorize the organic phase. The organic phase was removed, washed with brine, and then dried (Na_2SO_4). After removal of the solvents, the residual solid was crystallized from ethyl acetate-hexane. The mother liquor was chromatographed to afford additional pure material. The combined yield of ketone (**3**) was 2.77 g (95%): mp 90~91°C; $[\alpha]_D^{23}$ −5° (*c* 0.6, $CHCl_3$); IR (KBr disc) ν_{max} cm^{-1} 3200, 2150, 1750, 1715; ^1H NMR ($CDCl_3$) δ 1.16 (3H, d, J=7.0 Hz), 2.31 (3H, s), 3.95 (1H, dq, J=7.0 and 4.5 Hz), 4.07 (1H, dd, J=2.6 Hz), 4.25 (1H, dd, J=2.6 and 4.5 Hz), 4.70~5.98 (5H, m, $CHCH_2CH_2$).

Anal Calcd for $C_{13}H_{15}N_3O_5$: C 53.24, H 5.16.
Found: C 53.11, H 5.17.

(3*S*,4*R*)-1-*tert*-Butyldimethylsilyl-3-[1′-(*tert*-butyldimethylsilyloxy)-vinyl]-4-(1′*R*-methyl-3′-allyloxycarbonyl-2′-oxo-3′-diazopropyl)-azetidin-2-one (**4**)

A solution of the ketone (**3**) (2.93 g, 10 mmol) in dry methylene chloride (30 ml) was cooled to −20°C and *tert*-butyldimethylsilyl trifluoromethane-sulfonate (4.82 ml, 2.1 equiv) was added followed by triethylamine (2.92 ml, 2.1 equiv). After 0.5 hour, the reaction was allowed to warm to room temperature. It was diluted with hexane (150 ml) and was washed with water (20 ml), saturated aqueous $NaHCO_3$ solution (5 ml), water (5 ml) and brine. The organic phase was dried and then the solvent was removed. This left an oil which was chromatographed to afford the silyl enol ether (**4**) as a pale yellow oil (4.76 g, 91%): $[\alpha]_D^{23}$ 6° (*c* 0.56, $CHCl_3$); IR (film) ν_{max} cm^{-1} 2140, 1755, 1725; ^1H NMR ($CDCl_3$) δ 0.16 (3H, s), 0.19 (9H, s), 0.92 (9H, s), 0.93 (9H, s), 1.21 (3H, d, J=7.1 Hz), 3.70 (1H, dd, J=5.0 and 3.0 Hz), 4.03 (1H, dq, J=7.1 and 5.0 Hz), 4.14 (1H, d, J=1.6 Hz), 4.23 (1H, d, J=1.6 Hz), 4.25 (1H, d, J=3.0 Hz), 4.68~6.03 (5H, m, CH_2CHCH_2).

Anal Calcd for $C_{25}H_{43}N_3O_5Si_2$: C 57.63, H 8.32, N 8.07.
Found: C 57.84, H 8.33, N 8.08.

(3*S*,4*R*)-3-(1′*S*,2′-Epoxyethyl)-4-(1′*R*-methyl-3′-allyloxycarbonyl-2′-oxo-3′-diazopropyl)-azetidin-2-one (**8**)

A solution of the silyl enol ether (**4**) (10.2 g, 19.6 mmol) in dry tetrahydrofuran (100 ml) under Ar was cooled to −78°C. A solution of bromine (12.6 ml, 1.55 M in CCl_4, 1 equiv) was added dropwise. After the addition was complete, the reaction was left stirring for 25 minutes. The low temperature bath was then removed and after a further 25 minutes, the reaction was diluted with ethyl acetate (300 ml). After the reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$ (20 ml) and brine (25 ml),

it was dried and the solvents were removed. The residual oil was chromatographed to afford (3*S*,4*R*)-3-(2′-bromo-1′-oxo-ethyl)-1-*tert*-butyldimethylsilyl-4-(1′*R*-methyl-3′-allyloxycarbonyl-2′-oxo-3′-diazopropyl)-azetidin-2-one (**5**) as a pale yellow oil (6.7 g, 76%): $[\alpha]_D^{23}$ −8° (*c* 3.2, $CHCl_3$); IR (film) ν_{max} cm^{-1} 2150, 1750, 1725; ^1H NMR ($CDCl_3$) δ 0.13 (3H, s), 0.22 (3H, s), 0.91 (9H, s), 1.18 (3H, d, J=6.6 Hz), 4.10 (2H, m), 4.16 (2H, q, δ_A=4.13, δ_B=4.19, J_{AB}=13.4 Hz), 4.71~6.03 (5H, m, $-CH_2CHCH_2$), 5.25 (1H, d, J=2.3 Hz).

Sodium borohydride (154 mg, 1.15 hydride equiv) was added to a cooled solution (−78°C) of the α-bromoketone (**5**) (6.90 g, 14.2 mmol) in methanol (134 ml). This mixture was left stirring for 45 minutes after which a saturated aqueous solution of NH_4Cl (168 ml) was added. After warming to room temperature, this mixture was extracted with ethyl acetate (422 ml). The organic extract was washed with brine and then dried (Na_2SO_4). Removal of the solvents left an oil which was chromatographed to give a homogeneous mixture (7:1) of bromohydrin diastereomers as an oil (4.9 g, 71%). The major diastereomer, (3*S*,4*R*)-1-*tert*-butyldimethylsilyl-3-(2′-bromo-1′*S*-hydroxyethyl)-4-(1′*R*-methyl-3′-allyloxycarbonyl-2′-oxo-3′-diazopropyl)-azetidin-2-one (**6**), had the following ^1H NMR ($CDCl_3$) spectrum: δ 0.17 (3H, s), 0.22 (3H, s), 0.96 (9H, s), 1.25 (3H, d, J=6.99 Hz), 2.98 (1H, d, J=4.50 Hz, exchangeable with D_2O), 3.45 (4H, m), 3.93 (1H, dq, J=6.99 and 5.65 Hz), 4.05 (1H, m), 4.74 (2H, m), 5.29~5.95 (3H, m).

A solution of the mixture of bromohydrin isomers (4.9 g, 10 mmol) in dry tetrahydrofuran (32 ml) was added slowly to a stirred suspension of sodium hydride (440 mg, 60% w/w oil dispersion, 1.1 equiv) in tetrahydrofuran (62 ml) at room temperature. After 22 hours, the temperature was raised to 35°C and a further addition of sodium hydride (88 mg, 0.2 equiv) was made. The reaction was left for 24 hours. A saturated aqueous solution of NH_4Cl (62 ml) was then added and the resulting mixture was extracted with ethyl acetate (342 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed to leave a yellow oil. This was chromatographed to give an homogenous mixture of diastereomeric epoxides as an oil (3.55 g, 87%). The major isomer, (3*S*,4*R*)-1-*tert*-butyldimethylsilyl-3-(1′*S*,2′-epoxyethyl)-4-(1′*R*-methyl-3′-allyloxycarbonyl-2′-oxo-3′-diazopropyl)-azetidin-2-one (**7**) had the following ^1H NMR ($CDCl_3$) spectrum: δ 0.16 (3H, s), 0.23 (3H, s), 0.96 (9H, s), 1.19 (3H, d, J=7.0 Hz), 2.72 (1H, dd, J=4.5 and 2.7 Hz), 2.86 (1H, t, J=4.5 Hz), 3.21 (1H, ddd, J=4.5, 2.7 and 1.6 Hz), 3.50 (1H, dd, J=5.2 and 2.6 Hz), 3.66 (1H, dd, J=4.5 and 2.6 Hz), 4.00 (1H, dq, J=7.0 and 5.2 Hz), 4.73~5.95 (5H, m, CH_2CHCH_2).

Tetrabutylammonium fluoride (4.64 ml, 1.0 M in tetrahydrofuran, 1.2 equiv) was added to cooled (−15°C) solution of the mixture of epoxide isomers (1.89 g, 4.64 mmol) and acetic acid (0.69 ml, 2.6 equiv) in tetrahydrofuran (50 ml). After 3 hours, a saturated aqueous solution of $NaHCO_3$ (169 ml) was added. This was extracted with ethyl acetate. The organic extract was washed with brine and dried (Na_2SO_4). The solvents were removed and the residual oil was chromatographed to give, in order of elution, a mixture of diastereomeric, desilylated epoxy azetidinones (137 mg, 10%) and the pure 3-(1′*S*,2′-epoxyethyl)-azetidinone (**8**) (1.02 g, 75%) as colorless crystals (from diethyl ether-pentane): mp 75~77°C; $[\alpha]_D^{23}$ −22.6° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1} 3455, 2055, 1760, 1715, 1645; ^1H NMR ($CHCl_3$) δ 1.17 (3H, d, J=6.8 Hz), 2.72 (1H, dd, J=4.5 and 2.6 Hz), 2.87 (1H, t, J=4.5 Hz), 3.11 (1H, dd, J=5.1 and 2.3 Hz), 3.24 (1H, m), 3.72 (1H, dd, J=4.6 and 2.3 Hz), 3.87 (1H, dq, J=6.8 and 5.1 Hz), 4.73~5.94 (5H, m, CH_2CHCH_2), 5.97 (1H, br s).

Anal Calcd for $C_{13}H_{15}N_3O_5 \cdot \frac{1}{2}H_2O$: C 51.65, H 5.33, N 13.90.
Found: C 51.85, H 5.10, N 13.66.

Sodium (4*R*,5*S*)-(*Z*)-6-(2′-Hydroxyethylidene)-4-methyl-7-oxo-3-(pyridin-3-yl-methylthio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**11**)

A solution of the epoxide (**8**) (1.02 g, 3.48 mmol) and rhodium (II) octanoate (11 mg) in a mixture of ethyl acetate (7.6 ml) and hexane (2.4 ml) was heated at reflux for 15 minutes. The solvent was removed and the residual oil was dissolved in acetonitrile (5 ml) and cooled to −5°C. Chlorodiphenylphosphate (1.3 ml, 1.8 equiv) followed by *N*,*N*-diisopropylethylamine (0.67 ml, 1.1 equiv) were added. After 30 minutes, the reaction was cooled to −15°C and *N*,*N*-diisopropylethylamine (0.67 ml) followed by pyridin-2-yl methane thiol (0.76 g, 1.75 equiv) was added. The reaction was left for 30 minutes after which it was diluted with ethyl acetate (52 ml). This was washed with cold water, saturated aqueous $NaHCO_3$ and cooled to −5°C. After being dried (Na_2SO_4), the solvent was removed and the residual oil was chromatographed. This afforded allyl (4*R*,5*S*,6*S*)-6-(1′*S*,2′-epoxyethyl)-4-methyl-7-oxo-3-(pyridin-3-yl-methylthio)-1-

azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**9**) as a brown oil (555 mg, 43%): ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, d, J=7.3 Hz), 2.70 (1H, dd, J=4.4 and 2.4 Hz), 2.92 (1H, t, J=4.4 Hz), 3.13 (1H, dd, J=6.5 and 2.4 Hz), 3.30 (1H, ddd, J=6.5, 4.4 and 2.4 Hz), 3.72 (1H, dq, J=8.8 and 7.3 Hz), 4.05 (1H, d, J=14.1 Hz), 4.06 (1H, dd, J=8.8 and 2.4 Hz), 4.28 (1H, d, J=14.1 Hz), 4.76~5.48 (5H, m, CH_2CHCH_2), 7.22~8.51 (4H, m, arom.).

Zinc chloride (17 mg, 0.2 equiv) was added to a solution of the epoxide (**9**) (232 mg, 0.62 mmol) in a mixture of CH_2Cl_2 (16 ml) and benzene (3 ml) at -20°C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.5 ml, 1 M solution in toluene, 0.8 equiv) was added and the reaction was kept at -15°C for 1 day. The reaction was then diluted with ethyl acetate (60 ml) and washed with brine. The aqueous phase was back extracted with ethyl acetate and the combined organic phases were dried (Na_2SO_4). The solvent was removed and the residual oil was chromatographed to afford allyl (4*R*,5*S*)-(*Z*)-6-(2′-hydroxyethylidene)-4-methyl-7-oxo-3-(pyridin-3-yl-methylthio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**10**) as a light brown oil (92 mg, 40%): IR (film) ν_{max} cm^{-1} 3400, 1760, 1700; ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, d, J=7.3 Hz), 3.60 (1H, dq, J=9.1 and 7.3 Hz), 4.07 (1H, d, J=14.0 Hz), 4.24 (1H, d, J=14.0 Hz), 4.47 (2H, d, J=3.6 Hz), 4.76 (2H, m, CH_2CHCH_2), 4.75~4.87 (1H, m), 5.22~5.51 and 5.98 (3H, m, CH_2CHCH_2), 6.47 (1H, dt, J=3.6 and 1.5 Hz), 7.19~8.51 (4H, m, arom.).

A solution of the epoxide (**10**) (90 mg, 0.24 mmol) in tetrahydrofuran (1.5 ml) was added to a solution containing the palladium catalyst [prepared by allowing a solution of bis(dibenzylideneacetone)palladium (0) (7 mg, 0.05 equiv) and triphenylphosphine (13 mg, 0.2 equiv) in tetrahydrofuran (1.6 ml) to stir for 10 minutes] and sodium 2-ethylhexanoate (0.53 ml, 0.5 M solution in ethyl acetate, 1.1 equiv). A light yellow precipitate formed immediately. This was collected by filtration and washed with ether. Chromatography [medium pressure, using the adsorbant from a Waters C_{18} PrepPak-500 column and gradient elution beginning with water and ending with an acetonitrile-water mixture (3:97)] followed by lyophilization afforded the carbapenem (**11**) as a light yellow solid (38 mg, 48%): UV pH 7.4 buffer λ_{max} nm (ε) 266 (5,700), 328 (4,100); IR ν_{max} cm^{-1} 1740, 1590; ^{1}H NMR (D_2O) δ 1.01 (3H, d, J=7.2 Hz), 3.33 (1H, dq, J=9.0 and 7.2 Hz), 4.11 (1H, d, J=14.1 Hz), 4.24 (1H, d, J=14.1 Hz), 4.37 (2H, d, J=4.4 Hz), 4.74~4.94 (1H, m), 6.54 (1H, dt, J=4.4 and 1.4 Hz), 7.36~8.46 (4H, m, arom.).

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