

J. *J. Am. Chem. Soc.* 1992, 114, 4667.  
 25. Lange, G.; Hahn, H.; Dehnicke, K. *Z. Naturforsch.* 1969, 24b, 1498.

26. Rocchiccioli-Deltcheff, C.; Fournier, M.; Franck, R.; Thouvenot, R. *Inorg. Chem.* 1983, 22, 207.

## Synthesis of Aminophosphonopeptides Containing Carbapenem

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A new kind of aminophosphonopeptides containing carbapenem, allyl-(5*R*,6*S*)-3-(2-carbobenzyloxyamino-3-dialkylphosphonopropionyl-2-amino)ethanthio-6-[(1'*R*)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-carboxylate **1a-1d**, have been synthesized. 2-Carbobenzyloxyamino-3-dialkylphosphonopropionyl-2-amino-ethanethiol **7a-7d**, aminophosphonopeptides, were produced starting from *N*-carbobenzyloxyserine methyl ester (**2**) and 2-amino-3-dialkyl-phosphonopropionate (**4**) by way of methyl 2-carbobenzyloxyamino-3-dialkylphosphonopropionate **5a-5d**. The coupling of amino-phosphonopeptides **7a-7d** and allyl (5*R*,6*S*)-6-[(1'*R*)-hydroxyethyl]-1-aza-3,7-dioxobicyclo[3.2.0]-heptane-2-carboxylate yielded aminophosphonopeptides containing carbapenem **1a-1d**.

### Introduction

Since 2-aminoethylphosphonic acid (2-AEPn) was isolated from sheep rumen in 1959 by Horiguchi and his coworkers,<sup>1</sup> many aminophosphonic acids and their derivatives have been discovered in living organism. Aminophosphonic acids are also discovered in mammalian tissues such as human muscle, sheep liver, and bovine brain.<sup>2-8</sup> Its concentration in human tissues was higher in heart and skeletal muscle than in liver and brain. It has been known that the compounds having carbon-phosphorus bond are also stable. Aminophosphonic acids and their derivatives have attracted attention because of their antibiotic, herbicidal, pesticidal, anticancer, and enzyme inhibitory activities and because of particularly their structural similarities to biologically important amino acids.

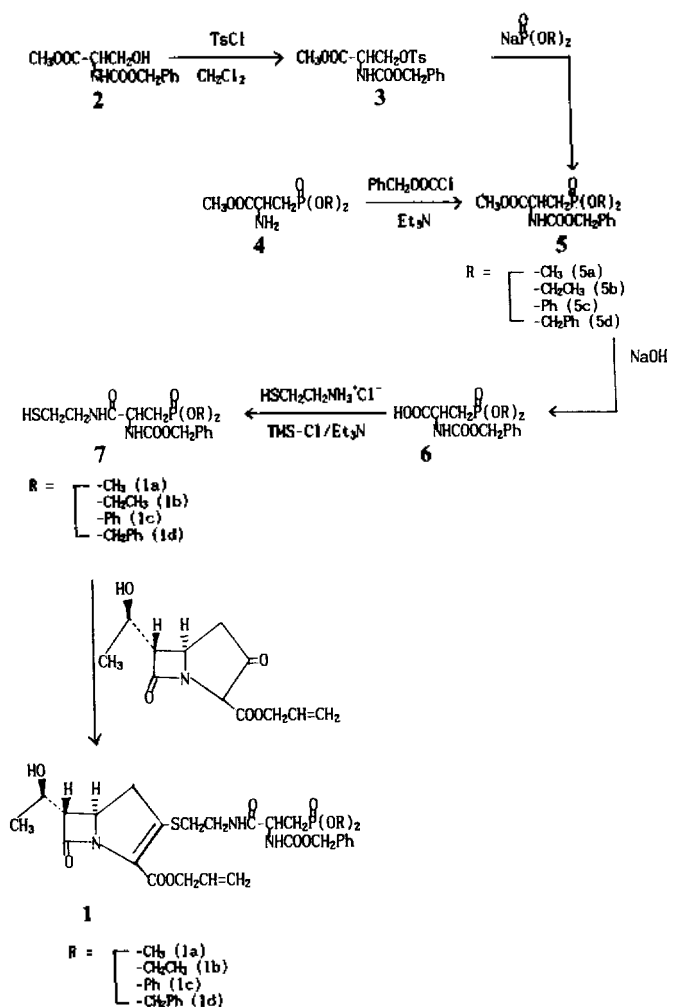
Recently, incorporated with synthetic derivatives, biological activity of aminophosphonopeptides were widely investigated. Kleinrok *et al.*<sup>9</sup> investigated central pharmacological properties of aminophosphonic acids and their derivatives. Among various disciplines neurochemistry and neuropharmacology are the most brisk areas concerning the activity of aminophosphonic acid. The effect of  $\omega$ -phosphono- $\alpha$ -aminocarboxylic acid on seizures and brain level in E1 mice was tested.<sup>10</sup> Carbapenem has a different structure from penicillin and cephalosporin and has a broader antibiotic, antibacterial activity and resistance to hydrolysis by  $\beta$ -lactamase. There were many carbapenem derivatives containing amide-bonded alkylthiol group at C-3 position which were synthesized because of their antibiotic activity.<sup>11-19</sup> Atherton<sup>20</sup> reported phosphonopeptides containing penicillin or cephalosporin synergized antibiotic activity. Phosphonopeptides are structurally divided into two groups, one containing carbon-nitrogen bond and the other amide containing phosphorus-nitrogen bond.

Phosphonopeptides containing C-N amide bond was found to be a strong competitive inhibitor of peptide hydrolysis enzyme. Jacobson<sup>21</sup> reported *N*-[[[(benzyloxycarbonyl)amino]methyl]hydroxyphosphonyl]-*L*-phenylalanylalanine was an active inhibitor of carboxypeptidase A. Elliott<sup>22</sup> also observed that phosphonopeptides containing C-N amide bond was an effective inhibitor of enkephalinase in kidney of rat and brain of man. Phosphonopeptides containing P-N amide bond have antibiotic activity because they inhibit biosynthesis of peptidoglycan in bacterial cellwall as well as penicillin and cephalosporin antibiotics. Allen<sup>23</sup> synthesized alaphosphorin which is a dipeptide of 1-aminoethylphosphonic acid and *L*-alanine and showed its antibacterial and antiviral activities. Niida<sup>24</sup> and Bayer<sup>25</sup> separated bialafos(phosphinothricylalanylalanine) from a fermentation broth of *Streptomyces hygrosopicus* and *Streptomyces viridochromogens*, and discovered its broad antibiotic activity for Gram positive and Gram negative bacteria.

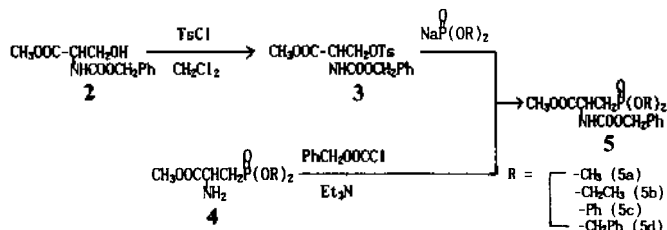
Now we accomplished a total synthesis of new aminophosphonopeptides containing carbapenem **1a-d**. In this paper, the authors wish to report the synthesis of allyl-(5*R*,6*S*)-3-(2-carbobenzyloxyamino-3-dialkylphosphonopropionyl-2-amino)ethanthio-6-[(1'*R*)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-carboxylate **1a-d**, as shown in Scheme 1.

### Results and Discussion

A synthesis of allyl (5*R*,6*S*)-(2-carbobenzyloxyamino-3-dialkylphosphonopropionyl-2-amino)ethanthio-6-[(1'*R*)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-carboxylate **1a-d** was carried out using inexpensive chemicals. *N*-carbobenzyloxyserine methyl ester (**2**) was tosylated to give *O*-tosyl *N*-carbobenzyloxyserine (**3**) in 86% yield. Methyl 2-carbobenzyloxyamino-3-dialkylphosphonopropionate (**5**) was prepared in



43% yield by reaction of *O*-tosyl *N*-carbobenzoxyserine (3) with sodium diethylphosphite under nitrogen. Phosphorylated ester 5 was also prepared in 82% yield by reaction of methyl 2-amino-3-dialkylphosphonopropionate (4) with benzoyloxy-carbonyl chloride.



2-Carbobenzoxyamino-3-dialkylphosphonopropionic acid (6) was prepared in 72% yield by saponification of phosphorylated ester (5) with sodium hydroxide solution. The coupling of 2-carbobenzoxyamino-3-dialkylphosphonopropionic acid (6) with 2-aminoethanethiolhydrochloride produced dipeptide 7a-d in 41-46% yield. Allyl-(5*R*,6*S*)-3-(2-carbobenzoyloxyamino-3-dialkylphosphonopropionyl-2-amino)ethanethio-6-[(1'*R*)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-carboxylate 1a-d was obtained by reaction of dipeptide 7a-d with allyl-(5*R*,6*S*)-6-[(1'*R*)-hydroxyethyl]-1-aza-3,7-dioxobicyclo[3.2.0]heptane-2-carboxylate<sup>26,27</sup> in 56-72% yield. In con-

clusion, allyl-(5*R*,6*S*)-3-(2-carbobenzoyloxyamino-3-dialkylphosphonopropionyl-2-amino)ethanethio-6-[(1'*R*)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-carboxylate 1a-d, a new kind of phosphorus compounds, were totally synthesized in two methods. One was prepared in 5 steps from 2 with 8.4-6.4% overall yield, the other in 4 steps from 4 with 19.7-16.2% overall yield.

## Experimental Part

All reactions were carried out with the precaution for rigorous exclusion of air or moisture. The solvents, ether and THF, were purified by refluxing for several hours in the presence of sodium metal and benzophenone followed by distillation under nitrogen prior to use. Melting points were measured by Mettler F61 melting point apparatus. IR spectra were recorded with Beckmann acculab T. M. I spectrometer, and proton NMR spectra were taken on Varian EM-360L (60 MHz) spectrometer with TMS as an internal standard.

***O*-Tosyl *N*-carbobenzoxyserine (3).** In a 500 ml three neck round bottomed flask fitted with a dropping funnel, were placed *L*-carbobenzoxyserine methyl ester (2)<sup>22</sup> (10.13 g, 0.04 mol) in dry methylene chloride (200 ml) and triethylamine (8.32 ml, 0.06 mol). To this flask tosyl chloride (8.39 g, 0.044 mol) in dry methylene chloride (50 ml) was added dropwise with careful stirring at  $-5^{\circ}\text{C}$ . After being stirred for 1 hr, the resulting yellow solution was washed with distilled water (200 ml), 5% HCl aqueous solution (50 ml), saturated sodium carbonate solution (50 ml), and saturated sodium chloride solution, successively. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was removed by evaporation *in vacuo*. Recrystallization with ethyl acetate and *n*-hexane gave a yellow crystalline (14.01 g) in 86% yield.

Anal. Calc. for  $\text{C}_{15}\text{H}_{21}\text{NO}_7\text{S}$ : C, 56.01; H, 5.19; N, 3.44; O, 27.48; S, 7.87. Found: C, 55.90; H, 5.07; N, 3.72; O, 27.38; S, 7.93; mp.  $92-95^{\circ}\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.85 (m, 2H,  $-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$ ), 7.43 (m, 2H,  $-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$ ), 7.35 (s, 5H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 5.1 (s, 2H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 4.5 (m, 3H,  $-\text{NHCH}_2\text{CH}_2-$ ), 2.50 (s, 3H,  $-\text{C}_6\text{H}_5\text{CH}_3$ ), IR (KBr): 3370 (N-H), 1720 (C=O), 1520 (CO-NH), 1320, 1150 ( $\text{SO}_2$ )  $\text{cm}^{-1}$ .

**Methyl-2-carbobenzoxyamino-3-dimethylphosphonopropionate (5a) from 3.** In a 1000 ml three neck round bottomed flask fitted with a dropping funnel, sodium metal (1.94 g, 0.084 mol) in dry THF (56 ml) was added. While stirring under nitrogen, dimethyl phosphite (9.24 g, 0.084 mol) was added carefully through a dropping funnel. After stirring for 5 hr, *O*-tosyl *N*-carbobenzoxyserine (3) (28.52 g, 0.07 mol) in dry THF (100 ml) was added carefully through a dropping funnel. After refluxing for 7 hr, the solvent was removed by evaporation *in vacuo*. The resulting crude product was chromatographed on a silica gel column using ethyl acetate and *n*-hexane (1:1, v/v) to give an oily product (10.39 g) in 43% yield.

Anal. Calc. for  $\text{C}_{14}\text{H}_{20}\text{NO}_7\text{P}$ : C, 48.70; H, 5.84; N, 4.06; O, 32.44; P, 9.00. Found: C, 48.53; H, 5.76; N, 4.21; O, 32.23; P, 9.27, mp.  $34^{\circ}\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.4 (s, 5H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 5.2 (s, 2H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 4.4 (m, 1H,  $-\text{NHCH}_2\text{CH}_2-$ ), 3.8 (d, 6H,  $J_{\text{H-P}}=7$  Hz,  $-\text{OCH}_3$ ), 3.6 (s, 3H,  $-\text{OCH}_3$ ), 2.5 (d, 1H,  $J_{\text{H-P}}=7.5$  Hz,  $-\text{CH}_2\text{P}=\text{O}$ ), 2.2 (d, 1H,  $J_{\text{H-P}}=7.5$  Hz,  $-\text{CH}_2\text{P}=\text{O}$ ), IR (neat): 3400 (NH), 1750 (C=O), 1230 (P=O), 1050 (P-O)  $\text{cm}^{-1}$ . (5b).

Anal. Calc. for  $C_{18}H_{24}NO_7P$ ; C, 51.48; H, 6.48, N, 3.75; O, 30.00; P, 8.30. Found: C, 51.39; H, 6.42; N, 3.82; O, 29.96; P, 8.41, mp. 37°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  4.1 (m, 4H,  $-OCH_2CH_3$ ), 1.3 (m, 6H,  $-OCH_2CH_3$ ). (5c) Anal. Calc. for  $C_{24}H_{24}NO_7P$ ; C, 61.41; H, 5.15; N, 3.00; O, 23.86; P, 6.60. Found: C, 61.20; H, 5.08; N, 3.15; O, 23.81; P, 6.76, mp. 38°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.15 (m, 10H,  $-OC_6H_5$ ). (5d) Anal. Calc. for  $C_{26}H_{28}NO_7P$ ; C, 62.77; H, 5.67; N, 2.81; O, 22.51; P, 6.23. Found: C, 62.74; H, 5.53; N, 2.89; O, 22.48; P, 6.36, mp. 40°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.25 (s, 10H,  $-CH_2C_6H_5$ ), 4.95 (d, 4H,  $J_{H-P}=8$  Hz,  $-CH_2C_6H_5$ ).

**Methyl-2-carbobenzyloxyamino-3-diethylphosphonopropionate (5b) from 4b.** In a 100 ml three neck round bottomed flask fitted with a dropping funnel, methyl 2-amino-3-diethylphosphonopropionate (**4b**)<sup>26</sup> (5.02 g, 0.021 mol) and potassium carbonate (6.95 g, 0.05 mol) and distilled water (35 ml) were added. While stirring at 0°C, benzyloxy-carbonyl chloride (3.2 ml, 0.022 mol) was added carefully through a dropping funnel over 30 min. After being stirred for 5 hr, this solution was extracted with ethyl acetate, the organic layer was dried over anhydrous magnesium sulfate. After the solvent was removed by evaporation *in vacuo*, the crude product was chromatographed on a silica gel column using ethyl acetate and n-hexane (1:1, v/v) to give an oily product (6.43 g) in 82% yield.

Found: C, 51.40; H, 6.39; N, 3.86; O, 29.92; P, 8.43, mp. 36°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  4.15 (m, 4H,  $-OCH_2CH_3$ ), 1.35 (m, 6H,  $-OCH_2CH_3$ ); IR (neat): 3350 (NH), 1730 (C=O), 1200 (P=O), 990 (P-O)  $cm^{-1}$ . (5a) Found: C, 48.49; H, 5.78; N, 4.19; O, 32.36; P, 9.18, mp. 33°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.9 (d, 6H,  $J_{H-P}=7$  Hz,  $-OCH_3$ ). (5c) Found: C, 61.37; H, 5.06; N, 3.17; O, 23.68; P, 6.72, mp. 38°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.20 (m, 10H,  $-OC_6H_5$ ). (5d) Found: C, 62.76; H, 5.57; N, 2.91; O, 22.42; P, 6.34, mp. 39°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.30 (s, 10H,  $-CH_2C_6H_5$ ), 4.9 (d, 4H,  $J_{H-P}=8$  Hz,  $-CH_2C_6H_5$ ).

**2-Carbobenzyloxyamino-3-diphenylphosphonopropionic acid (6c).** In a 50 ml three neck round bottomed flask fitted with a dropping funnel, Methyl 2-carbobenzyloxyamino-3-diphenylphosphonopropionate (**5c**) (0.39 g, 0.83 mmol) in acetone (3 ml) and distilled water (3 ml) were added. While stirring at room temperature, 1N NaOH (1.1 ml) was added carefully through a dropping funnel over 10 min and stirred for 1.5 hr at room temperature. After the solvent was removed by evaporation *in vacuo*, the crude product was washed with ether and chloroform successively and acidified with concentrated HCl. After the oily product was extracted with ethyl acetate, the solvent was removed by evaporation *in vacuo* to give an oily product (0.27 g) in 72% yield.

Anal. Calc. for  $C_{23}H_{22}NO_7P$ ; C, 60.66; H, 4.87; N, 3.07; O, 24.60; P, 6.80. Found: C, 60.58; H, 4.74; N, 3.21; O, 24.53; P, 6.94,  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  7.35 (s, 5H,  $-CH_2C_6H_5$ ), 7.15 (m, 10H,  $-OC_6H_5$ ), 5.1 (s, 2H,  $-CH_2C_6H_5$ ), 4.25 (m, 1H,  $-NHCH_2CH_2-$ ), 2.55 (d, 1H,  $J_{H-P}=7.5$  Hz,  $-CH_2P=O$ ), 2.2 (d, 1H,  $J_{H-P}=7.5$  Hz,  $-CH_2P=O$ ), IR (neat): 3370 (NH), 1710 (C=O), 1210 (P=O), 980 (P-O)  $cm^{-1}$ . (6a) Anal. Calc. for  $C_{13}H_{18}NO_7P$ ; C, 47.14; H, 5.48; N, 4.23; O, 33.81; P, 9.35. Found: C, 46.90; H, 5.47; N, 4.43; O, 33.69; P, 9.51;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.7 (d, 6H,  $J_{H-P}=7$  Hz,  $-OCH_3$ ). (6b) Anal. Calc. for  $C_{15}H_{22}NO_7P$ ; C, 50.14; H, 6.16; N, 3.90; O, 31.17; P, 8.62. Found: C, 50.01; H, 6.13; N, 3.98; O, 31.12; P, 8.76;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  4.3 (m, 4H,  $-OCH_2CH_3$ ), 1.35 (m, 6H,  $-OCH_2CH_3$ ). (6d) Anal. Calc.

for  $C_{25}H_{26}NO_7P$ ; C, 62.11; H, 5.42; N, 2.90; O, 23.17; P, 6.41. Found: C, 62.01; H, 5.37; N, 2.97; O, 23.11; P, 6.54;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.30 (s, 10H,  $-CH_2C_6H_5$ ), 5.0 (d, 4H,  $J_{H-P}=8$  Hz,  $-CH_2C_6H_5$ ).

**2-Carbobenzyloxyamino-3-dibenzylphosphonopropionyl-2-aminoethanethiol (7d).** In a 100 ml three neck round bottomed flask fitted with a dropping funnel, 2-aminoethanethiol hydrochloride (5.7 g, 0.05 mol) and acetonitrile (45 ml) were added. While stirring at 0°C under nitrogen, ethyldiisopropylamine (20 ml, 0.115 mol), imidazole (catalytic amount) and trimethylsilyl chloride (5.7 ml, 0.065 mol) were added carefully through a dropping funnel successively. After being stirred for 1 hr at 0°C and 15 min at room temperature, we called it "Solution A". In a 250 ml three neck round bottomed flask fitted with a dropping funnel, 2-carbobenzyloxyamino-3-dibenzylphosphonopropionic acid (**6d**) (22.24 g, 0.046 mol) and acetonitrile (46 ml) were added. While stirring at 0°C under nitrogen, triethylamine (6.35 ml) and ethyl chloroformate (4.43 ml, 0.046 mol) were added. After stirring for 30 min, "Solution A" was added carefully through a dropping funnel. The mixed solution was stirred for 24 hr at 0°C and added distilled water (20 ml). After the solvent was removed by evaporation *in vacuo*, the organic residue was added ethyl acetate and then was washed with brine and distilled water successively. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was removed by evaporation *in vacuo*. The crude product was chromatographed on a silica gel column using ethyl alcohol to give an oily product (10.18 g) in 43% yield.

Anal. Calc. for  $C_{26}H_{28}NO_6PS$ ; C, 60.69; H, 5.68; N, 2.72; O, 18.66; P, 6.02; S, 6.23. Found: C, 60.46; H, 5.62; N, 2.81; O, 18.59; P, 6.15; S, 6.37;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.35 (s, 5H,  $-CH_2C_6H_5$ ), 7.25 (s, 10H,  $-CH_2C_6H_5$ ), 4.9 (d, 4H,  $J_{H-P}=8$  Hz,  $-CH_2C_6H_5$ ), 4.3 (m, 1H,  $-CONHCH_2CH_2-$ ), 3.0 (m, 4H,  $-SCH_2CH_2-$ ), 2.5 (d, 1H,  $J_{H-P}=7.5$  Hz,  $-CH_2P=O$ ), 2.2 (d, 1H,  $J_{H-P}=7.5$  Hz,  $-CH_2P=O$ ), IR (neat): 3400 (NH), 1730 (C=O), 1210 (P=O), 1000 (P-O)  $cm^{-1}$ . (7a) Anal. Calc. for  $C_{14}H_{21}NO_6PS$ ; C, 46.41; H, 5.84; N, 3.86; O, 26.49; P, 8.55; S, 8.85. Found: C, 46.16; H, 5.78; N, 3.94; O, 26.43; P, 8.72; S, 8.97;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.8 (d, 6H,  $J_{H-P}=7$  Hz,  $-OCH_3$ ). (7b) Anal. Calc. for  $C_{16}H_{25}NO_6PS$ ; C, 49.22; H, 6.45; N, 3.59; O, 24.59; P, 7.93; S, 8.21. Found: C, 49.08; H, 6.37; N, 3.65; O, 24.51; P, 8.03; S, 8.36;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  4.15 (m, 4H,  $-OCH_2CH_3$ ), 1.2 (m, 6H,  $-OCH_2CH_3$ ). (7c) Anal. Calc. for  $C_{24}H_{28}NO_6PS$ ; C, 59.25; H, 5.18; N, 2.88; O, 19.73; P, 6.37; S, 6.59. Found: C, 59.01; H, 5.12; N, 2.96; O, 19.67; P, 6.51; S, 6.73;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.20 (m, 10H,  $-OC_6H_5$ ).

**Allyl-(5R,6S)-3-(2-carbobenzyloxyamino-3-dimethylphosphonopropionyl-2-amino)ethanethio-6-[(1'R)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1a).** In a 50 ml one neck round bottomed flask, allyl-(5R,6S)-6-[(1'R)-hydroxyethyl]-1-aza-3,7-dioxobicyclo[3.2.0]-heptane-2-carboxylate (0.184 g, 0.72 mmol)<sup>26,27</sup> in acetonitrile (11.3 ml) and dimethylaminopyridine (1.9 mg) were added. While stirring at 0°C under nitrogen, ethyldiisopropylamine (0.125 ml, 0.72 mmol) and diphenylchlorophosphate (0.194 mg, 0.72 mmol) were added carefully using a syringe. After the mixture was stirred for 30 minutes at 0°C and 10 minutes at -7°C, ethyldiisopropylamine (93 mg, 0.72 mmol) and 2-carbobenzyloxyamino-3-dimethylphosphonopropionyl-2-aminoethanethiol (**7a**) (0.28 g, 0.76 mmol) were ad-

ded carefully through another syringe. The resulting solution was stirred for 10 hr at  $-7^{\circ}\text{C}$  during which period white precipitate was formed. The mixture was filtered and the residual solid was washed with cold acetonitrile (5 ml). The solid was recrystallized from cold acetonitrile to give a product (0.31 g) in 69% yield.

Anal. Calc. for  $\text{C}_{27}\text{H}_{36}\text{N}_3\text{O}_{10}\text{PS}$ ; C, 51.84; H, 5.80; N, 6.72; O, 25.57; P, 4.95; S, 5.12 Found: C, 51.79; H, 5.73; N, 6.68; O, 25.49; P, 5.08; S, 5.23, mp.  $132^{\circ}\text{C}$  (acetonitrile);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.4 (s, 5H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 5.8 (m, 1H,  $-\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.25 (t, 2H,  $-\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.1 (s, 2H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 4.6 (br d, 2H,  $-\text{COOCH}_2\text{CH}=\text{CH}_2$ ), 4.35 (m, 2H,  $-\text{NCH}_2\text{CH}_2\text{CS}-$ ,  $-\text{CH}_2\text{CH}_2\text{P}-$ ), 3.85 (d, 6H,  $J_{\text{H-P}}=7$  Hz,  $-\text{OCH}_3$ ), 3.45 (d, 1H,  $J=5.5$  Hz,  $-\text{NCH}_2\text{CHCO}-$ ), 3.35 (d, 1H,  $J=12$  Hz,  $-\text{CH}_2\text{CS}-$ ), 3.2 (d, 1H,  $J=13$  Hz,  $-\text{CH}_2\text{CS}-$ ), 2.9 (m, 4H,  $-\text{SCH}_2\text{CH}_2-$ ), 2.5 (d, 1H,  $J_{\text{H-P}}=7.5$  Hz,  $-\text{CH}_2\text{P}=\text{O}$ ), 2.2 (d, 1H,  $J_{\text{H-P}}=7.5$  Hz,  $-\text{CH}_2\text{P}=\text{O}$ ), 1.6 (s, 1H,  $-\text{OH}$ ), 1.2 (m, 3H,  $-\text{CHCH}_3$ ), IR (neat); 3580 (OH), 1210 (COO), 930, 850 (vinyl), 1150 ( $\text{P}=\text{O}$ ), 980 ( $\text{P}-\text{O}$ )  $\text{cm}^{-1}$ . (1b) Anal. Calc. for  $\text{C}_{29}\text{H}_{40}\text{N}_3\text{O}_{10}\text{PS}$ ; C, 53.29; H, 6.17; N, 6.43; O, 24.48; P, 4.74; S, 4.90. Found: C, 53.10; H, 6.11; N, 6.54; O, 24.42; P, 4.86; S, 4.97; mp.  $135^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  4.3 (m, 4H,  $-\text{OCH}_2\text{CH}_3$ ), 1.35 (m, 6H,  $-\text{OCH}_2\text{CH}_3$ ), IR (neat); 3550 (OH), 1260 (COO), 930, 850 (vinyl), 1250 ( $\text{P}=\text{O}$ ), 1000 ( $\text{P}-\text{O}$ )  $\text{cm}^{-1}$ . (1c) Anal. Calc. for  $\text{C}_{37}\text{H}_{40}\text{N}_3\text{O}_{10}\text{PS}$ ; C, 59.27; H, 5.38; N, 5.60; O, 21.34; P, 4.13; S, 4.28. Found: C, 59.10; H, 5.32; N, 5.74; O, 21.26; P, 4.21; S, 4.37, mp.  $144^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.15 (m, 10H,  $-\text{OC}_6\text{H}_5$ ), IR (neat); 3560 (OH), 1230 (COO), 950 & 800 (vinyl), 1200 ( $\text{P}=\text{O}$ ), 1050 ( $\text{P}-\text{O}$ )  $\text{cm}^{-1}$ . (1d) Anal. Calc. for  $\text{C}_{39}\text{H}_{44}\text{N}_3\text{O}_{10}\text{PS}$ ; C, 60.22; H, 5.70; N, 5.40; O, 20.57; P, 3.98; S, 4.12. Found: C, 60.09; H, 5.62; N, 5.52; O, 20.48; P, 4.03; S, 4.26, mp.  $152^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.30 (s, 10H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 5.0 (d, 4H,  $J_{\text{H-P}}=8$  Hz,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), IR (neat); 3580 (OH), 1250 (COO), 920, 830 (vinyl), 1160 ( $\text{P}=\text{O}$ ), 980 ( $\text{P}-\text{O}$ )  $\text{cm}^{-1}$ .

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## References

- Horiguchi, M.; Kandatsu, M. *Nature* **1959**, *184*, 901.
- Kandatsu, M.; Horiguchi, M. *Agri. Bio. Chem.* **1965**, *29*, 781.
- Shimizu, H.; Kakimodo, Y.; Nagagima, T.; Danaza, A.; Sano, A. *Nature* **1965**, *207*, 1197.
- Alhadliff, J. A.; Davis, G. D. *J. Biochem.* **1970**, *9*, 48 66.
- Alhadliff, J. A.; Davis, G. D. *J. Biochem. Biophys. Acta* **1971**, *244*, 221.
- Ogita, K.; Gungi, H.; Fugazawa, Y.; Terahara, A.; Kinoshita, T.; Nagai, H. *Tetrahedron Lett.* **1983**, *24*, 2283.
- Gungi, H.; Beppu, T. *Abstracts of annual meeting of Agric. Chem. Soc. Jpn.* Tokyo, Japan, 1979; p 130.
- Ogita, K.; Fugazawa, Y.; Terahara, A.; Kinoshita, T.; Nagai, H.; Beppu, T. *Abstracts of annual Meeting of Agric. Chem. Soc. Jpn.* Sendai, Japan, 1983; p 213.
- Kleinrok, T.; Stirling, I. *Chemical Abstract* **1986**, *104*, 218953a.
- Shimada, M.; Kabuto, H.; Yokoi, I. *Res. Commun. Chem. Pathol. Pharmacol.* **1987**, *57*, 359.
- Korn, E. D.; Dearborn, D. G.; Fales, H. M.; Sokoloski, E. A. *J. Bio. Chem.* **1973**, *248*, 2257.
- Reider, P. J.; Grabowski, Edward, J. *J. Tetrahedron Lett.* **1981**, *22*, 3883.
- Tanaka, T.; Hashimoto, et al. *Tetrahedron Lett.* **1982**, *23*, 1075.
- Stirling, I.; Clarke, B. P. *J. Chem. Soc. Perkin Trans.* **1982**, 3011.
- Okano, K.; Kyotani, Y. *J. Am. Chem. Soc.* **1983**, *105*, 7186.
- Basker, M. J.; Boon, R. J. *J. Antibiot.* **1983**, *36*, 416.
- Tamura, N.; Natsugar, H. *Chem. Pharm. Bull.* **1987**, *35*, 996.
- Shimizu, H.; Kumagai, T. *Jpn. Kokai Tokkyo Koho JP* **63**, **1988**, *170*, 378.
- Ohta, T.; Sato, N. *Tetrahedron Lett.* **1988**, *29*, 4305.
- Atherton, F. R.; Hal, M. J. *European patent*, **1981**, 103, 654.
- Jacobson, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654.
- Elliott, R. L.; Marks, N.; Berg, M. J. *J. Med. Chem.* **1985**, *28*, 1208.
- Alen, J. S.; Atherton, F. R. *Nature* **1978**, *272*, 56.
- Niida, T.; Tsuruoka, T. *Ger. Offen.* **1973**, *22*, 559.
- Bayer, E.; Gugel, K. H. *Helv. Chim. Acta.* **1972**, *55*, 224.
- Sletzing, M.; Liu, T.; Reamer, R. A.; SinKai, I. *Tetrahedron Lett.* **1980**, *21*, 4221.
- Salzmann, T. N.; Ratcliff, R.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
- Chun, Y. J.; Oh, G. M.; Cho, S. K.; Kim, Y. J. *J. Korean Chem. Soc.* **1990**, *34*, 646.
- Deziel, R.; Favreau, D. *Tetrahedron Lett.* **1989**, *30*, 1345.
- Kitridge, J. S.; Huges, R. R. *Biochemistry* **1964**, *3*, 991.
- Spencer, E. Y.; Todd, A. R.; Webb, R. F. *J. Org. Chem.* **1967**, *32*, 1273.
- Majoral, J. P. *Tetrahedron*, **1976**, *32*, 2633.
- Vaughan, Jr. I. R.; Eichler, J. A. *J. Am. Chem. Soc.* **1953**, *75*, 5556.
- Hofmann, K.; Peckhan, W. D.; Heiner, A. R. *J. Am. Chem. Soc.* **1953**, *78*, 238.
- Elliott, R. L.; Marks, N.; Berg, M. J.; Portoghess, P. S. *J. Med. Chem.* **1985**, *28*, 1208.
- Kang, I. J.; Hong, S. I.; Kim, Y. J. *Bull. Korean Chem. Soc.* **1991**, *12*, 127.
- Kang, I. J.; Hong, S. I.; Kim, Y. J. *Bull. Korean Chem. Soc.* **1991**, *12*, 358.
- Kim, Y. J.; Kang, I. J. *The chemistry of C-P compounds having biophysiological activity*; Mineumsa: Seoul, **1993**.