elimination reaction from *trans*-isomer. Further studies on the removal of protecting groups as well as the attachment of suitable groups on N1 and C3 position to the synthesis of useful monobactam antibiotics are currently in progress.

Acknowledgment. This work was supported by Korea Minister of Science and Technology grants #2N03881.

References

1. R. Joyeau, R. Kobaiter, J. Sadet, and M. Wakselman, *Tetrahedron Lett.*, **30**, 337 (1989).
2. For a reviews on monobactam chemistry see: (a) R.B. Morin and M. Groman, Eds., *Chemistry and Biology of β-Lactam Antibiotics*, Academic, New York, Vol III, 339-375, 1982; (b) G.I. Georg, In *Studies in Natural Product Chemistry*, Atta-ur-Rahman Ed., Elsevier, Vol. 4, p. 431-487. 1989.
3. Other syntheses of 4-alkylidene β-Lactam ring; (a) R. Aumann, E. Kuckert, C. Kruger, R. Goddard, and K. Angermund, *Chem. Ber.*, **121**, 1475 (1988); (b) A. Battaglia, G. Cainelli, D. Giacomini, G. Martelli, and M. Panunzio, *Tetrahedron Lett.*, **28**, 4347 (1987); (c) I. Yamamoto, I. Abe, M. Mazawa, M. Kotani, J. Motoyoshiya, H. Gotoh, and K. Matsuzaki, *J. Chem. Soc. Perkin Trans. I.*, 2297 (1983); (d) K. Prasad, P. Kneuseel, G. Schulz, and P. Stutz, *Tetrahedron Lett.*, **23**, 1247 (1982); (e) C.W. Greengrass, and D.W.T. Hoople, *Tetrahedron Lett.*, **22**, 1161 (1981); (f) M. Bachi, O. Goldberg, A. Gross, and J. Veya, *J. Org. Chem.*, **45**, 1481 (1980); (g) M. Bachi, O. Goldberg, A. Gross, and J. Veya, *Tetrahedron Lett.*, 4167 (1978).
4. Other syntheses of β-lactam ring using [2+2] cyclization; (a) G. I. Georg, P. He, J. Kant, and J. Mudd, *Tetrahedron Lett.*, **31**, 4167 (1990); (b) D. Kronenthal, C. Y. Han, and M. K. Taylor, *J. Org. Chem.*, **47**, 2765 (1982).
5. All compounds described were chracterized by NMR, IR, and mass spectral data. Selected physical date are as follow: **2a**: mp. 180-1℃; IR (KBr) 1682, 1789, 3053, 3359 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.53 (d, 1, J=8.7 Hz NH), 2.86 (d, 1, J=3.0 Hz, $=CH_2$), 3.76 (s, 3, OCH_3), 4.20 (d, 1, J=3.0 Hz, $=CH_2$), 4.67 (d, 1, J=8.7 Hz, NHCH), 6.83-7.71 (m, 19, aromatic H); ^{13}C-NMR (200 MHz, $CDCl_3$, off resonance spectrum) δ 56.1 (q, OCH_3), 68.0 (d, NHCH), 71.8 (s, CPh_3), 82.1 (t, $=CH_2$), 115.2 (d, aromatic CH), 122.4 (d, aromatic CH), 127.4 (d, aromatic CH), 128.9 (d, aromatic CH), 129.3 (s, $C=CH_2$), 129.5 (d, aromatic CH) 146.8 (s, aromatic C), 149.5 (s, aromatic C), 159.2 (s, aromatic C), 170.6 (s, CO); mass spectrum (CI, 200 eV), m/z (relative intensity) 447 (M^++1, 3), 418 (8), 271 (7), 243 (100), 167 (8). **4a**: mp. 137-8℃; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.60 (dd, 1, J=3.0, 13.8 Hz, CH_2Se), 2.92 (dd, 1 J=3.0, 13.8 Hz, CH_2Se), 3.59-3.61 (m, 1, C_4H), 3.74 (s, 3, OCH_3), 3.77 (brs, 1, NH), 4.26 (s, 1, C_3H), 6.69-7.57 (m, 24, aromatic H); mas spectrum (CI, 200 eV), m/z (relative intensity) 605 (M^++1, 0.4), 603 (M^++1, 0.4), 576 (0.4), 527 (0.4), 475 (2), 447 (2), 271 (13), 244 (100), 243 (100), 203 (13), 189 (26), 167 (100). **4b**: mp. 116-9℃; m/z (relative intensity) 605 (M^++1, 2), 603(M^++1, 1), 576 (1), 527 (3), 475 (5), 447(7), 271 (34), 244 (100), 243 (100), 203 (13), 189 (8), 167 (100).

Synthesis of Fosfazinomycin B

Ik Joong Kang*, Suk In Hong†, and Yong Joon Kim†

Department of Chemical Engineering, Kyungwon University, Sungnam 461-701
†Department of Chemical Engineering, Korea University, Seoul 136-701.

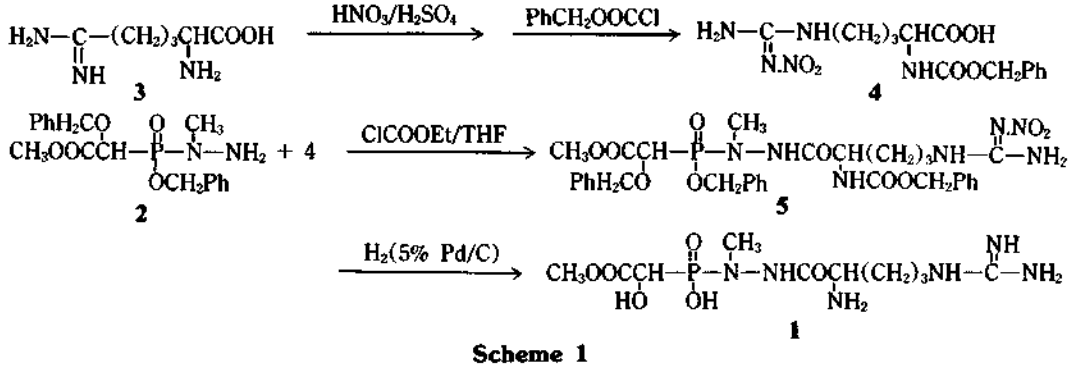
Received March 30, 1991

Fosfazinomycin B (**1**), methyl arginylmethylhydrazinohydroxyphosphonohydroxyacetate, is a new antifungal substance isolated from the fermentation broth of *Streptomyces lavendofoliae*[1-3]. It is a tripeptide which contains a carbon-phosphorus-amine bond. Most of the organic compounds in nature are composed of carbon-carbon bond. But it has been proved that the compounds having carbon-phosphorus bond are also stable. Recently aminophosphonic acids and their derivatives have attracted attention because of their antibacterial, herbicidal, pesticidal, anticancer and enzyme inhibitory activities, and particularly their structural similarity to the biologically important amino acids. Since 2-aminophosphonic acid (2-AEPn) was isolated from sheep rumen in 1959 by Horiguchi and his coworkers[4], twenty six aminophosphonic acids and their derivatives have been discovered form living organisms. Aminophosphonic acids are also discovered in mammalian tissues like human muscles, sheep liver, and ox brain[5-11]. Their concentrations in human tissues, in heart and skeletal muscles was higher than in liver and brain.

Here we report the synthesis of Fosfazinomycin B (**1**) from methyl methylhydrazinobenzyloxyphosphonoacetate (**2**)[12] which has carbon-phosphorus bond. N-Carbobenzyloxynitroarginine (**4**) was prepared in 82% yield from protecting guano group and amino group of L-arginine (**3**) by treatment with nitric acid and carbobenzyloxychloride, successively. The peptide (**5**) was prepared by coupling of acetate (**2**) with **4** in the presence of ethyl chloroformate in 67% yield. Fosfazinomycin B (**1**) was obtained by hydrogenation in 62% yield. In conclusion. Fosfazinomycin B (**1**), a new kind of phosphorus compound was synthesized from methyl methylhydrazinobenzyloxyphosphonoacetate efficiently in 4 steps in 24% overall yield.

Experimental

N-Carbobenzyloxynitroarginine(4). To a 250 m*l* three neck round-bottomed flask. 12.5 g (0.057 mol) of nitroarginine[12], 18.9 g (0.135 mol) of potassium carbonate and 100 m*l* of distilled water were added. With stirring at 0℃, the solution was added with 8.54 m*l* (0.06 mol) of benzyl chloroformate was added carefully through a dropping funnel over 30 minutes. After being stirred for 4 hours, the reaction mixture was washed with chloroform and ether successively, nd acidified with dilute HCl solution. White oily organic layer was extracted with ethyl acetate, and the extract 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 by eluting with ethyl acetate. The major compound eluted from the column was



Scheme 1

crystallized in ethyl alcohol and water to gave a white crystal in 85% yield. mp. 133℃; ^{1}H-NMR($CDCl_3$): δ 1.7 (m, 4H, -$NHCH_2C\underline{H}_2C\underline{H}_2CH$-), 3.2 (m, 3H, -$NHC\underline{H}_2CH_2CH_2C\underline{H}$-), 5.1 (s, 2H, -$OC\underline{H}_2C_6H_5$), 7.35 (s, 5H, -$OCH_2C_6\underline{H}_5$).; IR (KBr): 3500 (Guano group), 1700 cm^{-1} (C=O).

Methyl N-Carbobenzyloxynitroarginylmethylhydrazinobenzyloxyphosphonobenzyloxyacetate(5). In a 50 m*l* three neck round bottomed flask fitted with a dropping funnel 0.66 g (1.87 mmol) of N-Carbobenzyloxynitroarginine (**4**) in 3 m*l* of tetrahydrofuran and 0.26 m*l* of triethylamino were added under nitrogen. With stirring at 0℃, the solution was added with ethyl chloroformate (0.37 m*l*) through a dropping funnel. After the mixture was stirred for 30 minutes, it was added with 0.71 g (1.87 mmol) of methyl methylhydrazinobenzyloxyphosphonobenzyloxyacetate(**2**) in 2.4 m*l* of tetrafhydrofuran and 0.26 m*l* of triethylamine slowly at 0℃, and stirred further for 12 hours at 5℃. The reaction mixture was extracted with ethyl acetate and water successively. The extract was evaporated *under vacuo* to give a residue which was purfied by silica gel column chromatography. An oily product was obtained by eluting the column with ethyl acetate and n-hexane (3:2, v/v) in 67% yield. ^{1}H-NMR ($CDCl_3$): δ 1.7 (m ,4H, -$NHCH_2C\underline{H}_2C\underline{H}_2CH$-), 2.87 (d, 3H, J_{H-P}=6 Hz, -$NC\underline{H}_3$), 3.2 (m, 3H, -$NHC\underline{H}_2CH_2CH_2C\underline{H}$-) 3.8 (s, 3H, -$OC\underline{H}_3$), 4.6 (s, 2H, -$CHOC\underline{H}_2C_6H_6$), 5.0 (d, 2H, J=8 Hz, -$P(O)OC\underline{H}_2C_6H_5$), 5.1 (s, 2H, -$COOC\underline{H}_2C_6H_5$), 5.5 (s, 1H, -$C\underline{H}COOCH_3$), 7.35 (s, 15H, -$OCH_2C_6\underline{H}_5$).; IR (neat): 3500 (Guano group), 1760 (amide), 1220 (P=O), 1020 cm^{-1} (P-O-C).

Fosfazinomycin B(1). In a 250 m*l* parr low pressure hydrogenation apparatus, 0.57 g (0.8 mmol) of methyl N-Carbobenzyloxynitroarginylmethylhydrazinobenzyloxyphosphonobenzyloxyacetate(**5**) in 20 m*l* of methanol and 0.4 g of 5% palladium on charcoal were added. Hydrogenation was carried out with stirring at 15 psi of hydrogen pressure. After shaking for 4 hours at room temperature, 2.8 psi. of hydrogen pressure was comsumpted. After the mixture was filtered through Celite, the solvent was removed by evaporation *in vacuo* to give a yellow-green oil. The oil was chromatographed on a silica gel column using ethyl acetate and n-hexane (5:2, v/v) as an eluent, to give a white crystal in 62% yield. m.p.: 149℃[3]: ^{1}H-NMR (D_2O): δ 1.7 (m, 4H, -$NHCH_2C\underline{H}_2C\underline{H}_2$ CH-), 2.87 (d, 3H, J_{H-P}=6 Hz, -$NC\underline{H}_3$), 3.2 (m, 3H, -$NHC\underline{H}_2CH_2CH_2C\underline{H}$-), 3.8 (s, 3H, -$OC\underline{H}_3$), 5.35 (s, 1H, -$C\underline{H}COOCH_3$).; IR (neat): 3600 (OH), 1770 (C=O), 1200 (P=O), 980 cm^{-1} (P-O-C).

Acknowledgement. This work was supported by Post-Graduate Research Aid Program of the Daewoo Foundation, Republic of Korea.

References

1. H. Gunji and T. Beppu., *Annual Meeting of Agric. Chem. Soc. Jpn.*, Tokyo, Apr. 2-4, Abstr. 130 (1979).
2. K. Ogita, Y. Fugazawa, A. Terahara, T. Kinoshita, H. Nagai, and T. Beppu, *Annual meeting of Agric. Chem. Soc. Jpn.*, sendai, Mar. 29-Apr. 1, Abstr. 130 (1983).
3. T. Ogita, S. Gungi, Y. Fugazawa, A. Terahara, T. Kinoshita, and H. Nagai, *Tetrahedron Lett.*, **24**, 2283 (1983).
4. M. Horiguchi and M. Kandatsu, *Nature*, **184**, 901 (1959).
5. M. Kandatsu and M. Horiguchi, *Agr. Bio. Chem.*, **29**, 781 (1965).
6. H. Shimizu, Y. Kakimoto, T. Nakajima, A. Danaza, and I. sano, *Nature*, **207**, 1197 (1965).
7. J. A. Alhadelff and G. D. Davis, *J. Biochem.*, **9**, 4866 (1970).
8. J. A. Alhadelff and G. D. Davis, *J. Biochem. Biophy. Acta*, **244**, 221 (1971).
9. J. S. Kittridge and R. R. Hughes, *Biochemistry*, **3**, 991 (1964).
10. J. S. Kittridge, A. F. Isbell, and R. R. Hughes, *Biochemistry*, **6**, 289 (1967).
11. E. D. Korn, D. G. Dearborn, H. M. Fales, and E. A. Sokoloski, *J. Biol. Chem.*, **248**, 2257 (1973).
12. I. J. Kang, S. I. Hong, and Y. J. Kim, *Bull. Korean Chem. Soc.*, **12**(2), 127 (1991).
13. E. Y. Spencer, A. R. Todd, and R. F. Webb, *J. Org. Chem.*, **32**, 1273 (1967).
14. J. P. Majoral, *Tetrahedron*, **32**, 2633 (1976).
15. I. R. Vaughan Jr., and J. A. Eiechler, *J. Am. Chem. Soc.*, **75**, 5556 (1953).
16. K. Hofmann, W. D. Peckhan, and A. R. Hiener, *J. Am. Chem. Soc.*, **78**, 238(1953).
17. R. L. Elliot, N. Marks, M. J. Berg, and P. S. Portoghess, *J. Med. Chem.*, **28**, 1208 (1985).