Synthesis of Oxazolidinone Phosphonate Derivatives, Part I

Jae-Min Hwang, Woon-Seob Shin,† and Kang-Yeoun Jung*

Department of Environmental & Applied Chemistry, College of Engineering, Kangnung National University, Kangnung 210-702, Korea
†Department of Microbiology, Kwandong University College of Medicine, Kangnung 210-701, Korea
Received April 28, 2004

Several new derivatives of oxazolidinone phosphonate, that are expected to show biological activity, were prepared efficiently by previously published methods. γ-Ketophosphonate **1** was synthesized using pentacovalent oxaphosphorane chemistry followed by reductive amination with aromatic amine of oxazolidinone **4**. Biological activity of the synthetic compounds has been studied. One of the synthetic compounds showed promising result for us to pursue further studies.

Key Words : Oxazolidinone, Oxazolidinone phosphonates, Antibacterial agent, *N*-Arylation, γ-Ketophosphonate

Introduction

Oxazolidinones are very important class of antibacterial agents,[1] which are active against Gram-positive human pathogens including drug resistant strains MRSA (methicillin-resistant *Staphylococcus aureus*),[2] MRSE (methicillin-resistant *Staphylococcus epidermis*),[3] and VRE (vancomycin-resistant *Enterococci*)[4] as well as selected anaerobic organisms through a unique mechanism of action. To date many groups have reported the synthesis and biological activity of novel oxazolidinones since a few of synthetic oxazolidinone derivatives had shown antibacterial activity.[5a,b] The first oxazolidinone, linezolid (Zyvox™) is now being marketed for the treatment of multi-drug resistant Gram-positive infections.[5c]

Benzoxazolone moiety in many drugs has demonstrated to be very important group for the treatments of various diseases[6] and likewise, aminophosphonic acids which exist in many natural products, play very important role in biological system.[7] Our idea was to combine aminophosphonate moiety with variously substituted benzoxazolones giving access to a wide array of structures, which can be expected to show interesting biological and pharmacological properties.

We, therefore, selected the aminophosphonate group as a potential replacement for general substituents such as alcohol or carboxylic acid in our designed compounds, and report the preliminary synthesis of oxazolidinone phosphonate derivatives.

Results and Discussion

Synthetic route to target compounds is summarized in Scheme 1. γ-Ketophosphonate **1** was obtained using previously developed method[8] in excellent yield. Aromatic amine **4** derived from commercially available 2-amino-5-nitrophenol in three steps (amine protection with CBZCl, cyclization, and reduction) was coupled with **1** to give the reductive amination product **5**. Reductive amination method used in this coupling reaction was previously reported.[9]

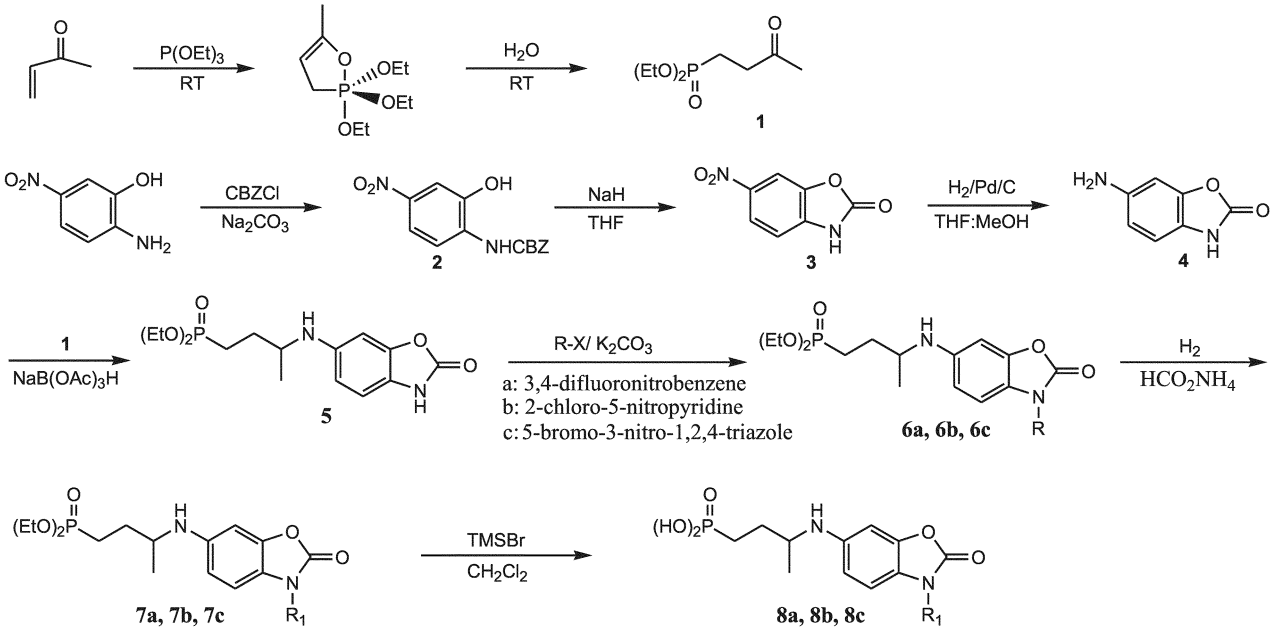
Regioselective arylation on the nitrogen of the benzoxazolone compound **5** was performed to give the desired derivatives, **6a-c**, in reasonable yields. This regioselective arylation was confirmed by NMR data comparison of compound **5** with compounds **6a-c**.

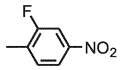
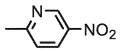
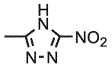
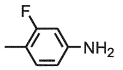
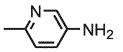
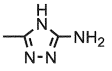
Amino products, **7a-c**, were obtained by the reduction of nitro compounds, **6a-c**, with H_2 and ammoniumformate. γ-Aminophosphonates, **7a-c**, were treated with TMSBr to give γ-aminophosphonic acids, **8a-c** for biological studies.

Biological activity of synthetic compounds was determined by 2-fold agar dilution method followed by procedure of National Committee for Clinical Laboratory Standards (NCCLS).[10] Standard strains of *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and *P. auroginosa* ATCC 27853 were used for the determination of antibacterial activity. Each compound was dissolved in methanol and added into sterilized Mueller-Hinton agar in 2-fold concentrations (0 to 500 μg/mL) prior to pouring into plates. After solidification, fresh bacterial suspensions were prepared in sterile saline and adjusted to an optical density of 0.2-0.3 at 600 nm. Adjusted inoculum (10 μL) was spotted on each plate. Plates were incubated for 24 to 48 h at 37 °C in ambient air. Preliminary biological data are shown below in Table 1.

In conclusion, several new compounds were synthesized efficiently by use of pentacovalent P(V) oxaphosphorane chemistry and reductive amination. All of the analogues were tested *in vitro* against a panel of Gram-positive and Gram-negative bacteria. Although the biological activity was not very promising compared to oxaciline, it allows us investigate other derivatives to obtain a better result in the future. Modification of the compound **8b**, particularly at the two amino groups and α position to the phosphonate group, will be studied.

*Corresponding Author. Tel: +82-33-640-2403; Fax: +82-33-640-2244; e-mail: kyjung@kangnung.ac.kr



Compounds		a	b	c
6	R :			
7	R_1:			

Scheme 1. Synthesis of Oxazolidinone γ-Aminophosphonic Acids.

Table 1. Minimum Inhibitory Concentration of Synthetic Compounds

Organisms	MIC (mg/mL)*				
	8a	**8b**	**8c**	**7a**	Oxacilin
S. aureus ATCC 25923	>500	>125	>500	>500	0.78
E. coli ATCC 25922	>500	>500	>500	>500	>500
P. auroginosa ATCC 27853	>500	>500	>500	>500	>500

*The minimum inhibitory concentration (MIC) was defined as the lowest concentration of synthetic compounds in agar plates showing no visible bacterial growth.

Experimental Section

General. Dichloromethane and Et_3N were distilled from CaH_2 immediately prior to use. All non-aqueous reactions were conducted in flame-dried glassware, under an atmosphere of argon, with magnetic stirring. NMR spectra were obtained on a JOEL Lamda 300 spectrometer and recorded at 300 MHz for ^1H (75 MHz for ^{13}C) with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards unless otherwise noted. All ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). FT-IR spectra were recorded on a JASCO FR-IR 460 series. High resolution FAB mass spectra were obtained from the Hybrid LC-Quarapole-TOF Tandem Mass Spectrometer at the Kangnung National University.

6-Amino-3*H*-benzoxazol-2-one 4: A flame-dried 250 mL round-bottom flask under argon was charged with benzoxazolone **3** (4.3 g, 23.93 mmol) and anhydrous mixture of THF : MeOH (35 : 65, 100 mL). To this solution was added ammonium formate (0.23 g, 3.7 mmol,). After bubbling Ar through the reaction solution for 30 min. Pd/C (catalyst 1.39 mg, 0.014 mmol) was added quickly. The reaction mixture were filtered after 3 hr and concentrated *in vacuo* to give the crude product. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography using a gradient solvent system with methylene chloride and methanol to give the desired product **4** (3.5 g, 23.32 mmol, 97%). ^1H NMR (DMSO) δ 11.06 (s, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.48 (d, J = 1.8 Hz, 1H), 6.33 (dd, J = 7.8, 1.8 Hz, 1H), 4.98 (s, 2H); ^{13}C NMR δ 154.74, 144.60, 144.37, 119.86, 109.92, 109.01, 96.13; HRFABMS calcd for $C_7H_6N_2O_2$ $(M+1)^+$: 151.0429, found: 151.0424.

[3-(2-Oxo-2,3-dihydro-benzoxazol-6-yl)aminobutyl]-phosphonic acid diethyl ester 5: A flame-dried 100 mL round-bottom flask under argon was charged with phosphonate **1** (0.53 g, 2.55 mmol) and anhydrous THF (20 mL). To this solution was added sodium tri-acetoxy borohydride (0.96 g, 4.53 mmol) and AcOH (153 mg, 2.55 mmol). After being stirred for 5 min at room temperature, benzoxazolone

4 (0.38 mL, 2.55 mmol) was added quickly. Reaction mixture was allowed to stir for 27 hr and quenched with 1 N NaOH. This aqueous mixture was extracted with CH_2Cl_2 and then the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography using a gradient solvent system with methylene chloride and methanol to give the desired product **5** (0.5 g, 1.45 mmol, 57%). ^{1}H NMR 9.74 (s, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.36 (dd, J = 8.4, 2.1 Hz, 1H), 4.11 (m, 4H), 3.49 (m, 1H), 1.86 (m, 4H), 1.28 (dt, J = 3.9, 7.2 Hz, 6H), 1.20 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 156.00, 145.21, 143.68, 120.68, 110.36, 109.08, 96.01, 61.78 (d, $J_{C\text{-}P}$ = 6.2 Hz), 49.42 (d, $J_{C\text{-}P}$ = 16.1 Hz), 29.11 (d, $J_{C\text{-}P}$ = 4.3 Hz), 21.98 (d, $J_{C\text{-}P}$ = 140.6 Hz), 20.38, 16.40 (d, $J_{C\text{-}P}$ = 6.2 Hz); ^{31}P NMR δ 32.7; HRFABMS calcd for $C_{15}H_{23}N_2O_5P$ $(M+1)^+$: 343.1345, found: 343.1350.

[3-{3-(2-Fluoro-4-nitro-phenyl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}aminobutyl]-phosphonic acid diethyl ester 6a: A flame-dried 100 mL round-bottom flask under argon was charged with benzophosphonate **5** (1.10 g, 3.5 mmol) and anhydrous CH_3CN (20 mL). To this solution was added activated K_2CO_3 (0.72 g, 5.25 mmol). After being stirred for 5 min at room temperature, 3,4-difluoronitrobenzene (0.47 mL, 4.2 mmol) was added quickly. The reaction mixture was refluxed for 5 hr and quenched with saturated ammonium chloride. This aqueous mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography using a gradient system with methylene chloride and methanol to give the desired product **6a** (1.19 g, 2.62 mmol, 75%). ^{1}H NMR δ 8.21 (m, 2H), 7.81 (m, 1H), 6.70 (dd, J = 2.94, 8.58 Hz, 1H), 6.60 (d, J = 2.19 Hz, 1H), 6.43 (dd, J = 2.22, 8.61 Hz, 1H), 4.10 (m, 4H), 3.53 (bs, 1H), 1.85 (m, 4H), 1.32 (dt, J = 5.31, 6.96 Hz, 6H), 1.23 (d, J = 6.24 Hz, 3H); ^{13}C NMR δ 158.02, 153.39 (d, $J_{C\text{-}F}$ = 179.55 Hz), 147.66 (d, $J_{C\text{-}F}$ = 8.03 Hz), 145.26, 144.26, 128.60 (d, $J_{C\text{-}F}$ = 1.8 Hz), 127.72 (d, $J_{C\text{-}F}$ = 12.3 Hz), 120.56, 120.31 (d, $J_{C\text{-}F}$ = 3.68 Hz), 113.31 (d, $J_{C\text{-}F}$ = 24.68 Hz), 110.39 (d, $J_{C\text{-}F}$ = 3.68 Hz), 109.05, 95.94, 61.67 (dd, $J_{C\text{-}P}$ = 1.8, 6.15 Hz), 49.42 (d, $J_{C\text{-}P}$ = 15.38 Hz), 29.38 (d, $J_{C\text{-}P}$ = 4.35 Hz), 22.32 (d, $J_{C\text{-}P}$ = 141.38 Hz), 20.48, 16.49 (dd, $J_{C\text{-}P}$ = 1.8, 6.15 Hz); ^{31}P NMR δ 32.78; IR (cm^{-1}): 3313, 2980, 2210, 1779, 1535, 1511, 1349; HRFABMS calcd for $C_{21}H_{25}N_3O_7PF$ $(M+1)^+$: 482.1415, found: 482.1413.

[3-{3-(4-Amino-2-fluoro-phenyl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}aminobutyl]-phosphonic acid diethyl ester 7a: A flame-dried 250 mL round-bottom flask under argon was charged with nitrobenzophosphonate **6a** (0.42 g, 0.93 mmol) and anhydrous mixture of THF : MeOH (35 : 65, 100 mL). To this solution was added ammonium formate (0.23 g, 3.7 mmol) quickly. After bubbling argon through the reaction solution for 30 min. Pd/C (catalyst 1.39 mg, 0.014 mmol) was added quickly. The reaction mixture were filtered after 3 hr and concentrated in vacuo to give the crude product. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography using a gradient solvent system with methylene chloride and methanol to give the desired product **7a** (0.27 g, 0.47 mmol, 69%). ^{1}H NMR δ 7.22 (m, 2H), 6.56 (m, 4H), 6.36 (dd, J = 2.19, 8.43 Hz, 1H), 4.09 (m, 4H), 3.49 (m, 1H), 1.82 (m, 4H), 1.31 (dt, J = 5.49, 7.14 Hz, 6H), 1.20 (d, J = 6.21 Hz, 3H); ^{13}C NMR δ 160.21, 155.31 (d, $J_{C\text{-}F}$ = 237.52 Hz), 149.24 (d, $J_{C\text{-}F}$ = 10.4 Hz), 144.41, 144.05, 129.34 (d, $J_{C\text{-}F}$ = 2.4 Hz), 123.06, 110.98 (d, $J_{C\text{-}F}$ = 2.4 Hz), 110.50 (d, $J_{C\text{-}F}$ = 12.9 Hz), 109.83 (d, $J_{C\text{-}F}$ = 1.2 Hz), 108.94, 102.63 (d, $J_{C\text{-}F}$ = 22.2 Hz), 96.00, 61.64 (dd, $J_{C\text{-}P}$ = 1.8, 6.7 Hz), 49.55 (d, $J_{C\text{-}P}$ = 16.0 Hz), 29.37 (d, $J_{C\text{-}P}$ = 4.9 Hz), 22.23 (d, $J_{C\text{-}P}$ = 140.6 Hz), 20.49, 16.45 (dd, $J_{C\text{-}P}$ = 1.8, 6.1 Hz); ^{31}P NMR δ 32.60; IR (cm^{-1}): 3320, 2981, 2214, 1790, 1534, 1351; HRFABMS calcd for $C_{21}FH_{27}N_3O_5P$ $(M+1)^+$: 452.1674, found: 452.1670.

[3-{3-(4-Amino-2-fluoro-phenyl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}aminobutyl]-phosphonic acid 8a: A flame-dried 100 mL round-bottom flask under argon was charged with aminobenzophosphonate **7a** (0.21 g, 0.5 mmol) and anhydrous CH_2Cl_2 (30 mL). Freshly distilled TMS-Br (1.95 mL, 14.9 mmol) was added through a syringe. The reaction mixture was allowed to stir for 26 hr and quenched with MeOH. This mixture was washed with ethyl acetate several times and then solidified from diethyl ether to get the desired product **8a** (0.15 g, 0.4 mmol, 80%). ^{1}H NMR (DMSO) δ 8.49 (d, J = 10.1 Hz, 1H), 8.32 (d, J = 8.6 Hz, 1H), 8.06 (t, J = 8.0 Hz, 1H), 7.48 (bs, 1H), 7.15 (bs, 2H), 3.67 (m, 1H), 1.88 (m, 4H), 1.19 (d, J = 5.9 Hz, 3H); ^{13}C NMR δ 158.17 (d, $J_{C\text{-}F}$ = 252.9 Hz), 154.93, 135.16 (d, $J_{C\text{-}F}$ = 6.7 Hz), 132.64, 130.83, 129.40, 121.00, 120.73 (d, $J_{C\text{-}F}$ = 3.7 Hz), 1120.12 (d, $J_{C\text{-}F}$ = 12.37 Hz), 113.20 (d, $J_{C\text{-}F}$ = 22.87 Hz), 111.81 (d, $J_{C\text{-}F}$ = 1.27 Hz), 107.43, 60.68 (d, $J_{C\text{-}P}$ = 17.92 Hz), 49.67, 23.79 (d, $J_{C\text{-}P}$= 135.07 Hz), 15.86; ^{31}P NMR δ 26.41; IR (cm^{-1}): 3418, 2930, 1796, 1536, 1512, 1352; HRFABMS calcd for $C_{17}H_{19}N_3O_5PF$ $(M+1)^+$: 396.1047, found: 396.1049.

[3-{3-(5-Nitro-pyridin-2-yl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}aminobutyl]-phosphonic acid diethyl ester 6b: A flame-dried 100 mL round-bottom flask under N_2 was charged with benzophosphonate **5** (0.57 g, 1.82 mmol) and anhydrous CH_3CN (20 mL). To this solution was added activated K_2CO_3 (0.38 g, 2.72 mmol). After being stirred for 5 min at room temperature, 2-chloro-5-nitropyridine (0.35 g, 2.18 mmol) was added quickly. The reaction mixture was refluxed for 5 hr and then quenched with saturated ammonium chloride. This aqueous mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography using a gradient solvent system with methylene chloride and methanol to give the desired product **6b** (0.48 g, 1.09 mmol, 60%). ^{1}H NMR δ 9.31 (dd, J = 0.9, 1.0 Hz, 1H), 8.55 (m, 2H), 8.09 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 4.4, 2.4 Hz, 1H), 4.11 (m, 4H), 3.56 (bs, 1H), 1.86 (m, 4H), 1.33 (dt, J = 5.5, 7.2 Hz, 6H), 1.25 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 159.57, 153.43, 151.85,

145.64, 143.88 (d, J = 22.8 Hz), 140.68, 133.31, 118.40, 116.76, 113.69, 108.87, 94.54, 61.50 (dd, $J_{C\text{-}P}$ = 1.8, 1.8 Hz), 48.98 (d, $J_{C\text{-}P}$ = 16.1 Hz), 29.78 (d, $J_{C\text{-}P}$ = 4.9 Hz), 22.06 (d, $J_{C\text{-}P}$ = 141.3 Hz), 20.21, 16.32 (dd, $J_{C\text{-}P}$ = 1.2, 1.8 Hz); ^{31}P NMR δ 32.82; IR (cm^{-1}): 3312, 2981, 2360, 2342, 1785, 1503, 1345; HRFABMS calcd for $C_{01}FH_{25}N_4O_7P$ $(M+1)^+$:465.1462, found: 465.1474.

[3-{3-(5-Amino-pyridin-2-yl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}aminobutyl]-phosphonic acid diethyl ester 7b: A flame-dried 250 mL round-bottom flask under N_2 was charged with benzophosphonate **6b** (0.3 g, 0.69 mmol) and anhydrous THF : MeOH (35 : 65, 100 mL). To this solution was added ammonium formate (0.17 g, 2.75 mmol). After being bubbled for 30 min with argon Pd/C (catalyst 1.39 mg, 0.014 mmol) was added quickly. The reaction mixture was allowed to stir for 3 hr, filtered, and concentrated in vacuo to give the crude product. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography with a gradient solvent system of methylene chloride and methanol to give the desired product **7b** (0.24 g, 0.59 mmol, 86%). ^{1}H NMR δ 7.99 (d, J = 2.94 Hz, 1H), 7.84 (d, J = 8.79 Hz, 1H), 7.68 (d, J = 8.61 Hz, 1H), 7.16 (dd, J = 2.94, 8.76 Hz, 1H), 6.54 (d, J = 2.37 Hz, 1H), 6.43 (dd, J = 2.19, 8.6 1 Hz, 1H), 4.09 (m, 4H), 3.51 (m, 1H), 1.83 (m, 4H), 1.32 (dt, J = 5.49, 6.93 Hz, 6H), 1.21 (d, J = 6.24 Hz, 3H); ^{13}C NMR δ 159.73, 153.67, 152.11, 145.74, 144.12 (d, J = 21.6 Hz), 140.94, 133.55, 118.77, 116.98, 113.97, 109.18, 94.82, 61.44 (dd, $J_{C\text{-}P}$ = 1.9, 2.5 Hz), 49.24 (d, $J_{C\text{-}P}$ = 15.5 Hz), 29.37 (d, $J_{C\text{-}P}$ = 5.0 Hz), 22.31 (d, $J_{C\text{-}P}$ = 140.6 Hz), 20.46, 16.50 (dd, $J_{C\text{-}P}$ = 1.8, 1.8 Hz); ^{31}P NMR δ 32.76; IR (cm^{-1}): 3311, 2979, 2359, 2341, 1785, 1503, 1340; HRFABMS calcd for $C_{20}H_{27}N_4O_5P$ $(M+1)^+$: 435.1721, found: 435.1728.

[3-{3-(5-Amino-pyridin-2-yl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}aminobutyl]-phosphonic acid 8b: A flame-dried 100 mL round-bottom flask under N_2 was charged with benzophosphonate **7b** (0.24 g, 0.59 mmol) and anhydrous CH_2Cl_2 (30 mL). Freshly distilled TMS-Br (2.3 mL, 17.7 mmol) was then added through a syringe. The reaction mixture was allowed to stir for 25 hr and quenched with distilled MeOH followed by adding of distilled water. This aqueous mixture was washed with ethyl acetate several times and the mixture was solidified from diethyl ether to give the desired product **8b** (0.2 g, 0.57 mmol, 97%). ^{1}H NMR (DMSO) δ 9.38 (d, J = 2.8 Hz, 1H), 8.82 (dd, J = 2.9, 2.7 Hz, 1H), 8.39 (d, J = 9.2 Hz, 2H), 8.23 (d, J = 8.8 Hz, 1H), 7.08 (m, 2H), 3.66 (q, 1H), 1.71 (m, 4H), 1.17 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ 159.55, 152.88, 151.23, 144.38, 143.23, 142.23, 139.51, 134.37, 118.94, 113.80, 102.45, 94.50, 48.68 (d, $J_{C\text{-}P}$ = 16.7 Hz), 29.32, 24.14 (d, $J_{C\text{-}P}$ = 135.8 Hz), 19.78; ^{31}P NMR δ 26.59; IR (cm^{-1}): 3397, 2978, 2462, 1794, 1580, 1349; HRFABMS calcd for $C_{16}H_{19}N_4O_5P$ $(M+1)^+$: 379.1094, found: 379.1090.

[3-{3-(5-Nitro-4*H*-[1,2,4]triazol-3-yl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}aminobutyl]-phosphonic acid diethyl ester 6c: A flame-dried 100 mL round-bottom flask under N_2 was charged with benzophosphonate **5** (0.57 g, 1.18 mmol) and anhydrous CH_3CN (20 mL). To this solution was added activated K_2CO_3 (0.38 g, 2.72 mmol) After being stirred for 5 min at room temperature, 5-bromo-3-nitro-1,2,4-triazole (0.42 mL, 2.18 mmol) was added quickly. The reaction mixture was refluxed for 5 hr and quenched with distilled water and ammonium chloride. This aqueous mixture was extracted with CH_2Cl_2 and then the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography using a gradient solvent system with methylene chloride and methanol to give the desired product **6c** (0.53 g, 1.13 mmol, 63%). ^{1}H NMR δ 9.18 (bs, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 6.36 (dd, J = 2.2, 2.2 Hz, 1H), 4.11 (m, 5H), 3.50 (m, 1H), 1.84 (m, 4H), 1.33 (dt, J = 3.3, 7.0 Hz, 6H), 1.20 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 155.72, 145.29, 143.73, 139.28, 120.63, 114.07, 110.31, 109.17, 96.20, 61.82 (d, $J_{C\text{-}P}$ = 6.2 Hz), 49.56 (d, $J_{C\text{-}P}$ = 16.1 Hz), 29.20 (d, $J_{C\text{-}P}$ = 5.0 Hz), 22.09 (d, $J_{C\text{-}P}$ = 140.7 Hz), 20.43, 16.45 (dd, $J_{C\text{-}P}$ = 1.2, 1.2 Hz); ^{31}P NMR δ 33.26; IR (cm^{-1}): 3355, 2979, 2370, 2340, 1763, 1498, 1026; HRFABMS calcd for $C_{17}H_{23}N_6O_7P$ $(M+1)^+$: 455.1372, found: 455.1376.

[3-{3-(5-Amino-4*H*-[1,2,4]triazol-3-yl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}amino-butyl]-phosphonic acid diethyl ester 7c: A flame-dried 250 mL round-bottom flask under N_2 was charged with benzophosphonate **6c** (0.47 g, 0.1 mmol) and anhydrous THF : MeOH (35 : 65, 100 mL). To this solution was added ammonium formate (0.25 g, 0.4 mmol). After being bubbled for 30 min for argon, Pd/C (catalyst 1.39 mg, 0.014 mmol) was added quickly. The reaction mixture was allowed to stir for 3 hr, filtered, and concentrated *in vacuo* to give the crude product. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography using a gradient solvent system with methylene chloride and methanol to give the desired product **7c** (0.46 g, 1.04 mmol, 69%). ^{1}H NMR δ 8.78 (s, 1H), 6.78 (d, J = 8.43 Hz, 1H), 6.50 (d, J = 2.19 Hz, 1H), 6.35 (dd, J = 2.19, 8.43 Hz, 1H), 4.11 (m, 4H), 3.48 (m, 1H), 1.85 (m, 4H), 1.32 (dt, J = 3.84, 6.96 Hz, 6H), 1.20 (d, J = 6.24 Hz, 3H); ^{13}C NMR δ 155.94, 145.23, 143.49, 139.25, 120.89, 114.03, 110.37, 109.26, 96.18, 61.83 (d, $J_{C\text{-}P}$ = 6.8 Hz), 49.59 (d, $J_{C\text{-}P}$ = 16.1 Hz), 29.62 (d, $J_{C\text{-}P}$ = 4.3 Hz), 22.00 (d, $J_{C\text{-}P}$ = 140.7 Hz), 20.33, 16.40 (dd, $J_{C\text{-}P}$ = 1.2, 1.2 Hz); ^{31}P NMR δ 30.21; IR (cm^{-1}): 3366, 2980, 2360, 1764, 1496, 1027.

[3-{3-(5-Amino-4*H*-[1,2,4]triazol-3-yl)-2-oxo-2,3-dihydro-benzoxazol-6-yl}amino-butyl]-phosphonic acid 8c: A flame-dried 100 mL round-bottom flask under N_2 was charged with benzophosphonate **7c** (0.4 g, 0.91 mmol) and anhydrous CH_2Cl_2 (30 mL). Freshly distilled TMS-Br (3.6 mL, 27.2 mmol) was then added through a syringe. The reaction mixture was allowed to stir for 26 hr and quenched with MeOH followed by adding of distilled water. This aqueous mixture was washed with ethyl acetate several times, and the mixture was solidified from diethyl ether to give the desired product **8c** (0.21 g, 0.64 mmol, 70%). ^{1}H NMR (DMSO) δ 11.06 (bs, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.52 (s, 1H), 6.35 (dd, J = 2.2, 2.2 Hz, 1H), 3.82 (m, 1H),

3.37 (m, 1H), 1.59 (m, 4H), 1.05 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ 154.70, 144.64, 144.54, 140.22, 119.54, 110.01, 108.00, 94.64, 64.90, 48.41 (d, $J_{C\text{-}P}$ = 18.6 Hz), 19.56, 16.50, 16.46, 15.15; ^{31}P NMR δ 26.84; IR (cm^{-1}): 3417, 2978, 1769, 1638, 1505, 1040; HRFABMS calcd for $C_{13}H_{17}N_6O_5P$ $(M+1)^+$: 369.1000, found: 369.1008.

Acknowledgement. This work has been supported by a grant from the Korea Science and Engineering Foundation (Grant R01-2001-000-00214-0).

References

1. Slee, A. M.; Wuonola, M. A.; McRipley, R. J.; Zajac, I.; Zawada, M. J.; Batholomew, P. T.; Gregory, W. A.; Forbes, M. *Abstracts of 27th Interscience Conference on Antimicrobial Agents and Chemotherapy*; New York, Oct. 4-7, 1987; abstract No. 244. ii. Bricker, S. J.; Hutchison, D. K.; Barbachyn, M. R.; Manninen, P. R.; Vlanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. V.; Zurenko, G. E. *J. Med. Chem*. **1996**, *39*, 673.
2. Brumfitt, W.; Hamilton-Miller, J. M. T. *Drugs Exp. Clin. Res.* **1994**, *XX*, 215.
3. (a) Brickner, S. J. *Curr. Pharm. Des.* **1996**, *2*, 175. (b) Brumfitt, W.; Hamilton-Miller, J. M. T. *Drugs Exp. Clin. Res.* **1994**, *XX*, 215.
4. Jones, R. N.; Sader, H. S. *Challenges Infect. Dis*. **1993**, *1*, 1.
5. (a) Fugitt, R. B.; Luckenbaugh, R. W. U.S. *Patent 4,128,654*, 1996. (b) Eustice, D. C.; Feldman, P. A.; Zajac, I.; Slee, A. M. *Antimicrob. Agents Chemother.* **1988**, *32*, 1218.
6. (a). Ucar, H.; Van depoorten, K.; Cacciaguerra, S.; Spampinato, S.; Stables, J. P.; Depovere, P.; Masereel, B.; Isa, M.; Delarge, J.; Poupaert, J. H. *J. Med. Chem*. **1998**, *41*, 1138. (b). Paskov, D.; Bakurdzhiev, A.; Kalcheva, V.; Simov, D.; Kamenova, L.; Boicheva, K. H. *Farmatsiya* **1975**, *25*, 61.
7. (a) Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, *J. Bioorg. Med. Chem.* **1996**, *4*, 1693. (b) Kase, H.; Yamamoto, M.; Koguchi, T.; Okachi, R.; Kasai, M.; Shirahata, K.; Kawamoto, I.; Shuto, K.; Karasawa, A.; Deguchi, T.; Nakayama, K. *Eur. Pat. Appl*. EP 0 061 172 A1, 1982; Chem. Abstr. **1983**, *98*, 107793. (c) Jung, K. Y.; Hwang, J. M. *Bull. Korean Chem. Soc.* **2002**, *23*(12), 1848.
8. (a) Jung, K. Y.; Lee, M. Y.; McClure, C. K. *Phosphorus, Sulfur, and Silicon* **1999**, *147*, 141. (b) McClure, C. K.; Hausel, R. C.; Hansen, K. B.; Grote, C. W.; Jung, K. Y. *Phosphorus, Sulfur, and Silicon* **1996**, *111*, 63.
9. (a) McClure, C. K.; Jung, K. Y. *J. Org. Chem.* **1991**, *56*, 867. (b) McClure, C. K.; Grote, C. W. *Terahedron Lett*. **1991**, *32*, 5313. (c) Jung, K. Y.; Lee, M. Y. *J. Ind. & Eng. Chem.* **1999**, *5*(3), 224.
10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: approved standard, 6th ed.; NCCLS document M7-A6 (ISBN 1-56238-486-4), NCCLS: Pennsylvania, USA, 2003.