Synthesis of Oxazolidinone Phosphonate Derivatives, Part II

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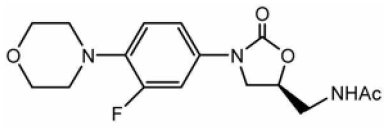
Several oxazolidinones, a new class of synthetic antibacterial agents, have shown biological activity against multidrug-resistant gram positive organisms such as *staphylococci*, *streptococci*, and *enterococci*. Previous results of our studies with benzoxazolidinone phosphonate derivatives have demonstrated very low antibacterial activity. In the course of our studies directed towards the discovery of noble antibacterial agents, we have synthesized several new derivatives of oxazolidinone phosphonates prepared efficiently from commercially available amino acids. These compounds are tested for *in vitro* antibacterial activity and one of the compounds showed promising results allowing us to pursue further studies.

Key Words : Oxazolidinone, Oxazolidinone phosphonates, Antibacterial agent

Introduction

Oxazolidinones are a promising new class of totally synthetic antibacterial agents active against numerous Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*.[1] While they share with other antimicrobials as ribosomal target, the oxazolidinones bind in a distinct region of 23S rRNA near the peptidyl transferase center and do not exhibit significant cross-resistance with the existing classes of antibacterials.[2]

Linezolid,[3] **1**, (Zyvox™, Pharmacia/Pfizer) is the first compound commercialized world wide from the oxazolidinone class of antibacterials to treat multi-drug resistant Gram-positive infections.



Linezolid 1

However, resistance against linezolid has already started to develop in *Enterococcus faecium*[4,5] and more alarmingly, in *S. aureus*, giving rise to linezolid-resistant MRSA strains.[6] Therefore, there is an urgent need for the further exploration of features of the oxazolidinone class and the synthesis of new compounds, which are more potent and less prone to resistance development.

In our previous work,[7] we described the synthesis of variously substituted benzoxazolidinone derivatives using pentacovalent oxaphosphorane chemistry followed by reductive amination with aromatic amine of oxazolidinones.[8] None of the synthetic benzoxazolidinone derivatives showed better biological activity than commercially available linezolid. As part of our ongoing efforts to improve biological activity, therefore, we have now designed and synthesized a range of oxazolidinone phosphonate derivatives from commercially available amino acids.

Results and Discussion

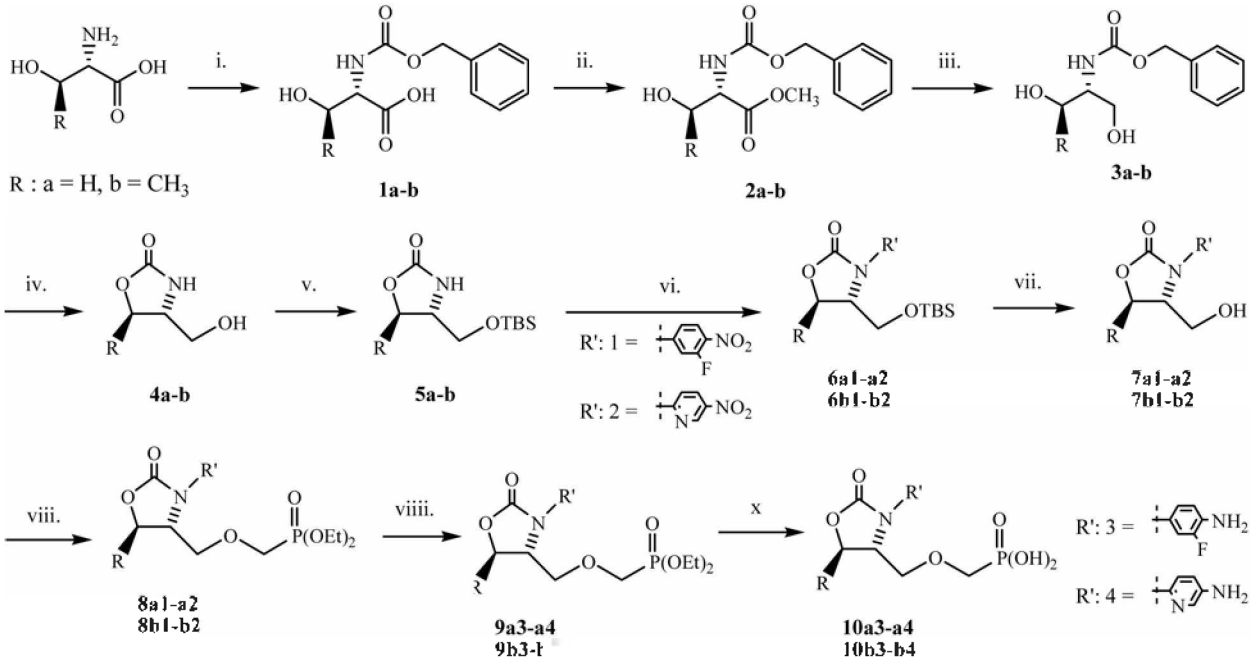
To date, many groups have reported the synthesis and biological activity of novel oxazolidinones since a few of synthetic oxazolidinone derivatives had shown antibacterial activity. In most studies, they used the reactions between oxirane derivatives and variously substituted amines in order to synthesize various oxazolidinone derivatives.[9]

In our work, however, we used L-serine and L-threonine as a starting material for the synthesis of oxazolidinone derivatives, which allows us to synthesize oxazolidine moiety more efficiently as shown in Scheme 1.

Two core compounds, 4-(*R*)-hydroxylmethyloxazolidin-2-one (**4a**)[10] and 4-(*R*)-hydroxylmethyl-5-(*R*)-methyloxazolidin-2-one (**4b**),[11] were prepared from commercially available L-serine and L-threonine in four steps, respectively. Protection of amino group with CbzCl followed by esterification under the presence of catalytic amount of TsOH gave the corresponding compounds **2a-b**, and then reduction of **2a-b** and subsequent cyclization of **3a-b** afforded the desired oxazolidinone compounds, **4a-b** in reasonable yields.

Selective protection of hydroxyl groups of **4a** and **4b** with TBSCl gave the corresponding TBS ethers **5a** and **5b** in 97% and 82% yields, respectively. Substitution of **5a** and **5b** with 2,4-difluoronitrobenzene (1: fluoronitrobenzene substituent, see Scheme 1 for the structure) or 2-chloro-5-nitropyridine (2: nitropyridine substituent) in the presence of K_2CO_3 in CH_3CN gave the *N*-substituted compounds. **6a1** and **6a2** from **5a**, **6b1** and **6b2** from **5b**, which were followed by deprotection of TBS group with TBAF gave *N*-substituted-5-hydroxyloxazolidinone derivatives **7a1-a2** and **7b1-b2** in 70-85% yields.

Oxazolidinone phosphonate products **8a** and **8b** were obtained (40-60% yields) from the reaction of **7a** and **7b**



Scheme 1. Synthesis of Oxazolidinone Phosphonic Acids. Reagents: i. $NaHCO_3$, H_2O, Cbz-Cl, ii. *p*-TsOH, MeOH, iii. $NaBH_4$, THF, iv. *t*-BuOK, THF, v. TBSCl, Imidazole, vi. R'-X, NaH, vii. TBAF, THF, viii. $TfOCH_2PO(OEt)_2$, CH_2Cl_2, ix. H_2, HCO_2NH_4, x. TMSBr, CH_2Cl_2.

with $TfOCH_2P(O)(OEt)_2$ in the presence of NaH at room temperature.

Catalytic hydrogenation of nitro groups on the aromatic ring of **8a1** and **8b1** with ammonium formate in the presence of 1.5 mol % of Pd/C in THF/methanol at room temperature gave *N*-4-amino-3-fluorophenyl derivatives **9a3** (R = H, 92% yield) and **9b3** (R = Me, 78% yield). Under the same conditions, **8a2** and **8b2** were converted into *N*-5-amino-pyridyl derivatives **9a4** (R = H, 50% yield) and **9b4** (R = CH_3, 83% yield). Treatment of diethyl phosphonate groups of **9a** and **9b** with TMSBr gave the corresponding oxazolidinone phosphonic acids **10a** and **10b** in 80-92% yields.

In summary, we have reported that a new series of *N*-substituted oxazolidinone phosphonic acid derivatives, which are expected to show improved antibacterial activity, were easily prepared from the commercially available amino acids. The biological activity of the compounds reported here will be studied and reported in the future.

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.

4-(*R*)-(*tert*-Butyldimethylsilyloxymethyl)-2-oxazolidinone (5a). A flame-dried 250 mL round-bottom flask under argon atmosphere was charged with oxazolidinone **4a** (2.17 g, 23.16 mmol), activated imidazole (3.47 g, 50.95 mmol, 2.2 equiv.), and anhydrous DMF (60 mL). After the solution was stirred for 5 min at room temperature, *tert*-butyldimethylsilylchloride (4.54 g, 30.11 mmol, 1.3 equiv.) was added quickly at the same temperature. This reaction mixture was allowed to stir for 5 hrs, and then quenched with distilled water. 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 with a gradient solvent system using methylene chloride and methanol to give the desired product **5a** (5.21 g, 22.55 mmol, 97%): ^1H NMR δ 6.47 (s, 1H), 4.40 (t, J = 8.7 Hz, 1H), 4.17 (dd, J = 8.8, 4.8 Hz, 1H), 3.89 (m, 1H), 3.58 (d, J = 5.3 Hz, 2H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 160.22, 67.17, 64.54, 53.63, 25.70, 18.11, −5.53 (d, J = 1.3 Hz); IR (cm^{-1}): 3441.3, 2928.3, 2249.5, 1730.8 HRFABMS calcd for $C_{10}H_{21}NO_3Si$ $(M+1)^+$: 232.1291, found: 232.1295.

4-(*R*)-(*tert*-Butyldimethylsilyloxymethyl)-5-(*R*)-methyl-2-oxazolidinone (5b). The desired product **5b** (2 g, 8.16 mmol, 82%) was prepared from the oxazolidinone **4b** (1.32 g, 10.07 mmol) following the same procedure as the compound **5a**: ^1H NMR δ 6.70 (bs, 1H), 4.42 (m, 1H), 3.56 (m, 2H), 3.42 (m, 1H), 1.38 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR δ 159.71, 76.18, 64.39, 60.43, 25.65 (d, J = 6.2 Hz), 20.75, 18.06, −5.56 (d, J = 2.5 Hz); IR

(cm^{-1}): 3434.6, 2293.9, 2257.3, 1635.3, 1037.5; HRFABMS calcd for $C_{11}H_{23}NO_3Si$ $(M+1)^+$: 246.1552, found: 246.1551.

4-(*R*)-(*tert*-Butyldimethylsilyloxymethyl)-*N*-(3-fluoro-4-nitrophenyl)-2-oxazolidinone (6a1). A flame-dried 100 mL round-bottom flask under argon was charged with oxazolidinone **5a** (1.11 g, 4.81 mmol) and activated K_2CO_3 (0.99 g, 7.22 mmol, 1.5 equiv.) in anhydrous CH_3CN (20 mL). After the solution was stirred for 5 min at room temperature, 3,4-difluoronitrobenzene (0.64 mL, 5.77 mmol, 1.2 equiv) was added quickly. This reaction mixture was refluxed for 1 hr, and then quenched with distilled water and ammonium chloride, respectively. The 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 with a gradient solvent system of methylene chloride and methanol to give the desired product **6a1** (1.37 g, 3.7 mmol, 77%): ^{1}H NMR δ 8.03 (m, 2H), 7.88 (dd, J = 8.9, 7.7 Hz, 1H), 4.61 (m, 2H), 4.35 (dd, J = 7.9, 4.0 Hz, 1H), 3.57 (d, J = 3.2 Hz, 2H), 0.97 (s, 9H), −0.07 (s, 3H), −0.14 (s, 3H); ^{13}C NMR δ 155.76, 155.24 (d, $J_{C\text{-}F}$ = 252.0Hz), 145.65 (d, $J_{C\text{-}F}$ = 8.3 Hz), 130.79 (d, $J_{C\text{-}F}$ = 10.2 Hz), 128.0 (d, $J_{C\text{-}F}$ = 2.2 Hz), 119.80 (d, $J_{C\text{-}F}$ = 3.4 Hz), 112.39 (d, $J_{C\text{-}F}$ = 25.0 Hz), 64.92, 61.53, 57.60 (d, J = 6.5 Hz), 25.42, 17.83, −5.93 (d, J = 1.0 Hz); IR (cm^{-1}): 3504.0, 2930.3, 2857.9, 1768.4, 1531.2, 1346.0; HRFABMS calcd for $C_{16}H_{23}N_2O_5FSi$ $(M+1)^+$: 371.1360, found: 371.1361.

4-(*R*)-(*tert*-Butyldimethylsilyloxymethyl)-*N*-(3-fluoro-4-nitrophenyl)-5(R)-methyl-2-oxazolidinone (6b1). The desired compound **6b1** (1.35 g, 3.6 mmol, 75%) was prepared from oxazolidinone **5b** (1.18 g, 4.81 mmol) following the same procedure as the compound **6a1**: ^{1}H NMR δ 7.98 (m, 3H), 4.63 (m, 1H), 4.17 (m, 1H), 3.58 (d, J = 3.3 Hz, 2H), 1.57 (d, J = 6.2 Hz, 3H), 0.81 (s, 9H), −0.06 (s, 3H), −0.13 (s, 3H); ^{13}C NMR δ 155.28, 155.30 (d, J = 251.7 Hz), 145.70 (d, $J_{C\text{-}F}$ = 8.0 Hz), 131.0 (d, $J_{C\text{-}F}$ = 10.5 Hz), 128.20 (d, $J_{C\text{-}F}$ = 2.5 Hz), 119.90 (d, $J_{C\text{-}F}$ = 3.1 Hz), 112.50 (d, $J_{C\text{-}F}$ = 25.3 Hz), 73.60, 64.41 (d, J = 6.2 Hz), 61.30, 25.51 (d, J = 8.0 Hz), 20.61, 17.90, -5.91 (d, J = 2.5 Hz); IR (cm^{-1}): 3425.0, 2930.3, 2858.0, 1766.5, 1531.2, 1346.1; HRFABMS calcd for $C_{17}H_{25}N_2O_5FSi$ $(M+1)^+$: 385.1517, found: 385.1515.

***N*-(3-Fluoro-4-nitrophenyl)-4-(*R*)-hydroxymethyl-2-oxazolidinone (7a1).** To a solution of oxazolidinone **6a1** (0.97 g, 2.62 mmol) in freshly distilled Et_2O (20 mL) was added tetrabutylammoniumfloride (1.03 mL, 3.54 mmol, 1.35 equiv.) quickly. The reaction mixture was stirred for 5 hrs and quenched with distilled water followed by aqueous 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 with a gradient solvent system using methylene chloride and methanol to give the desired product **7a1** (0.47 g, 1.84 mmol, 70%): ^{1}H NMR δ 8.03 (m, 2H), 7.84 (t, J = 8.1 Hz, 1H), 4.61 (m, 2H), 4.47 (m, 1H), 3.62 (s, 2H), 3.09 (s, 1H); ^{13}C NMR δ 156.23, 155.70 (d, $J_{C\text{-}F}$ = 252.6 Hz), 146.09 (d, $J_{C\text{-}F}$ = 8.3 Hz), 130.27 (d, $J_{C\text{-}F}$ = 10.8 Hz), 128.53 (d, $J_{C\text{-}F}$ = 2.2 Hz), 119.97 (d, $J_{C\text{-}F}$ = 3.5 Hz), 112.48 (d, $J_{C\text{-}F}$ = 25.4 Hz), 65.14, 60.48, 57.81 (d, J = 5.9 Hz); IR (cm^{-1}): 3426.8, 1747.1, 1530.2, 1410.6, 1349.9, 1205.2, 1141.6; HRFABMS calcd for $C_{10}H_9N_2O_5F$ $(M+1)^-$: 257.0495, found: 257.0495.

***N*-(3-Fluoro-4-nitrophenyl)-4-(*R*)-hydroxymethyl-5-(*R*)-methyl-2-oxazolidinone (7b1).** The procedure was the same as the preparation of compound **7a1**. Oxazolidinone **6b1** (0.82 g, 2.14 mmol) was converted to the desired product **7b1** (0.35 g, 1.34 mmol, 65%): ^{1}H NMR δ 8.07 (m, 2H), 7.85 (dd, J = 8.8, 7.9 Hz, 1H), 4.75 (m, 1H), 4.17 (m, 1H), 3.68 (d, J = 3. 5 Hz, 2H), 1.59 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 155.6 (d, $J_{C\text{-}F}$ = 251.6 Hz), 155.36, 146.11 (d, $J_{C\text{-}F}$ = 10.5 Hz), 130.66 (d, $J_{C\text{-}F}$ = 10.4 Hz), 128.55 (d, $J_{C\text{-}F}$ = 2.4 Hz), 120.16 (d, $J_{C\text{-}F}$ = 3.8 Hz), 112.65 (d, $J_{C\text{-}F}$ = 25.4 Hz), 73.62, 64.42 (d, J = 5.6 Hz), 60.7, 20.54; IR (cm^{-1}): 3398.9, 2939.0, 1735.6, 1528.3, 1348.0, 1077.1; HRFABMS calcd for $C_{11}H_{11}N_2O_5F$ $(M+1)^+$: 271.0652, found: 271.0650.

[*N*-(3-Fluoro-4-nitrophenyl)-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (8a1). To a suspension of NaH (0.88 g, 36.8 mmol, 20 equiv.) in freshly distilled THF (20 mL) was added hydroxyoxazolidinone **7a1** (0.47 g, 1.84 mmol) at 0 °C. After 5 min, the solution was treated with (diethoxyphosphono)methyltriflate (0.68 g, 3.05 mmol, 1.66 equiv.) quickly in anhydrous THF (10 mL). This reaction mixture was allowed to stir for 5 hrs at the same temperature and quenched with distilled water. 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 with a gradient solvent system using methylene chloride and methanol to afford pure compound **8a1** (0.45 g, 1.11 mmol, 60%): ^{1}H NMR δ 8.07 (m, 2H), 7.89 (dd, J = 8.8, 7.7 Hz, 1H), 4.69 (m, 2H), 4.47 (dd, J = 8.3, 4.3 Hz, 1H), 4.11 (m, 4H), 3.66 (m, 4H), 1.31 (m, 6H); ^{13}C NMR δ 155.43 (d, $J_{C\text{-}F}$ = 252.9 Hz), 155.26, 145.76 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.15 (d, $J_{C\text{-}F}$ = 10.5 Hz), 128.25 (d, $J_{C\text{-}F}$ = 2.5 Hz), 119.66 (d, $J_{C\text{-}F}$ = 3.7 Hz), 112.14 (d, $J_{C\text{-}F}$ = 25.4 Hz), 70.90 (d, J = 9.2 Hz), 65.47 (d, J = 96.8 Hz), 63.92, 62.15 (dd, J = 9.3, 6.2 Hz), 55.90 (d, J = 5.6 Hz), 16.07 (dd, J = 5.6, 1.9 Hz); ^{31}P NMR δ 19.65; IR (cm^{-1}): 3474.1, 2985.2, 2894.6, 1762.6, 1530.2, 1348.9, 1237.1, 1026.9; HRFABMS calcd for $C_{15}H_{20}N_2O_8PF$ $(M+1)^-$: 407.0941, found: 407.0943.

[*N*-(3-Fluoro-4-nitrophenyl)-5-(*R*)-methyl-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (8b1). The procedure was the same as the preparation of compound **8a1**. Hydroxyoxazolidinone **7b1** (0.3 g, 1.15 mmol) was converted to the desired product **8b1** (0.18 g, 0.44 mmol, 38%): ^{1}H NMR δ 7.93 (m, 1H), 7.84 (dd, J = 11.7, 2.6 Hz, 1H), 6.65 (t, J = 8.6 Hz, 1H), 4.26 (m, 1H), 4.12 (m, 4H), 3.79 (m, 4H), 1.31 (td, J = 7.0, 5.3 Hz, 6H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 151.57, 149.05 (d, J = 240.6 Hz), 142.50 (d, $J_{C\text{-}F}$ = 11.1 Hz), 136.39 (d, $J_{C\text{-}F}$ = 8.0 Hz), 122.20 (d, $J_{C\text{-}F}$ = 2.5 Hz), 111.03 (d, $J_{C\text{-}F}$ = 22.9 Hz), 109.27 (d, $J_{C\text{-}F}$ = 3.7 Hz), 72.11 (d, J = 6.2 Hz), 66.19, 64.73 (d, J = 111.1 Hz), 62.60 (dd, J = 6.8, 4.9 Hz), 56.48, 19.68,

16.35 (d, J = 5.6 Hz); ^{31}P NMR δ 21.42; IR (cm^{-1}): 3388.3, 2923.6, 2853.2, 1743.3, 1532.2, 1026.9; HRFABMS calcd for $C_{16}H_{22}N_2O_8PF$ (M+1)$^-$: 421.1098, found: 421.1096.

[*N*-(4-Amino-3-fluorophenyl)-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (9a3). A solution of oxazolidinone **8a1** (0.29 g, 0.71 mmol) in anhydrous THF:MeOH (35:65, 100 mL) was treated with ammoniumformate (0.18 g, 2.86 mmol, 4 equiv.) at room temperature. After being bubbled for 30 min with argon, Pd/C (catalyst 1.09 mg, 0.011 mmol, 0.015 equiv.) was added quickly and stirred. After 3 hrs, the reaction mixture was filtered and concentrated *in vacuo* to afford the crude product. This crude oil was purified by flash column chromatography with a gradient solvent system using ethyl acetate and methanol to give the desired product **9a3** (0.25 g, 0.66 mmol, 92%): ^{1}H NMR δ 7.06 (t, J = 8.4 Hz, 1H), 6.38 (m, 2H), 4.53 (t, J = 8.8 Hz, 1H), 4.39 (dd, J = 8.6, 5.3 Hz, 1H), 4.18 (m, 7H), 3.74 (m, 2H), 3.57 (m, 2H), 1.32 (m, 6H); ^{13}C NMR δ 158.87 (d, $J_{C\text{-}F}$ = 245.5 Hz), 157.02, 148.67 (d, $J_{C\text{-}F}$ = 10.5 Hz), 130.19 (d, $J_{C\text{-}F}$ = 2.5 Hz), 112.21 (d, $J_{C\text{-}F}$ = 12.3 Hz), 110.65 (d, $J_{C\text{-}F}$ = 3.1 Hz), 102.03 (d, $J_{C\text{-}F}$ = 22.9 Hz), 71.14 (d, J = 10.5 Hz), 65.70 (d, J = 113.5 Hz), 64.26, 62.42 (dd, J = 11.7, 6.5 Hz), 56.91 (d, J = 1.8 Hz), 16.26 (dd, J = 5.6, 1.9 Hz); ^{31}P NMR δ 19.96; IR (cm^{-1}): 3460.6, 3451.6, 3244.6, 2984.3, 1747.1, 1523.4, 1239.0, 1027.87; HRFABMS calcd for $C_{15}H_{22}N_2O_6PF$ (M+1)$^+$: 377.1200, found: 377.1201.

[*N*-(4-Amino-3-fluorophenyl)-5-(*R*)-methyl-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (9b3). The procedure was the same as the preparation of compound **9a3**. Oxazolidinone **8b1** (0.25 g, 0.59 mmol) was converted to **9b3** (0.17 g, 0.46 mmol, 78%): ^{1}H NMR δ 9.16 (dd, J = 2.3, 1.00 Hz, 1H), 8.47 (m, 2H), 4.84 (m, 1H), 4.59 (m, 1H), 4.07 (m, 8H), 3.79 (d, J = 7.7 Hz, 2H), 1.52 (d, J = 6.4 Hz, 3H), 1.32 (dt, J = 10.4, 8.5 Hz, 6H); ^{13}C NMR δ 156.92 (d, J = 245.3 Hz), 154.37, 144.19 (d, J = 18.5 Hz), 140.01, 133.25, 112.60, 111.33, 73.68, 70.67 (d, J = 8.6 Hz), 65.40 (d, J = 164.7 Hz), 62.36 (dd, J = 13.2, 6.5 Hz), 60.69, 20.58 (d, J = 36.7 Hz), 16.29 (dd, J = 8.6, 3.7 Hz); ^{31}P NMR δ 20.00; IR (cm^{-1}): 3466.41, 2984.3, 2938.98, 1768.4, 1597.73, 1345.11, 1117.55; HRFABMS calcd for $C_{16}H_{24}N_2O_6PF$ (M+1)$^+$: 391.1357, found: 391.1350.

[*N*-(4-Amino-3-fluorophenyl)-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid (10a3). To a solution of phosphonated oxazolidinone **9a3** (0.13 g, 0.35 mmol) in distilled CH_2Cl_2 (30 mL) was added freshly distilled TMSBr (1.36 mL, 10.5 mmol, 30 eq). After being stirred for 24 hrs at room temperature, the reaction was diluted with MeOH. This mixture was concentrated in vacuo and washed with methylene chloride and ether several times to give the desired product **10a3** (0.10 g, 0.31 mmol, 88.5%): ^{1}H NMR δ 7.43 (t, J = 8.6 Hz, 1H), 7.01 (m, 2H), 4.58 (m, 1H), 4.33 (m, 2H), 3.53 (m, 4H), 3.17 (s, 2H); ^{13}C NMR δ 158.27 (d, $J_{C\text{-}F}$ = 246.2 Hz), 156.31, 141.86 (d, $J_{C\text{-}F}$ = 9.2 Hz), 130.81 (d, $J_{C\text{-}F}$ = 2.5 Hz), 116.91 (d, $J_{C\text{-}F}$ = 12.4 Hz), 114.75, 106.03 (d, $J_{C\text{-}F}$ = 22.2 Hz), 70.38 (d, J = 8.0 Hz), 66.81 (d, J = 158.0 Hz), 65.08, 56.77; ^{31}P NMR δ 16.37; IR (cm^{-1}): 3433.6, 2252.4, 1651.7, 1026.9, 824.4, 762.7; HRFABMS calcd for $C_{11}H_{14}N_2O_6PF$ (M+1)$^+$: 321.0574, found: 321.0576.

[*N*-(4-Amino-3-fluorophenyl)-5-(*R*)-methyl-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid (10b3). The procedure was the same as the preparation of compound **10a3**. Phosphonated oxazolidinone **9b3** (0.2 g, 0.51 mmol) was converted to the desired product **10b3** (0.13 g, 0.39 mmol, 76%): ^{1}H NMR δ 9.22 (bs, 1H), 8.59 (d, J = 7.9 Hz, 1H), 8.40 (d, J = 9.2 Hz, 1H), 4.35 (m, 6H), 1.53 (d, J = 5.9 Hz, 3H); ^{13}C NMR δ 156.28 (d, J = 237.5 Hz), 155.65, 145.07, 140.94, 134.19, 113.34, 112.21, 74.83, 71.38, 61.60, 49.59, 21.09; ^{31}P NMR δ 15.62; IR (cm^{-1}): 3433.64, 2254.38, 2127.1, 1650.77, 1349.93, 1032.69; HRFABMS calcd for $C_{12}H_{16}N_2O_6PF$ (M+1)$^-$: 335.0730, found: 335.0738.

4-(*R*)-(*tert*-Butyldimethylsilyloxymethyl)-*N*-(5-nitro-pyridin-2-yl)-2-oxazolidinone (6a2). The procedure was the same as the preparation of compound **6a1**. Reaction of oxazolidinone **5a** (1.5 g, 6.49 mmol) and 2-chloro-5-nitropyridine (1.5 g, 9.74 mmol, 1.5 equiv.) gave the desired product **6a2** (2.03 g, 5.75 mmol, 89%): ^{1}H NMR δ 9.14 (t, J = 1.7 Hz, 1H), 8.45 (d, J = 1.8 Hz, 2H), 4.93 (m, 1H), 4.51 (t, J = 3.8 Hz, 2H), 4.03 (dd, J = 10.6, 4.2 Hz, 1H), 3.82 (dd, J = 10.6, 2.4 Hz, 1H), 0.82 (s, 9H), −0.02 (s, 3H), −0.13 (s, 3H); ^{13}C NMR δ 154.51, 154.43, 144.16, 139.92, 133.31, 112.39, 65.30, 61.34, 56.28, 25.53, 17.93, −5.7 (d, J = 4.4 Hz); IR (cm^{-1}): 2928.3, 1769.3, 1596.7, 1473.3, 1420, 1340.2, 1199.5; HRFABMS calcd for $C_{15}H_{23}N_3O_5Si$ (M+1)$^+$: 354.1407, found: 354.1409.

4-(*R*)-(*tert*-Butyldimethylsilyloxymethyl)-5(*R*)-methyl-*N*-(5-nitro-pyridin-2-yl)-2-oxazolidinone (6b2). The procedure was the same as the preparation of compound **6a1**. Reaction of oxazolidinone **5b** (1.18 g, 4.81 mmol) and 2-chloro-5-nitropyridine (0.92 g, 5.77 mmol, 1.2 equiv.) gave the desired product **6b2** (1.5 g, 4.08 mmol, 85%). ^{1}H NMR δ 9.20 (m, 1H), 8.47 (d, J = 1.6 Hz, 2H), 4.47 (m, 1H), 3.92 (m, 2H), 1.50 (d, J = 6.6 Hz, 3H), 0.83 (s, 9H), −0.01 (s, 3H), −0.11 (s, 3H); ^{13}C NMR δ 154.80, 154.10, 144.19, 140.01, 133.45(d, J = 17.9 Hz), 112.76, 73.77, 62.63, 61.17, 25.60, 21.08, 18.00, −5.62 (d, J = 8.0 Hz); IR (cm^{-1}): 2928.4, 2856.1, 1753.0, 1514.8, 1203.4; HRFABMS calcd for $C_{16}H_{25}N_3O_5Si$ (M+1)$^-$: 368.1546, found: 368.1545.

4-(*R*)-Hydroxymethyl-*N*-(5-nitro-pyridin-2-yl)-2-oxazolidinone (7a2). The procedure was the same as the preparation of compound **7a1**. Oxazolidinone **6a2** (2.03 g, 5.75 mmol) was converted to the desired product **7a2** (1.12 g, 4.69 mmol, 82%): ^{1}H NMR δ 9.17 (dd, J = 2.3, 1.0 Hz, 1H), 8.49 (m, 2H), 4.95 (m, 1H), 4.58 (t, J = 8.8 Hz, 1H), 4.48 (dd, J = 8.9, 4.0 Hz, 1H), 4.03 (m, 2H), 2.76 (s, 1H); ^{13}C NMR δ 154.48, 154.47, 144.09, 140.29, 133.67, 112.93, 65.29, 62.48, 57.08; IR (cm^{-1}): 3418.2, 2920.6, 2850.2, 1761.6, 1597.7, 1582.3, 1518.6, 1474.3, 1413.9, 1342.2, 1199.5; HRFABMS calcd for $C_9H_9N_3O_5$ (M+1)$^-$: 240.0542, found: 240.0543.

4-(*R*)-Hydroxymethyl-5-(*R*)-methyl-*N*-(5-nitro-pyridin-2-yl)-2-oxazolidinone (7b2). The procedure was the same as the preparation of compound **7a1**. Oxazolidinone **6b2** (0.5 g, 1.36 mmol) was converted to the desired product **7b2** (0.24 g, 0.95 mmol, 70%): ^{1}H NMR δ 9.15 (q, J = 1.3 Hz,

1H), 8.48 (s, 2H), 4.71 (m, 1H), 4.48 (q, J = 4.2 Hz, 1H), 3.97 (m, 2H), 3.07 (t, J = 4.9 Hz, 1H), 1.54 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 154.73, 154.01, 143.96, 140.19, 133.56, 113.14, 73.74, 63.68, 62.11, 20.67; IR (cm^{-1}): 3443.3, 2982.4, 2931.3, 2254.4, 1759.7, 1206.3; HRFABMS calcd for $C_{10}H_{11}N_3O_5$ (M+1)$^+$: 254.0699, found: 254.0698.

[*N*-(5-Nitro-pyridin-2-yl)-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (8a2). The procedure was the same as the preparation of compound **8a1**. Hydroxyoxazolidinone **7a2** (1.26 g, 5.27 mmol) was converted to the desired product **8a2** (1.27 g, 3.26 mmol, 61%): ^{1}H NMR δ 8.96 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 9.2, 2.5 Hz, 1H), 6.47 (d, J = 9.3 Hz, 1H), 4.20 (m, 5H), 3.84 (m, 6H), 1.34 (q, J = 7.1 Hz, 6H); ^{13}C NMR δ 160.78, 146.67, 144.41, 135.68, 134.43, 107.82, 71.95 (d, J = 6.8 Hz), 65.29, 65.30 (d, J = 164.7 Hz), 62.69 (dd, J = 8.7, 6.8 Hz), 51.74, 52.57, 16.39 (dd, J = 5.9, 1.5 Hz); ^{31}P NM R δ 21.99; IR (cm^{-1}): 3283.2, 2985.2, 2360.4, 1608.3, 1335.4, 1025.9; HRFABMS calcd for $C_{14}H_{20}N_3O_8P$ (M+1)$^-$: 390.0988, found: 390.0986.

[5-(*R*)-Methyl-*N*-(5-nitro-pyridin-2-yl)-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (8b2). The procedure was the same as the preparation of compound **8a1**. Hydroxyoxazolidinone **7b2** (0.3 g, 1.19 mmol) was converted to the desired product **8b2** (0.3 g, 0.74 mmol, 62.2%). ^{1}H NMR δ 8.98 (d, J = 2.6 Hz, 1H), 8.13 (dd, J = 2.8, 9.2 Hz, 1H), 6.44 (d, J = 9.3 Hz, 1H), 4.19 (m, 6H), 3.81 (m, 4H), 1.34 (q, J = 7.1 Hz, 6H), 1.22 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 161.02, 146.50, 144.47, 135.78, 134.45, 111.42, 73.34 (d, J = 6.2 Hz), 66.71, 65.30 (d, J = 164.7 Hz), 62.63 (dd, J = 11.8, 6.2 Hz), 55.31, 19.86, 16.44 (d, J = 5.6 Hz); ^{31}P NMR δ 21.79; IR (cm^{-1}): 3303.5, 2978.5, 2919.7, 1606.4, 1333.5, 1293.0, 1025.9; HRFABMS calcd for $C_{15}H_{22}N_3O_8P$ (M+1)$^+$: 404.1145, found: 404.1140.

[*N*-(5-Amino-pyridin-2-yl)-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (9a4). The procedure was the same as the preparation of compound **9a3**. Oxazolidinone **8a2** (0.11g, 0.28 mmol) was converted to the desired product **9a4** (0.05 g, 0.14 mmol, 50%): ^{1}H NMR δ 7.95 (dd, J = 2.8, 0.6 Hz, 1H), 6.93 (dd, J = 8.7, 2.8 Hz, 1H), 6.40 (dd, J = 8.7, 0.6 Hz, 1H), 4.15 (m, 4H), 3.8 (m, 7H), 3.48 (s, 2H), 1.33 (m, 6H); ^{13}C NMR δ 152.18, 138.02, 134.09, 133.41, 127.69, 109.85, 72.81 (d, J = 8.6 Hz), 65.22 (d, J = 164.3 Hz), 63.61, 62.56 (dd, J = 6.6, 3.5 Hz), 54.00, 16.48 (d, J = 5.3 Hz); ^{31}P NMR δ 21.57; IR (cm^{-1}): 3342.0, 2925.4, 2361.4, 1622.8, 1501.3, 1233.2, 1018.23; HRFABMS calcd for $C_{14}H_{22}N_3O_6P$ (M+1)$^+$: 360.1246, found: 360.1248.

[*N*-(5-Amino-pyridin-2-yl)-5-(*R*)-methyl-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid diethyl ester (9b4). The procedure was the same as the preparation of compound **9a3**. Oxazolidinone **8b2** (0.15 g, 0.37 mmol) was converted to the desired product **9b4** (0.1 g, 0.27 mmol, 83%): ^{1}H NMR δ 8.98 (d, J = 2.8 Hz, 1H), 8.13 (dd, J = 2.8, 9.2 Hz, 1H), 6.45 (d, J = 9.1 Hz, 1H), 4.15 (m, 6H), 3.81 (m, 4H), 1.72 (s, 1H), 1.34 (q, J = 7.1 Hz, 6H), 1.22 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 161.12, 146.75, 145.42, 136.02 (d, J = 20.4 Hz), 132.74 (d, J = 13.6 Hz), 105.77, 73.44, 66.77, 63.33 (d, J = 164.3 Hz), 62.64 (dd, J = 11.7, 6.8 Hz), 55.17, 19.88, 16.47 (d, J = 4.3 Hz); ^{31}P NMR δ 21.79; IR (cm^{-1}): 3290.0, 2993.0, 2912.0, 2360.4, 1606.4, 1293.0, 1025.9; HRFABMS calcd for $C_{15}H_{24}N_3O_6P$ (M+1)$^+$: 374.1404, found: 374.1401.

[*N*-(5-Amino-pyridin-2-yl)-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid (10a4). The procedure was the same as the preparation of compound **10a3**. Phosphonated oxazolidinone **9a4** (0.07 g, 0.19 mmol) was converted to the desired product **10a4** (0.04 g, 0.13 mmol, 68.4%): ^{1}H NMR δ 8.90 (d, J = 2.4 Hz, 1H), 8.41 (bs, 1H), 8.16 (d, J = 8.6 Hz, 1H), 6.79 (d, J = 9.3 Hz, 1H), 4.30 (bs, 1H), 3.54 (m, 7H); ^{13}C NMR δ 163.29, 160.29, 145.21, 134.59, 132.51, 110.11, 71.58 (d, J = 10.5 Hz), 6.83 (d, J = 159.2 Hz), 60.21, 48.79; ^{31}P NMR δ 17.10; IR (cm^{-1}): 3418.2, 2253.4, 1660.41, 1294, 1025.9, 825.38, 763.67; HRFABMS calcd for $C_{10}H_{14}N_3O_6P$ (M+1)$^+$: 304.0620, found: 304.0624.

[*N*-(5-Amino-pyridin-2-yl)-5-(*R*)-methyl-2-oxo-oxazolidin-4-(*R*)-yl-methoxymethyl]-phosphonic acid (10b4). The desired product **10b4** (0.08 g, 0.25 mmol, 78%) was prepared from the phosphonated oxazolidinone **9b4** (0.12 g, 0.32 mmol) following the same procedure as the compound **10a3**: ^{1}H NMR δ 8.87 (d, J = 2.2 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 9.4 Hz, 1H), 4.28 (bs, 1H), 3.94 (bs, 1H), 3.61(m, 4H), 1.02 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 161.73, 146.62, 134.19, 131.67, 108.86, 95.57, 71.43 (d, J = 11.7 Hz), 67.67, 65.54, 64.32, 19.84; ^{31}P NMR δ 16.97; IR (cm^{-1}): 3433.6, 2254.3, 2127.1, 1651.7, 1025.9, 1003.8; HRFABMS calcd for $C_{11}H_{16}N_3O_6P$ (M+1)$^+$: 318.0777, found: 318.0771.

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