

An expeditious construction of 3-aryl-5-(substituted methyl)-2-oxazolidinones: a short and efficient synthesis of Linezolid

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Abstract

A short, concise and efficient synthesis of Linezolid was accomplished through a convergent scheme utilizing either (*S*)-1-azido-3-chloropropan-2-yl chloroformate or (*S*)-1-phthalimido-3-chloropropan-2-yl chloroformate as a key starting material. The synthesis demonstrates utility of (*S*)-1-azido-3-chloropropan-2-yl chloroformate and/or (*S*)-1-phthalimido-3-chloropropan-2-yl chloroformate to facilitate the expeditious construction of 3-aryl-5-(substituted methyl)-2-oxazolidinones and offers the possibility of accessing related 2-oxazolidinone members easily as well as making additional analogues of Linezolid.

Keywords: (*S*)-1-Azido-3-chloropropan-2-yl chloroformate, (*S*)-phthalimido-3-chloropropan-2-yl chloroformate, linezolid, chloroformylation, 3-aryl-5-(substituted methyl)-2-oxazolidinone

Introduction

Oxazolidinones represent a milestone in antibacterial research as they represent the first new class of antibiotics to enter clinical usage within the past 30 years. As of 2011, Linezolid (Zyvox®, Pfizer, Figure 1) represents the first antibacterial with a new mechanism of action approved by the U.S. Food and Drug Administration (FDA).¹ Linezolid has excellent *in vitro* activity against all of the major Gram-positive bacteria that are pathogenic to humans.^{2,3} Linezolid has been approved for the treatment of patients with community-acquired and nosocomial pneumonia, complicated skin and soft tissue infections and infections due to vancomycin-resistant *Enterococcus faecium*, or for the treatment of heteroresistant vancomycin-

intermediate *Staphylococcus aureus* and penicillin-resistant pneumococci.⁴⁻⁶ Others of this class have entered development, such as Rivaroxaban (Bay-59-7939),⁷ Ranbezolid (RBx 7644),⁸ Posizolid (AZD 2563),⁹ Torezolid (TR-701),¹⁰ and Radezolid (RX-1741).¹¹

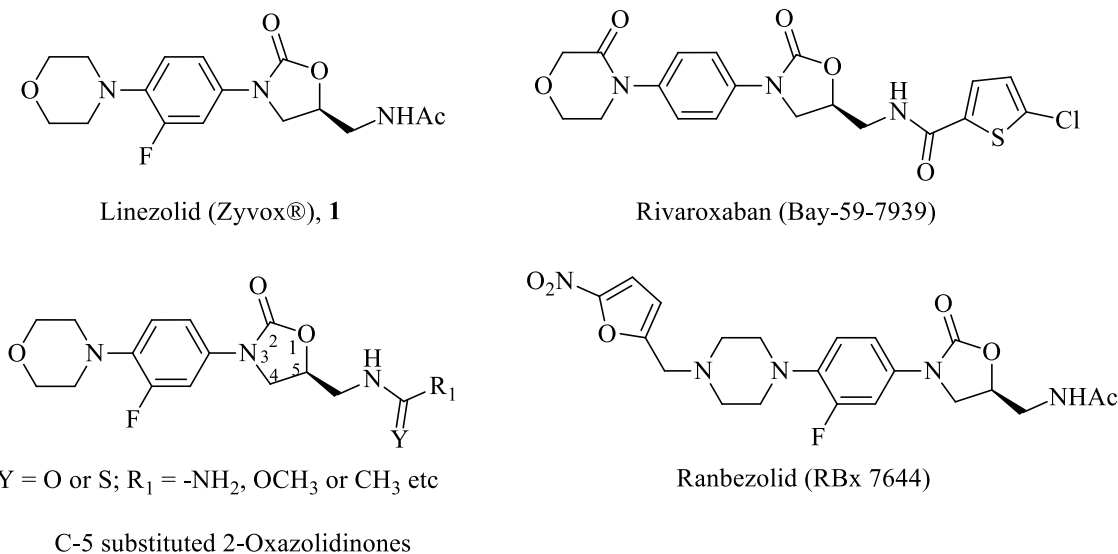


Figure 1. Various 3-aryl-5-(substituted methyl)-2-oxazolidinones.

In this context, the reported syntheses of Linezolid [3-aryl-5-(substituted methyl)-2-oxazolidinone] require mention. For instance, the classical method involves conversion of 3-fluoro-4-morpholinobenzenamine (ArNH₂) to corresponding carbamate which is deprotonated with *n*-BuLi or lithiumdiisopropyl amide (LDA) in THF followed by reaction with 2-substituted oxirane at -78 °C, or in another method, the aryl carbamate was reacted with 1-substituted 3-chloropropan-2-ol (halohydrin) using lithium *t*-butoxide (LiOtBu) or *n*-BuLi to generate (*R*)-3-aryl-5-(hydroxymethyl)-2-oxazolidinones. These 3-aryl-5-(hydroxymethyl)-2-oxazolidinone intermediates are elaborated to final products.^{12,13} However, in these methods for the synthetic key step to 2-oxazolidinone ring, severe conditions with low temperature (-78 °C) and an air-sensitive base (*n*-BuLi) are required, which limit the large-scale production in the industry. Other described synthetic methods involving aryl isocyanate instead of aryl carbamate are effective, but not general. The preparation of aryl isocyanates is cumbersome from multi-substituted aryl amines. Moreover, while preparing aryl isocyanates a major concern is the formation of the corresponding urea as a significant impurity.¹⁴

On the other hand, oxirane ring opening of 2-substituted oxirane using 3-fluoro-4-morpholinobenzenamine and carbonylation followed by further functional group transformations gave the Linezolid.¹⁵ One more method involves the conversion of (*R*)-1-azido-3-chloropropan-2-ol (halohydrin) to corresponding carbonate derivative followed by reaction with ArNH₂ giving required 2-oxazolidinone.¹⁶ In addition, there are some other articles describing the construction

of 5-(substituted methyl)-2-oxazolidinone followed by coupling with aryl halide using various reaction conditions and further transformations leading to Linezolid formation.^{17,18}

The latest analogs have common functionalities on the C-5 aminomethyl group, such as acetamides, carbamates, ureas, thioamides, thiocarbamates, and thioureas (Figure 1).¹⁹ During the conversion of amines to acetamides, carbamates, ureas, thioamides, thiocarbamates, and thioureas, there is a higher chance of obtaining the corresponding symmetrical derivatives.

Results and Discussion

In view of these limitations for accessing related 2-oxazolidinone members easily as well as making additional analogues of Linezolid and our interest in developing the small chiral building blocks,¹⁷ herein we wish to report the synthesis of novel chiral synthons, (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** or (*S*)-phthalimido-3-chloropropan-2-yl chloroformate **3b** by phosgenation of corresponding chlorohydrin with triphosgene (Scheme 1) and demonstrated their application in the synthesis of Linezolid (Figure 2). One of the early methods in the synthesis of 2-oxazolidinones involves the reaction of phosgene and aniline with β -chloroethanol to produce β -chloroethyl-*N*-phenyl carbamate which is cyclized by boiling in potassium hydroxide solution.²⁰ However, this methodology is not well utilized in synthetic organic chemistry and drug discovery probably due to the fear of limited (low) stability of 1-chloroalkan-2-yl chloroformates. Providentially, compounds **3a** and **3b** are quite stable for several days in the reaction condition and even after isolation.

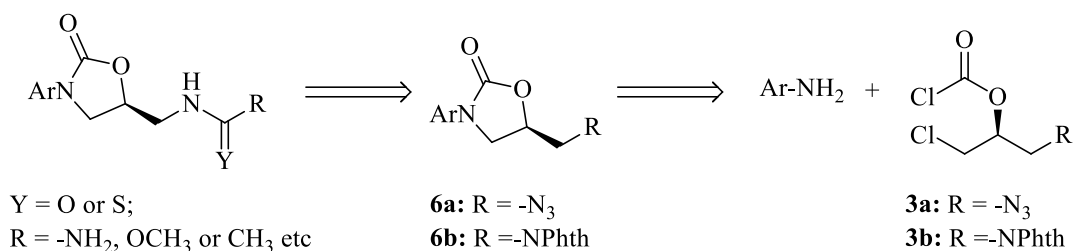
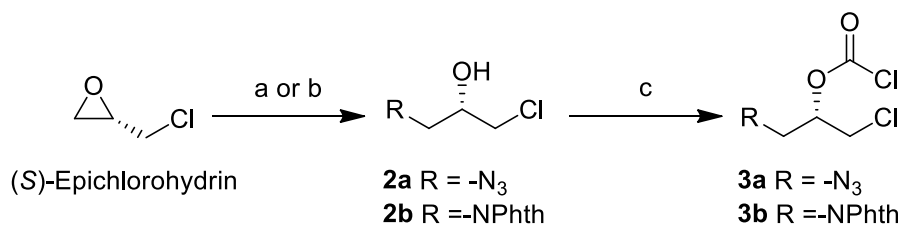


Figure 2. Application of (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** and (*S*)-1-phthalimido-3-chloropropan-2-yl chloroformate **3b** in the synthesis of 3-aryl-5-(substituted aminomethyl)-2-oxazolidinone.

Accordingly, (*S*)-epichlorohydrin was stereoselectively ring-opened with either NaN₃ or phthalimide to give corresponding chlorohydrin **2**. The chlorohydrin **2** on treatment with triphosgene using triethylamine as a base in tetrahydrofuran gave corresponding chloroformate **3**. It is worthwhile to mention that under these conditions (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** and (*S*)-1-phthalimido-3-chloropropan-2-yl chloroformate **3b** are quite stable and isolated readily without a trace of the corresponding chloride or symmetrical carbonate.



Reagents and conditions: (a) NaN₃, AcOH, H₂O, ambient temperature, 5 h, 80%; (b) Phthalimide, K₂CO₃ (cat.), IPA, reflux, 5 h, 75%; (c) Triphosgene, Et₃N, THF, 0 °C to r.t., 2-3 h, 72-89%.

Scheme 1. Preparation of (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** and (*S*)-1-phthalimido-3-chloropropan-2-yl chloroformate **3b**.

During initial reactions while preparing (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** (by using molar excess triethylamine), formation of a major impurity was observed (>25% by TLC), isolated (by column chromatography) and identified as ((*S*)-1-azido-3-chloropropan-2-yloxycarbonyl)triethylammonium chloride **4** (Figure 3). The formation of impurity **4** could be explained by either of the following two reasons: (i) side reaction of **3a** with Et₃N, or (ii) reaction of excess phosgene with Et₃N resulting in formation of corresponding unstable complex **4a** (Figure 3) which on further reaction with **2a** gave impurity **4**. The formation of ((*S*)-1-azido-3-chloropropan-2-yloxycarbonyl)triethylammonium chloride **4** was confirmed by its preparation starting from **3a** on reaction with triethylamine in tetrahydrofuran. However, the side formation of **4** was restricted in the preparation of **3a** by controlled addition of Et₃N and also by reducing the molar quantity. The impurity **4** formed is unstable and collapses, with elimination of ethyl chloride, to give a stable carbamoyl chloride derivative **4b**.

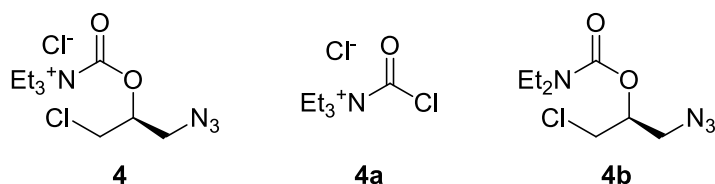
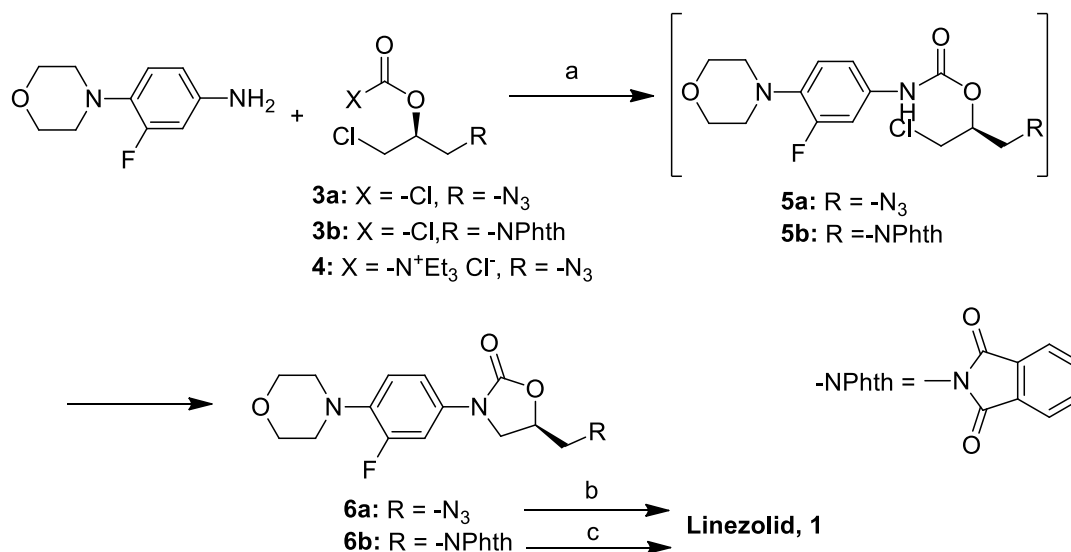


Figure 3. Chemical structures of **4**, **4a** and **4b**.

The chiral synthon **3a** can be derivatized on both ends to develop new oxazolidinone antibacterial analogs as well as monoamine oxidase-B (MAO-B) inhibitors used in the treatment of Parkinson's disease.²¹ The chlorocarbonyl functionality in **3a** and **3b** can be converted to either carbamate or 2-oxazolidinone by reaction with amines.²⁰ The azide functionality in **3a** provides the required site for preparing different analogues of the oxazolidinone. The azide functionality can also be converted to carbamates, ureas, thiocarbamates and thioureas via iminophosphorane²² and isocyanate or thiocyanate²³ intermediates, respectively. Many

established procedures are available for reductive conversion of azides to acetamides²⁴ and carbamates.²⁵

The utility of chiral synthons **3a** and **3b** has been exemplified by synthesizing Linezolid as shown in Scheme 2. The 2-oxazolidinone ring was constructed expeditiously by using chlorocarbonyl group in chloroformate **3** in a one-pot two step sequence. Accordingly, either **3a** or **3b** was treated with 3-fluoro-4-morpholinobenzenamine using molar excess K_2CO_3 in acetone resulting in corresponding 2-oxazolidinone **6**. This reaction proceeded *via* the carbamate **5** and the reaction mixture was maintained under reaction conditions until the completion of **3** as well as **5**. Initially, the carbamate **5a** was isolated exclusively using triethylamine or molar equivalent K_2CO_3 in dichloromethane. In these conditions no formation of **6a** was observed. As a summary, we developed a facile condition for the one-pot construction of 2-oxazolidinone ring (*via* carbamate) by the reaction of **3** with K_2CO_3 in acetone. Finally, the compound **6** was converted to Linezolid by reported conditions.^{12,15} The enantiomeric purity of Linezolid was readily assessed by chiral HPLC (Chiralpak ASH) and was found to be 99.9%. This was confirmed by comparing the chromatogram of the Linezolid to that of racemic Linezolid synthesized starting from racemic epichlorohydrin.



Reagents and conditions: (a) K_2CO_3 , Acetone, r.t., overnight, 82-86%; (b) H_2 , Pd/C, Ac_2O , MeOH, 20 psi, r.t., 3 h, 85%; (c) (i) Hydrazine hydrate, MeOH, reflux, 1 h; (ii) Ac_2O , Toluene, r.t., 1 h, 70%.

Scheme 2. Synthesis of Linezolid starting from either (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** or (*S*)-1-phthalimido-3-chloropropan-2-yl chloroformate **3b**.

Moreover, impurity **4** was not traceable in the initial reaction of **3a** (contains ~25% of **4**) with 3-fluoro-4-morpholinobenzenamine while synthesizing (*R*)-**6a**. In order to understand the further conversion of **4**, a reaction was performed on chemically pure **4** with K_2CO_3 in acetone at room

temperature which also resulted in the formation of (*R*)-**6a**. However, the reactivity of **4** with ArNH₂ is quite low when compared to (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** and **3b**.

Using either (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** or (*S*)-phthalimido-3-chloropropan-2-yl chloroformate **3b** as a starting material, we avoided the usage of *n*-BuLi, LDA, LiOtBu or cryogenic conditions and also increased the efficiency and atom economy of process during formation of 2-oxazolidinone in comparison to classical methods.

Conclusions

In summary, we describe herein the synthesis of novel chiral synthons, (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** and (*S*)-phthalimido-3-chloropropan-2-yl chloroformate **3b** which are precursors for further transformations into potential 2-oxazolidinone antibacterial agents. By using these chiral synthons, an efficient method has been demonstrated for 2-oxazolidinone ring construction in a one-pot two step sequence *via* the corresponding carbamate. The applicability of this approach was shown by the synthesis of Linezolid. The application of this strategy to develop a series of 2-oxazolidinone analogues where the morpholine moiety of Linezolid could be replaced with new heterobicyclic systems^{17b} is currently underway in our laboratory.

Experimental Section

General. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried at 200°C, flame-dried and flushed with dry nitrogen prior to use. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. TLC was performed on Kieselgel 60 F₂₅₄ silica-coated aluminium plates (Merck) and visualized by using either UV light ($\lambda = 254$ nm) or by spraying with a solution of ninhydrin or KMnO₄. Organic extracts were dried over anhydrous Na₂SO₄. Flash column chromatography was performed using Kieselgel 60 brand silica gel (230-400 mesh). The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. Optical rotations were measured on an Autopol V, serial number 80455 (manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA) at the sodium D line (589 nm) and are reported as follows: $[\alpha]^{t}_{D}$ (concentration in g/100 mL, solvent). The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz (¹H) and at 75 MHz (¹³C). Chemical shifts were given in ppm relative to trimethylsilane (TMS). Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintuplet; m, multiplet; and br, broad. Mass spectra were recorded on Waters Quattro Premier XE triple quadrupole spectrometer using either electrospray ionization (ESI) or

atmospheric pressure chemical ionization (APCI) technique. The chromatographic system used for the chiral HPLC studies consisted of a Shimadzu LC-10AT HPLC system equipped with a Shimadzu SPD-10A UV absorbance detector, with the wavelength set to 240 nm. Injections were made using an auto sampler Model Shimadzu SIL-20AC. Separation of the enantiomers of Linezolid were performed using a Chiralpak ASH column of dimensions $250 \times 4.6 \times 5.0$ mm. The column was fitted in a column oven Model Shimadzu CTO-10AS. UV absorbance ($\lambda = 240$ nm) chromatograms were recorded using an Advanced Computer Interface equipped with Chromatography Automation software Shimadzu CLASS-VP version 6.14 SP1. The isocratic mobile phase was a 60:40:0.1 (v/v) mixture of *n*-hexane : ethanol : diethylamine. The flow rate was 1.0 mL min^{-1} (Run time – 20 min).

Synthetic procedure for (S)-1-Azido-3-chloropropan-2-ol (2a). (*S*)-Epichlorohydrin (10 g, 0.108 mol) was dissolved in an aqueous solution of sodium azide (36.5 g, 0.561 mol in 100 mL), acetic acid (100 mL) then added and the resulting solution was stirred for 5 h at ambient temperature. The reaction mixture was extracted with EtOAc (3×50 mL) and the combined organic layer was washed with saturated NaHCO_3 solution followed by water. The organics were dried over anhydrous Na_2SO_4 and evacuated. The obtained crude compound was purified by column chromatography (97:3 *n*-hexane–EtOAc) to afford (*S*)-1-azido-3-chloropropan-2-ol, **2a** as a pale yellow thick liquid (11.7 g). Yield 80%, $[\alpha]_{\text{D}}^{20} -0.77^\circ$ (*c* 1, CHCl_3); IR (neat): ν 3436 (OH), 2109 (N_3) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 2.44 (br s, 1H, -OH, D_2O exchangeable), 3.48-3.64 (m, 4H), 4.0 (m, 1H); APCI-MS ($\text{C}_3\text{H}_6\text{ClN}_3\text{O}$): m/z (%) 136 (100, $\text{M}^+ + 1$).

2-((S)-3-Chloro-2-hydroxypropyl)isoindoline-1,3-dione (2b). To a stirred solution of (*S*)-epichlorohydrin (8.0 g, 0.086 mol), phthalimide (12.72 g, 0.086 mol) and isopropanol (60 mL), was added catalytic amount of potassium carbonate (1.1 g, 0.008 mol) at room temperature. The reaction mixture was heated to reflux and maintained at reflux temperature for 5-7 h. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was cooled to room temperature and solvent was removed under reduced pressure at below 40°C . The obtained residue was triturated with water, filtered and solid was slurry washed with water. The obtained solid was unloaded and dried at 60°C under reduced pressure to give 2-((*S*)-3-chloro-2-hydroxypropyl)isoindoline-1,3-dione **2b** as a white solid (15.5 g). Yield 75%, mp $95\text{-}96^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} -32.5^\circ$ (*c* 0.712, CHCl_3); IR (KBr): ν 3463 (OH), 1692 ($\text{C}=\text{O}$) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 2.82-2.84 (d, 1H, -OH, D_2O exchangeable), 3.59-3.71 (m, 2H), 3.85-4.01 (m, 2H), 4.15-4.21 (m, 1H), 7.72-7.78 (m, 2H), 7.85-7.89 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3): δ 41.5, 47.2, 69.64, 123.5, 131.8, 134.2, 168.6; ESI-MS ($\text{C}_{11}\text{H}_{10}\text{ClNO}_3$): m/z (%) 240 (100, $\text{M}^+ + 1$).

(S)-3-Azido-1-chloropropan-2-yl chloroformate (3a). Et_3N (10.1 g, 1.0 mol) rinsed with tetrahydrofuran (10 mL) is slowly added to a solution of (*S*)-1-azido-3-chloropropan-2-ol **2a** (9.0 g, 0.066 mol), triphosgene (9.8 g, 0.033 mol) and tetrahydrofuran (80 mL) at 0°C under inert atmosphere (N_2). After completion of addition, the reaction mixture was allowed to room temperature and stirred for 2-3 h. After completion of reaction (TLC), the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3×75 mL). The organics were dried over

anhydrous Na₂SO₄ and evacuated. The crude was purified by column chromatography (99:1 *n*-hexane–EtOAc) to afford the pure (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** as a pale yellow syrupy liquid (9.5 g). Yield 72%, $[\alpha]_D^{20}$ -3.3° (*c* 1, CHCl₃), IR (neat): ν 2109 (N₃), 1777 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 3.68-3.82 (m, 4H), 5.08-5.15 (m, 1H); ¹³C NMR (CDCl₃): δ 41.20, 50.35, 78.58, 150.33; ESI-MS (C₄H₅Cl₂N₃O₂): *m/z* (%) 161 (100) 196 (40, M⁺-1), 198 (50, M⁺+1), 200 (30, M⁺+3). Elemental Anal.calcd for C₄H₅Cl₂N₃O₂: C, 24.26; H, 2.55; N, 21.22. Found: C, 23.79; H, 2.35; N, 20.93.

(S)-3-Chloro-1-(1,3-dioxoisindolin-2-yl)propan-2-yl chloroformate (3b). Compound **3b** was prepared by using the method described for the preparation of **3a**. This compound was purified using isopropanol and obtained as a white colored solid. Yield 89%, mp 90-93°C, $[\alpha]_D^{20}$ -4.03° (*c* 1, CHCl₃), IR (KBr): ν 1771 (C=O), 1715 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 3.66-3.72 (m, 1H), 3.79-3.84 (m, 1H), 4.05-4.11 (m, 2H), 5.30-5.36 (m, 1H), 7.74-7.80 (m, 1H), 7.88-7.93 (m, 1H); ¹³C NMR (CDCl₃): δ 38.3, 42.4, 78.5, 123.5, 123.7, 131.5, 134.2, 134.4, 150.5, 167.8; ESI-MS (C₁₂H₉Cl₂NO₄): *m/z* (%) 302 (M⁺+1). Elemental Anal.calcd for C₁₂H₉Cl₂NO₄: C, 47.71; H, 3.00; N, 4.64. Found: C, 47.69; H, 2.95; N, 4.54.

((S)-1-Azido-3-chloropropan-2-yloxycarbonyl)triethylammonium chloride (4)

(a) From (S)-1-azido-3-chloropropan-2-ol (2a). Et₃N (3.95 g, 0.039 mol) rinsed with tetrahydrofuran (5 mL) is slowly added to a solution of (*S*)-1-azido-3-chloropropan-2-ol **2a** (2.0 g, 0.015 mol), triphosgene (2.2 g, 0.007 mol) and tetrahydrofuran (40 mL) at below 10 °C under inert atmosphere (N₂). After completion of addition, the reaction mixture was allowed to room temperature and stirred for 5-6 h. After completion of reaction (TLC), the reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 × 40 mL). The organics were dried over anhydrous Na₂SO₄ and evacuated to afford **4** as a pale yellow colored thick liquid (3.7 g). Yield 83%.

(b) From (S)-3-azido-1-chloropropan-2-yl chloroformate (3a). Et₃N (0.77 g, 0.008 mol) rinsed with tetrahydrofuran (2.5 mL) is slowly added to a solution of (*S*)-1-azido-3-chloropropan-2-yl chloroformate **3a** (1.2 g, 0.006 mol) and tetrahydrofuran (15 mL) at ambient temperature and stirred for 2-3 h. After completion of reaction (TLC), the reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 × 40 mL). The organics were dried over anhydrous Na₂SO₄ and evacuated to afford **4** as a pale yellow colored thick liquid (1.6 g). Yield 88%, $[\alpha]_D^{20}$ -9.3° (*c* 1, CHCl₃), IR (neat): ν 2974 (NEt₃), 2107 (N₃), 1755 (C=O), 1703, 1443 cm⁻¹; ¹H NMR (CDCl₃): δ 1.13-1.18 (t, 9H), 3.21-3.34 (m, 6H), 3.58-3.62 (m, 2H), 3.66-3.72 (m, 2H), 5.00-5.08 (m, 1H).

(S)-1-Azido-3-chloropropan-2-yl diethylcarbamate (4b). Compound **4** formed in the above procedure is found to be unstable and collapses (after a week on standing at room temperature), with elimination of ethyl chloride, to give a stable carbamoyl chloride derivative **4b**. ¹H NMR (CDCl₃): δ 1.13-1.18 (t, 6H), 3.30 (m, 4H), 3.58-3.60 (m, 2H), 3.67-3.76 (m, 2H), 5.03-5.06 (m, 1H); ¹³C NMR (CDCl₃): δ 13.25, 13.87, 41.40, 42.03, 42.81, 51.18, 71.88, 154.20; HRMS (ESI) found: 235.1002, [C₈H₁₅ClN₄O₂ + H]⁺ calcd: 235.0962.

(S)-3-Azido-1-chloropropan-2-yl 3-fluoro-4-morpholinophenylcarbamate (5a). To a stirred solution of (S)-3-azido-1-chloropropan-2-yl chloroformate, **3a** (4.0 g, 0.02 mol), 3-fluoro-4-morpholinobenzeneamine (3.33 g, 0.017 mol) and dichloromethane (40 mL) was added potassium carbonate (2.77 g, 0.02 mol) at room temperature. The mixture was stirred at room temperature for 4-5 h and reaction completion was monitored by TLC. The reaction mixture was filtered to remove solids and washed with CH₂Cl₂. The combined filtrate was washed with water, dried over anhydrous Na₂SO₄ and evacuated to give (S)-3-azido-1-chloropropan-2-yl 3-fluoro-4-morpholinophenylcarbamate **5a** as a brown colored gummy solid (5.2 g). This compound was used in the next step with out further purification. Yield 85%, IR (neat): ν 3304 (NH) 2106 (N₃), 1709 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 3.03-3.06 (t, 4H), 3.63-3.64 (d, 2H), 3.73-3.75 (m, 2H), 3.85-3.88 (t, 4H), 5.08-5.15 (m, 1H), 6.73 (br s, 1H), 6.86-6.92 (t, 1H), 6.98-7.01 (t, 1H), 7.26-7.30 (d, 1H); ESI-MS (C₁₄H₁₇ClFN₅O₃): m/z (%) 358 (100, M⁺+1) 360 (55, M⁺+3), 223 (75).

(S)-3-Chloro-1-(1,3-dioxisoindolin-2-yl)propan-2-yl 3-fluoro-4-morpholinophenylcarbamate (5b). Compound **5b** was prepared by using the method described for the preparation of **5a**. Yield 86%, mp. 200-202 °C; IR (KBr): ν 3302 (NH), 3123 (Ar-H), 2961 (C-H), 1648 (C=O), 1219 (C-O-C) cm⁻¹; ¹H NMR (CDCl₃): δ 3.00-3.03 (t, 4H), 3.73-3.74 (dd, 1H), 3.80-3.82 (dd, 1H), 3.84-3.87 (m, 4H), 3.99-4.00 (dd, 1H), 4.09-4.12 (dd, 1H), 5.30-5.33 (m, 1H), 6.66 (s, 1H, -NH), 6.84-6.90 (m, 2H), 7.20-7.21 (d, 1H), 7.72-7.75 (m, 2H), 7.85-7.88 (m, 2H); ESI-MS (C₂₂H₂₁ClFN₃O₅): m/z (%) 462 (100, M⁺+1).

(R)-5-(Azidomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (6a)

(a) From (S)-carbamate (5a). To a stirred solution of (S)-3-azido-1-chloropropan-2-yl 3-fluoro-4-morpholinophenylcarbamate **5a** (5.0 g, 0.014 mol) and acetone (25 mL) was added potassium carbonate (2.34 g, 0.017 mol) at room temperature. The mixture was stirred at room temperature for 8 h. After completion of reaction (TLC), solvent was removed under reduced pressure and the obtained residue was diluted with water. The aqueous was extracted with CH₂Cl₂ (3 × 50 mL). The organics were washed with saturated NaCl solution, dried over anhydrous Na₂SO₄ and evacuated. The crude compound was triturated with *n*-hexane (15 mL) to give (R)-5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one, **6a** as a off-white solid (3.7 g) in 83% yield.

(b) One-pot procedure from (S)-3-azido-1-chloropropan-2-yl chloroformate (3a). To a stirred solution of (S)-3-azido-1-chloropropan-2-yl chloroformate **3a** (5.0 g, 0.025 mol), 3-fluoro-4-morpholinobenzeneamine (4.12 g, 0.021 mol) and acetone (50 mL) was added potassium carbonate (12.2 g, 0.088 mol) at room temperature and stirred overnight. After completion of reaction (TLC), solvent was removed under reduced pressure and the obtained residue was diluted with water. The aqueous was extracted with CH₂Cl₂ (3 × 50 mL). The organics were washed with saturated NaCl solution, dried over anhydrous Na₂SO₄ and evacuated. The crude compound was triturated with *n*-hexane (15 mL) to give **6a** as a off-white colored solid (5.5 g). Yield 82%, mp 97-100 °C, (lit.²⁶ 102.5-103.5 °C); IR (KBr): ν 3109 (Ar-H), 2965 (C-H), 2103 (N₃) 1744 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 3.05-3.07 (t, 4H), 3.57-3.62 (dd, 1H), 3.68-3.74 (dd,

1H), 3.80-3.88 (m, 5H), 4.03-4.09 (t, 1H), 4.77-4.79 (m, 1H), 6.91-6.97 (t, 1H), 7.12-7.15 (d, 1H), 7.43-7.47 (d, 1H); ESI-MS (C₁₄H₁₆FN₅O₃): *m/z* (%) 322.1 (100, M⁺+1), 296 (40).

2-(((S)-3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione

(6b). Compound **6b** was prepared by using the method described for the preparation of **6a**. Yield 86%, mp 204-206 °C; IR (KBr): ν 3099 (Ar-H), 2962 (C-H), 1752 (C=O), 1711 (C=O), 1218 (C-O-C) cm⁻¹; ¹H NMR (CDCl₃): δ 3.03-3.07 (t, 4H), 3.86-3.89 (t, 4H), 3.94-4.19 (m, 4H), 4.96-5.00 (m, 1H), 6.89-6.95 (t, 1H), 7.10-7.13 (d, 1H), 7.39-7.45 (d, 1H), 7.76-7.80 (m, 2H), 7.87-7.91 (m, 2H); ¹³C NMR (CDCl₃): δ 40.7, 48.4, 50.9, 50.96, 66.9, 69.5, 107.4, 107.7, 113.9, 114.0, 118.7, 118.79, 123.6, 131.6, 132.8, 134.4, 136.4, 136.5, 153.7, 167.9. ESI-MS (C₂₂H₂₀FN₃O₅): *m/z* (%) 426.2 (100, M⁺+1).

N-(((S)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide 1 (Linezolid)

1 was prepared according to the method described in literature.^{12,15} Mp 182-183 °C, (lit.^{12a} 181.5-182.5 °C); enantiomeric purity 99.9% (by chiral HPLC); IR (KBr): ν 3343 (NH), 3075 (Ar-H), 2967 (CH), 1741 (C=O), 1660 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 2.03 (s, 3H), 3.04-3.07 (t, 4H), 3.56-3.77 (m, 3H), 3.86-3.89 (t, 4H), 4.00-4.06 (t, 1H), 4.74-4.79 (m, 1H), 5.96 (s, 1H), 6.90-6.96 (t, 1H), 7.06-7.10 (d, 1H), 7.43-7.48 (d, 1H). ¹³C NMR (DMSO-*d*₆): δ 22.4, 41.4, 47.3, 50.6, 66.1, 71.5, 106.4, 114.0, 119.1, 133.3, 135.5, 154.0, 156.2, 170.0; ESI-MS (C₁₆H₂₀FN₃O₄): *m/z* (%) 338.18 (100, M⁺+1).

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