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A new and alternate synthesis of Linezolid: An antibacterial agent

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ABSTRACT

*A New and alternate syntheses of Linezolid, an antibacterial agent are reported from by employing two different approaches and finalized the meritorious one. The key step in both the approaches involves N-alkylation of 3-fluoro-4-morpholinobenzenamine **3** with respective compounds by changing the leaving functionalities on other end and followed by functional group transformations yielded an antibacterial agent Linezolid. Among the both, later is more efficient one with respect to improved overall yield, easy process and less number of steps.*

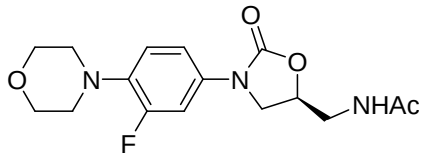
Keywords: Linezolid, antibacterial, 4-(chloromethyl)-2, 2-dimethyl-1, 3-dioxolane, *N*-alkylation, Mitsunobu conditions.

INTRODUCTION

2-Oxazolidinones have been remarkable antimicrobial agents, which act against numerous multidrug-resistant Gram-positive organisms [1]. Linezolid (**1**, **Figure 1**) as the promising candidate of this family works effectively against numerous serious Gram-positive human pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *enterococcus* (VRE) [2].

Several methods are reported in the literature for the synthesis of linezolid. Brickner S J reported a route to linezolid with good yield [3]. However, in this method for the synthetic key step to form 2-oxazolidinone ring, severe typical conditions including cryogenic conditions (–78 °C) and air-sensitive base (*n*-BuLi) were used which limit industrial preparation. Lohray presented another possibility to linezolid *via* asymmetric bis-epoxide using D-mannitol as a starting material [4]. However, the synthetic route was very long.

Another method was also reported in the literature starting from (*S*)-glyceraldehyde acetonide and 3-fluoro-4-morpholinobenzenamine [5]. However, the stability of both (*S*)-glyceraldehyde acetonide and respective condensed product (ie) imines restricts its application [5,7]. We aimed to identify an alternate synthetic method, by concerning the yields and mild reaction conditions to synthesize Linezolid starting from stable reactants such as 3-fluoro-4-morpholinobenzenamine **3** and chloro compound 4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane.



LINEZOLID, 1
Figure 1

MATERIALS AND METHODS

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 and $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

Preparation of (*S*)-4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane, (2) . To a solution of **(*S*)-epichlorohydrin** (50.0 g, 0.540 mol) and Acetone (500 mL), $BF_3.OEt_2$ (0.5 mL) was added at 0 °C. After stirring for 1 h, the reaction mixture was heated to 40 °C and again stirred for 5 h, After concentration under reduced pressure to give compound **(*S*)-2** as colorless oil (65.12 g); yield 80%; $[\alpha]^{25}_{D}$ = – 35.9 (*c* = 5.3, Bz); ^{1}H NMR ($CDCl_3$): δ 4.3-4.34 (m, 1H), 4.10-4.15 (m, 1H), 3.87-3.91 (m, 1H,) 3.56-3.61 (m, 1H), 3.50 (m, 1H), 1.45 (s, 3H), 1.37 (s, 3H); IR (neat): 2988, 1066, 845 cm^{-1}; ESI-MS: *m/z* (M^{+}+1) 151.0.

Preparation of 3-Fluoro-*N*-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-morpho lino benzenamine, (4) . To a stirred solution of **(*S*)-2** (10.0 g, 0.066 mol) and 3-fluoro-4-morpholino benzenamine (26.0 g, 0.132 mol) was added K_2CO_3 (27.6 g, 0.20 mol), TBAI (0.1 g) and NaI (0.1 g) at RT. The mixture was heated to 130 °C for 24 h. After completion of the reaction, cooled the reaction mass to RT, diluted with water (100 mL) and extracted with ethyl acetate (150 mL). The organic layer was dried over with anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. The resulted crude compound was purified by column

chromatography using silica gel (EtOAc : *n*-hexane) gave compound **(*R*)-4** as colorless oil (11.0 g); yield 70%; $[\alpha]^{20}_{D}$ = –1.7 (*c* = 4.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.84 (t, 1H), 6.39 (m, 2H), 4.35 (m, 1H), 4.09 (dd, 1H), 3.84 (t, 4H), 3.75 (dd, 1H), 3.24 (dd, 1H), 3.13 (dd, 1H), 2.95 (br s, 4H), 1.44 (s, 3H), 1.37 (s, 3H); IR (KBr): 3411, 1459, 1073 cm^{-1}; ESI-MS: *m/z* (M^+–1) 309.0.

Preparation of (*R*)-3-(3-fluoro-4-morpholinophenyl)-5-(hydroxyl methyl) oxazolidin-2-one, (6). To a solution of compound **(*R*)-4** (10.0 g, 0.032 mol) in Methanol (50.0 mL), PTSA (1.2 g, 0.0063 mol) was added and the mixture was stirred at room temperature for 5 h, then added K_2CO_3 (1.3 g, 0.0096). The mixture was cooled to 0 °C and treated lot wise with CDI (7.8 g, 0.048 mol) for 10 min. After being stirred for 8 h at room temperature, water was added (50.0 mL), organic phase was separated, and the aqueous layer was extracted with DCM (50 mL). The combined organic phase was washed with water (25 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was purified by crystallization from ethyl acetate and hexane to provide **(*R*)-6** as a solid (7.79 g); Yield 82% from **4**; mp 114–116 ^oC, $[\alpha]^{20}_{D}$ = –53° (*c* = 0.69, $CHCl_3$); ^{1}H NMR($CDCl_3$): *δ* 7.47 (dd, 1H), 7.12 (d, 1H), 7.00 (br s, 1H), 4.75 (m, 1H), 3.95 (m, 3H), 3.88 (t, 4H), 3.76 (d, 1H), 3.08 (t, 4H), 2.35 (br s, 1H); IR (KBr): 3314, 1745 cm^1; ESI-MS: *m/z* (M^++1) 297.0.

Preparation of 2-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) Iso indoline-1,3-dione, (7). To a solution of **(*R*)-6** (5.0 g, 0.0168 mol) in THF (25.0 mL), phthalimide (3.22 g, 0.021 mol), PPh_3 (5.7 g, 0.021 mol), the solution was cooled to 0 ^OC and added DEAD (3.81 g, 0.021 mol) drop wise, the mixture was stirred at room temperature for 3 h. After the completion of the reaction, water was added (50.0 mL), organic phase was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic phase was washed with water (25 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure to provide compound **(*S*)-7** as a solid (5.1 g); yield 72%; mp 205-207°C; ^{1}H NMR ($CDCl_3$): δ 7.87-7.91 (m, 2H), 7.76-7.80 (m, 2H), 7.39-7.45 (d, 1H), 7.10-7.13 (d, 1H), 6.89-6.95 (t, 1H), 4.96-5.00 (m, 1H), 3.94-4.19 (m, 4H), 3.86-3.89 (t, 4H), 3.03-3.07 (t, 4H); IR (KBr): 3099.3, 2962.2, 1752.3, 1711.3, 1217.8 cm^{-1}; ESI-MS: *m/z* (%) 426.2 (100, M^++1).

Preparation of (*S*)-5-(amino methyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one, (8). To a solution of **(*S*)-7** (20.0 g, 0.047 mol) in methanol (100.0 mL), hydrazine hydrate (13.0 g, 0.260 mol) added. The solution was heated to reflux and maintained for 2 h. After the completion of the reaction, cooled to 0 °C and water was added (100 mL) the phase was separated and extracted with DCM (100 mL). The combined organic phase was washed with water (50 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure to provide **(*S*)-8** as a solid (11.0 g) yield 79%; ^{1}H NMR ($CDCl_3$): δ 7.44-7.49 (dd, 1H), 7.12-7.15 (dd, 1H), 6.90-6.96 (t , 1H), 4.04 - 4.69 (m, 1H), 3.98-4.04 (t, 1H), 3.85-3.89 (t, 4H), 3.79 -3.84 (dd, 1H), 3.09-3.14 (dd, 1H), 3.03-3.06 (t, 4H), 2.94-3.0 (dd, 1H), 1.49 (br s, 2H); IR (KBr): 3404, 2958, 1726, 1229 cm^{-1}; ESI-MS: *m/z* (%) 296 (100, M^++1).

Preparation of *N*-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) acetamide, 1 (Linezolid). To a solution of **(*S*)-8** (10.0 g, 0.033 mol) in toluene (150.0 mL), acetic anhydride (10.0 g, 0.097 mol) added drop wise. The solution was maintained at RT for 2 hr. after reaction mass cooled to 0 °C and filtered. The resulted solid was recrystalized from

methanol to provide Linezolid **1** as a solid (8.55 g). yield 75%; mp 182-183 °C; ^{1}H NMR ($CDCl_3$): δ 7.43-7.48 (d, 1H), 7.06-7.10 (d, 1H), 6.90-6.96 (t, 1H), 5.96 (s, 1H), 4.74-4.79 (m, 1H), 4.00-4.06 (t, 1H), 3.56-3.77 (m, 3H), 3.04-3.07 (t, 4H), 2.03 (s, 3H); ^{13}C 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; IR (KBr): 3342, 2, 1741, 1660 cm^{-1}, ESI-MS: *m*/*z* (%) 338.18 (100, M^++1).

Preparation of *N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)acetamide, (3). To a solution of **(*R*)-2** (100.0 g, 0.664 mol) in DMSO (1000.0 mL), Potassium hydroxide (111.3 g, 1.992 mol), TBAI (24.5 g, 0.066 mol) and Acetamide (39.2 g, 0.664 mol) added. The solution was heated to 90 °C and maintained for 12 h. After the completion of the reaction, cooled to 0 °C and water was added (1000 mL) the phase was separated and extracted with Ethyl acetate (2 x 1000 mL). The combined organic phase was washed with water (500 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure to provide **(*S*)-3** as a liquid (97.0 g) yield 85%; ^{1}H NMR ($CDCl_3$): δ 5.80 (s, 1H), 4.30 (m, 1H), 4.10 (dd, 1H), 3.80 (dd, 1H), 3.70 (dd, 1H), 2.30 (dd, 1H), 2.00 (s, 3H), 1.43 (s, 1H), 1.35 (s, 3H); IR (KBr): 3341, 1654, 1077 cm^{-1}; ESI-MS: *m*/*z* (%) 174 (M^++1).

Preparation of *N*-((*S*)-2,3-dihydroxypropyl) acetamide, (4). To a solution of **(*S*)-3** (80.0 g, 0.462 mol) in methanol (800.0 mL), PTSA (39.7 g, 0.231 mol) added. The solution was maintained for 4 h at 25-30 ^{0}C. After the completion of the reaction, Most of the MeOH was then evaporated, and the residue was taken up in EtOAc (200 mL), washed with satd. $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4 and concentrated. Chromatography of the product on silica gel, eluting with [EtOAC/MeOH] (20:1), solvent was evaporated at reduced pressure to provide **(*S*)-4** as a liquid (43.0 g) yield 70 %; ^{1}H NMR (D_2O): δ 3.80 (m, 1H), 3.60 (m, 2H), 3.40 (m, 1H), 3.20 (m, 1H), 2.09 (s, 3H); IR (KBr): 3408, 1716 cm^{-1}; ESI-MS: *m*/*z* (%) 134 (M^++1).

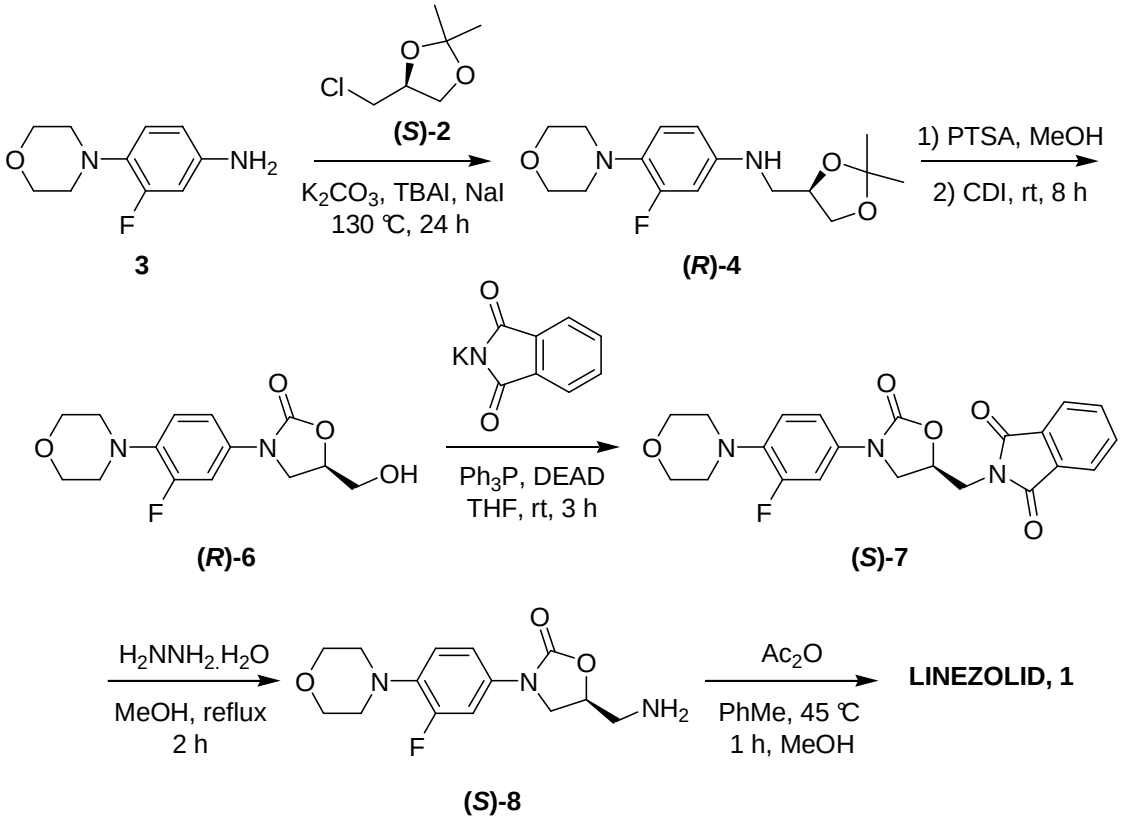
Preparation of *N*-((*R*)-3-(3-fluoro-4-morpholino phenyl amino)-2-hydroxypropyl) acetamide, (5). *p*-Toluenesulfonyl chloride (78.7 g, 0.413mol) was added to a solution of the **(*S*)-4** (50.0 g, 0.375 mol) in dry pyridine (250 ml) at 0 ^{0}C. After 15 mins the solution was warmed to 25-30 ^{0}C and stirred for 4 h. More *p*-toluene sulfonyl chloride (4.0 mg) was added and the mixture stirred for 2 h. The latter was added 3-fluoro-4-morpholino benzenamine (66.3 g, 0.33 mol) in dry pyridine *in-situ* and the mixture stirred for 12 h at 25-30 ^{0}C. Then evaporated Pyridine completely and the residue was taken up in EtOAc (200 mL), washed with water and brine, dried with anhydrous Na_2SO_4 and concentrated. Chromatography of the product on silica gel, eluting with [EtOAC/Hexane] (80:20), solvent was evaporated at reduced pressure to provide **(*R*)-5** as a solid (91.2 g) yield 78 %; ^{1}H NMR ($CDCl_3$): δ 7.43-7.48 (d, 1H), 7.06-7.10 (d, 1H), 6.90-6.96 (t, 1H), 5.96 (s, 1H), 4.74-4.79 (m, 1H), 4.00-4.06 (t, 1H), 3.56-3.77 (m, 3H), 3.04-3.07 (t, 4H), 2.03 (s, 3H); ESI-MS: *m*/*z* (%) 312 (M^++1).

Preparation of *N*-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) acetamide, 1 (Linezolid). A solution of **(*R*)-5** (35.0 g, 0.112 mol) in 150 mL dichloromethane was placed under an atmosphere of nitrogen and carbonyldiimidazole (54.6 g, 0.33 mol) was added with stirring. The mixture was allowed to stir at 35-40 ^{0}C for 8 h then was concentrated in vacuo. The resultant crude product was purified via chromatography using silica gel eluted with methanol in dichloromethane (0-10percent gradient). The fractions containing **1** were combined and concentrated in vacuo, the resulted solid was recrystalized from methanol to provide

Linezolid **1** as a solid (33.7 g). yield 89%; mp 182-183 °C; ^{1}H NMR ($CDCl_3$): δ 7.43-7.48 (d, 1H), 7.06-7.10 (d, 1H), 6.90-6.96 (t, 1H), 5.96 (s, 1H), 4.74-4.79 (m, 1H), 4.00-4.06 (t, 1H), 3.56-3.77 (m, 3H), 3.04-3.07 (t, 4H), 2.03 (s, 3H); ^{13}C 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; IR (KBr): 3342, 2, 1741, 1660 cm^{-1}, ESI-MS: *m*/*z* (%) 338.18 (100, M^++1).

RESULTS AND DISCUSSION

As a part of the ongoing research program [6] on synthesis of chiral 2-oxazolidinones such as Linezolid **1** and its derivatives, we wish to report herein a new and short synthesis of linezolid in two approaches starting from **(*S*)-2** & **(*R*)-2.** Toward this end, recently our group has become interested in exploring these types of approaches to synthetically valuable targets. To our knowledge, *N*-alkylation of 3-fluoro-4-morpholinobenzenamine **3** or acetamide has not yet been described. In conjunction with our ongoing studies on the synthesis of 2-oxazolidinone analogues, we have decided to develop an alternative, approach to construct chiral 2-oxazolidinone analogues architecture. Simplicity and environmental friendliness is the main scope of these routes. The synthetic route was outlined in (**Scheme 1** & **2**).



Scheme 1. Synthesis of linezolid by *N*-alkylation of compound 3 With chloro compound (*S*)-2

Hence, we targeted to synthesize the 3-fluoro-*N*-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-morpholinobenzenamine, **4** in one step by direct *N*-alkylation of 3-fluoro-4-morpholinobenzenamine, **3** using (*S*)-4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane, **2**. As of our

knowledge Approach-1 **(Scheme 1)**, the direct *N*-alkylation of **3** is un-reported in the literature. Various reaction conditions [8] such as solvent, base and temperature were screened to achieve direct *N*-alkylation of **3** with **(*S*)-2** with respect to (**Table 1**), unfortunately none of these conditions offered the corresponding *N*-alkylated product. It is interesting that the product **(*R*)-4** was obtained by the reaction of **3** with excess amount of **(*S*)-2** without solvent (*i.e*. neat) using K_2CO_3, tetrabutylammonium iodide (TBAI), sodium iodide (NaI) at 130 °C for 24 hrs. On the other hand, we found difficulty in isolation of pure product **(*R*)-4** from crude reaction mixture. However, the crude compound **(*R*)-4** was purified by column chromatography in 70% yield.

Table I - *N*-alkylation of 3 with (*S*)-2 with respect to solvent, base and temperature.

Entry No.	Solvent	Base /Temp (°C)
1	THF	*n*-BuLi/-78°C
2	DMF	KO*t*Bu / reflux
3	THF	NaH/ reflux
4	EtOH	KOH/ reflux
5	DMF	K_2CO_3/ reflux

After hydrolysis of the resulted dioxane **(*R*)-4** in methanol using *p*-toluenesulfonic acid (PTSA) followed by regio-selective cyclization with CDI in the presence of K_2CO_3 afforded the required oxazolidinone (*R*)-3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one, **6** with 82% yield and efforts were extended further to Linezolid **1.**

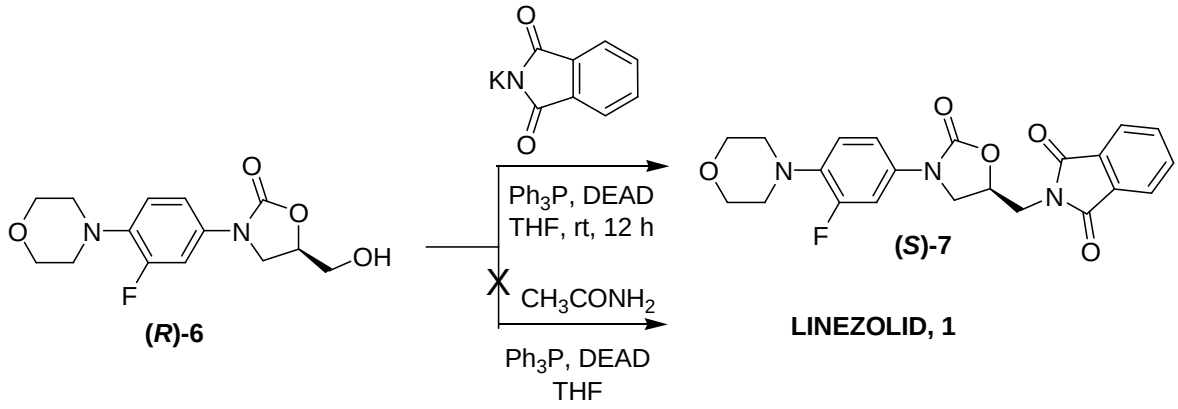
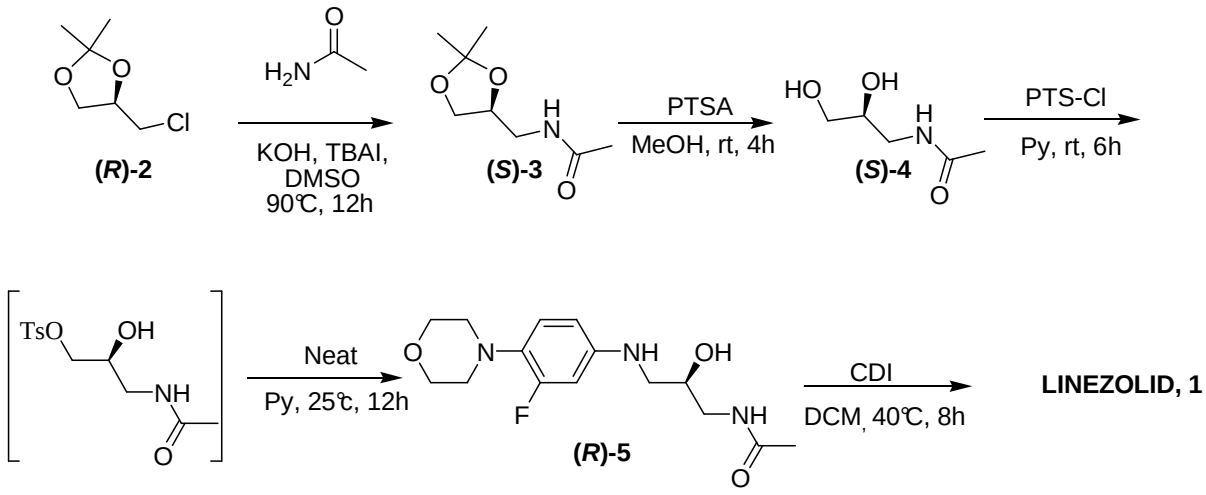


Figure 2

Incorporation of *N*-acetyl amine functionally was planned by employing mitsunobou conditions on primary hydroxyl functionality of **(*R*)-6**. Initially, the mentioned reaction was attempted using Acetamide, but hasn't offered any success, then efforts were further extended using pthalimide under same reaction conditions (**Figure 2**) and offered the phalimido compound **(*S*)-7**. Deprotection of pthalimide followed by acetylating using acetic anhydride yielded the targeted chemical entity Linezolid **1** with 75 % yield and 98% of HPLC purity.

Even though *N*-alkylation of Acetamide reactions has proved to be very efficient, there are few of the challenges are involved such as (i) tedious reaction conditions (ii) column purifications (iii) low to moderate yields, (iv) multi step sequences (6 steps). Therefore, developing an efficient synthetic strategy with fewer steps that provides diverse access to these

biologically/pharmaceutically active compounds is an important goal, especially to Linezolid, **1** through addressing all the issues of first approach **(Scheme-1)**.



Scheme 2. Synthesis of linezolid by *N*-alkylation of acetamide with chloro compound (*R*)-2

As shown in (**Scheme 2**), inexpensive and commercially readily available (*R*)-epichlorohydrin was chosen to prepare compound **(*R*)-2**, which was reacted with acetamide [9] in the presence of potassium hydroxide, TBAI in DMSO at 90°C to afford *N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)acetamide, **3** in 85% yield. The acetonide protecting group of compound **(*S*)-3** was deprotected using PTSA in methanol to give **(*S*)-4** in 70% yield. Tosylation of primary hydroxyl group of **(*S*)-4** in pyridine [10], followed by *in-situly* reacted with 3-fluoro-4-morpholinobenzenamine, **3** in previous step Pyridine as solvent offered the desired *N*-((*R*)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl) acetamide, **5** compound in 78% yield. Latter, 2-oxazolidinone ring was constructed by reacting the β- amino alcohol functionality of compound **(*R*)-5** with CDI afforded the required antibacterial agent Linezolid, **1** with 89% yield and 99.5% HPLC purity.

CONCLUSION

In conclusion, highly efficient method **(Scheme-2)** has been developed to prepare Linezolid, with in 4 steps and more than 40% of overall yield. This method overcomes many of the drawbacks associated with previously reported syntheses and offers an industrial viable procedure for the synthesis of linezolid and exploration of this method for the preparation of similar molecules is currently underway in our laboratory.

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