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A new and concise synthetic route to enantiopure Linezolid from (*S*)-epichlorohydrin

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ABSTRACT

*A new and short synthesis of Linezolid **1** has been emphasized in two path ways. The synthetic route in both the ways involves preparation of 2-((R)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl)isoindoline-1,3-dione **2** as a key intermediate starting from (S)-epichlorohydrin and phthalimide **3a**. One of these methods involves the direct N-alkylation of 3-fluoro-4-morpholinobenzenamine **3b** with 2-((S)-3-chloro-2-hydroxypropyl)isoindoline-1,3-dione **4a**. Alternatively, compound **2** was prepared by using one-pot three step sequence via 2-(((S)-oxiran-2-yl)methyl)isoindoline-1,3-dione **4b**.*

Keywords: *N*-Alkylation, Intermediate, (*S*)-Epichlorohydrin, Phthalimide, 1,2-Amino alcohol, Linezolid.

INTRODUCTION

1,2-Amino alcohols have an outstanding significance as chiral ligands and as precursors of chiral oxazolines and 2-oxazolidinones [1]. Applications of 2-oxazolidinones as chiral auxiliaries and as pharmaceuticals are well-known [1, 2]. 2-Oxazolidinones are a new class of synthetic antibacterial agents which exhibit activity against a large number of Gram-positive organisms and vancomycin-resistant *Enterococcus faecium* [3]. Their mode of action is by inhibition of protein synthesis at an early step [4]. As of 2010, Linezolid (**1, Figure 1**) is the only 2-oxazolidinone approved by the Food and Drug Administration (FDA) and became the first compound commercialized worldwide from the 2-oxazolidinone class of antibacterials [5]. Linezolid (Zyvox®, Pfizer) was introduced into the market which encouraged researchers to identify a high-yielding, economical and environmentally sound synthetic process.

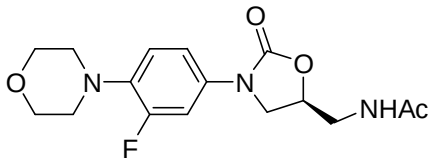


Figure 1. Chemical structure of Linezolid, 1

The first synthesis of linezolid starting from (5*S*)-5-(hydroxymethyl)oxazolidin-2-one which was obtained by the reaction of aryl carbamate with (*R*)-glycidyl butyrate in the presence of *n*-BuLi at −78°C [6]. A modified synthetic method using coupling of aryl carbamates with either (2*S*)-3-chloropropane-1,2-diol or (2*S*)-1-amino-3-chloropropan-2-ol promoted by LiO*t*-Bu has been developed [7]. Various other methods are also available in the literature for the synthesis of Linezolid [8, 9]. However, not all methods are practical on a large scale, due primarily to the overall low yields, high costs of reagents, more number of steps, usage of air sensitive bases (such as LiO*t*-Bu, *n*-BuLi, LDA) and low temperature reactions (−78°C). Thus, development of a more convergent, practical and rapid preparation of linezolid is highly desirable.

MATERIALS AND METHODS

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 F_{254} silica-coated aluminium plates (Merck) and visualized by using either UV light (λ = 254 nm) or by spraying with a solution of ninhydrin or $KMnO_4$. Organic extracts were dried over anhydrous Na_2SO_4. 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: $[\alpha]^{t^{\circ}C}_{D}$ (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 (^{1}H) and at 75 MHz (^{13}C). 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 ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

Synthesis of 2-((*S*)-3-Chloro-2-hydroxypropyl)isoindoline-1,3-dione (4a). To a stirred solution of (*S*)-epichlorohydrin (8.0 g, 0.086 mol), pthalimide **3a** (12.72 g, 0.086 mol) and isopropanol (60 mL), was added a catalytic amount of potassium carbonate (1.1 g, 0.008 mol) at RT. 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 RT, filtered 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 50°C under reduced pressure to give 2-((*S*)-3-chloro-2-hydroxypropyl)isoindoline-1,3-dione **4a** as a white colored solid (15.5 g); Yield 75%; Mp 95-96°C, $[\alpha]^{20}_{D}$ −32.5° (*c* = 0.712, $CHCl_3$); IR (KBr): ν 3463 (OH), 1692 (C═O) cm^{-1}; ^{1}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}C NMR ($CDCl_3$): δ 41.5, 47.2, 69.64, 123.5, 131.8, 134.2, 168.6; ESI-MS: *m*/*z* (%) 240 (100, M^++1).

Synthesis of 2-((*R*)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl)isoindoline-1,3-dione (2) (using path A). A mixture of 2-((*S*)-3-chloro-2-hydroxypropyl)isoindoline-1,3-dione **4a** (10 g, 0.041 mol) and 3-fluoro-4-morpholinobenzenamine **3b** (8.2 g, 0.041 mol) was suspended at 25°C in toluene (100 mL) and mixed with lutidine (5.4 g, 0.05 mol), and ethanol (8 mL). The reaction mixture is heated for 36 h at reflux (after 36 h, observed the formation of

product ~ 25% by TLC). After cooling to 30°C, the reaction mixture was evaporated to dryness and the residue was subjected to purification using column chromatography gave compound **2** as a pale yellow colored solid (3.2 g). Yield: 19 %; Mp 157-159°C; ^{1}H NMR ($CDCl_3$): δ 2.78-2.79 (d, 1H, D_2O exchangeable), 2.94-2.97 (t, 4H), 3.11-3.26 (m, 2H), 3.83-3.86 (t, 4H), 3.90-3.91 (d, 2H), 4.08 (br s, 1H, D_2O exchangeable) 4.11-4.16 (m, 1H), 6.38-6.45 (m, 2H), 6.79-6.85 (t, 1H), 7.73-7.78 (m, 2H), 7.85-7.89 (m, 2H); IR (KBr): 3463, 3337, 1776, 1704, 1047, 752 cm^{-1}; ESI-MS: *m/z* (M^++1) 400.

Synthesis of 2-(((*S*)-oxiran-2-yl)methyl)isoindoline-1,3-dione (4b). A mixture of 2-((*S*)-3-chloro-2-hydroxypropyl)isoindoline-1,3-dione **4a** (1.5 g, 0.006 mol) and potassium carbonate (2.6 g, 0.019 mol) was suspended in toluene (10 mL) at RT. The reaction mixture was heated to reflux and maintained at reflux temperature for 7 h. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was cooled to RT and solids were filtered-off. The filtrate was evaporated under reduced pressure at 50°C. The obtained residue was triturated with *n*-hexane, filtered and washed with *n*-hexane. The obtained solid was unloaded and dried at 50°C under reduced pressure to give 2-(((*S*)-oxiran-2-yl)methyl)isoindoline-1,3-dione **4b** as a white colored solid (1.0 g); Yield 80%; Mp 98-100°C, $[\alpha]^{20}_D$ –32.5° (*c* = 0.712, $CHCl_3$); IR (KBr): ν 1711, 1398, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.69 (dd, 1H), 2.81 (dd, 1H), 3.25 (m, 1H) 3.82 (dd, 2H), 3.96 (dd, 2H), 7.74 (m, 2H), 7.88 (dd, 2H); ESI-MS: *m/z* (%) 204 (100, M^++1).

Synthesis of 2-((*R*)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl)isoindoline-1,3-dione (2) starting from (*S*)-epichlorohydrin (one-pot process using path B). To a stirred solution of (*S*)-epichlorohydrin (15.7 g, 0.170 mol), pthalimide **3a** (25.0 g, 0.170 mol) and isopropanol (125 mL), was added a catalytic amount of potassium carbonate (2.3 g, 0.017 mol) at RT. 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 RT, filtered and solvent was removed under reduced pressure at below 40°C. The obtained residue was diluted with dichloromethane (85 mL) and toluene (85 mL) and was charged potassium carbonate (43.0 g, 0.31 mol) at RT. The mixture was heated to reflux for 7 h. After completion of **4a**, the reaction mixture was cooled to RT and filtered. The solvent was removed from the filtrate by evaporation under reduced pressure at 50°C and also co-distilled with ethanol at 50°C. To the residue was added 3-fluoro-4-morpholinobenzenamine **3b** (30.0 g, 0.153 mol), ethanol (113 mL) and water (12 mL) at RT. The mixture was heated to reflux for 20 h. The progress of the reaction was monitored by TLC. After completion of **4b**, the reaction mixture was cooled to RT and solvent was removed by evaporation under pressure at 40°C. The obtained residue was purified by column chromatography to give compound **2** as a pale yellow colored solid (40 g). Yield: 59 %. The analytical data was in agreement with the compound **2** prepared in path A.

Synthesis of 2-(((*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) isoindoline-1,3-dione (6). 2-((*R*)-3-(3-Fluoro-4-morpholinophenylamino)-2-hydroxypropyl) isoindoline-1,3-dione **2** (5.0 g, 0.012 mol) is dissolved in dichloromethane (50 mL), carbonyl diimidazole (3.0 g, 0.018 mol) is added at ambient temperature and the reaction mixture is stirred for 20 h. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was washed with water, organic layer was dried over Na_2SO_4, filtered and solvent was removed by evaporation under reduced pressure to give 2-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione **6** as a white colored solid (5.0 g); Yield 94 %; Mp 204-206°C; ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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; IR (KBr): ν 3099, 2962, 1752, 1711, 1217 cm^{-1}; ESI-MS: *m*/*z* (%) 426.2 (100, M$^+$+1).

Synthesis of (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (7). Hydrazine hydrate (3.9 g, 0.077 mol) was added to a stirred solution of 2-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione **6** (6.0 g, 0.014 mol) and methanol (50 mL). The mixture was stirred at reflux temperature for 1 h. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to RT, water was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated in vacuum to give (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one **7** as a white colored solid (3.66 g); Yield: 88 %; IR (KBr): ν 3404, 2958, 1726, 1229 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.49 (br s, 2H), 2.94-3.0 (dd, 1H), 3.03-3.06 (t, 4H), 3.09 -3.14 (dd, 1H), 3.79 -3.84 (dd, 1H), 3.85-3.89 (t, 4H), 3.98-4.04 (t, 1H), 4.04 - 4.69 (m, 1H), 6.90-6.96 (t , 1H), 7.12 - 7.15 (dd, 1H), 7.44-7.49 (dd, 1H); ESI-MS: *m*/*z* (%) 296 (100, M$^+$+1).

Synthesis of *N*-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) acetamide (Linezolid, 1). Acetic anhydride (3.1 g, 0.030 mol) was added dropwise to a stirred solution of (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one **7** (3.0 g, 0.010 mol) and toluene (30 mL) by maintaining the temperature at below 35°C. The mixture was stirred at RT for 1 h. The reaction progress can be monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool to 0°C and the obtained solids were filtrated to give *N*-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide **1** as a white colored solid (2.74 g); Yield: 80 %; Mp 181.5-182.5°C; IR (KBr): ν 3342, 3075, 2967, 1741, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 3H), 3.03-3.07 (t, 4H), δ 3.55-3.76 (m, 3H), 3.85-3.89 (t, 4H), 3.99-4.05 (t, 1H), 4.74-4.79 (m, 1H), 5.96 (s, 1H), 6.89-6.95 (t, 1H), 7.00-7.10 (d, 1H), 7.42-7.48 (d, 1H). ^{13}C NMR (DMSO): δ 22.4, 47.2, 50.6, 66.1, 71.5, 106.4, 114.0, 119.1, 113.3, 113.5, 152.9, 154.0, 156.1, 170.0; ESI-MS: *m*/*z* (%) 338.18 (100, M$^+$+1).

RESULTS AND DISCUSSION

As a part of the ongoing research programme on identifying new chiral synthons [9, 10] followed by developing and improving synthetic routes to antibacterial Linezolid [9, 10], it is wished to report herein the synthesis of 2-((*R*)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl) isoindoline-1,3-dione **2** as a key intermediate towards the synthesis of Linezolid **1**.

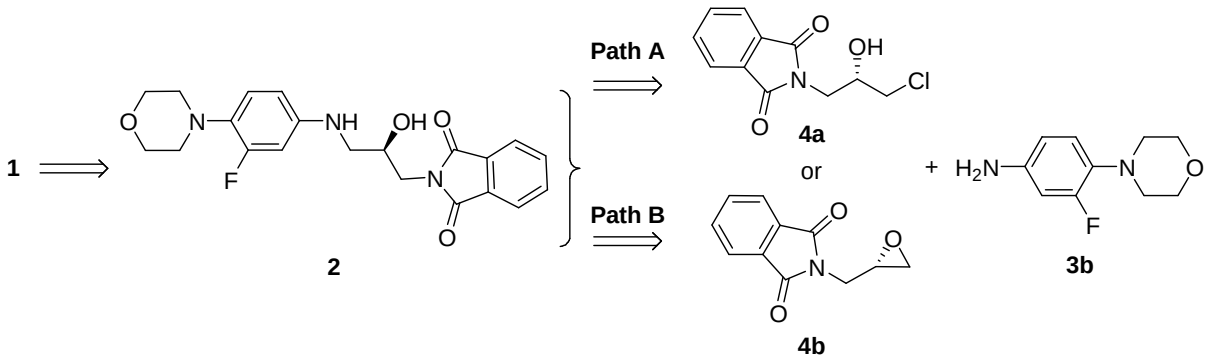
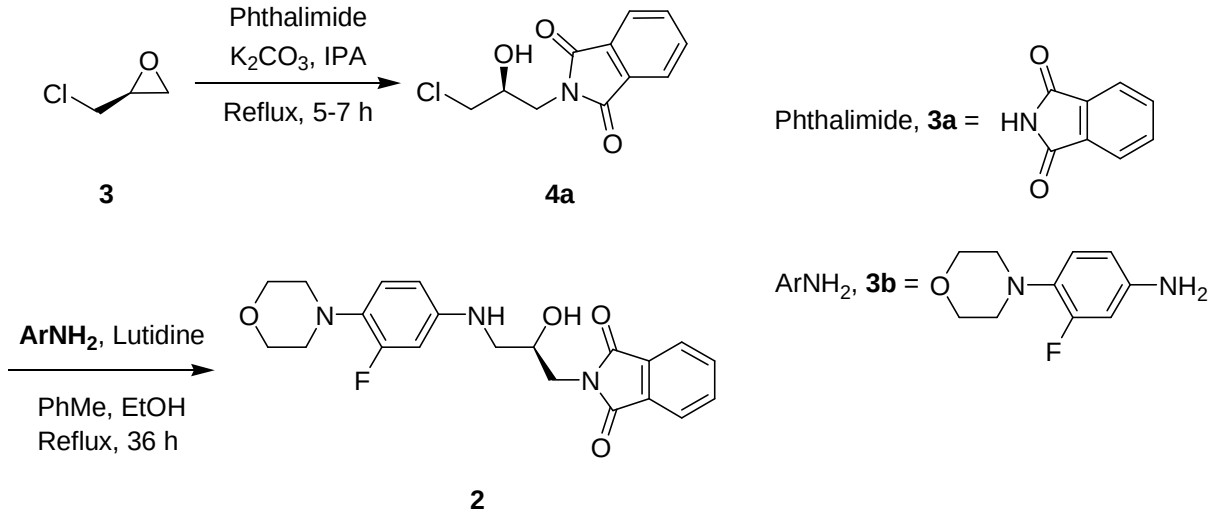


Figure 2. Retro synthetic analysis of 2-((*R*)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl) isoindoline-1,3-dione 2 towards the synthesis of Linezolid 1

Retro synthetic analysis of the projected amino alcohol **2** revealed two synthetic approaches either starting from halohydrin **4a** or epoxy compound **4b (Figure 2)**. In most of the cases while attempting path A approach, the reaction may proceeds via the formation of epoxy compound **4b** (halohydrin **4a** converts into epoxy compound **4b**) which finally results in the formation of expected compound **2**. To the best of our knowledge, *N*-alkylation of 3-fluoro-4-morpholinobenzenamine **3b** with any alkyl halide is un-reported and also the synthesis of Linezolid by utilizing **4b** is known in the literature [8f].

Anilines are generally sufficiently basic to undergo direct *N*-alkylation, often under mild conditions. However, the reactions are difficult to control because the reaction product (secondary amine) is often more nucleophilic than the precursor and will thus preferentially react with the alkylating agent. However, the *N*-alkylation of 4-(4-aminophenyl)morpholin-3-one with *N*-((*S*)-3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide using collidine (2,4,6-trimethylpyridine) as a base in toluene at 105°C is reported in the literature towards the synthesis of Rivaroxaban [11], an anti-coagulant. Other reaction conditions for the *N*-alkylation of anilines and/or substituted anilines using alkyl halides are also reported in the literature [12]. This prone us to utilize similar strategy for the synthesis of Linezolid as well by direct *N*-alkylation of 3-fluoro-4-morpholinobenzenamine **3b** with 2-((*S*)-3-chloro-2-hydroxypropyl)isoindoline-1,3-dione **4a**.

Initially, compound **4a** was prepared by the reaction of (*S*)-epichlorohydrin with phthalimide **3a** and K_2CO_3 (catalytic) in isopropanol at reflux temperature for 5 h with retention of stereochemistry. In our preliminary study, the reaction of 3-fluoro-4-morpholinobenzenamine **3b** with 2-((*S*)-3-chloro-2-hydroxypropyl)isoindoline-1,3-dione **4a** was tested using different reaction conditions such as CsF-Celite-acetonitrile, Na_2CO_3-acetone, $NaHCO_3$-water, Cs_2CO_3-TBAI-DMF, KI-acetonitrile, CsF-acetonitrile, K_2CO_3-KI-DMF, *N*,*N*-diisopropylethylamine-acetonitrile, KOH-EtOH and *n*-BuLi-THF at different temperatures. It was found that none of these reaction conditions resulted neither the compound **2** nor anticipated **4b**.



Scheme 1. Synthesis of compound 2 using path A

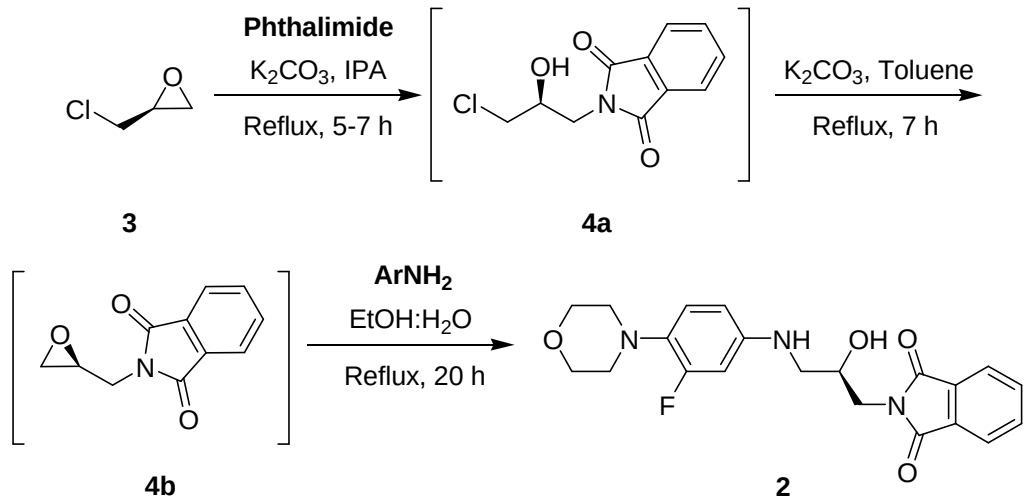
All attempts to achieve either compound **2** or **4b** were unsuccessful. Moreover, it has been observed either formation of various impurities or no reaction. To confirm no formation of intermediate **4b**, all previously mentioned conditions were again attempted independently using **4a** (without **3b**). It was again confirmed that no formation of **4b** under described conditions. Finally, the formation of 2-((*R*)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl)

isoindoline-1,3-dione **2** was observed (~25% by TLC) using lutidine (2,6-dimethylpyridine) as a base in toluene at reflux temperature for 36 h with an yield of 19% (**Scheme 1**).

Attempts were continued to enrich the product formation by varying solvent, molar quantity of lutidine and reaction temperature. None of these parameters played a significant role to increase the reaction conversion as well as yield. It was also confirmed that no formation of 2-(((*S*)-oxiran-2-yl)methyl)isoindoline-1,3-dione **4b** by the reaction of 2-((*S*)-3-chloro-2-hydroxypropyl) isoindoline-1,3-dione **4a** in equivalent reaction conditions (lutidine, toluene, reflux). Even though the formation of **2** was observed in path A approach, the low yield (19%) was not fulfilled our intention. Hence, alternative attempts were also performed to improve path B approach as well.

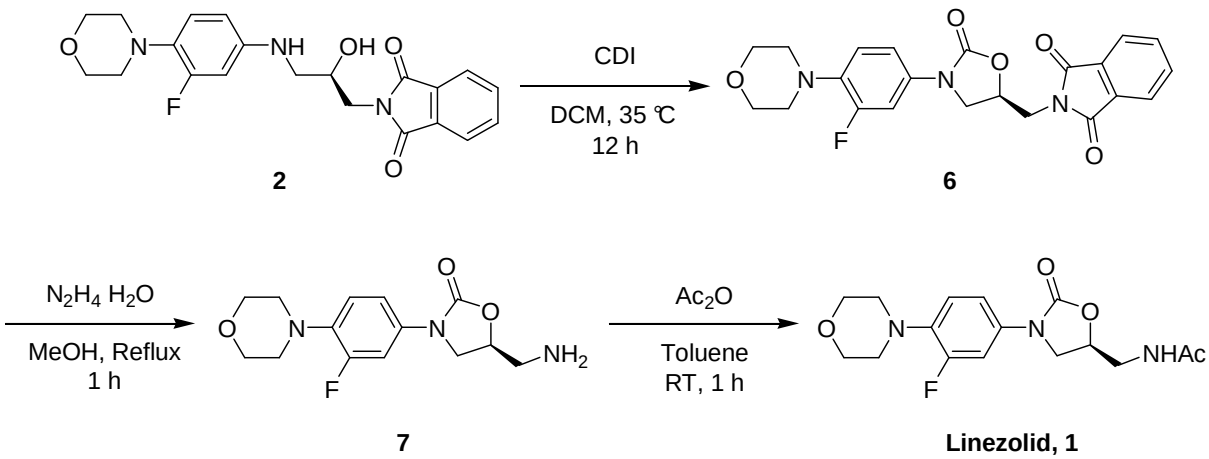
The preparation of 2-(((*S*)-oxiran-2-yl)methyl)isoindoline-1,3-dione **4b** was reported in the literature using various conditions. Compound **4b** can be produced directly from the reaction of epichlorohydrin with potassium phthalimide in one step. However, this reaction required significant excess epichlorohydrin and also there were issues with full retention of stereochemistry [13]. Alternatively epoxy compound **4b** can also be synthesized staring from chiral glycidol and phthalimide (Mitsunobu conditions) or from chiral 3-chloro-1-amino-2-proponal and phthalic anhydride (Et_3N, toluene, reflux) [14]. A few procedures were also reported for preparation of **4b** including varied reaction conditions starting from **4a**. Most of these methods reported are not practical primarily due to high costs of starting materials and poor enantiomeric excess. Thus, development of a more practical method for the preparation of **4b** was taken up as a task.

The halohydrin **4a** was further treated with K_2CO_3 in toluene at reflux temperature gave epoxy compound **4b** in moderate yield. After the successful preparation of **4b** it was further subjected to prepare amino alcohol **2** under the reported conditions. In initial two steps the base is K_2CO_3 and this made us to develop one-pot process and achieved successful preparation of **2** starting from phthalimide **3a** in one-pot with about 59% yield (**Scheme 2**).



Scheme 2. Synthesis of compound 2 using path B

Finally the resulted amino alcohol **2** in both approaches (path A and B) was further elaborated to Linezolid [6] which involves carbonylation using carbonyldiimidazole (CDI) followed by deprotection of phthalimide using hydrazine hydrate in methanol and finally acetylation using acetic anhydride and toluene (**Scheme 3**).



2 **6** **7** **Linezolid, 1**

Scheme 3. Synthesis of Linezolid from compound 2

CONCLUSION

As a summary, herein we have developed a new method for the synthesis of 2-((*R*)-3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl)isoindoline-1,3-dione **2** (path A) and also improved the reported method to prepare **2** starting from phthalimide and (*S*)-epichlorhydrin in one-pot three step sequence with about 59% yield (path B). Finally the resulted amino alcohol **2** was further elaborated to Linezolid using the literature procedure [6].

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REFERENCES

[1] Ager D J, Prakash I & Schaad D R, *Chem Rev*, 96, **1996,** 835.
[2] (a) Poce G, Zappia G, Porretta G C, Botta B & Biava M, *Expert Opin Ther Patents*, 18, **2008**, 97; (b) Endermann R & Riedl B, *Expert Opin Ther Patents*, 9, **1999**, 625; (c) Evans D A, *Aldrichimia Acta*, 15, **1982**, 23; (d) Ager D J, Prakash I & Schaad D R, *Aldrichimia Acta*, 30, **1997**, 3.
[3] Ford C W, Hamel J, Stapert D, Moerman J, Hutchinson D, Barbachyn M & Zurenko G, *Infect Med*, 16, **1999**, 435.
[4] Thompson J, O'Connor M, Mills J A & Dahlberg A E, *J Mol Biol*, 322, **2002**, 273.
[5] (a) Stefani S, Bongiorno D, Mongelli G & Campanile F, *Pharmaceuticals*, 3, **2010**, 1988; (b) Brickner S J, *Curr Pharm Des*, 2, **1996**, 175; (b) Renslo A R, Luehr G W & Gordeev M F, *Bioorg Med Chem*, 14, **2006**, 4227; (c) Mukhtar T A & Wright G D, *Chem Rev*, 105, **2005**, 529; (d) Barbachyn M R & Ford C W, *Angew Chem Int Ed*, 42, **2003**, 2010.
[6] (a) Brickner S J, Hutchinson D K, Barbachyn M R, Manninen P R, Ulanowicz D A, Garmon S A, Grega K C, Hendges S K, Toops D S, Ford C W & Zurenko G E, *J Med Chem*, 39, **1996**, 673; (b) Barbachyn M R, Brickner S J & Hutchinson D K, *US 5,688,792*, Nov 18, **1997**; *Chem Abstr*, 123, **1995**, 256742.
[7] (a) Pearlman B A, Perrault W R, Barbachyn M R, Manninen P R, Toops D S, Houser D J & Fleck T J, *US 5,837,870*, Nov 17, **1998**; *Chem Abstr*, 130, **1998**, 25061. (b) Perrault W R, Pearlman B A, Godrej D B, Jeganathan A, Yamagata K, Chen J J, Lu C V, Herrinton P M, Gadwood R C, Chan L, Lyster M A, Maloney M T, Moeslein J A, Greene M L & Barbachyn M R, *Org Proc Res Dev*, 7, **2003**, 533.

[8] (a) Dhananjay G S, Nandu B B, Avinash V N, Kamlesh D S, Anindya S B & Tushar A N, *PCT Int Appl 063505*, May 22 **2009**; *Chem Abstr*, 150, **2009**, 515152; (b) Rick J I, William R P & Michael R R, *PCT Int Appl 116284*, Oct 18, **2007**; *Chem Abstr*, 147, **2007**, 469356. (c) Yu D S, Huang L, Liang H & Gong P, *Chin Chem Lett*, 16, **2005**, 875; (d) Pearlman B A, *PCT Int Appl 9924393*, May 20, **1999**; *Chem Abstr*, 130, **1999**, 338099; (e) Mohan Rao D & Krishna Reddy P, *PCT Int Appl 099353*, Oct 27, **2005**; *Chem Abstr*, 143, **2005**, 440395; (f) Mohan Rao D & Krishna Reddy P, *PCT Int Appl 008754*, Jan 26, **2006**; *Chem Abstr* 144, **2006**, 170978; (g) Moran-Ramallal R, Liz R & Gotor V, *Org Lett*, 10, **2008**, 1935; (h) Mallesham B, Rajesh B M, Rajamohan Reddy P, Srinivas D & Sanjay T, *Org Lett*, 5, **2003**, 963.
[9] (a) Madhusudhan G, Om Reddy G, Ramanatham J & Dubey P K, *Indian J Chem*, 44B, **2005**, 1236; (b) Madhusudhan G, Om Reddy G, Rajesh T, Ramanatham J & Dubey P K, *Tetrahedron Lett*, 49, **2008**, 3060.
[10] (a) Rajesh T, Narayana Rao S P, Suresh K, Madhusudhan G & Mukkanti K, *J Hetercyclic Chem*, 47, **2010**, 1392; (b) Rajesh T, Suryanarayana Reddy, P. Manidhar M, Vijaya Lakshmi M & Madhusudhan G, *E-J Chem*, 8, **2011**, 1417; (c) Rajesh, T.; Kiran Kumar, V.; Ramadasu, G.; Ramesh, Y.; Madhusudhan, G.; *ARKIVOC* (Accepted, Ms. No. 11-6209AP).
[11] Thomas C R, *DE 1,030,0111*, Jul 15, **2004**; *Chem Abstr* 141, **2004**, 106454.
[12] (a) Hayat S, Rahman A, Choudhary M I, Mohammed Khan K, Schumann W & Bayer E, Tetrahedron Lett, 57, **2001**, 9951; (b) Ananthanarayanan C & Ramakrishnan V T, *Indian J Chem*, 27B, **1988**, 156; (c) Singh C B, Veerababurao K, Akshaya K S & Bhisma K P, *Eur J Org Chem*, 8, **2007**, 1369.
[13] (a) Wilkinson M C, Bell R, Landon R, Nikiforov P O & Walker A J, *Synlett* **2006**, 2151; (b) Madhusudhan G, Om Reddy G, Ramanatham J & Dubey P K, *Indian J Chem*, 45B, **2006**, 1264.
[14] (a) Coulton S & Gilpin M L, *PCT Int Appl 049023*, June 02, **2005**; *Chem Abstr*, 143, **2005**, 26497; (b) Kang H B, Quan L G, Lee J K & Kim S-J, *PCT Int Appl 132990*, Nov 22, **2007**; *Chem Abstr*, 147, **2007**, 541720.