A New Practical Synthesis of Linezolid: An Antibacterial Drug

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Received August 21, 2009: Revised November 23, 2009: Accepted November 24, 2009

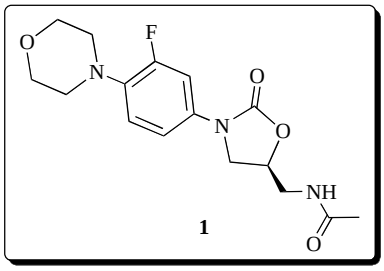
Abstract: A novel and practical asymmetric synthesis of (*S*)-*N*-[[3-(3-fluoro-4-morpholinyl phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide has been developed by a new approach without recourse to chromatography and it is employed for the synthesis of Linezolid. This involves the reaction of (*R*)-epichlorohydrin with *N*-arylcarbamates and subsequent regioselective epoxide ring opening of resulted intermediate by sodium azide.

Keywords: Linezolid, antibacterial drug, asymmetric synthesis, regioselective epoxide ring opening, one pot synthesis.

INTRODUCTION

Bacterial resistance development has become a very serious clinical problem for many classes of antibiotics. The 3-aryl-2-oxazolidinones are a relatively new class of synthetic antibacterial agents, having a new mechanism of action which involves very early inhibition of bacterial protein synthesis [1,2]. Only the oxazolidinone enantiomer with a (5*S*)-acetamidomethyl configuration possesses antibacterial activity [3]. They have potent activity against a variety of Gram-positive bacterial pathogens including methicillin-resistant *Staphylococcus aureas* (MRSA) and vancomycin-resistant *Enterococci* (VRE) [4]. Linezolid (**1**, Zyvox®, Pharmacia Upjohn) is currently the only antibacterial agent which can be administered orally (as well as intravenously) with strong activity against MRSA. It may be particularly useful as an alternative to vancomycin, in patients whose renal function is impaired, in cases of patients with poor or lack of intravenous access and in patients who require outpatient therapy, or who do not tolerate glycopeptides [5-8]. The oxazolidones have a novel mechanism of action that involves inhibition of protein synthesis as an early and unique step [2,9]. For these reasons, much attention has been given to the synthesis of these classes of compounds.

Linezolid (**1**) was earlier prepared by a route described in Scheme **1** [1,10]. The synthesis involves nucleophilic aromatic displacement (S_NAr reaction) of the 4-fluoro group of 2 with excess morpholine (**3**) in the presence of *N*,*N*-diisopropylethylamine to give 3-flouro-4-morpholinylnitro benzene (**4**). The nitro functionality of **4** was reduced using 10% Pd/C and ammonium formate to produce 3-flouro-4-morpholinylaniline (**5**) and subsequent attachment of a carbobenzyloxy (Cbz) to the arylamines **5** provided intermediate **6**. Deprotonation of carbamate **6** with *n*-BuLi in THF at -78 °C and reaction with (*R*)-glycidylbutyrate yielded (5*R*)-(hydroxymethyl)-2-oxazolidinone (**7**). Activation as the mesylate **8** and then displacement with NaN_3 yielded azide derivative **9**, whose catalytic hydrogenolysis of azide derivative **9** with 10% Pd/C followed by acetylation with acetic anhydride yielded **1**.



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This process suffers from disadvanges such as (a) a multistep synthesis for compound **1** (8 steps from compound **2**); (b) The use of (*R*)-glycidylbutyrate reagent is expensive and reaction has to be carried out at -78 °C and (c) addition of *n*-BuLi *via* syringe, which on large scale manufacturing process may pose handling difficulties.

Several other methods are available for the synthesis of linezolid and eperezolid. Gregory *et al.* [3] reported a method of producing oxazolidinones, which comprises reacting an isocyanate (R-N=C=O) with (*R*)-glycidylbutyrate in the presence of a catalytic amount of lithium bromide-tributylphosphine oxide complex to produce the corresponding 5(*R*)-butyryloxymethyl substituted oxazolidinone. The process was performed at 135-145 °C. The relative high cost and/or availability of the isocyanate starting material and requirement of high temperature detract significantly from the attractiveness of this method.

Fischer and Sweden [11] disclosed a method for converting primary alcohols to amines in a sealed reaction vessel under high pressure. It is also known that the mesylates of primary alcohols react with aqueous ammonia to give the corresponding primary amines, but high temperature and high pressure (85 psg) are required [11]. Normally this process cannot be used in ordinary general purpose reactors and must be run in special reactors rated for high pressure.

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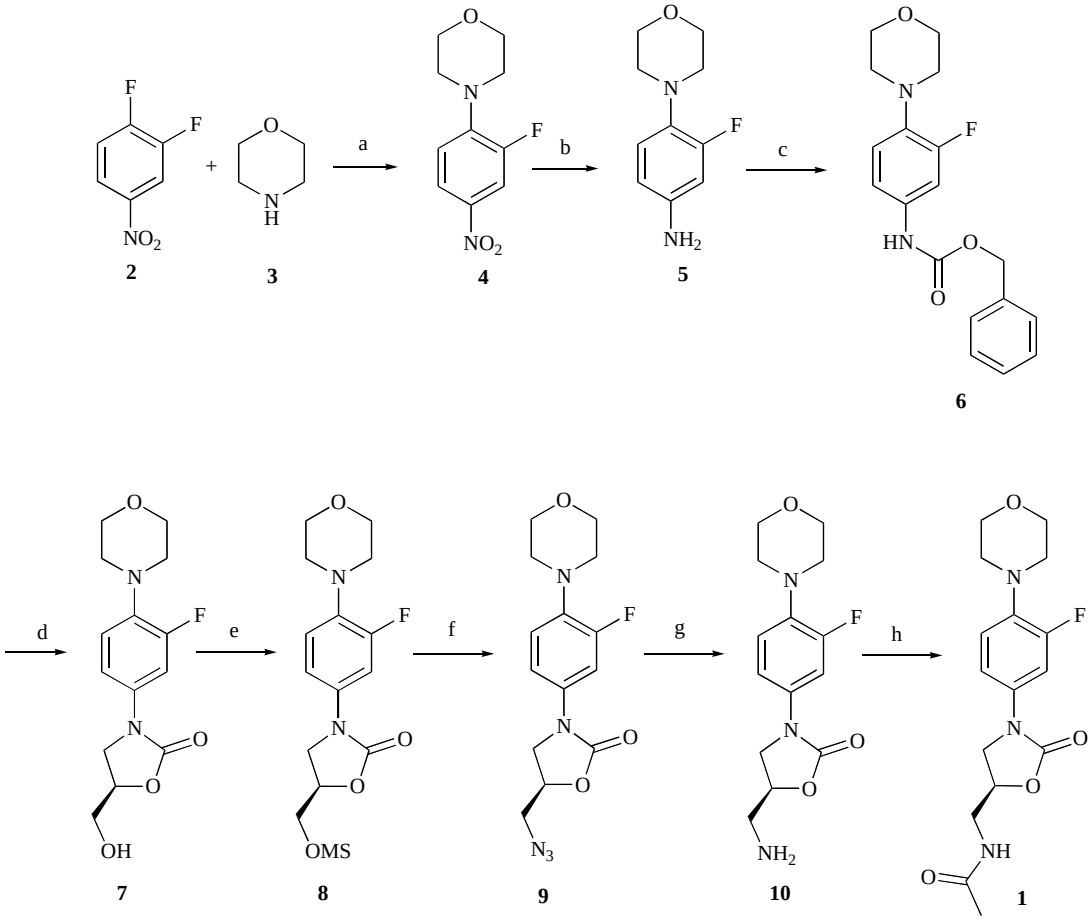
DRL-IPD Communication number. IPDOIPM-00108.

1570-1786/10 $55.00+.00



Scheme 1. Reagents and conditions: (**a**) *N*, *N*-diisopropylethylamine, EtOAc, CH_2Cl_2, 25-30 °C, overnight; (**b**) $HCOONH_4$, Pd/C, THF, 0 °C, 2 h; (**c**) $NaHCO_3$, benzylchloroformate, acetone, 0 °C, overnight; (**d**) (*R*)-glycidyl butyrate, n-BuLi, THF, -78 °C, 35 min; (e) methanesulfonyl chloride, TEA, CH_2Cl_2, 0 °C, 20 min; (**f**) NaN_3, DMF, 75 °C, 16 h; (**g**) 10% Pd/C, 24 h, 25-30 °C; (**f**) pyridine, Ac_2O, EtOAc, 0 °C, 30 min then 25-30 °C, 1 h.

Dostert *et al*. [12] reported a method of transforming 5-hydroxymethyl substituted oxazolidinones to the corresponding 5(*S*)-aminomethyl substituted oxazolidinones that involves treatment with methanesulfonyl chloride followed by potassium phthalimide then treating with hydrazine. This reaction sequence produces by-products (for example 2,3-dihyro-1,4-phthalazinedione) which are difficult to separate from the desired product.

Schaus and Jacobson reported [13] a route to oxazolidinones with good yields. However, in these methods for the synthetic key step to oxazolidinone ring, harsh conditions with low temperature (-78 °C) and air sensitive bases (n-BuLi or NaH) were required [14], which limit the large-scale production in the industry. Lohary *et .al.* [15] offered another possibility to oxazolidinones *via* asymmetric bis-epoxide using D-mannitol as a starting material. Though, the synthesis of asymmetric bis-epoxide suffers from a long-synthetic route and was reported without any optical data.

RESULTS AND DISCUSSION

On the basis of above limitations, we devised a safe, economically competitive new synthetic route for **1**, which was obtained from **2** in six steps using inexpensive, commercially available raw materials and reagents. To the best of our knowledge, this new route is economically advantageous over the earlier reported methods owing to the use of less expensive raw materials like (*R*)-epichlorohydrin thus circumventing the use of (*R*)-glycidylbutyrate.

Process for 3-fluoro-4-morpholinylnitrobenzene (4) without Using of Base

In our approach, reaction has been conducted without any base and avoided lot of multi solvent organic extractions. The workup is simple and it involves that once the reaction is completed, cool the reaction to 0-5 °C followed by filteration at same temperature.

Process for *N*-carboethyloxy intermediate (7) *via* (*R*)-epichlorohydrin

We opted ethylchloroformate and (*R*)-epichlorohydrin as key raw materials due to its commercial availability and low cost. In our approach, attachment of an ethylchloroformate to the aryl amines **5**, deprotonation of carbamate **6** with potassium carbonate in acetone at 50-55 °C and then reaction with (*R*)-epichlorohydrin provided a novel intermediate **12**.

Process for Azide Derivative 9 *via* One Pot Synthesis from 12

A general method for the preparation of oxazolidinone derivative from the *N*-carboethyl oxyepoxide derivative was developed. We have chosen to form an uncyclised **13** intermediate *in situ* and thus avoided the isolation of that intermediate. We belived this would give the simplest process for the intermediate **9**. In our approach, a solution of carboethyloxy intermediate **12** in methanol was added to a mixture of ammonium chloride and sodium azide in water at 80-85 °C, so that regio selective epoxide ring opens and followed by cyclisation takes place.

Synthesis of Linezolid 1 *via* One Pot Synthesis from 9

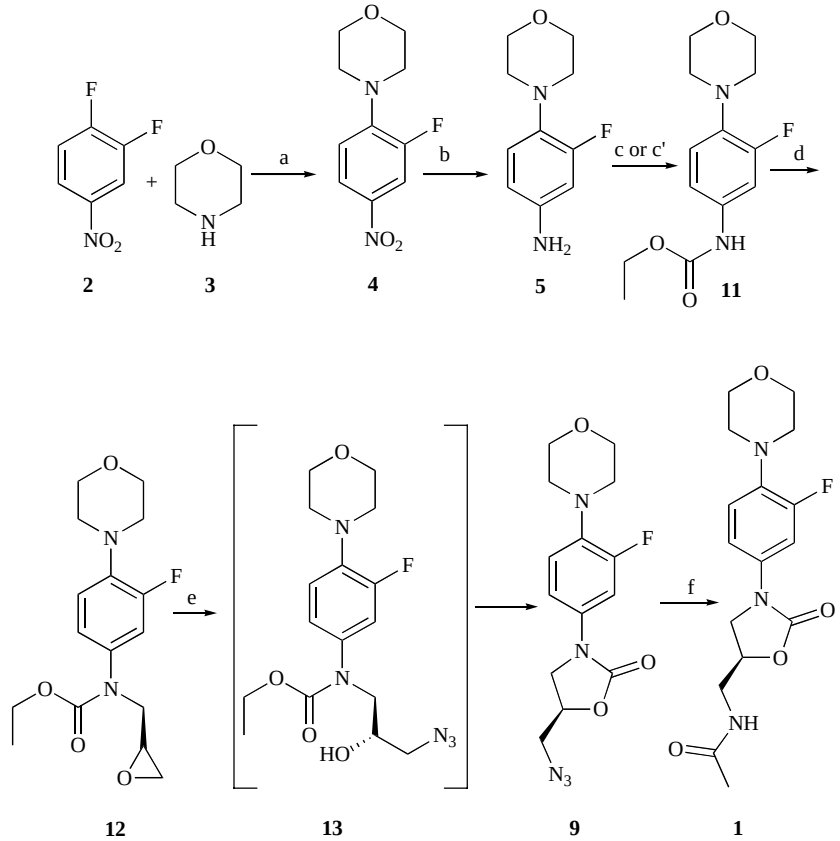
A general method for the synthesis of *N*-acetylated compound **1** from the azide derivative **9** was developed. In our approach, isolation of amine intermediate **10** was avoided, so that number of steps was reduced.

EXPERIMENTAL SECTION

The ^{1}H NMR spectra were measured in DMSO-d_6 and $CDCl_3$ using 200 MHz and 400 MHz on a Varian Gemini FT NMR spectrometer; The ^{1}H chemical shift values are reported on the δ ppm, relative to TMS (δ = 0.00). Coupling constants (*J*) are reported in hertz (Hz). The infrared absorption spectrums were obtained using Perkin Elmer, Spectrum One FT IR spectrophotometer with substances being pressed in a KBr pellet. The mass analysis was performed on AB-4000 Q-trap LC-MS mass spectrometer. The melting points were determined by using the capillary method on POLMON (Model no. M96). Solvent removal was accomplished by a rotator evaporator operating at in-house vacuum (40-50 Torr). The solvents and reagents were used without further purification.

3-Fluoro-4-morpholinylnitrobenzene (4)

To a solution of **3** (81.6 g, 0.93 mol) in 2-propanol (250 mL) was added **2** (50 g, 0.31 mol) *via* an addition funnel over a period of 4 h at 45-50 °C. The resulting suspension was stirred at 35-40 °C for an additional 7 h. The progress of the reaction was monitored by thin layer chromatography (*vide* TLC) and then reaction mass was cooled to 0-5 °C. Filtered the solid and washed with chilled 2-propanol (100.0 mL). Dried in vacuum oven to give a yellow solid **4** (Yield 65.6 g, 92 %). mp 121-126 °C; IR: (KBr, cm^{-1}); 3023 (Aromatic C-H), 2909 (Aliphatic C-H), 1604 (Aromatic C=C), 1516, 1328 (NO_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.97 (ddd, *J* = 9.2 Hz, *J'* = 2.6 Hz, *J''* = 2.6, 1H), 7.88 (dd, *J* = 12.8 Hz, *J'* = 2.6, 1H), 6.92 (t, *J* = 8.6 Hz, 1H), 3.88 (t, 4H), 3.28 (t, 4H); MS: *m/z* 227.4 [M^+ + H].



Scheme 2. Reagents and conditions: (**a**) *i*-PrOH, 45-50 °C, 7 h, 92%; (**b**) Raney Ni, H_2 , EtOAc, 25-30 °C, 10 h, 93%; (**c**) ethylchloroformate, K_2CO_3, acetone, 25-30 °C, 1.5 h, 90% or (**c'**) ethylchloroformate, TEA, DCM, 2 h, 25-30 °C, 87%; (**d**) (*R*)-epichlorohydrin, K_2CO_3, acetone, 50-55 °C, 24 h, 60%; (**e**) NH_4Cl, NaN_3, MeOH, water, 80-85 °C, 2 h, 76%; (**f**) Raney Ni, H_2, Ac_2O, TEA, EtOAc, 25-30 °C, 7 h. 77%.

3-Fluoro-4-morpholinylaniline (5)

To a solution of compound **4** (150 g, 0.66 mol) in methanol (1500 mL) was added Raney Ni (8.1 g) and water (21 mL), hydrogenated the solution for 10 h at 25-30 °C. On completion of the reaction (*vide* TLC), the reaction mixture was filtered through hyflow bed and distilled off ethyl acetate up to 30 % of mass left in the round bottom flask. The resulting mass was cooled to 10-15 °C and solid was collected by filtration, dried in vacuum oven to afford **5** as a brown solid (Yield 120.9 g, 93%).

***N*-Carboethyloxy-3-fluoro-4-morpholinylaniline (11)**

To a mixture of compound **5** (50 g, 0.25 mol) and sodium carbonate (27 g, 1.0 mol) in DCM (200 mL) was added ethylchloroformate (30 g, 0.27 mol) at 10-15 °C, and the reaction mixture was stirred for 1.5 h at 25-30 °C. On the completion of the reaction (*vide* TLC), the reaction mixture was poured into water (200 mL) and extracted with DCM (2 X 250 mL). The organics portions were dried over anhydrous sodium sulphate. Organics was distilled off completely and the solid was isolated from n-hexane to obtain **11** as a gray-purple solid (Yield 61.0 g, 90%). mp. 123-124 °C; IR (KBr, cm^{-1}): 3248 (NH), 1717 (C=O) 1600, 1510 (Aromatic C=C); MS *m/z* 269.0 [M^+ + H] ; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.27 (m, 1H), 6.93 (m, 2H), 6.59 (s, 1H), 4.21 (q, *J* = 14.2 Hz, *J'* = 7 Hz, 2H), 3.86 (t, *J* = 4.2 Hz, 4H), 3.03 (t, *J* = 4.8 Hz, 4H), 1.30 (t, *J* = 7.2 Hz, 3H).

(R)-N-(3-Fluoro-4-morpholinylphenyl)oxiranylmehtyl carbamic acid ethylester (12)

To a heterogeneous mixture of **11** (100 g, 0.37 mol) and K_2CO_3 (160 g, 1.14 mol) in acetone (1000 mL) was added (*R*)-epichlorohydrin (100 mL, 1.14 mol) over period of 1 h at 50-55 °C. Reaction was stirred over night at 50-55 °C, on completion of reaction (*vide* TLC), the resulting mass was filtered trough hyflow and filtrate was distilled off under reduced pressure. The crude was extracted with n-hexane (4 X 800 mL) and the combined extractions were concentrated to dryness below 50 °C to provide titled the compound as crude. The solid was isolated from 2-propanol (150 mL) by filtration and dried to afford **12** as a light yellow solid (Yield 73.0 g, 60%). IR (KBr, cm^{-1}): 3546 (NH), 1698 (C=O); MS: *m/z* 347.0 [M^+ + Na] ; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.07 (m, 3H), 4.05 (q, *J* = 14 Hz, *J'* = 6.8 Hz, 2H), 3.87 (dd, *J* = 15.2 Hz, *J'* = 4 Hz, 1H), 3.74 (m, 4H), 3.48 (dd, *J* = 15.2 Hz, *J'* = 6 Hz, 1H), 3.12 (m, 1H), 3.0 (t, 4H), 2.49 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H).

(R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl Azide (9)

To a mixture of ammonium chloride (4 g, 74 mmol) and sodium azide (8 g, 123 mmol) in water (100 mL) was added a solution of **12** (20 g, 61 mmol) in MeOH (150 mL) over 2 h at 80-85 °C and then reaction mass was stirred for an additional 2 h at 80-85 °C. On completion of reaction (*vide* TLC), reaction mass was cooled to 25-30 °C and extracted with ethylacetate (3 X 100 mL). Organic phase was washed with water (2 X 50 mL) and dried over anhydrous sodium sulphate. Organic phase was concentrated to dryness to provide **9** as brown colored solid (Yield 15.0 g, 76 %).

(S)-N-[[3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (1)

To a solution of compound **9** (5.0 g 74 5.5 mmol), acetic anhydride (2.0 g, 19 mmol) and triethylamine (3.2 g, 31mmol) in ethyl acetate (50 mL) was added Raney Ni (0.8 g) and the reaction mixture was hydrogenated in autoclave at 25-30 °C under hydrogen gas pressure 3 kg/cm^2 over 7 h. On completion of reaction (*vide* TLC), MeOH was added (25 mL) to the reaction mass and filtered through hyflow bed. The clear filtrate was partially concentrated under reduced pressure and the precipitated solid was filtered. This solid was purified from a mixture of ethyl acetate and acetonitrile. Dried the solid in a vacuum oven (20 mbr, 50 °C) to afford **1** as a white solid (Yield 3.67 g, 70%). mp. 181-182 °C {lit. [1] mp: 181.5-182.5 °C} ; **(**KBr, cm^{-1}): 3343 (N-H), 1741 (C= O, Oxazolidinone); MS: *m/z* 338 [M^+ + H], 360.1 [M^+ + Na]; SOR = $[\alpha]^{20}_D$= -9.4° (c 0.919 $CHCl_3$) {lit. [1] $[\alpha]^{20}_D$ = -9° (c 0.919 $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.23 (t, *J* = 5.4 Hz, 1H), 7.48 (dd, *J* = 14.0 Hz, *J'* = 2.4 Hz, 1H), 7.18 (dd, *J* = 8.8 Hz, *J'* = 2.4 Hz, 1H), 7.05 (t, *J* = 9.4 Hz, 1H), 4.64-4.70 (m, 1H), 4.07 (t, *J* = 8.8 Hz, 1H), 3.69-3.73 (m, 4H), 3.4 (t, *J* = 5.2 Hz, 3H), 2.95 (t, *J* = 4.6 Hz, 4H), 1.83 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 MHz) 22.39, 42.23, 47.28, 50.67 (d, *J* =3.05 Hz) 66.13, 71.52, 106.61 (d, *J* =26.2 Hz), 114.04 (d, *J* =3.0 Hz), 119.20 (d, *J* = 4.2 Hz), 133.41 (d, *J* = 10.6 Hz), 135.50 (d, *J* = 9.0 Hz), 154.02, 156.99 (d, *J* = 246.44 Hz), 169.98.

ACKNOWLEDGEMENT

We thank the management of Dr. Reddy's Laboratories Ltd for supporting this work. Authors wish to acknowledge the colleagues of Analytical Research Department of Dr. Reddy's Laboratories Ltd for their excellent cooperation.

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