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A Convenient Synthesis of Oxazolidinone Derivatives Linezolid and Eperezolid from (*S*)-Glyceraldehyde Acetonide

Guangyu Xu,[1] Yi Zhou,[1] Chunhao Yang,[2] and Yuyuan Xie[2]

[1]*Institute of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, People's Republic of China*

[2]*Shanghai Institute of Materia and Medica, Chinese Academy of Sciences, Shanghai 201023, People's Republic of China*

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ABSTRACT: *A new convenient method for the synthesis of oxazolidinone antibacterials Linezolid and Eperezolid from readily available (S)-glyceraldehyde acetonide was developed. The key steps include reductive amination of arylamine and (S)-glyceraldehyde acetonide in the presence of $NaBH_4$ and 4 Å sieve, followed by hydrolysis and regioselective cyclization.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:316–319, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20435

INTRODUCTION

Oxazolidinones as a new class of synthetic antimicrobial agents are active against numerous multidrug-resistant Gram-positive organisms [1]. Linezolid **1a** and Eperezolid **1b** (Fig. 1), which are well known as the promising candidates of this family, work effectively against numerous serious Gram-positive human pathogens such as MRSA (Methicillin resistant Staphylococcus aureus) and VRE (Vancomycin-resistant Enterococci) [2–4]. Linezolid has recently received approval for the treatment of community- and hospital-acquired pneumonia and skin structure infections.

Several methods are available for the synthesis of Linezolid and Eperezolid. Brickner et al. [2] and Schaus and Jacobson [5] reported separately a route to oxazolidinones with good yields. However, in these methods for the synthetic key step to oxazolidinone ring, severe conditions with low temperature (−78°C) and an air-sensitive base (*n*-BuLi) were required, which limit the large-scale production in the industry. Lohray et al. [6] offered another possibility to oxazolidinones via asymmetric bis-epoxide using D-mannitol as a starting material. However, the synthesis of asymmetric bis-epoxide suffers from a long-synthetic route and was reported without any optical data.

We wish to report herein a very convenient and efficient method for the synthesis of Linezolid and Eperezolid, using readily available (*S*)-glyceraldehyde acetonide as a chiral-building block.

RESULTS AND DISCUSSION

The synthesis of Linezolid and Eperezolid share a common route, as detailed in Scheme 1. (*S*)-Glyceraldehyde acetonide (**3**) was easily obtained

Correspondence to: Guangyu Xu; e-mail: gyxu@hunnu.edu.cn.
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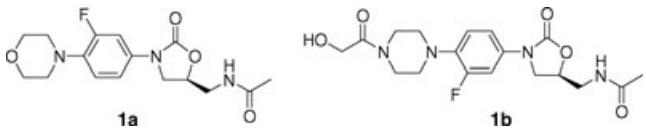


FIGURE 1 Linezolid (**1a**) and Eperezolid (**1b**).

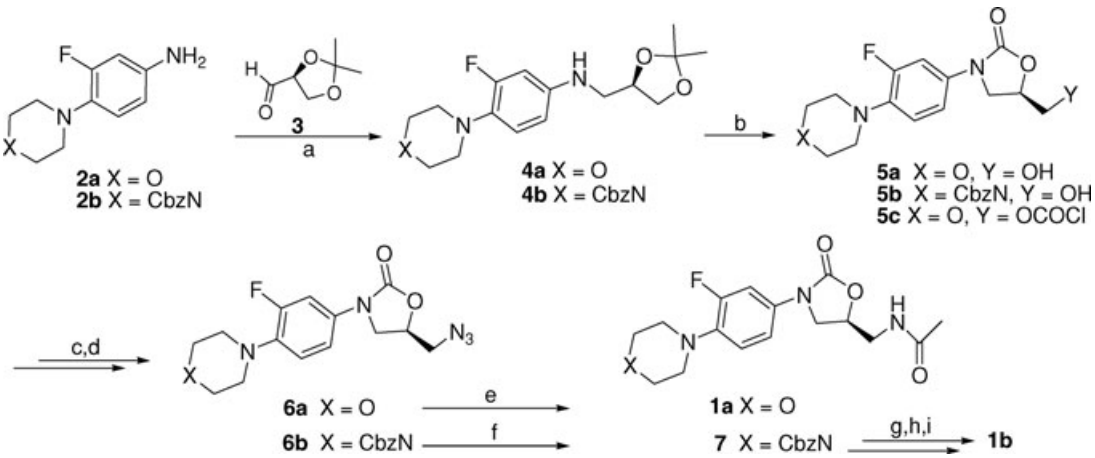
from L-ascorbic acid (vitamin C) via hydrogenation [7], acetonation, and oxidative cleavage [8,9]. Reductive amination of fluoroarylamine **2** with **3** in the presence of $NaBH_4$ and 4 Å molecular sieve at room temperature afforded dioxolanes **4** with good yields. The yields were considerably poor when Pd/C or Raney Ni was used as a catalyst in the reductive amination step, because unstable (*S*)-glyceraldehyde acetonide may polymerize during long reaction time. The addition of molecular sieve to $NaBH_4$ system could shorten the reaction time and minimize the polymerization of glyceraldehyde acetonide in the solvent. After hydrolysis of dioxolanes **4** in aqueous HCl/methanol, the regioselective cyclization with triphosgene in the presence of K_2CO_3 afforded oxazolidinones **5**. However, if NaOH [10] or triethylamine was used as an acid scavenger, the byproduct **5c** could form. The key intermediate **5** was activated as mesylate and then displaced with NaN_3 to give **6**. Hydrogenation of the azide **6a** over Pd/C and then treatment with Ac_2O provided the targeted antibacterial Linezolid. In our laboratory, we tried to synthesize **1a** via direct displacement of mesylate by acetamide anion in DMF or THF, and the yield was very low (10%) because **5a** mesylate was unstable and degraded under this condition. Reductive acetylation of azide **6b** with thioacetic acid [11] gave acetamide **7**. The compound **7** after side-chain manipulation [2] provided the targeted antibacterial Eperezolid with good yield. The final product's melting points and specific rotation data were identical to those reported in the literature.

In summary, we describe herein a simple, mild, and facile synthesis of Linezolid and Eperezolid from (*S*)-glyceraldehyde acetonide with reductive amination and regioselective cyclization as key steps with good yields.

EXPERIMENTAL

Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker-300 NMR spectrometer, and chemical shifts δ are in ppm (TMS was used as an internal standard). EI mass spectra were accomplished at 70 eV, using a MAT 90 spectrometer. Microanalyses were performed on a Leco CHN-2000 elemental analyzer. Optical rotations were taken on a Perkin-Elmer 341 polarimeter at the sodium-D line. Purification by column chromatography was carried out with silica gel 60 (70–230).

*N-[4(R)-(2,2-Dimethyl-1,3-dioxolane-4-yl)methyl]-3-fluoro-4-morpholinylaniline (**4a**).* A solution of **2a** (5.00 g, 25.5 mmol) and **3** (6.00 g, 46.1 mmol) in 25 mL THF and 25 mL methanol was added 6.25 g of molecular sieves (4 Å), then $NaBH_4$ (0.97 g, 25.6 mmol) was added portionwise. The mixture was stirred for 10 h at room temperature, ice water (150 mL) was added, and the molecular sieves were removed by filtration. The filtrate was extracted



SCHEME 1 Reagents and conditions: (a) $NaBH_4$, MeOH, 4 Å MS, r.t., 78%; (b) (*i*) H_3O^+, MeOH, r.t.; (*ii*) K_2CO_3, triphosgene, CH_2Cl_2, 30°C, 80%; (c) CH_3SO_2Cl, triethylamine, CH_2Cl_2, 0°C → r.t., 88%; (d) NaN_3, DMF, 80°C, 90%–92%; (e) (*i*) Pd/C, H_2, EtOH, r.t.; (*ii*) pyridine, Ac_2O, r.t., 51%; (f) CH_3COS H, r.t., 75%; (g) Pd/C, MeOH/EtOAc, r.t.; (h) $ClCOCH_2OBn$, triethylamine, CH_2Cl_2, 0°C → r.t.; (i) Pd/C, H_2, MeOH, 73%.

with ethyl acetate (50 × 3 mL) was and dried with Na_2SO_4. After removal of the solvent, 6.74 g of **4a** as a pale yellow oil was obtained without further purification. The analytic sample was obtained by chromatography on a silica-gel column (mobile phase PE/EtOAc from 6:1 to 4:1). $[\alpha]_D^{20}$–1.7° (*c* 4.54, $CHCl_3$); ^{1}H NMR($CDCl_3$): δ 6.84 (t, 1H, $J = 8.2$ Hz), 6.39 (m, 2H), 4.35 (m, 8 lines, 1H), 4.09 (dd, 1H, $J = 7.1$, 8.3 Hz), 3.84 (t, 4H, $J = 4.7$ Hz), 3.75 (dd, 1H, $J = 6.0$, 8.2 Hz), 3.24 (dd, 1H, $J = 3.7$, 12.3 Hz), 3.13 (dd, 1H, $J = 6.6$, 12.5 Hz), 2.95 (br s, 4H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 25.24, 26.86, 46.92, 51.73, 67.07, 67.12, 74.32, 101.70 (d, $J = 24.35$ Hz), 108.50, 109.50, 120.25, 130.99, 144.77 (d, $J = 9.56$ Hz), 156.94 (d, $J = 244.71$ Hz); MS: *m/z* 310 (61, M^+), 219 (12), 209 (100), 151 (16).

Compounds **4b** was prepared by using the method described for the preparation of **4a** except that the **4b** was recrystallized from petroleum ether and ethyl acetate.

*N-[4(R)-(2,2-Dimethyl-1,3-dioxolane-4-yl)methyl]-3-fluoro-4-(N-carbobenzoxypiperazinyl) Aniline (**4b**).* Yield 78%, mp 92.5—94°C, $[\alpha]_D^{20}$–1.0° (*c* 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 5H), 6.81 (t, 1H, $J = 7.6$ Hz), 6.36 (m, 2H), 5.16 (s, 2H), 4.35 (m, 8 lines, 1H), 4.10 (dd, 1H, $J = 6.4$, 8.3 Hz), 3.91 (br s, 1H), 3.76 (dd, 1H, $J = 6.1$, 8.2 Hz), 3.63 (br s, 4H), 3.25 (dd, 1H, $J = 4.2$, 12.5 Hz), 3.13 (dd, 1H, $J = 6.7$, 12.6 Hz), 2.89 (br s, 4H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 25.24, 26.86, 44.00, 46.86, 51.33, 67.06, 67.16, 74.29, 101.57 (d, $J = 24.35$ Hz), 108.51, 109.52, 120.88, 127.89, 128.02, 128.48, 130.71, 136.61, 145.09, 155.18, 157.03 (d, $J = 245.06$ Hz); MS: *m/z* 443 (96, M^+), 342 (25), 245 (66), 187 (27), 151 (24), 127 (20), 91 (100); Anal. calcd for $C_{24}H_{30}FN_3O_4$: C, 64.99; H, 6.82; N, 9.47. Found: C, 65.02; H, 6.79; N, 9.39.

*(R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol (**5a**).* A solution of benzamine (**4a**, 4.56 g) in dry HCl methanol (4 M, 40 mL) was added 0.5 mL of water, the mixture was stirred at room temperature for 8 h, and concentrated with rotary evaporator, the residue was diluted with methyl chloride (35 mL) then added aq. Na_2CO_3 solution (15%, 40 mL, 56.5 mmol). The mixture was cooled to 0°C and treated dropwise with a solution of triphosgene (1.30 g, 4.38 mmol) in methyl chloride (35 mL) for 30 min. After being stirred for 24 h at room temperature, the water phase was separated and extracted with methyl chloride (50 × 2 mL). The combined organic phase was washed with water (25 × 2 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was purified by crystallization from ethyl acetate and petroleum ether to provide 2.84 g (56% from **2a**) of **5a** as a light gray amorphous solid. mp 114–116°C, $[\alpha]_D^{20}$–53° (*c* 0.69, $CHCl_3$) (lit. [2] mp 112–114°C, $[\alpha]_D^{20}$–54° (*c* 0.990, $CHCl_3$)); ^{1}H NMR($CDCl_3$): δ 7.47 (dd, 1H, $J = 2.1$, 14.4 Hz), 7.12 (dt, 1H, $J = 2.4$, 8.9 Hz), 7.00 (br s, 1H), 4.75 (m, 1H), 3.95 (m, overlapping, 3H), 3.88 (t, 4H, $J = 4.7$ Hz), 3.76 (d, 1H, $J = 13.1$ Hz), 3.08 (t, 4H, $J = 4.2$ Hz), 2.35 (br s, 1H); MS: *m/z* 296 (100, M^+), 238 (55), 149 (20), 57 (36); Anal. calcd for $C_{14}H_{17}FN_2O_4$: C, 56.75; H, 5.78; N, 9.45. Found: C, 57.02; H, 5.78; N, 9.28.

*(R)-[N-3-[3-Fluoro-4-[N-1-(4-carbobenzoxy)piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methanol (**5b**).* Yield 78%, mp 155–157°C, $[\alpha]_D^{20}$–35° (*c* 1.01, $CHCl_3$), (lit. [2] mp 156–157°C, $[\alpha]_D^{20}$–32° (c 0.991, $CHCl_3$)); ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 1H, $J = 14.4$ Hz), 7.36 (m, 5H), 7.12 (m, 2H), 5.16 (s, 2H), 4.75 (m, 1H), 4.00 (m, 3H), 3.73 (m, 5H), 3.07 (br s, 4H).

6a and **6b** were prepared according to the method described in [2].

*(R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl Azide (**6a**).* Yield 79% (from **5a**). ^{1}H NMR ($CDCl_3$): δ 7.45 (dd, 1H, $J = 2.5$, 14.3 Hz), 7.13 (ddd, 1H, $J = 1.1$, 2.6, 8.9 Hz), 6.95 (t, 1H, $J = 9.1$ Hz), 4.78 (m, 1H), 4.05 (t, 1H, $J = 8.8$ Hz), 3.88 (t, 4H, $J = 4.6$ Hz), 3.83 (dd, 1H, $J = 6.2$, 8.8 Hz), 3.71 (dd, 1H, $J = 4.6$, 13.3 Hz), 3.59 (dd, 1H, $J = 4.3$, 13.1 Hz), 3.06 (t, 4H, $J = 4.6$ Hz).

*(R)-[N-3-[3-Fluoro-4-[N-1-(4-carbobenzoxy)piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl Azide (**6b**).* Yield 81% (from **5b**). ^{1}H NMR ($CDCl_3$): δ 7.46 (dd, 1H, $J = 2.6$, 14.3 Hz), 7.35 (m, 5H), 7.12 (ddd, 1H, $J = 0.8$, 2.5, 8.6 Hz), 6.93 (t, 1H, $J = 9.1$ Hz), 4.78 (m, 8 lines, 1H), 4.05 (t, 1H, $J = 8.8$ Hz), 3.83 (dd, 1H, $J = 6.3$, 8.9 Hz), 3.68 (m, 5H), 3.59 (dd, 1H, $J = 4.4$, 13.2 Hz), 3.01 (br s, 4H); MS: *m/z* 454 (14, M^+), 424 (38), 329 (32), 289 (16), 165 (16), 91 (100), 56 (37).

*(S)-N-[[3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (**1a**, Linezolid).* **1a** was prepared according to the method described in [2], except that the solvent was replaced by ethanol when reductive hydrogenation of azide **6a**. Yield 51% (from **6a**). mp 179–180.5°C, $[\alpha]_D^{20}$–10° (*c* 1.52, $CHCl_3$) (lit. [2] mp 181.5–182.5°C, $[\alpha]_D^{20}$–9° (*c* 0.919, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.46 (dd, 1H, $J = 2.2$, 14.6 Hz), 7.08 (dd, 1H, $J = 1.8$, 9.1 Hz), 6.96 (t, 1H, $J = 9.1$ Hz), 6.05 (t, 1H, $J = 6.0$ Hz), 4.77 (m, 1H),

4.02 (t, 1H, $J = 8.9$ Hz), 3.88 (t, 4H, $J = 4.5$ Hz), 3.73 (dd, 1H, $J = 1.8$, 7.0 Hz), 3.69 (dd, 1H, $J = 3.2$, 5.9 Hz), 3.61 (dt, 1H, $J = 5.5$, 8.5 Hz), 3.07 (t, 4H, $J = 4.6$ Hz), 2.02 (s, 3H); MS: *m/z* 337 (27, M^+), 293 (25), 234 (20), 209 (26), 149 (50), 91 (100); Anal. calcd for $C_{16}H_{20}FN_3O_4$: C, 56.97; H, 5.98; N, 12.46. Found: C, 57.16; H, 6.03; N, 12.22.

*(S)-N-[[3-[3-Fluoro-4-[N-1-(4-hydroxyacetyl)piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (***1b***, Eperezolid).* **1b** was prepared from **6b** according to the method described in [2,11], yield 55% (from **6b**). mp 172–174°C, $[\alpha]_D^{20}$–20° (*c* 0.93, DMSO), (lit. [2] mp 175–176°C, $[\alpha]_D^{20}$–21° (*c* 0.853, DMSO); ^{1}H NMR ($CDCl_3$): δ 7.50 (dd, 1H, $J = 2.5$, 14.0 Hz), 7.08 (d, 1H, $J = 8.7$ Hz), 7.00 (t, 1H, $J = 9.0$ Hz), 6.06 (t, 1H, $J = 2.7$ Hz), 4.77 (m, 1H), 4.21 (s, 2H), 4.02 (t, 1H, $J = 9.0$ Hz), 3.87 (t, 2H, $J = 5.1$ Hz), 3.75 (dd, 1H, $J = 6.8$, 9.1 Hz), 3.62 (m, 2H), 3.48 (t, 2H, $J = 5.0$ Hz), 3.09 (t, 4H, $J = 4.3$ Hz), 2.01 (s, 3H); MS: *m/z* 394 (28, M^+), 350 (56), 306 (27), 165 (26), 56 (100). Anal. calcd for $C_{18}H_{23}FN_4O_5$ C, 54.82; H, 5.88; N, 14.21. Found: C, 54.86; H, 5.99; N, 13.98.

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