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A Convenient Synthesis of Antibacterial Linezolid from (*S*)-Glyceraldehyde Acetonide

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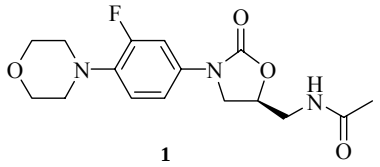
Abstract: A convenient synthesis of oxazolidinone antibacterial linezolid from readily available L-ascorbic acid is described. The key steps include reductive amination of arylamine and (*S*)-glyceraldehyde acetonide in the presence of $NaBH_4$ and 4Å sieve, followed by hydrolysis and regioselective cyclization.

Keywords: Linezolid, antibacterial, synthesis, ascorbic acid.

Oxazolidinones as a new class of synthetic antimicrobial agents are active against numerous multidrug-resistant Gram-positive organisms[1]. Linezolid **1** as the promising candidate of this family works effectively against numerous serious Gram-positive human pathogens as MRSA and VRE[2]. Recently linezolid has been marketed in the USA and is available in oral and i.v. formulations.



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Several methods are available for the synthesis of linezolid[2, 3]. Brickner[2] reported a route to linezolid with good yield. However, in this method for the synthetic key step to oxazolidinone ring, severe conditions with a low temperature (-78°C) and air-sensitive base (*n*-BuLi) were requested, which limit a large scale of production in industry. Lohray[3] offered another possibility to linezolid *via* asymmetric bis-epoxide using D-mannitol as a starting material. However, the synthetic route was very long and without optical data.

We wish to report herein a very convenient and efficient synthesis of linezolid from readily available (*S*)-glyceraldehyde acetonide **3**. The synthetic route was outlined in **Scheme 1**. Reductive amination of fluoroarylamine **2**[2] with L-(*S*)-glyceraldehyde acetonide in the presence of $NaBH_4$ and 4Å molecular sieve in methanol afforded

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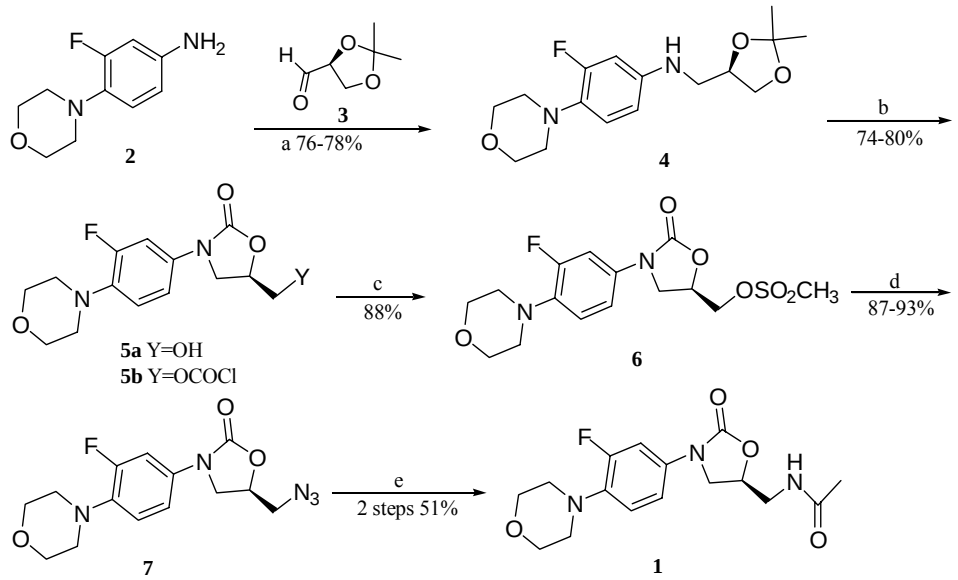
Scheme 1



Reagents and conditions: (a) $NaBH_4$, MeOH, 4Å MS, r.t.; (b) i. H_3O^+, MeOH, r.t.; ii. K_2CO_3, triphosgene, CH_2Cl_2, 30℃; (c) CH_3SO_2Cl, TEA, CH_2Cl_2, 0℃→r.t.; (d) NaN_3, DMF, 80℃; (e) i. Pd/C, H_2, EtOH, r.t.; ii. Pyridine, Ac_2O, r.t.

dioxane **4**[4] in good yields. (*S*)-Glyceraldehyde acetonide was easily obtained from L-ascorbic acid (vitamin C) *via* hydrogenation[5], acetonation and oxidative cleavage[6]. The yield was considerably poor, when Pd/C or Raney Ni was used as catalyst in reductive amination step, due to the fact that unstable (*S*)-glyceraldehyde acetonide may polymerize under the condition of long reaction time. The use of $NaBH_4$/molecular sieve system can shorten the reaction time and minimize the polymerization of glyceraldehyde acetonide. After hydrolysis of dioxane **4** in aq. HCl/methanol, the regioselective cyclization with triphosgene in the presence of K_2CO_3 afforded oxazolidinone **5**[7]. However, if NaOH or triethylamine was used as acid scavenger, the byproduct **5b** can be formed. The key intermediate **5a** after side-chain manipulation[2] provided the targeted antibacterial linezolid [8] in good yields.

In conclusion we have achieved a simple, mild and facile synthesis of linezolid in good yields.

Acknowledgments

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References and Notes

1. W. A. Gregory, D. R. Brittelli, C. L. J. Wang, *et al.*, *J. Med. Chem.*, **1989**, *32*(8), 1673.
2. S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, *et al.*, *J. Med. Chem.*, **1996**, *39*(3), 673.
3. B. B. Lohray, S. Baskaran, B. S. Rao, *et al.*, *Tetrahedron Lett.*, **1999**, *40*(26), 4855.

4. Spectral data: **4** ^{1}H NMR ($CDCl_3$, δ_{ppm}): 6.84 (t, 1H, *J*=8.2 Hz), 6.39 (m, 2H), 4.35 (m, 8lines, 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 (brs, 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, 144.7. MS: *m/z* 310 (M^+, 58), 209 (100), 151 (16). $[\alpha]_D^{20}$ -1.7 (c 4.54，$CHCl_3$).
5. G. C. Andrews, T. C. Crawford, B. E. Bacon, *J. Org. Chem.*, **1981**, *46*(14), 2976.
6. C. Hubschwerlen, J. L. Specklin, J. Higelin, *Org. Synth.*, **1993**, *72*, 1.
7. **5a**: white powder (EtOAc/Hex.), m.p.114-116℃, lit.[2] m.p.112-114℃, Spectral data: ^{1}H NMR ($CDCl_3$, δ_{ppm}): 7.47 (dd, 1H, *J*=2.1, 14.4 Hz), 7.12 (dt, 1H, *J*=2.4, 8.9 Hz), 7.00 (brs, 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 (brs, 1H). MS: *m/z* 296 (M^+, 100), 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. $[\alpha]_D^{20}$ -53 (c 0.69, $CHCl_3$), *lit.*[2] $[\alpha]_D^{20}$ -54 (c 0.990，$CHCl_3$). **5b**: ^{1}H NMR ($CDCl_3$, δ_{ppm}): δ 7.01 (m, 3H), 5.05 (m, 1H), 4.59 (t, 1H, *J*=8.7 Hz), 4.16 (dd, 1H, *J*=6.6, 9.1 Hz), 4.07 (dd, 1H, *J*=3.6, 14.7 Hz), 3.86 (m, 5H), 3.14 (t, 4H, *J*=4.8 Hz). MS: *m/z* 358 (M^+, 100), 300 (72), 213 (52), 208 (26), 164 (28), 150 (57). Anal. Calcd. for $C_{15}H_{16}ClFN_2O_5$: C, 50.22; H, 4.50; N, 7.81. Found: C, 50.39; H, 4.50; N, 7.57. $[\alpha]_D^{20}$ -32 (c 0.650, $CHCl_3$).
8. **1**: white needles (EtOAc/Hex.), m.p.179-180.5℃, lit.[2] m.p.181.5-182.5℃. Spectral data: ^{1}H NMR ($CDCl_3$, δ_{ppm}): 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 (M^+, 27), 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. $[\alpha]_D^{20}$ -9 (c 1.52，$CHCl_3$). lit.[2] $[\alpha]_D^{20}$ -9 (c 0.919，$CHCl_3$).

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