Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6799–6802

Short and practical enantioselective synthesis of linezolid and eperezolid via proline-catalyzed asymmetric α-aminooxylation

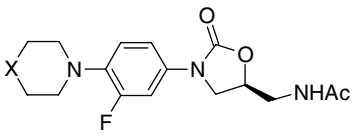
Srinivasarao V. Narina and Arumugam Sudalai*

Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India

Received 7 June 2006; revised 5 July 2006; accepted 14 July 2006
Available online 7 August 2006

Abstract—An efficient enantioselective synthesis of the antibacterials, linezolid (U-100766), and eperezolid (U-100592) using D-proline-catalyzed asymmetric α-aminooxylation of aldehydes as the key step is described here. This is the first report on the enantioselective synthesis of linezolid and eperezolid using asymmetric catalysis.

The 3-aryl-2-oxazolidinones are a relatively new class of synthetic antibacterial agents, having a new mechanism of action which involves early inhibition of bacterial protein synthesis. This class of compounds is particularly active against Gram-positive organisms such as methicilin-resistant *Saphylococcus aureus* and *Staphylococcus epidermitis* and vancomycin-resistant *enterococci*.[1,2e] Important representatives of this class include the morpholine derivative linezolid, **1**, and the piperazine derivative eperezolid, **2**. Most of the methods reported[2] for the asymmetric synthesis of linezolid and eperezolid involve either a chiral pool approach or classical resolution of racemates. Surprisingly, an asymmetric catalytic route for the construction of the 2-oxazolidinone moiety has not been reported so far. In this letter, we report a short and practical method for the enantioselective synthesis of the two important antibacterial antibiotics, linezolid **1** and eperezolid **2**, by employing D-proline-catalyzed asymmetric α-aminooxylation of aldehydes as the key step (Schemes 1 and 2).



1, X= O; Linezolid
2, X= $NCOCH_2OH$; Eperezolid

The field of asymmetric organocatalysis in organic synthesis is rapidly growing and has provided several new methods for obtaining chiral compounds in an environmentally benign manner.[3] In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[4] Proline has also been found to be an excellent asymmetric catalyst for α-functionalization[5] of aldehydes and ketones. The retrosynthetic analysis of linezolid **1** and eperezolid **2** is outlined in Figure 1. We envisioned that the oxazolidinones in **1** and **2** could be constructed by intramolecular cyclization of chiral diols **7** and **16**, which in turn would be obtained from the corresponding aldehydes **6** and **15** by D-proline-catalyzed asymmetric α-aminooxylation of the respective aldehydes **6** and **15**. Aldehydes **6** and **15** would in turn be prepared readily from amines **3** or **12** and 1,3-propane diol.

The asymmetric synthesis of linezolid **1** started with arylamine **3**, which was prepared following the reported procedure.[2e] Treatment of arylamine **3** with monotosyl protected 1,3-propane diol gave secondary amine **4**,[6] which was then protected using Cbz–Cl to furnish the key intermediate alcohol **5** in 85% overall yield. Alcohol **5** was then oxidized using standard Swern conditions[7] to aldehyde **6**, which was converted into the corresponding diol **7** by proline-catalyzed asymmetric α-aminooxylation in a two-step reaction sequence: (i) reaction of aldehyde **6** with nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at −20 °C[5a] followed by treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol and (ii) subsequent reduction

* Corresponding author. Tel.: +91 20 25902174; fax: +91 20 25902676; e-mail: a.sudalai@ncl.res.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.065

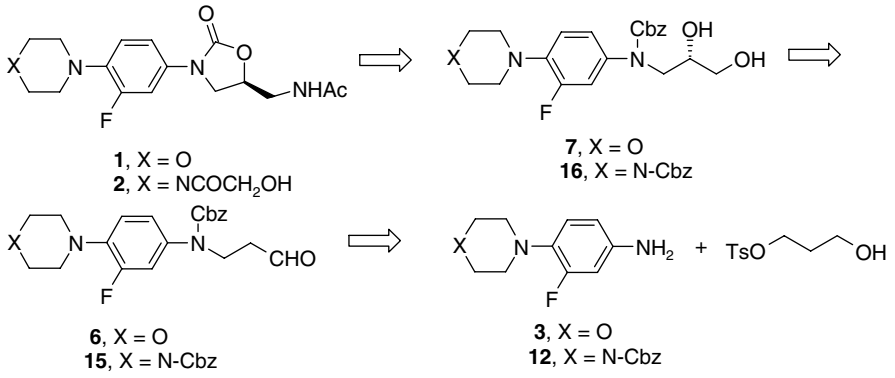
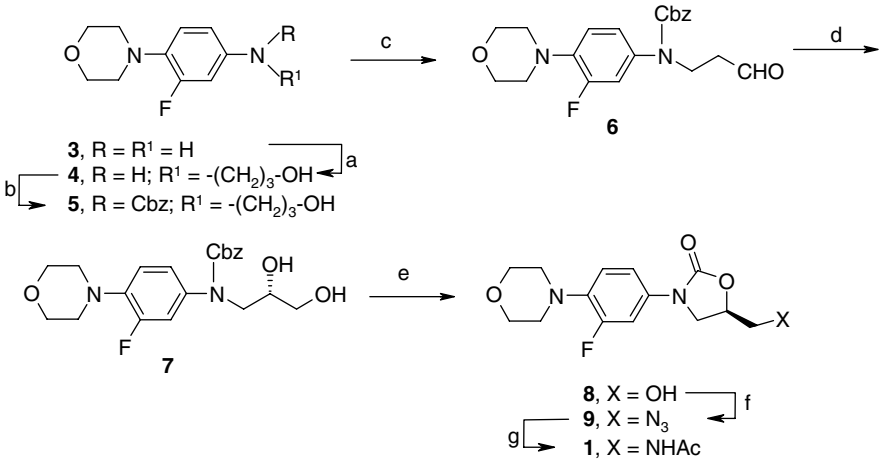
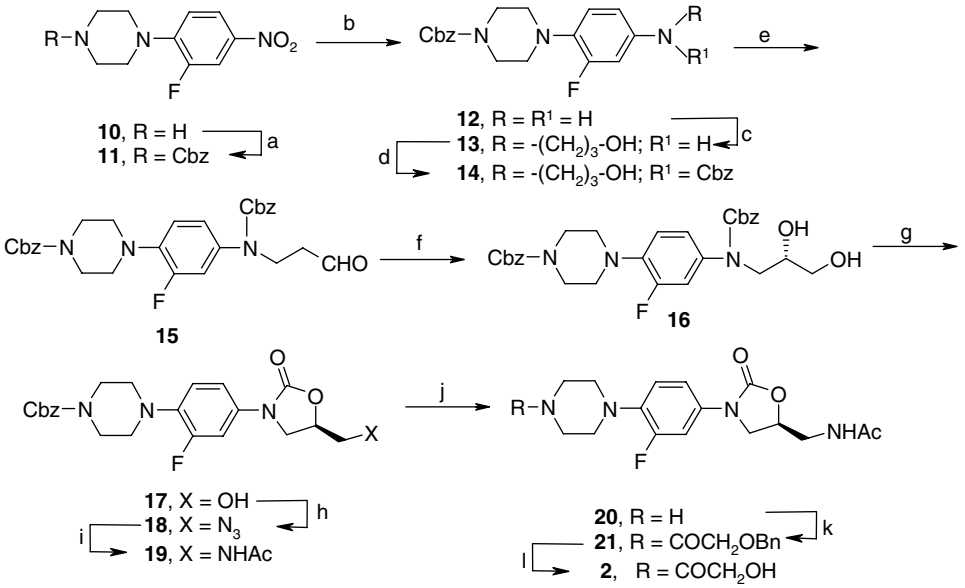


Figure 1. Retrosynthetic analysis of linezolid **1** and eperezolid **2**.



Scheme 1. Reactions and conditions: (a) TsO–$(CH_2)_3$–OH, NaI, Na_2CO_3, DMF, 65 °C; (b) Cbz–Cl, $NaHCO_3$, acetone–water, 85% (over two steps); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C, 95%; (d) (i) PhNO, D-proline (25 mol %), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$; (ii) $CuSO_4$ (30 mol %), MeOH, 86% (over two steps); (e) NaH, THF, 0 °C, 96%; (f) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 4 h; (ii) NaN_3, DMF, 75 °C, 92% (over two steps); (g) 10% Pd/C, H_2 (1 atm), EtOAc, 12 h then Ac_2O, py, 92%.



Scheme 2. Reagents and conditions: (a) Cbz–Cl, $NaHCO_3$, acetone–H_2O, 97%; (b) $CoCl_2$, $NaBH_4$, MeOH, 60 °C, 95%; (c) TsO–$(CH_2)_3$–OH, NaI, Na_2CO_3, DMF, 65 °C; (d) Cbz–Cl, $NaHCO_3$, acetone–H_2O, 79% (over two steps); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C, 94%; (f) (i) PhNO, D-proline (25 mol %), −20 °C, 24 h then MeOH, $NaBH_4$; (ii) $CuSO_4$ (30 mol %), MeOH, 82% (over two steps); (g) NaH, THF, 0 °C, 94%; (h) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 4 h; (ii) NaN_3, DMF, 75 °C, 89% (over two steps); (i) PPh_3, THF–water, 12 h then Ac_2O, py, 96%; (j) 10% Pd/C, H_2 (1 atm), MeOH–CH_2Cl_2 (3:1), 97%; (k) $ClCOCH_2OCH_2Ph$, Et_3N, CH_2Cl_2, 0 °C, 100%; (l) 10% Pd/C, H_2 (1 atm), MeOH–CH_2Cl_2 (3:1), 89%.

of the crude product with 30% $CuSO_4$ yielded chiral diol **7**[8] in 86% yield; $[\alpha]_D^{25}$ −4.0 (*c* 1.1, $CHCl_3$). The regioselective intramolecular cyclization[9] of diol **7** using sodium hydride in THF at 0 °C furnished the desired oxazolidinone **8** in 96% yield and 99% ee (determined by ^1H NMR analysis of its Mosher's ester). The physical and spectroscopic data of **8** were in complete agreement with the reported values.[2e] Oxazolidinone **8** was then converted into the corresponding azide **9** in two steps with 92% overall yield. Finally, the azide function was reduced with H_2 using Pd/C to furnish the crude amine, which was converted (Ac_2O, py) to linezolid **1**[2e] {mp 181–182.5 °C; $[\alpha]_D^{25}$ −9 (*c* 1, $CHCl_3$); lit.[2e] mp 181.5–182.5 °C; $[\alpha]_D^{25}$ −9 (*c* 1, $CHCl_3$)} in 92% yield and 99% ee (Scheme 1).

A similar strategy was extended to the asymmetric synthesis of eperezolid **2** (Scheme 2). Protection of the secondary amine group of **10**[2e] with Cbz–Cl gave **11** in quantitative yield. Reduction of the nitro group in **11** ($NaBH_4$, cobalt chloride, MeOH, 60 °C)[10] produced arylamine **12**, which was transformed to alcohol **14** in 79% overall yield (vide supra). Swern oxidation of alcohol **14** gave aldehyde **15**, which was subjected to D-proline catalyzed asymmetric α-aminooxylation with nitrosobenzene followed by reduction to furnish chiral diol **16**[11] in 82% yield (two steps) $[\alpha]_D^{25}$ −3.2 (*c* 1, $CHCl_3$). Subsequent regioselective intramolecular cyclization of diol **16** (NaH, THF, 0 °C) gave oxazolidinone **17** in 94% yield and 99% ee (determined by ^1H NMR analysis of its Mosher's ester), which was further converted into the corresponding azide **18** in two steps, in 94% overall yield. Reduction of azide **18** to the corresponding amine was readily achieved with PPh_3 in THF–H_2O mixture and the in situ generated amine was acetylated (Ac_2O, py) to give acetamide **19** in excellent yield. Deprotection of the Cbz group in **19** under catalytic hydrogenolysis conditions (Pd/C, H_2 (1 atm), MeOH–CH_2Cl_2) provided piperazine **20**, which was acylated ($ClCOCH_2OBn$, Et_3N, CH_2Cl_2, 0 °C) to give **21** in quantitative yield. Finally, debenzylation of **21** (Pd/C, H_2 (1 atm), MeOH–CH_2Cl_2) furnished eperezolid **2** {mp 174–176 °C; $[\alpha]_D^{25}$ −21 (*c* 1, DMSO); lit.[2e] mp 175–176 °C; $[\alpha]_D^{25}$ −21 (*c* 1, DMSO)} in 89% yield and 99% ee.

In conclusion, the enantioselective syntheses of two antibacterial antibiotics, linezolid **1** and eperezolid **2**, were achieved in 9 and 14 linear steps (56% and 39% overall yields, respectively). The applicability of the D-proline catalyzed asymmetric α-aminooxylation of aldehydes has been demonstrated. The advantages of our syntheses are the introduction of chirality using a catalytic amount of D-proline, which is cheap and readily available, and the high enantioselectivity associated with the process.

Acknowledgements

N.V.S.R. thanks CSIR, New Delhi, for the award of research fellowships. The authors are thankful to Dr. B. D. Kulkarni, Head, CEPD, for his support and encouragement.

References and notes

1. (a) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010; (b) Bobkova, E. V.; Yan, Y. P.; Jordan, D. B.; Kurilla, M. G.; Pompliano, D. L. *J. Biol. Chem.* **2003**, *278*, 9802; (c) Aoki, H.; Ke, L. Z.; Poppe, S. M.; Poel, T. J.; Weaver, E. A.; Gadwood, R. C.; Thomas, R. C.; Shinabarger, D. L.; Ganoza, M. C. *Antimicrob. Agents Chemother.* **2002**, *46*, 1080; (d) Halle, E.; Majcher-Peszynska, J.; Drewelow, B. *Chemother. J.* **2002**, *11*, 1; (e) Ford, C. W.; Zurenko, G. E.; Barbachyn, M. R. *Curr. Drug Targets* **2001**, *1*, 181; (f) Brickner, S. *J. Curr. Pharm. Des.* **1996**, *2*, 175; (g) Park, C. H.; Brittelli, D. R.; Wang, C. L. J.; Marsh, F. D.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Siee, A. M.; Forbes, M. *J. Med. Chem.* **1992**, *35*, 1156; (h) Gregory, W. A.; Brittelli, D. R.; Wang, C. L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.
2. (a) Madhusudhan, G.; Reddy, G. O.; Ramanatham, J.; Dubey, P. K. *Indian J. Chem. B* **2005**, *44*, 1236; (b) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963; (c) 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.* **2003**, *7*, 533; (d) Lohray, B. B.; Baskaran, S.; Rao, B. S.; Reddy, B. Y.; Rao, N. *Tetrahedron Lett.* **1999**, *40*, 4855; (e) 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.* **1996**, *39*, 673.
3. (a) List, B.; Seayad, J. *Org. Biomol. Chem.* **2005**, *3*, 719; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (c) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, *37*, 487; (d) List, B.; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 9; (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
4. For a review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.
5. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673.
6. Padwa, P.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Trans, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669.
7. For reviews of the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857; (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
8. Spectral data for diol **7**: $[\alpha]_D^{25}$ −4.0 (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 3.08 (t, $J = 4.66$ Hz, 4H), 3.49–3.61 (m, 2H), 3.65–3.80 (m, 3H), 3.86 (t, $J = 4.83$ Hz, 4H), 5.13 (s, 2H), 6.83–6.96 (m, 3H), 7.25–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 50.58 (d, $J = 3.52$ Hz), 52.89, 63.76, 66.70, 67.53, 69.92, 115.49 (d, $J = 32.71$ Hz), 118.33 (d, $J = 3.86$ Hz), 123.13 (d, $J = 2.92$ Hz), 127.38, 127.87, 128.29, 135.97, 138.69 (d, $J = 8.95$ Hz), 152.33, 156.40, 157.25; IR ($CHCl_3$) ν_{max}: 3433, 3018, 2966, 2862, 2399, 1685, 1514, 1452, 1215, 1117. Elemental analysis: $C_{21}H_{25}FN_2O_5$ requires C, 62.37; H, 6.23; F, 4.70; N, 6.93. Found: C, 62.30; H, 6.28; F, 4.81; N, 6.85.
9. Miyata, O.; Asai, H.; Naito, T. *Synlett* **1999**, *12*, 1915.
10. Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, *10*, 4555.

11. Spectral data for diol **16**: $[\alpha]_D^{25}$ −3.2 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 3.04 (t, $J = 5.12$ Hz, 4H), 3.49–3.61 (m, 2H), 3.67 (t, $J = 5.43$ Hz, 4H), 3.74–3.80 (m, 3H), 5.13 (s, 2H), 5.16 (s, 2H), 6.82–6.96 (m, 3H), 7.21–7.39 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 43.74, 50.15 (d, $J = 2.84$ Hz), 52.97, 63.79, 64.89, 67.18, 67.60, 70.04, 115.52 (d, $J = 21.83$ Hz), 118.87 (d, $J = 3.74$ Hz), 123.09 (d, $J = 3.01$ Hz), 126.79, 127.31, 127.45, 127.80, 127.97, 128.40, 131.89 (d, $J = 9.80$ Hz), 135.98, 136.38, 138.53 (d, $J = 8.45$ Hz), 152.44, 155.10, 156.42, 157.37; IR ($CHCl_3$) ν_{max}: 3410, 3018, 2361, 1685, 1514, 1436, 1215, 758. Elemental analysis: $C_{29}H_{32}FN_3O_6$ requires C, 64.79; H, 6.00; F, 3.53; N, 7.82. Found: C, 64.72; H, 6.07; F, 3.59; N, 7.81.