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A short enantioselective synthesis of the antiepileptic agent, levetiracetam based on proline-catalyzed asymmetric α-aminooxylation

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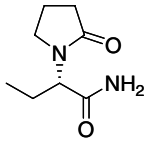
Abstract—An efficient enantioselective synthesis of a new antiepileptic drug, levetiracetam is described, in high optical purity (>99.5% ee), using proline-catalyzed α-aminooxylation of *n*-butyraldehyde as the key step.

Epilepsy is a chronic neurological disorder that consists of repeated occurrences of spontaneous seizures. Levetiracetam, [(*S*)-α-ethyl-2-oxopyrrolidine acetamide, **1**], has recently been approved as an add-on therapy for the treatment of refractory epilepsy.[1] The (*S*)-enantiomer of Etiracetam (levetiracetam), has shown outstanding pharmacokinetic and pharmacological activity which has led to the rapid approval of this antiepileptic drug by the FDA. Levetiracetam offers several advantages over traditional therapy, including twice daily dosing, a wide margin of safety with no requirements for serum drug concentration monitoring, no interactions with other anticonvulsants and has less adverse effects than traditional treatments.[2]

The literature methods for the synthesis of levetiracetam typically involve chiral pool approaches starting from enantiopure α-amino acids,[3] resolution of Etiracetam or advanced racemic intermediates,[3a,4] asymmetric hydrogenation over Rh(I) or Ru(II) complexes,[5] and deracemization of 2-bromobutyric acid using *N*-phenylpantolactam as a chiral auxiliary.[6] As a part of our research program aimed at developing stereocontrolled syntheses of bioactive molecules,[7] we report a highly efficient synthesis of levetiracetam **1** using proline-catalyzed α-aminooxylation[8] of *n*-butyraldehyde as the key step (Scheme 1).

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.[9] In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[10] Proline has also been found to be an excellent asymmetric catalyst for α-functionalization[8] of aldehydes and ketones. We employed proline-catalyzed α-aminooxylation coupled with S_N2 displacement of an *O*-mesyl group with 2-pyrrolidone in achieving the enantioselective synthesis of levetiracetam **1**.



1 Levetiracetam

Our synthesis started with α-aminooxylation[8a] of *n*-butyraldehyde which was carried out using nitrosobenzene and L-proline (25 mol %) at −20 °C to furnish the aminooxy aldehyde which was reduced in situ with sodium borohydride to afford (*R*)-α-aminooxy alcohol **2** in 85% yield; $[\alpha]_D^{25}$ +20.7 (*c* 1, $CHCl_3$), {lit.[8e] $[\alpha]_D^{25}$ +20.5 (*c* 1, $CHCl_3$)}. The protected alcohol **2** was then hydrogenated over Pd/C (10 mol %) to furnish (*R*)-1,2-butanediol **3** in 90% yield. Selective monobenzylation of diol **3** was carried out using Bu_2SnO and benzyl bromide to give **4** in 95% yield; $[\alpha]_D^{25}$ −10 (*c* 1, $CHCl_3$).

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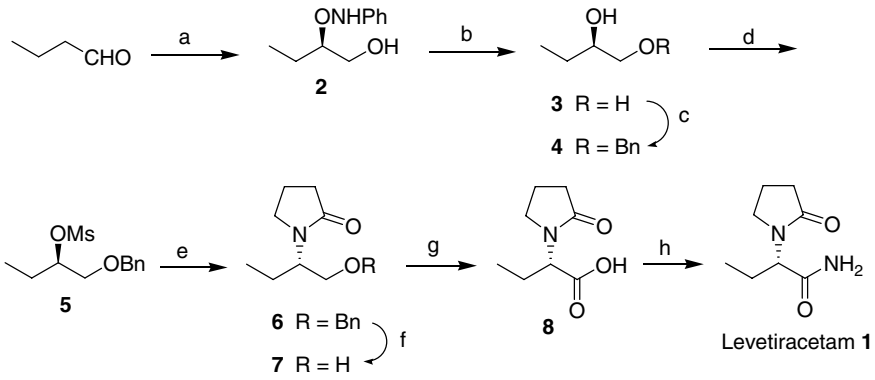

Scheme 1. Reagents and conditions: (a) PhNO, L-proline (25 mol %), −20 °C, 24 h then MeOH, $NaBH_4$, 85%; (b) H_2 (1 atm), Pd/C (10%), MeOH, 12 h, 90%; (c) Bu_2SnO, toluene, reflux, 12 h then Bu_4NBr, BnBr, reflux, 24 h, 95%; (d) MsCl, Et_3N, CH_2Cl_2, 0–25 °C, 4 h, 92%; (e) 2-pyrrolidone, NaH, DMF, 130 °C, 3 h, 62%; (f) H_2 (1 atm), Pd/C (10%), MeOH, 6 h, 97%; (g) TEMPO (7 mol %), NaClO–$NaClO_2$, acetonitrile, phosphate buffer (pH 6.8), 25 °C, 6 h, 90%; (h) $ClCO_2Et$, Et_3N, THF, 0 °C, 30 min then NH_4OH, 16 h, 75%, 99.5% ee.

Unfortunately, direct displacement of the secondary hydroxyl group in **4** with 2-pyrrolidone under Mitsunobu conditions was unsuccessful. Hence, alcohol **4** was treated with methanesulfonyl chloride and triethylamine to give mesylate **5** in 92% yield. Nucleophilic displacement of mesylate **5** with 2-pyrrolidone in dry DMF at 130 °C proceeded smoothly to give the benzyl ether (*S*)-**6**[11] in 62% yield. Debenzylation of **6** was carried out by catalytic hydrogenation over Pd/C (10 mol %) followed by oxidation of the resulting alcohol **7** with sodium hypochlorite–sodium chlorite in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[12] in acetonitrile–phosphate buffer (pH 6.8) to afford the corresponding acid **8** in 88% overall yield. Acid **8**, on treatment with ethyl chloroformate and ammonium hydroxide,[3a] produced levetiracetam[13] **1** in 82% yield (75% after recrystallization from acetone) and >99.5% ee (determined by chiral HPLC analysis of the recrystallized sample).[14]

In conclusion, a practical and short enantioselective synthesis of levetiracetam, **1**, has been achieved successfully by employing a proline-catalyzed α-aminooxylation strategy. The reactions are rapid and require a relatively low amount of the inexpensive and nontoxic proline as a catalyst which is available in both enantiomeric forms. The merit of the synthesis is that levetiracetam has been obtained with high enantioselectivity (>99.5% ee) and in a good overall yield (29.7%).

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11. Spectral data for **6**: $[\alpha]_D^{25}$ −35.0 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.4$ Hz, 3H), 1.46–1.63 (m, 2H), 1.93–2.05 (m, 2H), 2.38 (t, $J = 8.4$ Hz, 2H), 3.27–

3.38 (m, 2H), 3.47–3.51 (m, 2H), 4.19 (m, 1H), 4.43 (dd, $J = 12.2$, 15.1 Hz, 2H), 7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.42, 18.11, 21.26, 30.92, 43.04, 51.79, 70.15, 72.41, 127.19, 127.96, 137.88, 174.58. Elemental Analysis: $C_{15}H_{21}NO_2$ requires C, 72.84; H, 8.56; N, 5.66. Found: C, 72.88; H, 8.55; N, 5.63.

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13. Spectral data for levetiracetam: mp 116 °C, {lit.[3a] mp 117 °C}; $[\alpha]_D^{25}$ −90.3 (*c* 1, acetone) {lit.[3a] $[\alpha]_D^{25}$ −90.0 (*c* 1, acetone)}; IR ($CHCl_3$) ν_{max}: 3672, 3332, 3009, 2463, 1668, 1422, 1288, 1043, 754 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, $J = 7.5$ Hz, 3H), 1.60–1.75 (m, 1H), 1.90–2.09 (m, 3H), 2.38–2.47 (m, 2H), 3.34–3.55 (m, 2H), 4.42–4.50 (dd, $J = 6.7$, 8.6 Hz, 1H), 5.76 (br s, 1H), 6.52 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.27, 17.89, 21.09, 30.81, 43.57, 55.71, 172.59, 175.75. Elemental analysis: $C_8H_{14}N_2O_2$ requires C, 56.45; H, 8.29; N, 16.46. Found: C, 56.49; H, 8.34; N, 16.44.
14. HPLC conditions: Chiral OD-H column; hexane: *i*-PrOH (90:10 v/v); flow rate 1.0 mL/min; UV – 210 nm; column temperature 25 °C; retention time: 10.3 min (*R*-isomer) and 16.3 min (*S*-isomer). Compared with reported conditions: Rao, B. M.; Ravi, R.; Reddy, B. S.; Sivakumar, S.; Gopi Chand, I.; Praveen Kumar, K.; Acharyulu, P. V. R.; Om Reddy, G.; Srinivasu, M. K. *J. Pharm. Biomed. Anal.* **2004**, *35*, 1017.