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An alternate synthesis of enantiomerically pure levetiracetam (*Keppra*®)

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ABSTRACT

A simple and efficient synthesis of levetiracetam has been achieved with high enantiopurity (>99%) starting from commercially available benzyl glycidyl ether. The method is amenable for industrial scale-up.

1. Introduction

Enantioselectivity plays an important role in the design and development of many drugs, especially in the development of antiepileptic drugs (AEDs). Hence, the selective synthesis of individual enantiomers of targets is extremely important because the antipodes often display different pharmacological and physiological properties.[1] γ-Butyrolactam based analogues are an important structural class as they find prevalent use in treating epilepsy and brain related disorders (Fig. 1).[2] Among these substances, levetiracetam **1** [(*S*)-α-ethyl-2-oxo-pyrrolidine acetamide, *Keppra*®][3] is a novel antiepileptic drug with a unique antiepileptic mechanism of action related to an interaction with the synaptic vesicle protein 2A (SV2A).[4] The beneficial effects of levetiracetam **1** in patients with bipolar disorders, migraines, chronic or neuropathic pain, and diabetic complications are also reported.[5] As a result, it has attracted a great deal of attention from synthetic chemists and different methods for the preparation of levetiracetam have been extensively investigated. Generally, the reported methods for the preparation involve classical resolution processes[6] and asymmetric syntheses[7] and some of these methods have their own intrinsic disadvantages such as expensive chiral starting materials and catalysts; problems associated with the installation of the 2-pyrrolidone moiety with harsh reaction conditions which often leads to a loss of enantiomeric purity, usage of hazardous alkylating agents, tedious and time consuming experiments, and so on. Hence, to overcome these disadvantages, development of newer methods in the preparation of levetiracetam is highly desirable.

Epoxides constitute one of the most widely used functional groups in organic transformations and serve as important building blocks in the industrial production of a wide variety of organic materials.[8] Over the past few years, investigations in our laboratory have demonstrated the potential utility of these epoxides for the synthesis of many pharmaceutically important compounds.[9]

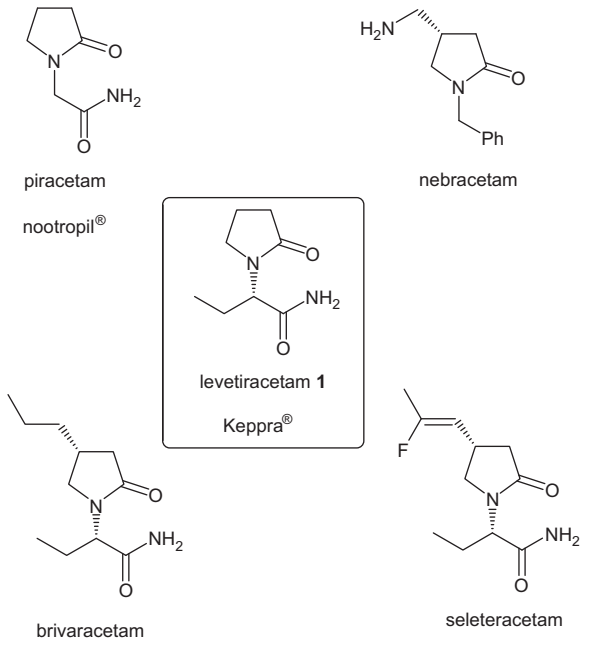

Figure 1. Examples of γ-butyrolactam based drugs used in epilepsy and related disorders.

Herein we report a concise and simple synthesis of levetiracetam **1** starting from commercially available benzyl glycidyl ether, thereby devising a new approach that would enable the synthesis of other γ-butyrolactam related antiepileptic drugs in high enantiomeric purity.

2. Results and discussion

A retrosynthetic analysis of levetiracetam is outlined in Scheme 1. As shown in Scheme 1, we envisaged that the secondary alcohol (*R*)-**4** would be an ideal key intermediate for the synthesis

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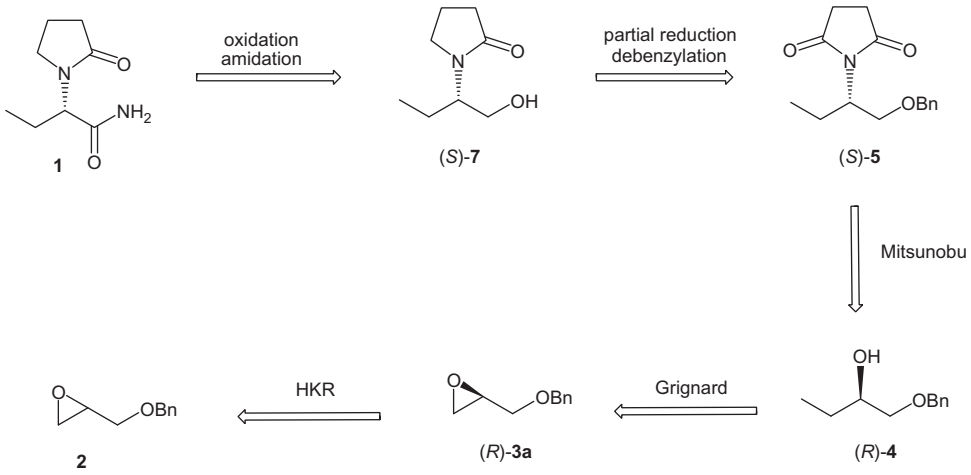
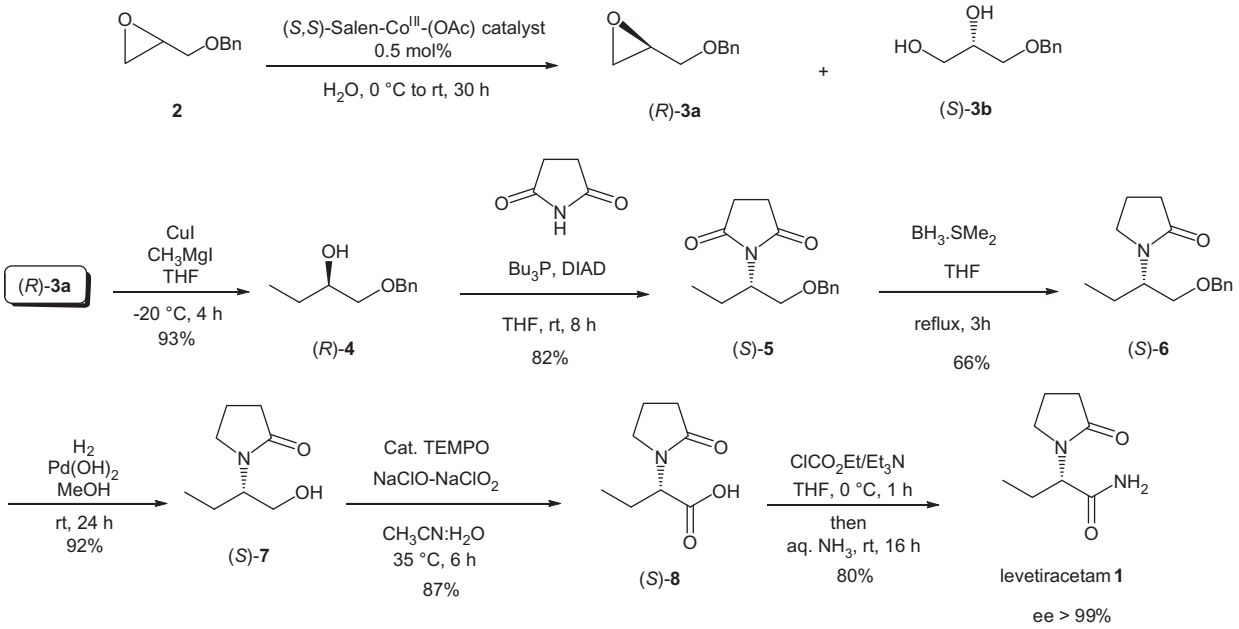


Scheme 1. Retrosynthetic analysis of levetiracetam **1**.

of levetiracetam **1**, which can be obtained easily from (*R*)-benzyl glycidyl ether (*R*)-**3a** by a Grignard reaction. The key intermediate (*R*)-**4** can be elaborated to the advanced amide precursor (*S*)-**7** by a Mitsunobu reaction followed by partial reduction protocols. The intermediate (*S*)-**7** can be transformed into the target molecule **1** by simple oxidation and amidation reactions.

Accordingly, our synthesis began with the commercially available *rac*-benzyl glycidyl ether **2**, which was subjected to hydrolytic kinetic resolution conditions to give enantiomerically pure epoxide (*R*)-**3a** from the racemic mixture in 48% yield and >99% ee {$[\alpha]_D^{25} = -7.9$ (*c* 0.4, EtOH); lit.[10] $[\alpha]_D = -5.8$ (*c* 0.4, EtOH)} along with its diol (*S*)-**3b** in 43% yield (Scheme 2). Next, the regioselective ring opening of (*R*)-epoxide (*R*)-**3a** was carried out with MeMgI and a catalytic amount of CuI in anhydrous THF at −20 °C to provide secondary alcohol (*R*)-**4** in 93% yield. Installation of the 2-pyrrolidone moiety onto secondary alcohol (*R*)-**4** was carried out by using a two step sequence via a Mitsunobu reaction followed by a partial reduction. Accordingly, the secondary alcohol (*R*)-**4** was readily transformed into succinimido ether (*S*)-**5** by stereospecific substitution of the hydroxyl group with succinimide using Bu_3P and DIAD in THF under Mitsunobu conditions. We observed that the yield of the compound (*S*)-**5** was very low when Ph_3P was used as a reagent. Several reaction conditions were tried for the mono reduction of succinimido ether (*S*)-**5** to obtain the compound (*S*)-**6.** The mono reduction of succinimido ether (*S*)-**5** employing a slow addition of 1 equiv of BH_3–DMS complex in anhydrous THF, conditions recently reported by Ortiz-Marciales et al.,[11] worked well and afforded the compound (*S*)-**6** in 66% yield.

It is noteworthy that installation of the 2-pyrrolidone moiety employing a Mitsunobu reaction followed by mono reduction using BH_3–DMS is a straightforward and mild protocol when compared to the harsh reaction conditions reported earlier. Compound (*S*)-**6** was next subjected to $Pd(OH)_2$ catalyzed hydrogenolysis, followed by oxidation with sodium chlorite catalyzed by TEMPO and bleach in an acetonitrile-phosphate buffer (pH 6.8) and afforded acid (*S*)-**8** in 80% yield (two steps). Finally, acid (*S*)-**8** was transformed into the corresponding amide by consecutive reactions with ethyl chloroformate and aq ammonia to give levetiracetam



Scheme 2. Synthesis of levetiracetam **1**.

1 in excellent enantioselectivity (>99% ee) without any additional crystallization (which is often required to obtain high enantiopurity in many reported methods) {$[\alpha]_D^{25} = -91.5$ (*c* 1, acetone) {lit.[6f] $[\alpha]_D^{25} = -90.5$ (*c* 0.99, acetone)}. The structure of levetiracetam **1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic analysis. The enantiomeric purity of levetiracetam **1** was determined by chiral HPLC analysis.

3. Conclusion

In conclusion, we have developed a concise and efficient new route for the synthesis of the antiepileptic drug levetiracetam, starting from readily available benzyl glycidyl ether. High enantiopurity (>99%) has been achieved without recrystallization of the final product. In addition, the required 2-pyrrolidone moiety was introduced conveniently via Mitsunobu and mono-reduction protocols. We envisage that this simple protocol may find application in the pharmaceutical industry for the large scale production of levetiracetum and that the strategy could be exploited further for the preparation of other pharmaceutically important γ-butyrolactam analogues.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures prior to use. IR spectra were obtained from Perkin–Elmer Spectrum one spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 NMR spectrometer. Spectra were obtained in $CDCl_3$. Monitoring of reactions was carried out using TLC plates Merck Silica Gel 60 F254, and visualization with UV light (254 and 365 nm), I_2, and anisaldehyde in ethanol as development reagents. Optical rotations were measured with a JASCO P 1020 digital polarimeter. LC-ESI-MS data were obtained by injecting the sample in Waters aquity ultra performance LC system equipped with a PDA and SQ detector. The enantiomeric excess was determined by chiral HPLC.

4.1.1. (*R*)-2-(Benzyloxymethyl) oxirane (*R*)-3a

A mixture of 2-(benzyloxymethyl)-oxirane **2** (10.00 g, 61 mmol) and (*S,S*)-salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) was vigorously stirred for 15 min, then cooled to 0 °C, and water added (0.6 mL, 34 mmol) over a period of 15 min through a micro-syringe. The reaction mixture was stirred at room temperature for 20 h, and then additional (*S,S*)-salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) was added and stirring was continued for an additional 10 h. The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/acetone (95:5). The less polar epoxide (*R*)-**3a** eluted first as a colorless oil (4.8 g, 48%), $[\alpha]_D^{25} = -7.9$ (*c* 0.4, EtOH) {lit.[10] $[\alpha]_D^{20} = -5.8$ (*c* 0.4, EtOH)}; ee > 99% [chiral HPLC analysis; CHIRALCEL OD-H (250 × 4.6 mm) column; eluent: *n*-hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector: 220 nm [(*S*)-isomer t_R = 15.25 min; (*R*)-isomer t_R = 16.46 min]; IR ($CHCl_3$): ν_{max} 3418, 3020, 2401, 1719, 1603, 1523, 1495, 1421, 1216, 1094, 929, 669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 2.60–2.64 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.78–2.82 (dd, *J* = 5.3, 4.2 Hz, 1H), 3.15–3.23 (m, 1H), 3.39–3.48 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.73–3.81 (dd, *J* = 11.4, 3.0 Hz, 1H), 4.60 (s, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 137.8 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.3 (CH_2), 70.7 (CH_2), 50.8 (CH), 44.2 (CH_2). MS: *m/z* 187 [M+Na]$^+$, followed by diol (*R*)-**3b** as a colorless oil (4.7 g, 43%); $[\alpha]_D^{25} = -2.3$ (*c* 6.5, $CHCl_3$) {lit.[12] $[\alpha]_D^{25} = -3.6$ (*c* 6.6, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3434, 3020, 1600, 1495, 1215, 1045, 1029, 929, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 2.73 (t, *J* = 5.8 Hz, 1H, OH), 3.13 (d, *J* = 5 Hz, 1H, OH), 3.51–3.54 (dd, *J* = 5.4, 2.6 Hz, 2H), 3.57–3.68 (m, 2H), 3.82–3.92 (m, 1H), 4.54 (s, 2H), 7.28–7.39 (m, 5H, Ph); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C = 137.6 (C), 128.4 (CH, 2 carbons), 127.8 (CH, 3 carbons), 73.5 (CH_2), 71.6 (CH_2), 70.7 (CH), 63.9 (CH_2).

4.1.2. (*R*)-1-(Benzyloxy)butan-2-ol (*R*)-4

To a pre-cooled (−20 °C) solution of epoxide (*R*)-**3a** (4.50 g, 27.4 mmol) and CuI (0.1 g) in dry THF (30 mL) was added dropwise methyl magnesium iodide (7.5 mL, 54.8 mmol) in diethyl ether for approximately 1 h. The reaction mixture was then allowed to return to ambient temperature and stirring continued for an additional 4 h. After completion of the reaction (as indicated by TLC), aqueous NH_4Cl was added, after which the reaction mixture was filtered, and washed with ethylacetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/acetone, 93:7) to yield (*R*)-**4** as a colorless oil. (4.6 g; 93%); $[\alpha]_D^{25} = -9.5$ (*c* 0.8, $CHCl_3$) {lit.[7c] $[\alpha]_D^{25} = -10.0$ (*c* 1, $CHCl_3$)}; IR ($CHCl_3$): 3435, 3020, 1601, 1422, 1118 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 0.96 (t, *J* = 7.4 Hz, 3H), 1.42–1.56 (m, 2H), 2.35 (d, *J* = 3.4 Hz, 1H), 3.28–3.38 (m, 1H), 3.49–3.60 (m, 1H), 3.68–3.81 (m, 1H), 4.56 (s, 2H), 7.31–7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 138.0 (C), 128.5 (CH, 2 carbons), 127.9 (CH), 127.8 (CH, 2 carbons), 73.5 (CH), 72.6 (CH_2), 69.9 (CH_2), 26.1 (CH_2), 9.3 (CH_3); MS: *m/z* 180 [M]$^+$.

4.1.3. (*S*)-1-(1-(Benzyloxy)butan-2-yl)pyrrolidine-2,5-dione (*S*)-5

A solution of DIAD (5.3 mL, 26.6 mmol) in dry THF (5 mL) was added dropwise to a solution of (*R*)-**4** (4.00 g, 22.2 mmol), succinimide (2.64 g, 26.6 mmol) and tributylphosphine (50% ethyl acetate solution; 19.1 mL, 53.2 mmol) in dry THF (50 mL) under an N_2 atmosphere at 0 °C. The reaction mixture was stirred at ambient temperature for 8 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 80:20) to yield (*S*)-**5** as a colorless oil. (4.8 g; 82%); $[\alpha]_D^{25} = +31.5$ (*c* 3.1, $CHCl_3$); IR ($CHCl_3$): 3458, 3020, 2970, 2938, 2877, 1773, 1699, 1496, 1455, 1377, 1296, 1216, 1199, 1124, 1028, 952, 907, 820; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 0.85 (t, *J* = 7.4 Hz, 3H), 1.60–1.99 (m, 2H), 2.65 (s, 4H), 3.55–3.63 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.98 (apparent t, *J* = 9.8 Hz, 1H), 4.25–4.37 (m, 1H), 4.41–4.51 (m, 2H), 7.23–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 177.7 (CO, 2 carbons), 138.0 (C), 128.3 (CH, 2 carbons), 127.6 (CH), 127.5 (CH, 2 carbons), 72.6 (CH_2), 68.7 (CH_2), 53.4 (CH), 27.9 (CH_2, 2 carbons), 21.1(CH_2), 10.7 (CH_3); MS: *m/z* 284 [M+Na]$^+$.

4.1.4. (*S*)-1-(1-(Benzyloxy)butan-2-yl)pyrrolidin-2-one (*S*)-6

To a solution of compound (*S*)-**5** (4.00 g, 15.3 mmol) in dry THF (20 mL) at 0 °C was added dropwise the BH_3–DMS complex (1.4 mL, 15.3 mmol) under an N_2 atmosphere. Next, the reaction mixture was refluxed for 3 h. After completion of the reaction, methanol (5 mL) was added carefully at 0 °C and the mixture was then stirred for 20 min. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (40 mL). After aqueous work-up the residue was purified by column chromatography (silica gel, petroleum ether/acetone, 70:30) to yield (*S*)-**6** as a colorless oil. (2.5 g; 66%); $[\alpha]_D^{25} = -30.5$ (*c* 1, $CHCl_3$) {lit.[7c] $[\alpha]_D^{25} = -35.0$ (*c* 1, $CHCl_3$)}; IR ($CHCl_3$): 3421, 3019, 1670, 1461, 1425, 1288, 1216, 1093, 928 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 7.5 Hz, 3H), 1.43–1.64 (m, 2H), 1.90–2.05 (m, 2H), 2.41 (apparent t, *J* = 8 Hz 2H), 3.23–3.39 (m, 2H), 3.44–3.58 (m, 2H), 4.17–4.30 (m, 1H), 4.40–4.50 (m, 2H),

7.24–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 175.5 (CO), 138.2 (C), 128.3 (CH, 2 carbons), 127.6 (CH, 3 carbons), 72.7 (CH_2), 70.4 (CH_2), 52.1 (CH), 43.3 (CH_2), 31.4 (CH_2), 21.5 (CH_2), 18.3 (CH_2), 10.6 (CH_3); MS: *m/z* 270 $[M+Na]^+$.

4.1.5. (*S*)-1-(1-Hydroxybutan-2-yl)pyrrolidin-2-one (*S*)-7

To a solution of (*S*)-**6** (2.00 g, 8.1 mmol) in methanol (10 mL) was added palladium hydroxide (0.2 g, 10–20 wt %) and the reaction mixture was stirred under hydrogen (60 psi) for 24 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of Celite and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, ethylacetate/methanol, 95:5) to yield (*S*)-**7** as a colorless oil. (1.2 g; 92%); $[\alpha]_D^{25} = -20.1$ (*c* 1.1, $CHCl_3$) {lit.[7b] $[\alpha]_D^{25} = -11.8$ (*c* 0.9, $CHCl_3$)} IR ($CHCl_3$): 3434, 3019, 1661, 1524, 1474, 1424, 1215, 1045, 928 cm^{-1}; ^{1}H NMR (200 MHz, $CDCL_3$): δ_H = 0.87 (t, *J* = 7.4 Hz, 3H), 1.36–1.62 (m, 2H), 1.93–2.1 (m, 2H), 2.39–2.47 (m, 2H), 3.24–3.50 (m, 2H), 3.54–3.72 (m, 3H), 3.87–4.01 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 176.8 (CO), 62.8 (CH_2), 55.8 (CH), 43.7 (CH_2), 31.5 (CH_2), 21.1 (CH_2), 18.2 (CH_2), 10.6 (CH_3); MS: *m/z* 157 $[M]^+$, 158 $[M+1]^+$, 180 $[M+Na]^+$.

4.1.6. (*S*)-2-(2-Oxopyrrolidin-1-yl)butanoic acid (*S*)-8

A mixture of (*S*)-**7** (1.00 g, 6.3 mmol), TEMPO (0.04 g, 0.31 mmol), acetonitrile (20 mL), and sodium phosphate buffer (9 mL, 0.67 M, pH 6.7) was heated to 35 °C. Sodium chlorite (0.6 g dissolved in 2 mL water, 6.4 mmol) and dilute bleach (4–6%, 2 mL diluted in 4 mL water) were then added simultaneously over 1 h. The reaction mixture was stirred at 35 °C until the reaction was complete (6 h, TLC), then cooled to room temperature. Water (20 mL) was added and the pH was adjusted to 8 with 2 M NaOH. The reaction was quenched by pouring into an ice cold Na_2SO_3 solution maintained at <20 °C. After stirring for 30 min at room temperature, ethyl acetate (20 mL) was added and continued the stirring for an additional 15 min. The organic layer was separated and discarded. More ethyl acetate (20 mL) was added, and the aqueous layer was acidified with 2 M HCl to pH 3–4. The organic layer was separated, washed with water (2 × 15 mL), brine (20 mL), and concentrated under reduced pressure to afford the carboxylic acid (*S*)-**8** (0.94 g, 87%); $[\alpha]_D^{25} = -27.1$ (*c* 1.1, $CHCl_3$) {lit.[7a] $[\alpha]_D^{25} = -23.6$ (*c* 0.97, $CHCl_3$)}; IR ($CHCl_3$): 3444, 3020, 1646, 1422, 1215, 1122, 1043, 929, 759 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 0.94 (t, *J* = 7.3 Hz, 3H), 1.64–1.81 (m, 2H), 2.01–2.18 (m, 2H), 2.50 (t, *J* = 7.7 Hz, 2H), 3.31–3.42 (m, 1H), 3.50–3.62 (m, 1H), 4.61–4.69 (dd, *J* = 10.7, 5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 177.1 (CO), 174.4 (CO), 55.5 (CH), 43.9 (CH_2), 30.8 (CH_2), 21.9 (CH_2), 18.2 (CH_2), 10.8 (CH_3); MS: *m/z* 171 $[M]^+$, 194 $[M+Na]^+$.

4.1.7. (*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide (levetiracetam) 1

To a solution of acid (*S*)-**8** (0.70 g, 4.1 mmol) and triethylamine (0.7 mL, 4.9 mmol) in dry THF (10 mL) was added ethyl chloroformate (0.4 mL, 4.5 mmol) at 0 °C under an argon atmosphere. After 1 h, ammonium hydroxide (25% w/v aqueous solution, 2.8 mL, 20.4 mmol) was added and the mixture was stirred at ambient temperature for another 16 h. After completion of the reaction, potassium carbonate (0.8 g, 6 mmol) was added and the reaction mixture was filtered, and washed with ethyl acetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, dichloromethane/methanol, 95:5) to yield **1** as a pale yellow solid (0.56 g, 80%); ee >99% [The ee was determined by chiral HPLC analysis: DAICEL CHIRALCEL OD-H (250 × 4.6 mm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector 210 nm [(*R*) isomer t_R = 33.30 min; (*S*) isomer t_R = 46.71 min]; mp = 116–17 °C {lit.[6f] mp = 115–117 °C}; $[\alpha]_D^{25} = -91.5$ (*c* 1, acetone) {lit.[6f] $[\alpha]_D^{25} = -90.5$ (*c* 0.99, acetone)}; IR ($CHCl_3$): 3409, 3019, 1670, 1523, 1422, 1215, 1045, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 0.90 (t, *J* = 7.4 Hz, 3H), 1.60–1.79 (m, 1H), 1.85–2.14 (m, 3H), 2.38–2.47 (m, 2H), 3.33–3.52 (m, 2H), 4.42–4.50 (dd, *J* = 8.9, 6.7 Hz, 1H), 5.77 (br s, 1H), 6.47 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 176.0 (CO), 172.5 (CO), 55.9 (CH), 43.7 (CH_2), 30.9 (CH_2), 21.1 (CH_2), 18.0 (CH_2), 10.4 (CH_3); MS: *m/z* 171 $[M+1]^+$, 193 $[M+Na]^+$.

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