Research Article

Enantioselective Synthesis of Antiepileptic Agent, (–)-Levetiracetam, through Evans Asymmetric Strategy

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A practical and efficient enantioselective synthesis of antiepileptic drug, (–)-Levetiracetam, has been described in five steps (33.0% overall yield) and high optical purity (99.0% *ee*), using Evans asymmetric strategy for α -alkylation of carbonyl functionality as the key step. The simplicity of the experimental procedures and high stereochemical outcome make this method synthetically attractive for preparing the target compound on multigram scales.

1. Introduction

Epilepsy is a chronic neurological disorder that consists of repeated occurrences of spontaneous seizures. Levetiracetam, [(S)- α -ethyl-2-oxopyrrolidine acetamide], (Figure 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 remarkable pharmacokinetic and pharmacological activity which has led to the quick 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 and no interactions with other anticonvulsants, and less adverse effects than traditional treatments [2–4].

Reported methods for the synthesis of levetiracetam typically involve chiral pool approaches starting from relevant enantiopure α -amino acids [5–8], resolution of etiracetam or advanced racemic intermediates [5–10], asymmetric hydrogenation over Rh(I) or Ru(II) complexes [11, 12], and deracemization of 2-bromobutyric acid using *N*-phenyl

pantolactam as a chiral auxiliary [13], proline catalyzed asymmetric α -aminooxylation [14].

The synthesis of **1** has been previously reported by S. P. Kotkar, A. Sudalai using proline-catalyzed α -aminooxylation of *n*-butyraldehyde in eight steps and 29.7% overall yield⁷ and to the best of our knowledge Evans type chiral auxiliary directed entioselective synthesis of (–)-Levetiracetam has not yet been reported. Chiral auxiliary derived asymmetric α -alkylation reactions have been identified as general method for asymmetric carbon-carbon bond formation [15, 16]. In this connection, Evans asymmetric strategy is the most powerful synthetic method that has been widely employed in natural product synthesis [17–23]. Moreover, the Evans type auxiliaries are inexpensive, nontoxic, available in both enantiomeric forms, and already explored for large scale synthesis of pharmaceutical important molecule like “Ezetimibe” (marketed as *Zetia* or *Ezetrol*) [24] antihyper lipidemic drug and “Tapentadol” (trade name *Nucynta*, in India *Zyntap*) is a centrally acting analgesic [25], and so forth.

In this paper, we report a practical and efficient enantioselective synthesis of levetiracetam, **1**, in five steps with good overall yield using Evans type asymmetric α -alkylation of

Levetiracetam, **1**

FIGURE 1

FIGURE 2: Retrosynthetic analysis of (-)-levetiracetam, **1**.

compound **4**. The retrosynthetic analysis of **1** is shown in (Figure 2).

2. Experimental Section

All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried at 200°C, flame-dried, and flushed with dry nitrogen prior to use. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. TLC was performed on Kieselgel 60 F254 silica-coated aluminium plates (Merck) and visualized by UV light ($\lambda = 254$ nm) or by spraying with a solution of KMnO_4 . Organic extracts were dried over anhydrous Na_2SO_4 . Flash chromatography was performed using Kieselgel 60 brand silica gel (230–400 mesh). The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury plus Spectrometer at 300 MHz (^1H) and at 75 MHz (^{13}C). Chemical shifts were given in ppm relative to trimethylsilane (TMS). Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) technique.

2.1. Preparation of (S)-3-(2-Chloroacetyl)-4-phenyloxazolidin-2-one (3). A solution of chloroacetyl chloride (9.76 mL, 0.122 mol) in DCM (100.0 mL) was added dropwise to a solution of (S)-4-phenyloxazolidin-2-one, **2** (10.0 g, 0.61 mol), Et_3N (35.0 mL, 0.244 mol) and DMAP (9.5 g, 4.0 mol) in DCM (150.0 mL) while maintaining temperature at 0–5°C. After 30 min additional chloroacetyl chloride was added (0.2 eq), and the mixture was gradually allowed to warm up to

room temperature. After mixture was vigorously stirred for 1 h, silica gel (20.0 g) was added and the reaction mixture was concentrated in vacuo. The resultant product was loaded on to a silica gel flash column. Elution with EtOAc /hexane (1 : 4) gave (S)-**3** (10.26 g, 70%) as white solid. Mp: 108–110°C. $[\alpha]_D^{25} = -78.5$ [c 1.0, CHCl_3].

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.32–7.46 (m, 5H), 5.45 (dd, $J = 3.9, 8.7$ Hz, 1H), 4.68–4.78 (m, $J = 12.4$ Hz, 3H), 4.38 (dd, $J = 3.9, 9.1$ Hz, 1H); IR (CHCl_3) ν_{max} : 1801, 1717, 695 cm^{-1} ; ESI-MS: m/z 239.1 [$\text{M}^+ + 1$].

2.2. Preparation of (S)-3-(2-(2-Oxopyrrolidin-1-yl)acetyl)-4-phenyloxazolidin-2-one (4). Sodium hydride (60% dispersion in oil, 5.4 g, 0.135 mol) was added in small portions to a solution of 2-pyrrolidone (10.6 g, 0.124 mol) in DMF (200.0 mL) at room temperature and the mixture was stirred for 30 min. To this mixture was added **3** (25.0 g, 0.104 mol), and the mixture was further stirred for another 30 min. The reaction mixture was poured onto ice/water (200.0 mL) and extracted with methylene dichloride (200.0 mL). The extract was washed with brine, dried, and evaporated to dryness. The residue was subjected to silica gel column chromatography (eluent: AcOEt /hexane 1 : 2) gave **4** (27.0 g, 90%) as colorless solid. Mp: 173–175°C. $[\alpha]_D^{20} = -60.7$ [c = 1.0, MeOH].

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.20–7.50 (m, 5H), 5.40 (t, 1H), 4.70 (dd, $J = 8.4, 2.8$ Hz, 1H), 4.50 (dd, $J = 17.0, 1.4$ Hz, 1H), 4.25 (dd, $J = 10.4, 1.4$ Hz, 1H), 3.40 (t, 2H), 2.25 (t, 2H), 2.00 (m, 2H); IR (CHCl_3) ν_{max} : 2978, 1779, 1683, 1071 cm^{-1} ; ESI-MS: m/z 289.1 [$\text{M}^+ + 1$]. Anal. calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$: C, 62.49; H, 5.59; N, 9.72; O, 22.20. Found: C, 62.85; H, 5.72; N, 9.98; O, 22.65.

2.3. 4(S)-3-((S)-2-(2-Oxopyrrolidin-1-yl)butanoyl)-4-phenyloxazolidin-2-one (5). A cooled (–78°C) solution of (5.0 g, 0.017 mol) of **4** in 50.0 mL of dry tetrahydrofuran was added to a precooled (–78°C) solution of (26.0 mL, 0.026 mol) of 1 M sodium bis(trimethylsilyl)amide in toluene diluted with 60.0 mL of dry THF, keeping the temperature below –60°C. After 30 min at –78°C, a precooled solution of (3.24 g, 0.020 mol) of ethyl iodide in 40.0 mL of dry THF was added. After 2 h at –75°C, 5.0 mL of glacial acetic acid was added and the mixture warmed immediately to 30°C for 1 h. The solution was partitioned between methylene dichloride (200.0 mL) and dilute brine (100.0 mL). The aqueous phase was extracted with three 75.0 mL portions of methylene chloride. Combined organic extracts were washed with saturated NaHCO_3 (100.0 mL) and dried (MgSO_4), and concentrated. Chromatography on silica gel with 1 : 9 (ethyl acetate: methylene chloride) gave **5** (4.4 g, 81%) of product as a white solid. Mp: 121–123°C. $[\alpha]_D^{20} = -87$ [c 1.0, CHCl_3].

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.32–7.41 (m, 3H), 7.26–7.28 (m, 2H), 5.63 (m, 1H), 5.40 (m, 1H), 4.73 (t, 1H), 4.25 (m, 1H), 3.66 (m, 1H), 3.33 (m, 1H), 2.46–2.32 (m, 2H), 2.10–1.95 (m, 3H), 1.67–1.55 (m, 1H), 0.98 (t, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 176.1, 171.79, 153.0, 138.9, 129.1, 128.6, 125.5, 70.2, 57.3, 55.1, 44.4, 30.8, 22.3, 18.5, 11.0 ppm; IR (KBr) ν_{max} : 2978, 1779, 1683, 1226 cm^{-1} ; ESI-MS: m/z

SCHEME 1: Synthesis of (-)-Levetiracetam, 1.

317.2 $[M^+ + 1]$. *Anal. calcd.* for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86; O, 20.23. *Found*: C, 64.96; H, 6.68; N, 8.97; O, 20.72.

2.4. Preparation of (S)-2-(2-Oxopyrrolidin-1-yl)butanoic Acid (6). To a cold (0°C) solution of **5** (5.0 g, 0.015 mol) in THF (30.0 mL), 30% w/v H_2O_2 (8.5 mL, 0.074 mol), and LiOH/ H_2O (1.13 g, 0.047 mol) were added sequentially and the mixture was stirred at this temperature for 7 h. A solution of Na_2SO_3 (75.0 mL) was added, the final pH being about 9. This mixture was extracted with Methylene dichloride (150 mL), was then it discarded and the aqueous phase was made acidic (pH = 2-3) with 1 M HCl and subsequently extracted with AcOEt (150 mL). The combined AcOEt organic extracts were dried over Na_2SO_4 and concentrated in vacuo. to give (S)-**6** (2.3 g, 85%) as a white solid. Mp: $124\text{--}125^\circ\text{C}$. $[\alpha]_D^{25} = -24.3$ [c 1.0, acetone].

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 4.64 (dd, $J = 10.6, 4.8$ Hz, 1H), 3.52–3.58 (m, 1H), 3.37 (m, $J = 8.7, 5.8$ Hz, 1H), 2.49 (t, $J = 7.7$ Hz, 2H), 1.99–2.13 (m, 3H), 1.67–1.76 (m, 1H), 0.93 (t, $J = 7.7$ Hz, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 177.1, 173.7, 55.4, 43.8, 30.7, 21.8, 18.1, 10.7 ppm; IR (CHCl_3) ν_{max} : 2975, 2358, 1731, 1620 cm^{-1} ; ESI-MS: m/z 170.0 $[M^- + 1]$.

2.5. Preparation of (S)-2-(2-Oxopyrrolidin-1-yl)butanemide (1, Levetiracetam). To a cold (0°C) solution of acid (S)-**6** (5.0 g, 0.292 mol) and Et_3N (4.3 mL, 0.307 mol) in anhydrous THF (20 mL) was added ethylchloroformate (2.9 mL, 0.304 mol) and the mixture stirred at 0°C for 30 min. Ammonium hydroxide (25% w/v aqueous solution, 19.0 mL) was added and the reaction mixture was left to stir at room temperature for 12 h. After the addition of K_2CO_3 (4.14 g, 30.0 mol), the mixture was filtered and the volatile materials (solvent and Et_3N) distilled off in vacuo. The solid residue was extracted with methylene dichloride (150 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated

in vacuo recrystallization from acetone (100.0 mL) gave **1** (4.3 g, 86%) a white solid. Mp: $113\text{--}114^\circ\text{C}$. $[\alpha]_D^{25} = -95.0$ [c = 1.0, acetone].

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 6.50 (br s, 1H), 5.70 (br s, 1H), 4.50 (t, $J = 8.7, 6.8$ Hz, 1H), 3.48 (m, 2H), 2.50 (m, 2H), 1.98–2.20 (m, 3H), 1.70 (m, 1H), 0.98 (t, $J = 7.7$ Hz, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 175.9, 172.7, 55.9, 43.7, 31.0, 21.2, 18.0, 10.4 ppm; IR (CHCl_3) ν_{max} : 3200, 1731, 1620 cm^{-1} ; ESI-MS: m/z 171.0 $[M^+ + 1]$. *Anal. calcd.* for $\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2$: C, 56.45; H, 8.29; N, 16.46; O, 18.80. *Found*: C, 56.76; H, 8.52; N, 16.87; O, 19.26. Chiral HPLC purity 99% ee. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material and 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 ; CHIRAL HPLC purity: $t_r = 14.4$ min (S)-isomer (major enantiomer) and 9.3 min (R)-isomer (minor enantiomer).

3. Results and Discussion

As shown in (Scheme 1), the synthesis of (-)-levetiracetam, **1**, was started from acylation of Evans type auxiliary (S)-4-phenyloxazolidin-2-one, **2**, with chloroacetyl chloride in the presence of Et_3N in methylene chloride using DMAP to afford (S)-3-(2-chloroacetyl)-4-phenyloxazolidin-2-one, **3**, in 70% yield. Reaction of **3** with 2-pyrrolidone in the presence of sodium hydride (NaH) in dimethyl formamide (DMF) to furnish (S)-3-(2-(2-oxopyrrolidin-1-yl)acetyl)-4-phenyloxazolidin-2-one, **4**, in 90% yield; $[\alpha]_D^{20} = -60.7$ (c = 1.0, MeOH). The diastereo selective alkylation on compound **4** was carried out using NaHMDS and ethyl iodide in dry THF at -78°C gave **5** in 81% yield with excellent diastereoselectivity; $[\alpha]_D^{20} = -87.0$ (c = 1.0, CHCl_3).

TABLE 1: Diastereoselective α -alkylation of **4a** & **4b**.

Entry no.	Starting material	R	Product	Observations ^a	Yield ^b (%)
1	4a	Ph	5a	Single diastereomer	81
2	4b	PhCH ₂	5b	Diastereomers mixture	53

^a Observed by monitoring on TLC and ^b isolated yield after purification.

The alkylation had indeed occurred from the least hindered face of the enolate delivering the required **S** stereochemistry.

3.1. Study of Selectivity during Alkylation with respect to Auxiliary and Size of Metal Ion. The discrepancy of stereoselectivity during α -alkylation with respect to substitution of auxiliary and size of metal ion was studied. The enolate derived from **4a** & **4b** with NaHMDS was alkylated under same conditions with ethyl iodide and the results are summarized in (Table 1).

(*S*)-phenyl substituted auxiliary showed higher diastereoselectivity (99% *ee*) as compared to (*S*)-benzyl auxiliary (<85% *ee*) with NaHMDS as the base, the diastereomeric ratios during alkylation were determined by chiral HPLC purity of final product (–)-Levetiracetam, **1**. Whereas LiHMDS provided similar results with **4a** & **4b**, but not as well as those with NaHMDS. Removal of the chiral auxiliary in compound **5** was carried out by LiOH/H₂O₂ in THF to afford the corresponding acid **6** in 85% yield. This is particularly noteworthy in a way that the (*S*)-4-phenyloxazolidin-2-one could be recovered in 85% yield, after a simple acid-base work-up operation. Acid **6** on treatment with ethyl chloroformate and ammonium hydroxide produced (–)-Levetiracetam, **1**, in 86% yield and 99.0% *ee* (determined by chiral HPLC analysis). The spectral data which were found to be in good agreement with reported values [26].

4. Conclusion

In conclusion, a practical and efficient enantioselective synthesis of levetiracetam, **1**, has been achieved successfully by employing Evans type asymmetric strategy. The merit of the mentioned approach is less number of steps (5 steps), improved overall yield (33.0%) and high enantioselectivity (99.0% *ee*). This sequence has also been applied to the preparation of the enantiomer of levetiracetam and brivaracetam, and so forth. The simplicity of the experimental procedures

and high stereochemical outcome make this method synthetically attractive for preparing the target compound on multigram scales and industrial applications. See Supplementary Material available online at doi:10.1155/2013/176512, including copies of the ¹H, ¹³C NMR, Mass, IR spectra of the new compounds.

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