Research Article

Enantioselective Synthesis of Antiepileptic Drug: (-)-Levetiracetam—Synthetic Applications of the Versatile New Chiral N-Sulfinimine

K. Chandra Babu,1,2 R. Buchi Reddy,3 E. Naresh,1 K. Ram Mohan,1 G. Madhusudhan,1 and K. Mukkanti2

1Department of Research and Development, Inogenent Laboratories Private Limited, 28A, IDA Nacharam, Hyderabad 500 076, India
2Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500 072, India
3R&D Centre, Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Sholinganallur, Chennai 600 119, India

Correspondence should be addressed to G. Madhusudhan; madhusudhan.gutta@yahoo.com

Received 11 January 2012; Accepted 3 May 2012

Academic Editor: Andreas G. Tzakos

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We report an asymmetric synthesis of (-)-Levetiracetam (1) in six steps starting from versatile new chiral N-sulfinimine (3). The key step, stereoselective 1,2-addition of ethylmagnesium bromide (EtMgBr) to chiral N-sulfinimine derived from (R)-glyceraldehyde acetonide and (S)-t-BSA, gave the corresponding sulfonamide (2) in high diastereoselectivity. Simultaneous deprotection and deacetylation followed by NaIO4 cleavage and reduction gave β-amino alcohol (6). Subsequent reactions yielded the targeted compound levetiracetam (1).

1. Introduction

Epilepsy is a chronic neurological disorder that consists of repeated occurrences of spontaneous seizures. Levetiracetam, (S)-α-ethyl-2-oxopyrrolidine acetamide (1), has 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 that has led to the rapid approval of this antiepileptic drug by the FDA (Figure 1). Levetiracetam offers several advantages over traditional therapy, including twice daily dosing, which includes a wide margin of safety with no requirements for serum drug concentration monitoring and no interactions with other anticonvulsants besides having less adverse effects than traditional treatments [2–4].

The literature methods for the synthesis of levetiracetam typically involve chiral pool approaches starting from enantiopure α-amino acids, resolution of etiracetam or advanced racemic intermediates [5–8], asymmetric hydrogenation over Rh(I) or Ru(II) complexes [9, 10], and deracemization of 2-bromobutyric acid using N-phenyl pantolactam as a chiral auxiliary [11]. As a part of our research program, aimed at developing stereo controlled syntheses of bioactive molecules [12–17], we report a new and enantioselective synthesis of levetiracetam (1) using versatile N-sulfinimine as starting material and (S)-t-BSA [18] as a chiral auxiliary. It demonstrates the versatility and important extended application of N-sulfinimine in the preparation of variety of biological active and pharmaceutical important molecules [19–29].

The field of asymmetric organocatalysis is rapidly developing and has attracted the attention of an increasing number of research groups around the world. In particular, organo catalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds. In this connection, t-BSA is abundant, inexpensive, and readily available in both enantiomeric forms and has emerged as arguably the most practical and versatile organo catalyst (S)-t-BSA has also been found to be an excellent asymmetric catalyst for β-amino alcohol functionalities (Figure 2).

We envisage the new chiral N-sulfinimine amongst the best starting material for functionalized amino alcohols,
amino acids [30–36], and amino diols. Hence, utilizing this versatile chiral building block, we successfully synthesized (S)-2-amino-1-butanol (6), a precursor for the asymmetric synthesis of 2-pyrrolidone derivatives like levetiracetam. Thus, we have successfully achieved the enantioselective synthesis of levetiracetam by employing (S)-t-BSA as a chiral catalyst and N-sulfinimine (3) as versatile chiral building block.

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 (λ = 254 nm) or by spraying with a solution of dry nitrogen. Reaction flasks were oven-dried at 200°C and maintained for 12 h. The reaction mass was allowed to cool to rt and filtered. The organic solution was dried over anhydrous Na2SO4. Flash chromatography was performed using Kieselgel 60 brand silica gel (230–400 mesh). The melting points were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz (1H) and at 75 MHz (13C). 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 ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

2.1. Preparation of (S,E)-N-((S),(S)-2,2-Dimethyl-1,3-dioxolan-4-yl) Methylene)-2-methyl Propane-2-sulfinamide (3). To a solution of aldehyde (R)-4 (30.0 g, 0.230 mol) in DCM (300 mL) were added (S)-t-butylsulfinamide (33.4 g, 0.276 mol) and anhydrous CuSO4 (110.1 g, 0.69 mol) with stirring at rt for 10 min. The temperature was gradually raised to 40°C and maintained for 12 h. The reaction mass was allowed to cool to rt and filtered. The organic solution was dried with (Na2SO4) distilled under vacuo to give compound 3 as an oil (51.0 g, 95%); δ 1.0 (s, 3H), 1.27 (s, 3H), 1.57 (m, 1H), 1.65 (m, 1H), 1.78 (d, 1H), 1.87–4.10 (m, 1H); 13C NMR (CDCl3, 125 MHz): δ 26.2, 26.3, 56.6, 66.5, 76.2, 109.8, 168.0; IR (CHCl3) νmax: 3280, 1376, 1153, 1063 cm−1; ESI-MS: m/z 234.0 [M+1]+.

2.2. Preparation of (S,N-((S),(S)-2,2-Dimethyl-1,3-dioxolan-4-yl)(Ethyl) Methyl)-2-methyl propane-2-sulfinamide (2). A solution of Sulfinimine 3 (10.0 g, 0.028 mol) in diethyl ether (50.0 mL) was cooled to −78°C. In another flask, ethylmagnesium bromide (30.0 mL, 0.85 mol, 3.0 M in ether) was added to a solution of TEMEDA (10.1 g, 0.87 mol) in diethyl ether (2.0 M). This mixture was then transferred to sulfinimine solution. After completion of reaction was added NH4Cl (50.0 mL) extracted with EtOAc (3 × 100 mL). The organic solution was dried with Na2SO4, distilled under vacuo to give compound 2 as oil. The residue was subjected to silica gel column chromatography (eluent: AcOEt/hexane 1:2) to give pure 2 (9.0 g, 80%) as light yellow liquid; [α]D25 + 0.60 (c 1.0, MeOH).

2.3. Preparation of (2S,3S)-3-Aminopentane-1,2-diol Hydrochloride (5). To a solution of protected chiral amine 2 (5.0 g, 0.018 mol) in methanol (50 mL) was added dropwise a solution of MeOH-HCl (10%) (34.0 mL, 0.094 mol). The solution was stirred for 2 h at room temperature and was then concentrated in vacuo. The amine hydrochloride was obtained as a white solid after precipitation from ether and was used without further purification of compound 5 (2.1 g, 75%) as a white solid; [α]D25 +12.0 (c 1.0, MeOH).

2.4. Preparation of (S)-2-Aminobutan-1-ol (6). Prepare solution of protected chiral amine diol 5 (2.0 g, 0.128 mol) by dropwise addition in water (10 mL). A few drops of acetone were needed for complete solubilization. NaIO4 (2.73 g, 0.128 mol) was added portionwise at 0°C. After 60 min NaBH4 (0.6 g, 0.153 mol) was added slowly. The solution was stirred for 3 h at room temperature, then acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 × 30 mL). The filtrate
was concentrated to yield the desired compound 6 as a colorless oil (1.5 g, 75%); [α]$_{D}^{25}$ = +10.1 (neat).

$^1$H NMR (CDCl$_3$, 300 MHz): δ 0.95 (t, 3H), 1.31–1.58 (m, 2H), 2.79 (m, 1H), 3.24 (s, 1H), 3.64 (m, 1H); IR (CHCl$_3$) $\nu_{max}$: 3346, 2933, 1571, 1463 cm$^{-1}$; ESI-MS: m/z $\pm 1$.

2.5. Preparation of 1-((S)-1-Hydroxybutan-2-yl) Pyrrolidine-2-one (7). To a cold (0°C) solution of 6 (10.0 g, 0.122 mol) in toluene (80 mL) was added anhydrous sodium sulfate (18.4 g, 0.129 mol), and the mixture stirred at this temperature for 1 h. Powdered potassium hydroxide (17.3 g, 0.122 mmol) with vigorous stirring. After completion of the reaction, the reaction mixture is filtered through a celite bed and washed with water (10 mL) to afford the pure compound 7 (178–180°C). $\alpha$-N-Methyl acid (2mL), addedsodiumphosphate (2.5 g, 0.0152 mol) and the reaction mixture was left for 30 min. The aqueous layer pH was adjusted to 3 using hydrochloric acid, and the mixture was filtered and washed with (Na$_2$SO$_4$) distilled under vacuum to give compound 8 as oil. To the residue toluene (10 mL) was added and stirred at 0°C for about 30 min. The solid was filtered and washed with toluene (5 mL) to afford the pure compound 8 (0.83 g, 76%); Mp: 124-125°C [Lit., [11] Mp: 124–126°C]; [α]$_{D}^{25}$ = -24.3 (c 1.0, acetone) [Lit., [38] [α]$_{D}^{10}$ = -24.0 (c1.0, acetone)].

$^3$H NMR (CDCl$_3$, 400 MHz): δ 0.93 (t, J = 7.7 Hz, 3H), 1.67–1.76 (m, 1H), 1.99–2.13 (m, 3H), 2.49 (t, J = 7.7 Hz, 2H), 3.37 (m, J = 8.7, 5.8 Hz, 1H), 3.52–3.58 (m, 1H), 4.64 (dd, J = 10.6, 4.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz); δ 10.8, 18.2, 21.9, 30.8, 43.9, 55.4, 173.7, 177.2; IR (CHCl$_3$) $\nu_{max}$: 2975, 1731, 1620 cm$^{-1}$; ESI-MS: m/z 170.0 [M$^+$ + 1].

2.6. Preparation of (S)-2-(2-Oxopyrrolidin-1-yl)butanoic Acid (8). Potassium hydroxide (1.0 g, 0.017 mol) was dissolved into water (18.0 mL). Tetra-n-butyl ammonium bromide (0.2 g, 0.0062 mol) and (S)-7 (1.0 g, 0.0063 mol) in methylene chloride (10 mL) were charged in 30 min charged potassium permanganate (1.5 g, 0.094 mol), after completion of reaction filtered through a celite bed and washed with water (10.0 mL). The aqueous layer pH was adjusted to 3 using hydrochloric acid (2 mL), added sodium phosphate (2.5 g, 0.0152 mol) and toluene (25.0 mL). The reaction mixture was extracted with dichloromethane (5 × 25 mL). The organic solution was dried with Na$_2$SO$_4$ and concentrated in vacuo recrystallization from acetone (100 mL) give 1 (3.3 g, 65%) a white solid, chiral HPLC.

![Figure 2: Versatility of N-sulfinimine](image-url)
3. Results and Discussion

In connection with a current research program, we required an efficient route for the preparation of chiral amino alcohols followed by synthesis of biologically active 2-pyrrolidone derivatives ((-)-levetiracetam, brivaracetam…). Despite the potential synthetic utility of the multiple functionalities present in N-sulfinimine (3), we have successfully synthesized taxol side chain precursor (4S,5S)-2-oxo-4-phenyloxazolidine-5-carboxylic acid [37] and (+)-cytoxazone. Herein, we report an asymmetric synthesis of (1) via stereoselective 1,2-addition of ethylmagnesium bromide (EtMgBr) to N-sulfinimine.

In this context, (R)-glyceraldehyde acetonide is regarded as a common starting material which has previously been synthesized using a new route in our laboratory in four steps and in 31% overall yield starting from commercially available (R)-epichlorohydrin. (R)-Glyceraldehyde acetonide was earlier elaborated in getting (S)-2,2-dimethyl-1,3-dioxolan-4-yl) methylene)-2-methyl propane-2-sulfinamide 3 by the CuSO₄ catalyzed reaction of (R)-glyceraldehyde acetonide with (S)-t-butylsulfinamide (S)-t-BSA in dichloromethane at room temperature in 98.94% de (Scheme 1) [37]. Among the various methods, nucleophilic 1,2-addition of aryl or alkyl carbanion to an imine double bond is a versatile and popular method for the preparation of functionalised amines. However, in this strategy both yield and stereoselectivity are predominantly influenced by electrostatic and steric factors of both substrates, that is, imine and the nucleophile. Incorporation of a stereo-directing motif such as chiral sulfinimines is evident for its potential to synthesize chiral amines in stereoselective fashion.

It is apparent that 1,2-addition of EtMgBr to chiral sulfinimine 3 proceeds via transition state (Figure 3). Stereoselectivity resulting from the addition of organometallic reagents to the C-N double bond of sulfinimines can generally

purity 99%; 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: ([S]-isomer rt = 14.4 min and (R)-isomer rt = 9.3 min; Mp: 113–114°C [Lit., [11] Mp: 113–114°C]; [α]D25 = −95.0 (c 1.0, acetone) [Lit., [11] [α]D25 = −95.0 (c 1.0, acetone)].

1H NMR (CDCl₃, 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 (t, 2H), 2.50 (t, 2H), 1.98–2.20 (m, 3H), 1.70 (m, 1H), 0.98 (t, J = 7.7 Hz, 3H); 13C NMR (CDCl₃, 125 MHz): δ 175.9, 172.7, 55.9, 43.7, 31.0, 21.2, 18.0, 10.4; IR (CHCl₃) νmax: 3200, 1731, 1620 cm⁻¹; ESI-MS: m/z 171.0 [M⁺ + 1].

Figure 3: Retrosynthetic analysis of (-)-levetiracetam (1).
be predicted by assuming chelated, chairlike transition states resulting from coordination of the metal ion with the sulfinyl oxygen.

The chiral \(\alpha\)-hydroxy-\(N\)-sulfinimines have recently received much attention as important precursors and intermediates for the preparation of a wide variety of natural products and drugs [39]. Furthermore, they can be easily converted into chiral \(\beta\)-amino alcohols and 2-oxazolidinones.

Therefore, development of methodologies for the stereoselective synthesis of chiral \(\beta\)-amino alcohols followed by 2-pyrrolidine ring formation to levetiracetam (1) is of considerable interest [40].

Only in diethyl ether as a solvent reaction completion within 5-6 hr was observed and alternate solvents such as THF, toluene, and \(\mathrm{CH}_2\mathrm{Cl}_2\) did not enhance the yields and selectivity (Table 1). The addition of the Grignard reagent to the imines 3 in THF at \(-78^\circ\text{C}\) gave good selectivity and observed single diastereomer in reaction monitored by TLC. Same reaction but in different solvents was carried out at the same temperature. However, incomplete reactions were observed. Rising to RT, complete conversion was observed but with low selectivity, and mixture of diastereomeric was observed by TLC. Higher temperatures lead, reaction completion. Deprotection of the \(t\)-butylsulfinyl group and 1,3-dimethyl acetal in compound 2 was performed in single step in acidic media (MeOH-HCl) to give the corresponding \(\beta\)-amino dial 5. Oxidation followed by reduction of amino dial in 5 using \(\mathrm{NaIO}_4/\mathrm{NaBH}_4\) gave the corresponding \(\beta\)-amino alcohol [41] 6. The compound 6 on reaction with 4-chlorobutyryl chloride [42] gave 2-pyrrolidone alcohol 7. The oxidation of 7 with \(\mathrm{KMnO}_4\) gave 8, and resultant amidation yielded (Scheme 2) the targeted (-)-levetiracetam 1. The spectral data for which were found to be in good agreement with reported values in the literature [38].

In conclusion, an efficient method has been developed for the preparation of levetiracetam 1 starting from chiral \(N\)-sulfinimine. The key step comprises a stereoselective 1,2-addition of ethylmagnesium bromide (EtMgBr) to chiral \(N\)-sulfinimine 3. The synthetic strategy detailed herein is equally applicable to the synthesis of the brivaracetam. Further application of this strategy to a variety of related natural products is currently underway in our laboratories.

**Acknowledgment**

The authors thank the Inogen Laboratories Private Limited (A GVK BIO Company) for the financial support and encouragement.

**References**


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**Table 1: 1,2-Addition of EtMgBr to chiral \(\alpha\)-hydroxy-\(N\)-sulfinimine 3.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et(_2)O</td>
<td>(-78^\circ\text{C})</td>
<td>5-6 h</td>
<td>80 (0)</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>(-78^\circ\text{C})</td>
<td>15 h</td>
<td>28 (47)</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>(-78^\circ\text{C})</td>
<td>15 h</td>
<td>32 (53)</td>
</tr>
<tr>
<td>4</td>
<td>(\mathrm{CH}_2\mathrm{Cl}_2)</td>
<td>(-78^\circ\text{C})</td>
<td>15 h</td>
<td>28 (65)</td>
</tr>
</tbody>
</table>

*Yields in parentheses are for recovered starting materials.*


