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Research Article

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

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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 $NaIO_4$ 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,

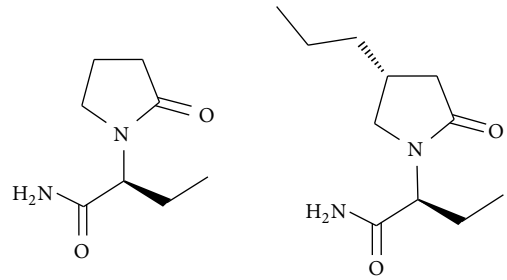


FIGURE 1: Structures of levetiracetam (**1**) and brivaracetam.

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 $KMnO_4$. 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 (^{1}H) 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 ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

*2.1. Preparation of (S,E)-N-(((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 $CuSO_4$(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 (Na_2SO_4) distilled under vacuo to give compound **3** as an oil (51.0 g, 95%); *de* (98.9%; determined by Chemical HPLC (X-BRIDGERP-18)), 0.02 M ammonium bicarbonate pH 7 with ACOH and ACN, gradient program, 1 mL/min, major enantiomer (*R*) tr = 9.338 min, minor enantiomer (*S*) tr = 8.90 min; $[\alpha]_D^{25}$ = +63.7 (*c* 1.0, EtOH) [Lit., [37] $[\alpha]_D^{20}$ = +63.7 (*c* 1.0, EtOH)].

^{1}H NMR (DMSO, 300 MHz): δ 1.19 (s, 9H), 1.44 (s, 3H), 1.50 (s, 3H), 3.99–4.04 (m, 1H), 4.18–4.23 (m, 1H), 4.89–4.93 (m, 1H), 7.87 (d,1H); ^{13}C NMR(DMSO, 125 MHz): δ 25.2, 26.3, 56.5, 66.5, 76.2, 109.8, 168.0; IR ($CHCl_3$) ν_{max}: 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, 0.428 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 TMEDA (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 NH_4Cl (50.0 mL) extracted with EtOAc (3 × 100 mL). The organic solution was dried with (Na_2SO_4) distilled under vacuo to give compound **2** as oil. The residue was subjected to silica gel column chromatography (eluent: AcOEt/hexane 1 : 2) give pure **2** (9.0 g, 80%) as light yellow liquid; $[\alpha]_D^{20}$ = + 0.60 (c 1.0, MeOH).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.97 (t, 3H), 1.27 (s, 9H),1.32 (s, 3H), 1.42 (s, 3H), 1.55 (m, 1H), 1.65 (m, 1H), 3.52 (m, 1H), 3.85 (dd, 1H), 4.03 (dd, 1H), 4.30–4.36 (m, 1H); ^{13}C NMR (CDCl, 100 MHz): δ 10.2, 22.6, 23.8, 24.7, 26.2, 55.9, 58.2, 65.4, 77.5, 109.1; IR ($CHCl_3$) ν_{max}: 3285, 1463, 1061 cm^{-1}; ESI-MS: *m/z* 263.8 [M$^+$+1].

*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; $[\alpha]_D^{25}$ = +12.0 (c 1.0, MeOH).

^{1}H NMR (DMSO, 300 MHz): δ 0.97 (t, 3H), 1.32 (m, 1H), 1.57 (m, 1H), 2.67 (m, 1H), 3.45 (m, 2H), 4.83 (m, 1H); IR (KBr) ν_{max}: 3343, 3085, 3036, 1612, 1492, 1386, 1063, 553 cm^{-1}; ESI-MS: *m/z* 120.0 [M$^+$+1].

*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 drop wise addition in water (10 mL). A few drops of acetone were needed for complete solubilization. $NaIO_4$ (2.73 g, 0.128 mol) was added portionwise at 0°C. After 60 min $NaBH_4$ (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

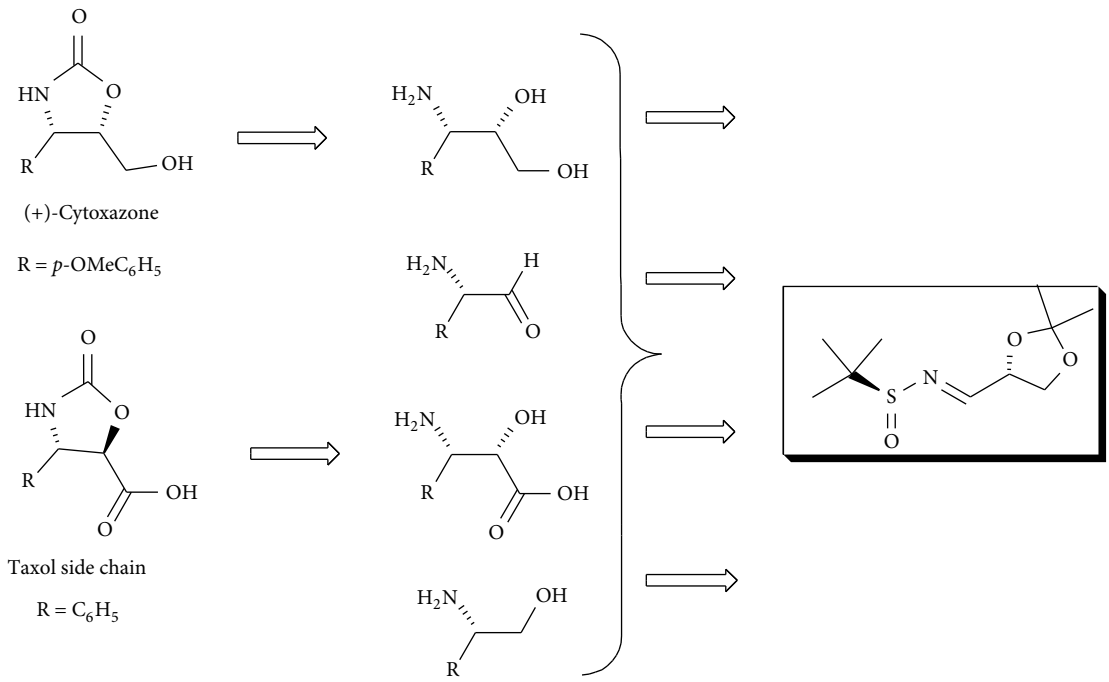


Figure 2: Versatility of *N*-sulfinimine **3** in the synthesis of various amine functionalized compounds.

was concentrated to yield the desired compound **6** as a colorless oil (1.5 g, 75%); $[\alpha]_D^{25} = +10.1$ (neat).

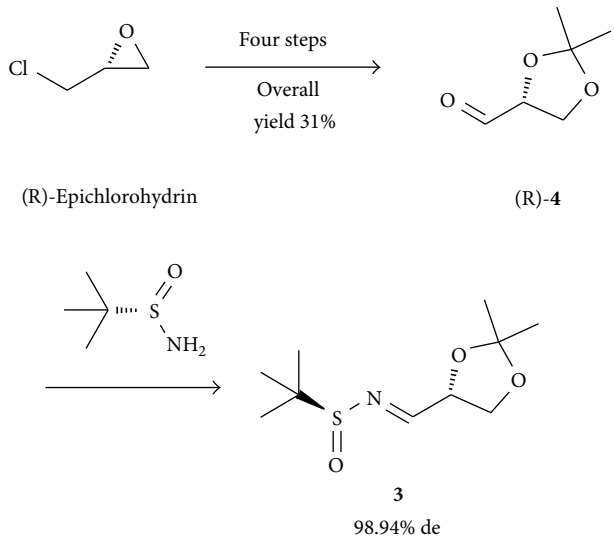
^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, 3 H), 1.31–1.58 (m, 2 H), 2.79 (m, 1H), 3.24 (s, 1H), 3.64 (m, 1H); IR ($CHCl_3$) ν_{max}: 3346, 2933, 1571, 1463 cm^{-1}; ESI-MS: *m/z* 89.8 [M^++1].

*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 (18.8 g, 0.335 mol) was gradually added followed by dropwise addition of 4-chlorobutyryl chloride (17.3 g, 0.122 mmol) with vigorous stirring. After completion of the reaction, the reaction mixture is filtered over Hyflo Super-Cel. Organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give (*S*)-**7** (137–140°C at 2 mm pressure). (14.0 g, 80%); $[\alpha]_D^{25} = -11.8$ (c 0.9, $CHCl_3$) [Lit., [38] $[\alpha]_D^{28} = -11.8$ (c 0.9, $CHCl_3$)].

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (t, 3H), 1.43–1.67 (m, 3H), 2.00–2.09 (m, 2H), 2.43–2.47 (m, 2H), 2.74 (br s, 1H), 3.31–3.45 (m, 2H), 3.61 (dd, 1H), 3.75 (dd, 1H), 3.86–3.93 (m, 1H). ^{13}C NMR (75 MHz): δ 10.5, 18.1, 21.0, 31.4, 43.4, 55.6, 62.6, 176.5; IR ($CHCl_3$) ν_{max}: 1668, 3379 cm^{-1}; ESI-MS: *m/z* 157.8 [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_2SO_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]; $[\alpha]_D^{25} = -24.3$ (c l.0, acetone) [Lit., [38] $[\alpha]_D^{19} = -24.0$ (c l.0, acetone)] ^{1}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 ($CHCl_3$) ν_{max}: 2975, 1731, 1620 cm^{-1}; ESI-MS: *m/z* 170.0 [M^-+1].

*2.7. Preparation of (S)-2-(2-Oxopyrrolidin-1-yl) Butanamide: (-)-Levetiracetam (***1***).* To a cold (0°C) solution of acid (*S*)-**8** (5.0 g, 0.292 mol) and Et_3N (4.3 mL, 0.307 mol) in anhydrous THF (20 mL) was added ethyl chloroformate (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, 136.0 mol) 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 CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated in vacuo recrystallization from acetone (100 mL) give **1** (3.3 g, 65%) a white solid, chiral HPLC



Scheme 1: Synthesis of (*R*)-glyceraldehyde acetonide (**4**) and imines (**3**) staring from (*R*)-epichlorohydrin.

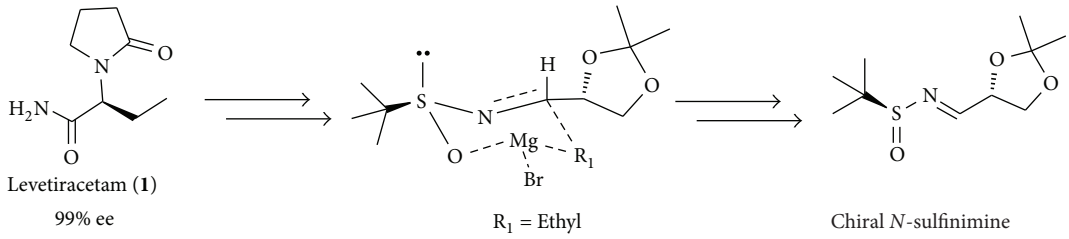


Figure 3: Retrosynthetic analysis of (-)-levetiracetam (**1**).

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 at rt = 14.4 min and (*R*)-isomer rt = 9.3 min; Mp: 113-114°C [Lit., [11] Mp: 113-114°C]; $[\alpha]_D^{25}$ = −95.0 (c l.0, acetone) [Lit., [11] $[\alpha]_D^{25}$ = −95.0 (c l.0, acetone)].

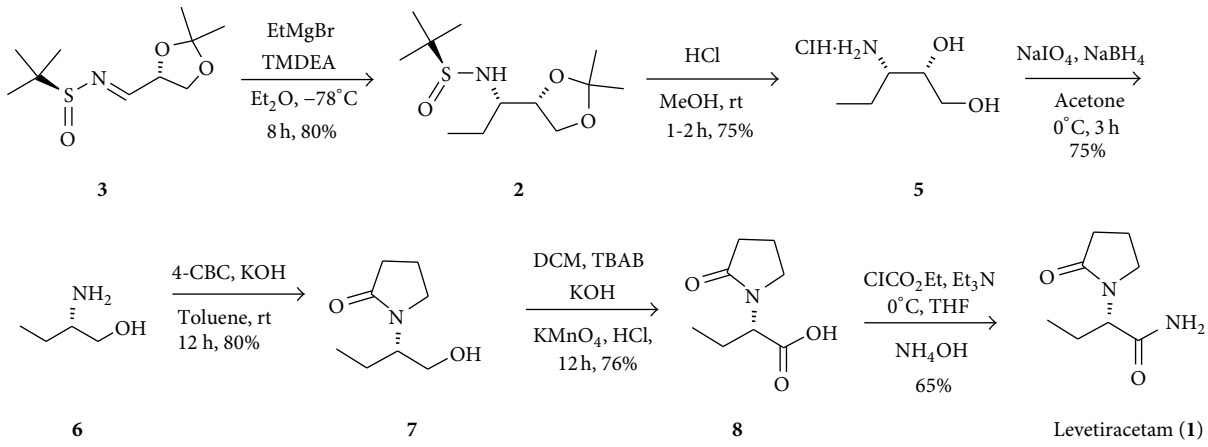
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.50 (br s, 1H), 5.70 (br s, 1H), 4.50 (t, J = 8.7, 6.8 Hz, 1H), 3.48 (t, 2H), 2.50 (t, 2H), 1.98–2.20 (m, 3H), 1.70 (m, 1H), 0.98 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.9, 172.7, 55.9, 43.7, 31.0, 21.2, 18.0, 10.4; IR ($CHCl_3$) ν_{max}: 3200, 1731, 1620 cm^{-1}; ESI-MS: m/z 171.0 [M$^+$+1].

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 (4*S*,5*S*)-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*,*E*)-*N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) methylene)-2-methyl propane-2-sulfinamide **3** by the $CuSO_4$ 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



Scheme 2: Synthesis of (-)-levetiracetam (**1**).

Table 1: 1,2-Addition of EtMgBr to chiral α-hydroxy-*N*-sulfinimine **3**.

Entry	Solvent	Temp.	Time	Yield[a] (%)
1	Et_2O	−78°C	5-6 h	80 (0)
2	THF	−78°C	15 h	28 (47)
3	Toluene	−78°C	15 h	32 (53)
4	CH_2Cl_2	−78°C	15 h	28 (65)

[a] Yields in parentheses are for recovered starting materials.

be predicted by assuming chelated, chairlike transition states resulting from coordination of the metal ion with the sulfinyl oxygen.

The chiral α-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 β-amino alcohols and 2-oxazolidinones.

Therefore, development of methodologies for the stereoselective synthesis of chiral β-Amino alcohols followed by 2-pyrrolidone 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 CH_2Cl_2 did not enhance the yields and selectivity (Table 1. Entries 2, 3, and 4). The addition of the Grignard reagent to the imines **3** in THF at −78°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 β-amino diol **5**. Oxidation followed by reduction of amino diol in **5** using $NaIO_4/NaBH_4$ gave the corresponding β-amino alcohol [41] **6**. The compound **6** on reaction with 4-chlorobutyryl chloride [42] gave 2-pyrrolidone alcohol 7. The oxidation of **7** with $KMnO_4$ 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.

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References

[1] B. Hurtado, M. J. Koepp, J. W. Sander, and P. J. Thompson, "The impact of levetiracetam on challenging behavior," *Epilepsy and Behavior*, vol. 8, no. 3, pp. 588–592, 2006.

[2] M. Dooley and G. L. Plosker, "Levetiracetam: a review of its adjunctive use in the management of partial onset seizures," *Drugs*, vol. 60, no. 4, pp. 871–893, 2000.

[3] C. A. Hovinga, "Levetiracetam: a novel antiepileptic drug," *Pharmacotherapy*, vol. 21, no. 11, pp. 1375–1388, 2001.

[4] S. D. Shorvon and K. Van Rijckevorsel, "A new antiepileptic drug," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 72, no. 4, pp. 426–429, 2002.

[5] J. Gobert, J. P. Greets, and G. Bodson, European Patent Application, E0162036; Chemistry Abstract 105, 018467.

[6] B. Z. Dolityzky, PCT International Application, WO 2004/069796; Chemistry Abstract 133, 183002.

[7] T. Futagawa, J. P. Canvat, E. Cavoy, M. Deleers, M. Hamende, and V. Zimmermann, US Patent 2000/6107492; Chemistry Abstract 133, 183002.

[8] E. Cavoy, M. Hamende, M. Deleers, J. P. Canvat, and V. Zimmermann, US Patent 2000/6124473; Chemistry Abstract 133, 268549.

[9] J. Surtees, V. Marmon, E. Differding, and V. Zimmermann, PCT International Application, WO 2001/64367.

[10] N. W. Boaz and S. D. Debenham, PCT International Application, WO 2002/26705; Chemistry Abstract 136, 279566.

[11] F. Boschi, P. Camps, M. Comes-Franchini, D. Muñoz-Torrero, A. Ricci, and L. Sánchez, "A synthesis of levetiracetam based on (*S*)-*N*-phenylpantolactam as a chiral auxiliary," *Tetrahedron Asymmetry*, vol. 16, no. 22, pp. 3739–3745, 2005.

[12] A. S. Paraskar and A. Sudalai, "Enantioselective synthesis of (-)-cytoxazone and (+)-epi-cytoxazone, novel cytokine modulators via Sharpless asymmetric epoxidation and l-proline catalyzed Mannich reaction," *Tetrahedron*, vol. 62, no. 24, pp. 5756–5762, 2006.

[13] A. S. Paraskar and A. Sudalai, "Co-catalyzed reductive cyclization of azido and cyano substituted α,β-unsaturated esters with $NaBH_4$: enantioselective synthesis of (*R*)-baclofen and (*R*)-rolipram," *Tetrahedron*, vol. 62, no. 20, pp. 4907–4916, 2006.

[14] I. A. Sayyed, V. V. Thakur, M. D. Nikalje, G. K. Dewkar, S. P. Kotkar, and A. Sudalai, "Asymmetric synthesis of aryloxypropanolamines via OsO_4-catalyzed asymmetric dihydroxylation," *Tetrahedron*, vol. 61, no. 11, pp. 2831–2838, 2005.

[15] I. A. Sayyed and A. Sudalai, "Asymmetric synthesis of l-DOPA and (*R*)-selegiline via, OsO_4-catalyzed asymmetric dihydroxylation," *Tetrahedron Asymmetry*, vol. 15, no. 19, pp. 3111–3116, 2004.

[16] V. V. Thakur, M. D. Nikalje, and A. Sudalai, "Enantioselective synthesis of (*R*)-(-)-baclofen via Ru(II)-BINAP catalyzed asymmetric hydrogenation," *Tetrahedron Asymmetry*, vol. 14, no. 5, pp. 581–586, 2003.

[17] I. S. Ali and A. Sudalai, "Pd-catalyzed kinetic resolution of benzylic alcohols: a practical synthesis of (*R*)-tomoxetine and (*S*)-fluoxetine hydrochlorides," *Tetrahedron Letters*, vol. 43, no. 31, pp. 5435–5436, 2002.

[18] D. A. Cogan, G. Liu, and J. Ellman, "Asymmetric synthesis of chiral amines by highly diastereoselective 1,2- additions of organometallic reagents to *N*-*tert*-butanesulfinyl imines," *Tetrahedron*, vol. 55, no. 29, pp. 8883–8904, 1999.

[19] N. R. Swamy, P. Krishnaiah, N. S. Reddy, and Y. Venkateswarlu, "A novel stereoselective total synthesis of (+)-5-epi-cytoxazone," *Journal of Carbohydrate Chemistry*, vol. 23, no. 4, pp. 217–222, 2004.

[20] Y.-L. Wu, W.-L. Wu, Y.-L. Li, X.-L. Sun, and Z.-H. Peng, "Stereoselective synthesis of acylic natural products containing vicinal diol," *Pure and Applied Chemistry*, vol. 68, no. 3, pp. 727–734, 1996.

[21] J. A. Marshall and G. P. Luke, *Journal of Organic Chemistry*, vol. 68, pp. 6229–6234, 1993.

[22] H. Arasaki, M. Iwata, M. Makida, and Y. Masaki, "Synthesis of (*R*)-(+)-tanikolide through stereospecific C-H insertion reaction of dichlorocarbene with optically active secondary alcohol derivatives," *Chemical and Pharmaceutical Bulletin*, vol. 52, no. 7, pp. 848–852, 2004.

[23] H. Matsunaga, T. Sakamaki, H. Nagaoka, and Y. Yamada, "Enantioselective synthesis of (*R*)- and (*S*)-4-[(methoxycarbonyl)-methyl]-2-azetidinones from D-glyceraldehyde acetonide," *Tetrahedron Letters*, vol. 24, no. 29, pp. 3009–3012, 1983.

[24] S. K. Kang and D. S. Shin, *Bulletin of the Korean Chemical Society*, vol. 8, p. 215, 1987.

[25] N. Minami, S. S. Ko, and Y. Kishi, "Stereocontrolled synthesis of D-pentitols, 2-amino-2-deoxy-D-pentitols, and 2-deoxy-D-pentitols from D-glyceraldehyde acetonide," *Journal of the American Chemical Society*, vol. 104, no. 4, pp. 1109–1111, 1982.

[26] D. R. Wagle, C. Garai, J. Chiang et al., "Studies on lactams. 81. Enantiospecific synthesis and absolute configuration of substituted β-lactams from D-glyceraldehyde acetonide," *Journal of Organic Chemistry*, vol. 53, no. 18, pp. 4227–4236, 1988.

[27] M. Kusakabe and F. Sato, *Chemistry Letters*, p. 1473, 1986.

[28] G. Y. Xu, Y. Zhou, and M. C. Xu, "A convenient synthesis of antibacterial linezolid from (*S*)-glyceraldehyde acetonide," *Chinese Chemical Letters*, vol. 17, no. 3, pp. 302–304, 2006.

[29] P. Zhou, B. C. Chen, and F. A. Davis, "Recent advances in asymmetric reactions using sulfinimines (*N*-sulfinyl imines)," *Tetrahedron*, vol. 60, no. 37, pp. 8003–8030, 2004.

[30] M. T. Robak, M. A. Herbage, and J. A. Ellman, "Synthesis and applications of *tert*-butanesulfinamide," *Chemical Reviews*, vol. 110, no. 6, pp. 3600–3740, 2010.

[31] L. R. Reddy, A. P. Gupta, and Y. Liu, "Asymmetric synthesis of α-amino acids by reduction of *N*-*tert*-butanesulfinyl ketimine esters," *Journal of Organic Chemistry*, vol. 76, no. 9, pp. 3409–3415, 2011.

[32] R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon, Oxford, UK, 1989.

[33] G. Cardillo, L. Gentilucci, and A. Tolomelli, "Aziridines and oxazolines: valuable intermediates in the synthesis of unusual amino acids," *Aldrichimica Acta*, vol. 36, no. 2, pp. 39–50, 2003.

[34] M. J. O'Donnell, "The enantioselective synthesis of α-amino acids by phase-transfer catalysis with achiral Schiff base esters," *Accounts of Chemical Research*, vol. 37, no. 8, pp. 506–517, 2004.

[35] K. Maruoka and T. Ooi, "Enantioselective amino acid synthesis by chiral phase-transfer catalysis," *Chemical Reviews*, vol. 103, no. 8, pp. 3013–3028, 2003.

[36] C. Nájera and J. M. Sansano, "Catalytic asymmetric synthesis of α-amino acids," *Chemical Reviews*, vol. 107, no. 11, pp. 4584–4671, 2007.

[37] K. C. Babu, R. Vysabhattar, K. S. V. Srinivas, S. Nigam, G. Madhusudhan, and K. Mukkanti, "Asymmetric synthesis of (4*S*,5*S*)-2-oxo-4-phenyloxazolidine-5-carboxylic acid using a 1,2-addition of PhMgBr to an *N*-sulfinimine derived from (*R*)-glyceraldehyde acetonide and (*S*)-*t*-BSA," *Tetrahedron Asymmetry*, vol. 21, no. 21-22, pp. 2619–2624, 2010.

[38] T. Imahori, K. Omoto, Y. Hirose, and H. Takahata, "Asymmetric synthesis of the antiepileptic drug levetiracetam," *Heterocycles*, vol. 76, no. 2, pp. 1627–1632, 2008.

[39] J. W. Evans and J. A. Ellman, "Stereoselective synthesis of 1,2-disubstituted β-amino alcohols by nucleophilic addition to *N*-*tert*-butanesulfinyl α-alkoxyaldimines," *Journal of Organic Chemistry*, vol. 68, no. 26, pp. 9948–9957, 2003.

[40] S. P. Kotkar and A. Sudalai, "Enantioselective synthesis of (*S*,*S*)-ethambutol using proline-catalyzed asymmetric α-aminooxylation and α-amination," *Tetrahedron Asymmetry*, vol. 17, no. 11, pp. 1738–1742, 2006.

[41] L. F. Jose, P. Albert, and G. Antonio, WO 2010/12789A1.

[42] A. K. Mandal, S. W. Mahajan, M. K. Sharma, A. Chetia, and N. D. Chauhan, WO 2006/095362A1.