A New Enantioselective Synthesis of the Anticonvulsant Drug Pregabalin (Lyrica) Based on a Hydrolytic Kinetic Resolution Method

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ABSTRACT A practical and efficient enantioselective synthesis of the anticonvulsant drug pregabalin is described for the first time using Jacobsen's hydrolytic kinetic resolution of a terminal epoxide as a key step and a source of chirality. *Chirality 25:965–969, 2013.*

KEY WORDS: pregabalin; anticonvulsant drug; hydrolytic kinetic resolution

INTRODUCTION

γ-Aminobutyric acid (GABA) is an important neurotransmitter that plays a major inhibitory role in the central nervous system.[1,2] An imbalance of GABA levels in the central nervous system is responsible for many diseases that exhibit several nervous system dysfunctions such as epilepsy, anxiety disorders, neuropathic pain, social phobia, etc.[3] Hence, analogs of GABA have significant therapeutic potential and in the last two decades numerous GABA mimetics (Fig. 1) were designed with the intention that they would be able to cross the blood–brain barrier and interact with GABAergic systems and enhance GABA-mediated inhibition.[4] Pregabalin (Lyrica (*S*)-**1**) is an important lipophilic, chiral analogue of GABA, approved by the U.S. FDA for the management of fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and as an adjunctive therapy for epilepsy.[5,6] Due to its unique mode of action it became Pfizer's best-selling drug, with worldwide sales of $4.15 billion in 2012, showing a 12% increase from the previous year.[7]

To date, several methods for the synthesis of enantiomerically pure pregabalin have been reported. Generally, the method includes chiral pool approaches,[8–10] classical resolution processes,[11–15] or using stereospecific procedures.[16–24] However, some of these methods have their own intrinsic disadvantages, such as expensive chiral starting materials, undesired side products, tedious and time-consuming experiments, and so on. Therefore, a new, practical, and expeditious stereoselective synthesis of pregabalin is still desirable.

In this context, as part of our ongoing program aimed at utilizing Jacobsen's hydrolytic kinetic resolution strategy (HKR)[25–28] for the synthesis of various pharmaceutically important compounds for industrial applications,[29–34] we herein report a new and simple synthesis of pregabalin employing Jacobsen's HKR strategy as a key step and a source of chirality.

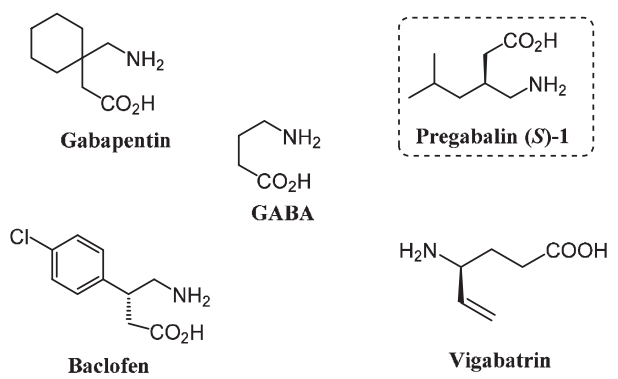

Fig. 1. Pharmaceutically important GABA mimetics.

EXPERIMENTAL

Chemicals and Reagents

All chemicals were purchased from Sigma Aldrich (St. Louis, MO) in the highest quality commercially available. Solvents were purified and dried by standard procedures prior to use. Tetrabutylammonium fluoride (TBAF) was used as a 1.0 M solution in tetrahydofuran (THF). Isopropyl magnesium chloride was used as a 2.0 M solution in THF.

Instrumentation

Infrared (IR) spectra were obtained with a Perkin–Elmer (Boston, MA) Spectrum one spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded with a Bruker (Billerica, MA) AC-200 NMR spectrometer. Spectra were obtained in $CDCl_3$. Monitoring of reactions was carried out using thin-layer chromatography (TLC) plates, Merck (Darmstadt, Germany) 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 Jasci (Tokyo, Japan) P 1020 digital polarimeter. Mass spectra were recorded at ionization energy 70 eV on API Q Star Pulsar spectrometer using electrospray ionization. High-resolution mass spectrometry (HRMS) (electrospray ionization, ESI) were recorded on an ORBITRAP mass analyzer (Thermo Scientific, Pittsburgh, PA; Q Exactive). Enantiomeric excess (*ee*) was determined by chiral high-performance liquid chromatography (HPLC).

Preparation

(*S*)-2-(2-(benzyloxy)ethyl)oxirane (*S*)-3a. A mixture of 2-(2-(benzyloxy)ethyl)oxirane **2** (10 g, 56.1 mmol) and (*S*,*S*) salen Co(III)OAc complex-A (0.1 g, 0.14 mmol) was vigorously stirred for 15 min, then cooled to 0°C, and water added (0.6 mL, 31 mmol) over a period of 15 min through a microsyringe. The reaction mixture was stirred at room temperature for 12 h, and then additional (*S*,*S*) salen Co(III)OAc complex-A (0.1 g, 0.14 mmol) was added and stirring was continued for an additional 12 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

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chromatography (silica gel, petroleum ether/acetone, 95:5). The less polar epoxide (*S*)-**3a** eluted first as a colorless oil (4.0 g, 40%); $[\alpha]_D^{25} = -15.2$ (*c* 2.5, $CHCl_3$) {lit.[26] $[\alpha]_D^{25} = -15.7$ (*c* 4.06, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3013, 2923, 2861, 1720, 1495, 1453, 1411, 1362, 1102; NMR (200 MHz, $CDCl_3$): δ_H 1.69-2.04 (m, 2H), 2.51 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.76 (dd, *J* = 5.2, 4.0 Hz, 1H), 3.03-3.12 (m, 1H), 3.60-3.66 (ddd, *J* = 7.0, 5.6, 1.0 Hz, 2H), 4.53 (s, 2H), 7.27-7.37 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 138.3 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.1 (CH_2), 67.1 (CH_2), 50.1 (CH), 47.2 (CH_2), 33.0 (CH_2); MS: *m/z* 201 $[M + Na]^+$; followed by diol (*R*)-**3b** as a colorless oil (4.7 g, 43%); $[\alpha]_D^{25} = +18.0$ (*c* 2.0, EtOH) {lit.[37] $[\alpha]_D^{25} = +22.7$ (*c* 5.16, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3600, 3435, 3013, 2923, 2861, 1495, 1453, 1411, 1362, 1102; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.70-1.79 (m, 2H), 3.47-3.67 (m, 5H), 3.88 (m, 1H), 4.50 (s, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.7 (C), 128.3 (CH, 2 carbons), 127.6 (CH, 3 carbons), 73.0 (CH_2), 70.6 (CH), 67.7 (CH_2), 66.2 (CH_2), 32.9 (CH_2); MS: *m/z* 219 $[M + Na]^+$.

(*R*)-1-(benzyloxy)-5-methylhexan-3-ol (*R*)-4. To a precooled (−20°C) solution of epoxide (*S*)-**3a** (3.8 g, 21.2 mmol) and CuI (0.1 g) in dry THF (30 mL) was added isopropyl magnesium chloride (2 M in THF, 15.8 mL, 31.8 mmol) in THF for about 30 min. Subsequently, the reaction mixture was allowed to attain ambient temperature and the stirring continued for an additional 2 h. After completion of the reaction (indicated by TLC), aqueous NH_4Cl was added, after which 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, petroleum ether/ethyl acetate, 85:15) to yield (*R*)-**4** as a colorless oil. (4.2 g; 90%); $[\alpha]_D^{25} = +17.5$ (*c* 2.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3502, 3018, 2957, 1603, 1454, 1366, 1307, 1092; NMR (200 MHz, $CDCl_3$): δ_H 0.91 (d, *J* = 6.6 Hz, 6H), 1.12-1.29 (m, 1H), 1.38-1.58 (m, 1H), 1.73 (dd, *J* = 11.7, 5.6 Hz, 2H), 1.74-1.85 (m, 1H), 2.84 (bd, *J* = 2.6 Hz, 1H), 3.60-3.78 (m, 2H), 3.82-3.96 (m, 1H), 4.53 (s, 2H), 7.27-7.37 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 138.0 (C), 128.5 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.4 (CH_2), 69.4 (CH), 69.3 (CH_2), 46.7 (CH_2), 36.9 (CH_2), 24.5 (CH), 23.4 (CH_3), 22.2 (CH_3); MS: *m/z* 245 $[M + Na]^+$; HRMS (ESI): m/z calculated for $C_{14}H_{22}O_2$ $[M + Na]^+$ 245.1512, found 245.1513.

(*S*)-2-(2-(benzyloxy)ethyl)-4- methylpentanenitrile (*S*)-5. To a precooled (0°C) solution of alcohol (*R*)-**4** (4.0 g, 17.9 mmol) in dry dichlormethane (DCM) (50 mL) was added triethylamine (5.4 mL, 39.3 mmol) followed by a slow addition of methanesulfonyl chloride (19.6 mmol, 1.5 mL) dropwise. The reaction mixture was stirred at 10°C for 2 h before quenching with water. The organic layer was washed with water (3 x 10 mL), brine, and evaporated under reduced pressure. The crude product was used for the next step without purification.

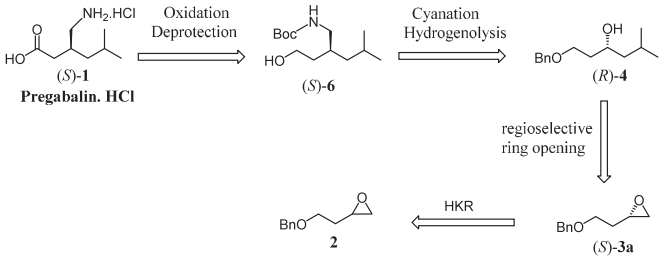
Trimethylsilyl cyanide (3.3 mL, 26.8 mmol) and TBAF (1 M in THF, 26.7 mL, 26.8 mmol) were added to a stirring solution of crude mesylated product as obtained above in acetonitrile under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 60°C for 24 h. After completion of the reaction (indicated by TLC), the solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate, 92:8) to yield (*S*)-**5** as a colorless oil. (2.9 g; 71%, 2 steps); $[\alpha]_D^{25} = +17.9$ (*c* 1.08, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3421, 2958, 2871, 2236, 1603, 1496, 1455, 1368, 1116; NMR (200 MHz, $CDCl_3$): δ_H 0.92 (d, *J* = 5.2 Hz, 3H), 0.95 (d, *J* = 5.4 Hz, 3H), 1.23-1.37 (m, 1H), 1.53-1.67 (m, 1H), 1.76-1.97 (m, 3H), 2.79-2.94 (m, 1H), 3.63 (apparent t, *J* = 6.1 Hz, 2H), 4.53 (d, *J* = 11.8 Hz, 2H), 7.26-7.41 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 138.0 (C), 128.5 (CH, 2 carbons), 127.7 (CH, 3 carbons), 122.1 (C), 73.3 (CH_2), 66.9 (CH_2), 41.2 (CH_2), 33.0 (CH_2), 26.7 (CH), 26.2 (CH), 23.0 (CH_3), 21.5 (CH_3); MS: *m/z* 254 $[M + Na]^+$; HRMS (ESI): m/z calculated for $C_{15}H_{21}NO$ $[M + Na]^+$ 254.1515, found 254.1514.

(*S*)-tert-butyl (2-(2-hydroxyethyl)-4-methylpentyl)carbamate (*S*)-6. To a solution of (*S*)-**5** (2.0 g, 8.6 mmol) and Boc_2O (2.0 g, 9.5 mmol) in methanol (30 mL) was added activated Raney-nickel catalyst (200 mg) and the reaction mixture was stirred under hydrogen (60 psi) for 20 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of celite bed (EtOAc as an eluent) and the solvent was evaporated under reduced pressure. The crude product was purified over column chromatography (silica gel, petroleum ether/ethyl acetate, 70:30) to yield (*S*)-**6** as a colorless oil (1.8 g, 86%); $[\alpha]_D^{25} = +1.8$ (c = 1.4,$CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3457, 3019, 2959, 2931, 1698, 1513, 1393, 1367, 1168; NMR (200 MHz, $CDCl_3$): δ_H 0.88 (apparent t, *J* = 6.2 Hz, 6H), 1.06-1.18 (m, 2H), 1.44 (s, 9H), 1.47-1.74 (m, 4H), 2.25 (bs, 1H), 3.10 (apparent t, *J* = 5.6 Hz, 2H), 3.65-3.79 (m, 2H), 4.80 (bs, 1H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 156.5 (CO), 79.5 (C), 60.7 (CH_2), 44.0 (CH_2), 42.0 (CH_2), 34.7 (CH_2), 33.6 (CH), 28.4 (CH_3, 3 carbons), 25.2 (CH), 22.8 (CH_3), 22.7 (CH_3); MS: *m/z* 268 $[M + Na]^+$; HRMS (ESI): m/z calculated for $C_{13}H_{27}NO_3$ $[M + Na]^+$ 268.1883, found 268.1883.

(*S*)-3-(((tert-butoxycarbonyl)amino)methyl)-5-methylhexanoic acid (*S*)-7. A mixture of (*S*)-**6** (1 g, 4.0 mmol), TEMPO (0.05 g, 0.32 mmol), acetonitrile (20 mL), and sodium phosphate buffer (16 mL, 0.67 M, pH 6.7) was heated to 35°C. Then sodium chlorite (1.3 g dissolved in 2 mL water, 14.6 mmol) and dilute bleach (4–6%, 1 mL diluted in 2 mL water) were added simultaneously over 1 h. The reaction mixture was stirred at 35°C until the reaction was complete (5 h, TLC), then cooled to room temperature. Water (30 mL) was added and the pH is adjusted to 8 with 2 N NaOH. The reaction was quenched by pouring into ice-cold Na_2SO_3 solution maintained at <20°C. After stirring for 30 min at room temperature, ethyl acetate (30 mL) was added and the stirring continued for an additional 15 min. The organic layer was separated and discarded. More ethyl acetate (30 mL) was added and the aqueous layer was acidified with 2 N HCl to pH 3–4. The organic layer was separated, washed with water (2 x 15 mL), brine (20 mL), and concentrated under reduced pressure to afford the carboxylic acid (*S*)-**7** (0.88 g, 85%); $[\alpha]_D^{25} = -8.6$ (*c* 1.1, $CHCl_3$) {lit.[6b] $[\alpha]_D^{25} = -1.4$ (*c* 3.3, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3450, 3020, 2927, 1646, 1521, 1423; NMR (200 MHz, $CDCl_3$): δ_H 0.90 (apparent t, *J* = 6.8 Hz, 6H), 1.16-1.19 (m, 2H), 1.45 (s, 9H), 1.62-1.69 (m, 1H), 2.10-2.35 (m, 3H), 3.05-3.09 (m, 1H), 3.21-3.25 (m, 1H), 4.78 (bs, 1H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 177.8 (CO), 156.5 (CO), 79.7 (C), 43.8 (CH_2), 41.4 (CH_2), 37.1 (CH_2), 33.8 (CH), 28.4 (CH_3, 3 carbons), 25.2 (CH), 22.7 (CH_3, 2 carbons); MS: *m/z* 282 $[M + Na]^+$

(*S*)-3-(aminomethyl)-5-methylhexanoic acid hydrochloride (Pregabalin) (*S*)-1. To a solution of compound (*S*)-**7** (0.25 g, 1 mmol) in acetone (5 mL) was added Conc. HCl (1 mL) and the reaction mixture was stirred at 60°C for 3 h, after which the solvent was

evaporated under reduced pressure. The residue was dissolved in water (10 mL) and extracted with DCM (2 x 5 mL). Heating of the aqueous layer with activated charcoal followed by filtration through Celite and concentration of the aqueous layer to dryness under reduced pressure furnished a residue that was dried at 50°C for 48 h to afford pregabalin hydrochloride (*S*)-**1** (0.18 g, 95%); $[\alpha]_D^{25} = +7.8$ (*c* 1.1, H_2O) {lit.[36] $[\alpha]_D^{25} = +7.0$ (*c* 1.03, H_2O)}; IR (Neat, cm^{-1}): ν_{max} 3448, 3211, 3130, 1720, 1431, 1215; NMR (200 MHz, D_2O): δ_H 0.87 (d, *J* = 4.7 Hz, 3H), 0.90 (d, *J* = 4.6 Hz, 3H), 1.25 (apparent t, *J* = 6.7 Hz, 2H), 1.58-1.75 (m, 1H), 2.22-2.28 (m, 1H), 2.50 (m, 2H), 3.02 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR(50 MHz, CD_3OD): δ_C 175.7 (CO), 44.2 (CH_2), 41.7 (CH_2), 37.0 (CH_2), 32.3 (CH), 25.8 (CH), 22.9 (CH_3), 22.2 (CH_3); MS: *m/z* 160 $[M+H]^+$; HRMS (ESI): m/z calculated for $C_8H_{18}NO_2$ $[M+H]^+$ 160.1332, found 160.1333.



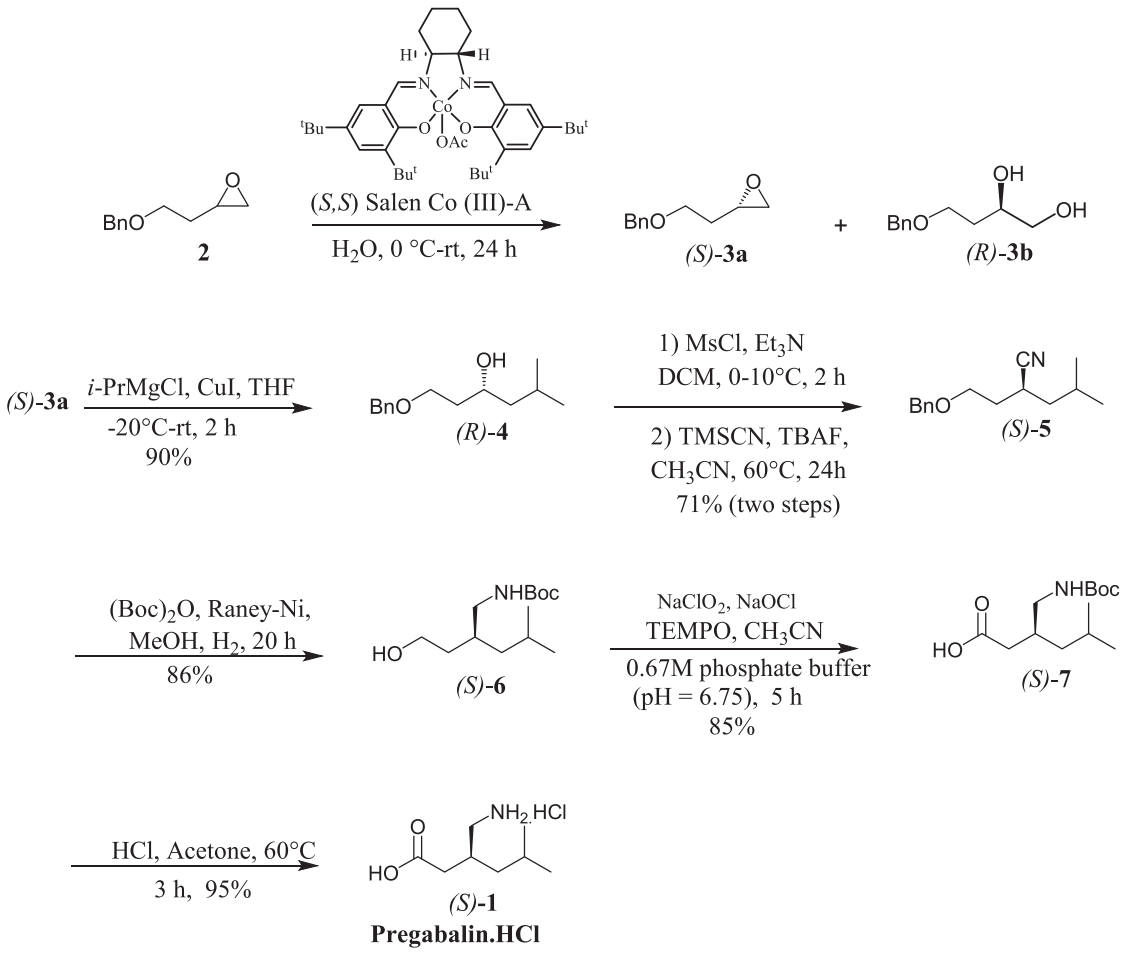
Scheme 1. Retrosynthetic analysis of pregabalin (*S*)-**1**.

For the purpose of *ee* determination of pregabalin (***S***)-**1**, *N*-benzyl amide of protected amino acid (***S***)-**8** was prepared and analyzed by chiral HPLC.

Method for the determination of ee: (*S*)-^{t}butyl (2-(2-(benzylamino)-2-oxoethyl)-4-methylpentyl)carbamate (*S*)-8. To a solution of acid (*S*)-**7** (0.11 g, 0.42 mmol) in dry THF was added *N*-methylmorpholine (50 μL, 0.46 mmol) at −78°C under argon atmosphere. After 5 min, isobutyl chloroformate (60 μL, 0.46 mmol) was added and the content stirred for another 5 min. To this reaction mixture benzylamine (50 μL, 0.46 mmol) was added at −78°C and the reaction mixture allowed to stir at room temperature for 2 h. After completion of the reaction, 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/ethylacetate, 65:35) to yield *N*-benzyl amide (*S*)-**8** (0.12 g, 85%); $[\alpha]_D^{25} = -3.5$ (*c* 0.8, $CHCl_3$); *ee* >99% (The *ee* was determined by chiral HPLC analysis: Chiralcel OJ-H [250 x 4.6 mm] column; eluent: pet ether/ethanol [90:10], flow rate 0.5 mL/min, detector: 220 nm, [(*R*)-isomer- t_R: 8.20 min; (*S*)-isomer- t_R: 8.80 min]).

RESULTS AND DISCUSSION

A retrosynthetic analysis of pregabalin (*S*)-**1** is outlined in Scheme 1. We envisaged that the secondary alcohol (*R*)-**4** would be an ideal intermediate for the synthesis which can be extended to the *Boc*-protected amino alcohol (*S*)-**6** via



Scheme 2. Synthesis of pregabalin (*S*)-**1**.

cyanation and hydrogenolysis. Simple oxidation and deprotection of compound (*S*)-**6** can lead to the target molecule (*S*)-**1**. Further, the key intermediate (*R*)-**4** in turn can be accessed from the enantiopure epoxide (*S*)-**3a** by employing regioselective ring opening using Grignard reagent. The enantiopure epoxide (*S*)-**3a** can be easily obtained with high enantiopurity from its racemic epoxide **2** employing Jacobsen's HKR method.

Accordingly, the substrate for HKR, the *rac*-epoxide **2**, was prepared from 3-buten-1-ol using the standard procedure.[35] The HKR of *rac*-epoxide **2** was performed with 0.55 equivalent of water using Jacobsen's catalyst (*S*,*S*)-Salen Co(III)OAc (0.5 mol%) at ambient temperature for 24 h (Scheme 2). After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give enantiomerically pure epoxide (*S*)-**3a** from the racemic mixture in 40% yield {$[\alpha]_D = -15.2$ (*c* 2.5, $CHCl_3$) Lit[26]: -15.7 (*c* 4.06, $CHCl_3$)} along with its diol (*R*)-**3b** in 43% yield. Subsequently, the epoxide (*S*)-**3a** was subjected to regioselective ring opening with isopropyl magnesium chloride in the presence of CuI in anhydrous THF at $-20°C$ to provide the key intermediate secondary alcohol (*R*)-**4** in 90% yield. The compound (*R*)-**4** was readily transformed into a cyano derivative (*S*)-**5** with an overall yield of 71% in two steps: (i) mesylation of the secondary alcohol (MsCl, Et_3N, DCM, 0°C) to afford mesylate and (ii) cyanation (TMSCN, TBAF, CH_3CN, 60°C) to obtain cyano derivative (*S*)-**5**. Performing cyanation reaction using the NaCN/DMF condition did not enhance the yield of the cyano product (*S*)-**5**. Further, compound (*S*)-**5** on simple hydrogenation/hydrogenolysis and concomitant *Boc*-protection using $(Boc)_2O$ and Raney-Ni as a catalyst in methanol furnished the protected amino alcohol derivative (*S*)-**6**.

Further, oxidation of compound (*S*)-**6** went smoothly using sodium chlorite catalyzed by TEMPO and bleach in an acetonitrile-phosphate buffer (pH 6.8) condition and afforded the corresponding acid (*S*)-**7** in 85% yield. Finally, simple Boc-deprotection of (*S*)-**7** using conc. HCl/ acetone completes the synthesis of pregabalin (*S*)-**1** in excellent enantioselectivity (>99 % *ee*) {$[\alpha]_D = +7.8$ (*c* 1.1, H_2O); lit[36] $[\alpha]_D = +7.0$ (*c* 1.1, H_2O)}. The structure of Pregabalin (*S*)-**1** was confirmed by its IR, ^1H NMR, ^{13}C NMR, and mass spectral analysis. The enantiomeric purity of pregabalin (*S*)-**1** (as its benzylamide derivative (**S**)-**8**) was determined by chiral HPLC analysis.

CONCLUSION

In conclusion, we have demonstrated the use of a Jacobsen's HKR strategy for the simple synthesis of pregabalin (*S*)-**1** for the first time. Simple procedures, high enantioselectivities, and the ready availability of the catalyst and starting materials are some of the salient features of this approach. We envisage that this simple protocol may find a viable alternative for the large-scale production of pregabalin in the pharmaceutical industry.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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