Organocatalytic approach for enantioselective total synthesis of anti-epileptic and anti-seizure drug (+)-lacosamide

Mr. Sanjay S. Gaikwad*

Department of Chemistry, MES, Abasaheb Garware College, Pune, Maharashtra-411004, India.

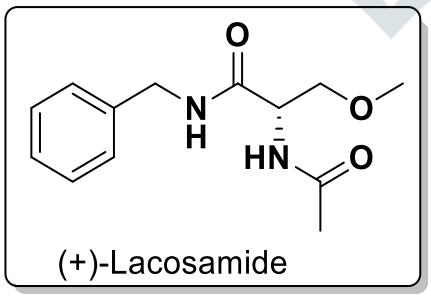
Abstract: A short and highly efficient enantioselective synthesis of (+)-lacosamide 1 from 3-methoxy propanal 2 in five high yielding steps, using L-proline catalysed α-amination, and acid-amine coupling as a key steps.

Key words: enantioselective, L-proline catalyzed, asymmetric α-amination, lacosamide

Introduction:

Epilepsy is a chronic neurological disorder that interrupts the typical activity of the brain cells by producing recurrent spontaneous seizures due to paroxysmal, excessive, synchronous neuronal discharges in the brain.[1-2] It is projected that about 1% of the world's population (about 50 million people) all over the world are exaggerated by this disease regardless of gender, age or socioeconomic status. In 1912, Hauptmann[3] synthesized and marketed the first synthetic organic compound, the Phenobarbital, possessing anticonvulsant activity. Since the 1970s, many antiepileptic so-called second-generation drugs have been synthesized.[4] (+)-Lacosamide (**7**) the (*R*)-enantiomer of *N*-benzyl-2-acetamido-3-methoxypropionamide, is a one of the most important second-generation antiepileptic drugs. It is an active substance flagged for adjunctive treatment of partial-onset seizures and diabetic neuropathic pain and is permitted as medical treatment in the U.S. and Europe in 2008 (Trade Name: Vimpat® owned by UCB Pharma (**Fig. 1**)). As of 2022, Vimpat's global net revenues reached ≤€1.5 billion.[4] This medication's precise mechanism of action in humans is still unidentified however, it is widely believed that it accelerates the voltage-gated sodium channels' slow inactivation, preventing repetitive neuronal shooting.

Fig. 1 Structure of (+)-lacosamide and its commercially available formulations



Due to the beneficial value of lacosamide, the synthesis of this D-serine derivative has pinched interest from both academic and industrial researchers.[5,7] An important disadvantage of earlier techniques was their preponderance of the non-natural amino acid D-serine as starting material, use of neutral but rather expensive Kuhn's *O*-methylation protocol,[6] which requires Ag_2O is another drawback. S. Stecko employed modified Overmann rearrangement for

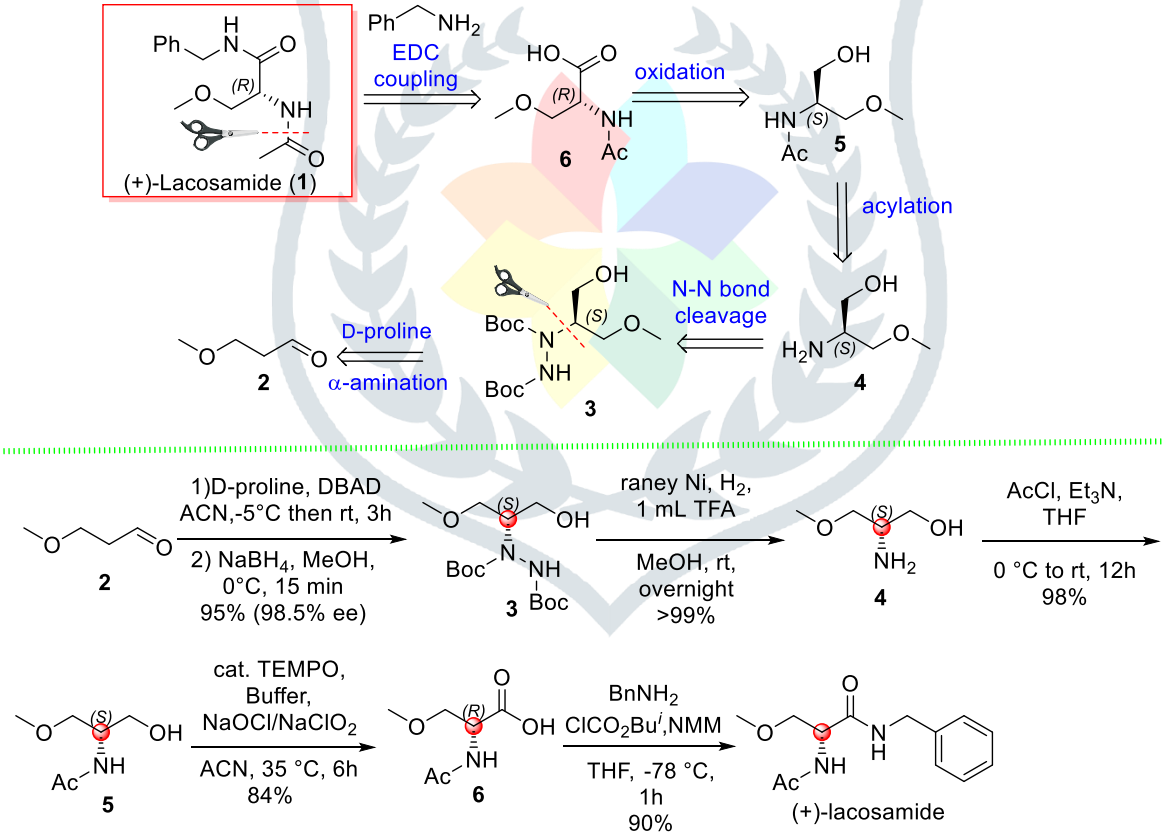
synthesis of lacosamide in which trichloro acetyl isocyanate expensive chemical is used.[7] Although few syntheses for (+)-lacosamide (**1**) have been reported,[5-7] but there is still need to develop a simple and quick method.

symmetric organo-catalysis has recently emerged as a promising tool for researchers to introduce chirality in the molecules with excellent optical purity.[8] Among various organocatalysts, proline is a versatile one and widely accessible in both its D and L forms.[8-10] The most promising techniques to introduce chirality in nonchiral aldehydes are asymmetric amination and aminooxylation.[11] As part of our research program on the development of new strategies for the total synthesis[12] and enantioselective syntheses of biologically active compounds and their key chiral intermediates based on proline-catalyzed asymmetric α-amination of aldehydes,[12a,b] we have established a new promising route for the synthesis of (+)-lacosamide (**1**) from an intermediate di-tert-butyl (S)-1-(1-hydroxy-3-methoxypropan-2-yl)hydrazine-1,2-dicarboxylate (**3**) obtained from L-proline catalyzed α-amination of 3-methoxypropanal (**2**).

Result and discussion:

In retrosynthetic analysis we envisioned that (+)-lacosamide could be obtained from acid (**5**) which can be easily accessible from the hyadrazinol (**3**) synthesised from aldehyde (**2**) by D-proline catalysed α-amination.

In actual synthesis 3-methoxypropanaldehyde (**2**) on D-proline catalysed α-amination using DBAD (di-tert-butyl azadicarboxylate) gives di-*tert*-butyl (*R/S*)-1-(1-hydroxy-3-



Scheme 1: Retrosynthetic analysis and sunthesis of (+)-lacosamide

methoxypropan-2-yl)hydrazine-1,2-dicarboxylate (**3**) from corresponding aldehyde via reduction in 95% yield and 98.5 % *ee*. Thus, obtained hydrazine alcohol (**3**) further treated with raney Ni in presence of H_2 at room temperature under acidic conditions (TFA 1.0 mL) to furnish amino alcohol (**4**) in comparative yield of >99%. Amino alcohol (**4**) on acylation with acetyl chloride in presence of triethyl amine (Et_3N) provides *N*-acylated amino alcohol (**5**) in 98%. This amino alcohol further on oxidation yields acid (**6**) in 84% yeild, and acid (**6**) on treatment with benzyl amine in presence of isobutyl chloroformate ($^iBuCO_2Cl$) and N-methyl morpoholine (NMM) furnishes the desired product (+)-lacosamide (1) in 70% overall yield in five steps with excellent *ee* (**Scheme 1**).

Conclusion:

In conclusion, we have developed a simple, and highly efficient way for the asymmetric total synthesis of (+)-lacosamide. Our route provided overall 70% from easily available commercial starting material aldehyde (2) in five steps. The intrinsic worth of the present synthetic approach is its shortness and high enantiomeric excess with high-yielding reaction steps. Additionally, this organocatalytic asymmetric synthetic strategy describes its potential significance for stereochemical variations at C-2 position and further easy access to other congeners for their SAR studies and minimal use of transition metal catalysts in overall synthesis.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

Experimental Section

1. General Information:

The solvents and chemicals were purchased from Merck and Sigma Aldrich chemical company. Solvents and reagents were purified and dried by standard methods prior to use. All reactions were carried out under argon or nitrogen in oven dried glassware using standard glass syringes and septa. Progress of the reactions was monitored by TLC using precoated aluminium plates of Merck kieselgel 60 F254. Column chromatography was performed on silica gel (100-200 mesh) using a mixture of n-hexane and ethyl acetate. 1H and 13C NMR spectra were recorded in CDCl3 (unless otherwise mentioned) on Bruker Avance III HD NMR 400 MHz instrument at 400 and 101 MHz, respectively. Chemical shifts are reported in δ (ppm), referenced to TMS. HRMS (ESI) were taken on Bruker Impact HD quadrupole plus ion trap at CIF, Savitribai Phule Pune University, Pune. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, bs: broad singlet dd: doublet of doublet for proton spectra. Optical rotations were measured on a digital polarimeter. Enantiomerically pure (+)-serinolamide A, B and (+)-lacosamide were synthesized according to literature procedures[14,15] for chiral HPLC analysis.

(*S*)-di-tert-butyl 1-(1-hydroxy-3-methoxypropan-2-yl)hydrazine-1,2-dicarboxylate (3)

Di-tert-butyl azodicarboxylate (1.74g, 7.57 mmol) and D-proline (87 mg, 0.076 mmol) in dry ACN (30 mL) were reacted with 3-methoxypropanal 7 (1.00 g, 11.35 mmol) at 0 °C. The reaction was stirred at same temperature for another 2 h and then warmed to room temperature (20 °C) for 3 h, till the color of the reaction changes from yellow to colorless. The reaction mixture again cooled to 0 °C and methanol (30 mL) was added followed by $NaBH_4$ (287 mg, 7.57 mmol) and stirred for 5 min. at same temperature. Then aq. NH_4Cl solution was added and the reaction mixture was extracted with ethyl acetate (3 X 25 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure and purified with silica gel column chromatography in EtOAc/hexane (1:6) to furnish white solid **3** in 2.30 g 95 % yield. *ee* 98% [The *ee* of **3** was determined by chiral HPLC analysis; Chiralpak

IA (4.6 X 250 nm) column; eluent: pet ether/isopropanol (95:5); flow rate 1 mL/min; detector: 220 nm [(*R*)-isomer tR = 49.02 min; (*S*)-isomer tR = 51.10 min]. $[\alpha]_{20}^{D}$ = +19.3 (c = 0.550, MeOH)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H), 4.73 – 4.21 (m, 1H), 3.77 – 3.38 (m, 3H), 3.32 (s, 4H), 1.91 (s, 1H), 1.49 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.3, 155.9, 155.1, 69.6, 63.0, 59.9, 58.7, 28.1, 28.1. HR-ESIMS: m/z calcd for $C_{14}H_{29}N_2O_6$: 221.2020 $[M+H]^+$ found: 221.2024.

(*S*)-2-amino-3-methoxypropan-1-ol (4)

To a solution of compound **3** (200 mg, 0.624 mmol) in MeOH (5 mL) Raney Ni (10 mol%), and 3 drops of acetic acid was added and stirred at room temperature in a Paar reactor with H_2 gas (100 psi) for 12 h. The reaction mixture then filtered through a bed of celite and washed with MeOH. The filtrate obtained is then concentrated in vacuo to obtain yellow oil **4** in quantitative yield of 99% (66 mg) as pale-yellow oil, which was used without purification in next step.

(*S*)-*N*-(1-hydroxy-3-methoxypropan-2-yl)acetamide (5)

To an anhydrous solution of THF in a 100 mL round bottom flask compound 4 (200 mg, 1.90 mmol) was added at 0 °C. To this cold solution Et_3N (211.75 mg, 2.09 mmol) was added dropwise followed by addition of acetyl chloride (164.25 mg, 2.09 mmol) and the reaction is stirred for 12 h at room temperature. After completion of reaction (monitored by tlc) saturated solution of ammonium chloride was added and the reaction is extracted in ethyl acetate (3 X 10 mL). Organic layer was dried over Na_2SO_4 and concentrated in vaccuo. The crude product (5) was purified using silica gel (100-200 mesh) column chromatography and eluted with ethyl acetate: hexane (3:7 v/v) solvent system to afford pure white solid (5) in 275 mg (98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (s, 1H), 4.36 – 4.27 (m, 1H), 3.82 (dd, *J* = 12.5, 1.4 Hz, 1H), 3.71 (dd, *J* = 12.5, 6.8 Hz, 1H), 3.62 (dd, *J* = 12.5, 1.2 Hz, 1H), 3.50 (bs,1H), 3.46 (dd, *J* = 12.5, 6.8 Hz, 1H), 3.34 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.17, 73.82, 62.29, 58.70, 51.24, 22.74. HR-ESIMS: m/z calcd for $C_6H_{13}NO_3Na$: 170.0793 $[M+H]^+$ found: 170.0809.

***N*-acetyl-*O*-methyl-D-serine (6)**

To a mixture of compound **5** (1 g, 4.9 mmol), TEMPO (0.05 g, 0.32 mmol) in ACN (20 mL), and sodium phosphate buffer (16 mL, 0.67 M, pH 6.7) was heated to 35 °C. Then, sodium chlorite (1.32 g dissolved in 2 mL water, 14.6 mmol) and diluted bleach (4–6%, 1 mL diluted in 2 mL water) were added simultaneously over 1 h. The reaction mixture was stirred at same temperature till the completion of reaction (6 h, monitored by tlc), and then cool the reaction mixture to room temperature. Water (30 mL) was added and the pH is adjusted to 8 using 2 M NaOH solution. The reaction was then quenched by pouring it into an ice cold Na_2SO_3 solution maintained at <20 °C. After stirring further for 30 min at room temperature, ethyl acetate (30 mL) was added and continued the stirring for 15 min. The organic layer was separated and discarded. More ethyl acetate (30 mL) was added, and the aqueous layer was acidified with 1 M HCl to pH 3–4. The organic layer was separated, washed with water (2 X 15 mL), brine (20 mL) and concentrated in vaccuo to afford the desired compound 16 as off-white solid (0.89 g, 84%). This compound without further purification directly used in next step. $[\alpha]\frac{D}{20}$ = -19.1 (c = 1.4, $CHCl_3$), [Lit.[6] $[\alpha]\frac{D}{20}$ = -19.2 (c = 1.4, $CHCl_3$).

(+)-lacosamide (1)

To a solution of crude amino acid **6** (0.7 g, 3.2 mmol) in dry THF was added *N*-methylmorpholine (0.43 mL, 3.8 mmol) at -78 °C under an argon atmosphere. After 5 min, isobutyl chloroformate (0.5 mL, 3.8 mmol) was added and stirred for another 5 min. To this reaction mixture benzylamine 17 (0.4 mL, 3.8 mmol) was added at -78 °C after which the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was filtered, and washed with ethyl acetate. The solvent was evaporated on rotary evaporator and crude product was subjected to silica gel column chromatography using eluent petroleum ether/acetone (85:15) to yield

pure product 18 as a white solid (0.9 g, 90%). $[\alpha]\frac{D}{20}$ = +16.1 (c = 1.2, MeOH), [Lit.: $[\alpha]\frac{D}{20}$ = +16.2 (c = 1, MeOH),[12] $[\alpha]\frac{D}{20}$ = +16.4 (c = 1, MeOH),[6] $[\alpha]\frac{D}{20}$ = +16.1 (c =1, MeOH)].

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.38 (m, 5H), 6.78 (br s, 1H), 6.48 (br s, 1H), 4.52–4.58 (m, 1H), 4.50 (d, *J* = 4.5 Hz, 2H), 3.83 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.45 (t, *J* = 9.7, 8.0 Hz, 1H), 3.40 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 170.0, 137.7, 128.6, 127.4, 71.8, 59.1, 52.6, 43.6, 23.2. HR-ESIMS: m/z calcd for $C_{23}H_{46}NO_3$ [M + H]+ 250.1317, found 250.1319. ee >98% [The *ee* of 1 was determined by chiral HPLC analysis; Chiralpak IA (4.6 X 250 nm) column; eluent: pet ether/isopropanol/TFA (60:40:0.1); flow rate 1 mL/min; detector: 220 nm [(*R*)-isomer tR = 10.43 min; (S)-isomer tR = 11.08 min].

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