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First asymmetric synthesis of the antiepileptic drug Lacosamide (Vimpat®) based on a hydrolytic kinetic resolution strategy

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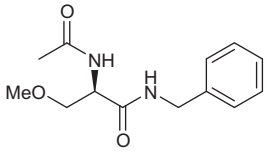
ABSTRACT

An efficient asymmetric synthesis of the new antiepileptic drug, Lacosamide is described in high enantiopurity (>98% ee), using Jacobsen's hydrolytic kinetic resolution strategy as a key step.

1. Introduction

Epilepsy is a complex neurological disorder characterized by recurrent spontaneous seizures and affects almost 50 million people worldwide.[1] The life time prevalence of this disease is 1% and it affects individuals of all ages regardless of gender or socio-economic status. Further, epilepsy requires prolonged and sometimes lifelong drug therapy. Lacosamide **1**[2,3] is the (*R*)-enantiomer of *N*-benzyl-2-acetamido-3-methoxypropionamide, recently approved by FDA (Oct, 2008) as an add-on therapy for partial-onset seizures in adults with epilepsy (Trade Name: Vimpat® owned by UCB Pharma). Although the mechanism of action of Lacosamide is not yet clearly understood, but it is believed that it enhances slow inactivation of voltage-gated Na^+ channels and binds to dihydropyrimidinase-related protein 2 (CRMP 2), and thus controls the seizures.[2a] Due to this unique mode of action, it differs from other antiepileptic drugs (AEDs). Commercially, Lacosamide is prepared using a chiral pool approach starting from unnatural amino acid D-serine and its derivatives.[2,3] To the best of our knowledge, there has been no asymmetric synthesis of this molecule reported.



Lacosamide (Vimpat®) **1**

Over the past few years, investigations in our laboratory have demonstrated the utility of Jacobsen's hydrolytic kinetic resolution strategy[4] for the synthesis of many pharmaceutically important compounds.[5] In this context, we herein report the first asymmetric synthesis of the antiepileptic drug Lacosamide.

2. Results and discussion

A retrosynthetic analysis of Lacosamide is outlined in Scheme 1. We envisaged that the azido compound (*R*)-**5** would serve as a key intermediate for the synthesis. It can be elaborated to the advanced acid precursor (*R*)-**7** by simple hydrogenation, hydrogenolysis, and oxidation sequences followed by amidation to give the target molecule **1**. Compound (*R*)-**5** can also be accessed from (*S*)-benzyl glycidyl ether (*S*)-**3a** by employing regioselective ring opening as well as Mitsunobu reaction protocols. (*S*)-Benzyl glycidyl ether (*S*)-**3a** can be easily obtained with high enantiopurity from its racemic benzyl glycidyl ether **3** using Jacobsen's hydrolytic kinetic resolution strategy.

The reaction of benzyl alcohol **2** with *rac*-epichlorohydrin in the presence of NaOH as a base gave *rac*-benzyl glycidyl ether **3** in 91% yield (Scheme 2). The *rac*- benzyl glycidyl ether **3** was subjected to Jacobsen's hydrolytic kinetic resolution conditions with 0.55 equiv of water using the catalyst (*R*,*R*)-Salen Co(III)OAc (0.5 mol %) at ambient temperature for 30 h. 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 47% yield and >99% ee {$[\alpha]_D = +8.1$ (*c* 0.4, EtOH); lit.[6] [α]D = +7.8 (*c* 0.4, EtOH)} along with its diol (*R*)-**3b** in 43% yield. The epoxide (*S*)-**3a** was subjected to regioselective ring opening with methanol in the presence of KOH as a base to give the corresponding secondary alcohol (*S*)-**4** in 98% yield (Scheme 2). The secondary alcohol (*S*)-**4** was converted into the desired azido derivative (*R*)-**5** in 83% yield using DPPA under Mitsunobu conditions. Next, the azido compound (*R*)-**5** was subjected to $Pd(OH)_2$ catalyzed hydrogenation/hydrogenolysis followed by N-acetylation using acetyl chloride under basic conditions to give compound (*S*)-**6** (Scheme 3) in 85% yield (two steps). Having successfully synthesized the precursor (*S*)-**6**, our next aim was to convert (*S*)-**6** into acid (*R*)-**7**, followed by coupling with benzylamine to complete the synthesis of Lacosamide **1**. However, oxidation of compound (*S*)-**6** to acid (*R*)-**7** posed a problem. Oxidative conditions with sodium chlorite catalyzed by TEMPO and bleach

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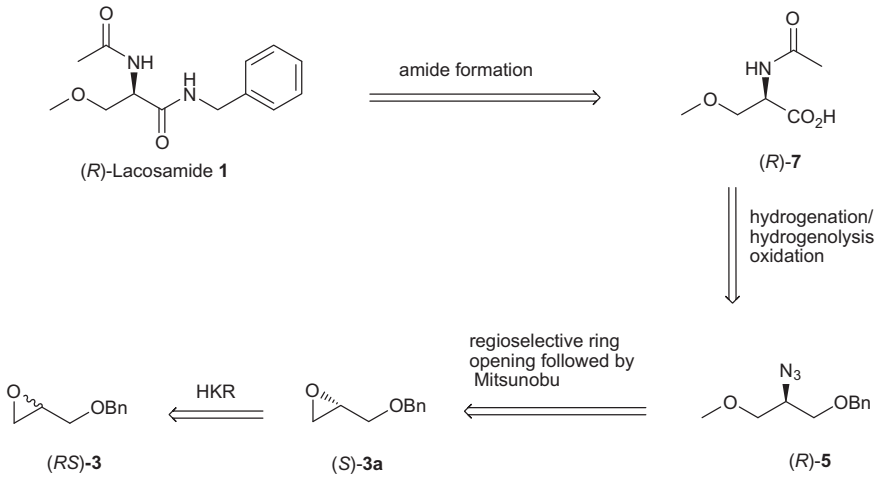
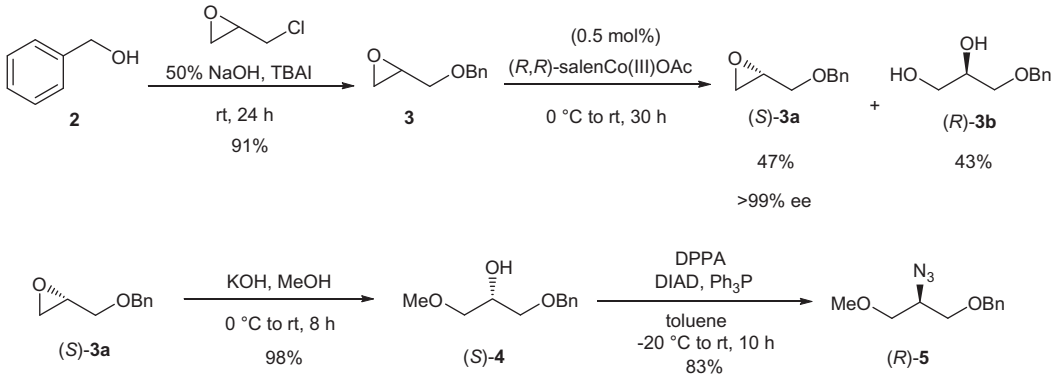
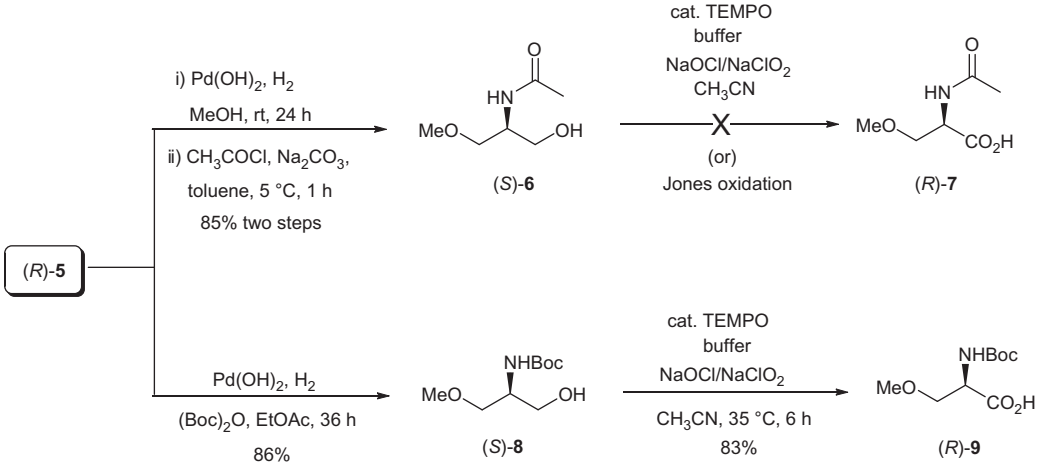


Scheme 1. Retrosynthetic analysis of Lacosamide **1**.



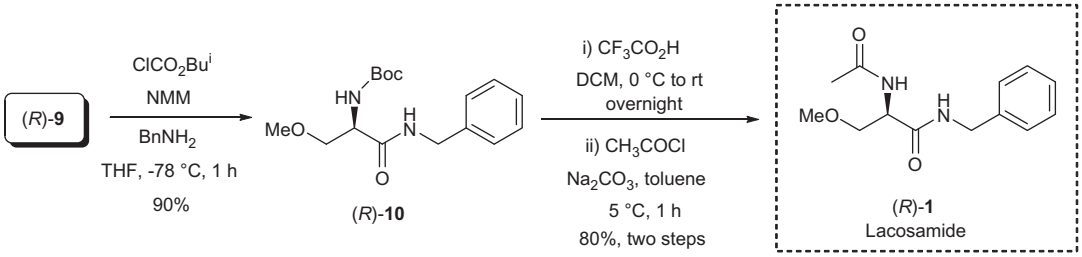
Scheme 2.



Scheme 3.

and Jones oxidative conditions failed to produce the desired acid (*R*)-**7**.

Consequently, the azido compound (*R*)-**5** was subjected to $Pd(OH)_2$ catalyzed hydrogenation/hydrogenolysis and concomitant protection with $(Boc)_2O$ and afforded the *N*-Boc protected aminoalcohol (*S*)-**8** in 86% yield. Compound (*S*)-**8** underwent oxidation very smoothly with sodium chlorite catalyzed by TEMPO and bleach in an acetonitrile–phosphate buffer (pH 6.8) and afforded the corresponding acid (*R*)-**9** in 83% yield. Acid (*R*)-**9** was then converted into amide (*R*)-**10** by coupling with benzylamine using a mixed anhydride procedure (Scheme 4). Finally, Boc-deprotection followed by N-acetylation using acetylchloride in the presence of Na_2CO_3 as a base, completed the synthesis of Lacosamide **1** in excellent enantioselectivity (>98% ee) {$[\alpha]_D = +16.1$ (*c* 1, MeOH); lit.[7] $[\alpha]_D = +16.4$



Scheme 4.

(*c* 1, MeOH)}. The structure of Lacosamide **1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic analysis.

3. Conclusion

In conclusion, a practical and highly enantioselective synthesis of Lacosamide **1** has been achieved using Jacobsen's hydrolytic kinetic resolution method as the key step and source of chirality. The main advantages of the present method include high enantioselectivity, the ready availability of the starting material and the catalyst, and the use of water (0.55 equiv) as the medium and reactant in the key step. Moreover, the Jacobsen catalyst can be regenerated by treatment with acetic acid and recycled.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures prior to use. IR spectra were obtained from Perkin–Elmer Spectrum one spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 NMR spectrometer. Spectra were obtained in $CDCl_3$. The reactions were monitored by using TLC plates Merck 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 JASCO P 1020 digital polarimeter. Mass spectra were recorded at ionization energy 70 eV on API Q Star Pulsar spectrometer using electrospray ionization. Enantiomeric excesses were determined by chiral HPLC, performed on 'SHIMADZU SCL-10A unit' system controller and UV monitor as detector.

4.2. 2-(Benzyloxymethyl) oxirane *rac*-3

To a stirred solution of aqueous sodium hydroxide (125 mL, 50% w/w), epichlorohydrin (54 mL, 925 mmol), and tetrabutylammonium iodide (3.4 g, 9.4 mmol) was added benzyl alcohol **2** (20 g, 185 mmol) below 25 °C and the resulting mixture was stirred at room temperature for 24 h. After completion of the reaction, cold water (250 mL) was added and the reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/acetone, 95:5) to afford 2-(benzyloxymethyl) oxirane **3** as a colorless oil (27.6 g, 91%); IR ($CHCl_3$, cm^{-1}): ν_{max} 3418, 3020, 2401, 1719, 1603, 1523, 1495, 1421, 1216, 1094, 929, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.60–2.64 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.78–2.82 (dd, *J* = 5.3, 4.2 Hz, 1H), 3.15–3.23 (m, 1H), 3.39–3.48 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.73–3.81 (dd, *J* = 11.4, 3.0 Hz, 1H), 4.60 (s, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.8 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.3 (CH_2), 70.7 (CH_2), 50.8 (CH), 44.2 (CH_2); MS: *m*/*z* 187 [M+Na]$^+$.

4.3. (*S*)-2-(Benzyloxymethyl) oxirane (*S*)-3a

A mixture of 2-(benzyloxymethyl)-oxirane **3** (10 g, 61 mmol) and (*R*,*R*)-salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) was vigorously stirred for 15 min, then cooled to 0 °C, and water added (0.6 mL, 34 mmol) over a period of 15 min, through a microsyringe. The reaction mixture was stirred at room temperature for 20 h, and additional (*R*,*R*) salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) was added and stirring was continued for additional 10 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 chromatography [silica gel, petroleum ether/acetone (95:5)]. The less polar epoxide (*S*)-3a eluted first as a colorless oil (4.7 g, 47%), $[\alpha]_D^{25} = +8.1$ (*c* 0.4, EtOH) {lit.[6] $[\alpha]_D^{23} = +7.8$ (*c* 0.4, EtOH)}; ee >99% [chiral HPLC analysis; CHIRALCEL OD-H (250 × 4.6 mm) column; eluent: *n*-hexane/isopropanol = 90:10; flow rate: 0.5 mL/min; detector: 220 nm [(*S*)-isomer t_R = 15.25 min; (*R*)-isomer t_R = 16.46 min], followed by diol (*R*)-**3b** as a colorless oil (4.8 g, 43%); $[\alpha]_D^{25} = -1.6$ (*c* 3.1, EtOH) {lit.[4b] $[\alpha]_D^{25} = -1.4$ (*c* 3.3, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 3020, 1600, 1495, 1215, 1045, 1029, 929, 697; NMR (200 MHz, $CDCl_3$): δ_H 2.73 (t, *J* = 5.8 Hz, 1H, OH), 3.13 (d, *J* = 5 Hz, 1H, OH), 3.51–3.54 (dd, *J* = 5.4, 2.6 Hz, 2H), 3.57–3.68 (m, 2H), 3.82–3.92 (m, 1H), 4.54 (s, 2H), 7.28–7.39 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.6 (C), 128.4 (CH, 2 carbons), 127.8 (CH, 3 carbons), 73.5 (CH_2), 71.6 (CH_2), 70.7 (CH), 63.9 (CH_2).

4.4. (*S*)-1-(Benzyloxy)-3-methoxypropan-2-ol (*S*)-4

To a stirred solution of epoxide (*S*)-**3a** (4 g, 24.3 mmol) in methanol (40 mL) was slowly added powdered KOH (4 g; 70 mmol) at 10 °C and the reaction mixture was stirred at ambient temperature for 8 h, after which the solvent was evaporated under reduced pressure. The residue was dissolved in ethylacetate (50 mL), washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 90:10) to afford (*S*)-1-(benzyloxy)-3-methoxypropan-2-ol (*S*)-**4** as a colorless oil (4.6 g, 98%); $[\alpha]_D^{25} = -2.0$ (*c* 1.55, EtOH) {lit.[8] $[\alpha]_D^{25} = -1.3$ (*c* 1.54, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3686, 3444, 3020, 2401, 1603, 1523, 1473, 1422, 1120, 1045, 758, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.38 (s, 3H), 3.43–3.47 (dd, *J* = 5.3, 3.4 Hz, 2H), 3.50–3.55 (dd, *J* = 5.8, 3.1 Hz, 2H), 3.94–4.04 (m, 1H), 4.56 (s, 2H), 7.29–7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.9 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.8 (CH_2), 73.4 (CH_2), 71.3 (CH_2), 69.4 (CH), 59.2 (CH_3); MS: *m*/*z* 219 [M+Na]$^+$.

4.5. (*R*)-((2-Azido-3-methoxypropoxy)methyl)benzene (*R*)-5

A solution of DIAD (3.1 mL, 15.9 mmol) in dry toluene (5 mL) was added dropwise to a solution of (*S*)-**4** (2.5 g, 13.2 mmol) and

triphenylphosphine (4.1 g, 15.9 mmol) in dry toluene (50 mL) under an N_2 atmosphere at 0 °C. After 15 min, diphenylphosphoryl azide (3.6 mL, 15.9 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 10 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 95:05) to yield (*R*)-**5** as a colorless oil (2.4 g, 83%); $[\alpha]_D^{25} = +8.3$ (*c* 2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3392, 2969, 2878,1661, 1542, 1463, 1441, 1384, 1289, 1073, 1017, 988, 930, 756, 667; ^1H NMR (200 MHz, $CDCl_3$): δ_H 3.37 (s, 3H), 3.46–3.52 (dd, *J* = 5.4, 3.7 Hz, 2H), 3.54–3.61 (m, 2H), 3.68–3.79 (m, 1H), 4.56 (s, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.7 (C), 128.5 (CH, 2 carbons), 127.8 (CH), 127.7 (CH, 2 carbons), 73.5 (CH_2), 72.2 (CH_2), 69.8 (CH_2), 60.6 (CH), 59.2 (CH_3); MS: *m*/*z* 244 $[M+Na]^+$; Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99; Found: C, 59.43; H, 7.11; N, 19.20.

4.6. (*S*)-*tert*-Butyl 1-hydroxy-3-methoxypropan-2-ylcarbamate (*S*)-8

To a solution of (*R*)-**5** (2.0 g, 9 mmol) and Boc_2O (2.1 g, 10 mmol) in ethyl acetate (30 mL) was added palladium hydroxide on activated charcoal (200 mg, 10–20 wt %) and the reaction mixture was stirred under hydrogen (60 psi) for 36 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of Celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 80:20) to yield (*S*)-**8** as a colorless oil (1.6 g, 86%); $[\alpha]_D^{25} = +3.8$ (*c* 0.95, $CHCl_3$) {lit.[9] $[\alpha]_D^{25} = +26.4$ (*c* 0.995, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3683, 3443, 3018, 2981, 2898, 1703, 1504, 1393, 1368, 1169, 1092, 928, 848, 669; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.45 (s, 9H), 2.94 (br s, 1H), 3.37 (s, 3H), 3.52–3.56 (apparent t, *J* = 3.7 Hz, 2H), 3.61–3.80 (m, 2H), 5.20 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 156.1 (CO), 79.2 (C), 73.1 (CH_2), 63.8 (CH_2), 59.2 (CH), 51.4 (CH_3), 28.3 (CH_3, 3 carbons); MS: *m*/*z* 228 $[M+Na]^+$.

4.7. (*R*)-2-(*tert*-Butoxycarbonylamino)-3-methoxypropanoic acid (*R*)-9

A mixture of (*S*)-**8** (1 g, 4.9 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. Next, 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 35 °C until the reaction was complete (6 h, TLC), then cooled to room temperature. Water (30 mL) was added and the pH adjusted to 8 with 2 M NaOH. The reaction was quenched by pouring it into an ice cold Na_2SO_3 solution maintained at <20 °C. After stirring for 30 min at room temperature, ethylacetate (30 mL) was added and the stirring continued for an additional 15 min. The organic layer was separated and discarded. More ethylacetate (30 mL) was added, and the aqueous layer was acidified with M HCl to pH 3–4. The organic layer was separated, washed with water (2 × 15 mL), brine (20 mL) and concentrated under reduced pressure to afford the carboxylic acid (*R*)-**9** (0.88 g, 83%); $[\alpha]_D^{25} = -19.2$ (*c* 1.4, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3443, 3019, 2982, 2932, 1708, 1501, 1393, 1369, 1216, 1164, 1119, 1064, 927, 757, 669; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.46 (s, 9H), 3.38 (s, 3H), 3.59–3.66 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.84–3.90 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.41–4.47 (m, 1H), 5.42 (d, *J* = 8.2 Hz, 1H) 8.16 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 175.4 (CO), 155.8 (CO), 80.3 (C), 72.1 (CH_2), 59.3 (CH), 53.7 (CH_3), 28.3 (CH_3, 3 carbons); MS: *m*/*z* 242 $[M+Na]^+$.

4.8. (*R*)-*tert*-Butyl 1-(benzylamino)-3-methoxy-1-oxopropan-2-ylcarbamate (*R*)-10

To a solution of acid (*R*)-**9** (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 (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 ethylacetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/acetone, 85:15) to yield (*R*)-**10** as a colorless solid (0.9 g, 90%); mp 63–64 °C; $[\alpha]_D^{25} = -20.5$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3683, 3431, 3020, 2931, 2401, 1714, 1523, 1496, 1368, 1165, 1119, 928, 758, 669; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.43 (s, 9H), 3.37 (s, 3H), 3.47–3.54 (dd, *J* = 9.2, 6.1 Hz, 1H), 3.82 (dd, *J* = 9.3, 3.7 Hz, 1H), 4.27 (m, 1H), 4.47 (d, *J* = 5.1 Hz, 1H), 5.41 (br s, 1H), 6.77 (m, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 170.3 (CO), 155.5 (CO), 137.9 (C), 128.7 (CH, 2 carbons), 127.5 (CH, 3 carbons), 80.4 (C), 72.1 (CH_2), 59.1 (CH_3), 54.0 (CH), 43.5 (CH_2), 28.3 (CH_3, 3 carbons); MS: *m*/*z* 331 $[M+Na]^+$.

4.9. (*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide (*R*)-1 (Lacosamide)

To a solution of compound (*R*)-**10** (0.6 g, 1.9 mmol) in dichloromethane (7 mL) was added trifluoroacetic acid (3 mL) and the reaction mixture was stirred at room temperature overnight, after which the solvent was evaporated under reduced pressure. The residue was then dissolved in dry toluene after which Na_2CO_3 (0.6 g, 5.7 mmol) was added. The reaction mixture was cooled to 0 °C after which acetyl chloride (0.14 mL, 2.0 mmol) was slowly added and the solution stirred at 5 °C for 1 h. After completion of the reaction, the solid was filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 95:05) to afford (*R*)-**1** (Lacosamide) as a colorless solid (0.38 g, 80%); Colorless solid; mp 139–40 °C (lit.[7] 143–44 °C); $[\alpha]_D^{25} = +16.1$ (*c* 1, MeOH) {lit.[7] +16.4 (*c* 1, MeOH)}; IR ($CHCl_3$): γ 3685, 3421, 3020, 1663, 1523, 1426, 1118, 1030, 929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 3.40 (s, 3H, OCH_3), 3.45 (apparent t, *J* = 9.7, 8.0 Hz, 1H, OCH_2), 3.83 (dd, *J* = 9.4, 3.4 Hz, 1H, OCH_2), 4.50 (d, *J* = 4.5 Hz, 2H, CH_2Ph), 4.52–4.58 (m, 1H), 6.48 (br s, 1H, NH), 6.78 (br s, 1H, NH), 7.26–7.38 (m, 5H, Ph);^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7 (CO), 170.0 (CO), 137.7 (C), 128.6 (CH, 2 carbons), 127.4 (CH, 3 carbons), 71.8 (CH_2), 59.1 (CH_3), 52.6 (CH), 43.6 (CH_2), 23.2 (CH_3); MS: *m*/*z* 273 $[M+Na]^+$; ee >98% [The ee of **1** was determined by chiral HPLC analysis; Chiralcel OD-H (250 × 4.6 mm) column; eluent: pet. ether/isopropanol/trifluoroacetic acid (60:40:0.1); flow rate 0.5 mL/min; detector: 220 nm [(*R*)-isomer t_R = 10.43 min; (*S*)-isomer t_R = 11.8 min].

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