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Journal of Chemical and Pharmaceutical Research, 2015, 7(7):1080-1083

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

New and alternate synthesis of lacosamide with chemoenzymatic method

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ABSTRACT

Lacosamide ((R)-2-acetamido-N-benzyl-3-methoxy propionamide) ***5*** *is a novel antiepileptic drug. Lacosamide was prepared by chemical method and resolution of racemic Lacosamide using new enzymatic method. Herein is reported an expedient four-steps enantio selective synthesis of Lacosamide* ***5*** *beginning with methyl 2,3-dibromo propionate* ***1****. A new resolution process catalyzed by* **Novozyme 435**. *The products were obtained in very good yields and in a state of high purity. All the newly synthesized compounds* ***(2-5)*** *were characterized by their spectral (IR, ^1H NMR, C^{13} NMR and MS) data.*

Keywords: Lacosamide, anticonvulsant, epilepsy, methyl-2,3-dibromopropionate, new enzymatic resolution method

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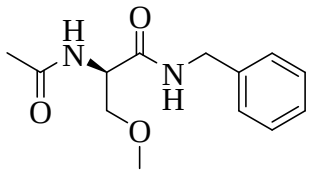
INTRODUCTION



(*R*)-2-acetamido-N-benzyl-3-methoxy propionamide

5

Figure-1

Epilepsy is a chronic neurological disorder complicated by neurobehavioral comorbidities and social consequences [1]. It is a type of recurrent seizures produced by paroxysmal, excessive, synchronous neuronal discharges in the brain [2,3], and affects 1% of the world's population [4-6]. The lifestyle restrictions and the large expense for treatment, lost productivity, and rehabilitation result in a huge cost to society [7]. In 1912, Hauptmann [8]

Introduced into the market the first synthetic organic compound posing anticonvulsant activity, the Phenobarbital. Since the 1970s, many drugs with antiepileptic action have been synthesized, so-called second generation drugs [9]. Lacosamide is an important one of the second generation drugs. Lacosamide [(*R*)-2-acetamido-*N*-benzyl-3-methoxy propionamide] has an empirical formula of $C_{13}H_{18}N_2O_3$ with a molecular weight of 250.30. It is an active substance indicated for adjunctive treatment of partial-onset seizures and diabetic neuropathic pain. Based on experimental studies, lacosamide appears to have a dual mode of action-enhancement of sodium-channel slow inactivation and modulation of collapsing response mediator protein-2 (CRMP-2) [10], both of which are novel mechanisms for an antiepileptic drug (AED). Without affecting fast inactivation, lacosamide appears to selectively enhance sodium-channel slow inactivation, which may help normalize activation thresholds and decrease path physiological neuronal activity, thus control ling neuronal hyper excitability [11]. In the United States, lacosamide is marketed under the

name VIMPAT TM for the treatment of epilepsy [12]. People have done a lot of researches for the synthesis of lacosamide, which can be made in three routes.

The first route is that *D*-serine is converted to methyl ester that reacts with benzylamine to get the corresponding benzyl amide. This intermediate reacts with acetic anhydride to get the *N*-acetyl derivative. Methylation by methyl iodide in the presence of silver oxide gave lacosamide. The second route is that *D*-serine reacts with acetic anhydride to get the corresponding *N*-acetyl derivative. This intermediate reacts with benzyl amine to get the corresponding benzyl amide derivative which gave lacosamide after methylation by methyl iodide and silver oxide. The third one is that the amino group of *D*-serine is protected by benzyl chloroformate followed by reaction with methyl iodide in the presence of silver oxide to get methyl ester of *O*-methyl derivative. The ester is hydrolyzed and converted to benzyl amide *via* mixed anhydride technique. The amino Protection group is removed by hydrogenation and converted to lacosamide by acetylation with acetic anhydride [13-21]. But, these methods have some difficulties in industrial production, such as chiral impurity, low yield, and costly reagent, rigorous reaction conditions, treating with poisonous reagent and requiring column chromatography in the intermediate isolation stage [19]. Recently, Narsaiah and co-workers [22] reported synthesis of 1 based on asymmetric dihydroxylation of the N-benzylacrylamide as a key step. To the best of our knowledge, there has been no chemical method coupled with enzymatic synthesis of this molecule reported. *D*,*L*-3-Methoxy-alanine (**1**) was synthesized by previously described procedures [23] from low-cost methyl acrylate.

Here we report an efficient chemo enzymatic synthesis of lacosamide with high enantiopurity was performed in the resolution process catalysed by Novozyme 435 activity as a key step (**Scheme 1**).

EXPERIMENTAL SECTION

General

Solvents were purified and dried by standard procedure prior to use. IR spectra were obtained from Perkin-Elmer Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-400 NMR spectrometer. Spectra were obtained in $CDCl_3$ and DMSO-d_6. The reactions were monitored by using TLC plates Merck Silica Gel 60 F254 and visualization with UV light (254 and 365 nm). Mass spectra were recorded at ionization energy 70 eV on API Q Star Pulsar spectrometer using electro spray ionization.

2-Bromo-3-methoxypropanoic acid (2)

To a solution of methyl 2,3-dibromopropionate **1** (10.0g, 37.34 mmol) in methanol (40mL, 4 vol) at 0-5°C was added 30% sodium methoxide in methanol (8.31mL, 46.16 mmol) at the 0-5°C. The contents were slowly warmed to 25-30°C and stirred for 3hr. To this reaction mixture 50% NaOH solution (2.3g, 57.71 mmol, and 4.6 mL of H_2O) was added and it was again stirred for 30min at 25-30°C. After completion of the reaction the mass was adjusted to pH~7 with the Conc. HCl and solvent was removed under reduced pressure. Again pH was adjusted to ~7 with Conc. HCl and extracted with dichloromethane (6x5vol). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain **2** (6.2g), yield: 88.2%

BP: 90-95°C, IR (KBr): υ 2997, 1734, 1457, 1407, 1221, 1118; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (q, J_1 = 6.0Hz, J =18.0 Hz, 1H), 3.90 (m, 1H), 3.90 (m, 1H), 3.80 (s, 3H –$COCH_3$), 3.71(m, 1H), 3.40 (s, 3H -CH_2-O-CH_2); EIMS *m/z* (%): 181 (M-1, 30), 155 (80), 113 (100).

N-Benzyl-2-(benzylamino)-3-methoxypropanamide (3)

A solution of **2** (5.0g, 27.32 mmol) and benzyl amine (8.94mL, 81.96 mmol) in sealed tube and warm to 120-125°C and stirred for 48hr. After completion of the reaction, the reaction mass was dissolved in ethyl acetate (100mL, 20vol) and washed with water (2x5vol) followed by brine solution (2x5vol), organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain pale brown liquid as a crude, purified by column chromatography using 100-200 silica gel eluting with 1:1 ethyl acetate in n-hexane, pure fractions were collected and concentrated to get light brown coloured liquid **3** (5.55g), yield: 68.1%

IR (KBr): υ 3327, 3029, 2925, 2359, 1665, 1521, 1455, 1328, 1247, 1105, 740; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (t, J = 5.6Hz, 1H), 7.33-7.20 (m, 10H), 4.32 (t, J = 5.2Hz, 2H), 3.72 (d, J = 13.2Hz, 1H), 3.61 (d, J = 13.6Hz, 1H), 3.47 (d, J = 5.6Hz, 1H), 3.29-3.22 (m, 4H), 2.43 (brs, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 171.8, 139.4, 138.7, 128.5, 128.1, 127.5, 127.3, 72.3, 61.8, 58.8, 52.7, 42.3; EIMS *m/z* (%): 299 (M+1, 100), 267 (40), 164 (90), 132(40).

2-Amino-*N*-benzyl-3-methoxypropanamide (4)

To a solution of 3 (4.0 g, 13.40 mmol) in methanol (40 mL, 10 vol) and added 10% Pd/C (0.6 g, 15% w/w) under nitrogen atmosphere at 25-30°C, reaction mass par vessel fix to the par hydrogenation and flushed with 2x10psi of

hydrogen gas and finally applied the 50 psi of hydrogen pressure and stirred for 4hr at 25-30°C, reaction mixture was filtered through celite bed and washed with methanol (40 mL, 10 vol) under nitrogen atmosphere. The filrate was concentrated completely under reduced pressure to afford pale yellow colored liquid **4** (2.5g), yield: 88.6%

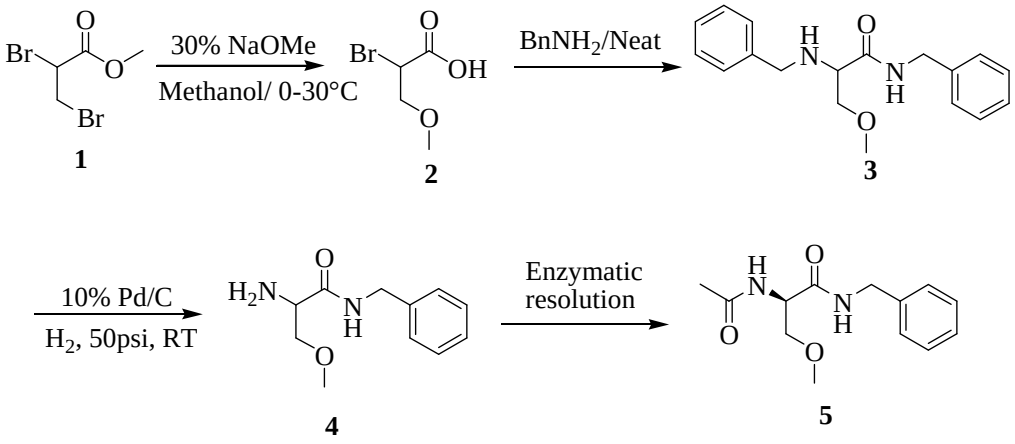
IR (KBr): υ 3311, 3062, 2925, 2825, 1656, 1524, 1454, 1251, 1106, 736, 700. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (brs, 1H), 7.32-7.20 (m, 5H), 4.29 (t, J = 5.6Hz, 2H), 3.45-3.41 (m, 3H), 3.25 (s, 5H), 2.82 (brs, 2H, -NH_2); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.5,138.2,128.5,127.5,127.2,72.4,58.7,54.7,43.02; EIMS *m/z* (%): 209 (M+1, 100), 177 (27), 164 (70), 149 (40), 132 (60), 115 (20), 108 (50).

(*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide (Lacosamide) (5)

To a solution of **4** (2.0g, 9.6mmol) in toluene (20mL, 10vol) at 25-30 °C was added Novozyme 435 (500mg) followed by vinyl acetate (5eq) drop wise at the same temperature. The reaction mass was heated to 55-60°C and stirred for 16hr. After completion of reaction, the reaction mixture was diluted with methanol (10v) and removed enzyme by filter through celite bed and washed with methanol (5vol). Filtrate was evoparated completly under reduced pressure. Obtained crude was purified by column chromatography on 100-200 silicagel by eluting Methnol/DCM (1:9) to obtain **5** (1.68g), yield: 70%

MP: 142-143°C, IR (KBr): υ 3290, 3081, 2924, 2880, 2358, 1639, 1550, 1453, 1384, 1135, 737; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (brs, 1H), 8.04 (d, 8.0Hz, 1H), 7.32-7.20 (m, 5H), 4.46 (q, J_1 = 5.6Hz, J_2 = 13.6Hz, 1H), 4.25 (d, J = 5.6Hz, 2H), 3.54-3.47 (m, 2H), 3.25 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.3, 169.9, 137.8, 128.5, 71.7, 58.9, 52.4, 43.4, 23.0; EIMS *m/z* (%): 251 (M+1, 100), 219 (16), 209 (20), 217 (14), 149 (40), 144 (43), 166 (18), 108 (70), 91 (12).

RESULTS AND DISCUSSION



Scheme- 1

The reaction of methyl 2,3-dibromopropionate, **1** converted in to corresponding acetate by treatment with 30% sodium methoxide in methanol under stirring conditions for 3 hr at 25-30°C, 50% NaOH solution was added and stirring continued for additional 30 min furnished 2-bromo-3-methoxypropanoic acid, **2** with 88.2% yield and compound **2** subjected to react with benzyl amine without any base and solvent coupling condition placed in a sealed tube and warm to at 120-125°C and stirred for 48hr afforded *N*-benzyl-2-(benzylamino)-3-methoxy propanamide, **3** with 68.1% yield. The compound **3** in methanol is treated with 10% Pd/C under nitrogen atmosphere at 25-30°C produced 2-amino-*N*-benzyl-3-methoxypropanamide, **4** with 88.6% yield.

Table-1: Enzymatic Reactions HPLC chromatograms

S.No	Enzymes	S-LCM	R-LCM
1	Lipozyme RM IM	45.57	54.53
2	Lipozyme TL 100L	86.22	13.78
3	NovozymebS1032	55.04	44.96
4	Alcalase 2.5L	56.66	43.34
5	Lipozyme TLIM	62.49	37.51
6	Patalase 20000L	52.48	47.52
7	Novozyme 435	6.21	93.79

Compound **4** was reaction with enzymatic resolution as tabulated aboue in table-1 to get (*R*)-2-amino- *N*-benzyl-3-methoxypropionamide, **5** precipitated were extracted with excellent enantioselectivity afford (*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide (Lacosamide) **5** was obtained in good yields (**Scheme I**).

CONCLUSION

We successfully synthesized In conclusion, new and alternate synthesis of Lacosamide, **5** with chemo enzymatic method has been described using chiral resolution method. The main advantages of the present method include high enantioselectivity, the ready availability of the starting material and reagents. Moreover, high yields of the products inexpensive and non-toxicity of the reagent are noteworthy advantages of this method.

Acknowledgements
The authors thank to *Osmania University*, Hyderabad for the support and encouragement.

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