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Chiral pool approach for the synthesis of functionalized amino acids: synthesis of antiepileptic drug (*R*)-lacosamide

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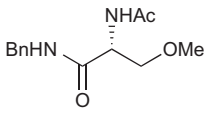
ABSTRACT

An efficient total synthesis of (*R*)-lacosamide **1** has been achieved from *N*-Boc-*N*,*O*-isopropylidene-L-serinol **2** which could easily be obtained from natural L-serine. Our synthesis of **1** starting from **2** using chiral pool strategy resulted in 54% overall yield.

Introduction

Epilepsy is a neurological disorder due to which patients suffering from this disease witness recurrent spontaneous seizures. It is believed that this disease affects approximately 50 million people worldwide and India alone accounts for approximately 10 million cases.[1] (*R*)-lacosamide **1** (Vimpat, Fig. 1) is currently being used clinically in the U.S. and Europe to treat people suffering from this disease. Although, the exact mode of action of this drug in humans is not yet deciphered however, it is widely believed that it increases the slow inactivation of the voltage-gated sodium channels thus inhibiting repetitive neuronal firing.[2]

Till date several synthesis of **1** have been reported using racemic epichlorohydrin[3] or acrylic acid[4] or ethyl L-lactate[5] or racemic butadiene monoepoxide[6] or D,L-serine[7] or D-serine,[8] respectively as starting materials. The kinetic resolution of the key intermediate using Hydrolytic Kinetic Resolution (HKR)[3] leads to the loss of yield during the resolution step whereas Trost's dynamic kinetic asymmetric transformation (DYKAT)[6] requires ligands, which are expensive. In some of the synthesis racemic lacosamide has been resolved to (*R*)-enantiomer either using crystallization[7a] with chiral carboxylic acid or chiral chromatography.[7b] The synthesis of **1** utilizing D-serine as a starting material involves *O*-methylation which undergoes racemization.[8c,g–j,l] In order to overcome this drawback, Kohn et al.[8c] used neutral but rather expensive Kuhn's *O*-methylation protocol,[8a] which requires Ag_2O.



(*R*)-Lacosamide (**1**)

Figure 1. Structure of antiepileptic drug, Lacosamide **1**.

Results and discussions

We thought of an efficient and straightforward synthesis of **1**, which could be achieved on an industrial scale at a much cheaper cost. We envisaged the synthesis of **1** could be achieved as delineated in Scheme 1. The key starting material, *N*-Boc-*N*,*O*-isopropylidene-L-serinol **2** could easily be synthesized[9] in gram scale from natural L-serine in four steps without the need of any purification of the intermediates. *N*-Boc-protected alcohol **4** would lead us to the desired product **1** after protection/deprotection and functional group manipulations. Also, our synthesis would enable the generation of various *O*-substituted congeners of (*R*)-lacosamide **1** for further development of new potent anti-epileptic agents.

We started the synthesis of (*R*)-lacosamide **1** from readily available *N*-Boc-*N*,*O*-isopropylidene-L-serinol **2**.[9] Methylation of the

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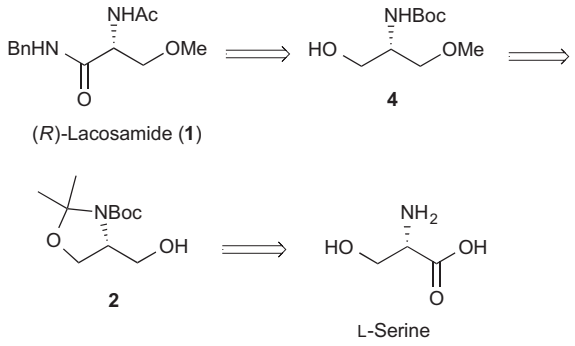
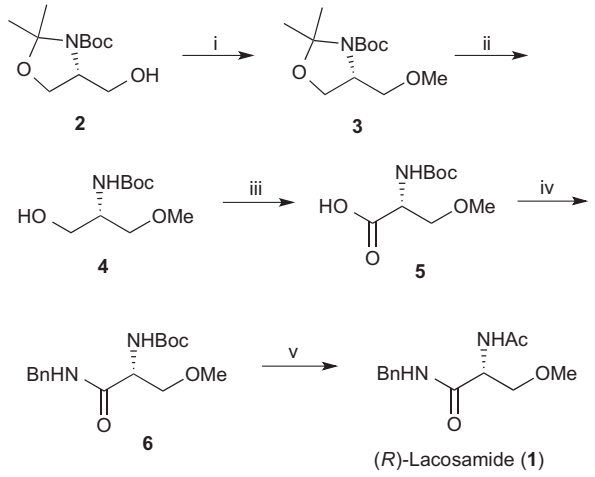
0040-4039/



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



Scheme 2. Synthesis of Lacosamide **1**. Reagents and conditions: (i) NaH, MeI, THF, rt, 30 min, 88%; (ii) PTSA, MeOH, rt, 5 h, 86%; (iii) TEMPO, NaOCl, $NaClO_2$, CH_3CN, rt, 3 h, 99%; (iv) $C_6H_5CH_2NH_2$, *N*-methyl morpholine, isobutyl chloroformate, THF, −78 °C to rt, 1 h, 90%; (v) (1) TFA, DCM, rt, overnight; (2) Ac_2O, DMAP, DCM, rt, 4 h, (80% over 2 steps).

alcohol **2**[10] with methyl iodide in THF in the presence of sodium hydride furnished the ether **3** in 88% yield (Scheme 2). Deprotection of acetonide group[10] of **3** with *p*-toluene sulphonic acid in methanol resulted in the formation of compound **4**, which on oxidation of the primary alcoholic group with TEMPO resulted in the clean formation of the acid **5** in 99% yield that was used in the next step as such. Next, the acid **5** was coupled with benzyl amine using *N*-methyl morpholine and isobutyl chloroformate in THF to furnish the amide **6** in 90% yield. The deprotection of the Boc group followed by acetylation of the resulting amine was achieved in one pot, which furnished the desired product (*R*)-lacosamide **1** in 80% over two-steps {mp 140–141 °C [Lit. 140–141 °C,[4] 142–143 °C,[5] 143–144 °C[6]]; $[\alpha]_D^{25}$ +15.9 (*c* 1.01, MeOH) [Lit. +16.2 (*c* 1, MeOH),[4] +16.1 (*c* 1.2, MeOH),[5] +16.1 (*c* 1, MeOH)[6]]}. The spectral data were in complete agreement with reported literature data.[3–8,11] The chiral HPLC analysis of compound **1** suggested that no racemization has occurred during the synthesis (see Supporting information).

Conclusion

In summary, a short and straightforward synthesis of (*R*)-lacosamide **1** has been achieved in five steps with an overall yield of 54%. The key starting material could be synthesized in gram scale from L-serine in four steps without requiring chromatography. The highlights of this synthesis are short and high yielding reaction steps without the need of any kinetic resolution or the use of chiral ligands thereby making it more commercially viable considering that the molecule is presently being used as a drug. Further using our synthesis, diverse *O*-substituted analogues of (*R*)-lacosamide **1** could be synthesized for further development of new potent anti-epileptic agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.077.

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11. *Spectral data of (R)-lacosamide (**1**):* mp 140–141 °C [Lit. 140–141 °C,[4] 142–143 °C,[5] 143–144 °C[6]]; $[\alpha]_D^{25}$ +15.9 (*c* 1.01, MeOH) [Lit. +16.2 (*c* 1, MeOH),[4] +16.1 (*c* 1.2, MeOH),[5] +16.1 (*c* 1, MeOH)[6]]; IR ($CHCl_3$) υ_{max}: 3671, 3421, 3304, 3015, 2933, 2404, 1657, 1515, 1456, 1376, 1218, 1115, 927, 762, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.21 (m, 5H), 7.02 (br s, 1H), 6.66 (d, *J* = 6.1 Hz, 1H), 4.60 (dt, *J* = 4.4, 7.0 Hz, 1H), 4.51–4.37 (m, 2H), 3.77 (ddd, *J* = 1.7, 4.2, 9.2 Hz, 1H), 3.46 (dd, *J* = 7.5, 8.7 Hz, 1H), 3.36 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 170.0, 137.9, 128.7, 127.4, 71.9, 59.1, 52.5, 43.5, 23.1; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}N_2O_3Na$ $[M+Na]^+$ 273.1210; found: 273.1195; ee >99.9% [The ee of (*R*)-lacosamide (**1**) was determined by chiral HPLC analysis: Chiralcel OD-H (0.46 cm × 25 cm), *iso*-propyl alcohol-^{n}hexane-trifluoroacetic acid (30:70:0.1), flow rate 0.5 mL/min; UV detection at 220 nm; t_R = 10.5 min]; for complete experimental procedures and spectral data of all the compounds, see Supporting information.