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Improved Synthesis and Impurity Identification of (*R*)-Lacosamide

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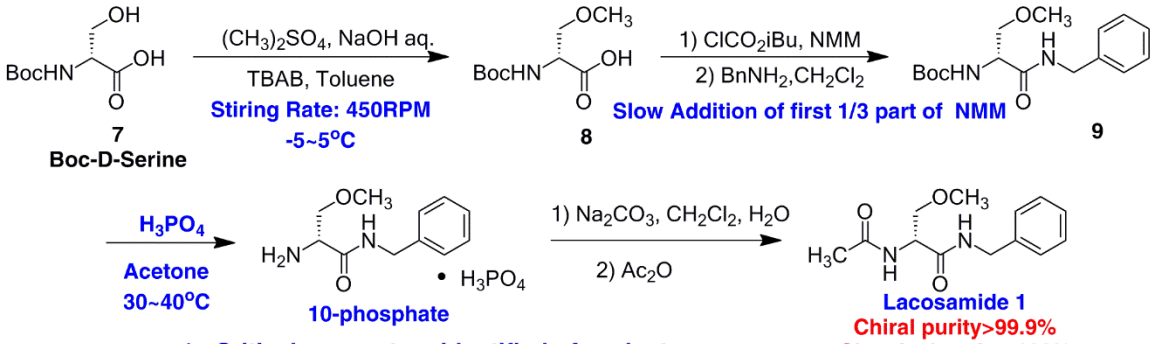


1. Critical parameters identified of each step
2. H_3PO_4 used for deprotecion of 9 instead of HCl
3. Improved chiral purity of 10 by forming salt with H_3PO_4
4. 16 Impurities recorded!
5. 68.4% overall yield with >99.9% chiral purity and 100% chemical purity

Abstract

An improved synthesis of Lacosamide **1** with high purity has been developed. Critical parameters of each step were identified as well as the impurities generated. Moreover, a creative method to improve chiral purity and stability of the key intermediate (*R*)-2-amino-N-benzyl-3-methoxypropionamide **10** by forming salt with an achiral acid (phosphoric acid) was discovered to ensure the chiral purity of (*R*)-Lacosamide. Phosphoric acid was further developed for the deprotection of the Boc group.

KEYWORDS

Lacosamide; improved synthesis; chiral purity; phosphoric acid; impurity

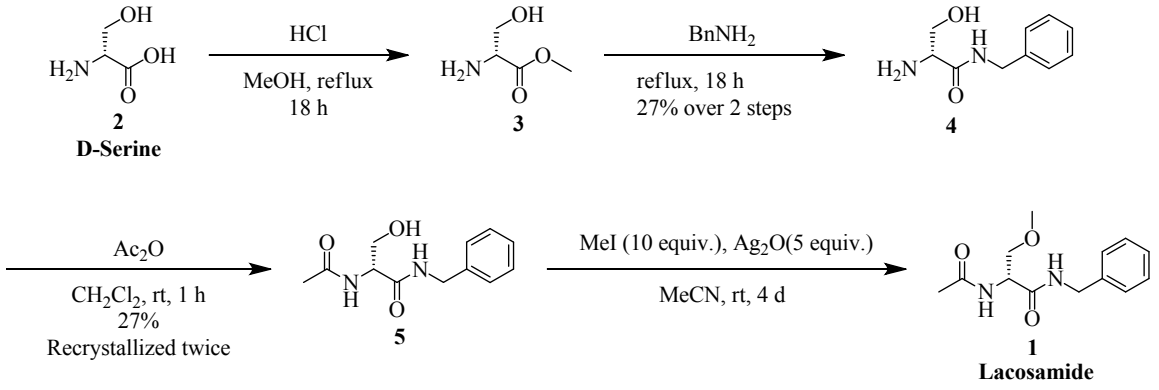
1. INTRODUCTION

(R)-Lacosamide **1** is chemically known as (R)-2-acetamido-N-benzyl-3-methoxypropionamide and the drug substance of Vimpat, which was first launched by UCB Pharma in the United States, Europe and Japan for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy[1].

Several methods were reported to synthesize *(R)*-Lacosamide **1** in the past decades, and the first-generation route was reported by Choi and colleagues[2] using D-serine as a starting material (**Scheme 1**). The advantage of this route was that the chiral center of *(R)*-Lacosamide **1** was directly introduced by D-serine. Moreover, it would be more efficient

and advantageous if there was no need to protect the amino group on D-serine. However, the fact was that the amino group of **3** could react with the ester group of itself, which would lead to a low yield (27%) for the first 2 steps. The second disadvantage of this route was the need of excessive silver oxide (Ag_2O, 5 equiv.), which was expensive and unaffordable for large-scale or industrial manufacture. The third disadvantage was racemization (approximately 33%), which was the biggest challenge to meet with for the synthesis of Lacosamide **1** with high chiral purity. In order to obtain optically pure **5**, repeated recrystallization was needed, which led to a low yield of the third step (29%) as well as the overall yield (6.9%).

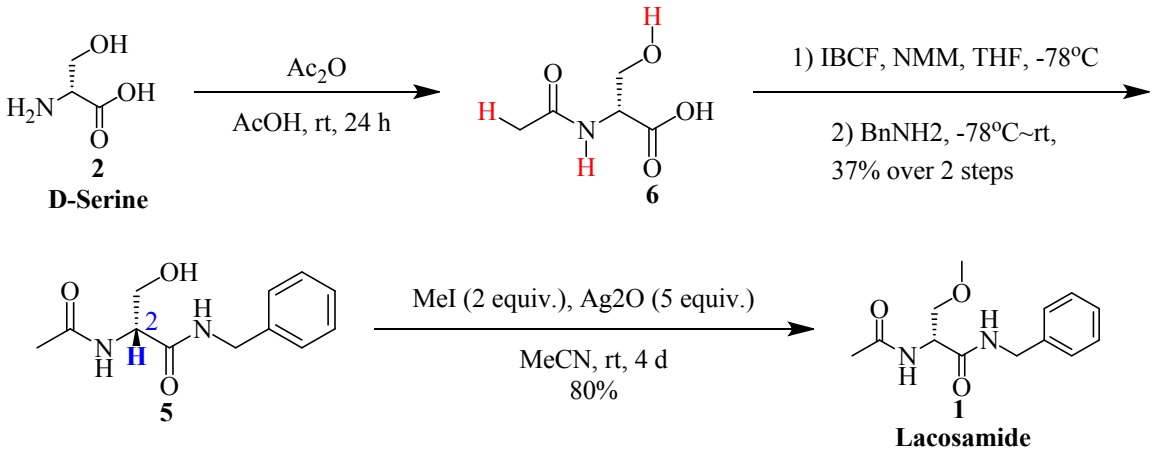
Scheme 1. First-Generation Synthetic Route of *(R)*-Lacosamide **1**



The second-generation synthetic route was also reported by Choi and colleagues[2] (**Scheme 2**), where acetyl group was installed first, followed by amidation and methylation. The advantage of this route was no racemization, while the yield over the first two steps was only 37% and it required column chromatography. The reason was

that the alcoholic hydroxyl group of **6** could be acetylated in the first step or react with isobutyl chloroformate (IBCF) in the second step respectively. Another disadvantage of this route was still the need of excessive silver oxide (5 equiv.). We have tried to use other conditions for the methylation. However, if extreme strong bases were used for the methylation, only almost totally racemized Lacosamide was obtained. The reason was that the hydrogen at C(2) position of **5** (marked in blue in **Scheme 2**) was easily deprotonated by strong bases, which promoted the racemization. In addition, if the base was too strong, N-acetyl group (N-Ac) of **5** could easily be methylated, which would lead to large amount of N-Ac methylated byproducts. As the properties of the byproducts were quite similar to Lacosamide **1**, column chromatography was needed for the purification of Lacosamide **1**, which limited the prospect for commercial manufacture. In contrast, if the base was too weak , the alcoholic hydroxyl group of **5** could not be deprotonated, which would lead to the failure of methylation. In summary, deprotonation of C(2)-H and alcoholic hydroxyl group of **5** should be balanced.

Scheme 2. Second-Generation Synthetic Route of *(R)*-Lacosamide **1**

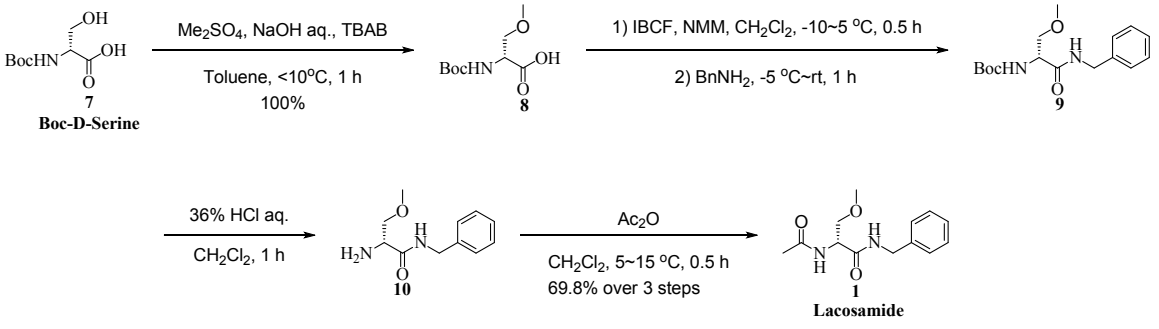


Another route[3] similar to the second-generation route, which installed N-Ac first but changed the order of amidation and methylation, was also reported. However, after N-Ac being installed, the next step methylation was problematic. The reason was that there were three positions of N-Ac product **6** (marked in red in **Scheme 2**) could be methylated by dimethyl sulfate in combination with lithium hydroxide as reported. It turned out to be a complex mixture of desired O-methylated product, two mono-methylated byproducts and some di-methylated byproducts, which made it difficult to isolate the desired O-methylated product by simple crystallization and limited the prospect for commercial manufacture.

To avoid the intrinsic defect of the first-generation and second-generation synthetic routes, the third-generation synthetic route[4] (**Scheme 3**) was developed and reported by UCB Pharma through protecting the amino group of D-serine with the t-butyloxycarbonyl

group (Boc group) before methylation, amidation and acetylation. The biggest advantage of this route was that racemization could be greatly reduced using tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in combination with medium-intensity base sodium hydroxide and dimethyl sulfate, which avoided the use of silver oxide. In addition, no obvious racemization occurred in the next three steps. The second advantage was that methylation on N-H of Boc-D-serine was greatly inhibited due to the steric hindrance of the Boc group compared with the Ac group of the second-generation route. The third advantage was high yield (69.8%) under mild reaction conditions with relatively simple work-up procedures. The first disadvantage of this route was its lack of robustness; the chiral purity of the product **8** showed a large batch to batch variation as we observed 4-8% of the wrong enantiomer.. The second disadvantage was that there was no purification for the intermediates and only the final product Lacosamide **1** was purified, which would make the quality control difficult.

Scheme 3. Third-Generation Synthetic Route of *(R)*-Lacosamide **1**



Other protecting groups were also reported, such as such as the carbobenzoxy group[5] (Cbz group) and the trityl group[6] (Tr group). While the yield of the route using the Cbz group (33.9%) or the Tr group (14.0%) was obviously lower. Moreover, the atom economy was the best in the route using the Boc group.

Some routes[7-8] similar to the third-generation route were reported as well, which just changed the order of methylation, amidation and acetylation. However, as we mentioned above, if the order was changed, the impurities would greatly increase, which would sacrifice the yield or purity significantly.

Other routes were also reported[9-16] such as introduction of chiral center by resolution or asymmetric synthesis, and some of them are novel and quite creative. However, considering the productivity and cost for scale-up, the third-generation route was advantageous. Therefore, it was determined that the third-generation route was more suitable for further investigation of scale-up, especially for commercial manufacture.

Herein, we report an improved synthetic process for *(R)*-Lacosamide **1**, which solved the slight partial racemization of the third-generation route. Moreover, the impurities generated in a process play an important role in researching the quality of a drug substance and evaluating a synthetic route, as well as helping researchers choose the best synthetic route and conditions. Therefore, we wish to report the impurities generated within this process, which have not yet been reported to our knowledge.

2. RESULTS AND DISCUSSION

The UCB Pharma's synthetic route involves the following four steps: methylation of Boc-D-serine **7**, condensation of **8** with benzylamine ($BnNH_2$), deprotection of **9**, and acetylation of **10** (**Scheme 3**).

2.1 The synthesis of 8

During the route selection period it was found that the chemical purity of **8** was 91.7% when a magnetic stirrer was employed. The major impurities (**Table 1)** were D-serine **11** (2.3%) and unreacted starting material, Boc-D-serine **7** (2.8%). D-serine **11** was introduced by the starting material, because the commercial Boc-D-serine **11** contained appoximately 5% D-serine **11**. Impurity **12** (0.23%) (**Table 1**) was also detected as a minor impurity, which was formed because N-H of Boc-D-serine **7** was also methylated. The major problem with this reaction was an unstable chiral purity of **8**, where the highest was 99.0% and the lowest was 88.2% for the first 3 batches. It was found that the reason for poor chiral purity might have been the discontinuous stirring, which led to a somewhat high concentration of base (high pH) and sequentially racemization. The discontinuous stirring resulted from the reaction mixture being viscous and hard to stir well using a magnetic stirrer. To ensure good stirring, we switched to a mechanical stirrer, and it was found that stirring speed was critical for this reaction. The reaction could not go completely at the

initial speed of 200 revolutions per min (RPM) until it was adjusted to 450 RPM. Meanwhile, both chemical and chiral purity were more stable at a speed of 450 RPM. The influence of temperature was further investigated. If the temperature was lower than -5°C, the reaction mixture started to freeze and could not be stirred well even by a mechanical stirrer. In contrast, if the temperature was higher than 10°C, both chemical and chiral purity decreased. In summary, stirring speed and temperature played important roles in the quality of **8**. Both chemical and chiral purity were improved through controlling both the temperature and stirring speed.

2.2 The synthesis of 9

A major impurity (**Table 1)** could attain up to 8.3% in one of the first three batches, which could not be removed during workup. After isolation and characterization, it was confirmed as **15** .

It might be formed because the mixture of **8** and chloroformate ($ClCO_2iBu$ or IBCF) only reacted when N-methylmorpholine (NMM) was added to form the carboxylate salt. When the base was added too fast, the exothermic neutralization heated up the mixture and caused the side reaction. Moreover, some **15** reacted with benzylamine and further produced a small amount of **16** (0.3%). To reduce **15** and **16**, the addition time of N-methylmorpholine was prolonged and the addition rate was also slowed down, especially

during the addition of the first 1/3 part of N-methylmorpholine. As a result, the amount of **15** dropped to less than 2.1%.

The other impurities (**Table 1)** were **14** (1.1%), **17** (0.83%) and **18** (0.27%). **14** was introduced because the unreacted Boc-D-serine of the previous step reacted with isobutyl chloroformate and benzylamine. **17** was formed due to the reaction of isobutyl chloroformate and benzylamine. **18** was formed because of the reaction of **12**, isobutyl chloroformate and benzylamine as the formation of **9**.

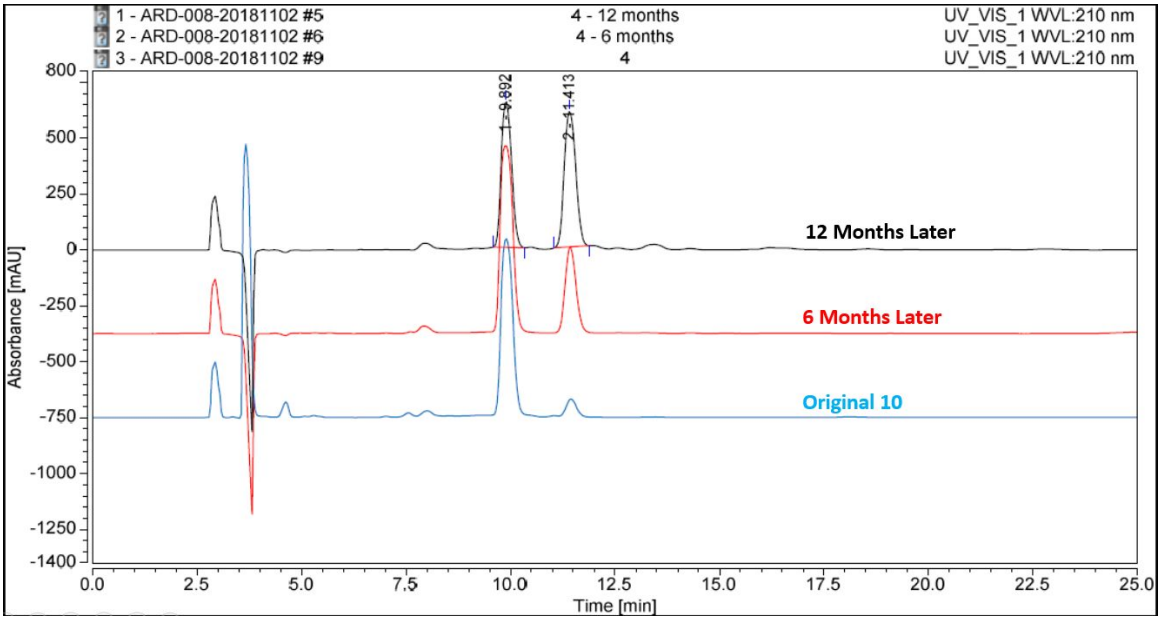
2.3 The synthesis of 10 and 10-phosphate (Scheme 4)

The major impurities (**Table 1)** were **15** (0.47%), **16** (0.27%), **20**(1.1%) and **21** (0.24%). **15** and **16** were formed in the previous step. **14**, which was formed in the second step, was deprotected in this step and formed **20** (1.1%). **21** (0.24%) was formed due to the reaction of **18** and hydrochloric acid.

As the intermediates of the entire process (**8, 9 and 10**) were oils, and the chiral purities of them were approximately 95% after optimization, which would produce Lacosamide **1** with low chiral purity according to the existing procedures. Moreover, it was found that the chiral purity of **10** could decrease from 95.66% (blue trace in Figure 1) to nearly 50% (black trace in Figure 1) in 12 months, which meant the chiral purity of **10** free base was not stable enough. As **10-hydrochloride** did not precipitate during the whole step of deprotection, we failed to obtain **10-hydrochloride** according to the existing procedure.

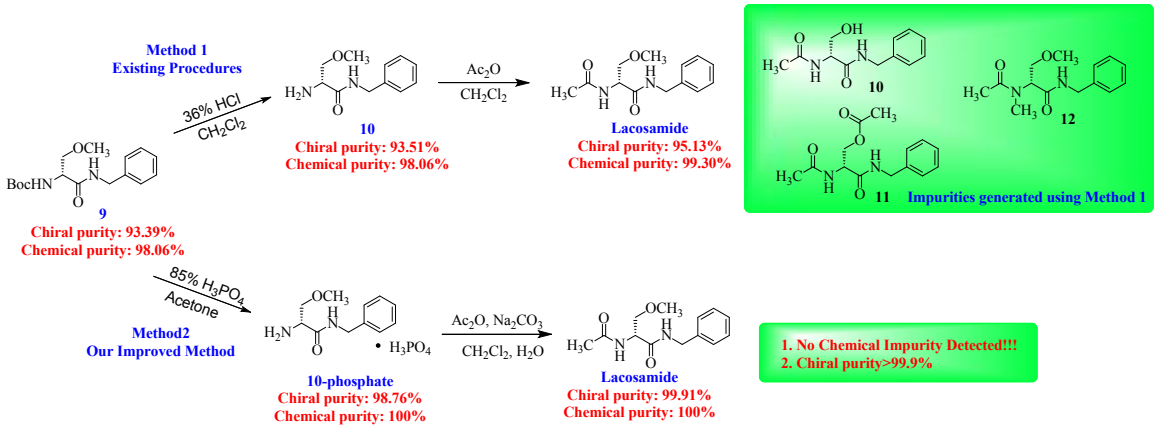
In order to eliminate the influence of water, we also tried to get **10-hydrochloride** by forming a salt with the obtained free base of **10** using hydrochloric acid – ethyl acetate solution instead of aqueous hydrochloric acid solution. However, **10-hydrochloride** could not be precipitated in different solvents such as ethyl acetate, isopropanol, tetrahydrofuran, acetone and dichloromethane. Therefore, to improve chiral purity and stability of **10**, several other acids (L-tartaric acid, fumaric acid, malic acid, succinic acid, sulfuric acid, phosphoric acid, acetic acid etc.) were screened to form a salt with **10**, which had a relatively lower chiral purity (93.51%). To our surprise, phosphoric acid turned out to be the best, with both improved chemical and chiral purity[17]. Additionally, the chiral stability was also improved significantly, and there was almost no change of chiral purity in 12 months for **10-phosphate**. Phosphoric acid was also further employed to deprotect **9** for the synthesis of **10** and **10-phosphate** in one pot. After screening several solvents like ethyl acetate, isopropanol, tetrahydrofuran, acetone, acetonitrile, isopropyl ether and dichloromethane, 10-phosphate could be precipitated successfully in acetone.

Figure 1. Chiral stability of intermediate **10:** HPLC chromatograms for the comparison of chiral purity. Original **10** (blue), 6 months later (red), 12 months later (black).



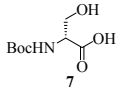
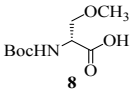
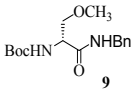
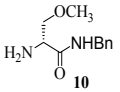
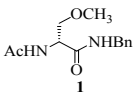
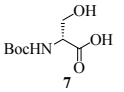
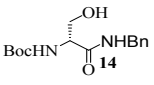
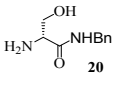
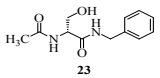
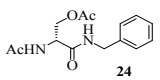
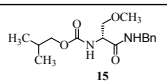
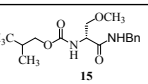
2.4 The synthesis of Lacosamide 1 (Scheme 4).

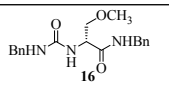
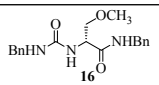
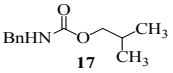
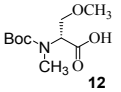
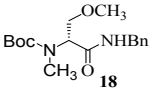
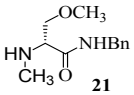
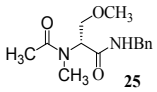
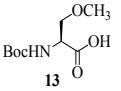
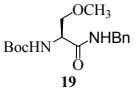
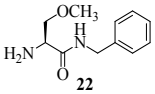
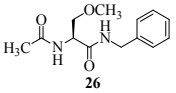
Scheme 4. Synthesis of Lacosamide: comparison between the existing procedures and our improved method.



As for the synthesis of Lacosamide (**Scheme 4)**, two different sources of **10** were adopted and compared. The first one was free base of **10**. Three major impurities (**Table 2)** detected were **23** (0.31%), **24** (0.23%) and **25** (0.19%). Additionally, if the chiral purity of **10** free base was lower than 95%, then the chiral purity of Lacosamide **1** synthesized from the free base would be lower than 96%. Lacosamide **1** derived from the second source of **10** as **10**-phosphate, was found to be both chemically (100 % HPLC) and chirally pure (>99.9 %), making the later as much superior choice of substrate 10.

Table 1. The impurity profiles for *(R)*-Lacosamide **1**

Step	0	1	2	3	4
SM& IM	 **7** **Boc-D-Serine**	 **8**	 **9**	 **10**	 **1**
Byproducts in steps	 **11** **D-Serine**	 **11** **D-Serine**			
		 **7** **Boc-D-Serine**	 **14**	 **20**	 **23**  **24**
			 **15**	 **15**	

			 16	 16	
			 17		
		 12	 18	 21	 25
		 13	 19	 22	 26

3. CONCLUSIONS

Anew strategy to ensure chiral purity of Lacosamide was discovered through controlling chiral purity of the intermediates **8** and **10**. For intermediate **8**, parameters were optimized to ensure a more stable and better chemical purity(>90%) as well as chiral purity (>95%). For intermediate **10**, a new method to improve its chiral purity and stability through forming a salt with achiral phosphoric acid was developed. Phosphoric acid was further developed for the deprotecting of **9** as well, which made the deprotecion and salt forming in one pot. Moreover, the impurity profiles of both existing method and our improved route were elucidated and compared, which showed our improved route to be advantageous.

4. EXPERIMENTAL SECTION

General Methods. All of the reagents and solvents were obtained from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded by a Bruker 400 or 600 MHz spectrometer. Chemical shift data are reported in δ (ppm) from the internal standard TMS. High resolution mass spectrum were recorded on a Bruker maXis 4G Q-TOF instrument. Melting points were measured on a WRS-1B apparatus. Purities of In-Progress-Control samples, the isolated intermediates and the final product were analyzed by high-performance liquid chromatography (HPLC, normalized area percentage). The HPLC analyses were recorded by a standard method on a Dionex UItiMate 3000 HPLC instrument. The chemical purity was analyzed by using an Angilent Eclipse XDB-C18 (5 μm,46 mm×250 mm), 30°C, 1 mL/min, 210 nm, 45 min. Mobile phase: A (20mM 1-octane sulfonic acid sodium salt, pH 2.1), B (acetonitrile). The mobile phase gradient is shown in **Table 2.** The chiral purity was analyzed by a Chiral Pak AD-H,(5 μm,46 mm×250 mm), 30°C, 1 mL/min, 210 nm, 25 min. Mobile phase: A (0.05% diethylamine in n-hexane), B (isopropyl alcohol). The gradient started with 15% of B; the ratio was maintained for 25 min.

Table 2: The HPLC mobile phase gradient for chemical purity

Time(min)	Mobile phase B(%,V/V)
0	15
4	15

7	20
15	20
25	45
40	45
40	15
45	15

Preparation of (R)-2-N-Boc-amino-3-methoxypropanoic acid (intermediate 8). A suspension of N-Boc-D-serine (100.0 g, 0.48 mol, 1.0 equiv.) and tetrabutylammonium bromide (TBAB, 5.2 g, 0.0195 mol, 0.04 equiv.) in toluene (500 ml) was cooled to 0~10°C. Then, 20% wt NaOH aq. (97.5 g, 0.48 mol, 1.0 equiv.) was added at 0~10°C, and the resultant mixture was aged for 30 minutes at 0~10°C. Dimethyl sulfate (246 g, 1.95 mol, 4.0 equiv.) and 50% wt NaOH aq. (179.5 g, 2.245 mol, 4.6 equiv.) were added at -5~5°C and the mixture was aged for 20 hours at -5~5°C. Water (300 ml) was added to the mixture. Then, the aqueous layer was separated and acidified to pH <3.5 with 50% citric acid and extracted with dichloromethane (2×500 ml，1×300 ml). The combined extracts of **8** were evaporated to dryness to give crude **8**. (107.1g, crude yield 100%).

Preparation of (R)-N-benzyl-2-N-Boc-amino-3-methoxypropionamide (intermediate 9). Intermediate **8** was dissolved in dichloromethane (800mL) and cooled to -10~0°C. Then, isobutyl chloroformateu (66.6 g, 0.49 mol, 1.0 equiv.) was added at -10~-5°C. The first 1/3 part of N-methylmorpholine (26.3 g, 0.26 mol, 0.53 equiv.) was added very slowly at -10~-5°C (1~2 h), and the rest 2/3 of N-methylmorpholine (52.6 g, 0.52 mol,

1.07 equiv.) was further added in 1 h. After addition of N-methylmorpholine, the mixture was aged for 30 minutes at -10~-5°C. A solution of benzylamine (53.8 g, 0.50 mol, 1.03 equiv.) in dichloromethane (200 mL) was added at -10~-5°C and the mixture was warmed to 10~15°C. After being aged for 2 hours, the mixture was washed with water (200 ml), 1N HCl (200 ml), 8% sodium bicarbonate aqueous (8% $NaHCO_3$ aq., 200 ml) and water (200 ml). The organic phase was evaporated to dryness to give crude **9**., (150.3g, crude yield 100%, chemical purity 94.72%, chiral purity 95.33%).

Preparation of (R)-2-amino-N-benzyl-3-methoxypropionamide phosphate (intermediate 10-phosphate). Phosphoric acid (85% wt, 280.9 g, 5.0 equiv.) was added dropwise to a solution of **9** (150.3 , 0.48 mol, 1.0 equiv.) in acetone (1000 mL) at 0~10°C.. The mixture was warmed to 40°C before being stirred for 6 hours and then cooled to 0~5°C by gradient cooling. The mixture was stirred at 0~5°C for additional 2 hours forming a suspension.The solid was collected by filtration, then washed with acetone (100 mL), and dried at 45°C under vacuum to give **10-phosphate** as a white solid (133.7g, 89.0% yield, chemical purity 100.0%, chiral purity 99.37%). Anal. Calc'd for $C_{11}H_{22}N_2O_6P$: C, 43.14; H, 6.25; N, 9.15. Found: C, 43.08; H, 6.23; N, 9.36; Mp: 178.1~179.0 °C; ^{1}H NMR (600 MHz, D_2O) δ 7.34 (ddd, J = 17.1, 11.6, 7.3 Hz, 5H), 4.42 (dd, J = 69.3, 15.2 Hz, 2H), 4.24 (t, J = 4.7 Hz, 1H), 3.82 (d, J = 4.8 Hz, 2H), 3.36 (s, 3H); ^{13}C NMR (600 MHz, D_2O) δ 167.29, 137.42, 128.79 (2×C), 127.59, 127.20 (2×C), 69.95, 58.78, 52.83, 43.16.

Preparation of (R)-2-acetamido-N-benzyl-3-methoxypropionamide (Lacosamide). Na_2CO_3 (41.5 g, 0.392 mol, 1.0 equiv.) was added to a mixture of **10**-phosphate (120.0 g, 0.392 mol, 1.0 equiv.), water (600 mL) and dichloromethane (1200 mL). Then, the reaction mixture was stirred for 30 min. The organic phase was collected and cooled to 0~5°C. Ac_2O (40.0 g, 0.392 mol, 1.0 equiv.) was added slowly to the organic phase at 0~5°C. Then, the mixture was stirred at 10~20°C for 2 hours. Water (600 mL) was added to the mixture and the organic phase was separated, which was then washed with 8% $NaHCO_3$ aaq. (240 mL) and water (240 mL) respectively. After organic phase being evaporated to dryness to obtain a crude product, ethyl acetate (600 mL) was added. The mixture was heated to reflux until it was dissolved, and then cooled to approximately 0°C by gradient cooling. Stirring was continued at 0°C for additional two hours forming a suspension. The precipitate was filtered and the obtained cake was dried at 40°C under vaccum (75.3 g, 76.8% yield, chemical purity 100.0%, chiral purity 99.94%). Anal. Calc'd for $C_{13}H_{18}O_3N_2$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.33; H, 7.22; N, 11.41; Mp 143.7−144.2°C (lit.[2] 143 - 144°C); $[\alpha]^{25}_D$ = +16.4° (c 1, MeOH) {lit.[2] 16.4° (c 1, MeOH)}; ^{1}H NMR (600 MHz, DMSO) δ 8.48 (t, J = 6.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.35 – 7.17 (m, 5H), 4.48 (dt, J = 8.0, 5.9 Hz, 1H), 4.28 (d, J = 6.0 Hz, 2H), 3.50 (ddd, J = 15.0, 9.7, 5.8 Hz, 2H), 3.25 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (151 MHz, DMSO) δ 170.22, 169.88, 139.76, 128.66(2×C), 127.42(2×C), 127.13, 72.58, 58.65, 53.11, 42.45, 23.03. HRMS(ESI) m/z calc'd for $C_{13}H_{18}O_3N_2$: 250.1317, found 251.1388($[M+H]^+$); 273.1212($[M+Na]^+$).

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, ^{13}C NMR, ESI-MS, HR-MS, DSC, XRPD and elemental analysis information for intermediate **10-phosphate** and **(*R*)-**Lacosamide; ^{1}H NMR, ^{13}C NMR and HR-MS information for impurities.

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Notes

The authors declare no competing financial interest.

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