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Total Synthesis of Lacosamide

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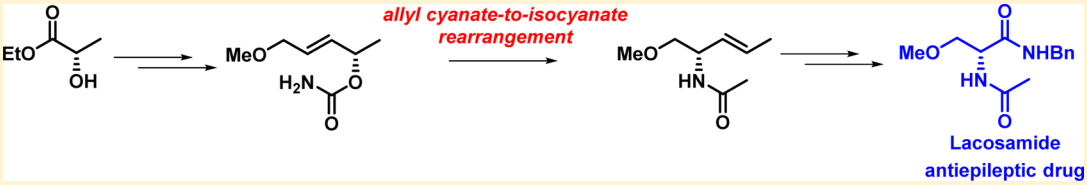
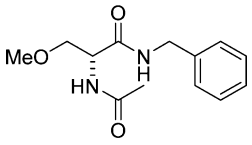
Supporting Information



ABSTRACT: Total synthesis of anticonvulsant amino acid, lacosamide, is reported. The key step is stereospecific allyl cyanate-to-isocyanate rearrangement, which proceeds with chirality transfer. The enantiopure starting material for the rearrangement step was accessed from ethyl L-lactate.

Epilepsy is the neurological disorder that disturbs the normal activity of the brain cells. It is estimated that this disease affects over 50 million people all over the world, and an additional hundreds of thousands are diagnosed with epilepsy every year.[1]

Lacosamide (**1**) is an active ingredient of Vimpat, which is dedicated for treatment of people with the above-mentioned disorder.[2−4] Although it was introduced to medical treatment in the U.S. and Europe just in 2008, the worldwide net sales of Vimpat strongly increases from year to year, from €211 million in 2011 to over €411 million in 2013.[4] The mechanism of action of lacosamide has not been completely unveiled, but it is believed that lacosamide operates on the sodium channels of the neurons, reducing their activity. In addition, lacosamide was also under clinical trials for treatment of a neuropathic pain.[5]



Lacosamide (**1**)

Because of the medicinal importance of **1**, the synthesis of this D-serine derivative has attracted many researchers at academia as well as in industry.[2,6,7] Early strategies mostly employed non-natural D-serine as a starting material, which is a serious drawback. The transformation of D-serine into **1** involves amidation, *N*-acylation, and *O*-methylation steps (including protective groups introduction and manipulation) in different order. The *O*-methylation step is the most problematic one because of a possible racemization of amino acid at this step.[2,7a−e] To avoid this, the *O*-methylation reaction is usually performed under neutral conditions by the Kuhn method[8] involving MeI and Ag_2O.[2,7a−e] Such an approach is rather expensive because of the costs of silver compounds and the necessity of a recovery and regeneration of silver byproducts after the methylation process. Other approches, which use *n*-BuLi/Me_2SO_4[7c] or bulky *N*-protective groups,[7e] are less commercially viable. In another approach, D-serine is transformed into the corresponding aziridine, which, upon BF_3·Et_2O catalyzed ring-opening with MeOH, furnishes lacosamide **1**.[6b]

Alternate strategies use D,L-serine as a starting material. The racemic lacosamide is then resolved to afford (*R*)-enantiomer (**1**) by employing chiral chromatography[7f] or crystallization of its non-*N*-acylated precursor (free amine) with a chiral carboxylic acid, for instance, mandelic acid.[7m] Other approaches apply enzymatic *N*-acylation, as either a kinetic or a dynamic kinetic resolution process.[7i,n]

The reports of asymmetric synthesis of **1** from a non-amino acid source are rare. For example, Muthukrishnan et al.[6e] described enantioselective synthesis of **1** based on hydrolytic kinetic resolution of the corresponding epoxide derivative. In another strategy, lacosamide **1** is prepared via enantioselective hydrogenation of the *β*-methoxy-substituted *α*-(acylamino)-acrylate derivative[6d,7o] Recently, Narsaiah and co-workers[6f] reported synthesis of **1** based on asymmetric dihydroxylation of the *N*-benzylacrylamide as a key step.

Since the so far developed strategies for preparation of **1** suffer from drawbacks, there is a need to find an alternative and improved process for the manufacture of lacosamide that would be competitive to the known ones, more cost-efficient, and lacking their major drawbacks. Recent reports by the Kohn group[9] revealed that also lacosamide analogues, for example, other *O*-substituted congeners, display interesting bioactivity and may be potent new anticonvulsant agents. Therefore, a need for a new and general synthetic strategy, which will lead to structurally diversified analogues of **1**, is even more urgent.

We sought a general and efficient procedure to prepare **1** that would eliminate the problem of partial racemization during the *O*-methylation step and, in addition, would permit different

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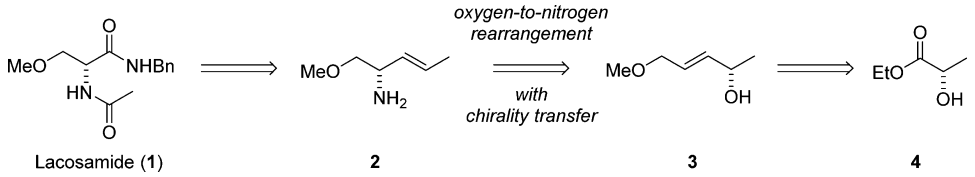
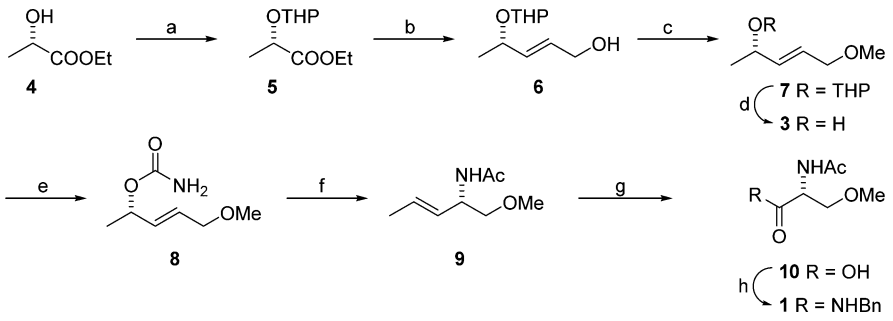
Scheme 1. Retrosynthetic Analysis of Lacosamide 1

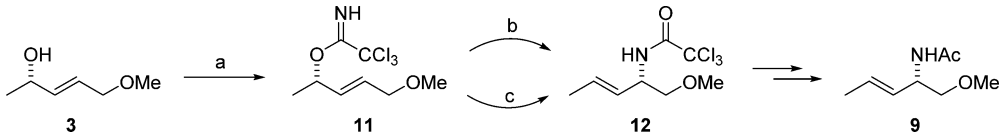


Scheme 2[a]



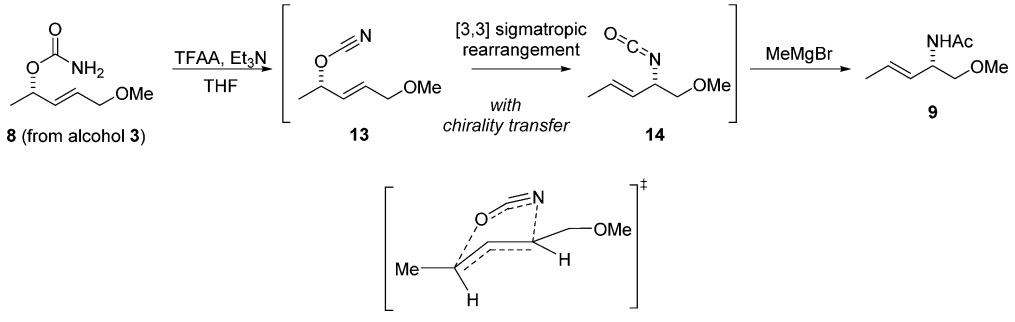
[a]Reagents and conditions: (a) DHP, PPTS, CH_2Cl_2, rt, 95%; (b) i. DIBAL-H (1.1 equiv), CH_2Cl_2, −78 °C; ii. NaH, $(EtO)_2P(O)CH_2COOEt$, THF, 0 °C; iii. DIBAL-H (2.2 equiv), CH_2Cl_2, −78 °C, 75% (3 steps); (c) NaH, MeI, THF, rt; (d) AcCl (5 mol %), MeOH, rt, 78% (2 steps − *O*-methylation and deprotection); (e) i. TCA-NCO, CH_2Cl_2, 0 °C, 1 h; ii. aq. K_2CO_3, MeOH, rt, 2 h, 82% (2 steps); (f) i. TFAA, Et_3N, THF, 0 °C, 30 min; ii. MeMgBr, THF, −10 °C to rt, 74% (3 steps); (g) $RuCl_3·H_2O$ (3 mol %), $NaIO_4$, acetone/water (5:1), 79%; (h) IBCF, NMM, $BnNH_2$, THF, −20 °C to rt, 82%.

Scheme 3. Transformation of Allylic Alcohol 3 into Amine 9 via Overman Rearrangement Approach[a]



[a]Reagents and conditions: (a) CCl_3CN, DBU (10 mol %), CH_2Cl_2, −10 °C, 80%; (b) K_2CO_3, xylene, 140 °C, 6 h, yield ∼ 15%; (c) $Pd(MeCN)_2Cl_2$ (5 mol %) THF, rt, 1 h, decomposition of starting material.

Scheme 4. Transformation of Allylic Carbamate 8 into Amine 9 via Allyl Cyanate-to-Isocyanate Rearrangement Approach



substituents at the 3-oxy, 2-aza, or amide site to provide other analogues of **1**. The proposed strategy of synthesis of lacosamide **1** is outlined in Scheme 1. It was envisaged that the allylic amine derivative **2** would serve as a key intermediate for the synthesis. We planned to access this amine from allylic alcohol **3** through oxygen-to-nitrogen [3,3] sigmatropic rearrangement.[10] It was assumed that the concerted nature of this reaction should establish the correct configuration of the stereogenic center in the resulting amine through [1,3]-chirality transfer. The allylic alcohol **3** can be accessed from ethyl L-lactate (**4**).

The reaction of ethyl L-lactate (**4**) with 3,4-dihydro-2*H*-pyrane (DHP) in the presence of a catalytic amount of pyridinium tosylate (PPTS) gave *O*-THP protected lactate **5** in 95% yield (Scheme 2). Treatment of ester **5** with 1 equiv of DIBAL-H provided the corresponding aldehyde that was directly treated with Horner−Wadsworth−Emmons reagent generated from triethyl phosphonoacetate and NaH. The resulting crude α,β-unsaturated ester, after extractive work-up, was directly reduced to provide allyl alcohol **6** in 75% overall yield after three steps.

Next, compound **6** was submitted to methylation, followed by deprotection of the hydroxyl group, to furnish allyl alcohol **3**. Treatment of **6** with NaH and MeI in THF at room temperature furnished methyl ether **7**. Crude ether **7** was dissolved in MeOH and treated with AcCl (5 mol %) to afford

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allylic alcohol **3** in 78% yield after 2 steps. Comparable results were obtained when Me_2SO_4 was applied as a methylation agent (yield 75%). *O*-Methylation under PTC conditions (Me_2SO_4, *n*-BuNBr, 50% aq. NaOH), followed by deprotection, gave **3** in 60% yield but required longer reaction time (24 h).

Next, the transformation of allyl alcohol **3** into allyl amine derivative **9** was investigated. In initial studies, the conversion of allylic alcohol **3** into the corresponding trichloroacetimidate (**11**), followed by Overman rearrangement[11] leading to **12**, was considered, as outlined in Scheme 3.

Although the corresponding trichloroacetimidate **11** was obtained smoothly (80%), its rearrangement under Isobe's conditions, with refluxing xylene in the presence of K_2CO_3,[12] gave only small amounts (∼15%) of desired *N*-trichloroacetamide **12** (full conversion of starting material) along with tar byproducts. Under milder reaction conditions (boiling toluene or benzene), no reaction was observed and starting material was recovered only. Unsatisfactory results were also obtained for Pd-catalyzed Overman rearrangement; complete decomposition of starting material was observed. Inefficient formation of **12** forced us to reject the initial synthetic plan, and therefore, other way of transformation of **3** into **9** was considered.

The method of choice was less popular: [3,3]-sigmatropic allyl cyanate-to-isocyanate rearrangement (Scheme 4). In contrast to Overman transformation, the allyl cyanate-to-isocyanate rearrangement proceeds smoothly under mild conditions and does not require metal catalyst.[10] The concerted mechanism of rearrangement should guarantee efficient chirality transfer in the case of nonracemic allyl carbamates.[10b] In addition, the initial allyl carbamates (e.g., **8**) are easily available and more stable than the corresponding imidates (e.g., **11**). Finally, the resulting isocyanate (e.g., **14**) can be directly functionalized.

The carbamate **8** was readily prepared by reacting alcohol **3** with trichloroacetyl isocyanate (TCA-NCO), followed by hydrolysis (82% overall yield). It was found out that trichloroacetyl isocyanate can be replaced by cheaper chlrosulfonyl isocyanate (CSI). In the case of the use of CSI, carbamate **8** was obtained in 78% yield. Dehydration of **8** was carried out with TFAA in the presence of Et_3N at 0 °C for 30 min and provided allyl cyanate **13**, which spontaneously underwent [3,3] sigmatropic rearrangement to afford allyl isocyanate **14** (Scheme 4). Compound **14** was not isolated but directly treated with an excess of MeMgBr to afford *N*-acetylated allyl amine **9**. Aqueous workup and chromatography gave **9** in 74% yield. The dehydration of **8** can be also performed under Ichikawa's (CBr_4, PPh_3, Et_3N, 0 °C, 20 min)[10a] or Baldwin's conditions (Tf_2O, *i*-Pr_2NEt, −78 °C);[13] however, these protocols were less satisfactory from a practical point of view. The former one provided **9** contaminated with Ph_3PO, which was difficult to remove, whereas the latter one required low temperature and an expensive dehydration agent. In both cases, *N*-acetamide **9** was obtained in lower yield (51% and 63%, respectively).

Allyl amide **9** was submitted to oxidative cleavage of the double bond to afford serine derivative **10**. An ozonolysis of olefin **9** and subsequent Lindgren−Pinnick oxidation[14] of the resulting aldehyde provided the corresponding acid in low yield (ca. 30%). Slightly better results were obtained in the case of one-pot oxidation with a $RuCl_3/NaIO_4$ in $MeCN/CCl_4/H_2O$ (2:2:3) mixture. In both cases, the main problem was isolation of highly polar carboxylic acid. The solution that allowed to increase the isolated yield of **10** was a change in the solvent mixture used. When $RuCl_3/NaIO_4$ oxidation was performed in an acetone/water mixture (5:1), amino acid **10** was obtained in 79% yield (determined by ^1H NMR of crude product). Compound **10** was not purified, but after filtration and drying, it was submitted directly to the final amidation step.

For this purpose, amino acid **10** was treated with isobutyl chloroformate (IBCF) in the presence of *N*-methyl morpholine in THF at −20 °C, followed by treatment with $BnNH_2$, to furnish lacosamide **1** in 79% yield, after 2 h. The product was isolated by filtration and crystallization from ethyl acetate. An alternative method of amide formation by reacting amino acid **10** with $BnNH_2$ in the presence of HOBt and EDCI at 0 °C to room temperature gave product **1** in 69% yield. However, isolation of **1** required chromatographic purification. The comparison of the optical rotation values of **1** with the literature ones ($[\alpha]_D^{20}$ +16.1 (*c* 1.2, MeOH); Lit.: +16.2 (*c* 1, MeOH),[6f] +16.4 (*c* 1, MeOH)[2]), along with HPLC analysis, confirmed formation (*R*)-lacosamide **1** without loss of enantiomeric purity at any synthetic step.

In summary, enantiospecific total synthesis of lacosamide (**1**) starting from an ethyl L-lactate has been reported. The target molecule was obtained with an overall yield of 22%. The synthetic strategy presented above can be regarded as a general method for preparation of serine derivatives. A change of either *O*-alkylation agent, or Grignard reagent, or amine reagent should install different substituents at the 3-oxy, 2-aza, or amide site, respectively, to provide other analogues of **1**, which also display interesting neurological activity as recently reported.[9]

EXPERIMENTAL SECTION

(*S*)-Ethyl 2-(Tetrahydropyranyloxy)propionate (5).[10b] To a stirred solution of L-(−)-ethyl lactate (15 g, 127 mmol) and 3,4-dihydro-2*H*-pyran (18.9 g, 225 mmol, 20.5 mL) in 100 mL of dry CH_2Cl_2 was added a solution of PPTS (0.8 g, 3 mmol) in 5 mL of CH_2Cl_2 at 0 °C and under Ar. The resulting mixture was stirred overnight. After the reaction was completed, 100 mL of CH_2Cl_2 was added and the resulting solution was shaken three times with 35 mL portions of water and once with saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on a short pad of silica gel (10% AcOEt in hexanes) to give 24.8 g (95%) of **5** as a mixture of two diastereomers.

(4*S*,*E*)-4-((Tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-en-1-ol (6).[10b] To a solution of **5** (15 g, 74.2 mmol) in dry CH_2Cl_2 (250 mL) at −78 °C was added a 1 M solution of DIBAL-H (75 mL) over 1 h. In the second flask, to a suspension of NaH (111.2 mmol, 4.45 g of 60% disp. in mineral oil) in dry THF (150 mL) was added slowly triethyl phosphonoacetate (111.2 mmol, 24.9 g, 23 mL), and the mixture was stirred for 30 min at rt. When reduction was completed (according to TLC, 20% of AcOEt in hexanes), a solution of HWE reagent was cannulated into the aldehyde solution at −78 °C. The resulting mixture was adjusted to room temperature and stirred for 3 h. Water was added (10 mL) to the mixture, and it was stirred until precipitation appeared, and then the mixture was diluted with Et_2O, and stirred for 1 h. Celite (∼6 g) was added, and stirring was continued for an additional 30 min. Solids were filtered off and washed with Et_2O. The organic solution was dried over Na_2SO_4, and solvents were removed under diminished pressure to obtain the crude unsaturated ester as a mixture of diastereoisomers (yield 94% according to ^1H NMR with internal standard), which was used directly in the next step. [HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{20}O_4Na$ [M + Na^+] 251.1256. Found: 251.1255] To a solution of the crude *α*,*β*-unsaturated ester (69 mmol) in dry CH_2Cl_2 (250 mL) at −75 °C was added slowly a 1 M solution of DIBAL-H (154 mL). Progress of reduction was followed by TLC (20% AcOEt in

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hexanes). After 2 h, sat. aqueous Na_2SO_4 (8.5 mL) was added and the resulting mixture was adjusted to rt. When precipitation appeared, the mixture was diluted with Et_2O, Celite was added, and stirring was continued for 1 h. Solids were filtered off and washed with Et_2O. The organic solutions were dried over anhydr. Na_2SO_4, and solvents were removed under diminished pressure to afford a mixture of diastereomeric allyl alcohols **6** (10.3 g, 75%, overall after 3 steps) pure enough to use in the next step. The analytically pure sample was obtained by short pad chromatography on silica gel (15% AcOEt in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereoisomers) δ: 5.85 (dt, *J* 16.4, 6.4 Hz, 2 × 1H), 5,60 (dd, *J* 16.4, 7.2 Hz, 2 × 1H), 4.75 (t, *J* 3.2 Hz, 1H), 4.60 (t, *J* 3 Hz, 1H), 4.36−4.32 (m, 2H), 4.20−4,14 (m, 4H), 3.93−3.90 (m, 2H), 3.52−3.46 (m, 2H), 1.95−1.65 (m, 14H), 1.30 (d, *J* 6.6 Hz, 3H), 1.22 (d, *J* 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.4, 131.9, 131.3, 129.0, 96.1, 95.3, 71.5, 71.3, 62.5, 62.3, 62.1, 30.7, 30.5, 25.3, 25.2, 19.6, 19.4, 19.3; IR (film) ν: 3415, 1022 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{18}O_3Na$ [M + Na$^+$] 209.1154. Found: 209.1151.

(*S*,*E*)-5-Methoxypent-3-en-2-ol (3). *Method A.* To a suspension of NaH (45.1 mmol, 1.8 g of 60% disp. in mineral oil) in dry THF (150 mL) was added a solution of alcohol **6** (37.6 mmol, 7 g) in dry THF (60 mL). When evolution of hydrogen was finished (ca. 2−3 h), MeI (45.1 mmol, 6.4 g, 2.8 mL) was added. After stirring for 3 h, the reaction was quenched carefully with water (50 mL), and the mixture was stirred for 30 min. Solvent was removed under diminished pressure, and the aqueous residue was extracted with AcOEt. The combined organic phases were dried over anhydr. Na_2SO_4. Removal of solvent under diminished pressure gave crude methyl ether **7** (diastereomeric mixture), which was used directly in the next step (yield 90% according to ^{1}H NMR with internal standard). Crude ether **7** was dissolved in dry MeOH (100 mL), and AcCl (5 mol %, 160 μL) was added dropwise. After 1.5 h, acid was neutralized by addition of Et_3N (1 mL) and stirring was continued for 30 min. After removal of solvent, the residue was chromatographed on silica gel (50% AcOEt in hexanes) to afford 3.8 g of alcohol **3** (87%, 2 steps). $[\alpha]_D^{24}$ +2 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.85−5.66 (m, 2H), 4.38−4.28 (m, 1H), 3.91 (d, *J* 5.0 Hz, 2H), 3.34 (s, 3H), 1.28 (d, *J* 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.1, 126.1, 72.4, 68.2, 58.0, 23.2; IR (film) ν: 3404, 1123 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_6H_{12}O_2Na$ [M + Na$^+$] 139.0735. Found: 139.0735.

Method B. To a suspension of NaH (45.1 mmol, 1.8 g of 60% disp. in mineral oil) in dry THF (150 mL) was added a solution of alcohol **6** (37.6 mmol, 7 g) in dry THF (60 mL). When evolution of hydrogen was finished (ca. 2−3 h), Me_2SO_4 (45.1 mmol, 5.8 mL) was added. After stirring for 4 h, the reaction was quenched as in method A and the crude product was submitted to the deprotection step. Product **3** was obtained in 75% yield (3.2 g) after 2 steps.

Method C. A two-phase mixture of 50% aq. NaOH (1 g), alcohol **6** (2.1 g, 11.27 mmol), Me_2SO_4 (1.6 mL, 22 mmol), and TBABr (320 mg, 1 mmol) in 10 mL of CH_2Cl_2 was stirred vigorously for 20 h. After extractive workup, the crude ether **8** was directly submitted to the deprotection step. Product **3** was obtained in 60% yield (0.79 g) after 2 steps.

(*S*,*E*)-5-Methoxypent-3-en-2-yl Carbamate (8). *Method A.* To a cooled to −10 °C solution of allyl alcohol **3** (4 g, 34.4 mmol) in 50 mL of CH_2Cl_2 was added 5.2 mL of TCA-NCO (8.4 g, 44.7 mmol). After 1 h, solvent was removed. The residue was dissolved in a mixture of MeOH/H_2O (4:1 v/v, 200 mL), and 19.2 g of K_2CO_3 was added in one portion. After 1.5 h, MeOH was removed and the aqueous residue was extracted with AcOEt. The combined organic extracts were dried over Na_2SO_4 and filtered through a silica gel pad, and solvent was removed under diminished pressure. Carbamate **8** was obtained in 82% yield (4.5 g) as a colorless oil. $[\alpha]_D^{21}$ −14.4 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.83−5.69 (m, 2H), 5.29−5.21 (m, 1H), 4.75 (s, 2H), 3.94−3.86 (m, 2H), 3.32 (s, 3H), 1.32 (d, *J* 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.5, 132.6, 128.0, 72.4, 71.1, 58.2, 20.4; IR (film) ν: 3443, 3350, 3203, 1714, 1376, 1051 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_{13}NO_3Na$ [M + Na$^+$] 182.0793. Found: 182.0788.

Method B. To a cooled to −50 °C solution of allylic alcohol **3** (1 g, 8.6 mmol) in 20 mL of THF was added 0.82 mL of CSI (1.34 g, 9.5 mmol). After 1 h, the reaction was carefully quenched with water (10 mL). Extractive workup, filtration through a silica gel pad, and concentration gave 1.07 g of carbamate **8** (78%).

(*S*,*E*)-*N*-(1-Methoxypent-3-en-2-yl)acetamide (9). To a cooled to 0 °C solution of allyl carbamate **8** (1.6 g, 10 mmol) and Et_3N (8.35 mL, 60 mmol) in 100 mL of THF was added 2.8 mL of TFAA (20 mmol). After 30 min, the reaction mixture was cooled to −20 °C and 20 mL of 3 M soln. of MeMgBr in THF was added. After 4 h, reaction was quenched carefully by addition of aq. NH_4Cl. The organic phase was separated, and the aqueous one was extracted with EtOAc (6 × 50 mL). The combined organic solutions were dried over Na_2SO_4, and solvent was removed under diminished pressure. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH 50:1) to afford 1.17 g of acetamide **9** (74%) as a brown oil. $[\alpha]_D^{20}$ +6.3 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.80 (s, 1H, N*H*), 5.72−5.63 (m, 1H, CH_3CH=CH), 5.46 (ddd, *J* 15.4, 6.1, 1.6 Hz, 1H, CH_3CH=C*H*), 4.58−4.56 (m, 1H, C*H*NHAc), 3.46−3.42 (m, 2H, CH_2OMe), 3.36 (s, 3H, OCH_3), 2.01 (s, 3H, CH_3CO), 1.71−1.68 (br d, *J* 6.1 Hz, 3H, CH_3CH=CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.8, 128.5, 127.8, 74.81, 59.3, 50.7, 23.5, 17.9; IR (film) ν: 3284, 1651, 1548, 1126, 966 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{15}NO_2Na$ [M + Na$^+$] 180.1000. Found 180.0995.

***N*-Acetyl-*O*-methyl-D-serine (10).** To a solution of allyl amide **2** (1.15 g, 7.3 mmol) in an acetone/water mixture (5:1, 60 mL) were added solid $NaIO_4$ (3.2 g, 15 mmol) and $RuCl_3{\cdot}H_2O$ (20 mg, 0.09 mmol, 1.5 mol %). After 8 h, the reaction mixture was filtered through a Celite pad and collected solids were washed with acetone (4 × 10 mL). After removal of solvent, the residue was dissolved in CH_2Cl_2 (50 mL) and dried over anhydrous Na_2SO_4, and solvent was removed under diminished pressure to afford crude amino acid **10** (0.93 g, 79% yield determined by ^{1}H NMR), which was used directly in the next step. The analytical sample was obtained by chromatography on silica gel (CH_2Cl_2/MeOH 50:1 v/v) as a white solid; mp 108−109 °C [Lit.[6b] mp 108−109 °C]. $[\alpha]_D^{20}$ −16.3 (*c* 1.78, MeOH) [Lit.[6a] $[\alpha]_D^{25}$ −16.9 (*c* 1.2, MeOH)]; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.50 (d, *J* 7.5 Hz, 1H), 4.75−4.69 (m, 1H), 3.87 (dd, *J* 9.5, 3.3 Hz, 1H), 3.63 (dd, *J* 9.6, 3.6 Hz, 1H), 3.37 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 173.5, 171.4, 71.8, 59.5, 52.7, 23.1; IR (film) ν: 3334, 1732, 1658, 1546, 1197, 1118 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_6H_{11}NO_4Na$ [M + Na$^+$] 184.0586. Found: 184.0581. Anal. Calcd for $C_6H_{11}NO_4$ C, 44.72, H, 6.88, N, 8.69. Found C, 44.67, H, 6.82, N, 8.67.

(*S*,*E*)-5-Methoxypent-3-en-2-yl 2,2,2-Trichloroacetimidate (11). To a cooled solution of allyl alcohol **3** (300 mg, 1.15 mmol) and DBU (30 μL, 30 mg, 0.2 mmol) in CH_2Cl_2 (15 mL) was added neat CCl_3CN (188 mg, 130 μL, 1.3 mmol). After 30 min, solvent was removed under reduced pressure and the residue was chromatographed on silica gel (30% AcOEt in hexanes) to afford **11** as a yellow oil (80%, 240 mg). $[\alpha]_D^{20}$ −14.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ: 8.32 (s, 1H), 5.84−5.69 (m, 2H), 5.60−5.52 (m, 1H), 3.70−3.61 (m, 2H), 3.06 (s, 3H), 1.23 (d, *J* 6.4 Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ: 161.8, 130.7, 129.4, 92.4, 75.5, 72.1, 57.6, 19.5; IR (film) ν: 3344, 1660, 1082, 795 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{12}NO_2Cl_3Na$ [M + Na$^+$] 281.9831; Found 281.9828.

***N*-Trichloroacetyl-*O*-methyl-D-serine (12).** To a solution of imidate **11** (100 mg, 0.38 mmol) in xylene (5 mL) was added K_2CO_3 (55 mg, 0.38 mmol), and the reaction mixture was put into a preheated oil bath (140 °C). After 6 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and filtered, and solvents were removed under diminished pressure. The residue was purified by chromatography on silica gel to afford 30 mg of amide **12** (30%) as a colorless oil. $[\alpha]_D^{20}$ −16.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (s, 1H, NH), 5.81−5.71 (m, 1H, CH_3CH=CH), 5.53−5.46 (m, 1H, CH_3CH=C*H*), 4.57−4.42 (m, 1H, C*H*NH), 3.56−3.48 (m, 2H, CH_2OMe), 3.39 (s, 3H, CH_3O), 1.72 (br d, *J* 6.5 Hz, 3H, CH_3CH=CH); IR (film) ν: 3420, 3335, 1703, 1514, 1119, 821 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{12}NO_2Cl_3Na$ [M + Na$^+$] 281.9831; Found 281.9830.

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Lacosamide (1). To a cooled to −20 °C solution of amino acid **10** (0.90 g, 5.58 mmol) in THF (90 mL) was added NMM (0.92 mL, 8.37 mmol). After 5 min, isobutyl chloroformate (0.8 mL, 6.12 mmol) was added. After an additional 10 min, benzylamine (0.7 mL) was added, and the reaction mixture was kept at −20 °C for 1 h and then for 30 min at room temperature. The reaction mixture was filtered through a short pad of silica gel (CH_2Cl_2), and collected filtrates were evaporated under diminished pressure. The residue was recrystallized from AcOEt to afford 1.14 g of lacosamide **1** (82%) as a white solid. mp 142−143 °C [Lit. 140−141 °C,[6f] 143−144 °C[2]]; $[\alpha]_D^{20}$ +16.1 (*c* 1.2, MeOH) [Lit.: +16.2 (*c* 1, MeOH),[6f] +16.4 (*c* 1, MeOH)[2]]; 99% *ee* (HPLC); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.37−7.23 (m, 5H), 6.78 (s, 1H), 6.45 (d, *J* 4.8 Hz, 1H), 4.55 (td, *J* 7.6, 4.8, 4.1 Hz, 1H), 4.52−4.42 (m, 2H), 3.80 (dd, *J* 9.2, 4.1 Hz, 1H), 3.44 (dd, *J* 9.2, 7.6 Hz, 1H), 3.37 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ*: 170.4, 170.1, 138.03, 128.8, 127.6, 127.6, 71.8, 59.2, 52.6, 43.7, 23.4; IR (film) *ν*: 3286, 1633, 1547 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{18}N_2O_3Na$ [M + Na^+] 273.1215. Found 273.1212. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38, H, 7.25, N, 11.19. Found: C, 62.32, H, 7.21, N, 11.13. HPLC: Chiralcel OD-H (0.46 nm × 25 cm), *n*-hexane*i*-PrOH (60:40); flow rate 0.5 mL/min; UV det. UV: 220 nm): t_R = 10.40 (*R*-isomer), 11.6 min (*S*-isomer). A sample of ***rac*-1** was prepared following the Kohn protocol[2] starting from D,L-serine.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, and HPLC of ***rac*-1** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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