Synthesis H. Jeong et al. Paper

Synthesis of Lacosamide (Vimpat) and Its Derivatives from Aziridine-(2*R*)-carboxylate

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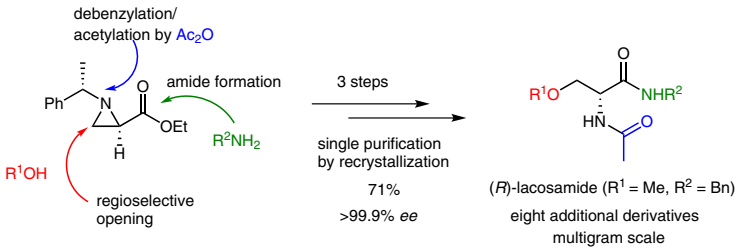

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Abstract An efficient and scalable synthesis of the antiepileptic drug (*R*)-lacosamide and its derivatives has been achieved from commercially available aziridine-(2*R*)-carboxylate in three simple sequential steps, including regioselective aziridine ring opening, debenzylation followed by acetylation in one pot, and amide formation. The advantage of this protocol is that the starting material and reagents are commercially available and a single purification by recrystallization is required after all the chemical transformations, providing the final drug in >99.9% ee.

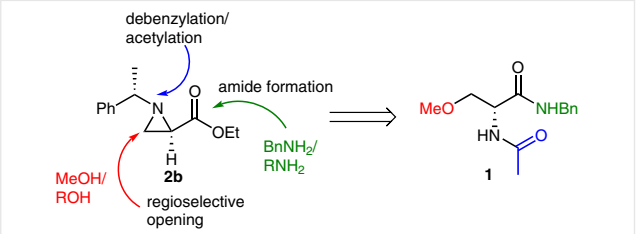
Key words (R)-lacosamide, Vimpat, antiepileptic drug, aziridine, regioselectivity

Epilepsy is a chronic neurological disorder with recurrent seizures produced by paroxysmal, excessive, synchronous neuronal discharges in the brain that disturbs the normal activity of the brain.[1,2] This disease affects about 1% of the population and the number of new patients continues to grow every year.[3] Lacosamide (**1**) was recently approved in the United States and the European Union for the treatment of epilepsy.

The medicinal and commercial importance of lacosamide led many synthetic chemists to attempt its synthesis with the introduction of an acetamide and a methoxy group at the α- and β-positions of *N*-benzyl propionamide. Most synthetic methods in the reports and patents utilize a chiral pool of D-serine and its derivatives,[1a,b,4] which is an unnatural form with a high price and low availability compared with the natural form of L-serine. The enantiopure starting material, ethyl L-lactate, was also used via chirality transfer through stereospecific allyl cyanate-to-isocyanate rearrangement, which requires a multistep reaction sequence and resulted in low overall yield.[5a] Chemical methods to generate the chiral center were also reported by using asymmetric dihydroxylation with the tedious requisite conversion of the hydroxyl group into amine functionality.[5b] Dynamic kinetic asymmetric transformation (DYKAT) has also been used for the generation of amine chirality (which requires further multiple conversions to complete the synthesis).[5c,d] The synthesis utilizing Ugi reaction in a single operation was applied to obtain lacosamide in decent yield.[5e] However there were some drawbacks, including preparation of prerequisite malodourous isocyanide and methoxyacetaldehyde, and low diastereoselectivity of the Ugi reaction with chiral amines. Upon completion of the reaction, multiple recrystallizations were required to obtain the desired enantiomerically pure product in moderate yield. Thus far, the challenge has been to overcome the aforementioned difficulties posed by divergent methods for the synthesis of lacosamide and its derivatives. To our knowledge, there is no single-step simple purification procedure that yields large quantities of lacosamide of excellent chiral purity.

Long-term extensive studies on the use of chiral aziridine for the asymmetric synthesis of amines and amino acids[6,7] inspired us to prepare lacosamide by using a similar synthetic strategy that included aziridine ring opening and functional group transformations (Scheme 1). Aziridine ring opening by methanol at C3, N-acetylation and debenzylation, and amide formation with benzylamine from an ester delivered the target molecule.

These reactions do not conflict with each other, which allows us to carry out individual steps without purification after each reaction. To achieve this goal, the aziridine ring opening should be highly regioselective, and the removal of phenylethyl group at the ring nitrogen should proceed smoothly in high yield. Furthermore, the formation of two amides should proceed in a controlled manner without interfering with each other. This report describes a highly efficient and scalable synthesis of enantiopure lacosamide

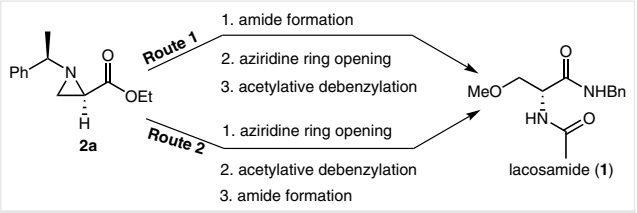


Scheme 1 Strategic analysis of (*R*)-lacosamide synthesis from aziridine-(2*S*)-carboxylate

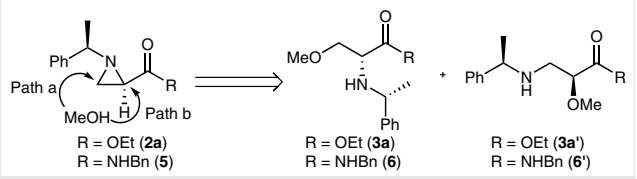
from the commodity chemical, aziridine-(2*R*)-carboxylate in three simple sequential steps, including regioselective aziridine ring opening, acetylative debenzylation, and benzylamide formation. This synthesis consists of three non-competing, high-yielding operational steps from commercially available starting materials and reagents with a single purification by recrystallization at the last stage to yield the final product lacosamide (**1**) in >99.9% *ee*.

The key to the success of this synthetic method is the aziridine ring opening. This depends on the stage at which the aziridine ring opening is performed; it can take place either at the stage of the starting material aziridine-2-carboxylate (Route 2) or from the aziridine-2-carboxamide (Route 1), which is prepared from aziridine-2-carboxylate through benzyl amide formation (Scheme 2).

Based on a previous study, the regiochemical pathway that is followed depends on the substituents at C2; that is,



Scheme 2 Two routes for the synthesis of Lacosamide from ester **2**



Scheme 3 Formation of regioisomers through aziridine ring opening at two reaction sites

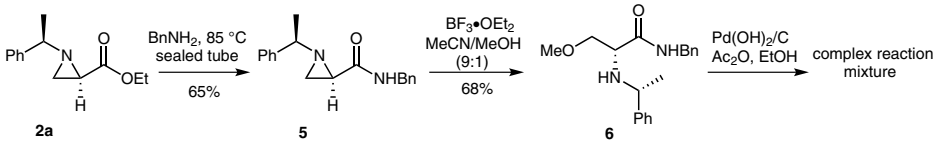
whether it is an ester or an amide.[8] Initially, we assumed that the ratio of amine **6** and its regioisomer **6′** derived from two different reaction sites of ring opening of aziridine-2-carboxamide would favor **6** compared with the ratio of the corresponding ring opening products obtained from the ester (**3a**/**3a′**; Scheme 3).

Aziridine-2-carboxybenzylamide (**5**) was prepared in 65% yield by reacting ester **2a**[9] with benzylamine in a sealed tube at 85 °C. Several trial runs for the ring opening reactions under various reaction conditions always delivered the required product **6** in 68% yield, with typical **6**/**6′** ratio of 8:2. Having obtained compound **6** in a moderate overall yield of 44% from ester **2a**, the subsequent removal of the phenylethyl group from benzylamide **6** remained an unresolved challenge. Removal of the phenylethyl group from **6** under hydrogenation conditions gave a complex mixture of the product without generating the desired lacosamide as a major product (Scheme 4).

Therefore we investigated the ring opening of ethyl aziridine-2-carboxyester (**2a**) as a first step. The expected ring-opened product, 3-methoxy-2-aminopropionate (**3a**), was obtained with $BF_3{\cdot}OEt_2$ in MeCN containing methanol in 75% yield, with an 85:15 regioisomeric ratio of **3a**/**3a′** bearing the same configuration at the α-position as the starting aziridine (Table 1). In an effort to improve the selectivity and yields, we varied the temperature, solvent, acid catalyst and substrate from ethyl 1-[(*R*)-1-phenylethyl]aziridine-(2*R*)-carboxylate (**2a**) to its (1*S*)-isomer (**2b**), and (–)-menthyl ester (**2c**). Changing solvents from MeCN to either MeOH or CH_2Cl_2 (entries 1–3) did not change the product ratio; instead, low yields were observed because of incomplete conversion of starting materials.

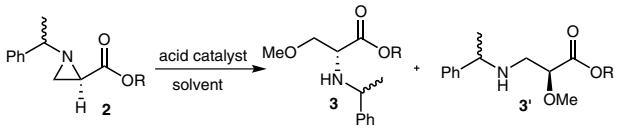
Similarly, changing either the reaction temperature (90 °C to room temperature) or the concentration did not alter the product ratio in the reaction, although the reaction yields were reduced from 75 to 61% (Table 1, entries 3–6).

The use of *p*-toluenesulfonic acid as acid catalyst did not improve either the yield of the reaction or its regioselectivity, whereas the use of camphor sulfonic acid (CSA) gave a better selectivity but generated some unidentified byproducts and the majority of the starting aziridine remained unreacted (Table 1, entries 7 and 9). Changing the substrate from ethyl 1-[(*R*)-1-phenylethyl]aziridine-(2*R*)-carboxylate (**2a**) to its (1*S*)-isomer (**2b**) improved the regioselectivity of the reaction from a ratio of 83:17 to 94:6, because of differences in the steric environment encountered during the ap-



Scheme 4 Synthesis of lacosamide by following Route 1

Table 1 Optimization of Regioselective Opening of Aziridine-2-carboxylate



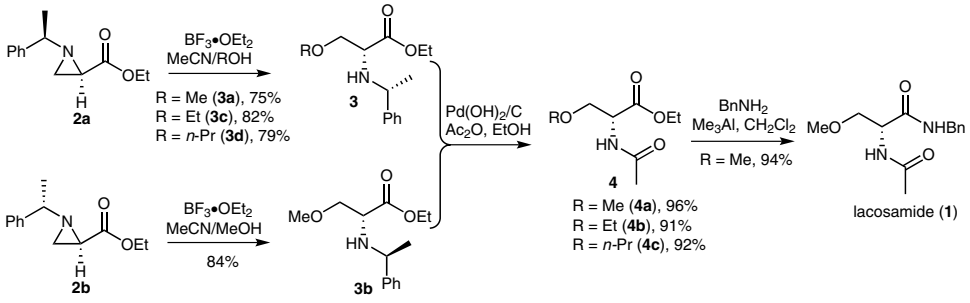
Entry	R	Acid	Solvent[a]	Temp. (°C)	Conc. (M)	Time (h)	Ratio (**3**/**3**′)[b]	Yield (%)[c]
1	ethyl (**2a**)	$BF_3{\cdot}OEt_2$	MeCN	90	0.3	3.0	85:15	75
2	ethyl (**2a**)	$BF_3{\cdot}OEt_2$	MeOH	90	0.3	6.0	80:20	74
3	ethyl (**2a**)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	25	0.3	72	82:18	42[d]
4	ethyl (**2a**)	$BF_3{\cdot}OEt_2$	MeCN	25	0.3	70	83:17	51[d]
5	ethyl (**2a**)	$BF_3{\cdot}OEt_2$	MeCN	60	0.3	5.0	83:17	63
6	ethyl (**2a**)	$BF_3{\cdot}OEt_2$	MeCN	90	0.15	4.5	87:13	61
7	ethyl (**2a**)	*p*TsOH	MeCN	90	0.3	12	78:22	58[d]
8	ethyl (**2b**)	$BF_3{\cdot}OEt_2$	MeCN	90	0.3	3.0	94:6	84
9	ethyl (**2a**)	CSA	MeCN	90	0.3	6.0	>95:5[c]	25[d]
10	(–)-menthyl (**2c**)	$BF_3{\cdot}OEt_2$	MeCN	90	0.3	3.0	80:20	67

[a] Used in combination with MeOH in 9:1 ratio.
[b] Determined by NMR analysis of the crude mixture.
[c] Yield of pure product **3**.
[d] Starting material remained and other impurities were observed.

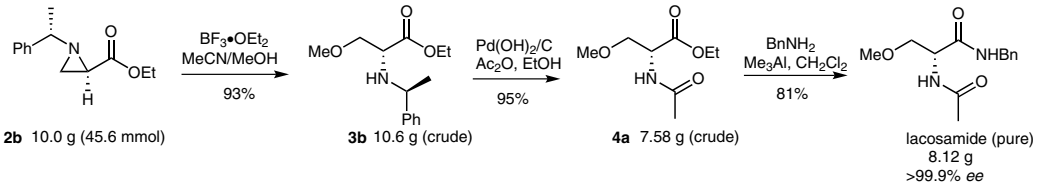
proach of the nucleophile (entry 8).[10] However, the use of the bulky (–)-menthyl ester did not improve the selectivity of the aziridine ring opening reaction (entry 10).

Having achieved the ring-opening reaction, we removed the phenylethyl group and conducted the subsequent acetamide formation in one pot, with the two reactions promoting each other in a synergic manner based on our early study.[6,7] Removal of the phenylethyl group at the amine nitrogen by catalytic hydrogenation is dependent on the substrates and was affected by the nature of the neighboring groups; in some cases the reaction barely proceeded. However, the addition of reagents to help form the amide, including $(Boc)_2O$, prompted the debenzylation reaction under mild conditions such as with atmospheric hydrogen in the presence of a Pd catalyst.[11] Debenzylation of compound **3a** under hydrogenation in the presence of $Pd(OH)_2$ did not give the free amine. Therefore, a molar equivalent of acetic anhydride was added to the reaction vessel for the catalytic hydrogenation under atmospheric hydrogen in the presence of $Pd(OH)_2$ in EtOH, which resulted in the formation of amide **4a** in 96% yield (Scheme 5). The final reaction was benzylamide formation from ester **4a**. Amide formation to generate lacosamide (**1**) was achieved by treating ester **4a** with benzylamine and Me_3Al in CH_2Cl_2 at room temperature in 94% yield.[12] The biggest advantage of this step is that we were able to use excess benzylamine to complete the reaction and remaining amines could be easily removed by aqueous extraction.

Having optimized the three steps to provide the expected products in reasonable yields, we scaled the protocol for the synthesis of lacosamide in large quantities with a single purification step without chromatography. Aziridine ring opening of (*S*,*R*)-aziridine-2-carboxyester (**2b**) under the optimized reaction conditions gave the desired crude prod-



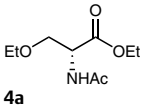
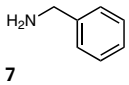
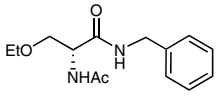
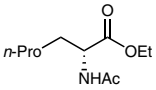
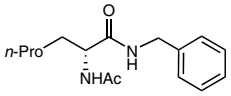
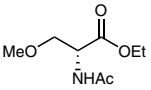
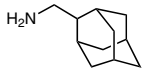
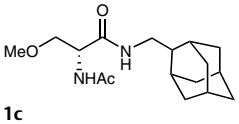
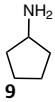
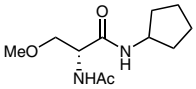
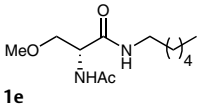
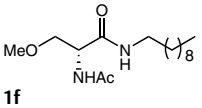
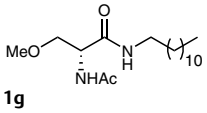
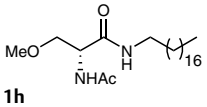
Scheme 5 Completion of the synthesis of lacosamide



Scheme 6 Multigram synthesis of lacosamide

uct **3b** with a 94:6 regioisomeric ratio. Acetylative debenzylation of crude **3b** under hydrogenation with $Pd(OH)_2$ and acetic anhydride gave the corresponding crude compound **4a**, which was used as such for subsequent amide formation with benzylamine (Scheme 6). The reaction of ethyl ester **4a** with benzylamine in the presence of Me_3Al gave crude lacosamide (**1**) with a chiral purity of 99:1. The crude lacosamide was recrystallized from ethyl acetate to give highly pure lacosamide as a white solid with >99.9 *ee* in 71% overall yield. The analytical data is in complete

Table 2 Synthesis of Analogues of Lacosamide

Entry	*N*-Acetyl ester	Amines	Product (**1**)[a]	Yield (%)[b]
1	 **4a**	 **7**	 **1a**	89
2	 **4c**	**7**	 **1b**	87
3	 **4a**	 **8**	 **1c**	83
4	**4a**	 **9**	 **1d**	81
5	**4a**	 **10**	 **1e**	89
6	**4a**	 **11**	 **1f**	78
7	**4a**	 **12**	 **1g**	80
8	**4a**	 **13**	 **1h**	76

[a] All products were characterized by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.
[b] Yield of pure product after recrystallization.

agreement with reported data.[5] The overall yield of lacosamide from aziridine-(2*R*)-carboxylate with single crystallization after finishing all necessary reactions was >71% with >99.9% *ee*, as determined by chiral high-performance liquid chromatography (HPLC) analysis.

After successful synthesis of enantiopure lacosamide, our attention turned to applying this synthetic protocol for the preparation of lacosamide derivatives by replacing methoxy and benzyl groups by other alkoxy and alkyl groups, respectively. Since lacosamide analogues exhibit interesting bioactivity,[13] the development of a new and general synthetic strategy for the generation of structurally diversified analogues is urgently needed. The synthetic method we developed from aziridine-2-carboxylate allowed various lacosamide derivatives to be prepared in good to excellent yields (Table 2). The same amides as lacosamide (**1**) with ethoxy- (**1a**) and *n*-propanoxy (**1b**) instead of methoxy group were prepared in 89 and 87% yields, respectively. Several amines were also attached instead of benzylamine in lacosamide, including adamantalmethyl (**1c**), cyclopentyl (**1d**), *n*-hexyl (**1e**), *n*-decyl (**1f**), *n*-dodecyl (**1g**), and *n*-octadecyl (**1h**) in similar reaction yields.

In conclusion, we have achieved the large-scale synthesis of the anticonvulsant amino acid, lacosamide and derivatives, starting from a commodity chemical, aziridine-(2*R*)-carboxylate, in three consecutive steps, including regioselective aziridine ring opening, acetylative debenzylation, and benzylamide formation, with a single purification after finishing all necessary reactions. Lacosamide was obtained in 71% overall yield with >99.9% *ee*.

Chiral aziridines are available from Sigma–Aldrich as reagents and also from Imagene Co. Ltd. (http://www.imagene.co.kr/) in bulk quantities. All commercially available compounds were used as received unless stated otherwise. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with a magnetic stirrer. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA), followed by heating on a hot plate for about 10 s. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were obtained with a Varian UNITY INOVA 400WB (400 MHz) or a Bruker AVANCE III HD (400 MHz) spectrometer. Chemical shifts are reported relative to chloroform (δ = 7.26 ppm) for ^{1}H NMR and chloroform (δ = 77.2 ppm) for ^{13}C NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet). Coupling constants are given in Hz. Ambiguous assignments were resolved on the basis of standard one-dimensional proton decoupling experiments. Optical rotations were obtained with a Rudolph Autopol III digital polarimeter and JASCO P-2000. Optical rotation data is reported as $[\alpha]^{20}$ (concentration *c* = g/100 mL, solvent). High-resolution mass spectra were recorded with a 4.7 Tesla IonSpec ESI-TOFMS, JEOL (JMS-700) and AB Sciex 4800 Plus MALDI TOF™; 2,5-dihydroxybenzoic acid (DHB) matrix was used to prepare samples for MS. Data was obtained in the reflector positive mode with internal standards for calibration.

N-Benzyl-1-[(*R*)-1-phenylethyl]aziridine-(2*R*)-2-carboxamide (5)

A mixture of ethyl ester **2a** (1.0 g, 4.56 mmol) and benzylamine (1.5 mL, 13.6 mmol) in EtOH (2 mL) was taken in a sealed tube and heated to 85 °C with stirring for 12 h. EtOH was then removed under vacuum and the crude product was purified by column chromatography on silica gel (EtOAc/hexane, 30%; R_f 0.2) to give the pure product **5**.

Yield: 0.83 g (65%); white solid; mp 93–94 °C; $[\alpha]_D^{20}$ +71.9 (*c* = 1.0, $CHCl_3$).

IR (neat): 3281, 2911, 2331, 1719, 1349, 1081, 871 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 10 H), 7.13–7.01 (m, 1 H), 4.50–4.35 (m, 2 H), 2.57 (q, *J* = 6.5 Hz, 1 H), 2.26 (dd, *J* = 7.0, 3.1 Hz, 1 H), 1.83 (d, *J* = 3.1 Hz, 1 H), 1.61 (d, *J* = 7.0 Hz, 1 H), 1.41 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 170.1, 143.1, 138.1, 128.3, 128.0, 127.0, 126.9 (2C), 126.2, 68.0, 42.2, 39.1, 34.4, 22.7.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{21}N_2O$: 281.1649; found: 281.1642.

N-Benzyl-3-methoxy-(2*R*)-2-{[(*R*)-1-phenylethyl]amino}propanamide (6)

To a stirred solution of amide **5** (0.5 g, 1.78 mmol) in a mixture of MeCN and MeOH (9:1, 10 mL) was added $BF_3{\cdot}OEt_2$ (0.25 mL, 1.96 mmol), and the resulting mixture was stirred and heated at 90 °C for 3.0 h. Upon complete conversion of starting material as confirmed by TLC (product R_f 0.1; EtOAc/hexane, 50%), the mixture was cooled to r.t. and the reaction was quenched with saturated $NaHCO_3$ solution (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by chromatography on silica gel (EtOAc/hexane, 50%; R_f 0.3) to afford the pure product **6**.

Yield: 0.38 g (68%); viscous liquid; $[\alpha]_D^{20}$ +60.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 3288, 2908, 2335, 1720, 1215, 1078, 847 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.69 (m, 1 H), 7.43–7.18 (m, 10 H), 4.59–4.42 (m, 2 H), 3.70 (q, *J* = 6.7 Hz, 1 H), 3.55 (dd, *J* = 9.8, 6.7 Hz, 1 H), 3.41 (dd, *J* = 9.8, 4.3 Hz, 1 H), 3.23 (dd, *J* = 6.6, 4.3 Hz, 1 H), 3.19 (s, 3 H), 2.00 (br s, 1 H), 1.33 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 172.2, 144.4, 138.2, 128.4, 128.3, 127.2, 127.1, 127.0, 126.2, 72.8, 59.7, 58.2, 57.1, 42.8, 23.9.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{24}N_2O_2Na$: 335.1731; found: 335.1725.

Ethyl 3-Methoxy-(2*R*)-2-{[(*R*)-1-phenylethyl]amino}propanoate (3a)

To a stirred solution of ethyl ester **2a** (2.0 g, 9.12 mmol) in a mixture of MeCN and MeOH (9:1, 20 mL) was added $BF_3{\cdot}OEt_2$ (1.27 mL, 10.03 mmol), and the resulting mixture was stirred and heated at 90 °C for 3.0 h. Upon complete conversion of starting material as confirmed by TLC (product R_f 0.3; EtOAc/hexane, 25%), the mixture was cooled to r.t. and the reaction was quenched with saturated $NaHCO_3$ solution (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by chromatography on silica gel (EtOAc/hexane, 15%) to give the pure product **3a**.

Yield: 1.72 g (75%); viscous liquid; $[\alpha]_D^{20}$ +95.2 (*c* = 1.0, $CHCl_3$).

IR (neat): 2930, 1726, 1434, 1232, 1077, 864 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.16 (m, 5 H), 4.28–4.14 (m, 2 H), 3.82 (q, *J* = 6.5 Hz, 1 H), 3.57 (dd, *J* = 9.1, 4.6 Hz, 1 H), 3.48 (dd, *J* = 9.1, 4.6 Hz, 1 H), 3.29 (s, 3 H), 3.18 (t, *J* = 4.5 Hz, 1 H), 2.20 (br s, 1 H), 1.36 (d, *J* = 6.5 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 173.5, 144.8, 128.3, 126.9, 126.8, 74.3, 60.6, 59.0, 58.7, 56.4, 25.1, 14.2.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{21}NO_3Na$: 274.1414; found: 274.1413.

Ethyl 3-Methoxy-(2*R*)-2-{[(*S*)-1-phenylethyl]amino}propanoate (3b)

The procedure was analogous to that used for the preparation of **3a**. From ester **2b** (2.0 g, 9.12 mmol) and $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol) in a mixture of MeCN and MeOH (9:1, 20 mL) was obtained the amine compound **3b**.

Yield: 1.92 g (84%); viscous liquid; $[\alpha]_D^{20}$ –23.9 (*c* = 1.0, $CHCl_3$).

IR (neat): 2887, 1724, 1439, 1348, 1153, 1082, 917 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.14 (m, 5 H), 4.15–3.97 (m, 2 H), 3.84 (q, *J* = 6.5 Hz, 1 H), 3.61–3.53 (m, 2 H), 3.44 (t, *J* = 4.9 Hz, 1 H), 3.32 (s, 3 H), 2.18 (br s, 1 H), 1.36 (d, *J* = 6.6 Hz, 3 H), 1.19 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 144.8, 128.1, 126.8, 126.5, 73.0, 60.4, 58.9, 58.8, 55.9, 23.0, 13.9.

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{24}NO_3$: 266.1751; found: 266.1759.

Ethyl 3-Ethoxy-(2*R*)-2-{[(*R*)-1-phenylethyl]amino}propanoate (3c)

The procedure was analogous to that used for the preparation of compound **3a**. From ester **2a** (2.0 g, 9.12 mmol) and $BF_3{\cdot}OEt_2$ (1.27 mL, 10.03 mmol) in a mixture of MeCN and EtOH (9:1, 20 mL) was obtained amine compound **3c**.

Yield: 1.98 g (82%); viscous liquid; $[\alpha]_D^{20}$ +92.1 (*c* = 1.0, $CHCl_3$).

IR (neat): 2933, 1725, 1442, 1346, 1231, 1069, 873 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.18 (m, 5 H), 4.30–4.12 (m, 2 H), 3.82 (q, *J* = 6.5 Hz, 1 H), 3.61 (dd, *J* = 9.3, 4.8 Hz, 1 H), 3.52 (dd, *J* = 9.3, 4.7 Hz, 1 H), 3.48–3.37 (m, 2 H), 3.18 (t, *J* = 4.7 Hz, 1 H), 2.18 (br s, 1 H), 1.36 (d, *J* = 6.6 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.14 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.7, 144.9, 128.3, 126.9, 126.8, 72.0, 66.5, 60.6, 58.8, 56.4, 25.2, 14.8, 14.2.

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{24}NO_3$: 266.1751; found: 266.1761.

Ethyl (2*R*)-2-{[(*R*)-1-Phenylethyl]amino}-3-propoxypropanoate (3d)

The procedure was analogous to that used for the preparation of compound **3a**. From the ester **2a** (2.0 g, 9.12 mmol) and $BF_3{\cdot}OEt_2$ (1.27 mL, 10.03 mmol) in a mixture of MeCN and *n*-PrOH (9:1, 20 mL) was obtained amine compound **3d**,

Yield: 2.01 g (79%); viscous liquid; $[\alpha]_D^{20}$ +86.3 (*c* = 1.0, $CHCl_3$).

IR (neat): 2935, 1721, 1431, 1346, 1197, 1086, 870 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.16 (m, 5 H), 4.28–4.10 (m, 2 H), 3.82 (q, *J* = 6.5 Hz, 1 H), 3.61 (dd, *J* = 9.2, 4.8 Hz, 1 H), 3.52 (dd, *J* = 9.2, 4.7 Hz, 1 H), 3.38–3.25 (m, 2 H), 3.19 (t, *J* = 4.8 Hz, 1 H), 2.20 (br s, 1 H), 1.59–1.48 (m, 2 H), 1.36 (d, *J* = 6.6 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.87 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.4, 144.7, 128.1, 126.8, 126.7, 72.7, 72.1, 60.3, 58.7, 56.3, 25.0, 22.4, 14.0, 10.2.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{26}NO_3$: 280.1908; found: 280.1904.

Ethyl (2*R*)-2-Acetamido-3-methoxypropanoate (4a)

To a stirred solution of amine **3a**/**3b** (1.7 g, 6.76 mmol) in EtOH (17 mL), was added acetic anhydride (1.27 mL, 13.52 mmol) and 20% $Pd(OH)_2/C$ (170 mg, 50% wet). The resulting heterogeneous mixture was hydrogenated under an atmospheric pressure of hydrogen for 12 h. The reaction mixture was filtered through a pad of Celite, washed with EtOH (30 mL), and the solvents were removed under vacuum to obtain the crude residue. The resulting residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give crude acetamide **4a**, which was recrystallized from hexane to give pure acetamide **4a**.

Yield: 1.23 g (96%); white solid; mp 71–72 °C; $[\alpha]_D^{20}$ –53.8 (*c* = 1.0, $CHCl_3$).

IR (neat): 3290, 2912, 1726, 1631, 1524, 1370, 1107 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.45 (d, *J* = 6.6 Hz, 1 H), 4.78–4.68 (m, 1 H), 4.34–4.18 (m, 2 H), 3.81 (dd, *J* = 9.5, 3.1 Hz, 1 H), 3.63 (dd, *J* = 9.5, 3.1 Hz, 1 H), 3.35 (s, 3 H), 2.06 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 169.8, 72.2, 61.5, 59.1, 52.5, 23.0, 14.0.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{15}NO_4Na$: 212.0893; found: 212.0880.

Ethyl (2*R*)-2-Acetamido-3-ethoxypropanoate (4b)

The procedure was analogous to that used for the preparation of compound **4a**. From amine **3c** (1.5 g, 5.65 mmol), acetic anhydride (1.07 mL, 11.3 mmol), and 20% $Pd(OH)_2/C$ (150 mg, 50% wet) in EtOH (15 mL) was obtained acetamide compound **4b**.

Yield: 1.04 g (91%); viscous liquid; $[\alpha]_D^{20}$ –47.3 (*c* = 1.0, $CHCl_3$).

IR (neat): 3252, 2900, 1728, 1651, 1230, 1077, 930 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (d, *J* = 8.2 Hz, 1 H), 4.51–4.39 (m, 1 H), 4.03–3.84 (m, 2 H), 3.55 (dd, *J* = 9.6, 3.9 Hz, 1 H), 3.38 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.30–3.13 (m, 2 H), 1.77 (s, *J* = 9.5 Hz, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H), 0.89 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 169.6, 69.4, 66.0, 60.6, 52.1, 22.1, 14.1, 13.4.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{17}NO_4Na$: 226.1050; found: 226.1064.

Ethyl (2*R*)-2-Acetamido-3-propoxypropanoate (4c)

The procedure was analogous to that used for the preparation of compound **4a**. From amine **3d** (1.5 g, 5.37 mmol), acetic anhydride (1.01 mL, 10.7 mmol), and 20% $Pd(OH)_2/C$ (150 mg, 50% wet) in EtOH (15 mL) was obtained acetamide compound **4c**.

Yield: 1.07 g (92%); viscous liquid; $[\alpha]_D^{20}$ –46.2 (*c* = 1.0, $CHCl_3$).

IR (neat): 3238, 2931, 1725, 1646, 1363, 1227, 1112, 911 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (d, *J* = 8.0 Hz, 1 H), 4.73 (dt, *J* = 8.2, 3.4 Hz, 1 H), 4.29–4.13 (m, 2 H), 3.83 (dd, *J* = 9.6, 3.5 Hz, 1 H), 3.65 (dd, *J* = 9.6, 3.4 Hz, 1 H), 3.47–3.29 (m, 2 H), 2.05 (s, 3 H), 1.61–1.48 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 169.7, 72.7, 70.0, 61.1, 52.4, 22.6, 22.2, 13.8, 10.0.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{19}NO_4Na$: 240.1207; found: 240.1200.

(*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide [(*R*)-Lacosamide] (1)

To a stirred solution of benzylamine (0.86 mL, 7.92 mmol) in CH_2Cl_2 (5 mL) was added Me_3Al (2.0 M in toluene, 3.96 mL, 7.92 mmol) at r.t. and the solution was stirred for 10 min. The resulting solution was transferred to a solution of compound **4a** (500 mg, 2.64 mmol) in CH_2Cl_2 (5 mL) under N_2 and stirred for another 3.0 h. The reaction was quenched with 0.1 N HCl (20 mL) and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude **1**, which was recrystallized from EtOAc to give pure lacosamide (**1**).

Yield: 621 mg (94%); white solid; mp 143–144 °C {Lit.[5a] mp 142–143 °C}; $[\alpha]_D^{20}$ +15.8 (*c* = 1.2, MeOH) {Lit.[5a] $[\alpha]_D^{20}$ +16.1 (*c* 1.2, MeOH)}.

IR (neat): 3283, 2341, 1627, 1538, 1142, 678 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 5 H), 6.79 (br s, 1 H), 6.46 (d, *J* = 5.6 Hz, 1 H), 4.55 (td, *J* = 7.1, 4.2 Hz, 1 H), 4.52–4.42 (m, 2 H), 3.81 (dd, *J* = 9.1, 4.1 Hz, 1 H), 3.44 (dd, *J* = 9.1, 7.6 Hz, 1 H), 3.38 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 169.9, 137.8, 128.5, 127.3, 71.8, 58.9, 52.4, 43.4, 23.0.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}N_2O_3Na$: 273.1210; found: 273.1210.

Multigram Synthesis of (*R*)-Lacosamide (1) with a Single Purification by Recrystallization

To a stirred solution of ethyl ester **2b** (10.0 g, 45.6 mmol) in a mixture of MeCN and MeOH (9:1, 100 mL) was added $BF_3{\cdot}OEt_2$ (6.35 mL, 50.16 mmol). The resulting mixture was stirred and heated at 90 °C for 3.0 h. Upon complete conversion of starting material as confirmed by TLC (product R_f 0.3; EtOAc/hexane, 25%), the mixture was cooled to r.t., the solvents were removed under vacuum, and the crude product was dissolved in CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ solution (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give the crude product **3b** as a pale-yellow viscous liquid (10.6 g, 93% yield, 94:6 regioisomeric ratio), which was used as such for the next step without purification.

To a stirred solution of amine **3b** (10.6 g, 42.17 mmol) in EtOH (106 mL), was added acetic anhydride (8.0 mL, 84.3 mmol) and 20% $Pd(OH)_2/C$ (1.0 g, 50% wet). The resulting heterogeneous mixture was hydrogenated under an atmospheric pressure of hydrogen for 14 h. The mixture was filtered through a pad of Celite, washed with EtOH (2 × 50 mL) and the solvents were removed under vacuum to give a crude residue. The resulting residue was dissolved in CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ solution (2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give crude acetamide **4a** (7.58 g, 95% yield), which was used as such for next step without purification.

To a stirred solution of benzylamine (10.0 mL, 91.0 mmol) in CH_2Cl_2 (35 mL) was slowly added Me_3Al (2.0 M in toluene, 45.5 mL, 91.0 mmol) in 30 min at r.t. and the solution was stirred for another 10 min. The resulting solution was transferred slowly to the solution of compound **4a** (7.58 g, 40.06 mmol) in CH_2Cl_2 (75 mL) under N_2 at r.t. and the mixture was stirred for another 3.0 h. The mixture was cooled to 0 °C and the reaction was quenched by slow addition of 0.5 N HCl (200 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude **1** (chiral purity 99:1), which was recrystallized from EtOAc to give pure lacosamide **1** (8.12 g, 81% yield, chiral purity >99.9 by HPLC) as a white solid.

(*R*)-2-Acetamido-*N*-benzyl-3-ethoxypropanamide (1a)

The procedure was analogous to that used for the preparation of **1**. From compound **4a** (200 mg, 0.98 mmol), benzylamine (0.32 mL, 2.95 mmol), and Me_3Al (2.0 M in toluene, 1.48 mL, 2.95 mmol) was obtained compound **1a**.

Yield: 231 mg (89%); white solid; mp 132–133 °C {Lit.[1b] mp 129–130 °C}; $[\alpha]_D^{20}$ –34.9 (*c* = 1.0, $CHCl_3$) {Lit.[1b] $[\alpha]_D^{25}$ –34.1 (*c* 0.64, $CHCl_3$)}.

IR (neat): 3274, 2846, 1732, 1623, 1530, 1364, 1117, 687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.12 (m, 5 H), 6.91 (br s, 1 H), 6.52 (d, *J* = 6.4 Hz, 1 H), 4.49 (td, *J* = 7.3, 4.3 Hz, 1 H), 4.43 (dd, *J* = 15.0, 6.1 Hz, 1 H), 4.34 (dd, *J* = 15.0, 5.6 Hz, 1 H), 3.74 (dd, *J* = 9.2, 4.3 Hz, 1 H), 3.52–3.36 (m, 3 H), 1.94 (s, 3 H), 1.07 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 170.1, 137.8, 128.4, 127.3, 127.2, 69.7, 66.6, 52.5, 43.3, 22.9, 14.8.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}N_2O_3Na$: 287.1366; found: 287.1369.

(*R*)-2-Acetamido-*N*-benzyl-3-propoxypropanamide (1b)

The procedure was analogous to that used for the preparation of **1**. From compound **4b** (200 mg, 0.92 mmol), benzylamine (0.30 mL, 2.76 mmol), and Me_3Al (2.0 M in toluene, 1.38 mL, 2.76 mmol) was obtained compound **1b**.

Yield: 223 mg (87%); white solid; mp 131–132 °C; $[\alpha]_D^{20}$ –38.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 3274, 2914, 1716, 1629, 1537, 1132, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 5 H), 6.91 (br s, 1 H), 6.52 (d, *J* = 6.2 Hz, 1 H), 4.55 (ddd, *J* = 7.9, 6.8, 4.2 Hz, 1 H), 4.46 (qd, *J* = 15.1, 5.9 Hz, 2 H), 3.82 (dd, *J* = 9.2, 4.2 Hz, 1 H), 3.52–3.34 (m, 3 H), 2.02 (s, 3 H), 1.60–1.45 (m, 2 H), 0.84 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.21, 170.1, 137.8, 128.6, 127.4, 73.1, 69.7, 52.4, 43.5, 23.1, 22.6, 10.4.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}N_2O_3Na$: 301.1523; found: 301.1539.

(*R*)-2-Acetamido-*N*-(adamantan-2-ylmethyl)-3-methoxypropanamide (1c)

The procedure was analogous to that used for the preparation of **1**. From compound **4** (50 mg, 0.26 mmol), 1-adamantanemethylamine (131 mg, 0.79 mmol), and Me_3Al (2.0 M in toluene, 0.40 mL, 0.79 mmol) was obtained compound **1c**.

Yield: 68 mg (83%); white solid; mp 150–151 °C; $[\alpha]_D^{20}$ –21.9 (*c* = 1.0, $CHCl_3$).

IR (neat): 3265, 2883, 1628, 1533, 1105, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (d, *J* = 4.0 Hz, 2 H), 4.50 (ddd, *J* = 7.9, 6.6, 4.3 Hz, 1 H), 3.77 (dd, *J* = 9.0, 4.3 Hz, 1 H), 3.41 (s, 3 H), 3.40 (dd, *J* = 8.9, 8.1 Hz, 1 H), 3.08 (dd, *J* = 13.4, 7.0 Hz, 1 H), 2.86 (dd, *J* = 13.4, 5.6 Hz, 1 H), 2.04 (s, 3 H), 2.01–1.95 (m, 3 H), 1.67 (dd, *J* = 40.9, 11.9 Hz, 6 H), 1.47 (d, *J* = 1.9 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 170.0, 72.0, 58.8, 52.2, 50.8, 39.9, 36.7, 33.6, 28.0, 22.9.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{28}N_2O_3Na$: 331.1993; found: 331.1986.

(*R*)-2-Acetamido-*N*-cyclopentyl-3-methoxypropanamide (1d)

The procedure was analogous to that used for the preparation of **1**. From compound **4** (150 mg, 0.79 mmol), cyclopentylamine (0.23 mL, 2.38 mmol), and Me_3Al (2.0 M in toluene, 1.19 mL, 2.38 mmol) was obtained compound **1d**.

Yield: 147 mg (81%); white solid; mp 165–166 °C; $[\alpha]_D^{20}$ –28.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 3271, 2909, 1619, 1532, 1255, 984, 693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 7.3 Hz, 1 H), 4.67–4.54 (m, 1 H), 4.00 (dq, *J* = 13.5, 6.8 Hz, 1 H), 3.55 (dd, *J* = 9.5, 5.2 Hz, 1 H), 3.38 (dd, *J* = 9.5, 6.0 Hz, 1 H), 3.21 (s, 3 H), 1.87 (s, 3 H), 1.76 (qd, *J* = 12.4, 6.4 Hz, 2 H), 1.60–1.21 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 169.3, 72.3, 58.5, 52.2, 50.8, 32.5, 32.2, 23.4, 23.3, 22.5.

HRMS (MALDI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{21}N_2O_3$: 229.1547; found: 229.1545.

(*R*)-2-Acetamido-*N*-hexyl-3-methoxypropanamide (1e)

The procedure was analogous to that used for the preparation of **1**. From compound **4** (150 mg, 0.79 mmol), hexylamine (0.32 mL, 2.38 mmol), and Me_3Al (2.0 M in toluene, 1.19 mL, 2.38 mmol) was obtained compound **1e**.

Yield: 172 mg (89%); white solid; mp 112–114 °C; $[\alpha]_D^{20}$ –30.0 (*c* = 1.0, $CHCl_3$).

IR (neat): 3278, 2920, 1625, 1533, 1130, 972, 693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.84–6.57 (m, 2 H), 4.54 (td, *J* = 7.1, 4.5 Hz, 1 H), 3.74 (dd, *J* = 9.2, 4.4 Hz, 1 H), 3.44 (dd, *J* = 9.1, 7.4 Hz, 1 H), 3.38 (s, 3 H), 3.35–3.17 (m, 2 H), 2.03 (s, 3 H), 1.57–1.43 (m, 2 H), 1.32–1.26 (m, 2 H), 0.88 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 169.8, 71.8, 58.9, 52.2, 50.8, 32.5, 32.2, 23.4, 23.3, 22.5.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{24}N_2O_3Na$: 267.1680; found: 267.1689.

(*R*)-2-Acetamido-*N*-decyl-3-methoxypropanamide (1f)

The procedure was analogous to that used for the preparation of **1**. From compound **4** (150 mg, 0.79 mmol), decylamine (0.48 mL, 2.38 mmol), and Me_3Al (2.0 M in toluene, 1.19 mL, 2.38 mmol) was obtained compound **1f**.

Yield: 186 mg (78%); white solid; mp 110–111 °C; $[\alpha]_D^{20}$ –27.4 (*c* = 1.0, $CHCl_3$).

IR (neat): 3267, 2911, 1628, 1527, 1117, 693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.94–6.67 (m, 2 H), 4.55 (td, *J* = 7.1, 4.7 Hz, 1 H), 3.74 (dd, *J* = 9.2, 4.4 Hz, 1 H), 3.44 (dd, *J* = 9.2, 7.3 Hz, 1 H), 3.38 (s, 3 H), 3.33–3.16 (m, 2 H), 2.03 (s, 3 H), 1.56–1.43 (m, 2 H), 1.41–1.16 (m, *J* = 8.1 Hz, 14 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 169.8, 71.9, 58.9, 52.2, 39.5, 31.7, 29.4, 29.3, 29.2, 29.1, 26.7, 23.0, 22.5, 14.0.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{32}N_2O_3Na$: 323.2306; found: 323.2296.

(*R*)-2-Acetamido-*N*-dodecyl-3-methoxypropanamide (1g)

The procedure was analogous to that used for the preparation of **1**. From compound **4** (150 mg, 0.79 mmol), dodecylamine (441 mg, 2.38 mmol), and Me_3Al (2.0 M in toluene, 1.19 mL, 2.38 mmol) was obtained compound **1f**.

Yield: 208 mg (80%); white solid; mp 104–105 °C; $[\alpha]_D^{20}$ –24.3 (*c* = 1.0, $CHCl_3$).

IR (neat): 3274, 2912, 2334, 1733, 1627, 1364, 1199, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.68–6.50 (m, 2 H), 4.50 (td, *J* = 7.2, 4.4 Hz, 1 H), 3.75 (dd, *J* = 9.2, 4.3 Hz, 1 H), 3.48–3.36 (m, 4 H), 3.33–3.15 (m, 2 H), 2.03 (s, 3 H), 1.56–1.44 (m, 2 H), 1.40–1.17 (m, *J* = 9.3 Hz, 18 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 169.7, 71.8, 59.0, 52.2, 39.6, 31.8, 29.59, 29.57, 29.53, 29.50, 29.3, 29.29, 29.21, 26.7, 23.1, 22.6, 14.0.

HRMS (MALDI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{37}N_2O_3$: 329.2800; found: 329.2814.

(*R*)-2-Acetamido-3-methoxy-*N*-octadecylpropanamide (1h)

The procedure was analogous to that used for the preparation of **1**. From compound **4** (50 mg, 0.26 mmol), octadecylamine (214 mg, 0.79 mmol), and Me_3Al (2.0 M in toluene, 0.40 mL, 0.79 mmol) was obtained compound **1f**.

Yield: 83 mg (76%); white solid; mp 128–130 °C; $[\alpha]_D^{20}$ –18.9 (*c* = 1.0, $CHCl_3$).

IR (neat): 3281, 2913, 2848, 1726, 1630, 1364, 691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.50 (br s, *J* = 5.1 Hz, 2 H), 4.48 (td, *J* = 7.2, 4.5 Hz, 1 H), 3.76 (dd, *J* = 9.1, 4.2 Hz, 1 H), 3.44–3.36 (m, 4 H), 3.33–3.18 (m, 2 H), 2.04 (s, 3 H), 1.56–1.44 (m, 2 H), 1.37–1.18 (m, 30 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 169.8, 71.7, 59.0, 52.2, 39.6, 31.8, 29.65, 29.61, 29.55, 29.51, 29.38, 29.31, 29.2, 26.7, 23.1, 22.6, 14.0.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{48}N_2O_3$: 435.3559; found: 435.3548.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588093.

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