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3-Azaspiro[5,5]undecan-2,4-dioxo-3-yl diphenyl phosphate (ASUD-diphenyl phosphate), a new reagent for the synthesis of the *N*-protected amino acid-ASUD ester

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ABSTRACT

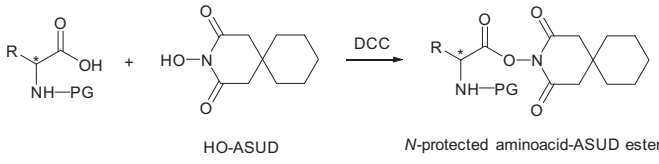
A new reagent, 3-azaspiro[5,5]undecan-2,4-dioxo-3-yl diphenyl phosphate (ASUD-diphenyl phosphate) is described for the synthesis of *N*-protected amino acid-ASUD esters which are active esters useful in the synthesis of peptides. This compound was synthesized by reacting *N*-hydroxy-3-azaspiro[5,5]undecane-2,4-dione (HO-ASUD) with diphenyl chlorophosphate in the presence of a base at room temperature and was obtained in high yields. The ASUD-diphenyl phosphate reagent reacts with *N*-protected amino acids under mild conditions to give the corresponding ASUD active esters, while preserving the enantiomeric purity of the amino acid. The new reagent is a stable crystalline compound and eliminates the need for DCC, a potent skin allergen, used previously for the synthesis of *N*-protected amino acid-ASUD ester.

1. Introduction

Mild and racemization free methods for the synthesis of peptide bonds remain a focus of much research activity. Over the past decade, a number of new methods for the construction of peptide bond have been discovered.[1] Several *N*-hydroxy compounds such as *N*-hydroxy succinimide,[2,3] 1-hydroxy benzotriazole,[4,5] 1-hydroxy-7-aza-1*H*-benzotriazole,[6] *N*-hydroxyphthalimide,[7] have been used to activate the carboxylic group during peptide synthesis. Recently, *N*-hydroxy-3-azaspiro[5,5]undecane-2,4-dione (HO-ASUD) has been used successfully to prepare activated amino acids as an alternative for *N*-hydroxy succinimide.[8] The activated *N*-protected amino acid-ASUD esters were prepared by reacting the *N*-protected amino acid with the HO-ASUD, using DCC as a coupling agent (Scheme 1).[8]

The coupling agent DCC is a potent allergen and sensitizer, often causing skin rashes.[9] Another major drawback of DCC is the formation of dicyclohexyl urea as a by-product, which is difficult to remove because of its poor solubility in most organic solvents.

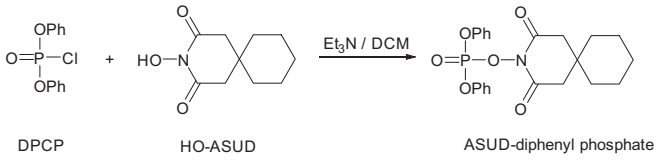
Herein we report a new reagent, ASUD-diphenyl phosphate, for the easy synthesis of *N*-protected amino acid-ASUD esters. The new reagent is stable, crystalline and reacts with *N*-protected amino acids directly to give ASUD esters without the need for DCC. The amino acid-ASUD esters prepared by this method maintain chiral integrity without undergoing any racemization during the reaction.



Scheme 1.

2. Results and discussion

The new reagent, ASUD-diphenyl phosphate, can be conveniently prepared by the reaction of HO-ASUD with diphenyl chlorophosphate under the condition of Schotten–Baumann reaction in the presence of a base such as triethylemine (Scheme 2).



Scheme 2. Synthesis of ASUD-diphenyl phosphate.

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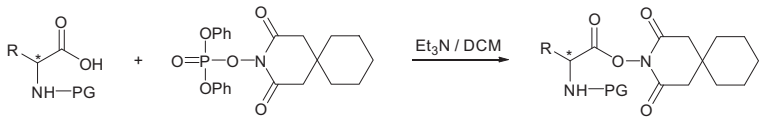
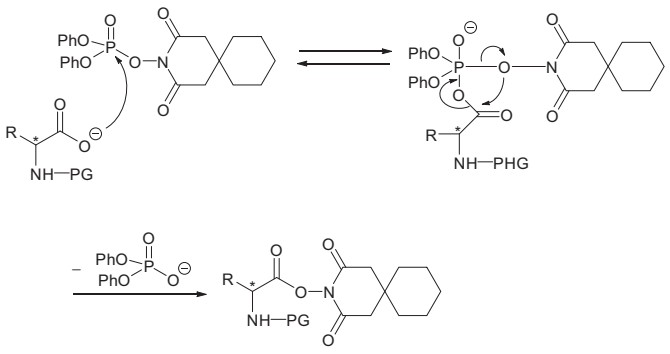


Scheme 3.

The reaction is fast (<30 min) and gives almost quantitative yields (>95%). The reagent, ASUD-diphenyl phosphate, is a stable colorless solid of >99% purity (^{31}P NMR and HPLC) and can be stored at ambient temperature for several weeks without any decomposition.

The ASUD-diphenyl phosphate is an excellent reagent for the synthesis of *N*-protected aminoacid active ASUD esters. The *N*-protected amino acid-ASUD ester can be prepared by simply stirring equimolar amounts of the *N*-protected amino acid with ASUD-diphenyl phosphate in the presence of an organic base in a suitable solvent, as shown in Scheme 3.

A wide range of solvents can be used, such as toluene, dichloromethane, chloroform, ethyl acetate, acetone, acetonitrile, THF, DMF and NMP. The reaction takes approximately 4–8 h at ambient temperature and can be easily monitored by HPLC or TLC. A mechanism has been proposed for the synthesis of ASUD-diphenyl phosphate (Scheme 4).



Scheme 4.

In the presence of a base, the *N*-protected amino acid is ionized and the carboxylate ion attacks the phosphorus atom of the ASUD-diphenyl phosphate. The resulting intermediate rearranges via elimination of diphenyl phosphite to give a stable *N*-protected amino acid-ASUD ester.

The reagent is compatible with all of the *N*-protected groups generally used and no deprotection was observed, even, in the case of Boc, Cbz, and FMOC groups. A list of *N*-protected aminoacid-ASUD esters prepared using ASUD-diphenyl phosphate is shown in Table 1.

Dipeptides can be prepared in a facile manner by condensing *N*-protected amino acid-ASUD ester with another amino acid as reported in the literature.[8] The condensation can be carried out in THF or THF-water mixture using a base such as sodium carbonate or trimethylamine at room temperature. The overall yield of dipeptides obtained is very high ranging between 70% and 90%. Table 2 lists the dipeptides synthesized using *N*-protected amino acid-ASUD esters. The enantiomeric purity was measured by the specific rotation and compared with standard samples. In some cases, the enantiomeric purity was also measured using HPLC. In all cases, it was found that the dipeptide formation takes place with complete preservation of enantiomeric purity.

We also report a new scheme for the synthesis of lacosamide, an anti-epileptic drug using ASUD-diphenyl phosphate (Scheme 5).

The starting compound required, *N*-Boc-*O*-methyl-D-serine **Ia** was prepared as reported by Muddasani et al.[20] and reacted with ASUD-diphenyl phosphate to obtain the corresponding ASUD derivative **Ib**. Reaction of **Ib** with benzyl amine resulted in **Ic** in good yields. The deprotection of the Boc group of **Ic** followed by *N*-acetylation to obtain lacosamide is reported in the literature.[21,22] The lacosamide thus obtained showed very high enantiomeric purity (>99.5%) in addition to high chemical purity. This further confirms that the new reagent, ASUD-diphenyl phosphate is very effective for amide formation, which maintains the chiral integrity during the reaction.

3. Conclusion

Herein we have shown that the ASUD-diphenyl phosphate is an excellent new reagent for the synthesis of *N*-protected amino acid-ASUD esters useful in the synthesis of peptides. The new reagent is a stable crystalline material and reacts with *N*-protected amino acids in a facile manner under mild conditions and gives *N*-protected amino acid-ASUD esters in high yields while preserving the chiral integrity of the amino acid. The new reagent eliminates the requirement of DCC, a skin allergen, which was used previously in preparing ASUD esters.

4. Experimental

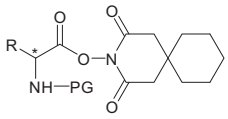
4.1. General

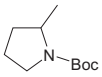
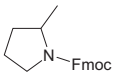
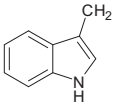
All of the chemicals used were obtained from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed on Merck (TLC Silica gel 60 F254) and visualized using a UV lamp (254 nm) and stains such as iodine, ninhydrin. The melting points were determined by using Polmon melting point apparatus and are uncorrected. Optical rotations were recorded on Jasco DIP-1000 polarimeter. IR spectra were obtained from Perkin–Elmer Spectrum one, Spectrophotometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker 300 MHz NMR spectrometer. Mass spectra were recorded on a Thermo scientific LCQ Fleet spectrometer with ion trap mass spectrometer.

4.2. Synthesis of ASUD-diphenyl phosphate

ASUD-OH (5.0 g, 25.35 mmol), diphenylchlorophosphate (7.50 g, 27.9 mmol) and triethyl- amine (2.82 g, 27.9 mmol) were dissolved in dichloromethane (50 mL). The solution was stirred for 30 min at room temperature. The triethylamine hydrochloride salt was filtered and the filtrate was washed with water (25 mL), brine (25 mL), and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuum to yield a solid, which was slurried in methyl *tert*-butyl ether (30 mL) to give 10.50 g (96.4%) of title product as a white crystalline solid; mp 99–101 °C, TLC: Single, R_f 0.8 (Hexanes:EtOAc-1:2) 99.97% purity by HPLC (Method b, Table 1); IR (KBr, cm^{-1}): ν_{max} 3420, 3287, 2935, 2924, 2859, 1791, 1760, 1716, 1589, 1526, 1488, 1456, 1389, 1365, 1318, 1236, 1214; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.46 (s, 10H), 2.70 (s, 4H), 7.19–7.39

Table 1
N-ASUD esters of *N*-substituted amino acids using ASUD-diphenyl phosphate



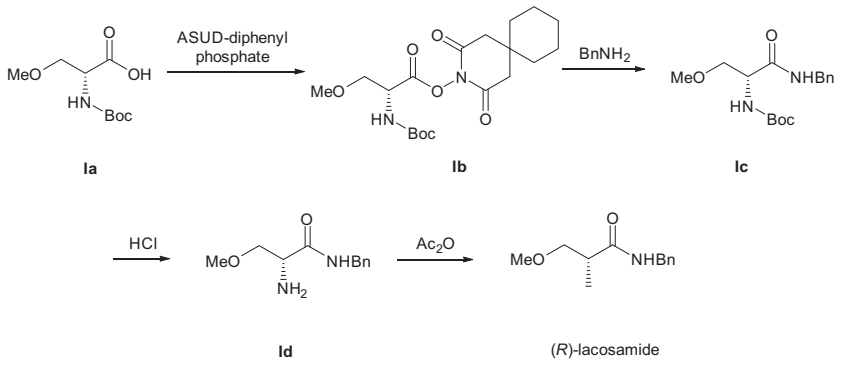
Entry	R	PG	*L/D	Yield (%)	M.R. (°C)	Purity by HPLC (%)	ee[a]
1	H	Boc	—	87	138–142	98.63[b]	—
2	H	Cbz	—	91	129–132	98.49[b]	—
3	H	Fmoc	—	90	140–142	97.92[c]	—
4	CH_3	Cbz	L	89	109–111	99.77[b]	100[e]
5	CH_3	Cbz	D	86	111–113	99.82[b]	100[e]
6	$PhCH_2$	Boc	L	85	127–139	100[b]	99.35[f]
7	$PhCH_2$	Boc	D	80	128–130	99.79[b]	99.60[f]
8	$PhCH_2$	Cbz	L	85	88–91	97.49[b]	100[f]
9	$PhCH_2$	Fmoc	L	87	102–105	96.36[c]	99.72[g]
10			L	78	Oil	99.34[b]	100[h]
11			L	78	87–90	98.60[c]	100[i]
12		Fmoc	L	83	92–95	95.02[c]	100[g]
13	CH_2OMe	Boc	D	91.3	Oil	98.37[d]	99.21[j]
14	CH_2OMe	Boc	L	89.2	Oil	98.46[d]	98.24[j]

[*] L-Isomer/D-isomer.
[a] Determined using chiral HPLC.
[b] Purity by HPLC: Xterra RP-18, 4.6 mm × 250 mm (5 μm), water/CH_3CN (50:50), Flow rate: 1.0 mL/min, Detection: 210 nm.
[c] Purity by HPLC: Symmetry C 18, 4.6 mm × 150 mm (5 μm), water/CH_3CN (50:50), Flow rate: 1.0 mL/min, Detection: 220 nm.
[d] Purity by HPLC: Hypersil BDS C 18, 4.6 mm × 250 mm (5 μm), water: CH_3CN (20:80), Flow rate: 1.0 mL/min, Detection: 210 nm.
[e] Chiral HPLC: Chiralpak IA; *n*-hexane/EtOH (30:70).
[f] Chiral HPLC: Chiralpak IA; *n*-hexane/EtOAc/TFA (70:30:0.1%).
[g] Chiral HPLC: Chiralcel OD-H; *n*-hexane/EtOH/TFA (70:30:0.1%).
[h] Chiral HPLC: Chiralpak IA; *n*-hexane/EtOH (40:60).
[i] Chiral HPLC: Chiralcel OD-H; *n*-hexane/EtOH/TFA (60:40:0.1%).
[j] Chiral HPLC: Chiralcel OD-H, *n*-hexane/IPA/TFA (60:40:0.1%).

Table 2
Dipeptides prepared involving the activated amino acid-ASUD ester

Entry	Starting material	Product	Yield (%)	Lit.Y (%)	Obtained specific rotation[*]	Lit. specific rotation $[\alpha]_D$ (c 1)
1	Boc-L-Phe-ASUD	Boc-L-Phe-Phe-OMe	82	70[a]	−13.8	−13.9 (MeOH)
2	Boc-L-Phe-ASUD	Boc-L-Phe-Ser-OMe	84	74[b]	+17.2	+17 ($CHCl_3$)
3	Boc-L-Pro-ASUD	Boc-L-Pro-Ala-OMe	81	75[c]	−94.8	−92.3 (MeOH)
4	Fmoc-L-Pro-ASUD	Fmoc-L-Pro-Pro-OH	91	74[d]	−79.2	−79.8 ($CHCl_3$)
5	Fmoc-L-Trp-ASUD	Fmoc-L-Trp-Ser-OH	85	87[e]	−13.5	−13.7 (DMF)
6	Fmoc-L-Trp-ASUD	Fmoc-L-Trp-Ala-OH	75	70[f]	−15.9	−15.7 (DMF)
7	Boc-L-Ala-ASUD	Boc-L-Ala-Pro-OH	78	80[g]	−94.2	−92.5 (MeOH)
8	Cbz-L-Ala-ASUD	Cbz-L-Ala-Ala-OMe	90	94[h]	−48.8	−49 (MeOH)
9	Cbz-L-Ala-ASUD	Cbz-L-Ala-Pro-OH	80	77[i]	−90.1	−91.2 (MeOH)
10	Boc-Gly-ASUD	Boc-Gly-Gly-OEt	92	90[j]	—	—

[*] The observed values were obtained under identical conditions to those reported in the literature.
[a] Ref. 10.
[b] Ref. 11.
[c] Ref. 12.
[d] Ref. 13.
[e] Ref. 14.
[f] Ref. 15.
[g] Ref. 16a (Lit. yield) and 16b (Lit. specific rotation);
[h] Ref. 17.
[i] Ref. 18.
[j] Ref. 19.



Scheme 5.

(m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.44, 25.50, 32.47, 37.76, 44.31, 120.35, 120.42, 125.78, 129.67, 150.43, 150.53, 165.73; DEPT 135: δ_C 21.43, 25.49, 35.74, 44.27 (–CH_2), 120.35, 120.42, 125.82, 129.69 (–CH); ^{31}P NMR (121 MHz, $CDCl_3$): δ –11.57 (s); MS: *m*/*z* 430.20 $[M+H]^+$.

4.3. Synthesis of *N*-ASUD esters of *N*-substituted amino acids

4.3.1. Synthesis of 2,4-dioxo-3-azaspiro[5.5]undecan-3-yl (*tert*-butoxycarbonyl)-L-phenyl-alaninate (Table 1, entry 6)

At first, *N*-Boc-L-Phenyl alanine (5.0 g, 18.8 mmol) was dissolved in dichloromethane (50 mL); to the clear solution were added ASUD-diphenyl phosphate (8.1 g, 18.8 mmol) and triethylamine (2.1 g, 20.73 mmol). The reaction mixture was stirred at room temperature for 4 h and washed with water (2 × 25 mL), brine (2 × 25 mL). The DCM layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to yield 8.5 g (>100%) of viscous oil. The oil was purified by silica gel chromatography (ethyl acetate: hexane = 3: 7) and crystallized from n-propanol to give the product as a white solid (7.12 g, 85%); mp 127–129 °C; TLC: Single, R_f 0.7 (Hexanes:EtOAc-2:1); 100% Purity by HPLC (Method b, Table 1);% ee: 99.35% (Method f, Table 1) (D-isomer R_t = 13.1 min; L-isomer R_t = 22.1 min); IR (KBr, cm^{-1}): ν_{max} 3421, 3288, 2983, 2934, 1802, 1791, 1748, 1714, 1698, 1604, 1526, 1497, 1455, 1389, 1365, 1240; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.38 (s, 9H), 1.48–1.59 (m, 10H), 2.64–2.83 (m, 4H), 3.12–3.16 (dd, 1H), 3.32–3.39 (dd, 1H), 4.90–4.95 (m, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.44, 24.53, 27.20, 31.65, 34.14, 35.53, 37.23, 43.15, 51.64, 79.17, 126.10, 127.51, 128.68, 134.29, 153.58, 164.53, 164.76, 167.62; MS: *m*/*z* 461.96 $[M+H_2O]^+$.

The other active esters given in Table 1 were prepared and characterized in a similar manner.

4.4. Synthesis of dipeptides

4.4.1. Synthesis of Boc-L-Phe-Phe-OMe (Table 2, entry 1)

A mixture of Boc-L-phenyl alanine-ASUDester (Table 1, entry 6) (3.0 g, 6.7 mmol), L-phenyl alanine methyl ester hydrochloride (1.46 g, 6.7 mmol), and triethylamine (1.71 g, 16.9 mmol) in dry THF (15 mL) was stirred overnight at room temperature (15 h). After completion of the reaction, the reaction mixture was filtered (remove TEA·HCl salt) and washed with THF (5 mL). The filtrate was concentrated under vacuum to obtain an oily crude. The oily crude was dissolved in ethyl acetate, washed with 1.0% $NaHCO_3$ solution and water. The ethyl acetate layer was dried over Na_2SO_4 and distilled under vacuum to give an oily crude product. The oily crude product obtained was crystallized using ethyl acetate and hexanes to yield Boc-L-Phe-Phe-OMe as a white crystalline solid (2.36 g, 82%); mp 113–115 °C (lit.[10] 114–116 °C); $[\alpha]_D^{20}$ = –13.8 (*c* 1, CH_3OH) [lit.[10] –13.9].

The other dipeptides listed in Table 2 were prepared in a similar manner and characterized.

4.5. Synthesis of lacosamide

To a solution of *N*-(*tert*-butoxycarbonyl)-*O*-methyl-D-serine **Ia**, (Scheme 5) (5.0 g, 22.8 mmol) in dichloromethane (25 mL) was added triethyl amine (2.54 g, 25.1 mmol) and the reaction mixture was stirred under an N_2 atmosphere. After 10 min, ASUD-Di phenyl phosphate (10.8 g, 25.1 mmol) was added and the reaction mixture was stirred at ambient temperature for 5 h. After completion of the reaction, the reaction mixture was washed with water (15 ml), brine (15 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 80:20) to afford 2,4-dioxo-3-azaspiro[5.5]undecan-3-yl *N*-(*tert*-butoxycarbonyl)-*O*-methyl-D-serinate **Ib** as a colorless oil (8.3 g, 91.3%); 98.37% purity by HPLC (Method d, Table 1);% ee: 99.21% (Method j, Table 1) (D-isomer R_t = 11.89 min; L-isomer R_t = 14.74 min); IR ($CHCl_3$, cm^{-1}): ν_{max} 3441, 3019, 2980, 2933, 2859, 1812, 1750, 1715, 1502, 1455, 1393, 1368, 1342, 1282, 1244, 1215, 1196, 1170, 1135, 1116, 1107, 1064, 966, 926, 878, 851, 758, 668; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.45–1.59 (m, 19H), 2.60–2.69 (m, 2H), 2.76–2.82 (m, 2H), 3.42 (s, 3H), 3.74–3.78 (dd, *J* = 9.6, 3.6 H_Z, 1H), 3.86–3.91, *J* = 9.6, 3.6 H_Z, 1H), 4.82 (m, 1H), 5.37 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.5, 165.5, 154.8, 80.2, 72.0, 59.2, 52.3, 44.1, 36.6, 35.0, 32.6, 28.2, 25.5, 21.4; MS: *m*/*z* 398.58 $[M]^+$, 415.79 $[M+H_2O]^+$, 420.9 $[M+Na]^+$.

A mixture of 2,4-dioxo-3-azaspiro[5.5]undecan-3-yl *N*-(*tert*-butoxycarbonyl)-*O*-methyl-D-serinate **Ib** (Scheme 5) (3.0 g, 7.53 mmol) and benzyl amine (0.97 g, 9.05 mmol) was vigorously stirred for 3 h at ambient temperature. After completion of the reaction, methyl *tert*-butyl ether (20 mL) was added and stirred at room temperature for 1 h. The reaction mixture was filtered, and washed with methyl *tert*-butyl ether (5 mL). The filtrate was washed with 5% aq HCl solution (10 mL), water (2 × 10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product solidified while standing overnight at room temperature to yield *tert*-butyl (*R*)-(1-(benzylamino)-3-methoxy-1-oxopropan-2-yl) carbamate **Ic** as a colorless solid (2.1 g, 90.4%); mp 62–64 °C (lit.[23] 63–64 °C); $[\alpha]_D^{25}$ = –20.8 (*c* 0.9, $CHCl_3$) [lit.[23] –20.5]; 97.68% purity by HPLC (Method-d, Table 1); ee%: 99.44% (Method-j, Table 1) [(*R*)-isomer R_t = 7.65 min; (*S*)-isomer R_t = 8.51 min]. IR (KBr, cm^{-1}): ν_{max} 3326, 3030, 2971, 2950, 2927, 2852, 2824, 1684, 1650, 1528, 1496, 1453, 1393, 1364, 1351, 1317, 1284, 1252, 1227, 1171, 1115, 1095, 1046, 1021, 919, 870, 750, 697, 652; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.43

(s, 9H), 3.36 (s, 3H), 3.47–3.52 (dd, J = 9.3, 6.3 Hz, 1H), 3.82–3.86 (dd, J = 9.3, 3.9 Hz, 1H), 4.27 (br, 1H), 4.48 (br s, 2H), 5.41 (br, 1H), 6.74 (br, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 169.3, 154.5, 137.0, 127.5, 126.4, 79.2, 71.1, 58.0, 53.0, 42.3, 27.2; MS: m/z 331 $[M+Na]^+$.

The above obtained **Ic**, (5.0 g, 16.2 mmol) was dissolved in dichloromethane (30 mL) after which was added concentrated hydrochloric acid (3 mL) at 0–5 °C and stirred at 25–30 °C for 2 h. The reaction mixture was diluted with water (20 mL), stirred for 10 min and then both layers were separated. The aqueous layer pH was adjusted to 10 with 25% NaOH, saturating with sodium chloride and extracted with dichloromethane (3 × 20 mL). The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to yield (*R*)-2-amino-*N*-benzyl-3-methoxypropanamide **Id** as an oil (3.38 g, 100%). Compound **Id** was used directly in the next step without further purification.

Compound **Id** (3.38 g, 16.2 mmol) was dissolved in dichloromethane (35 mL) and the resulting solution was treated with acetic anhydride (1.82 g, 17.8 mmol) after which the reaction mixture was stirred at ambient temperature for 4 h. After completion of the reaction (indicated by TLC), the mixture washed with 5% aqueous sodium carbonate solution (20 mL), followed by 10% aqueous citric acid solution (15 mL), water (15 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was dissolved in ethyl acetate (12 mL), stirred at 70–75 °C for 1 h and then stirred at 25–30 °C for 10 h. The solid was filtered, washed with ethyl acetate (5 mL) and dried under vacuum at 50 °C for 6 h to yield (*R*)-lacosamide as a colorless solid (3.53 g, 87%); mp 143–44 °C (lit.[24] 142–43 °C); $[\alpha]_D^{25}$ = +16.0 (*c* 1, MeOH) {lit.[24] $[\alpha]_D^{20}$ = +16.1 (*c* 1.2, MeOH)}; 99.88% purity by HPLC [Method: Hypersil BDS C 18, 4.6 mm × 250 mm (5 µm), water: CH_3CN (80:20), Flow rate: 1.0 mL/min, Detection: 210 nm];% ee: 99.68% (Method-j, Table 1) [(*R*)-isomer R_t = 8.90 min; (*S*)-isomer R_t = 10.45 min]; IR (KBr, cm^{-1}): ν_{max} 3289, 3086, 3026, 3003, 2923, 2875, 1637, 1547, 1497, 1454, 1395, 1370, 1306, 1276, 1245, 1220, 1159, 1138, 1098, 945, 748, 694, 605; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.02 (s, 3H), 3.37 (s, 3H), 3.41–3.46 (m, 1H), 3.78–3.82 (dd, J = 9.0, 4.2 Hz, 1H), 4.45–4.48 (m, 2H), 4.53–4.59 (m, 1H), 6.5 (br s, 1H), 6.82 (br s, 1H), 7.24–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.5, 170.1, 137.9, 128.5, 127.4, 127.3, 72.0, 58.9, 52.5, 43.4, 22.9; MS: m/z 250.9 $[M+H]^+$.

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