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Enantioselective Synthesis of (+)-α-Conhydrine and (–)-Sedamine by L-Proline-Catalysed α-Aminooxylation

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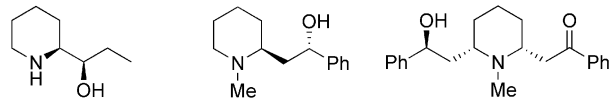
An efficient organocatalytic approach to the enantioslective synthesis of two important piperidine alkaloids, namely (+)-α-conhydrine (98 % *ee*) and (–)-sedamine (95 % *ee*), by L-proline-catalysed α-aminooxylation of aldehydes has been developed. The strategy involves an intramolecular cyclization to construct the piperidine core.

Introduction

Alkaloids with piperidine structural units often display interesting biological activities[1] and include (+)-conhydrine (**1**), (–)-sedamine (**2**), (–)-lobeline (**3**) and their stereoisomers (Figure 1). Their stereoselective synthesis is important for organic and medicinal chemists,[2] and they have been the subject of intense study due to their structural diversity and varied biological activities.[3] (+)-α-Conhydrine (**1**) was isolated in 1856 from the seeds and leaves of the poisonous plant *Conium maculatum L.*,[4a] its structure being elucidated in 1933,[4b] and (–)-sedamine (**2**) was isolated from *Sedum acre*[5] and other *Sedum* species.[6] In particular, these alkaloids have been shown to display memory-enhancing properties and are effective in the treatment of cognitive disorders.[7] Owing to their biological importance, a number of total syntheses of (+)-α-conhydrine[8] (**1**) and (–)-sedamine[9] (**2**), both in racemic and optically active forms, have been established. However, many of the reported methods either make use of chiral building blocks or involve longer reaction sequences, often accompanied by low product selectivity. For example, Takahata and coworkers reported the synthesis of azido diol **5** with low enantioselectivity (88% *ee*) by Sharpless asymmetric dihydroxylation of 5-hexenyl azide.[10] As part of our research aimed at developing a stereocontrolled synthesis of bioactive molecules,[11] we herein report an organocatalytic approach to a high-yielding synthesis of (+)-α-conhydrine (**1**) and (–)-sedamine (**2**), namely by L-proline-catalysed α-aminooxylation of azido aldehyde **6** as the chiral inducing step.



(+)-α-Conhydrine (**1**) (–)-Sedamine (**2**) (–)-Lobeline (**3**)

Figure 1. Structures of piperidine alkaloids **1**–**3**.

Results and Discussion

The retrosynthetic analysis of (+)-conhydrine (**1**) and (–)-sedamine (**2**) is shown in Scheme 1. The secondary alcohol moiety in (+)-conhydrine (**1**) can be obtained by the addition of ethylmagnesium bromide to aldehyde **4**, which may be derived from the azido diol **5** by intramolecular reductive amination. The diol **5** can in turn be obtained from 6-azidohexanal (**6**) by L-proline-catalysed α-aminooxylation. Similarly, (–)-sedamine (**2**) can be synthesized by the addition of phenylmagnesium bromide to aldehyde **7**, which can be derived from amino 1,3-diol **8** by intramolecular cyclization. The 1,3-diol **8** can be envisaged to arise from azido 1,2-diol **5**, the common intermediate in the synthesis of **1** and **2**.

The synthetic route to azido diol **5**, in which the L-proline-catalysed α-aminooxylation[12] of the aldehyde **6** is a key step for the introduction of chirality, is presented in Scheme 2. 6-Azidohexan-1-ol (**10**) was obtained from 1,6-hexanediol (**9**) in two steps by simple organic transformations, namely selective monotosylation followed by nucleophilic displacement with NaN_3, in an overall yield of 80%. Azido alcohol **10** was then subjected to Swern oxidation [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C] to obtain the corresponding aldehyde **6**, which was converted into the azido diol **5** in 61% yield by a two-step reaction sequence: (i) L-proline-catalysed asymmetric α-aminooxylation by using nitrosobenzene as the electrophilic oxygen source followed by reduction of the aldehyde function with $NaBH_4$ and (ii) cleavage of the aminooxy moiety of **11** (N–O bond) with $CuSO_4$ in methanol.

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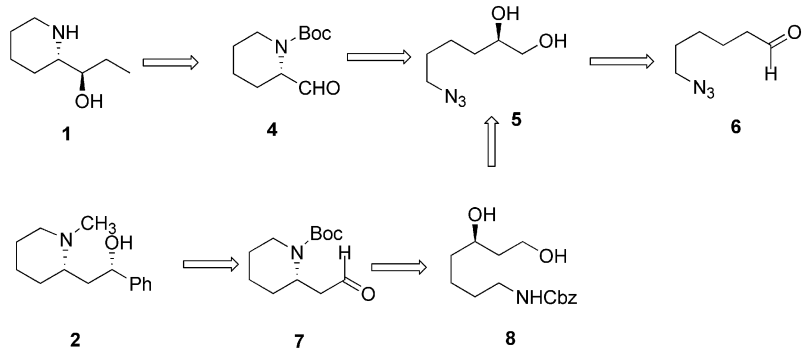
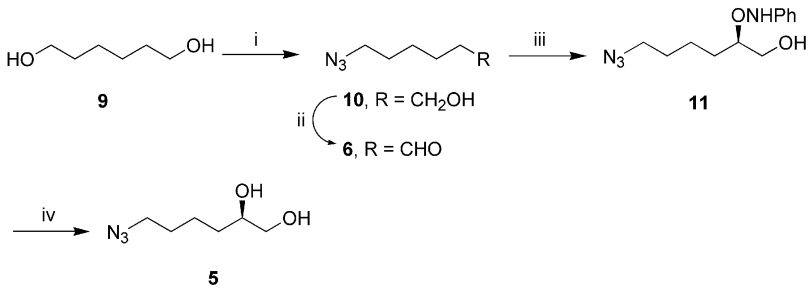


Scheme 1. Retrosynthetic analysis of (+)-conhydrine (**1**) and (–)-sedamine (**2**).



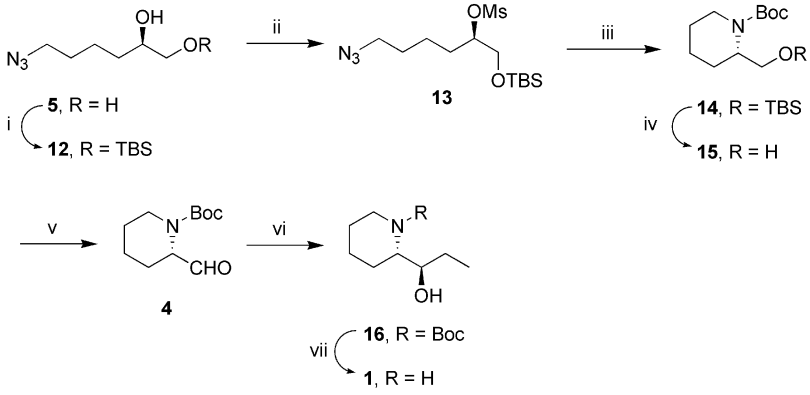
Scheme 2. Reagents and conditions: (i) TsCl, Et_3N, CH_2Cl_2, 0 °C; then NaN_3, dry DMF, 80 °C, 16 h, 80%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, 96%; (iii) L-proline (25 mol-%), PhNO, CH_3CN, –20 °C, 24 h; then MeOH, $NaBH_4$, 0 °C, 1 h; (iv) $CuSO_4$ (30 mol-%), MeOH, 12 h, 61%.

Synthesis of (+)-α-Conhydrine

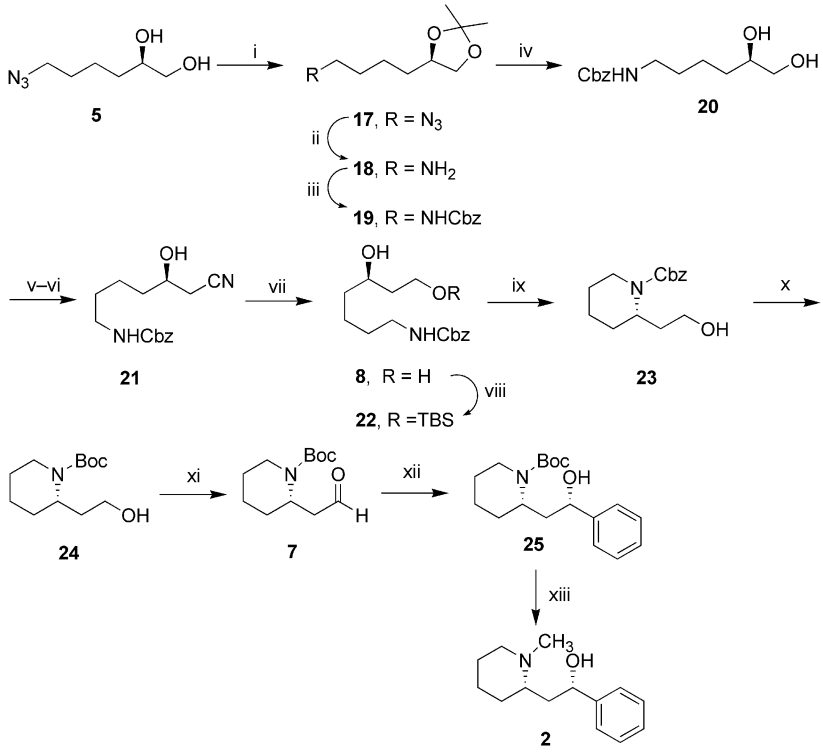
The primary hydroxy group in diol **5** was then protected (TBSCl, imidazole) selectively to give *tert*-butyldimethylsilyl ether **12** in 95% yield (Scheme 3). The secondary hydroxy group in the TBS ether **12** was then converted into the corresponding mesylate **13** in situ, which was subjected to reductive cyclization by catalytic hydrogenation with 10% Pd/C and H_2 (20 psi). This was followed by treatment with $(Boc)_2O$ and I_2 (10 mol-%),[13] which resulted in the chiral Boc-protected piperidine core **14** in 76% yield. Deprotection of the TBS ether (TBAF, THF) in **14** afforded piperidine alcohol **15** in 92% yield and 98% *ee*, as determined by chiral HPLC. The primary hydroxy group in piperidine alcohol **15** was then oxidized under Swern conditions to give aldehyde **4** in 90% yield. The aldehyde **4** was subsequently treated with ethylmagnesium bromide to afford the Boc-protected (+)-conhydrine **16** as a single diastereomer in 87% yield. The Boc group was finally deprotected under acidic conditions to furnish (+)-α-conhydrine (**1**) {$[a]_D^{25}$ = +8.7 (*c* = 0.85, EtOH); ref.[8u] $[a]_D^{22}$ = +8.33 (*c* = 0.81, EtOH)}.

Synthesis of (–)-Sedamine

The synthetic sequence for (–)-sedamine (**2**), starting from the key intermediate diol **5** derived by L-proline-catalysed α-aminooxylation, is presented in Scheme 4. Diol **5**



Scheme 3. Reagents and conditions: (i) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 95; (ii) MsCl, Et_3N, CH_2Cl, 0 °C, 1 h; (iii) 10% Pd/C, H_2 (20 psi), MeOH, Et_3N, 25 °C, 7 h; then $(Boc)_2O$, I_2 (10 mol-%), 3 h, 76%; (iv) TBAF, THF, 0 °C, 8 h, 92%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, 90%; (vi) excess EtMgBr, Et_2O, –78 °C, 3 h, 87%; (vii) TFA/CH_2Cl_2 (1:1), 25 °C, 12 h, 86%.



Scheme 4. Reagents and conditions: (i) *p*TsOH (10 mol-%), 2,2-dimethoxypropane, CH_2Cl_2, 25 °C, 12 h, 98%; (ii) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 8 h, 95%; (iii) CbzCl, K_2CO_3, CH_2Cl_2/H_2O (1:1), 25 °C, 7 h, 92%; (iv) excess 80% aq. AcOH, 25 °C, 18 h, 98%; (v) *p*TsCl, Et_3N, CH_2Cl_2, –20 °C, 15 h; (vi) NaCN, EtOH/H_2O (3:2), 0–25 °C, 18 h, 89%; (vii) 1.0 M DIBAL-H; CH_2Cl_2, –78 °C, 5 h; then 10% aq. HCl, –78 °C; then $NaBH_4$, MeOH, 25 °C, 5 h, 83%; (viii) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 85%; (ix) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h; then NaH (1 equiv.), THF, –40 °C, 1 h; then 50 °C, 2 h; then 3 N HCl in MeOH, 25 °C, 2 h, 68%; (x) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 5 h, 91%; then $(Boc)_2O$, I_2 (10 mol-%), 3 h, 95%; (xi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, 84%; (xii) PhMgBr, THF, –78 °C, 4 h, 61%; (xiii) $LiAlH_4$, THF, 70 °C, 8 h, 78%.

was protected as its acetonide **17** (2,2-dimethoxypropane, *p*-toluenesulfonic acid).[14a] Reduction of the azide function in **17** by catalytic hydrogenation [10% Pd/C, H_2 (20 psi), MeOH, 25 °C] produced amine **18** in 95% yield, which on protection [CbzCl (1.5 equiv.) and K_2CO_3 (2 equiv.), CH_2Cl_2/H_2O (1:1)] afforded Cbz-protected[14b] amine **19** in 92% yield. Removal of the acetonide group in **19** (excess of 80% aq. AcOH) afforded diol **20**. Diol **20** was then transformed into the cyano derivative **21** in two steps: selective monotosylation[14c] of the primary alcohol and S_N2 displacement of the tosylate with the CN^- ion to give nitrile **21** in 89% yield. Selective in situ reduction of the nitrile **21** (1.0 M DIBAL-H, CH_2Cl_2) to the corresponding aldehyde followed by treatment with $NaBH_4$ in MeOH produced 1,3-diol **8** in 83% yield. The primary alcohol function in 1,3-diol **8** was selectively protected as its TBS ether (TBSCl, imidazole) to give **22**, the secondary free hydroxy group of which was converted into the mesylate, which was employed in the next step without purification. The crude mesylate ($\tilde{\nu}_{max}$ = 1351 and 1142 cm^{-1}) underwent intramolecular cyclization under basic conditions (NaH),[15c,15d] and subsequent treatment with 3 N HCl in MeOH produced piperidine alcohol **23**. We then turned our attention to the stereoselective construction of the secondary hydroxy functionality of (–)-sedamine (**2**). To achieve this, we converted alcohol **23** into the corresponding Boc-protected alcohol **24** [catalytic hydrogenation followed by treatment with $(Boc)_2O$ and I_2]. Then the 2-(piperidin-2-yl)ethanol **24** was subjected to oxidation under Swern conditions to give the corresponding aldehyde **7** in 84% yield. Finally, the addition[9j] of PhMgBr to aldehyde **7** resulted in a mixture of *syn* and *anti* alcohols in a ratio of 2:1 and an overall yield of 90%. However, these diastereomers were readily separated by simple column chromatography. The major isomer (61% isolated yield) was subjected to reduction with $LiAlH_4$ to give (–)-sedamine **2** in 78% yield. The spectroscopic data of **2** were in complete agreement with reported values.[9i,9j,9t]

Conclusions

We have achieved an efficient synthesis of two important alkaloids, namely (+)-α-conhydrine (**1**; overall yield 25% and 98% *ee*) and (–)-sedamine (**2**; overall yield 31.5% and 95% *ee*). Both routes employed L-proline-catalysed α-aminooxylation as the key chiral-inducing reaction. The synthetic strategy described herein has significant potential for the synthesis of a variety of other biologically important piperidine alkaloids.

Experimental Section

General: All solvents were distilled and dried before use. IR spectra were recorded with a Perkin-Elmer model 683 B or 1605 FT-IR, and absorptions are expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with Bruker FT AV-200, AV-400 and AV-500 MHz instruments. Optical rotations were carried out with a JASCO-181 digital polarimeter at 25 °C by using sodium D light. Elemental analysis was done with a Carlo ERBA EA 110B instrument.

6-Azidohexan-1-ol (10): *p*-Toluenesulfonyl chloride (11.0 g, 57.8 mmol) was added to a stirred solution of 1,6-hexanediol (**9**; 7.2 g, 60.9 mmol) and Et_3N (8.4 mL, 60.9 mmol) in CH_2Cl_2 (200 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was poured into ice/water (150 mL), washed with aq. H_2SO_4 (10%), saturated aq. $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4, and the solvent was removed by distillation under reduced pressure to give the crude product (12.0 g). The crude tosylate (6.0 g, 22.0 mmol) was then dissolved in DMF (110 mL), and sodium azide (5.7 g, 88.1 mmol) was added. The reaction mixture was then heated at 80 °C for 15 h and then quenched by the addition of water. The aq. phase was extracted with Et_2O (3 × 100 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, the solvent was removed by distillation under reduced pressure and the crude product purified by column chromatography on silica gel by using petroleum ether/EtOAc (90:10) as eluent to yield pure azido alcohol **10**. Yield: 80% (2.52 g). IR ($CHCl_3$): $\tilde{\nu}$ = 3228, 2105, 1452, 1338, 1225, 1110, 1040, 935, 784 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (br. s, 1 H), 1.33–1.45 (m, 4 H), 1.49–1.64 (m, 4 H), 3.26 (t, J = 6.8 Hz, 2 H), 3.64 (t, J = 6.2 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.1, 26.3, 28.5, 32.2, 51.1, 62.2 ppm. $C_6H_{13}N_3O$ (143.19): calcd. C 50.33, H 9.15, N 29.35; found C 49.99, H 9.30, N 29.02.

Synthesis of (*R*)-6-Azidohexane-1,2-diol (5)

Swern Oxidation of 6-Azidohexan-1-ol (10): DMSO (3.7 mL, 52.3 mmol) was added to a stirred solution of oxalyl chloride (4.4 g, 34.9 mmol) in CH_2Cl_2 (30 mL) at –78 °C. The reaction mixture was stirred for 20 min, and then a solution of 6-azidohexan-1-ol (**10**; 2.5 g, 17.4 mmol) in CH_2Cl_2 (20 mL) was added. After stirring at –78 °C for 1 h, the reaction was quenched by the addition of Et_3N (9.7 mL, 69.8 mmol). The reaction mixture was then stirred for 30 min, and then water (70 mL) was added. The organic layer was separated and the aq. phase extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with water (3 × 30 mL), dried with anhydrous Na_2SO_4 and concentrated to give the corresponding crude aldehyde **6**. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.31–1.65 (m, 6 H), 2.31–2.48 (m, 2 H), 3.26 (t, J = 6.6, 13.2 Hz, 2 H), 9.75 (t, J = 1.7 Hz, 1 H) ppm.

α-Aminooxylation: Aldehyde **6** (2.0 g, 14.16 mmol) was dissolved in CH_3CN (60 mL), and the solution was cooled to –20 °C, and then nitrosobenzene (1.44 g, 13.45 mmol) and L-proline (407 mg, 25 mol-%) were added. After 24 h, the reaction mixture was warmed to 0 °C and then diluted with anhydrous methanol (20 mL). $NaBH_4$ (1.07 g, 28.3 mmol) was subsequently added. The reaction was quenched after 20 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aq. NH_4Cl. The organic layer was separated, and the aq. phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to give the crude product **11**, which was dissolved in MeOH (40 mL). $CuSO_4$ (0.675 g, 4.2 mmol) was then added. After stirring at 25 °C for 24 h, the reaction mixture was quenched by the addition of a solution of saturated aq. NH_4Cl (40 mL). The organic layer was separated and the aq. phase extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography on silica gel by using petroleum ether/EtOAc (60:40) as eluent to give pure diol **5**. Yield: 61% (0.780 g). $[\alpha]_D^{25}$ = +33.5 (c = 0.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3127, 3020, 2115, 1540, 1452, 1330, 1212, 1125, 1035, 932, 775, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.39–1.39 (m, 6 H), 1.98 (br. s, 2 H), 3.28 (t, J = 6.3 Hz, 2 H), 3.33–3.48 (m, 1 H), 3.66 (br. d, J = 11.0 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8, 28.8, 32.4, 51.3, 66.6, 72.0 ppm. $C_6H_{13}N_3O_2$ (159.19): calcd. C 45.27, H 8.23, N 26.40; found C 45.41, H 8.17, N 25.98.

Synthesis of (+)-Conhydrine (1)

(2*R*)-6-Azido-1-(*tert*-butyldimethylsilyloxy)hexan-2-ol (12): TBDMSCl (1.89 g, 12.5 mmol) was added to a stirred solution of diol **5** (2.0 g, 12.5 mmol) and imidazole (1.0 g, 15.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, the solvent was removed by distillation under reduced pressure and the crude product purified by column chromatography on silica gel by using petroleum ether/EtOAc (95:5) as eluent to give TBS ether **12**. Yield: 95% (3.26 g). IR ($CHCl_3$): $\tilde{\nu}$ = 3305, 2930, 2812, 1460, 1230, 1020, 745, 700, 605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.89 (s, 9 H), 1.38–1.64 (m, 6 H), 2.44 (br. d, J = 2.9 Hz, 1 H), 3.24–3.42 (m, 3 H), 3.58–3.69 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.47, 18.23, 22.78, 25.8, 28.8, 32.1, 51.29, 67.11, 71.4 ppm. $C_{12}H_{27}N_3O_2Si$ (273.45): calcd. C 52.71, H 9.95, N 15.37; found C 52.66, H 10.01, N 15.29.

***tert*-Butyl (2*S*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]piperidine-1-carboxylate (14):** Methanesulfonyl chloride (0.707 mL, 9.14 mmol) was added dropwise through a syringe to a stirred solution of TBS ether **12** (2.5 g, 9.14 mmol) and Et_3N (1.78 mL, 12.7 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After stirring at 0 °C for 0.5 h, the mixture was poured into ice/water (40 mL), washed with aq. $NaHCO_3$ and brine, and dried with anhydrous Na_2SO_4. The solvent was removed by distillation under reduced pressure to give the crude mesylate **13** (3.2 g), which was added to a stirred suspension of 10% Pd/C (40 mg) and Et_3N (1.27 mL, 12.6 mmol) in MeOH (10 mL) under hydrogen (20 psi) at 25 °C. After 7 h, the mixture was filtered through a pad of Celite, which was rinsed with MeOH (3 × 30 mL). The combined organic layers were concentrated under reduced pressure, and the crude product (2.0 g, 8.7 mmol) was stirred with $(Boc)_2O$ (2.0 mL, 8.7 mmol) and I_2 (220 mg, 10 mol-%) for 3 h and extracted with EtOAc (3 × 20 mL) and washed with water followed by aq. $Na_2S_2O_3$ (2 × 20 mL) to give crude **14**, which was purified by column chromatography by using petroleum ether/EtOAc (9:1) as eluent to give the pure TBS ether **14**. Yield: 76% (2.3 g). $[\alpha]_D^{25}$ = –35.8 (c = 0.7, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3442, 2812, 1650, 1020, 745, 700, 605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.87 (s, 9 H), 1.21–1.32 (m, 1 H), 1.44 (s, 9 H), 1.49–1.61 (m, 4 H), 1.75–1.87 (m, 1 H), 2.63–2.79 (m, 1 H), 3.57 (dd, J = 6.9, 9.8 Hz, 1 H), 3.67 (dd, J = 8.4, 9.6 Hz, 1 H), 3.97 (br. d, J = 12.1 Hz, 1 H), 4.16 (br., 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.41, 18.1, 19.0, 24.4, 25.2, 25.8, 28.4, 39.9, 51.5, 60.7, 79.0, 155.1 ppm. $C_{17}H_{35}NO_3Si$ (329.55): calcd. C 61.96, H 10.70, N 4.25; found C 60.99, H 10.79, N 4.58.

***tert*-Butyl (*S*)-2-(Hydroxymethyl)piperidine-1-carboxylate (15):** A solution of tetrabutylammonium fluoride (TBAF; 1.19 g, 1 M in THF, 4.5 mmol) was added to a stirred solution of carbamate **14** (1.5 g, 4.5 mmol) in THF at 0 °C and the mixture stirred for 8 h. The reaction was quenched by the addition of water, and the organic layer was separated. The aq. phase was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried with an-

hydrous Na_2SO_4, the solvent was removed by distillation under reduced pressure and the crude product purified by column chromatography on silica gel by using petroleum ether/EtOAc (7:3) as eluent to give alcohol **15** as a gum in 92% yield. Yield: 92% (0.897 g). Chiral column: Chiralcel OD-H, length 25 × 4.6 mm, wavelength 230 nm, flow rate 1.0 mL/min; mobile phase: 5% isopropyl alcohol in hexane; *ee* = 98%. $[a]_D^{25}$ = –40.1 (*c* = 1, $CHCl_3$) {ref.[15a] $[a]_D^{25}$ = –40.5 (*c* = 1, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3442, 2940, 2890, 1655, 1422, 1370, 1280, 1170, 1150, 1060, 1050, 870 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 1.51–1.76 (m, 6 H), 2.11 (br. s, 1 H), 2.78–2.92 (m, 1 H), 3.5–3.6 (m, 1 H), 3.74–3.96 (m, 2 H), 4.23–4.34 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.9, 24.4, 24.9, 28.0, 39.5, 51.7, 60.0, 79.1, 155.5 ppm. $C_{11}H_{21}NO_3$ (215.29): calcd. C 61.37, H 9.83, N 6.51; found C 61.40, H 9.79, N 6.49.

***tert*-Butyl (*S*)-2-Formylpiperidine-1-carboxylate (4):** DMSO (0.77 mL, 10.86 mmol) was added to a stirred solution of oxalyl chloride (0.625 mL, 7.24 mmol) in CH_2Cl_2 (25 mL) at –78 °C. The reaction mixture was stirred for 20 min, and then a solution of alcohol **15** (0.780 g, 3.64 mmol) in CH_2Cl_2 (20 mL) was added. After stirring at –78 °C for 1 h, the reaction was quenched by the addition of Et_3N (2.01 mL, 14.49 mmol). The reaction mixture was then stirred at 25 °C for 30 min, and then water (100 mL) was added. The organic layer was separated and the aq. phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with water (3 × 30 mL), dried with anhydrous Na_2SO_4 and concentrated to give the corresponding crude aldehyde, which was purified by column chromatography on silica gel by using petroleum ether/EtOAc (7:3) as a eluent to give aldehyde **4** as colourless gum. Yield: 90% (0.7 g). $[a]_D^{25}$ = –77.8 (*c* = 1.21, $CHCl_3$) {ref.[15b] $[a]_D^{25}$ = –77.9 (*c* = 1.49, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 2940, 2872, 1740, 1702, 1485, 1411, 1372, 1280, 1250, 1167, 1051, 1002, 1062, 871, 778 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.16–1.20 (m, 2 H), 1.38 (s, 9 H), 1.50–1.62 (m, 3 H), 2.06–2.11 (m, 1 H), 2.77–2.87 (br. s, 1 H), 3.80–3.93 (br. s, 1 H), 4.40–4.53 (br. s, 1 H), 9.49 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 23.3, 24.6, 28.1, 41.7, 42.9, 60.4, 61.4, 80.1, 155.0, 155.6, 200.8 ppm. $C_{11}H_{19}NO_3$ (213.27): calcd. C 61.95, H 8.98, N 6.57; found C 62.01, H 8.70, N 6.45.

(+)-Conhydrine (1): Grignard reagent EtMgBr, freshly prepared from ethyl bromide (0.62 g, 5.68 mmol) and Mg (0.165 g, 6.82 mmol) in diethyl ether (15 mL) at 0 °C, was added dropwise to a solution of aldehyde **4** (0.5 g, 2.34 mmol) in diethyl ether (7 mL). After stirring at this temperature for 3 h, saturated aq. NH_4Cl (40 mL) was added, and the mixture was extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. After flash chromatography by using petroleum ether/EtOAc (6:4), compound **16** (0.5 g) was obtained as a colourless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3421, 2932, 2867, 2351, 1686, 1165, 921 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 6 Hz, 3 H), 1.33–1.45 (m, 6 H), 1.45 (s, 9 H), 1.53–1.63 (m, 2 H), 2.02 (t, *J* = 8 Hz, 2 H), 2.97 (br. s, 1 H), 3.32–4.31 (m, 2 H) ppm. Trifluoroacetic acid (1 mL, 8.77 mmol) was added to a solution of **16** (100 mg, 0.411 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the mixture was washed with aq. $NaHCO_3$, extracted with dichloromethane (3 × 10 mL) and the aq. layer extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography by using CH_3OH/CH_2Cl_2 (4:6) as eluent to give (+)-conhydrine (**1**). Yield: 86% (50 mg). $[a]_D^{25}$ = +8.7 (*c* = 0.85, EtOH) {ref.[8u] $[a]_D^{22}$ = +8.33 (*c* = 0.81, EtOH)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3280, 3110, 2971, 2945, 2815, 1422, 1348, 1250, 1106, 1062, 1005, 972, 940, 811 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.0 Hz, 3 H), 1.24–1.57 (m, 7 H), 1.62–1.89 (m, 1 H), 2.47 (br. s, 2 H), 2.65–2.72 (m, 1 H), 2.73–2.88 (m, 1 H), 3.12–3.31 (m, 1 H), 3.40–3.57 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.0, 24.3, 25.5, 25.9, 29.9, 47.3, 60.4, 75.9 ppm. $C_8H_{17}NO$ (143.23): calcd. C 67.09, H 11.96, N 9.78; found C 66.99, H 11.89, N 9.85.

Synthesis of (–)-Sedamine (2)

(*R*)-4-(4-Azidobutyl)-2,2-dimethyl-1,3-dioxolane (17): *p*-Toluenesulfonic acid (0.27 g, 10 mol-%) was added to a mixture of diol **5** (2.5 g, 15.7 mmol), 2,2-dimethoxypropane (7.7 mL, 62.2 mmol) and dry CH_2Cl_2 (25 mL), and the reaction mixture was stirred at 25 °C for 12 h. After completion of the reaction, as monitored by TLC, it was neutralized with triethylamine, concentrated and purified by silica gel chromatography by using petroleum ether/EtOAc (9:1) as eluent to yield **17** as an oil. Yield: 98% (3.07 g). $[a]_D^{25}$ = –20.0 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2984, 2939, 2864, 2091, 1738, 1457, 1371, 1247, 1216, 1151, 1055, 853 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.38 (s, 3 H), 1.43–1.70 (m, 6 H), 3.27 (t, *J* = 6.5 Hz, 2 H), 3.44–3.53 (m, 1 H), 3.98–4.12 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8, 25.4, 26.7, 28.6, 32.9, 51.0, 69.1, 75.5, 108.5 ppm. $C_9H_{17}N_3O_2$ (199.25): calcd. C 54.25, H 8.60, N 21.09; found C 54.50, H 8.32, N 20.98.

4-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]butan-1-amine (18): 10% Pd/C (40 mg) was added to a stirred mixture of azide **17** (2.8 g, 14.0 mmol) in dry methanol (20 mL) under H_2 (20 psi), and the reaction mixture was stirred at 25 °C for 8 h. After completion of the reaction, as monitored by TLC, the mixture was filtered through a pad of Celite, which was rinsed with MeOH (3 × 30 mL). The combined organic layers were concentrated under reduced pressure to give the crude amine **18**, which was purified by column chromatography by using $CHCl_3$/MeOH (9:1) as eluent to give pure amine **18** as a colourless oil. Yield: 95% (2.32 g). $[a]_D^{25}$ = –16.7 (*c* = 2.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3420, 2980, 2932, 2860, 1632, 1559, 1460, 1364, 1251, 1055, 856, 605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.37 (s, 3 H), 1.46–1.68 (m, 6 H), 2.77 (t, *J* = 7.3 Hz, 1 H), 3.43–3.53 (m, 1 H), 3.72 (br. s, 2 H), 3.97–4.14 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7, 25.3, 26.6, 31.0, 32.9, 40.6, 69.0, 75.4, 108.3 ppm. $C_9H_{19}NO_2$ (173.25): calcd. C 62.39, H 11.05, N 8.08; found C 62.52, H 10.97, N 7.99.

Benzyl 4-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]butylcarbamate (19): Potassium carbonate (3.19 g, 23.0 mmol) was added to a stirred solution of amine **18** (2 g, 11.5 mmol) in a mixture of water (15 mL) and dichloromethane (15 mL). After 15 min, benzyl chloroformate (1.97 mL, 13.85 mmol) was introduced through a syringe, and the reaction mixture was stirred at 25 °C for 7 h. After completion of the reaction, the organic layer was decanted and the aq. phase extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, the solvent was evaporated in vacuo and the residue purified by column chromatography by using petroleum ether/EtOAc (7:3) to give pure carbamate **19** as a colourless oil. Yield: 92% (3.25 g). $[a]_D^{25}$ = –19.0 (*c* = 2.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3347, 3035, 3063, 2977, 2936, 2867, 1710, 1535, 1450, 1367, 1244, 1052, 853, 736 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.38 (s, 3 H), 1.44–1.59 (m, 6 H), 3.18 (dd, *J* = 6.1, 12.5 Hz, 2 H), 3.43–3.52 (m, 1 H), 3.97–4.11 (m, 2 H), 4.78 (br. s, 1 H), 5.08 (s, 2 H), 7.29–7.39 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8, 25.5, 26.7, 29.7, 32.9, 40.6, 66.3, 69.2, 75.6, 108.5, 127.8, 128.3, 136.4, 156.3 ppm. $C_{17}H_{25}NO_4$

(307.38): calcd. C 66.43, H 8.20, N 4.56; found C 66.51, H 7.97, N 4.49.

Benzyl (*R*)-5,6-Dihydroxyhexylcarbamate (20): A solution of acetonide **19** (3.0 g, 9.75 mmol) and 80% aq. AcOH (15 mL) was stirred at 25 °C for 18 h. After completion of the reaction, the acetic acid and water were removed under reduced pressure, and the crude mixture was extracted with EtOAc (3 × 20 mL) and washed with 10% aq. $NaHCO_3$. The combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by column chromatography by using petroleum ether/EtOAc (5:5) to give pure diol **20**. Yield: 98% (2.55 g). $[\alpha]_D^{25}$ = +18 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3401, 2941, 1640, 1527, 1340, 1066, 1028, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.33–1.59 (m, 6 H), 1.98 (br. s, 1 H), 2.74 (br. s, 1 H), 2.90 (br. s, 1 H), 3.16 (t, *J* = 6.0 Hz, 2 H), 3.34–3.42 (m, 1 H), 3.55–3.71 (m, 2 H), 5.06 (s, 2 H), 7.28–7.34 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4, 29.5, 32.2, 40.5, 64.6, 66.3, 71.8, 126.7, 127.2, 127.8, 128.2, 128.3, 136.3, 140.8, 156.6 ppm. $C_{14}H_{21}NO_4$ (267.32): calcd. C 62.90, H 7.92, N 5.24; found C 63.02, H 7.58, N 5.41.

Benzyl (*R*)-6-Cyano-5-hydroxyhexylcarbamate (21): *p*-Toluenesulfonyl chloride (1.1 g, 6.1 mmol) was added portionwise through an addition funnel for solids to a stirred solution of diol **20** (1.5 g, 5.6 1.3 mmol) and triethylamine (0.858 mL, 6.1 mmol) in dry CH_2Cl_2 (180 mL) at –20 °C. After stirring at –20 to 0 °C for 15 h, the reaction mixture was poured into ice/water (30 mL), washed with 20% aq. H_2SO_4, saturated aq. $NaHCO_3$ and brine, and dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give the monotosylate. The crude tosylate (1 g, 2.37 mmol) was taken up in EtOH/H_2O (3:2 v/v, 15 mL), cooled to 0 °C, and NaCN (0.697 g, 14.2 mmol) was added. The mixture was slowly warmed to room temperature. After stirring for 18 h, it was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine and water, dried with anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography by using petroleum ether/EtOAc (7:3) as eluent to give pure cyano compound **21** as a colourless oil. Yield: 89% (0.585 mg). IR ($CHCl_3$): $\tilde{\nu}$ = 3378, 3066, 2936, 2860, 2249, 1704, 1525, 1453, 1254, 1134, 1024, 746, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.28–1.64 (m, 6 H), 2.46 (br. d, *J* = 2.1 Hz, 2 H), 2.87 (br. s, 1 H), 3.15–3.224 (m, 2 H), 3.83–3.96 (m, 1 H), 4.87 (t, *J* = 5.8, 10.5 Hz, 1 H), 5.06 (s, 2 H), 7.33 (s, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 25.7, 29.2, 35.5, 40.4, 66.3, 66.8, 117.8, 127.6, 127.8, 128.2, 136.3, 156.5 ppm. $C_{15}H_{20}N_2O_3$ (276.33): calcd. C 65.20, H 7.30, N 10.14; found C 65.39, H 7.12, N 9.98.

Benzyl (*R*)-5,7-Dihydroxyheptylcarbamate (8): DIBAL-H (4.7 mL, 4.7 mmol, 1.0 M in hexanes) was added dropwise to a stirred solution of nitrile **21** (1.0 g, 3.61 mmol) in CH_2Cl_2 (26 mL) at –78 °C. After 5 h, aq. HCl (10%, 10 mL) was added, and the mixture was stirred at –78 °C for 30 min before being warmed to room temperature. After 30 min, further aq. HCl (10%, 20 mL) was added, and the mixture was extracted with Et_2O (6 × 30 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to give the crude aldehyde. The aldehyde (0.86 g) was dissolved in MeOH (20 mL) at room temperature, and the solution was cooled to 0 °C. Then $NaBH_4$ (380 mg, 10.0 mmol) was added in portions. After being stirred at room temperature for 5 h, the mixture was concentrated, and the residue was partitioned between ethyl acetate (40 mL) and water (20 mL). The aq. phase was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel by using petroleum ether/EtOAc (1:1) as eluent to afford diol **8**. Yield: 83% (0.720 g). $[\alpha]_D^{25}$ = +18.7 (*c* = 1.04, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 2940, 2872, 1740, 1702, 1485, 1411, 1372, 1280, 1250, 1167, 1051, 1002, 1062, 871, 778 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24–1.69 (m, 8 H), 2.66 (br. s, 2 H), 3.18 (dd, *J* = 6.0, 12.2 Hz, 2 H), 3.54–3.92 (m, 3 H), 4.89 (br. s, 1 H), 5.06 (s, 2 H), 7.27–7.37 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4, 29.6, 36.9, 38.3, 40.7, 60.7, 66.4, 70.7, 127.9, 128.1, 128.3, 136.5, 156.6 ppm. $C_{15}H_{23}NO_4$ (281.35): calcd. C 64.03, H 8.24, N 4.98; found C 63.97, H 8.16, N 5.01.

Benzyl (*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxyheptylcarbamate (22): TBDMSCl (0.536 g, 3.5 mmol) was added to a stirred solution of diol **8** (1.0 g, 3.5 mmol) and imidazole (290 mg, 4.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, the solvent was removed by distillation under reduced pressure and the crude product purified by column chromatography on silica gel by using petroleum ether/EtOAc (80:20) as eluent to give TBS ether **22** in 85% yield. Yield: 85% (1.2 g). $[\alpha]_D^{25}$ = +21.8 (*c* = 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.89 (s, 9 H), 1.31–1.57 (m, 8 H), 3.18 (dd, *J* = 6.3, 11.9 Hz, 2 H), 3.45–3.63 (m, 1 H), 3.76–3.82 (m, 1 H), 3.85–3.90 (m, 1 H), 4.81 (br. s, 1 H), 5.06 (s, 2 H), 7.28–7.33 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.4, 18.1, 22.6, 25.9, 29.7, 29.9, 37.0, 38.3, 40.9, 62.9, 66.5, 71.9, 128.0, 128.1, 128.4, 136.7, 156.3 ppm.

Benzyl (*S*)-2-(2-Hydroxyethyl)piperidine-1-carboxylate (23): Methanesulfonyl chloride (0.195 mL, 2.5 mmol) was added dropwise through a syringe to a stirred solution of TBS ether **22** (1 g, 2.5 mmol) and Et_3N (0.527 mL, 3.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After stirring at 0 °C for 0.5 h, the mixture was poured into ice/water (30 mL), washed with aq. $NaHCO_3$ and brine, and dried with anhydrous Na_2SO_4. The solvent was removed by distillation under reduced pressure to give the crude mesylate (1.2 g). A suspension of NaH (84 mg, 2.11 mmol) in THF (10 mL) was added over a period of 15 min to a stirred solution of the crude mesylate (1 g, 2.11 mmol) in THF (200 mL) at –40 °C. After stirring at this temperature for 1 h, the mixture was warmed to 50 °C and stirred for another 2 h. The reaction was then quenched by the addition of saturated aq. NH_4Cl, and the aq. phase was extracted with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was stirred in 3 N HCl in MeOH at 25 °C for 2 h, then the reaction was quenched by the addition of cold water (5 mL), and the aq. phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel by using petroleum ether/EtOAc (1:1) as eluent to afford pure alcohol **23**. Yield: 68% (0.45 g). $[\alpha]_D^{25}$ = –18.5 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3427, 2940, 2864, 1674, 1497, 1429, 1265, 1172, 1054, 755, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.37–1.74 (m, 7 H), 1.89–2.02 (m, 1 H), 2.68–2.82 (m, 1 H), 3.26–3.41 (m, 1 H), 3.47–3.55 (m, 1 H), 4.05 (br. d, *J* = 11.2 Hz, 1 H), 4.38–4.51 (m, 1 H), 5.10 (d, *J* = 11.7 Hz, 1 H), 5.17 (d, *J* = 12.6 Hz, 1 H), 7.29–7.38 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.7, 25.1, 28.7, 32.0, 38.9, 46.7, 58.3, 67.0, 127.5, 127.7, 128.2, 136.3, 156.3 ppm. $C_{15}H_{21}NO_3$ (263.33): calcd. C 68.42, H 8.04, N 5.32; found C 68.39, H 7.98, N 5.27.

***tert*-Butyl (*S*)-2-(2-Hydroxyethyl)piperidine-1-carboxylate (24):** 10% Pd/C (30 mg) was added to a solution of alcohol **23** (0.4 g, 1.5 mmol) in MeOH (10 mL), and the mixture was stirred under hydrogen (20 psi) at 25 °C. After 5 h, the mixture was filtered through a pad of Celite, which was rinsed with MeOH (3 × 30 mL).

The combined organic layers were concentrated under reduced pressure, and the crude product (196 mg) was stirred with $(Boc)_2O$ (0.349 mL, 1.5 mmol) and I_2 (38 mg, 10 mol-%) for 3 h. This crude mixture was extracted with EtOAc (3 × 20 mL) and washed with water followed by aq. $Na_2S_2O_3$ to give crude **24**, which was purified by column chromatography by using petroleum ether/EtOAc (9:1) as eluent to give the pure Boc alcohol **24**. Yield: 95% (0.33 g). $[a]_D^{25}$ = –19.2 (*c* = 1, $CHCl_3$) {ref.[9j] $[a]_D^{25}$ = –18.9 (*c* = 1, $CHCl_3$, 95% *ee*)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3434, 2935, 2864, 1688, 1419, 1391, 1254, 1164, 1254, 1142, 1052, 711 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 1.48–2.09 (m, 8 H), 2.58–2.72 (m, 1 H), 3.30 (br. t, *J* = 11.6 Hz, 1 H), 3.54–3.66 (m, 1 H), 3.92 (br. d, *J* = 12.6 Hz, 1 H), 4.37–4.51 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.0, 25.3, 28.2, 29.0, 32.1, 39.0, 45.8, 58.3, 79.7, 155.9 ppm. $C_{12}H_{23}NO_3$ (229.32): calcd. C 62.85, H 10.11, N 6.11; found C 62.77, H 9.98, N 6.27.

***tert*-Butyl (*S*)-2-(Formylmethyl)piperidine-1-carboxylate (7):** DMSO (0.278 mL, 3.92 mmol) was added to a stirred solution of oxalyl chloride (0.224 mL, 2.6 mmol) in CH_2Cl_2 (15 mL) at –78 °C. The reaction mixture was stirred for 20 min, and then a solution of alcohol **24** (0.3 g, 1.3 mmol) in CH_2Cl_2 (5 mL) was added. After stirring at –78 °C for 1 h, the reaction was quenched by the addition of Et_3N (0.728 mL, 5.22 mmol). The reaction mixture was then stirred at 25 °C for 30 min, and water (25 mL) was added. The organic layer was separated, and the aq. phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL), dried with anhydrous Na_2SO_4 and concentrated to give the corresponding crude aldehyde, which was purified by column chromatography on silica gel by using petroleum ether/EtOAc (7:3) as eluent to give aldehyde **7** as a colourless oil. Yield: 84% (0.250 g). $[a]_D^{25}$ = –51.1 (*c* = 0.9, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 2872, 1741, 1700, 1480, 1411, 1372, 1160, 1055, 872, 770 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 1.50–1.76 (m, 6 H), 2.53–2.58 (m, 1 H), 2.71–2.82 (m, 2 H), 3.98 (br. d, *J* = 12.8 Hz, 1 H), 4.83 (br. s, 1 H), 9.73 (t, *J* = 3.1 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 24.9, 28.0, 28.5, 38.9, 44.2, 45.3, 79.3, 154.1, 199.8 ppm. $C_{12}H_{21}NO_3$ (227.3): calcd. C 63.41, H 9.31, N 6.16; found C 63.28, H 9.45, N 5.99.

***tert*-Butyl (*S*)-2-[(*S*)-2-Hydroxy-2-phenylethyl]piperidine-1-carboxylate (25):** A solution of aldehyde **7** (250 mg, 1.09 mmol) in THF (5 mL) was added dropwise to a solution of PhMgBr (0.398 g, 2.19 mmol) in THF (20 mL) at – 78 °C under nitrogen. The solution was warmed up to –20 °C and stirred for 4 h. The reaction was then quenched by the addition of saturated aq. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give the corresponding diastereomeric mixture (90% yield, 305 mg) of *syn* and *anti* alcohols (*dr* = 2:1), which was purified by column chromatography by using petroleum ether/EtOAc (7:3) as eluent to give the major isomer **25**. Yield: 60.6% (185 mg). $[a]_D^{25}$ = –128.3 (*c* = 1.5, $CHCl_3$) {ref.[9t] $[a]_D^{25}$ = –127.2 (*c* = 1, $CHCl_3$, 94.2% *ee*)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 2943, 1685, 1410, 920, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 1.57–1.89 (m, 7 H), 2.12–2.26 (m, 1 H), 2.79 (t, *J* = 13.5 Hz, 1 H), 3.88–4.02 (m, 2 H), 4.41 (br. s, 1 H), 4.68–4.81 (m, 1 H), 7.21–7.38 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.99, 25.3, 28.4, 29.1, 39.2, 40.2, 48.2, 72.3, 79.6, 125.6, 127.1, 128.2, 144.7, 155.3 ppm. $C_{18}H_{27}NO_3$ (305.41): calcd. C 70.79, H 8.91, N 4.59; found C 70.67, H 8.77, N 4.72.

(–)-Sedamine (2): A solution of carbamate **25** (125 mg, 0.40 mmol) in THF (2 mL) was added to a solution of $LiAlH_4$ (31 mg, 0.81 mmol) in THF (10 mL). The reaction mixture was heated to 70 °C under nitrogen for 8 h, then cooled to 0 °C, then the reaction was carefully quenched by the sequential addition of water (0.2 mL) and 15% (w/v) aq. NaOH (0.2 mL). The resulting mixture was filtered through a pad of Celite and anhydrous Na_2SO_4 to remove solids by rinsing with ethyl acetate. The mixture was concentrated under reduced pressure, and the resulting oil was purified by column chromatography to provide (–)-sedamine (**2**). Yield: 78% (70 mg). M.p. 58–59 °C (ref.[9l] m.p. 58–60 °C). $[a]_D^{25}$ = –89.2 (*c* = 0.86, EtOH) {ref.[9l] $[a]_D^{25}$ = –89.4 (*c* = 0.9, EtOH)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3367, 3060, 2928, 2851, 1450, 1264, 1061, 752, 659 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.63 (m, 1 H), 1.66–1.80 (m, 6 H), 2.05–2.18 (m, 1 H), 2.50 (s, 3 H), 2.54–2.68 (m, 1 H), 2.98–3.09 (m, 2 H), 4.89 (dd, *J* = 10.7, 2.6 Hz, 1 H), 5.80 (br. s, 1 H), 7.28–7.39 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 22.2, 26.2, 39.3, 39.9, 52.7, 61.4, 73.3, 125.1, 127.1, 128.2, 145.5 ppm. $C_{14}H_{21}NO$ (219.32): calcd. C 76.67, H 9.65, N 6.39; found C 76.59, H 9.72, N 6.27.

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[1] a) C. Schneider, C. Borner, A. Schuffenhauer, *Eur. J. Org. Chem.* **1999**, 3353–3362; b) J.-C. Braekman, A. Charlier, D. Daloze, S. Heliporn, J. Pasteels, V. Plasman, S. Wang, *Eur. J. Org. Chem.* **1999**, 1749–1755; c) P. Laurent, J.-C. Braekman, D. Daloze, *Eur. J. Org. Chem.* **2000**, 2057–2062; d) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; e) M. Amat, N. Lior, J. Hidalgo, C. Escolano, J. Bosch, *J. Org. Chem.* **2003**, *68*, 1919–1928; f) A. Bariau, W. B. Jatoi, P. Calinaud, Y. Troin, J.-L. Canet, *Eur. J. Org. Chem.* **2006**, 3421–3433; g) F. A. Davies, M. Santhanaraman, *J. Org. Chem.* **2006**, *71*, 4222–4226; h) A. Voituriez, F. Ferreira, A. Perez-Luna, F. Chemla, *Org. Lett.* **2007**, *9*, 4705–4708.

[2] a) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.* **1998**, 633–640; b) B. B. Toure, H. R. Hoveyda, J. Tailor, A. Ulaczyk-Lesanko, D. G. Hall, *Chem. Eur. J.* **2003**, *9*, 466–474; c) P. M. Weintraub, J. S. Sabol, J. A. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953–2989; d) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729; e) B. B. Toure, D. G. Hall, *Angew. Chem. Int. Ed.* **2004**, *43*, 2001–2004; f) D. S. Tan, *Nat. Chem. Biol.* **2005**, *1*, 74–84; g) G. Zheng, L. P. Dwoskin, A. G. Deaciuc, S. D. Norrholm, P. A. Crooks, *J. Med. Chem.* **2005**, *48*, 5551–5560; h) L. V. Adriaenssens, C. A. Austin, M. Gibson, D. Smith, R. C. Hartley, *Eur. J. Org. Chem.* **2006**, 4998–5001; i) G. Wang, E. Vedejs, *Org. Lett.* **2009**, *11*, 1059–1061.

[3] a) H. Kunz, W. Pfrengle, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1067–1068; b) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781–1813.

[4] a) T. Wertheim, *Justus Liebigs Ann. Chem.* **1856**, *100*, 328–330; b) E. Spath, E. Adler, *Monatsh. Chem.* **1933**, *63*, 127–140.

[5] a) S. Adamkova, I. Frebort, M. Sebela, P. Pec, *J. Enzyme Inhib. Med. Chem.* **2001**, *16*, 367–372; b) L. Marion, R. Lavigne, L. Lemay, *Can. J. Chem.* **1951**, *29*, 347–351; c) B. Franck, *Chem. Ber.* **1958**, *91*, 2803–2818; d) B. Franck, *Chem. Ber.* **1960**, *93*, 2360–2371; e) D. Butruille, G. Fodor, C. S. Huber, F. Letourneau, *Tetrahedron* **1971**, *27*, 2055–2067.

[6] J. H. Kim, H. T. Hart, J. F. Stevens, *Phytochemistry* **1996**, *41*, 1319–1324.

[7] a) O. Meth-Cohn, C-Y. Yu, M-C. Lestage, D.-H. Lebrun, P. Caignard, P. Renard, "Pyridine and piperidine derivatives for treating neurodegenerative diseases", Eur. Pat. 1050531, **2000**; *Chem. Abstr.* **2000**, *133*, 350144.

[8] a) G. Fodor, E. Bauerschmidt, *J. Heterocycl. Chem.* **1968**, *5*, 205–209; b) Y. Masaki, T. Imaeda, K. Nagata, H. Oda, A. Ito, *Tetrahedron Lett.* **1989**, *30*, 6395–6396; c) M. Dockner, N. A. Sasaki, C. Riche, P. Potier, *Liebigs Ann./Recueil* **1997**, *6*, 1267–1272; d) P. Guerreiro, V. Ratovelomanana-Vidal, J.-P. Genet, *Chirality* **2000**, *12*, 408–410; e) D. L. Comins, A. L. Williams, *Tetrahedron Lett.* **2000**, *41*, 2839–2842; f) C. Agami, F. Couty, N. Rabasso, *Tetrahedron Lett.* **2000**, *41*, 4113–4116; g) D. Enders, B. Nolte, G. Raabe, J. Runsink, *Tetrahedron: Asymmetry* **2002**, *13*, 285–291; h) I. L. Lysenko, A. V. Bekish, O. G. Kulinkovich, *Russ. J. Org. Chem.* **2002**, *38*, 875–879; i) K. Nagata, Y. Toriizuka, T. Itoh, *Heterocycles* **2005**, *66*, 107–109; j) S. R. V. Kandula, P. Kumar, *Tetrahedron: Asymmetry* **2005**, *16*, 3268–3274; k) S. K. Pandey, P. Kumar, *Tetrahedron Lett.* **2005**, *46*, 4091–4093; l) M.-Y. Chang, Y.-H. Kung, S.-T. Chen, *Tetrahedron* **2006**, *61*, 10843–10848; m) A. G. Jamieson, A. Sutherland, *Org. Lett.* **2007**, *9*, 1609–1611; n) A. Voituriez, F. Ferreira, F. Chemla, *J. Org. Chem.* **2007**, *72*, 5358–5361; o) D. Rodriguez, A. Pico, A. Moyano, *Tetrahedron Lett.* **2008**, *49*, 6866–6869; p) P. P. Saikia, G. Baishya, A. Goswami, N. C. Barua, *Tetrahedron Lett.* **2008**, *49*, 6508–6511; q) K. S. Petersen, G. H. Posner, *Org. Lett.* **2008**, *10*, 4685–4687; r) A. K. Srivastava, S. K. Das, G. Panda, *Tetrahedron* **2009**, *65*, 5322–5327; s) A. Kamal, S. R. Vangala, N. V. S. Reddy, V. S. Reddy, *Tetrahedron: Asymmetry* **2009**, *20*, 2589–2593; t) S. Liu, J.-H. Xie, W. Li, W.-L. Kong, L.-X. Wang, Q.-L. Zhou, *Org. Lett.* **2009**, *11*, 4994–4997; u) S. Roy, A. Sharma, S. Mula, S. Chattopadhyay, *Chem. Eur. J.* **2009**, *15*, 1713–1722; v) M. Venkataiah, N. W. Fadnavis, *Tetrahedron* **2009**, *65*, 6950–6952; w) E. Bandini, G. Corda, A. D′Aurizio, M. Panunzio, *Tetrahedron Lett.* **2010**, *51*, 933–934.

[9] a) C. Schopf, G. Dummer, W. Wust, R. Rausch, *Justus Liebigs Ann. Chem.* **1959**, *626*, 134–149; b) K. Irie, K. Aoe, T. Tanaka, S. Saito, *J. Chem. Soc., Chem. Commun.* **1985**, 633–635; c) S. G. Pyne, P. Bloem, S. L. Chapman, C. E. Dixon, R. Griffith, *J. Org. Chem.* **1990**, *55*, 1086–1093; d) D. L. Comins, H. Hong, *J. Org. Chem.* **1993**, *58*, 5035–5036; e) D. Compere, C. Maranzano, B. C. Das, *J. Org. Chem.* **1999**, *64*, 4528–4532; f) C.-Y. Yu, O. Meth-Cohn, *Tetrahedron Lett.* **1999**, *40*, 6665–6668; g) R. W. Bates, K. Sa-Ei, *Tetrahedron* **2002**, *58*, 5957–5978; h) J. Cossy, C. Willis, V. Bellosta, S. Bouzbouz, *J. Org. Chem.* **2002**, *67*, 1982–1992; i) F.-X. Felpin, J. Lebreton, *J. Org. Chem.* **2002**, *67*, 9192–9199; j) M. Angoli, A. Barilli, G. Lesma, D. Passarella, S. Riva, A. Silvani, B. Danieli, *J. Org. Chem.* **2003**, *68*, 9525–9527; k) N. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735; l) G. Zheng, L. P. Dwoskin, P. A. Crooks, *J. Org. Chem.* **2004**, *69*, 8514–8517; m) F.-X. Felpin, J. Lebreton, *Tetrahedron* **2004**, *60*, 10127–10153; n) R. W. Bates, J. Boonsombat, *Org. Biomol. Chem.* **2005**, *3*, 520–523; o) J. S. Yadav, M. S. Reddy, P. P. Rao, A. R. Prasad, *Tetrahedron Lett.* **2006**, *47*, 4397–4401; p) S. Fustero, D. Jimenez, J. Moscardo, S. Catalan, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283–5286; q) V. B. Birman, H. Jiang, X. Li, *Org. Lett.* **2007**, *9*, 3237–3240; r) A. Bisai, V. K. Singh, *Tetrahedron Lett.* **2007**, *48*, 1907–1910; s) R. W. Bates, J. A. Nemeth, R. H. Snell, *Synthesis* **2008**, 1033–1038; t) S. Krishnan, J. T. Bagdanoff, D. C. Ebner, Y. K. Ramtohul, U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 13745–13754; u) S. G. Davies, A. M. Fletcher, P. M. Roberts, A. D. Smith, *Tetrahedron* **2009**, *65*, 10192–10213; v) T. Spangenberg, B. Breit, A. Mann, *Org. Lett.* **2009**, *11*, 261–264.

[10] a) H. Takahata, M. Kubota, S. Takahashi, T. Momose, *Tetrahedron: Asymmetry* **1996**, *7*, 3047–3054; b) H. Takahata, M. Kubota, N. Ikota, *J. Org. Chem.* **1999**, *64*, 8594–8601.

[11] a) S. P. Kotkar, A. Sudalai, *Tetrahedron: Asymmetry* **2006**, *17*, 1738–1742; b) A. R. Jagdale, S. R. Reddy, A. Sudalai, *Tetrahedron: Asymmetry* **2009**, *20*, 335–339; c) T. M. Shaikh, A. Sudalai, *Tetrahedron: Asymmetry* **2009**, *20*, 2287–2292.

[12] a) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem. Int. Ed.* **2004**, *43*, 1112–1115; b) A. Cordova, H. Sunden, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673–3684; c) G. Zhong, *Angew. Chem. Int. Ed.* **2003**, *42*, 4247–4250; d) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809; e) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293–8296.

[13] R. Varala, S. Nuvula, S. R. Adapa, *J. Org. Chem.* **2006**, *71*, 8283–8286.

[14] a) M. K. Gurjar, V. S. Kumar, B. V. Rao, *Tetrahedron* **1999**, *55*, 12563–12576; b) C. Cinquin, M. Bortolussi, R. Bloch, *Tetrahedron* **1996**, *52*, 6943–6952; c) R. A. Fernandes, P. Kumar, *Tetrahedron: Asymmetry* **1999**, *10*, 4349–4356.

[15] a) F. Sanchez-Sancho, B. Herradon, *Tetrahedron: Asymmetry* **1998**, *9*, 1951–1965; b) A. Stehl, G. Seitz, K. Schulz, *Tetrahedron* **2002**, *58*, 1343–1354; c) T. L. Suyama, W. H. Gerwick, *Org. Lett.* **2006**, *8*, 4541–4543; d) P.-Q. Huang, Z.-Q. Guo, Y.-P. Ruan, *Org. Lett*. **2006**, *8*, 1435–1438.

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