Asymmetric Total Synthesis of (+)-2-*epi*-Deoxoprosopinine

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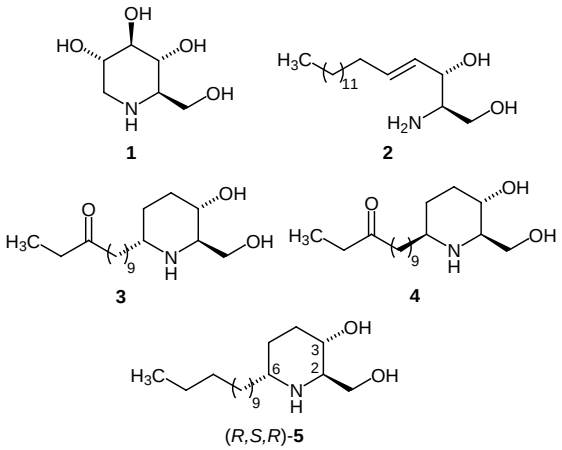
Abstract: The asymmetric synthesis of (+)-2-*epi*-deoxoprosopinine [(*S*,*S*,*R*)-**5**] in eleven steps and with excellent diastereomeric and enantiomeric purity (de, ee ≥96%) is described. As key steps, the 1,2-addition of a dodecyl nucleophile to an aldehyde-SAMP hydrazone and the α-alkylation of 2,2-dimethyl-1,3-dioxan-5-one SAMP hydrazone are employed to generate two of the three stereogenic centers. Creation of the third stereogenic center was achieved in a domino deprotection/cyclisation/reduction sequence.

Key words: asymmetric synthesis, deoxoprosopinine, SAMP/RAMP hydrazone method, natural products, piperidine alkaloids

Hydroxylated piperidine alkaloids are abundantly found in living systems. The wide range of their potent physiological effects stems from their ability to mimic carbohydrates in a variety of enzymatic processes.[1] *Prosopis* alkaloids form a small subgroup of alkaloid lipids containing a 2,6-disubstituted 3-piperidinol framework with a long aliphatic appendage at the 6-position. At one end of these molecules is the polar head group with a configuration of the 1,3-diol unit similar to those in deoxynojirimycin **1**, a potent α-glucosidase I and II inhibitor,[2] while the lipophilic tail resembles the membrane lipid sphingosine **2**. Seven piperidine alkaloids, among them (+)-prosopinine **3** and (+)-prosophylline **4** have been isolated from the leaves of the West African savanna tree *Prosopis africana* Taub.[3]

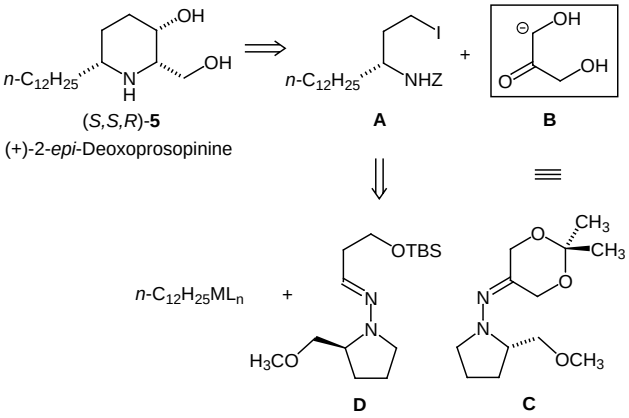


Due to their structural features mentioned above these polysubstituted piperidine alkaloids and their deoxygenated derivatives (e.g. (+)-deoxoprosopinine **5**) exhibit a wide variety of physiological properties, including analgesic, anaesthetic and antibiotic activity.[4]

During the last few years these molecules have become interesting targets in total synthesis. Some syntheses of the racemates have been reported,[5] however, in most approaches to this class of molecules an enantiopure substance was used as starting material ("ex chiral pool synthesis")[6] and only a few examples employing asymmetric synthesis have been published.[7]

As part of our continuing studies towards the asymmetric total synthesis of piperidine- and pyrrolidine alkaloids,[8] we herein wish to disclose an efficient asymmetric synthesis of (*S*,*S*,*R*)-(+)-2-*epi*-deoxoprosopinine [(*S*,*S*,*R*)-**5**] employing the SAMP/RAMP hydrazone method as key steps.

As disclosed in the retrosynthetic analysis (Scheme 1), the title alkaloid (*S*,*S*,*R*)-**5** can be traced back to electrophilic iodo amine **A** and the dihydroxyacetone enolate synthon **B** of which the SAMP hydrazone **C** is an enantiopure synthetic equivalent.[9] Amine **A** in turn may be prepared by nucleophilic 1,2-addition[10] of a dodecyl nucleophile to the CN double bond of SAMP hydrazone **D**. Accordingly, the final synthetic transformation would be an intramolecular reductive amination.

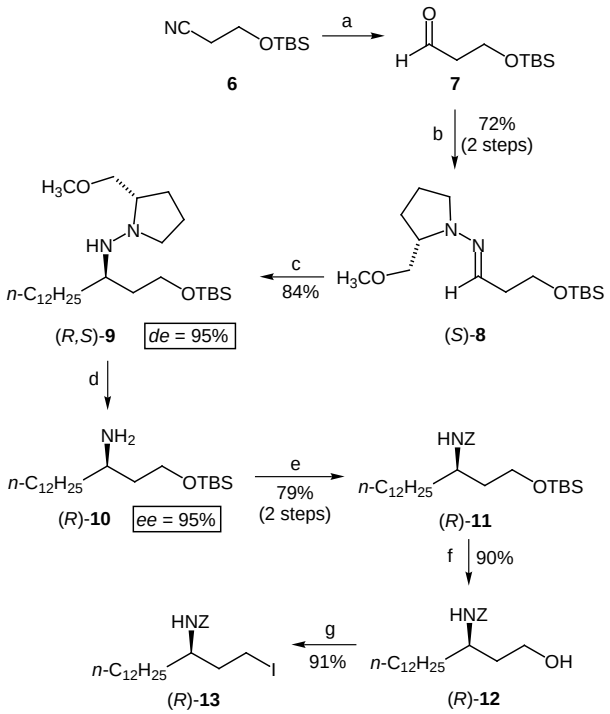


Retrosynthetic analysis

Scheme 1

As outlined in Scheme 2, the synthesis starts from 3-(*tert*-butyldimethylsiloxy)propanenitrile **6**, readily prepared via TBS protection of commercially available 3-hydroxypropanenitrile.[11] Aldehyde **7**[12] was obtained by reduction

of nitrile **6** with diisobutylaluminium hydride following an analogous literature procedure.[13] The crude aldehyde was treated with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) affording hydrazone (*S*)-**8** in 72% yield over 2 steps. As the first key step in the synthesis, the diastereoselective 1,2-addition of a dodecyl nucleophile to the CN double bond of hydrazone (*S*)-**8** (**D**) by several nucleophiles, such as organolithium, -cerium, -ytterbium and Grignard reagents was investigated. The best results were achieved by treatment of hydrazone (*S*)-**8** with three equivalents of a dodecylytterbium reagent, obtained from dodecyllithium and dry ytterbium(III) chloride, at −100 °C, furnishing hydrazine (*R*,*S*)-**9** in 84% yield and excellent diastereomeric excess of 95% (determined by ^{13}C NMR). N-N bond cleavage affording α-branched amine (*R*)-**10** was accomplished by heating with borane-tetrahydrofuran complex (10 equivalents) in THF under reflux for 4 hours, followed by methanolysis according to a standard procedure developed by our group.[14] To ensure that the N-N bond cleavage proceeded without racemisation, a sample of amine (*R*)-**10** was converted to the Mosher amide with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl).[15] As expected, the diastereomeric excess of the amide was determined to be 95% by ^{13}C NMR, revealing that no racemisation during N-N bond cleavage had occurred.



Reagents and conditions: a) DIBAL-H, THF, 0 °C to r.t., 2 h, then 1 M tartaric acid; b) SAMP, 0 °C to r.t., 16 h; c) $YbCl_3$6 H_2O, *n*-$C_{12}H_{25}Li$, −100 °C, then (*S*)-**8**/THF, 2 h, −100 °C to r.t.; d) BH_3•THF (excess), THF, reflux, 4 h; e) BnOC(O)Cl (ZCl), *n*-Bu_4NI, Na_2CO_3, $CHCl_3/H_2O$, reflux, 3 days; f) TBAF, NH_4F, THF, r.t., 5 h; g) imidazole, PPh_3, I_2, Et_2O/CH_3CN 3:2, 0 °C, 5 h

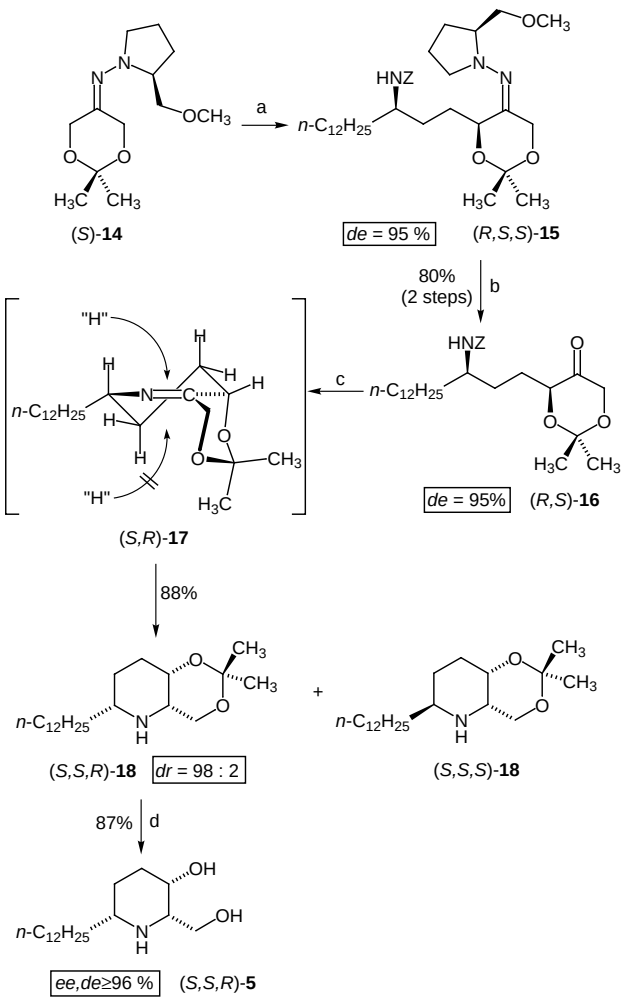
Scheme 2

For protection, amine (*R*)-**10** was transformed to a benzylcarbamate. Introduction of the Z-protecting group with excess benzyl chloroformate and triethylamine in dichloromethane turned out to be unsatisfactory because of the long reaction times and the unacceptable yields. It therefore proved advantageous to carry out the reaction in a two-phase solvent system of water and chloroform using catalytic amounts of tetra-*n*-butylammonium iodide and Na_2CO_3, as base, to yield carbamate (*R*)-**11** in a yield of 79% over two steps from hydrazine (*R*,*S*)-**9**.

To obtain a suitable electrophile for the α-alkylation of hydrazone (*S*)-**14** (**C**), carbamate (*R*)-**11** was transformed into iodide (*R*)-**13** (**A**). First, the silyl ether in (*R*)-**11** was cleaved with excess tetra-*n*-butylammonium fluoride (TBAF) in THF in the presence of ammonium fluoride, which buffered the solution to a neutral pH value. The resulting alcohol (*R*)-**12**, obtained in 90% yield, was then converted into its corresponding iodide.[16] Treatment of alcohol (*R*)-**12** with imidazole, triphenylphosphine and elemental iodine in a mixture of ether and acetonitrile furnished iodide (*R*)-**13** in 91% yield. With this key compound in hand, the α-alkylation of SAMP hydrazone (*S*)-**14** to establish the second stereogenic center was next examined (Scheme 3).

Thus, SAMP hydrazone (*S*)-**14** was metalated at −78 °C with *tert*-butyllithium in THF and the resulting aza-enolate was alkylated with the iodide (*R*)-**13** affording the α-alkylated hydrazone (*R*,*S*,*S*)-**15** with a diastereomeric excess of 95% (determined by ^{13}C NMR analysis). Due to the acidity of the carbamate proton in (*R*)-**13**, it was necessary to employ two equivalents of the metalated SAMP-hydrazone (*S*)-**14**. Hexamethylphosphoramide (HMPA) was needed as an additive to keep the lithiated carbamate (*R*)-**13** in solution. The reaction was complete after 18 h. This extraordinarily long reaction time can be rationalised by considering the negative charge of the electrophile. Separation of the product (*R*,*S*,*S*)-**15** and excess hydrazone (*S*)-**14** by column chromatography could not be achieved on a preparative scale, so that the hydrolytic cleavage of the auxiliary was carried out on a mixture of both. Therefore, a solution of hydrazones (*R*,*S*,*S*)-**15** and (*S*)-**14** in ether was treated with aqueous oxalic acid.[17] Because of the high volatility of the ketone derived from (*S*)-**14**, pure ketone (*R*,*S*)-**16** was obtained without chromatographic purification in 80% yield (2 steps) and a diastereomeric excess of 95% (^{1}H, ^{13}C NMR). It should be noted that under these mild conditions even acid sensitive protecting groups like acetals and carbamates are tolerated. Furthermore the method allows recycling of the chiral auxiliary.

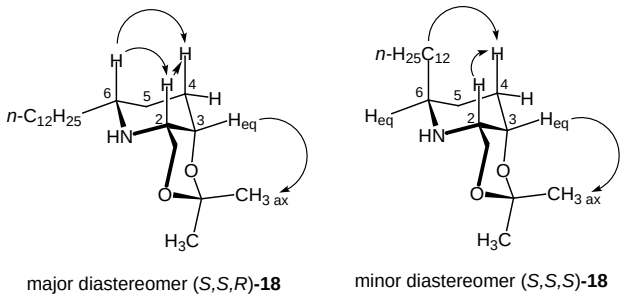
The next steps in the synthesis were the deprotection of the amine functionality, with subsequent formation of piperidine **18** via the cyclic imine intermediate (*S*,*R*)-**17**. In a domino reaction, the amine protecting group was removed by catalytic hydrogenolysis over palladium on charcoal, and the released amine cyclised under reductive amination conditions to furnish piperidines (*S*,*S*,*R*)-**18** and (*S*,*S*,*S*)-**18** in a ratio of 98:2 and an overall yield of 88%.



Reagents and conditions: a) *t*-BuLi, THF, −78 °C, 2 h, then HMPA, (*R*)-**13**/THF, −78 °C, 16 h; b) sat. oxalic acid, Et_2O, r.t., 5 h; c) H_2, Pd/C (10%), EtOH, r.t., 2 h; d) Lewatit S 100™, MeOH, reflux 2 h, then sat. NH_4OH

Scheme 3

After chromatographic separation of both epimers, stereochemical assignments were established through NOE-NMR techniques on each isomer leading to the structures sketched in the Figure.



major diastereomer (*S,S,R*)-**18** minor diastereomer (*S,S,S*)-**18**

Figure

For the major diastereomer (*S,S,R*)-**18**, strong nuclear Overhauser effects are observed between the protons at C-2, C-$4_{ax.}$ and C-6, indicating a 2,4,6 *cis*-substitution pattern with the protons in the axial position, and between the proton at C-3 and the axial methyl group of the acetonide, revealing an equatorial *cis* position of the proton at C-3 with respect to that at C-2. In contrast, the axial protons at C-2 and C-4 of the minor diastereomer (*S,S,S*)-**18** exhibit no interaction with the proton at C-6 due to its equatorial position, but instead with the methylene protons of the carbon chain. Again a strong resonance between the equatorial proton at C-3 and the methyl group of the acetonide is observed, indicating a 2,3-*cis*-substitution pattern at the piperidine ring.

These results clearly indicate that the reductive amination leads exclusively to the 2,3-*cis*-substituted epimers of acetonide-protected (+)-2-*epi*-deoxoprosopinine [(*S,S,R*)-**18**] and (+)-2-*epi*-deoxoprosophylline [(*S,S,S*)-**18**]. The observed configuration can be explained by sterical shielding of the *re* face of imine (*S,R*)-**18** by the acetonide group, leading to an attack of hydrogen from the *si* face, resulting in a 2,3-*cis*-substitution pattern (Scheme 3).

At this stage of the synthesis, the enantiomeric excess of diastereomerically pure acetonide (*S,S,R*)-**18** was determined by treatment with (*S*)-MTPA-chloride yielding a diastereomerically pure amide with a diastereomeric excess greater than 96% (NMR, HPLC), revealing that acetonide (*S,S,R*)-**18** is enantiomerically pure and during the synthesis no racemisation occurred.

The final step in the synthesis towards (*S,S,R)*-(+)-2-*epi*-deoxoprosopinine [(*S,S,R*)-**5**] was the hydrolytic cleavage of the acetal group. In contrast to a literature procedure,[6a] involving hydrochloric acid in methanol, an improved yield of 87% could be achieved by using an acidic ion exchange resin. In this way, the target molecule (*S,S,R*)-**5** was isolated as a colourless amorphous solid with a diastereo- and enantiomeric excess greater than 96%.

In conclusion, an efficient asymmetric synthesis of (+)-2-*epi*-deoxoprosopinine [(*S,S,R*)-**5**] was successfully carried out in 11 steps to afford the target molecule in 23% overall yield and with excellent diastereomeric and enantiomeric excess. The applicability of the SAMP/RAMP hydrazone method with respect to α-alkylation and 1,2-addition for the synthesis of polyhydroxylated piperidine alkaloids has been demonstrated. Biological tests towards the physiological activity of (*S,S,R*)-(+)-2-*epi*-deoxoprosopinine are now in progress.

All chemicals were of reagent grade and used from freshly opened containers. Ytterbium(III) chloride hexahydrate was purchased from Aldrich, *t*-BuLi (1.6 M in hexane) from Merck, Darmstadt, 1-Iodododecane and Florisil™ from Acros, ion exchange resin Lewatit S 100™ from Fluka. *tert*-Butyldimethylsilyl chloride was used as a 50% solution in toluene obtained from Wacker Silan, München. Solvents were dried and purified by conventional methods prior to use. Et_2O and THF were freshly distilled from benzophenone and Na/lead alloy under Ar; DMF and MeCN from CaH_2. Preparative column chromatography: Merck silica gel 60, particle size 0.040−

0.063 mm (230−400 mesh, flash). Analytical TLC: Silica gel 60 F_{254} plates, Merck, Darmstadt. Optical rotation values were measured on a Perkin−Elmer P241 (589 nm), solvents used were of Merck UVASOL-quality. Microanalyses were obtained from a Heraeus CHN-O-RAPID element analyser. Mp: Büchi 510. HRMS: Finnigan MAT 95. Mass spectra: Finnigan MAT 212 (EI 70 eV). IR spectra: Perkin−Elmer FT/IR 1750. ^{1}H NMR spectra (300 MHz, 400 MHz and 500 MHz), ^{13}C NMR (75 MHz, 100 MHz and 125 MHz): Gemini 300, Varian VXR 300, Varian Inova 400 and Varian Unity 500 (TMS as internal standard). HPLC: Gilson Abimed, column: Lichrosorb™ Si 60 (7µm), UV detector. (*S*)-1-Amino-2-(methoxymethyl)pyrrolidine (SAMP),[18] 2,2-dimethyl-1,3-dioxan-5-one[19] and 2,2-dimethyl-1,3-dioxan-5-one SAMP hydrazone[9a] were prepared according to published procedures.

(2*S*)-(*E*)-(−)-3-[(1-*tert*-Butyldimethylsilyloxy)propylidene)-2-(methoxymethyl)-1-pyrrolidinamine [(*S*)-8]

3-(*tert*-Butyldimethylsiloxy)propanal (**7**) was prepared following an analogous literature procedure:[13] A solution of diisobutylaluminium hydride (1 M in hexane, 200 mL, 200 mmol, 1.33 equiv) was added dropwise at 0 °C to a stirred solution of 3-(*tert*-butyldimethylsiloxy)propanenitrile **6**[11] (24.2 g, 150 mmol) in anhyd THF (350 mL) under Ar. The reaction was allowed to warm to r.t. and stirred for an additional 2 h. The reaction mixture was quenched by dropwise addition to a rapidly stirred mixture of 1 M tartaric acid (700 mL) and Et_2O (300 mL) at 0 °C. After separation, the aqueous phase was extracted with Et_2O (3 × 150 mL) and the combined organic phases were washed with brine, and dried ($MgSO_4$). After concentration in vacuo, the crude product was obtained as a reddish-brown oil; yield: 20.4 g, which was used without further purification in the next step. The crude aldehyde **7** was cooled to 0 °C and SAMP (19.5 g, 150 mmol, 1.0 equiv) was added dropwise. The reaction mixture was allowed to warm to r.t. overnight, poured into Et_2O (400 mL) and dried ($MgSO_4$). After removal of the solvent under reduced pressure and purification of the brown residue by flash chromatography (silica gel; pentane/Et_2O, 4:1, 1% Et_3N), hydrazone (*S*)-**8** was obtained as a colourless oil; yield: 32.3 g (72% over 2 steps).

$[\alpha]_D^{28}$ −133° (*c* 1.20, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 6H, SiCH_3), 0.84 [s, 9H, C(CH_3)$_3$], 1.69−1.95 (m, 4H, NCH$_2$CH_2CH_2), 2.38 (dt, 2H, *J* = 5.5, 6.59 Hz, N=CHCH_2), 2.67 (m, 1H, NCH*H*), 3.26−3.40 (m, 3H, H$_3$COC*H*HC*H*, NCH*H*), 3.32 (s, 3H, OCH_3), 3.51 (m, 1H, H$_3$COCH*H*), 3.70 (t, 2H, *J* = 6.59 Hz, CH_2OSi), 6.60 (t, 1H, *J* = 5.5 Hz, *H*C=N).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.73 (Si*C*H$_3$), 18.83 [*C*(CH$_3$)$_3$], 22.70 (NCH$_2$*C*H$_2$), 26.46 [C(*C*H$_3$)$_3$], 27.16 (NCH$_2$CH$_2$*C*H$_2$), 37.08 (N=CH*C*H$_2$), 50.73 (N*C*H$_2$), 59.71 (O*C*H$_3$), 62.37 (*C*H$_2$OSi), 63.88 (N*C*HCH$_2$CH$_3$), 75.36 (*C*H$_2$CH$_3$), 136.18 (N=*C*).

IR (film): ν = 2954−2826 (C-H), 1604 (C=N), 1472, 1462, 1386, 1361, 1340, 1255, 1197, 1097 (Si-O), 1006, 940, 837 (Si-O-C), 776 (Si-C), 728 cm^{-1}.

MS (EI): *m/z* (%) = 300 (2, M$^+$), 255 (100, M$^+$−CH$_2$OCH$_3$), 186 (1, M$^+$−SMP), 123 (7), 99 (7), 73 (29), 70 (14, *c*-C$_4$H$_8$N$^+$), 45 (5, H$_2$C = OCH$_3^+$).

Anal. Calcd. for $C_{15}H_{32}N_2O_2Si$ (300.521): C, 59.95; H, 10.73; N, 9.32. Found: C, 59.81; H 10.73; N, 9.62.

(1*R*,2*S*)-(−)-*N*-{1-[2-(1-*tert*-Butyldimethysiloxy)ethyl]tridecyl}-*N*-2-(methoxymethyl)-1-pyrrolidinamine [(*R*,*S*)-9]

In a 500 mL Schlenk flask, equipped with an oval stirring bar, ytterbium(III) chloride hexahydrate (9.26 g, 24 mmol, 3 equiv) was dried at 140 °C and 0.1 Torr under stirring for 2 h. After cooling to r.t., the dry colourless powder suspended in anhyd THF (140 mL) was placed under an Ar atm, and stirred under ultrasonication for 16 h. A solution of 1-iodododecane (21.32 g, 72 mmol, 9 equiv) in anhyd Et_2O (60 mL) was cooled to −20 °C and treated dropwise with *t*-BuLi (1.6 M in hexane, 77 mL, 122 mmol), whilst the reaction mixture was slowly cooled to −40 °C. After stirring for 0.5 h at that temperature, the mixture was warmed to r.t. and stirred for an additional 2 h. The ytterbium(III) chloride/THF suspension was cooled to −78 °C and the organolithium solution was added dropwise via a canula. The suspension was stirred for 2 h at this temperature, turning to an orange colour. After cooling to −100 °C, a solution of hydrazone (*S*)-**8** (2.40 g, 8 mmol, 1 equiv) in anhyd THF (12 mL) was added dropwise. The mixture was stirred at this temperature for an additional 2 h, then warmed to r.t. overnight and quenched with sat. $NaHCO_3$ (40 mL). The resulting slurry was extracted with Et_2O (4 × 100 mL) and dried ($MgSO_4$). After removal of the solvent, the yellow residue was purified by flash chromatography (silica gel, pentane/Et_2O, 10:1 to 4:1, 1% Et_3N) to yield hydrazine (*R*,*S*)-**9** as a pale yellow oil; yield: 3.16 g (84%).

$[\alpha]_D^{25}$ −56.5° (*c* 1.01, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.01 (s, 6H, SiCH_3), 0.88 (m, 12H, C(CH_3)$_3$, CH$_2$CH_3), 1.16−1.39 [m, 22H, H$_3$C(CH_2)$_{11}$], 1.42−1.79 (m, 5H, NCH$_2$CH*H*CH_2, CH_2CH$_2$OSi), 1.82−1.95 (m, 1H, NCH*H*), 2.11 (m, 1H, NCH$_2$CH*H*), 2.55 (m, 1H, NCH_2), 2.82 (m, 1H, HNC*H*), 3.28−3.33 (m, 1H, H$_3$COCH$_2$C*H*), 3.30 (s, 3H, OCH_3), 3.37 (m, 1H, H$_3$COCH*H*), 3.54 (dd, 1H, *J* = 9.06, 3.69 Hz, H$_3$COCH*H*), 3.69 (m, 2H, CH_2OSi).

^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.82 (Si*C*H$_3$), 14.65 (CH$_2$*C*H$_3$), 18.77 [*C*(CH$_3$)$_3$], 21.57 (*C*H$_2$CH$_3$), 23.23 (NCH$_2$*C*H$_2$), 25.89 (*C*H$_{2\ chain}$), 26.51 [C(*C*H$_3$)$_3$], 26.77 (NCH$_2$CH$_2$*C*H$_2$), 29.91−30.35 (6 C-atoms, *C*H$_{2\ chain}$), 30.67 (*C*H$_{2\ chain}$), 32.47 (HNCHCH$_{2\ chain}$), 34.52 (*C*H$_{2\ chain}$), 36.04 (*C*H$_2$CH$_2$OSi), 57.67 (N*C*H$_2$), 57.81 (HN*C*H), 59.54 (O*C*H$_3$), 62.44 (*C*H$_2$OSi), 66.45 (N*C*HCH$_2$CH$_3$), 75.59 (*C*H$_2$CH$_3$).

IR (film):ν = 2954−2850 (C-H), 1464, 1387, 1361, 1255, 1187, 1097 (Si-O), 1006, 939, 919, 836 (Si-O-C), 776 (Si-C), 723, 663 cm^{-1}.

MS (EI): *m/z* (%) = 470 (29, M$^+$), 425 (100, M$^+$−CH$_2$OCH$_3$), 395 (10), 365 (23), 311 (5, M$^+$−CH$_2$CH$_2$OTBS), 285 (7), 169 (5, C$_{12}$H$_{25}^+$), 129 (15), 96 (11), 73 (17), 70 (22, *c*-C$_4$H$_8$N$^+$), 57 (22, *t*-C$_4$H$_9^+$).

Anal. Calcd. for $C_{27}H_{58}N_2O_2Si$ (470.861): C, 68.87; H, 12.42; N, 5.95. Found: C, 68.51; H, 12.63; N, 6.51.

HRMS: *m/z* calcd for $C_{27}H_{58}N_2O_2Si^+$: 470.4268. Found: 470.4267.

(1*R*)-(−)-Benzyl-*N*-[1-(2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)tridecyl]carbamate [(1*R*)-11]

Hydrazine (*R*)-**9** (2.56 g, 5.45 mmol) was dissolved in anhyd THF (20 mL) under Ar. After addition of borane-tetrahydrofuran-complex (1 M THF, 55 mL, 55 mmol, 10 equiv), the mixture was heated under reflux for 4 h. After cooling to r.t., MeOH (30 mL) was cautiously added and the solvent was removed under reduced pressure. MeOH (80 mL) was added and the mixture was heated under reflux for an additional hour. After cooling to r.t., the solvent was evaporated and the residue was dried in vacuo to yield a turbid oil; 2.68 g. The crude amine (*R*)-**10** was dissolved in $CHCl_3$ (100 mL), and tetra-*n*-butylammonium iodide (61 mg, 0.15 mmol, 3 mol%), a solution of Na_2CO_3 (6.90 g) in H_2O (30 mL) and benzyl chloroformate (2.32 g, 13.6 mmol, 2.5 equiv) were added and the mixture was heated under reflux for 3 days. After cooling to r.t., the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with sat. Na_2CO_3 (2 × 10 mL), H_2O (10 mL), and brine (10 mL), and dried ($MgSO_4$). The residue obtained after removal of the solvent was purified by column chromatography (pentane/Et_2O, 7:1 to 4:1, 1% Et_3N) to

yield carbamate (*R*)-**11** as a colourless oil; yield: 2.11 g (79% over 2 steps).

$[\alpha]_D^{25}$ −3.5° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$), 0.88 [m, 12H, C(C*H*$_3$)$_3$, CH$_2$C*H*$_3$], 1.22−1.33 [m, 18H, H$_3$C(C*H*$_2$)$_9$], 1.48 (m, 2H, C*H*$_{2\ chain}$), 1.58 (m, 1H, NC*H*), 1.69−1.88 (m, 2H, NCHC*H*$_{2\ chain}$), 3.64−3.79 (m, 4H, C*H*$_2$CH$_2$OSi, C*H*$_2$OSi), 5.08 (s, 2H, OC*H*$_2$Ph), 5.17 (d, 1H, *J* = 7.5 Hz, N*H*), 7.28−7.36 (m, 5H, *H*$_{arom}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.49 (Si*C*H$_3$), 14.14 (CH$_2$*C*H$_3$), 18.15 [*C*(CH$_3$)$_3$], 22.71 (*C*H$_2$CH$_3$), 25.89 [C(*C*H$_3$)$_3$], 29.38−29.79 (8 C-atoms, *C*H$_{2\ chain}$), 31.94 (*C*H$_{2\ chain}$), 34.88 (NCHC*H*$_{2\ chain}$), 36.64 (*C*H$_2$CH$_2$OSi), 49.56 (N*C*H), 60.31 (*C*H$_2$OSi), 66.27 (O*C*H$_2$Ph), 127.88 (4 C-atoms), 128.41 (*C*$_{arom}$), 136.9 (*C*$_{ipso}$), 156.0 (*C*O).

IR (film): ν = 3750−3120 (N-H), 3100−2855 (C-H), 1701 (C=O), 1532, 1511, 1464, 1254, 1094 (Si-O), 837 (Si-O-C), 777 (Si-C), 735, 697, 664 (C-H$_{oop}$) cm^{-1}.

MS (EI): *m/z* (%) = 434 (42, M$^+$−C$_4$H$_9$), 390 (8, M$^+$−C$_4$H$_9$,-CO$_2$), 208 (11), 130 (8), 100 (6), 91 (100, C$_7$H$_7^+$), 73 (6), 57 (5, C$_4$H$_9^+$).

Anal. alcd. for $C_{29}H_{53}NO_3Si$ (491.350): C, 70.82; H, 10.86; N, 2.85. Found: C, 70.68; H, 11.29; N, 3.25.

(1*R*)-(−)-Benzyl-*N*-[1-(2-hydroxyethyl)tridecyl]carbamate [(*R*)-12]

Carbamate (*R*)-**11** (4.59 g, 9.34 mmol) was dissolved in THF (70 mL), ammonium fluoride (6.90 g, 187 mmol, 20 equiv) was added and the suspension was treated with a solution of tetra-*n*-butylammonium fluoride (1 M in THF, 47 mL, 47 mmol, 5 equiv) and stirred for 5 h. After complete conversion (TLC control), the mixture was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$). After removal of the solvent, the resulting residue was purified by flash chromatography (pentane/Et_2O, 2:1, 1% Et_3N) to yield alcohol (*R*)-**12** as a colourless amorphous solid; yield: 3.17 g (90%); mp: 76 °C.

$[\alpha]_D^{24}$ −4.8° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.9 Hz, C*H*$_3$), 1.20−1.56 [m, 22H, H$_3$C(C*H*$_2$)$_{11}$], 1.81 (m, 1 H, NC*H*), 2.70 (br s, 2H, C*H*$_2$CH$_2$OH), 3.63 (dd, 2H, *J* = 7.7, 3.30 Hz, C*H*$_2$OH), 3.80 (br s, 1H, O*H*), 4.70 (br s, 1H, N*H*), 5.08 (d, 1H, *J* = 12.09 Hz, OCH*H*-Ph), 5.12 (d, 1H, *J* = 12.09 Hz, OCH*H*Ph), 7.29−7.39 (m, 5H, *H*$_{arom}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.11 (*C*H$_3$), 22.67 (*C*H$_2$CH$_3$), 26.07 (*C*H$_{2\ chain}$), 29.32−29.63 (7 C-atoms, *C*H$_{2\ chain}$), 31.89 (*C*H$_{2\ chain}$), 35.54 (NCH*C*H$_{2\ chain}$), 38.65 (*C*H$_2$CH$_2$OH), 48.06 (N*C*H), 58.75 (*C*H$_2$OH), 66.87 (O*C*H$_2$Ph), 127.88, 128.03, 128.38 (*C*$_{arom}$), 136.18 (*C*$_{ipso}$), 157.16 (*C*=O).

IR (KBr): ν = 3800−3120 (O-H, N-H), 3066, 3035 (C$_{ar}$-H), 2919, 2851 (C-H), 1690 (C=O), 1542, 1469 (C=C$_{ar}$), 1455, 1430, 1353, 1250, 1093, 1063, 869, 740, 694 (C-H$_{oop}$) cm^{-1}.

MS (EI): *m/z* (%) = 377 (15, M$^+$), 332 (11, M$^+$−C$_2$H$_5$O), 288 (40), 242 (13, H$_{25}$C$_{12}$CNH$_2$CH$_2$CH$_2$OH$^+$), 208 (69, M$^+$−C$_{12}$H$_{25}$), 164 (61, CbzNHCH$_2^+$), 108 (15), 91 (100, C$_7$H$_7^+$).

Anal. Calcd. for $C_{23}H_{39}NO_3$ (377.572): C, 73.17; H, 10.41; N, 3.71. Found: C, 73.02; H, 10.61; N 3.54.

(1*R*)-(−)-Benzyl-*N*-[1-(2-iodoethyl)tridecyl]carbamate [(*R*)-13]

Alcohol (*R*)-**12** (500 mg, 1.32 mmol) was dissolved in a mixture of anhyd Et_2O and anhyd MeCN (3:2, 33 mL) under Ar and cooled to 0 °C. Imidazole (167 mg, 2.45 mmol, 1.85 equiv) and triphenylphosphine (607 mg, 2.32 mmol, 1.75 equiv) were added and the mixture was treated portion-wise with iodine, until a pale yellow colour remained. After stirring for 5 h at this temperature, the reaction was complete (TLC control) and the mixture was poured into Et_2O (70 mL), washed with sat. $Na_2S_2O_3$ (10 mL), brine (10 mL), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the obtained residue was purified by flash chromatography (pentane/Et_2O, 10:1 to 1:1, 1% Et_3N) affording iodide (*R*)-**13** as a colourless amorphous solid; yield: 585 mg (91%); mp: 67 °C.

$[\alpha]_D^{28}$ −4.75° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.9 Hz, C*H*$_3$), 1.17−1.34 [m, 20H, H$_3$C(C*H*$_2$)$_{10}$], 1.42 (m, 2H, NCHC*H*$_{2\ chain}$), 1.96 (m, 1H, CH*H*CH$_2$I), 2.07 (m, 1H, CH*H*CH$_2$I), 3.17 (m, 2H, C*H*$_2$I) 3.68 (dquintet, 1H, *J* = 9.34, 4.40 Hz, NC*H*), 4.55 (d, 1H, *J* = 9.34 Hz, N*H*), 5.09 (s, 2H, OC*H*$_2$Ph), 7.29−7.38 (m, 5H, *H*$_{arom}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.44 (*C*H$_2$I), 14.14 (*C*H$_3$), 22.70 (*C*H$_2$CH$_3$), 25.73 (*C*H$_{2\ chain}$), 29.36−29.65 (7 C-atoms, *C*H$_{2\ chain}$), 31.92 (*C*H$_{2\ chain}$), 35.01 (NCH*C*H$_{2\ chain}$), 40.04 (*C*H$_2$CH$_2$I), 52.46 (N*C*H), 66.74 (O*C*H$_2$Ph), 128.10, 128.17, 128.55 (*C*$_{arom}$), 136.23 (*C*$_{ipso}$), 156.11 (*C*=O).

IR (KBr): ν = 3315 (N-H), 3059, 3032 (C$_{ar}$-H), 2917, 2849 (C-H), 1686 (C=O), 1541, 1473, 1469 (C=C$_{ar}$), 1444, 1351, 1297, 1285, 1270, 1257, 1196, 1171, 1156, 1139, 1126, 1089, 1053, 1042, 1024, 1009, 735, 697 (C-H$_{oop}$) cm^{-1}.

MS (EI): *m/z* (%) = 487 (2, M$^+$), 360 (6), 332 (25, M$^+$−C$_2$H$_4$I), 318 (5, M$^+$−C$_{12}$H$_{25}$), 288 (52), 274 (10), 108 (17), 91 (100, C$_7$H$_7^+$).

Anal. Calcd. for $C_{23}H_{38}INO_2$ (487.464): C, 56.67; H, 7.86; N, 2.87. Found: C, 56.29; H, 7.61; N, 2.69.

(1*R*,2*S*,4*S*)-(5*Z*)-(+)-Benzyl-*N*-{1-[2-(5-{[2-methoxymethyl]pyrrolidin-1-yl]imino}-2,2-dimethyl-1,3-dioxan-4-yl)ethyltridecyl]carbamate [(*R*,*S*,*S*)-15]

A solution of hydrazone (*S*)-**14**[9a] (1.05 g, 4.32 mmol, 2.3 equiv) in anhyd THF (45 mL) under Ar was treated at −78 °C with *t*-BuLi (1.6 M in hexane, 2.60 mL, 4.14 mmol, 2.2 equiv) and stirred for 2 h. Hexamethylphosphoramide (HMPA) (7.6 mL) was added followed by dropwise addition of a solution of iodide (*R*)-**13** (915 mg, 1.88 mmol, 1 equiv) in anhyd THF (20 mL). The mixture was stirred for an additional 16 h at −78 °C and quenched with pH 7 buffer (10 mL) at this temperature. Et_2O (100 mL) was added and the organic layer washed with brine (4 × 10 mL). After drying ($MgSO_4$) and removal of the solvent under reduced pressure, the remaining pale yellow residue was purified by flash chromatography (pentane/Et_2O, 4:1 to 1:2, 3% Et_3N). The product was obtained as a colourless, oily mixture of hydrazone (*R*,*S*,*S*)-**15** and unreacted hydrazone (*S*)-**14**, which was used in the next step without further separation; yield: 1.50 g (89% by NMR). An analytical sample was obtained by HPLC chromatography (pentane/Et_2O, 1:1, 0.3% Et_3N) as a colourless oil.

(*Z*)-Isomer

$[\alpha]_D^{28}$ +77.9° (*c* 0.77, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.7 Hz, C*H*$_3$), 1.22−1.55 [m, 24H, C*H*$_2$CHO, H$_3$C(C*H*$_2$)$_{11}$], 1.37 (s, 3H, [(*H*$_3$C)$_2$C$_{eq.}$], 1.39 [s, 3H, (*H*$_3$C)$_2$C$_{ax.}$], 1.58−1.86 (m, 4H, NCH$_2$C*H*$_2$ CH$_{2\ pyrrolidine\ ring}$), 1.94 (m, 2H, C*H*$_2$CH$_2$CHO), 2.39 (m, 1H, NCH-*H*$_{eq.}$), 3.01 (dt, 1H, *J* = 8.8, 6.04 Hz, NCH*H*$_{ax.}$), 3.19 (m, 1H, NC*H*-$_{pyrrolidine\ ring}$), 3.29−3.42 (m, 2H, H$_3$COC*H*$_2$), 3.32 (s, 3H, *H*$_3$CO), 3.61 (m, 1H, HNC*H*), 4.11 [dd, 1H, *J* = 15.66, 1.8 Hz, (H$_3$C)$_2$COCH*H*$_{ax.}$], 4.34 [m, 1H, (H$_3$C)$_2$COC*H*], 4.49 [d, 1H, *J* = 15.66 Hz, (H$_3$C)$_2$COCH*H*$_{eq.}$], 4.76 (d, 1H, *J* = 8.79 Hz, N*H*), 5.06 (d, 1H, *J* = 12.2 Hz, OCH*H*Ph), 5.11 (d, 1H, *J* = 12.2 Hz, OCH*H*Ph), 7.25−7.43 (m, 5H, *H*$_{arom}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.14 (CH$_2$*C*H$_3$), 22.70 (*C*H$_2$CH$_3$), 22.79 (NCH$_2$*C*H$_{2\ pyrrolidine\ ring}$), 24.03 [(H$_3$*C*)$_2$C], 24.16 [(H$_3$*C*)$_2$C], 25.83 (*C*H$_{2\ chain}$), 26.70 (*C*H$_2$CHO), 27.74 (NCH*C*H$_{2\ pyrrolidine\ ring}$),

29.37−30.12 (9 C-atoms, $CH_{2\ chain}$), 31.93 (CH_2CH_2CHO), 35.52 ($NCHCH_{2\ chain}$), 51.15 (HN*C*H), 55.65 ($NCH_{2\ pyrrolidine\ ring}$), 59.18 ($OCH_3$), 59.83 [$(H_3C)_2COCH_2$], 66.42 ($OCH_2Ph$), 66.66 ($NCH_{pyrrolidine\ ring}$), 70.29 [$(H_3C)_2COCH$], 75.55 ($CH_2CH_3$), 100.23 [$(H_3C)_2C$], 127.99, 128.03, 128.48 (C_{arom}), 136.81 (C_{ipso}), 156.14 (*C*=O), 162.63 (*C*=N).

IR (film): ν = 3334 (N-H), 3065 (C_{ar}-H), 2926, 2854 (C-H), 1713 (C=O), 1587, 1514, 1455, 1380 (C=C_{ar}), 1336, 1226, 1162, 1104, 1063, 1028, 909, 865, 757 (C-H_{oop}), 698, 667 (H_{oop}) cm^{-1}.

MS (EI): *m/z* (%) = 601 (4, M^+), 556 (80, $M^+-CH_2OCH_3$), 543 [13, $M^+-(H_3C)_2CO$], 498 (100), 480 (12), 412 (12), 328 (21), 321 (48), 91 (41, $C_7H_7^+$).

HRMS: m/z calcd for $C_{35}H_{59}N_3O_5^+$: 601.4455. Found: 601.4453.

(1*R*,4*S*)-(−)-Benzyl-*N*-{1-[2-(2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)ethyltridecyl]carbamate [(*R*,*S*)-16]

The crude mixture of hydrazones (*R*,*S*,*S*)-**15** and (*S*)-**14** (1.50 g) in Et_2O (35 mL) was stirred vigorously at r.t. with sat. oxalic acid (8 mL) for 5 h. After complete conversion (TLC control), the phases were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic layers were washed with pH 7 buffer (5 mL) and brine (5 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Et_2O (5 mL) was added and the solution passed through a plug of cottonwool and Florisil™. After drying in vacuo, pure ketone (*R*,*S*)-**16** was obtained as a yellow oil; yield: 737 mg (80% over 2 steps).

$[\alpha]_D^{28}$ −89.3° (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.7 Hz, CH_3), 1.22−1.52 [m, 22H, CH_2CHO, $H_3C(CH_2)_{10}$], 1.42 (s, 3H, [$(H_3C)_2C_{eq.}$], 1.47 [s, 3H, $(H_3C)_2C_{ax.}$], 1.60 (m, 2H, NCHC$H_{2\ chain}$), 1.87 (m, 2H, CH_2CH$_2$CHO), 3.65 (m, 1H, NC*H*), 4.00 [d, 1H, *J* = 16.76 Hz, $(H_3C)_2$COCH$H_{eq.}$], 4.27 [dd, 1H, *J* = 16.76, 1.37 Hz, $(H_3C)_2$CO CH$H_{ax.}$], 4.27 [m, 1H, $(H_3C)_2$COC*H*], 4.55 (d, 1H, *J* = 9.06 Hz, N*H*), 5.06 (d, 1H, *J* = 12.36 Hz, OCH_2Ph), 5.11 (d, 1H, *J* = 12.36 Hz, OCH_2Ph), 7.25−7.43 (m, 5H, H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.14 (CH_2CH_3), 22.70 (CH_2CH_3), 23.64 [$(H_3C)_2C_{eq.}$], 23.88 [$(H_3C)_2C_{ax.}$], 24.50 ($CH_{2\ chain}$), 25.85 (CH_2CHO), 29.30−30.33 (9 C-atoms, $CH_{2\ chain}$), 31.92 (CH_2CH_2CHO), 35.57 ($NCHCH_{2\ chain}$), 50.64 (N*C*H), 66.59 (2 C-atoms, $(H_3C)_2COCH_2$, (OCH_2Ph), 73.96 [$(H_3C)_2COCH$], 100.83 [$(H_3C)_2C$], 128.03, 128.06, 128.51 (C_{arom}), 136.64 (C_{ipso}), 156.17 (*C*=O amide), 209.63 (*C*=O ketone).

IR ($CHCl_3$): ν = 3323 (N-H), 3035, 3020 (C_{ar}-H), 2923, 2853 (C-H), 1751 (C=O amide), 1682 (C=O ketone), 1541, 1468, 1456, 1382, 1351, 1313, 1293 (C=C_{ar}), 1253, 1223, 1163, 1124, 1087, 1062, 1011, 907, 858, 776, 753, 725, 696 (C-H_{oop}) cm^{-1}.

MS (EI): *m/z* (%) = 431 [16, $M^+-(H_3C)_2CO$], 332 (5, $M^+-C_{12}H_{25}CHNHZ$), 296 (11), 288 (20), 278 (15), 238 (8), 91 (100, $C_7H_7^+$), 72 (14).

Anal. Calcd. for $C_{29}H_{47}NO_5$ (489.702): C, 71.07; H, 9.67; N, 2.86. Found: C, 71.07; H, 9.42; N, 2.73.

(1*S*,5*S*,8*R*)-(−)-8-Dodecyl-3,3-dimethyl-2,4-dioxa-7-azabicyclo-[4.4.0]decane [(*S*,*S*,*R*)-18]

Through a suspension of ketone (*R*,*S*)-**16** (517 mg, 1.06 mmol) and Pd/C (10% on charcoal, 500 mg) in EtOH (30 mL), a stream of hydrogen was passed for 2 h. After complete conversion (TLC control) the mixture was flushed with Ar and filtered through Celite™ and the solvent removed under reduced pressure. After flash column chromatography (Et_2O, 1% Et_3N), piperidine (*S*,*S*,*R*)-**18** was obtained as colourless oil; yield: 306 mg (85%).

$[\alpha]_D^{28}$ −0.5° (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 7.0 Hz, CH_3), 1.24−1.32 [m, 22H, $H_3C(CH_2)_{11}$], 1.37 (m, 1H, NCHCH$H_{ax.}$), 1.42 [s, 3H, $(H_3C)_2C_{eq.}$], 1.47 [s, 3H, $(H_3C)_2C_{ax.}$], 1.47−1.51 (m, 1H, NCHCH$H_{eq.}$), 1.63 (tdd, 1H, *J* = 14.04, 4.58, 3.05 Hz, NCHCHCH-$H_{ax.}$), 1.89 (tdd, 1H, *J* = 14.04, 3.35, 3.05 Hz, NCHCHCH$H_{eq.}$), 2.50 (m, 1H, NC*H*CH_2O), 2.56 (m, 1H, NC*H*C_{chain}), 3.78 [dd, 1H, *J* = 12.2, 1.1 Hz, $(H_3C)_2$COCH$H_{eq.}$], 3.91 (m, 1H, NCHC*H*), 4.11 [dd, 1H, *J* = 12.2, 1.1 Hz, $(H_3C)_2$COCH$H_{ax.}$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.13 (CH_2CH_3), 18.63 [$(H_3C)_2C_{eq.}$] 22.70 (CH_2CH_3), 25.98 ($NCHCH_{2\ ring}$), 26.03 ($NCHCH_{2\ chain}$), 29.37 ($CH_{2\ chain}$), 29.62−29.70 (5 C-atoms, $CH_{2\ chain}$), 29.82 [$(H_3C)_2C_{ax.}$], 29.87 ($NCHCHCH_2$), 30.02 ($CH_{2\ chain}$), 31.93 ($CH_{2\ chain}$), 37.27 ($CH_{2\ chain}$), 51.75 (N*C*HCH), 55.66 ($NCHCH_2$), 64.35 (NCH*C*H), 65.03 ($NCHCH_2O$), 98.41 ($(H_3C)_2C$).

IR ($CHCl_3$): ν = 3800−3100 (NH), 2988, 2952, 2919, 2870, 2850, 2814 (C-H), 2749, 2712, 2682, 2632, 2572, 2534 (C-H), 2370, 1578, 1509, 1498, 1463, 1421, 1401, 1381, 1343, 1295, 1276, 1257, 1222, 1205, 1099, 1077 cm^{-1}.

MS (EI): *m/z* (%) = 339 (7, M^+), 324 (22, M^+-CH_3), 264 (6), 224 (13), 170 (100, $M^+-C_{12}H_{25}$), 112 [26, $M^+-C_{12}H_{25}-(H_3C)_2CO$], 82 (11).

HRMS: *m/z* calcd for $C_{21}H_{41}NO_2^+$: 339.3137. Found: 339.3133.

Further elution with Et_2O afforded piperdine (*S*,*S*,*S*)-**18** as a colourless oil; yield: 11 mg (3.1%).

$[\alpha]_D^{28}$ +2.0° (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.9 Hz, CH_3), 1.24−1.33 [m, 21H, $H_3C(CH_2)_{10}$, NCHCH$H_{eq.}$], 1.44 [s, 3H, $(H_3C)_2C_{eq.}$], 1.45 [s, 3H, $(H_3C)_2C_{ax.}$], 1.49 (m, 1H, NCHCHH_{chain}), 1.61 (m, 1H, NCHCHH_{chain}), 1.65 (dq, 1H, *J* = 14.04, 3.05 Hz, NCHCHCH$H_{eq.}$), 1.80 (dddd, 1H, *J* = 14.04, 13.74, 3.66, 3.05 Hz, NCHCHCH$H_{ax.}$), 1.90 (dddd, 1H, *J* = 13.74, 13.43, 4.58, 4.27 Hz, NCHCH$H_{ax.}$), 2.58 (m, 1H, NC*H*CH_2O), 3.04 (m, 1H, NC*H*C_{chain}), 3.70 [d, 1H, *J* = 12.0 Hz, $(H_3C)_2$COCH$H_{eq.}$], 3.91 (m, 1H, NCHC*H*), 4.08 [dd, 1H, *J* = 12.0, 2.5 Hz, $(H_3C)_2$COCH$H_{ax.}$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.13 (CH_2CH_3), 18.68 [$(H_3C)_2C_{eq.}$] 22.19 (CH_2CH_3), 22.70 ($NCHCH_{2\ ring}$), 24.71 (NCH $CHCH_2$), 27.27 ($CH_{2\ chain}$), 29.36 ($CH_{2\ chain}$), 29.66−30.10 [8 C-atoms, $CH_{2\ chain}$, $(H_3C)_2C_{ax.}$], 31.93 ($CH_{2\ chain}$), 45.34 (N*C*HCH), 51.45 ($NCHCH_2$), 64.64 (NCH*C*H), 64.87 ($NCHCH_2O$), 98.35 [$(H_3C)_2C$].

(2*S*,3*S*,5*R*)-(+)-6-Dodecyl-2-(hydroxymethyl)piperdin-3-ol [(*S*,*S*,*R*)-5]

Acetonide (*S*,*S*,*R*)-**18** (110 mg, 0.324 mmol) was dissolved in MeOH (10 mL), ion exchange resin Lewatit S 100™ (621 mg) was added and the mixture was heated for 2 h under reflux. After cooling to r.t., sat. NH_4OH (1 mL) was added and the mixture was passed through silica gel followed by a mixture of CH_2Cl_2/MeOH (5:1, 20 mL). After evaporation of the solvent under reduced pressure and repetition of this procedure, the resulting solid was crystallised from acetone/pentane to yield the deprotected product as a colourless solid; yield: 84 mg (87%); mp: 59 °C.

$[\alpha]_D^{26}$ +2.7° (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz, CD_3OD): δ = 0.88 (t, 3H, *J* = 6.9 Hz, CH_3), 1.25−1.31 [m, 22H, $H_3C(CH_2)_{11}$], 1.33−1.61 (m, 3H, NCHCH_2, NCHCHCH$H_{ax.}$), 1.85 (dddd, 1H, *J* = 13.74, 3.57, 3.05, 2.74 Hz, NCHCHCH$H_{eq.}$), 2.52 (m, 1H, NC*H*C_{chain}), 2.67 (td, 1H, *J* = 5.77, 1.65 Hz, NC*H*CH_2OH), 3.60 (dd, 2H, *J* = 6.87, 5.77 Hz, CH_2OH), 3.79 (m, 1H, NCHC*H*).

^{13}C NMR (100 MHz, CD_3OD): δ = 13.47 (CH_3), 22.72 (CH_2CH_3), 25.89 ($NCHCH_{2\ chain}$), 26.09 ($NCHCH_2$), 29.45−29.89 (7 C-atoms, $CH_{2\ chain}$), 31.67 ($NCHCHCH_2$), 32.04 ($CH_{2\ chain}$), 36.58 ($CH_{2\ chain}$), 56.71 (N*C*HCH$_2$), 61.31 (N*C*HCH), 63.22 (CH_2OH), 64.60 (NCH*C*H).

IR (KBr): ν = 3800−3170 (NH, OH), 2953, 2916, 2850, 2800, 2506, 2413, 1724, 1584, 1472, 1079, 886, 719 cm^{-1}.

MS (EI): *m/z* (%) = 299 (2.0, M^+), 268 (100, M^+-OCH_3), 130 (78.7, $M^+-C_{12}H_{25}$).

HRMS: *m/z* calcd for $C_{18}H_{37}NO_2^+$: 299.2824. Found: 299.2825.

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