Asymmetric Synthesis of 2-Mono- and 2,3-*trans*-Disubstituted Azetidines

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A versatile and efficient asymmetric synthesis of 2-mono- and 2,3-*trans*-disubstituted azetidines with excellent diastereomeric (*de* = 93 to ≥ 96%) and enantiomeric excesses (*ee* ≥ 96%) in good overall yields is described. Virtually stereoisomerically pure differently *N*,*O*-protected 3-amino-1-alkanols were prepared as intermediates. Key steps are a diastereoselective α-alkylation of aldehyde SAMP-hydrazones with benzyloxymethyl chloride as the electrophile, and a nucleophilic 1,2-addition of various organocerium reagents to the hydrazone CN double bond. An epimerisation-free reductive removal of the auxiliary gave *O*-benzyl-protected 3-amino-1-alkanols. After *N*-tosylation and hydrogenolytic cleavage of the benzylic protecting group, ring closure to the corresponding *N*-tosylazetidines was achieved in good yields under Mitsunobu conditions. Detosylation was easily accomplished employing sodium/naphthalene.

Introduction

Azetidines have been less studied in the past than related nitrogen heterocycles, although they show significant biological activities.[1] One explanation could be the small number of natural products containing a four-membered N-heterocycle in contrast to the large number of pyrrolidine and piperidine compounds. The three-membered aziridines also received significant attention as soon as convenient methods for their asymmetric preparation and their application as chiral building blocks in organic synthesis were at hand.[2] Nevertheless, chiral azetidines have recently triggered much interest as potential active pharmaceutical ingredients as indicated by the growing number of publications and patents emerging in this field.[3] One of the most prominent biologically active azetidines is the non-opiate analgesic agent ABT-594.[4]

Furthermore, ligands with an azetidine backbone have been employed in various asymmetric catalytic processes with convincing results, such as reductions,[5] diethylzinc additions,[6] cycloadditions[7] and cyclopropanations.[8] Enantiopure azetidines have also been used as substrates in stereoselective ring enlargement reactions.[9] Despite these promising developments in azetidine chemistry, the lack of general diastereo- and enantioselective routes to these heterocycles is evident by the relatively low number of reports on azetidines in the literature.[10]

Different approaches for the construction of nonracemic azetidine ring systems have been reported, such as reduction of β-lactams,[11] double alkylation of primary amines,[12] intramolecular *C*-alkylation or Michael addition,[13] cyclisation of β-amino allenes,[14] carbene insertion into the NH bond via α-amino diazo ketones[15] amongst others.[16] One of the most reliable ways for the asymmetric synthesis of substituted azetidines remains the synthesis of a straight chain precursor, such as 3-amino-1-alkanols, with established stereochemistry and subsequent ring closure by intramolecular *N*-alkylation.[17]

The synthesis of enantiomerically enriched 3-amino-1-alkanols has recently received much attention, as the direct catalytic asymmetric Mannich reaction was reported as a promising new method for their synthesis. The use of organometallic and amine catalysts in this reaction has recently been reviewed.[18]

As part of our continuing interest in the asymmetric synthesis of nitrogen heterocycles[19] we herein wish to report an efficient and flexible synthesis of substituted azetidines. Our synthetic strategy comprises the synthesis of virtually enantiopure γ-amino alcohols as key intermediates employing the SAMP/RAMP-hydrazone methodology.[20] Subsequent conversion into the azetidines is then carried out by intramolecular nucleophilic substitution.

Results and Discussion

The asymmetric synthesis of 2-mono- and 2,3-*trans*-disubstituted azetidines was achieved following the well established protocols for the α-alkylation and 1,2-addition of aldehyde SAMP/RAMP-hydrazones with subsequent N−N bond cleavage, followed by ring closure as depicted in Scheme 1.

The SAMP-hydrazones **1** were obtained by condensation of the chiral auxiliary with aldehydes.[21] For the synthesis

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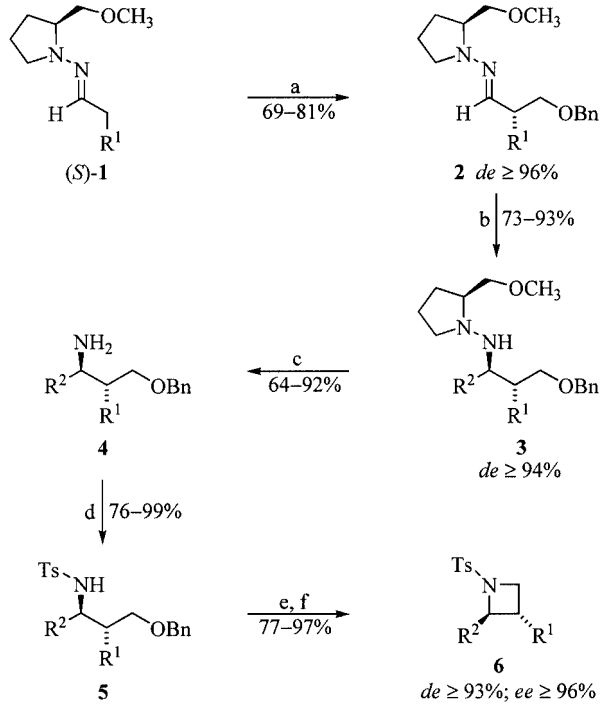


Scheme 1. Asymmetric synthesis of azetidines **6**: a) LDA, benzyloxymethyl chloride, THF; b) $CeCl_3$, R^2Li, THF; c) BH_3·THF, THF, then HCl; d) TsCl, K_2CO_3, NEt_3, CH_2Cl_2; e) Pd/C, H_2, EtOAc; f) PPh_3, *i*$PrO_2CN{=}NCO_2$*i*Pr, THF

of the 2,3-*trans*-disubstituted azetidines the SAMP-hydrazones **1** were first α-alkylated with benzyloxymethyl chloride corresponding effectively to a hydroxymethylation with benzyl protection in a single step. Benzyloxymethyl chloride had previously been successfully utilized for the alkylation of hydrazones.[22] While **2d** was obtained in good yield, we achieved only moderate results with the aliphatic hydrazones **2a**−**c** following the standard alkylation protocol. β-Elimination of benzyl alcohol and oligomerisation of benzyloxymethyl chloride were the side reactions as observed by NMR spectroscopic analysis of the crude reaction mixtures. They could be circumvented by using lower hydrazone concentrations, shorter reaction times and quenching the reaction at low temperature. The use of other bases like LTMP and LHMDS instead of LDA did not improve yields. Under optimised reaction conditions the hydrazones **1a**−**c** were deprotonated with LDA at −5 °C over 2.5 h. A significantly lower hydrazone concentration had to be used (9−12 mL THF/mmol hydrazone) than usually employed in the hydrazone alkylation protocols (typically 2−3 mL THF/mmol hydrazone). In order to achieve complete deprotonation another 0.9 equivalents of *n*BuLi had to be added to regenerate LDA and to complete the metalation of the hydrazones. The aza-enolates thus obtained were alkylated at −100 °C with benzyloxymethyl chloride. After 2−3 h the reaction mixtures were subjected to an aqueous workup and the crude products were purified by flash column chromatography to give the alkylated, diastereomerically pure hydrazones **2** (*de* ≥ 96%) in 69−81% yield (Table 1).

Table 1. Diastereoselective α-alkylation of the hydrazones **1** with benzyloxymethyl chloride

Product	R^1	Yield [%]	*de*[a] [%]
(*R*,*S*)-**2a**	Me	70	≥ 96
(*R*,*S*)-**2b**	Et	69	≥ 96
(*R*,*S*)-**2c**	*n*Bu	79	≥ 96
(*R*,*S*)-**2d**	Ph	81	≥ 96

[a] Determined by ^1H and ^{13}C NMR spectroscopy.

The absolute configuration of the newly formed stereogenic centre of the hydrazones **2** was assigned according to previous results obtained in α-alkylation reactions of aldehyde SAMP-hydrazones.[19a,20,23]

In the following step the second substituent was introduced by the nucleophilic 1,2-addition of an organometallic reagent to the hydrazone CN double bond.[24] Initial experiments with alkyllithiums led to poor yields and the elimination of benzyl alcohol as a side reaction. The use of less basic and more nucleophilic organocerium compounds, which were freshly prepared from $CeCl_3$ and organolithium compounds following Imamoto's procedure,[25] gave the corresponding hydrazines **3** in good yields (73−93%) and high diastereoselectivities (*de* = 94 to at least 96%) (Table 2).

Table 2. Diastereoselective nucleophilic addition of organocerium reagent to the hydrazones **2**

Product	R^1	R^2	Yield [%]	*de*[a] [%]
(*R*,*R*,*S*)-**3a**	Me	*n*Bu	90	≥ 96
(*R*,*R*,*S*)-**3b**	Et	*n*Bu	93	≥ 96
(*R*,*R*,*S*)-**3c**	*n*Bu	*n*-Hex	73	≥ 96
(*S*,*R*,*S*)-**3d**	*n*Bu	*t*Bu	91	≥ 96
(*R*,*R*,*S*)-**3e**	Ph	*n*-Hex	93	94 (91[b])
(*R*,*S*)-**3f**	H	*n*-Hex	76	96

[a] Determined by ^1H and ^{13}C NMR spectroscopy. [b] Before flash column chromatography.

The preparation of monosubstituted azetidines started with the 1,2-addition to the unsubstituted hydrazone **2e** (R^1 = H), which was derived via condensation of 3-benzyloxypropanal[26] and SAMP in 81% yield, without a preceding α-alkylation. **3f** was obtained by the nucleophilic addition of the *n*-hexylcerium reagent to hydrazone **2e**.

The α-alkylation of hydrazone (*S*)-**2e** as an alternative way for the preparation of stereoisomers of the hydrazones **2a**−**d** was not possible due to decomposition during the deprotonation.

It is important to note that an reverse addition of the cerium reagent to the hydrazone solution was necessary in order to obtain high yields. Addition of the hydrazone solution to the organocerium compound was only possible in the cases of the less reactive *tert*-butyl reagent leading to the hydrazine **3d** and the unsubstituted hydrazone **2e** leading to the hydrazine **3f**.

The absolute configuration of the newly generated stereogenic centre of the hydrazines **3** was assigned according to the previously confirmed mechanism for 1,2-additions to SAMP-hydrazones.[23b,27]

The *O*-benzyl-protected 3-amino-1-alkanols **4a**−**f** were obtained after the N−N bond cleavage of the corresponding hydrazines **3**. This was accomplished by heating the hydrazines with an excess of borane tetrahydrofuran complex according to a standard procedure developed in our group.[28] Purification by flash column chromatography afforded the pure amines **4** in good yields (64−92%) as shown in Table 3.

Table 3. Hydrazine cleavage with the borane tetrahydrofuran complex

Product	R^1	R^2	Yield [%]	*de*[a] [%]	*ee*[b] [%]
(*R*,*R*)-**4a**	Me	*n*Bu	92	≥ 96	≥ 96
(*R*,*R*)-**4b**	Et	*n*Bu	83	≥ 96	≥ 96
(*R*,*R*)-**4c**	*n*Bu	*n*-Hex	78	≥ 96	≥ 96
(*S*,*R*)-**4d**	*n*Bu	*t*Bu	64	≥ 96	≥ 96
(*R*,*R*)-**4e**	Ph	*n*-Hex	88	94	≥ 96
(*R*)-**4f**	H	*n*-Hex	−[c]	−	−

[a] Determined by ^{1}H and ^{13}C NMR spectroscopy. [b] In correlation with the *de* value of the corresponding hydrazine as determined by ^{1}H and ^{13}C NMR spectroscopy and racemisation-free hydrazine cleavage. [c] Not isolated and directly converted into **5f**.

The tosyl group appeared to be the protecting group of choice in this synthesis. Other protecting groups such as *N*-benzyl and *N*-*p*-methoxybenzyl were tested in the course of this work giving only poor yields during their introduction.

Alternatively, various carbamates gave undesired side products during the ring closure by nucleophilic substitution due to their ambident N- and O-nucleophilic character. The NMR spectroscopic examination of the crude reaction mixtures indicated the formation of oxazines by alkylation of the carbamate oxygen. This was in accordance with observations made by Baldwin et al. during attempted carbamate alkylations.[29]

The generation of the sulfonamides **5** was accomplished in good yields (84−99%) by heating the amines with tosyl chloride in the presence of K_2CO_3. For the preparation of the tosylamine **5f** with satisfactory yield triethylamine was necessary as an additional base. In several cases the diastereomeric excesses determined by ^{1}H and ^{13}C NMR could be confirmed by GC (Table 4).

The *O*-benzyl ethers **5a**−**f** were cleaved by hydrogenolysis in the presence of palladium on charcoal affording the corresponding protected amino alcohols. Finally, cyclisation to the desired azetidines **6** was achieved in analogy to Mitsunobu's procedure for the alkylation of amines.[30] The 2,3-disubstituted azetidines **6a**−**e** and the 2-monosubstituted azetidine **6f** were obtained in good yields (Table 5).

The enantiomeric excesses given are based on the diastereomeric excesses of the corresponding SAMP-hydrazones and hydrazines. The following steps leading to the azetidines were assumed to be racemisation-free. This was indeed a valid assumption that could be proven in the case of (*R*,*S*)-**6e**, of which the enantiomer (*S*,*R*)-**6e** ($[\alpha]_D^{22}$ = +51.7 (*c* = 1.0, $CHCl_3$)) was also synthesized starting from the RAMP-hydrazone (*R*)-**1d**. This enabled us to confirm the *ee* values by HPLC on chiral stationary phases and to confirm the racemisation-free course of the azetidine synthesis.

Table 4. Protection of the amines **4** as tosyl amides **5**

Product	R^1	R^2	Yield [%]	*de*[a] [%]	*ee*[b] [%]
(*R*,*R*)-**5a**	Me	*n*Bu	89	≥ 96	≥ 96
(*R*,*R*)-**5b**	Et	*n*Bu	92	98[c]	≥ 96
(*R*,*R*)-**5c**	*n*Bu	*n*-Hex	99	98[c]	≥ 96
(*S*,*R*)-**5d**	*n*Bu	*t*Bu	76	≥ 96	≥ 96
(*R*,*R*)-**5e**	Ph	*n*-Hex	89	≥ 96	97[d]
(*R*)-**5f**	H	*n*-Hex	84 (2 steps)	−	≥ 96

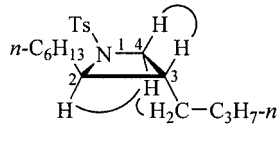
[a] Determined by ^{1}H and ^{13}C NMR spectroscopy. [b] In correlation with the *de* value of the corresponding hydrazine as determined by ^{1}H and ^{13}C NMR spectroscopy. The following steps are racemisation-free. [c] Determined by gas chromatography. [d] Determined by HPLC on a chiral stationary phase. Optical rotation of the RAMP derived tosylamino alcohol (*S*,*S*)-**5e**: $[\alpha]_D^{23}$ = −20.7 (*c* = 0.9, $CHCl_3$).

Table 5. Hydrogenolytic cleavage of the *O*-benzyl ether **5** and ring closure to the azetidines **6**

Product	R^1	R^2	Yield [%] (2 steps)	*de*[a] [%]	*ee*[b] [%]
(*R*,*S*)-**6a**	Me	*n*Bu	97	93	≥ 96
(*R*,*S*)-**6b**	Et	*n*Bu	92	96	≥ 96
(*R*,*S*)-**6c**	*n*Bu	*n*-Hex	92	95	≥ 96
(*S*,*S*)-**6d**	*n*Bu	*t*Bu	93	≥ 96[c]	≥ 96
(*R*,*S*)-**6e**	Ph	*n*-Hex	94	≥ 96[c]	96[d]
(*R*)-**6f**	H	*n*-Hex	77	−	≥ 96

[a] Determined by gas chromatography. [b] In correlation with the *de* value of the corresponding hydrazine as determined by ^{1}H and ^{13}C NMR spectroscopy. The following steps are racemisation-free. [c] Determined by ^{1}H and ^{13}C NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase.

The *trans*-configuration of the disubstituted azetidines **6a**−**e** was proven by NOE-measurements on **6c** as shown in Figure 1. On radiation of one of the protons at C-4 a strong nuclear Overhauser effect was observed with the proton at C-2 and with the protons of the alkyl substituent at C-3. The other proton at C-4 showed strong interaction with the proton at C-3. No enhancement was visible between the protons at C-2 and C-3, all this indicating their relative *trans*-configuration.



6c

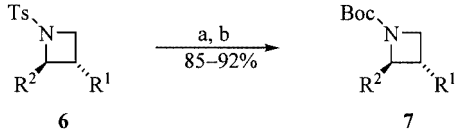
Figure 1. NOE measurements on azetidine **6c**, confirming the *trans*-configuration of the 2,3-disubstituted azetidines **6**

The removal of the tosyl group was carried out in the cases of the aliphatic azetidines **6c** and the aromatic azetidine **6e** as depicted in Scheme 2. The cleavage of the tosyl group proceeded cleanly with Na/naphthalene in dimethoxyethane (DME) at −45 °C. The free azetidines were subsequently protected as *tert*-butyl carbamates for easier isolation and purification. No epimerisation was detected with the aliphatic azetidine (*R*,*S*)-**7a**. Unfortunately, a slight drop in the diastereomeric excess of the aromatic azetidine (*R*,*S*)-**7b** from ≥ 96% to 91% was detected by ^{1}H NMR and HPLC. Nevertheless the *ee* value was confirmed to be 96% by HPLC on a chiral stationary phase {(*S*,*R*)-**7b**: $[\alpha]_D^{23} = +5.8$ (c = 1.1, $CHCl_3$)}.

Table 6. Reductive detosylation and Boc-protection of the chiral azetidines **6**

Product	R^1	R^2	Yield [%] (2 steps)	*de* [%]	*ee* [%]
(*R*,*S*)-**7a**	*n*Bu	*n*-Hex	85	95[a]	≥ 96[b]
(*R*,*S*)-**7b**	Ph	*n*-Hex	92	91[c]	96[d]

[a] Determined by gas chromatography. [b] In correlation with the *de* value of the corresponding hydrazine determined by ^{1}H and ^{13}C NMR spectroscopy. The following steps are racemisation-free. [c] Determined by ^{1}H and ^{13}C NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase.



6 **7**

Scheme 2. Tosyl cleavage and subsequent Boc protection: a) Na/naphthalene, DME, −45 °C; b) $(Boc)_2O$, TEA, DCM

Conclusion

In summary, we have developed a versatile and efficient asymmetric synthesis of 2-mono- and 2,3-*trans*-disubstituted azetidines starting from aldehyde-SAMP/RAMP-hydrazones including a short three-step asymmetric synthesis of 3-amino-1-alkanols on the way. The amino alcohols and azetidines were obtained in very good diastereomeric and enantiomeric purities. Furthermore, the removal of the tosyl protecting group of the azetidines was shown for selected examples.

Experimental Section

General Remarks: All solvents were dried and purified by conventional methods prior to use. THF and dimethoxyethane were freshly distilled from sodium/lead alloy and benzophenone under argon. All moisture sensitive reactions were carried out under argon using standard Schlenk techniques. Diisopropylamine was distilled from CaH_2 under argon and stored over molecular sieves. Sodium metal was cleaned and rinsed with dry methanol before use. Flash column chromatography was carried out with Merck silica gel 60, 0.040−0.063 mm particle size. Optical rotation values were measured on a Perkin−Elmer P 241 polarimeter with solvents of Merck UVASOL quality. IR spectra: Perkin−Elmer FT/IR. NMR spectra: Varian VXR 300, Varian Gemini 300 and Varian Inova 400, using TMS as internal standard. Mass spectra: Varian MAT 212 and Finnigan SSQ 7000. Microanalyses: Heraeus, CHN-O-Rapid. Merck TLC plates with silica gel 60 F_{254} were used for analytical TLC. Benzyloxymethyl chloride was prepared from formaldehyde and benzyl alcohol.[31] The SAMP/RAMP-hydrazones were prepared from (*S*)- or (*R*)-proline according to the literature procedures.[21]

General Procedure for the α-Alkylation of SAMP-Hydrazones 1 with Benzyloxymethyl Chloride (GP 1): LDA (1.1 equiv.) was freshly prepared by addition of *n*BuLi (1.1 equiv.) to a solution of diisopropylamine in dry THF (9−12 mL/mmol hydrazone) under argon at −5 °C and stirring for 15 min. The SAMP-hydrazones **1** (1 equiv.) were added drop wise to this solution. After stirring for 2 to 3 h another portion of *n*BuLi (0.9 equiv.) was added. The mixture was then cooled to −100 °C and benzyloxymethyl chloride (1.2 equiv.) in dry THF (0.5 mL/mmol) was slowly added at this temperature. This solution was warmed to −65 °C over 2 to 3 h. The reaction mixture was quenched with water and after warming up pH-7 buffer solution was added. The mixture was extracted three times with CH_2Cl_2 and the combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The pure products where obtained by flash column chromatography.

(2*R*,2*S*)-(−)-[3-Benzyloxy-2-methylpropylidene][2-(methoxymethyl)-pyrrolidin-1-yl]amine [(*R*,*S*)-2a]: Hydrazone (*S*)-**1a** (3.41 g, 20.0 mmol) was alkylated according to GP 1. Purification by flash column chromatography (pentane/Et_2O, 6:1, 1% Et_3N) gave (*R*,*S*)-**2a** as a colourless oil (4.03 g, 70%). $[\alpha]_D^{23} = -89.4$ (c = 1.0, $CHCl_3$). R_t = 15.79 min (CP-Sil-8, 80−10−300). R_f = 0.60 (pentane/Et_2O, 1:1). IR (film): $\tilde{\nu}$ = 3063 (m), 3030 (m), 2875 (s), 2080 (w), 1952 (w), 1874 (w), 1811 (w), 1726 (w), 1602 (m), 1495 (m), 1455 (s), 1363 (m), 1304 (w), 1199 (s), 1103 (s), 1028 (w), 1000 (w), 973 (m), 903 (m), 878 (m), 740 (s), 700 (s), 611 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 1.75−1.99 (m, 4 H, $NCH_2CH_2CH_2$), 2.71 (m, 2 H, N=CHCH, NCHH), 3.36 (s, 3 H, OCH_3), 3.30−3.60 (m, 6 H, NCHH, CH_2OCH_2Ph, $NCHCH_2OCH_3$), 4.51 (s, 2 H, OCH_2Ph), 6.56 (d, J = 5.9 Hz, 1 H, N=CH), 7.26−7.33 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8 (CH_2CH_3), 22.1 (NCH_2CH_2), 26.6 ($NCH_2CH_2CH_2$), 37.5 (N=CHCH), 50.1 (NCH_2), 59.2 (OCH_3), 63.4 (NCH), 72.9 (CH_2OCH_2Ph), 74.1 (OCH_2Ph), 74.7 (CH_2OCH_3), 127.5, 127.6, 128.3 (Ar *C*), 138.6 (Ar C_q), 140.2 (N=CH) ppm. MS (EI, 70 eV): *m*/*z* (%) = 290 (7) [M^+], 245 (100), 169 (2), 123 (3), 91 (29), 70 (13). $C_{17}H_{26}N_2O_2$ (290.40): calcd. C 70.31, H 9.02, N 9.65; found C 70.72, H 8.93, N 9.96.

(2*R*,2*S*)-(−)-[2-(Benzyloxymethyl)butylidene][2-(methoxymethyl)-pyrrolidin-1-yl]amine [(*R*,*S*)-2b]: Hydrazone (*S*)-**1b** (2.76 g, 15.0 mmol) was alkylated according to GP 1. Purification by flash column chromatography (pentane/Et_2O, 5:1, 1% Et_3N) gave (*R*,*S*)-**2b** as a colourless oil (3.15 g, 69%). $[\alpha]_D^{24} = -60.3$ (c = 1.2, $CHCl_3$). R_t = 10.80 min (CP-Sil-8, 140−10−300). R_f = 0.38 (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3063 (m), 3029 (m), 2961 (s), 2927 (s), 2873 (s), 1950 (w), 1874 (w), 1810 (w), 1726 (w), 1602 (m), 1456 (s), 1363 (m), 1341 (m), 1303 (m), 1199 (m), 1111 (s), 1028 (m), 973 (m), 905 (m), 737 (s), 699 (m), 612 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.49 (m, 1 H, $CHHCH_3$), 1.62 (m, 1 H, $CHHCH_3$), 1.75−2.00 (m, 4 H, $NCH_2CH_2CH_2$), 2.47 (m, 1 H, N=CHCH), 2.74 (q, J = 8.4 Hz, 1 H, NCHH), 3.32 (m, 1 H, NCHH), 3.36 (s, 3 H, OCH_3), 3.39−3.60 (m, 5 H, CH_2OCH_2Ph,

NC*H*C*H*$_2$OCH$_3$), 4.48 (d, J = 12.4 Hz, 1 H, OC*H*HPh), 4.53 (d, J = 12.4 Hz, 1 H, OCH*H*Ph), 6.54 (d, J = 6.7 Hz, 1 H, N=C*H*), 7.26−7.33 (m, 5 H, C*H*$_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5 (CH_2CH_3), 22.1 (NCH_2CH_2), 23.4 (CH_2CH_3), 26.6 ($NCH_2CH_2CH_2$), 44.4 (N=CHCH), 50.2 (NCH_2), 59.2 (OCH_3), 63.4 (NCH), 72.4 (CH_2OCH_2Ph), 72.9 (OCH_2Ph), 74.7 (CH_2OCH_3), 127.4, 127.6, 128.3 (Ar *C*), 138.7 (Ar C_q), 139.8 (N=*C*H) ppm. MS (EI, 70 eV): *m*/*z* (%) = 304 (6) [M^+], 259 (100), 183 (3), 91 (34), 70 (13). $C_{18}H_{28}N_2O_2$ (304.43): calcd. C 71.02, H 9.27, N 9.20; found C 70.99, H 9.43, N 9.68.

(2*R*,2*S*)-(−)-[2-(Benzyloxymethyl)hexylidene][2-(methoxymethyl)-pyrrolidin-1-yl]amine [(*R*,*S*)-2c]: Hydrazone (*S*)-**1c** (2.11 g, 9.9 mmol) was alkylated according to GP 1. Purification by flash column chromatography (pentane/Et_2O, 8:1 to 6:1, 1% Et_3N) gave (*R*,*S*)-**2c** as a colourless oil (2.61 g, 79%). $[\alpha]_D^{25}$ = −81.7 (c = 1.1, $CHCl_3$). R_t = 14.19 min (CP-Sil-8, 120−10−300). R_f = 0.48 (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3062 (m), 3028 (m), 2927 (s), 2860 (s), 1956 (w), 1873 (w), 1809 (w), 1728 (w), 1601 (m), 1456 (s), 1361 (m), 1304 (w), 1199 (m), 1108 (s), 1026 (w), 972 (w), 902 (m), 739 (m), 699 (m), 612 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.31 (m, 4 H, $CH_2CH_2CH_3$), 1.44 [m, 1 H, CH*H*$(CH_2)_2CH_3$], 1.55 [m, 1 H, CH*H*$(CH_2)_2CH_3$], 1.76−1.98 (m, 4 H, $NCH_2CH_2CH_2$), 2.54 (m, 1 H, N=CHC*H*), 2.72 (q, J = 8.2 Hz, 1 H, NC*H*H), 3.32 (m, 1 H, NCH*H*), 3.36 (s, 3 H, OCH_3), 3.50 (m, 5 H, CH_2OCH_2Ph, NC*H*C*H*$_2$OCH$_3$), 4.48 (d, J = 12.2 Hz, 1 H, OC*H*HPh), 4.52 (d, J = 12.2 Hz, 1 H, OCH*H*Ph), 6.53 (d, J = 6.6 Hz, 1 H, N=C*H*), 7.26−7.33 (m, 5 H, C*H*$_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 22.1 (NCH_2CH_2), 22.8 (CH_2CH_3), 26.5 ($NCH_2CH_2CH_2$), 29.1 ($CH_2CH_2CH_3$), 30.1 ($CH_2CH_2CH_2CH_3$), 42.9 (N=CHCH), 50.1 (NCH_2), 59.1 (OCH_3), 63.3 (NCH), 72.7 (CH_2OCH_2Ph), 72.8 (OCH_2Ph), 74.6 (CH_2OCH_3), 127.2, 127.4, 128.1 (Ar *C*H), 138.5 (Ar C_q), 139.9 (*C*H=N) ppm. MS (EI, 70 eV): *m*/*z* (%) = 332 (6) [M^+], 287 (100), 211 (3), 91 (24), 70 (15). $C_{20}H_{32}N_2O_2$ (332.48): calcd. C 72.25, H 9.70, N 8.43; found C 72.74, H 9.68, N 8.82.

(2*R*,2*S*)-(−)-[3-Benzyloxy-2-phenylpropylidene][2-(methoxymethyl)-pyrrolidin-1-yl]amine [(*R*,*S*)-2d]: Hydrazone (*S*)-**1d** was alkylated with a slight variation of GP 1. SAMP-hydrazone (3.48 g, 15.0 mmol) was added dropwise to a solution of LDA (1.1 equiv.) in dry THF (30 mL) at 0 °C. After stirring for 3 h at this temperature the mixture was cooled to −90 °C and a solution of benzyloxymethyl chloride (2.82 g, 18.0 mmol) dissolved in dry THF (6.0 mL) was slowly added. After 45 min at this temperature the solution was warmed to room temperature over 16 h. Purification by flash column chromatography (pentane/Et_2O, 10:1 to 4:1) gave (*R*,*S*)-**2d** as a colourless oil (4.30 g, 81%). $[\alpha]_D^{24}$ = −93.8 (c = 0.9, $CHCl_3$). R_t = 18.86 min (CP-Sil-8, 100−10−300). R_f = 0.76 (pentane/Et_2O, 1:1). IR (film): $\tilde{\nu}$ = 3060 (m), 3028 (m), 2874 (s), 1951 (w), 1877 (w), 1811 (w), 1745 (w), 1601 (m), 1494 (m), 1454 (s), 1359 (m), 1305 (m), 1199 (m), 1107 (s), 1027 (m), 971 (m), 902 (m), 742 (s), 700 (s), 608 (w), 569 (w), 540 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74−1.97 (m, 4 H, $NCH_2CH_2CH_2$), 2.76 (q, J = 8.2 Hz, 1 H, NC*H*H), 3.28 (m, 1 H, NCH*H*), 3.33 (s, 3 H, OCH_3), 3.34−3.49 (m, 2 H, NC*H*C*H*HOCH$_3$), 3.56 (dd, J = 3.6, 9.1 Hz, 1 H, NCHCH*H*OCH$_3$), 3.75 (dd, J = 6.6, 9.2 Hz, 1 H, C*H*HOCH$_2$), 3.85 (m, 1 H, N=CHC*H*), 3.92 (dd, J = 6.8, 9.2 Hz, 1 H, CH*H*OCH$_2$), 4.50 (s, 2 H, OCH_2Ph), 6.54 (d, J = 5.8 Hz, 1 H, N=C*H*), 7.19−7.33 (m, 10 H, C*H*$_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (NCH_2CH_2), 26.6 ($NCH_2CH_2CH_2$), 49.1 (N=CHCH), 49.8 (NCH_2), 59.2 (OCH_3), 63.2 (NCH), 72.8 (CH_2OCH_2Ph), 72.8 (OCH_2Ph), 74.7 (CH_2OCH_3), 126.6, 127.4, 127.5, 128.2, 128.3, 128.4 (Ar *C*), 136.9 (N=*C*H), 138.5, 140.9 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 352 (9) [M^+], 307 (100), 231 (17), 114 (5), 91 (52), 70 (11). $C_{22}H_{28}N_2O_2$ (352.47): calcd. C 74.97, H 8.01, N 7.95; found C 74.83, H 8.35, N 8.44.

(2*S*)-(−)-[3-(Benzyloxy)propylidene][2-(methoxymethyl)pyrrolidin-1-yl]amine [(*S*)-2e]:[32] SAMP (6.11 g, 46.9 mmol) was added dropwise to benzyloxypropanal (**7**) (7.69 g, 46.9 mmol) at 0 °C. The reaction mixture was warmed to room temperature over 16 h, diluted with diethyl ether (100 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and hydrazone (*S*)-**2e** (10.44 g, 81%) was obtained as a colourless oil after flash column chromatography (pentane/EtO_2, 4:1, 2% Et_3N). $[\alpha]_D^{25}$ = −94.7 (c = 1.0, $CHCl_3$). R_t = 18.86 min (CP-Sil-8, 100−10−300). R_f = 0.40 (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3087 (m), 3029 (m), 2954 (s), 2874 (s), 1603 (w), 1496 (w), 1454 (m), 1363(m), 1341(m), 1303(m), 1282 (m), 1198 (s), 1100 (s), 1029 (m), 972 (m), 909 (m), 874 (m), 735 (s), 699 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74−1.98 (m, 4 H, $NCH_2CH_2CH_2$), 2.54 (dt, J = 5.5, 6.6 Hz, 2 H, N=CHC*H*$_2$), 2.72 (m, 1 H, NCH*H*), 3.31−3.35 (m, 1 H, NC*H*), 3.36 (s, 3 H, OCH_3), 3.40−3.45 (m, 2 H, $NCHCH_2$), 3.55 (m, 1 H, NC*H*H), 3.62 (t, J = 6.6 Hz, 2 H, OCH_2CH_2), 4.51 (s, 2 H, OCH_2Ph), 6.65 (t, J = 5.5 Hz, 1 H, *H*C=N), 7.24−7.34 (m, 5 H, Ph-C*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.13 (NCH_2CH_2), 26.54 ($NCH_2CH_2CH_2$), 33.54 (N=CHCH$_2$), 50.05 (NCH_2), 59.08 (NC*H*), 63.23 (OCH_3), 68.57 (CH_2OCH_2Ph), 72.75 (OCH_2Ph), 74.67 (CH_2OCH_3), 127.32, 127.45, 128.12 (Ar *C*H), 134.74 (Ar C_q), 138.21 (N=*C*H) ppm. MS (EI, 70 eV): *m*/*z* (%) = 276 (9) [M^+], 231 (100), 91 (19), 70 (6). $C_{16}H_{24}N_2O_2$ (276.38): calcd. C 69.53, H 8.75, N 10.14; found C 69.44, H 8.44, N 10.28.

General Procedure for the 1,2-Addition of Organocerium Reagents to SAMP-Hydrazones 2 (GP 2): $CeCl_3 \cdot 7\,H_2O$ (4.0 equiv.) was dehydrated for 2 h at 140 °C under reduced pressure (0.1 Torr) in a Schlenk flask equipped with a magnetic stirrer. It was then suspended in dry THF (15 mL/mmol) by sonification for 15 min and additional stirring for 12 h. The suspension was cooled to −78 °C and the organolithium reagent (4.0 equiv.) was added. The mixture was stirred for 2 h at this temperature, giving a yellow or orange coloured suspension. After the mixture had been cooled to −100 °C it was transferred through a double ended needle into a solution of the hydrazone (1.0 equiv.) in dry THF (15 mL/mmol), that was also cooled to −100 °C. The reaction mixture was warmed to −78 °C over approximately 2 h and then quenched with H_2O. After a saturated aqueous solution of $NaHCO_3$ had been added the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The crude hydrazine was purified by flash column chromatography.

(1*R*,1′*R*,2*S*)-(−)-[1-(2′-Benzyloxy-1′-methylethyl)pentyl][2-(methoxymethyl)pyrrolidin-1-yl]amine [(*R*,*R*,*S*)-3a]: According to GP 2 $CeCl_3$/*n*BuLi (4.0 equiv.) was reacted with hydrazone (*R*,*S*)-**2a** (1.74 g, 6.0 mmol). Compound (*R*,*R*,*S*)-**3a** (1.89 g, 90%) was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 4:1, 1% Et_3N). $[\alpha]_D^{27}$ = −59.0 (c = 1.0, $CHCl_3$). R_t = 15.88 min (CP-Sil-8, 100−10−300). R_f = 0.29 (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3063 (w), 3029 (m), 2957 (s), 2871 (s), 1948 (w), 1807 (w), 1605 (w), 1457 (m), 1368 (m), 1199 (m), 1100 (s), 917 (m), 738 (m), 699 (m), 610 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.6 Hz, 3 H, CH_2CH_3), 0.93 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 1.23−1.44 [m, 6 H, $(CH_2)_3CH_3$], 1.52−2.16 (m, 5 H, $NCH_2CH_2CH_2$, NCHC*H*), 2.18 (q, J = 8.5 Hz, 1 H, NC*H*H), 2.56 (m, 2 H, NC*H*CH$_2$O, N*H*), 2.78 (m, 1 H, NC*H*CH), 3.34 (s, 3 H, OCH_3), 3.29−3.60 (m, 5 H, NCH*H*, CH_2OCH_3, CH_2OCH_2Ph), 4.47 (d, J = 12.1 Hz, 1 H, OC*H*HPh), 4.52 (d, J = 12.1 Hz, 1 H, OCH*H*Ph), 7.24−7.33 (m, 5 H, C*H*$_{arom.}$)

ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 14.2 (CH_3), 21.0 (CH_2CH_3), 23.3 (NCH_2CH_2), 26.4 ($NCH_2CH_2CH_2$), 28.0 ($CH_2CH_2CH_3$), 29.5 ($CH_2CH_2CH_2CH_3$), 34.6 (NCHCH), 57.4 (NCH_2), 59.0 (OCH_3), 61.3 (NCHCH), 66.3 ($NCHCH_2O$), 73.0 (CH_2OCH_2Ph), 74.2 (CH_2Ph), 75.4 (CH_2OCH_3), 127.5, 127.6, 128.3 (Ar CH), 138.7 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 348 (40) [M^+], 303 (100), 291 (11), 199 (37), 129 (17), 114 (8), 91 (34), 70 (18). $C_{21}H_{36}N_2O_2$ (348.52): calcd. C 72.37, H 10.41, N 8.04; found C 72.29, H 10.51, N 8.41.

(1*R*,1′*R*,2*S*)-(−)-{1-[(1′-Benzyloxymethyl)propyl]pentyl}[2-(methoxymethyl)pyrrolidin-1-yl]amine [(*R*,*R*,*S*)-3b]: According to GP 2 $CeCl_3$/*n*BuLi (4.0 equiv.) was reacted with hydrazone (*R*,*S*)-**2b** (0.63 g, 2.1 mmol). Compound (*R*,*R*,*S*)-**3b** (0.69 g, 93%) was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 4:1). $[\alpha]_D^{23}$ = −65.1 (*c* = 2.0, $CHCl_3$). R_t = 16.18 min (CP-Sil-8, 100−10−300). R_f = 0.36 (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3087 (w), 3063 (w), 3030 (m), 2958 (s), 2929 (s), 2872 (s), 1954 (w), 1878 (w), 1807 (w), 1726 (w), 1623 (m), 1496 (m), 1455 (s), 1250 (s), 1098 (s), 914 (m), 734 (s), 698 (m), 646 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.6 Hz, 3 H, CH_2CH_3), 0.93 (t, *J* = 6.5 Hz, 3 H, CH_2CH_3), 1.12−1.45 [m, 8 H, $(CH_2)_3CH_3$, $CHCH_2CH_3$), 1.52−1.96 (m, 5 H, $NCH_2CH_2CH_2$, NCHCH), 2.14 (q, *J* = 8.7 Hz, 1 H, NCHH), 2.46 (m, 2 H, $NCHCH_2O$, NH), 2.86 (m, 1 H, NCHCH), 3.33 (s, 3 H, OCH_3), 3.29−3.58 (m, 5 H, NCHH, CH_2OCH_3, CH_2OCH_2Ph), 4.46 (d, *J* = 12.2 Hz, 1 H, OCHHPh), 4.51 (d, *J* = 12.2 Hz, 1 H, OCHHPh), 7.24−7.33 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6, 14.4 (CH_2CH_3), 21.1, 21.2 (CH_2CH_3), 23.4 (NCH_2CH_2), 26.6 ($NCH_2CH_2CH_2$), 28.5 ($CH_2CH_2CH_3$), 30.5 ($CH_2CH_2CH_2CH3$), 41.7 (NCHCH), 57.4 (NCH_2), 59.2 (OCH_3), 60.0 (NCHCH), 66.3 ($NCHCH_2O$), 71.6 (CH_2OCH_2Ph), 73.2 (CH_2Ph), 75.5 (CH_2OCH_3), 127.6, 127.7, 128.5 (Ar CH), 139.0 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 362 (36) [M^+], 317 (100), 305 (12), 199 (63), 129 (20), 114 (9), 91 (38), 70 (19). $C_{22}H_{38}N_2O_2$ (362.55): calcd. C 72.88, H 10.56, N 7.73; found C 72.47, H 10.78, N 7.93.

(1*R*,1′*R*,2*S*)-(−)-{1-[1′-(Benzyloxymethyl)pentyl]heptyl}[2-(methoxymethyl)pyrrolidin-1-yl]amine [(*R*,*R*,*S*)-3c]: According to GP 2 $CeCl_3$/*n*-hexyllithium (4.0 equiv.) was reacted with hydrazone (*R*,*S*)-**2c** (1.00 g, 3.0 mmol). Compound (*R*,*R*,*S*)-**3c** (0.92 g, 73%) was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 6:1). $[\alpha]_D^{24}$ = −48.9 (*c* = 1.3, $CHCl_3$). R_t = 16.65 min (CP-Sil-8, 120−10−300). R_f = 0.44 (pentane/Et_2O, 4:1). IR (film): $\tilde{\nu}$ = 3062 (w), 3029 (m), 2926 (s), 2858 (s), 1946 (w), 1871 (w), 1807 (w), 1725 (w), 1604 (w), 1458 (s), 1363 (m), 1251(w), 1199 (m), 1101 (s), 1028 (w), 918 (w), 735 (m), 698 (m), 609 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 0.90 (t, *J* = 6.5 Hz, 3 H, CH_2CH_3), 1.29 [m, 16 H, $(CH_2)_5CH_3$, $CH(CH_2)_3CH_3$], 1.52−1.89 (m, 5 H, $NCH_2CH_2CH_2$, NCHCH), 2.14 (q, *J* = 8.6 Hz, 1 H, NCHH), 2.46 (m, 2 H, $NCHCH_2O$, NH), 2.86 (m, 1 H, NCHCH), 3.33 (s, 3 H, OCH_3), 3.29−3.58 (m, 5 H, NCHH, CH_2OCH_3, CH_2OCH_2Ph), 4.44 (d, *J* = 12.2 Hz, 1 H, OCHHPh), 4.50 (d, *J* = 12.2 Hz, 1 H, OCHHPh), 7.24−7.33 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 2 × 14.3 (2 × CH_2CH_3), 21.20 (CH_2), 22.9 (NCH_2CH_2), 23.3, 26.3, 26.7, 28.0, 30.0, 30.4, 30.8, 32.2 (CH_2), 40.0 (NCHCH), 57.5 (NCH_2), 59.2 (OCH_3), 60.2 (NCHCH), 66.3 ($NCHCH_2O$), 71.8 (CH_2OCH_2Ph), 73.1 (CH_2Ph), 75.5 (CH_2OCH_3), 127.6, 127.7, 128.5 (Ar CH), 139.0 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 418 (50) [M^+], 373 (100), 333 (15), 227 (88), 211 (7), 129 (17), 91 (28), 85 (7), 70 (13). $C_{26}H_{46}N_2O_2$ (418.66): calcd. C 74.59, H 11.07, N 6.69; found C 74.26, H 10.92, N 7.12.

(1*S*,2*R*,2′*S*)-(−)-[2-(Benzyloxymethyl)-1-(*tert*-butyl)hexyl][2′-methoxymethyl)pyrrolidin-1′-yl]amine [(*S*,*R*,*S*)-3d]: A suspension of $CeCl_3$/*t*BuLi (4.0 equiv.) in dry THF was prepared as described in GP 2 and then cooled to −100 °C. A solution of hydrazone (*R*,*S*)-**2c** (0.85 g, 2.5 mmol) in dry THF (5 mL) was slowly added to this orange coloured mixture. The solution was warmed to room temperature over 16 h and worked up as described in GP 2. Compound (*S*,*R*,*S*)-**3d** (0.89 g, 91%) was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 7:1). $[\alpha]_D^{24}$ = −66.0 (*c* = 1.0, $CHCl_3$). R_t = 14.85 min (CP-Sil-8, 120−10−300). R_f = 0.39 (pentane/Et_2O, 4:1). IR (film): $\tilde{\nu}$ = 3064 (w), 3030 (m), 2954 (s), 2868 (s), 1945 (w), 1806 (w), 1728 (w), 1604 (w), 1458 (m), 1391 (m), 1363 (m), 1250 (w), 1200 (m), 1100 (s), 1027 (w), 919 (w), 737 (m), 698 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 0.92 [s, 9 H, $C(CH_3)_3$], 1.25−1.91 (m, 11 H, $CHCH_2CH_2CH_2$, $NCH_2CH_2CH_2$), 2.17 (q, *J* = 8.4 Hz, 1 H, NCHH), 2.46 (m, 3 H, $NCHCH_2O$, NHCHCH), 3.33 (s, 3 H, OCH_3), 3.15−3.67 (m, 5 H, NCHH, CH_2OCH_3, CH_2OCH_2Ph), 4.44 (s, 2 H, OCH_2Ph), 7.24−7.33 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 20.9 (CH_2CH_3), 23.0 (NCH_2CH_2), 26.7 ($NCH_2CH_2CH_2$), 27.9 [$C(CH_3)_3$], 30.3, 33.1 ($CH_2CH_2CH_2CH_3$), 35.5 [$C(CH_3)_3$], 39.0 (NCHCH), 56.5 (NCH_2), 58.8 (OCH_3), 66.1 ($NCHCH_2O$), 67.5 (NCHCH), 72.0 (CH_2OCH_2Ph), 72.3 (CH_2Ph), 75.3 (CH_2OCH_3), 127.1, 127.3, 128.0 (Ar CH), 138.6 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 390 (7) [M^+], 333 (100), 199 (9), 114 (8), 91 (19), 70 (8). $C_{24}H_{42}N_2O_2$ (390.60): calcd. C 73.80, H 10.84, N 7.17; found C 73.45, H 10.92, N 7.57.

(1*R*,1′*R*,2*S*)-(−)-[1-(2′-Benzyloxy-1′-phenylethyl)heptyl][2-(methoxymethyl)pyrrolidin-1-yl]amine [(*R*,*R*,*S*)-3e]: According to GP 2 $CeCl_3$/*n*-hexyllithium (4.0 equiv.) was reacted with hydrazone (*R*,*S*)-**2d** (1.41 g, 4.0 mmol). Compound (*R*,*R*,*S*)-**3e** (1.50 g, 93%) was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 6:1, Et_3N 0.5%). $[\alpha]_D^{27}$ = −60.1 (*c* = 1.0, $CHCl_3$). R_t = 16.99 min (CP-Sil-8, 140−10−300). R_f = 0.38 (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3062 (m), 3028 (m), 2926 (s), 2857 (s), 1948 (w), 1874 (w), 1808 (w), 1722 (w), 1602 (w), 1495 (m), 1455 (m), 1364 (m), 1198 (w), 1101 (s), 1028 (w), 917 (m), 754 (s), 701 (s), 606 (w), 549 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.12−1.30 [m, 8 H, $(CH_2)_4CH_3$], 1.31−1.91 (m, 6 H, $NCH_2CH_2CH_2$, $CH_2(CH_2)_4CH_3$], 1.95 (q, *J* = 8.5 Hz, 1 H, NCHH), 2.56 (m, 1 H, $NCHCH_2O$), 2.85 (s, 1 H, NH), 3.11 (m, 2 H, NCHCH), 3.32 (s, 3 H, OCH_3), 3.30 (m, 2 H, NCHH, $CHHOCH_3$), 3.55 (dd, *J* = 9.1, 3.9 Hz, 1 H, $CHHOCH_3$), 3.76 (m, 2 H, CH_2OCH_2Ph), 4.49 (s, 2 H, OCH_2Ph), 7.17−7.34 (m, 10 H, $CH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 21.0, 22.6, 24.5, 26.4, 29.6, 31.0 ($NCH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_3$), 33.8 ($CH_2(CH_2)_4CH_3$], 46.8 (NCHCH), 56.3 (NCH_2), 58.9 (OCH_3), 61.7 (NCHCH), 65.8 ($NCHCH_2O$), 72.2 (CH_2OCH_2Ph), 73.0 (CH_2Ph), 75.0 (CH_2OCH_3), 126.2, 127.3, 127.4, 128.0, 128.1, 128.3 (Ar CH), 138.0, 141.2 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 438 (3) [M^+], 227 (100), 114 (8), 91 (12), 70 (10). HRMS calcd. for $C_{28}H_{42}N_2O_2$: 438.3246; found 438.3248.

(1*R*,2*S*)-(−)-[1-(2-Benzyloxyethyl)heptyl][2-(methoxymethyl)-pyrrolidin-1-yl]amine [(*R*,*S*)-3f]: A suspension of $CeCl_3$/*n*-hexyllithium (4.0 equiv.) in dry THF was prepared as described in GP 2 and then cooled to −100 °C. A solution of hydrazone (*S*)-**2e** (0.83 g, 3.0 mmol) in dry THF (45 mL) was slowly added to this yellow coloured mixture. The solution was warmed to room temperature over 16 h and worked up as described in GP 2. Compound (*R*,*S*)-**3f** (0.82 g, 76%) was obtained as a colourless oil after purifi-

cation by flash column chromatography (pentane/Et_2O, 2:1). $[\alpha]_D^{25} = -77.3$ ($c = 1.1$, $CHCl_3$). $R_t = 17.19$ min (CP-Sil-8, 100−10−300). $R_f = 0.11$ (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3087 (w), 3062 (w), 3030 (m), 2926 (s), 2856 (s), 1946 (w), 1873 (w), 1807 (w), 1604 (w), 1494 (m), 1457 (s), 1363 (m), 1306 (w), 1198 (m),1102 (s), 1027 (w), 919 (m), 859 (w), 812 (w), 738 (m), 698 (m), 610 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, 3 H, $J = 6.9$ Hz, CH_2CH_3), 1.20−1.38 [m, 9 H, $CH(CH_2)_4CH_3$], 1.45−1.77 [m, 6 H, $CH_3(CH_2)_4CH$, $NCHCH_2CH_2O$, NCH_2CH_2CHH], 1.88 (m, 1 H, NCH_2CH_2CHH), 2.12 (q, $J = 8.6$ Hz, 1 H, NC*H*H), 2.55 (m, 2 H, N*H*, $NCHCH_2O$), 2.84 (m, 1 H, $NCHCH_2CH_2O$), 3.30−3.42 (m, 2 H, NCH*H*, $NCHCHHO$), 3.35 (s, 3 H, OCH_3) 3.44−3.63 (m, 3 H, CH_2OCH_2Ph, $NCHCHHO$), 4.50 (s, 2 H, OCH_2Ph), 7.26−7.37 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 21.0, 22.7, 25.3, 26.2 ($CH_3CH_2CH_2$, $NCH_2CH_2CH_2$), 29.8, 32.0, 32.7 ($NCHCH_2CH_2CH_2$), 33.9 ($NCHCH_2CH_2O$), 57.2 ($NCHCH_2CH_2O$), 57.3 (NCH_2), 59.0 (OCH_3), 65.9 ($NCHCH_2O$), 68.9 (CH_2OCH_2Ph), 73.0 (OCH_2Ph), 75.1 (CH_2OCH_3), 127.5, 127.7, 128.3 (Ar *C*H), 138.5 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 362 (22) [M^+], 318 (23), 317 (100), 227 (6), 129 (13), 91 (23), 85 (5), 70 (8). $C_{22}H_{38}N_2O_2$ (362.56): calcd. C 72.88, H 10.56, N 7.73; found C 72.96, H 10.46, N 8.15.

General Procedure for the Preparation of *O*-Benzyl-Protected 3-Amino-1-alkanols 4 by N−N-Cleavage of the Hydrazines 3 (GP 3): Hydrazines **3** were dissolved in dry THF (1.5 mL/mmol) in a Schlenk flask under an argon. After a 1 M solution of BH_3·THF in THF (10 equiv.) had been added, the mixture was heated to reflux until complete conversion of the starting material was indicated by TLC (4−6 h). The solution was then cooled to −5 °C and a 1 M aqueous HCl solution (10 mL/mmol hydrazine) was added. After heating to reflux for 2 min the solvent was removed under reduced pressure and the aqueous residue was neutralized with a saturated $NaHCO_3$ solution. Extraction with CH_2Cl_2 followed by drying of the combined organic phases over Na_2SO_4 and subsequent removal of the solvent in vacuo yielded the crude amines **4**, which were purified by flash column chromatography.

(2*R*,3*R*)-(+)-2-(Benzyloxymethyl)heptan-3-amine [(*R*,*R*)-4a]: Prepared by N−N cleavage of the corresponding hydrazine (*R*,*R*,*S*)-**3a** (1.60 g, 4.6 mmol) with BH_3·THF as described in GP 3. Compound (*R*,*R*)-**4a** was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 1:1, 2% Et_3N). Yield: 1.00 g (92%). $[\alpha]_D^{24} = +8.0$ ($c = 1.0$, $CHCl_3$). $R_t = 10.41$ min (CP-Sil-8, 100−10−300). $R_f = 0.43$ (MeOH/CH_2Cl_2, 2:1). IR (film): $\tilde{\nu}$ = 3380 (w), 3062 (m), 3029 (m), 2929 (s), 2860 (s), 1948 (w), 1871 (w), 1808 (w), 1607 (m), 1525 (w), 1495 (m), 1456 (s,), 1365 (m), 1205 (m), 1100 (s), 1028 (w), 738 (s), 699 (m), 610 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 7.0$ Hz, 3 H, CH_2CH_3), 0.92 (d, $J = 6.9$ Hz, 3 H, $CHCH_3$), 1.12−1.50 [m, 8 H, $(CH_2)_3CH_3$, NH_2), 1.75 (m, 1 H, NCHC*H*), 2.71 (m, 1 H, NC*H*), 3.43 (m, 2 H, CH_2OCH_2Ph), 4.49 (s, 2 H, OCH_2Ph), 7.25−7.34 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.1 (CH_2CH_3, $CHCH_3$), 22.9 (CH_2CH_3), 28.7 ($CH_2CH_2CH_2CH_3$), 34.2 ($NCHCH_2$), 39.4 (NCHCH), 53.7 (NCH), 73.1 (CH_2OCH_2Ph), 73.3 (CH_2OCH_2Ph), 127.4, 127.5, 128.3 (Ar *C*H), 138.7 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 178 (8) [$M^+ - C_4H_9$], 144 (6), 105 (9), 91 (30), 86 (100), 72 (11), 57 (5). $C_{15}H_{25}NO$ (235.37): calcd. C 76.55, H 10.71, N 5.95; found C 76.49, H 10.33, N 6.34.

(3*R*,4*R*)-(+)-3-(Benzyloxymethyl)octan-4-amine [(*R*,*R*)-4b]: Prepared by N−N cleavage of the corresponding hydrazine (*R*,*R*,*S*)-**3b** (0.42 g, 1.7 mmol) with BH_3·THF as described in GP 3. Compound (*R*,*R*)-**4b** was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 1:1, 2% Et_3N). Yield: 0.35 g (83%). $[\alpha]_D^{24} = +8.3$ ($c = 1.6$, $CHCl_3$). $R_t = 10.92$ min (CP-Sil-8, 100−10−300). $R_f = 0.46$ (MeOH/CH_2Cl_2, 2:1). IR (film): $\tilde{\nu}$ = 3381 (w), 3064 (m), 3030 (m), 2958 (s), 2929 (s), 2871 (s), 1948 (w), 1872 (w), 1808 (w), 1606 (m), 1495 (m), 1456 (s,), 1363 (m), 1204 (m), 1100 (s), 908 (w), 819 (w), 736 (m), 699 (m), 606 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 [t, J = 7.1 Hz, 3 H, (CH_2CH_3), 0.92 (t, $J = 7.4$ Hz, 3 H, CH_2CH_3), 1.24−1.50 [m, 9 H, $(CH_2)_3CH_3$, $CHCH_2CH_3$), 2.84 (m, 1 H, NC*H*), 3.51 (d, $J = 4.7$ Hz, 2 H, CH_2OCH_2Ph), 4.47 (d, J = 12.1 Hz, 1 H, OC*H*HPh), 4.49 (d, $J = 12.1$ Hz, 1 H, OCH*H*Ph), 7.25−7.34 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (CH_3), 14.1 (CH_3), 21.6, 22.8, 29.0, 35.0 ($CH_2CH_2CH_2CH_3$, $CHCH_2CH_3$), 45.6 (NCHCH), 52.3 (NCH), 70.2 (CH_2OCH_2Ph), 73.1 (CH_2OCH_2Ph), 127.3, 127.4, 128.1 (Ar *C*H), 138.4 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 192 (7) [$M^+ - C_4H_9$], 184 (5), 114 (17), 112 (12), 91 (36), 86 (100), 60 (10). $C_{16}H_{27}NO$ (249.39): calcd. C 77.06, H 10.91, N 5.62; found C 76.68, H 10.88, N 6.00.

(5*R*,6*R*)-(+)-5-(Benzyloxymethyl)dodecan-6-amine [(*R*,*R*)-4c]: Prepared by N−N cleavage of the corresponding hydrazine (*R*,*R*,*S*)-**3c** (0.92 g, 2.2 mmol) with BH_3·THF as described in GP 3. Compound (*R*,*R*)-**4c** was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 1:1, 3% Et_3N). Yield: 0.52 g (78%). $[\alpha]_D^{24} = +14.5$ ($c = 1.0$, $CHCl_3$). R_t = 14.68 min (CP-Sil-8, 100−10−300). $R_f = 0.46$ (MeOH/CH_2Cl_2, 1:10). IR (film): $\tilde{\nu}$ = 3389 (w), 3062 (m), 3030 (m), 2926 (s), 2857 (s), 1947 (w), 1875 (w), 1806 (w), 1607 (w), 1495 (w), 1457 (m), 1363 (m), 1205 (w), 1100 (m), 1027 (w), 736 (m), 698 (m), 608 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.9$ Hz, 3 H, CH_3), 0.90 (t, $J = 6.9$ Hz, 3 H, CH_3), 1.17−1.46 [m, 16 H, $(CH_2)_5CH_3$, $CH(CH_2)_3CH_3$], 1.53 (m, 1 H, NCHC*H*), 2.80 (m, 1 H, NC*H*), 3.47 (dd, $J = 5.4$, 9.3 Hz, 1 H, C*H*HOCH$_2$Ph), 3.50 (dd, $J = 4.9$, 9.3 Hz, 1 H, CH*H*OCH$_2$Ph), 4.45 (d, $J = 12.1$ Hz, 1 H, OC*H*HPh), 4.49 (d, $J = 12.1$ Hz, 1 H, OCH*H*Ph), 7.25−7.34 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 2 \times 14.1$ ($2 \times CH_3$), 22.6, 23.0, 26.8, 28.5, 29.5, 29.9, 31.9 (CH_2), 35.4 ($NCHCH_2$), 44.0 (NCHCH), 52.6 (NCH), 70.5 (CH_2OCH_2Ph), 73.0 (CH_2OCH_2Ph), 127.2, 127.3, 128.1 (Ar *C*H), 138.5 (Ar C_q) ppm. MS (CI, 100 eV): *m*/*z* (%) = 306 (75) [MH^+], 290 (7), 228 (5), 220 (20), 114 (100), 91 (17). $C_{20}H_{35}NO$ (305.50): calcd. C 78.63, H 11.55, N 4.58; found C 78.36, H 11.35, N 5.01.

(3*S*,4*R*)-(−)-4-(Benzyloxymethyl)-2,2-dimethyloctan-3-amine [(*S*,*S*)-4d]: Prepared by N−N cleavage of the corresponding hydrazine (*S*,*R*,*S*)-**3d** (0.55 g, 1.4 mmol) with BH_3·THF as described in GP 3. Compound (*S*,*R*)-**4d** was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 3:1, 1.5% Et_3N). Yield: 0.25 g (64%). $[\alpha]_D^{24} = -10.0$ ($c = 1.0$, $CHCl_3$). R_t = 12.01 min (CP-Sil-8, 100−10−300). $R_f = 0.46$ (MeOH/CH_2Cl_2, 1:10). IR (film): $\tilde{\nu}$ = 3398 (w), 3334 (w), 3064 (m), 3031 (m), 2955 (s), 2863 (s), 1948 (w), 1871 (w), 1806 (w), 1608 (m), 1460 (m), 1393 (m), 1363 (m), 1206 (w), 1098 (s), 1027 (w), 924 (w), 823 (w), 736 (s), 698 (m), 608 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ [t, $J = 7.0$ Hz, 3 H, (CH_2CH_3), 0.90 [s, 9 H, $C(CH_3)_3$], 1.23−1.38 (m, 5 H, $CHHCH_2CH_2CH_3$), 1.62 (m, 1 H, $CHHCH_2CH_2CH_3$), 1.80 (m, 1 H, NCHC*H*), 2.44 (d, $J = 2.2$ Hz, 1 H, NC*H*), 3.41 (dd, $J = 5.9$, 9.2 Hz, 1 H, C*H*HOCH$_2$Ph), 3.59 (dd, $J = 4.3$, 9.2 Hz, 1 H, CH*H*OCH$_2$Ph), 4.44 (d, $J = 12.0$ Hz, 1 H, OC*H*HPh), 4.48 (d, $J = 12.0$ Hz, 1 H, OCH*H*Ph), 7.24−7.34 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_2CH_3), 23.4 (CH_2CH_3), 27.1 [$C(CH_3)_3$], 30.0 ($CH_2CH_2CH_3$), 33.2 ($CH_2CH_2CH_2CH_3$), 35.6 [$C(CH_3)_3$], 39.1 (NCHCH), 62.6 (NCH),

71.5 (CH_2OCH_2Ph), 73.3 (OCH_2Ph), 127.4, 127.5, 128.3 (Ar *C*H), 138.7 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 278 (4) [MH^+], 262 (4), 220 (100), 114 (86), 91 (97), 86 (72). $C_{18}H_{31}NO$ (277.44): calcd. C 77.92, H 11.26, N 5.05; found C 77.54, H 11.41, N 5.47.

(2*R*,3*R*)-(+)-1-Benzyloxy-2-phenylnonan-3-amine [(*R*,*R*)-4e]: Prepared by N−N cleavage of the corresponding hydrazine (*R*,*R*,*S*)-**3e** (1.24 g, 2.8 mmol) with BH_3·THF as described in GP 3. Compound (*R*,*R*)-**4e** was obtained as a colourless oil after purification by flash column chromatography (pentane/Et_2O, 1:1, 3% Et_3N). Yield: 0.81 g (88%). $[\alpha]_D^{30}$ +28.6 (*c* = 1.0, $CHCl_3$). R_t = 13.22 min (CP-Sil-8, 140−10−300). R_f = 0.44 (MeOH/CH_2Cl_2, 1:10). IR (film): $\tilde{\nu}$ = 3382 (w), 3061 (m), 3028 (m), 2926 (s), 2856 (s), 1950 (w), 1875 (w), 1808 (w), 1601 (m), 1494 (m), 1455 (s,), 1363 (m), 1205 (w), 1103 (s), 1028 (m), 909 (w), 826 (w), 738 (s), 701 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.08−1.42 [m, 10 H, $(CH_2)_5CH_3$], 2.79 (dt, *J* = 5.7, 7.3 Hz, 1 H, NCHC*H*), 3.08 (m, 1 H, NC*H*), 3.82 (d, *J* = 5.7 Hz, 2 H, CH_2OCH_2Ph), 4.46 (d, *J* = 12.1 Hz, 1 H, OC*H*HPh), 4.51 (d, *J* = 12.1 Hz, 1 H, OCH*H*Ph), 7.18−7.34 (m, 10 H, $CH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2CH_3), 26.1 ($CH_2CH_2CH_3$), 29.3 ($CH_2(CH_2)_2CH_3$], 31.8 ($CH_2(CH_2)_3CH_3$], 35.4 (NCHCH_2), 52.5 (NCH*C*H), 54.1 (N*C*H), 72.1 (CH_2OCH_2Ph), 73.1 (CH_2OCH_2Ph), 126.4, 127.5, 127.5, 128.3, 128.3, 128.5 (Ar *C*H), 138.4, 142.0 (Ar C_q) ppm. MS (CI, 100 eV): *m*/*z* (%) = 326 (100) [MH^+], 310 (5), 248 (6), 240 (8), 218 (4), 114 (70), 91 (8). $C_{22}H_{31}NO$ (325.49): calcd. C 81.18, H 9.60, N 4.30; found C 80.88, H 9.39, N 4.70.

General Procedure for the Tosylation of the Amines 4 (GP 4): The amines **4** were dissolved in CH_2Cl_2 (10 mL/mmol). K_2CO_3 (10 equiv.) and tosyl chloride (1.5 equiv.) were added. The mixture was heated to reflux for 2 h and stirred for 12 h at ambient temperature. Filtration through a pad of SiO_2 with CH_2Cl_2 and removal of the solvent under reduced pressure gave the crude products, which were further purified by flash column chromatgraphy.

(2*R*,3*R*)-(+)-2-(Benzyloxymethyl)-*N*-tosylheptan-3-amine [(*R*,*R*)-5a]: According to GP 4 amine (*R*,*R*)-**4a** (0.81 g, 3.4 mmol) was treated with tosyl chloride in the presence of K_2CO_3. Tosylamine (*R*,*R*)-**5a** was obtained as a colourless oil after flash column chromatography (pentane/Et_2O, 3:1). Yield: 1.20 g (89%); *de* ≥ 96% (^1H NMR). $[\alpha]_D^{24}$ = +8.9 (*c* = 0.6, $CHCl_3$). R_t = 20.34 min (CP-Sil-8, 100−10−300). R_f = 0.64 (pentane/Et_2O, 1:1). IR (film): $\tilde{\nu}$ = 3285 (s), 3063 (m), 3031 (m), 2957 (s), 2932 (s), 2864 (s), 1918 (w), 1809 (w), 1655 (w), 1599 (m), 1495 (m), 1455 (s), 1425 (m), 1326 (s), 1209 (w), 1160 (s), 1095 (s), 1029 (m), 947 (m), 875 (w), 816 (m), 739 (m), 700 (m), 667 (s), 584 (m), 552 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 6.9 Hz, 3 H, CH_2CH_3), 0.80 (d, *J* = 7.1 Hz, 3 H, $CHCH_3$), 1.01−1.17 (m, 4 H, $CH_2CH_2CH_2CH_3$), 1.37 (m, 2 H, NCHCH_2), 1.88 (m, 1 H, NCHC*H*), 2.39 (s, 3 H, Ar−CH_3), 3.26 (m, 2 H, C*H*HOCH$_2$Ph, NC*H*), 3.42 (dd, *J* = 4.4, 9.6 Hz, 1 H, CH*H*OCH$_2$Ph), 4.39 (d, *J* = 11.8 Hz, 1 H, COC*H*HPh), 4.44 (d, *J* = 11.8 Hz, 1 H, OCH*H*Ph), 5.34 (d, *J* = 8.0 Hz, 1 H, N*H*), 7.21−7.37 (m, 7 H, $CH_{arom.}$), 7.72 (d, *J* = 8.2 Hz, 2 H, $SO_2CCH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 14.3 ($CHCH_3$), 21.7 (Ar−CH_3), 22.6, 27.8, 32.5 ($CH_2CH_2CH_2CH_3$), 36.0 (NCH*C*H), 57.2 (N*C*H), 72.4 (CH_2OCH_2Ph), 73.2 (OCH_2Ph), 127.1, 127.6, 127.6, 128.4, 129.4 (Ar *C*H), 138.1, 138.7, 142.8 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 389 (1) [M^+], 332 (6), 240 (100), 226 (15), 155 (26), 91 (59). $C_{22}H_{31}NO_3S$ (389.55): calcd. C 67.83, H 8.02, N 3.60; found C 67.40, H 8.08, N 4.05.

(3*R*,4*R*)-(+)-3-(Benzyloxymethyl)-*N*-tosyloctan-4-amine [(*R*,*R*)-5b]: According to GP 4 amine (*R*,*R*)-**4b** (0.35 g, 1.4 mmol) was treated with tosyl chloride in the presence of K_2CO_3. Tosylamine (*R*,*R*)-**4b** was obtained as a colourless oil after flash column chromatography (pentane/Et_2O, 4:1). Yield: 0.52 g (92%); *de* = 98% (GC, CP-Sil-8). $[\alpha]_D^{22}$ = +7.8 (*c* = 1.0, $CHCl_3$). R_t = 20.66 [major *anti*-isomer], 20.72 min [minor *syn*-isomer] (CP-Sil-8, 100−10−300). R_f = 0.34 (pentane/Et_2O, 4:1). IR (film): $\tilde{\nu}$ = 3286 (s), 3063 (m), 3031 (m), 2958 (s), 2870 (s), 1953 (w), 1918 (w), 1872 (w), 1810 (w), 1755 (w), 1598 (m), 1496 (m), 1456 (m), 1422 (m), 1326 (s), 1241 (w), 1209 (m), 1160 (s), 1095 (s), 1030 (m), 947 (m), 887 (w), 815 (s), 739 (s), 700 (s), 667 (s), 552 (m), 461 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.78 (t, *J* = 6.9 Hz, 3 H, CH_2CH_3), 1.01−1.32 [m, 6 H, $(CH_2)_2CH_3$, $CHCH_2CH_3$], 1.43 (m, 2 H, NCHCH_2), 1.51 (m, 1 H, NCHC*H*), 2.39 (s, 3 H, Ar − CH_3), 3.35 (m, 2 H, C*H*HOCH$_2$Ph, NC*H*), 3.55 (dd, *J* = 3.3, 9.6 Hz, 1 H, CH*H*OCH$_2$Ph), 4.41 (d, *J* = 12.1 Hz, 1 H, OC*H*HPh), 4.47 (d, *J* = 12.1 Hz, 1 H, OCH*H*Ph), 5.52 (d, *J* = 7.7 Hz, 1 H, N*H*), 7.22−7.38 (m, 7 H, $CH_{arom.}$), 7.70 (d, *J* = 8.0 Hz, 2 H, $SO_2CCH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 13.9 (CH_2CH_3), 21.4 (Ar − CH_3), 21.7, 22.4,28.0 ($CH_2CH_2CH_3$, $CHCH_2CH_3$), 33.5 (NCHCH_2), 42.3 (NCH*C*H), 56.0 (N*C*H), 69.5 (CH_2OCH_2Ph), 73.2 (OCH_2Ph), 126.7, 127.4, 127.6, 128.2, 129.1 (Ar *C*H), 137.7, 138.8, 142.4 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 403 (1) [M^+], 346 (8), 248 (10), 240 (100), 155 (18), 91 (53). $C_{23}H_{33}NO_3S$ (403.58): calcd. C 68.45, H 8.24, N 3.47; found C 68.06, H 8.55, N 3.86.

(5*R*,6*R*)-(+)-5-(Benzyloxymethyl)-*N*-tosyldodecan-6-amine [(*R*,*R*)-5c]: According to GP 4 amine (*R*,*R*)-**4c** (0.37 g, 1.2 mmol) was treated with tosyl chloride in the presence of K_2CO_3. Tosylamine (*R*,*R*)-**5c** was obtained as a colourless solid after flash column chromatography (pentane/Et_2O, 5:1). Yield: 0.55 g (99%); *de* ≥ 98% (GC, CP-Sil-8); m.p. 54 °C. $[\alpha]_D^{24}$ = +5.9 (*c* = 1.0, $CHCl_3$). R_t = 19.84 [major *anti*-isomer], 19.90 min [minor *syn*-isomer] (CP-Sil-8, 140−10−300). R_f = 0.33 (pentane/Et_2O, 4:1). IR (KBr): $\tilde{\nu}$ = 3315 (s), 3033 (w), 2932 (s), 2859 (s), 1952 (w), 1925 (w), 1814 (w), 1598 (m), 1497 (m), 1457 (m), 1428 (m), 1326 (s), 1256 (w), 1209 (w), 1158 (s), 1082 (s), 1025 (m), 1002 (m), 910 (m), 817 (m), 748 (m), 702 (m), 669 (s), 583 (m), 540 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 0.85 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 0.99−1.25 [m, 14 H, $(CH_2)_4CH_3$, $CH(CH_2)_3CH_3$], 1.44 (m, 2 H, NCHCH_2), 1.57 (m, 1 H, NCHC*H*), 2.39 (s, 3 H, Ar−CH_3), 3.31 (m, 2 H, C*H*HOCH$_2$Ph, NC*H*), 3.50 (dd, *J* = 3.0, 9.7 Hz, 1 H, CH*H*OCH$_2$Ph), 4.40 (d, *J* = 12.1 Hz, 1 H, OC*H*HPh), 4.47 (d, *J* = 12.1 Hz, 1 H, OCH*H*Ph), 5.55 (d, *J* = 8.0 Hz, 1 H, N*H*), 7.22−7.37 (m, 7 H, $CH_{arom.}$), 7.70 (d, *J* = 8.3 Hz, 2 H, $SO_2CCH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 14.3 (CH_2CH_3), 21.6 (Ar−CH_3), 22.7, 22.9, 26.1, 28.7, 29.2, 29.7, 31.8 (CH_2), 34.2 (NCHCH_2), 40.8 (NCH*C*H), 56.6 (N*C*H), 69.9 (CH_2OCH_2Ph), 73.4 (OCH_2Ph), 127.0, 127.5, 127.8, 128.5, 129.4 (Ar−*C*H), 137.9, 138.0, 142.6 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 459 (1) [M^+], 374 (8), 304 (9), 268 (100), 183 (6), 154 (15), 91 (34). $C_{27}H_{41}NO_3S$ (459.68): calcd. C 70.55, H 8.99, N 3.05; found C 71.03, H 9.21, N 3.08.

(3*S*,4*R*)-(+)-4-(Benzyloxymethyl)-2,2-dimethyl-*N*-tosyloctan-3-amine [(*S*,*R*)-5d]: According to GP 4 amine (*S*,*R*)-**4d** (0.24 g, 1.2 mmol) was treated with tosyl chloride in the presence of K_2CO_3. Tosylamine (*S*,*R*)-**5d** was obtained as a colourless oil after flash column chromatography (pentane/Et_2O, 6:1). Yield: 0.27 g (76%); *de* ≥ 96% (NMR). $[\alpha]_D^{23}$ = +42.5 (*c* = 1.0, $CHCl_3$). R_t = 17.09 min (CP-Sil-8, 140−10−300). R_f = 0.32 (pentane/Et_2O, 4:1). IR (film): $\tilde{\nu}$ = 3309 (s), 3062 (m), 3032 (m), 2957 (s), 2868 (s), 1918 (w), 1808 (w), 1719 (w), 1599 (m), 1456 (s), 1367 (m), 1334 (s), 1209 (w), 1158 (s), 1094 (s), 1025 (m), 906 (m), 816 (m), 740 (m), 701

(m), 667 (s), 551 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82 [t, J = 7.1 Hz, 3 H, CH_2CH_3], 0.84 [s, 9 H, $C(CH_3)_3$], 1.04−1.22 [m, 6 H, $(CH_2)_3CH_3$], 1.84 (m, 1 H, NCHC*H*), 2.39 (s, 3 H, Ar−CH_3), 3.03 (dd, J = 3.3, 9.6 Hz, 1 H, NC*H*), 3.20 (dd, J = 8.0, 9.3 Hz, 1 H, C*H*HOCH$_2$Ph), 3.47 (dd, J = 4.0, 9.3 Hz, 1 H, CH*H*OCH$_2$Ph), 4.41 (d, J = 11.8 Hz, 1 H, OC*H*HPh), 4.45 (d, J = 11.8 Hz, 1 H, OCH*H*Ph), 5.67 (d, J = 9.3 Hz, 1 H, N*H*), 7.18−7.40 (m, 5 H, C$H_{arom.}$), 7.62 (d, J = 8.2 Hz, 2 H, $SO_2CCH_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 21.4 (Ar−CH_3), 22.7 (CH_2CH_3), 27.0 [$C(CH_3)_3$], 29.8 ($CH_2CH_2CH_3$), 33.0 ($CH_2CH_2CH_2CH_3$), 36.0 [$C(CH_3)_3$], 38.3 (NCH*C*H), 66.3 (N*C*H), 71.5 (CH_2OCH_2Ph), 73.2 (CH_2OCH_2Ph), 126.7, 127.5, 127.6, 128.3, 129.1 (Ar *C*H), 137.6, 139.2, 142.3 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 374 (34) [$M^+ - C_4H_9$], 344 (6), 268 (48), 240 (121), 184 (14), 173 (8), 155 (15), 91 (100). $C_{25}H_{37}NO_3S$ (431.63): calcd. C 69.57, H 8.64, N 3.25; found C 69.31, H 8.80, N 3.63.

(2*R*,3*R*)-(+)-1-Benzyloxy-2-phenyl-*N*-tosylnonan-3-amine [(*R*,*R*)-5e]: According to GP 4 amine (*R*,*R*)-**4e** (0.19 g, 0.6 mmol) was treated with tosyl chloride in the presence of K_2CO_3. Tosylamine (*R*,*R*)-**5e** was obtained as a colourless solid after flash column chromatography (pentane/Et_2O, 4:1). Yield: 0.25 g (89%); *de* ≥ 96% (^1H NMR); *ee* = 97% (HPLC, Chiralpak AD 2); m.p. 125 °C. $[\alpha]_D^{24}$ = +21.9 (*c* = 0.9, $CHCl_3$). R_t = 24.81 min (CP-Sil-8, 140−10−300). R_f = 0.40 (pentane/Et_2O, 2:1). IR (KBr): $\tilde{\nu}$ = 3319 (s), 3060 (m), 3031 (m), 2925 (s), 2859 (s), 1949 (w), 1877 (w), 1811 (w), 1599 (m), 1497 (m), 1453 (m), 1430 (m), 1329 (s), 1258 (w), 1208 (w), 1157 (s), 1090 (s), 1046 (m), 10245 (m), 1002 (m), 909 (m), 819 (m), 744 (m), 700 (s), 671 (s), 596 (m), 567 (m), 544 (m), 494 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.2 Hz, 3 H, CH_3), 0.97−1.25 [m, 9 H, [C*H*H(CH_2)$_4$$CH_3$], 1.42 (m, 1 H, CH*H*($CH_2$)$_4$$CH_3$], 2.41 (s, 3 H, Ar−$CH_3$), 3.02 (dt, J = 4.7, 7.4 Hz, 1 H, NCHC*H*), 3.58 (dd, J = 4.7, 9.6 Hz, 1 H, C*H*HOCH$_2$Ph), 3.70 (m, 2 H, CH*H*OCH$_2$Ph, NC*H*), 4.44 (d, J = 12.1 Hz, 1 H, $CH_2OCHHPh$), 4.49 (d, J = 12.1 Hz, 1 H, $CH_2OCHHPh$), 5.00 (d, J = 7.7 Hz, 1 H, N*H*), 7.06 (m, 2 H, C$H_{arom.}$), 7.22−7.37 (m, 10 H, C$H_{arom.}$), 7.70 (d, J = 8.4 Hz, 2 H, $SO_2CCH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 21.5 (Ar−CH_3), 22.5, 24.7, 29.0, 31.6, 32.1 [(CH_2)$_5$$CH_3$], 48.7 (NCH*C*H), 56.9 (N*C*H), 72.0 (CH_2OCH_2Ph), 73.2 (CH_2OCH_2Ph), 2 × 127.1, 2 × 127.8, 128.4, 128.5, 128.6, 129.5 (Ar *C*H), 137.8, 138.4, 139.2, 143.0 (Ar C_q) ppm. MS (CI, 100 eV): *m*/*z* (%) = 480 (47) [MH^+], 371 (30), 309 (8), 291 (30), 280 (26), 268 (100), 262 (61), 201 (21), 184 (8), 171 (7), 154 (16), 119 (13), 104 (76), 91 (59). $C_{29}H_{37}NO_3S$ (479.67): calcd. C 72.61, H 7.77, N 2.92; found C 72.58, H 7.61, N 2.85.

(*R*)-(+)-1-Benzyloxy-*N*-tosylnonan-3-amine [(*R*)-5f]: The amine (*R*)-**4f** was prepared by N−N cleavage of the corresponding hydrazine (*R*,*S*)-**3f** (1.81 g, 5.0 mmol) with BH_3·THF as described in GP 3 and then treated with tosyl chloride according to GP 4 in the presence of K_2CO_3 and additional Et_3N (1.51 g, 15.0 mmol). Tosylamine (*R*)-**5f** was obtained as a colourless oil after flash column chromatography (pentane/Et_2O, 1:1). Yield: 1.24 g (84%, 2 steps). $[\alpha]_D^{24}$ = +2.24 (*c* = 1.0, $CHCl_3$). R_t = 21.99 min (CP-Sil-8, 100−10−300). R_f = 0.27 (pentane/Et_2O, 1:1). IR (KBr): $\tilde{\nu}$ = 3283 (m), 3064 (m), 3031 (m), 2929 (s), 2859 (s), 1726 (w), 1599 (m), 1495 (m), 1454 (s), 1327 (s), 1208 (w), 1159 (s), 1096 (s), 1031 (m), 912 (m), 815 (m), 739 (s), 700 (m), 667 (s), 577 (m), 552 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.04−1.26 [m, 8 H, (CH_2)$_4$$CH_3$], 1.40 [m, 2 H, NCHC$H_2$($CH_2$)$_4$], 1.56 (m, 1 H, NCHC*H*HCH$_2$O), 1.68 (m, 1 H, NCHCH*H*CH$_2$O), 2.41 (s, 3 H, Ar−CH_3), 3.38 (m, 2 H, C*H*HOCH$_2$Ph, NC*H*), 3.50 (dt, J = 4.5, 8.9 Hz, 1 H, CH*H*OCH$_2$Ph), 4.40 (s, 2 H, OCH_2Ph), 5.13 (s, 1 H, N*H*), 7.22−7.39 (m, 7 H, C$H_{arom.}$), 7.32 (d, J = 8.4 Hz, 2 H, $SO_2CCH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 21.5 (Ar−CH_3), 22.5, 25.4, 29.0, 31.7 ($CH_3CH_2CH_2CH_2CH_2$), 33.7 (NCHCH_2CH_2O), 35.0 (NCHCH_2(CH_2)$_4$], 52.7 (N*C*H), 67.2 (CH_2OCH_2Ph), 73.2 (OCH_2Ph), 127.1, 127.6, 127.7, 128.4, 129.5 (Ar *C*H), 138.0, 138.4, 143.0 (Ar C_q) ppm. MS (EI, 70 eV): *m*/*z* (%) = 403 (1) [M^+], 318 (5), 268 (27), 248 (45), 212 (24), 171 (5), 154 (21), 142 (7), 114 (5), 91 (100), 65 (6). $C_{23}H_{33}NO_3S$ (403.59): calcd. C 68.45, H 8.24, N 3.47; found C 68.36, H 8.60, N 3.81.

General Procedure for the Hydrogenolytic Alcohol Deprotection and the Ring Closure to Azetidines 6 (GP 5): A catalytic amount of Pd/C (10 wt%, 54 wt% H_2O) was added to a solution of the tosylamines **5** in EtOAc or MeOH. The reaction mixture was hydrogenated at atmospheric pressure until complete conversion of the starting material was indicated by TLC (2−3 h). After filtration through a pad of Celite® and removal of the solvent in vacuo, the resulting *N*-tosylamino alcohols and PPh_3 (1.5 equiv.) were dissolved in dry THF (15 mL/mmol) under argon. Diisopropyl azodicarboxylate (DIAD, 1.5 equiv.) was added dropwise at 0 °C with stirring. The solution was warmed to room temperature and stirred for 72 h. The reaction mixture was then filtered through a pad of SiO_2 and concentrated in vacuo. The crude tosylazetidines **6** were purified by flash column chromatography.

(2*R*,3*S*)-(−)-2-Butyl-3-methyl-1-tosylazetidine [(*R*,*S*)-6a]: According to GP 5 compound (*R*,*R*)-**5a** (0.57 g, 1.5 mmol) was hydrogenated in EtOAc (25 mL) in the presence of Pd/C (0.31 g). A mixture of the crude amino alcohol and PPh_3 in dry THF was then treated with DIAD. After flash column chromatography (pentane/Et_2O, 6:1) the tosylazetidine (*R*,*S*)-**6a** was obtained as a colourless solid. Yield: 0.38 g (97%, 2 steps); *de* = 93% (GC, CP-Sil-8); m.p. 62 °C. $[\alpha]_D^{23}$ = −87.5 (*c* = 1.1, $CHCl_3$). R_t = 11.82 [major *trans*-isomer], 12.31 min [minor *cis*-isomer] (CP-Sil-8, 120−10−300). R_f = 0.53 (pentane/Et_2O, 2:1). IR (KBr): $\tilde{\nu}$ = 3100 (w), 3033 (m), 2965 (s), 2931 (s), 2863 (s), 1942 (w), 1833 (w), 1676 (w), 1597 (m), 1496 (w), 1459 (m), 1382 (m), 1341 (s), 1290 (m), 1161 (s), 1025 (s), 910 (m), 821 (s), 714 (m), 669 (s), 603 (s), 548 (s), 497 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 0.90 [t, J = 6.9 Hz, 3 H, CH_2CH_3], 1.22−1.38 (m, 4 H, $CH_2CH_2CH_3$), 1.68 (m, 1 H, NCHC*H*H), 1.84 (m, 1 H, NCHCH*H*), 2.24 (m, 1 H, C*H*CH_3), 2.46 (s, 3 H, Ar−CH_3), 3.08 (t, J = 7.7 Hz, 1 H, NC*H*H), 3.37 (m, 1 H, NC*H*), 3.81 (t, J = 7.7 Hz, 1 H, NCH*H*), 7.36 (d, J = 8.4 Hz, 2 H, $CH_{arom.}CCH_3$), 7.71 (d, J = 8.4 Hz, 2 H, $CH_{arom.}CSO_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 18.5 ($CHCH_3$), 21.6 (Ar−CH_3), 22.6 (CH_2CH_3), 26.4 ($CH_2CH_2CH_3$), 30.9 (NCH*C*H), 35.3 (NCHCH_2), 54.8 (NCH_2), 71.2 (N*C*H), 128.2 (Ar *C*HCSO$_2$), 129.4 (Ar *C*HCCH$_3$), 132.0 (Ar C_qSO_2), 143.5 (Ar C_qCH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 281 (4) [M^+], 240 (6), 224 (30), 197 (12), 184 (23), 175 (10), 155 (100), 133 (42), 112(8), 106 (12), 98 (34), 91 (93), 84 (9), 70 (7), 65 (13). $C_{15}H_{23}NO_2S$ (281.41): calcd. C 64.02, H 8.24, N 4.98; found C 63.77, H 8.55, N 5.00.

(2*R*,3*S*)-(−)-2-Butyl-3-ethyl-1-tosylazetidine [(*R*,*S*)-6b]: According to GP 5 compound (*R*,*R*)-**5b** (0.50 g, 1.2 mmol) was hydrogenated in EtOAc (25 mL) in the presence of Pd/C (0.30 g). A mixture of the crude amino alcohol and PPh_3 in dry THF was then treated with DIAD. After flash column chromatography (pentane/Et_2O, 6:1) the tosylazetidine (*R*,*S*)-**6b** was obtained as a colourless oil. Yield: 0.34 g (92%, 2 steps); *de* = 96% (GC, CP-Sil-8). $[\alpha]_D^{22}$ = −63.8 (*c* = 1.1, $CHCl_3$). R_t = 10.67 [major *trans*-isomer], 11.15 min [minor *cis*-isomer] (CP-Sil-8, 140−10−300). R_f = 0.60 (pen-

tane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 3030 (w), 2959 (s), 2932 (s), 2871 (s), 1924 (w), 1817 (w), 1671 (w), 1598 (m), 1495 (w), 1462 (m), 1380 (m), 1345 (s), 1162 (s), 1091 (m), 1021 (w), 815 (m), 713 (m), 668 (s), 603 (s), 551 (s), 498 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.65 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.90 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.03 (m, 1 H, CHCHHCH$_3$), 1.17 (m, 1 H, CHCHHCH$_3$) 1.26−1.35 [m, 4 H, $(CH_2)_2CH_3$], 1.68 (m, 1 H, NCHCHH), 1.82 (m, 1 H, NCHCHH), 2.08 (m, 1 H, NCHCH), 2.46 (s, 3 H, Ar−CH_3), 3.12 (t, J = 7.8 Hz, 1 H, NCHH), 3.46 (m, 1 H, NCH), 3.79 (t, J = 7.8 Hz, 1 H, NCHH), 7.36 (d, J = 8.1 Hz, 2 H, $CH_{arom.}CCH_3$), 7.70 (d, J = 8.1 Hz, 2 H, $CH_{arom.}CSO_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8 (CH_2CH_3), 14.0 ($(CH_2)_3CH_3$], 21.5 (Ar−CH_3), 22.6 (CH_2CH_3), 26.5 (CH$CH_2CH_2CH_3$), 26.7 ($CH_2CH_2CH_2CH_3$), 35.5 (NCHCH_2), 37.2 (NCHCH), 53.1 (NCH_2), 69.5 (NCH), 128.1 (Ar $CHCSO_2$), 129.4 (Ar $CHCCH_3$), 132.1 (Ar C_qSO_2), 143.5 (Ar C_qCH_3) ppm. MS (EI, 70 eV): m/z (%) = 295 (9) [M^+], 266 (6), 240 (40), 238 (50), 197 (16), 189 (12), 183 (26), 155 (100), 146 (14), 140 (18), 133 (37), 126 (10), 98 (22), 91 (72), 84 (12), 65 (9). $C_{16}H_{25}NO_2S$ (295.44): calcd. C 65.05, H 8.53, N 4.74; found C 64.90, H 8.54, N 5.23.

(2*R*,3*S*)-(−)-3-Butyl-2-hexyl-1-tosylazetidine [(*R*,*S*)-6c]: According to GP 5 compound (*R*,*R*)-**5c** (0.48 g, 1.1 mmol) was hydrogenated in EtOAc (50 mL) in the presence of Pd/C (0.26 g). A mixture of the crude amino alcohol and PPh_3 in dry THF was then treated with DIAD. After flash column chromatography (pentane/Et_2O, 7:1) the tosylazetidine (*R*,*S*)-**6c** was obtained as a colourless oil. Yield: 0.34 g (92%, 2 steps); *de* = 95% (GC, CP-Sil-8). $[\alpha]_D^{22}$ = −53.9 (c = 1.1, $CHCl_3$). R_t = 15.97 [major *trans*-isomer], 16.37 min [minor *cis*-isomer] (CP-Sil-8, 120−10−300). R_f = 0.69 (pentane/Et_2O, 2:1). IR (film): $\tilde{\nu}$ = 2928 (s), 2858 (s), 1921 (w), 1670 (w), 1598 (m), 1494 (w), 1463 (m), 1379 (m), 1346 (s), 1216 (w), 1163 (s), 1092 (m), 1036 (w), 816 (m), 712 (m), 670 (s), 606 (m), 551 (m), 504 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 0.89 (t J = 6.7 Hz, 3 H, CH_2CH_3), 0.97 (m, 3 H, NCHCHCHH, CH_2), 1.14 (m, 3 H, NCHCHCHH, CH_2) 1.25−1.33 (m, 8 H, CH_2), 1.67 (m, 1 H, NCHCHH), 1.80 (m, 1 H, NCHCHH), 2.11 (m, 1 H, NCHCH), 2.45 (s, 3 H, Ar−CH_3), 3.13 (t, J = 7.7 Hz, 1 H, NCHH), 3.46 (ddd, J = 8.0, 6.8, 5.0 Hz, 1 H, NCH), 3.79 (t, J = 7.7 Hz, 1 H, NCHH), 7.36 (d, J = 8.1 Hz, 2 H, $CH_{arom.}CCH_3$), 7.71 (d, J = 8.1 Hz, 2 H, $CH_{arom.}CSO_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.1 (CH_2CH_3), 21.5 (Ar−CH_3), 22.4, 22.6, 24.5, 28.6, 29.2, 31.7, 33.2 (CH_2), 35.6 (NCHCH), 35.8 (NCHCH_2), 53.4 (NCH_2), 69.7 (NCH), 128.1 (Ar $CHCSO_2$), 129.4 (Ar $CHCCH_3$), 132.2 (Ar C_qSO_2), 143.5 (Ar C_qCH_3) ppm. MS (EI, 70 eV): m/z (%) = 351 (4) [M^+], 294 (7), 284 (9), 268 (59), 266 (53), 217 (10), 202 (17), 196 (36), 184 (52), 155 (100), 133 (36), 126 (29), 112 (19), 91 (85). $C_{20}H_{33}NO_2S$ (351.55): calcd. C 68.33, H 9.46, N 3.98; found C 68.34, H 9.11, N 4.43.

(2*S*,3*S*)-(−)−3-Butyl-2-*tert*-butyl-1-tosylazetidine [(*S*,*S*)-6d]: According to GP 5 compound (*S*,*R*)-**5d** (0.26 g, 0.6 mmol) was hydrogenated in EtOAc (15 mL) in the presence of Pd/C (0.19 g). A mixture of the crude amino alcohol and PPh_3 in dry THF was then treated with DIAD. After flash column chromatography (pentane/Et_2O, 8:1) the tosylazetidine (*S*,*S*)-**6d** was obtained as a colourless solid. Yield: 0.18 g (93%, 2 steps); *de* ≥ 96% (NMR); m.p. 53 °C. $[\alpha]_D^{23}$ = −28.1 (c = 1.0, $CHCl_3$). R_t = 13.57 min (CP-Sil-8, 120−10−300). R_f = 0.58 (pentane/Et_2O, 4:1). IR (KBr): $\tilde{\nu}$ = 3063 (w), 2964 (s), 2879 (s), 1934 (w), 1827 (w), 1626 (w), 1598 (m), 1494 (m), 1464 (m), 1387 (m), 1366 (m), 1342 (s), 1303 (m), 1214 (m), 1156 (s), 1094 (m), 1033 (m), 1010 (m), 983 (m), 848 (m), 823 (m), 713 (m), 673 (s), 620 (m), 574 (m), 546 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.75 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 0.95 [s, 9 H, C(CH_3)$_3$], 0.95−1.02 [m, 4 H, CH(CH_2)$_2$], 1.10 (m, 2 H, CH_2CH_3), 2.06 (m, 1 H, NCHCH), 2.45 (s, 3 H, Ar−CH_3), 3.25 (m, 2 H, NCHH, NCH), 3.81 (t, J = 8.5 Hz, 1 H, NCHH), 7.36 (d, J = 8.2 Hz, 2 H, $CH_{arom.}CCH_3$), 7.73 (d, J = 8.2 Hz, 2 H, $CH_{arom.}CSO_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 21.5 (Ar−CH_3), 22.4 (CH_2CH_3), 25.4 [C(CH_3)$_3$], 28.4 ($CH_2CH_2CH_3$), 31.1 (NCHCH), 33.6, 33.7 (CHCH_2, C(CH_3)$_3$], 53.6 (NCH_2), 78.8 (NCH), 128.1 (Ar $CHCSO_2$), 129.3 (Ar $CHCCH_3$), 133.1 (Ar C_qSO_2), 143.4 (Ar C_qCH_3) ppm. MS (EI, 70 eV): m/z (%) = 323 (3) [M^+], 266 (100), 155 (29), 139 (7), 110 (6), 91 (22). $C_{18}H_{29}NO_2S$ (323.49): calcd. C 66.83, H 9.04, N 4.33; found C 66.54, H 8.96, N 4.27.

(2*R*,3*S*)-(−)-2-Hexyl-3-phenyl-1-tosylazetidine [(*R*,*S*)-6e]: According to GP 5 compound (*R*,*R*)-**5e** (0.15 g, 0.3 mmol) was hydrogenated in EtOAc (15 mL) in the presence of Pd/C (0.10 g). A mixture of the crude amino alcohol and PPh_3 in dry THF was then treated with DIAD. After flash column chromatography (pentane/Et_2O, 7:1) the tosylazetidine (*R*,*S*)-**6e** was obtained as a colourless solid. Yield: 0.11 g (94%, 2 steps); *de* ≥ 96% (NMR); *ee* = 95.5% (HPLC, OD.M); m.p. 69 °C. $[\alpha]_D^{23}$ = −50.8 (c = 1.0, $CHCl_3$). R_t = 14.34 min (CP-Sil-8, 160−10−300). R_f = 0.36 (pentane/Et_2O, 6:1). IR (KBr): $\tilde{\nu}$ = 3064 (w), 3025 (m), 2957 (m), 2931 (s), 2898 (m), 2861 (m), 1959 (w), 1879 (w), 1825 (w), 1596 (m), 1495 (m), 1462 (m), 1380 (m), 1343 (s), 1299 (m), 1165 (s), 1094 (s), 1023 (m), 978 (m), 822 (m), 757 (m), 706 (s), 664 (s), 612 (s), 551 (s), 527 (m), 496 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 6.3 Hz, 3 H, CH_2CH_3), 1.18−1.26 [m, 8 H, $(CH_2)_4CH_3$], 1.80 (m, 1 H, NCHCHH), 1.92 (m, 1 H, NCHCHH), 2.51 (s, 3 H, Ar−CH_3), 3.30 (q, J = 8.2 Hz, 1 H, NCHCH), 3.57 (t, J = 8.2 Hz, 1 H, NCHH), 3.88 (dt, J = 8.2, 4.2 Hz, 1 H, NCH), 4.04 (t, J = 8.2 Hz, 1 H, NCHH), 6.69 (m, 2 H, $CH_{arom.}$), 7.15 (m, 3 H, $CH_{arom.}$), 7.36 (d, J = 8.3 Hz, 2 H, $CH_{arom.}CCH_3$), 7.78 (d, J = 8.3 Hz, 2 H, $CH_{arom.}CSO_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 21.6 (Ar−CH_3), 22.5, 24.1, 29.0, 31.5, 36.0 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 40.9 (NCHCH), 54.9 (NCH_2), 71.7 (NCH), 126.9, 127.0, 128.4, 128.4, 129.6 (Ar CH), 131.8 (Ar C_qSO_2), 139.9 (Ar C_qCH), 143.8 (Ar C_qCH_3) ppm. MS (EI, 70 eV): m/z (%) = 371 (1) [M^+], 155 (3), 117 (4), 104 (100), 91 (10). $C_{22}H_{29}NO_2S$ (371.54): calcd. C 71.12, H 7.87, N 3.77 found; C 70.66, H 7.81, N 3.60.

(2*R*)-(−)-2-Hexyl-1-tosylazetidine [(*R*)-6f]: According to GP 5 compound (*R*)-**5f** (0.81 g, 2.0 mmol) was hydrogenated in MeOH (30 mL) in the presence of Pd/C (0.40 g). A mixture of the crude amino alcohol and PPh_3 in dry THF was then treated with DIAD. After flash column chromatography (pentane/Et_2O, 4:1) the tosylazetidine (*R*)-**6f** was obtained as a colourless oil. Yield: 0.46 g (77%, 2 steps). $[\alpha]_D^{25}$ = −80.0 (c = 1.8, $CHCl_3$). R_t = 15.57 min (CP-Sil-8, 60−10−300). R_f = 0.17 (pentane/Et_2O, 4:1). IR (film): $\tilde{\nu}$ = 2928 (s), 2860 (m), 1922 (w), 1808 (m), 1770 (m), 1598 (m), 1495 (m), 1461 (m), 1404 (w), 1380 (w), 1345 (s), 1305 (m), 1161 (s), 1096 (s), 1020 (m), 946 (m), 818 (s), 770 (m), 714 (m), 670 (s), 608 (s), 553 (s), 500 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.5 Hz, 3 H, CH_2CH_3), 1.18−1.30 [m, 8 H, $(CH_2)_4CH_3$], 1.68 (m, 1 H, NCHCHH), 1.90 (m, 3 H, NCHCHH, NCH_2CH_2), 2.44 (s, 3 H, Ar−CH_3), 3.49 (m, 1 H, NCHH), 3.67 (m 1 H, NCHH), 3.84 (m, 1 H, NCH), 7.39 (d, J = 8.2 Hz, 2 H, $CH_{arom.}CCH_3$), 7.71 (d, J = 8.2 Hz, 2 H, $CH_{arom.}CSO_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 21.6 (Ar−CH_3), 22.2 (NCH_2CH_2), 22.65, 24.2, 29.1, 31.7, 36.1 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 47.6 (NCH_2), 64.2 (NCH), 128.4 (Ar $CHCSO_2$), 129.7 (Ar $CHCCH_3$), 132.1 (Ar C_qSO_2), 143.8 (Ar C_qCH) ppm. MS (EI, 70 eV): m/z (%) = 295 (1)

[M^+], 238 (8), 210 (37), 184 (42), 155 (100), 140 (26), 91 (55), 65 (9). $C_{16}H_{25}NO_2S$ (295.44): calcd. C 65.05, H 8.53, N 4.74; found C 64.60, H 8.34, N 4.96.

General Procedure for the Reductive Detosylation and Boc-Protection of the Azetidines 6 (GP 6): Sodium metal (6.0 equiv.) was rinsed with dry methanol and was put in a Schlenk flask together with naphthalene (6.0 equiv.). After the flask had been evacuated and filled with argon, the mixture was dissolved in dry dimethoxyethane (DME, 15 mL/mmol) at 0 °C and stirred for 2.5 h at this temperature. The resulting dark green solution was then cooled to −45 °C and the tosylazetidines **6** (1.0 equiv.) dissolved in DME (9 mL/mmol) were slowly added at this temperature. After complete conversion of the starting material had been indicated by TLC the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with CH_2Cl_2 for several times. The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The crude mixture was then again dissolved in CH_2Cl_2 (10 mL/mmol) and stirred with Et_3N (1.2 equiv.) and $(Boc)_2O$ (1.2 equiv.) for 20 h at ambient temperature. After addition of a saturated $NaHCO_3$ solution the aqueous phase was extracted with CH_2Cl_2, dried with Na_2SO_4 and concentrated under reduced pressure. The pure *N*-Boc-azetidines **7** were obtained by flash column chromatography.

***tert*-Butyl (2*R*,3*S*)-(−)-3-Butyl-2-hexylazetidine-1-carboxylate [(*R*,*S*)-7a]:** The tosylazetidine (*R*,*S*)-**6c** (0.10 g, 0.3 mmol) was treated with sodium naphthalide in DME for 30 min at −45 °C and converted into the corresponding Boc-protected azetidine as described in GP 6. A pure product was obtained by flash column chromatography (pentane/Et_2O, 15:1) as a colourless oil. Yield: 0.07 g (85%, 2 steps); *de* = 95% (GC, CP-Sil-8). $[\alpha]_D^{23} = -22.6$ (*c* = 1.1, $CHCl_3$). R_t = 9.12 [major *trans*-isomer], 9.67 min [minor *cis*-isomer] (CP-Sil-8, 120−10−300). R_f = 0.60 (pentane/Et_2O, 6:1). IR (film): $\tilde{\nu}$ = 2928 (s), 2860 (s), 1704 (s), 1460 (m), 1394 (s), 1367 (s), 1254 (m), 1142 (s), 1069 (w), 903 (w), 876 (w), 769 (m), 731 (m), 655 (m), 622 (m), 509 (m), 464 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 6.9 Hz, 3 H, CH_2CH_3), 0.82 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.12−1.27 (m, 12 H, CH_2), 1.37 [s, 9 H, $C(CH_3)_3$] 1.38−1.55 (m, 3 H, NCHC*H*H, NCHCHCH_2), 1.78 (m, 1 H, NCHCH*H*), 1.97 (m, 1 H, NCHC*H*), 3.32 (dd, *J* = 8.3, 5.8 Hz, 1 H, NC*H*H), 3.46 (dt, *J* = 7.0, 5.2 Hz, 1 H, NC*H*), 3.79 (t, *J* = 8.3 Hz, 1 H, NCH*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (2 × CH_2CH_3), 2 × 22.7, 24.8, 29.3, 29.5, 31.9 (CH_2), 28.6 [$C(CH_3)_3$], 34.2 (NCHCHCH_2), 35.0 (NCHCH_2), 35.9 (NCHCH), 52.2 (br, NCH_2), 68.0 (NCH), 79.0 [$C(CH_3)_3$], 156.6 (*C*=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 297 (11) [M^+], 241 (17), 224 (16), 184 (16), 170 (17), 156 (100), 140 (12), 126 (14), 112 (63), 74 (14), 57 (96). $C_{18}H_{35}NO_2$ (297.48): calcd. C 72.68, H 11.86, N 4.71; found C 72.73, H 12.05, N 5.02.

***tert*-Butyl (2*R*,3*S*)-(−)-2-Hexyl-3-phenylazetidine-1-carboxylate [(*R*,*S*)-7b]:** The tosylazetidine (*R*,*S*)-**6e** (0.10 g, 0.3 mmol) was treated with sodium naphthalide in DME for 10 min at −45 °C and transferred into the corresponding Boc-protected azetidine as described in GP 6. A pure product was obtained by flash column chromatography (pentane/Et_2O, 15:1) as a colourless oil. Yield: 0.06 g (67%, 2 steps); *de* = 90.5 (HPLC, SI-60); *ee* = 96% (HPLC, (*S*,*S*)-Whelk 01), $[\alpha]_D^{23} = -5.0$ (*c* = 0.4, $CHCl_3$). R_f = 0.47 (pentane/Et_2O, 6:1). IR (film): $\tilde{\nu}$ = 3063 (m), 3030 (m), 2929 (s), 2859 (s), 1948 (w), 1872 (w), 1703 (s), 1604 (w), 1457 (m), 1391 (s), 1253 (m), 1136 (s), 864 (w), 755 (m), 700 (m), 521 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.5 Hz, 3 H, CH_2CH_3), 1.26−1.35 (m, 8 H, CH_2), 1.47 [s, 9 H, $C(CH_3)_3$], 1.74 (m, 1 H, NCHC*H*H), 1.97 (m, 1 H, NCHCH*H*), 3.29 (dt, *J* = 8.7, 6.4 Hz, 1 H, NCHC*H*), 3.87 (dd, *J* = 8.7, 6.7 Hz, 1 H, NC*H*H), 4.18 (m, 2 H, NC*H*, NCH*H*), 7.20−7.37 (m, 5 H, $CH_{arom.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 22.6 (CH_2CH_3), 24.5 ($CH_2CH_2CH_3$), 28.5 [$C(CH_3)_3$], 29.3 ($CH_2(CH_2)_2CH_3$], 31.7 ($CH_2(CH_2)_3CH_3$], 35.4 (NCHCH_2), 40.9 (NCHCH), 53.7 (br, NCH_2), 70.0 (NCH), 79.4 [$C(CH_3)_3$], 126.9, 127.0, 128.7 (Ar CH), 142.0 (Ar C_q), 156.8 (*C*=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 317 (3) [M^+], 261 (7), 217 (8), 170 (7), 104 (100), 91 (5), 57 (34). $C_{20}H_{31}NO_2$ (317.47): calcd. C 75.67, H 9.84, N 4.41 found C 75.45, H 9.92, N 4.80.

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