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Asymmetric synthesis of 2-substituted piperidin-3-ols

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Abstract—Starting from a protected glycol aldehyde hydrazone a flexible asymmetric synthesis of 2-substituted piperidin-3-ols was achieved. An α-alkylation/1,2-addition sequence furnished the intermediate hydrazines which were subjected to reductive cleavage of the chiral auxiliary. After acidic workup and simultaneous deprotection the title compounds were obtained in moderate overall yields and excellent diastereomeric and enantiomeric excesses (*de*, *ee* >96%) by ring closure under reductive amination conditions.

1. Introduction

Piperidine alkaloids are an important class of natural products and due to their broad range of bioactivities are of great pharmacological interest. 2,3-Disubstituted derivatives, especially the 2-substituted piperidin-3-ol skeleton, play an important role as natural and synthetic bioactive compounds (Fig. 1). The pyrrolidinyl substituted derivative **1** for example was tested for its activity as κ-opioid receptor agonist.[1] The hydroxy piperidinyl substituted propanoic acid **2** is a new potent analogue of baclofen, which shows significant in vitro activity as a GABA receptor binder.[2]

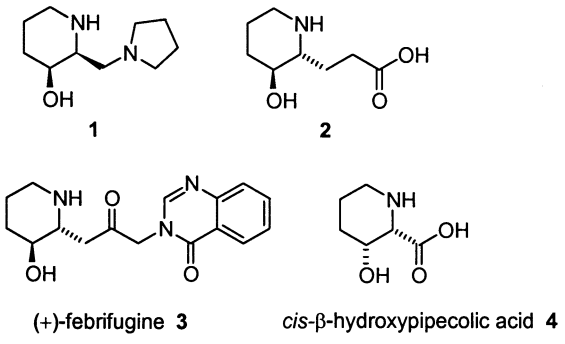

Figure 1. Examples of natural and synthetic pharmacologically active 2-substituted piperidin-3-ols.

(+)-Febrifugine **3** was first isolated from the Chinese medicinal plant *Dichroa febrifuga* (Chinese name: Chang Shan) and exhibits strong antimalarial properties comparable to that of the clinically used drug chloroquinine.[3,4] As the rare amino acid building block hydroxypipecolic acid **4** is present in certain bioactive natural products such as tetrazomine, a promising candidate with antitumor and antimicrobial activity.[5] Most of the reported syntheses of 2-substituted piperidin-3-ols were directed to specific molecules, such as (+)-febrifugine **3**[4b,6] and hydroxy pipecolic acid **4**,[7] or focused on special substitution patterns which are necessary for further transformations into more complex structures, e.g. indolizidine alkaloids.[8] Only a few publications describe a more general and flexible method for the preparation of 2-substituted piperidin-3-ols, which allows the introduction of different substituents in the 2-position of the ring.[9]

2. Results and discussion

In a previous article we described an efficient methodology for the synthesis of 2-(α-hydroxyalkyl)-piperdines, which was also applied to accomplish the first asymmetric synthesis of (−)-α-conhydrine.[10] Herein, we wish to report on the extension of our versatile procedure to another class of hydroxylated piperidines, the 2-substituted piperidin-3-ols.

2.1. Retrosynthetic analysis

A retrosynthetic analysis of the target molecule **5** leads to the amino aldehyde precusor **6**. The construction of

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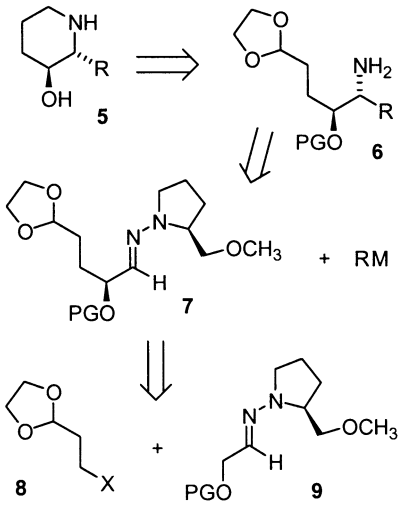
the piperidine skeleton can be achieved by ring closure performed under reductive amination conditions (Scheme 1). The key intermediate **6** is based on a disubstituted 1,2-amino alcohol subunit. The desired substitution pattern can be obtained by a diastereoselective nucleophilic 1,2-addition of various organometallic compounds to the chiral, α-substituted glycol aldehyde hydrazone **7**.[11] The required carbonyl functionality can be introduced by α-alkylation of the protected glycol aldehyde SAMP hydrazone **9** with the acetal-containing electrophile **8**. The use of this class of hydrazones as versatile chiral synthons for the synthesis of miscellaneous substituted 1,2-amino alcohol units applying the SAMP/RAMP hydrazone method[12] has already been reported by our group.[13]

The enantiopure TBS-protected glycol aldehyde SAMP hydrazone **10** is readily available in high yield by a three-step sequence on a multigram scale from commercially available (*Z*)-butenediol, which is first protected prior to ozonolytic cleavage under reductive workup conditions and final condensation with the hydrazine SAMP to yield **10**.[13c]

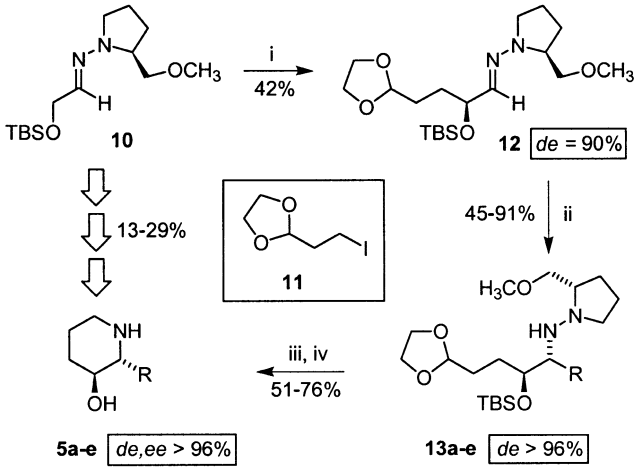


Scheme 1. Retrosynthetic analysis of 2-substituted piperidin-3-ols **5**.

According to the proposed mechanisms for the α-alkylation and subsequent 1,2-addition supported by this auxiliary, the formation of the (2*R*,3*S*)-*trans* products are expected.[10,13]

2.2. Asymmetric synthesis of 2-substituted piperidin-3-ols

As depicted in Scheme 2, treatment of hydrazone **10** with LDA at low temperature gave the intermediate lithium azaenolat, which was trapped at the same temperature with the acetal protected β-iodo propanal **11** to form the α-substituted hydrazine **12** in moderate yield and good diastereomeric excess. The functionalized electrophile **11** is easily available from acroleine by the one-pot procedure described by Larson and Klesse.[14] Treatment of the key intermediate **12** with various alkyllithium reagents afforded the light- and air-sensitive hydrazines **13a–e** (Table 1). Commercially



Scheme 2. Asymmetric synthesis of 2-substituted piperidin-3-ols **5a–e**. *Reagents and conditions*: (i) LDA, THF, −78°C, then **11**, −78°C; (ii) RLi, THF, −78°C, then $NaHCO_3$ (aq.); (iii) BH_3·THF, THF, Δ, then 3 M HCl (aq.), CH_2Cl_2, rt; (iv) $NaBH_4$, EtOH, rt.

Table 1. Results of the asymmetric synthesis of 2-substituted piperidin-3-ols **5a–e**

R	Product	Yield (%)[b]	*de* (%)[c]	Prod.	Yield (%)[d]	*de* (%)[e]	*ee* (%)[f]
Me[a]	**13a**	53	>96	**5a**	59	>96	>96
n-Bu	**13b**	75	>96	**5b**	62	>96	>96
t-Bu	**13c**	77	>96	**5c**	51	>96	>96
n-Hex[a]	**13d**	45	>96	**5d**	67	>96	>96
$(CH_2)_2Ph$[g]	**13e**	91	>96	**5e**	76	>96	>96

[a] Due to the less reactive organolithium reagents the addition reaction was carried out at −30°C.
[b] Isolated by flash column chromatography.
[c] Determined by ^{13}C NMR spectroscopy after purification.
[d] Isolated by flash column chromatography. Yield after two steps.
[e] Determined by ^{13}C NMR spectroscopy.
[f] In correlation to the *de* value of the corresponding hydrazines **13a–e** assuming the following steps take place without any detectable racemization.[16,17]
[g] Prepared from the corresponding iodide and *t*-butyllithium according to a procedure of Negishi and Bailey.[15]

available organolithium compounds as well as 2-phenylethyllithium, prepared by halogen–metal exchange reaction[15] from the corresponding iodide, reacted well in moderate to excellent yields in the highly diastereoselective 1,2-addition (*de* >96%) to the carbon–nitrogen double bond of hydrazone **12**.[13] Due to their lower reactivity, reactions of methyl- and *n*-hexyllithium were carried out at higher temperature (−30°C). The lower chemical yields of **13a**,**d** were due to side reactions, which occured at that temperature.

Because of the incomplete asymmetric induction in the alkylation of **10** to form **12**, the minor diastereomers of **13a–e** were expected, but NMR spectroscopic investigations showed no significant signals. We assume that the undesired isomers were separated during the purification procedure.

The chiral auxiliary was removed from the hydrazines **13a–e** after isolation by flash chromatography. Nitrogen–nitrogen bond cleavage was achieved with a BH_3THF complex in refluxing THF.[16] After completion, the reaction mixtures were treated with hydrochloric acid to destroy excess borane. In addition, acid-catalyzed silyl ether cleavage and acetal hydrolysis occured and the resulting amino aldehydes underwent spontaneous cyclization to the corresponding imines. The solvents were evaporated and the remaining residue was dissolved in EtOH without further purification. Finally, $NaBH_4$ reduction completed the reductive amination to afford the 2-substituted piperidin-3-ols **5a–e** in moderate to good yields over two steps (Table 1). Due to the longer and less polar side chains the isolation of **5b**, **5d** and **5e** by flash chromatography were achieved in higher yields in comparison to the more polar compounds **5a** and **5c**. Starting from glycol aldehyde hydrazone **10** the title compounds **5a–e** were obtained in overall yields of 13–29% with both diastereomeric and enantiomeric excesses greater than 96%, as determined by ^{1}H and ^{13}C NMR.

Finally, the proposed (2*R*,3*S*)-configuration for the products **5a–e** was confirmed by NOESY experiments on **5b** (Fig. 2). Due to the *trans* configured product a less strong interaction between the relevant hydrogen atoms was expected. In fact, irradiation of the C(2) proton of **5b** gave no significant enhancement of the C(3) proton resonance due to the greater distance between these nuclei. Other interactions confirming the *trans* stereochemistry of **5b** could not be observed. The determined relationship was in accord with that reported in previous publications for the α-alkylation/1,2-addition sequence[10,13] and confirmed the (2*R*,3*S*)-absolute configuration of the 2-substituted piperidin-3-ols **5a–e** starting from protected glycol aldehyde SAMP hydrazone **10**.

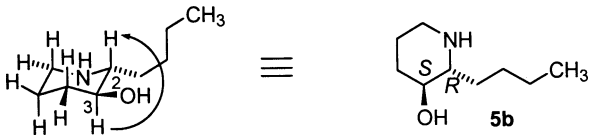


Figure 2. Determination of the relative configuration of **5b** by NOESY experiments.

3. Conclusion

In summary, we have successfully extended our method for the synthesis of hydroxylated piperidines. Applying our SAMP/RAMP hydrazone methodology for the α-alkylation/1,2-addition of chiral glycol aldehyde hydrazones, the 2-substituted piperidin-3-ols were obtained in moderate to good overall yields and excellent diastereo- and enantiomeric excesses. Investigations towards the employment of functionalized nucleophiles in the 1,2-addition, which would allow the application of the 2-substituted piperidine-3-ols as building blocks in the synthesis of bioactive compounds (Fig. 1), are currently in progress.

4. Experimental

4.1. General

Methyllithium (1.6 M in diethyl ether), *n*-butyllithium (1.6 M in hexane) and *t*-butyllithium (1.6 M in hexane) were purchased from Merck, Darmstadt. *n*-Hexyllithium (2.5 M in hexane) was purchased from Aldrich. 2-Phenylethyllithium was freshly prepared from the corresponding iodide.[15] Melting points were determined on a Tottoli melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1750 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively, on Varian VXR 300, Varian Gemini 300 or Varian Unity spectrometers. $^3J_{H,H}$ coupling constants were expressed in Hz. All measurements were performed in $CDCl_3$ and chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Varian MAT 212 or Finnigan SSQ 7000. Optical rotations were measured on a Perkin Elmer P 241 polarimeter. Microanalyses were performed on Elementar Vario EL. In case of sensitive compounds high resolution mass spectra (HR-MS) were obtained on a Finnigan MAT 95.

4.1.1. General procedures

4.1.1.1. 1,2-Addition of organolithium reagents to hydrazone 12. A solution of the corresponding organolithium compound was slowly added to a solution of **12** in dry THF (5 mL/mmol) at −100°C. In the case of a freshly prepared lithium reagent, the hydrazone solution was added. After stirring the mixture for 15 h at this temperature the reaction mixture was allowed to warm to room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL/mmol) and the aqueous portion was extracted with Et_2O (3×10 mL/mmol). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography of the residue on silica gel eluting with pentane–Et_2O gave the hydrazines **13a–e** as pale yellow liquids.

4.1.1.2. N–N bond cleavage of hydrazines 13a–e and ring closure by reductive amination to 2-substituted piperidin-3-ols 5a–e. A solution of BH_3·THF (1 M, 10.0 equiv.) in THF was slowly added to a solution of **13** in dry THF (2 mL/mmol) at room temperature. After heating the mixture under reflux for 4 h, the mixture was allowed to cool to room temperature and carefully quenched with 3 M aqueous HCl (10 mL/mmol). CH_2Cl_2 (8 mL/mmol) was added and the mixture was stirred for 1 h at this temperature. The solvents were removed in vacuo and the residue was dissolved in EtOH (10 mL/mmol). $NaBH_4$ (6.0 equiv.) was added slowly to the solution at room temperature and the mixture was then stirred at this temperature for 2 h. The reaction was quenched with 3 M HCl (1 mL/mmol) and conc. NH_3 was added until a basic pH value was measured. H_2O (10 mL/mmol) and CH_2Cl_2 (15 mL/mmol) were added and after separation of the organic layer the aqueous portion was extracted further with CH_2Cl_2 (4×10 mL/mmol). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The isomer ratio was determined and flash column chromatography of the residue on silica gel eluting with CH_2Cl_2–MeOH gave **5a–e** as colourless solids.

4.2. Synthesis of 2-substituted piperidin-3-ols

4.2.1. (2*S*,2*S*)-(−)-(*E*)-*N*-[2-(*tert*-Butyldimethylsilyloxy)-4-([1,3]dioxolan-2-yl)-but-1-ylidene]-*N*-(2-methoxymethylpyrrolidin-1-yl)-amine 12. A solution of **10** (2.87 g, 10 mmol) in dry THF (5 mL) was slowly added to a solution of 2.0 equiv. LDA (freshly prepared from a solution of *n*-butyllithium (1.6 M) in hexane (12.5 mL, 20 mmol) and diisopropylamine (2.9 mL, 20.5 mmol) in dry THF (20 mL) at −78°C. The mixture was stirred at this temperature for 15 h. Iodide **11** (6.84 g, 30 mmol) was added at −100°C. The solution was stirred for 1 h and then allowed to warm to room temperature within 20 h. The reaction mixture was quenched with a saturated NH_4Cl solution (15 mL). The aqueous portion was extracted with Et_2O (3×10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. After the isomer ratio was determined, flash column chromatography of the residue on silica gel eluting with pentane–Et_2O (1:1, 1 vol.% of Et_3N) gave **12** (940 mg, 42%, 85% conversion). R_f (silica, pentane–Et_2O, 1:1): 0.6. *de* 90% (^{1}H, ^{13}C NMR). $[\alpha]_D^{24}$ −50.1 (*c* 1.04, $CHCl_3$). ^{1}H NMR (400 MHz): δ 0.03 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.88 (s, 9H, SiC(CH_3)$_3$), 1.63–2.00 (m, 8H, NCH$_2$CH_2CH_2CH, (CH$_2$O)$_2$CHCH_2CH_2), 2.79 (m, 1H, NCHHCH$_2$), 3.24–3.74 (m, 3H, NCHHCH$_2$, NCH-CHHOCH$_3$), 3.36 (s, 3H, OCH_3), 3.54 (d/d, *J*=3.3/8.7, 1H, NCHCHHOCH$_3$), 3.85 (m, 2H, OCH_2CH$_2$O), 3.96 (m, 2H, OCH$_2$CH_2O), 4.20 (m, 1H, *C*HOSi), 4.88 (m, 1H, (CH$_2$O)$_2$CH), 6.38 (d, *J*=6.6, 1H, *H*C=N). ^{13}C NMR (100 MHz): δ −4.73 (SiCH_3), −4.10 (SiCH_3), 18.15 (*C*(CH$_3$)$_3$), 22.08 (NCH$_2$CH_2), 25.88 (C(CH_3)$_3$), 26.62 (NCHCH_2), 29.76 ((CH$_2$O)$_2$CHCH_2), 31.28 ((CH$_2$O)$_2$CHCH$_2$CH_2), 49.44 (NCH_2), 59.10 (OCH_3), 62.81 (N*C*H), 64.74 ((*C*H$_2$O)$_2$CH), 73.28 (*C*HOSi), 74.60 (*C*H$_2$OCH$_3$), 104.40 ((CH$_2$O)$_2$*C*H), 138.11 (N=*C*H). MS (CI): *m*/*z* (%) 389 (6, M$^{+\bullet}$+3), 388 (23, M$^{+\bullet}$+2), 387 (96, M$^{+\bullet}$+1), 386 (18, M$^{+\bullet}$), 341 (6), 329 (6), 256 (14), 255 (100), 133 (25). IR (film): *v* 3077, 2955, 2929, 2887, 2857, 2857 (CH), 2709, 1589 (C=N), 1472, 1463, 1409, 1389, 1360, 1341, 1301, 1283, 1253, 1198, 1124, 1097, 1075, 1039, 1006, 991, 941, 837, 815, 777, 678. Anal. calcd for $C_{19}H_{38}O_4N_2Si$: C, 59.03; H, 9.91; N, 7.25. Found: C, 58.71, H, 10.15; N, 7.47%.

4.2.2. (1*R*,2*S*,2*S*)-(−)-*N*-[2-(*tert*-Butyldimethylsilyloxy)-4-([1,3]dioxolan-2-yl)-1-methyl-butyl]-*N*-(2-methoxymethylpyrrolidin-1-yl)-amine 13a. Hydrazone **12** (780 mg, 2.0 mmol) was allowed to react with 3.0 equiv. of methyllithium according to the procedure described in Section 4.1.1.1 at −30°C. Flash column chromatography (silica, pentane–Et_2O, 2:1) gave **13a** (426 mg, 53%). R_f (silica, pentane–Et_2O, 2:1): 0.2. *de* >96% (^{13}C NMR). $[\alpha]_D^{27}$ −52.7 (*c* 1.01, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.06 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.87 (s, 9H, C(CH_3)$_3$), 0.94 (d, *J*=7.2, 3H, CHCH_3), 1.50–2.22 (m, 8H, NCH$_2$CH_2CH_2, (CH$_2$O)$_2$CHCH_2CH_2), 2.56 (m, 1H, NCHCH$_2$OCH$_3$), 2.92 (m, 1H, NCHCH$_3$), 3.27 (d/d, *J*=9.0/3.0, 1H, CHHOCH$_3$), 3.36 (s, 3H, OCH_3), 3.46 (m, 2H, NCH_2CH$_2$), 3.54 (m, 1H, CHHOCH$_3$), 3.77 (m, 1H, CHOSi), 3.85 (m, 2H, OCH_2CH$_2$O), 3.96 (m, 2H, OCH$_2$CH_2O), 4.87 (m, 1H, (CH$_2$O)$_2$CHCH$_2$). ^{13}C NMR (75 MHz): δ −4.52 (SiCH_3), −4.37 (SiCH_3), 14.21 (NCH*C*H$_3$), 18.05 (*C*(CH$_3$)$_3$), 21.10 (NCH$_2$*C*H$_2$), 25.17 (NCH*C*H$_2$), 25.92 (C(*C*H$_3$)$_3$), 26.58 ((CH$_2$O)$_2$CHCH$_2$*C*H$_2$), 30.66 ((CH$_2$O)$_2$CH*C*H$_2$), 57.53 (N*C*H$_2$), 58.11 (N*C*HCH$_3$), 59.08 (CH$_2$O*C*H$_3$), 64.81 ((*C*H$_2$O)$_2$CH), 65.84 (N*C*HCH$_2$), 73.51 (*C*HOSi), 75.39 (*C*H$_2$OCH$_3$), 104.97 ((CH$_2$O)$_2$*C*H). MS (EI): *m*/*z* (%) 402 (16, M$^{+\cdot}$), 158 (9), 157 (100), 129 (11), 114 (5), 113 (5), 85 (7), 73 (10), 70 (8). IR (film): *v* 2957, 2857 (CH), 2709, 1729, 1472, 1463, 1448, 1408, 1390, 1377, 1361, 1255, 1198, 1123, 1096, 1061, 1041, 987, 939, 917, 835, 814, 775, 665. HR-MS calcd for $C_{20}H_{42}N_2O_4Si^{+\bullet}$: 402.2914. Found: 402.2912.

4.2.3. (1*R*,2*S*,2*S*)-(−)-*N*-{1-[1-(*tert*-Butyldimethylsilyloxy)-3-[1,3]dioxolan-2-yl-propyl]-pentyl}-*N*-(2-methoxymethylpyrrolidin-1-yl)-amine 13b. Hydrazone **12** (740 mg, 1.9 mmol) was allowed to react with 2.0 equiv. of *n*-butyllithium according to the procedure described in Section 4.1.1.1. Flash column chromatography (silica, pentane–Et_2O, 3:1) gave **13b** (635 mg, 75%). R_f (silica, pentane–Et_2O, 2:1): 0.3. *de* >96% (^{13}C NMR). $[\alpha]_D^{28}$ −75.9 (*c* 1.48, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.08 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), 0.90 (s, 9H, C(CH_3)$_3$), 1.16–1.37 (m, 9H, CH(CH_2)$_3$CH_3), 1.40–2.05 (m, 8H, NCH$_2$CH_2CH_2, (CH$_2$O)$_2$CHCH_2CH_2), 2.50 (m, 1H, NCHCH$_2$OCH$_3$), 2.82 (m, 1H, NCH(CH$_2$)$_3$CH$_3$), 3.27–3.50 (m, 3H, NCH_2CH$_2$, CHHOCH$_3$), 3.37 (s, 3H, OCH_3), 3.55 (d/d, *J*=9.0/4.0, 1H, CHHOCH$_3$), 3.74–4.01 (m, 5H, CHOSi, OCH_2CH_2O), 4.80 (t, *J*=4.5, 1H, (CH$_2$O)$_2$CH). ^{13}C NMR (75 MHz): δ −4.61 (SiCH_3), −4.05 (SiCH_3), 14.22 (CH$_2$CH_3), 18.07 (*C*(CH$_3$)$_3$), 20.93 (NCH$_2$CH_2), 23.28 (*C*H$_2$CH$_3$), 24.77 (NCHCH_2), 25.98 (C(*C*H$_3$)$_3$), 26.06 ((CH$_2$O)$_2$CHCH$_2$CH_2), 28.53 (*C*H$_2$CH$_2$CH$_3$), 30.64 ((CH$_2$O)$_2$CH*C*H$_2$), 31.03 (*C*H$_2$(CH$_2$)$_2$CH$_3$), 56.60 (N*C*H$_2$), 59.00 (CH$_2$O*C*H$_3$), 62.97 (N*C*H(CH$_2$)$_3$CH$_3$), 64.85 ((*C*H$_2$O)$_2$CH), 65.84

(NCHCH$_2$), 72.84 (*C*HOSi), 74.75 (*C*H$_2$OCH$_3$), 104.90 ((CH$_2$O)$_2$*C*H). MS (EI): *m*/*z* (%) 444 (6, M$^{+\cdot}$), 200 (13), 199 (100), 129 (8), 114 (7), 113 (5), 85 (6), 73 (10), 70 (9). IR (film): *v* 2955, 2858 (CH), 1729, 1471, 1408, 1380, 1361, 1256, 1198, 1131, 1097, 1062, 1005, 941, 919, 897, 836, 813, 775, 738, 663. HR-MS calcd for $C_{23}H_{48}N_2O_4Si^{+\cdot}$: 444.3383. Found: 444.3384.

4.2.4. (1*R*,2*S*,2*S*)-(−)-*N*-[1-*tert*-Butyl-2-(*tert*-butyldimethylsilyloxy)-4-[1,3]dioxolan-2-yl-butyl]-*N*-(2-methoxymethylpyrrolidin-1-yl)-amine 13c. Hydrazone **12** (880 mg, 2.3 mmol) was allowed to react with 2.0 equiv. of *t*-butyllithium according to the procedure described in Section 4.1.1.1. Flash column chromatography (silica, pentane–Et$_2$O, 3:1) gave **13c** (780 mg, 77%). R_f (silica, pentane–Et$_2$O, 2:1): 0.6. *de* >96% (^{13}C NMR). $[\alpha]_D^{30}$ −91.4 (*c* 1.15, CHCl$_3$). ^{1}H NMR (300 MHz): δ 0.08 (s, 3H, SiC*H*$_3$), 0.09 (s, 3H, SiC*H*$_3$), 0.91 (s, 9H, SiC(C*H*$_3$)$_3$), 1.01 (s, 9H, NCHC(C*H*$_3$)$_3$), 1.45–1.99 (m, 8H, NCH$_2$C*H*$_2$C*H*$_2$, (CH$_2$O)$_2$CHC*H*$_2$C*H*$_2$), 2.50 (m, 1H, NC*H*CH$_2$OCH$_3$), 2.71 (m, 1H, NC*H*C(CH$_3$)$_3$), 3.31–3.52 (m, 3H, NC*H*$_2$CH$_2$, C*H*HOCH$_3$), 3.35 (s, 3H, OC*H*$_3$), 3.74 (m, 1H, CH*H*OCH$_3$), 3.71–4.01 (m, 5H, C*H*OSi, OC*H*$_2$C*H*$_2$O), 4.80 (m, 1H, (CH$_2$O)$_2$C*H*). ^{13}C NMR (75 MHz): δ −4.64 (Si*C*H$_3$), −3.70 (Si*C*H$_3$), 18.08 (Si*C*(CH$_3$)$_3$), 20.69 (NCH$_2$*C*H$_2$), 26.05 (SiC-(*C*H$_3$)$_3$), 26.64 (NCH*C*H$_2$), 27.05 ((CH$_2$O)$_2$CH-CH$_2$*C*H$_2$), 28.86 (SiC(*C*H$_3$)$_3$), 31.35 ((CH$_2$O)$_2$CH*C*H$_2$), 34.26 (NH*C*(CH$_3$)$_3$), 56.22 (N*C*H$_2$), 58.96 (CH$_2$O*C*H$_3$), 64.81 ((*C*H$_2$O)$_2$CH), 66.33 (N*C*HC(CH$_3$)$_3$), 70.23 (N*C*HCH$_2$), 72.86 (*C*HOSi), 75.36 (*C*H$_2$OCH$_3$), 104.74 ((CH$_2$O)$_2$*C*H). MS (EI): *m*/*z* (%) 444 (5, M$^{+\bullet}$), 200 (13), 199 (100), 129 (5), 114 (6), 99 (6), 73 (9), 70 (9), 57 (6). IR (film): *v* = 2955, 2858 (CH), 1472, 1392, 1361, 1256, 1216, 1200, 1128, 1075, 1037, 1006, 982, 941, 835, 813, 774, 759, 666. HR-MS calcd. for $C_{23}H_{48}N_2O_4Si^{+\bullet}$: 444.3383. Found: 444.3383.

4.2.5. (1*R*,2*S*,2*S*)-(−)-*N*-{1-[1-(*tert*-Butyldimethylsilyloxy)-3-[1,3]dioxolan-2-yl-propyl]-heptyl}-*N*-(2-methoxymethylpyrrolidin-1-yl)-amine 13d. Hydrazone **12** (615 mg, 1.59 mmol) was allowed to react with 3.0 equiv. of *n*-hexyllithium according to the procedure described in Section 4.1.1.1 at −30°C. Flash column chromatography (silica, pentane–Et$_2$O, 3:1) gave **13d** (342 mg, 45%). R_f (silica, pentane–Et$_2$O, 2:1): 0.7. *de* >96% (^{13}C NMR). $[\alpha]_D^{26}$ −99.8 (*c* 1.03, CHCl$_3$). ^{1}H NMR (300 MHz): δ = 0.04 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$), 0.88 (s, 9H, C(C*H*$_3$)$_3$), 1.20 (t, *J* = 8.3, 3H, CH(CH$_2$)$_5$C*H*$_3$), 1.26 (m, 10H, CH(C*H*$_2$)$_5$CH$_3$), 1.46–2.09 (m, 8H, NCH$_2$C*H*$_2$C*H*$_2$, (CH$_2$O)$_2$CHC*H*$_2$C*H*$_2$), 2.52 (m, 1H, NC*H*CH$_2$OCH$_3$), 2.70 (m, 1H, NC*H*(CH$_2$)$_5$CH$_3$), 3.22 (d/d, *J* = 18.0/8.8, 1H, C*H*HOCH$_3$), 3.35 (s, 3H, OC*H*$_3$), 3.54 (d/d, *J* = 9.2/4.0, 1H, CH*H*OCH$_3$), 3.83 (m, 2H, OC*H*$_2$CH$_2$O), 3.97 (m, 2H, OCH$_2$C*H*$_2$O), 4.87 (m, 1H, C*H*(OCH$_2$)$_2$) ppm. ^{13}C NMR (75 MHz): δ −4.48 (Si*C*H$_3$), −4.42 (Si*C*H$_3$), 14.09 (CH$_2$*C*H$_3$), 18.05 (*C*(CH$_3$)$_3$), 21.03 (NCH$_2$*C*H$_2$), 22.65 (*C*H$_2$CH$_3$), 24.92 (NCH*C*H$_2$), 25.94 (C(*C*H$_3$)$_3$), 25.98 (*C*H$_2$CH$_2$CH$_3$), 26.81 ((CH$_2$O)$_2$CHCH$_2$*C*H$_2$), 27.11 (*C*H$_2$(CH$_2$)$_2$CH$_3$), 29.63 (*C*H$_2$(CH$_2$)$_3$CH$_3$), 31.68 ((CH$_2$O)$_2$CH*C*H$_2$), 31.75 (*C*H$_2$(CH$_2$)$_4$CH$_3$), 56.73 (N*C*H$_2$), 59.09 (CH$_2$O*C*H$_3$), 62.98 (N*C*H(CH$_2$)$_4$CH$_3$), 64.83 ((*C*H$_2$O)$_2$CH), 65.11 (N*C*HCH$_2$), 72.90 (*C*HOSi), 75.74 (*C*H$_2$OCH$_3$), 105.06 ((CH$_2$O)$_2$*C*H). MS (EI): *m*/*z* (%) 472 (11, M$^{+\bullet}$), 228 (15), 227 (100), 129 (10), 114 (7), 113 (6), 73 (8), 70 (9). IR (film): *v* 2955, 2928, 2856 (CH), 1471, 1407, 1390, 1361, 1255, 1197, 1128, 1095, 1060, 1041, 1006, 940, 916, 836, 814, 775, 665. HR-MS calcd. for $C_{25}H_{52}N_2O_4Si^{+\bullet}$: 472.3696. Found: 472.3699.

4.2.6. (1*R*,2*S*,2*S*)-(−)-*N*-{1-[2-(*tert*-Butyldimethylsilyloxy)-4-[1,3]dioxolan-2-yl-1-phenylethylbutyl]}-*N*-(2-methoxymethylpyrrolidin-1-yl)-amine 13e. Hydrazone **12** (610 mg, 1.58 mmol) was allowed to react with 3.0 equiv. of 2-phenylethyllithium according to the procedure described in Section 4.1.1.1. Flash column chromatography (silica, pentane–Et$_2$O, 3:1) gave **13e** (710 mg, 91%). R_f (silica, pentane–Et$_2$O, 1:1): 0.7. *de* >96% (^{13}C NMR). $[\alpha]_D^{24}$ −79.95 (*c* 1.10, CHCl$_3$). ^{1}H NMR (300 MHz): δ 0.08 (s, 3H, SiC*H*$_3$), 0.10 (s, 3H, SiC*H*$_3$), 0.91 (s, 9H, C(C*H*$_3$)$_3$), 1.15–2.08 (m, 10H, C*H*$_2$CH$_2$Ph, NCH$_2$C*H*$_2$C*H*$_2$, (CH$_2$O)$_2$CHC*H*$_2$C*H*$_2$), 2.55 (m, 1H, NC*H*CH$_2$OCH$_3$), 2.68 (m, 1H, CH$_2$C*H*$_2$Ph), 3.27–3.52 (m, 5H, NC*H*$_2$CH$_2$, NC*H*CH$_2$CH$_2$Ph, C*H*$_2$OCH$_3$), 3.32 (s, 3H, OC*H*$_3$), 3.62 (m, 1H, C*H*OSi), 3.76–4.05 (m, 4H, (C*H*$_2$O)$_2$CH), 4.88 (m, 1H, CH$_2$O)$_2$C*H*), 7.16–7.28 (m, 5H, Ar–*H*). ^{13}C NMR (75 MHz): δ −4.68 (Si*C*H$_3$), −4.17 (Si*C*H$_3$), 18.07 (*C*(CH$_3$)$_3$), 20.98 (NCH$_2$*C*H$_2$), 24.92 (NCH*C*H$_2$), 25.95 (C(*C*H$_3$)$_3$), 26.26 (*C*H$_2$CH$_2$Ph), 30.89, 32.25, 32.85 ((CH$_2$O)$_2$CH*C*H$_2$-*C*H$_2$, CH$_2$*C*H$_2$Ph), 56.44 (N*C*H$_2$), 58.96 (CH$_2$O*C*H$_3$), 62.03 (NC*H*CH$_2$CH$_2$Ph), 64.78, 64.79 ((*C*H$_2$O)$_2$CH), 65.79 (N*C*HCH$_2$), 73.16 (*C*HOSi), 75.01 (*C*H$_2$OCH$_3$), 104.75 ((CH$_2$O)$_2$*C*H), 125.59 (Ar–C_{para}), 128.19, 128.39 (Ar–$C_{ortho,meta}$), 142.63 (Ar–C_{ipso}). MS (EI): *m*/*z* (%) 492 (8, M$^{+\bullet}$), 341 (16), 261 (9), 248 (17), 247 (100), 245 (8), 201 (11), 131 (6), 129 (12), 117 (17), 115 (14), 114 (11), 113 (25), 99 (13), 91 (33), 85 (8), 75 (25), 73 (65), 70 (13). IR (film): *v* 3014, 2953, 2930, 2884, 2857, 1469, 1254, 1217, 1127, 1090, 1047, 1006, 835, 716, 700. HR-MS calcd. for $C_{27}H_{48}N_2O_4Si^{+\bullet}$: 492.3383. Found: 492.3384.

4.2.7. (2*R*,3*S*)-(+)-2-Methyl-piperidin-3-ol 5a. According to the procedure described in Section 4.1.1.2. Hydrazine **13a** (400 mg, 0.99 mmol) was employed in the cleavage of the auxiliary and the subsequent ring closure. Flash column chromatography (silica, CH$_2$Cl$_2$–MeOH, 1:1) gave **5a** (59 mg, 59%). R_f (silica, MeOH): 0.1. *de*, *ee* >96% (^{1}H, ^{13}C NMR). $[\alpha]_D^{26}$ 16.2 (*c* 0.92, CHCl$_3$). Mp 130°C. ^{1}H NMR (400 MHz): δ 0.93 (t, *J* = 7.4, 3H, NCHC*H*$_3$), 1.35–1.62 (m, 2H, C*H*HCHO, NCH$_2$-C*H*H), 1.77 (m, 1H, NCH$_2$CH*H*), 1.97 (m, 1H, CH*H*-CHO), 2.41 (m, 1H, NC*H*), 2.49 (br s, 2H, N*H*, O*H*), 2.54 (m, 1H, NC*H*H), 2.81 (m, 1H, NCH*H*), 3.25 (m, 1H, C*H*O). ^{13}C NMR (100 MHz): δ 15.32 (NCH*C*H$_3$), 22.89 (NCH$_2$*C*H$_2$), 33.76 (*C*H$_2$CHO), 45.71 (N*C*H$_2$), 62.64 (N*C*H), 71.65 (O*C*H). Mass (CI): *m*/*z* (%) 117 (6, M$^{+\bullet}$+2), 116 (100, M$^{+\bullet}$+1), 84 (7, M$^{+\bullet}$–OH, –CH$_3$), 70 (8). IR (CHCl$_3$): *v* 3399 (br s, NH, OH), 2943, 2757, 2685, 2490, 1626, 1460, 1397, 1120, 1068, 1039. Anal. calcd for $C_6H_{13}NO$: C, 62.57; H, 11.34; N, 12.16. Found: C, 62.43, H, 11.21; N, 12.25%.

4.2.8. (2*R*,3*S*)-(+)-2-*n*-Butyl-piperidin-3-ol 5b. According to the procedure described in Section 4.1.1.2 hydrazine **13b** (800 mg, 1.79 mmol) was employed in the cleavage of the auxiliary and the subsequent ring closure. Flash column chromatography (silica, CH_2Cl_2–MeOH, 1:1) gave **5b** (170 mg, 62%). R_f (silica, CH_2Cl_2–MeOH): 0.2. *de*, *ee* >96% (^1H, ^{13}C NMR). $[\alpha]_D^{26}$ 28.6 (*c* 1.90, $CHCl_3$). Mp 117°C. ^1H NMR (400 MHz): δ 0.91 (t, $J=7.1$, 3H, CH_2CH_3), 1.23–1.57 (m, 7H, $CH_2CH_2CH_3$, CHHCHO, NCH_2CHH, NCHCHH), 1.72 (m, 1H, NCH_2CHH), 1.86 (m, 1H, NCHCHH), 2.03 (m, 1H, CHHCHO), 2.33 (t/d, $J=8.2/3.1$, 1H, CHN), 2.42 (s, 2H, OH, NH), 2.55 (t/d, $J=11.6/3.0$, 1H, NCHH), 2.96 (m, 1H, NCHH), 3.32 (d/d/d, $J=6.1/8.5/10.2$, 1H, CHO). ^{13}C NMR (100 MHz): δ 14.05 (CH_2CH_3), 22.93 (CH_2CH_3), 25.27 (NCH_2CH_2), 27.96 ($CH_2CH_2CH_3$), 31.75 ($NCHCH_2$), 33.83 (CH_2CHO), 45.66 (NCH_2), 62.74 (NCH), 71.76 (OCH). Mass (EI): *m*/*z* (%) 157 (10, $M^{+\bullet}$), 128 (11), 101 (5), 100 (100, $M^{+\bullet}$–*n*Bu), 84 (19), 71 (6), 56 (13). IR (KBr): *v* 3434 (OH), 3291 (NH), 2933, 2858, 2875 (CH), 1653, 1636, 1496, 1469, 1383, 1341, 1177, 1153, 1122, 1103, 1081, 1051, 1010, 985, 952, 929, 895, 871, 854, 828, 773, 740, 593, 455. Anal. calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.93, H, 11.89; N, 8.59%.

4.2.9. (2*R*,3*S*)-(+)-2-*tert*-Butyl-piperidin-3-ol 5c. According to the procedure described in Section 4.1.1.2 hydrazine **13c** (780 mg, 1.75 mmol) was employed in the cleavage of the auxiliary and the subsequent ring closure. Flash column chromatography (silica, CH_2Cl_2–MeOH, 1:1) gave **5c** (140 mg, 51%). R_f (silica, CH_2Cl_2–MeOH, 1:2): 0.3. *de*, *ee* >96% (^1H, ^{13}C NMR). $[\alpha]_D^{26}$ 35.7 (*c* 1.04, $CHCl_3$). Mp. 109°C. ^1H NMR (400 MHz): δ 0.95 (s, 9H, $C(CH_3)_3$), 1.41–1.72 (m, 2H, NCH_2CH_2), 1.84 (m, 1H, CHHCHO), 2.01 (m, 1H, CHHCHO), 2.11 (d, $J=8.8$, NCH), 2.50 (t/d, $J=11.8/3.0$, $NCHHCH_2$), 2.61 (s, 2H, NH, OH), 3.01 (m, 1H, $NCHHCH_2$), 3.54 (m, 1H, CHO). ^{13}C NMR (100 MHz): δ 25.94 (NCH_2CH_2), 26.73 (CH_2CHO), 27.70 ($C(CH_3)_3$), 34.47 ($C(CH_3)_3$), 47.12 (NCH_2), 65.47 (NCH), 71.43 (OCH). Mass (CI): *m*/*z* (%) 159 (4, $M^{+\bullet}$+2), 158 (49, $M^{+\bullet}$+1), 141 (10), 140 (100, $M^{+\bullet}$–OH), 100 (10, $M^{+\bullet}$–*tert*-butyl). IR ($CHCl_3$): *v* 3364 (OH, NH), 2951, 2868 (CH), 1476, 1396, 1364, 1261, 1120, 1073, 1000, 755. Anal. calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.91, H, 12.03; N, 8.69%.

4.2.10. (2*R*,3*S*)-(+)-2-*n*-Hexyl-piperidin-3-ol 5d. According to the procedure described in Section 4.1.1.2 hydrazine **13d** (270 mg, 0.57 mmol) was employed in the cleavage of the auxiliary and the subsequent ring closure. Flash column chromatography (silica, CH_2Cl_2–MeOH, 1:1) gave **5d** (70 mg, 67%). R_f (silica, CH_2Cl_2–MeOH, 1:1): 0.2. *de*, *ee* >96% (^1H, ^{13}C NMR). $[\alpha]_D^{26}$ 32.7 (*c* 1.06, $CHCl_3$). Mp 101°C. ^1H NMR (400 MHz): δ 0.89 (t, $J=6.6$, 3H, CH_2CH_3), 1.26–1.58 (m, 11H, $CHH(CH_2)_4CH_3$, CHHCHO, NCH_2CHH), 1.74 (m, 1H, NCH_2CHH), 1.86 (m, 1H, NCHCHH), 2.03 (m, 1H, CHHCHO), 2.37 (t/d, $J=3.0/8.3$, 1H, CHN), 2.54–2.64 (m, 3H, NCHH, OH, NH), 3.01 (d, $J=11.8$, 1H, NCHH), 3.27 (d/d/d, $J=4.2/8.8/18.7$, 1H, CHO). ^{13}C NMR (100 MHz): δ 14.07 (CH_2CH_3), 22.60 (CH_2CH_3), 24.97 (NCH_2CH_2), 25.75, 29.40, 31.76 ($CH_2(CH_2)_3CH_3$), 31.92 ($NCHCH_2$), 33.61 (CH_2CHO), 45.49 (NCH_2), 62.69 (NCH), 71.52 (OCH). Mass (EI): *m*/*z* (%) 185 (8, $M^{+\bullet}$), 128 (13, $M^{+\bullet}$–*n*Bu), 126 (5), 101 (6), 100 (100, $M^{+\bullet}$–*n*hex), 84 (19), 71 (5), 70 (5). IR (KBr): *v* 3421 (OH), 3291 (NH), 3154 (OH), 2933, 2854, 2823 (CH), 1470, 1341, 1176, 1122, 1103, 1061, 1045, 1022, 980, 929, 911, 888, 846, 724, 592. Anal. calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.05, H, 12.62; N, 7.67%.

4.2.11. (2*R*,3*S*)-(+)-2-(2-Phenylethyl)-piperidin-3-ol 5e. According to the procedure described in Section 4.1.1.2 hydrazine **13e** (700 mg, 1.42 mmol) was employed in the cleavage of the auxiliary and the subsequent ring closure. Flash column chromatography (silica, CH_2Cl_2–MeOH, 1:1) gave **5e** (220 mg, 76%). R_f (silica, CH_2Cl_2–MeOH, 1:1): 0.3. *de*, *ee* >96% (^1H, ^{13}C NMR). $[\alpha]_D^{26}$ 26.8 (*c* 1.0, $CHCl_3$). Mp 116°C. ^1H NMR (300 MHz): δ 1.22–1.90 (m, 4H, NCH_2CH_2CHH, $CHHCH_2Ph$), 1.95–2.10 (m, 1H, NCH_2CH_2CHH), 2.15–2.28 (m, 1H, $CHHCH_2Ph$), 2.35–2.71 (m, 5H, NH, OH, CHHPh, NCHH, NCH), 2.73–2.84 (m, 1H, CHHPh), 2.92–3.05 (m, 1H, NCHH), 3.18–3.30 (m, 1H, CHO), 7.14–7.29 (m, 5H, Ar–H). ^{13}C NMR (75 MHz): δ 25.48 (NCH_2CH_2), 32.23 (CH_2Ph), 34.06, 34.13 ($NCHCH_2$, CH_2CHO), 45.74 (NCH_2), 62.54 (NCH), 71.68 (OCH), 125.78 (Ar–C_{para}), 128.33, 128.38 (Ar–$C_{ortho,meta}$), 142.23 (Ar–C_{ipso}). Mass (EI): *m*/*z* (%) 205 (22, $M^{+\bullet}$), 174 (16), 160 (8), 134 (18), 133 (8), 132 (22), 117 (11), 114 (23), 100 (100, $M^{+\bullet}$–$(CH_2)Ph$), 90 (44), 84 (6), 70 (8), 69 (8). IR (KBr): *v* 3439 (OH), 3286 (NH), 3155 (OH), 3061 (Ar–H), 2944, 2894, 2859, 2825 (CH), 1601, 1494, 1463, 1336, 1177, 1107, 1075, 1052, 1025, 982, 931, 898, 878, 854, 741, 695, 585. Anal. calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.95, H, 9.24; N, 7.04%.

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