Enantioselective Synthesis of Differently Protected 1,2-Diamines via α-Alkylation of Dibenzylaminoacetaldehyde SAMP-Hydrazone

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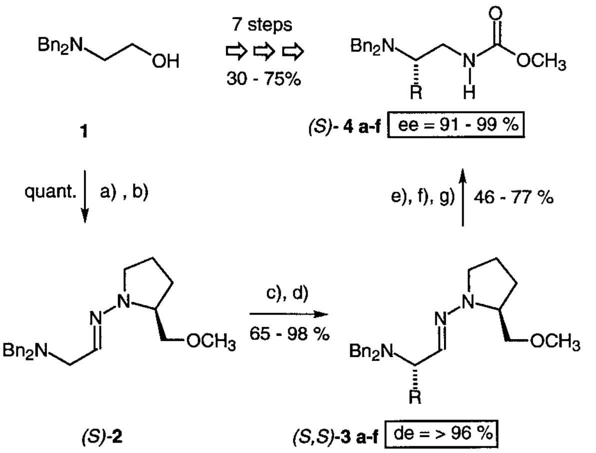
Dedicated to Professor Richard Neidlein on the occasion of his 60th birthday

Chiral, unsymmetrically and differently protected 1,2-diamines **4** were prepared in moderate to good overall yields and with high asymmetric inductions (ee = 91–99 %) by α-alkylation of *N*,*N*-dibenzylaminoacetaldehyde SAMP-hydrazone (*S*)-**2** with subsequent oxidative cleavage to the corresponding α-aminonitriles, reduction to the diamines, and protection of the latter.

Vicinal diamines are not only of great importance in medicinal chemistry, for example in cancer therapy, but there is also a growing interest in these compounds because of their use as chiral ligands and auxiliaries in asymmetric synthesis, for instance, in the enantioselective reduction of prochiral ketones, enantioselective 1,2-addition of organometallics to aldehydes, Diels–Alder, Michael, and aldol reactions, or for asymmetric dihydroxylation of prochiral alkenes with osmium tetroxide.[1] A new method for the determination of enantiomeric excesses of chiral alcohols, thiols and amines is also based on the use of vicinal 1,2-diamines.[2]

Most recent syntheses of enantiopure 1,2-diamines started from amino acids (ex-chiral pool).[1,3–6] A novel protocol for the preparation of racemic 1,2-diamines is based on *N*-alkylaminomethyl carbanion equivalents.[7]

We now wish to report the enantioselective synthesis of unsymmetrical, differently protected 1,2-diamines, based on our SAMP/RAMP-hydrazone method[8] via the α-alkylation of *N*,*N*-dibenzylaminoacetaldehyde (SAMP-hydrazone (*S*)-**2**.



Reactions / conditions: a) DMSO, $(COCl)_2$, NEt_3, –78°C to rt. b) SAMP, molecular sieves, 0°C to rt, quantitative. c) 1.2 to 3.0 eq. hexane free LDA, THF, –78°C, then d) 1.5 to 3.5 eq. RX, –100°C to rt. e) 1.1 eq. MMPP, MeOH, –78° C to 0°C, then f) 1.0 eq. LAH, –78°C to rt, then g) 1.5 eq. NEt_3, 1.0 eq. $ClCO_2Me$, 0°C to rt.

Scheme 1

Hydrazone (*S*)-**2**, easily prepared in good overall yield starting from glycine, was deprotonated with lithium diisopropylamide in tetrahydrofuran and alkylated with various electrophiles. For complete deprotonation it was neccessary to use an excess of three equivalents of base and/or to keep the reaction mixture at – 78 °C for 24 hours. Complete degradation occurred when the reaction mixtures were allowed to warm up to 0 °C after the addition of the hydrazone **2**, presumably by kinetically favoured deprotonation of the aldehyde proton, followed by elimination of (*S*)-methoxymethylpyrrolidine to give *N*,*N*-dibenzylaminoacetonitrile. It was also impossible to use *tert*-butyllithium for the deprotonation because of competitive addition to the CN double bond under these conditions. In the case of more sensitive electrophiles such as benzyl bromide better yields were obtained when only a slight excess of LDA was used to avoid side reactions. To obtain high asymmetric inductions it was crucial to use hexane-free LDA. After complete deprotonation it was cooled to – 100 °C and the electrophiles were added slowly. After reaction overnight and workup, the *N*,*N*-dibenzylamino-SAMP-hydrazones (*S*,*S*)-**3a–f** were obtained in good to very good yields and with high diastereomeric excess (de ≥ 96 %, see Table 1).

In cases of incomplete alkylation, the products could easily be separated by simple flash column chromatography on silica gel (petrol ether/diethyl ether, 1 : 1) with recycling of the starting material (*S*)-**2**. To avoid partial racemisation at this stage it was crucial to deactivate the silica gel by the addition of 2 % triethylamine. Diastereomeric enrichment during chromatography was disproven by NMR spectroscopy, indicating the original asymmetric induction of the crude material. Nevertheless, a

Table 1. α-Alkylated Dibenzylamino-SAMP-Hydrazones (*S*,*S*)-**3** Prepared

Product	R	X	Yield[a] (%)	$[\alpha]_D^{RT}$ (*c*, $CHCl_3$)	de[b] (%)
(*S*,*S*)-**3a**	methyl	I	98[c]	– 181.3 (1.21)	> 96
(*S*,*S*)-**3b**	ethyl	I	97[c]	– 142.1 (1.30)	> 96
(*S*,*S*)-**3c**	isopropyl	I	93[c]	– 154.1 (1.34)	> 96
(*S*,*S*)-**3d**	benzyl	Br	68[d]	– 109.9 (1.31)	> 96
(*S*,*S*)-**3e**	allyl	Br	90[d]	– 146.3 (1.67)	> 96
(*S*,*S*)-**3f**	benzyloxymethyl	Cl	61[d]	– 97.69 (1.52)	> 96

[a] Yield of product **3** based on dibenzylaminoacetaldehyde SAMP-hydrazone **2**.
[b] Determined by ^1H and ^{13}C NMR spectroscopy.
[c] Deprotonation with 3.0 eq. LDA, alkylation with 3.5 eq. RX.
[d] Deprotonation with 1.2 eq. LDA, alkylation with 1.5 eq. RX.

Table 2. 2-Dibenzyl-1-methoxycarbonyl-Protected 1,2-Diamines (*S*)-**4** Prepared

Product	R	Yield[a] (%)	$[\alpha]_D^{RT}$ (c, $CHCl_3$)	ee[b] (%)
(*S*)-**4a**	methyl	77	+ 12.7 (1.61)	99
(*S*)-**4b**	ethyl	74	− 2.5 (1.61)	99
(*S*)-**4c**	isopropyl	66	− 20.6 (1.10)	99
(*S*)-**4d**	benzyl	68	+ 22.8 (1.06)	91
(*S*)-**4e**	allyl	73	+ 2.3 (1.45)	99
(*S*)-**4f**	benzyloxymethyl	49	+ 31.9 (1.16)	97

[a] Yield of product **4** based on the alkylated SAMP-hydrazones **3**.

[b] Determined by HPLC employing the chiral stationary phase Daicel OD® (cyclohexane/isopropanol, 95 : 5).

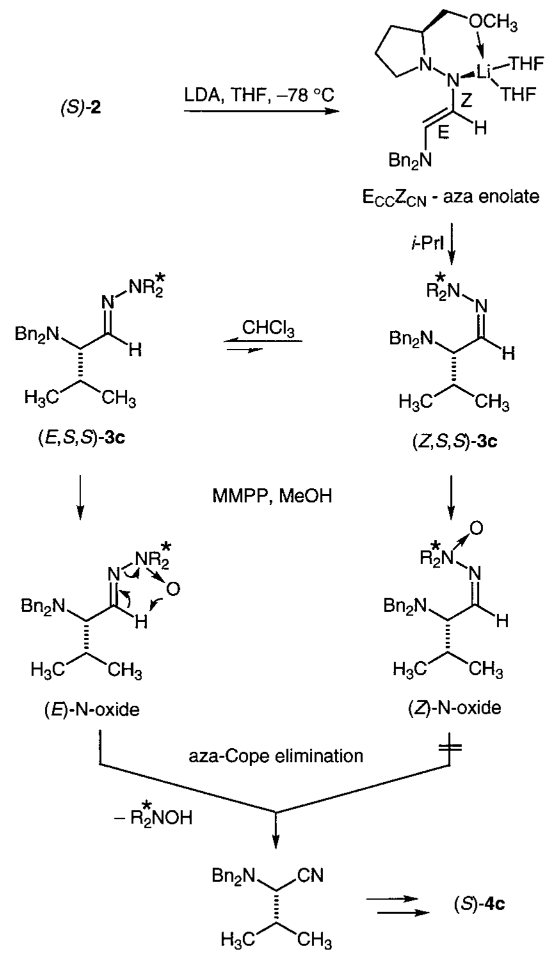
(*Z*)/(*E*)-isomerisation towards the thermodynamically favoured (*E*)-hydrazone occurred during chromatography to give almost completely (*E*)-hydrazones. One notable exception was example (*S*,*S*)-**3c** (R = *i*-Pr, *vide supra*).

The absolute configuration at the new stereogenic centre was assigned by comparison with optical rotation values of the SAMP-hydrazones prepared starting from the corresponding (*S*)-amino acids in examples (*S*,*S*)-**3a** [(*S*)-alanine] and (*S*,*S*)-**3c** [(*S*)-valine]. In both cases the hydrazones formed by α-alkylation were shown to have the (*S*)-configuration at the new stereogenic centre, as was predicted from the mechanism of the SAMP-hydrazone alkylations.[9]

Unfortunately, so far it has not been possible to obtain the corresponding synthetically interesting *N*,*N*-dibenzylaminoaldehydes by one-step cleavage of the hydrazones (*S*,*S*)-**3a–f**, but the oxidative cleavage with magnesium monoperoxyphthalate (MMPP) gave the corresponding α-aminonitriles in good yield. These crude aminonitriles were directly reduced to the unsymmetrical 1,2-diamines with lithium aluminium hydride and were then protected as their methyl carbamates because of the high sensitivity of the free primary amines in air and their difficult purification. The differently protected 1,2-diamines (*S*)-**4a–f** could be obtained in moderate to good overall yields and with high asymmetric inductions (ee = 91–99 %, see Table 2).

The enantiomeric excesses were determined by HPLC, indicating that no racemisation occurred in the reactions from the hydrazones (*S*,*S*)-**3** to the corresponding 1,2-diamines (*S*)-**4**, except in the case of compound (*S*,*S*)-**3d** where R was benzyl. Here partial racemisation was found and the best ee value that could be obtained was 91 %.

In the case of (*S*,*S*)-**3c** (R = *i*-Pr) an interesting observation was made. According to the proposed metallo-retentive mechanism for electrophilic substitutions with SAMP-hydrazones, the aza-enolate adopts the $E_{CC}Z_{CN}$-configuration with the pyrrolidine ring virtually perpendicular to the CCNN-plane and intramolecular methoxy chelation of the lithium ion. Regeneration of the hydrazone CN double bond via electrophilic α-alkylation of the aza-enolate thus affords the kinetic (*Z*)-hydrazone, which is readily isomerised to the thermodynamically more stable (*E*)-isomer upon warming, isolation, and purification procedures. This was observed in all cases except (*S*,*S*)-**3c**, which was isolated after chromatographic purification as the (*Z*)-hydrazone. Attempts to cleave the hydrazone CN double bond of (*Z*,*S*,*S*)-**3c** with MMPP failed. However, isomerisation to (*E*,*S*,*S*)-**3c** by prolonged standing in chloroform and subsequent oxidative cleavage with MMPP proved facile, supporting the proposed aza-Cope-type elimination mechanism of the hydrazone/nitrile conversion (Scheme 2).[10]



Scheme 2

In summary, an efficient enantioselective synthesis of differently protected unsymmetrical 1,2-diamines via α-alkylation of *N*,*N*-dibenzylaminoacetaldehyde SAMP-hydrazone (*S*)-**2** followed by oxidative cleavage to the corresponding intermediate α-aminonitriles with subsequent reduction and methoxycarbonyl protection to the 1,2-diamines has been developed. Because a selective deprotection of either amine function should be possible, the compounds could serve as novel chiral building blocks, for example in the synthesis of heterocycles[11] or bioactive compounds in general. An extension of this new diamine synthesis by combination with the highly diastereoselective 1,2-addition to aldehyde SAMP-hydrazones[14] is currently being investigated in our laboratories.[15]

Table 3. Spectroscopic Data of the 2-Dibenzylamino-SAMP-Hydrazones (*S*,*S*)-**3a–f**[a]

	IR (neat) ν ($\mathrm{cm^{-1}}$)	^{1}H NMR ($\mathrm{CDCl_3}$/TMS) δ (ppm), J (Hz)	^{13}C NMR ($\mathrm{CDCl_3}$/TMS) δ (ppm)	MS (70 eV) m/z (%)
3a	2975, 2930, 2879, 2828, 1494, 1454, 1217, 1117, 1075, 1029, 757, 699	1.22 (d, 6.9 Hz, 3 H, $\mathrm{CH_3}$), 1.73–2.00 (m, 4 H, $\mathrm{N-CHR-C}H_2$), 2.69 (m, 1 H, $\mathrm{N-C}H\mathrm{-CH_2-OCH_3}$), 3.37 (s, 3 H, $\mathrm{OCH_3}$), 3.64 (s, 2 H, $\mathrm{N-CH_2-Ph}$), 3.65 (s, 2 H, $\mathrm{N-CH_2-Ph}$), 3.25–3.62 (m, 5 H, $\mathrm{N=CH-C}H\mathrm{R}$, $\mathrm{C}H_2\mathrm{-OCH_3}$), $\mathrm{N-CH_2}$), 6.63 (d, 4.7 Hz, 1 H, $\mathrm{N=CH}$), 7.15–7.42 (m, 10 H, CH-arom)	13.9 ($\mathrm{CH_3}$), 22.6, 27.2 ($\mathrm{N-CHR-}C\mathrm{H_2}$), 50.3 ($\mathrm{N-CH_2}$), 54.5 ($\mathrm{N-CH_2-Ph}$), 55.9 ($\mathrm{N=CH-}C\mathrm{HR}$), 59.9 ($\mathrm{N-}C\mathrm{H-CH_2-OCH_3}$), 63.8 ($\mathrm{OCH_3}$), 75.3 ($C\mathrm{H_2-OCH_3}$), 127.3, 128.7, 129.3 (CH-arom.), 139.7 ($\mathrm{N=CH}$), 141.2 (C-arom)	365 (1.1, $\mathrm{M^{+\bullet}}$), 350 (16, $\mathrm{M^{+\bullet}}$ – 15), 274 (13), 224 (23), 196 (15), 170 (100), 169 (18), 125 (22), 91 (44).
3b	2969, 2930, 2874, 2825, 1494, 1454, 1245, 1119, 1074, 1028, 963, 906, 746, 699	0.98 (t, 7.4 Hz, 3 H, $\mathrm{CH_3}$), 1.61–2.10 (m, 6 H, $\mathrm{N-CHR-C}H_2$, $\mathrm{N-CH-C}H_2$), 2.81 (m, 1 H, $\mathrm{N-C}H\mathrm{-CH_2-OCH_3}$), 3.20 (m, 1 H, $\mathrm{N=CH-C}H\mathrm{R}$), 3.48 (s, 3 H, $\mathrm{OCH_3}$), 3.61 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.86 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.35–3.75 (m, 4 H, $\mathrm{C}H_2\mathrm{-OCH_3}$, $\mathrm{N-CH_2}$), 6.64 (d, 6.6 Hz, 1 H, $\mathrm{N=CH}$), 7.17–7.49 (m, 10 H, CH-arom.).	11.3 ($\mathrm{CH_3}$), 22.6, 24.1 ($\mathrm{N-CHR-}C\mathrm{H_2}$), 27.1 ($\mathrm{N-CH-}C\mathrm{H_2}$), 50.3 ($\mathrm{N-CH_2}$), 54.5 ($\mathrm{N-CH_2-Ph}$), 59.9 ($\mathrm{N=CH-}C\mathrm{HR}$), 62.0 ($\mathrm{N-}C\mathrm{H-CH_2-OCH_3}$), 63.9 ($\mathrm{OCH_3}$), 75.2 ($C\mathrm{H_2-OCH_3}$), 127.2, 128.7, 129.4 (CH-arom.), 137.5 ($\mathrm{N=CH}$), 141.2 (C-arom.)	350 (18, $\mathrm{M^{+\bullet}}$ – 29), 264 (4), 235 (5), 174 (23), 146 (13), 106 (6), 92 (10), 91 (100), 65 (12)
3c	2957, 2926, 2873, 2827, 1494, 1454, 1374, 1323, 1304, 1281, 1242, 1110, 1070, 974, 740, 699	0.79 (d, 6.6 Hz, 3 H, $\mathrm{CH_3}$), 1.06 (d, 6.6 Hz, 3 H, $\mathrm{CH_3}$), 1.81–2.12 (m, 5 H, $\mathrm{N-CHR-C}H_2$, $\mathrm{CH_3-C}H$)/2.72 (d/d, 8.0, 10.4 Hz, 1 H, $\mathrm{N=CH-C}H\mathrm{R}$), 2.81 (m, 1 H, $\mathrm{N-C}H\mathrm{-CH_2-OCH_3}$), 3.44 (d, 13.5 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.87 (d, 13.5 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.45 (s, 3 H, $\mathrm{OCH_3}$), 3.36–3.72 (m, 4 H, $\mathrm{C}H_2\mathrm{-OCH_3}$, $\mathrm{N-CH_2}$), 6.59 (d, 8.0 Hz, 1 H, $\mathrm{N=CH}$), 7.16–7.46 (m, 10 H, CH-arom.)	20.3, 20.6 ($\mathrm{CH_3}$), 22.0, 26.4 ($\mathrm{N-CHR-}C\mathrm{H_2}$), 28.3 ($\mathrm{CH_3-}C\mathrm{H}$), 49.9 ($\mathrm{N-CH_2}$), 53.9 ($\mathrm{N-CH_2-Ph}$), 59.4 ($\mathrm{N=CH-}C\mathrm{HR}$), 63.2 ($\mathrm{N-}C\mathrm{H-CH_2-OCH_3}$), 66.2 ($\mathrm{OCH_3}$), 74.4 ($C\mathrm{H_2-OCH_3}$), 126.6, 128.1, 128.9 (CH–arom), 136.8 ($\mathrm{N=CH}$), 140.5 (C-arom.)	351 (17, $\mathrm{M^{+\bullet}}$ – 42), 350 (68, $\mathrm{M^{+\bullet}}$ – 43), 302 (12), 252 (17), 204 (14), 198 (17), 159 (10), 92 (9), 91 (100), 70 (8)
3d	3026, 2973, 2926, 2876, 2827, 1495, 1454, 1339, 1242, 1197, 1154, 1120, 1072, 905, 745, 698	1.84–2.10 (m, 4 H, $\mathrm{N-CHR-C}H_2$), 2.80 (m, 1 H, $\mathrm{N-C}H\mathrm{-CH_2-OCH_3}$), 3.10 (m, 2 H, $\mathrm{N-CH-C}H_2\mathrm{-Ph}$), 3.46 (s, 3 H, $\mathrm{OCH_3}$), 3.36–3.76 (m, 5 H, $\mathrm{CX}H_2\mathrm{-OCH_3}$, $\mathrm{N-CH_2}$, $\mathrm{N=CH-C}H\mathrm{R}$), 3.72 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.85 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 6.70 (d, 5.8 Hz, 1 H, $\mathrm{N=CH}$), 7.14–7.38 (m, 15 H, CH-arom.)	22.6, 27.1 ($\mathrm{N-CHR-}C\mathrm{H_2}$), 36.0 ($\mathrm{N-CH-}C\mathrm{H_2-Ph}$), 50.2 ($\mathrm{N-CH_2}$), 54.4 ($\mathrm{N-CH_2-Ph}$), 59.9 ($\mathrm{N=CH-}C\mathrm{HR}$), 61.5 ($\mathrm{N-}C\mathrm{H-CH_2-OCH_3}$), 63.8 ($\mathrm{OCH_3}$), 75.2 ($C\mathrm{H_2-OCH_3}$), 126.3, 127.3, 128.5, 128.7, 129.3, 130.3 (CH-arom), 136.3 ($\mathrm{N=CH}$), 140.7, 140.9 (C-arom.)	441 (0.1, $\mathrm{M^{+\bullet}}$), 351 (18), 350 (72, $\mathrm{M^{+\bullet}}$ – 91), 235 (10), 204 (20), 199 (24), 159 (10), 106 (21), 103 (6), 92 (11), 91 (100), 77 (5), 70 (13), 65 (11)
3e	3027, 2974, 2925, 2877, 2826, 1640, 1494, 1454, 1303, 1245, 1197, 1119, 1072, 908, 747, 699	1.66–1.94 (m, 4 H, $\mathrm{N-CHR-C}H_2$), 2.39 (m, 2 H, $\mathrm{N-CH-C}H_2$), 2.64 (m, 1 H, $\mathrm{N-C}H\mathrm{-CH_2-OCH_3}$), 3.31 (s, 3 H, $\mathrm{OCH_3}$), 3.50 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.68 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.20–3.55 (m, 5 H, $\mathrm{C}H_2\mathrm{-OCH_3}$, $\mathrm{N-CH_2}$, $\mathrm{N=CH-C}H\mathrm{R}$), 4.86–5.08 (m, 2 H, $\mathrm{CH_2}$-alkene), 5.74 (d/d/d/d, 6.6, 10.2, 13.7, 17.0 Hz, 1 H, CH-alkene), 6.48 (d, 6.0 Hz, 1 H, $\mathrm{N=CH}$), 7.06–7.34 (m, 10 H, CH-arom.)	22.6, 27.1 ($\mathrm{N-CHR-}C\mathrm{H_2}$), 35.0 ($\mathrm{N-CH-}C\mathrm{H_2}$), 50.2 ($\mathrm{N-cH_2}$), 54.8 ($\mathrm{N-CH_2-Ph}$), 59.9 ($\mathrm{N=CH-}C\mathrm{HR}$), 60.3 ($\mathrm{N-}C\mathrm{H-CH_2-OCH_3}$), 63.8 ($\mathrm{OCH_3}$), 75.1 ($C\mathrm{H_2-OCH_3}$), 116.3 ($\mathrm{CH_2}$-alkene), 127.3, 128.7, 129.4 (CH-arom.), 136.6 (CH-alkene), 137.5 ($\mathrm{N=CH}$), 141.0 (C-arom.)	351 (13), 350 (43.8, $\mathrm{M^{+\bullet}}$ – 41), 235 (10), 204 (21), 196 (9), 159 (11), 149 (12), 106 (15), 92 (10), 91 (100), 70 (14), 65 (8)
3f	2971, 2922, 2876, 1454, 1341, 1304, 1283, 1245, 1200, 1113, 1075, 1028, 970, 908, 751, 698	1.75–2.00 (m, 4 H, $\mathrm{N-CHR-C}H_2$), 2.74 (m, 1 H, $\mathrm{N-C}H_2$), 2.74 (m, 1 H, $\mathrm{N-C}H\mathrm{-CH_2-OCH_3}$), 3.38 (s, 3 H, $\mathrm{OCH_3}$), 3.28–3.84 (m, 5 H, $\mathrm{C}H_2\mathrm{-OCH_3}$, $\mathrm{N-CH_2}$, $\mathrm{N=CH-C}H\mathrm{R}$), 3.69 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 3.85 (d, 13.7 Hz, 2 H, $\mathrm{N-CH_2-Ph}$), 4.48 (s, 2 H, $\mathrm{O-CH_2-Ph}$), 4.75 (m, 2 H, $\mathrm{N-CH-C}H_2\mathrm{-O}$), 6.60 (d, 5.2 Hz, 1 H, $\mathrm{N=CH}$), 7.16–7.42 (m, 15 H, CH-arom.)	22.0, 26.6 ($\mathrm{N-CHR-}C\mathrm{H_2}$), 49.4 ($\mathrm{N-Ch_2}$), 54.7 ($\mathrm{N-CH_2-Ph}$), 59.0 ($\mathrm{N-}C\mathrm{H-CH_2-OCH_3}$), 59.3 ($\mathrm{N=CH-}C\mathrm{HR}$), 63.1 ($\mathrm{OCH_3}$), 70.6 ($\mathrm{N-CH-}C\mathrm{H_2-O}$), 72.9 ($\mathrm{O-CH_2-Ph}$), 74.6 ($C\mathrm{H_2-OCH_3}$), 126.6, 127.5, 128.1, 128.2, 128.8, 127.8 (CH-arom.), 134.7 ($\mathrm{N=CH}$), 138.7, 140.5 (C-arom.)	380 (0.3, $\mathrm{M^{+\bullet}}$ – 91), 351 (19), 350 (79, $\mathrm{M^{+\bullet}}$ – 121), 235 (8), 204 (16), 159 (9), 123 (7), 106 (12), 92 (11), 91 (100), 70 (7)

[a] Satisfactory microanalyses obtained for **3a–f**: C ± 0.30, H ± 0.40, N ± 0.41.

All reagents were of commercial quality from freshly opened containers or distilled before use. The chiral auxiliary (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) was prepared according to the literature procedure.[9] THF was freshly distilled from potassium/benzophenone. Analytical TLC plates (silica gel 60 $\mathrm{F_{254}}$) and silica gel 60 (230–400 mesh) were purchased from Merck, Darmstadt, *n*-BuLi (1.6 N in *n*-hexane) was purchased from Aldrich. The melting point (Büchi apparatus, system Dr. Tottoli) is uncorrected. Optical rotation values were measured using a Perkin-Elmer P 241 polarimeter. Microanalyses were obtained with a Heraeus CHN-O-RAPID element analyser. Mass spectra were recorded on a Varian MAT 212 (70 eV 1 mA) spectrometer with DEI ionisation (relative

Table 4. Spectroscopic Data of the Differently Protected Vicinal Diamines (*S*)-**4a–f**[a]

	IR (neat) ν (cm^{-1})	^{1}H NMR (CDCl$_3$/TMS) δ (ppm), J (Hz)	^{13}C NMR (CDCl$_3$/TMS) δ (ppm)	MS (70 eV) m/z (%)
4a	3420, 3026, 2966, 2934, 1718, 1504, 1495, 1454, 1241, 1218, 1194, 1151, 753, 700	1.03 (d, 6.6 Hz, 3 H, CH$_3$), 2.69–2.93 (m, 1 H, N$-$CHR), 3.00–3.25 (m, 2 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 3.34 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.77 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.63 (s, 3 H, $\mathrm{O{-}CH_3}$), 5.18 (s, 1 H, NH), 7.20–7.36 (m, 10 H, CH-arom.)	10.1 (CH$_3$), 43.5 ($\mathrm{O{=}C{-}NH{-}}C\mathrm{H_2}$), 52.0 (N$-$CHR), 52.3 ($\mathrm{O{-}CH_3}$), 53.1 ($\mathrm{N{-}CH_2{-}Ph}$), 127.1, 128.4, 128.8 (CH-arom), 139.7 (C-arom.), 157.0 ($\mathrm{O{=}}C\mathrm{{-}O{-}CH_3}$)	225 (8), 224 (46, $M^{+\cdot}-88$), 132 (5, $M^{+\cdot}-180$), 92 (10), 91 (100), 65 (15), 56 (12), 44 (56), 41 (17)
4b	3418, 3026, 2962, 2933, 1718, 1495, 1454, 1370, 1233, 1218, 1194, 1148, 754, 700	0.92 (t, 7.4 Hz, 3 H, CH$_3$), 1.18–1.34 (m, 1 H, $\mathrm{N{-}CH{-}C}H_2$), 1.79 (m, 1 H, $\mathrm{N{-}CH{-}C}H_2$), 2.54 (m, 1 H, N$-$CHR), 3.00 (d/d/d, 12.9, 10.2, 2.5, 1 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 3.20–3.40 (m, 1 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 3.43 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.75 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2Ph}$), 3.45 (s, 3 H, $\mathrm{O{-}CH_3}$), 5.08 (s, 1 H, NH), 7.20–7.36 (m, 10 H, CH-arom.)	11.8 (CH$_3$), 19.0 ($\mathrm{N{-}CH{-}}C\mathrm{H_2}$), 40.8 ($\mathrm{O{=}C{-}NH{-}}C\mathrm{H_2}$), 52.0 (N$-$CHR), 53.2 ($\mathrm{N{-}CH_2{-}Ph}$), 58.9 ($\mathrm{O{-}CH_3}$), 127.1, 128.4, 128.9 (CH-arom.), 139.7 (C-arom.), 157.0 ($\mathrm{O{=}}C\mathrm{{-}O{-}CH_3}$).	326 (0.1, $M^{+\cdot}$), 239 (11), 238 (54, $M^{+\cdot}-88$), 181 (10), 146 (4, $M^{+\cdot}-180$), 92 (8), 91 (100), 65 (7)
4c	3333, 2990, 2968, 2953, 1724, 1699, 1667, 1558, 1471, 1452, 1278, 1194, 1113, 1020, 750, 699	0.93 (d, 6.9 Hz, 3 H, CH$_3$), 1.04 (d, 6.9 Hz, 3 H, CH$_3$), 2.06 (d/q, 6.9, 6.9 Hz, 1 H, $\mathrm{N{-}CH{-}C}H$), 2.40 (m, 1 H, N$-$CHR), 3.13 (d/d/d, 16.8, 9.3, 3.3 Hz, 1 H, $\mathrm{O{=}C{-}NH{-}}CH_2$), 3.33 (m, 1 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 3.63 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.77 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.64 (s, 3 H, $\mathrm{O{-}CH_3}$), 5.08 (s, 1 H, NH), 7.19–7.36 (m, 10 H, CH-arom.)	20.1, 22.4 (CH$_3$), 27.6 ($\mathrm{N{-}CH{-}}C\mathrm{H}$), 38.9 ($\mathrm{O{=}C{-}NH{-}}C\mathrm{H_2}$), 52.0 (N$-$CHR), 54.6 ($\mathrm{N{-}CH_2{-}Ph}$), 62.5 ($\mathrm{O{-}CH_3}$), 127.0, 128.4, 129.0 (CH-arom.), 156.9 ($\mathrm{O{=}}C\mathrm{{-}O{-}CH_3}$)	253 (17), 252 (82), $M^{+\cdot}-88$), 181 (11), 160 (3, $M^{+\cdot}-180$), 92 (8), 91 (100), 65 (7)
4d	3389, 3059, 3022, 2945, 2982, 1733, 1689, 1548, 1493, 1455, 1432, 1276, 1238, 1130, 1000, 745, 730, 695	2.44 (d/d, 13.2, 9.6 Hz, 1 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 2.87–2.99 (m, 1 H, N$-$CHR), 3.14 (m, 3 H, $\mathrm{O{=}C{-}NH{-}C}H_2$, $\mathrm{N{-}CH{-}C}H_2$), 3.47 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.87 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.59 (s, 3 H, $\mathrm{O{-}CH_3}$), 5.06 (s, 1 H, NH), 7.04–7.37 (m, 10 H, CH-arom.)	32.8 ($\mathrm{N{-}CH{-}}C\mathrm{H_2}$), 40.8 ($\mathrm{O{=}C{-}NH{-}}C\mathrm{H_2}$), 51.9 (N$-$CHR), 53.2 ($\mathrm{N{-}CH_2{-}Ph}$), 59.0 ($\mathrm{O{-}CH_3}$), 126.2, 127.2, 128.5, 128.6, 128.8, 129.0 (CH-arom.), 139.2, 139.4 (C-arom.), 156.8 ($\mathrm{O{=}}C\mathrm{{-}O{-}CH_3}$)	388 (0.1, $M^{+\cdot}$), 301 (20), 300 (76, $M^{+\cdot}-88$), 297 (22.0, $M^{+\cdot}-91$), 208 (2, $M^{+\cdot}-180$), 206 (6), 181 (9), 132 (7), 92 (9), 91 (100), 65 (9)
4e	3420, 3064, 3014, 1717, 1640, 1602, 1504, 1496, 1454, 1367, 1243, 1218, 756, 700	2.00 (m, 1 H, $\mathrm{N{-}CH{-}C}H_2$), 2.55 (m, 1 H, $\mathrm{N{-}CH{-}C}H_2$), 2.74 (m, 1 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 3.31 (m, 1 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 3.03 (d/d/d, 13.5, 10.4, 2.8, 1 H, N$-$CHR), 3.43 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.62 (s, 3 H, $\mathrm{O{-}CH_3}$), 3.79 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 5.06 (m, 3 H, NH, CH$_2-$alkene), 5.72 (m, 1 H, CH-alkene), 7.20–7.36 (m, 10 H, CH-arom.)	31.0 ($\mathrm{N{-}CH{-}}C\mathrm{H_2}$), 41.0 ($\mathrm{O{=}C{-}NH{-}}C\mathrm{H_2}$), 52.0 (N$-$CHR), 53.3 ($\mathrm{N{-}CH_2{-}Ph}$), 57.0 ($\mathrm{O{-}CH_3}$), 117.2 (CH$_2$-alkene), 127.1, 128.4, 128.9 (CH-arom.), 135.7 (CH-alkene), 139.5 (C-arom.), 156.9 ($\mathrm{O{=}}C\mathrm{{-}O{-}CH_3}$)	338 (0.1, $M^{+\cdot}$), 297 (14, $M^{+\cdot}-41$), 251 (20), 250 (100, $M^{+\cdot}-88$), 181 (6), 158 (1, $M^{+\cdot}-180$), 92 (7), 91 (90), 65 (6)
4f	3410, 3320, 3020, 2940, 2850, 1715, 1600, 1510, 1495, 1445, 1365, 1250, 1145, 1100, 1075, 1030, 745, 700	2.99 (m, 1 H, N$-$CH$-$R), 3.18–3.39 (m, 2 H, $\mathrm{O{=}C{-}NH{-}C}H_2$), 3.50–3.74 (m, 2 H, $\mathrm{N{-}CH{-}C}H_2$), 3.57 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 3.62 (s, 3 H, $\mathrm{O{-}CH_3}$), 3.82 (d, 13.5 Hz, 2 H, $\mathrm{N{-}CH_2{-}Ph}$), 4.51 (s, 2 H, $\mathrm{O{-}CH_2{-}Ph}$), 5.07 (s, 1 H, NH), 7.18–7.40 (m, 15 H, CH-Arom)	40.0 ($\mathrm{O{=}C{-}N{-}}C\mathrm{H_2}$), 52.0 (N$-CH-$R), 54.1 ($\mathrm{N{-}CH_2{-}Ph}$), 56.5 ($\mathrm{O{-}CH_3}$), 68.7 ($\mathrm{N{-}CH{-}}C\mathrm{H_2}$), 73.3 ($\mathrm{O{-}CH_2{-}Ph}$), 127.0, 127.5, 128.4, 127.7, 128.4, 128.8 (CH-Arom), 138.1, 139.1 (C-arom.), 157.0 ($\mathrm{O{=}}C\mathrm{{-}O{-}CH_3}$)	418 (0.3, $M^{+\cdot}$), 331 (10), 330 (42, $M^{+\cdot}$ 88), 327 (0.2, $M^{+\cdot}-91$), 297 (11, $M^{+\cdot}-121$), 238 (2, $M^{+\cdot}-180$), 224 (5), 206 (4), 181 (9), 132 (5), 92 (8), 91 (100), 65 (5)

[a] Satisfactory microanalyses obtained for **4a–f**: C ± 0.47, H ± 0.18, N ± 0.40.

intensities in parantheses). IR spectra were obtained using a Perkin-Elmer FT 1750 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Varian VXR 300 (300 and 75 MHz).

Compounds **1** and (*S*)-**2** gave C,H,N analysis ± 0.29%.

2-Dibenzylaminoethanol (1):

The amino alcohol **1** was prepared according to a procedure of Reetz et al.:[12] Glycine (37.5 g, 0.5 mol), KOH (84.0 g, 1.5 mol), and Na$_2$CO$_3$ (159.0 g, 1.5 mol) were dissolved in water (0.5 L) and benzyl bromide (257.0 g, 1.5 mol) was added. The mixture was heated to reflux for 2 h, cooled, and then extracted with Et$_2$O, dried (Na$_2$SO$_4$), and concentrated in vacuo. The crude *N*,*N*-dibenzylglycine benzyl ester was then dissolved in THF (0.5 mL) and added dropwise to a suspension of LiAlH$_4$ (19.0 g, 0.5 mol) in THF (1.0 L). The mixture was heated to reflux for 2 h, cooled, and hydrolyzed carefully with a 20% solution of KOH (0.2 L) and then heated again for 15 minutes. The aluminium hydroxide was removed by filtration, the THF dried (Na$_2$SO$_4$), and the alcohol concentrated in vacuo. Distillation of the crude product gave pure 2-dibenzylaminoethanol (**1**) which crystallized; mp 43 °C. Yield: 96.5 g (80%).

IR (KBr): ν = 3304, 3083, 3060, 3023, 2946, 2883, 2834, 2997, 1953, 1875, 1814, 1600, 1584, 1494, 1451, 1370, 1327, 1291, 1255, 1232, 1203, 1130, 1073, 1055, 1025, 996, 977, 951, 920, 909, 873, 746, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (t, 5.5 Hz, 2 H, CH_2–N), 2.66 (s, 1 H, OH), 3.53 (t, 5.5 Hz, 2 H, CH_2–OH), 3.58 (s, 4 H, N–CH_2–Ph), 7.18–7.32 (m, 10 H, CH-arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.72 (CH_2–N), 58.13 (N–CH_2–Ph), 58.57 (CH_2–OH), 127.12, 128.33, 128.88, 138.74 (CH-arom).

MS: m/z (%) = 242 (0.04, MH^+), 241 (2.6 $M^{+\bullet}$), 211 (12.3, $M^{+\bullet}$ – OMe), 210 (74.2, $M^{+\bullet}$ – MeOH), 182 (1.0), 181 (6.9), 118 (2.0), 92 (8.3), 91 (100, $PhCH_2^+$), 65 (9.3), 51 (1.1), 42 (3.7), 41 (1.2), 39 (2.2).

(*S*)-1-(2-Dibenzylaminoethylideneamino)-2-methoxymethylpyrrolidine [(*S*)-2]:

Swern oxidation[13] of the alcohol **1** and subsequent reaction with SAMP gave hydrazone (*S*)-**2**: DMSO (5.2 g, 66 mmol) was diluted in dry CH_2Cl_2 (100 mL) and cooled under argon to – 78 °C. Oxalyl chloride (8.4 g, 66 mmol) was added dropwise and the mixture was stirred for additional 15 min, then alcohol **1** (14.5 g, 60 mmol), diluted in CH_2Cl_2 (25 mL) was added dropwise. After one hour Et_3N (13.4 g, 132 mmol) was added and the mixture was allowed to warm to r. t., poured into a phosphate pH-7-buffer solution (100 mL), extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude aldehyde was dissolved in Et_2O under Ar molecular sieves (20 g, 4 Å) were added, and the mixture was cooled to 0 °C. SAMP (8.6 g, 66 mmol) was added dropwise with stirring. Upon complete reaction, the mixture was filtered through Celite and concentrated in vacuo to give hydrazone **2** (21.1 g, 60 mmol, 100%) as a slightly yellow oil containing traces of SAMP and dimethyl sulfide, which was used in the alkylation reactions without further purification. $[\alpha]_D^{20}$ – 69.02 (c = 2.15, $CHCl_3$).

IR (neat): ν = 3061, 3027, 2923, 2876, 2825, 2809, 1601, 1494, 1453, 1366, 1340, 1320, 1302, 1283, 1245, 1197, 1117, 1072, 1028, 973, 750, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.90 (m, 4 H, N–CHR–CH_2, N–CH_2–CH_2–OCH_3), 3.10–3.80 (m, 4 H, CH_2–OCH_3, N–CH_2), 3.21 (d, 5.4 Hz, 2 H, N=CH–CH_2), 3.28 (s, 3 H, OCH_3), 3.59 (s, 4 H, N–CH_2–Ph), 6.48 (t, 5.4 Hz, 1 H, N=CH), 7.12–7.38 (m, 10 H, CH-arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.01, 26.56 (N–CHR–CH_2, N–CH_2–CH_2), 49.49 (N=CH–CH_2), 56.04 (N–CH_2), 58.13 (N–CH_2–Ph), 58.99 (N–CH–CH_2–OCH_3), 62.94 (OCH_3), 74.65 (CH_2–OCH_3), 126.72, 128.06, 128.84 (CH-arom.), 134.43 (N=CH), 139.46 (C-arom).

MS: m/z (%) = 352 (0.3, MH^+), 351 (0.9, $M^{+\bullet}$), 306 (1.1, $M^{+\bullet}$ – CH_2OMe), 260 (9.3), 235 (2.2), 210 (14.3), 197 (3.6), 196 (35.2), 159 (8.2), 157 (5.3), 156 (58.3), 155 (5.5), 145 (4.8), 116 (3.6), 112 (4.0), 111 (38.7), 92 (10.5), 91 (100, $PhCH_2^+$), 71 (6.8), 70 (4.2), 68 (3.9), 65 (9.8), 55 (5.3), 45 (11.3), 42 (10.0), 41 (9.5).

α-Alkylation of Hydrazone (*S*)-2; General Procedure:

BuLi (1.6 N in hexane, 7.2–18 mmol) was added dropwise to a solution of diisopropylamine (1.2–3.0 equiv, 7.2–18 mmol) in THF (5 mL) at – 78 °C under Ar. The mixture was allowed to warm to r. t. and was carefully evacuated until only lithium diisopropylamide remained as a dry, colourless solid. The system was flushed with argon again, cooled to – 78 °C, and THF (60 mL) was added. The hydrazone (*S*)-**2** (2.11 g, 6 mmol) was added dropwise, the mixture was kept at – 78 °C for 24 h, and then cooled to – 100 °C. The electrophile (1.5–3.5 equiv) was added dropwise and the reaction mixture was allowed to warm to r. t. overnight. The mixture was then poured into a phosphate-pH-7-buffer solution (50 mL), extracted several times with Et_2O, dried (Na_2SO_4), and concentrated in vacuo. Where necessary, the crude products were purified by flash column chromatography (silica gel, petroleum ether/Et_2O, 1 : 1, deactivated with 2% Et_3N).

Synthesis of Protected Diamines 4; General Procedure:

This synthesis starting from hydrazones **3a–f** had three steps: Cleavage of the hydrazones with MMPP to the corresponding α-aminonitriles,[10] reduction of the nitriles to the diamines, and subsequent protection:

MMPP · $6H_2O$ (1.1 equiv, 2.0–3.0 mmol) was dissolved in dry MeOH (20 mL) and cooled to – 78 °C. The hydrazone (*S,S*)-**3**, dissolved in MeOH (5 mL), was added dropwise. The mixture was stirred for 1 h and then allowed to warm to 0 °C, and stirred until the reaction was complete (TLC control). Then, the mixture was poured into a phosphate-pH-7-buffer solution (20 mL) and extracted several times with Et_2O. The ether phase was dried with molecular sieves (4 Å) and the crude aminonitrile concentrated in vacuo. The nitrile then was added to a suspension of $LiAlH_4$ (1.0 equiv) in absolute diethyl ether (10–20 mL) at – 78 °C, stirred overnight at this temperature, warmed to 0 °C and then stirred at r. t. (TLC control). To the mixture was added carefully a concentrated solution of sodium potassium tartrate (10 mL) and then a 20% solution of KOH (5 mL). This mixture was extracted several times with CH_2Cl_2, the organic phases dried (Na_2SO_4) and then concentrated in vacuo.

The crude diamine was dissolved in CH_2Cl_2 (10 mL), Et_3N (1.5 equiv) was added, the mixture cooled to 0 °C, and then methyl chloroformate (1.0 equiv) was added dropwise. The mixture was allowed to warm to r. t. overnight, then poured into a phosphate-pH-7-buffer solution (10 mL), extracted several times with CH_2Cl_2, dried (Na_2SO_4), and concentrated in vacuo. The crude protected diamines were purified by flash column chromatography (silica gel, petroleum ether/Et_2O 1 : 1).

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