Enantiomerically Pure Amino Alcohols and Diamino Alcohols from L-Aspartic Acid. Application to the Synthesis of Epi- and Diepislaframine

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Starting from natural aspartic acid (6) a practical method for the synthesis of enantiomerically pure 3-amino alcohols 6 including 3,4-diamino derivatives is described. After perbenzylation of 6 and reduction of both carboxylates, position 4 of the resultant (dibenzyland)butanediol (11) could be regioselectively blocked to afford the silyloxy-protected intermediate 12a. Functionalization of position 1 was accomplished by nucleophilic displacement reactions including a 2-fold migration of the dibenzylamino substituent or by reductive amination of the amino aldehyde 15. Both routes proceeded under complete preservation of the optical purity. For envisaged SAR studies, we, furthermore, report on the application of this method to a chiroselective synthesis of epi- and diepislaframine (9a and 9b) as diastereomers of the highly bioactive indolizidine alkaloid slaframine (9c). Our first approach including reductive coupling of the chiral amino aldehyde 15 with 3-hydroxypropyrrolidine failed when formation of a quaternary ammonium salt occurred, preventing the anticipated anionic cyclization. Therefore, we turned out attention to methodology developed by Wasserman. In fact, introduction of a 3-hydroxypyrrole-2-carboxylate fragment gave a cyclization precursor (80b) which could be successfully transformed into epi- and diepislaframine.

Introduction

Chemoselective functionalization of α-amino acids has become an attractive method for the synthesis of natural products, bioactive compounds, and nonproteinogenic amino acids.1 We have recently demonstrated that L-asparagine (1) can be converted very efficiently into enantiomerically pure β-amino acids 3a and 3,8-amino alcohols 3b through the activated β-homoserine derivative 2 when organocuprates, LiBH4, or NaN3 have been employed for displacement of the mesyloxy group (Scheme 1).2 On the other hand, use of amines or related basic nucleophiles as well as polar solvents resulted in formation of the aminobutenenitrile 5 instead of the projected substitution products.2b This side reaction obviously proceeds through an aziridinium intermediate (4) and is facilitated by the acidity of the nitrite α-position.

To overcome this problem, we planned to work out a more flexible approach from L-aspartic acid (6) involving N,N-dibenzyl protection, reduction of both carboxyl groups, and regioselective functionalization of the thus generated chiral building block.3 Using this plan of synthesis, we herein communicate a short and practical EPC synthesis of 1,3-amino alcohols 8 included in the respective diamino derivatives (Nu = NRR'), through the key intermediate 7 (Scheme 2). As a part of our program on the synthesis of bioactive compounds we, furthermore, demonstrate an application of this method for the preparation of the enantiomerically pure indolizidines 8a-epi- and 1,5-diepislaframine 9a,9b which are of major interest for structure–activity relationship (SAR) studies including the indolizine alkaloid slaframine (9c).5 Slaframine was isolated from forages contaminated with the fungus Rhizoctonia leguminicola and exhibits strong muscarinic agonistic activity.6

Results and Discussion

Synthesis of the Selectively Protected Intermediate 12. For the conversion of the chiral educt 6 into the diol 11 a convenient and high yielding two-step synthesis was elaborated (Scheme 3). Thus, natural aspartic acid and an excess of benzyl bromide were refluxed in aqueous K2CO3 to give the tetrabenzyl derivative 10, which could

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be reduced by LiAlH₄. Our strategy depended upon a specific protection of the primary alcohol in position 4. Due to the bulky dibenzylamino group the two primary alcohol functions of 11 could be differentiated very efficiently. Treatment of 11 with TBDMS-Cl/imidazole resulted in preferred attack at the less hindered position 4 affording 12a in 66% yield. The regioisomer 13a (2%) and the bis-protected derivative 14a (11%) could be easily separated by chromatography. A similar distribution of products has been observed employing tert-butyldiphenylsilyl chloride (TBDDS-Cl)/imidazole yielding 12b (52%), 13b (15%), and 14b (12%).

**Activation of Alcohol 12a.** For the projected coupling with nuclophiles the position 1 of 12a needs to be transformed into a leaving group. Furthermore, Swern oxidation of 12a should be accomplished since the resulting amino aldehyde 15 was expected to make possible a convenient introduction of amines by reductive amination.

Reaction of 12a with MsCl/Et₃N in CH₂Cl₂ gave the projected product 16a (Scheme 4). However, the mesylate 16a could be only detected in pure form (by NMR) immediately after addition of the reagents since, in a following reaction step, rearrangement occurred. Obviously, the secondary chloride 18b was formed through the aziridinium species 17b. After 5 h 18b was isolated as a single product in 94% yield. When THF was used as a solvent a small amount (5%) of the regioisomeric byproduct 16b was detected by NMR spectroscopy of the crude reaction product. We reason that the preferred formation of the secondary alkyl halide instead of the kinetically favored ring-opening product 16b is not due to regioselective cleavage of the aziridinium ring but to thermodynamic control. By analogy, the rearranged methanesulfonic ester 18a could be prepared from 12a and Ms₂O/Et₃N via 17a. Compound 18a turned out to be moisture sensitive and was used as a solution in CH₂Cl₂.

Alternatively, activation of 12a by Swern oxidation (oxalyl chloride, Et₃N, CH₂Cl₂, -60 °C) needs to be performed.

**Amination of 15.** Coupling with primary or secondary amines could be accomplished by reductive amination of the amino aldehyde 15 (Scheme 5; Table 1, first three entries). Thus, treatment of 15 with pyrrolidine, in the presence of NaCNBH₃, yielded the tertiary amine 19a. Coupling with Gly-OEt or L-Ala-OEt resulted in formation of the protected peptidomimetics 19b and 19c.

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**Scheme 2**

\[
\text{P: protecting group} \quad \text{Nu: nucleophile} \quad \text{L: leaving group}
\]

**Scheme 3**

**Scheme 4**

4 affording 12a in 66% yield. The regioisomer 13a (2%) and the bis-protected derivative 14a (11%) could be easily separated by chromatography. A similar distribution of products has been observed employing tert-butyldiphenylsilyl chloride (TBDDS-Cl)/imidazole yielding 12b (52%), 13b (15%), and 14b (12%).

Activation of Alcohol 12a. For the projected coupling with nuclophiles the position 1 of 12a needs to be transformed into a leaving group. Furthermore, Swern oxidation of 12a should be accomplished since the resulting amino aldehyde 15 could be only detected in pure form (by NMR) immediately after addition of the reagents since, in a following reaction step, rearrangement occurred. Obviously, the secondary chloride 18b was formed through the aziridinium species 17b. After 5 h 18b was isolated as a single product in 94% yield. When THF was used as a solvent a small amount (5%) of the regioisomeric byproduct 16b was detected by NMR spectroscopy of the crude reaction product. We reason that the preferred formation of the secondary alkyl halide instead of the kinetically favored ring-opening product 16b is not due to regioselective cleavage of the aziridinium ring but to thermodynamic control. By analogy, the rearranged methanesulfonic ester 18a could be prepared from 12a and Ms₂O/Et₃N via 17a. Compound 18a turned out to be moisture sensitive and was used as a solution in CH₂Cl₂.

Alternatively, activation of 12a by Swern oxidation (oxalyl chloride, Et₃N, CH₂Cl₂, -60 °C) resulted in the protected α-amino aldehyde 15 in 85% yield.

Amination of 15. Coupling with primary or secondary amines could be accomplished by reductive amination of the amino aldehyde 15 (Scheme 5; Table 1, first three entries). Thus, treatment of 15 with pyrrolidine, in the presence of NaCNBH₃, yielded the tertiary amine 19a. Coupling with Gly-OEt or L-Ala-OEt resulted in formation of the protected peptidomimetics 19b and 19c.

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representing reduced peptide bond analogs of the Homoser-Gly or Homoser-Ala dipeptide.\textsuperscript{11} \textsuperscript{1}H NMR investigation of 19e, including appropriate doping experiments with the diastereomeric mixture obtained by reductive amination of 15 with d,l-Ala-OEt, proved the isomeric purity of 19e and the stability of the amino alcohol 15 toward racemization.

**Displacement Reactions.** Reaction of 18a,b with nucleophiles caused migration of the dibenzylamine group back to position 2 indicating that the aziridinium species 17a,b served again as intermediates. Using the chloride 18h as an electud reagent, NaCN, phthalimide-K, or Na\textsubscript{2}S\textsubscript{2}O\textsubscript{8} attacked predominantly at the less crowded position (kinetic control), when the protected 1,3-amino alcohols 19d-f were formed as the main products besides the regiosomers 20d-f. For substitutions with organocuprates at low temperature the chloride 18b was not reactive enough. However, the more electrophilic mesylate 18a gave a highly regioselective reaction with Me\textsubscript{2}CuLi or Bu\textsubscript{4}CuLi to afford the protected 1,3-amino alcohols 19g and 19h, respectively. The reaction of 18a with the potassium salts of indole as well as its 4- and 5-substituted derivatives proceeded also under high regiocontrol affording the major isomers 19i-k and the byproducts 20i-k in ratios between 11:1 and 18:1. On the other hand, employment of nucleophiles with leaving group character, such as NaCl or NaBr, afforded the protected 1,4-amino alcohols 18b or 20l. Obviously, this is due to thermodynamic control.

Using phthalimide as an example, it was shown that nucleophiles can also be induced by reacting 12a under Mitsunobu conditions.\textsuperscript{12} The convenient one-pot procedure afforded 57% of 19f besides 23% of the easily separable regiosomer 20f.

Selective removal of the TBDMS protecting group was accomplished by treatment of 19a-k, 18b, and 20d-k with HOAc or NaOH to give the chiral 1,3-amino alcohols 8a-k, 21b, and 21d-k, respectively, in 60-99% yield.

Starting from the fully protected diamino alcohols 19f and 20f the optical integrity and the stereospecificity of both synthetic alternatives was demonstrated (Scheme 6). Thus, selective removal of the phthaloyl groups by hydrazinolysis of 19f and 20f (prepared using both routes) gave the primary amines 22a and 23a. Subsequent derivatization with optically pure (R)-1-phenylethyl isocyanate followed by HPLC and \textsuperscript{1}H-NMR studies of the ureas 22b and 23b revealed the synthetic material to be configurationally pure. Furthermore, the formation of the enantiomers 22c and 23c with opposite optical values by reductive benzylation of 22a and 23a, respectively, indicates that the synthesis of 20f occurred exclusively through an aziridinium intermediate and not by a direct S\textsubscript{N}2 reaction of 18.

**Optically Active Slaframine Isomers.** Our first approach for the construction of a suitable chiral indolizidine skeleton was based on reductive coupling of the amino alcohol 15 as a chiral C-4 equivalent with 3-hydroxy-3-carboxylic acid, followed by oxidation of the secondary hydroxyl function, activation of the protected primary OH group, and base-induced 6-(enol exo)-exo,exo\textsuperscript{13} cyclization to give 26, a valuable precursor for 9a,b. As outlined in Scheme 7 reaction of 15 with racemic 3-hydroxy-3-carboxylic acid in the presence of NaCNBH\textsubscript{3} gave a 1:1 diastereomeric mixture of the amines which, in a following step, could be readily oxidized under Swern conditions to afford the ketone 25a. Subsequently, the OTBDMS group, which was unaffected during the preceding oxidation,\textsuperscript{14} was deprotected by HOAc to give the diamino alcohol 25b. Unfortunately, reaction of 25b with methanesulfonic chloride resulted in immediate formation of the quaternary ammonium salt 27b (observed as a 1:1 mixture of diastereomers) by intramolecular nucleophilic attack of the intermediate sulfonic ester. Attempts to activate the terminal position of 25b under Appel conditions (CBr\textsubscript{4}, PPh\textsubscript{3})\textsuperscript{16} were also disappointing. Again the spiro derivative 27b was isolated as the reaction product. The structure of 27b was confirmed by the analogy of \textsuperscript{1}H and \textsuperscript{13}C NMR data when compared with those of the methylene analog 27a which we could synthesize by treatment of the pyrrolidine coupling product 8a with methanesulfonic chloride. Starting from 25b, various efforts to direct the cyclization toward C-alkylation by enolate formation and subsequent activation failed. Furthermore, attempts to construct the indolizidine framework by rearrangement of the spiro compound 27b proved fruitless.

To circumvent the problems arising from the nucleophilic character of the pyrrolidine nitrogen we turned to methodology developed by Wasserman\textsuperscript{15} for the synthesis of indolizidines by alkylation of 3-hydroxy-3-carboxylic acid esters. In fact, the diamino alcohol 28, readily available by O-deprotection of 22a, was reacted with the vinyl tricarbonyl reagent 29\textsuperscript{17} to give the condensation product 30a which was subsequently converted into the cyclization precursor 30b by CBr\textsubscript{4}/PPh\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} (Scheme 7). Ring closure of 30b was induced by NaH yielding a 2:1 ratio of the separable diastereomers 31a and 31b. (Since epimerization takes place on a following reaction step the synthesis can be continued with a mixture of isomers). Stereochemical effects\textsuperscript{18} favor a chairlike transition state during the ring closure and thus lead to a chair conformation of the piperidin ring. This is consistent with diagnostic NMR coupling constants which, furthermore, indicate an equato-


\textsuperscript{12} Mitsunobu, O. Synthesis 1981, 1-28.


\textsuperscript{14} For a review on the stability of silyl ethers under oxidation conditions, see: Muzart, J. Synthesis 1993, 11-27.


\textsuperscript{17} Compound 29 was prepared according to: (a) Cooke, M. P., Jr.; Burman, D. L. J. Org. Chem. 1992, 47, 4955-4963. (b) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; Van Duzer, J.; Lombardo, L.; McCarthy, K. J. Am. Chem. Soc. 1989, 111, 371-372. It turned out to be crucial to the success of the reactions that the ozonolysis product was dehydrochlorinated by saturated NaHCO\textsubscript{3}/THF for only 5 min. Subsequently, the product was extracted by EtOAc and purified by flash chromatography (n-hexane-EtOAc 7:3).

Table 1

<table>
<thead>
<tr>
<th>educt</th>
<th>reagent</th>
<th>product</th>
<th>yield (%)</th>
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<tbody>
<tr>
<td>15</td>
<td>pyrrolidine, NaCNBH₃</td>
<td>19a (Nu = 1-pyrrolidinyl)</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>Gly-OEt, NaCNBH₃</td>
<td>19b (Nu = NHCH₂CO₂Et)</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>L-Ala-OEt, NaCNBH₃</td>
<td>19c (Nu = NHCH(CH₃)CO₂Et)</td>
<td>75</td>
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<tr>
<td>18b</td>
<td>NaCN</td>
<td>19d (Nu = CN)</td>
<td>73</td>
</tr>
<tr>
<td>18b</td>
<td>NaN₃</td>
<td>19e (Nu = N₃)</td>
<td>98</td>
</tr>
<tr>
<td>18b</td>
<td>phthalimide-K</td>
<td>19f (Nu = NPhth)</td>
<td>52</td>
</tr>
<tr>
<td>12a</td>
<td>phthalimide, DEAD, PPh₃</td>
<td>20f (Nu = NPhth)</td>
<td>19</td>
</tr>
<tr>
<td>18a</td>
<td>Me₂CuLi</td>
<td>19g (Nu = Me)</td>
<td>46⁶</td>
</tr>
<tr>
<td>18a</td>
<td>Bu₂CuLi</td>
<td>19h (Nu = Bu)</td>
<td>30⁶</td>
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<tr>
<td>18a</td>
<td>1-(4-MeO-indolyl)-K</td>
<td>19i, 201 (Nu = 1-indolyl), 18:1 mixture</td>
<td>94⁶</td>
</tr>
<tr>
<td>18a</td>
<td>1-(5-MeO-indolyl)-K</td>
<td>19j, 20k (Nu = 1-(5-MeO-indolyl), 12:1</td>
<td>98⁶</td>
</tr>
<tr>
<td>18a</td>
<td>LiBr</td>
<td>20l (Nu = Br)</td>
<td>68⁶</td>
</tr>
<tr>
<td>18a</td>
<td>LiCl</td>
<td>18b (Nu = Cl)</td>
<td>72⁶</td>
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⁶ Used as a hydrochloride salt. Based on 12a.

Scheme 6

Scheme 7

26a. Upon treatment of 26a with NaBH₄/MeOH at 0 °C a 1:1 mixture of the 8α-epi- and 1,8α-diepislaframine precursors 33a and 34a was formed. At this point we were not able to establish the stereochemistry at the newly generated chiral center unambiguously; however, comparison of chemical shifts and W₁₂ values with those described for racemic 33c and 34c strongly supported our assignment which was confirmed on later stages in the synthesis. The isomers are easily separable by flash chromatography. Employing the bulky Li(sBu)₃BH selective attack of the si-side was observed resulting in exclusive formation of 34a (de > 99, determined by HPLC). The conformational representation of the theoretical global minimum energy conformation of 26a, established by cuffed force field calculations followed by MOPAC-based geometry optimizations (20) (Figure 1), indicates that the axially positioned protons at C-3 and C-8 obviously preclude the approach of a sterically demanding nucleophile from the bottom side (re-side). Several


(20) Conformational studies were performed employing the cuffed force field of the program DISCOVER (Biosym, Tech. Inc., San Diego) followed by minimization of the geometry, when the AM1 parameter set of the program system MOPAC 6.0 (Stewart, J. J. P. J. Comput. Chem. 1989, 10, 208-220) was used. Visualization of the structures was done by the Insight 2.1.2 program (Biosym Tech., San Diego).
transformation into the target compounds with acetic anhydride gave the N-acetyl derivatives with a rotatory evaporator. Flash chromatography was carried out with 230-400 mesh silica gel. Melting points: Buchi melting point apparatus, uncorrected. IR spectra: Perkin-Elmer 851 spectrometer. Mass spectra: Varian CH7 instru-


tments to reverse the diastereoselectivity including the application of Yamamoto's methodology failed. Finally, transformation into the target compounds 9a and 9b was accomplished by acetylation and hydrogenolytic debenzylation of the resultant esters 33b and 34b. The overall yield of 9a and 9b was 2.4 and 3.7%, respectively. Reaction of the air sensitive primary amines 9a and 9b with acetic anhydride gave the N-acetyl derivatives 33c and 34c. The spectral data of the final products were identical with those reported for 9b as well as for racemic 9a, 9b, 33c, and 34c.

Conclusion

In summary, a general chiroselective synthesis of 3-amino alcohols 8 including 3,4-diamino derivatives is reported employing natural aspartic acid 6 as an educt. The key strategy is a regioselective functionalization of the (dibenzylamino)butanediol (11). Application of this methodology leads to 8a-epi- and 1,8a-diepialafamine 9a,b in 2.4 and 3.7% overall yield, respectively.

Experimental Section

General. THF was distilled from Na/benzophenone, DMF, and CHCl₃ from CaH₂, in all cases immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted, reactions were conducted under dry N₂. Evaporation of final product solutions were done under vacuo with a rotary evaporator. Flash chromatography was carried out with 230-400 mesh silica gel. Melting points: Büchi melting point apparatus, uncorrected. IR spectra: Perkin-Elmer 851 spectrometer. Mass spectra: Varian CH7 instru-

(21) Reduction reagent: tBuMgCl/MA. The reaction was performed according to: Maruska, K., Itoh, T., Nonoshita, K.; Yamamoto, H. J. Am. Chem. Soc. 1988, 110, 3588-3597.
Synthesis of Epi- and Diepislaframine

2930, 2870, 1600 cm⁻¹; ¹H NMR δ 0.81 (t, 3H, J = 7.3), 1.12–1.21 (m, 1H), 1.41–1.49 (m 1H), 1.721.85 (m, 2H), 2.56–2.62 (m, 1H), 3.26 (d, 2H, 13.2), 3.39–3.45 (m, 1H), 3.66–3.71 (m, 1H), 3.81 (d, 2H, J = 13.2), 7.16–7.26 (m, 10H); CIMS 254 (M + 1). Anal. Calcd for C₃₂H₃₂NO: C, 80.5; H, 8.9; N, 4.9. Found: C, 80.2; H, 9.3; N, 4.8.

(R)-3-(N-Dibenzylamino)-1-octanol (8b). A solution of 18.3 mg (0.042 mmol) in THF/POAcH₂O (2 mL, 1:3) was reacted and worked up as described for 8a to give 8b (12.1 mg, 90%) as a colorless oil (solvent for flash chromatography: CH₂Cl₂-MeOH 98.5:1.5); [α]D₃~ 21ı = -402°.

To a solution of (R)-4-(N-Dibenzylamino)-3-[1-(4-methoxyindolyl)-1-pentanol (8c) and (R)-4-(N-Dibenzylamino)-3-[1-(5-methoxyindolyl)-1-pentanol (8j) were reacted and worked up as described for 8a to give 8c (21.9 mg, 93%) and 8j (21.2 mg, 95%) as a colorless oil.

IR 3390, 3040, 2930, 2960 cm⁻¹; ¹H NMR δ 0.80–0.85 (3H, J = 6.9, 6.2, 6.7); 1.57–1.69 (m, 2H, J = 13.8); 1.70–1.77 (m, 2H, J = 13.9); 2.14–2.20 (m, 2H, J = 13.7); 3.31–3.34 (m, 1H), 3.53–3.55 (m, 1H), 3.59 (d, 2H, J = 13.9), 5.10 (d, 1H, J = 13.9), 7.16–7.26 (m, 10H); CIMS 379 (M + 1), 254 (M – 71). Anal. Calcd for C₃₂H₃₂NO: C, 81.2; H, 9.6; N, 4.3. Found: C, 81.1; H, 9.7; N, 4.3.

(S)-3-(N-Dibenzylamino)-4-(1-indolyl)-1-butanol (8i) and (R)-4-(N-Dibenzylamino)-3-(1-indolyl)-1-butanol (21i). The compounds 19i and 20i (544 mg, 1.59 mmol) were reacted and worked up as described for 8a to give 19i (156 mg, 97%) and 20i (159 mg, 96%) as a colorless oil. To a solution of (R)-4-(N-Dibenzylamino)-3-[1-(5-methoxyindolyl)-1-pentanol (8k) and (R)-4-(N-Dibenzylamino)-3-[1-(4-methoxyindolyl)-1-pentanol (21k) the compounds 19k and 20k (250 mg, 0.47 mmol) were reacted and worked up as described for 8a to give 19k (14 mg, 7%) followed by 20k (15 mg, 8%) as a colorless oil.}

IR 3380, 3030, 2930, 2960 cm⁻¹; ¹H NMR δ 1.23–1.31 (m, 3H), 1.87–1.96 (m, 1H), 3.26–3.33 (m, 1H), 1.89 (d, 2H, J = 13.2), 3.50–3.55 (m, 1H), 3.89 (d, 2H, J = 13.9), 3.54 (d, 2H, J = 13.9), 4.54–4.62 (m, 1H), 6.42 (d, 1H, J = 2.9), 6.84 (d, 1H, J = 2.9), 7.01–7.26 (m, 13H), 7.55 (d, 1H, J = 8.0), 7.64 (d, 1H, J = 7.9).

Anal. Calcd for C₃₃H₃₃NO: C, 81.2; H, 7.3; N, 6.5. Found: C, 75.3; H, 7.5; N, 6.5. 21ı: δ 1.33–1.39 (J = 7.3), 1.72–1.85 (m, 2H), 2.55–2.62 (m, 1H), 3.26–3.33 (m, 1H), 1.38 (d, 2H, J = 13.2), 3.89 (d, 2H, J = 13.9), 3.54 (d, 2H, J = 13.9), 4.54–4.62 (m, 1H), 6.42 (d, 1H, J = 2.9), 7.01–7.26 (m, 13H), 7.55 (d, 1H, J = 8.0), 7.64 (d, 1H, J = 7.9).

Found: C, 75.3; H, 7.5; N, 6.5. 21ı: δ 1.33–1.39 (J = 7.3), 1.72–1.85 (m, 2H), 2.55–2.62 (m, 1H), 3.26–3.33 (m, 1H), 1.38 (d, 2H, J = 13.2), 3.89 (d, 2H, J = 13.9), 3.54 (d, 2H, J = 13.9), 4.54–4.62 (m, 1H), 6.42 (d, 1H, J = 2.9), 7.01–7.26 (m, 13H), 7.55 (d, 1H, J = 8.0), 7.64 (d, 1H, J = 7.9).

Anal. Calcd for C₃₃H₃₃NO: C, 81.2; H, 7.3; N, 6.5. Found: C, 75.3; H, 7.5; N, 6.5.
DMF (60 mL) was added TDBMS-Cl (1.85 g, 12.2 mmol) and then imidazole (1.67 g, 24.5 mmol) at 0 °C. After 2 h at 0 °C saturated NH₄Cl and Et₂O were added. The organic layer was dried (MgSO₄) and evaporated and the residue purified by flash chromatography (petroleum ether–EtOAc 9:1) to give 14a (0.63 g, 11%). Followed by 12a (2.95 g, 66%) and 13a (59 mg, 2%).

12a: [α]D +43° (c 1, CHCl₃); IR 3440, 3030, 2930 cm⁻¹; ¹H NMR δ 0.00 (s, 6H), 0.85 (s, 6H), 1.35–1.48 (m, 4H), 2.18–2.01 (m, 1H), 2.87–2.94 (m, 1H), 3.38 (d, 2H, J = 13.2, 13.9), 3.53–3.53 (m, 2H), 3.58 (d, 2H, J = 16.2, 17.3), 7.24–7.28 (m, 10H); MS 400 (M⁺). Anal. Calc. for C₂₉H₂₂N₂O₂Si: C, 74.3; H, 9.8; N, 6.2. Found: C, 74.1; H, 10.0; N, 6.0.

To a solution of crude 18a, prepared from the crude mixture, when Et₂N (31.7 mL, 227 mmol) was added. After 15 min the ice bath was removed and stirring was continued for 1 h. After addition of saturated NaHCO₃ the mixture was extracted with CH₂Cl₂. The organic layer was dried (MgSO₄) and evaporated and the residue purified by flash chromatography to give 18b (2.33 g, 94%) as a colorless oil. To a solution of crude 12b, prepared from the crude mixture, 1H NMR data from the crude mixture. EIMS of 18b. Anal. Calc. for C₂₈H₅₁NO₂Si: C, 76.8; H, 10.2; N, 5.9.

(R)-N,N-Dibenzylation-(l)-[[l)-(tert-butyldimethylsilyl)oxy]butyllysine (19a). To a solution of 12c (1.87 g, 5.52 mmol) and Et₂N (453 mg, 5.52 mmol) in DMF (60 mL) were reacted and worked up as described for 18a which can be used for displacement reactions. For NMR analysis, saturated NaHCO₃ was added, the mixture extracted with CH₂Cl₂ and the organic layer dried (MgSO₄); [α]D -29° (c 6H, 0.79 (s, 9H), 1.54–1.61 (m, 1H), 1.9–1.98 (m, 1H), 2.14–2.3 (m, 1H), 2.3–2.35 (m, 1H)). After 5 min the ice bath was removed and stirring was continued for 1 h to give a solution of crude 18a which can be used for displacement reactions. For NMR analysis, saturated NaHCO₃ was added, the mixture extracted with CH₂Cl₂ and the organic layer dried (MgSO₄); [α]D -29° (c 6H, 0.79 (s, 9H), 1.54–1.61 (m, 1H), 1.9–1.98 (m, 1H), 2.14–2.3 (m, 1H), 2.3–2.35 (m, 1H)). 1H NMR δ 0.00 (s, 6H), 0.85 (s, 6H), 1.35–1.48 (m, 4H), 2.18–2.01 (m, 1H), 2.87–2.94 (m, 1H), 3.38 (d, 2H, J = 13.2, 13.9), 3.53–3.53 (m, 2H), 3.58 (d, 2H, J = 16.2, 17.3), 7.24–7.28 (m, 10H); MS 400 (M⁺). Anal. Calc. for C₂₉H₂₂N₂O₂Si: C, 74.3; H, 9.8; N, 6.2. Found: C, 74.1; H, 10.0; N, 6.0.
19a to 19c (21 mg, 75%) as a colorless liquid (solvent for flash chromatography: n-hexane–EtOAc 3:1; [α]D 23 +7° (c = 1, CHCl₃); IR 3040, 2930, 1730 cm⁻¹; 1H NMR δ 6.00 (s, 6H), 0.84 (s, 6H), 1.20 (d, 3H, J = 6.6), 1.24 (t, 3H, J = 7.3), 1.42–1.56 (m, 1H), 1.85–1.96 (m, 1H), 2.54–2.63 (m, 2H), 2.91–2.80 (m, 1H), 3.11 (q, 1H, J = 6.6), 3.48 (d, 2H, J = 13.2), 3.52–3.63 (m, 2H), 3.74–3.84 (m, 2H). Found: C, 70.1; H, 9.7; N, 5.6.

(R)-3-(N,N-Dibenzylaminol)-5-(4-chlorobenzyl)-4-[(tert-butyldimethylsilyl)oxy]pentanenitrile (19d) and (R)-2-[(NJV-Dibenzylamino)-4-[(tert-butyldimethylsilyl)oxy]butyl]amine (19e). A mixture of (R)-3-(N,N-Dibenzylamino)-4-[(tert-butyldimethylsilyl)oxy]butyl]amine (19d) (40 mg, 0.14 mmol), MszO (24.4 mg, 0.14 mmol), and CH₂Cl₂ (3.5 mL) were reacted and worked up as described for 19g to give 19g (40 mg, 52%) as a colorless liquid (solvent for flash chromatography: petroleum ether–EtOAc 98:2) to give [α]D 23 +10° (c = 0.5, CHCl₃); IR 3040, 2930, 1770, 1720 cm⁻¹; 1H NMR δ 0.01 (s, 6H), 0.89 (s, 6H), 1.23–1.28 (m, 1H), 1.51–1.60 (m, 1H), 1.76–1.81 (m, 1H), 1.96–2.09 (m, 1H), 2.75–2.85 (m, 1H), 3.48–3.58 (m, 2H), 3.65–3.75 (m, 2H), 7.11–7.28 (m, 10H); CIMS 396 (M + 1). Anal. Calcd for C₃₂H₄₅NOSi: C, 75.5; H, 9.9; N, 3.5. Found: C, 75.3; H, 10.1; N, 3.5.

(R)-N,N-Dibenzyl-1-[(4-chlorobenzyl)amino]-3-phenyl-1-buta-1,3-diene (19h). To a stirred suspension of Cul (243 mg, 1.28 mmol) in EtO (5 mL) was added MeLi (1.6 mL, 1 M in EtO) at −50 °C. Then the mixture was allowed to warm to −20 °C. After 30 min it was cooled to −50 °C, when a solution of crude 18a (prepared from 12a (51 mg, 0.13 mmol), Et₂N (14 mg, 0.14 mmol), MeSO₃ (24.4 mg, 0.14 mmol), and CH₂Cl₂ (1 mL)) was added. After the mixture was stirred for 16 h at −20 °C saturated NaHCO₃ and EtO were added. The organic layer was dried (MgSO₄) and evaporated, and the residue was purified by flash chromatography (petroleum ether–EtOAc 98:2) to give 19g (23 mg, 46%) as a colorless liquid: [α]D 23 +10° (c = 0.5, CHCl₃); IR 3040, 2930, 1770, 1720 cm⁻¹; 1H NMR δ 0.05 (s, 6H), 0.79 (s, 6H), 0.82 (s, 6H), 0.85 (s, 6H), 0.97 (s, 6H), 1.12 (m, 1H), 1.39–1.49 (m, 1H), 1.64–1.79 (m, 1H), 2.51–2.58 (m, 1H), 3.47–3.52 (m, 1H), 3.51 (d, 2H, J = 13.9), 3.55 (d, 2H, J = 13.9), 3.64–3.67 (m, 1H), 7.11–7.16 (m, 1H), 7.22–7.26 (m, 10H); CIMS 409 (M + 1). Anal. Calcd for C₃₂H₄₆N₂O₃: C, 76.3; H, 10.2; N, 3.4. Found: C, 76.3; H, 10.2; N, 3.4.
Determination of the Enantiomeric Purity of 22a and 23a. To a stirred solution of 22a (20 mg, 0.056 mmol) in THF (2 mL) was added (R)-1-phenylethyl isocyanate (6.8 µL, 0.05 mmol) at 0°C. After 1 h the solvent was evaporated to give crude 22b (27 mg, 130%) as a colorless oil. Coupling was also carried out with (S)-1-phenylethyl isocyanate 22b. 1H NMR of 0.00 (s, 6H), 0.84 (s, 3H), 1.37-1.45 (m, 1H), 1.39 (d, 3H, J = 6.3, 6.6, 1.81-2.20 (m, 1H), 3.31 (d, 2H, J = 9.2, 2.5); 7.15-1.38 (m, 1H). Mass: 229.1 (M+1, 100%), 228.1 (M, 12%), 227.1 (M-1, 21%), 226.1 (M-2, 5%).

23b was prepared from 23a (23 mg, 0.058 mmol) as described for 22b. Coupling was also carried out with (S)-1-phenylethyl isocyanate. 23b. 1H NMR of 0.00 (s, 5H), 0.84 (s, 3H), 1.44 (m, 1H), 1.52-1.72 (m, 2H), 1.9-2.3 (m, 2H), 3.46-3.58 (m, 1H), 3.58-3.68 (m, 2H), 4.64-4.66 (m, 1H), 7.23-7.35 (m, 1H), 7.68-7.80 (m, 1H).

Analysis of the crude product of 22a and 23a by HPLC (silica gel, solvent: n-hexane-ethyl acetate 3:1) and 1H NMR studies including doping experiments established 22a and 23a to be >96% ee.

S-(N,N-Dibenzy1-1-(N,N-dibenzylamino)-4-(tert-butyl dimethylsilyloxy)-2-butylamine (22a). A solution of 19f (20 mg, 0.058 mmol) in THF/EtOAc (4.5 mL) was reacted and worked up as described for 8f to give 21f (225 mg, 77%) (solvent for flash chromatography: petroleum ether–EtOAc 4:1). 1H NMR of 0.00 (s, 6H), 0.84 (s, 3H), 1.46-1.70 (m, 2H), 2.21-2.35 (m, 1H), 2.70-3.00 (m, 2H). Mass: 229.1 (M+1, 100%), 228.1 (M, 12%), 227.1 (M-1, 21%), 226.1 (M-2, 5%).

Analysis of the crude product of 22a and 23a by HPLC (silica gel, solvent: n-hexane-ethyl acetate 3:1) and 1H NMR studies including doping experiments established 22a and 23a to be >96% ee.

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(S)-4-Amino-3-(N,N-dibenzylamino)-1-butanol (28). Compound 22a (4.4 g, 11.2 mmol) was reacted and worked up as described for 8a to give pure 28b (3.0 g, 99%) as a colorless liquid; \( \text{CIMS} \ 353 \ (M+) \). Anal. Calcd for C\(_{37}\)H\(_{4}N\(_{2}\)O\(_{2}\)Si: C, 76.0; H, 8.5; N, 9.8. Found: C, 76.3; H, 8.5; N, 9.8.

tert-Butyl (S)-1-[2-(N,N-Dibenzy1amino)-4-hydroxybutyl]-3-hydroxypyrrole-2-carboxylate (30a). To a solution of 28 (7.43 g, 22.5 mmol) in CH\(_2\)Cl\(_2\) (250 mL) was added the tricarbonyl compound 29. After 16 h at rt silica gel (22.5 g) was added, and stirring was continued for further 16 h. After filtration the solvent was evaporated and the residue purified by flash chromatography (petroleum ether–EtOAc 7:3) to give 30a (5.0 g, 63%) as a colorless liquid; \( \text{CIMS} \ 353 \ (M+) \). Anal. Calcd for C\(_{37}\)H\(_{4}N\(_{2}\)O\(_{2}\)Si: C, 76.0; H, 8.5; N, 9.8. Found: C, 76.3; H, 8.5; N, 9.8.

tert-Butyl (S)-1-[2-(N,N-Dibenzy1amino)-3-bromobutyl]-3-hydroxypyrrole-2-carboxylate (30b). To a mixture of NaH (0.65 g, 27 mmol) in THF (200 mL) was slowly added triphenylphosphine (6.22 g, 23.7 mmol) at 0 °C. After 5 min the solution was evaporated and the residue purified by flash chromatography to give 30b (8.4 g, 80%) as a colorless liquid; \( \text{CIMS} \ 353 \ (M+) \). Anal. Calcd for C\(_{37}\)H\(_{4}N\(_{2}\)O\(_{2}\)Si: C, 76.0; H, 8.5; N, 9.8. Found: C, 76.3; H, 8.5; N, 9.8.

terr-Butyl (6S,8aR)-6-(N,N-Dibenzy1amino)-6,6,7,8-tetrahydro-1-oxo-8a(1H)-indolizinecarboxylate (31a) and tert-Butyl (6S,8aS)-6-(N,N-Dibenzy1amino)-6,6,7,8-tetrahydro-1-oxo-8a(1H)-indolizinecarboxylate (31b). To a mixture of NaH (0.65 g, 27 mmol) in THF (200 mL) was slowly added 30b (6.3 g, 12.3 mmol), dissolved in THF (100 mL), at 0 °C. After 30 min at 0 °C the mixture was stirred for further 30 min at 46 °C. Then, it was cooled to 0 °C and added to saturated NH\(_4\)Cl. After extraction with CH\(_2\)Cl\(_2\) as a colorless liquid; \( \text{CIMS} \ 353 \ (M+ \ - 99) \). Anal. Calcd for C\(_{37}\)H\(_{4}N\(_{2}\)O\(_{2}\)Si: C, 76.0; H, 8.5; N, 9.8. Found: C, 76.3; H, 8.5; N, 9.8.}

(S)-(2S,5S,8S,11S)-2-(N,N-Dibenzy1amino)-5-azaspiro[4.4]nonane (27a). To a stirred solution of Et\(_3\)N (0.02 mL, 0.15 mmol) in THF (1 mL) was added Et\(_3\)AlCl (2.5 mmol, 0.074 mmol) in THF (1 mL) at 0 °C. When MeCl (0.07 mL, 0.88 mmol) was added, THF was removed. After 2 h the mixture was filtered and the solvent evaporated to give 27a. \( \text{H NMR} \ 1.88-2.50 \ (m, 10H) \); 3.49 (dd, 2H, J = 13.9) 3.65 (dd, 1H, J = 13.1), 3.67-3.80 (m, 2H), 3.72 (d, 2H, J = 13.9), 3.99-4.10 (m, 2H), 4.25 (d, 1H, J = 16.9), 4.37-4.49 (m, 2H), 4.46 (d, 1H, J = 16.9), 7.17-7.24 (m, 1OH); \( \text{13CNMR} \ 52.6/26.1, 25.0/35.1, 56.5/65.6, 51.0/61.1, 63.1/63.2, 64.6/63.4, 67.3, 67.9/68.1, 128.5, 128.9, 129.3, 130.1, 203.6.}
a 2:1 mixture of 32a and 32b (1.59 g, 3.68 mmol) in THF (125 mL) was added BF₃·Et₂O (0.588 mm, 4.78 mmol) at −78 °C. After 5 min LiEt₂BH (Super-Hydride, 4.77 mL, 1 M in THF) was added, and stirring was continued for 30 min. Then saturated NaCl and saturated NaHCO₃ were added and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc 5:1) to give 32a (0.85 g, 55%) followed by 32b (0.43 g, 27%).

32a: mp 103 °C; [α]D +85° (c = 0.76, CHCl₃); IR 3030, 2930, 1760, 1720 cm⁻¹; ¹H NMR δ 1.26 (dt, 1H, J = 13.9, 3.6), 1.92 (dd, 1H, J = 13.9, 3.6), 2.29 (dt, 1H, J = 13.9, 3.6), 2.33-2.44 (m, 2H), 2.82-2.88 (m, 1H), 2.99 (dd, 1H, J = 11.7, 5.1), 2.95-3.05 (m, 1H), 3.13 (t, 1H, J = 11.1), 3.18 (dd, 1H, J = 11.1, 3.7), 3.22 (dd, 1H, J = 11.1, 7.2), 7.21 (t, 2H, J = 7.3), 7.29 (t, 2H, J = 7.3), 7.35 (d, 4H, J = 7.3); ¹C NMR δ 22.5, 27.5, 28.1, 35.9, 46.1, 48.3, 52.9, 54.3, 71.3, 82.4, 126.8, 128.2, 128.3, 140.5, 168.4, 209.1; CIMS 435 (M + 1). Anal. Calcd for C₂₇H₃₂Cl₂N₂O₂: C, 76.2; H, 8.4; N, 8.5. Found: C, 76.2; H, 8.1; N, 8.3.

32b: (1R,6S,8aR)-6-VV'-Dibenzylamino-1-acetoxyoctahydroindolizine (32b). To a solution of 32a (50 mg, 0.252 mmol) in Ac₂O (1 mL) and pyridine (1 mL) was stirred for 2 h at rt. After evaporation the residue was purified by flash chromatography (CH₂Cl₂–MeOH 95:5) to give 32b (30 mg, 50%) as a colorless solid: [α]D +1° (c = 2, CHCl₃); mp 198 °C; IR 3030, 2940, 1730, 1640, 1460, 1380, 1260, 1170, 1015, 880 cm⁻¹; ¹H NMR δ 1.24-1.39 (m, 2H), 1.67-1.75 (m, 3H), 1.94 (s, 3H), 1.94-1.99 (m, 4H), 2.19 (q, 1H, J = 7.3), 2.22 (m, 1H), 3.05 (dt, 1H, J = 9.1, 1.5), 3.23 (dd, 1H, J = 10.3, 2.9), 3.56 (d, 2H, J = 2.9); CIMS 172 (M + 1). Anal. Calcd for C₂₇H₃₂Cl₂N₂O₂: C, 76.2; H, 8.1; N, 11.3. Found: C, 76.0; H, 8.0; N, 11.5.