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

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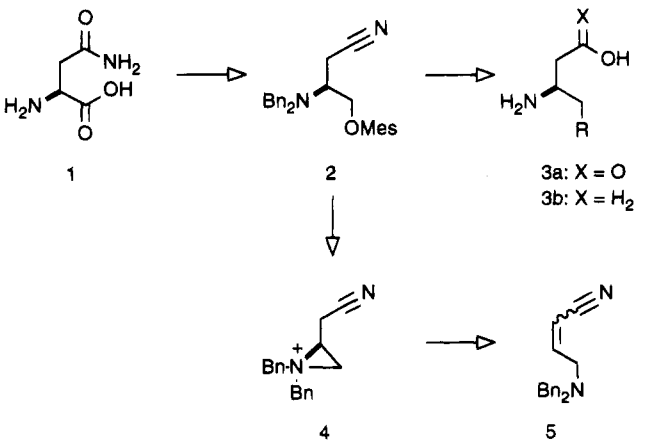
Starting from natural aspartic acid (**6**) a practical method for the synthesis of enantiomerically pure 3-amino alcohols **8** including 3,4-diamino derivatives is described. After perbenzylation of **6** and reduction of both carboxylates, position 4 of the resultant (dibenzylamino)butanediol (**11**) 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 envisioned SAR studies, we, furthermore, report on the application of this method to a chirospecific 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-hydroxypyrrolidine 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 (**30b**) 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 1,3-amino alcohols **3b** through the activated β-homoserine derivative **2** when organocuprates, $LiBH_4$, or NaN_3 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 nitrile 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**[4] including the respective diamino derivatives (Nu = NRR′), through the key intermediate **7** (Scheme 2). As a part of our program on the synthesis

Scheme 1



of bioactive compounds we, furthermore, demonstrate an application of this method for the preparation of the enantiomerically pure indolizidines 8a-epi- and 1,8a-diepislaframine **9a,b** 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 K_2CO_3 to give the tetrabenzyl derivative **10**, which could

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(1) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; Wiley: New York, 1987.

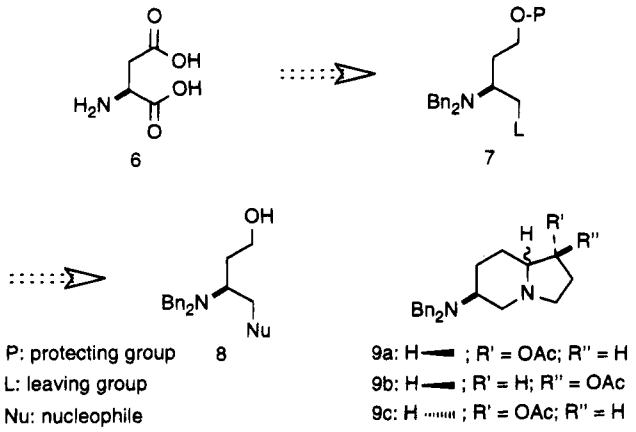
(2) (a) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717–5720. (b) Gmeiner, P. *Arch. Pharm. (Weinheim)* **1991**, *324*, 551–557. (c) Gmeiner, P. *Liebigs Ann. Chem.* **1991**, 501–502. (d) Gmeiner, P. *Heterocycles* **1991**, *32*, 1499–1504.

(3) For recent examples on regioselective functionalizations of aspartic acid, see: (a) Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3832–3890. (b) Takahashi, Y.; Hasegawa, S.; Izawa, T.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 3020–3024. (c) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068–3074. (d) Lee, K.-I.; Kim, J. H.; Ko, K. Y.; Kim, W. J. *Synthesis* **1991**, 935–936. (e) Misiti, D.; Santaniello, M.; Zappia, G. *Synth. Commun.* **1992**, *22*, 883–891. (f) Dener, J. M.; Zhang, L.-H.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1159–1166. (g) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019–5022.

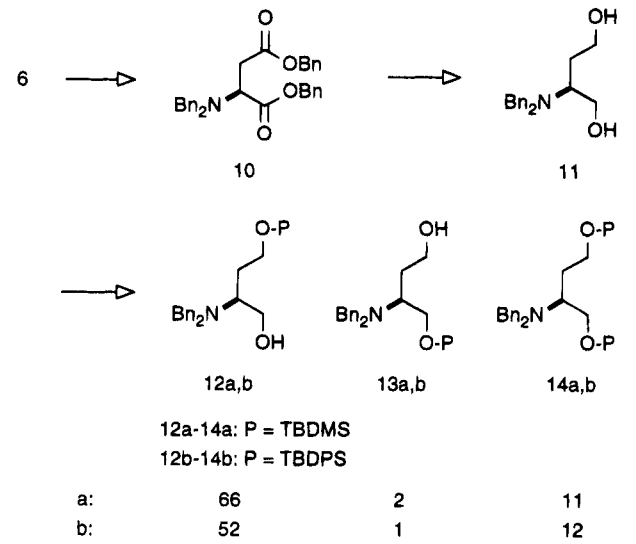
(4) (a) Preliminary communication: Gmeiner, P.; Kärtner, A.; Junge, D. *Tetrahedron Lett.* **1993**, *34*, 4325–4326. (b) For examples of stereoselective syntheses of 1,3-amino alcohols, see: Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A. L. *J. Org. Chem.* **1992**, *57*, 1219 and references cited therein.

0022-3263/94/1959-6766$04.50/0

Scheme 2



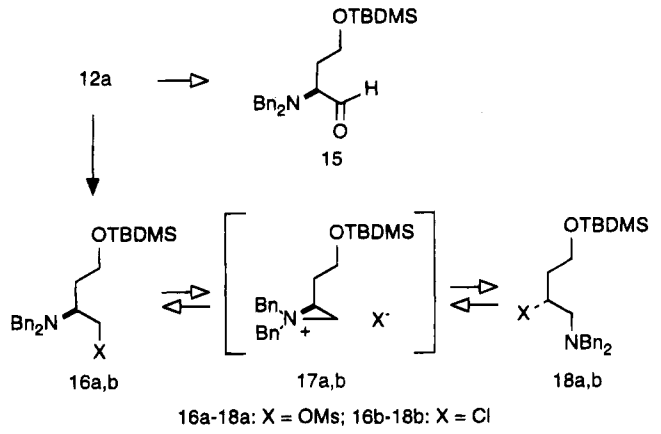
Scheme 3



a:	66	2	11
b:	52	1	12

be reduced by $LiAlH_4$. 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**[2b,7] could be differentiated very efficiently. Treatment of **11** with TBDMS-Cl/imidazole resulted in preferred attack at the less hindered position

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 (TBDPS-Cl)/imidazole yielding **12b** (52%), **13b** (1%), and **14b** (12%).

Activation of Alcohol 12a. For the projected coupling with nucleophiles 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**[8] was expected to make possible a convenient introduction of amines by reductive amination.

Reaction of **12a** with $MsCl/Et_3N$ in CH_2Cl_2 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**.[9] 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 Ms_2O/Et_3N via **17a**. Compound **18a** turned out to be moisture sensitive and was used as a solution in CH_2Cl_2.

Alternatively, activation of **12a** by Swern oxidation (oxalyl chloride, Et_3N, CH_2Cl_2, −60 °C)[10] 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 $NaCNBH_3$, yielded the tertiary amine **19a**. Coupling with Gly-OEt or L-Ala-OEt resulted in formation of the protected peptidomimetics **19b** and **19c**,

(5) Syntheses of racemic slaframine: (a) Cartwright, D.; Gardiner, R. A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 7615–7617. (b) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848–3853. (c) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7806. (d) Schneider, M. J.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3681–3684. (e) Dartmann, M.; Flitsch, W.; Krebs, B.; Pandl, K.; Westfechtel, A. *Liebigs Ann. Chem.* **1988**, 695–704. (f) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368–2372. Syntheses of (−)-slaframine: (g) Pearson, W. H.; Bergmeier, C. *J. Org. Chem.* **1991**, *56*, 1976–1978. (h) Choi, J. R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469–6472. (i) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1992**, *57*, 3977–3987. (j) Sibi, M. P.; Christensen, J. W.; Li, B.; Renhowe, P. A. *J. Org. Chem.* **1992**, *57*, 4329–4330. (k) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802–4809. (l) Hua, D. H.; Park, J.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144–2150. (m) Knight, D. W.; Sibley, A. W. *Tetrahedron Lett.* **1993**, *34*, 6607–6610.

(6) For biological effects of slaframine, see: (a) Rainey, D. P.; Smalley, E. B.; Crumpp, M. P.; Strong, F. M. *Nature (London)* **1965**, *205*, 203–204. (b) Aust, S. D.; Broquist, H. P. *Nature (London)* **1965**, *205*, 204. (c) Guengenich, F. P.; Aust, S. D. *Mol. Pharmacol.* **1977**, *13*, 185. (d) Guengenich, F. P.; Broquist, H. P. In *Bioorganic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, 1979; Vol. 2, pp 97–109. (e) Elbein, A. D.; Molyneux, R. J. In *Alcaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, pp 1–54.

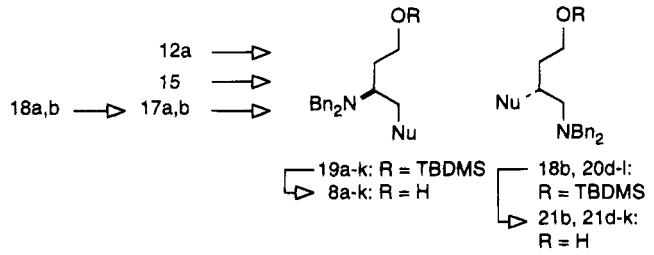
(7) Pedrocchi-Fantoni, G.; Servi, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1029–1033.

(8) For a review on *N,N*-dibenzylamino aldehydes, see: Reetz, M. T. *Angew. Chem.* **1991**, *103*, 1559–1573.

(9) (a) For examples of related migration reactions, see: Shanzer, A.; Somekh, L. *J. Am. Chem. Soc.* **1982**, *104*, 5836. Setoi, H.; Taheno, H.; Hashimoto, M. *Heterocycles* **1986**, *24*, 1261. McDonald, F. E.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 7001–7002. (b) For a review on aziridinium salts, see: Crist, D. R.; Leonard, N. J. *Angew. Chem.* **1969**, *81*, 953–1008; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 962–974.

(10) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

Scheme 5



representing reduced peptide bond analogs of the Homoser-Gly or Homoser-Ala dipeptide.[11] ^{1}H NMR investigation of **19c**, including appropriate doping experiments with the diastereomeric mixture obtained by reductive amination of **15** with D,L-Ala-OEt, proved the isomeric purity of **19c** and the stability of the amino aldehyde **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 **18b** as an educt, NaCN, phthalimide–K, or NaN_3 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 regioisomers **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_2CuLi or Bu_2CuLi 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-methoxy 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 introduced by reacting **12a** under Mitsunobu conditions.[12] The convenient one-pot procedure afforded 57% of **19f** besides 23% of the easily separable regioisomer **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 stereospecifity 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 ^{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 α_D 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_N2 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 aldehyde **15** as a chiral C-4 equivalent with 3-hydroxypyrrolidine, followed by oxidation of the secondary hydroxyl function, activation of the protected primary OH group, and base-induced 6-(enol exo)-*exo,tet*[13] cyclization to give **26**, a valuable precursor for **9a,b**. As outlined in Scheme 7 reaction of **15** with racemic 3-hydroxypyrrolidine in the presence of $NaCNBH_3$ gave a 1:1 diastereomeric mixture of the amination product **23** 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,[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 intermediately produced sulfonic ester. Attempts to activate the terminal position of **25b** under Appel conditions (CBr_4, PPh_3)[15] were also disappointing. Again the spiro derivative **27b** was isolated as the reaction product. The structure of **27b** was confirmed by the analogy of ^{1}H and ^{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[16] for the synthesis of indolizidines by alkylation of 3-hydroxypyrrole-2-carboxylate derivatives. In fact, the diamino alcohol **28**, readily available by O-deprotection of **22a**, was reacted with the vinyl tricarbonyl reagent **29**[17] to give the condensation product **30a** which was subsequently converted into the cyclization precursor **30b** by CBr_4/PPh_3 in CH_2Cl_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). Stereoelectronic effects[18] favor a chairlike transition state during the ring closure and thus lead to a chair conformation of the piperidine fragment. This is consistent with diagnostic NMR coupling constants which, furthermore, indicate an equato-

(11) For a review on peptidomimetics, see: Giannis, A.; Kolter, T. *Angew. Chem.* **1993**, *105*, 1303–1326; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267. For recent developments, see: Symposia-in-Print No. 50. *Tetrahedron* **1993**, *49*, 3433–3689.

(12) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(13) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939–2947.

(14) For a review on the stability of silyl ethers under oxidation conditions, see: Muzart, J. *Synthesis* **1993**, 11–27.

(15) Appel, R. *Angew. Chem.* **1975**, *87*, 863–874; *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–812.

(16) Wasserman, H. H.; Chi, B. V.; Cook, J. D. *Tetrahedron* **1992**, *48*, 2101–2112.

(17) Compound **29** was prepared according to: (a) Cooke, M. P., Jr.; Burman, D. L. *J. Org. Chem.* **1982**, *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 dehydrohalogenated by saturated $NaHCO_3$/THF for only 5 min. Subsequently, the product was extracted by EtOAc and purified by flash chromatography (*n*-hexane–EtOAc 7:3).

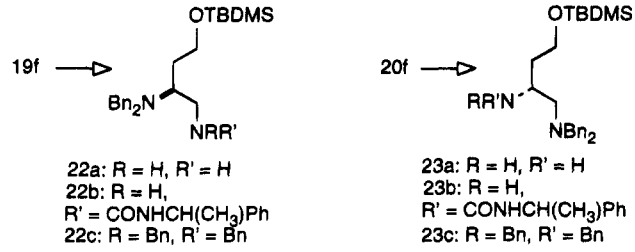
(18) Deslongchamps, P. *Stereoelectronics Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

Table 1

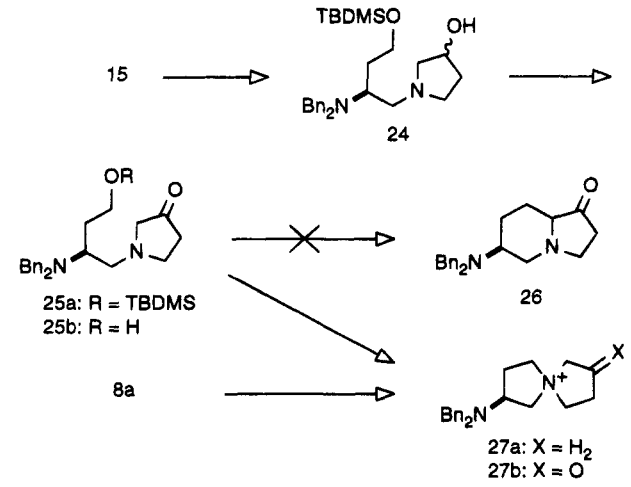
educt	reagent	product	yield (%)
15	pyrrolidine[a], $NaCNBH_3$	**19a** (Nu = 1-pyrrolidinyl)	50
15	Gly-OEt,[a] $NaCNBH_3$	**19b** (Nu = $NHCH_2CO_2Et$)	50
15	L-Ala-OEt,[a] $NaCNBH_3$	**19c** (Nu = $NHCH(CH_3)CO_2Et$)	75
18b	NaCN	**19d** (Nu = CN)	73
		20d (Nu = CN)	7
18b	NaN_3	**19e, 20e** (Nu = N_3), 3:2	98
18b	phthalimide–K	**19f** (Nu = NPhth)	52
		20f (Nu = NPhth)	19
12a	phthalimide, DEAD, PPh_3	**19f** (Nu = NPhth)	57
		20f (Nu = NPhth)	23
18a	Me_2CuLi	**19g** (Nu = Me)	46[b]
18a	Bu_2CuLi	**19h** (Nu = Bu)	32[b]
18a	1-indolyl–K	**19i, 20i** (Nu = 1-indolyl), 18:1 mixture	94[b]
18a	1-(4-MeO-indolyl)–K	**19j, 20j** (Nu = 1-(4-MeO-indolyl), 11:1	99[b]
18a	1-(5-MeO-indolyl)–K	**19k, 20k** (Nu = 1-(5-MeO-indolyl), 12:1	98[b]
18a	LiBr	**20l** (Nu = Br)	68[b]
18a	LiCl	**18b** (Nu = Cl)	72[b]

[a] Used as a hydrochloride salt. [b] Based on **12a**.

Scheme 6



Scheme 7



rial orientation of the dibenzylamine group for the major isomer **31a** and an axially positioned substituent in position 6 of the minor component **31b**. Under these conditions, for both diastereomers only a pseudo-trans junction including axial disposition of the *tert*-butyl ester group is possible since the endocyclic nitrogen is a part of a vinylogous lactam structure resulting in a trigonal planar geometry.

The C,C double bonds of **31a** and **31b** could be reduced by a Lewis acid assisted reaction with $LiEt_3BH$[19] to give **32a** and **32b**, respectively. Subsequently saponification and decarboxylation was induced by TFA. Due to the tendency of the dibenzylamino group to achieve an equatorial disposition, decarboxylation of the intermediately formed β-keto acid was accompanied by complete epimerization to give the diastereomerically pure ketone

(19) Comins, D. L.; LaMuyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053–5056.

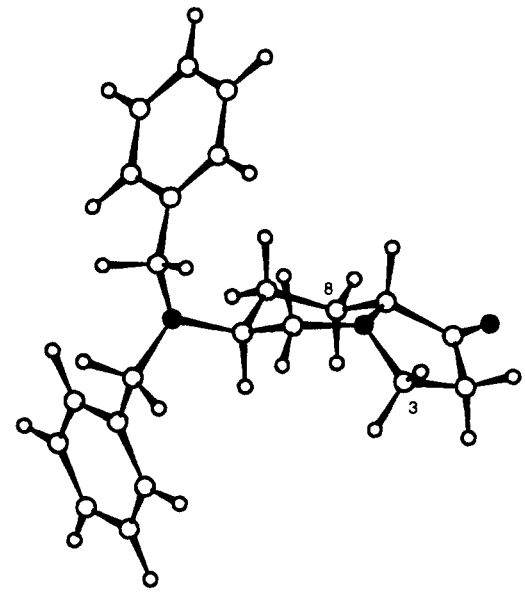
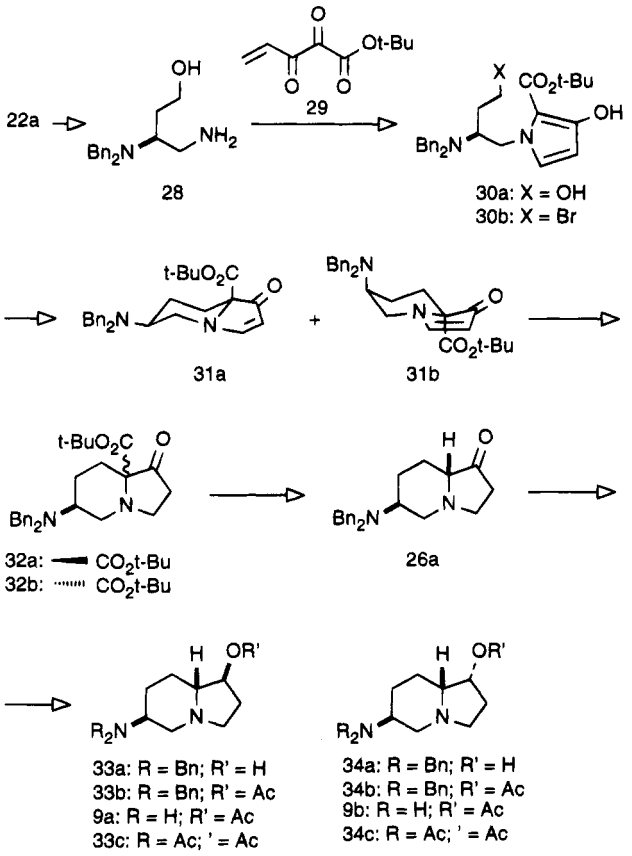


Figure 1

26a. Upon treatment of **26a** with $NaBH_4$/MeOH at 0 °C a 1:1 mixture of the 8a-epi- and 1,8a-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 $W_{1/2}$ values with those described for racemic **33c** and **34c**[5a] 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 *cvff* 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 *cvff* 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*, 209–220) was used. Visualization of the structures was done by the Insight 2.1.2 program (Biosym Tech., San Diego).

Scheme 8



attempts to reverse the diastereoselectivity including the application of Yamamoto's methodology[21] 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**.[5a,i]

Conclusions

In summary, a general chirospecific 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-diepislaframine **9a,b** in 2.4 and 3.7% overall yield, respectively.

Experimental Section

General. THF was distilled from Na/benzophenone, DMF, and CH_2Cl_2 from CaH_2, in all cases immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted reactions were conducted under dry N_2. Evaporations of final product solutions were done under vacuo with a rotatory evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. Melting points: Büchi melting point apparatus, uncorrected. IR spectra: Perkin-Elmer 881 spectrometer. Mass spectra: Varian CH7 instrument, methane was employed for CIMS. NMR spectra: JEOL JNM-GX 400 spectrometer at 400 MHz, spectra were measured as $CDCl_3$ solutions using tetramethylsilane as internal standard. Unless specified otherwise, J values are given in Hz. Elemental analyses: Heraeus CHN Rapid instrument.

(*S*)-1-[2-(*N*,*N*-Dibenzylamino)-4-hydroxybutyl]-*N*-pyrrolidine (8a). A solution of **19a** (530 mg, 1.2 mmol) in EtOH (80 mL) and NaOH (2 N, 70 mL) was stirred at 60 °C for 24 h. After addition of saturated $NaHCO_3$ the mixture was extracted with Et_2O and the organic layer dried ($MgSO_4$) and evaporated to give pure **8a** (400 mg, 98%) as a colorless oil: $[\alpha]^{23}_D$ −54° (c = 1, $CHCl_3$); IR 3400, 3030, 2930 cm^{-1}; ^{1}H NMR δ 1.60–1.69 (m, 5H), 2.02 (dt, 1H, J = 13.2, 2.2), 2.34 (dd, 2H, J = 6.6, 2.2), 2.44 (dd, 2H, J = 6.6, 2.2), 2.53 (d, 1H, J = 11.0), 2.68 (dt, 1H, J = 8.8, 2.2), 2.80 (t, 1H, J = 11.0), 3.33 (dt, 1H, J = 12.1, 2.2), 3.52 (d, 2H, J = 13.9), 3.55 (d, 2H, J = 13.9), 3.62 (ddt, 1H, J = 11.7, 2.9, 2.2), 7.15 (t, 2H, J = 7.3), 7.23 (t, 4H, J = 7.3), 7.28 (d, 4H, J = 7.3); CIMS 339 (M^+), 268 (M − 70). Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.1; H, 8.9; N, 8.3. Found: C, 78.1; H, 8.9; N, 8.2.

(*R*)-3-(*N*,*N*-Dibenzylamino)-5-hydroxypentanenitrile (8d). A solution of **19d** (49 mg, 0.12 mmol) in EtOH (4 mL) and NaOH (2N, 4 mL) was reacted and worked up as described for **8a** to give pure **8d** (31 mg, 88%) after flash chromatography (petroleum ether–EtOAc 65:35): $[\alpha]^{23}_D$ −74° (c = 1, $CHCl_3$); IR 3430, 3030, 2930, 2840, 2250, 1600 cm^{-1}; ^{1}H NMR δ 1.61–1.68 (m, 1H), 2.00–2.09 (m, 1H), 2.44 (dd, 1H, J = 17.8, 6.6), 2.60 (dd, 1H, J = 17.8, 5.8), 2.61–2.65 (m, 1H), 3.23–3.30 (m, 1H), 3.43 (d, 2H, J = 13.2), 3.56–3.61 (m, 1H), 3.72–3.76 (m, 1H), 3.86 (d, 2H, J = 13.29), 7.23–7.35 (m, 10H); CIMS 295 (M + 1), 354 (M − 40). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.5; H, 7.5; N, 9.5. Found: C, 77.6; H, 7.6; N, 9.3.

(*S*)-4-Azido-3-(*N*,*N*-dibenzylamino)-1-butanol (8e) and (*R*)-3-Azido-4-(*N*,*N*-dibenzylamino)-1-butanol (21e). A solution of **19e** and **20e** (198 mg, 0.47 mmol) in EtOH (16 mL) and NaOH (2 N, 16 mL) was stirred at 60 °C for 2 h. After addition of saturated $NaHCO_3$ the mixture was extracted with Et_2O and the organic layer dried ($MgSO_4$) and evaporated to give **8e** and **21e** (136 mg, 94%). Subsequent purification by HPLC (silica gel, *n*-hexane–EtOAc 4:1) afforded **21e** (52 mg, 37%) followed by **8e** (78 mg, 54%), both as colorless oils. **8e**: $[\alpha]^{23}_D$ −84° (c = 1, $CHCl_3$); IR 3360, 3030, 2930, 2100, 1600 cm^{-1}; ^{1}H NMR δ 1.42–1.49 (m, 1H), 1.80–1.89 (m, 1H), 3.93–3.00 (m, 1H), 3.24 (dd, 1H, J = 12.5, 6.6), 3.43 (d, 2H, 13.2), 3.46–3.51 (m, 1H), 3.56 (dd, 1H, J = 12.5, 5.8), 3.61–3.69 (m, 1H), 3.83 (d, J = 13.2), 7.17–7.27 (m, 10H); CIMS 311 (M + 1), 254 (M − 56). Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.7; H, 7.1; N, 18.0. Found: C, 69.9; H, 7.3; N, 17.6. **21e**: $[\alpha]^{23}_D$ +37° (c = 1, $CHCl_3$); IR 3380, 3030, 2930, 2800, 2100, 1600 cm^{-1}; ^{1}H NMR δ 1.39–1.50 (m, 1H), 1.58–1.66 (m, 1H), 2.48 (dd, 1H, J = 13.2, 5.8), 2.61 (dd, 1H, J = 13.2, 7.4), 3.50 (d, 2H, J = 13.2), 3.53–3.58 (m, 3H), 3.63 (d, J = 13.2), 7.17–7.31 (m, 10H); CIMS 311 (M + 1), 210 (M − 100). Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.7; H, 7.1; N, 18.0. Found: C, 69.5; H, 7.2; N, 17.7.

(*S*)-1-[2-(*N*,*N*-Dibenzylamino)-4-hydroxy]butyl-*N*-phthalimide (8f). A solution of **19f** (50 mg, 0.095 mmol) in THF/HOAc/H_2O (5 mL, 1:3:1) was stirred for 4 d at rt. Then, the reaction mixture was basified with 2 N NaOH and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether–EtOAc 3:2) to give **8f** (23 mg, 60%) as a colorless oil: $[\alpha]^{23}_D$ −18° (c = 1, $CHCl_3$); IR 3460, 3030, 2930, 1770, 1710 cm^{-1}; ^{1}H NMR δ 1.39–1.46 (m, 1H), 1.92–1.99 (m, 1H), 3.05–3.12 (m, 1H), 3.42–3.48 (m, 1H), 3.58 (dd, 1H, J = 13.2, 7.3), 3.61 (d, 2H, J = 13.2), 3.62–3.71 (m, 1H), 3.73 (d, 2H, J = 13.2), 4.01 (dd, 1H, J = 13.2, 5.1), 7.10–7.19 (m, 6H), 7.26 (d, 4H, J = 6.6), 7.66 (dd, 2H, J = 5.1, 2.9), 7.76 (dd, 2H, J = 5.1, 2.9); CIMS 415 (M + 1). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.3; H, 6.3; N, 6.8. Found: C, 75.5; H, 6.5; N, 6.5.

(*R*)-3-(*N*,*N*-Dibenzylamino)-1-pentanol (8g). A solution of **19g** (18 mg, 0.045 mmol) in EtOH (1.5 mL) and NaOH (2N, 1.5 mL) was reacted and worked up as described for **8a** to give pure **8g** (9 mg, 71%) after flash chromatography (petroleum ether–EtOAc 9:1): $[\alpha]^{23}_D$ −47° (c = 1, $CHCl_3$), IR 3390, 3030,

(21) Reduction reagent: ^{t}BuMgCl/MAD. The reaction was performed according to: Maruoka, K.; Itoh, T.; Nonoshiita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588–3597.

2930, 2870, 1600 cm^{-1}; ^{1}H NMR δ 0.81 (t 3H, J = 7.3), 1.12–1.21 (m, 1H), 1.41–1.48 (m 1H), 1.721.85 (m, 2H), 2.56–2.62 (m, 1H), 3.26 (d, 2H, 13.2), 3.39–3.45 (m, 1 H), 3.66–3.71 (m, 1H), 3.81 (d, 2H, J = 13.2), 7.16–7.26 (m, 10H); CIMS 284 (M + 1). Anal. Calcd for $C_{19}H_{25}NO$: C, 80.5; H, 8.9; N, 4.9. Found: C, 80.2; H, 9.3; N, 4.8.

(*R*)-3-(*N*,*N*-Dibenzylamino)-1-octanol (8h). A solution of **19h** (18.3 mg, 0.042 mmol) in THF/HOAc/H_2O (2 mL, 1:3:1) was reacted and worked up as described for **8f** to give **8h** (12.1 mg, 90%) as a colorless oil (solvent for flash chromatography: CH_2Cl_2–MeOH 98.5:1.5); $[\alpha]^{23}_D$ −85° (c = 0.5, $CHCl_3$); IR 3400, 3030, 2930, 2850, 1600 cm^{-1}; ^{1}H NMR δ 0.83 (t, 3H, J = 7.3), 1.08–1.28 (m, 7H), 1.39–1.46 (m, 1H), 1.70–1.83 (m, 2H), 2.64–2.69 (m, 1H), 3.26 (d, 2H, J = 13.2), 3.42 (dt, 1H, J = 10.3, 2.9), 3.65–3.70 (m, 1H), 3.80 (d, 2H, J = 13.2), 7.16–7.27 (m, 10H); CIMS 326 (M + 1), 254 (M − 71). Anal. Calcd for $C_{22}H_{31}NO$: C, 81.2; H, 9.6; N, 4.3. Found: C, 81.1; H, 9.7; N, 4.3.

(*S*)-3-(*N*,*N*-Dibenzylamino)-4-(1-indolyl)-1-butanol (8i) and (*R*)-4-(*N*,*N*-Dibenzylamino)-3-(1-indolyl)-1-butanol (21i). The compounds **19i** and **20i** (544 mg, 1.09 mmol) were reacted and worked up as described for **8a** to give **8i** (372 mg, 89%) followed by **21i** (22 mg, 5%) after flash chromatography (petroleum ether–EtOAc 4:1). **8i**: $[\alpha]^{23}_D$ 12° (c = 1, $CHCl_3$); IR 3380, 3030, 2930, 1600 cm^{-1}; ^{1}H NMR δ 1.25–1.34 (m, 1H), 1.87–1.95 (m, 1H), 3.27–3.34 (m, 1H), 3.36–3.42 (m, 1H), 3.38 (d, 2H, 13.9), 3.52–3.58 (m, 1H), 3.89 (d, 2H, J = 13.9), 3.99 (dd, 1H, J = 13.9, 7.1), 4.39 (dd, 1H, J = 13.9, 5.1), 6.45 (D, 1H, J = 2.9), 6.95 (d, 1H, J = 2.9), 7.0–7.23 (m, 13H), 7.55 (d, 1H, J = 7.0); CIMS 385 (M + 1), 254 (M − 130). Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.2; H, 7.3; N, 7.3. Found: C, 81.3; H, 7.6; N, 6.9. **21i**: ^{1}H NMR δ 1.77–1.86 (m, 1H), 1.89–1.97 (m, 1H), 2.77 (dd, 1H, J = 13.2, 6.6), 2.86 (dd, 1H, J = 13.2, 8.0), 3.40–3.45 (m, 1H), 3.17–3.24 (m, 1H), 3.48 (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 = 7.3).

(*S*)-3-(*N*,*N*-Dibenzylamino)-4-[1-(4-methoxyindolyl)]-1-butanol (8j) and (*R*)-4-(*N*,*N*-Dibenzylamino)-3-[1-(4-methoxyindolyl)]-1-butanol (21j). The compounds **19j** and **20j** (250 mg, 0.47 mmol) were reacted and worked up as described for **8a** to give **21j** (14 mg, 7%) followed by **8j** (160 mg, 82%) after flash chromatography (petroleum ether–EtOAc 7:3). **8j**: $[\alpha]^{23}_D$ −14° (c = 0.5, $CHCl_3$); IR 3380, 3030, 2930 cm^{-1}; ^{1}H NMR δ 1.23–1.31 (m, 1H), 1.87–1.96 (m, 1H), 3.26–3.33 (m, 1H), 3.34–3.40 (m, 1H), 3.47 (d, 2H, J = 13.2), 3.50–3.55 (m, 1H), 3.89 (d, 2H, J = 13.2), 3.89 (s, 3H), 3.96 (dd, 1H, J = 13.9, 8.8), 4.38 (dd, 1H, J = 13.9, 5.9), 6.44 (d, 1H, J = 7.3), 6.65 (d, 1H, J = 2.9), 6.76 (d, 1H, J = 7.3), 6.86 (d, 1H, J = 2.9), 7.01 (t, 1H, J = 7.3), 7.15–7.27 (m, 10H); CIMS 415 (M + 1), 254 (M − 160). Anal. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.2; H, 7.3; N, 6.8. Found: C, 78.3; H, 7.5; N, 6.5. **21j**: $[\alpha]^{23}_D$ +58° (c = 1, $CHCl_3$); IR 2310, 3030, 2960, 2920 cm^{-1}; ^{1}H NMR δ 1.82–1.90 (m, 1H), 2.11–2.20 (m, 1H), 2.84 (dd, 1H, J = 13.2, 6.6), 2.91 (dd, 1H, J = 13.2, 7.3), 3.23–3.29 (m, 1H), 3.45–3.53 (m, 1H), 3.55 (d, 2H, J = 13.9), 3.60 (d, 2H, J = 13.9), 3.96 (s, 3H), 4.58–4.66 (m, 1H), 6.50 (d, 1H, J = 7.3), 6.60 (d, 1H, J = 2.9), 6.80 (d, 1H, J = 2.9), 6.84 (d, 1H, J = 7.3), 7.06 (t, 1H, J = 7.3), 7.20–7.30 (m, 10H); CIMS 415 (M + 1), 210 (M − 204). Anal. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.2; H, 7.3; N, 6.7. Found: C, 78.3; H, 7.7; N, 6.3.

(*S*)-3-(*N*,*N*-Dibenzylamino)-4-[1-(5-methoxyindolyl)]-1-butanol (8k) and (*R*)-4-(*N*,*N*-Dibenzylamino)-3-[1-(5-methoxyindolyl)-1-butanol (21k). The compounds **19k** and **20k** (125 mg, 0.24 mmol) were reacted and worked up as described for **8a** to give **21k** (7 mg, 7%) followed by **8j** (78 mg, 80%) after flash chromatography (petroleum ether–EtOAc 65:35). **8j**: $[\alpha]^{23}_D$ −1° (c = 1, $CHCl_3$); IR 3400, 3030, 2930, 2830, 1620 cm^{-1}; ^{1}H NMR δ 1.31–1.38 (m, 1H), 1.93–2.04 (m, 1H), 3.32–3.39 (m, 1H), 3.43–3.50 (m, 1H), 3.54 (d, 2H, J = 13.2), 3.61–3.64 (m, 1H), 3.85 (s, 3H), 3.96 (d, 2H, J = 13.2), 4.02 (dd, 1H, J = 13.9, 8.1), 4.44 (dd, 1H, J = 13.9, 5.1), 6.43 (d, 1H, J = 2.9), 6.81 (dd, 1H, J = 8.8, 2.2), 7.00 (d, 1H, J = 2.9), 7.06 (d, 1H, J = 8.8), 7.09 (d, 1H, J = 2.2), 7.12–7.30 (m, 10H); CIMS 415 (M + 1), 254 (M − 160). Anal. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.2; H, 7.3; N, 6.7. Found: C, 78.5; H, 7.5; N, 6.4. **21j**: $[\alpha]^{23}_D$ +39° (c = 1, $CHCl_3$); IR 3390, 3030, 2930, 2830, 1620 cm^{-1}; ^{1}H NMR δ 1.81–1.91 (m, 1H), 2.10–2.19 (m, 1H), 2.83 (dd, 1H, J = 13.2, 7.3), 2.90 (d, 1H, J = 13.2, 7.3), 3.25–3.31 (m, 1H), 3.46–3.52 (m, 1H), 3.55 (d, 2H, J = 13.2), 3.60 (d, 2H, J = 13.2), 3.85 (s, 3H), 4.53–4.60 (m, 1H), 6.41 (d, 1H, J = 3.6), 6.79 (dd, 1H, J = 8.8, 2.2), 6.89 (d, 1H, J = 3.6), 7.06 (d, 1H, J = 8.8), 7.08 (d, 1H, J = 2.2), 7.20–7.30 (m, 10H); CIMS 415 (M + 1), 210 (M − 205).

(1*S*,6*S*,8a*R*)-1-Acetoxy-6-aminooctahydroindolizine (9a). A mixture of **33b** (31 mg, 0.082 mmol) and $Pd(OH)_2$/C (19 mg, 20%) in MeOH (3.5 mL) was stirred for 2 h at rt under a balloon of H_2. The reaction mixture was filtered and the solvent evaporated to give **9a** (25.3 mg, 95%) as a colorless oil: $[\alpha]^{23}_D$ +38° (c = 0.75, EtOH); IR 3310, 2940, 1730 cm^{-1}; ^{1}H NMR δ 1.07 (dq, 1H, J = 12.4, 3.6), 1.36 (dq, 1H, J = 13.2, 3.6), 1.54–1.61 (m, 1H), 1.81 (t, 1H, J = 10.3), 1.87–2.00 (m, 3H), 2.04 (s, 3H), 2.30–2.38 (m, 2H), 2.84–2.93 (m, 1H), 2.95 (dt, 1H, J = 7.3, 2.2), 3.12 (dd, 1H, J = 10.3, 4.4), 4.73–4.78 (m, 1H); EIMS 155 (M − 43).

(1*R*,6*S*,8a*R*)-1-Acetoxy-6-aminooctahydroindolizine (9b). Compound **9b** (23 mg, 94%) was prepared from **34b** (46 mg, 0.122 mmol) as described for **9a**: $[\alpha]^{23}_D$ +7° (c = 1, EtOH)[22] (lit.[5i] $[\alpha]^{23}_D$ +20° (c = 0.5, EtOH)< for *ent*-**9b**; lit.[5i] $[\alpha]^{23}_D$ −11.6° (c = 0.37, EtOH)); IR 3340, 2950, 1740 cm^{-1}; ^{1}H NMR δ 1.16 (dq, 1H, J = 12.4, 3.6), 1.51 (dq, 1H, J = 11.0, 3.6), 1.70–1.91 (m, 3H), 1.99–2.23 (m, 4H), 2.06 (s, 3H), 2.98–3.04 (m, 1H), 3.14 (dt, 1H, J = 9.5, 2.2), 3.30 (dd, 1H, J = 10.3, 3.6), 5.20–5.23 (m, 1H); EIMS 198 (M$^+$), 155 (M − 43).

(*S*)-*N*,*N*-Dibenzylaspartic Acid Dibenzyl Ester (10). To a solution of L-aspartic acid (**6**) (15.0 g, 113 mmol) in aqueous K_2CO_3 (20%) was slowly added benzyl bromide (130 g, 765 mmol) at rt. The mixture was stirred at 100 °C for 4 h. After being cooled to rt, the reaction mixture was extracted with ether and the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc 97:3) to give **10** (41 g, 75%) as a colorless oil: $[\alpha]^{23}_D$ −63° (c = 1, $CHCl_3$); IR 3060, 2850, 1730 cm^{-1}; ^{1}H NMR δ 2.71 (dd, 1H, J = 15.4, 7.3), 2.93 (dd, 1H, J = 15.4, 8.1), 3.53 (d, 2H, J = 13.9), 3.78 (d, 2H, J = 13.9), 3.96 (t, 1H, J = 8.1), 4.92 (d, 1H, J = 12.5), 5.11 (d, 1H, J = 12.5), 5.14 (d, 1H, J = 12.5), 5.26 (d, 1H, J = 12.5), 7.18–7.42 (m, 20H); EIMS 402 (M − 91). Anal. Calcd for $C_{32}H_{31}NO_4$: C, 77.8; H, 6.3; N, 2.8. Found: C, 77.7; H, 6.5; N, 2.8.

(*S*)-2-(*N*,*N*-Dibenzylamino)butane-1,4-diol (11). To a stirred solution of **10** (12.71 g, 25.8 mmol) was added $LiAlH_4$ (77.5 mL, 1 M solution in THF) at −78 °C. The temperature was allowed to warm to −55 °C. After 1 h saturated Na_2SO_4 was added, followed by saturated $NaHCO_3$ and Et_2O. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether–EtOAc 2:3) to give **11** (7.4 g, 70%); α^{23}_D +17° (c = 1, $CHCl_3$); IR and NMR data were in agreement with those previously reported.[2b]

(*S*)-2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]-1-butanol (12a), (*S*)-2-(*N*,*N*-Dibenzylamino)-1-[(*tert*-butyldimethylsilyl)oxy]-4-butanol (13a), and (*S*)-2-(*N*,*N*-Dibenzylamino)-1,4-bis[(*tert*-butyldimethylsilyl)-oxy]butane (14a). To a solution of **11** (3.18 g, 11.1 mmol) in

(22) The inequality of the compared α_D values can be explained by the instability of **9b** in solution. We proved the isomeric purity of **9b** by derivatization with (*R*)- as well as (*S*)-1-phenylethyl isocyanate as described for the determination of the enantiomeric purity of **22a** and **23a**. ^{1}H NMR investigation (J values in Hz) of the resulting ureas including appropriate doping experiments revealed the synthetic material to be isomerically pure. Coupling with (*S*)-1-phenylethyl isocyanate: ^{1}H NMR δ 0.98 (dq, 1H, J = 12.5, 4.4), 1.38 (d, 3H, J = 6.6), 1.48 (dq, 1H, J = 13.2, 3.7), 1.61–1.65 (m, 1H), 1.70–1.82 (m, 2H), 1.96–2.08 (m, 3H), 1.98 (s, 3H), 2.14–2.24 (m, 1H), 3.03 (dt, 1H, J = 1.5, 8.8), 3.25 (dd, 1H, J = 10.3, 2.9), 3.58–3.68 (m, 1H), 4.12 (bs, 1H), 4.65 (bs, 1H), 4.75 (q, 1H, J = 6.6), 5.11–5.14 (m, 1H), 7.19–7.28 (m, 5H); CIMS 346 (M + 1). Coupling with (*R*)-1-phenylethyl isocyanate: ^{1}H NMR δ 1.01–1.04 (m, 1H), 1.44 (d, 3H, J = 6.8), 1.52 (dq, 1H, J = 13.2, 3.8), 1.68–1.79 (m, 1H), 1.81–1.87 (m, 1H), 1.96–1.99 (m, 1H), 1.94–2.10 (m, 3H), 2.06 (s, 3H), 2.23–2.32 (m, 1H), 3.13 (dt, 1H, J = 8.9, 1.7), 3.36 (dd, 1H, J = 10.7, 3.8), 3.73–3.76 (m, 1H), 4.44 (bs, 1H), 4.82 (q, 1H, J = 6.8), 4.94 (bs, 1H), 5.19–5.22 (m, 1H), 7.23–7.27 (m, 1H), 7.30–7.36 (m, 4H); CIMS 346 (M + 1).

DMF (60 mL) was added TBDMS-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 NH_4Cl and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated and the residue purified by flash chromatography (petroleum ether–EtOAc 9:1) to give **14a** (0.63 g, 11%), followed by **12a** (2.93 g, 66%) and **13a** (89 mg, 2%). **12a**: $[\alpha]^{23}_D$ +43° (c = 1, $CHCl_3$); IR 3440, 3030, 2930 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.83 (s, 9H), 1.37–1.45 (m, 1H), 1.93–2.01 (m, 1H), 2.87–2.94 (m, 1H), 3.38 (d, 2H, J = 13.2), 3.43–3.53 (m, 2H), 3.58 (t, 2H, J = 6.6), 3.76 (d, 2H, J = 13.2), 7.24–7.28 (m, 10H); MS 400 (M^+). Anal. Calcd for $C_{24}H_{37}NO_2Si$: C, 72.1; H, 9.3; N, 3.5. Found: C, 72.1; H, 8.9; N, 3.9. **13a**: $[\alpha]^{23}_D$ −54° (c = 0.5, $CHCl_3$); IR 3400, 3030, 2930 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.91 (s, 9H), 1.38–1.45 (m, 1H), 1.84–1.93 (m, 1H), 2.93–3.00 (m, 1H), 3.46–3.52 (m, 1H), 3.57 (d, 2H, J = 13.2), 3.66–3.70 (m, 1H), 3.69 (dd, 1H, J = 10.3, 5.1), 3.81 (dd, 1H, J = 10.3, 6.6), 3.90 (d, 2H, J = 13.2), 7.20–7.30 (m, 10H); MS 400 (M^+). Anal. Calcd for $C_{24}H_{37}NO_2Si$: C, 72.1; H, 9.3; N, 3.5. Found: C, 71.9; H, 9.2; N, 3.8. **14a**: $[\alpha]^{23}_D$ −18° (c = 1, $CHCl_3$); IR 3030, 2930 cm^{-1}; ^1H NMR δ 0.05 (s, 6H), 0.06 (s, 6H), 0.85 (s, 9H), 0.91 (s, 9H), 1.61–1.67 (m, 1H), 1.79–1.85 (m, 1H), 2.77–2.83 (m, 1H), 3.53–3.60 (m, 1H), 3.68 (d, 2H, J = 13.9), 3.68–3.75 (m, 3H), 3.77 (d, 2H, J = 13.9), 7.17–7.36 (m, 10H); MS 514 (M^+). Anal. Calcd for $C_{30}H_{51}NO_2Si_2$: C, 70.1; H, 10.0; N, 2.7. Found: C, 69.8; H, 10.4; N, 2.9.

(*S*)-2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldiphenylsilyl)oxy]-1-butanol (12b), (*S*)-2-(*N*,*N*-Dibenzylamino)-1-[(*tert*-butyldiphenylsilyl)oxy]-4-butanol (13b), and (*S*)-2-(*N*,*N*-Dibenzylamino)-1,4-[(*tert*-butyldiphenylsilyl)oxy]-butane (14b). Compound **11** (500 mg, 1.77 mmol), TBDPS-Cl (520 mg, 19.3 mmol), and imidazole (262 mg, 3.85 mmol) in DMF (10 mL) were reacted and worked up as described for **12a**–**14a** to give **14b** (110 mg, 12%), followed by **12b** (482 mg, 52%) and **13b** (10 mg, 1%). **12b**: $[\alpha]^{23}_D$ +37° (c = 1, $CHCl_3$); IR 3450, 3030, 2850 cm^{-1}; ^1H NNMR δ 0.96 (s, 9H), 1.17–1.22 (m, 1H), 1.92–1.98 (m, 1H), 2.36–2.92 (m, 1H), 3.29 (d, 2H, J = 13.2), 3.32–3.43 (m, 2H), 3.54–3.60 (m, 2H), 3.70 (d, 2H, J = 13.2), 7.13–7.22 (m, 10H), 7.30–7.39 (m, 6H), 7.56–7.59 (m, 4H). Anal. Calcd for $C_{34}H_{41}NO_2Si$: C, 78.0; H, 7.9; N, 2.7. Found: C, 78.0; H, 7.9; N, 2.7. **13b**: IR 3430, 3030, 2860 cm^{-1}; ^1H NMR δ 1.09 (s, 9H), 1.49–1.56 (m, 1H), 1.88–1.97 (m, 1H), 3.04–3.10 (m, 1H), 3.48–3.54 (m, 1H), 3.55 (d, 2H, J = 13.2), 3.72–3.76 (m, 1H), 3.76 (dd, 1H, J = 11.0, 5.9), 3.85 (dd, 1H, J = 11.0, 5.9), 3.94 (d, 2H, J = 13.2), 7.22–7.33 (m, 10H), 7.39–7.48 (m, 6H), 7.67–7.71 (m, 4H). **14b**: IR 3070, 2930, 2850 cm^{-1}; ^1H NMR δ 0.89 (s, 9H), 1.00 (s, 9H), 1.57–1.68 (m, 1H), 1.74–1.82 (m, 1H), 2.84–2.90 (m, 1H), 3.51–3.61 (m, 1H), 3.62–3.69 (m, 7H), 7.08–7.19 (m, 10H), 7.22–7.36 (m, 12H), 7.49–7.59 (m, 8H); CIMS 763 (M + 1). Anal. Calcd for $C_{50}H_{59}NO_2Si_2$: C, 78.8; H, 7.8; N, 1.8. Found: C, 78.8; H, 8.3; N, 1.7.

(*S*)-2-(*N*,*N*-Dibenzylamino)-4-hydroxybutanal (15). To a solution of oxalyl chloride (4.96 mL, 56.8 mmol) in CH_2Cl_2 was added at −60 °C DMSO (8.07 mL, 113.7 mmol), dissolved in CH_2Cl_2 (20 mL), and subsequently, **12a** (18.2 g, 45.5 mmol), also dissolved in CH_2Cl_2. The mixture was stirred for 15 min when Et_2N (31.7 mL, 227 mmol) was added. After 5 min, saturated $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated to leave pure **15** (15.4 g, 85%) as colorless crystals: $[\alpha]^{23}_D$ −62° (c = 1, $CHCl_3$); mp 32 °C; IR 3060, 2930, 1730 cm^{-1}; ^1H NMR δ 0.02 (s, 6H), 0.85 (s, 9H), 1.81–1.95 (m, 1H), 1.97–2.05 (m, 1H), 3.44 (dd, 1H, J = 8.1, 4.4), 3.69 (d, 2H, J = 13.2), 3.62–3.69 (m, 1H), 3.73–3.79 (m, 1H), 3.79 (d, 2H, J = 13.2), 7.25–7.29 (m, 2H), 7.31–7.35 (m, 4H), 7.39–7.41 (m, 4H), 9.29 (s, 1H); EIMS 368 (M − 29). Anal. Calcd for $C_{24}H_{35}NO_2Si$: C, 72.5; H, 8.9; N, 3.5. Found: C, 72.4; H, 8.9; N, 3.5.

(*R*)-2-[1-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl Methanesulfonate (18a). To a solution of **12a** (204 mg, 0.51 mmol) and Et_3N (155 mg, 1.53 mmol) in CH_2Cl_2 (3 mL) was slowly added Ms_2O (222 mg, 1.28 mmol) at 0 °C. 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 $NaHCO_3$ was added, the mixture extracted with $CDCl_3$ and the organic layer dried ($MgSO_4$): ^1H NMR δ 0.0 (s, 6H), 0.79 (s, 9H), 1.54–1.61 (m, 1H), 1.9–1.98 (m, 1H), 2.58 (dd, 1H, J = 13.2, 5.6), 2.77 (dd, 1H, J = 13.2, 5.9), 3.52 (d, 2H, J = 13.2), 3.57 (d, 2H, J = 13.2), 3.59–3.69 (m, 2H), 4.84–4.90 (m, 1H), 7.16–7.29 (m, 10H).

(*R*)-*N*,*N*-Dibenzyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-chloro-1-butylamine (18b). A. To a solution of **12a** (2.37 g, 5.92 mmol) and Et_3N (1.80 g, 14.8 mmol) in CH_2Cl_2 (50 mL) was slowly added MsCl (1.70 g, 18.8 mmol) at 0 °C. After 5 min the ice bath was removed and stirring was continued for 1 h. After addition of saturated $NaHCO_3$ the mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography to give **18b** (2.33 g, 94%) as a colorless oil.

B. To a solution of crude **18a**, prepared from **12a** (24 mg, 0.06 mmol), Et_3N (18 mg, 0.18 mmol), Mes_2O (26 mg, 0.15 mmol), and CH_2Cl_2 (1 mL), was added LiCl (42 mg, 1 mmol). After being stirred for 16 h the mixture was filtered and evaporated and the residue purified by flash chromatography (petroleum ether–EtOAc 95:5) to give **18b** (18 mg, 72%): $[\alpha]^{23}_D$ +18° (c = 1, $CHCl_3$); IR 3030, 2930, 1600 cm^{-1}; ^1H NMR δ 0.01 (s, 6H), 0.83 (s, 9H), 1.40–1.49 (m, 1H), 2.14–2.20 (m, 1H), 2.66 (dd, 1H, J = 13.2, 8.1), 2.75 (dd, 1H, J = 13.2, 6.6), 3.51 (d, 2H, J = 13.2), 3.64 (d, 2H, J = 13.2), 3.66–3.70 (m, 2H), 4.10–4.17 (m, 1H), 7.17–7.32 (m, 10H); EIMS 418 (M^+). Anal. Calcd for $C_{24}H_{37}ClNO_2Si$: C, 68.9; H, 8.7; Cl, 8.5; N, 3.3. Found: C, 68.9; H, 8.6; Cl, 8.3; N, 3.2. By employing THF as a solvent, the above-mentioned reaction afforded **18b** and **16b** as a 3:1 mixture of isomers in 64% yield. ^1H NMR data of **16b** from the crude mixture: −0.01 (s, 6H), 0.81 (s, 9H), 1.71–1.77 (m, 1H), 1.86–1.95 (m, 1H), 3.07 (qui, 1H, J = 6.6), 3.68–3.77 (m, 4H), 3.70 (s, 4H), 7.20–7.38 (m, 10H). By performing the above-mentioned procedure in $CDCl_3$, **16a** could be observed, 5 min after addition of MesCl, as the main reaction product by ^1H NMR spectroscopy of the crude mixture. **16a**: ^1H NMR δ 0.00 (s, 6H), 0.84 (s, 9H), 1.68–1.77 (m, 1H), 1.86–1.95 (m, 1H), 3.02–3.07 (m, 1H), 3.53–3.60 (m, 2H), 3.70 (s, 4H), 4.28 (dd, 1H, J = 10.2, 4.4), 4.35 (dd, 1H, J = 10.2, 5.9 Hz), 7.20–7.37 (m, 10H).

(*S*)-1-[1-[2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl]pyrrolidine (19a). To a solution of $NaCNBH_3$ (201 mg, 3.2 mmol) in MeOH (40 mL) was added first pyrrolidine·HCl (1.29 g, 12 mmol) and then **15** (1.59 g, 4 mmol) in MeOH (20 mL). After being stirred for 1 h at rt the solvent was evaporated, followed by addition of saturated $NaHCO_3$ and Et_2O. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether–EtOAc 3:2) to give **19a** (0.9 g, 50%) as a colorless liquid: $[\alpha]^{23}_D$ −29° (c = 1, $CHCl_3$); IR 3030, 2930 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.84 (s, 9H), 1.68–1.73 (m, 5H), 1.73–1.80 (m, 1H), 2.34–2.36 (m, 2H), 2.40–2.42 (m, 2H), 2.48 (dd, 1H, J = 11.7, 8.8), 2.65 (dd, 1H, J = 11.7, 5.14), 2.78–2.85 (m, 1H), 3.52–3.60 (m, 1H), 3.59 (d, 2H, J = 13.9), 3.71 (d, 2H, J = 13.9), 3.73–3.79 (m, 1H), 7.19 (t, 2H, J = 7.3), 7.27 (t, 4H, J = 7.3), 7.34 (d, 4H, J = 7.3). Anal. Calcd for $C_{28}H_{44}N_2OSi$: C, 74.3; H, 9.8; N, 6.2. Found: C, 74.1; H, 10.0; N, 6.0.

(*S*)-*N*-[1-[2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl]glycine Ethyl Ester (19b). Compound **15** (11 mg, 0.028 mmol), $NaCNBH_3$ (1.4 mg, 0.022 mmol), and glycine ethyl ester·HCl (19.3 mg, 0.14 mmol) in MeOH (2 mL) were reacted and worked up as described for **19a** to give **19b** (6.7 mg, 50%) as a colorless liquid (solvent for flash chromatography: n-hexane–EtOAc 3:1): $[\alpha]^{23}_D$ +9° (c = 0.25, $CHCl_3$); IR 3420, 3030, 2930, 1740 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.85 (s, 9H), 1.23 (t, 3H, J = 6.6), 1.36–1.45 (m, 1H), 1.93–2.01 (m, 1H), 2.45 (dd, 1H, J = 11.7, 4.4), 2.69 (dd, 1H, J = 11.7, 10.3), 2.83–2.90 (m, 1H), 3.06 (d, 1H, J = 17.6), 3.15 (d, 1H, J = 17.6), 3.40 (d, 2H, J = 13.2), 3.58 (t, 2H, J = 6.6), 3.71 (d, 2H, J = 13.2), 4.13 (q, 2H, J = 7.3), 7.17 (t, 2H, J = 7.3), 7.23–7.31 (m, 8H). Anal. Calcd for $C_{28}H_{44}N_2O_3Si$: C, 69.4; H, 9.2; N, 5.8. Found: C, 69.1; H, 9.6; N, 5.6.

(2*S*)-*N*-[1-[2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl]]-(*S*)-alanine Ethyl Ester (19c). Compound **15** (25 mg, 0.063 mmol), $NaCNBH_3$ (3.2 mg, 0.05 mmol), and (*S*)-alanine ethyl ester·HCl (48.6 mg, 0.315 mmol) in MeOH (2 mL) were reacted and worked up as described for

19a to give **19c** (21 mg, 75%) as a colorless liquid (solvent for flash chromatography: *n*-hexane–EtOAc 3:1): $[\alpha]^{23}_D$ −7° (*c* = 1, $CHCl_3$); IR 3340, 3030, 2930, 1730 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.84 (s, 9H), 1.20 (d, 3H, *J* = 6.6), 1.24 (t, 3H, *J* = 7.3), 1.42–1.56 (m, 1H), 1.88–1.96 (m, 1H), 2.54–2.63 (m, 2H), 2.81–2.86 (m, 1H), 3.11 (q, 1H, *J* = 6.6), 3.48 (d, 2H, *J* = 13.2), 3.53–3.68 (m, 2H), 3.66 (d, 2H, *J* = 13.2), 4.08–4.20 (m, 2H), 7.14 (d, 2H, *J* = 6.6), 7.23–7.30 (m, 8H). Anal. Calcd for $C_{29}H_{46}N_2O_3Si$: C, 69.8; H, 9.3; N, 5.6. Found: C, 70.1; H, 9.7; N, 5.6.

(*R*)-3-(*N*,*N*-Dibenzylamino)-5-[(*tert*-butyldimethylsilyl)oxy]pentanenitrile (19d) and (*R*)-2-[(*N*,*N*-Dibenzylamino)methyl]-4-[(*tert*-butyldimethylsilyl)oxy]butanenitrile (20d). A mixture of **18b** (250 mg, 0.6 mmol) and NaCN (250 mg, 510 mmol) in DMF (15 mL) was stirred for 5 d at 50 °C. After the mixture was cooled to 0 °C it was added to saturated $NaHCO_3$ and Et_2O. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether–EtOAc 96:4) to give **20d** (16 mg, 7%) followed by **19d** (180 mg, 73%), both as colorless liquids. **19d**: $[\alpha]^{23}_D$ −28.2° (*c* = 1, $CHCl_3$); IR 3030, 2930 cm^{-1}; ^1H NMR δ −0.01 (s, 6H), 0.83 (s, 9H), 1.58–1.67 (m, 1H), 1.97–2.05 (m, 1H), 2.46 (dd, 1H, *J* = 16.9, 7.3), 2.56 (dd, 1H, *J* = 16.9, 5.1), 3.18–3.25 (m, 1H), 3.58–3.72 (m, 2H), 3.65 (s, 4H), 7.24 (d, 2H, *J* = 7.3), 7.31 (t, 4H, *J* = 7.3), 7.39 (d, 4H, *J* = 7.3); CIMS 409 (M + 1), 368 (M − 40). Anal. Calcd for $C_{25}H_{36}N_2OSi$: C, 73.5; H, 8.9; N, 6.9. Found: C, 73.5; H, 8.9; N, 6.9. **20d**: $[\alpha]^{23}_D$ −1° (*c* = 0.8, $CHCl_3$); IR 3030, 2950, 2240 cm^{-1}; ^1H NMR δ −0.01 (s, 6H), 1.53 (s, 6H), 1.54–1.59 (m, 1H), 1.71–1.77 (m, 1H), 2.54 (dd, 1H, *J* = 13.2, 6.6), 2.77 (dd, 1H, *J* = 13.2, 8.8), 2.90–2.96 (m, 1H), 3.55 (d, 2H, *J* = 13.9), 3.65 (d, 2H, *J* = 13.9), 3.62–3.67 (m, 2H), 7.22 (d, 2H, *J* = 7.3), 7.29 (t, 4H, *J* = 7.3), 7.35 (d, 4H, *J* = 7.3); CIMS 409 (M + 1), 210 (M − 198). Anal. Calcd for $C_{25}H_{36}N_2OSi$: C, 73.5; H, 8.9; N, 8.9. Found: C, 73.1; H, 9.3; N, 6.7.

(*S*)-*N*,*N*-Dibenzyl-1-azido-4-[(*tert*-butyldimethylsilyl)oxy]-2-butylamine (19e) and (*R*)-*N*,*N*-Dibenzyl-2-azido-4-[(*tert*-butyldimethylsilyl)oxy]-1-butylamine (20e). A mixture of **18b** (198 mg, 0.474 mmol) and NaN_3 (270 mg, 417 mmol) in DMF (12 mL) was stirred for 3 d at 60 °C. After the mixture was cooled to 0 °C it was added to saturated $NaHCO_3$ and Et_2O. The organic layer was dried ($MgSO_4$) and evaporated to leave **19e** and **20e** (200 mg, 99%) as a hardly separable mixture of isomers. ^1H NMR of the crude product: δ 0.0 (s, 3/5 × 6H), 0.01 (s, 2/5 × 6H), 0.81 (s, 2/5 × 9H), 0.84 (s, 3/5 × 9H), 1.28–1.34 (m, 2/5 × 1H), 1.49–1.56 (m, 3/5 × 1H), 1.61–1.66 (m, 2/5 × 1H), 1.87–1.95 (m, 3/5 × 1H), 2.45 (dd, 2/5 × 1H, *J* = 13.2, 4.4), 2.62 (dd, 2/5 × 1H, *J* = 13.2, 8.1), 2.96–3.01 (m, 3/5 × 1H), 3.27 (dd, 3/5 × 1H, *J* = 12.4, 5.1), 3.45 (dd, 3/5 × 1H, *J* = 12.4, 7.4), 3.48 (d, 2/5 × 2H, *J* = 13.2), 3.53–3.63 (m, 3/5 × 2H), 3.55–3.65 (m, 2/5 × 3H), 3.63 (d, 3/5 × 2H, *J* = 13.9), 3.68 (d, 3/5 × 2H, *J* = 13.9), 3.70 (d, 2/2 × 2H, *J* = 13.2), 7.20 (d, 2/5 × 2H, *J* = 7.3), 7.22 (d, 3/5 × 2H, *J* = 7.3), 7.28 (d, 2/5 × 4H, *J* = 7.3), 7.30 (d, 3/5 × 4H, *J* = 7.3), 7.34 (d, 2/5 × 4H, *J* = 7.3), 7.37 (d, 3/5 × 4H, *J* = 7.3).

(*S*)-1-[2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl]-*N*-phthalimide (19f) and (*S*)-2-[1-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl]-*N*-phthalimide (20f). A. To a solution of **12a** (4.98 g, 12.5 mmol), phthalimide (1.84 g, 12.5 mmol), and PPh_3 (3.28 g, 12.5 mmol) in THF was added dropwise diethyl azodicarboxylate (2.18 g, 12.5 mmol) at rt. After 16 h the solvent was evaporated and the crude residue purified by flash chromatography (petroleum ether–EtOAc 95:5) to give **20f** (1.52 g, 23%) followed by **19f** (3.76 g, 57%), both as colorless liquids.

B. A mixture of **18b** (61 mg, 0.146 mmol) and phthalimide–K (238 mg, 1.28 mmol) in DMF (3.5 mL) was stirred for 2 d at 50 °C. After the mixture was cooled to 0 °C it was added to saturated $NaHCO_3$ and Et_2O. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether–EtOAc 95:5) to give **20f** (15 mg, 19%) followed by **19f** (40 mg, 52%). **19f**: $[\alpha]^{23}_D$ +13° (*c* = 1, $CHCl_3$); IR 3030, 2930, 1770, 1720, 1600 cm^{-1}; ^1H NMR δ 0.02 (s, 6H), 0.83 (s, 9H), 1.50–1.56 (m, 1H), 1.99–2.04 (m, 1H), 3.08–3.12 (m, 1H), 3.49 (d, 2H, *J* = 13.2), 3.51 (dd, 1H, *J* = 13.9, 5.9), 3.57–3.64 (m, 1H), 3.71–3.77 (m, 1H), 3.75 (d, 2H, *J* = 13.2), 3.97 (dd, 1H, *J* = 13.9, 8.1), 7.10–7.26 (m, 10H), 7.71–7.75 (m, 2H), 7.79–7.83 (m, 2H); ^{13}C NMR −5.5, 18.3, 25.9, 31.2, 38.4, 53.2, 53.8, 61.3, 123.0, 126.7, 127.9, 128.9, 132.3, 133.6, 139.8, 168.1; CIMS 529 (M + 1). Anal. Calcd for $C_{32}H_{40}N_2O_3Si$: C, 72.7; H, 7.6; N, 5.3. Found: C, 72.7; H, 7.6; N, 5.3. **20f**: $[\alpha]^{23}_D$ −28° (*c* = 1, $CHCl_3$); IR 3030, 2930, 1770, 1710 cm^{-1}; ^1H NMR δ 0.01 (s, 6H), 0.89 (s, 9H), 1.93–1.99 (m, 1H), 2.22–2.31 (m, 1H), 2.63 (dd, 1H, *J* = 13.2, 4.0), 3.22 (dd, 1H, *J* = 13.2, 10.3), 3.37 (d, 2H, *J* = 13.2), 3.59–3.72 (m, 2H), 3.86 (d, 2H, *J* = 13.2), 4.73–4.80 (m, 1H), 7.14–7.25 (m, 10H), 7.77–7.83 (m, 4H); CIMS 529 (M + 1). Anal. Calcd for $C_{32}H_{40}N_2O_3Si$: C, 72.7; H, 7.6; N, 5.3. Found: C, 72.6; H, 7.6; N, 5.2.

(*R*)-*N*,*N*-Dibenzyl-1-[(*tert*-butyldimethylsilyl)oxy]-3-pentylamine (19g). To a stirred suspension of CuI (243 mg, 1.28 mmol) in Et_2O (5 mL) was added MeLi (1.6 mL, 1.6 M in Et_2O) 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), Et_3N (14 mg, 0.14 mmol), Ms_2O (24.4 mg, 0.14 mmol), and CH_2Cl_2 (1 mL)) was added. After the mixture was stirred for 16 h at −20 °C saturated $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purifed by flash chromatography (petroleum ether–EtOAc 98:2) to give **19g** (23 mg, 46%) as a colorless liquid: $[\alpha]^{23}_D$ +10° (*c* = 0.5, $CHCl_3$); IR 3030, 2960 cm^{-1}; ^1H NMR δ 0.05 (s, 6H), 0.79 (s, 9H), 0.82 (t, 3H, *J* = 7.3), 1.35–1.44 (m, 1H), 1.51–1.60 (m, 2H), 1.78–1.83 (m, 1H), 1.37–1.43 (m, 1H), 3.46 (d, 2H, *J* = 13.9), 3.51 (d, 2H, *J* = 13.9), 3.59–3.65 (m, 2H), 7.11–7.28 (m, 10H); CIMS 398 (M + 1). Anal. Calcd for $C_{25}H_{39}NOSi$: C, 75.5; H, 9.9; N, 3.5. Found: C, 75.3; H, 10.1; N, 3.5.

(*R*)-*N*,*N*-Dibenzyl-1-[(*tert*-butyldimethylsilyl)oxy]-3-octylamine (19h). CuI (682 mg, 3.58 mmol) and BuLi (4.48 mL, 1.6 M in *n*-hexane) in Et_2O (15 mL) and crude **18a** (prepared from **12a** (143 mg, 0.36 mmol), Et_3N (80 mg, 0.79 mmol), Ms_2O (137 mg, 0.79 mmol), and CH_2Cl_2 (2.5 mL)) were reacted and worked up as described for **19g** to give **19h** (51 mg, 32%) as a colorless liquid: $[\alpha]^{23}_D$ +3° (*c* = 1, $CHCl_3$); IR 3030, 2930 cm^{-1}; ^1H NMR δ 0.0 (s, 6H), 0.84 (s, 9H), 0.85 (t, 3H, *J* = 7.3), 1.07–1.45 (m, 9H), 1.84–1.91 (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), 3.64–3.71 (m, 1H), 7.16–7.35 (m, 10H); CIMS 440 (M + 1). Anal. Calcd for $C_{28}H_{45}NOSi$: C, 76.5; H, 10.3; N, 3.2. Found: C, 76.3; H, 10.2; N, 3.4.

(*S*)-*N*,*N*-Dibenzyl-4-[(*tert*-butyldimethylsilyl)oxy]-1-(1-indolyl)-2-butylamine (19i) and (*R*)-*N*,*N*-Dibenzyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(1-indolyl)-1-butylamine (20i). To a stirred solution of indole (315 mg, 2.67 mmol) in THF (4 mL) was added KHMDS (4.93 mL, 0.6 M in toluene) at −40 °C. Then the mixture was allowed to warm to 0 °C. After 30 min it was cooled to −78 °C, when a solution of crude **18a** (prepared from **12a** (108 mg, 0.27 mmol), Et_3N (82 mg, 0.81 mmol), Ms_2O (117 mg, 0.67 mmol), and CH_2Cl_2 (2 mL)) was added. After the mixture was stirred for 16 h at −20 °C saturated $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether–EtOAc 98:2) to give an 18:1 mixture of **19i** and **20i** (126 mg, 94%) as a colorless oil: ^1H NMR (main isomer) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.50–1.57 (m, 1H), 2.02–2.09 (m, 1H), 3.36–3.43 (m, 1H), 3.54–3.60 (m, 1H), 3.67 (d, 2H, *J* = 13.9), 3.69–3.72 (m, 1H), 3.76 (d, 2H, *J* = 13.9), 4.19 (dd, 1H, *J* = 14.0, 6.7), 4.31 (dd, 1H, *J* = 14.0, 8.20), 6.55 (d, 1H, *J* = 3.0), 7.07 (d, 1H, *J* = 3.0), 7.08–7.31 (m, 13H), 7.68 (d, 1H, *J* = 7.3). Anal. Calcd for $C_{32}H_{42}N_2OSi$: C, 77.1; H, 8.5; N, 5.6. Found: C, 77.1; H, 8.3; N, 5.7.

(*S*)-*N*,*N*-Dibenzyl-4-[(*tert*-butyldimethylsilyl)oxy]-1-[1-(4-methoxyindolyl)]-2-butylamine (19j) and (*R*)-*N*,*N*-Dibenzyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-[1-(4-methoxyindole)]-1-butylamine (20j). 4-Methoxyindole (751 mg, 5.10 mmol), KHMDS (9.35 mL, 0.6 M in toluene), THF (7.5 mL), and crude **18a** (prepared from **12a** (204 mg, 0.51 mmol), Et_3N (155 mg, 1.53 mmol), Ms_2O (222 mg, 1.27 mmol), and CH_2Cl_2 (3.5 mL)) were reacted and worked up as described for **19i** and **20i** to give an 11:1 mixture of **19j** and **20j** (267

mg, 99%) as a colorless oil (solvent for flash chromatography (petroleum ether–EtOAc 95:5): ^{1}H NMR (main isomer) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.49–1.58 (m, 1H), 2.00–2.06 (m, 1H), 3.34–3.39 (m, 1H), 3.52–3.58 (m, 1H), 3.66 (d, 2H, J = 13.9), 3.68–3.72 (m, 1H), 3.67 (d, 2H, J = 13.9), 4.03 (s, 3H), 4.15 (dd, 1H, J = 13.9, 5.5), 4.28 (dd, 1H, J = 13.9, 8.9), 6.53 (d, 1H, J = 7.3), 6.65 (d, 1H, J = 2.9), 6.74 (d, 1H, J = 7.3), 6.97 (d, 1H, J = 2.9), 6.99 (t, 1H, J = 7.3), 7.17–7.22 (m, 10H).

(*S*)-*N,N*-Dibenzyl-4-[(*tert*-butyldimethylsilyl)oxy]-1-[1-(5-methoxyindolyl)]-2-butylamine (19k) and (*R*)-*N,N*-Dibenzyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-[1-(5-methoxyindolyl)]-1-butylamine (20k). 5-Methoxyindole (397 mg, 2.70 mmol), KHMDS (4.95 mL, 0.6 M in toluene), THF (4 mL), and crude **18a** (prepared from **12a** (108 mg, 0.27 mmol), Et_3N (82 mg, 0.81 mmol), Mes_2O (118 mg, 0.68 mmol), and CH_2Cl_2 (2 mL)) were reacted and worked up as described for **19i** and **20i** to give a 12:1 mixture of **19k** and **20k** (267 mg, 98%) as a colorless oil (solvent for flash chromatography (petroleum ether–EtOAc 95:5): ^{1}H NMR (main isomer) δ 0.00 (s, 6H), 0.84 (s, 9H), 1.47–1.55 (m, 1H), 2.00–2.06 (m, 1H), 3.31–3.39 (m, 1H), 3.51–3.57 (m, 1H), 3.65 (d, 2H, J = 13.9), 3.68–3.74 (m, 1H), 3.72 (d, 2H, J = 13.9), 3.89 (s, 3H), 4.12 (dd, 1H, J = 14.6, 5.7), 4.25 (dd, 1H, J = 14.6, 8.0), 6.45 (d, 1H, J = 2.9), 6.71 (dd, 1H, J = 8.8, 2.2), 6.94 (d, 1H, J = 8.8), 7.02 (d, 1H, J = 2.9), 7.12–7.30 (m, 11H).

(*R*)-*N,N*-Dibenzyl-2-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-1-butylamine (20l). To a solution of crude **18a** (prepared from **12a** (502 mg, 1.26 mmol), Et_3N (635 mg, 6.28 mmol), Ms_2O (547 mg, 3.14 mmol), and CH_2Cl_2 (9 mL)) was added LiBr (870 mg, 10 mmol). After being stirred for 16 h the mixture was evaporated and the residue purified by flash chromatography (petroleum ether–EtOAc 98:2) to give **20l** (392 mg, 68%): $[\alpha]^{23}_D$ +19° (c = 1, $CHCl_3$); IR 3030, 2960 cm^{-1}; ^{1}H NMR δ −0.01 (s, 6H), 0.82 (s, 9H), 1.52–1.57 (m, 1H), 2.22–2.31 (m, 1H), 2.72 (d, 1H, J = 13.2), 2.85 (dd, 1H, J = 13.2, 6.6), 3.47 (d, 2H, J = 13.2), 3.62 (d, 2H, J = 13.2), 3.65–3.69 (m, 2H), 4.17–4.24 (m, 1H), 7.16–7.31 (m, 10H); CIMS 462 (M^+), 382 (M − 80). Anal. Calcd for $C_{24}H_{36}BrNOSi$: C, 62.3; H, 7.8; N, 3.0. Found: C, 62.0; H, 8.2; N, 3.0.

(*R*)-1-(*N,N*-Dibenzylamino)-2-chloro-1-butanol (21b). Compound **18b** (402 mg, 0.96 mmol) in THF/HOAc/H_2O (50 mL, 1:3:1) was reacted and worked up as described for **8f** to give **21b** (225 mg, 77%) (solvent for flash chromatography: petroleum ether–EtOAc 4:1): $[\alpha]^{23}_D$ +29° (c = 1, $CHCl_3$); IR 3370, 3030, 2920, 2800, 1600 cm^{-1}; ^{1}H NMR δ 1.62–1.70 (m, 1H), 2.01–2.10 (m, 1H), 2.70–2.77 (m, 2H), 3.48 (d, 2H, J = 13.9), 3.59–3.61 (m, 2H), 3.64 (d, 2H, J = 13.9), 3.95–4.01 (m, 1H), 7.16–7.29 (m, 10H); CIMS 304 (M + 1), 210 (M − 93). Anal. Calcd for $C_{18}H_{22}ClNO$: C, 71.2; H, 7.3; N, 4.6. Found: C, 71.1; H, 7.4; N, 4.7.

(*R*)-2-[1-(*N,N*-Dibenzylamino)-4-hydroxybutyl]-*N*-phthalimide (21f). A solution of **20f** (300 mg, 0.567 mmol) in HOAc/THF/H_2O (42.5 mL, 3:1:1) was reacted and worked up as described for **8f** to give **21f** (235 mg, 99%) as a colorless solid (235 mg, 99%): $[\alpha]^{23}_D$ −21° (c = 0.8, $CHCl_3$); mp 114 °C; IR 3470, 3030, 2930, 1770, 1710 cm^{-1}; ^{1}H NMR δ 1.91–1.99 (m, 1H), 2.09–2.23 (m, 1H), 2.72 (dd, 1H, J = 13.2, 5.1), 3.18 (dd, 1H, J = 13.2, 8.8), 3.41 (d, 2H, J = 13.2), 3.49–3.55 (m, 1H), 3.59–5.65 (m, 1H), 3.74 (d, 2H, J = 13.2), 4.60–4.67 (m, 1H), 7.10–7.19 (m, 10H), 7.72 (dd, 2H, J = 5.1, 2.9), 7.78 (dd, 2H, J = 5.1, 2.9); CIMS 415 (M + 1). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.4; H, 6.3; N, 6.8. Found: C, 75.7; H, 6.7; N, 6.1.

(*S*)-2-(*N,N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]-1-butylamine (22a). A solution of **19f** (12.0 g, 22.8 mmol) and hydrazine hydrate (11.4 g, 228 mmol) in EtOH (240 mL) was refluxed for 16 h. After being cooled to rt the solvent was evaporated. Then, Et_2O and saturated $NaHCO_3$ were added to the residue. The organic layer was dried ($MgSO_4$) and evaporated to leave pure **22a** (8.6 g, 95%) as a colorless liquid: $[\alpha]^{23}_D$ +37° (c = 1, $CHCl_3$); IR 3310, 3060, 2880 cm^{-1}; ^{1}H NMR δ 0.03 (s, 6H), 0.87 (s, 9H), 1.33–1.43 (m, 1H), 1.96–2.01 (m, 1H), 2.57–2.71 (m, 3H), 3.41 (d, 2H, J = 13.9), 3.57–3.65 (m, 2H), 3.77 (d, 2H, J = 13.9), 7.20–7.32 (m, 10H); EIMS 398 (M^+). Anal. Calcd for $C_{24}H_{38}N_2OSi$: C, 72.3; H, 9.6; N, 7.0. Found: C, 72.3; H, 9.7; N, 7.1.

Determination of the Enantiomeric Purity of 22a and 23a. To a stirred solution of **22a** (20 mg, 0.05 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, 100%) as a colorless oil. Coupling was also carried out with (*S*)-1-phenylethyl isocyanate **22b**: ^{1}H NMR δ 0.00 (s, 6H), 0.84 (s, 9H), 1.37–1.45 (m, 1H), 1.39 (d, 3H, J = 6.6), 1.81–1.89 (m, 1H), 2.72–2.78 (m, 1H), 3.00 (dt, 1H, J = 12.5, 2.2), 3.25–3.30 (m, 1H), 3.37 (d, 2H, J = 13.2), 3.55–3.62 (m, 2H), 3.66 (d, 2H, J = 13.2), 4.21 (d, 1H, J = 6.6), 4.64–4.66 (m, 1H), 4.68–4.75 (m, 1H), 7.18–7.33 (m, 15H).

Compound **23b** (32 mg, 100%) was prepared from **23a** (23 mg, 0.058 mmol) as described for **22b**. Coupling was also carried out with (*S*)-1-phenylethyl isocyanate. **23b**: ^{1}H NMR δ 0.00 (s, 6H), 0.86 (s, 9H), 1.49 (d, 3H, J = 6.6), 1.49–1.56 (m, 1H), 1.74–1.82 (m, 1H), 2.42 (dd, 1H, J = 12.5, 7.3), 2.49 (dd, 1H, J = 12.5, 6.6), 3.49 (d, 2H, J = 13.2), 3.49–3.60 (m, 2H), 3.62 (d, 2H, J = 13.2), 3.92–3.96 (m, 1H), 4.58 (bs, 1H), 4.64–4.66 (m, 1H), 4.88–4.95 (m, 1H), 7.23–7.33 (m, 15H) HPLC (silica gel, solvent: *n*-hexane–EtOAc 3:1) and ^{1}H-NMR studies including doping experiments established **22a** and **23a** to be of >99 ee.

(*S*)-*N,N*-Dibenzyl-1-(*N,N*-dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]-2-butylamine (22c). To a solution of **22a** (50 mg, 0.125 mmol) in MeOH was added benzaldehyde (132 mg, 1.25 mmol) and $NaCNBH_3$ (15.7 mg, 0.25 mmol). The mixture was stirred for 16 h at rt. Then it was evaporated, and the residue was purified by flash chromatography (petroleum ether–EtOAc 95:5) to give **22c** (25 mg, 35%) as a colorless oil: $[\alpha]^{23}_D$ −54° (c = 1, $CHCl_3$); IR 3030, 2930 cm^{-1}; ^{1}H NMR δ 0.01 (s, 6H), 0.85 (s, 9H), 1.62–1.70 (m, 2H), 2.32 (dd, 1H, J = 12.5, 7.3), 2.72 (dd, 1H, J = 12.5, 5.1), 2.92–2.99 (m, 1H), 3.40 (d, 4H, J = 13.2), 3.46–3.53 (m, 3H), 3.55 (d, 2H, J = 13.2), 3.68–3.74 (m, 1H), 7.14–7.28 (m, 20H); CIMS 409 (M + 1). Anal. Calcd for $C_{38}H_{50}N_2OSi$: C, 78.8; H, 8.7; N, 4.8. Found: C, 78.8; H, 9.3; N, 4.8.

(*R*)-1-(*N,N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]-2-butylamine (23a). Compound **20f** (2.0 g, 3.8 mmol) and hydrazine hydrate (1.83 g, 37.8 mmol) in EtOH (90 mL) were reacted and worked up as described for **19f** to give pure **23a** (1.38 g, 91%) as a colorless liquid: $[\alpha]^{23}_D$ −40° (c = 1, $CHCl_3$); IR 3380, 3030, 2930 cm^{-1}; ^{1}H NMR δ 0.00 (s, 6H), 0.84 (s, 9H), 1.24–1.31 (m, 1H), 1.55–1.62 (m, 1H), 2.26–2.35 (m, 2H), 3.05–3.11 (m, 1H), 3.39 (d, 2H, J = 13.9), 3.64–3.72 (m, 2H), 3.71 (d, 2H, J = 13.9), 7.21–7.24 (m, 2H), 7.27–7.32 (m, 8H); CIMS 399 (M + 1). Anal. Calcd for $C_{24}H_{38}N_2OSi$: C, 72.3; H, 9.6; N, 7.0. Found: C, 72.3; H, 9.8; N, 6.8.

(*R*)-*N,N*-Dibenzyl-1-(*N,N*-dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]-2-butylamine (23c). Compound **23c** (18 mg, 25%) was prepared from **23a** (50 mg, 0.125 mmol) as described for **22c**: $[\alpha]^{23}_D$ +57° (c = 1.1, $CHCl_3$); spectroscopical data are identical to those reported for **22c**. Anal. Calcd for $C_{38}H_{50}N_2OSi$: C, 78.8; H, 8.7; N, 4.8. Found: C, 78.8; H, 8.9; N, 4.8.

(*S*)-1-[1-[2-(*N,N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl]-(*R,S*)-pyrrolidin-3-ol (24). Compound **15** (15.5 g, 27.3 mmol), $NaCNBH_3$ (1.37 g, 21.8 mmol), and (*R,S*)-3-hydroxypyrrolidine·HCl (10.12 g, 82 mmol) in MeOH (300 mL) were reacted and worked up as described for **19a** (solvent for flash chromatography: *n*-hexane–2-propanol–NEt_3 97:0.3:0.1) to give **24** (3.9 g, 30% of isomer 1 followed by 3.9 g, 30% of isomer 2) as a mixture of colorless oils. Isomer I: $[\alpha]^{23}_D$ −28° (c = 1, $CHCl_3$); IR 3450, 3030, 2930 cm^{-1}; ^{1}H NMR δ 0.00 (s, 6H), 0.84 (s, 9H), 1.64–1.72 (m, 2H), 1.72–1.83 (m, 1H), 1.91 (bs, 1H), 2.05–2.12 (m, 2H), 2.39 (dd, 1H, J = 10.3, 5.1), 2.46 (dd, 1H, J = 11.7, 8.1), 2.69 (dd, 1H, J = 11.7, 5.1), 2.56 (d, 1H, J = 9.5), 2.79–2.86 (m, 2H), 3.52–3.55 (m, 1H), 3.57 (d, 2H, J = 13.9), 3.69 (d, 2H, J = 13.9), 3.72–3.79 (m, 1H), 4.21 (m, 1H), 7.19 (t, 2H, J = 7.3), 7.27 (t, 4H, J = 7.3), 7.34 (d, 4H, J = 7.3); CIMS 469 (M + 1), 368 (M − 100). Anal. Calcd for $C_{28}H_{44}N_2O_2Si$: C, 71.7; H, 9.5; N, 6.0. Found: C, 71.9; H, 9.9; N, 6.1. Isomer II: $[\alpha]^{23}_D$ −17° (c = 1, $CHCl_3$); IR 3380, 3030, 2930 cm^{-1}; ^{1}H NMR δ 0.05 (s, 6H), 0.85 (s, 9H), 1.62–1.71 (m, 2H), 1.77–1.86 (m, 1H), 1.97–2.07 (bs, 1H), 2.08–2.14 (m, 2H), 3.32 (dd, 1H, J = 9.5, 5.1), 2.42 (dd, 1H, J

= 12.8, 7.3), 2.61 (d, 1H, J = 9.5), 2.67–2.71 (m, 1H), 2.69 (dd, 1H, J = 12.8, 5.8), 2.78–2.85 (m, 1H), 3.53–3.59 (m, 1H), 3.58 (d, 2H, J = 13.2), 3.68 (d, 2H, J = 13.2), 3.69–3.78 (m, 1H), 4.23 (bs, 1H), 7.19 (t, 2H, J = 6.6), 7.27 (t, 4H, J = 6.6), 7.34 (d, 4H, J = 7.3); CIMS 469 (M + 1), 368 (M − 100). Anal. Calcd for $C_{28}H_{44}N_2O_2Si$: C, 71.7; H, 9.5; N, 6.0. Found: C, 71.4; H, 9.7; N, 6.1.

(*S*)-1-[1-[2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]butyl]pyrrolidin-3-one (25a). To a stirred solution of oxalyl chloride (0.124 mL, 1.44 mmol) in CH_2Cl_2 (3.5 mL) was added DMSO (0.204 mL, 2.88 mmol), dissolved in CH_2Cl_2 (0.6 mL). After 10 min **24** (540 mg, 1.15 mmol) was dissolved in CH_2Cl_2 (1.8 mL) and after a further 15 min Et_3N (0.8 mL, 5.67 mmol) was added. Five min later saturated $NaHCO_3$ was added and the mixture was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated to leave pure **25a** (480 mg, 80%) as a colorless oil: $[\alpha]^{23}_D$ −33° (c = 0.5, $CHCl_3$); IR 3030, 2930, 1760 cm^{-1}; ^{1}H NMR δ 0.01 (s, 6H), 0.85 (s, 9H), 1.61–1.71 (m, 1H), 1.81–1.90 (m, 1H), 2.33 (t, 2H, J = 7.3), 2.51 (dd, 1H, J = 11.7, 7.3), 2.74–2.79 (m, 3H), 2.75 (d, 1H, J = 16.8), 2.85–2.90 (m, 1H), 2.87 (d, 1H, J = 16.8), 3.56–3.60 (m, 1H), 3.60 (d, 2H, J = 13.2), 3.71 (d, 2H, J = 13.2), 3.71–3.77 (m, 1H), 7.21 (t, 2H, J = 7.3), 7.28 (t, 4H, J = 7.3), 7.34 (d, 4H, J = 7.3); EIMS 466 (M$^+$), 368 (M − 98). Anal. Calcd for $C_{28}H_{42}N_2O_2Si$: C, 72.1; H, 9.1; N, 6.0. Found: C, 72.0; H, 9.5; N, 6.3.

(*S*)-1-[1-[2-(*N*,*N*-Dibenzylamino)-4-hydroxybutyl]]pyrrolidin-3-one (25b). A solution of **25a** (3.61 g, 7.73 mmol) in THF/HOAc/H_2O (125 mL, 1:3:1) was reacted and worked up as described for **8h** to give **25b** (2.18 g, 80%) as a colorless oil (solvent for flash chromatography: CH_2Cl_2–MeOH 98.5:1.5): $[\alpha]^{23}_D$ −85° (c = 0.5, $CHCl_3$); IR 3400, 3030, 2930, 1760 cm^{-1}; ^{1}H NMR δ 1.61–1.69 (m, 1H), 1.90–1.97 (m, 1H), 2.24–2.31 (m, 2H), 2.66–2.85 (m, 5H), 2.68 (d, 1H, J = 16.8), 2.87 (d, 1H, J = 16.8), 3.44–3.49 (m, 1H), 3.45 (d, 2H, J = 13.2), 3.53–3.61 (m, 1H), 3.65 (d, 2H, J = 13.2), 7.15–7.24 (m, 10H); CIMS 353 (M + 1), 254 (M − 98). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 75.0; H, 8.0; N, 7.9. Found: C, 75.0; H, 8.3; N, 7.6.

(6*S*,8a*R*)-6-(*N*,*N*-Dibenzylamino)-2,3,6,7,8,8a-hexahydro-1-(5*H*)-indolizinone (26a). A solution of **32a** and **32b** (826 mg, 1.9 mmol) and TFA (8.68 mL) in CH_2Cl_2 was stirred for 3 h at rt. Then saturated $NaHCO_3$ and Et_2O were added at 0 °C. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (n-hexane–acetone 4:1) to give **26a** (480 mg, 76%) as a colorless oil: $[\alpha]^{23}_D$ +92° (c = 1, $CHCl_3$); IR 3030, 2930, 1750 cm^{-1}; ^{1}H NMR δ 1.09–1.21 (m, 1H), 1.36 (dq, 1H, J = 12.6, 3.7), 1.94–2.02 (m, 3H), 2.20–2.27 (m, 3H), 2.39 (q, 1H, J = 8.8), 2.77–2.84 (m, 1H), 3.14–3.21 (m, 2H), 3.58 (d, 2H, J = 13.9), 3.64 (d, 2H, J = 13.9), 7.13 (t, 2H, J = 7.3), 7.22 (t, 4H, J = 7.3), 7.29 (d, 4H, J = 7.3); CIMS 335 (M + 1). Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.0; H, 7.8; N, 8.4. Found: C, 79.0; H, 7.8; N, 8.5.

(*S*)-2-(*N*,*N*-Dibenzylamino)-5-azaspiro[4.4]nonane (27a). To a stirred solution of Et_3N (0.02 mL, 0.15 mmol) in THF (1 mL) was added **8a** (25 mg, 0.074 mmol) in THF (1 mL) at 0 °C. Then MsCl (0.07 mL, 0.088 mmol) was added. After 2 h the mixture was filtered and the solvent evaporated to give **27a**: ^{1}H NMR δ 1.81–1.91 (m, 1H), 1.95–2.09 (m, 1H), 2.10–2.21 (m, 2H), 2.23–2.30 (m, 1H), 2.36–2.45 (m, 1H), 3.53–3.61 (m, 1H), 3.57 (d, 2H, J = 13.9), 3.63 (dd, 1H, J = 8.1, 5.1), 3.69–3.87 (m, 6H), 3.80 (d, 2H, J = 13.9), 3.88–3.96 (m, 1H), 7.22–7.33 (m, 10H); ^{13}C NMR δ 21.6, 21.8, 26.9, 56.2, 60.1, 61.9, 63.4, 63.7, 63.9, 127.5, 128.6, 138.7.

(2*S*,5*RS*)-2-(*N*,*N*-Dibenzylamino)-5-azaspiro[4.4]nonan-7-one (27b). Compound **25b** (30 mg, 0.085 mmol), Et_3N (9.5 mg, 0.094 mmol), and MsCl (10.8 mg, 0.094 mmol) in THF (0.7 mL) were reacted and worked up as described for **27a** to give **27b** (10 mg, 35%) as a mixture of diastereomers after flash chromatography (CH_2Cl_2–MeOH 9:1): IR 3420, 3000, 2930, 1770 cm^{-1}; ^{1}H NMR δ 1.78–1.90 (m, 2H), 2.23–2.32 (m, 2H), 3.46–3.60 (m, 1H), 3.48 (d, 2H, J = 13.9), 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, 10H); ^{13}C NMR δ 25.6/26.1, 35.0/35.1, 56.5/56.6, 61.0/61.1, 63.1/63.2, 64.0/64.2, 67.3, 67.9/68.1, 128.5, 128.9, 129.3, 130.1, 203.6.

(*S*)-4-Amino-3-(*N*,*N*-dibenzylamino)-1-butanol (28). Compound **22a** (4.48 g, 11.2 mmol) was reacted and worked up as described for **8a** to give pure **28** (3.0 g, 95%) as a colorless liquid: $[\alpha]^{23}_D$ −19° (c = 1, $CHCl_3$); IR 3350, 3060, 2930 cm^{-1}; ^{1}H NMR δ 1.52–1.60 (m, 1H), 1.89–2.02 (m, 1H), 2.55–2.60 (m, 2H), 3.04 (dd, 1H, J = 11.0, 3.7), 3.48–3.61 (m, 2H), 3.52 (d, 2H, J = 13.9), 3.59 (d, 2H, J = 13.9), 7.15–7.28 (m, 10H); CIMS 284 (M$^+$). Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.0; H, 8.5; N, 9.8. Found: C, 76.3; H, 8.8; N, 9.6.

***tert*-Butyl (*S*)-1-[1-[2-(*N*,*N*-Dibenzylamino)-4-hydroxybutyl]]-3-hydroxypyrrole-2-carboxylate (30a).** To a solution of **28** (7.43 g, 22.5 mmol) in CH_2Cl_2 (250 mL) was added the tricarbonyl compound **29**.[17] 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** (6.39 g, 63%) as a colorless liquid: $[\alpha]^{23}_D$ +117° (c = 1, $CHCl_3$); IR 3450, 1680, 1640 cm^{-1}; ^{1}H NMR δ 1.40 (s, 9H), 1.40–1.49 (m, 1H), 1.95–2.04 (m, 1H), 3.06–3.14 (m, 1H), 3.51–3.60 (m, 1H), 3.54 (d, 2H, J = 13.9), 3.58 (d, 2H, J = 13.9), 3.67–3.74 (m, 1H), 4.16–4.23 (m, 2H), 5.76 (d, 1H, J = 2.9), 6.73 (d, 1H, J = 2.9), 7.17–7.22 (m, 10H); CIMS 451 (M + 1). Anal. Calcd for $C_{27}H_{34}N_2O_4$: C, 72.0; H, 7.6; N, 6.2. Found: C, 72.0; H, 7.7; N, 6.1.

***tert*-Butyl (*S*)-1-[1-[2-(*N*,*N*-Dibenzylamino)-4-bromobutyl]]-3-hydroxypyrrole-2-carboxylate (30b).** To a solution of **30a** (7.12 g, 15.8 mmol) and CBr_4 (6.55 g, 19.8 mmol) in CH_2Cl_2 (200 mL) was slowly added triphenylphosphine (6.22 g, 23.7 mmol) at 0 °C. After 5 min the solvent was evaporated and the residue was purified by flash chromatography to give **31b** (6.49 g, 80%) as a colorless oil: $[\alpha]^{23}_D$ +110° (c = 1, $CHCl_3$); IR 3450, 3030, 2970, 1640 cm^{-1}; ^{1}H NMR (MeOH) δ 1.44 (s, 9H), 1.75–1.79 (m, 1H), 2.16–2.26 (m, 1H), 3.11 (bs, 1H), 3.32 (dd, 1H, J = 15.4, 8.8), 3.49 (dd, 1H, J = 15.4, 8.8), 3.57–3.65 (m, 4H), 4.07–4.12 (m, 1H), 4.24 (dd, 1H, J = 13.6, 5.1), 5.81 (d, 1H, J = 2.2), 6.55 (d, 1H, J = 2.2), 7.19–7.29 (m, 10H); CIMS 513 (M$^+$). Anal. Calcd for $C_{27}H_{33}BrN_2O_3$: C, 63.2; H, 6.5; N, 5.5. Found: C, 63.3; H, 6.5; N, 5.2.

***tert*-Butyl (6*S*,8a*R*)-6-(*N*,*N*-Dibenzylamino)-5,6,7,8-tetrahydro-1-oxo-8a(1*H*)-indolizinecarboxylate (31a) and *tert*-Butyl (6*S*,8a*S*)-6-(*N*,*N*-Dibenzylamino)-5,6,7,8-tetrahydro-1-oxo-8a(1*H*)-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 a further 30 min at 40 °C. Then, it was cooled to 0 °C and added to saturated NH_4Cl. After extraction with Et_2O the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc 3:2) to give **31a** (3.25 g, 61%), followed by **31b** (1.49 g, 28%). **31a**: $[\alpha]^{23}_D$ +299° (c = 1, $CHCl_3$); mp 129 °C; IR 3030, 2930, 1660 cm^{-1}; ^{1}H NMR δ 1.29 (dt, 1H, J = 13.2, 3.6), 1.46 (s, 9H), 1.61 (dq, 1H, J = 13.2, 3.6), 2.01–2.04 (m, 1H), 2.68–2.73 (m, 2H), 3.41 (t, 1H, J = 12.4), 3.59 (dd, 1H, J = 12.4, 4.4), 3.62 (d, 2H, J = 13.9), 3.71 (d, 2H, J = 13.9), 4.90 (d, 1H, J = 3.6), 7.24–7.34 (m, 10H), 7.68 (d, 1H, J = 2.9); ^{13}C NMR δ 22.2, 27.9, 29.7, 49.3, 54.3, 57.3, 73.1, 82.9, 94.4, 127.2, 128.3, 128.4, 139.6, 163.9, 164.6, 197.2; CIMS 433 (M + 1), 333 (M − 99). Anal. Calcd for $C_{27}H_{32}N_2O_3$: C, 75.0; H, 7.5; N, 6.5. Found: C, 75.5; H, 7.5; N, 6.4. **31b**: $[\alpha]^{23}_D$ −338° (c = 1, $CHCl_3$); IR 3030, 2980, 1730, 1660 cm^{-1}; ^{1}H NMR δ 1.37 (s, 9H), 1.50–1.58 (m, 1H), 1.92 (dt, 1H, J = 13.2, 2.2), 2.18 (d, 1H, J = 14.7), 2.40 (dt, 1H, J = 13.2, 2.9), 2.85 (bs, 1H), 3.33 (dd, 1H, J = 14.7, 3.7), 3.47 (d, 2H, J = 14.7), 3.72 (d, 1H, J = 14.7), 3.79 (d, 2H, J = 14.7), 4.82 (d, 1H, J = 3.7), 6.79 (d, 1H, J = 3.7), 7.15–7.23 (m, 10H); ^{13}C NMR δ 24.4, 25.5, 27.9, 49.5, 55.5, 57.6, 73.2, 82.7, 94.7, 127.2, 128.5, 128.6, 139.4, 165.2, 165.7, 198.0; CIMS 433 (M + 1). Anal. Calcd for $C_{27}H_{32}N_2O_3$; C, 75.0; H, 7.5; N, 6.5. Found: C, 75.5; H, 7.5; N, 6.4.

***tert*-Butyl (6*S*,8a*R*)-6-(*N*,*N*-Dibenzylamino)-2,3,5,6,7,8-hexahydro-1-oxo-8a(1*H*)-indolizinecarboxylate (32a) and *tert*-Butyl (6*S*,8a*S*)-6-(*N*,*N*-Dibenzylamino)-2,3,5,6,7,8-hexahydro-1-oxo-8a(1*H*)-indolizinecarboxylate (32b).** To

a 2:1 mixture of **31a** and **31b** (1.59 g, 3.68 mmol) in THF (125 mL) was added $BF_3{\cdot}Et_2O$ (0.588 mL, 4.78 mmol) at −78 °C. After 5 min $LiEt_3BH$ (Super-Hydride, 4.77 mL, 1 M in THF) was added, and stirring was continued for 30 min. Then saturated NaCl and saturated $NaHCO_3$ were added at −30 °C. The mixture was extracted with Et_2O, and the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether−EtOAc 85:15) to give **32a** (0.85 g, 53%) followed by **32b** (0.43 g, 27%). **32a**: mp 103 °C; $[\alpha]^{23}_D$ +85° (c = 0.76, $CHCl_3$); IR 3030, 2930, 1760, 1720 cm^{-1}; ^1H NMR δ 1.26 (dt, 1H, J = 13.9, 3.6), 1.45 (s, 9H), 1.68 (dq, 1H, J = 13.9, 3.6), 1.92 (dd, 1H, J = 13.9, 3.6), 2.29 (dt, 1H, J = 13.9, 3.6), 2.39−2.44 (m, 2H), 2.82−2.88 (m, 1H), 2.99 (dt, 1H, J = 11.7, 5.1), 2.95−3.05 (m, 1H), 3.13 (t, 1H, J = 11.0), 3.27 (q, 1H, J = 8.1), 3.63 (d, 2H, J = 13.9), 3.69 (d, 2H, J = 13.9), 7.21 (t, 2H, J = 7.3), 7.29 (t, 4H, J = 7.3), 7.35 (d, 4H, J = 7.3); ^{13}C 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 $C_{27}H_{34}N_2O_3$: C, 74.6; H, 7.9; N, 6.5. Found: C, 74.6; H, 7.7; N, 6.7. **32b**: $[\alpha]^{23}_D$ −68° (c = 0.7, $CHCl_3$); IR 3030, 2930, 1760, 1720 cm^{-1}; ^1H NMR δ 1.32 (s, 9H), 1.40−1.47 (m, 1H), 1.67−1.74 (m, 1H), 1.81−1.88 (m, 1H), 2.07 (dt, 1H, J = 14.6, 5.1), 2.28−2.32 (m, 2H), 2.51 (dd, 1H, J = 11.0, 8.1), 2.73−2.79 (m, 1H), 2.83−2.89 (m, 1H), 3.11 (dd, 1H, J = 11.0, 3.7), 3.22 (dq, 1H, J = 8.0, 2.9), 3.51 (d, 2H, J = 13.9), 3.65 (d, 2H, J = 13.9), 7.12 (t, 2H, J = 7.3), 7.20 (t, 4H, J = 7.3), 7.25 (d, 4H, J = 7.3); CIMS 435 (M + 1). Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.6; H, 7.9; N, 6.5. Found: C, 74.5; H, 8.0; N, 6.4.

(1*S*,6*S*,8a*R*)-6-(*N*,*N*-Dibenzylamino)-1-octahydroindolizinol (33a) and (1*R*,6*S*,8a*R*)-6-(*N*,*N*-Dibenzylamino)-1-octahydroindolizinol (34a). A. To a solution of **26a** (372 mg, 1.11 mmol) in MeOH (35 mL) was added $NaBH_4$ (41.5 mg, 1.11 mmol) at 0 °C. After the solution was stirred for 1 h HCl (1 mL, 2 N) was added, followed by addition of saturated $NaHCO_3$ and Et_2O. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (CH_2Cl_2−MeOH 9:1) to give **33a** (180 mg, 48%) followed by **34a** (180 mg, 48%).

B. To a solution of **26a** (40 mg, 0.12 mmol) in THF (7.5 mL) was added Li(s-Bu)$_3$BH (L-Selectride, 0.13 mL, 1 M in THF) at −78 °C. After the solution was stirred for 30 min at −78 °C saturated $NaHCO_3$ was added and the mixture was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2−MeOH 9:1) to give **34a** (32 mg, 80%). **33a**: $[\alpha]^{23}_D$ −11° (c = 1, $CHCl_3$); mp 103 °C; IR 3380, 2930 cm^{-1}; ^1H NMR δ 1.37−1.51 (m, 2H), 1.65−1.79 (m, 3H), 1.99−2.07 (m, 3H), 2.12−2.20 (m, 1H), 2.82−2.99 (m, 1H), 3.07 (dt, 1H, J = 8.8, 2.2), 3.25 (dd, 1H, J = 10.3, 2.9), 3.64 (d, 2H, J = 13.9), 3.70 (d, 2H, J = 13.9), 4.02 (bs, 1H), 7.20 (t, 2H, J = 7.3), 7.28 (t, 4H, J = 7.3), 7.36 (d, 4H, J = 7.3). Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.5; H, 8.4; N, 8.3. Found: C, 78.5; H, 8.3; N, 8.5. **34a**: $[\alpha]^{23}_D$ +24° (c = 1, $CHCl_3$); IR 3410, 2930 cm^{-1}; ^1H NMR δ 1.19 (dq, 1H, J = 12.5, 3.6), 1.43 (dq, 1H, J = 12.5, 3.6), 1.51−1.53 (m, 1H), 1.74−1.78 (m, 1H), 2.02−2.09 (m, 2H), 2.16−2.28 (m, 2H), 2.41 (q, 1H, J = 8.8), 2.81−2.88 (m, 1H), 2.93 (dt, 1H, J = 8.8, 2.2), 3.64 (d, 2H, J = 14.7), 3.70 (d, 2H, J = 14.7), 3.85−3.88 (m, 1H), 7.19 (t, 2H, J = 7.3), 7.27 (t, 4H, J = 7.3), 7.35 (d, 4H, J = 7.3).

(1*S*,6*S*,8a*R*)-6-(*N*,*N*-Dibenzylamino)-1-acetoxyoctahydroindolizine (33b). A solution of **33a** (250 mg, 0.74 mmol) and Ac_2O (5 mL) in THF (50 mL) was stirred for 7 d at rt. After addition of saturated $NaHCO_3$ the mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2−MeOH 9:1) to give **33b** (242 mg, 87%) as a colorless oil: $[\alpha]^{23}_D$ +34° (c = 1, $CHCl_3$); IR 3030, 2930, 1740 cm^{-1}; ^1H NMR δ 1.22 (dq, 1H, J = 12.4, 2.9), 1.40 (dq, 1H, J = 12.4, 3.6), 1.55 (m, 1H), 1.87−2.04 (m, 3H), 2.03 (s, 3H), 2.15 (t, 1H, J = 10.3), 2.23−2.37 (m, 2H), 2.81−2.89 (m, 1H), 2.91−2.93 (m, 1H), 3.18 (dd, 1H, J = 10.3, 3.6), 3.63 (d, 2H, J = 13.9), 3.69 (d, 2H, J = 13.9), 4.67−4.74 (m, 1H), 7.19 (t, 2H, J = 7.3), 7.27 (t, 4H, J = 7.3), 7.32 (d, 4H, J = 7.3); ^{13}C NMR δ 21.1, 25.2, 27.2, 30.2, 52.6, 54.4, 54.9, 55.1, 68.3, 77.4, 126.7, 128.2, 128.3, 140.5, 170.7; CIMS 379 (M + 1). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.2; H, 8.0; N, 7.4. Found: C, 76.0; H, 8.0; N, 7.6.

(1*S*,6*S*,8a*R*)-6-Acetamido-1-acetoxyoctahydroindolizine (33c). A solution of **9a** (50 mg, 0.252 mmol) in Ac_2O (1 mL) and pyridine (1 mL) was stirred for 2 h at rt. After evaporation the residue was purified by flash chromatography (CH_2Cl_2−MeOH 95:5) to give **33c** (30 mg, 50%) as a colorless solid: $[\alpha]^{23}_D$ −1° (c = 2, $CHCl_3$); mp 198 °C; IR 3290, 2940, 1730, 1640; ^1H NMR δ 1.24 (dq, 1H, J = 11.0, 2.2), 1.47 (dq, 1H, J = 13.2, 4.4), 1.65−1.71 (m, 1H), 1.97−2.13 (m, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.35−2.45 (m, 2H), 2.59−2.61 (m, 1H), 2.99−3.05 (dt, 1H, J = 8.8, 2.2), 3.21 (dd, 1H, J = 11.0, 4.4), 4.00−4.11 (m, 1H), 4.82−4.87 (m, 1H), 5.71 (br s, 1H); CIMS 241 (M + 1). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 60.0; H, 8.4; N, 11.7. Found: C, 60.0; H, 8.1; N, 11.3.

(1*R*,6*S*,8a*R*)-6-(*N*,*N*-Dibenzylamino)-1-acetoxyoctahydroindolizine (34b). Compound **34a** (250 mg, 0.74 mmol) and Ac_2O (5 mL) in THF (50 mL) were reacted and worked up as described for **33b** to give **34b** (230 mg, 82%) as a colorless oil (solvent for flash chromatography: petroleum ether−EtOAc 7:3): $[\alpha]^{23}_D$ +28° (c = 0.5, $CHCl_3$); IR 3030, 2930, 1740 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, 3H), 2.19 (q, 1H, J = 7.3), 2.82 (m, 1H), 3.04 (dt, 1H, J = 9.1, 1.5), 3.23 (dd, 1H, J = 10.3, 2.9), 3.56 (d, 2H, J = 13.9), 3.62 (d, 2H, J = 13.9), 5.10−5.13 (m, 1H), 7.12 (t, 2H, J = 7.3), 7.20 (t, 4H, J = 7.3), 7.28 (d, 4H, J = 7.3); ^{13}C NMR δ 21.1, 23.9, 24.9, 31.1, 53.0, 54.4, 55.1, 55.5, 67.4, 74.4, 126.7, 128.1, 128.5, 140.5, 170.9; CIMS 379 (M + 1), 368 (M − 40). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.2; H, 8.0; N, 7.4. Found: C, 76.2; H, 8.0; N, 7.3.

(1*R*,6*S*,8a*R*)-6-Acetamido-1-acetoxyoctahydroindolizine (34c). Compound **9b** (18 mg, 0.075 mmol) in Ac_2O (0.5 mL) and pyridine (0.5 mL) was reacted and worked up as described for **33c** to give **34c** (12 mg, 55%) as a colorless solid: $[\alpha]^{23}_D$ −12° (c = 0.7, $CHCl_3$); mp 205 °C; IR 3290, 2930, 1730, 1630 cm^{-1}; ^1H NMR δ 1.15 (dq, 1H, J = 12.4, 3.7), 1.54 (dq, 1H, J = 13.2, 3.7), 1.69−1.72 (m, 2H), 1.77−1.90 (m, 2H), 1.93 (s, 3H), 2.04 (s, 3H), 2.02−2.11 (m, 2H), 2.20−2.27 (m, 1H), 3.12 (dt, 1H, J = 9.0, 1.0), 3.38 (dd, 1H, J = 9.5, 4.4), 3.91−4.04 (m, 1H), 5.18−5.20 (m, 1H), 5.28 (bs, 1H); CIMS 241 (M + 1). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 60.0; H, 8.3; N, 11.7. Found: C, 60.3; H, 8.2; N, 11.5.

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