Synthesis of Optically Active α,β-Disubstituted β-Amino Nitriles and β-Amino Acids Starting from Asparagine

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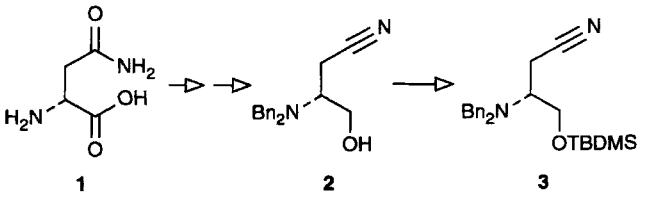
Starting from the enantiomerically pure building block **2** which is readily available from D-asparagine α,β-disubstituted β-amino nitriles and β-amino acids could be synthesized. After deprotonation of the nitrile α-position the introduction of substituents was performed by alkylation of either **2** or the TBDMS-protected derivative **3**. Starting from the β-homoserine equivalent **2** the reaction proceeds via a dianionic intermediate resulting in a preferred formation of the *threo*-configured products **6a,b** (ratio of isomers: 7:1). Modification of the side chain was demonstrated by displacement reactions with $LiBH_4$ or potassium thioacetate.

Enantiomerically pure β-amino acids are highly important building blocks in medicinal chemistry[1] and serve as valuable intermediates for β-lactam synthesis[2]. Furthermore, β-amino acids attract special interest for the construction of peptidomimetics[3]. Especially, α,β-disubstituted β-amino acids are components in a number of molecules which display interesting biological properties. Thus, (2*S*,3*R*)-2-methyl-3-aminopentanoic acid was isolated as a hydrolysis fragment of the marine peptide antitumor agents dolastatin 11 and 12[4] and of the antifungal peptides majusculamide C[5] and 57-normajusculamide C[6]. Furthermore, the activity of a variety of peptide transition state analogs including the HIV-1 protease inhibitors KNI-227 and KNI-272 is due to their β-amino-α-hydroxy acid motif[7]. Last but not least, taxol, a sophisticated diterpene which is currently considered as one of the most promising anti-tumor agents contains an essential α,β-disubstituted β-amino acid side chain[8]. As a consequence, the synthesis of non-racemic β-amino acids has become a very active field of research in the preceding five years[9].

Recent studies in this laboratory resulted in a practical method for the synthesis of homochiral β-amino acids from L-asparagine[10]. The strategy was based on a chemoselective reduction of the α-carboxylic acid and its subsequent transformation into different side chains giving access to 3-aminobutyric acid and its 4-alkyl-[11] 4-aryl-[12] 4-azido-[13] or 4-amino-substituted[14] derivatives. As an extension of this methodology we herein report a novel approach to α,β-disubstituted β-amino nitriles and β-amino acids[15,16] which allows an individual construction of both the α substituent and the β side-chain.

Applying to the previously reported protocol[12], we transformed D-asparagine (**1**) into the enantiomerically pure β-homoserine derivative **2** in 61% overall yield (Scheme 1). For a projected introduction of substituents into the nitrile α-position by deprotonation and subsequent alkylation, protection of the OH group was envisioned. Therefore, the building block **2** was treated with TBDMS-Cl and imidazole to afford the silyl ether **3** in 82% yield.

Scheme 1



C-Alkylation was performed by deprotonation of **3** with 2 equivalents of LDA (−78 °C) and trapping of the resulting anion with benzyl bromide[17]. When THF was used as a solvent a 1:1 mixture of the diastereomers **4a** and **5a** was isolated in 92% yield (Scheme 2). Methylation with methyl iodide under the above mentioned conditions gave a 85% yield of **4b** and **5b** (1:1 mixture). The configurational assignment of the isomers was performed in a later step of the synthesis. Variation of the reaction conditions for the benzylation and observation of turnover and the ratio of isomers by HPLC analysis showed that reduction of the amount of base to 1 equivalent did not change the stereochemical outcome of the reaction. However, only 50% of **3** were converted. Employing Et_2O as a solvent resulted in modest diastereoselectivity when formation of the *threo* isomer **4a** was preferred (**4a**:**5a** = 2:1). The same distribution of products was detected when KHMDS (2 equivalents) was used as a base. Very recent investigations of Reetz et al. of the alkylation of β-amino nitriles showed also *threo* selectivity[16]. Whereas deprotonation by *t*BuLi turned out

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to give the same results as LDA, treatment of **3** with the more nucleophilic *n*BuLi caused decomposition. Improvement of the stereoselectivities by chelation control which was supposed to be induced by transmetalation of the LDA derived salt with $TiCl_4$ failed[18]. Under these conditions no alkylation reaction was observed, even after the reaction mixture hed been stirred for 1 d at room temp. Separation of the diastereomers **4a, 5a** and **4b, 5b** was possible in small amounts by flash chromatography. However, it turned out to be advantageous to proceed in the synthesis with the diastereomeric mixtures and to purify the isomers after the following *O*-deprotection. Desilylation of **4a,b** and **5a,b** was accomplished with a mixture of acetic acid, THF and H_2O at room temp. when the alcohols **6a,b** and **7a,b** were formed almost quantitatively.

Furthermore, we found an efficient and diastereoselective approach to **6a,b** when we started from unprotected **2**. When treated with an excess of LDA the resuting dianion of **2** could be *C*-alkylated with benzyl bromide or methyl iodide giving a 7:1 ratio of the diastereomers **6a,b** and **7a,b** respectively. This can be explained by a preferred attack from the *re* side of the nucleophile, when existing in a chelated structure (Figure 1).

For the determination of the relative configuration lactonization of the hydroxy nitriles **6a,b** and **7a,b** was attempted. Employing conc. aqueous HCl we could only transform the *threo* isomers **6a.b** into the *trans* configured γ-lactones **9a,b**. For **7a,b** decomposition was observed. The synthesis of diastereomerically pure **9a** could be also accomplished by LDA induced deprotonation of the dibenzylamino-γ-lactone **8**[12,19] and subsequent trapping with benzyl bromide. Due to signal overlaps in the ^{1}H-NMR spectrum of **9a** an unambiguous structure determination was not possible. However, diagnostic data of **9c** (significant NOEs between 4-H and 5-H_a and between 3-H and 5-H_b), which were obtained by catalytic hydrogenolysis of **9a**, allowed us to prove the *trans* configuration. Additionally, there is only a very week NOE between the protons in the positions 3 and 4 as well as between 4-H and 5-H_b. These data are in total agreement with the results of NOESY experiments comparing *cis*- and *trans*-configured 3,4-disubstituted amino-γ-lactams and thus corroborate our assignement[20]. Furthermore, this reference provides typical vicinal coupling constants between the *trans*-positioned protons at C-4 and C-5 (^3J = 8.8–9.6 Hz for the *trans*- and < 1 Hz for the *cis* isomers) indicating the *trans* configuration of **9c** ($^3J_{4\text{-H}/5b\text{-H}}$ = 7.3 Hz). The configuration of **9b** was also estimated to be *trans* by proceeding as described above.

We have recently demonstrated that the α-unsubstituted β-homoserine equivalent **2** can be transformed into a variety of β-amino nitriles and β-amino acids by activation of the primary alkohol and subsequent displacement reaction with organo cuprates, $LiBH_4$, NaN_3 as well as under Mitsunobu conditions[10–14].

As an example of a modification of the β-substituents of α-substituted analogues we envisioned to displace the hydroxy substituents of the amino nitriles **6a,b** and **7a,b** by

Scheme 2

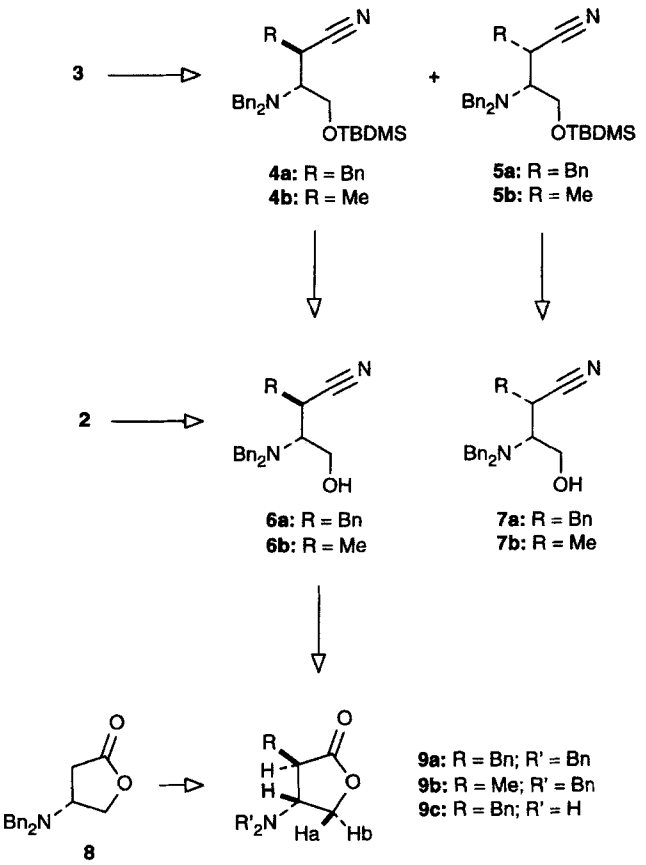
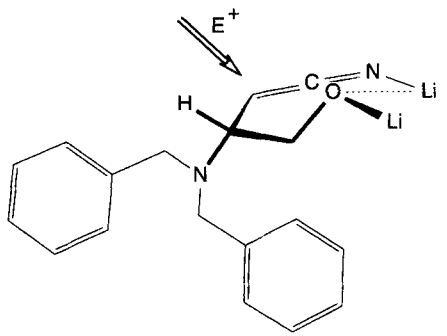


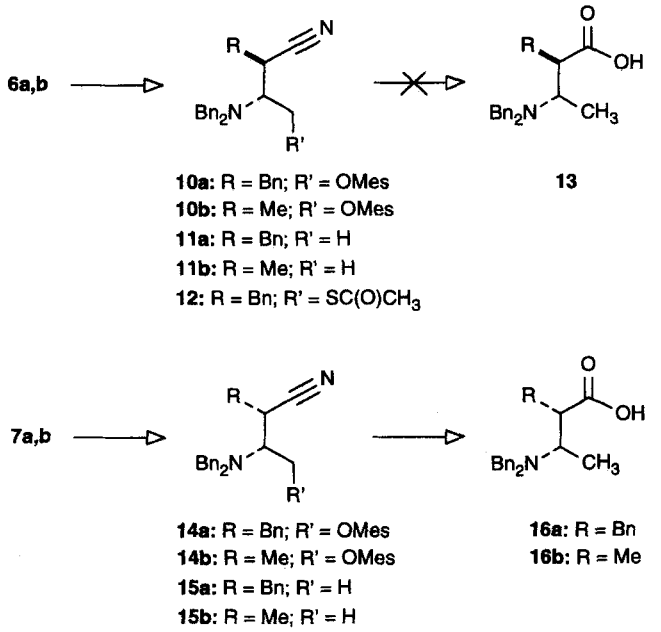
Figure 1. Simplified conformational representation for the preferred electrophilic attack from the *re* side after double deprotonation of **2**



hydrogen resulting in precursors of α-substituted β-homoalanines. Starting from the *threo*-configured benzylation product **6 a**, we planned the introduction of a thioacetate group to obtain a protected β-homocysteine equivalent. In practice, the primary OH groups of **6a,b** and **7a,b** were activated by treatment with methanesulfonic chloride in the presence of triethylamine when the sulfonates **10a,b** and **14a,b** were formed in 69–96% yield (Scheme 3). Subsequent reaction of **10a,b** and **14a,b** with $LiBH_4$ resulted in displacement of the mesyloxy function by hydrogen. Although a temperature of 40 °C was necessary for the reaction to proceed, the butanenitriles **11a,b** and **15a,b** were formed chemoselectively[16]. Reduction of the nitrile func-

tion could not be observed as a side reaction. Nucleophilic displacement by thioacetate was performed by starting from **10a** to afford the β-homocysteine precursor **12**. Preparation of the respective amino acids **13** and **16** by hydrolysis was not possible for the *threo* isomers **11a,b** when the nitrile function was stable towards conc. HCl at 80 °C as well as $LiOH/H_2O_2$. On the other hand, complete hydrolysis of the *erythro* amino nitriles **15a,b** could be accomplished when the dibenzyl protected β-amino acids **16a** and **16b** were isolated in 73 and 59% yield, respectively. Epimerization at the chiral α-center was not detected.

Scheme 3



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Experimental

General: THF was distilled from Na/benzophenone 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. Concentrations of final product solutions were performed 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 HNM-GX 400 spetrometer at 400 MHz, spectra were measured as $CDCl_3$ solutions by using tetramethylsilane as internal standard. – Elemental analyses: Heraeus CHN Rapid instrument.

(R)-4-(tert-Butyldimethylsiloxy)-3-(dibenzylamino)butane-1-nitrile (**3**): To a solution of **2**[12] {$[\alpha]_D^{20} = -40$ ($c = 1.12$ in $CHCl_3$)}, 6.46 g, 23.1 mmol) in DMF (150 ml) were added TBDMS-Cl 7.79 g, 50.9 mmol) and then imidazole (6.69 g, 97.1 mmol) at 0 °C. After being stirred for 16 h at room temp., satd. aqueous NH_4Cl and Et_2O were added at 0 °C. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatoraphy (petroleum ether/Et_2O, 95:5) to give **3** (7.48 g, 82%) as a colorless oil, {$[\alpha]_D^{20} = +16$ ($c = 0.93$ in $CHCl_3$)}. – IR (NaCl): $\tilde{\nu} = 3020$ cm^{-1}, 2930, 2250. – ^1H NMR ($CDCl_3$): δ = 0.01 (s, 6H, $SiCH_3$), 0.84 [s, 9H, $C(CH_3)_3$], 2.52–2.57 (m, 2H, 2-H), 3.10–3.16 (m, 1H, 3-H), 3.66 (d, $J = 13.9$ Hz, 2H, NCH_2), 3.71–3.76 (m, 2H, 4-H), 3.77 (d, $J = 13.9$ Hz, 2H, NCH_2), 7.17–7.21 (m, 4H, *p*-Ar), 7.26–7.29 (m, 4H, *m*-Ar), 7.36 (d, $J = 7.3$ Hz, 2H, *o*-Ar). – $C_{24}H_{34}N_2OSi$ (394.6): calcd. C 73.05, H 8.68, N 7.10; found C 72.85, H 8.48, N 7.50. – Mol. mass 395 (CIMS).

(2R,3R)-2-Benzyl-4-(tert-butyldimethylsiloxy)-3-(dibenzylamino)butane-1-nitrile (**4a**), *(2S,3R)-2-Benzyl-4-(tert-butyldimethylsiloxy)-3-(dibenzylamino)butane-1-nitrile* (**5a**): To a solution of **3** (1.065 g, 2.7 mmol) in THF (35 ml) was added freshly prepared LDA (18.4 ml, 0.32 M in THF) at −78 °C. After being stirred for 40 min benzyl bromide (1.64 ml, 13.5 mmol) was added. 10 min. later, 5% aqueous $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether/Et_2O, 98:2) to give a 1:1 mixture of **4a** and **5a** (1.203 g, 92%) as a colorless oil. Separation of the diastereomers was possible by repeated flash chromatography on a small scale (**4a** was eluted first); **4a** (colorless oil): {$[\alpha]_D^{20} = -9$ ($c = 1.08$ in $CHCl_3$)}. – IR (NaCl): $\tilde{\nu} = 3030$ cm^{-1}, 2930, 2240. – ^1H NMR ($CDCl_3$): δ = 0.12 (s, 3H, CH_3Si), 0.15 (s, 3H, CH_3Si), 0.94 [s, 9H, $(CH_3)_2C$], 2.56 (dd, $J = 13.9$, 10.3 Hz, 1H, $PhCH_2CH$), 2.95–2.99 (m, 1H, 2-H), 3.01–3.07 (m, 1H, 3-H), 3.33 (dd, $J = 13.9$, 4.4 Hz, 1H, $PhCH_2CH$), 3.67 (d, $J = 13.9$ Hz, 2H, $PhCH_2N$), 3.89 (d, $J = 13.9$ Hz, 2H, $PhCH_2N$), 3.95 (dd, $J = 11.0$, 5.1 Hz, 1H, 4-H), 4.17 (dd, $J = 11.0$, 2.9 Hz, 1H, 4-H), 7.12 (d, $J = 5.9$ Hz, 2H, Ar), 7.22–7.35 (m, 13H, Ar). – $C_{31}H_{40}N_2OSi$ (484.8): calcd. C 76.81, H 8.32, N 5.78; found C 76.93, H 8.43, N 5.54. – Mol. mass 485 (CIMS).

5a (colorless oil): {$[\alpha]_D^{20} = -7$ ($c = 1.07$ in $CHCl_3$)}. – IR (NaCl): $\tilde{\nu} = 3020$ cm^{-1}, 2930, 2240. – ^1H NMR ($CDCl_3$): δ = 0.12 (s, 3H, CH_3Si), 0.94 [s, 9H, $(CH_3)_3C$], 2.76–2.79 (m, 2H, $PhCH_2CH$, 2-H), 2.95–2.99 (m, 1H, $PhCH_2CH$), 3.30–3.36 (m, 1H, 3-H), 3.54 (d, $J = 13.9$ Hz, 2H, $PHCH_2N$), 3.82 (dd, $J = 10.9$, 4.4 Hz, 1H, 4-H), 4.01 (dd, $J = 10.9$, 4.0 Hz, 1H, 4-H), 4.10 (d, $J = 13.9$ Hz, 2H, $PhCH_2N$), 7.12–7.17 (m, 2H, Ar), 7.21–7.34 (m, 9H, Ar), 7.43 (d, $J = 7.3$ Hz, 4H, Ar). – $C_{31}H_{40}N_2OSi$ (484.8): calcd. C 76.81, H 8.32, N 5.54; found C 76.73, H 8.25, N 5.94. – Mol. mass 485 (CIMS).

(2R,3R)-4-(tert-Butyldimethylsiloxy)-3-(dibenzylamino)-2-methylbutane-1-nitrile (**4b**), *(2S,3R)-4-(tert-Butyldimethylsiloxy)-3-(dibenzylamino)-2-methylbutane-1-nitrile* (**5b**): To a solution of **3** (1.403 g, 3.55 mmol) in THF (40 ml) was added freshly prepared LDA (24.1 ml, 0.32 M in THF) at −78 °C. After being stirred for 90 min. methyl iodide (1.11 ml, 17.8 mmol) was added. 30 min later, 5% aqueous $NaHCO_3$ and Et_2O were added. The org. layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether/Et_2O, 95:5) to give a 1:1 mixture of **4b** and **5b** (1.247 g, 85%) as a colorless oil. Separation of the diastereomers was possible by repeated flash chromatography on a small scale (**4b** was eluted first); **4b** (colorless oil): {$[\alpha]_D^{20} = +23$ ($c = 1.07$ in $CHCl_3$)}. – IR (NaCl): $\tilde{\nu} = 3050$ cm^{-1}, 2930, 2240. – ^1H NMR ($CDCl_3$): δ = 0.12 (s, 3H, CH_3Si), 0.13 (s, 3H, CH_3Si), 0.93 [s, 9H, $(CH_3)_3C$], 1.31 (d, $J = 7.3$ Hz, 3H, $CHCH_3$), 2.76–2.80 (m, 1H, 2-H), 2.91–2.99 (m, 1H, 3-H), 3.57 (d, $J = 13.9$ Hz, 2H, $PhCH_2$), 3.87 (d, $J = 13.9$, 2H, $PhCH_2$), 3.89 (dd, $J = 11.0$, 5.1 Hz, 1H, 4-H), 4.11 (dd, $J = 11.0$, 2.9 Hz, 1H, 4-H), 7.20–7.26 (m, 2H, Ar), 7.29–7.32 (m, 8H, Ar). – $C_{25}H_{36}N_2OSi$ (408.7): calcd. C 73.48, H 8.88, N 6.85; found C 73.61, H 8.92, N 6.76. – Mol. mass 409 (CIMS).

5b (colorless oil): $\{[\alpha]_D^{20} = +60$ ($c = 1.08$ in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu} = 3050\ cm^{-1}$, 2930, 2240. – ^1H NMR ($CDCl_3$): $\delta = 0.07$ (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si), 0.91 [s, 9H, $(CH_3)_3C$], 1.21 (d, J = 6.6 Hz, 3H, CH_3), 2.76–2.81 (m, 1H, 2-H), 3.11–3.19 (m, 1H, 3-H), 3.51 (d, J = 13.9 Hz, 2H, $PhCH_2$), 3.69 (dd, J = 11.0, 3.7 Hz, 1H, 4-H), 3.96 (dd, J = 11.0, 2.9 Hz, 1H, 4-H), 4.04 (d, J = 13.9 Hz, 2H, $PhCH_2$), 7.22 (dd, J = 10.7, 2.6 Hz, 2H, *p*-Ar), 7.28–7.33 (m, 4H, *m*-Ar), 7.43 (d, J = 7.3 Hz, 4H, *o*-Ar). – $C_{25}H_{36}N_2OSi$ (408.7): calcd. C 73.48, H 8.88, N 6.85; found C 73.82, H 8.45, N 6.83. – Mol. mass 409 (CIMS).

(2R,3R)-2-Benzyl-3-(dibenzylamino)-4-hydroxybutane-1-nitrile (**6a**), *(2S,3R)-2-Benzyl-3-(dibenzylamino)-4-hydroxybutane-1-nitrile* (**7a**). – *Method A:* A solution of **4a, 5a** (774 mg, 1.60 mmol, 1:1 mixture of diastereomers) in THF/HOAc/H_2O (80 ml, 1:3:1) was stirred for 8 d at room temp. After slow addition of $NaHCO_3$ the mixture was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give **6a** (254 mg, 43%) followed by **7a** (284 mg, 48%). – *Method B:* To a solution of **2** (140 mg, 0.5 mmol) in THF (35 ml) was added freshly prepared LDA (7.95 ml, 0.32 M in THF) at –78 °C. After being stirred for 1 h benzyl bromide (0.24 ml, 2.0 mmol) was added. 2 h later, 5% aqueous $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and concentrated and the residue was purified as described above to give **6a** (72 mg, 39%) and **7a** (10 mg, 6%).

6a (colorless solid): m.p. 126 °C; $\{[\alpha]_D^{20} = -72$ ($c = 1.09$ in $CHCl_3$)$\}$. – IR (KBr): $\tilde{\nu} = 3490\ cm^{-1}$, 3030, 2930, 2240. – ^1H NMR ($CDCl_3$): $\delta = 2.87$ (dd, J = 13.2, 8.8 Hz, 1H, $PhCH_2CH$), 2.91 (dd, J = 13.2, 6.6 Hz, 1H, $PhCH_2CH$), 2.95–3.00 (m, 1H, 2-H), 3.12–3.17 (m, 1H, 3-H), 3.48 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.90 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.95–4.04 (m, 2H, 4-H), 7.10–7.24 (m, 6H, Ar), 7.25–7.36 (m, 9H, Ar). – $C_{25}H_{26}N_2O$ (370.5): calcd. C 81.05, H 7.07, N 7.56; found C 80.86, H 6.82, N 7.50. – Mol. mass 372 (M + 1, CIMS).

7a (colorless oil): $\{[\alpha]_D^{20} = -57$ ($c = 1.06$ in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu} = 3490\ cm^{-1}$, 3020, 2960, 2250. – ^1H NMR ($CDCl_3$): δ = 2.77–2.87 (m, 2H, $PhCH_2CH$), 3.06–3.12 (m, 1H, 2-H), 3.13–3.19 (m, 1H, 3-H), 3.70 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.77 (dd, J = 11.0, 6.6 Hz, 1H, 4-H), 3.88 (dd, J = 11.0, 4.8 Hz, 1H, 4-H), 4.06 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 7.19–7.35 (m, 15H, Ar). – $C_{25}H_{26}N_2O$ (370.5): calcd. C 81.05, H 7.07, N 7.50; found C 81.31, H 7.27, N 7.26. – Mol. mass 372 (M + 1, CIMS).

(2R,3R)-3-(Dibenzylamino)-4-hydroxy-2-methylbutane-1-nitrile (**6b**), *(2S,3R)-3-(Dibenzylamino)-4-hydroxy-2-methylbutane-1-nitrile* (**7b**). – *Method A:* A solution of **4b, 5b** (874 mg, 12.14 mmol, 1:1 mixture of diasteromers) in THF/HOAc/H_2O (80 ml, 1:3:1) was allowed to react and the reaction mixture was worked up as described for **6a, 7a** to give **6b** (309 mg, 49%) followed by **7b** (296 mg, 47%). – *Method B:* A solution of **2** (140 mg, 0.5 mmol) in THF (35 ml), LDA (7.95 ml, 0.32 M in THF) and methyl iodide (0.12 ml, 2.0 mmol) was allowed to react and the reaction mixture was worked up as described for **6a, 7a** (method B) to give **6b** (58 mg, 39%) and **7b** (9 mg, 5%).

6b (colorless oil): $\{[\alpha]_D^{20} = -30$ ($c = 1.07$ in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu} = 3460\ cm^{-1}$, 3030, 2940, 2240. – ^1H NMR ($CDCl_3$): $\delta = 1.34$ (d, J = 7.3 Hz, 3H, CH_3), 2.84–2.89 (m, 1H, 2-H), 2.98–3.04 (m, 1H, 3-H), 3.60 (d, J = 13.5 Hz, 2H, $PhCH_2$), 3.90 (d, J = 13.5 Hz, 2H, $PhCH_2$), 3.94–3.97 (m, 2H, 4-H), 7.22–7.35 (m, 10H, Ar). – $C_{19}H_{22}N_2O$ (294.4): calcd. C 77.52, H 7.53, N 9.52; found C 77.76, H 7.36, N 9.30. – Mol. mass 295 (CIMS).

7b (colorless solid): m.p. 92 °C; $\{[\alpha]_D^{20} = -12°$ ($c = 1.05$, $CHCl_3$)$\}$. – IR (KBr): $\tilde{\nu} = 3500\ cm^{-1}$, 3020, 2930, 2240, 2240. – ^1H NMR ($CDCl_3$): $\delta = 1.29$ (d, J = 6.6 Hz, 3H, CH_3), 2.94–3.03 (m, 2H, 2-H, 3-H), 3.62 (dd, J = 11.0, 6.6 Hz, 1H, 4-H), 3.73–3.77 (m, 1H, 4-H), 3.75 (d, J = 13.9 Hz, 2H, $PhCH_2$), 4.02 (d, J = 13.9 Hz, 2H, $PhCH_2$), 7.24–7.28 (m, 3H, Ar), 7.31–7.38 (m, 7H, Ar). – $C_{19}H_{22}N_2O$ (294.4): calcd. C 77.52, H 7.53, N 9.52; found C 77.20, H 7.67, N 9.39. – Mol. mass 295 (CIMS).

(3R,4R)-3-Benzyl-4-(dibenzylamino)-4,5-dihydro-2(3H)-furanone (**9a**). – *Method A:* A mixture of **6a** (120 mg, 0.32 mmol) in Et_2O (3 ml) and conc. aqueous HCl (15 ml) was stirred for 2 h at 80 °C. After being cooled to room temp. the reaction mixture was basified with $NaHCO_3$ and subsequently extracted with Et_2O. The organic layer was dried ($MgSO_4$), the solvent evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 9:1) to give **9a** (66 mg, 55%) as a colorless solid. – *Method B:* To a solution of **8** (30 mg, 0.11 mmol, prepared from D-asparagine, according to ref.[12] was added freshly prepared LDA (0.73 ml, 3.2 M solution in THF) at –78 °C. After 75 min benzyl bromide was added and stirring was continued for 60 min. Then satd. $NaHCO_3$ and Et_2O were added and the mixture was worked up as described above to give **8** (7 mg, 17%).

9a: m.p. 95 °C; $\{[\alpha]_D^{20} = +53$ ($c = 1.24$ in $CHCl_3$)$\}$. – IR (KBr): $\tilde{\nu} = 3020\ cm^{-1}$, 2930, 1770. – ^1H NMR ($CDCl_3$): $\delta = 2.87$ (dd, J = 15.4, 8.8 Hz, 1H, $PhCH_2CH$), 3.01–3.06 (m, 2H, $PhCH_2CH$, 3-H), 3.47 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.51–3.55 (m, 1H, 4-H), 3.56 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.97 (dd, J = 9.9, 7.3 Hz, 1H, 5a-H), 4.24 (dd, J = 9.9, 4.4 Hz, 1H, 5b-H), 7.01–7.03 (m, 2H, Ar), 7.16–7.18 (m, 3H, Ar), 7.20–7.30 (m, 10H, Ar). – $C_{25}H_{25}NO_2$ (371.5): calcd. C 80.83, H 6.78, N 3.77; found C 80.84, H 6.45, N 3.78. – Mol. mass 373 (M + 1, CIMS).

(3R,4R)-4-(Dibenzylamino)-4,5-dihydro-3-methyl-2(3H)-furanone (**9b**): A mixture of **6b** (63 mg, 0.21 mmol) in MeOH (2 ml) and conc. aqueous HCl (10 ml) was allowed to react and worked up as described for **9a** to give **9b** (45 mg, 71%) as a colorless solid; m.p. 57 °C; $\{[\alpha]_D^{20} = +31$ ($c = 1.13$ in $CHCl_3$)$\}$. – IR (KBr): $\tilde{\nu}$ = 3030 cm^{-1}, 2920, 1780. – ^1H NMR ($CDCl_3$): $\delta = 1.28$ (d, J = 7.3 Hz, 3H, CH_3), 2.72 (quint, J = 7.3 Hz, 1H, 3-H), 3.42 (q, J = 7.3 Hz, 1H, 4-H), 3.67 (d, J = 13.9 Hz, 2H, $PhCH_2$), 3.70 (d, J = 13.9 Hz, 2H, $PhCH_2$), 4.15 (dd, J = 9.5, 6.6 Hz, 1H, 5a-H), 4.26 (dd, J = 9.5, 7.3 Hz, 1H, 5b-H), 7.23–7.28 (m, 2H, Ar), 7.30–7.35 (m, 8H, Ar). – $C_{19}H_{21}NO_2$ (295.4): calcd. C 77.26, H 7.17, N 4.74; found C 77.12, H 7.21, N 4.84. – Mol. mass 296 (CIMS).

(3R,4R)-4-Amino-3-benzyl-4,5-dihydro-2(3H)furanone (**9c**): To a mixture of **9a** (30 mg, 0.008 mmol) in EtOAc (9 ml) and MeOH (1 ml) was added $Pd(OH)_2/C$ (20 mg, 20%). After being stirred for 1 h under a balloon of H_2 the mixture was filtered and the filtrate was evaporated to give **9c** (10 mg, 66%) as a colorless oil. – ^1H NMR ($CDCl_3$): $\delta = 2.66–2.72$ (m, 1H, 3-H), 2.96 (dd, J = 14.1, 6.8 Hz, 1H, $PhCH_2$), 3.09 (dd, J = 14.1, 5.6 Hz, 1H, $PhCH_2$), 3.46 (q, 6.8 Hz, 1H, 4-H), 3.80 (dd, J = 9.0, 6.9 Hz, 1H, 5-H_a), 4.21 (dd, J = 9.0, 7.3 Hz, 1H, 5-H_b), 7.18–7.30 (m, 5H, Ar).

(2R,3R)-1-[3-Cyano-2-(dibenzylamino)-4-phenyl]butyl Methanesulfonate (**10a**): To a solution of **6a** (189 mg, 0.51 mol) and Et_3N (171 µl, 1.27 mmol) in THF (15 ml) was slowly added MesCl (86 µl, 1.12 mmol) at 0 °C. After being stirred for 16 h the mixture was filtered and evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 7:3) to give **10a** (221 mg, 96%) as a colorless oil; $\{[\alpha]_D^{20} = -11$ ($c = 1.35$ in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu} = 3030\ cm^{-1}$, 2930, 2240. – ^1H NMR ($CDCl_3$): $\delta = 2.66$ (dd, J = 13.7, 9.9 Hz, 1H, 4-H), 3.04 (s, 3H, CH_3), 3.20–3.24 (m, 1H, 3-H), 3.24 (dd, J = 13.7, 5.1 Hz, 1H, 4-H), 3.71 (d, J = 13.9 Hz, 2H, $PhCH_2N$), 3.81 (d, J = 13.9 Hz, 2H, $PhCH_2N$), 3.93–3.99

(m, 1H, 2-H), 4.52 (dd, J = 10.9, 5.9 Hz, 1H, 1-H), 4.66 (dd, J = 10.9, 4.1 Hz, 1H, 1-H), 7.10–7.37 (m, 15H, Ar). – $C_{26}H_{28}N_2O_3S$ (448.6): calcd. C 69.62, H 6.29, N 6.24, S. 7.15; found C 69.39, H 6.06, N 6.52, S 7.44. – Mol. mass 449 (CIMS).

(2R,3R)-1-[3-Cyano-2-(dibenzylamino)butyl Methanesulfonate (**10b**): A solution of **6b** (28 mg, 0.095 mmol) and Et_3N (32 µl, 0.24 mmol) in THF (4 ml) and MesCl (16 µl, 0.21 mmol) were allowed to react and the reaction mixture was worked up as described for **10a** to give **10b** (26 mg, 74%) as a colorless oil; $\{[\alpha]_D^{20} = +13$ (c = 0.94 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2940, 2240. – ^1H NMR ($CDCl_3$): δ = 1.37 (d, J = 7.3 Hz, 3H, 4-H), 3.04–3.08 (m, 1H, 3-H), 3.09 (s, 3H, SO_3CH_3), 3.65 (d, J = 13.5 Hz, 2H, $PhCH_2$), 3.85 (d, J = 13.5 Hz, 2H, $PhCH_2$), 3.93–3.98 (m, 1H, 2-H), 4.50 (dd, J = 10.9, 5.5 Hz, 1H, 1-H), 4.64 (dd, J = 10.9, 3.7 Hz, 1H, 1-H), 7.27–7.38 (m, 10H, Ar). – $C_{20}H_{24}N_2O_3S$ (372.5): calcd. C 64.49, H 6.49, N 7.52, S 8.61; found C 64.09, H 6.40, N 7.81, S 8.98. – Mol. mass 373 (CIMS).

(2R,3S)-2-Benzyl-3-(dibenzylaminobutane)-1-nitrile (**11a**): To a solution of **10a** (221 mg, 0.49 mmol) in THF (20 ml) was added $LiBH_4$ (0.50 ml, 2 M in THF) at room temp. After being stirred for 1 d at 40 °C and subsequently for 3 d at room temp. 5% aqueous $NaHCO_3$ was added. The mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography (hexane/Et_2O, 9:1) to give **11a** (122 mg, 70%) as colorless oil; $\{[\alpha]_D^{20} = -20$ (c = 0.98 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2920, 2240. – ^1H NMR ($CDCl_3$): δ = 1.34 (d, J = 6.6 Hz, 3H, CH_3), 2.55 (dd, J = 13.3, 9.7 Hz, 1H, PhCH_2CH), 2.85–2.91 (m, 1H, 2-H), 2.94–2.99 (m, 1H, 3-H), 3.20 (dd, J = 13.3, 5.1 Hz, 1H, PhCH_2CH), 3.53 (d, J = 13.9 Hz, 2H, $PhCH_2N$), 3.72 (d, J = 13.9 Hz, 2H, $PhCH_2N$), 7.09 (d, J = 8.1 Hz, 2H, Ar), 7.25–7.35 (m, 13H, Ar). – $C_{25}H_{26}N_2$ (354.5): calcd. C 84.70, H 7.39, N 7.90; found C 84.96, H 7.59, N 8.29. – Mol. mass 355 (CIMS).

(2R,3S)-3-(Dibenzylamino)-2-methylbutane-1-nitrile (**11b**): A solution of **10b** (178 mg, 0.50 mmol) in THF (20 ml) and $LiBH_4$ (0.50 ml, 2 M in THF) were allowed to react and the reaction mixture was worked up as described for **11a** to give **11b** (74 mg, 53%) as a colorless oil; $\{[\alpha]_D^{20} = +18$ (c = 1.01 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2920, 2240. – ^1H NMR ($CDCl_3$): δ = 1.29 (d, 6.6 Hz, 6H, 2 × CH_3), 2.70–2.75 (m, J = 6.6 Hz, 1H, 2-H), 2.77–2.84 (m, J = 6.6 Hz, 1H, 3-H), 3.46 (d, J = 13.5 Hz, 2H, $PhCH_2$), 3.70 (d, J = 13.5 Hz, 2H, $PhCH_2$), 7.22–7.35 (m, 10H, Ar). – $C_{19}H_{22}N_2$ (278.4): calcd. C 81.97, H 7.97, N 10.06; found C 81.65, H 7.58, N 10.44. – Mol. mass 279 (CIMS).

(2R,3R)-S-{1-[3-Cyano-2-(dibenzylamino)-4-phenyl]butyl} Thioacetate (**12**): To a solution of **6a** (53 mg) in DMF (10 ml) was added potassium thioacetate (15 mg, 0.13 mmol). After being stirred for 2 d at room temp. H_2O and EtOAc were added. The organic layer was washed with 5% aqueous $NaHCO_3$ and 10% aqueous NaCl, then dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to give **12** (19 mg, 37%) as a colorless oil; $\{[\alpha]_D^{20} = -90$ (c = 0.96 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2930, 2230, 1690. – ^1H NMR ($CDCl_3$): δ = 2.26 (s, 3H, CH_3), 2.88–2.91 (m, 1H, 3-H), 2.89 (dd, J = 13.4, 7.3 Hz, 1H, 4-H), 2.99 (dd, J = 13.4, 7.7 Hz, 1H, 4-H), 3.11–3.16 (m, 1H, 2-H), 3.26 (dd, J = 13.9, 10.3 Hz, 1H, 1-H), 3.33 (d, J = 13.9 Hz, 2H, $PhCH_2$), 3.37 (dd, J = 13.9, 4.4 Hz, 1H, 4-H), 3.89 (d, J = 13.9 Hz, 2H, $PhCH_2$), 7.15–7.29 (m, 15H, Ar). – $C_{27}H_{28}N_2OS$ (428.6): calcd. C 75.67, H 6.59, N 6.54, S. 7.48; found C 75.32, H 6.83, N 6.88, S 7.12. – Mol. mass 429 (CIMS).

(2R,3S)-1-[3-Cyano-2-(dibenzylamino)-4-phenyl]butyl Methanesulfonate (**14a**): A solution of **7a** (303 mg, 0.82 mmol) and Et_3N (274 µl, 2.05 mmol) in THF (20 ml) and MesCl (138 µl, 1.80 mmol) were allowed to react and the reaction mixture was worked up as described for **10a** to give **14a** (272 mg, 74%) as a colorless oil; $\{[\alpha]_D^{20} = -9$ (c = 1.01 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2930, 2240. – ^1H NMR ($CDCl_3$): δ = 2.71 (dd, J = 13.7, 4.4 Hz, 1H, 4-H), 2.95 (dd, J = 13.7, 9.9 Hz, 1H, 4-H), 3.05 (s, 3H, CH_3), 3.25–3.29 (m, 1H, 3-H), 3.59 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.91–3.99 (m, 2-H), 4.13 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 4.47 (dd, J = 10.9, 5.9 Hz, 1H, 1-H), 4.57 (dd, J = 10.9, 4.8 Hz, 1H, 1-H), 7.08–7.42 (m, 15H, Ar). – $C_{26}H_{28}N_2O_3S$ (448.6): calcd. C 69.62, H 6.29, N 6.24, S 7.15; found C 69.35, H 5.91, N 5.89, S 7.37. – Mol. mass 449 (CIMS).

(2R,3S)-1-[3-Cyano-2-(dibenzylamino)]butyl Methanesulfonate (**14b**): A solution of **7b** (71 mg, 0.24 mol) and Et_3N (81 µl, 0.24 mmol) in THF (7 ml) and MesCl (41 µl, 0.53 mmol) were allowed to react and the reaction mixture was worked up as described for **10a** to give **14b** (62 mg, 69%) as a colorless oil; $\{[\alpha]_D^{20} = +34$ (c = 1.03 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3020 cm^{-1}, 2910, 2240. – ^1H NMR ($CDCl_3$): δ = 1.30 (d, J = 6.6 Hz, 3H, 4-H), 3.08 (s, 3H, CH_3, SO_3CH_3), 3.09–3.16 (m, 1H, 3-H), 3.58 (d, J = 13.5 Hz, 2H, $PhCH_2$), 3.93–3.98 (m, 1H, 2-H), 4.07 (d, J = 13.5 Hz, 2H, $PhCH_2$), 4.46 (d, J = 5.1 Hz, 2H, 1-H), 7.23–7.43 (m, 10H, Ar). – $C_{20}H_{24}N_2O_3S$ (372.5): calcd. C 64.49, H 6.49, N 7.52, S 8.61; found C 64.32, H 6.82, N 7.16, S 8.34. – Mol. mass 373 (CIMS).

(2S,3S)-2-Benzyl-3-(dibenzylaminobutane)-1-nitrile (**15a**): A solution of **14a** (124 mg, 0.28 mmol) in THF (17 ml) and $LiBH_4$ (0.28 ml, 2 M in THF) were allowed to react and the reaction mixture was worked up as described for **11a** to give **15a** (65 mg, 65%) as a colorless oil; $\{[\alpha]_D^{20} = -55$ (c = 1.08 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2920, 2240. – ^1H NMR ($CDCl_3$): δ = 1.21 (d, J = 7.3 Hz, 3H, CH_3), 2.79 (dd, J = 10.3, 6.6 Hz, 1H, CHCH_2CH), 2.81–2.84 (m, 2H, 2-H, CHCH_2CH), 3.00–3.06 (m, 1H, 3-H), 3.39 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.93 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 7.16 (d, J = 8.1 Hz, 2H, Ar), 7.22–7.34 (m, 9H, Ar), 7.45 (d, J = 7.3 Hz, 4H, Ar). – $C_{25}H_{26}N_2$ (354.5): calcd. C 84.70, H 7.39, N 7.90; found C 84.87, H 7.19, N 8.10. – Mol. mass 355 (CIMS).

(2S,3S)-3-(Dibenzylamino)-2-methylbutane-1-nitrile (**15b**): A solution of **14b** (54 mg, 0.15 mmol) in THF (8 ml) and $LiBH_4$ (0.15 ml, 2 M in THF) were allowed to react and the reaction mixture was worked up as described for **11a** to give **15b** (19 mg, 46%) as a colorless oil; $\{[\alpha]_D^{20} = +23$ (c = 1.23 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2920, 2240. – ^1H NMR ($CDCl_3$): δ = 1.09 (d, J = 6.6 Hz, 3H, 4-H), 1.23 (d, J = 7.3 Hz, 3H, CH_3), 2.67–2.75 (m, 1H, 2-H), 2.84–2.92 (m, 1H, 3-H), 3.57 (d, J = 13.5 Hz, 2H, $PhCH_2$), 3.86 (d, J = 13.5 Hz, 2H, $PhCH_3$), 7.23 (d, J = 7.3 Hz, 2H, *p*-Ar), 7.31–7.35 (m, 4H, *m*-Ar), 7.47 (d, J = 8.1 Hz, 4H, *o*-Ar). – $C_{19}H_{22}N_2$ (278.4): calcd. C 81.97, H 7.97, N 10.06; found C 81.52, H 7.59, N 10.39. – Mol. mass 279 (CIMS).

(2S,3S)-2-Benzyl-3-(dibenzylamino)butyric Acid (**16a**): To a solution of **15a** (60 mg, 0.17 mmol) in MeOH (0.5 ml) was added conc. aqueous HCl (10 ml). After being stirred for 2 d at 80 °C the mixture was cooled to room temp. Then $NaCO_3$ was slowly added. The mixture was extracted with THF, and the organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to give **16a** (46 mg, 73 as a colorless oil; $\{[\alpha]_D^{20} = +43$ (c = 0.36 in $CHCl_3$)$\}$. – IR (NaCl): $\tilde{\nu}$ = 3380 cm^{-1}, 3010, 2950, 1720. – ^1H NMR ($CDCl_3$): δ = 1.20 (d, J = 6.6 Hz, 3H, 4-H), 2.70–2.75 (m, 1H, 2-H), 2.85 (dd, J = 15.1, 5.9 Hz, 1H, PhCH_2CH), 3.05–3.13 (m,

1H, 3-H), 3.36 (d, J = 13.2 Hz, 2H, $PhCH_2N$), 3.45 (dd, J = 15.1, 3.7 Hz, 1H, $PhCH_2CH$), 3.97 (d, J = 13.2 Hz, 2H, $PhCH_2N$), 7.00–7.02 (m, 2H, Ar), 7.08–7.10 (m, 3H, Ar), 7.23–7.30 (m, 10H, Ar). – $C_{25}H_{27}NO_2$ (373.5): calcd. C 80.40, H 7.29, N 3.75; found C 80.11, H 6.97, N 3.95. – Mol. mass 374 (CIMS).

(2S,3S)-3-(Dibenzylamino)-2-methylbutyric Acid (**16b**): To a solution of **15b** (19 mg, 0.07 mmol) in MeOH (0.2 ml) was added conc. aqueous HCl (5 ml). After being stirred for 5 h at 80°C the mixture was worked up as described for **16a** to give **16b** (12 mg, 59%) as a colorless oil; {$[\alpha]_D^{20}$ = +40 (c = 0.58 in $CHCl_3$)}. – IR (NaCl): $\tilde{\nu}$ = 3690 cm^{-1}, 3050, 2930, 1710. – ^1H NMR ($CDCl_3$): δ = 1.17 (d, J = 6.6 Hz, 3H, 4-H), 1.23 (d, J = 6.6 Hz, 3H, CH_3), 2.44–2.55 (m, 1H, 2-H), 2.96–3.05 (m, 1H, 3-H), 3.41 (d, J = 13.2 Hz, 2H, $PhCH_2$), 4.02 (d, J = 13.2 Hz, 2H, $PhCH_2$), 7.26–7.38 (m, 10H, Ar). – $C_{19}H_{23}NO_2$ (297.4): calcd. C 76.74, H 7.80, N 4.71; found C 76.39, H 8.12, N 4.51. – Mol. mass 298 (CIMS).

[1] For examples, see: J. Xie, J.-M. Soleilhac, C. Schmidt, J. Peyroux, B. P. Roques, M.-C. Fournie-Zaluski, *J. Med. Chem.* **1989**, *32*, 1497–1503; M. Namikoshi, K. L. Rinehart, A. M. Dahlem, V. R. Beasley, W. W. Carmichael, *Tetrahedron Lett.* **1989**, *30*, 4349–4352; P. Gmeiner, J. Mierau, G. Höfner, *Arch. Pharm. (Weinheim, Ger.)* **1992**, *325*, 57–60; P. Gmeiner, E. Hummel, *Synthesis* **1994**, 1026–1028.

[2] For examples, see: D. J. Hart, D.-C. Ha, *Chem. Rev.* **1989**, *89*, 1447–1465 and references cited therein; T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, F. A. Bouffard, *J. Am. Chem. Soc.* **1980**, *102*, 6161–6163.

[3] C. N. C. Drey, in: *Chemistry and Biochemistry of Amino Acids* (Ed. G. C. Barret), Chapman and Hall, London, New York **1985**, pp. 25–54; M. Amblard, M. Rodriguez, M.-F. Lignon, M.-C. Galas, N. Bernard, A.-M. Artis-Noel, L. Hauad, J. Laur, J.-C. Califano, A. Aumelas, J. Martinez, *J. Med. Chem.* **1993**, *36*, 3021–3028.

[4] G. R. Pettit, Y. Kamano, H. Kizu, C. Dufresne, C. L. Herald, R. J. Bontemps, J. M. Schmidt, F. E. Boettner, R. A. Nieman, *Heterocycles* **1989**, *28*, 553–558.

[5] D. C. Carter, R. E. Moore, J. S. Mynderse, W. P. Niemczura, J. S. Todd, *J. Org. Chem.* **1984**, *49*, 236–241.

[6] J. S. Mynderse, H. Hunt, *J. Nat. Prod.* **1988**, *51*, 1299–1301.

[7] T. Mimoto, J. Imai, S. Kisanuki, H. Enomoto, N. Hattori, K. Akaji, Y. Kiso, *Chem. Pharm. Bull.* **1992**, *40*, 2251–2253.

[8] For review, see: K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38–69; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15–46.

[9] For review, see: E. Juaristi, D. Quintana, J. Escalante, *Aldrichimica Acta* **1994**, *27*, 3–11; D. C. Cole, *Tetrahedron* **1994**, *50*, 9517–9582.

[10] P. Gmeiner, *Tetrahedron Lett.* **1990**, *31*, 5717–5720.

[11] P. Gmeiner, *Liebigs Ann. Chem.* **1991**, 501–502.

[12] P. Gmeiner, *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 551–557.

[13] P. Gmeiner, *Heterocycles* **1991**, *32*, 1499–1504.

[14] P. Gmeiner, E. Hummel, C. Haubmann, G. Höfner, *Arch. Pharm. (Weinheim. Ger.)* **1995**, *328*, 265–268.

[15] For a very recent example on the synthesis of α-substituted β-amino acids, see: D. Enders, W. Bettray, G. Raabe, J. Runsink, *Synthesis* **1994**, 1322–1326; see also ref.[16].

[16] M. T. Reetz, F. Kayser, K. Harms, *Tetrahedron Lett.* **1994**, *35*, 8769–8772.

[17] For studies on the structure of lithiated nitriles, see: G. Raabe, E. Zobel, J. Fleischbauer, P. Gerdes, D. Mannes, E. Müller, D. Enders, *Z. Naturforsch.* **1991**, *46a*, 275–288.

[18] For a review on chelation-controlled reactions, see: M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556.

[19] For similar observations, see: G. J. McGarvey, J. M. Williams, R. N. Hiner, Y. Matsubara, T. Oh, *J. Am. Chem. Soc.* **1986**, *108*, 4943–4952.

[20] J.-P. Wolf, H. Rapoport, *J. Org. Chem.* **1989**, *54*, 3164–3173.

[95158]