Synthesis of γ-Amino Acid Esters by 1,4-Addition of Deprotonated α-Aminonitriles and α-(Alkylideneamino)nitriles to α,β-Unsaturated Esters

Ines Bergner, Till Opatz*

Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10-14, 55128 Mainz, Germany
Fax +49(6131)3924786; E-mail: opatz@uni-mainz.de

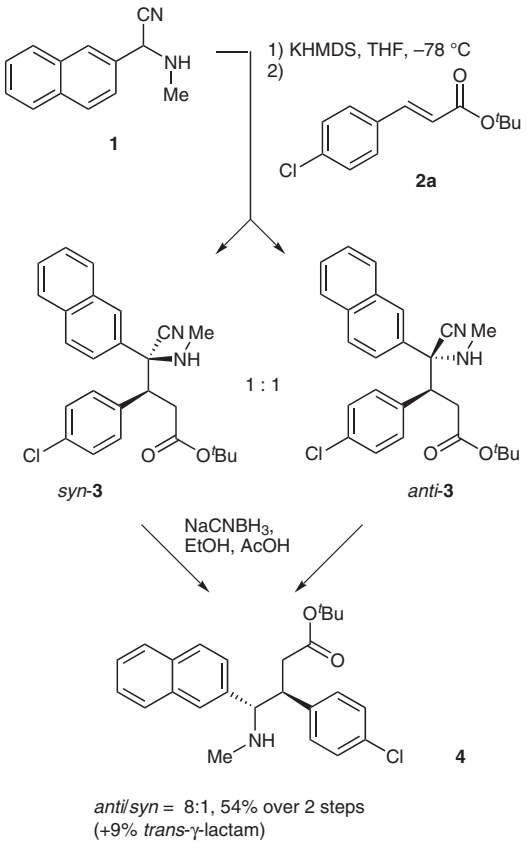
Received 20 September 2006; revised 20 December 2006

Abstract: α-Aminonitriles and α-(alkylideneamino)nitriles can serve as readily available α-aminocarbanion equivalents. Their conjugate addition to α,β-unsaturated esters followed by reduction furnishes polysubstituted γ-amino acid esters in moderate to high yield.

Key words: Michael addition, reduction, α-aminonitriles, α-aminocarbanions, γ-amino acids

Due to their close relation to the inhibitory neurotransmitter γ-aminobutyric acid (GABA), γ-amino acid derivatives represent interesting targets for the development of drugs for the treatment of imbalances in GABAergic signal transmission. C-Substituted GABA derivatives are for example used for the treatment of epilepsy, spasticity or as medication in pain therapy.[1–5] Moreover, γ-amino acid derivatives have been employed as building blocks for the preparation of peptidomimetics.[2,6–9] Among the methods used for their preparation, the 1,4-addition of nitronates to α,β-unsaturated esters[10] and the 1,4-addition of ester enolates to nitroolefins[11] are most widely applied. A technique for the preparation of N-substituted products is the samarium-mediated reductive addition of nitrones to α,β-unsaturated esters developed by Masson, Vallée and Py.[12,13] Unfortunately, this elegant method requires two equivalents of samarium diiodide as well as the subsequent reduction of the produced hydroxylamine. Here, we report on a two-step procedure for the synthesis of γ,N-di- and β,γ,N-trisubstituted γ-amino acids from deprotonated α-aminonitriles and α-(alkylideneamino)nitriles.

Strecker products derived from primary amines or from ammonia can be deprotonated in α-position without using protecting groups to prevent the retro-Strecker reaction.[14–17] The vinylogous addition of their conjugate anions to α,β-unsaturated aldehydes or ketones allows the preparation of highly substituted pyrrolidines in a one-pot reaction sequence.[18,19] If α,β-unsaturated esters are used as the electrophiles,[20] the reductive removal of the cyano group[21] from the products of the 1,4-addition yields γ-amino acid esters. As an example, the Strecker product from 2-naphthaldehyde and methylamine (**1**) was deprotonated with KHMDS in THF at –78 °C. To the resulting solution of the potassium salt of **1** was added *tert*-butyl 4-chlorocinnamate (**2a**) to yield the diastereomeric products of the 1,4-addition **3** in a 1:1 ratio. Chromatographic separation and reductive decyanation of the diastereomers with $NaCNBH_3$ in both cases gave the same 8:1 mixture of the diastereomeric γ-amino acid esters **4** (Scheme 1). As the diastereoselectivity of the reduction is independent of the relative configuration of the starting material, the reductive decyanation most likely proceeds via an elimination–addition sequence.



Scheme 1

The relative configuration of the major product could be established to be *anti* by X-ray crystallography (Figure 1). Along with compounds **4**, the *trans*-configured γ-lactam was formed by intramolecular aminolysis of the *tert*-butyl ester of *syn*-**4** during the reduction step. The selectivity of this side reaction can be explained by the fact that *anti*-**4** adopts an extended conformation (Figure 1), whereas in the *syn*-diastereomer, the repulsion between the β- and the

SYNTHESIS 2007, No. 6, pp 0918–0928
Advanced online publication: 20.02.2007
DOI: 10.1055/s-2007-965937; Art ID: T14506SS

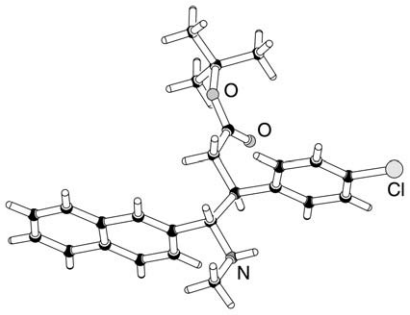


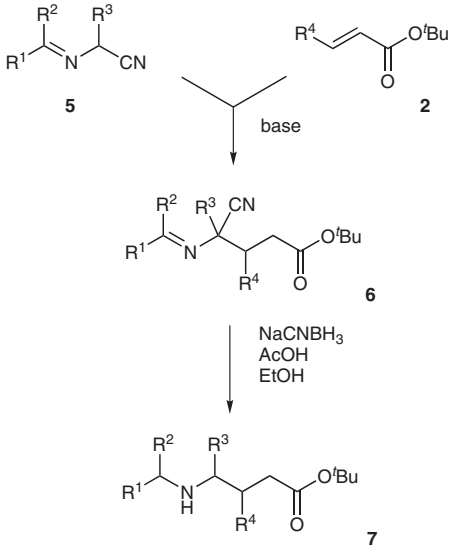
Figure 1 Crystal structure of *anti*-**4**

γ-substituent may induce a bent conformation in which the N-terminus is closer to the π*-orbital of the carbonyl group (*vide infra*).

Whereas the non-destructive deprotonation of α-aminonitriles with free NH protons requires the presence of a stabilizing α-substituent such as an aromatic, heteroaromatic or olefinic group in order to prevent a retro-Strecker reaction,[22] α-(alkylideneamino)nitriles **5** are much more CH-acidic and can be easily deprotonated even if no stabilizing α-substituent is present.[23–25] We tested several conditions for the addition reaction and found that either phase-transfer conditions (7.9 M KOH/CH_2Cl_2, 10 mol% $BnNEt_3Cl$)[26,27] or the use of metal-free bases such a DBU or Me_4NOH furnishes the desired products. In most cases, the biphasic system gives somewhat higher yields although side reactions may occur.[23] However, no general rules could yet be devised to determine the optimal base for a given transformation. The Michael adducts **6** were obtained in moderate to good yield. Whereas Tsuge and Kanemasa described fast additions to α,β-unsaturated methyl esters, the *tert*-butyl esters used in this work to prevent lactam formation reacted slower.[23]

We found that the complete reduction of the stable addition products **6** with $NaCNBH_3$ under mild conditions furnishes γ-amino acid esters **7** in moderate to excellent yield (Scheme 2, Tables 1 and 2). Presumably, the first hydride equivalent is consumed by the reduction of the C=N bond while the second reduction step involves elimination of HCN and reduction of the formed imine. Interestingly, the γ- and the N-substituent play a major role in the reductive decyanation: N-unsubstituted aminonitriles obtained by acid hydrolysis of compounds **6** did not yield the corresponding N-unsubstituted γ-amino acids. Moreover, compounds **6** devoid of a γ-substituent were quickly reduced to the N-alkylated aminonitriles but the decyanation proceeded sluggishly. For example, reduction of **6h** furnished only a 4.5:1-mixture of the α-(benzhydrylamino)nitrile **9** and the decyanated γ-amino acid ester **7h** after nine days.

On the other hand, the reduction of the γ-substituted Michael adducts **6b–g** was usually complete overnight. Although similar reactivity trends have been reported for the reductive cleavage of aminonitriles during catalytic hydrogenation,[28] the origin of these effects is not yet fully understood.



Scheme 2 General reaction course to γ-aminobutyric esters

Table 1 1,4-Addition of α-(Alkylideneamino)nitriles to α,β-Unsaturated Esters

Imine	R^1	R^2	R^3	Ester	R^4	Method[a]	Product	Yield (%)	dr
5a	Ph	Ph	H	**2b**	H	A	**6a**	80	–
5b	H	3,4-$(MeO)_2C_6H_3$	Bn	**2b**	H	A	**6b**	95	–
5b	H	3,4-$(MeO)_2C_6H_3$	Bn	**2b**	H	B	**6b**	43	–
5b	H	3,4-$(MeO)_2C_6H_3$	Bn	**2c**	Me	C	**6c**	64	1.2:1
5b	H	3,4-$(MeO)_2C_6H_3$	Bn	**2a**	4-ClC_6H_4	A	**6d**	51	1.3:1
5c	H	3,4-$(MeO)_2C_6H_3$	Ph	**2a**	4-ClC_6H_4	B	**6e**	61	1.5:1
5d	H	2-naphthyl	Me	**2b**	H	A	**6f**	94	–
5e	H	2- naphthyl	Bn	**2b**	H	A	**6g**	99	–
5a	Ph	Ph	H	**2a**	4-ClC_6H_4	A	**6h**	84	1.2:1

[a] Method A: $BnNEt_3Cl$ (0.1 equiv), KOH (7.9 M, 20 equiv), CH_2Cl_2; Method B: DBU (1.1 equiv), THF; Method C: Me_4NOH (1 equiv, 25 wt% in MeOH), THF.

Table 2 γ-Aminobutyric Acid Esters via Reduction with Sodium Cyanoborohydride

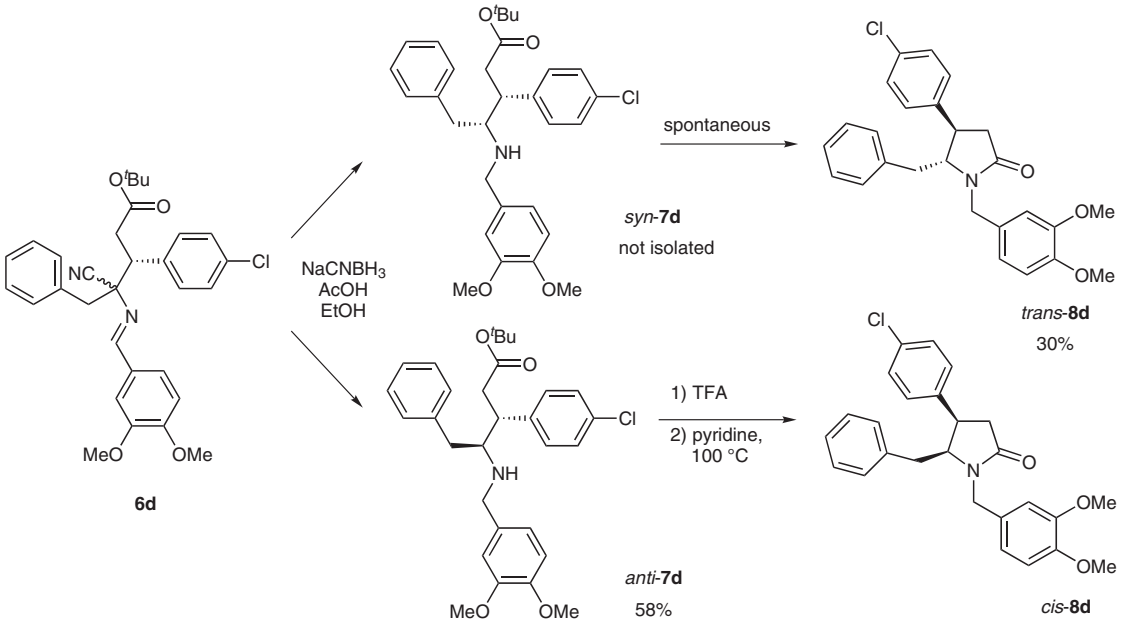
1,4-Adduct	R^1	R^2	R^3	R^4	Product	Yield (%)	*anti*/*syn*[a]
6a	Ph	Ph	H	H	**7a**	71	–
6b	H	3,4-$(MeO)_2C_6H_3$	Bn	H	**7b**	81	–
6c	H	3,4-$(MeO)_2C_6H_3$	Bn	Me	**7c**	54	1.6:1
6d	H	3,4-$(MeO)_2C_6H_3$	Bn	4-ClC_6H_4	**7d**	58	>98:2
6e	H	3,4-$(MeO)_2C_6H_3$	Ph	4-ClC_6H_4	**7e**	60	6.5:1
6f	H	2- naphthyl	Me	H	**7f**	94	–
6g	H	2- naphthyl	Bn	H	**7g**	89	–
6h	Ph	Ph	H	4-ClC_6H_4	**7h**	–[b]	

[a] Determined by ^{1}H NMR spectroscopy.
[b] A 4.5:1-mixture of the α-(benzhydrylamino)nitrile (**9**) and the doubly reduced product **7h** was obtained.

In the reduction of compound **6d**, a seemingly complete selectivity in favor of *anti*-**7d** is observed. The relative configuration of this material could be assigned by its conversion to the corresponding γ-lactam **8d**. NMR measurements revealed the *cis*-configuration of the product.[29] As a side product, the reduction of compound **6d** also furnished the *trans*-configured γ-lactam **8d** in 30% yield. Thus, the reduction of **6d** presumably yields both diastereomers of **7d** but only the *syn*-diastereomer quantitatively cyclized to the corresponding γ-lactam, leaving behind pure *anti*-**7d** (Scheme 3). A similar, though less impressive, observation was also made in the case of compound **4** (*vide supra*) as well as compound **7e**, where a 2.6:1-diastereomeric mixture of γ-lactams **8e** in favor of the sterically less encumbered *trans*-**8e** was formed.

In summary, we have found a short and efficient method for the preparation of polysubstituted γ-amino acid derivatives from readily available starting materials. α-Aminonitriles are accessible via Strecker reaction of aldehydes and amines, whereas α-(alkylideneamino)nitriles can be prepared by condensing Strecker products derived from ammonia with aldehydes. As α,β-unsaturated esters can also be assembled in a modular fashion, the presented methodology is amenable to the combinatorial variation of substituents.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 or AMX-400 spectrometer, chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.24, δ_C = 77.0). FD-MS spectra were measured on a Finnigan MAT-95 spectrometer. ESI-HRMS spectra were measured on a Waters Q-TOF-Ultima 3 equipped with a LockSpray interface (HCO_2Na or NaI/CsI as external reference). IR spectra were recorded on a Perkin-Elmer 1760X FTIR spectrometer. The melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected. THF was freshly dis-



Scheme 3

tilled from potassium/benzophenone under argon. EtOAc and petroleum ether (PE) were distilled from K_2CO_3 and CaH_2, respectively, before use. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. Petroleum ether (PE) used had a boiling range of 40–70 °C. TLC was performed on aluminum sheets coated with silica gel (60 F_{254}, E. Merck). Flash column chromatography was carried out on silica gel (32–63 μm, 60 Å, MP Biomedicals GmbH). Imines **5a–c** were synthesized via known literature procedures.[19,30,31]

tert-Butyl 3-(4-Chlorophenyl)-4-(methylamino)-4-(2-naphthyl)butanoate (4)

(Methylamino)-2-naphthylacetonitrile (**1**; 400 mg, 2.04 mmol) was dissolved in anhyd THF (10 mL) and cooled to –78 °C under argon. A solution of KHMDS (447 mg, 2.24 mmol) in anhyd THF (5 mL) was added within 1 min. After 1 more min, a solution of (*E*)-*tert*-butyl 4-chlorocinnamate[34] [**2a**; 487 mg, 2.04 mmol, prepared from (*E*)-4-chlorocinnamic acid after a protocol by Ahmad et al.[35]] in anhyd THF (5 mL) was added to the deep red solution. After 1 h, TLC indicated no further conversion. To the mixture were added aq sat. NH_4Cl solution (5 mL) and Et_2O (15 mL). The organic layer was separated, washed with brine (30 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo yielded the crude product (974 mg) as a yellow oil. Purification by flash chromatography (*n*-hexane–EtOAc, 8:1 → 5:1) furnished the diastereomeric addition products P1 (315 mg, 36%) and P2 (327 mg, 37%) as colorless oils.

P1

R_f = 0.43 (*n*-hexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 1.8 Hz, 1 H, H1′), 7.94–7.83 (m, 3 H, H4′, H5′, H8′), 7.70 (dd, 1 H, *J* = 8.8, 1.8 Hz, 1 H, H3′), 7.54 (mc, 2 H, H6′, H7′), 7.44 (AA′-part of AA′BB′ system, 2 H, ClC_6H_4), 7.37 (BB′-part of AA′BB′ system, 2 H, ClC_6H_4), 3.59 (dd, *J* = 11.8, 4.4 Hz, 1 H, β-CH), 2.78 (dd, J_{gem} = 15.5, J_{vic} = 11.8 Hz, 1 H, CH_2-a), 2.33 (dd, J_{gem} = 15.5, J_{vic} = 4.4 Hz, 1 H, CH_2-b), 2.13 (d, *J* = 5.5 Hz, 3 H, NCH_3), 1.50 (br q, *J* = 5.5 Hz, 1 H, NH), 1.06 (s, 9 H, *t*-C_4H_9).

P2

R_f = 0.34 (*n*-hexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.76 (m, 4 H, H1′, H4′, H5′, H8′), 7.84–7.76 (m, 3 H, H3′, H6′, H7′), 7.13 (AA′ part of AA′BB′ system, 2 H, Cl-C_6H_4), 6.98 (BB′ part of AA′BB′ system, 2 H, Cl-C_6H_4), 3.66 (dd, *J* = 9.3, 6.4 Hz, 1 H, β-CH), 2.86–2.82 (m, 2 H α-CH_2), 2.31 (br s, 3 H, NCH_3), 1.86 (br s, 1 H, NH), 1.15 (s, 9 H, *t*-C_4H_9).

The diastereomer P1 (305 mg) was dissolved in EtOH (7.5 mL) and after addition of $NaCNBH_3$ (88.1 mg, 1.40 mmol) and AcOH (120 μL, 2.10 mmol), the mixture was stirred for 24 h at r.t. The mixture was partitioned between Et_2O (30 mL) and aq 1 N NaOH (25 mL) solution, the organic layer was separated, washed with brine (25 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo yielded a colorless crystalline solid (240.8 mg). Reduction of the diastereomer P2 (315 mg) under identical conditions furnished a colorless crystalline solid (269.8 mg). NMR spectroscopic analysis revealed that both samples had an identical composition and contained an 8:1 diastereomeric mixture of the γ-amino acid esters **4** along with 15% of the *trans*-γ-lactam. Overall yield from **4**: 54%, 9% γ-lactam.

An attempt to remove the cyclized product from a sample (487 mg) of the material by column chromatography led to partial decomposition. Crystallization of the resulting diastereomeric mixture of **4** (282 mg, colorless crystals) from EtOAc yielded crystals of *anti*-**4** suitable for X-ray crystallography.

γ-Lactam [*trans*-4-(4-Chlorophenyl)-1-methyl-5-(2-naphthyl)pyrrolidin-2-one]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.5 Hz, 1 H, H4′), 7.88–7.76 (m, 2 H, H5′, H8′), 7.53–7.49 (m, 3 H, H1′, H6′, H7′), 7.28–7.25 (m, 3 H, H3′, H3″,5″), 7.06 (BB′ part of AA′BB′ system, 2 H, H2″,6″), 4.54 (d, *J* = 6.7 Hz, 1 H, H5), 3.41 (dt, J_t = 9.0 Hz, J_d = 6.7 Hz, 1 H, H4), 3.03 (dd, J_{gem} = 17.0 Hz, J_{vic} = 9.0 Hz, 1 H, H3a), 2.74 (s, 3 H, NCH_3), 2.70 (dd, J_{gem} = 17.0 Hz, J_{vic} = 9.0 Hz, 1 H, H3b).

Irradiation (transient NOE) at 4.54 ppm (H5) enhances the signals at 7.52 (H1′, 4.3%), 7.26 (H3′, 2.2%), 7.06 (H2″,6″, 2.6%), 3.41 (H4, 1.2%), 2.74 (NCH_3, 2.1%), 2.70 (H3b, 0.8%). Irradiation at 3.41 ppm (H4) enhanced the signals at 7.52 (H1′, 1.0%), 7.26 (H3′, 2.6%), 7.06 (H2″,6″, 4.3%), 4.54 (H5, 1.3%), 3.03 (H3a, 3.2%), 2.70 (H3b, 0.9%).

^{13}C NMR, HSQC (100.6 MHz, $CDCl_3$): δ = 174.0 (C2), 139.7, 136.3, 133.25, 133.17, 133.1 (C2′, C4a′,C8a′, C1″, C4″), 129.3 (C4′), 129.0 (2 C, C3″,5″), 128.5 (2 C, C2″,6″), 127.84, 127.75 (C5′, C8′), 126.6, 126.4, 126.2 (C1′, C6′, C7′), 123.6 (C3′), 72.8 (C5), 47.4 (C4), 38.2 (C3), 28.5 (NCH_3).

4 (Ratio of *anti*/*syn* = 8:1)

IR (KBr): 3423 (br, NH), 2977, 2933, 2780, 1718 (vs), 1491, 1368, 1319, 1255, 1158 (sh), 1142, 1091, 1015, 832, 748 cm^{-1}.

ESI-MS: *m*/*z* (%) = 410.2 (100, $[M + H]^+$), 354.2 (18, $[M - C_4H_8 + H]^+$), 323.1 (11, $[M - CH_3NH]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{25}H_{28}ClNO_2 + H]^+$: 410.1887; found: 410.1877.

anti-**4**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.78 (m, 3 H, H4′, H5′, H8′), 7.70 (br s, 1 H, H1′), 7.51–7.40 (m, 3 H, H3′, H6′, H7′), 7.30 (AA′ part of AA′BB′ system, 2 H, H3″,5″), 7.22 (BB′ part of AA′BB′ system, 2 H, H2″,6″), 3.68 (d, *J* = 9.2 Hz, 1 H, H4), 3.34 (ddd, *J* = 10.4, 9.2, 5.3 Hz, 1 H, H3), 2.37 (dd, J_{gem} = 15.3 Hz, J_{vic} = 10.4 Hz, 1 H, H2-a), 2.28 (dd, J_{gem} = 15.3 Hz, J_{vic} = 5.3 Hz, 1 H, H2-b), 2.08 (s, 3 H, NCH_3), 1.11 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 170.9 (C=O), 139.7, 138.6 (C1″, C4″), 133.19, 133.18, 132.8 (C2′, C4a′, C8a′), 129.8 (2 C, Cl-C_6H_4), 128.7 (2 C, Cl-C_6H_4), 128.4, 127.75, 127.66, 127.6, 126.1, 125.8, 125.5 (C1′, C3′, C4′, C5′, C6′, C7′, C8′), 80.3 [*C*(CH_3)$_3$], 70.3 (C4), 48.5 (C3), 39.5 (C2), 34.8 (NCH_3), 27.7 [3 C, C(*C*H_3)$_3$].

syn-**4**

^{1}H NMR (300 MHz, $CDCl_3$): δ (characteristic chemical shifts) = 7.10 (AA′ part of AA′BB′ system, 2 H, H3″,5″), 6.91 (BB′ part of AA′BB′ system, 2 H, H2″,6″), 3.76 (d, *J* = 7.0 Hz, 1 H, H4), 3.51 (ddd, *J* = 9.0, 7.0, 6.3 Hz, 1 H, H3), 2.85 (dd, J_{gem} = 15.4 Hz, J_{vic} = 6.3 Hz, 1 H, H2-a), 2.54 (dd, J_{gem} = 15.4 Hz, J_{vic} = 9.0 Hz, 1 H, H2-b), 2.21 (s, 3 H, NCH_3), 1.27 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ (characteristic chemical shifts) = 171.8 (C=O), 139.5, 138.2 (C1″, C4″), 133.0, 132.7, (naph-C_q), 129.9 (2 C, C3″,5″), 128.0 (2 C, C2″,6″), 127.7, 127.5, 127.0, 125.9, 125.6 (2 C) (naph), 80.3 [*C*(CH_3)$_3$], 69.7 (C4), 47.7 (C3), 38.4 (C2), 34.6 (NCH_3), 27.9 [C(*C*H_3)$_3$].

2-[(2-Naphthylmethylene)amino]propionitrile (5d)

2-Naphthaldehyde (6.0 g, 38.4 mmol) was dissolved in CH_2Cl_2 (40 mL). To this solution were added $MgSO_4$ (13.9 g, 115.2 mmol), 2-aminopropionitrile hydrochloride[32] (5.3 g, 50.0 mmol) and Et_3N (5.9 mL, 42.2 mmol). After stirring the mixture overnight under argon, $MgSO_4$ was filtered off and the solvent was removed in vacuo. Crystallization from Et_2O and petroleum ether gave a crude yellow solid (2.95 g). The solid was dissolved in CH_2Cl_2 (100 mL), washed with aq sat. $NaHCO_3$ solution (100 mL) and dried (Na_2SO_4). Re-

moval of the solvent and crystallization from Et_2O and petroleum ether gave the pure title compound as slightly yellow crystals (1.16 g). The mother liquor was evaporated and the resulting residue (4.44 g) was reacted once again with equivalent amounts of aminonitrile hydrochloride, Et_3N and $MgSO_4$ and yielded after purification 4.12 g pure product. The combined yield amounted to 66%; R_f = 0.48 (PE–EtOAc, 2:1); mp 86–88 °C.

IR (film): 2990 (w), 2939 (w), 2869 (w), 2250 (vw, C≡N), 1635 (s), 1347 (w), 1311 (w), 1123 (m), 973 (m), 869 (m), 827 (s), 757 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6): δ = 8.65 (s, 1 H, CH=N), 8.30 (s, 1 H, naph-H1), 8.07–7.88 (m, 4 H, naph-H3, -H4, -H5, -H8), 7.62–7.52 (m, 2 H, naph-H6, -H7), 4.95 (q, J = 7.1 Hz, 1 H, CNCH), 1.58 (d, J = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 163.6 (C=N), 134.6 (naph-C4a), 132.7 (naph-C2), 132.6 (naph-C8a), 131.2, 128.9, 128.7, 127.9, 127.9 (partly overlapping signals), 127.0, 123.3 (naph-C3), 120.1 (CN), 52.9 (*C*CN), 20.9 (CH_3).

FD-MS: m/z = 208.2 (100%, $[M]^+$).

Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.93; H, 5.85; N, 13.05.

2-[(2-Naphthylmethylene)amino]-3-phenylpropionitrile (5e)

2-Naphthaldehyde (1.6 g, 10.2 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL). To this solution were added, $MgSO_4$ (3.68 g, 30.6 mmol), 2-amino-3-phenylpropionitrile[33] (2.04 g, 14.0 mmol) and AcOH (3 mL, 52.4 mmol) and the mixture was refluxed for 8 h under argon. After filtration of $MgSO_4$, the filtrate was washed with aq sat. $NaHCO_3$ solution (10 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo yielded the crude product. After crystallization from EtOAc–cyclohexane, yellow crystals (1.50 g, 52%) were obtained; R_f = 0.51 (PE–EtOAc, 10:1); mp 81–83 °C.

IR (film): 3061 (w), 3031 (w), 2885 (w), 2232 (vw, C≡N), 1646 (s, C = N), 1498 (m), 1455 (m), 1342 (w), 1018 (w), 867 (m), 869 (m), 824 (m), 755 (s), 698 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.42 (s, 1 H, CH=N), 8.05 (s, 1 H, naph-H1), 8.01–7.96 (m, 1 H, naph-H3), 7.92–7.82 (m, 3 H, naph-H4, -H5, -H8), 7.58–7.49 (m, 2 H, naph-H6, -H7), 7.37–7.24 (m, 5 H, C_6H_5), 4.95–4.88 (m, 1 H, CHCN), 3.38 (dd, J = 13.6, 5.9 Hz, 1 H, PhCH_2-H_a), 3.24 (dd, J = 13.6, 7.4 Hz, 1 H, PhCH_2-H_b).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 163.3 (C=N), 135.1 (C_6H_5-C1), 135.1, 132.9, 132.5, 131.4, 129.9 (2 C), 128.9, 128.7, 128.6 (2 C) (partly overlapping signals), 127.9, 127.7, 127.5, 126.7, 123.5, 117.5 (CN), 60.1 (*C*CN), 40.8 (Ph*C*H_2).

FD-MS: m/z = 284.2 (100%, $[C_{20}H_{16}N_2]^+$).

γ-(Alkylideneamino)-γ-cyanoesters 6a–h; General Procedure (Table 1)

Method A: To a stirred mixture of imine **5** (1 equiv) and $BnNEt_3Cl$ (0.1 equiv) in CH_2Cl_2, were added a solution of ester **2** (1.01–1.1 equiv) in CH_2Cl_2 and an aq solution of KOH (33.5 wt%, 20 equiv) simultaneously under argon. The color of the solution changed to yellow or orange. After stirring for several hours, the mixture was washed with sat. aq $NaHCO_3$ solution (3 × 5–10 mL) and H_2O (1 × 5–10 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo.

Method B: To a stirred solution of imine **5** (1 equiv) and ester **2** (1 equiv) in anhyd THF, was added DBU (1.1 equiv) under argon. The color change of the solution was pronounced in most cases. After stirring for several hours, EtOAc (5–20 mL) and aq $NaHCO_3$ solution (5–20 mL) were added to the mixture. After separation of the aqueous layer, the organic layer was washed with sat. aq $NaHCO_3$ solution (2 × 5–20 mL) and with H_2O (5 –20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo.

Method C: In an oven-dried flask, imine **5** (1 equiv) and ester **2** (1 equiv) were dissolved in anhyd THF under argon. A solution of Me_4NOH (25 wt% in MeOH, 1 equiv) in THF was added dropwise within 30 min at –8 °C. After 1.5 h at –8 °C, aq 1 N NaOH (25 mL) was added. After extraction with EtOAc (3 × 15 mL) and washing with H_2O (3 × 15 mL), the organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo.

***tert*-Butyl 4-Cyano-4-[(diphenylmethylene)amino]butyrate (6a)**

Following method A, imine **5a** (500 mg, 2.27 mmol) and $BnNEt_3Cl$ (51.7 mg, 0.227 mmol) in CH_2Cl_2 (10 mL), ester **2b** (332.8 μL, 293.8 mg, 2.29 mmol) in CH_2Cl_2 (10 mL), and KOH (2.55 g, 45.4 mmol) in H_2O (5.05 mL) were used. Complete conversion was achieved after 100 min. Purification of the crude product (719.5 mg, yellow oil) by flash chromatography (PE–EtOAc, 8:1) furnished **6a** (632.3 mg, 80%) as a slightly yellow oil; R_f = 0.66 (PE–EtOAc, 1:1).

IR (film): 2978 (m), 2242 (vw, C≡N), 1728 (s, C=O), 1619 (m), 1596 (m), 1578 (m), 1447 (m), 1368 (m), 1317 (m), 1291 (m), 1257 (m), 1152 (s), 784 (w), 698 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.18 (m, 10 H, C_6H_5), 4.30 (t, J = 6.4 Hz, 1 H, CHCN), 2.52–2.35 (m, 2 H, CH_2), 2.26–2.09 (m, 2 H, CH_2CO), 1.37 (s, 9 H, t-C_4H_9).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.5 (C=O), 171.3 (C=N), 138.3 (*ipso*-C), 135.0 (*ipso*-C), 131.2, 129.3, 129.0 (4 C), 128.2 (2 C), 127.3 (2 C), 119.1 (CN), 80.8 (*C*Me_3), 51.9 (*C*HCN), 31.1 (β-CH_2), 30.0 (CH_2CO), 28.0 [3 C, C(CH_3)$_3$].

ESI-MS: m/z (%) = 400.1 (51), 349.0 (70, $[M + H]^+$), 292.97 (100, $[M - C_4H_8]^+$).

ESI-HRMS: m/z calcd for $[C_{22}H_{24}N_2O_2 + H]^+$: 349.1916; found: 349.1943.

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.09; H, 6.80; N, 8.10.

***tert*-Butyl 4-Cyano-4-[(3,4-dimethoxybenzylidene)amino]-5-phenylpentanoate (6b)**

Following method A, imine **5b** (500 mg, 1.699 mmol) and $BnNEt_3Cl$ (38.7 mg, 0.170 mmol) in CH_2Cl_2 (5 mL), ester **2b** (247 μL, 218 mg, 1.70 mmol) in CH_2Cl_2 (5 mL), and KOH (1.91 g, 33.97 mmol) in H_2O (3.78 mL) were reacted. After 2 h, 701.3 mg of a slightly yellow oil was isolated. A portion (682.9 mg) of the crude product was purified by flash chromatography (cyclohexane–EtOAc, 3:1 + 1% Me_2NEt) to give **6b** (662.0 mg, 95%) as a colorless oil.

According to method B, the crude product (76.6 mg, brown oil) was obtained after 20 h from a solution of **5b** (60 mg, 2.204 mmol), **2b** (29.6 μL, 26.1 mg, 0.204 mmol), and DBU (33.5 μL, 34.1 mg, 0.224 mmol) in anhyd THF (0.6 mL). Purification of the crude product by flash chromatography (PE–EtOAc, 3:1) led to **6b** (37 mg, 43%) as a colorless oil; R_f = 0.23 (PE–EtOAc, 3:1).

IR (film): 2934 (m), 1729 (s, C=O), 1642 (m), 1586 (m), 1513 (s), 1456 (m), 1422 (m), 1368 (m), 1269 (s), 1242 (m) 1154 (s), 1026 (m), 705 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (s, 1 H, CH=N), 7.37 [d, J = 1.8 Hz, 1 H, 3,4-$(OMe)_2C_6H_3$-H2], 7.22–7.15 [m, 6 H, C_6H_5, 3,4-$(OMe)_2C_6H_3$], 6.87 [d, J = 8.3 Hz, 1 H, 3,4-$(OMe)_2C_6H_3$-H5], 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.15 (s, 2 H, PhCH_2), 2.37–2.23 (m, 4 H, β-CH_2, CH_2CO), 1.39 (s, 9 H, t-C_4H_9).

ESI-MS: m/z (%) = 423.1 (100, $[M + H]^+$), 367.0 (78, $[M - C_4H_8 + H]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{25}H_{30}N_2O_4 + H]^+$: 423.2284; found: 423.2266.

tert-Butyl 4-Cyano-4-[(3,4-dimethoxybenzylidene)amino]-3-methyl-5-phenylpentanoate (6c)

According to method C, the crude product (601 mg, slightly yellow oil) was obtained from a solution of **5b** (414.2 mg, 1.407 mmol) and **2c** (200.1 mg, 1.41 mmol) in anhyd THF (5 mL) after addition of Me_4NOH (25 wt% in MeOH, 570 μL, 1.41 mmol) in anhyd THF (5 mL) after a reaction time of 75 min. A portion (165 mg) of the crude product was purified by flash chromatography (cyclohexane–EtOAc, 4:1 + 1% Me_2NEt) to give **6c** (108.6 mg) as a colorless oil. Ratio of isomers: 1.2:1 (based on crude product); R_f = 0.44 (PE–EtOAc, 2:1).

IR (film): 2976 (m), 1728 (s, C=O), 1644 (m), 1601 (m), 1586 (m), 1513 (s), 1456 (m), 1421 (m), 1368 (m), 1269 (s), 1242 (m), 1162 (s), 1142 (m), 1026 (m), 706 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ (ratio of isomers a/b = 1.7:1) = 7.79 (s, 1 H, CH=N^b), 7.78 (s, 1 H, CH=N^a), 7.33 [s, 1 H, 3,4-$(OMe)_2$-C_6H_3-H2^{a+b}], 7.18–7.09 [m, 6 H, $C_6H_5^{a+b}$, 3,4-$(OMe)_2C_6H_3$-H6^{a+b}], 6.85 [d, *J* = 8.2 Hz, 1 H, 3,4-$(OMe)_2C_6H_3$-H5^{a+b}], 3.93 (s, 3 H, OCH_3^{a+b}), 3.91 (s, 3 H, OCH_3^{a+b}), 3.30–3.05 (m, 2 H) [contains: 3.26 (d, *J* = 13.3 Hz, 1 H, PhCH_2-H$_a^a$), 3.16 (s, 2 H, PhCH_2^b), 3.10 (d, *J* = 13.3 Hz, 1 H, PhCH_2-H$_b^a$)], 2.77 (dd, *J* = 15.2, 4.3 Hz, 1 H, CH_2CO-H$_a^b$), 2.64 (mc, 1 H, MeCH^{a+b}), 2.53 (dd, *J* = 15.4, 3.3 Hz, 1 H, CH_2CO-H$_a^a$), 2.25–2.05 (m, 2 H) [contains: 2.19 (dd, *J* = 15.2, 10.3 Hz, 1 H, CH_2CO-H$_b^b$), 2.11 (dd, *J* = 15.4, 10.6 Hz, 1 H, CH_2CO-H$_b^a$)], 1.45 (s, 9 H, *t*-$C_4H_9^b$), 1.41 (s, 9 H, *t*-$C_4H_9^a$), 1.27 (d, *J* = 6.7 Hz, 3 H, CH_3^a), 1.14 (d, *J* = 6.7 Hz, 3 H, CH_3^b).

ESI-MS: *m*/*z* (%) = 459.3 (14, $[M + Na]^+$), 437.4 (100, $[M + H]^+$), 412.4 (40, $[M – CN + 2 H]^+$), 381.3 (57, $[M – C_4H_8 + H]^+$), 356.2 (12).

Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.33; H, 7.27; N, 6.48.

tert-Butyl 3-(4-Chlorophenyl)-4-cyano-4-[(3,4-dimethoxybenzylidene)amino]-5-phenylpentanoate (6d)

Following method A, imine **5b** (250 mg, 0.849 mmol) and $BnNEt_3Cl$ (19.3 mg, 0.085 mmol) in CH_2Cl_2 (2.5 mL), ester **2a** (223 mg, 0.934 mmol) in CH_2Cl_2 (2.5 mL), and KOH (0.95 g, 16.9 mmol) in H_2O (1.89 mL) were used. After 3 h, a slightly yellow foam (431.7 mg) was isolated. A portion (421 mg) of the crude product was purified by flash chromatography (PE–EtOAc, 4:1). Two diastereomerically pure fractions of **6d** (60 mg,^{a} colorless foam, 103.5 mg,^{b} colorless amorphous material) and a mixture of the two diastereomers (63.4 mg,$^{a+b}$) were obtained. The combined yield of **6d** amounted to 51%. Ratio of isomers: 1.3:1 (based on crude product).

Minor Diastereomer

R_f = 0.29 (PE–EtOAc, 3:1).

IR (film): 2976 (m), 1729 (s, C=O), 1643 (m), 1600 (m), 1586 (m), 1513 (s), 1456 (m), 1421 (m), 1369 (m), 1269 (s), 1241 (m), 1146 (s), 1026 (m), 705 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (s, 1 H, CH=N), 7.40–7.34 (m, 2 H, C_6H_5-H3,5), 7.29–7.26 (m, 3 H), 7.16–7.00 (m, 6 H), 6.86 [d, *J* = 8.3 Hz, 1 H, 3,4-$(OMe)_2C_6H_3$-H5], 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.73 (dd, *J* = 11.5, 4.3 Hz, 1 H, 4-ClC_6H_4-CH), 3.08 (d, *J* = 13.3 Hz, 1 H, PhCH_2-H$_a$), 2.96 (dd, *J* = 15.4, 4.3 Hz, 1 H, CH_2CO-H$_a$), 2.90 (d, *J* = 13.3 Hz, 1 H, PhCH_2-H$_b$), 2.70 (dd, *J* = 15.4, 11.6 Hz, 1 H, CH_2CO-H$_b$), 1.21 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 169.9 (C=O), 160.9 (CH=N), 152.1 [3,4-$(OMe)_2C_6H_3$-C4], 149.3 [3,4-$(OMe)_2C_6H_3$-C3], 135.9 (C_6H_5-C1), 134.0 (4-ClC_6H_4-C1), 133.6 [3,4-$(OMe)_2C_6H_3$-C1], 131.7 (2 C), 131.0 (2 C), 128.0 (2 C), 127.9 (2 C) (partly overlapping signals), 127.3 (4-ClC_6H_4-C4), 127.5 (C_6H_5-C4), 123.5 [3,4-$(OMe)_2C_6H_3$-C6], 117.8 (CN), 110.7 [3,4-$(OMe)_2C_6H_3$-C2], 110.0 [3,4-$(OMe)_2C_6H_3$-C5], 81.0 (*C*Me_3), 71.5 (*C*CN), 56.0 (OCH_3), 55.9 (OCH_3), 50.6 (4-ClC_6H_4-CH), 44.4 (Ph*C*H_2), 38.1 (*C*H_2CO), 27.8 [3 C, C(*C*$H_3)_3$].

ESI-MS: *m*/*z* (%) = 533.2 (100%, $[M + H]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{31}H_{33}ClN_2O_4 + H]^+$: 533.2207; found: 533.2212.

Anal. Calcd for $C_{31}H_{33}ClN_2O_4$: C, 69.85; H, 6.24; N, 5.26. Found: C, 69.73; H, 6.13; N, 5.18.

Major Diastereomer

R_f = 0.24 (PE–EtOAc, 3:1).

IR (film): 2934 (w), 1728 (s, C=O), 1641 (m), 1600 (m), 1586 (m), 1513 (s), 1495 (m), 1456 (m), 1422 (m), 1368 (m), 1269 (s), 1241 (m), 1145 (s), 1026 (m), 734 (m), 702 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (s, 1 H, CH=N), 7.46–7.29 (m, 5 H), 7.16–7.07 (m, 4 H), 7.00–6.93 (m, 2 H), 6.86 [d, *J* = 8.3 Hz, 1 H, 3,4-$(OMe)_2C_6H_3$-H5], 3.96 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.75 (t, *J* = 8.0 Hz, 1 H, 4-ClC_6H_4-CH), 3.06 (d, *J* = 13.3 Hz, 1 H, PhCH_2-H$_a$), 2.85 (d, *J* = 13.3 Hz, 1 H, PhCH_2-H$_b$), 2.76 (d, *J* = 8.0 Hz, 2 H, CH_2CO), 1.17 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 170.3 (C=O), 161.7 (CH=N), 152.2 [3,4-$(OMe)_2C_6H_3$-C4], 149.3 [3,4-$(OMe)_2C_6H_3$-C3], 136.2, 133.9 [2 C, C_6H_5-C1, 4-ClC_6H_4-C1, 3,4-$(OMe)_2C_6H_3$-C1], 131.1 (2 C), 131.0 (2 C), 128.6 (2 C), 127.9 (2 C), 127.8 (4-ClC_6H_4-C4), 127.3 (C_6H_5-C4), 123.8 [3,4-$(OMe)_2C_6H_3$-C6], 117.3 (CN), 110.6 [3,4-$(OMe)_2C_6H_3$-C2], 109.6 [3,4-$(OMe)_2C_6H_3$-C5], 80.9 (*C*Me_3), 72.3 (*C*CN), 56.0 (OCH_3), 56.0 (OCH_3), 50.4 (4-ClC_6H_4-CH), 44.4 (Ph*C*H_2), 37.4 (*C*H_2CO), 27.7 [3 C, C(*C*$H_3)_3$].

ESI-MS: *m*/*z* (%) = 555.2 (51, $[M + Na]^+$), 533.2 (100, $[M + H]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{31}H_{33}ClN_2O_4 + H]^+$: 533.2207; found: 533.2199.

tert-Butyl 3-(4-Chlorophenyl)-4-cyano-4-[(3,4-dimethoxybenzylidene)amino]-4-phenylbutyrate (6e)

According to method B, the crude product (820 mg, yellow oil) was obtained after 2 h 20 min from a solution of **5c** (400 mg, 1.43 mmol), **2a** (340.6 mg, 1.43 mmol), and DBU (234.5 μL, 239.0 mg, 1.57 mmol) in anhyd THF (4 mL). Purification of the crude product by flash chromatography (PE–EtOAc, 3:1) afforded **6e** (117.0 mg, 61%) as a slightly yellow oil. Ratio of isomers: 1.5:1 (based on crude product); R_f = 0.32 (PE–EtOAc, 3:1).

IR (film): 2977 (w), 1709 (s, C = O), 1639 (m), 1597 (m), 1514 (m), 1493 (m), 1368 (m), 1322 (m), 1270 (m), 1152 (s), 1092 (m), 1027 (m), 823 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ (ratio of isomers a/b = 1.4:1) = 8.34 (s, 1 H, CH=N^a), 8.16 (s, 1 H, CH=N^b), 7.61–6.86 [m, 12 H, 3,4-$(OMe)_2C_6H_3$, 4-ClC_6H_4, C_6H_5], 3.99 (s, 3 H, OCH_3^a), 3.95 (s, 3 H, OCH_3^b), 3.94 (s, 3 H, OCH_3^a), 3.92 (s, 3 H, OCH_3^b), 3.90–3.77 (m, 1 H, 4-ClC_6H_4-CH^{a+b}), 2.89–2.61 (m, 2 H, CH_2CO^{a+b}), 1.14 (s, 9 H, *t*-$C_4H_9^b$), 1.13 (s, 9 H, *t*-$C_4H_9^a$).

ESI-MS: *m*/*z* (%) = 519.1 (100, $[M + H]^+$), 463.0 (30, $[M – C_4H_8 + H]^+$).

Anal. Calcd for $C_{30}H_{31}ClN_2O_4$: C, 69.42; H, 6.02; N, 5.40. Found: C, 69.35; H, 5.89; N, 5.46.

tert-Butyl 4-Cyano-4-methyl-4-[(2-naphthylmethylene)amino]butyrate (6f)

Following method A, imine **5d** (200 mg, 0.960 mmol) and $BnNEt_3Cl$ (21.9 mg, 0.096 mmol) in CH_2Cl_2 (2 mL), ester **2b** (123.2 mg, 0.960 mmol) in CH_2Cl_2 (2 mL), and KOH (1.08 g, 19.2 mmol) in H_2O (2.14 mL) were used. After 2.5 h, **6f** (308.2 mg, 94%) was

obtained as a yellow oil. No further purification was required; R_f = 0.57 (PE–EtOAc, 3:1).

IR (film): 2980 (m), 2935 (w), 2228 (vw, C≡N), 1729 (s, C=O), 1641 (m), 1393 (w), 1368 (m), 1156 (s), 1125 (m), 861 (w), 823 (m), 750 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.66 (s, 1 H, CH=N), 8.13 (s, 1 H, naph-H1), 8.01–7.97 (m, 1 H, naph-H3), 7.92–7.81 (m, 3 H, naph-H4, -H5, -H8), 7.53 (mc, 2 H, naph-H6, -H7), 2.43–2.19 (m, 4 H, CH_2CO, β-CH_2), 1.68 (s, 3 H, CH_3), 1.40 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 171.4 (C=O), 160.2 (C=N), 135.1, 132.9, 132.5, 131.4, 128.8, 128.6, 127.9, 127.7, 126.7, 123.7 (naph), 119.5 (CN), 80.8 (*C*Me_3), 62.8 (*C*CN), 36.3 (CH_2), 30.9 *C*H_2CO), 28.0 [4 C, C(*C*H_3)$_3$, CH_3].

ESI-MS: *m*/*z* (%) = 337.2 (81, $[M + H]^+$), 327.2 (38), 310.3 [M – CN]$^+$, 281.2 (100, $[M – C_4H_8 + H]^+$), 254.1 (28), 192.2 (23).

tert-Butyl 4-Cyano-4-[(2-naphthylemthylene)amino]-5-phenylpentanoate (6g)

Following method A, imine **5e** (200 mg, 0.703 mmol) and $BnNEt_3Cl$ (16.0 mg, 0.070 mmol) in CH_2Cl_2 (2 mL), ester **2b** (102.1 μL, 90.1 mg, 0.703 mmol) in CH_2Cl_2 (2 mL), and KOH (0.78 g, 13.9 mmol) in H_2O (1.57 mL) were used. After 2 h, **6g** (286.8 mg, 99%) was obtained as a slightly brown and viscous oil. No further purification was required; R_f = 0.51 (PE–EtOAc, 3:1).

IR (film): 2978 (m), 2931 (w), 2229 (vw, C≡N), 1729 (s, C=O), 1640 (m), 1456 (m), 1393 (w), 1368 (m), 1288 (w) 1154 (s), 893 (w), 848 (w), 823 (m), 749 (m), 704 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 1 H, CH=N), 8.03–7.95 (m, 2 H, naph-H1, -H3), 7.89–7.81 (m, 3 H, naph-H4, -H5, -H8), 7.57–7.49 (m, 2 H, naph-H6, -H7), 7.20 (m, 5 H, C_6H_5), 3.21 (s, 2 H, Ph*C*H_2), 2.45–2.25 (m, 4 H, CH_2CO, β-CH_2), 1.40 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 171.4 (C=O), 161.4 (CH=N), 135.1 (C_6H_5-C1), 134.0, 132.9, 132.4, 131.4, 130.9 (2 C), 128.8, 128.6, 128.1 (2 C), 127.9, 127.7, 127.4, 126.7, 123.7 (C_6H_5-C4), 118.2 (CN), 80.8 [*C*Me_3], 68.2 (*C*CN), 46.4 (Ph*C*H_2), 35.2 (β-CH_2), 30.8 (*C*H_2CO), 28.0 [3 C, C(*C*H_3)$_3$].

ESI-MS: *m*/*z* (%) = 413.4 (83, $[M + H]^+$), 402.3 (18), 386.3 (100, $[M – CN]^+$), 357.2 (59, $[M – C_4H_8 + H]^+$), 330.2 (14, $[M – C_4H_8 – CN]^+$), 192.2 (39).

tert-Butyl 4-(Benzhydrylidene)amino-3-(4-chlorophenyl)-4-cyanobutyrate (6h)

Following method A, imine **5a** (1 g, 4.54 mmol) and $BnNEt_3Cl$ (103 mg, 0.454 mmol) in CH_2Cl_2 (20 mL), ester **2a** (1.09 g, 4.59 mmol) in CH_2Cl_2 (20 mL), and KOH (5.09 g, 90.8 mmol) in H_2O (10.1 mL) were used. After 3 h, the crude product (2.12 g, quant) was obtained as a slightly brown viscous oil. Purification by flash chromatography (PE–EtOAc, 9:1) afforded **6h** (1.74 g, 84%) as a yellow solid. Ratio of isomers: 1.2:1 (based on crude product); R_f = 0.28 (PE–EtOAc, 9:1).

IR (film): 3436 (vs), 1728 (m, C=O), 1624 (s, C=N), 1493 (w), 1446 (w), 1368 (w), 1288 (w), 1150 (m), 1094 (w), 1015 (w), 829 (w), 784 (w), 698 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ (ratio of isomers a/b = 1.4:1) = 7.61–6.86 (m, 14 H, 2 C_6H_5 , 4-ClC_6H_4), 4.35 (d, *J* = 5.9 Hz, 1 H, CHCN^a), 4.31 (d, *J* = 5.6 Hz, 1 H, CHCN^b), 3.66 (td, J_t = 10.8 Hz, J_d = 5.6 Hz, 1 H, C*H*Ar^b), 3.57 (td, J_t = 11.0 Hz, J_d = 5.9 Hz, 1 H, C*H*Ar^a), 3.09 (dd, *J* = 15.9, 5.3 Hz, 1 H, CH_2CO-H_a^{a}), 2.99 (dd, *J* = 15.9, 5.2 Hz, 1 H, CH_2CO-H_a^{b}), 2.88–2.71 (m, 1 H, CH_2CO-$H_b$$^{a+b}$), 1.25 (s, 9 H, *t*-$C_4H_9$^{a}), 1.23 (s, 9 H, *t*-C_4H_9^{b}).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$,): δ (ratio of isomers a/b = 1.4:1) = 174.4 (C=O^a), 174.0 (C=O^b), 170.1 (C=N^b), 170.1 (C=N^a), 138.2 (C1′^{a}), 138.0 (C1′^{b}), 134.9, 134.8, 133.5, 131.5, 131.4, 129.9, 129.8, 129.5, 129.3, 129.1, 129.0, 128.6, 128.3, 128.2, 127.3, 127.0 (partly overlapping signals), 118.0 (CN^{a+b}), 81.1 (*C*$Me_3$$^{a+b}$), 57.9 (*C*HCN^a), 57.6 (*C*HCN^b), 45.7 (Ar*C*H^b), 45.6 (Ar*C*H^a), 37.0 (*C*H_2CO^a), 36.95 (*C*H_2CO^b), 27.8 [3 C, C(*C*H_3)$_3$$^{a+b}$].

ESI-MS: *m*/*z* (%) = 481.1 (14, $[M + Na]^+$) 403.1 (41, $[M – C_4H_8 + H]^+$), 385.0 (33, $[M – C_4H_8 – H_2O + H]^+$) 330.0 (27), 221.0 (100, $[Ph_2CNCH_2CN + H]^+$), 192.9 (28), 182.0 (37, $[Ph_2C=NH_2]^+$), 164.9 (96, $[4\text{-}ClC_6H_4CH=CHCO]^+$).

γ-Aminobutyric Acid Esters 7a–h (Table 2); General Procedure

To a stirred solution of the γ-(alkylideneamino)-γ-cyanoester **6** (1 equiv) in EtOH (60 equiv) was added solid $NaCNBH_3$ (3 equiv) under argon. After addition of AcOH (6 equiv), the mixture was stirred at least for 24 h at r.t. Two different work-up procedures were applied.

Method A: EtOAc (3–20 mL) and aq sat. $NaHCO_3$ solution (3–20 mL) were added to the reaction mixture. The organic layer was separated; the aqueous layer was extracted with EtOAc (2 × 3–20 mL). The combined organic layers were washed with H_2O (5–10 mL), dried (Na_2SO_4) and the solvent was removed in vacuo.

Method B: After addition of ethanolamine, the mixture was stirred at r.t. for several hours and partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic layer was washed with aq sat. $NaHCO_3$ solution (1 × 5 mL) and with H_2O (3 × 5 mL), dried (Na_2SO_4) and the solvent was removed in vacuo.

tert-Butyl 4-(Benzhydrylamino)butyrate (7a)

Following the general method, **6a** (200 mg, 0.574 mmol), $NaCNBH_3$ (108.2 mg, 1.72 mmol), and AcOH (197 μL, 3.44 mmol) in EtOH (2 mL) were used. After stirring for 4 d at r.t., the addition of more $NaCNBH_3$ (108.2 mg, 1.72 mmol) was necessary because the conversion of the intermediate product [*tert*-butyl 4-(benzhydrylamino)-4-cyanobutyrate] did not proceed further. After 2 d, another portion of $NaCNBH_3$ (108.2 mg, 1.72 mmol) was added. The work-up procedure (method A) was performed even though the intermediate was not converted completely. A portion (171.4 mg) of the crude product (181.4 mg) was purified by flash chromatography (cyclohexane–EtOAc, 3:1 + 1% Me_2NEt) to give **7a** (129.6 mg, 71%) as a colorless oil; R_f = 0.58 (PE–EtOAc, 1:1).

IR (film): 2977 (m), 2931 (m), 1728 (s, C=O), 1493 (m), 1454 (m), 1367 (m), 1256 (m), 1151 (s), 746 (m), 703 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 4 H, C_6H_5-H3,5), 7.32–7.25 (m, 4 H, C_6H_5-H2,6), 7.20–7.16 (m, 2 H, C_6H_5-H4), 4.80 (s, 1 H, Ph_2CH), 2.59 (t, *J* = 6.9 Hz, 2 H, NCH_2), 2.30 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 1.79 (quint, *J* = 7.1 Hz, 2 H, β-CH_2), 1.51 (br s, 1 H, NH), 1.41 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.0 (C=O), 144.2 (2 C, C_6H_5-C1), 128.4 (4 C, C_6H_5-C3,5), 127.2 (4 C, C_6H_5-C2,6), 126.9 (2 C, C_6H_5-C4), 80.1 (*C*Me_3), 67.5 (Ph_2CH), 47.4 (NCH_2), 33.5 (*C*H_2CO), 28.1 [3 C, C(*C*H_3)$_3$], 25.7 (β-CH_2).

ESI-HRMS: *m*/*z* calcd for $[C_{21}H_{27}NO_2 + Na]^+$: 348.1940, found: 348.1947.

Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.57; H, 8.26; N, 4.36.

tert-Butyl 4-(3,4-Dimethoxybenzylamino)-5-phenylpentanoate (7b)

Following the general method, **6b** (295 mg, 0.698 mmol), $NaCNBH_3$ (131.6 mg, 2.095 mmol) and AcOH (239.8 μL, 4.19 mmol) in EtOH (2.5 mL) were used. After stirring overnight, ethanolamine (1.5 mL) was added. The mixture was stirred at r.t. for 4 h. Following work-up procedure B, **7b** (224.8 mg, 81%) was obtained as a colorless oil; R_f = 0.12 (PE–EtOAc, 1:1).

IR (film): 2933 (s), 1724 (s), 1591 (m), 1514 (s), 1454 (m), 1417 (m), 1365 (m), 1261 (s), 1149 (s), 1030 (m), 847 (m), 806 (m), 700 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.12 (m, 5 H, C_6H_5), 6.76–6.70 [m, 3 H, 3,4-$(OMe)_2C_6H_3$], 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.68 [AB system, J = 13.1 Hz, 2 H, 3,4-$(OMe)_2C_6H_3CH_2$], 2.78 (mc, 1 H, BnC*H*), 2.74–2.67 (m, 2 H, PhCH_2), 2.32 (t, J = 7.6 Hz, 2 H, CH_2CO), 1.75–1.68 (m, 3 H, NH, β-CH_2), 1.40 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 173.3 (C=O), 148.9 [3,4-$(OMe)_2C_6H_3$-C3], 147.9 [3,4-$(OMe)_2C_6H_3$-C4], 139.0 (C_6H_5-C1), 132.8 [3,4-$(OMe)_2C_6H_3$-C1], 129.3 (2 C), 128.4 (2 C), 126.2 (C_6H_5-C4), 120.1 [3,4-$(OMe)_2C_6H_3$-C6], 111.2 [3,4-$(OMe)_2C_6H_3$], 110.9 [3,4-$(OMe)_2C_6H_3$], 80.2 (*C*Me_3), 57.3 (Bn*C*H), 55.9 (OCH_3), 55.8 (OCH_3), 50.6 [3,4-$(OMe)_2C_6H_3CH_2$], 40.4 (PhCH_2), 32.0 (β-CH_2), 28.9 (CH_2CO), 28.1 [3 C, C(*C*H_3)$_3$)].

ESI-MS: *m*/*z* (%) = 423.1 (13, $[M + Na]^+$), 400.2 (90, $[M + H]^+$), 344.0 (100, $[M - C_4H_8 + H]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{24}H_{33}NO_4 + H]^+$: 400.2488; found: 400.2469.

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 71.96; H, 8.18; N, 3.54.

tert-Butyl 4-(3,4-Dimethoxybenzylamino)-3-methyl-5-phenylpentanoate (7c)

Following the general method, **6c** (430.1 mg, 0.985 mmol, dr 1.2:1), $NaCNBH_3$ (185.7 mg, 2.96 mmol) and AcOH (338.4 μL, 5.91 mmol) in EtOH (3.5 mL) were used. The mixture was stirred overnight at r.t. Following work-up procedure A, 356.1 mg of a slightly yellow oil were obtained. A portion (325.0 mg) of the crude product was purified by chromatography (cyclohexane–EtOAc, 1:1.5). Two fractions of **7c** were obtained as slightly yellow oils (125.2 mg, dr 3.2:1 and 76.3 mg, dr 1:1). The combined yield amounted 54%. Ratio of isomers (based on crude product): *anti*/*syn* = 1.6:1; R_f = 0.44 (PE–EtOAc, 2:3).

IR (film): 2966 (m), 2934 (m), 1724 (s, C=O), 1515 (s), 1456 (m), 1367 (m), 1262 (s), 1237 (m), 1155 (s), 1031 (m), 701 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ (ratio of isomers: *anti*/*syn* = a/b = 3.2:1) = 7.28–7.11 (m, 5 H, $C_6H_5{}^{a+b}$), 6.73–6.61 [m, 3 H, (3,4-$(OMe)_2C_6H_3$-H2, -H5, -H6^{a+b}], 3.82 (s, 3 H, $OCH_3{}^a$), 3.82 (s, 3 H, $OCH_3{}^b$), 3.76 (s, 3 H, $OCH_3{}^a$), 7.75 (s, 3 H, $OCH_3{}^b$) (partly overlapping signals), 3.69–3.48 (m, 2 H, [3,4-$(OMe)_2C_6H_3CH_2$], 2.79–2.65 (m, 2 H, BnCH^{a+b}, PhCH_2-$H_a{}^{a+b}$), 2.60–2.35 (m, 3 H, Ph$CH_2{}^{a+b}$, CH_2CO-$H_a{}^b$) [contains: 2.57 (dd, J = 14.7, 4.7 Hz, 1 H, CH_2CO-$H_a{}^a$)], 2.24 (mc, 1 H, MeCH^{a+b}), 2.13 (dd, J = 13.9, 1.8 Hz, 1 H, CH_2CO-$H_b{}^b$), 2.01 (dd, J = 14.7, 9.3 Hz, 1 H, CH_2CO-$H_b{}^a$), 1.42 (s, 9 H, *t*-$C_4H_9{}^b$), 1.41 (s, 9 H, *t*-$C_4H_9{}^a$), 1.00 (d, J = 5.4 Hz, 3 H, $CH_3{}^b$), 0.98 (d, J = 6.8 Hz, 3 H, $CH_3{}^a$).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ (ratio of isomers: *anti*/*syn* = a/b = 3.2:1) = 173.2 (C=O^a), 172.7 (C=O^b), 148.8 [3,4-$(OMe)_2C_6H_3$-C3^{a+b}], 147.8 [3,4-$(OMe)_2C_6H_3$-C4^{a+b}], 139.8 (C_6H_5-C1^a), 139.7 (C_6H_5-C1^b), 133.3 [3,4-$(OMe)_2C_6H_3$-C1^{a+b}], 129.2 (2 C^b), 129.1 (2 C^a), 128.4 (2 C^a), 128.4 (2 C^b), 126.1 (C_6H_5-C4^{a+b}), 120.1 [3,4-$(OMe)_2C_6H_3$-C6^a], 120.0 [3,4-$(OMe)_2C_6H_3$-C6^b], 111.1 [3,4-$(OMe)_2C_6H_3$-C5^{a+b}], 110.8 [3,4-$(OMe)_2C_6H_3$-C2^{a+b}], 80.1 (*C*$Me_3{}^b$), 79.9 (*C*$Me_3{}^a$), 61.8 (Bn*C*H^a), 61.8 (Bn*C*H^b), 55.9 ($OCH_3{}^{a+b}$), 55.7 ($OCH_3{}^{a+b}$), 51.5 [3,4-$(OMe)_2C_6H_3CH_2{}^a$], 51.3 [3,4-$(OMe)_2C_6H_3CH_2{}^b$], 40.0 (Ph$CH_2{}^b$), 38.4 (Ph$CH_2{}^a$), 37.1 (CH_2CO^a), 36.4 (CH_2CO^b), 32.4 (Me*C*H^b), 31.9 (Me*C*H^a), 28.1 [3 C, C(*C*H_3)$_3{}^{a+b}$], 15.5 ($CH_3{}^a$), 15.1 ($CH_3{}^b$).

ESI-MS: *m*/*z* (%) = 414.4 (73, $[M + H]^+$), 358.2 (100, $[M - C_4H_8 + H]^+$), 151.1 (38, $[3,4\text{-}(OMe)_2C_6H_3CH_2]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{25}H_{35}NO_4 + H]^+$: 414.2644; found: 414.2630.

tert-Butyl 3-(4-Chlorophenyl)-4-(3,4-dimethoxybenzylamino)-5-phenylpentanoate (7d) and 5-Benzyl-4-(4-chlorophenyl)-1-(3,4-dimethoxybenzyl)pyrrolidin-2-one (8d)

Following the general method, **6d** (95 mg, 0.178 mmol, *anti*/*syn* >98:2), $NaCNBH_3$ (33.6 mg, 0.535 mmol) and AcOH (61.2 μL, 1.07 mmol) in a mixture of EtOH (0.6 mL) and THF (0.6 mL) were used. The mixture was stirred overnight at r.t. Because the conversion (monitored by TLC) was incomplete, an additional amount of $NaCNBH_3$ (10 mg, 0.159 mmol) was added. The mixture was stirred for 24 h. Following work-up procedure A, a slightly yellow oil (76.2 mg) was obtained. A portion (65.8 mg) of the crude product was purified by chromatography (PE–EtOAc, 1:1) and yielded **7d** (45.3 mg, 58%) and **8d** (20.3 mg, 30%) as colorless viscous oils.

7d

Ratio of isomers: *anti*/*syn* = >98:2 (based on crude product); R_f = 0.41 (PE–EtOAc, 2:1).

IR (film): 2933 (m), 1725 (s, C=O), 1515 (s), 1494 (m), 1455 (m), 1367 (m), 1262 (s), 1238 (m), 1151 (s), 1093 (m), 1031 (m), 734 (m), 702 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$), HMQC (400 MHz, $CDCl_3$): δ = 7.27–7.16 (m, 7 H, C_6H_5, 4-ClC_6H_4-H3,5), 7.06–7.03 (BB′ part of AA′BB′ system, 2 H, 4-ClC_6H_4-H2,6), 6.73 [d, J = 8.1 Hz, 1 H, 3,4-$(OMe)_2C_6H_3$-H5], 6.34–6.60 [m, 1 H, 3,4-$(OMe)_2C_6H_3$-H6], 6.57–6.56 [m, 1 H, 3,4-$(OMe)_2C_6H_3$-H2], 3.84 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.57 [AB system, J = 13.0 Hz, 2 H, 3,4-$(OMe)_2C_6H_3CH_2$], 3.31 (dt, J_t = 5.1 Hz, J_d = 9.9 Hz, 1 H, BnC*H*), 2.95 (mc, 1 H, 4-ClC_6H_4CH), 2.87 (dd, J = 15.4, 5.5 Hz, 1 H, CH_2CO-H_a), 2.68–2.40 (m, 3 H) [contains: 2.64 (dd, J = 15.4, 9.9 Hz, 1 H, CH_2CO-H_b), 2.57 (dd, J = 13.7, 4.7 Hz, 1 H, PhCH_2-H_a), 2.44 (dd, J = 13.7, 8.6 Hz, 1 H, PhCH_2-H_b)], 1.26 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$), HMQC (400 MHz, $CDCl_3$): δ = 171.9 (C=O), 148.9 [3,4-$(OMe)_2C_6H_3$-C3], 147.9 [3,4-$(OMe)_2C_6H_3$-C4], 139.7 (C_6H_5-C1), 139.3 (4-ClC_6H_4-C1), 132.9 (4-ClC_6H_4-C4), 132.3 [3,4-$(OMe)_2C_6H_3$-C1], 130.1 (2 C, 4-ClC_6H_4-C2,6), 129.1 (2 C, 4-ClC_6H_4-C3,5), 128.5 (2 C), 128.2 (2 C), 126.3 (C_6H_5-C4), 120.2 [3,4-$(OMe)_2C_6H_3$-C6], 111.2 [3,4-$(OMe)_2C_6H_3$-C5], 110.8 [3,4-$(OMe)_2C_6H_3$-C2], 80.3 (*C*Me_3), 61.9 (Bn*C*H), 55.9 (OCH_3), 55.7 (OCH_3), 51.8 [3,4-$(OMe)_2C_6H_3CH_2$], 44.0 (4-ClC_6H_4CH), 37.9 (PhCH_2), 36.8 (CH_2CO), 27.9 [3 C, C(*C*H_3)$_3$].

ESI-MS: *m*/*z* (%) = 512.2 (29), 511.2 (29), 510.2 (100, $[M + H]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{30}H_{36}ClNO_4 + Na]^+$: 532.2231; found: 532.2206.

Anal. Calcd for $C_{30}H_{36}ClNO_4$: C, 70.64; H, 7.11; N, 2.75. Found: C, 70.70; H, 6.97; N, 2.82.

trans-8d

Ratio of isomers: *trans*/*cis* = >98:2; R_f = 0.09 (PE–EtOAc, 2:1).

IR (film): 2934 (w), 1686 (s, C=O), 1593 (w), 1516 (m), 1494 (m), 1454 (m), 1418 (m), 1263 (m), 1236 (m), 1140 (m), 1028 (m), 825 (w), 703 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–6.66 [m, 12 H, 3,4-$(OMe)_2C_6H_3$, 4-ClC_6H_4, C_6H_5], 5.11 [d, J = 14.8 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_a], 3.90 [d, J = 14.8 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_b], 3.85 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.52 (mc, 1 H, H5), 3.12 (td, J_d = 9.2 Hz, J_t = 2.8 Hz, 1 H, H4), 3.03 (dd, J = 13.8, 4.5 Hz, 1 H, PhCH_2-H_a), 2.76–2.70 (m, 2 H, PhCH_2-H_b, $H3_a$), 2.36 (dd, J = 17.4, 3.3 Hz, 1 H, $H3_b$).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 173.5 (C=O), 149.3 [3,4-$(OMe)_2C_6H_3$-C3], 148.7 [3,4-$(OMe)_2C_6H_3$-C4], 142.5 (C_6H_5-C1), 136.5 (4-ClC_6H_4-C1), 132.5 (4-ClC_6H_4-C4), 129.3 (2 C, 4-ClC_6H_4-C2,6), 128.7 (4 C, C_6H_5-C2,6, C3,5), 128.5 [3,4-$(OMe)_2C_6H_3$-C1], 127.7 (2 C, 4-ClC_6H_4-C3,5), 127.0 (C_6H_5-C4), 120.8 [3,4-$(OMe)_2C_6H_3$-C6], 111.3 [3,4-$(OMe)_2C_6H_3$], 110.9 [3,4-$(OMe)_2C_6H_3$], 65.7 (C5), 55.9 (OCH_3), 55.8 (OCH_3), 44.5 [3,4-$(OMe)_2C_6H_3CH_2$], 40.4 (C4), 38.7 (C3), 37.7 (CH_2Ph).

ESI-MS: *m*/*z* (%) = 499.3 (17, [M + Na + MeCN]$^+$), 477.2 (16, [M + H + MeCN]$^+$), 458.2 (13, [M + Na]$^+$), 436.3 (100, [M + H]$^+$), 298.2 (13), 236.3 (17), 151.1 (28, [3,4-$(OMe)_2C_6H_3CH_2$]$^+$).

ESI-HRMS: *m*/*z* calcd for [$C_{26}H_{26}ClNO_3$ + Na]$^+$: 458.1499; found: 458.1513.

cis-8d

A portion of **7d** (13.2 mg, 26 μmol) was dissolved in THF (100 μL). After addition of CF_3CO_2H (100 μL, 1.35 mmol) and H_2O (100 μL, 5.56 mmol), the mixture was stirred at 50 °C for 3.5 h. Stirring was continued at r.t. for 12 h, the pH of the solution was adjusted to 6 by addition of pyridine and the solution was heated to 100 °C. After TLC had indicated complete conversion (5.5 h), the mixture was partitioned between sat. aq citric acid solution (3 mL) and EtOAc (5 mL). The organic layer was washed with sat. aq citric acid solution (3 mL) and H_2O (5 mL), dried (Na_2SO_4) and the solvent was removed in vacuo to furnish a greenish oil (20 mg) which still contained some CF_3CO_2H. Comparison of the ^{1}H NMR spectrum with the data of *trans*-**8d** showed that the *cis*-isomer had been formed.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.16 (m, 5 H), 7.04–6.98 (m, 2 H), 6.83–6.70 (m, 3 H), 6.55–6.49 (m, 2 H), 5.03 [d, *J* = 14.8 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_a], 3.98 (mc, 1 H, H5), 3.86 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.59 (mc, 1 H, H4), 3.35 [d, *J* = 14.8 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_b], 2.85 (dd, *J* = 16.6, 10.2 Hz, 1 H, PhCH_2-H_a), 2.75 (dd, *J* = 16.6, 8.4 Hz, 1 H, PhCH_2-H_b), 2.61 (dd, *J* = 14.1, 7.8 Hz, 1 H, H3a), 2.41 (dd, *J* = 14.1, 5.7 Hz, 1 H, H3b).

tert-Butyl 3-(4-Chlorophenyl)-4-(3,4-dimethoxybenzylamino)-4-phenylbutyrate (7e) and 4-(4-Chlorophenyl)-1-(3,4-dimethoxybenzyl)-5-phenylpyrrolidin-2-one (8e)

Following the general method, **6e** (130 mg, 0.250 mmol, dr 1.4:1), $NaCNBH_3$ (47.2 mg, 0.751 mmol) and AcOH (86.0 μL, 1.503 mmol) in EtOH (1.4 mL) were used. The mixture was stirred overnight at r.t. Because the conversion (monitored by TLC) was incomplete, an additional amount of $NaCNBH_3$ (49 mg, 0.780 mmol) was added. The mixture was stirred for 3 d. Following work-up procedure B, a colorless oil (93.9 mg) was obtained. A portion (84.0 mg) of the crude product was purified by chromatography (cyclohexane–EtOAc, 3:1 + 1% Me_2NEt) to give *anti*-**7e** (49.1 mg), **7e** as a mixture of isomers (17.9 mg, ratio of isomers: *anti*/*syn* = 1:1.5) and **8e** (24.4 mg, 26%) as colorless viscous oils. Combined yield of **7e**: 67.0 mg (60%).

7e

Ratio of isomers: *anti*/*syn* = a:b = 6.5:1 (based on crude product).

Major Diastereomer (*anti*)

R_f = 0.35 (PE–EtOAc, 2:1).

IR (film): 2976 (m), 2933 (m), 1727 (s, C=O), 1515 (s), 1493 (m), 1455 (m), 1368 (m), 1261 (m), 1237 (m), 1142 (s), 1093 (m), 1030 (m), 1014 (m), 704 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$), HMQC (400 MHz, $CDCl_3$): δ = 7.37–7.06 (m, 9 H, C_6H_5, 4-ClC_6H_4), 6.73 [d, *J* = 8.1 Hz, 1 H, 3,4-$(OMe)_2C_6H_3$-H2], 6.51–6.45 [m, 2 H, 3,4-$(OMe)_2C_6H_3$-H5,6], 3.84 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.59 (d, *J* = 8.9 Hz, 1 H, PhC*H*), 3.50 [d, *J* = 13.6 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_a], 3.28–3.17 (m, 2 H) [contains: 3.24 (q, *J* = 8.2 Hz, 1 H, 4-ClC_6H_4CH), 3.19 [d, *J* = 13.6 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_b)], 2.27 (d, *J* = 7.9 Hz, 2 H, CH_2CO), 1.12 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$), HMQC (400 MHz, $CDCl_3$): δ = 171.0 (C=O), 148.8 [3,4-$(OMe)_2C_6H_3$-C3], 147.8 (4-ClC_6H_4-C1), 141.3 [3,4-$(OMe)_2C_6H_3$-C4], 139.6 (C_6H_5-C1), 132.7 (4-ClC_6H_4-C4), 132.6 [3,4-$(OMe)_2C_6H_3$-C1], 129.9 (2 C), 128.4 (2 C), 128.4 (2 C), 128.3 (2 C), 127.6 (C_6H_5-C4), 120.1 [3,4-$(OMe)_2C_6H_3$-C6], 111.0 [3,4-$(OMe)_2C_6H_3$-C5], 110.7 [3,4-$(OMe)_2C_6H_3$-C2], 80.3 (CMe_3), 65.8 (Ph*C*H), 55.9 (OCH_3), 55.6 (OCH_3), 50.7 [3,4-$(OMe)_2C_6H_3CH_2$], 48.7 (4-ClC_6H_4CH), 39.5 (CH_2CO), 27.7 [3 C, $C(CH_3)_3$].

ESI-MS: *m*/*z* (%) = 518.2 (15, [M + Na]$^+$), 496.2 (100, [M + H]$^+$), 421.0 (12), 345.0 (30), 263.0 (28).

ESI-HRMS: *m*/*z* calcd for [$C_{29}H_{34}ClNO_4$ + Na]$^+$: 518.2074; found: 518.2059.

Anal. Calcd for $C_{29}H_{34}ClNO_4$: C, 70.22; H, 6.91; N, 2.82. Found: C, 70.09; H, 6.93; N, 2.88.

Minor Diastereomer (*syn*)

R_f = 0.30 (PE–EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ratio of isomers: *anti*/*syn* = a/b = 1:1.5) = 7.36–6.45 [m, 12 H, C_6H_5, 4-ClC_6H_4, 3,4-$(OMe)_2C_6H_3$$^{a+b}$], 3.88 (s, 3 H, OCH_3^{b}), 3.86 (s, 3 H, OCH_3^{b}), 3.85 (s, 3 H, OCH_3^{a}), 3.75 (s, 3 H, OCH_3^{a}), 3.60–3.48 [m, 2 H, PhC*H*, 3,4-$(OMe)_2C_6H_3CH_2$-$H_a$$^{a+b}$], 3.31–3.17 [m, 2 H, 4-$ClC_6H_4CH$, 3,4-$(OMe)_2C_6H_3CH_2$-$H_b$], 2.30–2.26 (m, 2 H, $CH_2CO$$^{a+b}$), 1.14 (s, 9 H, *t*-$C_4H_9$^{b}), 1.12 (s, 9 H, *t*-C_4H_9^{a}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ratio of isomers: *anti*/*syn* = a/b = 1:1.5) = 171.1 (C=O^b), 171.0 (C=O^a), 149.1 [3,4-$(OMe)_2C_6H_3$-C3^b], 148.8 [3,4-$(OMe)_2C_6H_3$-C3^a], 148.4 (4-ClC_6H_4-C1^b), 147.9 (4-ClC_6H_4-C1^a), 141.3 [3,4-$(OMe)_2C_6H_3$-C4^a], 140.2 [3,4-$(OMe)_2C_6H_3$-C4^b], 139.6 (C_6H_5-C1^{a+b}), 133.5 (4-ClC_6H_4-C4^b), 132.7 [4-ClC_6H_4-C4^a, 3,4-$(OMe)_2C_6H_3$-C1^b], 132.6 [3,4-$(OMe)_2C_6H_3$-C1^a], 129.9 (2 C^a), 129.9 (2 C^b), 128.4 (2 C^{a+b}), 128.4 (2 C^a), 128.3 (2 C^a), 128.2 (2 C^b), 128.0 (2 C^b), 127.6 (C_6H_5-C4^a), 126.8 (C_6H_5-C4^b), 120.9 [3,4-$(OMe)_2C_6H_3$-C6^b], 120.1 [3,4-$(OMe)_2C_6H_3$-C6^a], 111.1 [3,4-$(OMe)_2C_6H_3$-C5^a], 110.8 [3,4-$(OMe)_2C_6H_3$-C2^a], 110.7 [3,4-$(OMe)_2C_6H_3$-C5^b], 110.5 [3,4-$(OMe)_2C_6H_3$-C2^b], 80.3 ($CMe_3$$^{a+b}$), 65.9 (Ph*C*H^b), 65.8 (Ph*C*H^a), 55.9 (2 C, OCH_3^{b}, 1 C OCH_3^{a}), 55.6 (OCH_3^{a}), 51.0 [3,4-$(OMe)_2C_6H_3CH_2$^{b}], 50.7 [3,4-$(OMe)_2C_6H_3CH_2$^{a}], 48.7 (4-ClC_6H_4CH^{b}), 48.7 (4-ClC_6H_4CH^{a}), 39.5 (CH_2CO^{a}), 39.4 (CH_2CO^{b}), 27.7 [3 C, $C(CH_3)_3$$^{a+b}$].

8e

Ratio of isomers: *trans*/*cis* = 2.6:1 (based on crude product).

R_f = 0.09 (PE–EtOAc, 2:1).

IR (film): 1691 (s, C=O), 1516 (m), 1594 (m), 1408 (m), 1263 (m), 1239 (m), 1140 (m), 1028 (m), 732 (m), 703 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ratio of isomers: *trans*/*cis* = a/b = 2.6:1) = 7.35–6.50 [m, 12 H, 3,4-$(OMe)_2C_6H_3$, 4-ClC_6H_4, C_6H_5], 5.10 [d, *J* = 14.3 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_a^{a}], 5.07 [d, *J* = 14.4 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_a^{b}], 4.20 (d, *J* = 6.2 Hz, 1 H, H5^a), 4.15 (d, *J* = 6.8 Hz, 1 H, H5^b), 3.87 (s, 3 H, OCH_3^{b}), 3.83 (s, 3 H, OCH_3^{a}), 3.77 (s, 3 H, OCH_3^{b}), 3.75 (s, 3 H, OCH_3^{a}), 3.56 [d, *J* = 14.4 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_b^{b}], 3.44 [d, *J* = 14.3 Hz, 1 H, 3,4-$(OMe)_2C_6H_3CH_2$-H_b^{a}], 3.28 (mc, 1 H, H4^{a+b}), 3.01 (dd, *J* = 17.0, 9.1 Hz, 1 H, H3$_a$$^{a+b}$), 2.69–2.66 (m, 1 H) [contains: 2.65 (dd, *J* = 17.0, 8.7 Hz, 1 H, H3$_b$^{b}), 2.60 (dd, *J* = 17.0, 7.8 Hz, 1 H, H3$_b$^{a})].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ratio of isomers: *trans*/*cis* = a/b = 2.6:1) = 173.7 (C=O^{a+b}), 149.5 [3,4-$(OMe)_2C_6H_3$-C3^b], 149.1 (4-ClC_6H_4-C1^b), 149.0 [3,4-$(OMe)_2C_6H_3$-C3^a], 148.5 (4-ClC_6H_4-C1^a),

139.9 [3,4-$(OMe)_2C_6H_3$-C4^a], 139.6 [3,4-$(OMe)_2C_6H_3$-C4^b], 138.9 (C_6H_5-C1^a), 136.1 (C_6H_5-C1^b), 133.0 (4-ClC_6H_4-C4^a), 132.9 (4-ClC_6H_4-C4^b), 130.9, 129.5, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.0, 128.0, 127.6, 127.3, 127.0 (partly overlapping signals), 121.2 [3,4-$(OMe)_2C_6H_3$-C6^a], 119.8 [3,4-$(OMe)_2C_6H_3$-C6^b], 111.8 [3,4-$(OMe)_2C_6H_3$-C5^a], 111.2 [3,4-$(OMe)_2C_6H_3$-C5^b], 110.9 [3,4-$(OMe)_2C_6H_3$-C2^a], 109.5 [3,4-$(OMe)_2C_6H_3$-C2^b], 69.3 (C5^b), 69.2 (C5^a), 55.9 ($OCH_3{}^b$), 55.9 ($OCH_3{}^b$), 55.8 ($OCH_3{}^a$), 55.8 ($OCH_3{}^a$) (partly overlapping signals), 47.2 [3,4-$(OMe)_2C_6H_3CH_2{}^b$], 47.1 [3,4-$(OMe)_2C_6H_3CH_2{}^a$], 44.7 (C3^b), 44.4 (C3^a), 38.4 (C4^a), 38.3 (C4^b).

ESI-MS: *m*/*z* (%) = 563.6 (12), 444.1 (15, $[M + Na]^+$), 422.2 (95, $[M + H]^+$), 282.3 (100).

ESI-HRMS: *m*/*z* calcd for $[C_{25}H_{24}ClNO_3 + Na]^+$: 444.1343; found: 444.1338.

tert-Butyl 4-[(2-Naphthylmethyl)amino]pentanoate (7f)

Following the general method, **6f** (298.0 mg, 0.886 mmol), $NaCNBH_3$ (167.0 mg, 2.66 mmol) and AcOH (304.2 μL, 5.32 mmol) in EtOH (3.1 mL) were used. The mixture was stirred overnight at r.t. Following work-up procedure A, **7f** (261.4 mg, 94%) was obtained as a yellow oil. No further purification was required; R_f = 0.10 (PE–EtOAc, 2:1).

IR (film): 2975 (m), 2931 (m), 1728 (s, C=O), 1456 (m) 1367 (m), 1257 (m), 1154 (s), 854 (m), 819 (m), 751 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.77 (m, 3 H, naph-H4, -H5, -H8), 7.74 (s, 1 H, naph-H1), 7.47–7.39 (m, 3 H, naph-H3, -H6, -H7), 3.98 (d, *J* = 13.3 Hz, 1 H, $naphCH_2$-H_a), 3.89 (d, *J* = 13.3 Hz, 1 H, $naphCH_2$-H_b), 2.72 (mc, 1 H, MeC*H*), 2.31–2.26 (m, 2 H, CH_2CO), 1.85–1.58 (m, 3 H, NH, β-CH_2), 1.40 (s, 9 H, *t*-C_4H_9), 1.10 (d, *J* = 6.3 Hz, 3 H, CH_3).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 173.2 (C=O), 138.3 (naph-C2), 133.4, 132.6, 128.8, 127.7, 127.6, 126.7, 126.3, 125.9, 125.4 (naph), 80.1 (*C*Me_3), 51.8 (Me*C*H), 51.3 ($naphCH_2$), 32.1, 32.0 (β-CH_2, *C*H_2CO), 28.0 [3 C, C(*C*H_3)$_3$], 20.2 (CH_3).

ESI-MS: *m*/*z* (%) = 314.2 (48, $[M + H]^+$), 258.2 (100, $[M - C_4H_8 + H]^+$).

ESI-HRMS: *m*/*z* calcd for $[C_{20}H_{27}NO_2 + H]^+$: 314.2120; found: 314.2113.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.65; H, 8.58; N, 4.29.

tert-Butyl 4-[(2-Naphthylmethyl)amino]-5-phenylpentanoate (7g)

Following the general method, **6g** (269.1 mg, 0.652 mmol), $NaCNBH_3$ (123.0 mg, 1.96 mmol) and AcOH (224.1 μL, 3.91 mmol) in EtOH (2.3 mL) were used. The mixture was stirred overnight at r.t. Following work-up procedure A, **7g** (225.7 mg, 89%) was obtained as a yellow oil. No further purification was required; R_f = 0.08 (PE–EtOAc, 2:1).

IR (film): 2977 (m), 2931 (m), 1725 (s, C=O), 1661 (m), 1602 (m), 1455 (m), 1367 (m), 1150 (s), 819 (m), 748 (m), 701 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.73 (m 3 H, naph-H4, -H5, -H8), 7.60 (s, 1 H, naph-H1), 7.47–7.40 (m, 2 H, naph-H6, -H7), 7.34–7.14 (m, 6 H, naph-H3, C_6H_5), 3.93 (AB system, *J* = 13.6 Hz, 2 H, $naphCH_2$), 2.85 (mc, 1 H, BnC*H*), 2.75 (d, *J* = 6.4 Hz, 2 H, Ph*C*H_2), 2.36 (t, *J* = 7.6 Hz, 2H, CH_2CO), 1.85–1.70 (m, 3 H, β-CH_2, NH), 1.40 (s, 9 H, *t*-C_4H_9).

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ = 173.3 (C=O), 139.0 (C_6H_5-C1), 137.8 (naph-C2), 133.3, 132.6, 129.3 (2 C), 128.4 (2 C), 127.9, 127.8, 127.6, 126.5, 126.3 (2 C), 125.8, 125.4 (naph), 80.1 (*C*Me_3), 57.4 (*C*HBn), 50.9 ($naphCH_2$), 40.5 (Ph*C*H_2), 31.9 (CH_2), 29.0 (*C*H_2CO), 28.0 [3 C, C(*C*H_3)$_3$].

ESI-MS: *m*/*z* (%) = 421.0 (10), 390.3 (100, $[M + H]^+$), 345.0 (24), 334.2 (18, $[M - C_4H_8 + H]^+$), 263.0 (22).

ESI-HRMS: *m*/*z* calcd for $[C_{26}H_{31}NO_2 + H]^+$: 390.2433; found: 390.2432.

Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 80.18; H, 7.94; N, 3.55.

tert-Butyl 4-(Benzhydrylamino)-3-(4-chlorophenyl)butyrate (7h) and *tert*-Butyl 4-(Benzhydrylamino)-3-(4-chlorophenyl)-4-cyanobutyrate (9)

Following the general method, **6h** 100 mg, 0.218 mmol), $NaCNBH_3$ (41.2 mg, 0.655 mmol) and AcOH (75 μL, 1.31 mmol) in EtOH (1 mL) were used. The mixture was stirred for 4 d at r.t. Because the conversion (monitored by TLC) was incomplete, more $NaCNBH_3$ (30 mg, 0.478 mmol) was added. After stirring for 2 d, an additional portion of $NaCNBH_3$ (108.2 mg, 1.72 mmol) was added. Following work-up procedure A, a slightly yellow resin (60 mg) was obtained after additional 5 d. According to the ^{1}H NMR spectrum, a mixture of **7h** and **9** in a ratio of 1:4.5 was obtained. Product **9** contained two diastereomers in the ratio of 1.1:1; R_f = 0.15 (PE–EtOAc, 9:1); no separation of **7h** and **9** was achieved.

^{1}H NMR (300 MHz, $CDCl_3$): δ [**9** (a/b = 1.1:1)/**7h** (c) = 4.5:1] = 7.43–7.09 (m, 14 H), 5.03 (s, 1 H, Ph_2CH^a), 4.97 (s, 1 H, Ph_2CH^b), 3.62–3.43 (m, 2 H, CNCH, 4-$ClC_6H_4CH^{a+b}$), 3.31–3.23 (m, 1 H, 4-$ClC_6H_4CH^c$), 2.97–2.86 (m, 1 H) [contains: 2.94 (dd, *J* = 13.6, 6.9 Hz, 1 H, CH_2CO-$H_a{}^b$), 2.89 (dd, *J* = 13.1, 6.7 Hz, 1 H, CH_2CO-$H_a{}^a$)], 2.81–2.41 (m, 5 H, CH_2CO-$H_b{}^{a+b}$, $NCH_2{}^c$, CH_2CO^c), 1.71 (t, *J* = 13.0 Hz, 1 H, NH^{a+b+c}), 1.27 (s, 9 H, *t*-$C_4H_9{}^c$), 1.26 (s, 9 H, *t*-$C_4H_9{}^b$), 1.25 (s, 9 H, *t*-$C_4H_9{}^a$).

The assignment of some signals to the diastereomers a and b, respectively, was complicated because of the similar signal intensities in a mixture of isomers with a dr of 1.1:1. The superscript c denotes signals of the doubly reduced product **7h**.

^{13}C NMR, DEPT (75.5 MHz, $CDCl_3$): δ (**9**: a/b = 1.1:1; **7h**: c) = 170.1 (C=O), 169.9 (C=O), 142.8, 142.8, 140.9, 136.4, 136.1, 134.0, 133.9, 129.9, 129.7, 129.1, 129.0, 129.0, 128.9, 128.9, 128.8, 128.6, 128.5, 127.9, 127.7, 127.4, 127.2, 126.9, 126.8, 118.9 ($CN^{a/b}$), 118.4 ($CN^{a/b}$), 81.3 (*C*Me_3), 81.3 (*C*Me_3), 80.7 (*C*$Me_3{}^c$), 67.2 (Ph_2CH^c), 65.4 (Ph_2CH), 65.3 (Ph_2CH), 53.4 (CN*C*H^b), 53.2 (CN*C*H^c), 52.1 (CN*C*H^a), 44.2 (4-$ClC_6H_4CH^b$), 43.9 (4-$ClC_6H_4CH^a$), 42.0 (4-$ClC_6H_4CH^c$), 40.4 (*C*H_2CO^c), 38.7 (*C*H_2CO^a), 37.2 (*C*H_2CO^b), 27.9 [3 C, C(*C*H_3)$_3{}^c$], 27.854 [3 C, C(*C*H_3)$_3{}^{a+b}$].

X-ray Crystallography of *anti*-4[36]

The crystal was measured on a Turbo-CAD4 diffractometer with Cu-K_α radiation (graphite monochromator) at 193 K. Crystal structure solution and refinement were performed using the SIR-92 and SHELXL-97 program, respectively. $C_{25}H_{28}ClNO_2$, M = 409.94 g·mol^{-1}, monoclinic, space group $P2_1/n$, Z = 4, *a* = 5.6612(8) Å, *b* = 20.354(2) Å, *c* = 19.17(2) Å, β = 93.54(6)°, *R*1 = 0.0798, *wR*2 = 0.2245.

Acknowledgment

The help of Dr. D. Schollmeyer (X-ray crystallography) and H. Kolshorn (NMR spectroscopy) is gratefully acknowledged. We thank the Deutsche Forschungsgemeinschaft, the University of Mainz and the Fonds der Chemischen Industrie for financial support.

References

(1) *Analgesics*; Buschmann, H.; Christoph, T.; Friderichs, E.; Maul, C.; Sundermann, B., Eds.; Wiley-VCH: Weinheim, **2002**.
(2) Trabocchi, A.; Guarna, F.; Guarna, A. *Curr. Org. Chem.* **2005**, *9*, 1127.
(3) Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149.
(4) Satzinger, G. *Arzneim.-Forsch.* **1994**, *44*, 261.
(5) Silverman, R. B.; Andruszkiewicz, R.; Nanavati, S. M.; Taylor, C. P.; Vartanian, M. G. *J. Med. Chem.* **1991**, *34*, 2295.
(6) Baldauf, C.; Guenther, R.; Hofmann, H.-J. *Helv. Chim. Acta* **2003**, *86*, 2573.
(7) Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573.
(8) Seebach, D.; Schaeffer, L.; Brenner, M.; Hoyer, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 776; *Angew. Chem.* **2003**, *115*, 800.
(9) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983.
(10) Andruszkiewicz, R.; Silverman, R. B. *Synthesis* **1989**, 953.
(11) Brenner, M.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 2365.
(12) Masson, G.; Cividino, P.; Py, S.; Vallee, Y. *Angew. Chem. Int. Ed.* **2003**, *42*, 2265; *Angew. Chem.* **2003**, *115*, 2367.
(13) Masson, G.; Zeghida, W.; Cividino, P.; Py, S.; Vallee, Y. *Synlett* **2003**, 1527.
(14) Kison, C.; Meyer, N.; Opatz, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 5662; *Angew. Chem.* **2005**, *117*, 5807.
(15) von Miller, W.; Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2718.
(16) Bodforss, S. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 1111.
(17) Treibs, A.; Derra, R. *Liebigs Ann. Chem.* **1954**, *589*, 176.
(18) Meyer, N.; Opatz, T. *Synlett* **2003**, 1427.
(19) Meyer, N.; Werner, F.; Opatz, T. *Synthesis* **2005**, 945.
(20) (a) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207; and references cited therein. For an asymmetric variant of the 1,4-addition, see: (b) Enders, D.; Gerdes, P.; Kipphardt, H. *Angew. Chem. Int. Ed.* **1990**, *29*, 179; *Angew. Chem.* **1990**, *102*, 226.
(21) Mattalia, J.-M.; Marchi-Delapierre, C.; Hazimeh, H.; Chanon, M. *ARKIVOC* **2006**, *(iv)*, 90.
(22) Opatz, T.; Ferenc, D. *Org. Lett.* **2006**, *8*, 4473.
(23) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3347.
(24) Tsuge, O.; Kanemasa, S.; Yorozu, K.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3359.
(25) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523.
(26) Roux-Schmitt, M. C.; Croisat, D.; Seyden-Penne, J.; Wartski, L.; Cossentini, M. *Pol. J. Chem.* **1996**, *70*, 325.
(27) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3.
(28) Zymalkowski, F. *Katalytische Hydrierungen im Organisch-Chemischen Laboratorium (Sammlung Chemischer und Chemisch-Technischer Beiträge, Neue Folge Nr. 61)*; Enke: Stuttgart, **1965**.
(29) A NOESY-spectrum of *trans*-**8d** was recorded and the distance between H4 and H5 was calculated from the cross-peak volume integrals using the diastereotopic NCH_2 protons as a reference. The obtained value (3.3 Å) was in good accordance with a 3D model of the *trans*-isomer (3.1 Å) but not with the *cis*-isomer (2.4 Å). Moreover, a transient NOE experiment on *trans*-**8d** revealed a close contact between H4 and one of the benzylic protons of the substituent in 5-position. The γ-lactam obtained by cyclization of **7d** was not identical with *trans*-**8d**.
(30) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.
(31) Meyer, N.; Opatz, T. *Synlett* **2004**, 787.
(32) Paventi, M.; Edward, J. T. *Can. J. Chem.* **1987**, *65*, 282.
(33) Lagriffoul, P.-H.; Tadros, Z.; Taillades, J.; Commeyras, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1279.
(34) Liu, J.; Zhao, Y.; Zhou, Y.; Li, L.; Zhang, H.; Zhang, T. Y. *Org. Biomol. Chem.* **2003**, *1*, 3227.
(35) Ahmad, S.; Doweyko, L. M.; Dugar, S.; Grazier, N.; Ngu, K.; Wu, S. C.; Yost, K. J.; Chen, B.-C.; Gougoutas, J. Z.; DiMarco, J. D.; Lan, S.-J.; Gavin, B. J.; Chen, A. Y.; Dorso, C. R.; Serafino, R.; Kirby, M.; Atwal, K. S. *J. Med. Chem.* **2001**, *44*, 3302.
(36) CCDC 621580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.