Asymmetric Strecker Synthesis of the Four α-Quaternary 1-Amino-2-methylcyclohexanecarboxylic Acids☆

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The synthesis of the four 1-amino-2-methylcyclohexanecarboxylic acids **13**, **14**, **15**, and **16** from diastereomeric mixtures of the α-amino nitriles **1**–**4** by successive application of conc. H_2SO_4, Pd/C H_2, and conc. HCl is described. The amino nitriles **1**–**4** were prepared by asymmetric Strecker synthesis under various reaction conditions. The formation of **1**–**4** is thermodynamically controlled in protic solvents (e.g. MeOH), whereas the reaction is under kinetic control in non-protic solvents (e.g. hexane). The separation of the α-amino amides **5**–**8**, which were obtained by partial hydrolysis of **1**–**4**, was achieved by CC, LPLC, and HPLC. The absolute configuration of all synthesized compounds was determined by means of only two X-ray analyses with consecutive correlations. The steric control of the asymmetric Strecker synthesis is discussed.

The asymmetric Strecker synthesis that was described first by Harada[1] for the preparation of L-alanine, starting with acetaldehyde, *S*-α-methylbenzylamine (**S-α-MBA**) and NaCN, is a convenient method for the synthesis of proteinogenous and non-proteinogenous[2] α-amino acids. Numerous modifications of Harada's experimental protocol are described[3]. Various aliphatic aldehydes[4], acyclic ketones[5], and in one case a ketal[6] were applied as carbonyl compounds. The use of the most widely applied chiral auxiliary, α-MBA, as well as further arylalkylamines like α-*t*-butylbenzylamine, α-ethylbenzylamine, α-naphthylbenzylamine, α-phenylglycinol[7] and *N*-benzylphenylglycinol[8] resulted in d.e. values up to 13:1[8] for the respective α-amino nitriles. However the synthesis of α-arylglycines from aromatic aldehydes or ketones and arylalkylamines as chiral auxiliaries is impossible. They can be obtained in good optical yields by using either (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane[9] or 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine[10] as chiral auxiliaries. The use of the aminodioxane derivative introduced for asymmetric Strecker synthesis by Weinges et al. is limited to ketones, whereas the amino sugar, first described by Kunz et al., can also be converted to the corresponding α-amino acids by starting from aromatic and aliphatic aldehydes. Besides NaCN, trimethylsilyl cyanide[11] (TMSCN), diethyl phosphorocyanidate[12], and a cyanide-modified hemin copolymer[13] are suitable cyanide sources for asymmetric Strecker syntheses. In the first step of asymmetric Strecker synthesis the crucial α-amino nitriles with already-fixed configuration at the new chiral center are formed. Due to the reversible addition of hydrogen cyanide to imines, postulated as precursors[14], these α-amino nitrile intermediates show high configurational instability in solution. Therefore epimeric α-amino nitrile mixtures formed under kinetic control undergo thermodynamic equilibration unless a crystallization allows the isolation of pure diastereomers.

All previous works concerning asymmetric Strecker and α-aminonitrile syntheses started with prochiral carbonyl compounds, most of them with aldehydes and only a few with acyclic ketones, and gave two diastereomeric α-amino nitriles in the first reaction step. We now describe for the first time the preparation of cyclic α-quaternary α-amino acids with vicinal chiral centers stemming from cyclic ketones. The sterical hindrance and the conformational rigidity of these compounds make them interesting building blocks for the synthesis of peptidomimetics as enzyme inhibitors with an increased resistance to hydrolysis. For that purpose we exemplarily studied the reaction of rac-2-methylcyclohexanone [(*RS*)-2-MC] with *S*-α-MBA and TMSCN leading to the corresponding α-amino nitriles. In order to achieve a high diastereoselectivity in the synthesis of the crucial α-amino nitrile intermediates we carried out a systematic investigation of the first reaction steps described in this paper.

Results

The α-Amino Nitriles **1**–**4**: The asymmetric Strecker syntheses with (*RS*)-2-MC and *S*-α-MBA via the four different reaction pathways **A** = "one-pot synthesis" with NaCN, **B** = "one-pot synthesis" with TMSCN, **C** = "two-step synthesis" with NaCN, and **D** = "two-step synthesis" with TMSCN gave the 2-methyl-1(α-methylbenzylamino)-

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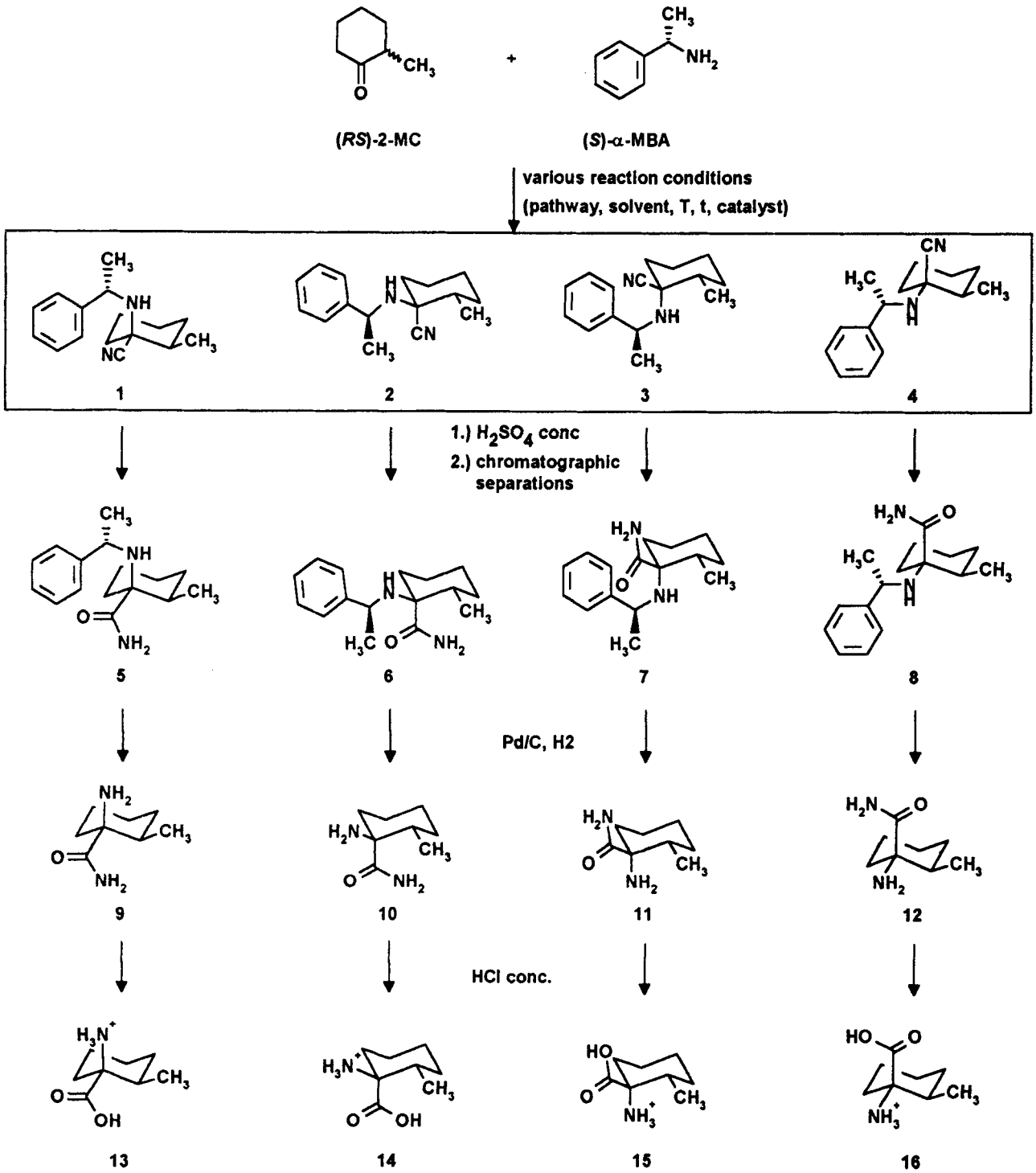
Scheme 1. Synthesis of the α-amino acids **13**–**16**



cyclohexanecarbonitriles **1**–**4** as oily mixtures of the four possible diastereomers (Scheme 1) in good total yields.

The "two-step syntheses" **C** and **D** include the condensation of (*RS*)-2-MC with *S*-α-MBA affording the ketimine mixture **17**–**20** in the first step, to which NaCN or TMSCN was added in the second step. Since the chromatographic separation of **1**–**4** into pure stereomers failed, the quantitative analysis of the diastereomeric mixtures had to be carried out in situ by ^{13}C-NMR spectroscopy. The ^{13}C-NMR spectra show fourfold signal sets. The stereochemical composition of the mixtures of **1**–**4** was derived from the suitable integrals of the four α-methine carbon signals with the chemical shifts δ = 54.7 for the α*S*,1*S*,2*R*, δ = 54.4 for the α*S*,1*S*,2*S*, δ = 53.9 for the α*S*,1*R*,2*S* and δ = 53.5 for the α*S*,1*R*,2*R* diastereomer, and does not depend on the chosen reaction pathway. The α-amino nitrile mixtures obtained

Table 1. Stereochemical composition of the diastereomeric mixtures of **1**–**4** obtained under various reaction conditions[a]

reaction conditions (pathway, solvent, *T*, *t*)	**1**	**2**	**3**	**4**	total yield	diastereomeric mixture
A, MeOH, Δ	16%	59%	5%	20%	75%	
B, MeOH, Δ	18%	56%	6%	20%	97%	
C, MeOH, 0 °C, 3 h	22%	48%	6%	24%	65%	
D, MeOH[a]	19%	54%	5%	22%	98%	**M-1**
D, R-OH[a]	15–21%	52–62%	4–6%	18–23%	quant.	
D, dioxane[a]	19%	56%	7%	18%	67%	
D, $CHCl_3$[a]	23%	54%	7%	16%	50%	
D, TBME[a]	28%	49%	6%	17%	60%	
D, THF[a]	30%	50%	7%	13%	75%	
D, Et_2O[a]	36%	43%	11%	10%	45%	
D, hexane[a]	48%	31%	15%	6%	70%	**M-2**
D, hexane, 0 °C, 3 h	57%	20%	19%	4%	30%	**M-2'**
D, MeOH, –78 °C, 3 h	18%	54%	5%	23%	quant.	
D, hexane, –78 °C, 3 h	60%	20%	17%	3%	30%	
D, hexane, –78 °C, 48 h	45%	36%	14%	5%	95%	**M-3**

[a] Standard conditions: 5 mol-% $ZnCl_2$, 0 °C, 3 h, room temperature 24 h. – R: Et, Pr, *i*Pr, Bu, *s*Bu, *t*Bu, nC_5H_{11}, nC_6H_{13}, nC_7H_{15}, nC_8H_{17}.

according to the pathways **A**, **B**, **C** and **D** consist of 48% to 59% of the *trans*-configured (α*S*,1*S*,2*S*)-2-methyl-1-(α-methylbenzylamino)cyclohexanecarbonitrile (**2**) as the major compound (Table 1).

The following variations of the reaction conditions (solvent, temperature, catalysts) were carried out by the "two step synthesis" **D**, which is the most convenient protocol for the α-amino nitrile synthesis. Under standard reaction conditions (3 h, 0 °C; 24 h, room temp.; 5 mol-% $ZnCl_2$) the following solvent effects were observed (Table 1): The use of polar protic solvents (R-OH) resulted in the formation of nearly identically composed mixtures of **1**–**4** in quantitative yields. The same compositions of diastereomers were obtained if the reaction in MeOH was stopped after 3 h, and if the sample is heated for 3 h in a sealed bottle. The thermodynamic equilibrium mixture of **1**–**4** (**M-1**) consists of 19% of the *cis*-configured (α*S*,1*S*,2*R*)-, 54% of the *trans*-configured (α*S*,1*S*,2*S*)-, 5% of the *cis*-configured (α*S*,1*R*,2*S*)-, and 22% of the *trans*-configured (α*S*,1*R*,2*R*)-2-methyl-1-(α-methylbenzylamino)cyclohexanecarbonitrile. Diastereomeric mixtures that are not in accordance with the thermodynamic equilibrium mixture **M-1** were obtained by using nonprotic solvents, under otherwise unchanged reaction conditions. The resulting differences from **M-1** increase in the solvent series dioxane/$CHCl_3$/TBME/THF/Et_2O/hexane since the solvent polarity is the major factor that influences the rate of the thermodynamic equilibration (Table 1). When the reaction in hexane is stopped after 3 h the diastereomeric mixture **M-2'** results, which shows the biggest differences from **M-1** observed so far, but this was obtained in only 30% total yield (Table 1). With increasing reaction time the total yield rises in hexane, in parallel with the thermodynamic equilibration proceeding. Little by little the diastereomeric mixtures, formed under kinetic control, convert to the thermodynamic equilibrium mixture **M-1**, if they stay in solution at room temperature (Table 2).

Table 2. Diastereomeric mixture **M-2** after 0, 48 and 72 h in $CDCl_3$[a]

t	**1**	**2**	**3**	**4**
0 h	48%	31%	15%	6%
48 h	31%	47%	8%	14%
72 h	22%	50%	7%	21%

[a] *T* = 20 °C.

Lowering of the reaction temperature from 0 °C to –78 °C resulted neither in MeOH nor in hexane in remarkable changes of the solvent-specific compositions **M-1** and **M-2'**, respectively. After 48 h at –78 °C the yield of α-amino nitriles had risen to 95% in hexane. Simultaneously the equilibration proceeds and results in the formation of the diastereomeric composition **M-3** (Table 1).

Reactions carried out below –150 °C in a suitable isopentane/isohexane (4:1) mixture also gave diastereomeric mixtures of **1**–**4**[15]. An increase of the percentage of $ZnCl_2$ from 5 mol-% to 100 mol-% resulted in a decreased total yield of 30%, whereas the composition of the diastereomeric mixture **1**–**4** remained unchanged[15]. The synthesis of **1**–**4** in the presence of quaternary ammonium salts as phase-transfer catalysts required temperatures of 45 °C. Consequently, the formation of the α-amino nitrile mixtures **1**–**4** was under thermodynamic control[15]. By addition of α-cyclodextrine (α-CD) to the reaction mixtures, an α-aminonitrile mixture with obviously increased percentages of the two *cis* diastereomers **1** (α*S*,1*S*,2*R*) and **3** (α*S*,1*R*,2*S*) was obtained[15].

The α-Amino Acids **13**–**16**: Since the chromatographic separation of **1**–**4** into diastereomerically pure compounds

failed, hydrolysis to the corresponding α-amino amides **5**–**8** as a consecutive reaction step had to be carried out with α-amino nitrile mixtures. The conversion of the mixtures of **1**–**4** to the secondary α-amino carboxyamide mixtures **5**–**8** was achieved exclusively by means of concentrated sulfuric acid. The enzymatic degradation of the α-amino nitriles **1**–**4**[16] as well as other hydrolytic reaction conditions[17] (conc. HCl; HCO_2H/HCl; dry HCl gas/EtOH; H_2SO_4 conc./Δ) failed, probably because of the extremely sterically hindered attack at the cyano group of the 2-methyl-1-(α-methylbenzylamino)cyclohexanecarbonitriles. As expected, the products of the hydrolysis consist of the four possible α-amino amides **5**–**8** as diastereomeric mixtures, discernible by fourfold signal sets in the respective ^{1}H- and ^{13}C-NMR spectra. The stereochemical composition of these mixtures was determined by integration of the four α-methine carbon signals with the chemical shifts δ = 53.0 for the αS,1S,2R-(**5**), δ = 53.6 for the αS,1S,2S-(**6**), δ = 52.0 for the αS,1R,2S-(**7**), and δ = 52.3 for the αS,1R,2R diastereomer (**8**), respectively. The stereochemical composition of the diastereomeric mixtures of **5**–**8** depends on the composition of the α-amino nitrile mixture used for hydrolysis, as well as on the reaction conditions chosen (Table 3).

Table 3. Stereochemical composition of the α-amino nitrile mixtures **1**–**4** and their hydrolysis products **5**–**8** in the entries **I**–**III** (values in %)

compound \ entry	I	II	III	I	II	III	I	II	III	I	II	III
1	19	40	49									
2				53	40	30						
3							7	13	19			
4										21	7	2
5	15	11	33									
6				61	74	50						
7							6	3	12			
8										18	12	5
Δ	–4	–29	–16	+8	+34	+20	–1	–10	–7	–3	+5	+3

The corresponding α-amino nitrile mixtures **1**–**4** were dissolved *directly* in conc. H_2SO_4 at −10°C (entries **I** and **II**). The resulting solution was stirred for 3 h at −10°C, for 3 h at 0°C and for a further 4–6 d at room temperature. In entry **III** the sulfuric acid was added at −10°C to a *solution* of an α-amino nitrile mixture in hexane, which was then stirred for 3 h at −10°C, for 3 h at 0°C and for a further 4 d at room temperature. The total chemical yield of **5**–**8** varied from 61 to 78%. These results prove, that in all cases (entries **I**–**III**) a solvent-specific (partial) thermodynamic equilibration of the α-amino nitrile mixtures **1**–**4** used for hydrolysis occurs. This equilibration precedes the conversion into the corresponding α-amino amides. The equilibration rate of the diastereomeric mixtures **1**–**4**, formed under kinetic control (entries **II** and **III**), was retarded by dissolving these α-amino nitriles in hexane (entry **III**).

The diastereomerically pure α-amino amides **5**, **6**, **7**, and **8** were obtained by the following stepwise chromatographic procedures:

(**1.**) CC of the α-amino amide mixtures of **5**–**8** yielded two (entry **II**) or three (entries **I** and **III**) combined fractions: the first (**F-1**) contained the *cis*-configured (αS,1R,2S)- and the *trans*-configured (αS,1R,2R)-2-methyl-1-(α-methylbenzylamino)cyclohexanecarboxamides **7** and **8**, the second (**F-2**) all the four α-amino amides **5**–**8**, whereas the third (**F-3**) consisted of the *cis*-configured (αS,1S,2R)- and the *trans*-configured (αS,1S,2S)-2-methyl-1-(α-methylbenzylamino)cyclohexanecarboxamides **5** and **6**. The α-amino amides **5**–**8** were eluted in the following order of increasing retention times: *trans*-αS,1R,2R-(**8**) → *cis*-αS,1R,2S-(**7**) → *cis*-αS,1S,2R-(**5**) → *trans*-αS,1S,2S-(**6**).

(**2.**) The mixtures **7/8** (**F-1**) and **5/6** (**F-3**) were separated into diastereomerically pure compounds by preparative HPLC under the conditions given in Table 4.

Table 4. Preparative HPLC conditions for the separation of the **5/6** and **7/8** mixtures

diastereomeric mixture	**5/6**	**7/8**
stationary phase:	LiChroSorb® RP-18 (5 μm) 250-20	LiChroSorb® Si 60 (5 μm) 250-10
mobile phase:	MeOH/H_2O (70:30)	CH_2Cl_2/EtOAc (95:5)
flow rate:	15.0 ml/min	6.0 ml/min
detection:	UV: λ= 254 nm	UV: λ= 254 nm
retention interval:	**6**: 19.5–23 min **5**: 22–25 min	**8**: 30–40 min **7**: 40–50 min

The diastereomerically pure amides **5** and **6** can alternatively be obtained by LPLC applying LiChroSorb RP-18 material as the stationary phase and MeOH/H_2O (70:30) as the mobile phase. However, separation of **5** and **6** failed under these conditions.

(**3.**) The diastereomeric purity of the separated α-amino amides **5**, **6**, **7**, and **8** as well as the stereochemical composition of **F-1** and **F-3** was determined by analytical HPLC, under the conditions given in Table 5.

Table 5. Analytical HPLC conditions for the separation of the **5/6** and **7/8** mixtures

diastereomeric mixture	**5/6**	**7/8**
stationary phase:	LiChroSorb® RP-18 (5 μm) 250-4	LiChroSorb® Si 60 (5 μm) 250-4
mobile phase:	MeOH/H_2O (70:30)	CH_2Cl_2/dioxane (95:5)
flow rate:	0.6 ml/min	0.7 ml/min
detection:	UV: λ= 254 nm	UV: λ= 254 nm
retention interval:	**6**: 16.6 min **5**: 18.8 min	**8**: 7.0 min **7**: 9.5 min

Hydrogenolysis of the pure secondary α-amino amides **5**, **6**, **7**, and **8** gave the corresponding 1-amino-2-methylcyclohexanecarboxamides **9**, **10**, **11**, and **12**, respectively, in up to 99% yield, which form the two enantiomeric pairs **9/11** and **10/12**, respectively. That means that all possible stereomeric α-amino amides **9**, **10**, **11**, and **12** and α-amino acids **13**, **14**, **15**, and **16** can be obtained as described in Scheme 1. The experiment with *R*-α-MBA as chiral auxiliary was

only necessary for the synthesis of the enantiomeric set of secondary α-amino amides *ent*-**5**, *ent*-**6**, *ent*-**7**, and *ent*-**8**.

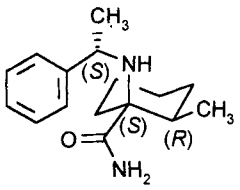
In the final reaction step the primary α-amino amides **9**, **10**, **11**, and **12** were hydrolyzed at reflux for several hours in concentrated hydrochloric acid to afford the α-amino acid hydrochlorides **13**, **14**, **15** and **16**, respectively, also in up to 99% yield. They were purified by ion-exchange chromatography to furnish the zwitterionic forms which were finally converted into the corresponding hydrochlorides.

Analysis of The Absolute Configuration of All Synthesized Compounds

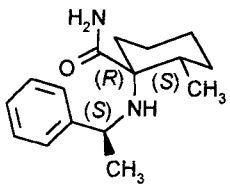
Within each of the reaction sequences **1** ⇒ **5** ⇒ **9** ⇒ **13**, **2** ⇒ **6** ⇒ **10** ⇒ **14**, **3** ⇒ **7** ⇒ **11** ⇒ **15** and **4** ⇒ **8** ⇒ **12** ⇒ **16**, respectively (Scheme 1), the four outlined compounds possess the same absolute configuration. The α-amino nitriles **1**–**4** were always obtained as oily diastereomeric mixtures which could not be separated into diastereomerically pure compounds, whereas chromatography of the α-amino amides **5**–**8** gave the pure crystalline compounds **5**, **6**, **7**, and **8**, respectively, so that their absolute configuration could be elucidated according to steps **1.**–**5.** as follows:

(**1.**) By X-ray analysis (three-beam method[18]) **5** was determined unambiguously as the *cis*-(α*S*,1*S*,2*R*)-2-methyl-1-(α-methylbenzylamino)cyclohexanecarboxamide[19] (Scheme 2).

Scheme 2. The *cis*-configured secondary α-amino amides **5** and **7**



cis-(α*S*,1*S*,2*R*)-2-Methyl-1(α-methylbenzylamino)-cyclohexanecarboxamide (**5**)

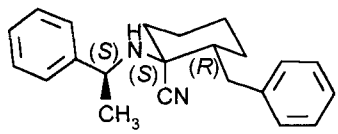


cis-(α*S*,1*R*,2*S*)-2-Methyl-1(α-methylbenzylamino)-cyclohexanecarboxamide (**7**)

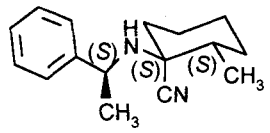
(**2.**) The secondary α-amino amide (α*S*,1*S*,2*R*)-**5** was hydrogenolyzed to the primary α-amino amide (1*S*,2*R*)-**9**, the hydrolysis of which gave the α-amino acid (1*S*,2*R*)-**13**. Since the two primary α-amino amides (1*S*,2*R*)-**9** and **11** form an enantiomeric pair, identical in their NMR data and discernible by the sign of their optical rotation values, the configuration of **11** is conclusively 1*R*,2*S*, which is also the case with α-amino acid (1*R*,2*S*)-**15** as its hydrolysis product. Consequently, the chemical precursor of **11**, the secondary α-amino amide **7** possesses the *cis*-α*S*,1*R*,2*S* configuration (Scheme 2).

(**3.**) The absolute configuration of the *trans*-configured secondary α-amino amides **6** and **8** could be deduced from the X-ray analytical data of a 2-benzyl-substituted α-amino nitrile crystal[20] as *trans*-(α*S*,1*S*,2*R*)-2-benzyl-1-(α-methylbenzylamino)cyclohexanecarbonitrile (**A**) (Scheme 3). Since **A** is the major product in a thermodynamic equilibrium mixture of the four possible 2-benzyl-substituted secondary α-amino nitriles[15], we concluded that the major product **2** of the 2-methyl-substituted α-amino nitriles **1**–**4** possesses the same configuration as **A**. This assumption was additionally supported by the similar ^{13}C-NMR shifts of **A** and **2** (Table 6). Therefore, according to the C.I.P. rules, the absolute configuration of α-amino nitrile **2** is α*S*,1*S*,2*S* (Scheme 3).

Scheme 3. The *trans*-configured secondary α-amino nitriles **2** and **A**



trans-(α*S*,1*S*,2*R*)-2-Benzyl-1(α-methylbenzylamino)-cyclohexanecarbonitrile (**A**)



trans-(α*S*,1*S*,2*S*)-2-Methyl-1(α-methylbenzylamino)-cyclohexanecarbonitrile (**2**)

(**4.**) The hydrolysis of (α*S*,1*S*,2*S*)-**2**, as the major compound in a thermodynamically controlled mixture of **1**–**4** gave **6** as the respective major product in a mixture of the secondary α-amino amides **5**–**8**, which therefore also exhibits the configuration α*S*,1*S*,2*S*. The secondary α-amino amide (α*S*,1*S*,2*S*)-**6** was hydrogenolyzed to the primary α-amino amide (1*S*,2*S*)-**10** the hydrolysis of which afforded the α-amino acid (1*S*,2*S*)-**14**.

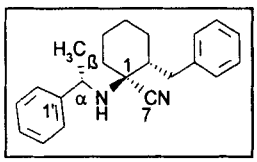
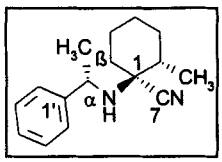
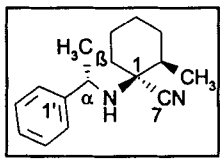
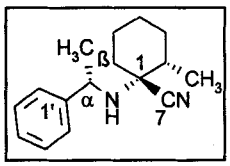
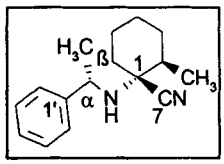
(**5.**) Consequently, the primary α-amino amide **12**, as the enantiomer of (1*S*,2*S*)-**10**, must be 1*R*,2*R*-configured, which also applies to its precursor **8** with the α*S*,1*R*,2*R* configuration and the α-amino acid (1*R*,2*R*)-**16** as its hydrolysis product.

A correlation between each of the α-amino nitrile precursors **1**, **2**, **3**, and **4** and one of the α-amino amides **5**, **6**, **7**, and **8** with known configuration was then established by a comparison of the composition of the diastereomeric mixtures in the entries **II** and **III** (Table 3) of the respective compounds via steps **6.**–**9.**:

(**6.**) **2** as the (α*S*,1*S*,2*S*)-configured α-amino nitrile is the precursor of the α*S*,1*S*,2*S*-configured α-amino amide **6** (see **3.** and **4.**).

(**7.**) Under kinetic control **1** is the major product with contents of 40% (entry **II**) and 49% (entry **III**) in the mixtures of **1**–**4**. Under thermodynamic control the content of **1** is only 19% (entry **I**). Thus when we start hydrolysis with kinetically controlled mixtures of **1**–**4** an epimerization at C-1 and/or C-2 of **1** occurs to yield either (α*S*,1*S*,2*R*)-**5**, (α*S*,1*R*,2*S*)-**7**, or (α*S*,1*R*,2*R*)-**8** with hypothetical epimerization rates of 29%, 37% or 28%, respectively, for entry **II**. The α-amino amide (α*S*,1*S*,2*S*)-**6** was excluded because it was determined previously as the reaction product of (α*S*,1*S*,2*S*)-**2**. Since the thermodynamic equilibration was retarded by dissolution of **1**–**4** in hexane (entry **III**) a minor epimerization of **1** occurred. Consequently, the (α*S*,1*S*,2*R*)-configured α-amino amide **5** with an epimerization rate of only 16% for entry **III** was derived as the hydrolysis product of **1**. The α-amino amides **7** and **8** could be excluded on the grounds of very high hypothetical epimerization rates, of

Table 6. Selected ^{13}C-NMR shift values for the α-amino nitriles **A**, **2**, **1**, **3** and **4**

	 (αS,1S,2R)-A	 (αS,1S,2S)-2	 (αS,1S,2R)-1	 (αS,1R,2S)-3	 (αS,1R,2R)-4
1	62.9	63.3	60.1	59.1	61.5
7	120.9	120.8	123.0	122.7	120.4
1'	147.5	147.5	146.8	145.4	145.5
a	54.4	54.4	54.7	53.9	53.5
ß	26.5	26.5	26.2	25.4	25.8

37% and 44% respectively, with respect to the configuration of **1**.

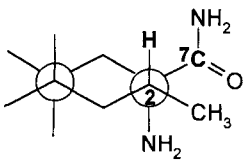
(**8.**) Under kinetic control **4** is the minor product with contents of 7% (entry **II**) and 2% (entry **III**) in the mixtures of **1**–**4**. Under thermodynamic control the amount of **4** *increases* to 21% (entry **I**). Since **5** and **6** were already correlated with **1** and **2**, respectively, only the (αS,1R,2R)-configured α-amino amide **8** with *positive* Δ values (+5% for entry **II**; +3% for entry **III**) can be the hydrolysis product of **4** with the identical αS,1R,2R configuration.

(**9.**) Under thermodynamic control **3** is the minor product with a content of 7% in a mixture of **1**–**4** (entry **I**). Under kinetic control the amounts of **3** increase to 13% (entry **II**) and 19% (entry **III**). Consequently, the α-amino amide (αS,1R,2S)-**7** with negative Δ values (−10% for entry **II**; −7% for entry **III**) was identified as the reaction poduct of **3** with αS,1R,2S configuration.

The assignments of the absolute configuration, derived from two X-ray structures, were confirmed by the relative configuration of the primary amino amides **9** and **10** via their C-H-coupled ^{13}C-NMR spectra. Since the C-1 of all synthesized compounds is a quaternary carbon atom, the relative configuration of these cyclohexane derivatives could not be derived as usual from ^{3}JH-^{1}H coupling constants, the size of which depend on the dihedral angle of vicinal protons. The respective heteronuclear ^{13}C-^{1}H coupling constants are decreased by a factor of ≈ 0.6[21]. Since both diastereomers, **9** and **10**, prefer conformations with two equatorial substituents and one axial substituent, **10** forms a dihedral angle of 180° between the carbonyl atom C-7 and the proton 2-H, whereas **9** displays one of only 60° (Scheme 4).

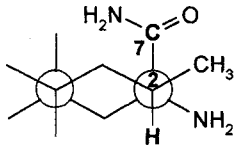
The corresponding C-H-coupled ^{13}C-NMR spectra unfortunately show unresolved signals for the crucial carboxamide carbon atoms which are due to additional couplings of C-7 with 6-H_{ax} and 6-H_{eq}, respectively. However, the half-band widths of 14.0 Hz for **10** and 6.5 Hz for **9**, which may be regarded as equivalent indicators, prove the *trans* configuration of **10** and the *cis* configuration of **9** and thus confirm the absolute configuration of the synthesized secondary (**5**–**8**), and primary (**9**–**12**) α-amino amides, of the α-amino acids (**13**–**16**), and finally the α-amino nitriles (**1**–**4**).

Scheme 4. Dihedral angles between C-7 and 2-H for the primary α-amino amides **9** and **10**



9

cis-(1S,2R)-1-Amino-2-methylcyclohexanecarboxamide



10

trans-(1S,2S)-1-Amino-2-methylcyclohexanecarboxamide

Calculation of Optical Rotation Increments for the Secondary α-Amino Amides **5**–**8** *and* **ent-5**–**ent-8**

From the $[\alpha]_D^{25}$ values (Table 7) of the secondary α-amino amides **5**–**8** and **ent-5**–**ent-8**, respectively, the optical rotation increments *X*, *Y* and *Z* for C-α, C-1 and C-2, respectively, as well as a conformational correction factor *C* were calculated from a fourfold set of equations with four variables.

a) $-X + Y + Z + C = -3.7$ b) $-X + Y - Z - C = -25.2$
c) $-X - Y - Z + C = -92.2$ d) $-X - Y + Z - C = -80.6$

and led to the increment values: $X = 50.4$, $Y = 35.9$, $Z = 8.3$ and $C = 2.5$.

Table 7. $[\alpha]_D^{25}$ values for the α-amino amides **5**–**8** and **ent-5**–**ent-8**

α-amino amide	absolute configuration	$[\alpha]_D^{25}$
5	αS,1S,2R	–3.7
6	αS,1S,2S	–25.2
7	αS,1R,2S	–92.2
8	αS,1R,2R	–80.6
ent-5	αR,1R,2S	+4.0
ent-6	αR,1R,2R	+25.2
ent-7	αR,1S,2R	+92.3
ent-8	αR,1S,2S	+77.1

Table 8. $\Delta[\alpha]_D^{25}$ values for the secondary α-amino amides **5**–**8** and **ent-5**–**ent-8**

compounds	constant configuration at two centers	switched configuration at the third center	$\Delta[\alpha]_D^{25}$
ent-5 / 7	1*R*,2*S*	α*R* → α*S*	–96.2
ent-6 / 8	1*R*,2*R*	α*R* → α*S*	–105.2
8 / 5	α*S*,2*R*	1*R* → 1*S*	+76.9
7 / 6	α*S*,2*S*	1*R* → 1*S*	+67.0
8 / 7	α*S*,1*R*	2*R* → 2*S*	–11.6
5 / 6	α*S*,1*S*	2*R* → 2*S*	–21.5

The signs of *X*, *Y*, and *Z* were ascertained by calculation of $\Delta[\alpha]_D^{25}$ values from two selected secondary α-amino amides each with a constant configuration pattern at two of the three chiral centers and a configurational change from *R* to *S* at the third chiral center. As shown in Table 8 a change e.g. from α*R* to α*S* configuration causes a strong decrease of the $\Delta[\alpha]_D^{25}$, of between −96.2 and −105.2. Thus, the sign for the C-α increment *X* must be (−) for the α*S*-configured α-amino amides **5**–**8** and (+) for the α*R*-configured compounds **ent-5**–**ent-8**. The signs of the C-1 increment *Y* [(+) for the 1*S*-configured α-amino nitriles **5**, **6**, **ent-7**, and **ent-8**; (−) for the 1*R*-configured compounds **ent-5**, **ent-6**, **7** and **8**], as well as that of the C-2 increment *Z* [(−) for the 2*S*-configured α-amino amides **ent-5**, **6**, **7**, and **ent-8**; (+) for the 2*R*-configured compounds **5**, **ent-6**, **ent-7** and **8**], were derived in the same manner. Within the series **5**–**8** the conformational correction factor *C* shows the (+)-sign if the bulky α-methylbenzylamino substituent is in the axial position and the (−)-sign if the substituent occupies the equatorial position. For **ent-5**–**ent-8** it shows the opposite sign each. The $[\alpha]_D^{25}$ values of the α-amino amides are based mainly on the increments *X* for C-α and *Y* for C-1, whereas the increment *Z* for C-2 as well as the conformational correction factor *C* contribute only to a minor extent.

Discussion

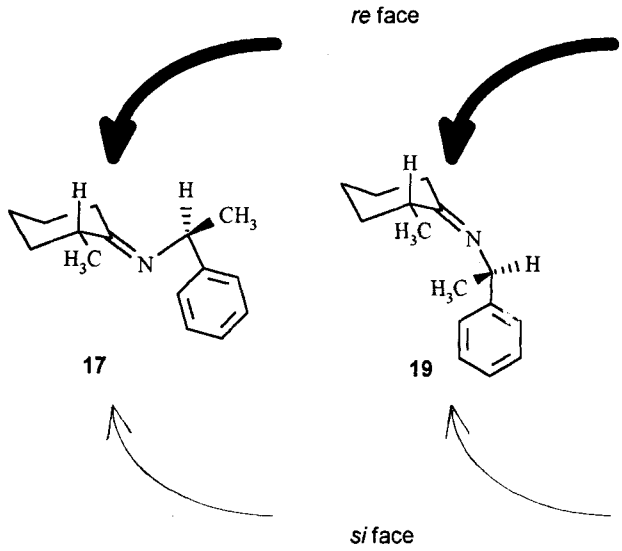
Under all the tested reaction conditions (pathway, solvent, temperature, catalyst), the asymmetric syntheses of the α-amino nitriles **1**–**4** yielded oily mixtures of the four possible diastereomers. The stereochemical composition of these mixtures was dominantly influenced by the solvent. Thermodynamically (**M-1**) as well as variably kinetically controlled (**M-2**, **M-2'**, **M-3**) diastereomeric mixtures could be obtained by the choice of appropriate solvents (see Table 1). The thermodynamic equilibrium mixture **M-1** shows the following characteristics:

- The ratio of the *trans*-configured (α*S*,1*S*,2*S* and α*S*,1*R*,2*R*) α-amino nitriles **2** and **4** to the *cis*-configured (α*S*,1*S*,2*R* and α*S*,1*R*,2*S*) α-amino nitriles **1** and **3** is 3:1.
- The buttressing α*S*,2*S* substitution in the epimeric 1*S*- and 1*R*-configured α-amino nitriles leads to a selectivity of ca. 11:1 between the *trans*-configured (α*S*,1*S*,2*S*), and the *cis*-configured (α*S*,1*R*,2*S*) α-amino nitriles **2** and **3**.
- In contrast, the buttressing α*S*,2*R* substitution in the epimeric 1*S*- and 1*R*-configured α-amino nitriles leads to a nearly 1:1 ratio between the *trans*-configured (α*S*,1*R*,2*R*) and the *cis*-configured (α*S*,1*S*,2*R*) α-amino nitriles **4** and **1**.

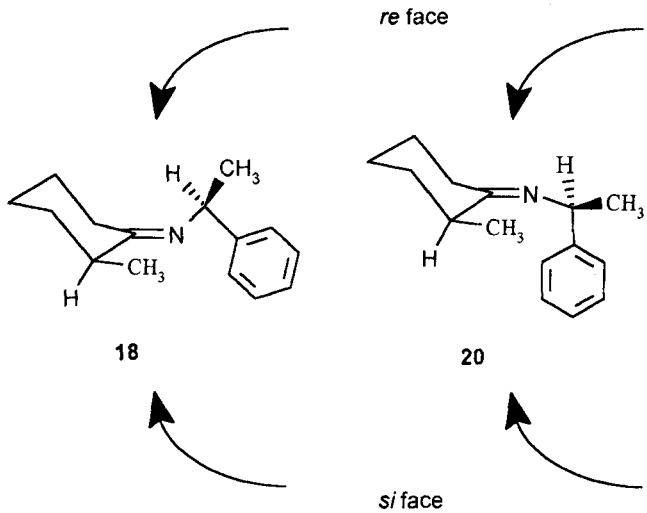
The kinetically controlled mixture with the lowest equilibration rate (**M-2'**) shows the following characteristics:

- The ratio of the *cis*-configured (α*S*,1*S*,2*R* and α*S*,1*R*,2*S*) α-amino nitriles **1** and **3** to the *trans*-configured (α*S*,1*S*,2*S* and α*S*,1*R*,2*R*) α-amino nitriles **2** and **4** is 3:1.
- The addition of the cyanide anion to the α*S*,2*R*-configured part of the ketimine mixture occurs with a rather high facial diastereoselectivity from the *re* face of the *E*-α*S*,2*R*-configured ketimine **17** and is reflected in a 1*S*:1*R* ratio of ≈14:1 (Scheme 5).

Scheme 5. Nucleophilic attack at the *E*-α*S*,2*R*-ketimine **17** and the *Z*-α*S*,2*R*-ketimine **19**



Scheme 6. Nucleophilic attack at the *E*-α*S*,2*S*-ketimine **18** and the *Z*-α*S*,2*S*-ketimine **20**



- In contrast, the addition of the cyanide anion to the *E*-α*S*,2*S*-configured ketimine **18** occurs without facial diastereoselectivity and is mirrored in a 1*S*:1*R* ratio of nearly 1:1 (Scheme 6).
- The addition of the cyanide ion to the minor ketimines *Z*-α*S*,2*R*-**19** and *Z*-α*S*,2*S*-**20** occurs with the same facial diastereoselectivity as observed for the *E* isomers **17** and **18** (Schemes 5 and 6).
- The 61:39 ratio of the 2*R*- (**1**, **4**) to the 2*S*-configured (**2**, **3**) α-amino nitriles is due to a kinetic resolution between the α*S*,2*R*-configured ketimines **17** and **19** on the one hand and the α*S*,2*S*-configured ketimines **18** and **20** on the other hand. With increasing total yields of α-amino nitriles the 2*R*:2*S* ratio reaches 1:1 (54:46 under **M-2** and 50:50 under **M-3** conditions).

Experimental

General Remarks: Melting points were determined with a Reichert melting point apparatus and are uncorrected. – Elemental analyses were carried out with a Perkin-Elmer elemental analyzer PE240. – ^{1}H-NMR spectra were recorded at 300 MHz with a Varian U300 spectrometer using TMS (δ = 0.0) as internal standard. – ^{13}C-NMR spectra were recorded at 75 MHz with the same instrument using the solvent peak ($CDCl_3$, δ = 77.0) as the reference. – Infrared spectra were obtained with a Perkin-Elmer Model PE 841 spectrometer. – Optical rotations were measured in a 1-dm cell with a Perkin Elmer 241 polarimeter. – MS and HRMS were obtained with a Finnigan MAT 312 (EI) and a Finnigan MAT 44S (CI) mass spectrometer. – Solvents were purified by standard procedures. – Starting materials were purchased from either Merck-Schuchardt or Fluka companies and were used without further purification.

E/Z-[2(RS)]-2-Methyl-N-(S-α-methylbenzyl)-cyclohexaneimines (**17**–**20**) *(Mixtures of Four Diastereomers). – General Procedure:* A solution of 11.2 g (0.1 mol) of (*RS*)-2-methylcyclohexanone (**5**), 12.1 g (0.1 mol) of *S*-α-methylbenzylamine and a catalytic amount of p-TosOH in 100 ml of toluene is refluxed in a Dean–Stark apparatus for 6 h. The solvent is evaporated in vacuo and the residue distilled in vacuo over a 20-cm Vigreux column yielding 15.0 g (70%) of the ketimine mixture as a pale yellow oil; b.p. 147–149 °C/12 Torr (ref.[17] 147–148 °C/12 Torr). – IR (neat): $\tilde{\nu}$ = 3080 cm^{-1}, 3055, 3020, 2960, 2910, 2850, 1655, 1595, 1490, 1440, 1315, 760, 695. – ^{1}H NMR ($CDCl_3$): δ = 0.91, 1.0, 1.1, 1.13 (4 d, *J* = 6.8 Hz, 3H, 8-CH_3), 1.37, 1.40, 1.45, 1.47 (4 d, *J* = 6.6 Hz, 3H, β-CH_3), 1.2–2.7 (m, 9H, cycloaliphatic H), 4.69, 4.70, 4.74 (3 q, *J* = 6.6 Hz, 1H, α-CH), 7.1–7.4 (m, 5H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 16.6 (*Z*), 17.29 (*Z*), 17.34 (*E*), 17.43 (*E*) (4 q, C-8), 20.17 (*Z*), 20.27 (*Z*), 24.27 (*E*), 24.41 (*E*) (4 t, C-4), 25.21 (*Z*), 25.22 (*Z*), 25.4 (*E*), 25.5 (*E*) (4 q, C-β), 27.2 (*E*), 27.6 (*E*) (2 t, C-5), 27.9 (*E*), 28.0 (*E*), 32.5 (*Z*), 33.0 (*Z*) (4 t, C-6), 35.6 (*Z*), 35.7 (*E*), 35.8 (*E*) (2 t, C-3), 31.4 (*Z*), 31.6 (*Z*), 42.1 (*E*) (2 d, C-2), 56.8 (*Z*), 57.3 (*E*), 57.4 (*E*) (3 d, C-α), 125.9 (*E*), 126.0 (*E*) (2 d, C-4′), 126.3 (*E*), 126.4 (*E*) (2 d, C-2′/6′), 128.0 (*E*) (d, C-3′/5′), 146.2 (*Z*), 146.9 (*E*), 147.0 (*E*) (2 s, C-1′), 173.2 (*E*), 173.5 (*E*), 175.1 (*Z*), 175.6 (*Z*) (4 s, C-1); (*E*): chemical shift for one of the *E* isomers **7** and **8**; (*Z*): chemical shift for one of the *Z* isomers **9** and **10**. – $C_{15}H_{21}N$ (215.3): calcd. C 83.7, H 9.83, N 6.5; found C 83.6, H 9.80, N 6.5.

2-Methyl-1-(α-methylbenzylamino)cyclohexanecarbonitriles (**1**–**4**) *(Mixtures of Four Diastereomers). – Method* **A** *("One-Pot Synthesis"):* To a solution of 5.6 g (0.05 mol) of (*RS*)-2-MC (**5**), 6.06 g (0.05 mol) of (*S*)-α-MBA and 2.7 g (0.055 mol) of NaCN in 60 ml of MeOH, 4.8 g (0.08 mol) of AcOH is added dropwise. The solution is heated at 60 °C for 2 h and then stirred at room temperature for about 12 h. The MeOH is evaporated in vacuo, the white residue is dissolved in 50 ml of H_2O, the solution adjusted to pH 8 with NaOH and then extracted three times with Et_2O. The combined organic layers are washed twice with H_2O, dried with Na_2SO_4, filtered and the Et_2O is evaporated yielding 9.14 g (76%) of **1**–**4** as diastereomeric mixtures that are dried in vacuo.

Method **B** *("One-Pot Synthesis"):* A mixture of 5.6 g (0.05 mol) of (*RS*)-2-MC (**5**), 340 mg (5 mol-%) of $ZnCl_2$ and 6.7 ml (5.0 g, 0.05 mol) of TMSCN is stirred for 15 min at room temperature. A solution of 6.06 g (0.05 mol) of (*S*)-α-MBA in 30 ml of MeOH is added, and the mixture is heated at 60 °C for 5 h (12 h for 0.3 mol). The MeOH is evaporated in vacuo to yield 11.8 g (97%) of **1**–**4** as a pale yellow oil that is dried in vacuo.

Method **C** *("Two-Step Synthesis"):* A solution of 2.15 g (0.01 mol) of **17**–**20** and 2.45 g (0.05 mol) of NaCN in 30 ml of MeOH is stirred at 0 °C for 3 h. To this is added H_2O (50 ml) and the mixture is extracted twice with Et_2O. The combined organic layers are washed twice with H_2O, dried over Na_2SO_4, filtered and the Et_2O is evaporated to yield 1.57 g (65%) of the diastereomeric mixtures of **1**–**4** as pale yellow oils.

Method **D** *("Two-Step Synthesis"):* To a solution of 10.75 g (0.05 mol) of **17**–**20** and 340 mg (5 mol-%) of $ZnCl_2$ in 100 ml of MeOH, 8.3 ml (6.2 g, 0.0625 mol) of TMSCN is added cautiously at 0 °C. The solution is stirred for 3 h at 0 °C. The MeOH is evaporated in vacuo, yielding 11.75 g (97%) of the diastereomeric mixtures of **1**–**4** as pale yellow oils, which are dried in vacuo.

General Procedure for Reactions by Method **D** *in Different Solvents (Except Hexane) and at Variable Temperatures:* To a solution of 650 mg (3 mmol) of **17**–**20** and 20 mg (5 mol-%) of $ZnCl_2$ in 15 ml of the respective solvent (see Table 1), 0.5 ml (375 mg, 3.75 mmol) of TMSCN is added cautiously at 0 °C and −78 °C, respectively. The resulting mixture is stirred for 3 h at 0 °C, for 24 h at room temperature, and for 3 h at −78 °C, respectively. The reaction mixture is filtered and the solvent is evaporated. The resulting diastereomeric mixtures **1**–**4** (for yields, see Table 2) are dried in vacuo and were analyzed without further purification.

General Procedure for Reactions by Method **D** *in Hexane at 0 °C and −78 °C, Respectively:* To a solution of 650 mg (3 mmol) of **17**–**20** in 20 ml of hexane, 0.5 ml (375 mg, 3.75 mmol) of TMSCN is added vigorously at 0 °C and −78 °C, respectively. The solution is stirred for 3 h, 24 h, and 48 h, respectively. If the reactions are carried out in the presence of 20 mg (5 mol-%) of $ZnCl_2$ the catalyst is suspended in hexane before TMSCN is added and is removed again by filtration before work-up. Hexane is evaporated in vacuo yielding diastereomeric mixtures of **1**–**4** (for yields, see Table 1) as pale yellow oils, which are dried in vacuo and analyzed without further purification.

IR (diastereomeric mixture of **1**–**4**) (neat): $\tilde{\nu}$ = 3357 cm^{-1}, 3024, 2931, 2861, 2218, 1602, 1493, 1446, 1384, 1372, 1263, 1211, 1150, 1130, 1049, 987, 945, 885, 858, 761, 701.

(αS,1S,2R)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarbonitrile (**1**): ^{1}H NMR ($CDCl_3$): δ = 1.12 (d, *J* = 7.1 Hz, 3H, 8-CH_3), 1.39 (d, *J* = 6.6 Hz, 3H, β-CH_3), 0.8–2.2 (m, 10H, cycloaliphatic H, NH), 4.06 (q, *J* = 6.6 Hz, 1H, α-CH), 7.1–7.5 (m, 5H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 15.2 (q, C-8), 20.0 (t, C-4), 23.1 (t, C-5), 26.2 (q, C-β), 28.4 (t, C-6), 32.8 (t, C-3), 38.9 (d, C-2), 54.7 (d, C-α), 60.1 (s, C-1), 123.0 (s, C-7), 126.3 (d, C-3′/5′), 126.6 (d, C-4′), 128.0 (d, C-2′/6′), 146.8 (s, C-1′).

(αS,1S,2S)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarbonitrile (**2**): ^{1}H NMR ($CDCl_3$): δ = 1.12 (d, *J* = 6.4 Hz, 3H, 8-CH_3), 1.37 (d, *J* = 6.6 Hz, 3H, β-CH_3), 0.8–2.2 (m, 10H, cycloaliphatic H, NH), 4.09 (q, *J* = 6.6 Hz, 1H, α-CH), 7.1–7.5 (m, 5H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 16.5 (q, C-8), 22.7 (t, C-4), 24.7 (t, C-5), 26.5 (q, C-β), 31.5 (t, C-6), 36.1 (t, C-3), 40.0 (d, C-2), 54.4 (d, C-α), 63.3 (s, C-1), 120.8 (s, C-7), 126.1 (d, C-3′/5′), 126.4 (d, C-4′), 128.1 (d, C-2′/6′), 147.5 (s, C-1′).

(αS,1R,2S)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarbonitrile (**3**): ^{1}H NMR ($CDCl_3$): δ = 0.82 (d, *J* = 7.1 Hz, 3H, 8-CH_3), 1.41 (d, *J* = 6.6 Hz, 3H, β-CH_3), 0.8–2.2 (m, 10H, cycloaliphatic H, NH), 4.04 (q, *J* = 6.6 Hz, 1H, α-CH), 7.1–7.5 (m, 5H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 14.5 (q, C-8), 20.0 (t, C-4), 23.1 (t, C-5), 25.4 (q, C-β), 28.3 (t, C-6), 33.2 (t, C-3), 37.6 (d, C-2), 53.9 (d, C-α), 59.1 (s, C-1), 122.7 (s, C-7), 126.9 (d, C-3′/5′), 128.2 (d, C-4′), 128.7 (d, C-2′/6′), 145.4 (s, C-1′).

(αS,1R,2R)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarbonitrile (**4**): ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, *J* = 6.4 Hz, 3H, 8-CH_3), 1.40 (d, *J* = 6.6 Hz, 3H, β-CH_3), 0.8–2.2 (m, 10H, cycloaliphatic H, NH), 4.07 (q, *J* = 6.6 Hz, 1H, α-CH), 7.1–7.5 (m, 5H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 16.5 (q, C-8), 22.6 (t, C-4), 24.4 (t, C-5), 25.8 (q, C-β), 31.0 (t, C-6), 36.0 (t, C-3), 39.8 (d, C-2), 53.5 (d, C-α), 61.5 (s, C-1), 120.4 (s, C-7), 126.2 (d, C-3′/5′), 127.0 (d, C-4′), 128.4 (d, C-2′/6′), 145.5 (s, C-1′).

2-Methyl-1-(α-methylbenzylamino)cyclohexanecarboxamides (**5**–**8** *and ent-***5**–*ent-***8**) *(Mixtures of Four Diastereomers)*

Entries I and II in Table 3: To 60 ml (150 ml) of conc. H_2SO_4, which was cooled to −10 °C, 7.26 g (0.03 mol) [70.0–71.2 g (0.3 mol)] of the α-amino nitrile mixtures **1**–**4** and *ent-***1**–*ent-***4**, respectively (entry **I**: *"method* **D***"*; entry **II**: *"general procedure for reactions by method* **D** *in hexane"*), was added slowly. The mixture was stirred for 3 h at −10 °C, for 3 h at 0 °C and then for a further 96 h (144 h) at room temperature. The solution was poured onto 250 g of crushed ice, filtered, and the filtrate was adjusted to pH 8 with conc. ammonia. The aqueous layer was extracted three times with 100 ml of Et_2O. The combined organic layers were dried with Na_2SO_4, filtered, and the Et_2O was evaporated yielding 4.8–5.0 g (61–64%) [56.0–61.0 g (72–78%)] of the diastereomeric mixtures of the α-amino amides **5**–**8** and **ent-5**–**ent-8**, respectively, as pale yellow oils which were dried in vacuo.

Entry III in Table 3: To a solution of 9.25 g (0.038 mol) of the α-amino nitrile mixture **1**–**4** *("general procedure for reactions by method* **D** *in hexane")* in 60 ml of hexane, cooled to −10 °C, 60 ml of conc. H_2SO_4 was added dropwise, whereby the temperature should not rise above −5 °C. The mixture was stirred for 3 h at −10 °C, for 3 h at 0 °C, and for 96 h at room temperature and then worked up according to the procedure used for the entries **I** and **II** to yield 7.0 g (71%) of the α-amino amides **5**–**8**.

Column Chromatography of the α-Amino Carboxamide Mixtures **5**–**8** *and* **ent-5**–**ent-8**: Stationary phase: Merck Kieselgel 60 (70–230 mesh), mobile phase: cyclohexane/EtOAc (60:40), compound/stationary phase = 1:100, fraction size: 6 min, flow rate: 30 drops/min; detection: Merck DC-Alufolien Kieselgel F_{254} with ninhydrine reagent.

Analytical HPLC of the **ent-5/ent-6**, **ent-6** *and the* **7/8**, **ent-7/ent-8** *Mixtures:* Diastereomeric mixtures of **5/6** and **ent-5/ent-6**: stationary phase: Bischoff LiChroSorb® RP-18 (5 μm) 250-4, mobile phase: MeOH/H_2O (70:30), flow rate: 0.6 ml/min, detection: UV (254 nm). – Diastereomeric mixtures of **7/8** and **ent-7/ent-8**: stationary phase: Merck LiChroSorb® Si 60 (5 μm) 250-4, mobile phase: CH_2Cl_2/dioxane (95:5); flow rate: 0.7 ml/min, detection: UV (254 nm).

LPLC of the **5/6** *and* **ent-5/ent-6** *Mixtures:* Stationary phase: Merck Lobar®-Fertigsäulen A and B, respectively, mobile phase: MeOH/H_2O (70:30), substance: Lobar® A: 70 mg of a **5/6** mixture, Lobar® B: max. 400 mg of a **5/6** mixture, flow rate: Lobar® A: 0.7 ml/min, Lobar® B: 0.8 ml/min, detection: UV (254 nm), fraction size: 2–3 min (1.4–2.4 ml).

cis-(αS,1S,2R)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarboxamide (**5**): M.p. 49–50 °C. – $[\alpha]_D^{25}$ = −3.7 (*c* = 1.15, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 3H, 8-CH_3), 1.33 (d, *J* = 6.6 Hz, 3H, β-CH_3), 1.1–2.1 (m, 9H, aliphatic H), 1.6 (br. s, 1H, NH), 3.9 (q, *J* = 6.6 Hz, 1H, α-H), 5.6 [br. s, 1H, NH (amide)], 7.4 [br. s, 1H, NH (amide)], 7.1–7.4 (m, 5H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 16.4 (q, C-8), 21.5 (t, C-4), 25.0 (q, C-β), 25.4 (t, C-5), 28.3 (t, C-6), 30.4 (t, C-3), 39.2 (d, C-2), 53.0 (d, C-α), 64.0 (s, C-1), 126.4 (d, C-3′/5′), 127.1 (d, C-4′), 128.6 (d, C-2′/6′), 147.0 (s, C-1′), 180.2 (s, C=O). – For elemental analysis **5** was converted into its hydrochloride salt with HCl saturated Et_2O. – $C_{16}H_{25}ClN_2O$ (296.8): calcd. C 64.7, H 8.49, N 9.4; found C 64.3, H 8.43, N 9.3.

trans-(αS,1S,2S)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarboxamide (**6**): M.p. 95–97 °C. – $[\alpha]_D^{25}$ = −25.2 (*c* = 1.47, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, *J* = 7.3 Hz, 3H, 8-CH_3), 1.29 (d, *J* = 6.6 Hz, 3H, β-CH_3), 1.0–2.0 (m, 9H, aliphatic H), 1.8 (br. s, 1H, NH), 3.82 (q, *J* = 6.6 Hz, 1H, α-H), 5.7 [br. s, 1H, NH (amide)], 6.9 [br. s, 1H, NH (amide)], 7.1–7.4 (m, 5H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 15.8 (q, C-8), 20.4 (t, C-4), 21.6 (t, C-5), 24.4 (t, C-6), 24.5 (q, C-β), 28.8 (t, C-3), 38.2 (d, C-2), 53.6 (d, C-α), 63.8 (s, C-1), 126.4 (d, C-3′/5′), 127.0 (d, C-4′), 128.5 (d, C-2′/6′), 147.1 (s, C-1′), 180.3 (s, C=O). – $C_{16}H_{24}N_2O$ (260.4): calcd. C 73.8, H 9.29, N 10.7; found C 73.5, H 9.36, N 10.6.

cis-(αR,1R,2S)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarboxamide (**ent-5**): M.p. 48–50 °C. – $[\alpha]_D^{25}$ = +4.0 (*c* = 0.85, MeOH). – ^{1}H-NMR and ^{13}C-NMR data are identical with those of **5**. – MS (CI/isobutane, 70 eV); *m/z* (%): 261 (100) [M^+ + 1], 216 (8) [$C_{15}H_{22}N$], 157(23) [$C_8H_{17}N_2O$]. – $C_{15}H_{22}N$ (M^+ − $CONH_2$): calcd. 216.1752; found 216.1756 (MS).

trans-(αR,1R,2R)-2-Methyl-1-(α-methylbenzylaminocyclo)-hexanecarboxamide (**ent-6**): M.p. 94–96 °C. – $[\alpha]_D^{25}$ = +25.2 (*c* = 1.505, MeOH). – ^{1}H-NMR and ^{13}C-NMR data are identical with those of **6**. – $C_{16}H_{24}N_2O$ (260.4): calcd. C 73.8, H 9.29, N 10.7; found C 73.5, H 9.22, N 10.6.

Preparative HPLC of the **5/6**, **ent-5/ent-6** *and the* **7/8**, **ent-7/ent-8** *Mixtures:* Diastereomeric mixtures of **5/6** and **ent-5/ent-6**: stationary phase: Bischoff LiChroSorb® RP-18 (5 μm) 250-20, mobile phase: MeOH/H_2O (70:30), flow rate: 15.0 ml/min, detection: UV (254 nm). – Diastereomeric mixtures of **7/8** and **ent-7/ent-8**: stationary phase: Merck LiChroSorb® Si 60 (5 μm) 250-10 (Hibar® Fertigsäule), mobile phase: CH_2Cl_2/dioxane (95:5) and CH_2Cl_2/EtOAc (95:5), respectively, flow rate: 6.0 ml/min, detection: UV (254 nm).

cis-(αS,1R,2S)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarboxamide (**7**): Colorless oil. – $[\alpha]_D^{25}$ = −92.2 (*c* = 0.41, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.84 (d, *J* = 7.1 Hz, 3H, 8-CH_3), 1.40 (d, *J* = 6.8 Hz, 3H, β-CH_3), 1.1–2.1 (m, 9H, aliphatic H), 2.0 (br. s, 1H, NH), 3.79 (q, *J* = 6.8 Hz, 1H, α-H), 5.2 [br. s, 1H, NH (amide)], 6.4 [br. s, 1H, NH (amide)], 7.1–7.4 (m, 5H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 16.3 (q, C-8), 21.4 (t, C-4), 25.5 (t, C-5), 29.1 (t, C-6), 26.8 (q, C-β), 30.3 (t, C-3), 38.8 (d, C-2), 52.0 (d, C-α), 65.0 (s, C-1), 126.2 (d, C-3′/5′), 126.7 (d, C-4′), 128.6 (d, C-2′/

6'), 147.6 (s, C-1'), 179.1 (s, C=O). – $C_{16}H_{24}N_2O$ (260.4): calcd. C 73.8, H 9.29, N 10.7; found C 73.4, H 8.99, N 10.4.

trans-(αS,1R,2R)-2-Methyl-1-(α-methylbenzylamino)-cyclohexanecarboxamide (**8**): M.p. 77–79°C. – $[\alpha]_D^{25} = -80.6$ (c = 0.98, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.96 (d, J = 7.1 Hz, 3H, 8-CH_3), 1.38 (d, J = 6.8 Hz, 3H, β-CH_3), 1.1–2.1 (m, 9H, aliphatic H), 1.7 (br. s, 1H, NH), 3.80 (q, J = 6.8 Hz, 1H, α-H), 4.8 [br. s, 1H, NH (amide)], 6.3 [br. s, 1H, NH (amide)], 7.1–7.4 (m, 5H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 16.0 (q, C-8), 21.8 (t, C-4), 22.1 (t, C-5), 27.4 (t, C-6), 27.0 (q, C-β), 29.4 (t, C-3), 38.4 (d, C-2), 52.3 (d, C-α), 64.5 (s, C-1), 126.3 (d, C-3'/5'), 126.5 (d, C-4'), 128.3 (d, C-2'/6'), 147.6 (s, C-1'), 178.2 (s, C=O). – $C_{16}H_{24}N_2O$ (260.4): calcd. C 73.8, H 9.29, N 10.7; found C 73.7, H 9.23, N 10.7.

cis-(αR,1S,2R)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarboxamide (**ent-7**): Colorless oil. – $[\alpha]_D^{25} = +92.3$ (c = 0.62, MeOH). – ^{1}H-NMR and ^{13}C-NMR data are identical with those of **7**. – $C_{16}H_{24}N_2O$ (260.4): calcd. C 73.8, H 9.29, N 10.7; found C 73.5, H 9.12, N 10.7.

trans-(αR,1S,2S)-2-Methyl-1-(α-methylbenzylamino)cyclohexanecarboxamide (**ent-8**): M.p. 76–77°C. – $[\alpha]_D^{25} = +77.1$ (c = 1.10, MeOH). – ^{1}H-NMR and ^{13}C-NMR data are identical with those of **8**. – $C_{16}H_{24}N_2O$ (260.4): calcd. C 73.8, H 9.29, N 10.7; found C 74.0, H 9.37, N 10.6.

1-Amino-2-methylcyclohexanecarboxamides **9–12**. – *General Procedure:* In a Parr apparatus X mg of Pd/C (10%) was suspended in Y ml of EtOH. After evacuation the mixture was shaken under 5 bar H_2 pressure for 1 h at 45°C. A solution of Z mg of the respective diastereomerically pure α-amino amides (**ent-5**, **ent-6**, **ent-7** and **ent-8**) in EtOH (8–20 ml) was added, and the reaction mixture was shaken for 24 h at 45°C under 5 bar H_2 pressure. The cooled solution was filtered through Celite. The EtOH was evaporated to yield the oily α-amino amides **9**, **10**, **11**, and **12**, respectively, which were dried in vacuo.

	X	Y	Z	yield
ent-5 (αR,1R,2S)	10	10	17	10 mg (98%) of **11**
ent-6 (αR,1R,2R)	100	40	200	116 mg (97%) of **12**
ent-7 (αR,1S,2R)	20	15	45	25 mg (93%) of **9**
ent-8 (αR,1S,2S)	75	30	150	89 mg (99%) of **10**

cis-(1S,2R)-1-Amino-2-methylcyclohexanecarboxamide (**9**): Colorless oil. – $[\alpha]_D^{25} = +0.7$ (c = 1.4, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.75 (d, J = 6.8 Hz, 3H, 8-CH_3), 1.6 (br. s, 2H, NH_2), 1.1–2.1 (m, 9H, aliphatic H), 5.8 [br. s, 1H, NH (amide)], 7.6 [br. s, 1H, NH (amide)]. – ^{13}C NMR ($CDCl_3$): δ = 16.2 (q, C-8), 20.7 (t, C-4), 25.6 (t, C-5), 29.3 (t, C-6), 35.7 (t, C-3), 35.8 (d, C-2), 60.5 (s, C-1), 180.9 (s, C=O). – MS (CI/isobutane, 70 eV); m/z (%): 157 (100) [M^+ + 1], 112 (8) [$C_7H_{14}N$]. – $C_7H_{14}N$ (M^+ – $CONH_2$): calcd. 112.1126; found 112.1128 (MS).

trans-(1S,2S)-1-Amino-2-methylcyclohexanecarboxamide (**10**): Colorless oil. – $[\alpha]_D^{25} = +7.1$ (c = 1.57, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.93 (d, J = 6.8 Hz, 3H, 8-CH_3), 2.0 (br. s, 2H, NH_2), 1.1–2.1 (m, 9H, aliphatic H), 6.0 [br. s, 1H, NH (amide)], 7.2 [br. s, 1H, NH (amide)]. – ^{13}C NMR ($CDCl_3$): δ = 15.9 (q, C-8), 22.5 (t, C-4), 24.0 (t, C-5), 30.3 (t, C-6), 37.1 (t, C-3), 41.5 (d, C-2), 59.3 (s, C-1), 178.7 (s, C=O). – MS (CI/isobutane, 70 eV); m/z (%): 157 (100) [M^+ + 1], 112 (12) [$C_7H_{14}N$]. – $C_7H_{14}N$ (M^+ – $CONH_2$): calcd. 112.1126; found 112.1128 (MS).

trans-(1S,2S)-1-Amino-2-methylcyclohexanecarboxamide Hydrochloride (**10-HCl**): M.p. ~240°C (dec.). – $C_8H_{17}ClN_2O$ (192.7): calcd. C 49.9, H 8.90, N 14.5; found C 49.9, H 8.76, N 14.3.

cis-(1R,2S)-1-Amino-2-methylcyclohexanecarboxamide (**11**): Colorless oil. – $[\alpha]_D^{25} = +2.0$ (c = 0.5, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.75 (d, J = 6.8 Hz, 3H, 8-CH_3), 1.6 (br. s, 2H, NH_2), 1.1–2.1 (m, 9H, aliphatic H), 5.4 [br. s, 1H, NH (amide)], 7.6 [br. s, 1H, NH (amide)]. – ^{13}C NMR ($CDCl_3$): δ = 16.2 (q, C-8), 20.7 (t, C-4), 25.6 (t, C-5), 29.3 (t, C-6), 35.7 (t, C-3), 35.9 (d, C-2), 60.6 (s, C-1), 180.8 (s, C=O). – MS (CI/isobutane, 70 eV); m/z (%): 157 (100) [M^+ + 1], 112 (8) [$C_7H_{14}N$]. – $C_7H_{14}N$ (M^+ – $CONH_2$): calcd. C 112.1126; found 112.1129 (MS).

trans-(1R,2R)-1-Amino-2-methylcyclohexanecarboxamide (**12**): Colorless oil. – $[\alpha]_D^{25} = -6.4$ (c = 0.556, MeOH). – ^{1}H NMR ($CDCl_3$): δ = 0.93 (d, J = 6.8 Hz, 3H, 8-CH_3), 2.0 (br. s, 2H, NH_2), 1.1–2.1 (m, 9H, aliphatic H), 6.0 [br. s, 1H, NH (amide)], 7.2 [br. s, 1H, NH (amide)]. – ^{13}C NMR ($CDCl_3$): δ = 15.9 (q, C-8), 22.5 (t, C-4), 24.0 (t, C-5), 30.3 (t, C-6), 37.1 (t, C-3), 41.4 (d, C-2), 59.3 (s, C-1), 178.7 (s, C=O). – MS (CI/Isobutane, 70 eV); m/z (%): 157 (100) [M^+ + 1], 112 (11) [$C_7H_{14}N$]. – $C_7H_{14}N$ (M^+ – $CONH_2$): calcd. 112.1126; found 112.1128 (MS).

trans-(1R,2R)-1-Amino-2-methylcyclohexanecarboxamide Hydrochloride (**12-HCl**): M.p. ~240°C (decompn.). – $C_8H_{17}ClN_2O$ (192.7): calcd. C 49.9, H 8.90, N 14.5; found C 49.6, H 8.67, N 14.3.

1-Amino-2-methylcyclohexanecarboxylic Acids **13–16**. – *General Procedure: X* mg of the diastereomerically pure primary α-amino amides **9**, **10**, **11**, and **12**, respectively, was dissolved in Y ml of conc. hydrochloric acid. The mixture was stirred for 2 h at room temp. refluxed at 80°C for 10 h and evaporated to dryness in vacuo. The residue was dissolved in H_2O and purified by ion exchange chromatography [strong acidic ion exchanger (Merck 4765), NH_4OH (1 M), ninhydrine detection]. The combined fractions were concentrated in vacuo, the residue was dissolved in acetone and converted into the α-amino acid hydrochlorides **13**, **14**, **15**, and **16**, respectively, with HCl-saturated Et_2O.

	X	Y	yield
9 (1S,2R)	8	3	8 mg (99%) of **13**
10 (1S,2S)	77	10	76 mg (98%) of **14**
11 (1R,2S)	13	5	13 mg (99%) of **15**
12 (1R,2R)	50	10	37 mg (75%) of **16**

cis-(1S,2R)-1-Amino-2-methylcyclohexanecarboxylic Acid Hydrochloride (**13**): M.p. >310°C (decompn.). – $[\alpha]_D^{25} = +11.9$ (c = 0.88, MeOH). – ^{1}H NMR (CD_3OD): δ = 0.91 (d, J = 6.8 Hz, 3H, 8-CH_3), 1.2–2.3 (m, 9H, aliphatic H). – ^{13}C NMR (CD_3OD): δ = 15.9 (q, C-8), 21.3 (t, C-4), 25.7 (t, C-5), 29.8 (t, C-6), 34.3 (t, C-3), 37.0 (d, C-2), 65.6 (s, C-1), 175.0 (s, C=O). – $C_8H_{16}ClNO_2$ (192.7): calcd. C 49.9, H 8.37, N 7.3; found C 49.6, H 8.27, N 7.4.

trans-(1S,2S)-1-Amino-2-methylcyclohexanecarboxylic Acid Hydrochloride (**14**): M.p. >310°C (decompn.). – $[\alpha]_D^{25} = +11.9$ (c = 1.4, MeOH). – ^{1}H NMR (CD_3OD): δ = 0.91 (d, J = 6.8 Hz, 3H, 8-CH_3), 1.2–2.3 (m, 9H, aliphatic H). – ^{13}C NMR (CD_3OD): δ = 16.2 (q, C-8), 22.7 (t, C-4), 25.5 (t, C-5), 31.3 (t, C-6), 34.2 (t, C-3), 38.7 (d, C-2), 64.2 (s, C-1), 172.2 (s, C=O). – $C_8H_{16}ClNO_2$ (192.7): calcd. C 49.9, H 8.37, N 7.3; found C 48.7, H 7.96, N 8.2.

cis-(1R,2S)-1-Amino-2-methylcyclohexanecarboxylic Acid Hydrochloride (**15**): M.p. >310°C (decompn.). – $[\alpha]_D^{25} = -12.0$ (c =

0.4, MeOH). – ^{1}H NMR (CD_3OD): δ = 0.92 (d, J = 6.8 Hz, 3H, 8-CH_3), 1.2–2.3 (m, 9H, aliphatic H). – ^{13}C NMR (CD_3OD): δ = 15.9 (q, C-8), 21.3 (t, C-4), 25.7 (t, C-5), 29.8 (t, C-6), 34.3 (t, C-3), 37.0 (d, C-2), 65.6 (s, C-1), 175.0 (s, C=O). – $C_8H_{16}ClNO_2$ (192.7): calcd. C 49.9, H 8.37, N 7.3; found C 49.4, H 8.19, N 7.5.

trans-(1R,2R)-1-Amino-2-methylcyclohexanecarboxylic Acid Hydrochloride (**16**): M.p. >310°C (decompn.). – $[\alpha]_D^{25}$ = −11.5 (c = 1.5, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.05 (d, J = 6.8 Hz, 3H, 8-CH_3), 1.2–2.2 (m, 9H, aliphatic H). – ^{13}C NMR (CD_3OD): δ = 16.2 (q, C-8), 22.7 (t, C-4), 25.5 (t, C-5), 31.3 (t, C-6), 34.3 (t, C-3), 38.8 (d, C-2), 64.2 (s, C-1), 172.3 (s, C=O). – $C_8H_{16}ClNO_2$ (192.7): calcd. C 49.9, H 8.37, N 7.3; found C 49.5, H 8.22, N 7.5.

☆ Dedicated to Professor *J. Knabe*, Saarbrücken, on the occasion of his 75th birthday.

[1] K. Harada, *Nature* **1963**, *200*, 1201.

[2] [2a] R. Schwyzer, M. Oppliger, *Helv. Chim. Acta* **1977**, *60*, 43–47. – [2b] R. Schwyzer, K. Do, P. Thanei, M. Caviezel, *Helv. Chim. Acta* **1980**, *62*, 956–964. – [2c] J. Fauchere, C. Petermann, *Helv. Chim. Acta* **1980**, *63*, 824–831. – [2d] J. Fauchere, C. Petermann, *J. Pept. Prot. Res.* **1983**, *48*, 5369–5373. – [2e] K. Subramanian, R. Woodard, *Synth. Comm.* **1986**, *16(3)*, 337–342. – [2f] T. K. Chakraborty, A. V. Rao, K. Tushar, S. Joshi, *Tetrahedron Lett.* **1992**, *33*, 4045–4058.

[3] Reviews: [3a] K. Weinges, B. Stemmle, *Recent Dev. Chem. Nat. Carbon Compd.* **1976**, *7*, 86. – [3b] K. A. Kochetkov, V. M. Belikov, *Russ. Chem. Rev. (Engl. Transl.)* **1987**, *56(11)*, 1060. – [3c] R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, vol. 7 of Organic Chemistry Series, (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon Press, Oxford, **1989**, chapter *5*, 208–229. – [3d] R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539–1650.

[4] [4a] K. Harda, T. Okawara, *J. Org. Chem.* **1973**, *38*, 707. – [4b] K. Harada, T. Okawara, K. Matsumoto, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1865. – [4c] M. S. Patel, M. Worsley, *Can. J. Chem.* **1970**, *48*, 1881. – [4d] D. Stout, L. Black, W. Matier, *J. Org. Chem.* **1983**, *48*, 5369–5373.

[5] [5a] K. Weinges, G. Graab, D. Nagel, B. Stemmle, *Chem. Ber.* **1971**, *104*, 3594–3606. – [5b] K. Weinges, B. Stemmle, *Chem. Ber.* **1973**, *106*, 2291–2297. – [5c] K. Weinges, K. Greis, W. Schrank, *Chem. Ber.* **1977**, *110*, 2098–2105. – [5d] K. Weinges, K. Klotz, H. Droste, *Chem. Ber.* **1980**, *113*, 710–721. – [5e] K. Weinges, H. Blackholm, *Chem. Ber.* **1980**, *113*, 3098–3102. – [5f] K. Weinges, G. Brune, H. Droste, *Liebigs Ann. Chem.* **1980**, 212–218. – [5g] K. Weinges, H. Brachmann, P. Stahnecker, H. Rodewald, M. Nixdorf, H. Irngartinger, *Liebigs Ann. Chem.* **1985**, *566*.

[6] A. Fadel, *Synlett* **1993**, 503–505.

[7] [7a] T. K. Chakraborty, G. V. Raddy, K. Hussain, *Tetrahedron Lett.* **1991**, *32*, 7597–7600. – [7b] T. Inaba, K. Ogura, M. Fulita, I. Kozono, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2359–2365. – [7c] T. K. Chakraborty, K. A. Hussain, G. V. Reddy, *Tetrahedron* **1995**, *51*, 9179.

[8] C. Andres, A. Maestro, R. Pedrosa, A. Perze-Encabo, M. Vicente, *Synlett* **1992**, *30*, 45–47.

[9] See [5a], [5b], [5d–g].

[10] [10a] H. Kunz, W. Sager, *Angew. Chem.* **1987**, *99*, 595–597; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 557–559. – [10b] H. Kunz, W. Sager, D. Schanzenbach, M. Decker, *Liebigs Ann. Chem.* **1991**, 649–654. – [10c] H. Kunz, W. Sager, W. Pfrengle, D. Schanzenbach, *Tetrahedron Lett.* **1988**, *29*, 4397–4400.

[11] I. Ojima, S. Inaba, *Chem. Lett.* **1975**, 737–740.

[12] T. Shiori, S. Harusawa, Y. Hamada, *Tetrahedron Lett.* **1979**, *20*, 4663.

[13] K. Harada, T. Saito, *Tetrahedron Lett.* **1989**, *30*, 4535–4538.

[14] [14a] Y. Ogata, A. Kawasaki, *J. Chem. Soc. B* **1971**, 325. – [14b] J. Stanley, J. Beasley, I. Mathison, *J. Org. Chem.* **1972**, *37*, 3746. – [14c] J. Walia, S. Bannore, A. Walia, L. Guillot, *Chem. Lett.* **1974**, 1005.

[15] For details: F.-J. Volk, *Ph. D. Thesis*, University of Freiburg, **1995**.

[16] The enzymatic reactions were carried out with the immobilized enzyme mixture Nitrilase SP409 from the Novo Nordisk company. For a review see: M. Michihiko, S. Shimizu, *Microbiol. Lett.* **1994**, *120*, 217–224.

[17] Reviews: [17a] R. Sustmann, H. G. Korth in *Methoden Org. Chem.* (Houben-Weyl), 4th ed. **1985**, vol. E5/1, p. 264–268. – [17b] W. Stein, *Methodicum Chimicum* **1975**, *5*, 566–572. – [17c] P. L. Campagnon, M. Mioque, *Ann. Chim. (Paris)*, **1970**, *511*, 23–45. – [17d] E. N. Zilberman, *Russ. Chem. Rev. (Engl. Transl.)*, **1984**, *53*, 1548–1571. – [17e] M. A. Ogliaruso, J. F. Wolfe in *Synthesis of Carboxylic Acids, Esters and Their Derivatives* (in Updates from the Chemistry of Functional Groups, Ed.: S. Patai, Z. Rappoport) Interscience, Chichester, **1991**, pp. 7–9, 183–185, 253–263.

[18] K. Hümmer, E. Weckert, H. Bondza, *Acta Crystallogr.*, **1989**, *A45*, 182–187.

[19] F.-J. Volk, E. Weckert, A. W. Frahm, *Acta Crystallogr.*, submitted.

[20] K. Hümmer, F.-J. Volk, E. Weckert, A. W. Frahm, unpublished results.

[21] J. L. Marshall in *Carbon-Carbon and Carbon-Proton NMR Couplings (Applications to Organic Stereochemistry and Conformational Analysis)* in Methods in Stereochemical Analysis (Ed.: A. P. Marchand) VCH International, Deerfield Beach, **1983**, vol. 2, p. 11–64.

[96138]