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# Asymmetric Strecker synthesis of enantiopure 2,4-ethanothreonines

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Dedicated to Professor Dr. F. Zymalkowski on the occasion of his 90th birthday

**Abstract**—The second generation asymmetric synthesis reported herein proceeds via a Strecker reaction of chiral ketimines, obtained from the condensation of racemic 2-methoxycyclopentanone and (*S*)- and (*R*)-1-phenylethylamine. In the key stereodifferentiating step, the cyanide addition leads to mixtures of diastereomeric nitriles, the composition of which dramatically changes under the influence of protic and aprotic solvents. Hydrolysis of the nitriles to carboxamides with concd $H_2SO_4$ yielded diastereomeric mixtures of carboxamides each of which was hydrogenolysed and hydrolysed after separation to the four stereoisomers of the 1-amino-2-methoxy- and 1-amino-2-hydroxy-cyclopentanecarboxylic acid. Their stereochemistry was established by NMR methods and by X-ray analyses of the *trans* as well as the *cis* configured compounds.
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## 1. Introduction

Over the last few decades, the structural features of α,α-disubstituted α-amino acids have gained increasing attention in the field of medicinal chemistry. These compounds act as agonists and antagonists at various binding sites of both ionotropic and metabotropic glutamate receptors.[1] α,α-Dialkyl-α-amino acids also participate in enzymatic processes for plant growth and fruit ripening.[2] They also exhibit useful biological properties in the isosteric replacement of proteinogenic amino acids in peptides, favouring specific backbone conformations and, thus, leading to stabilised secondary peptide structures.[3] Moreover, this incorporation increases the stability of these peptides towards chemical and enzymatic degradation.[3] Hence, α,α-disubstituted-α-amino acids are utilised as building blocks for the design and synthesis of new peptide hormones and enzyme inhibitors.[4]

Title compounds **1a**–**d** and **2a**–**d** are 2,3-propano-bridged analogues of natural L-serine as well as 2,4-ethano analogues of L-threonine (Scheme 1) and have been the subject of a number of synthetic studies.[5] Recently a cyclic variant of the Strecker reaction, which was successfully applied to the synthesis of other β-hydroxy-α-amino acids, provided exclusively the *cis* configured enantiomers **1c** notably **1d**.[6] Incorporated into the 2-position of Leu-enkephalins, the (1*R*,2*S*)-enantiomer **1d** remarkably increased the δ-receptor affinity and was postulated to promote a β-turn-structure.[7] More recently, the *trans*-(1*S*,2*S*) configured stereomer **1a** has been utilised as the central building block of a novel class of patented bicyclic cruzipain-related cysteine protease inhibitors.[8]

Since the asymmetric Strecker reaction has proven to be a powerful and convenient experimental protocol for the synthesis of β-substituted-α-disubstituted amino acids,[9] we designed the preparation of the stereoisomeric α-amino-β-hydroxycyclopentanecarboxylic acids starting from racemic 2-methoxycyclopentanone **3** and 1-phenylethylamine (1-PEA) as the chiral auxiliary, yielding all four stereomers (Scheme 2). The results of these investigations are reported herein.

## 2. Results and discussion

The discussion is based on the compounds obtained with the chiral auxiliary (*S*)-1-PEA. The respective enantiomeric compounds (**ent**-) were synthesised with its antipode (*R*)-1-PEA.

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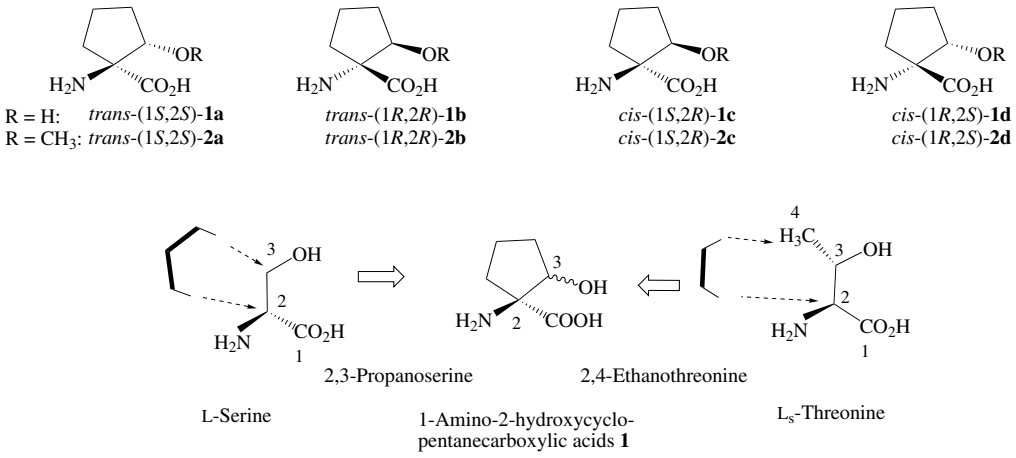
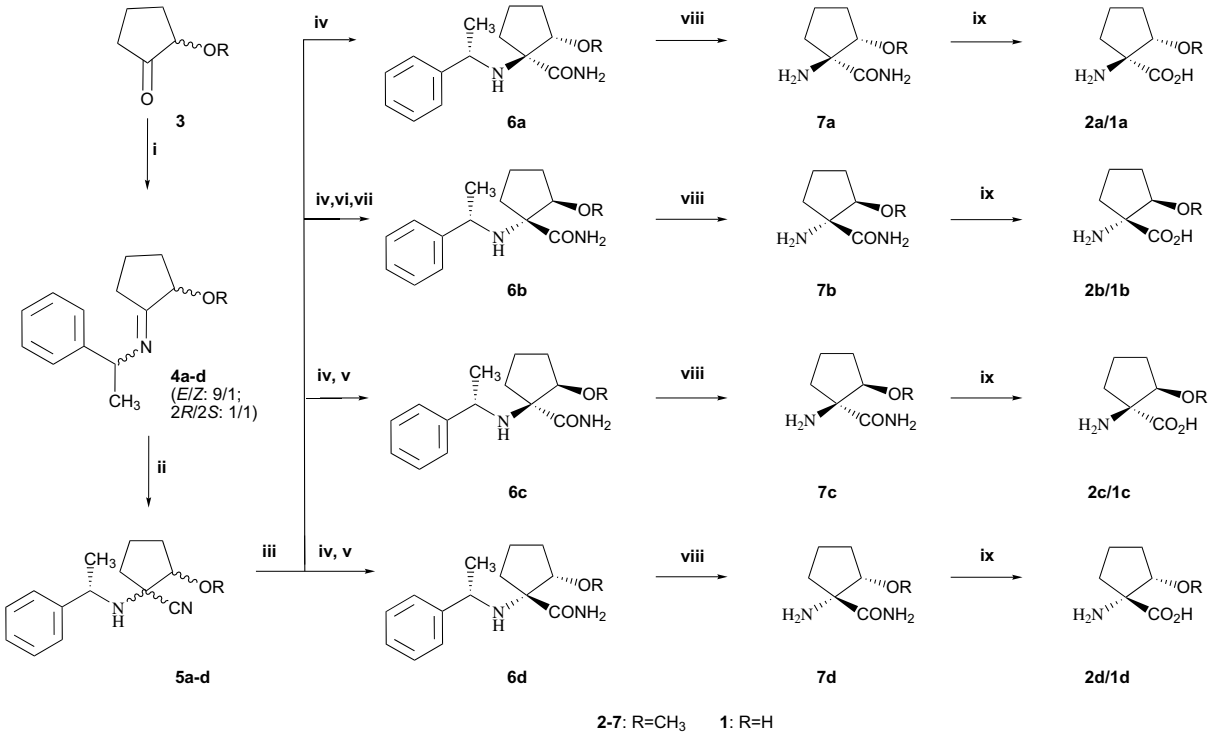



**Scheme 1.**




**Scheme 2.** Asymmetric Strecker synthesis of the 2,4-ethanothreonines **1a**–**d** and **2a**–**d**. Reagents and conditions: (i) (*S*)-1-PEA, TsOH, toluene, reflux, 9 h, ca. 99%; (ii) TMSCN, MeOH, $ZnCl_2$, 20 °C, 12 h, 98% or TMSCN, hexane, $ZnCl_2$, −10 °C, 18 h, 75%; (iii) concd $H_2SO_4$, −10 °C, 3 h, 0 °C, 3 h, rt, 96 h, 62%; (iv) CC: silica gel Si60 (230–400 mesh), EtOAc–cyclohexane (6:4), 86% recovery; (v) CC: silica gel Si60 (230–400 mesh), EtOAc–cyclohexane–$Et_2NH$ (68:29:3), 72% recovery rate; (vi) crystallisation from MeOH–$H_2O$; (vii) RP18-Lobar® chromatography MeOH–$H_2O$ (7:3); (viii) MeOH, Pd/C (10%), $HCO_2NH_4$, reflux, 2 h, 96%; (ix) HCl (7.0 M → **1**; 0.7 M → **2**), reflux, 48 h.

## 2.1. α-Amino nitrile synthesis

The asymmetric synthesis of the 1-amino-2-hydroxycyclopentanecarboxylic acids was designed with racemic 2-methoxycyclopentanone **3** prepared in two steps from cyclopentanone.[11] Condensation of **3** with a slight excess of (*S*)-1-PEA **2**, under azeotropic removal of water gave a mixture of two diastereomeric (*E*)-imines **4a** and **b** and two diastereomeric (*Z*)-imines **4c** and **d** in a ratio of 4.5:4.5:0.5:0.5 (Scheme 2). The **4a/b/c/d** mixture was subsequently subjected to Lewis acid-catalysed cyanide addition using trimethylsilylcyanide (TMSCN). Since an additional stereogenic centre at C-1 arises from this step, four diastereomeric α-amino nitriles (*cis*/*trans*-2*RS*) are theoretically feasible. In fact, we observed the formation of three and four component mixtures under varying reaction conditions. It is noteworthy that the overall *cis*/*trans* diastereoselectivity could be reversed upon solvent and temperature changes.

**Table 1.** Stereochemical distributions of the α-amino nitriles **5a–d** obtained under different reaction conditions

| Reaction conditions | | | *trans*-(α*S*,1*R*,2*S*)-**5a** | *trans*-(α*S*,1*S*,2*R*)-**5b** | *cis*-(α*S*,1*R*,2*R*)-**5c** | *cis*-(α*S*,1*S*,2*S*)-**5d** |
|---|---|---|---|---|---|---|
| Solvent | Temperature (°C) | Time (h) | | | | |
| | | | (%) | (%) | (%) | (%) |
| Methanol | +20 | 12 | 41 | 22 | 29 | 8 |
| *n*-Hexane | −10 | 18 | 10 | 0 | 61 | 29 |

While *cis*-(α*S*,1*R*,2*R*)-**5c** prevailed over *trans*-(α*S*,1*R*,2*S*)-**5a** in hexane, *trans*-**5a** was preferred over *cis*-**5c** in methanol. The second diastereomer *trans*-(α*S*,1*S*,2*R*)-**5b** only formed in methanol. The stereochemical compositions of the α-amino nitrile mixtures **5a–d** (obtained in nearly quantitative yields) are presented in Table 1 and are derived from our previously established $^{13}C$ NMR analysis.[10]

## 2.2. Acidic hydrolysis of α-amino nitriles 5 and separation of the resulting α-amino carboxamide mixtures 6

The nitrile mixture **5a–d** was hydrolysed in situ to the corresponding carboxamides **6a–d** with concd $H_2SO_4$ at 25 °C in a reaction monitored by means of NMR spectroscopy (Scheme 2). The reaction was completed after 4 days. $^{13}C$ NMR analysis of the crude reaction mixture showed four sets of signals, all containing the characteristic signal groups accounting for the 1-phenylethyl and the 2-methoxy moiety, thus indicating selective hydrolysis of the nitrile group. Carboxamides **6a–d** could be isolated by means of combined chromatographic methods and recrystallisation procedures. Compound *trans*-**6a** was separated directly from the crude α-amino carboxamide mixture by a single standard column chromatography, whereas separation of the *cis* configured compounds **6c** and **d** required a second column, which provided **6c** as well as **6d**. Compound *trans*-**6b** was crystallised from enriched fractions and cleaned by subsequent Lobar® chromatography.

## 2.3. Hydrogenolysis and final hydrolysis

The diastereomerically pure α-amino carboxamides **6a–d** obtained in this way, were separately hydrogenolysed using palladium on charcoal (10%) and ammonium formate to yield the corresponding primary α-amino carboxamides **7a–d**, respectively. Finally, **7a–d** were hydrolysed chemoselectively to the α-amino acid hydrochlorides **2a–d** under reflux in 0.7 M HCl for 24 h. Final hydrolysis to **1a–d** was achieved by refluxing either **7a–d** or **2a–d** for 96 h in 7.0 M HCl.

## 2.4. Absolute configuration

The structure and the relative configurations of all stereomers **1a–d**, **2a–d**, **5a–d**–**7a–d** were assigned by complete NMR analysis ($^1H$, $^{13}C$, $^1H$–$^1H$ COSY, and $^1H$–$^{13}C$ HETCOR). Finally, the absolute configuration of all compounds was unambiguously established by deductive conclusions from only two crystal X-ray analyses of the *trans* configured **6b** and the *cis* configured **ent-6c-HCl** (Fig. 1).

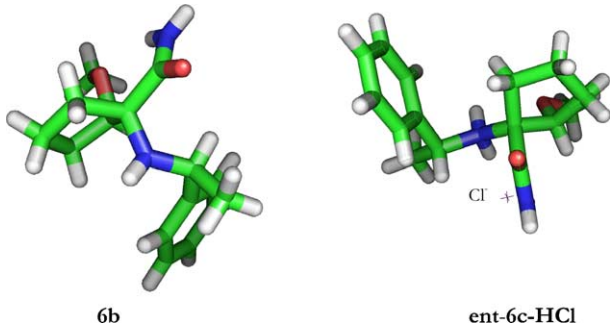



**Figure 1.** ORTEP plots of crystal structures.

The absolute configuration of the *trans* configured α-amino carboxamide **6b** was determined as *trans*-(α*S*,1*R*,2*R*). Thus the absolute configuration of **ent-6b** must be *trans*-(α*R*,1*S*,2*S*). Hydrogenolysis of the α-amino carboxamide **6b** led to **7b**, which turned out to be the enantiomer of **7a**, according to NMR data and specific rotation values. Therefore, the (1*S*,2*S*)-configuration was assigned to **7a**. The α-amino carboxamide **6a** was therefore *trans*-(α*S*,1*S*,2*S*) configured. Furthermore, the absolute configuration of the *trans* configured α-amino carboxamide hydrochloride **ent-6c** was established as *cis*-(α*R*,1*R*,2*S*). Hence, its enantiomer **6c** must be *cis*-(α*S*,1*S*,2*R*) configured. Hydrogenolysis of the α-amino carboxamide **6c** yielded **7c**, which is the enantiomer of **7d**, according to NMR data and specific rotation values. Therefore, a (1*R*,2*S*)-configuration was deduced for **7d**. Its precursor **6d** possesses the *cis*-(α*S*,1*R*,2*S*) configuration. The absolute configuration of the *cis* configured diastereomers is in accordance with earlier assignments in a series of asymmetric Strecker reactions.[9] The absolute configurations of the α-amino nitriles **5a–d** were correlated with those of the α-amino carboxamides **6a–d**. According to Cahn Ingold Prelog rules, the denotation of the absolute configuration of C-1 reverses formally because of a priority switch of the C-1 substituents after the conversion of α-amino nitriles **5** to the corresponding α-amino carboxamides **6**.

## 3. Conclusion

Starting from racemic 2-methoxycyclopentanone, the asymmetric Strecker synthesis yielded mixtures of three or four detectable α-amino nitriles **5** the stereochemical composition of which was influenced by the solvent and the temperature. Thermodynamically controlled reactions (MeOH, 25 °C) predominantly gave *trans* configured α-amino nitriles **5a** and **b** with a *trans*/*cis* diastereoselectivity (**5a**+**b**/**5c**+**d**) of 63:37. In contrast the kinetically controlled formation (*n*-hexane, −10 °C) yielded the *cis* configured products **5c** and **d** with a *cis*/*trans* ratio (**5c**+**d**/**5a**+**b**) of 90:10.

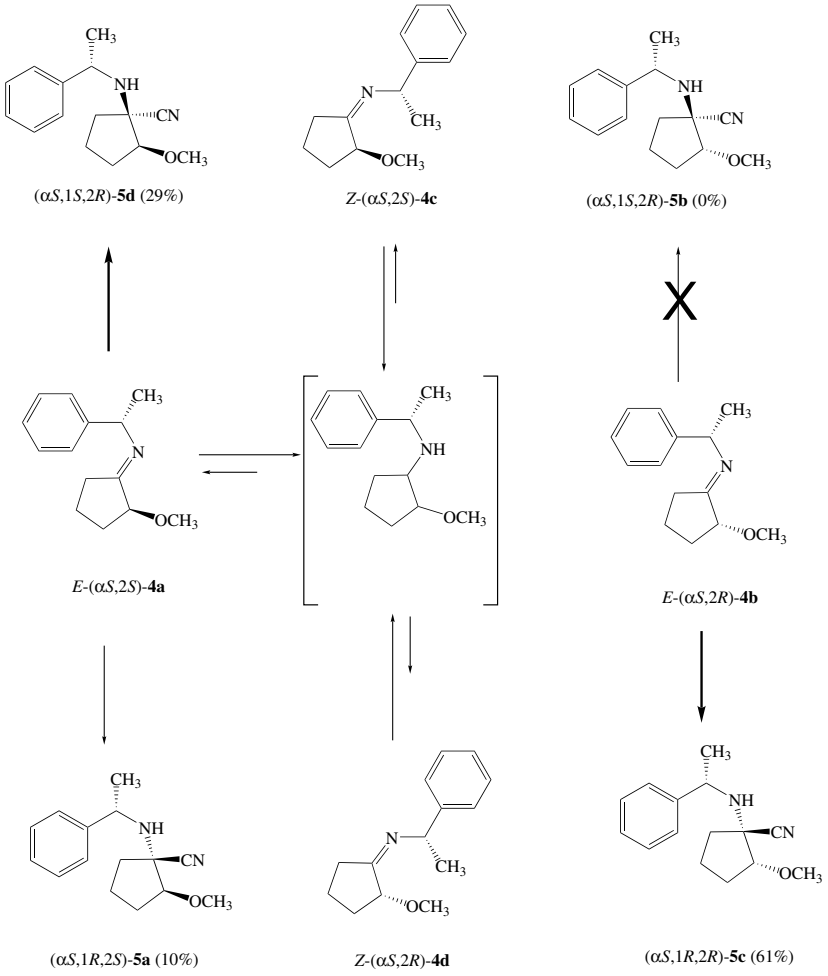
Regarding the zinc-mediated nucleophilic attack of cyanide to the ketimines **4a**–**d** (Scheme 3) the following conclusions can be drawn. *Si*-facial attack of the (*E*-α*S*,2*S*) and *re*-facial attack of the (*E*-α*S*,2*R*) configured ketimine **4a** and **4b** is under kinetic control resulting in the major *cis* products **5c** (61%) and **5d** (29%). Under kinetic control, the facial attack of the (*E*-α*S*,2*R*) configured ketimine **4b** does not occur. An enhanced complexation of the zinc ion in aprotic media increases the steric hindrance by the 1-(1-phenylethyl)-substituent and therefore hampers the facial attack of the (*E*-α*S*,2*S*) ketimine. Under thermodynamic control, both the (*E*-α*S*,2*S*) and the (*E*-α*S*,2*R*) configured ketimines **4a** and **4b** led to products **5a** (41%) and **5b** (22%) together with the *cis* configured **5c** in a rather high yield of 29%. The contribution of an attack of the thermodynamically less favoured (*Z*-α*S*,2*S*) and (*Z*-α*S*,2*R*) configured ketimines **4c** and **4d**, which are in equilibrium with the (*E*-α*S*,2*S*) and the (*E*-α*S*,2*R*) configured ketimine **4a** and **4b** is regarded as negligible. The shift of the 1:1 ratio of the 2*R*/2*S*-ketimines **4a**–**d** to a 6:4 ratio of the 2*R*/2*S*-α-amino nitriles **5a**–**d** under kinetic control may occur via an amino-enolether intermediate, which enables both the *E*/*Z* diastereomers to invert and the C-2 to epimerise rapidly.

In summary, we have reported on the asymmetric Strecker synthesis of stereomerically pure *trans*-(1*S*,2*S*)-, *trans*-(1*R*,2*R*)-, *cis*-(1*S*,2*R*)- and *cis*-(1*R*,2*S*)-1-amino-2-hydroxy- and 2-methoxycyclopentanecarboxylic acids.

## 4. Experimental

### 4.1. General methods

Melting points were determined with a Mel-Temp II apparatus (Devices Laboratory USA) and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded at 300 and 75.4 MHz, respectively, on a Varian Unity 300




**Scheme 3.** Reaction equilibria of the kinetically controlled Strecker addition of TMSCN to the ketimines **4a**–**b**.

spectrometer. The chemical shifts are reported as $\delta$-values using the solvent peaks as references. Optical rotations were measured on a Perkin–Elmer 241 spectrometer. Column chromatography was carried out with Merck silica gel Si60 (0.2–0.063 mm). TLC was performed on Si60 $F_{254}$ TLC plates from Merck. Drying of organic extracts during the workup of reactions was performed over anhydrous $Na_2SO_4$. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Microanalysis and HRMS were performed at the Department of Biochemistry and Organic Chemistry, University of Freiburg.

### 4.2. (*RS*)-2-Methoxycyclopentanone 3

(*RS*)-2-Methoxycyclopentanone **3** was prepared in two steps from cyclopentanone via chlorination (chlorine gas) to 2-chlorocyclopentanone followed by nucleophilic substitution in methanol with an overall yield of 43% (lit.: 47%).[11]

### 4.3. (*E*/*Z*)-2-(*RS*)-[*N*-(*S*)-1-Phenylethyl]methoxycyclopentylidenamines 4a–d (mixture of four diastereomers)

A mixture of (*RS*)-2-methoxycyclopentanone **3** (11.4 g, 0.1 mol), (*S*)-1-phenylethylamine (12.7 g, 0.105 mol) and a catalytic amount of *p*-toluenesulfonic acid was dissolved in toluene (50 mL) and heated under reflux for 3 h using a Dean–Stark apparatus. The solvent was evaporated in vacuum and the residue dried further under high vacuum to yield **4** (21.5 g, 99%) as a reddish oil, which was used in situ in further reactions.

**4.3.1. (*E*/*Z*)-2-(*RS*)-[*N*-(*S*)-1-Phenylethyl]methoxycyclopentylidenamines 4a–d.** IR (film), *v*: 3332, 3062, 3028, 2945, 2823, 1672, 1603, 1492, 1449, 1405, 1356, 1267, 1199, 1088, 1028, 761, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.2–2.5 (**a**–**d**) (m, 6H, cycloaliphatic *H*), 1.52 (**a**)/1.53 (**b**) (d, $J = 6.6$ Hz, 3H, 3 × β-C$H_3$), 3.49 (**a**)/3.41 (**b**)/3.38 (**c**)/3.50 (**d**) (s, 3H, OC$H_3$), 4.44 (**a**)/4.45 (**b**)/4.68 (**c**)/4.94 (**d**) (q, $J = 6.6$ Hz, 1H, α-*H*), 3.84 (**a**)/3.86 (**b**)/4.10 (**c**)/4.12 (**d**) (dd, 1H, 2-*H*), 7.1–7.5 (**a**–**d**) (m, 5H, aromatic *H*); $^{13}C$ NMR ($CDCl_3$): 20.50 (*E*)/20.36 (*E*) (t, C-4), 24.42 (*E*)/24.22 (*E*) (q, C-β), 26.63 (*E*)/26.55 (*E*) (t, C-3), 30.47 (*E*)/30.15 (*E*) (t, C-5), 56.23 (*E*)/56.09 (*E*) (d, C-α), 61.85 (*E*)/61.81 (*E*) (q, C-6), 84.88 (*Z*)/84.81 (*Z*)/82.71 (*E*)/82.68 (*E*) (d, C-2), 145.09 (*E*)/144.99 (*E*)/(s, C-1′), 175.36 (*E*)/175.05 (*E*) (s, C-1).

### 4.4. 2-Methoxy-1-(1-phenylethylamino)cyclopentanecarbonitrile mixture 5a–d (conditions of thermodynamic control)

To a solution of **4** (4.34 g, 0.02 mol) and dry zinc chloride (136 mg, 5 mol%) in methanol (20 mL) trimethylsilylcyanide (2.6 mL, 0.21 mol) was added at 20 °C over a period of 15 min. The reaction mixture was stirred for 12 h at 20 °C, filtered, concentrated under reduced pressure and dried under high vacuum to give a diastereomeric mixture of the α-amino nitriles **5a**–**d** (4.88 g, 98%), which was used in situ in further reactions.

### 4.5. 2-Methoxy-1-(1-phenylethylamino)cyclopentanecarbonitrile mixture 5a, 5c and 5d (conditions of kinetic control)

To a solution of **4** (4.34 g, 0.02 mol) and dry zinc chloride (136 mg, 5 mol%) in hexane (100 mL), trimethylsilylcyanide (2.6 mL, 0.21 mol) was added at −10 °C over a period of 30 min. The reaction mixture was stirred for 18 h at −10 °C, quenched with an equimolar volume (1 mL) of methanol, filtered, concentrated under reduced pressure and finally dried under high vacuum to yield a diastereomeric mixture of the α-amino nitriles **5a**, **5c** and **5d** (4.88 g, 98%), which was used in situ in further reactions.

**4.5.1. 2-Methoxy-1-(1-phenylethylamino)cyclopentanecarbonitrile mixture 5a–d.** IR (film), *v*: 3332, 2945, 2224, 1741, 1632, 1602, 1492, 1451, 1372, 1276, 1207, 1121, 1028, 764, 702 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.2–2.5 (**a**–**d**) (m, 6H, cycloaliphatic *H*), 1.52 (**a**)/1.53 (**b**) (d, $J = 6.7$ Hz, 3H, 3 × β-C$H_3$), 3.49 (**a**)/3.41 (**b**)/3.38 (**c**)/3.50 (**d**) (s, 3H, OC$H_3$), 4.44 (**a**)/4.45 (**b**)/4.68 (**c**)/4.94 (**d**) (q, 1H, α-*H*), 3.84 (**a**)/3.86 (**b**)/4.10 (**c**)/4.12 (**d**) (dd, 1H, 2-*H*), 7.1–7.5 (**a**–**d**) (m, 5H, aromatic *H*); $^{13}C$ NMR ($CDCl_3$): 18.80/18.61/22.02/20.13 (t, 4 × C-4), 25.61/25.98/25.61/25.00 (q, 4 × C-β), 26.60/27.39/27.74/27.47 (t, 4 × C-3), 34.56/33.45/37.83/35.82 (t, 4 × C-5), 66.14/60.99/65.76/61.04 (s,4 × C-1), 120.30/121.95/120.63/121.49 (s, 4 × C-6), 145.76/146.76/145.83/145.02 (s, 4 × C-1′).

### 4.6. General procedure: hydrolysis of the α-amino nitrile mixture 5

The diastereomeric α-amino nitrile mixture **5** (2.44 g, 0.01 mmol) was slowly added to concd $H_2SO_4$ (15 mL) at −10 °C. The mixture was stirred for 3 h at −10 °C, 3 h at 0 °C and for 96 h at 20 °C, decomposed on ice (80 g) and filtered. The filtrate was adjusted to pH 8 with $NH_3$ (14 M) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with water (1 × 50 mL), dried over anhyd $Na_2SO_4$, filtered, and the ether was evaporated, yielding the 3.35 g (63%) of the α-amino carboxamide mixture **6**, which was applied to gravity chromatography (stationary phase: Si60, 230–400 mesh; mobile phase: ethyl acetate–cyclohexane (6:4); fraction size: 10 mL; compound: stationary phase: 1:120; detection: TLC with ninhydrin reagent).

**4.6.1. Compounds 5a–d (see Section 4.4).** The α-amino nitrile mixture **5a**–**d** yielded the α-amino carboxamide **6a** (878 mg, 36%) and diastereomerically enriched fractions of **6b**, **6c**, and **6d**, respectively. The diastereomerically enriched fraction containing the diastereomer **6b** was crystallised from MeOH–water (8:2) and purified by Lobar® chromatography [stationary phase: RP18,

230–400 mesh; mobile phase: MeOH–water (8:2); fraction size: 10 mL; stationary phase: 120:1; detection: GC/MS] providing the diastereomerically pure α-amino carboxamide **6b** (340 mg, 14%).

**4.6.2. Compounds 5a, 5c and 5d (see Section 4.5).** The α-amino nitrile mixture **5a**, **5c** and **5d** yielded the α-amino carboxamide **6a** (195 mg, 8%) and diastereomerically enriched fractions of **6c** and **6d**, respectively, which were subjected to subsequent gravity chromatography [stationary phase: Si60, 230–400 mesh; mobile phase: ethyl acetate–cyclohexane–diethylamine (68:29:3); fraction size: 10 mL; stationary phase: 200:1; detection: GC/MS and TLC with UV-detection] yielding the diastereomerically pure α-amino carboxamides **6c** (970 mg, 37%) and **6d** (445 mg, 17%).

**4.6.2.1. *trans*-(α*S*,1*S*,2*S*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, 6a.** $[\alpha]_D^{25} = -3$ (*c* 0.81, $CH_3OH$); IR (film), *v*: 3453, 3334, 3187, 2982, 1657, 1611, 1451, 1380, 1176, 1130, 762, 702, 547, 484 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.31 (d, $^3J_{\beta\text{-H3}/\alpha\text{-H}} = 6.7$ Hz, 3H, β-$H_3$), 1.34/1.56 (m, 2H, 4-$H_2$), 1.34/1.92 (m, 2H, 5-*H*), 1.57/2.00 (m, 2H, 3-$H_2$), 2.16 (s, 1H, N–*H*), 3.27 (s, 3H, 6-$H_3$), 3.49 (m, 1H, 2-$H_2$), 3.80 (q, $^3J_{\alpha\text{-H}/\beta\text{-H3}} = 6.7$ Hz, 1H, α-*H*), 6.10/6.75 (s, 2H, amide *H*), 7.28 (m, 5H, aromatic *H*); $^{13}C$ NMR ($CDCl_3$): 19.42 (t, C-4), 25.74 (q, C-β), 27.21 (t, C-3), 29.12 (t, C-5), 54.11 (d, C-α), 57.01 (q, C-6), 72.35 (s, C-1), 88.99 (d, C-2), 147.29 (s, C-1′), 176.93 (s, C-8). Compound **6a-HCl**: MS (EI, 70 eV): *m*/*z* (%) 218 (100) [$M^+$−44 ($CONH_2$)]; 120 (9), 114 (65), 105 (50), 82 (11), 71 (9); MS (CI, isobutane, 200 eV): *m*/*z* (%) 263 (100) [$M^+$]. Anal. Calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38. Found: C, 59.98; H, 7.98; N, 9.06.

**4.6.2.2. *trans*-(α*S*,1*R*,2*R*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, 6b.** $[\alpha]_D^{25} = -93$ (*c* 1.10, $CH_3OH$); IR (KBr), *v*: 3409, 3306, 3251, 2964, 1666, 1451, 1387, 1123, 1070, 763, 703, 564, 468 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.32 (d, $^3J_{\beta\text{-H3}/\alpha\text{-H}} = 6.7$ Hz, 3H, β-$H_3$), 1.53/1.92 (m, 2H, 3-$H_2$), 1.65/2.20 (m, 2H, 5-$H_2$), 1.71 (m, 2H, 4-$H_2$), 1.98 (s, 1H, N-*H*), 3.08 (s, 3H, 6-$H_3$), 3.44 (m, 1H, 2-*H*), 3.76 (q, $^3J_{\alpha\text{-H}/\beta\text{-H3}} = 6.7$ Hz, 1H, α-*H*), 5.53/7.30 (s, 2H, amide-*H*), 7.28 (m, 5H, aromatic *H*); $^{13}C$ NMR ($CDCl_3$): 19.50 (t, C-4), 26.62 (q, C-β), 27.81 (t, C-3), 35.30 (t, C-5), 55.03 (d, C-α), 56.75 (q, C-6), 72.09 (s, C-1), 86.83 (d, C-2), 147.69 (s, C-1′), 177.01 (s, C-8). Compound **6b-HCl**: MS (EI, 70 eV): *m*/*z* (%) 218 (100) [$M^+$−44 ($CONH_2$)]; 120 (9), 114 (65), 105 (50), 97 (9), 82 (11), 77 (6), 71 (9); MS (CI, isobutane, 200 eV): *m*/*z* (%) 263 (100) [$M^+$]. Anal. Calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38. Found: C, 59.41; H, 7.87; N, 8.94.

**4.6.2.3. *cis*-(α*S*,1*S*,2*R*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, 6c.** $[\alpha]_D^{25} = -26$ (*c* 1.12, $CH_3OH$); IR (film), *v*: 3440, 3534, 3027, 2961, 1675, 1453, 1371, 1185, 1105, 762, 703, 552 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.38 (d, $^3J_{\beta\text{-H3}/\alpha\text{-H}} = 6.3$ Hz, 3H, β-$H_3$), 1.50 (m, 2H, 4-$H_2$), 1.69/1.98 (m, 2H, 5-$H_2$), 1.69/1.92 (m, 2H, 3-$H_2$), 2.24 (s, 1H, N-*H*), 3.30 (s, 3H, 6-$H_3$), 3.75 (dd, 1H, 2-*H*), 3.84 (q, $^3J_{\alpha\text{-H}/\beta\text{-H3}} = 6.7$ Hz, 1H, α-*H*), 5.83/7.30 (s, 2H, amide-*H*), 7.28 (m, 5H, aromatic *H*); $^{13}C$ NMR ($CDCl_3$): δ 19.81 (t, C-4), 25.47 (q, C-β), 28.16 (t, C-3), 29.71 (t, C-5), 53.95 (d, C-α), 57.33 (q, C-6), 70.44 (s, C-1), 86.96 (d, C-2), 147.31 (s, C-1′), 179.77 (s, C-8). Compound **6c-HCl**: anal. calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38; found: C, 60.35; H, 7.60; N, 8.91.

**4.6.2.4. *cis*-(α*S*,1*R*,2*S*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, 6d.** $[\alpha]_D^{25} = -18$ (*c* 1.05, $CH_3OH$); IR (film), *v*: 3460, 3344, 2967, 1722, 1651, 1450, 1380, 1316, 1273, 1163, 1032, 757, 699, 531 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.38 (d, $^3J_{\beta\text{-H3}/\alpha\text{-H}} = 6.7$ Hz, 3H, β-$H_3$), 1.69/1.98 (m, 2H, 5-$H_2$), 1.72 (m, 2H, 4-$H_2$), 1.85/2.16 (m, 2H, 3-$H_2$), 2.24 (s, 1H, N-*H*), 3.30 (s, 3H, 6-$H_3$), 3.80 (dd, 1H, 2-*H*), 3.84 (q, $^3J_{\alpha\text{-H}/\beta\text{-H3}} = 6.7$ Hz, 1H, α-*H*), 5.50, 7.00 (s, 2H, amide-*H*), 7.28 (m, 5H, aromatic *H*); $^{13}C$ NMR ($CDCl_3$): 20.46 (t, C-4), 26.04 (q, C-β), 28.76 (t, C-3), 31.50 (t, C-5), 53.95 (d, C-α), 57.33 (q, C-1″), 70.76 (s, C-1), 86.89 (d, C-2), 126.34 (C-2′/C-6′), 126.71 (C-4′), 128.40 (C-3′/C-5′), 147.14 (s, C-1′), 179.36 (s, C-8). Compound **6d-HCl**: anal. calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38; found: C, 60.06; H, 7.98; N, 9.10.

**4.6.2.5. *trans*-(α*R*,1*R*,2*R*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, ent-6a.** $[\alpha]_D^{25} = +1$ (*c* 1.10, $CH_3OH$); **ent-6a-HCl**: anal. calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38; found: C, 59.96; H, 7.65; N, 9.00.

**4.6.2.6. *trans*-(α*R*,1*S*,2*S*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, ent-6b.** $[\alpha]_D^{25} = +78$ (*c* 1.00, $CH_3OH$); **ent-6b-HCl**: anal. calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38; found: C, 59.82; H, 7.90; N, 9.10.

**4.6.2.7. *cis*-(α*R*,1*R*,2*S*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, ent-6c.** $[\alpha]_D^{25} = +32$ (*c* 1.08, $CH_3OH$); **ent-6c-HCl**: MS (EI, 70 eV): *m*/*z* (%) 218 (100) [$M^+$−44 ($CONH_2$)]; 120 (7), 114 (67), 105 (47), 97 (8), 82 (11), 77 (8), 71 (8); MS (CI, isobutane, 200 eV): *m*/*z* (%) 263 (100) [$M^+$]. Anal. Calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38. Found: C, 60.04; H, 7.98; N, 9.13.

**4.6.2.8. *cis*-(α*R*,1*S*,2*R*)-2-Methoxy-1-(1-phenylethylamino)cyclopentanecarboxamide, ent-6d.** $[\alpha]_D^{25} = +18$ (*c* 1.10, $CH_3OH$); **ent-6d-HCl**: anal. calcd for $C_{15}H_{23}N_2O_2Cl$: C, 60.29; H, 7.76; N, 9.38; found: C, 59.94; H, 7.87; N, 9.11.

### 4.7. General procedure: hydrogenolysis of the α-amino amides 6a–d to the α-amino amides 7a–d

To a solution of a diastereomerically pure α-amino carboxamide **6a–d** (260 mg, 1 mmol), in methanol (30 mL), Pd/C (10%, 280 mg) and ammonium formate (510 mg) were added and the resulting mixture heated under reflux for 2 h. The catalyst was removed by fil-

tration through Celite and the solvent evaporated yielding **7a**–**d** as colourless oils, which were converted into their hydrochloride salts using ether saturated with HCl gas.

**4.7.1. *trans*-(1*S*,2*S*)-1-Amino-2-methoxycyclopentanecarboxamide hydrochloride, 7a-HCl.** Mp 217–218 °C; $[\alpha]_D^{25} = +53$ (*c* 0.77, $CH_3OH$); IR (KBr), *v*: 2963, 1681, 1612, 1501, 1427, 1333, 1197, 1112, 1027, 915 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ 1.74–2.06 (m, 4H), 2.09–2.24 (m, 1H), 2.33–2.49 (m, 1H), 3.38 (s, 3H), 3.87 (dd, 1H); $^{13}C$ NMR ($CD_3OD$): 21.56 (t, C-4), 30.68 (t, C-3), 34.68 (t, C-5), 58.33 (q, C-1″), 69.62 (s, C-1), 88.33 (d, C-2), 172.82 (d, C-6); MS (CI, isobutane, 200 eV): *m*/*z* (%) 159 (100) [M−H$^+$], 114 (20), MS (EI, 70 eV): *m*/*z* (%) 126 (44), 114 (68), 109 (23), 97 (30), 82 (100), 55 (28). HRMS (EI, 70 eV): *m*/*z* 126 [M$^+$−32 ($CH_3OH$)], $C_6H_{10}N_2O$: calcd 126.0793, found 126.0793, 114 [M$^+$−44 ($CONH_2$)], $C_6H_{12}NO$: calcd 114.0919, found 114.0919.

**4.7.2. *trans*-(1*R*,2*R*)-1-Amino-2-methoxycyclopentanecarboxamide hydrochloride, 7b-HCl.** Mp 210–214 °C; $[\alpha]_D^{25} = -54$ (*c* 1.00, $CH_3OH$); IR (film), $^1H$ NMR ($CD_3OD$) and $^{13}C$ NMR ($CD_3OD$) data are identical with those of **7a-HCl**, HRMS (EI, 70 eV): *m*/*z* 126 [M$^+$−32 ($CH_3OH$)], $C_6H_{10}N_2O$: calcd 126.0793, found 126.0793, 114 [M$^+$-44 ($CONH_2$)], $C_6H_{12}NO$: calcd 114.0919, found 114.0918.

**4.7.3. *cis*-(1*S*,2*R*)-1-Amino-2-methoxycyclopentanecarboxamide hydrochloride, 7c-HCl.** Colourless oil; $[\alpha]_D^{25} = -6$ (*c* 1.03, $CH_3OH$); IR (film), $^1H$ NMR ($CD_3OD$) and $^{13}C$ NMR ($CD_3OD$) data are identical with those of **7d-HCl**, MS (EI, 70 eV): *m*/*z* (%) 126 (44), 114 (100), 109 (24), 97 (24), 87 (27), 82 (54), 55 (20). HRMS (EI, 70 eV): *m*/*z* 126 [M$^+$−32 ($CH_3OH$)], $C_6H_{10}N_2O$: calcd 126.0793, found 126.0790.

**4.7.4. *cis*-(1*R*,2*S*)-1-Amino-2-methoxycyclopentanecarboxamide hydrochloride, 7d-HCl.** Mp 214–216 °C (decomp.); $[\alpha]_D^{25} = +9$ (*c* 1.05, $CH_3OH$); IR (KBr), *v*: 3144, 2931, 1683, 1624, 1569, 1489, 1388, 1363, 1180, 1122, 1083, 1018 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ 1.68–1.84 (m, 1H), 1.85–2.08 (m, 3H), 2.19–2.39 (m, 2H), 3.40 (s, 3H), 4.20 (dd, 1H); $^{13}C$ NMR ($CD_3OD$): 20.78 (t, C-4), 30.06 (t, C-3), 34.77 (t, C-5), 58.69 (q, C-1″), 68.21 (s, C-1), 86.67 (d, C-2), 174.54 (d, C-6); MS (EI, 70 eV): *m*/*z* (%) 159 (0.5), 126 (39), 114 (100), 109 (21), 97 (20), 87 (30), 82 (52), 55 (19). HRMS (EI, 70 eV): *m*/*z* 159 [MH$^+$], $C_7H_{15}N_2O_2$: calcd 159.1134, found 159.1137.

### 4.8. General procedure: hydrolysis of the α-amino amides 7a–d to the α-amino acid hydrochlorides 2a–d

The α-amino amide hydrochloride **7a**–**d** (1 mmol) was dissolved in 0.70 M hydrochloric acid (10 mL) and heated under reflux at 100 °C for 24 h. The solution was evaporated to dryness. The residue was twice dissolved in 10 mL of water and evaporated again. The crude α-amino acid hydrochlorides **2a**–**d** were washed with small amounts of diethyl ether and ethyl acetate and finally dried in high vacuum.

**4.8.1. *trans*-(1*S*,2*S*)-1-Amino-2-methoxycyclopentanecarboxylic acid hydrochloride, 2a-HCl.** Mp >250 °C (decomp.); $[\alpha]_D^{25} = +43$ (*c* 0.85, $CH_3OH$); IR (KBr), *v*: 2943, 1682, 1578, 1509, 1467, 1412, 1355, 1190, 1117, 1029, 944, 832 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ 1.78–2.07 (m, 4H), 2.15–2.28 (m, 1H), 2.38–2.51 (m, 1H), 3.38 (s, 3H), 3.98 (dd, 1H); $^{13}C$ NMR ($CD_3OD$): 21.23 (t, C-4), 29.92 (t, C-3), 33.39 (t, C-5), 58.65 (q, C-1″), 68.78 (s, C-1), 88.79 (d, C-2), 171.70 (d, C-6); HRMS (EI, 70 eV): *m*/*z* 127 [M$^+$−32 ($CH_3OH$)], $C_6H_9NO_2$: calcd 127.0633, found 127.0634.

**4.8.2. *trans*-(1*R*,2*R*)-1-Amino-2-methoxycyclopentanecarboxylic acid hydrochloride, 2b-HCl.** Mp >250 °C (decomp.); $[\alpha]_D^{25} = -34$ (*c* 0.70, $CH_3OH$); IR (film), $^1H$ NMR ($CD_3OD$) and $^{13}C$ NMR ($CD_3OD$) data are identical with those of **2a-HCl**, MS (CI, isobutane, 200 eV): *m*/*z* (%) 160 (100) [MH$^+$], 114 (7) [M$^+$−45 (COOH)], MS (EI, 70 eV): *m*/*z* (%) 127 (64), 114 (56), 109 (42), 97 (21), 82 (100), 55 (23), 42 (31). HRMS (EI, 70 eV): *m*/*z* 127 [M$^+$−32 ($CH_3OH$)], $C_6H_9NO_2$: calcd 127.0633, found 127.0635, 114; [M$^+$−45 (COOH)], $C_6H_{12}NO$: calcd 114.0919, found 114.0919.

**4.8.3. *cis*-(1*S*,2*R*)-1-Amino-2-methoxycyclopentanecarboxylic acid hydrochloride, 2c-HCl.** Mp >223 °C (decomp.); $[\alpha]_D^{25} = -19$ (*c* 0.93, $CH_3OH$); IR (film), $^1H$ NMR ($CD_3OD$) and $^{13}C$ NMR ($CD_3OD$) data are identical with those of **2d-HCl**, HRMS (EI, 70 eV): *m*/*z* 127 [M$^+$−32 ($CH_3OH$)], $C_6H_9NO_2$: calcd 127.0633, found 127.0634; 114 [M$^+$−45 (COOH)], $C_6H_{12}NO$: calcd 114.0919, found 114.0919.

**4.8.4. *cis*-(1*R*,2*S*)-1-Amino-2-methoxycyclopentanecarboxylic acid hydrochloride, 2d-HCl.** Mp >215 °C (decomp.); $[\alpha]_D^{25} = +24$ (*c* 0.91, $CH_3OH$); IR (KBr), *v*: 2934, 1695, 1572, 1493, 1363, 1119 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ 1.70–2.00 (m, 4H), 2.19–2.39 (m, 2H), 3.38 (s, 3H), 4.11 (dd, 1H); $^{13}C$ NMR ($CD_3OD$): 21.73 (t, C-4), 30.66 (t, C-3), 35.11 (t, C-5), 58.39 (q, C-1″), 67.02 (s, C-1), 85.91 (d, C-2), 173.56 (d, C-6); MS (CI, isobutane, 200 eV): *m*/*z* (%) 160 (100) [MH$^+$], MS (EI, 70 eV): *m*/*z* (%) 127 (76), 114 (84), 109 (62), 100 (23), 97 (35), 82 (100), 55 (44); HRMS (EI, 70 eV): *m*/*z* 160 [MH$^+$], $C_7H_{14}NO_3$: calcd 160.0974, found 160.0973; 127 [M$^+$−32 ($CH_3OH$)], $C_6H_9NO_2$: calcd 127.0633, found 127.0635; 114 [M$^+$−45 (COOH)] $C_6H_{12}NO$: calcd 114.0919, found 114.0918.

### 4.9. General procedure: hydrolysis of the α-amino amides 7a–d and α-amino acid hydrochlorides 2a–d, respectively, to the α-amino acid hydrochlorides 1a–d

One of the α-amino amide hydrochlorides **7a**–**d** (1 mmol) or one of the α-amino acid hydrochlorides **2a**–**d** was dissolved in 7.0 M hydrochloric acid (10 mL) and heated under reflux for 48 h. The solution was evaporated to

dryness. The residue was dissolved twice in 10 mL of water and evaporated again. The crude α-amino acid hydrochlorides **1a–d** were washed with small amounts of diethyl ether and ethyl acetate and finally dried in high vacuum.

**4.9.1. *trans*-(1*S*,2*S*)-1-Amino-2-hydroxycyclopentanecarboxylic acid hydrochloride, 1a-HCl.** Mp 214 °C; $[\alpha]_D^{25} = +21$ (*c* 0.68, $CH_3OH$); IR (KBr), *v*: 2911, 1732, 1582, 1503, 1446, 1409, 1207, 1094, 1069, 1013, 968 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): δ 1.72–2.14 (m, 5H), 2.35–2.52 (m, 1H), 4.32 (dd, 1H); $^{13}C$ NMR ($CD_3OD$): 21.23 (t, C-4), 33.46 (t, C-3), 33.53 (t, C-5), 69.64 (s, C-1), 80.09 (d, C-2), 172.24 (d, C-6); MS (CI, isobutane, 200 eV): *m/z* (%) 146 (100) [$M^+$], 128 (28) [$M^+-(H_2O)$], 100 (14) [$M-H^+-45$ (COOH)], MS (EI, 70 eV): *m/z* (%) 127 (27), 109 (28), 100 (100), 98 (32), 82 (56), 56 (56), 42 (69). HRMS (EI, 70 eV): *m/z* 127 [$M+H^+-H_3O^+$], $C_6H_9NO_2$: calcd 127.0633, found 127.0634; 100 [$M^+-45$ (COOH)] $C_5H_{10}NO$: calcd 100.0762, found. 100.0762.

**4.9.2. *trans*-(1*R*,2*R*)-1-Amino-2-hydroxycyclopentanecarboxylic acid hydrochloride, 1b-HCl.** Mp 223 °C; $[\alpha]_D^{25} = -29$ (*c* 1.03, $CH_3OH$); IR (film), $^1H$ NMR ($CD_3OD$) and $^{13}C$ NMR ($CD_3OD$) data are identical with those of **1a-HCl**, HRMS (EI, 70 eV): *m/z* 127 [$M+H^+-H_3O^+$] $C_6H_9NO_2$: calcd 127.0633, found 127.0634.

**4.9.3. *cis*-(1*S*,2*R*)-1-Amino-2-hydroxycyclopentanecarboxylic acid hydrochloride, 1c-HCl.** Mp 218 °C; $[\alpha]_D^{25} = -14$ (*c* 0.63, $CH_3OH$); IR (film), $^1H$ NMR ($CD_3OD$) and $^{13}C$ NMR ($CD_3OD$) data are identical with those of **1d-HCl**, MS (EI, 70 eV): *m/z* (%) 146 (1), 127 (23), 109 (22), 100 (100), 88 (31), 82 (53), 70 (22), 55 (45), 44 (34). HRMS (EI, 70 eV): *m/z* 127 [$M+H^+-H_3O^+$], $C_6H_9NO_2$: calcd 127.0633, found 127.0635.

**4.9.4. *cis*-(1*R*,2*S*)-1-Amino-2-hydroxycyclopentanecarboxylic acid hydrochloride, 1d-HCl.** Mp 193–195 °C; $[\alpha]_D^{25} = +17$ (*c* 0.97, $CH_3OH$); IR (KBr), *v*: 2945, 1727, 1497, 1399, 1207, 1111, 825, 702 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): δ 1.68–2.03 (m, 4H), 2.08–2.23 (m, 1H), 2.28-2.42 (m, 1H), 4.47 (dd, 1H); $^{13}C$ NMR ($CD_3OD$): 21.67 (t, C-4), 34.18 (t, C-3), 34.88 (t, C-5), 67.80 (s, C-1), 76.83 (d, C-2), 173.80 (d, C-6); MS (CI, isobutane, 200 eV): *m/z* (%) 146 (100) [$MH^+$], 100 (8) [$M^+-45$ (COOH)], MS (EI, 70 eV): *m/z* (%) 146 (2), 127 (25), 109 (22), 100 (100), 98 (22), 88 (29), 82(53), 55 (38), 42 (48). HRMS (EI, 70 eV): *m/z* 146 [$MH^+$], $C_6H_{12}NO_3$: calcd 146.0817, found 146.0817.

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