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Carbocyclic α,β-diamino acids: asymmetric Strecker synthesis of stereomeric 1,2-diaminocyclohexanecarboxylic acids

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Abstract—Asymmetric syntheses of *trans*-(*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexanecarboxylic acids have been achieved with ee >99% while the respective *cis*-(*R*,*S*)- and (*S*,*R*)-stereoisomers were obtained as 1-amino-2-benzoylaminocyclohexanecarboxylic acids. The underlying second generation asymmetric synthesis proceeds via Strecker reaction with commercially available (*R*)- and (*S*)-1-phenylethylamine (1-PEA) as chiral auxiliaries, TMSCN as cyanide source and racemic 2-benzoylaminocyclohexanone. The key stereodifferentiating step of the cyanide addition to the chiral ketimine intermediates has been studied under the influence of protic and aprotic solvents. Hydrolysis of the nitriles to the carboxamides with conc. H_2SO_4 yielded dramatic changes in the product composition as a function of temperature and time. Hydrolysis of both the attendant amido groups are concomitant processes in case of the *trans*-configured carboxamides while the *cis*-stereoisomers undergo selective carboxamide hydrolysis, with the benzoyl protecting group remaining intact, leading to orthogonally protected α,β-diamino acids. The absolute configurations of the amino acids and their intermediates have been assigned based on detailed NMR spectroscopic analysis and X-ray data.

1. Introduction

In recent years, the structural features of both α,α-disubstituted α-amino acids and the β-amino acids have gained increasing attention in the field of medicinal chemistry due to a variety of interesting biological properties they may account for.

α,α-Dialkyl α-amino acids are widely used in the isosteric replacement of proteinogenic amino acids in peptides,[1] favoring specific backbone conformations and, thus, leading to stabilized secondary peptide structures.[2] Moreover, this incorporation increases the stability of these peptides towards chemical and enzymatic degradation. Hence, α,α-disubstituted α-amino acids are building blocks for the design and synthesis of new peptide hormones and enzyme inhibitors.[3] Furthermore, α,α-dialkyl α-amino acids such as α-alkylated phenylglycine derivatives, the respective carbocyclic analogue 1-aminoindanedicarboxylic acid (AIDA), and the stereoisomeric 1-aminocyclopentane-1,3-dicarboxylic acids (ACPD), have been described as ligands at both the ionotropic and metabotropic glutamate receptors.[4] They have also been used as tools in the family- and subtype-classification of mGluRs.[5]

β-Amino acids, such as the neurotoxin β-*N*-methylamino-L-alanine (BMAA), are reported to function as modulators of the glycine binding site of the NMDA receptor complex.[6] In addition, β-peptides, the short oligomers of β-amino acids, can adopt all types of secondary peptide structures (helix, sheets and turns) and are considered as alternatives to α-amino acid oligomers since the β-peptide backbone offers greater opportunities for conformational rigidity than the α-peptides do.[7] We reasoned that chimeric compounds bearing both the structural features of α,α-disubstituted α-amino acids and of β-amino acids are of considerable interest in various fields of medicinal chemistry.

Since the asymmetric Strecker reaction[8] has proved to be a powerful and convenient experimental protocol for the synthesis of β-substituted α-amino acids,[9] we planned the preparation of the stereoisomeric α,β-diaminocyclohexanecarboxylic acids starting from the *N*-protected cyclohexanone **1** or **1′** and 1-phenylethylamine as the chiral auxiliary. The results of these investigations are discussed in this paper.

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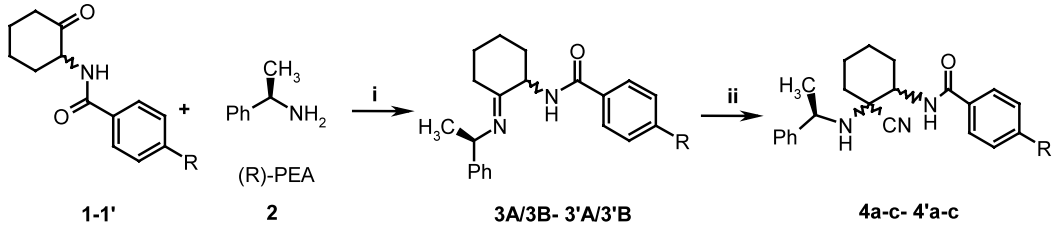
2. Results and discussion

The whole of this discussion is based on the compounds obtained with the chiral auxiliary (*R*)-1-PEA. The respective enantiomeric compounds (**ent-Xa-c**) were synthesized via the same sequence upon replacement of this chiral auxiliary with its antipode (*S*)-1-PEA.

Asymmetric synthesis of the 1,2-diamino acids was designed with racemic 2-protected-amino-cyclohexanone **1** or **1′** prepared from cyclohexene oxide following a procedure previously reported from our laboratory.[10] Condensation of **1** or **1′** with a threefold excess of (*R*)-1-PEA **2** under azeotropic removal of water gave a mixture of only two diastereomeric (*E*)-imines **3A**/**B** or **3′A**/**B** in a ratio of 1:1 (Scheme 1). In contrast to our earlier studies no (*Z*)-isomers were observed. The **3A**/**B** or **3′A**/**B** mixture was subsequently subjected to Lewis acid-catalyzed cyanide addition using trimethylsilylcyanide (TMSCN). Since an additional stereo center at C-1 is generated in this step, four diastereomeric α-amino nitriles (two with *cis* and two with *trans* configuration) are theoretically feasible. In a series of earlier works we had observed dramatic changes in the *cis*/*trans* diastereoselectivity as a factor of the nature of the solvent.[9] Indeed, while protic solvents favored the thermodynamically more stable *trans* isomers, aprotic solvents led to diastereomeric mixtures with predominance of the *cis* isomer. In the study presented herein, although variation of the product composition was observed upon solvent and temperature changes, the overall *cis*/*trans* diastereoselectivity was not reversed and under all conditions investigated, the *trans*-(α*R*,1*R*,2*R*)-α-amino nitrile **4a** or **4′a** was the major reaction product. However, while the formation of *trans*-(α*R*,1*S*,2*S*)-**4b** or **4′b** is preferred over *cis*-(α*R*,1*R*,2*S*)-**4c** or **4′c** in methanol, *cis*-**4c** or **4′c** predominates *trans*-**4b** or **4′b** in hexane. The fourth diastereomer *cis*-(α*R*,1*S*,2*R*)-**4d** or **4′d** is formed neither in methanol nor in hexane. The stereochemical composition of the α-amino nitrile mixtures **4a–c** and **4′a–c** (obtained in quantitative yields) is presented in Table 1 and is derived from our previously established ^{13}C NMR analysis.[9]

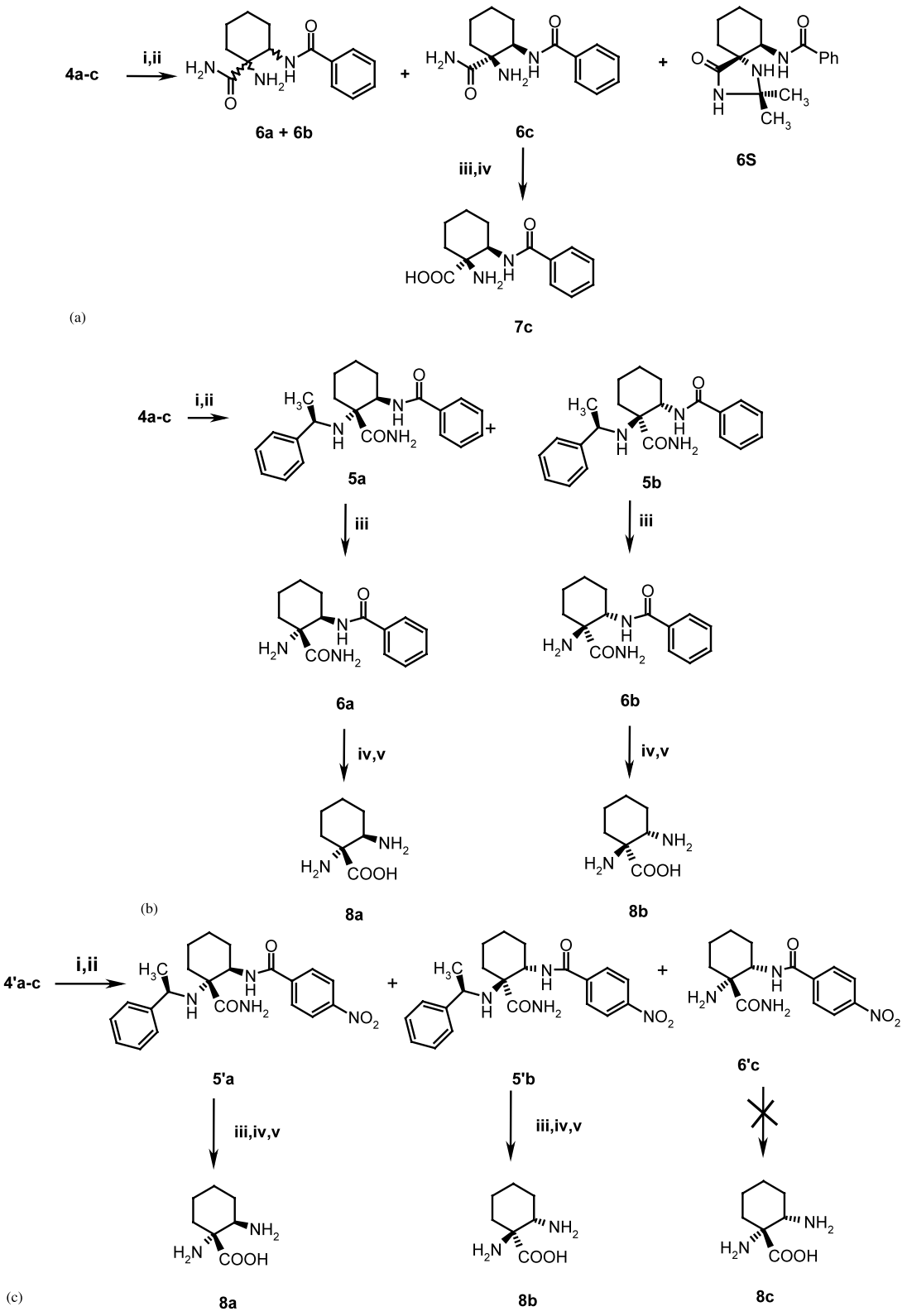
Subsequently, the nitrile mixture **4a–c** was hydrolyzed to the corresponding carboxamides with conc. H_2SO_4 at 25°C in a reaction monitored by means of infrared spectroscopy (Scheme 2(a)). The reaction was completed after 3 days. ^{13}C NMR analysis of the crude reaction mixture showed two sets of signals, both devoid of the characteristic signal groups accounting for the 1-phenylethyl moiety, thus indicating simultaneous hydrolysis and hydrogenolysis. Standard column chromatography followed by low pressure liquid chromatography (LPLC) resulted in the separation of the homochiral α-amino carboxamide *cis*-**6c** from the mixture of the two *trans*-configured enantiomers **6a** and **6b**. Furthermore, a *trans* spiro heterocyclic compound **6S** could be isolated and characterized by means of NMR and HRMS analysis. This compound is assumed to arise from a silica gel-catalyzed imine formation between the primary amine and the acetone co-eluent, followed by ring-closure via nucleophilic attack of the amido-nitrogen on the imine carbon during column chromatography. Refluxing the *cis* configured **6c** for 2 days in conc. HCl gave only orthogonally protected **7c** as the sole product (Scheme 2(a)), which could neither be hydrolyzed to *N*-unprotected α,β-diamino acid by increasing reaction time up to 2 weeks nor by using base-catalyzed hydrolysis with aqueous sodium hydroxide, Claisen's alkali (KOH, methanol, water) and



Scheme 1. R = H: **1–4** series; R = NO_2: **1′–4′** series. *Reagents and conditions*: (i) *p*-toluenesulfonic acid, toluene, reflux, 5 h; (ii) TMSCN, $ZnCl_2$, methanol (or hexane), 0°C, 3 h.

Table 1. Stereochemical distributions of the α-amino nitriles **4a–c** and **4′a–c**, respectively, obtained under different reaction conditions

Reaction conditions [solvent, T, t]	**4a**/**4′a** α*R*,1*R*,2*R* (*trans*)	**4b**/**4′b** α*R*,1*S*,2*S* (*trans*)	**4c**/**4′c** α*R*,1*R*,2*S* (*cis*)	**4d**/**4′d** α*R*,1*S*,2*R* (*cis*)
MeOH; 0°C; 3 h	51/–	25/–	24/–	0/–
Hexane; 0°C; 3 h	53/50	33/37	14/13	0/0
Hexane; −20°C; 24 h	52/–	31/–	17/–	0/–



Scheme 2. *Reagents and conditions*: (a) (i) conc. H_2SO_4, −10°C for 30 min and 25°C for 3 days; (ii) CC, EtOAc/acetone (1:1), followed by LPLC; (iii) conc. HCl, 0°C, 2 h, then reflux for 2 days; (iv) Dowex 50WX.8.100 (NH_4^+ form), 1 M NH_3. (b) (i) conc. H_2SO_4, −20°C, 10 days; (ii) CC, cyclohexane/EtOAc (1:1); (iii) Pd/C (10%), HCO_2NH_4, methanol, reflux, 2 h; (iv) conc. HCl, 0°C, 2 h, then reflux for 2 days; (v) Dowex 50WX.8.100 (NH_4^+ form), 1 M NH_3. (c) (i) conc. H_2SO_4, CH_2Cl_2, −10°C for 30 min then 3 days at rt; (ii) CC, EtOAc/acetone (1/1), followed by CC, EtOAc/cyclohexane/diethylamine (4/6/5 drops); (iii) Pd/C (10%), HCO_2NH_4, methanol, reflux, 2 h; (iv) conc. HCl, 0°C, 2 h, then reflux for 2 days; (v) Dowex 50WX.8.100 (NH_4^+ form), 1 M NH_3.

KOH/ethylene glycol at high temperatures. After several trials to change the protecting group (acetyl, Boc) we reasoned that among the more reactive *N*-protecting groups, not affected by conc. H_2SO_4 at room temperature, the *p*-nitro substituted benzoyl moiety should be more suitable for final deprotection. Thus, the Strecker sequence was repeated with this protecting group.

In order to obtain the non-hydrogenolyzed products, the ^{13}C NMR-monitored hydrolysis was performed at −20°C. After 10 days the complete set of amino nitriles had been consumed. Subsequent chromatographic separation of the reaction products yielded the two diastereomerically pure *trans*-configured carboxamides **5a** and **5b** (Scheme 2(b)) with the intact 1-phenylethylamino moiety.

The structure and the relative stereochemistry of the minor diastereomer **5b** was assigned by complete NMR analysis (^1H, ^{13}C, ^1H–^1H COSY, ^1H–^{13}C HETCOR and 2D-INEPT). Finally, its absolute stereochemistry was established as α*R*,1*S*,2*S* by single crystal X-ray analysis (Fig. 1). Since the primary amino amides **6a** and **6b** obtained from the hydrogenolysis of **5a** and **5b**, respectively, showed opposite specific rotation values, the absolute stereochemistry α*R*,1*R*,2*R* was assigned to the second parent compound **5a**. All of our efforts to isolate any of the *cis* configured stereoisomer failed under these conditions. Since benzoic acid could be isolated from the crude reaction mixture, the 2-benzoylamino group must have been hydrolysed and the resulting *cis*-2-amino-1-(1-phenylethylamino)cyclohexanecarbonitrile is probably further degraded. The catalytic transfer hydrogenolysis of the *trans* configured compounds **5a** and **5b** underwent smoothly with Pd/C and ammonium formate in methanol to give the corresponding *trans*-(1*R*,2*R*)-**6a** and *trans*-(1*S*,2*S*)-**6b**, respectively, in 89–92% yield. Concomitant hydrolysis of both the amide groups occurred upon refluxing **6a** and **6b**, respectively, in concentrated HCl for 2 days yielding the diamino acid hydrochlorides *trans*-(1*R*,2*R*)-**8a·2HCl** and *trans*-(1*S*,2*S*)-**8b·2HCl**, respectively. The respective free zwitterionic α-amino acids **8a** and **8b** were obtained by means of ion-exchange chromatography on a Dowex 50WX column. All of our efforts to prepare the *trans*-configured 1-amino-2-benzoylamino-cyclohexanecarboxylic acids considered to be orthogonally protected *trans* α-amino acids, by selective hydrolysis of only the carboxamide group to the respective carboxylic acid, preserving the 2-benzoylamino group, failed. Hydrolysis of **6a** with hydrochloric acid under varying concentration and temperature conditions gave only differing product compositions (presented in Table 2).

Table 2. Product distribution of the acidic hydrolysis of **6a** versus HCl concentration

Conditions	Time (h)	**8a** (%)	**7a** (%)
Conc. HCl/reflux	48	100	0
Conc. HCl/reflux	24	95	5
6N HCl/reflux	6	88	12
2N HCl/reflux	6	86	14
2N HCl/reflux	2	41	34*

* 25% unreacted **6a**.

Further lowering of the temperature of the nitrile hydrolysis to −30°C did not allow the isolation of the *cis* α-amino carboxamide **5c**. However, chromatographic separation of the complex mixture, obtained after not less than 30 days, gave *trans*-**5a** (α*R*,1*R*,2*R*) along with the 2-benzoylamino ketone **1** and 1-PEA. Neither *trans*-**5b** nor any of the *cis* secondary α-amino carboxamide were isolated, indicating that the cyanide elimination reaction and subsequent imine hydrolysis are successfully competing with cyanide hydrolysis under these reaction conditions.

The very sensitive hydrolysis of the amino nitrile mixture was performed under slightly modified conditions in the case of the **4′a–c** mixture. Thus, the cyanide mixture was taken up in CH_2Cl_2, added to pre-cooled (−10°C) conc. H_2SO_4, and subsequently reacted at room temperature leading to the isolation of **5′a**, **5′b** and **6′c** after standard workup and column chromatography (Scheme 2(c)). Unfortunately, analogously to **6c**,

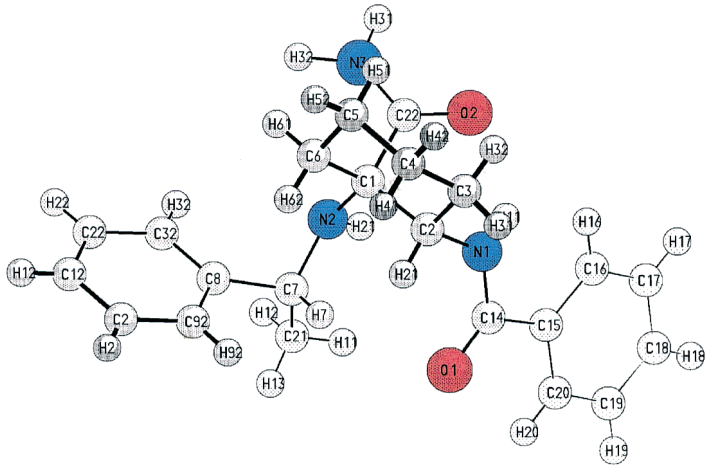


Figure 1. ORTEP plot of the crystal structure of **5b**.

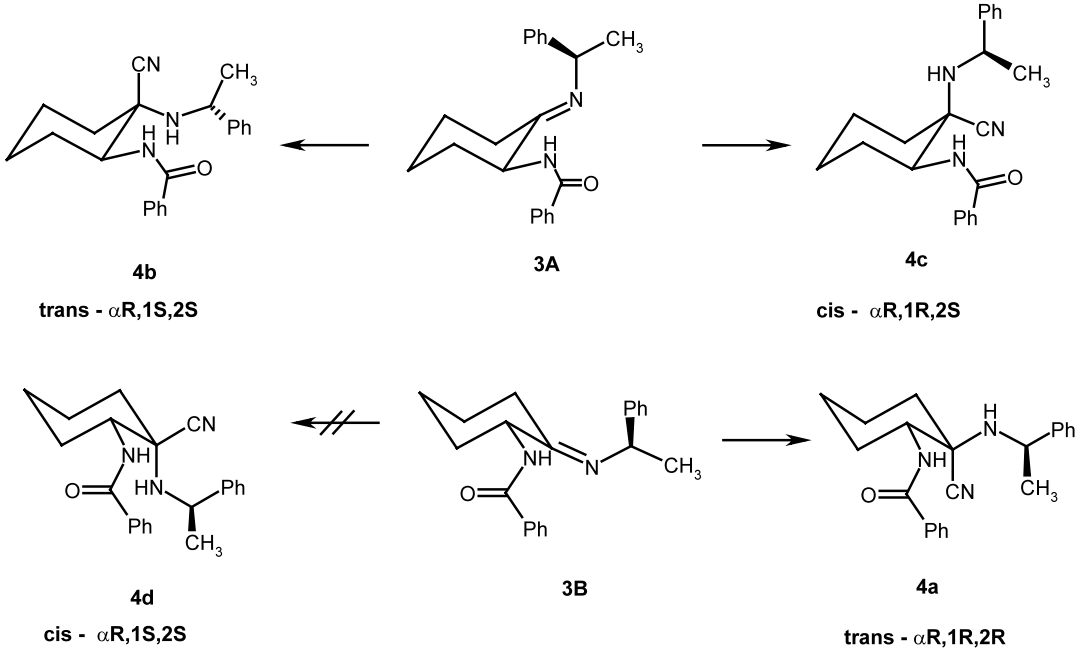
the intermediate **6′c** could not be hydrolyzed to the corresponding free diamino acid under any of the conditions investigated.

The determination of the absolute stereochemistry of the theoretically feasible cyanide addition products **4a–c**, which were identified in the crude ^{13}C NMR spectrum by three sets of signals, corresponding to three amino nitriles, proved particularly challenging (Scheme 3). As was observed earlier for 2-substituted cyclohexylimines in methanol,[7,8,10] the addition of cyanide to chiral imines occurs under thermodynamic control resulting in the formation of a major *trans*-configured diastereomer. Based on these findings, the major reaction product (≈50%) in methanol was tentatively assigned the *trans* configuration. The same diastereomer also predominates when the reaction is carried out in a non-polar solvent (hexane). The second major diastereomer in methanol becomes the minor in hexane and the minor diastereomer in methanol becomes second major in hexane. Accordingly, they were assigned the *trans*- and *cis*-configuration, respectively. Since nitrile hydrolysis at −20°C yielded a carboxamide mixture of (α*R*,1*R*,2*R*)-**5a** and (α*R*,1*S*,2*S*)-**5b** with **5a** as the major product, the absolute configurations of their precursors, **4a** and **4b**, respectively, could be assigned accordingly. Thus, the major *trans* diastereomer **4a** has α*R*,1*R*,2*R* configuration, whilst the second *trans* diastereomer **4b** has α*R*,1*S*,2*S* configuration. Obviously the imine (*E*,α*R*,2*R*)-**3B** was consumed completely for the formation of the major *trans* diastereomer (α*R*,1*R*,2*R*)-**4a** in ≈50% yield. Hence, the simultaneous formation of a *cis*-configured compound with **2*R*** configuration is theoretically impossible. Consequently, the *cis* configured compound **4c** must have the absolute configuration α*R*,1*R*,2*S* and originates along with the minor *trans* diastereomer **4b** (α*R*,1*S*,2*S*) from the imine **3A** (*E*,α*R*,2*S*) contained also with 50% in the (*E*)-imine mixture (Scheme 3). These findings support our earlier observations of a 'like induction' at C-1 during the addition of cyanide to ketimines.[9,11]

Since the stereocenters are not affected in the following steps we could assign the absolute configurations to the α,β-diamino acids as follows: 1*R*,2*R* to **8a**, 1*S*,2*S* to **8b**, 1*R*,2*S* to **7c** and 1*S*,2*R* to *ent*-**7c**. The ee values of the *trans*-configured α,β-diamino acids were determined by means of chiral HPLC according to a method developed in our laboratory (column: D-Penicillamine, mobile phase: 0.3 mM $CuSO_4$ in H_2O, temp. 20°C, flow rate:0.8 mL/min) and were found to be >99% for **8a** and **8b**, respectively.[11] The enantiomeric unity of **7c** and *ent*-**7c** is assumed since they arise from the respective unique *cis*-α-amino nitrile formed in the stereodetermining cyanide addition step as discussed earlier.

3. Conclusion

In conclusion, in this contribution we have reported on the asymmetric Strecker synthesis of *trans*-(1*R*,2*R*)- and (1*S*,2*S*)-1,2-diaminocyclohexanecarboxylic acids with ee values >99% and enantiomerically pure, orthogonally protected *cis*-(1*R*,2*S*)- and (1*S*,2*R*)-1-amino-2-benzoylaminocyclohexanecarboxylic acids.



Scheme 3. Mechanistic aspects of the cyanide addition to the ketimine mixture **3A**/**B**.

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 spectrometer. The chemical shifts are reported as δ values using the solvent peaks as reference. 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 with 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. Preparation of the aminocyclohexanones, 1 and 1′

4.2.1. (*RS*)-2-Benzoylaminocyclohexanone, 1. Prepared from cyclohexeneoxide according to literature procedure.[10] For NMR data see Ref. 10.

4.2.2. (*RS*)-2-*p*-Nitrobenzoylaminocyclohexanone, 1′. Prepared according to Ref. 10: ^{1}H NMR ($CDCl_3$) 1.40–1.54 (m, 1H), 1.64–1.98 (m, 3H), 2.14–2.26 (m, 1H), 2.42–2.64 (m, 2H), 2.78–2.88 (m, 1H), 4.68 (m, $J=5.5$ Hz, 1H), 7.26 (brs., NH) 7.96 (d, $J=8.8$ Hz, 2H), 8.28 (d, $J=8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 23.75 (CH_2), 27.84 (CH_2), 35.12 (CH_2), 40.83 (CH_2), 58.45 (CH), 123. 59 (CH), 123.59 (CH), 128.05 (CH), 128.05 (CH), 149.53 (CH), 164.51 (CO), 207.21 (CO).

4.3. Imine condensation

A solution of **1** or **1′** (1.09 g, 5 mmol), *p*-toluenesulfonic acid (15 mg) and (*R*)-1-phenylethylamine (0.43 g, 7 mmol) in dry toluene was heated under reflux using a Dean–Stark apparatus. After 90 min 0.3 g (5 mmol) and after a further 60 min 0.24 g (4 mmol) of (*R*)-1-phenylethylamine were added and reflux was continued for 3 h. The solvent was removed under reduced pressure and the residue was dried under high vacuum to yield crude imine which was used without further purification for the next step.

4.3.1. (*E*)-2-(*RS*)-[*N*-(*R*)-1-Phenylethyl]benzoylaminocyclohexaneimine 3A/B. For spectral data see Ref. 10.

4.3.2. (*E*)-2-(*RS*)-[*N*-(*R*)-1-Phenylethyl]*p*-nitrobenzoylaminocyclohexaneimine 3′A/B. ^{1}H NMR ($CDCl_3$) 1.1–1.4 (m, 3H), 1.1.42/1.48 (d, $J=6.6$ Hz, 3H), 1.6–1.9 (m, 3H), 2.7–2.9 (m, 1H), 3.0–3.2 (m, 1H), 4.35 (m, 1H), 4.7 (m, 1H), 7.12–7.30 (m, 5H), 7.88 (m, 2H), 8.16 (m, 2H), 8.52 (brs., NH); ^{13}C NMR ($CDCl_3$) 23.8/24.0 (CH_2), 25.0/22.2 (CH_3), 26.9/27.6 (CH_2), 29.0/29.1 (CH_2), 34.9/35.0 (CH_2), 54.9/55.0 (CH), 57.7/57.6 (CH), 123.6/123.6 (CH), 126.2/126.7 (CH), 126.7/126.8 (CH), 128.0/128.3 (CH), 128.4/128.4 (CH), 140.4/140.5 (C), 145.2/145.7 (C), 147.5/149.4 (C), 163.8/163.9 (CO), 167.2/167.4 (CO).

4.4. Cyanide addition to the ketimine mixtures 3A/B and 3′A/B, respectively

Method A: To a solution of the mixed ketimines **3A**/**B** (8 g, 25 mmol) and anhydrous $ZnCl_2$ (170 mg, 5 mol%) in MeOH (140 mL), TMSCN (4 mL, 33 mmol) was added at 0°C over a period of 30 min. The reaction mixture was stirred for 3 h, filtered, concentrated and dried to yield a mixture of the α-amino nitriles **4a**–**c** (8.6 g, 99%) and further reacted without purification.

Method B: The above procedure was repeated with **3A**/**B** and **3′A**/**B**, respectively, using hexane as a solvent, yielding 99% of the α-amino nitrile mixture **4a**–**c** and **4′a**–**c**, respectively.

4.5. Hydrolysis of the amino nitriles mixtures 4a–c and 4′a–c, respectively

Method A: To 4.7 g (13.6 mmol) of the α-amino nitrile mixture **4a**–**c** pre-cooled (−10°C) conc. H_2SO_4 (20 mL) was added slowly. The resulting mixture was stirred at −10°C for 30 min and was then allowed to stir at 25°C for 3 days. The crude product was decomposed on ice and filtered. The filtrate was adjusted to pH 8 with conc. ammonia and extracted with EtOAc. The organic extracts were washed with water, brine, dried, filtered, concentrated and finally dried under high vaccum to yield an oily residue (2.6 g, 79%). The above residue was separated on silica gel, eluted with a gradient of acetone/EtOAc mixtures (1/1 to 9/1) resulting in the isolation of **6a**/**6b** mixture (1.1 g) and further fractions containing 6S and *cis*-**6c**/*trans*-**6a**/**6b** mixtures. The latter were further separated by means of LPLC [stationary phase: Merck LOBAR column, mobile phase: EtOAc–acetone (1:1), flow rate: 1 mL/min, fraction size: 5 mL, detector: 254 nm] yielding pure **6c**, which was further converted into its hydrochloride salts with HCl saturated ether.

Method B: To the α-amino nitrile mixture **4a**–**c** (8.6 g, 24.8 mmol) pre-cooled (−20°C) conc. H_2SO_4 (80 mL) was added slowly. The resulting mixture was stirred at −20°C for 10 days. The crude product was decomposed on ice and filtered. The filtrate was adjusted to pH 8 with conc. ammonia and extracted with EtOAc. The organic extracts were washed with water, brine, dried, filtered, concentrated and finally dried in a high vaccum, yielding the crude product (7.1 g, 78%). A quantity of this residue (7 g) was separated on silica gel (700 g) using cyclohexane/EtOAc (1:1) as the eluent to yield **5a** (1.71 g, 19%), a **5a**/**5b** mixture (257 mg, 2.8%) and finally **5b** (721 mg, 8%).

Method C: The same procedure was repeated with 8.6 g (24.8 mmol) of **4a**–**c**, 80 mL conc H_2SO_4 maintaining the temperature between −30 to −35°C for 30 days. A crude yield of 7.8 g was isolated. A quantity of 7 g of the residue was separated on silica gel (600 g) and eluted with cyclohexane–EtOAc (1:1) to yield racemic **1** (1.92 g), diastereomerically pure **5b** (1.01 g) and phenylethylamine (2.4 g).

Method D: The α-amino nitriles (3.6 g, 9.7 mmol) mixture **4′a–c** was dissolved in dry dichloromethane (20 mL) and added slowly to pre-cooled (−10°C) conc. H_2SO_4 (15 mL). The resulting mixture was kept at −10°C for 30 min and then allowed to stir at room temperature for 3 days. The crude product was decomposed on ice and filtered. The filtrate was adjusted to pH 8 with conc. ammonia and extracted with EtOAc. The organic extract was washed with water, brine, dried with $MgSO_4$, filtered, concentrated and finally dried in high vacuum to yield an oily residue (3.2 g, 86%). The above residue was separated on silica gel column eluted with EtOAc/acetone (1/1) yielding a mixture of **5′a**/**5′b** (1.02 g, 27%) along with **6′c** (96 mg, 2.6%). The **5′a**/**5′b** mixture (1 g) was further purified on silica gel column eluted with EtOAc/cyclohexane/diethylamine 4/6/5 drops mixture yielding the diastereomerically pure *trans*-secondary amino amides **5′a** (542 mg) and **5′b** (307 mg), respectively.

4.5.1. *trans*-(α*R*,1*R*,2*R*)-2-Benzoylamino-1-(1-phenylethylamino)cyclohexanecarboxamide, 5a. Mp 92°C; $[\alpha]_D^{20}=-4.3$ (*c* 1.02, MeOH); ^{1}H NMR ($CDCl_3$) 1.26 (d, $J=6.6$ Hz, 3H), 1.20–1.90 (m, 8H), 2.30 (bs, 1H) 3.90 (q, $J=6.6$ Hz, 1H), 4.24 (ddd, $J=8.9$, 8.9, 3.7 Hz, 1H), 6.30 (s, 1H), 6.90 (s, 1H), 7.10–7.50 (m, 8H), 7.6 (d, $J=8.4$ Hz, 1H), 7.70–7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) 21.8 (CH_2), 22.9 (CH_2), 26.2 (CH_3), 29.1 (CH_2), 31.6 (CH_2), 53.4 (CH), 54.6 (CH), 63.9 (C), 126.2 (CH), 126.7 (CH), 126.9 (CH), 128. 2 (CH), 128.4 (CH), 131.2 (CH), 134.5 (C), 147. 3 (C), 167.0 (CO), 178.5 (CO); HRMS calcd for $C_{21}H_{25}N_2O$ (100%, M^+-CONH_2) 321.1967, found 321.1968.

4.5.2. *trans*-(α*R*,1*S*,2*S*)-2-Benzoylamino-1-(1-phenylethylamino)cyclohexanecarboxamide, 5b. Mp 170°C; $[\alpha]_D^{20}=+51.2$ (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$) 1.25 (d, $J=6.6$ Hz, 3H), 1.20–2.20 (m, 9H), 4.13 (q, $J=6.6$ Hz, 1H), 4.48 (ddd, $J=11.0$, 11.0, 5.1 Hz, 1H), 5.6 (bs, 1H), 6.9 (s, 1H), 7.07 (d, $J=9.6$ Hz, 1H), 7.18 (dd, $J=7.2$, 7.2 Hz, 1H), 7.28 (dd, $J=7.6$, 7.2 Hz, 2H), 7.34–7.52 (m, 5H); 7.89 (dd, $J=7.6$, 1.7 Hz, 2H), ^{13}C NMR ($CDCl_3$) 22.2 (CH_2), 24.8 (CH_2), 27.4 (CH_3), 30.6 (CH_2), 34.6 (CH_2), 50.4 (CH), 52.2 (CH), 66.0 (C), 126.1 (CH), 126.5 (CH), 126.9 (CH), 128.4 (CH), 128.6 (CH), 131.5 (CH), 134.5 (C), 149.0 (C), 167.0 (CO), 178.7 (CO); HRMS calcd for $C_{21}H_{25}N_2O$ (100%, M^+-CONH_2) 321.1967, found 321.1963.

4.5.3. *trans*-(α*S*,1*S*,2*S*)-2-Benzoylamino-1-(1-phenylethylamino)cyclohexanecarboxamide, ent-5a. Mp 92°C; $[\alpha]_D^{20}=+2.0$ (*c* 1.02, MeOH); HRMS calcd for $C_{21}H_{25}N_2O$ (100%, M^+-CONH_2) 321.1967, found 321.1967.

4.5.4. *trans*-(α*S*,1*R*,2*R*)-2-Benzoylamino-1-(1-phenylethylamino)cyclohexanecarboxamide, ent-5b. Mp 170°C; $[\alpha]_D^{20}=-51.2$ (*c* 1.00, MeOH); HRMS calcd for $C_{21}H_{25}N_2O$ (100%, M^+-CONH_2) 321.1967, found 321.1966.

4.5.5. *trans*-(α*R*,1*R*,2*R*)-2-*p*-Nitrobenzoylamino-1-(1-phenylethylamino)cyclohexanecarboamide, 5′a. Mp 217°C; $[\alpha]_D^{20}=-3.4$ (*c* 0.93, MeOH); ^{1}H NMR ($CDCl_3$) 1.20–1.90 (m, 8H), 1.28 (d, $J=6.6$ Hz, 3H), 2.1 (brs, 1H), 3.95 (q, $J=6.6$ Hz, 1H), 4.24 (ddd, $J=9.0$, 8.8, 3.8 Hz, 1H), 6.01 (s, 1H), 6.66 (s, 1H), 7.18–7.40 (m, 6H), 7.90 (d, $J=8.4$ Hz, 2H), 8.24 (d, $J=8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 22.05 (CH_2), 23.20 (CH_2), 26.36 (CH_3), 29.31 (CH_2), 32.43 (CH_2), 53.34 (CH), 55.26 (CH), 63.76 (C), 123.66 (CH), 126.20 (CH), 126.95 (CH), 128.10 (CH), 128.43 (CH), 140.18 (C), 147.06 (C), 149.45 (C), 164.06 (CO), 178.26 (CO). HRMS calcd for $C_{21}H_{24}N_3O_3$ (100%, M^+-CONH_2) 367.4479, found 367.4471.

4.5.6. *trans*-(α*R*,1*S*,2*S*)-2-*p*-Nitrobenzoylamino-1-(1-phenylethylamino)cyclohexanecarboamide, 5′b. Mp >250°C (decomp.); $[\alpha]_D^{20}=+50.0$ (*c* 1.12, MeOH); ^{1}H NMR ($CDCl_3$) 1.18 (d, $J=6.4$ Hz, 3H), 1.20–2.05 (m, 8H), 2.1 (brs, 1H), 4.14 (q, $J=6.7$ Hz, 1H), 4.50 (ddd, $J=11.2$, 9.6, 5.0 Hz, 1H), 5.62 (s, 1H), 6.68 (s, 1H), 7.14–7.42 (m, 6H) 7.92 (d, $J=8.8$ Hz, 2H), 8.24 (d, $J=8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 22.13 (CH_2), 24.57 (CH_2), 27.30 (CH_3), 30.51 (CH_2), 51.10 (CH), 52.17 (CH), 65.73 (C), 123.73 (CH), 125.99 (CH), 126.57 (CH), 128.12 (CH), 128.45 (CH), 139.96 (C), 148.57 (C), 149.56 (C)), 164.86 (CO), 178.54 (CO). HRMS calcd for $C_{21}H_{24}N_3O_3$ (100%, M^+-CONH_2) 367.4479, found 367.4481.

4.5.7. *cis*-(1*R*,2*S*)-1-Amino-2-benzoylaminocyclohexanecarboxamide hydrochloride, 6c·HCl. Mp 226–228°C (decomp.); $[\alpha]_D^{20}=-5.8$ (*c* 1.36, MeOH); ^{1}H NMR (CD_3OD) 1.52–1.84 (m, 5H), 2.00–2.24 (m, 3H), 4.64 (dd, $J=5.5$, 5.3 Hz, 1H), 7.67 (dd, $J=8.1$, 7.5 Hz, 3H), 7.83 (d, $J=7.5$, 1H); 7.99 (dd, $J=14.0$, 8.1 Hz, 1H); ^{13}C NMR (CD_3OD) 18.3 (CH_2), 18.7 (CH_2), 26.5 (CH_2), 29.3 (CH_2), 60.2 (CH), 69.4 (C), 123.4 (C), 129.8 (CH), 130.8 (CH), 136.4 (CH), 166.5 (CO), 174.1 (CO).

4.5.8. *cis*-(1*S*,2*R*)-1-Amino-2-benzoylaminocyclohexanecarboxamide hydrochloride, ent-6c·HCl. Mp 226–228°C (decomp.); $[\alpha]_D^{20}=+7.4$ (*c* 0.76, MeOH).

4.5.9. 6-Benzoylamino-3,3-dimethyl-2,4-diazaspiro[4,5]-dec-1-one, 6S. Mp 231°C; ^{1}H NMR ($CDCl_3$) 1.25 (s, 3H), 1.36 (m, 1H), 1.39 (s, 3H), 1.50–1.68 (m, 2H), 1.74–1.88 (m, 3H), 2.12–2.34 (m, 2H), 3.20 (bs, 1H), 4.12 (ddd, $J=11.5$, 8.6, 4.4 Hz, 1H), 6.31 (bs, 1H), 6.52 (d, $J=7.6$ Hz, 1H), 7.40–7.90 (m, 5H); ^{13}C NMR ($CDCl_3$) 21.7 (CH_2), 24.1 (CH_2), 28.9 (CH_2), 30.2 (CH_3), 32.8 (CH_3), 38.8 (CH_2), 53.1 (CH), 66.0 (C), 70.7 (C), 127.0 (CH), 128.6 (CH), 131.7 (CH), 134.3 (C), 168.8 (CO), 177.1 (CO). Anal. calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94; found: C, 67.71; H, 7.74; N, 13.80%. MS (EI, 70 eV) 301 (M^+).

4.5.10. *cis*-(1*R*,2*S*)-1-Amino-2-*p*-nitrobenzoylamino-cyclohexanecarbamide, 6′c. ^{1}H NMR ($CDCl_3$) 1.20–2.36 (m, 8H), 4.15 (t, $J=4.73$ Hz, 1H), 5.61 (s, 1H), 6.80 (s, 1H), 7.96 (d, $J=8.8$ Hz, 2H), 8.24 (d, $J=8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 18.68 (CH_2), 19.32 (CH_2), 27.39 (CH_2), 32.32 (CH_2), 59.15 (C), 74.01 (CH), 123.71

(CH×2), 128.04 (CH×2), 135.97 (C), 149.29 (C), 161.41 (CO), 178.52 (CO).

4.6. Hydrogenolytic cleavage of the chiral auxiliary

To a solution of **5a** or **5b** (or **5′a** and **5′b**, respectively) (312 mg, 0.85 mmol) and Pd/C (10%, 215 mg) in methanol (43 mL), ammonium formate (436 mg) were added. The reaction mixture was heated under reflux for 2 h, cooled, filtered over a pad of Celite, washed with methanol, concentrated and dried in high vacuum to yield a yellow oil. The crude product was purified on a small silica gel column using EtOAC as a solvent to yield **6a** and **6b**, respectively (or **6′a** and **6′b**, respectively) (204 mg, 92%) as white solids.

4.6.1. *trans*-(1*R*,2*R*)-1-Amino-2-benzoylaminocyclohexanecarboxamide, 6a. Mp 44°C; $[\alpha]_D^{20}=+15.3$ (*c* 1.09, MeOH); ^{1}H NMR ($CDCl_3$) 1.30–1.70 (m, 4H), 1.72–1.86 (m, 2H), 2.10–2.30 (m, 4H), 4.06 (ddd, $J=11.6$, 9.5, 4.6 Hz, 1H), 5.78 (s, 1H), 7.03 (d, $J=9.5$ Hz, 1H), 7.28 (bs, 1H), 7.35–7.50 (m, 3H); 7.72–7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) 22.1 (CH_2), 24.8 (CH_2), 30.5 (CH_2), 38.3 (CH_2), 57.5 (CH), 60.9 (C), 127.0 (CH), 128. 5 (CH), 131.5 (CH), 134.2 (C), 167.8 (CO), 178.3 (CO); HRMS calcd for $C_{13}H_{17}N_2O$ (85%, M^+-CONH_2) 217.1341, found 217.1341.

4.6.2. *trans*-(1*S*,2*S*)-1-Amino-2-benzoylaminocyclohexanecarboxamide, 6b. Yield: 89% as a white solid. Mp 44°C; $[\alpha]_D^{20}=-14.2$ (*c* 1.03, MeOH); HRMS calcd for $C_{13}H_{17}N_2O$ (85%, M^+-CONH_2) 217.1341, found 217.1338.

4.6.3. *trans*-(1*R*,2*R*)-1-Amino-2-*p*-nitrobenzoylaminocyclohexanecarboxamide, 6′a. Mp 152°C; $[\alpha]_D^{20}=+16.5$ (0.82, MeOH); ^{1}H NMR ($CDCl_3$) 1.2–1.9 (m, 6H), 2.0–2.3 (m, 4H), 3.9–4.1 (m, 1H), 5.75 (s, 1H), 7.1–7.3 (m, 2H), 7.89 (d, $J=8.8$, 2H), 8.22 (d, $J=8.8$, 2H); ^{13}C (NMR) 22.06 (CH_2), 24.48 (CH_2), 30.23 (CH_2), 38.23 (CH_2), 57.91 (CH), 60.55 (C), 123.67 (CH), 128. 20 (CH), 139.85 (C), 149.56 (C), 165.57 (CO), 178.58 (CO). HRMS calcd for $C_{13}H_{17}N_3O_3$ (100%, M^+-CONH_2) 263.2964, found 263.2963.

4.6.4. *trans*-(1*S*,2*S*)-1-Amino-2-*p*-nitrobenzoylaminocyclohexanecarboxamide, 6′b. Mp 152°C; $[\alpha]_D^{20}=-17.1$ (0.97, MeOH). HRMS calcd for $C_{13}H_{17}N_3O_3$ (100%, M^+-CONH_2) 263.2964, found 263.2958.

4.7. Hydrolysis of the *trans*-carboxamides 6a/6′a and 6b/6′b, respectively

The *trans*-carboxamide mixture (**6a**/**6′a** or **6b**/**6′b**) (300 mg, 0.9 mmol) was dissolved in conc. HCl (15 mL) at 0°C, stirred at rt for 2 h and then heated under reflux for 2 days. Concentration under reduced pressure followed by drying under high vacuum yielded **8a·2HCl** and **8b·2HCl**, respectively, which was dissolved in water (5 mL) and then applied to a Dowex 50WX.8.100 ion-exchange column (10 g) pre-treated with HCl and washed with distilled water. The free α,β-diamino acid was eluted with 100 mL of 1 M NH_3. The NH_3 was evaporated in vacuum, the crude product was dissolved in water, evaporated to dryness, and finally dried for 24 h under high vacuum to yield **8a** and **8b**, respectively, as yellowish solids (135 mg, 97%).

4.7.1. *trans*-(1*R*,2*R*)-1,2-Diaminocyclohexanecarboxylic acid, 8a. Mp >250°C; $[\alpha]_D^{20}=+7.4$ (*c* 1.00, H_2O); ^{1}H NMR (D_2O) 1.32–1.50 (m, 2H), 1.52–1.74 (m, 3H), 1.80–2.00 (m, 2H), 2.18 (m, 1H), 3.53 (dd, $J=9.0$, 4.9 Hz, 1H); ^{13}C NMR (D_2O) 20.3 (CH_2), 21.1 (CH_2), 26.8 (CH_2), 31.9 (CH_2), 51.9 (CH), 60.6 (C), 172.2 (CO). HRMS calcd for $C_7H_{14}N_2O_2$ 158.1055, found 158.1055.

4.7.2. *trans*-(1*S*,2*S*)-1,2-Diaminocyclohexanecarboxylic acid, 8b. Yield: 98%; mp >250°C; $[\alpha]_D^{20}=-8.0$ (*c* 1.01, H_2O). HRMS calcd for $C_7H_{14}N_2O_2$ 158.1055, found 158.1052.

4.8. Hydrolysis of the *cis*-carboxamide, 6c·HCl

cis-Carboxamide **6c**·HCl (70 mg, 0.23 mmol) was dissolved in conc. HCl (10 mL) at 0°C. The mixture was stirred at rt for 2 h and then heated under reflux for 2 days. Concentration under reduced pressure, followed by drying under high vacuum, yielded a yellowish solid which was dissolved in water (10 mL) and washed with ether. The aqueous extract was concentrated and dried in high vacuum to yield a yellowish white solid (62.6 mg, 89%).

4.8.1. *cis*-(1*R*,2*S*)-1-Amino-2-benzoylaminocyclohexanecarboxylic acid hydrochloride, 7c·HCl. Mp 212°C (dec.); $[\alpha]_D^{20}=-9.9$ (*c* 0.93. CH_3OH); ^{1}H NMR (CD_3OD) 1.30–1.68 (m, 5H), 1.80–2.08 (m, 3H), 4.49 (dd, $J=5.0$, 5.0 Hz, 1H), 7.44–7.74 (m, 5H); ^{13}C NMR (CD_3OD) 16.0 (CH_2), 16.5 (CH_2), 24.3 (CH_2), 27.6 (CH_2), 58.5 (CH), 68.1 (C), 121.5 (C), 128.0 (CH), 129.5 (CH), 135.1 (CH), 164.8 (CO), 175.3 (CO). MS 245 (100%, M^+-OH).

4.8.2. *cis*-(1*S*,2*R*)-1-Amino-2-benzoylaminocyclohexanecarboxylic acid hydrochloride, *ent*-7c·HCl. Mp 212°C (dec.); $[\alpha]_D^{20}=+10.4$ (*c* 1.61. CH_3OH). MS 245 (100%, M^+-OH).

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