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Carbocyclic α-amino acids: asymmetric synthesis of all four 1-amino-2-hydroxycyclohexanecarboxylic acids †

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Abstract

Starting from racemic 2-methoxycyclohexanone and (*S*)- or (*R*)-1-phenylethylamine, respectively, the four stereoisomers of 1-amino-2-hydroxycyclohexanecarboxylic acid are obtained via an asymmetric Strecker synthesis with *ee* values ranging from 87 to 98%. Their stereochemistry is established by NMR methods and by X-ray analyses. Hydrogenolysis of a benzylic C–N bond by conc. sulphuric acid as well as cleavage of a methoxy ether by conc. HCl are two intriguing reactions which are observed within the five-step procedure described herein.

1. Introduction

Recently, diverse biological effects of carbocyclic α-amino acids have been described. They act as agonists and/or antagonists at both ionotropic and metabotropic glutamate receptors.[1,2] Furthermore, they are involved in enzymatic processes for plant growth and fruit ripening.[3] They are also reported to modify biological activities in a useful way when incorporated as building blocks into peptides or proteins.[4] These findings demand the development of straightforward syntheses of this type of α-quaternary α-amino acids from readily available starting materials. As part of our research efforts towards conformationally restricted analogues of naturally occurring α-amino acids, we previously described the preparation of the four cyclic isoleucines **1a**–**d** (Scheme 1) by means of asymmetric Strecker synthesis.[5] More recently, Ohfune and co-workers reported the syntheses of the 5- and 6-membered carbocyclic serine analogues **2a**,**b** and **3a**,**b** (Scheme 1) via an intramolecular version of the Strecker reaction.[6]

Herein we describe the stereoselective preparation of the 1-amino-2-hydroxycyclohexanecarboxylic acids **10a**,**b**, representing 2,4-propano analogues of the natural L$_s$-threonine (Scheme 2), starting from

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† Dedicated to Professor Dr. P. Nickel on the occasion of his 65th birthday.

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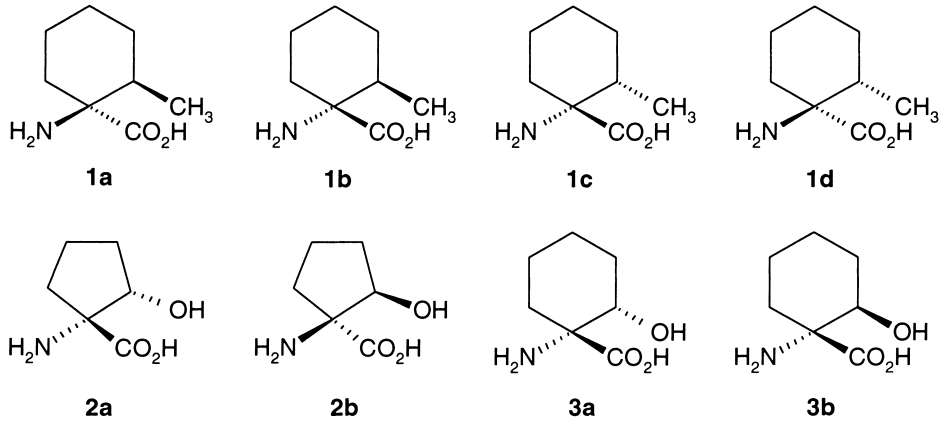
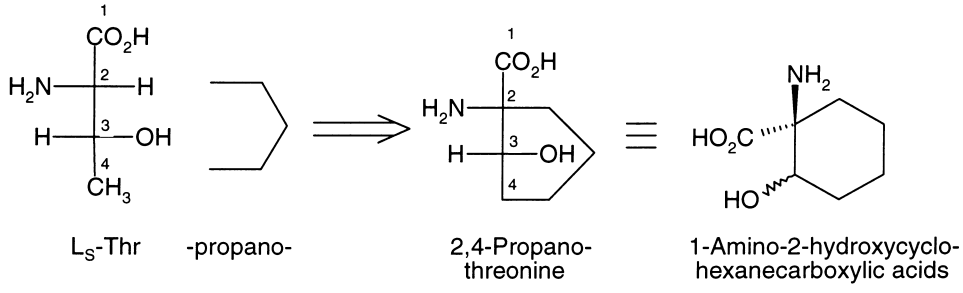


Scheme 1.

racemic 2-methoxycyclohexanone **4** and (*S*)-1-phenylethylamine **5** as the chiral auxiliary (Scheme 3). Using (*R*)-1-PEA instead of (*S*)-1-PEA the amino acids **3a**,**b** were obtained.



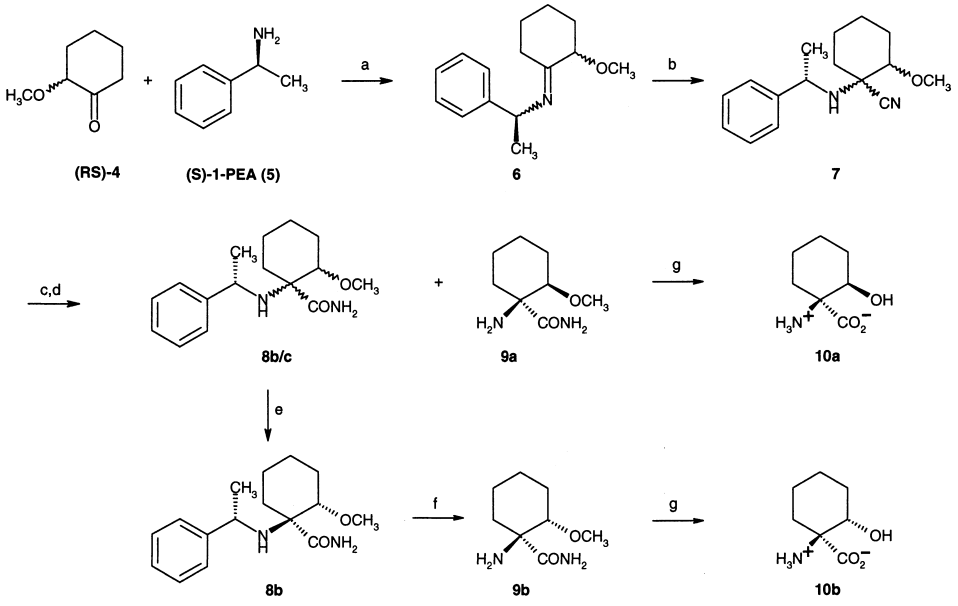
Scheme 2.

2. Results and discussion

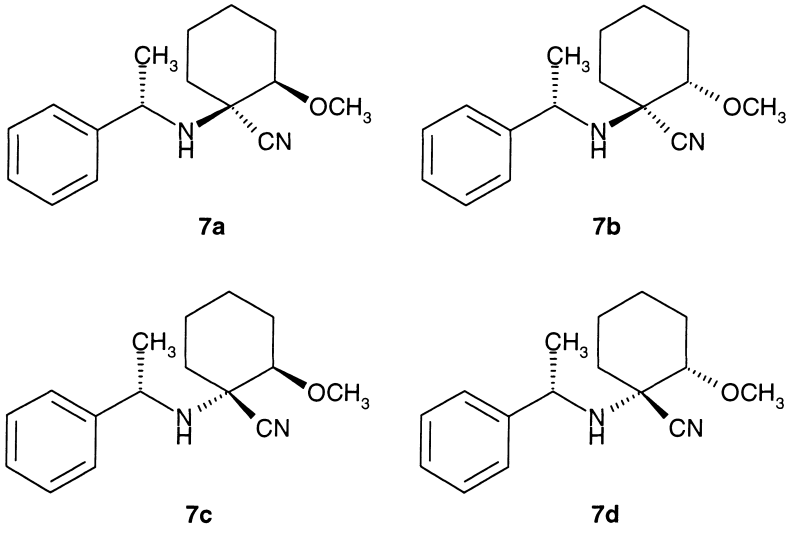
The racemic starting ketone **4** was prepared as described previously.[7] Azeotropic condensation of (*RS*)-**4** with an equimolar quantity of (*S*)-1-PEA **5** gave imines **6** as diastereomeric mixtures with *E*-α*S*,2*R*-, *E*-α*S*,2*S*-, *Z*-α*S*,2*R*- and *Z*-α*S*,2*S* configuration and an *E*:*Z* ratio of ~10:1 as derived from ^{1}H NMR in 93% yield. The crude imines **6** were then reacted with trimethylsilylcyanide (TMSCN)/$ZnCl_2$ yielding the α-amino nitriles **7** in quantitative yields as a mixture of all four possible diastereomers **7a**–**d** (Scheme 4).

As observed earlier,[5] the *trans*/*cis* diastereoselectivity of the α-amino nitrile formation was dependent on the solvent (Table 1).

Thus, in MeOH (procedure **A**) the α-amino nitrile formation was under thermodynamic control leading predominantly to the *trans* configured products **7b** and **7c** (*trans*:*cis*=74:26), whereas in hexane (procedure **B**) it was kinetically controlled, with the *cis* configured compounds **7a** and **7d** being the major products (*trans*:*cis*=25:75). The stereochemical compositions of the α-amino nitrile mixtures **7**, outlined in Table 1, are based on our previously established ^{13}C NMR analyses.[5] On treatment of the α-amino nitrile mixture **7** with conc. sulphuric acid for 6 days a complex crude product was obtained, which was then chromatographed on silica gel using petrol ether/ethyl acetate as the eluent yielding (i) a mixture of the two *trans* configured α-amino amides **8b**/**c** and (ii) the hydrogenolysed *cis* configured primary



Scheme 3. Reaction conditions: (a) toluene, reflux; (b) (i) MeOH, TMSCN, $ZnCl_2$ (5 mol%), 0°C (30 min), rt (3 h); (ii) hexane, TMSCN, $ZnCl_2$ (5 mol%), 0°C (30 min), rt (48 h); (c) conc. H_2SO_4, −10°C (3 h), 0°C (3 h), rt (7 days); (d) CC: silica gel, petrol ether:ethyl acetate (1:1) then (1:3); (e) LPLC: Lobar®, MeOH:H_2O (85:15); (f) EtOH, Pd/C (10%), 45°C, 5 bar H_2, 24 h; (g) 12 M HCl, reflux, 7 days; Dowex 50WX.8.100 (NH_4^+ form), 1 M NH_3

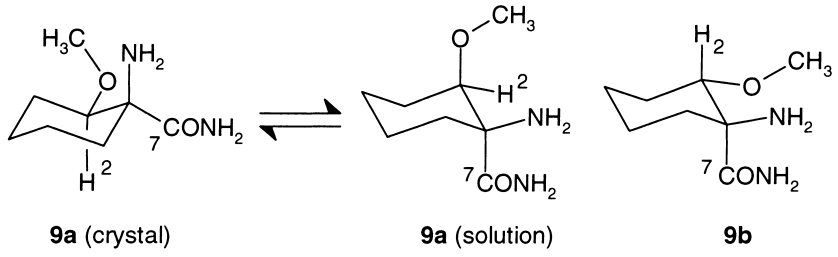


Scheme 4.

α-amino amide **9a**. Subsequent Lobar® purification of the **8b**,**c** mixture to diastereomerically pure **8b** followed by catalytic hydrogenolysis of the benzylic C–N bond on Pd/C at 5 bar H_2 and 45°C gave the second primary α-amino amide **9b**. In the final reaction step the primary α-amino amides **9a** and **9b**, respectively, were refluxed with conc. HCl for 7 days, whereby the carboxamide was hydrolysed along with the demethylation of the methoxy group and, after treatment with ion-exchange resin (activated Dowex 50WX.8.100), the 1-amino-2-hydroxycyclohexanecarboxylic acids **10a** and **10b** were obtained. Shorter reaction times and lower concentrations of HCl led to the selective hydrolysis of the carboxamide

Table 1
Diastereoselective α-amino nitrile formation

	7a	**7b**	**7c**	**7d**	Diastereoselectivity
	cis	*trans*	*trans*	*cis*	(trans : cis)
solvent	α*S*,1*R*,2*R*	α*S*,1*R*,2*S*	α*S*,1*S*,2*R*	α*S*,1*S*,2*S*	
MeOH	22%	54%	20%	4%	74 : 26
hexane	46%	22%	3%	29%	25 : 75



9a (crystal) **9a** (solution) **9b**

Figure 1.

function.[8] The respective enantiomers of **10a** and **10b**, the α-amino acids **3a** and **3b** were prepared by the same reaction sequence starting from (*RS*)-**4** and (*R*)-1-PEA instead of (*S*)-1-PEA.

The *ee* values of 95% and 98% for the *trans* α-amino acids **3b** and **10b**, respectively, are within the range of the optical purity of the chiral auxiliary used in the reaction sequence. The lower *ee* values of 88% and 87% for the *cis* α-amino acids **3a** and **10a** are due to the simultaneous hydrolysis and hydrogenolysis of the 93:7 mixtures of the two *cis* configured α-amino nitriles **7a**:**7d** and *ent*-**7a**:*ent*-**7d**, respectively, on treatment with conc. sulphuric acid. Thus, the *cis* configured compounds **9a** and *ent*-**9a** as well as the corresponding α-amino acids **3a** and **10a** are obtained as enantiomeric mixtures with the given *ee* values which were determined by means of chiral HPLC on a Chirobiotic T™ column, using EtOH:H_2O (30:70) as the eluent.[9]

2.1. Stereochemical assignments

The relative configuration of the primary α-amino amides **9a** and **9b** was deduced on the basis of NMR spectroscopic data using the heteronuclear coupling constants between the carboxamide carbon C-7 and the proton 2-H (Fig. 1). Thus, the $^3J_{C\text{-}7/2\text{-}H}$ value of 1.6 Hz for **9a** correlates with *cis* configuration and that of 6.3 Hz for **9b** with *trans* configuration.

Furthermore, assuming 'like-induction' at C-1, we predicted 1*S*,2*R* configuration for **9a** and 1*S*,2*S* for **9b**. In fact, this assignment was finally proved by the X-ray analysis of the primary α-amino amide hydrochloride **9a**·HCl.[10]

3. Experimental

Solvents were purified according to standard procedures. Melting points are uncorrected. Analytical TLC was performed on Merck Si60 F_{254} (0.2 mm) precoated alumina foils. CC was carried out on Merck silica gel (0.2–0.063 mm). Infrared spectra were recorded on a Perkin–Elmer IR 298 spectrometer. The NMR spectra were obtained on a Varian XL 300 spectrometer at 300 MHz (^{1}H) and 75.4 MHz (^{13}C)

respectively. Chemical shifts are reported as δ values using either TMS (^{1}H) or the solvent peak (^{13}C) as the reference. Optical rotation values are measured in a 1 dm cell with a Perkin–Elmer 214 polarimeter. HPLC was performed on a Chirobiotic T™ column equipped with a Waters 515 pump and a Waters 2487 dual λ absorbance detector. Elemental analyses were carried out with a Perkin–Elmer elemental analyser PE240 at the Department of Biochemistry and Organic Chemistry, University of Freiburg. MS and HRMS were obtained with a Finnigan MAT312 (EI) and a Finnigan 44S mass spectrometer.

*3.1. (*RS*)-2-Methoxycyclohexanone **4***

Compound **4** was prepared from 2-chlorocyclohexanone following the procedure described in the literature.[7]

3.2. E/Z*-2-(*RS*)-[*N*-(*S*)-α-Phenylethyl]methoxycyclohexaneimine **6***

An equimolar mixture of (*RS*)-2-methoxycyclohexanone **4** (12.7 g, 0.1 mol) and (*S*)-(−)-1-PEA **5** (12.1 g, 0.1 mol) was taken up in 100 mL of dry toluene and refluxed for 8 h using a Dean–Stark apparatus. The solvent was then evaporated under reduced pressure and the residue was dried under high vacuum to yield 21.5 g (93%) of **6** as a reddish oil. IR (film): 1658 (C=N), 1098 (C–O) cm^{-1}; ^{13}C NMR ($CDCl_3$): 20.4(*E*), 20.5(*E*), 21.1(*Z*), 22.8(*Z*), 23.6(*Z*), 24.6(*E*), 24.7(*E*), 24.9(*E*), 24.9(*E*), 25.7(*Z*), 25.7(*Z*), 26.4(*E*), 26.5(*Z*), 27.0(*Z*), 27.4(*E*), 31.9(*Z*), 33.0(*E*), 33.1(*E*), 33.9(*Z*), 52.7(*Z*), 53.2(*Z*), 55.7(*E*), 55.8(*E*), 57.4(*Z*), 57.5(*Z*), 57.7(*E*), 57.8(*E*), 82.1(*Z*), 83.6(*E*), 83.6(*E*), 83.9(*Z*), 125.4(*Z*), 125.5(*Z*), 125.5(*E*), 126.0(*E*), 126.1(*Z*), 126.2(*Z*), 126.2(*E*), 126.3(*E*), 127.9(*Z*), 128.0(*E*), 128.1(*E*), 128.2(*Z*), 139.3(*Z*), 145.7(*E*), 145.8(*E*), 146.0 (*Z*), 171.0(*E*), 171.3(*E*).

*3.3. 2-Methoxy-1-(α-phenylethylamino)cyclohexanecarbonitriles **7a–d***

3.3.1. Procedure A

To a solution of 11.5 g (0.05 mol) **6** and 340 mg (5 mol%) of dry $ZnCl_2$ in 150 mL methanol, 8.3 mL (0.0625 mol) TMSCN were added slowly at 0°C over a period of 30 min. The reaction mixture was then stirred for a further 3 h, filtered, concentrated under reduced pressure and dried under high vacuum to yield 13.4 g (99%) diastereomeric mixture of the α-amino nitriles **7a–d**. IR (film): 3347 (N–H), 2224 (C≡N), 1101 (C–O) cm^{-1}; ^{13}C NMR ($CDCl_3$): 21.9, 21.7, 18.8, 20.3 (C-4), 23.1, 22.7, 23.1, 22.1 (C-5), 26.4, 24.7, 25.7, 24.3 (C-3), 26.4, 26.0, 25.9, 24.5 (C-β), 34.1, 32.9, 34.8, 33.1 (C-6), 54.4, 54.9, 54.0, 53.9 (C-α), 56.5, 56.4, 57.5, 56.7 (O*C*H$_3$), 63.6, 61.7, 60.2, 63.7 (C-1), 83.4, 82.4, 82.8, 83.9 (C-2), 120.2, 122.4, 120.3, 121.7 (C≡N), 126.3, 126.3, 126.5, 126.0 (C-3′), 126.5, 127.0, 126.6, 126.9 (C-4′), 128.1, 128.4, 128.3, 128.5 (C-2′), 147.5, 146.6, 145.5, 145.9 (C-1′).

3.3.2. Procedure B

To a solution of 9.0 g (0.04 mol) **6** and 270 mg (5 mol%) of dry $ZnCl_2$ in 150 mL of hexane, 6.7 mL (0.05 mol) TMSCN was added slowly at 0°C over a period of 30 min. The reaction mixture was then stirred for a further 48 h and then an equimolar volume of methanol (1.6 mL) was added. The resulting mixture was stirred for 30 min more, filtered, concentrated under reduced pressure and dried under high vacuum to yield 10.3 g (98%) diastereomeric mixture of the α-amino nitriles **7a–d**.

3.4. Hydrolysis of the 2-methoxy-1-(α-phenylethylamino)cyclohexanecarbonitriles **7a–d**

A diastereomeric mixture of α-amino nitriles **7a**–**d** (11.0 g, 0.04 mol) was added slowly to 80 mL of conc. H_2SO_4 at −10°C and stirred for 3 h at same temperature. The solution was then stirred at 0°C for 3 h and at rt for 7 days. The reaction mixture was decomposed on ice (250 g), filtered, and the filtrate was adjusted to pH 8 with conc. ammonia and then extracted with ethyl acetate (3×100 mL). The crude organic extracts were dried over anhyd. Na_2SO_4, concentrated under reduced pressure and dried under high vacuum to yield 7.1 g of an oily residue. A quantity (5.0 g) of the above residue was chromatographed over silica gel (350 g) and eluted with petrol ether (40–60°C):ethyl acetate (1:1) to yield a diastereomeric mixture of unreacted α-amino nitriles **7a**–**d** (360 mg, fraction **A**); continuing elution with same polarity resulted in 1.8 g of a mixture of the two diastereomeric α-amino carboxamides **8b**,**c** (fraction **B**). Further elution with petrol ether (40–60°C):ethyl acetate (1:3) yielded 630 mg of diastereomerically pure **9a**.

3.4.1. cis-*(1*S,*2*R*)*-1-Amino-2-methoxycyclohexanecarboxamide ***9a***

Mp: 92°C; ^{1}H NMR ($CDCl_3$): 1.0–1.8 (m, 9H, cycloaliphatic and amino-H), 1.94 (m, 1H, 3-H), 3.30 (s, 3H, -OCH_3), 3.76 (dd, *J*=11.0, 4.5 Hz, 1H, 2-H), 5.9 (s(b), 1H, -NH (amido)), 7.7 (s(b), 1H, -NH (amido)); ^{13}C NMR ($CDCl_3$): 20.2 (C-5), 23.6 (C-4), 25.5 (C-3), 34.0 (C-6), 56.7 (OCH_3), 60.8 (C-1), 79.8 (C-2), 180.4 (C=O).

3.4.2. cis-*(1*S,*2*R*)*-1-Amino-2-methoxycyclohexanecarboxamide hydrochloride ***9a**·HCl*

Compound **9a** was converted into its hydrochloride salt using ether saturated with HCl gas. Mp: 207°C; $[\alpha]_D^{20}$=+7.7 (*c* 0.963, CH_3OH); ^{1}H NMR ($CDCl_3$): 1.3–2.3 (m, 8H, cycloaliphatic -H), 3.42 (s, 3H, -OCH_3), 3.84 (dd, *J*=11.0, 5.1 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$): 20.9 (C-5), 23.76 (C-4), 26.5 (C-3), 33.0 (C-6), 57.4 (OCH_3), 65.4 (C-1), 79.7 (C-2), 174.2 (C=O); HRMS (EI, 70 eV): m/z (%) 140 (2) [M^+−32 (H_3COH), $C_7H_{12}N_2O_1$: calcd 140.094963, found 140.094451], 128 (100) [M^+−44 ($CONH_2$), $C_7H_{14}N_1O_1$: calcd 128.107539, found 128.107555], 96 (66), 79 (41), 69 (20); MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 173 (100) [M^+].

3.4.3. cis-*(1*R,*2*S*)*-1-Amino-2-methoxycyclohexanecarboxamide hydrochloride* ent-***9a**·HCl*

Mp: 206°C; $[\alpha]_D^{20}$=−7.5 (*c* 1.0, CH_3OH); MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 173 (100) [M^+].

3.4.4. trans-*(*αS,*1*S,*2*S*)*-2-Methoxy-1-(*α*-phenylethylamino)cyclohexanecarboxamide ***8b***

Compound **8b** was isolated from the **8b**,**c** mixture (fraction **B**) by means of LPLC [stationary phase: Merck LobarB®, mobile phase: CH_3OH:H_2O (85:15), flow rate: 0.7 mL/min, fraction size: 4.2 mL, detector: UV (254 nm)] and then converted into its hydrochloride salt using ether saturated with HCl gas. **8b**·HCl: mp: 234°C (dec.); $[\alpha]_D^{20}$=+24.9 (*c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD): 1.2–1.8 (m, 6H, cycloaliphatic-H), 1.72 (d, *J*=6.8 Hz, 3H, β-CH_3), 2.20 (m, 1H, 3-H), 2.45 (m, 1H, 6-H), 3.42 (s, 3H, -OCH_3), 3.68 (dd, *J*=10.0, 3.7 Hz, 1H, 2-H), 4.68 (q, *J*=7.0 Hz, 1H, α-H), 7.4–7.65 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$): 21.7 (C-5), 22.9 (C-4), 23.3 (C-3), 26.8 (C-β), 30.7 (C-6), 57.2 (C-α), 58.1 (OCH_3), 70.1 (C-1), 81.5 (C-2), 129.1 (C-3′), 130.3 (C-2′), 130.7 (C-4′), 139.3 (C-1′), 169.5 (C=O). $C_{16}H_{25}ClN_2O_2$: calcd C 61.43, H 8.05, N 8.95, found C 61.22, H 8.02, N 8.82.

3.4.5. trans-*(αR,1R,2R)-2-Methoxy-1-(α-phenylethylamino)cyclohexanecarboxamide hydrochloride* ent-***8b*·*HCl***

Mp: 234°C (dec.); $[\alpha]_D^{20}$=−23.5 (*c* 1.03, CH_3OH); $C_{16}H_{25}ClN_2O_2$: calcd C 61.43, H 8.05, N 8.95, found C 61.38, H 8.09, N 8.93.

3.4.6. trans-*(1S,2S)-1-Amino-2-methoxycyclohexanecarboxamide hydrochloride* ***9b*·*HCl***

In a Parr apparatus, 100 mg of Pd/C (10%) was suspended in 50 mL of EtOH. After evacuation, the mixture was shaken under 5 bar H_2 pressure for 1 h at 45°C. A solution of 200 mg (0.6 mmol) **8b**·HCl in EtOH (50 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 and concentrated to yield 127 mg (95%) of **9b**·HCl. Mp: 195°C; $[\alpha]_D^{20}$=−4.9 (*c* 0.657, CH_3OH); ^{1}H NMR (CD_3OD): 1.4–1.76 (m, 5H, cycloaliphatic-H), 1.78 (m, 1H, 4-H), 2.08 (m, 1H, 3-H), 2.42 (m, 1H, 6-H), 3.49 (s, 3H, -OCH_3), 3.61 (dd, *J*=9.3, 3.7 Hz, 1H, 2-H); ^{13}C NMR (CD_3OD): 22.4 (C-5), 22.9 (C-4), 26.4 (C-3), 32.0 (C-6), 57.6 (OCH_3), 63.4 (C-1), 81.4 (C-2), 171.6 (C≡O); HRMS (EI, 70 eV): m/z (%) 140 (2) [M^+−32 (H_3COH), $C_7H_{12}N_2O_1$: calcd 140.094963, found 140.094726], 128 (100) [M^+−44 ($CONH_2$), $C_7H_{14}N_1O_1$: calcd 128.107539, found 128.107555]; MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 173 (100) [M^+].

3.4.7. trans-*(1R,2R)-1-Amino-2-methoxycyclohexanecarboxamide hydrochloride* ent-***9b*·*HCl***

Mp: 195°C; $[\alpha]_D^{20}$=+5.5 (*c* 0.657, CH_3OH); MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 173 (100) [M^+].

3.4.8. trans-*(1S,2S)-1-Amino-2-methoxycyclohexanecarboxamide* ***9b*** *(free base)*

A colourless oil; ^{1}H NMR ($CDCl_3$): 0.8–2.3 (m, 10H, cycloaliphatic and amino-H), 3.20 (dd, *J*=10.4, 3.7 Hz, 1H, 2-H), 3.41 (s, 3H, -OCH_3), 6.15 (s(b), 1H, -NH (amido)), 7.24 (s(b), 1H, -NH (amido)); ^{13}C NMR ($CDCl_3$): 22.2 (C-5), 23.5 (C-4), 26.1 (C-3), 35.2 (C-6), 57.2 (OCH_3), 60.3 (C-1), 85.8 (C-2), 177.7 (C≡O).

3.5. 1-Amino-2-hydroxycyclohexanecarboxylic acids ***10a,b*** *and* ***3a,b*** *(general procedure)*

40 mg of **9a**·HCl, **9b**·HCl, *ent*-**9a**·HCl and *ent*-**9b**·HCl, respectively, were dissolved in 10 mL conc. HCl, stirred for 2 h at rt and then refluxed for one week in an oil bath. Concentration under reduced pressure followed by drying under high vacuum yielded the α-amino acid hydrochlorides **10a**·HCl, **10b**·HCl, **3a**·HCl and **3b**·HCl, respectively, which were dissolved in 5 mL distilled water and then applied to a Dowex 50WX.8.100 ion-exchange column (10 g) in the NH_4^+-form. The column was first washed with distilled water, and then the free α-amino acids were eluted with 100 mL of 1 M NH_3. The eluant was concentrated in vacuo. In order to complete the removal of NH_3, the substances were taken up in water, evaporated to dryness, and finally dried for 3 h on the oil pump yielding the α-amino acids **10a**,**b** and **3a**,**b**, respectively in quantitative yields.

3.5.1. cis-*(1S,2R)-1-Amino-2-hydroxycyclohexanecarboxylic acid hydrochloride* ***10a*·*HCl***

Yield: 86%; mp: >300°C (dec.); ^{1}H NMR (CD_3OD): 1.38 (m, 3H, 3-H, 4-H, 5-H), 1.68 (m, 1H, 5-H), 1.81 (m, 1H, 4-H), 1.93 (m, 1H, 5-H), 2.01 (m, 2H, 6-H), 4.12 (dd, *J*=10.7, 5.1 Hz, 1H, 2-H); ^{13}C NMR (CD_3OD): 20.3 (C-5), 23.8 (C-4), 30.3 (C-3), 31.8 (C-6), 65.5 (C-1), 70.3 (C-2), 173.2 (C=O).

3.5.2. cis-*(1*S,*2*R*)-1-Amino-2-hydroxycyclohexanecarboxylic acid* ***10a***

Mp: >270°C (dec.); $[\alpha]_D^{20}$=+4.5 (*c* 1.085, H_2O); ^{1}H NMR (D_2O; HOD, 4.80 ppm): 1.1–1.4 (m, 3H, cycloaliph. H), 1.5–2.0 (m, 5H, cycloaliph. H), 4.05 (dd, *J*=11.2, 5.0 Hz, 1H, 2-H); ^{13}C NMR (D_2O): 19.1 (C-5), 22.7 (C-4), 28.7 (C-3), 30.9 (C-6), 65.7 (C-1), 69.7 (C-2), 175.7 (C=O); HRMS (EI, 70 eV): m/z (%) 159 (1) [M^+, $C_7H_{13}N_1O_3$: calcd 159.089544, found 159.089704], 141 (7) [M^+−18 (H_2O), $C_7H_{11}N_1O_2$: calcd 141.078979, found 141.078994], 114 (100) [M^+−45 (CO_2H)]; MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 160 (100) [M^++1].

3.5.3. cis-*(1*R,*2*S*)-1-Amino-2-hydroxycyclohexanecarboxylic acid* ***3a*** *(antipode of* ***10a****)*

Mp: >270°C (dec.); $[\alpha]_D^{20}$=−4.0 (*c* 0.15, H_2O) (lit.[6]: $[\alpha]_D^{20}$=−33.1); MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 160 (100) [M^++1].

3.5.4. trans-*(1*S,*2*S*)-1-Amino-2-hydroxycyclohexanecarboxylic acid hydrochloride* ***10b***·*HCl*

Yield: 89%; mp: >300°C (dec.); ^{1}H NMR (CD_3OD): 1.42 (m, 1H, 4-H), 1.60–1.76 (m, 2H, 3-H, 5-H), 1.76–1.96 (m, 3H, 4-H, 5-H, 6-H), 2.00–2.20 (m, 2H, 3-H, 6-H), 3.76 (dd, *J*=11.0, 4.9 Hz, 1H, 2-H); ^{13}C NMR (CD_3OD): 22.1 (C-5), 24.4 (C-4), 31.3 (C-6), 32.9 (C-3), 65.1 (C-1), 73.8 (C-2), 171.6 (C=O).

3.5.5. trans-*(1*S,*2*S*)-1-Amino-2-hydroxycyclohexanecarboxylic acid* ***10b***

Mp: >270°C (dec.); $[\alpha]_D^{20}$=+3.1 (*c* 1.06, H_2O); ^{1}H NMR (D_2O; HOD, 4.80 ppm): 1.1–2.2 (m, 8H, cycloaliph. H), 3.6 (dd, *J*=10.2, 4.6 Hz, 1H, 2-H); ^{13}C NMR (D_2O): 21.0 (C-5), 22.5 (C-4), 29.9 (C-3), 31.6 (C-6), 64.1 (C-1), 72.3 (C-2), 174.0 (C=O); HRMS (EI, 70 eV): m/z (%) 159 (1) [M^+, $C_7H_{13}N_1O_3$: calcd 159.089544, found 159.089715], 141 (7) [M^+−18 (H_2O), $C_7H_{11}N_1O_2$: calcd 141.078979, found 141.078987], 114 (100) [M^+−45 (CO_2H)]; MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 160 (100) [M^++1].

3.5.6. trans-*(1*R,*2*R*)-1-Amino-2-hydroxycyclohexanecarboxylic acid* ***3b*** *(antipode of* ***10b****)*

Mp: >270°C (dec.); $[\alpha]_D^{20}$=−3.0 (*c* 0.965, H_2O) (lit.[6]: $[\alpha]_D^{20}$=−28.9); MS (ESI, 1 μL/min, spray 3.8 kV, 200°C, 30 psi): m/z (%) 160 (100) [M^++1].

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