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Cyclobutane amino acids (CBAAs): asymmetric Strecker synthesis of enantiopure *cis*- and *trans*-2,4-methanovalines

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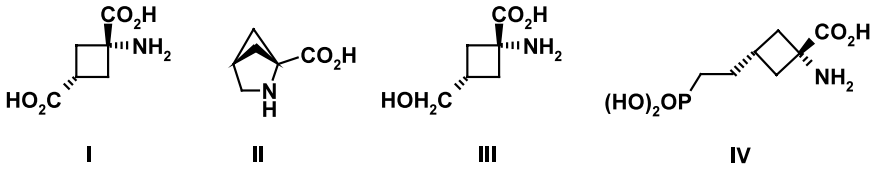
Abstract—Synthesis of enantiopure 2,4-methanovalines has been achieved by means of asymmetric Strecker synthesis starting from racemic 2-methylcyclobutanone. The *trans*-configured α-amino acids were obtained from cyanide additions carried out in methanol, whereas the *cis*-configured 2,4-methanovalines were accessible via reactions in hexane. Relative stereochemistry was elucidated from NOESY experiments, while absolute configurations were assigned from X-ray crystallographic analysis.

1. Introduction

The structure of 1-aminocyclobutane carboxylic acids has received increasing attention in the field of medicinal chemistry in recent years. Thus, in 1980 Bell et al. reported on the first isolation of 2,4-methano amino acids (2,4-MAAs) (Scheme 1), namely *cis*-2,4-methanoglutamic acid (2,4-MGlu, **I**) and 2,4-methanoproline (2,4-MPro, **II**) from the seeds of *Ateleia herbert smithii*.[1] Later, *cis*-1-amino-3-hydroxymethylcyclobutane carboxylic acid (**III**) was isolated by Fellows et al. from the same source.[2] In 1990 *trans*-2,4-methanoglutamic acid was described as a highly potent NMDA agonist,[3] whereas other 1,3-disubstituted cyclobutane derived α-amino acids such as **IV** operate as NMDA antagonists and anticonvulsive drugs,[4] respectively. Furthermore, incorporation of various 2,4-MAAs into bioactive peptides increased their stability towards enzymatic degradation and altered their biological properties remarkably.[5] From a synthetic point of view it is noteworthy that the Gaoni approach[6] provides access only to a wide range of either achiral or racemic 1-aminocyclobutanecarboxylic acids and corresponding 1,3-dicarboxylic acids, leading us to investigate asymmetric Strecker synthesis as a tool for the preparation of enantiomerically and diastereomerically pure 1-amino-2-methylcyclobutane carboxylic acids. Herein, we report on the first synthesis of homochiral 2,4-methanovalines (2,4-MVals) starting from racemic 2-methylcyclobutanone and 1-phenylethylamine as a chiral auxiliary.

2. Results and discussion

The racemic starting material 2-methylcyclobutanone **1** was prepared in two steps from 1,3-dibromobutane and tosylmethylioscyanide (TosMiC) according to a literature procedure.[7] The racemic ketone **1** was allowed to condense with an equimolar amount of (*R*)-1-phenylethylamine under azeotropic removal of water, yielding the ketoimine **2** in quantitative yields but as a diastereomeric mixture of *E*-α*R*,2*R*-, *E*-α*R*,2*S*-, *Z*-α*R*,2*R*- and *Z*-α*R*,2*S*-configured components. Accord-



Scheme 1. Structures of 2,4-methano α-amino acids **I**–**IV**.

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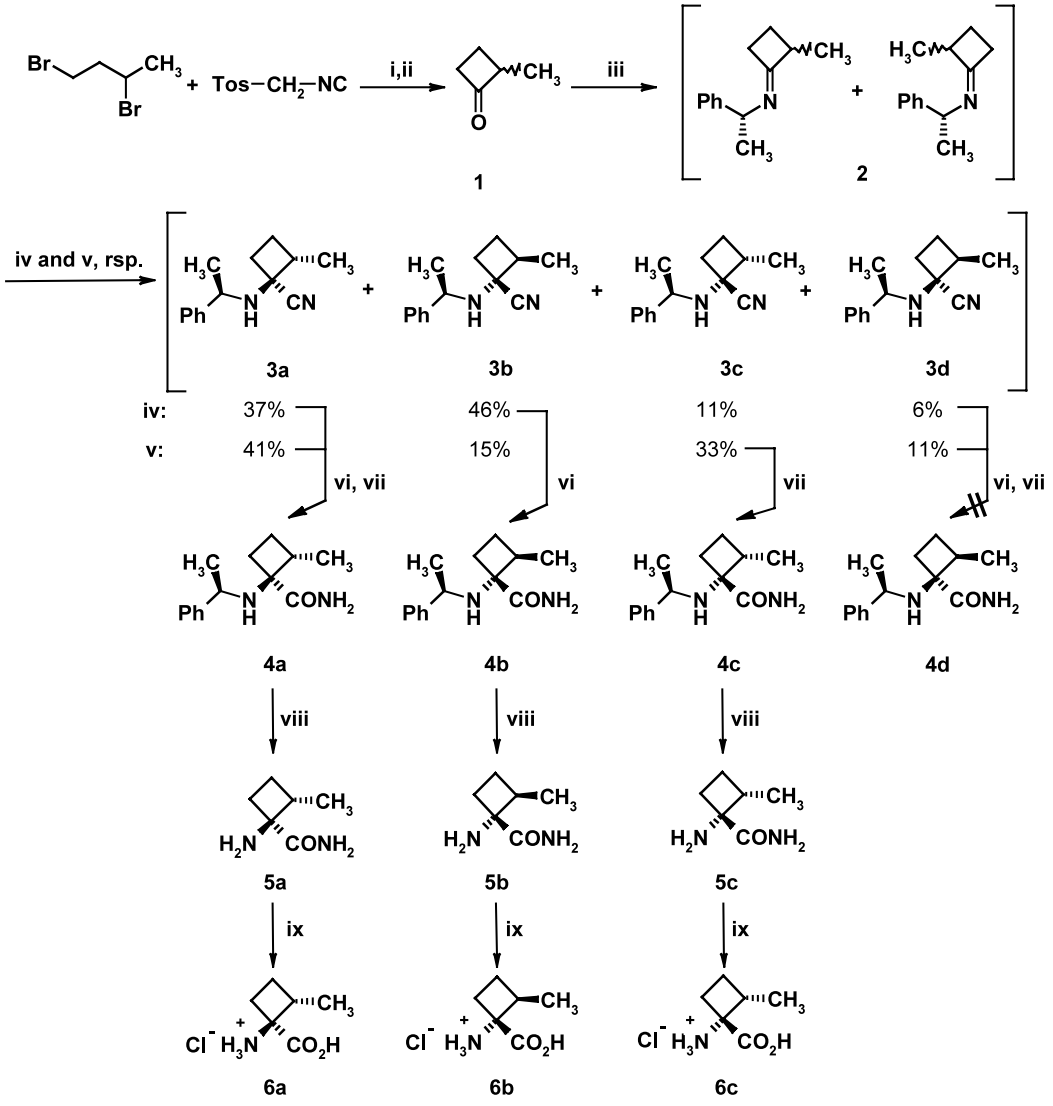
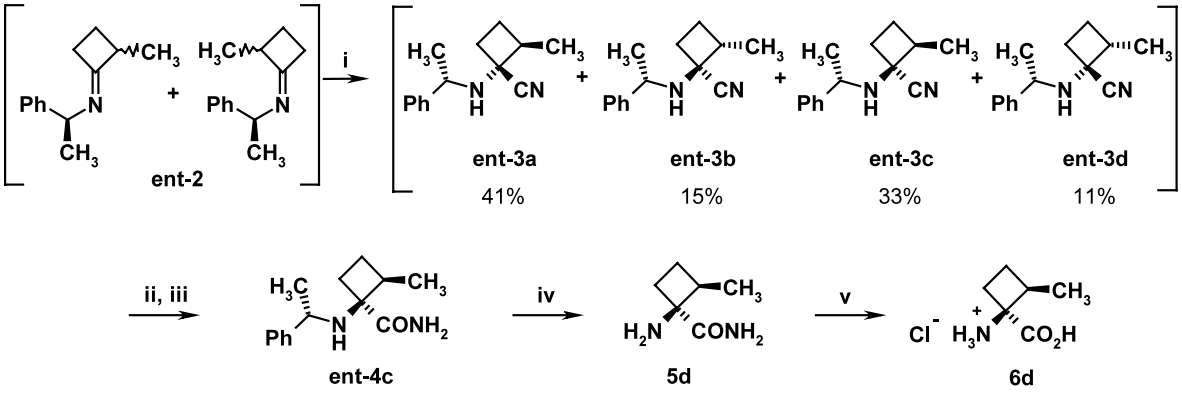
ing to ^{13}C NMR analysis the E/Z ratio of the ketoimine mixture was ≈8:1, whereas the $2R/2S$ quotient (1:1) of the starting material was the same, indicating that no epimerisation at C-2 took place during ketoimine formation. The crude imine mixture **2** was then applied to Lewis acid-catalyzed addition of trimethylsilylcyanide (TMSCN) to yield the respective α-amino nitriles **3**. In this step, the prochiral sp^2 hybridised imino carbon atom of **2** is converted into the new third stereogenic center. Since the configuration of the chiral auxiliary is fixed, up to four diastereomeric α-amino nitriles **3a–d** can theoretically be formed in this reaction. In practice, we observed the formation of four component mixtures even under different reaction conditions (Scheme 2). However, our earlier results[8] on the solvent dependent reversal of the *trans*/*cis*-diastereoselectivity could be confirmed and accordingly, the use of methanol in the α-amino nitrile synthesis led to the preferential formation of the *trans* products (reaction conditions **iv** in Scheme 2), whereas completing the reaction with hexane as the solvent drove the reaction towards *cis* configured diastereomers as the major products (reaction conditions **v** in Scheme 2). This difference in behavior enabled us to subsequently isolate the two *trans*-2,4-methanovalines and the two *cis*-2,4-methanovalines starting from α-amino nitrile synthesis carried out in different solvents (vide infra).

2.1. Preparation of *trans*-2,4-MVals (Scheme 2)

Treatment of the α-amino nitrile mixture **3a–d** obtained in MeOH (**iv**) with concentrated sulfuric acid for 3 h at −10°C, 3 h at 0°C and finally 4 days at 25°C gave the respective α-amino carboxamide in 55% yield again as



Scheme 2. Asymmetric Strecker synthesis of the 2,4-methanovalines **6a**, **6b** and **6c**. *Reagents and conditions*: (i) NaH, DMSO/Et_2O, rt, 2 h, 62%; (ii) sulfolane, H_2O/H_2SO_4, 110°C, 2 h, 70%; (iii) (*R*)-1-PEA, TsOH, toluene, reflux, 5 h, ca. 100%; (iv) TMSCN, MeOH, $ZnCl_2$, 0°C, 3 h, 98%; (v) TMSCN, hexane, $ZnCl_2$, −10°C, 48 h, 75%; (vi) conc. H_2SO_4, −10°C 3 h, 0°C 3 h, rt 96 h, 55%; CC: silica gel Si60 (230–400 mesh), EtOAc–cyclohexane (1:1), 78% recovery rate; (vii) conc. H_2SO_4–CH_2Cl_2, −10°C, 96 h, 80%; CC: silica gel Si60 (70–230 mesh), EtOAc–cyclohexane–Et_2NH; (viii) MeOH, Pd/C (10%), $HCOONH_4$, reflux, 2 h, 96%; (ix) HCl conc., reflux, 12 h.



Scheme 3. Asymmetric Strecker synthesis of the *cis*-2,4-methanovaline **6d**. *Reagents and conditions*: (i) TMSCN, hexane, $ZnCl_2$, −10°C, 48 h, 75%; (ii) conc. H_2SO_4–CH_2Cl_2, −10°C, 96 h, 80%; (iii) silica gel Si60 (70–230 mesh), EtOAc–cyclohexane–Et_2NH; (iv) MeOH, Pd/C (10%), $HCOONH_4$, reflux, 2 h, 96% (v) HCl conc., reflux, 12 h.

four component mixtures with practically unchanged diastereomeric composition with respect to the **3a**–**d** mixture. The two *trans*-configured components **4a** and **4b** could be isolated from this crude α-amino carboxamide mixture by simple flash column chromatography, whereas isolation of any *cis*-configured compounds failed in this series. The diastereomerically pure α-amino amides **4a** and **4b**, obtained in this way, were separately hydrogenolysed using palladium on charcoal (10%) and ammonium formate to yield the corresponding primary α-amino amides **5a** and **5b**, respectively. Finally, **5a** and **5b** were hydrolysed to the α-amino acid hydrochlorides **6a** and **6b** by refluxing in 12 M HCl for 24 h.

2.2. Preparation of *cis*-2,4-MVals

Since the relative amount of *cis* configured compounds in the α-amino nitrile mixtures **3a**–**d**, obtained from reactions in methanol (**iv**), was very small, it was unfeasible to isolate any of them after partial hydrolysis to the corresponding α-amino amides. Therefore, we needed to set up a second series, in which the hydrolysis step with concentrated sulfuric acid started from the α-amino nitrile mixture yielded from cyanide addition in hexane (reaction conditions **v**). As shown in Scheme 2, this mixture contains 33% of the *cis*-configured nitrile **3c**. On hydrolysis, the stereochemical composition of this mixture remained almost unchanged. Subsequent column chromatography on silica gel using cyclohexane/ethyl acetate/diethylamine as the mobile phase yielded three fractions: the first contained the diastereomerically pure *trans*-configured **4a**, the second consisted of a mixture of *trans*-**4b** and the minor *cis* component **4d** in a ratio of 85:15, and the third was made up of the pure *cis*-configured α-amino amide **4c**. The conversion of *cis*-**4c** into the target cis-α-amino acid **6c** was done as described for **4a** and **4b**, respectively (Scheme 2). Although the separation of the **4b**/**4d** mixture from above failed, the second *cis*-amino acid **6d** was easily accessible from the same sequence starting with Strecker synthesis using the enantiomerically pure chiral auxiliary (*S*)-1-phenylethylamine. In this case diastereomerically pure **ent-4c**, the precursor of **6d**, was obtained by column chromatography and transformed into the respective α-amino acid **6d** (Scheme 3).

In conclusion, all four stereomeric 1-amino-2-methylcyclobutanecarboxylic acids (2,4-methanovalines) could be synthesised via asymmetric Strecker reactions carried out in different solvents using (*R*)- and (*S*)-1-phenylethylamine, respectively.

3. Remarks on the stereochemistry

The relative stereochemistry of the α-amino amides **4a** and **4b** could be derived from 2D NMR experiments carried out in $CDCl_3$. As a result, we observed NOEs between the carboxamide NH_2-protons and the methyl group at position 2 of the cyclobutane on the one site, and between the amino NH-proton of the chiral auxiliary moiety and the methin proton at position 2 on the other site, both indicating the *trans* configuration of the methyl and the 1-phenylethylamino substituents (Fig. 1). The absolute stereochemistry of the *trans* compounds was obtained from X-ray analysis, which allowed us to unambiguously assign the α*R*,1*S*,2*S* configuration to compound **4a**. Consequently, the second *trans* α-amino amide **4b** must be α*R*,1*R*,2*R* configured. In a series of earlier papers we have already shown that the major product gained from α-amino nitrile synthesis in hexane (kinetically controlled reactions) always possesses the same absolute configuration at C-1 as the chiral auxiliary ('like-induction'). By analogy, we can deduce the α*R*,1*R*,2*S* configuration for the *cis* configured α-amino amide **4c** and finally the α*S*,1*S*,2*R* configuration for the second *cis* compound

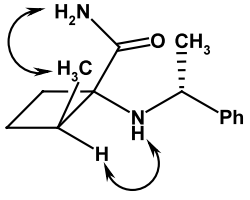


Figure 1. NOE effects observed for compound **4b**.

ent-4c. Given that the hydrogenolysis of the chiral auxiliary moiety as well as the final hydrolysis of the carboxamides proceed under retention of the absolute stereochemistry all assignments made above apply for the primary amino amides **5a–d** as well as for the 2,4-methanovalines **6a–d**.

4. Experimental

Melting points are uncorrected. Solvents were purified according to standard procedures. The given yields are for isolated products. Elemental analyses were obtained with a Perkin–Elmer elemental analyzer PE 240 at the Department of Biochemistry and Organic Chemistry, University of Freiburg. NMR spectra were run at 300 MHz (^{1}H) and 75.4 MHz (^{13}C), respectively, on a Varian Unity 300 spectrometer. Chemical shifts are reported as δ values using either TMS (^{1}H) or the solvent peak (^{13}C) as a reference. Optical rotation values were measured in a 1 dm cell with a Perkin–Elmer 241 polarimeter. Column chromatography was performed on Merck silica gel (70–230 mesh ATSM). Flash chromatography was carried out with silica gel Si60 0.04–0.063 mm, Sigma-Aldrich Chemie GmbH.

4.1. (*RS*)-2-Methylcyclobutanone, 1

Compound **1** was prepared from 1,3-dibromobutane and tosylmethylisocyanide (TosMic) following the procedure described in the literature.[7] Overall yield: 43% (lit.:[7] 57%).

4.2. (*E*/*Z*)-2-(*R*/*S*)-[*N*-(*R*)-1-Phenylethyl]methylcyclobutylidenamines 2 (mixture of four diastereomers)

A mixture of (*RS*)-2-methylcyclobutanone **2** (1.68 g, 0.02 mol), (*R*)-(+)-1-phenylethylamine (2.42 g, 0.02 mol) and a catalytic amount of *p*-toluenesulfonic acid was dissolved in toluene (50 ml) and heated under reflux for 6 h using a Dean–Stark apparatus. The solvent was evaporated in vacuum and the residue was further dried under high vacuum to yield **2** (3.74 g, 99%) as a reddish oil, which was used directly in further reactions without purification.

4.3. 2-Methyl-1-(1-phenylethylamino)cyclobutanecarbonitrile mixture 3a–d (reaction conditions iv)

To a solution of **2** (1.87 g, 0.01 mol) and dry zinc chloride (70 mg, 5 mol%) in methanol (20 ml) trimethylsilylcyanide (1.66 ml, 0.0125 mol) were added at 0°C over a period of 15 min. The reaction mixture was stirred at 0°C for additional 3 h, filtered, concentrated under reduced pressure and dried under high vacuum to give diastereomeric mixture of the α-amino nitriles **3a–d** (2.03 g, 95%) which was used directly in further reactions without purification.

4.4. 2-Methyl-1-(1-phenylethylamino)cyclobutanecarbonitrile mixture 3a–d (reaction conditions v)

To a solution of **2** (3.74 g, 0.02 mol) and dry zinc chloride (140 mg, 5 mol%) in hexane (100 ml) trimethylsilylcyanide (3.4 ml, 0.025 mol) were added at −10°C over a period of 30 min. The reaction mixture was stirred for 48 h at −10°C, quenched with an equimolar volume (1 ml) of methanol, stirred for further 2 h at −10°C, filtered, concentrated under reduced pressure and finally dried under high vacuum to yield diastereomeric mixture of the α-amino nitriles **3a–d** (3.28 g, 77%), which was used directly in further reactions without purification.

4.5. Hydrolysis of the α-amino nitrile mixture 3a–d obtained in MeOH

The diastereomeric mixture **3a–d** (obtained under reaction conditions **iv**, 1.85 g, 8.5 mmol) was added slowly to conc. 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 conc. NH_3, 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 1.1 g (55%) of a crude reaction product, which was applied to flash chromatography (stationary phase: Si60, 230–400 mesh; mobile phase: ethyl acetate/cyclohexane = 1/1; fraction size: 10 ml; compound: stationary phase = 1:100; detection: TLC with ninhydrin reagent), providing the diastereomerically pure α-amino amides **4a** (332 mg, 18%) and **4b** (344 mg, 19%), respectively.

4.5.1. (α*R*,1*S*,2*S*)-2-Methyl-1-(1-phenylethylamino)-cyclobutanecarboxamide, 4a. Mp 219°C (HCl-salt, decomp.); $[\alpha]_D^{25} = +61.9$ (*c* 0.879, H_3COH); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, $J = 6.84$ Hz, 3H), 1.41 (d, $J = 6.59$ Hz, 3H), 1.5–1.7 (m, 2H), 1.82–2.0 (m, 2H), 2.2–2.34 (m, 1H), 2.73–2.83 (m, 1H), 3.75 (q, $J = 6.59$ Hz, 1H), 4.9 (br.s, 1H), 6.4 (br.s, 1H), 7.15–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.9 (q), 22.6 (t), 25.6 (q), 28.8 (t), 43.4 (d), 54.2 (d), 67.7 (s), 126.3 (d), 126.7 (d), 128.3 (d), 146.1 (s), 176.1 (s). Anal. calcd for $C_{14}H_{20}N_2O$: C, 62.56; H, 7.87; N, 10.42. Found: C, 62.44; H, 7.80; N, 10.43%.

4.5.2. (α*R*,1*R*,2*R*)-2-Methyl-1-(1-phenylethylamino)-cyclobutanecarboxamide, 4b. Mp 210°C (HCl-salt, decomp.); $[\alpha]_D^{25} = -19.3$ (*c* 0.846, H_3COH); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, $J = 6.84$ Hz, 3H), 1.28 (d, $J = 6.59$ Hz, 3H), 1.46–1.62 (m, 2H), 1.67 (br.s, 1H); 1.74–1.84 (m, 1H), 2.1–2.23 (m, 1H), 2.32–2.45 (m, 1H), 3.86 (q, $J = 6.59$ Hz, 1H), 5.5 (br.s, 1H), 7.1 (br.s, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.9 (q), 22.7 (t), 23.8 (q), 26.5 (t), 43.4 (d), 54.7 (d), 67.2 (s), 126.3 (d), 127.0 (d), 128.4 (d), 146.5 (s), 177.5 (s). Anal. calcd for $C_{14}H_{20}N_2O$: C, 62.56; H, 7.87; N, 10.42. Found: C, 62.32; H, 7.77; N, 10.35%.

4.6. Hydrolysis of the α-amino nitrile mixture 3a–d obtained in hexane

The diastereomeric mixture **3a–d** (obtained under reaction conditions **v**, 3.2 g, 15 mmol) was dissolved in

dichloromethane (40 ml) and added slowly to conc. H_2SO_4 (30 ml) at −10°C. The mixture was kept for 3 h at −10°C, allowed to warm up to rt, and stirring was continued for 96 h. The reaction mixture was worked-up as described above, to yield crude product (2.78 g, 80%), which was purified by column chromatography (stationary phase: Si 60, 70–230 mesh; mobile phase: cyclohexane/ethyl acetate/diethylamine = 6/4/0.3) to give the diastereomerically pure α-amino amides **4a** (110 mg, 3.2%) and **4c** (620 mg 18%), respectively.

4.6.1. (α*R*,1*R*,2*S*)-2-Methyl-1-(1-phenylethylamino)-cyclobutanecarboxamide, 4c. Mp 208°C (HCl-salt, decomp.); $[\alpha]_D^{25} = +2.6$ (*c* 0.74, H_3COH); ^1H NMR ($CDCl_3$) δ 1.06 (d, $J = 7.17$ Hz, 3H), 1.26 (d, $J = 6.72$ Hz, 3H), 1.28–1.40 (m, 1H), 1.66–1.78 (m, 1H), 1.96 (br.s, 1H), 2.0–2.1 (m, 1H), 2.36–2.46 (m, 1H), 2.50–2.64 (m, 1H), 3.80 (q, $J = 6.72$ Hz, 1H), 5.8 (br.s, 1H), 6.9 (br.s, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 23.3 (t), 23.9 (q), 24.1 (t), 39.1 (d), 54.3 (d), 64.2 (s), 126.2 (d), 126.9 (d), 128.4 (d), 146.6 (s), 180.1 (s). Anal. calcd for $C_{14}H_{20}N_2O$: C, 62.56; H, 7.87; N, 10.42. Found: C, 62.92; H, 7.45; N, 10.50%.

4.6.2. (α*S*,1*S*,2*R*)-2-Methyl-1-(1-phenylethylamino)-cyclobutanecarboxamide, *ent*-4c. Mp 206°C (HCl-salt, decomp); $[\alpha]_D^{25} = -3.0$ (*c* 1.01, H_3COH); ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data are identical with those of **4c**. Anal. calcd for $C_{14}H_{20}N_2O$: C, 62.56; H, 7.87; N, 10.42. Found: C, 62.75; H, 7.51; N, 10.55%.

4.7. General procedure for the hydrogenolysis of the α-amino amides 4a–c and ent-4c

To a solution of the diastereomerically pure α-amino carboxamides **4a–c** and **ent-4c** (230 mg, 1 mmol), respectively, in methanol (30 ml), Pd/C (10%, 280 mg) and ammonium formate (510 mg) were added and the resulting mixture was heated under reflux for 2 h. The catalyst was removed by filtration through Celite and the solvent was evaporated yielding **5a–d** as colorless oils, which were converted into their hydrochloride salts using ether saturated with HCl gas.

4.7.1. (1*S*,2*S*)-1-Amino-2-methylcyclobutanecarboxamide hydrochloride, 5a. Mp 209°C (decomp); $[\alpha]_D^{25} = +86.1$ (*c* 1.015, H_3COH); ^1H NMR (CD_3OD) δ 1.09 (d, $J = 7.02$ Hz, 3H), 1.70–1.84 (m, 1H), 2.16–2.42 (m, 2H), 2.56–2.66 (m, 1H), 2.70–2.88 (m, 1H); ^{13}C NMR (CD_3OD) δ 16.0 (q), 23.5 (t), 26.7 (t), 39.6 (d), 63.2 (s), 172.2 (s); MS (CI, isobutane, 200 eV): *m*/*z* (%) 129 (100) [M^+], 111.9 (23) [M^+-17 (NH_3)], 85 (7) [M^+-44 ($CONH_2$)]; HRMS (EI, 70 eV): *m*/*z* (%) 128 [$M-1^+$], $C_6H_{12}N_2O$: calcd 128.0947, found 128.0949.

4.7.2. (1*R*,2*R*)-1-Amino-2-methylcyclobutanecarboxamide hydrochloride, 5b. Mp 206°C (decomp.); $[\alpha]_D^{25} = -86.8$ (*c* 0.875, H_3COH); ^1H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) data are identical with those of **5a**; MS (CI, isobutane, 200 eV): *m*/*z* (%) 129 (100) [M^+], 111.9 (22) [M^+-17 (NH_3)], 85 (7) [M^+-44 ($CONH_2$)].

4.7.3. (1*R*,2*S*)-1-Amino-2-methylcyclobutanecarboxamide hydrochloride, 5c. Mp 198°C (decomp.); $[\alpha]_D^{25} = +7.1$ (*c* 1.03, H_3COH); ^1H NMR (CD_3OD) δ 1.13 (d, $J = 7.33$ Hz, 3H), 1.88–2.02 (m, 1H), 2.10–2.36 (m, 2H), 2.62–2.76 (m, 1H), 2.98–3.12 (m, 1H); ^{13}C NMR (CD_3OD) δ 14.7 (q), 23.9 (t), 28.3 (t), 38.3 (d), 63.2 (s), 174.3 (s); MS (CI, isobutane, 200 eV): *m*/*z* (%) 129 (100) [M^+], 111.9 (23) [M^+-17 (NH_3)], 85 (6) [M^+-44 ($CONH_2$)]; HRMS (EI, 70 eV): *m*/*z* (%) 128 [$M-1^+$], $C_6H_{12}N_2O$: calcd 128.0947, found 128.0950.

4.7.4. (1*S*,2*R*)-1-Amino-2-methylcyclobutanecarboxamide hydrochloride, 5d. Mp 199°C (decomp.); $[\alpha]_D^{25} = -7.4$ (*c* 1.015, H_3COH); ^1H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) data are identical with those of **5c**; MS (CI, isobutane, 200 eV): *m*/*z* (%) 129 (100) [M^+], 111.9 (23) [M^+-17 (NH_3)], 85 (7) [M^+-44 ($CONH_2$)].

4.8. General procedure for the hydrolysis of the α-amino amides 5a–d

The stereochemically pure α-amino amide hydrochloride **5a–d** (1 mmol) was dissolved in conc. hydrochloric acid (10 ml) and heated under reflux at 100°C for 24 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 **6a–d** were washed with small amounts of diethyl ether and ethyl acetate and finally dried in high vacuum.

4.8.1. (1*S*,2*S*)-1-Amino-2-methylcyclobutanecarboxylic acid hydrochloride, 6a. Mp >250°C (decomp.); $[\alpha]_D^{25} = +13.8$ (*c* 0.105, water); ^1H NMR (CD_3OD) δ 1.13 (d, $J = 7.02$ Hz, 3H), 1.84–2.0 (m, 1H), 2.12–2.32 (m, 2H), 2.52–2.64 (m, 1H), 2.78–2.92 (m, 1H); ^{13}C NMR (CD_3OD) δ 15.8 (q), 23.7 (t), 27.6 (t), 39.8 (d), 62.6 (s), 171.9 (s); MS (CI, isobutane, 200 eV): *m*/*z* (%) 130 (100) [M^+], 113 (3) [M^+-17 (NH_3)], 85 (10) [M^+-45 (COOH)]; HRMS (EI, 70 eV): *m*/*z* (%) 87 [$M+1^+-44$ (CO_2)], $C_5H_{13}N_1$: calcd 87.1048, found 87.1051.

4.8.2. (1*R*,2*R*)-1-Amino-2-methylcyclobutanecarboxylic acid hydrochloride, 6b. Mp >250°C (decomp.); $[\alpha]_D^{25} = -14.5$ (*c* 0.112, water); ^1H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) data are identical with those of **6a**; MS (CI, isobutane, 200 eV): *m*/*z* (%) 130 (100) [M^+], 113 (3) [M^+-17 (NH_3)], 85 (10) [M^+-45 (COOH)].

4.8.3. (1*R*,2*S*)-1-Amino-2-methylcyclobutanecarboxylic acid hydrochloride, 6c. Mp >250°C (decomp.); $[\alpha]_D^{25} = +23.5$ (*c* 0.190, water); ^1H NMR (CD_3OD) δ 1.19 (d, $J = 7.33$ Hz, 3H), 1.81–2.0 (m, 1H), 2.16–2.38 (m, 2H), 2.63–2.76 (m, 1H), 3.02–3.16 (m, 1H); ^{13}C NMR (CD_3OD) δ 15.1 (q), 24.1 (t), 27.9 (t), 37.3 (d), 61.8 (s), 173.1 (s); MS (CI, isobutane, 200 eV): *m*/*z* (%) 130 (100) [M^+], 113 (3) [M^+-17 (NH_3)], 85 (5) [M^+-45 (COOH)]; HRMS (EI, 70 eV): *m*/*z* (%) 87 [$M+1^+-44$ (CO_2), $C_5H_{13}N_1$: calcd 87.1048, found 87.1041.

4.8.4. (1*S*,2*R*)-1-Amino-2-methylcyclobutanecarboxylic acid hydrochloride, 6d. Mp >250°C (decomp.); $[\alpha]_D^{25} = -24.0$ (*c* 0.088, water); ^1H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) data are identical with those of **6c**; MS (CI, isobutane, 200 eV): *m*/*z* (%) 130 (100) [M^+], 113 (3) [M^+-17 (NH_3)], 85 (5) [M^+-45 (COOH)].

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References

1. Bell, E.; Qureshi, M.; Pryce, R.; Janzen, D.; Lemke, P.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 1409.
2. Austin, G. N.; Baird, P. D.; Chow, H. F.; Fellows, L. E.; Fleet, G. W. J.; Nash, R. J.; Peach, J. M.; Pryce, R. J.; Stirton, C. H. *Tetrahedron* **1987**, *43*, 1857.
3. (a) Allan, R. D.; Hanrahan, J. R.; Hambley, T. W.; Johnston, G. A.; Mewett, K. N.; Mitrovic, A. D. *J. Med. Chem.* **1990**, *33*, 2905; (b) Lanthorn, T. H.; Hood, W. F.; Watson, G. B.; Compton, R. P.; Rader, R. K.; Gaoni, Y.; Moanhan, J. B. *Eur. J. Pharmacol.* **1990**, *182*, 397.
4. Gaoni, Y.; Chapman, A. G.; Parvez, N.; Pook, P. C. K.; Jane, D. E.; Watkins, J. C. *J. Med. Chem.* **1994**, *37*, 4288.
5. Fridkin, M.; Gaoni, Y.; Gershonov, E.; Granoth, R.; Tzehoval, E. *J. Med. Chem.* **1996**, *39*, 4833.
6. (a) Gaoni, Y. *Org. Prep. Proc. Int.* **1995**, *27*, 185; (b) Gaoni, Y. *Tetrahedron Lett.* **1988**, *29*, 1591.
7. van Leusen, D.; van Leusen, A. *Synthesis* **1980**, 325.
8. Wede, J.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **2000**, *11*, 3231 and references cited therein.