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Stereoselective synthesis of (1*R*,2*S*)- and (1*S*,2*R*)-1-amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochlorides: bicyclic glutamic acid derivatives

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Abstract—Asymmetric synthesis of (1*R*,2*S*)- and (1*S*,2*R*)-1-amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-diones has been achieved. The underlying second generation asymmetric synthesis proceeds via a Strecker reaction with commercially available (*R*)-1-phenylethylamine (1-PEA) as chiral auxiliary, TMSCN as cyanide source and racemic ethyl 2-(2-oxocyclohex-1-yl)ethanoate. A ring closure addition–elimination reaction between an amide nitrogen and the ester functionality leads to the 1-amino-3-azabicyclo[4.4.0]decan-2,4-diones. The absolute configurations of the title compounds have been assigned based on detailed NMR-spectroscopic analysis and X-ray data.

1. Introduction

As early as 1850, the German chemist Adolf Strecker described the one-pot synthesis of the amino acid alanine by means of heating a mixture of acetaldehyde, ammonia and hydrogen cyanide in the presence of hydrochloric acid.[1,2a–k] This procedure, named after its originator and extended to a variety of carbonyl substrates, is still the most common method of preparing large amounts of α-amino acids. Nevertheless and in contrast to his assumption, Strecker did not prepare one single compound but a racemic mixture of the enantiomeric D- and L-alanines. Since nowadays enantiomeric purity is one of the major issues in α-amino acid synthesis, tremendous efforts have been put into the development of asymmetric versions of Strecker's protocol. In 1963, a 'Nature' paper of Harada et al.[3] describes a modified three-step asymmetric synthesis of L-alanine with an enantiomeric excess (ee) of 90% and an overall chemical yield of 17%. Starting from acetaldehyde, (*S*)-(−)-phenylethylamine ((*S*)-1-PEA) and hydrogen cyanide, the authors obtained the corresponding secondary α-aminonitriles, which were subsequently hydrolysed and hydrogenolysed to L-alanine. Nevertheless, later investigations showed that the enantiomeric excess was essentially due to fractional crystallisation of the intermediate secondary α-amino acid hydrochlorides. The actual diastereoselectivity of the stereodetermining step of this sequence, namely the cyanide addition, was shown to yield enantiomeric excesses of around 30%.[4]

As medicinal chemists we were particularly interested in stereomerically pure and conformationally restricted analogues of naturally occuring α-amino acids. In order to get access to compounds bearing such structural features we have developed and extensively studied the asymmetric Strecker procedure starting from racemic 2-substituted cycloaliphatic ketones. Depending on the reaction conditions (temperature and nature of the solvent), the established reaction sequence has proven to be a powerful tool for the diastereoselective synthesis of all four feasible stereomers of a series of carbocyclic α-amino acids with vicinal stereocentres.[5,6a–c]

Carbocyclic α-amino acids as representatives of the α,α-disubstituted α-amino acid family are widely used in the isosteric replacement of proteinogenic amino acids resulting in specific backbone conformations and increased stability towards chemical and enzymatic degradations.[7a–c] Moreover, conformationally restricted analogues of glutamic acid such as 1-aminoindanedicarboxylic acid (AIDA) or 1-aminocyclopentane-1,3-dicarboxylic acids (ACPD) have been described as agonists and/or antagonists at both the ionotropic (iGluRs) and the metabotropic glutamate receptors (mGluRs). Recently, they have been used in the characterisation and the subtype classification of mGluRs.[8a,b]

Keywords: Asymmetric Strecker synthesis; 3-Azabicyclo[4.4.0]decan-2,4-dione; Diastereoselectivity; X-ray analysis; Glutamic acid derivatives.
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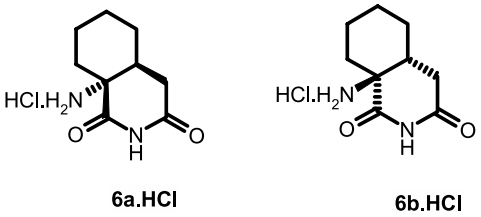


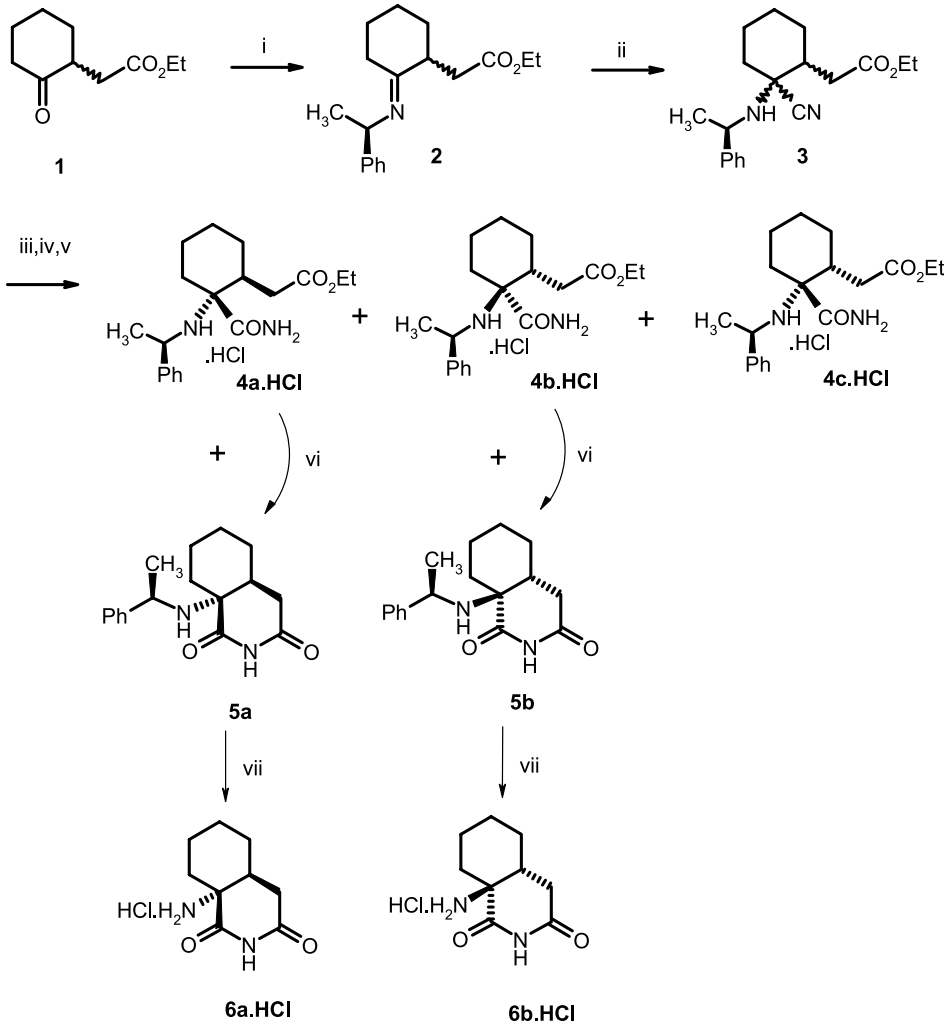
Figure 1. 1-Amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-diones.

Herein, we wish to report on the synthesis of the bicyclic imides **6a**,**b** (Fig. 1) as conformationally restricted templates, which mimic folded conformations of glutamic acid, with a focus on the elucidation of the relative and the absolute stereochemistry of the intermediate α-aminonitriles.

2. Results and discussion

The synthetic route is exemplified using (*R*)-1-phenylethylamine as the chiral auxiliary. Racemic ethyl 2-(2-oxocyclohex-1-yl)ethanoate (**1**), prepared according to the standard Stork-enamine procedure from cyclohexanone, was reacted with enantiomerically pure (*R*)-1-phenylethylamine under acidic catalysis and azeotropic removal of water in benzene to yield a diastereomeric mixture of only the two (*E*)-imines **2**. It is noticable that, if the imine condensation is run in higher boiling solvents, some aminolysis of the ester could be observed.

The imine mixture was subsequently subjected to a Lewis acid ($ZnCl_2$) catalysed cyanide addition using trimethysilylcyanide (TMSCN) affording the four feasible diastereomeric α-aminonitriles **3**. Indeed, since the cyanide addition to the prochiral imine carbon atom provides a new stereocentre, the α-aminonitriles exhibit two adjacent asymmetrically substituted carbon atoms. The stereochemical outcome of this stereodetermining step depends upon the reaction conditions, that is, the nature of the solvent and the reaction temperature which allows the reaction to be carried out either under kinetic (aprotic solvents and low temperatures) or under thermodynamic (protic solvents and higher temperatures) conditions.[5,6a,b] For the purposes of developing a straight-forward synthesis of the bicyclic amino imides **6a**,**b** presented here, the



Scheme 1. Reagents and conditions: (i) (*R*)-1-PEA, *p*-TsOH, benzene, reflux, 16 h; (ii) TMSCN, $ZnCl_{2\ anhyd}$, MeOH, 0 °C to rt, overnight; (iii) $H_2SO_{4\ concd}$, CH_2Cl_2, −20 °C, 3 days; (iv) CC on SiO_2, cyclohexane/EtOAc 3:2; (v) for **4a**–**c**, ether–HCl; (vi) extraction of the base with EtOAc, then stirring with SiO_2, cyclohexane/EtOAc 3:2, rt, 5 days; (vii) $NH_4^+HCO_2^-$, Pd/C (10%), EtOH, reflux, 2 h.

cyanide addition was carried out under thermodynamic control leading preferentially to the required *trans* amino nitriles. Thus, at room temperature in methanol the four feasible α-aminonitriles were obtained in a 44:30:18:8 ratio as determined by ^{13}C NMR-analysis of selected significant carbon atoms.[5]

The subsequent hydrolysis of the nitriles to the corresponding stable secondary α-amino amidoesters **4** proved troublesome. Indeed, the hydrolysis of the sterically hindered cyano group of the α,α-disubstituted aminonitriles needs drastic reaction conditions and the aminonitriles are prone to undergo a 'retro-Strecker-reaction' even in acidic milieu under such conditions. Finally, the hydrolysis was achieved in 73% yield with concd H_2SO_4 at −20 °C over a period of 3 days avoiding any cleavage of the chiral auxiliary. It could be shown by means of ^{13}C NMR spectroscopy that the stereochemical distribution of the four stereoisomers was not altered during this specific type of mild hydrolysis. Thus, we reasoned that the assignment of the configuration of the different stereoisomeric secondary aminonitriles **3** should be deducible from the corresponding derived secondary amino amides **4**. For this purpose, the amino amidoesters **4** were separated by means of column chromatography (CC) on silica gel eluted with cyclohexane/ethyl acetate 3:2. Surprisingly, the CC did not lead to the expected four compounds but to five different structures. Three of the structures could be identified as the amino amidoesters **4a–c**, and two of them, which lack the ethyl ester moiety, as the amino imides **5a**,**b** by means of 1D- and 2D NMR techniques. We reasoned that the imides are the desired follow-up products of the *trans*-amino amidoesters and arise from a ring closure addition–elimination reaction between the amide nitrogen and the ester functionality. In this case, the low nucleophilicity of the amide nitrogen is compensated by the geometric proximity of the electrophilic reaction partner and finally by the extreme thermodynamic stability of the bicyclic imides. We could show that ester **4a**, by far the major compound, is converted to **5a** if stirred with silica gel under exactly the conditions of the CC. The same occurs with **4b**, the second major ester, which is converted to **5b**. The third ester **4c**, with *cis* configuration, did not yield a bicyclic analogue under those reaction conditions. Indeed, neither a bicyclic imide nor the theoretically feasible bicyclic lactam rising from a nucleophilic displacement of the ethyl ester moiety by the secondary amine nitrogen were observed. Note, that neither the fourth diastereomeric ester nor any of the possible follow-up compounds could be traced after column chromatography (Scheme 1).

The relative stereochemistry of **5a** was deduced from a positive NOE effect between H_α and H_2 indicating a *cis*-fusion of the rings (Fig. 2a).

The absolute configuration of **5a** was finally derived from a single crystal X-ray structure analysis and established as α*R*,1*R*,2*S* (Fig. 2b). Thus, the absolute configuration of the parent **4a** could be deduced as *trans*-α*R*,1*R*,2*S*. Subsequent hydrogenolysis of **5a** under transfer catalysis conditions with ammonium formate and Pd on charcoal affords the primary amino imide **6a** with 1*R*,2*S* configuration, whereas hydrogenolysis of **5b** yields the corresponding primary amino imide **6b** with the opposite optical rotation as

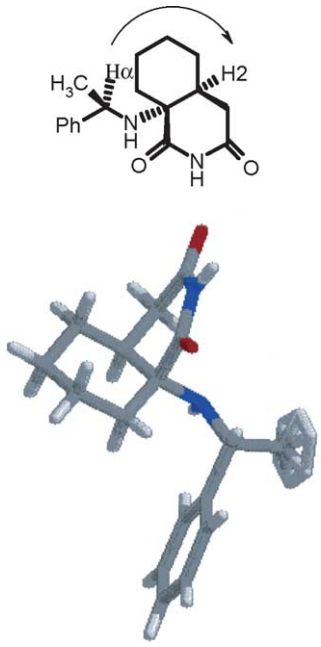


Figure 2. (a) (top) NOE-effect between H-α and H-2 in compound **5a** and (b) (bottom) X-ray structure of **5a**.

compared to **6a**. Thus, the enantiomeric 1*S*,2*R* configuration could be assigned to the parent compounds **4b** and **5b**. Since **4a** and **4b** represent the two feasible *trans* configured esters, the third ester **4c** has to exhibit a *cis* configuration. In this case, the relative stereochemistry cannot be unambiguously confirmed by a NMR analysis since earlier investigations from our group have shown that the exclusively accessible ^3J C–H coupling constants are not a reliable parameter in assessing the relative stereochemistry of 1,1-disubstituted-2-substituted cyclohexane derivatives.[9]

Interestingly, the major ester **4a** features 1*R*-configuration which is the configuration of the chiral auxiliary. This means that the diastereoselective cyanide addition occurs with like-induction at C1 which is in accordance with all our previous observations.[4,5a–c] The two feasible *cis*-aminonitriles represent 18 and 8% of the crude aminonitrile mixture, repectively. Since the amino amidoester **4c** is isolated in more than 8%, it has to arise from the major *cis* aminonitrile formed during the cyanide addition and as we observe like-induction at C1, **4c** must be 1*R*,2*R* configured. The enantiomeric *cis* amino amidoester with 1*S*,2*S* configuration would be accessible by the same pathway, using (*S*)-1-phenylethylamine as chiral auxiliary. The final bicyclic imides **6a** and **6b** are obtained in an approximate ratio of 3:1 from a reaction sequence carried out with the chiral auxiliary (*R*)-1-PEA. The same sequence run with the enantiomeric auxiliary would lead to the same final products with the opposite ratio.

3. Conclusions

The application of the asymmetric Strecker protocol followed by a ring closure reaction led to the synthesis of the previously unknown 1*R*,2*S*- and 1*S*,2*R*-1-amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochlorides.

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 with chloroform-*d* and methanol-d_4, respectively, as internal standards. The chemical shifts are reported as δ values using the solvent peaks as reference. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. 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 with subsequent filtration. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. HRMS (EI, 70 eV) was performed on a Finnigan MAT 8200 spectrometer at the Department of Biochemistry and Organic Chemistry, University of Freiburg.

4.1.1. (*RS*)-Ethyl 2-(2-oxocyclohex-1-yl)ethanoate (1). Prepared from cyclohexanone by classical 'Stork-enamine' synthesis in a 0.1 M batch (30% yield). For NMR data see Ref. 10.

4.1.2. *E*-Ethyl-2-[(2-(1(*R*)-phenylethyl)imino)cyclohex-1(*RS*)-yl]ethanoate (2). A solution of **1** (5.5 g, 30 mmol), *p*-toluenesulfonic acid (15 mg) and (*R*)-1-phenylethylamine (4.5 g, 37 mmol) in dry benzene was refluxed using a Dean–Stark apparatus for 16 h. The solvent was removed under reduced pressure and the residue was dried under high vacuum to yield the crude ketimine mixture which was used without further purification in the cyanide addition step. ^{13}C NMR ($CDCl_3$) δ 14.0/14.1, 25.4/25.5, 25.5/25.7, 26.9/27.6, 28.7/28.9, 33.9/34.1, 36.6/36.8, 43.8/44.0, 57.4/57.5, 59.6/59.7, 125.9/126.0, 126.3/126.3, 127.8/128.0, 146.5/147.0, 169.2/169.9, 173.2/173.4.

4.1.3. Ethyl-2-[2(*RS*)-cyano-(2(*RS*)-(1(*R*)-phenylethyl)-amino)cyclohex-1(*RS*)-yl]ethanoate (3). To a solution of the ketimine mixture **2** (8.5 g, 29.6 mmol) and anhydrous $ZnCl_2$ (200 mg) in MeOH (100 mL), TMSCN (4.4 mL, 35 mmol) was added at 0 °C over a period of 30 min. The reaction mixture was allowed to warm up to room temperature and stirred over night. The solids were filtered off, the solvent was evaporated and the residue was dried to yield a mixture of the α-amino nitrile mixture **3** (8.9 g, 96%) which was further reacted without purification.

4.2. Hydrolysis of the nitrile mixture 3

A solution of the nitrile mixture **3** (5 g, 16 mmol) in CH_2Cl_2 (3 mL) was added dropwise to concd H_2SO_4 (50 mL) at −20 °C. Stirring was maintained for a period of 3 days. The reaction mixture was poured onto ice (600 mL) and the solids filtered off. The filtrate was adjusted to pH 8 with concd ammonia and extracted with EtOAc (3×150 mL). The combined organic extracts were washed with water, brine, dried with $MgSO_4$, filtered, concentrated and finally dried in high vacuum to yield 4.77 g (89%) of an oily residue. 3 g of the above residue were separated by means of silica gel column chromatography eluting with cyclohexane/EtOAc 3:2 yielding four fractions **A**, **B**, **C**, and **D**. Fraction **D** consisted of pure **4a** (1.04 g, 31%). Fraction **A** consisted of pure **5a** (292 mg, 10%). Fraction **B** was rechromatographed on silica gel eluting with cyclohexane/EtOAc 2:1 yielding **5b** (170 mg, 6%) and **4c** (328 mg, 10%). Fraction **C** was rechromatographed on silica gel eluting with cyclohexane/EtOAc 2:1 yielding **4b** (295 mg, 9%).

The amine bases **4a**–**c** were each taken up in ether and treated with ether–HCl to yield the corresponding hydrochlorides in quantitative yields (**4a·HCl** can be precipitated directly from the crude oily residue upon treatment with acetone and ether–HCl).

4.2.1. *trans*-Ethyl-2-[2(*S*)-carbamoyl-(2(*S*)-(1(*R*)-phenylethyl)amino)cyclohex-1(*R*)-yl]ethanoate hydrochloride (4a·HCl). White solid, mp 200 °C; $[\alpha]_D^{25}=+1.85$ (EtOH, *c* 1.03); ^{1}H NMR (CD_3OD) δ 1.22 (t, $J=7.0$ Hz, 3H), 1.1–1.3 (m, 3H), 1.3–1.6 (m, 3H), 1.74 (d, $J=6.7$ Hz, 3H), 1.7–1.8 (m, 1H), 1.9–2.1 (m, 1H), 2.4–2.6 (m, 2H), 2.7–2.80 (m, 1H), 4.13 (q, $J=7.0$ Hz, 2H), 4.51 (q, $J=6.7$ Hz, 1H), 7.4–7.5 (m, 3H), 7.6–7.7 (m, 2H); ^{13}C NMR (CD_3OD) δ 14.5, 20.8, 21.5, 22.4, 25.8, 26.0, 35.7, 38.9, 60.1, 62.1, 71.7, 129.0, 130.4, 130.9, 138.8, 172.4, 173.4; MS (CI, NH_3, 45 eV): *m/z* (%) 333 (100) $[M+H^+]$; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}NO_2$ $[M-CONH_2]$ 288.1963. Found 288.1968.

4.2.2. *trans*-Ethyl-2-[2(*R*)-carbamoyl-(2(*R*)-(1(*R*)-phenylethyl)amino)cyclohex-1(*S*)-yl] ethanoate hydrochloride (4b·HCl). White solid, mp 195 °C; $[\alpha]_D^{25}=-22.04$ (EtOH, *c* 1.00); ^{1}H NMR (CD_3OD) δ 1.1 (t, $J=7.1$ Hz, 3H), 1.4–1.6 (m, 3H), 1.6–1.8 (m, 2H), 1.78 (d, $J=6.8$ Hz, 3H), 1.9–2.2 (m, 2H), 2.2–2.4 (m, 1H), 2.45 (dd, $J=16.9$, 10.7 Hz, 1H), 2.5–2.7 (m, 2H), 4.12 (q, $J=7.1$ Hz, 2H), 4.50 (q, $J=6.8$ Hz, 1H), 7.3–7.4 (m, 3H), 7.4–7.6 (m, 2H); ^{13}C NMR (CD_3OD) δ 14.5, 22.0, 22.5, 22.6, 27.3, 27.5, 36.1, 39.4, 58.8, 62.0, 70.7, 129.6, 129.9, 130.5, 138.2, 171.6, 173.7; MS (CI, NH_3, 45 eV): *m/z* (%) 333 (100) $[M+H^+]$; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}NO_2$ $[M-CONH_2]$ 288.1963. Found 288.1972.

4.2.3. *cis*-Ethyl-2-[2(*R*)-carbamoyl-(2(*R*)-(1(*R*)-phenylethyl)amino)cyclohex-1(*R*)-yl]ethanoate hydrochloride (4c·HCl). White solid, mp 210 °C; $[\alpha]_D^{25}=+10.8$ (EtOH, *c* 1.12); ^{1}H NMR (CD_3OD) δ 1.12 (t, $J=7.0$ Hz, 3H), 1.4–1.9 (m, 11H with 1.77 (d, $J=6.7$ Hz, 3H)), 2.2–2.4 (m, 3H), 4.12 (q, $J=7.0$ Hz, 2H), 4.47 (q, $J=6.7$ Hz, 1H), 7.3–7.4 (m, 3H), 7.5–7.6 (m, 2H); ^{13}C NMR (CD_3OD) δ 13.3, 20.8, 21.4, 23.0, 26.2, 28.4, 34.3, 39.0, 58.6, 61.0, 70.9, 128.1, 128.8, 129.2, 138.4, 171.0, 172.6; MS (CI, NH_3, 45 eV): *m/z* (%) 333 (100) $[M+H^+]$; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}NO_2$ $[M-CONH_2]$ 288.1963. Found 288.1967.

4.2.4. (1*R*,2*S*)-1-((1(*R*)-Phenylethyl)amino)-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione (5a). White solid, mp 170 °C; $[\alpha]_D^{25}=+12.5$ (EtOH, *c* 1.00); ^{1}H NMR ($CDCl_3$) δ 1.0–1.4 (m, 7H with 1.28 (d, $J=6.7$ Hz, 3H)), 1.4–1.5 (m, 1H), 1.6–1.8 (m, 2H), 1.8–2.0 (m, 1H), 2.18 (dd, $J=18.0$, 2.8 Hz, 1H), 2.3–2.4 (m, 1H), 2.97 (dd, $J=17.9$, 5.5 Hz, 1H), 4.0 (q, $J=6.7$ Hz, 2H) 7.2–7.4 (m, 5H), 7.6 (s br, 1H); ^{13}C NMR (CD_3OD) δ 23.0, 24.5, 26.6, 30.0, 32.1, 35.2,

37.7, 51.9, 61.1, 126.3, 126.83, 128.48, 147.52, 171.90, 173.65; MS (CI, NH_3, 45 eV): *m/z* (%) 287 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_{17}H_{22}N_2O_2$ 286.1681. Found 286.1674.

4.2.5. (1*S*,2*R*)-1-((1(*R*)-Phenylethyl)amino)-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione (5b). White solid, mp 156 °C; $[\alpha]_D^{25} = -8.5$ (EtOH, *c* 1.00); ^{1}H NMR ($CDCl_3$) δ 0.9–1.1 (m, 1H), 1.1–1.5 (m, 6H, with 1.32 (d, $J=6.72$ Hz, 3H)), 1.5–1.8 (m, 3H), 1.8–1.9 (m, 1H), 1.9–2.0 (m, 1H), 2.2–2.4 (m, 1H), 2.49 (dd, $J=17.7$, 7.0 Hz, 1H), 2.9–3.0 (m, 1H), 3.82 (q, $J=6.6$ Hz, 1H), 7.1–7.4 (m, 5H), 8.1 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.4, 27.1, 27.3, 32.5, 34.8, 35.6, 53.15, 61.19, 126.3, 126.6, 128.1, 146.9, 172.3, 175.4; MS (CI, NH_3, 45 eV): *m/z* (%) 287 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_{17}H_{21}NO_2$ 286.1681. Found 286.1688.

4.3. Hydrogenolytic cleavage of the chiral auxiliary

Ammonium formate (150 mg) was added to a solution of **5a** and **5b**, respectively, (100 mg, 0.35 mmol) and Pd/C (10%) (80 mg) in ethanol (10 mL). The reaction mixture was refluxed for 2 h, cooled, filtered through a pad of celite, washed with methanol, concentrated and dried in high vacuum yielding **6a** (49 mg, 76%) and **6b** (52 mg, 81%), respectively. Each of the residues were treated with ether–HCl to yield **6a·HCl** and **6b·HCl**, respectively, in quantitative yields.

4.3.1. (1*R*,2*S*)-1-Amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochloride (6a·HCl). White solid, mp >250 °C (dec); $[\alpha]_D^{25} = +13.1$ (EtOH, *c* 1.00); ^{1}H NMR (CD_3OD) δ 1.5–2.0 (m, 7H), 2.1–2.4 (m, 1H), 2.4–2.6 (m, 1H), 2.70 (dd, $J=18.0$, 5.3 Hz, 1H), 3.00 (dd, $J=18.2$, 10.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 20.29, 21.01, 25.90, 29.32, 33.98, 34.38, 59.65, 172.67, 172.99; MS (CI, NH_3, 45 eV): *m/z* (%) 183 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_9H_{14}N_2O_2$ 182.1055. Found 182.1051.

4.3.2. (1*S*,2*R*)-1-Amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochloride (6b·HCl). White solid, mp >250 °C (dec); $[\alpha]_D^{25} = -14.1$ (EtOH, *c* 0.9); ^{1}H NMR (CD_3OD) δ 1.5–2.0 (m, 7H), 2.1–2.4 (m, 1H), 2.4–2.6 (m, 1H), 2.70 (dd, $J=18.0$, 5.3 Hz, 1H), 3.00 (dd, $J=18.2$, 10.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 20.29, 21.01, 25.90, 29.32, 33.98, 34.38, 59.65, 172.67, 172.99; MS (CI, NH_3, 45 eV): *m/z* (%) 183 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_9H_{14}N_2O_2$ 182.1055. Found 182.1053.

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References and notes

1. Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27–45.
2. For reviews on asymmetric Strecker synthesis see the following: (a) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225–227. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650. (c) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Organic Chemistry Series: Pergamon: Oxford, 1989; Vol. 7, Chapter 5, pp 208–229. For recent work on asymmetric Strecker synthesis see: (d) Byrne, J.; Chavarot, M.; Chavant, P.; Vallee, Y. *Tetrahedron Lett.* **2000**, *41*, 873–876. (e) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762–766. (f) Ma, D.; Guozhi, T.; Zou, G. *Tetrahedron Lett.* **1999**, *40*, 9385. (g) Ma, D.; Guozhi, T.; Zou, G. *Tetrahedron Lett.* **1999**, *40*, 5753–5756. (h) Corey, E. J.; Grogan, M. *Org. Lett.* **1999**, *1*, 157–160. (i) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120–124. (j) Dominguez, C.; Ezquerra, J.; Baker, S. R.; Borrelly, S.; Prieto, L.; Espada, M.; Pedregal, C. *Tetrahedron Lett.* **1998**, *39*, 9305–9307. (k) Vergne, C.; Bouillon, J.-P.; Chastanet, J.; Bois-Choussy, M.; Zhu, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3095–3103.
3. Harada, K. *Nature* **1963**, *200*, 1201–1202.
4. Harada, K.; Okawara, T. *J. Org. Chem.* **1973**, *38*, 707–710.
5. Volk, F. J.; Frahm, A. W. *Liebigs Ann.* **1996**, 1893–1903.
6. (a) Fondekar, K. P. F.; Volk, F. J.; Khaliq-zu-Zaman, S. M.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2002**, *13*, 2241–2249. (b) Pai Fondekar, K. P.; Volk, F. J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1999**, *10*, 727–735. (c) Wede, J.; Volk, F. J.; Frahm, A. W. *Tetrahedron: Asymmetry* **2000**, *11*, 3231–3252.
7. (a) Kaul, R.; Balaram, B. *Bioorg. Med. Chem. Lett.* **1999**, *7*, 105–117. (b) Ohfune, Y.; Nanba, K.; Takada, I.; Kann, T. *Chirality* **1997**, *9*, 459–462. (c) Horikawa, M.; Shigeni, Y.; Yumato, N.; Yoshikawa, S.; Nakajima, T.; Ohfune, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2027–2032.
8. (a) Trist, D. G. *Pharm. Acta Helv.* **2000**, *74*, 221–229. (b) Karcz-Kubicha, M.; Wedzony, K.; Zajaczkowski, W.; Danysz, W. J. *Neural Transm.* **1999**, *105*, 1189–1204.
9. Frahm, A. W. Unpublished results.
10. Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705–3716.