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Stereoselective synthesis of 2,4-methanoproline homologues

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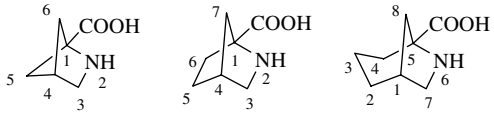
Abstract—The stereoselective synthesis of 2-azabicyclo[2.2.1]heptane-1-carboxylic acid and 6-azabicyclo[3.2.1]octane-5-carboxylic acid, novel rigid bicyclic proline analogues, is reported. The synthesis was performed in five steps from the corresponding 2-cycloalken-1-ones. A known approach to 2,4-methanoproline is improved. The three amino acids constitute a library of conformationally constrained proline analogues, which can be used for the design of peptidomimetics and peptide models.

1. Introduction

Conformationally restricted molecules have become increasingly popular in those areas of chemistry where efficient intermolecular interaction is important. In medicinal chemistry, conformationally restricted drug molecules often exhibit more efficient interactions with the corresponding biological targets than the flexible analogues.[1,2] For example, many peptidomimetics reported to date contain rigid fragments; this is usually achieved by incorporation of conformationally restricted amino acid residues.[3]

Libraries of conformationally constrained or rigid amino acids, designed to vary torsion angles in peptidomimetics in a systematic manner, are of particular interest. Such libraries can be composed of either isomers or homologues of amino acids. While the fixed torsion angles in the common rigid fragments are different within the set of compounds in such a library, other properties (steric bulkiness, lipophilicity, etc.) are similar. Therefore, the libraries could be used to study the structure-property relationships. However, there are not many examples of the libraries of isomeric and especially homologic amino acids in the literature.[4]

Herein we report the design and synthesis of a library, which consists of three amino acids—bicyclic proline analogues. Proline is often found in those secondary structure elements of peptides which are responsible for their biological action.[2,5] One of the compound in the library is well-known 2-azabicyclo[2.1.1]hexane-1-carboxylic acid (trivial name 2,4-methanoproline) **1**, which was found in *Atheleia herbert smithii* in 1980.[6] Several syntheses of this compound have been reported since then.[7,8] Two other amino acids, the methanoproline homologues **2** and **3**, are novel.



1 **2** **3**

Analysis of molecular models for the *N*-acetyl *N*′-methylamide derivatives of compounds **1**–**3** showed that torsion angle φ at the residues of these amino acids in peptides should change in consequential manner when going from **1** to **3**. This difference is achieved by minimal structural changes within the set, allowing one to assume that the observed regularities in the properties of the peptides are caused at first approximation by changes of φ.

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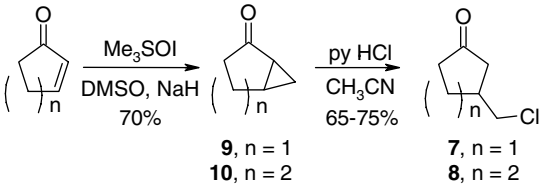
2. Results and discussion

In principle, the synthesis of novel amino acids **2** and **3** could be performed using a strategy reported by de Kimpe for 2,4-methanoproline **1**.[8] The key step in the synthesis of **1** is tandem cyanide addition—intramolecular cyclization of the imine **4**, which was prepared from 3-chloromethylcyclobutanone **5**. Compound **6** was then converted to **1** by the hydrolysis of the nitrile group and subsequent Pd-catalysed hydrogenolysis (Scheme 1).

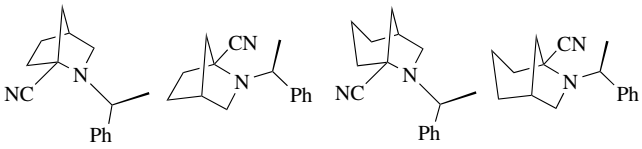
The corresponding chloromethylcycloalkanones **7** and **8**, which can be used as the starting compounds for the synthesis of **2** and **3** using de Kimpe's strategy, are known compounds. They can be obtained from 2-cycloalken-1-ones in two steps in 45–50% overall yield (Scheme 2).[9]



Scheme 2.

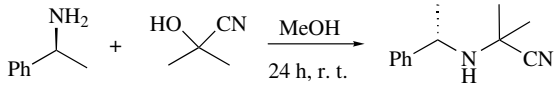
However, it was necessary to modify the reported strategy for at least two reasons. First, while the 2,4-methanoproline is achiral, the novel amino acids here contain two stereogenic centers. A stereoselective synthesis has to be developed in order to obtain nonracemic compounds **2** and **3**. Another problem is related to the difficulties in imine formation from **7** and **8**, and following cyclization under treatment of the acetone cyanohydrine. In our hands, the reported procedures led to complex mixtures of unidentified compounds, containing only minor amounts of the desired aminonitriles.

The stereoselectivity problem could be solved, if nonracemic chloromethylcycloalkanones **7** and **8** were used. These could be prepared from the corresponding nonracemic cyclopropane derivatives **9** and **10**, the synthesis of which has already been reported.[10] However, the synthesis involves the use of a rather expensive chiral auxiliary—1,4-bis(benzyloxy)butane-2,3-diol (1,4-di-*O*-benzylthreitol), therefore we abandoned this approach. Our strategy was based on the separation of stereoisomers rather than on chiral induction. The use of racemic **7** or **8** and enantiomerically pure (e.g., *S*) α-phenylethylamine in reactions analogous to those shown in Scheme 1 should yield equimolar mixtures of diastereomers **11a** and **11b** (or **12a** and **12b**, respectively), which could hopefully be separated.

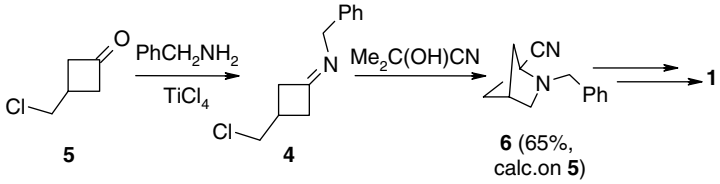


The second problem can be solved by avoiding imine isolation during the synthesis of **11** and **12**. We achieved this using a tandem Strecker-intramolecular cyclization reaction. Only a few papers on the synthesis of α-aminonitriles directly from γ-chloromethylketones using this strategy have been published, all of them exploiting achiral α-aminonitrile **13** as a cyanide source (Scheme 3).[11]

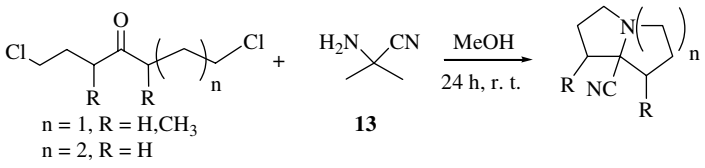
An analogous reaction of **7** or **8** with chiral α-aminonitrile **14** (instead of **13**) leads to the desirable nitriles **11a**, **11b** or **12a**, **12b**. Surprisingly, compound **14** was not described in the literature, but was found to be easily formed from α-phenylethylamine and acetone cyanohydrine in quantitative yield (Scheme 4).



Scheme 4.



Scheme 1.



Scheme 3.

The reaction of **14** with 3-chloromethylcyclohexanone **8** in methanol proceeded uneventfully; compounds **12a** and **12b** were formed in 80% total yield. Column chromatography on silica gel turned out to be very efficient for their separation. It has been found that the preliminary isolation of **14** is not necessary: the reaction was equally efficient when chloromethylketone **8**, α-phenylethylamine and acetone cyanohydrin were mixed simultaneously in methanol (Scheme 5).

Analogous reaction proceeded smoothly with 3-chloromethylcyclobutanone **5** (achiral benzylamine was taken in this case, Scheme 6). This approach to 2,4-methanoproline precursor **6** is simpler than reported earlier.[8]

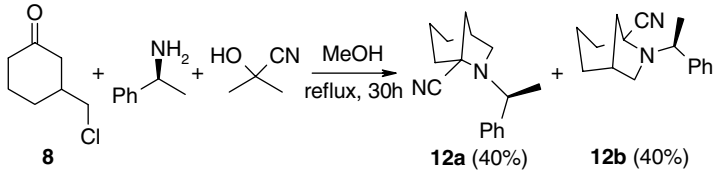
When we applied the reaction conditions described above to 3-chloromethylcyclopentanone **7**, which has a less reactive carbonyl group when compared to compounds **5** and **8**, none of the expected products were obtained. Optimization of the reaction conditions was performed, and it was found that a mixture of **11a**, **11b**, and **15** was formed in acetonitrile as the solvent in 38% overall yield (Scheme 7). Chromatographic separation of the isomers was analogous to that for **12**. The mechanism of formation of **15** is currently under investigation.

All three isomers **11a**, **11b**, and **15** were indistinguishable by ^{1}H and ^{13}C NMR spectroscopy. Structural assignments were performed using ^{13}C DEPT-135 experiments. There are three carbon atoms connected to nitrogen in each isomer; secondary, tertiary, and quaternary in the case of **11a**(**11b**) or tertiary, tertiary, and quaternary in the case of **15**. Therefore, the DEPT-135 spectra were different and characteristic for **11a**, **11b**, and **15** in the region of 55–65 ppm (Fig. 1).

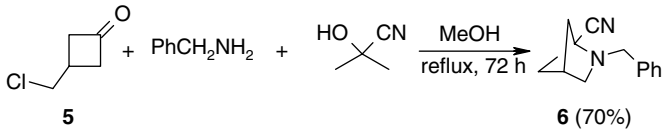
The structure of **15** was also confirmed by its transformation to the known 7-azabicyclo[2.2.1]heptane-1-carboxylic acid **16** (Scheme 8).[12]

To determine the absolute configuration of compounds **11a**, **11b** and **12a**, **12b**, X-ray analysis of aminonitriles (1*S*,4*R*)-**11b** and (1*S*,5*R*)-**12a** was performed (Fig. 2). The absolute configuration of these compounds was established using the known (*S*)-configuration of the stereogenic center of the α-phenylethylamine moiety. The asymmetric part of the crystal unit cell contains one molecule in the case of **11b** and two molecules (A and B) for **12a**. The N(2)–C(9) bond (1.496(2) Å **11b**, 1.496(3) Å, and 1.492(3) Å for molecules A and B of **12a**) is slightly longer compared to average value[13] 1.475 Å. The N(2) atom has pyramidal configuration, the sum of bond angles centered at this atom is 334.7(4)° for **11b** and 339.5(6)° (A) and 338.7(6)° (B) for **12a**. The α-phenylethyl substituent possesses *endo* orientation relative to the polycyclic fragment (the C(10)–C(9)–N(2)–C(7) torsion angle is −133.0(2)° for **11b**, −140.5(2)° (A) and −141.6(2)° (B) for **12a**). Molecules **11b** and **12a** differ by orientation of the α-phenylethylamine substituent with respect to the nitrile group. The C(8) methyl group adopts *ap* conformation with respect to the N(2)–C(9) bond in **11b** and *–sc* conformation in **12a** (the C(9)–N(2)–C(7)–C(8) torsion angle is 175.3(2)° for **11b**, −54.9(2)° (A) and −57.3(2)° (B) for **12a**). The phenyl subtituent has almost orthogonal orientation relative to the C(7)–C(8) bond in all molecules (the C(8)–C(7)–C(1)–C(2) torsion angle is 93.2(2)° in **11b**, −111.6(3)° (A) and −109.9(3)° (B) in **12a**).

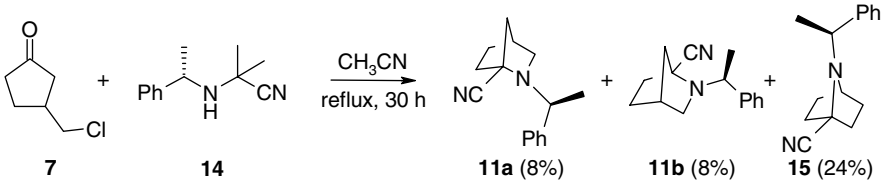
Hydrolysis of the cyano group in compounds **11** and **12** was accompanied by partial N-deprotection. This does not pose a problem since after hydrogenation and



Scheme 5.



Scheme 6.



Scheme 7.

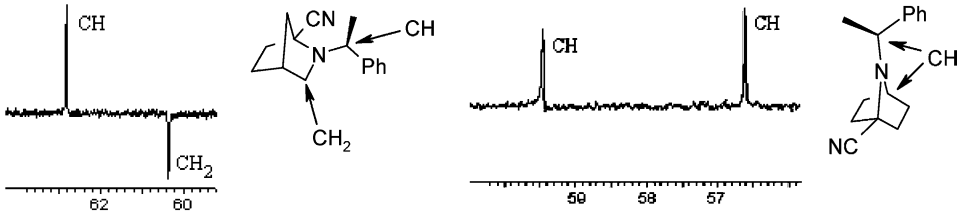
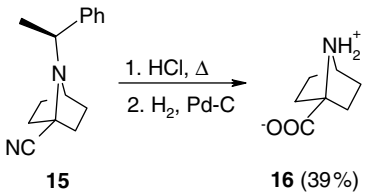


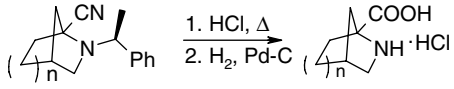
Figure 1.



15 **16** (39%)

Scheme 8.

recrystallization, pure N-deprotected amino acids **2** and **3** were obtained as hydrochlorides in moderate yields (35–50% over two steps) (Scheme 9).



11a,b, n = 1
12a,b, n = 2

35-50%

2a,b, n = 1
3a,b, n = 2

Scheme 9.

3. Conclusions

A library, consisting of three amino acids—bicyclic proline analogues (compounds **1**–**3**) has been designed. A simple and convenient method for the synthesis of 2,4-methanoproline homologues as pure enantiomers was developed. A convenient synthetic route to 2,4-methanoproline has been proposed.

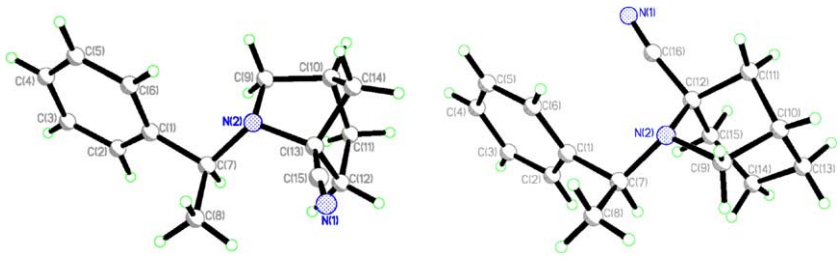
4. Experimental

All air- and moisture-sensitive reactions were performed under an argon atmosphere using standard Schlenk technique. Solvents were purified according to standard procedures.[14] 3-Chloromethylcyclobutanone **5**,[15] 3-chloromethylcyclopentanone **7**,[9] and 3-chloromethylcyclohexanone **8**[9] were prepared according to the procedures described in the literature. All other starting materials were purchased from Acros, Merck, Aldrich, and Fluka chemicals. Melting points are uncorrected. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) stationary phase. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Unity Plus 400 spectrometer at 400.4 and 100.7 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS as an internal standard. IR spectra were obtained on Nicolet Nexus 470 spectrometer. ν_{max} (cm^{-1}) values in IR spectra are given for the main absorption bands. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument with chemical ionization (CI). Optical rotation values were measured on Perkin–Elmer 341 polarimeter.

4.1. General procedure for the cyclopropanation (compounds 9 and 10)

The procedure is a modification of the method reported by Gassman and Atkins.[16] The synthesis of bicyclo-[4.1.0]heptan-2-one **10** is representative.

All operations were performed under a constant argon flow through the reaction flask. To a flame-dried three-necked flack, equipped with an efficient stirrer, inert gas inlet, thermometer, and dropping funnel, 250 ml of dry dimethylsulfoxide were placed. Vigorous stirring was started and 9.0 g (0.356 mol) of sodium hydride (95%) carefully added in small portions (less than 1 g) in such a manner that each next portion was only added after gas evolution from the previous addition ceased. The temperature of the reaction mixture had to be kept within the range of 20–35 °C



(1*S*,4*R*)-**11b** (1*S*,5*R*)-**12a**

Figure 2. Molecular structure of compounds **11b** and **12a**.

by external cooling. After the addition of NaH, 78.4 g (0.356 mol) of trimethylsulfoxonium iodide[17] was added, also in small portions. Temperature control (20–35 °C) is particularly critical at this stage. The white milky suspension obtained was stirred for an additional 30–45 min to complete the ylide formation. The reaction mixture was cooled to 20 °C, and a solution of 30 ml (0.324 mol) of 2-cyclohexen-1-one in 50 ml of dimethylsulfoxide was slowly added dropwise under vigorous stirring. When all the cycloalkenone was added, the reaction mixture was stirred for 0.5 h at an ambient temperature and for an additional 2 h at 50 °C, then cooled and poured onto 300 g of ice. The suspension formed was filtered, and the filtrate thoroughly extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated at a reduced pressure (temperature of the bath was kept not higher than 30 °C) to give 25.2 g (0.229 mol, 70%) of bicyclo[4.1.0]heptan-2-one **10**, sufficiently pure for the next step. Further purification can be performed as described elsewhere.[16]

4.2. General procedure for the synthesis of α-aminonitriles 11, 12, and 15

Synthesis of 6-[(1*S*)-1-phenylethyl]-6-azabicyclo[3.2.1]-octane-5-carbonitriles **12a** and **12b** is representative.

Method A: To a solution of 25.6 g (0.174 mol) of 3-chloromethylcyclohexanone **8** in 150 ml of dry methanol 47.7 ml (0.522 mol) of acetone cyanohydrin and 23.6 ml (0.183 mol) of (*S*)-α-phenylethylamine were added. The mixture obtained was refluxed under an argon atmosphere for 30 h, then poured into 500 ml of 10% sodium hydroxide solution and extracted with dichloromethane. The combined extracts were dried over $MgSO_4$ and evaporated under a reduced pressure. The residue was chromatographed (gradient hexane–ethylacetate, 5:1–2:1 as an eluent) to give 16.6 g (0.069 mol, 40%) of **12b** first, and then 16.9 g (0.070 mol, 40%) of **12a**.

Method B: To a solution of 0.39 g of 3-chloromethylcyclohexanone **8** in 10 ml of dry acetonitrile, 0.53 g of aminonitrile **14** (see the synthesis below) was added. The mixture obtained was refluxed under an argon atmosphere for 30 h and then worked up as described above.

4.2.1. 2-Benzyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile 6. 2-Benzyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile was prepared by method A [using benzylamine instead of (*S*)-α-phenylethylamine] in 70% yield. The reaction time was increased to 72 h. There was no need in chromatographic purification of crude product (more than 90% of the main compound). For spectral and physical data see Ref. 8.

4.2.2. (1*R*,4*S*)-2-((1*S*)-1-Phenylethyl)-2-azabicyclo[2.2.1]-heptane-1-carbonitrile 11a. (1*R*,4*S*)-2-((1*S*)-1-Phenylethyl)-2-azabicyclo[2.2.1]heptane-1-carbonitrile was prepared by method B from **7** in 8% yield. $[\alpha]_D = -5.1$ (*c* 0.66, MeOH). ^{1}H NMR ($CDCl_3$), δ: 7.41 (m, 2H), 7.33 (m, 3H), 3.75 (q, $J = 6.5$ Hz, 1H, C*H*(CH_3)), 3.30 (dt, $J = 9.0$ Hz and 3.2 Hz, 1H), 2.47 (m, 1H), 2.40 (s, 1H), 2.33 (d, $J = 8.5$ Hz, 1H), 2.14 (d, $J = 9.0$ Hz, 1H), 1.6–1.8 (m, 3H), 1.49 (m, 1H), 1.43 (d, $J = 6.5$ Hz, 3H, CH(C*H*$_3$)). ^{13}C NMR ($CDCl_3$), δ: 143.2, 128.5, 128.4, 128.1, 60.1, 58.9, 57.5, 45.5, 37.2, 30.3, 29.9, 22.6. IR (KBr): 2236 (ν C≡N). MS (*m*/*z*): 227 (M+1), 123, 105 (PhCH(CH_3)).

4.2.3. (1*S*,4*R*)-2-((1*S*)-1-Phenylethyl)-2-azabicyclo[2.2.1]-heptane-1-carbonitrile 11b. (1*S*,4*R*)-2-((1*S*)-1-Phenylethyl)-2-azabicyclo[2.2.1]heptane-1-carbonitrile was prepared from **7** by method B in 8% yield. Mp 65–66 °C. $[\alpha]_D = -43.3$ (*c* 0.60, MeOH). ^{1}H NMR ($CDCl_3$), δ: 7.3 (m, 5H, C_6H_5), 3.69 (q, $J = 6.5$ Hz, 1H, C*H*(CH_3)), 2.93 (dt, $J = 9.5$ and 3.2 Hz, 1H), 2.45 (m, 1H), 2.3 (s, 1H), 2.27 (d, $J = 9.0$ Hz, 1H), 1.8–1.9 (m, 4H), 1.54 (d, $J = 6.5$ Hz, CH(C*H*$_3$)), 1.27 (m, 1H). ^{13}C NMR ($CDCl_3$), δ: 145.2, 128.4, 127.1, 127.0, 122.3, 62.7 (*C*H(CH_3)), 60.1 (3-*C*H_2), 58.1 (1-*C*), 40.6 (*C*H_2), 37.3 (4-*C*H), 29.3 (*C*H_2), 29.3 (CH_2), 24.2 (*C*H_3). IR (KBr): 2240 (ν C≡N). MS (*m*/*z*): 227 (M+1), 123, 105 (PhCH(CH_3)). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found C, 79.72; H, 8.06; N, 12.42.

4.2.4. 7-((1*S*)-1-Phenylethyl)-7-azabicyclo[2.2.1]heptane-1-carbonitrile 15. 7-((1*S*)-1-Phenylethyl)-7-azabicyclo-[2.2.1]heptane-1-carbonitrile was prepared by method B from **7** in 24% yield. Mp 64–65 °C. $[\alpha]_D = -37.6$ (*c* 0.84, MeOH). ^{1}H NMR ($CDCl_3$), δ: 7.41 (d, $J = 7.0$ Hz, 2H, *o*-C_6H_5), 7.33 (m, 3H, C_6H_5), 3.55 (q, $J = 6.5$ Hz, 1H, C*H*(CH_3)), 3.14 (t, $J = 4.0$ Hz, 1H, 4-C*H*), 2.20 (m, 2H), 1.84 (m, 4H), 1.50 (d, $J = 6.5$ Hz, 3H, CH(C*H*$_3$)), 1.36 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 145.25, 128.4, 127.5, 127.2, 120.5, 59.5 (*C*H), 57.1 (*C*-4), 56.6 (*C*H), 35.3 (*C*H_2), 35.2 (*C*H_2), 28.0 (*C*H_2), 28.0 (CH_2), 23.9 (CH(*C*H_3)). IR (KBr): 2230 (ν C≡N). MS (*m*/*z*): 227 (M+1), 123, 105 (PhCH(CH_3)). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found C, 79.68; H, 7.97; N, 12.34.

4.2.5. (1*S*,5*R*)-6-((1*S*)-1-Phenylethyl)-6-azabicyclo[3.2.1]-octane-5-carbonitrile 12a. (1*S*,5*R*)-6-((1*S*)-1-Phenylethyl)-6-azabicyclo[3.2.1]octane-5-carbonitrile was prepared by both A and B methods. Mp 176–178 °C. $[\alpha]_D = -18.6$ (*c* 0.16, MeOH). ^{1}H NMR ($CDCl_3$), δ: 7.44 (d, $J = 8$ Hz, 2H, *o*-C_6H_5), 7.33 (m, 3H, C_6H_5), 4.12 (q, $J = 6.5$ Hz, 1H, C*H*(CH_3)), 3.34 (dd, $J = 9.2$ and 6.2 Hz, 1H, *exo*-7-C*H*), 2.79 (d, $J = 9.0$ Hz, 1H, *endo*-7-C*H*), 2.39 (s, 1H), 2.33 (d, $J = 11$ Hz, 1H, 8-C*H*), 2.24 (d, $J = 11.5$ Hz, 1H), 1.81 (d, $J = 11$ Hz, 1H, 8-C*H*), 1.70 (m, 3H), 1.5–1.6 (m, 2H), 1.50 (d, $J = 7.0$ Hz, 3H, CH(C*H*$_3$)). ^{13}C NMR ($CDCl_3$), δ: 143.4, 128.4, 128.3, 127.8, 121.4, 57.9, 57.6, 53.6, 45.4, 33.4, 33.0, 30.0, 22.6, 19.6. IR (KBr): 2232 (ν C≡N). MS (*m*/*z*): 241 (M+1), 137, 105 (PhCH(CH_3)). Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found C, 79.81; H, 8.48; N, 11.59.

4.2.6. (1*R*,5*S*)-6-((1*S*)-1-Phenylethyl)-6-azabicyclo[3.2.1]-octane-5-carbonitrile 12b. (1*R*,5*S*)-6-((1*S*)-1-Phenylethyl)-6-azabicyclo[3.2.1]octane-5-carbonitrile was prepared by both A and B methods. $[\alpha]_D = -26.2$ (*c* 0.54, MeOH). ^{1}H NMR ($CDCl_3$), δ: 7.38 (d,

$J = 7.5$ Hz, 2H, *o*-C_6H_5), 7.31 (t, $J = 7.0$ Hz, *m*-C_6H_5), 7.23 (t, $J = 7.5$ Hz, 1H, *p*-C_6H_5), 4.13 (q, $J = 6.7$ Hz, 1H, C*H*(CH_3)), 3.05 (dd, $J = 9.2$ and 5.2 Hz, 1H, *exo*-7-C*H*), 2.42 (m, 1H, 8-C*H*), 2.36 (dd, $J = 13$ and 5.2 Hz, 2-C*H*), 2.28 (br s, 1H, 1-C*H*), 2.24 (d, $J = 10.0$ Hz, *endo*-7-C*H*), 1.90 (d, $J = 11.5$ Hz, 8-C*H*), 1.82 Hz (td, $J = 12.6$ and 6.0 Hz, 1H, 2-C*H*), 1.70 (m, 1H, 3-C*H*), 1.61 (m, 1H, 3-C*H*), 1.61 (d, $J = 6.5$ Hz, 3H, C*H*(CH_3)), 1.49 (m, 2H, 4-CH_2). ^{13}C NMR ($CDCl_3$), δ: 145.7, 128.4, 127.1, 127.0, 123.9 (*C*N), 59.9 (*C*H(CH_3)), 56.9 (5-*C*), 56.7 (2-*C*H_2), 45.9 (*C*H_2), 33.3 (1-*C*H), 32.9 (*C*H_2), 30.1 (*C*H_2), 24.1 (CH(*C*H_3)), 19.2 (*C*H_2). IR (KBr): 2240 (ν C≡N). MS (*m*/*z*): 241 (M+1), 137.

4.2.7. 2-Methyl-2-(((1*S*)-1-phenylethyl)amino)propanenitrile 14. 2-Methyl-2-(((1*S*)-1-phenylethyl)amino)propanenitrile 14.5 ml (0.159 mol) of acetone cyanohydrine and 20 ml (0.155 mol) of (*S*)-α-phenylethylamine were mixed in 50 ml of absolute methanol and allowed to stand overnight. Then the mixture was evaporated to dryness to give 29.1 g (0.155 mol, 100%) of pure **14**. An analytical sample of **14** was obtained by recrystallization from hexane. Mp 77–78 °C. $[\alpha]_D = -146.3$ (*c* 0.64, MeOH). ^{1}H NMR ($CDCl_3$), δ: 7.41 (d, $J = 7.0$ Hz, 2H, *o*-C_6H_5), 7.32 (t, $J = 7.5$ Hz, 2H, *m*-C_6H_5), 7.23 (t, $J = 7.2$ Hz), 4.11 (q, $J = 6.6$ Hz, 1H, C*H*CH_3), 1.53 (s, 3H, CH_3), 1.41 (d, $J = 6.5$ Hz, 3H, CHCH_3), 1.12 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 146.6 (*C*N), 128.5, 127.0, 126.5, 125.8, 55.6, 52.2, 29.2, 27.8, 26.3. IR (KBr): 3323 (ν N–H), 2223 (ν C≡N). Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57; N, 14.88. Found C, 76.48; H, 8.61; N, 14.84.

4.3. General procedure for the synthesis of amino acids 2, 3, and 16

The synthesis of (1*R*,5*S*)-6-azabicyclo[3.2.1]octane-5-carboxylic acid **3b** hydrochloride is representative. To 16.6 g (0.069 mol) of compound **12b**, 60 ml of concentrated hydrochloric acid was added. The resulting mixture was refluxed for 72 h, then cooled, filtered and evaporated under reduced pressure. Water (20 ml) was added and subsequently removed by evaporation under reduced pressure. This operation was repeated twice to remove the excess of HCl. To the obtained solid residue, 70 ml of absolute ethanol were added, the resulting mixture was refluxed, then cooled and left in an ice bath for 3 h. Ammonium hydrochloride was filtered off, the filtrate was evaporated to dryness. The solid obtained was dissolved in 80 ml of methanol and hydrogenated (10% Pd/C, 35 atm, 35 °C) for 36 h. The catalyst was filtered off, and the solvent was removed by rotary evaporation. The crude product was recrystallized from 10 ml of concentrated hydrochloric acid to obtain 4.52 g of pure **3b**. The additional 1.84 g of pure **3b** were obtained from the mother liquor by further crystallization. Total yield—6.36 g (0.033 mol, 48%). Mp >250 °C. $[\alpha]_D = -19.9$ (*c* 1.30, MeOH). ^{1}H NMR (DMSO-d_6), δ: 10.20 (br s, 1H, N*H*), 9.24 (br s, 1H, N*H*), 3.32 (br s, 1H, 3-C*H*), 3.14 (br s, 1H, 3-C*H*), 2.56 (s, 1H, 4-C*H*), 1.97 (m, 2H), 1.85 (m, 3H), 1.65 (m, 1H), 1.56 (m, 1H), 1.50 (m, 2H). ^{13}C NMR (DMSO-d_6), δ: 171.8 (*C*OOH), 69.1 (5-*C*), 48.9 (7-*C*H_2), 39.2(1-*C*H), 34.3, 31.6, 28.8, 17.8 (3-*C*H_2). IR (KBr): 1731 (ν C=O). Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; N, 7.31. Found C, 50.09; H, 7.30; N, 7.35.

4.3.1. (1*S*,5*R*)-6-Azabicyclo[3.2.1]octane-5-carboxylic acid hydrochloride 3a. (1*S*,5*R*)-6-Azabicyclo[3.2.1]octane-5-carboxylic acid hydrochloride was prepared analogously to **3b** from **12a** in 38% yield. Mp >250 °C. $[\alpha]_D = +17.5$ (*c* 0.95, MeOH). NMR and IR spectra were identical to that for **3b** enantiomer. Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; N, 7.31. Found C, 50.19; H, 7.41; N, 7.29.

4.3.2. (1*R*,4*S*)-2-Azabicyclo[2.2.1]heptane-1-carboxylic acid 2a. (1*R*,4*S*)-2-Azabicyclo[2.2.1]heptane-1-carboxylic acid was prepared analogously to **3b** from **11a**, except the purification was performed using ion-exchange chromatography (strong cationite, 10% aqueous pyridine as an eluent), in 33% yield. Mp >230 °C (dec.). $[\alpha]_D = +10.5$ (*c* 0.28, MeOH). ^{1}H NMR (CD_3OD), δ: 3.22 (d, $J = 10.0$ Hz, 1H, 3-C*H*), 3.01 (d, $J = 9.5$ Hz, 1H, 3-C*H*), 2.69 (s, 1H, 4-C*H*), 2.19 (m, 1H), 1.9–2.0 (m, 4H), 1.63 (m, 1H). ^{13}C NMR (CD_3OD), δ: 171.2 (*C*OOH), 71.9 (1-*C*), 49.1 (3-*C*H_2), 38.5, 35.9, 28.7, 25.9. IR (KBr): 1640 (ν_{as} COO^-), 1600 (δ NH_2^+), 1409 (ν_s COO^-). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found C, 59.50; H, 7.79; N, 9.90.

4.3.3. (1*S*,4*R*)-2-Azabicyclo[2.2.1]heptane-1-carboxylic acid 2b. (1*S*,4*R*)-2-Azabicyclo[2.2.1]heptane-1-carboxylic acid was prepared analogously to **2a** from **11b** in 35% yield. Mp >230 °C (dec.). $[\alpha]_D = -13.7$ (*c* 0.26, MeOH). NMR and IR spectra were identical to that for **2a** enantiomer. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found C, 59.51; H, 7.89, N, 9.88.

4.3.4. 7-Azabicyclo[2.2.1]heptane-1-carboxylic acid 16. 7-Azabicyclo[2.2.1]heptane-1-carboxylic acid was prepared analogously to **2a** from **15** in 39% yield. For spectral and physical data see Ref. 12.

4.4. X-ray analysis

Crystals for X-ray diffraction studies were obtained by slow evaporation of hexane–ethyl acetate (4:1) solution of **11b** and heptane solution of **12a**, respectively. The crystals of **11b** ($C_{15}H_{18}N_2$) are orthorhombic. At 100 K $a = 6.3333(3)$, $b = 10.7795(8)$, $c = 18.511(1)$ Å, $V = 1263.8(1)$ Å^3, $M_r = 226.31$, $Z = 4$, space group $P2_12_12_1$, $d_{calcd} = 1.189$ g/cm^3, μ (Mo K_α) = 0.071 mm^{-1}, $F(000) = 488$. Intensity of 16,391 reflections (2095 independent, $R_{int} = 0.088$) were measured on an automatic «Xcalibur 3» diffractometer (graphite monochromated Mo K_α radiation, CCD-detector $\Theta/2\Theta$ scanning, $2\Theta_{max} = 60°$).

The crystals of **12a** ($C_{16}H_{20}N_2$) are monoclinic. At 293 K, $a = 8.4708(5)$, $b = 14.8404(6)$, $c = 11.2447(5)$ Å, $\beta = 98.950(4)°$, $V = 1396.36(12)$ Å^3, $M_r = 240.34$, $Z = 4$, space group $P2_1$, $d_{calcd} = 1.143$ g/cm^3, μ (Mo K_α) =

0.068 mm^{-1}, $F(000) = 520$. Intensity of 7128 reflections (4607 independent, R_{int}=0.024) were measured on an automatic «Xcalibur 3» diffractometer (graphite monochromated Mo K_α radiation, CCD-detector $\Theta/2\Theta$ scanning, $2\Theta_{max} = 50°$).

Both structures were solved by direct method using SHELX97 package.[18] Positions of hydrogen atoms were located from electron density difference maps and refined by 'riding' model with $U_{iso} = nU_{eq}$ of nonhydrogen atom is bonded with given hydrogen atom ($n = 1.5$ for methyl group and $n = 1.2$ for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation was converged to $wR_2 = 0.116$ for 2095 reflections ($R_1 = 0.049$ for 2011 reflections with $I > 4\sigma(I)$, $S = 1.05$) for **11b** and to $wR_2 = 0.120$ for 4607 reflections ($R_1 = 0.046$ for 3788 reflections with $I > 4\sigma(I)$, $S = 1.08$) for **12a**. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request by quoting the deposition number CCDC 289018 (**11b**) and CCDC 289081 (**12a**).

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