Synthesis of 2,4-Methanoproline Analogues via an Addition−Intramolecular Substitution Sequence

Thomas Rammeloo, Christian V. Stevens,* and Norbert De Kimpe

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure links 653, B-9000 Gent, Belgium

chris.stevens@rug.ac.be

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A new two-step synthetic approach toward 3-(chloromethyl)cyclobutanone is described and used in the synthesis of 2,4-methanoproline analogues. The key step consists of a reversible addition of hydrogen cyanide onto the imines **12** in 50−74% yield under conditions that allow ring closure. 2-Alkyl-2-azabicyclo[2.1.1]hexane-1-carbonitriles **19**, synthesized in four steps, can also be converted to the corresponding amines.

Introduction

2,4-Methanoproline **1** is a nonproteinogenic amino acid that was isolated from the seeds of *Ateleia herbert smithii* Pittier,[1] which are ignored by at least 100 seed predators. It is know that some legume species accumulate large quantities of rare amino acids to protect them from predators. Therefore, it was suggested that 2,4-methanoproline could be acting as an antifeedant responsible for the ignorance of the seeds by predators.

During our search for biologically active compounds with potential applications in agrochemisrty, 2,4-methanoproline rose to our attention. Besides the interesting activity being attributed to this molecule, it is also a structural analogue of proline, which plays an important role in the *cis*−*trans* isomerization of peptide bonds in enzymes. Bicyclic analogues of proline are therefore useful for peptide design if the *cis* or *trans* peptide bond needs to be selectively stabilized. Introduction of 2,4-methanoproline (Figure 1) into peptides is known to selectively stabilize the *trans* tertiary peptide bond.[2]

Most of the syntheses of 2,4-methanoproline are accomplished by an intramolecular light-induced [2 + 2] cycloaddition of an appropriate diene.[3] Only Gaoni used an intramolecular cyclization strategy for his approach.[4] Also analogues containing the 2-azabicyclo[2.1.1]hexane skeleton are often synthesized by the light-induced [2 + 2] cyclization.[5] The rearrangement of an appropriate bromohydrine to synthesize 5-hydroxy-2-azabicyclo[2.1.1]hexanes has been described by Krow.[6] The use of an intramolecular nucleophilic substitution of a cyclobutane derivative to get access to 5-methylamino-2-azabicyclo[2.1.1]hexane has recently been published by Huet and co-workers.[7]

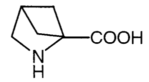

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FIGURE 1. 2,4-Methanoproline.

Recently, we developed a short method for the synthesis of 2,4-methanoproline in which the 2-azabicyclo[2.1.1]hexane skeleton was constructed by the intramolecular ring closure of an amino acid containing the four-membered ring.[8] The currently described methodology is inspired by earlier work in which the skeleton was formed via a hydride-induced intramolecular nucleophilic ring closure of a *N*-[3-(chloromethyl)-1-cyclobutylidene]amine **3**.[9] At that time, the method was limited to the use of hydride as nucleophile for the ring closure, and in addition, the synthesis of the intermediate 3-(chloromethyl)cyclobutanone **2** was problematic (Scheme 1).

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* To whom correspondence should be addressed. Ph: + 32-9-264 59 57. Fax: +32-9-264 62 43.

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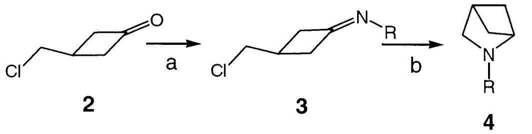
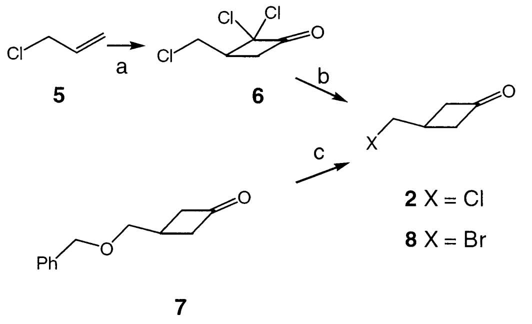
SCHEME 1[a]



[a] Reagents: (a) RNH_2, Ti(IV)Cl_4, Et_2O, rt 16 h; (b) $LiAlH_4$, ether or THF, Δ 16−18 h.

SCHEME 2[a]



a Reagents: (a) allyl chloride, Zn−Cu couple, $POCl_3$, Cl_3CCOCl, ether, Δ 1 d, 37%; (b) Zn, HOAc, Δ 4 h, 85%; (c) X = Cl, 12 N HCl, $ZnCl_2$, Δ 1 d, yield 48%; X = Br, 48% HBr in H_2O, Δ 7 h, yield 54%.

Until now, there was only one synthesis of 3-(chloromethyl)cyclobutanone **2** in eight steps with an overall yield of 6%.[9] Therefore, we now present a two-step synthesis of this precursor and its use for the synthesis of novel 2,4-methanoproline analogues.

Results and Discussion

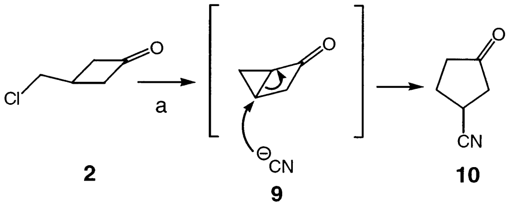
A new synthesis for the key compound 3-(chloromethyl)cyclobutanone **2** was developed for its synthesis on a multigram scale. In the first step, a [2 + 2] cycloaddition of dichloroketene and allyl chloride leads to the cyclobutanone **6** (Scheme 2). Many different reaction conditions were evaluated to improve the yield of this reaction. Despite this effort, the isolated yield is still moderate (37%). The best results were obtained generating the dichloroketene from trichloroacetyl chloride and a zinc−copper couple. Formation of the dichloroketene from dichloroacetyl chloride and a base (triethylamine, lutidine) always led to mixtures of compounds, probably as a result of the instability of the end product in basic medium.

Although the cyclobutanone **6** could be distilled, a severe loss of product was observed during the distillation. Since almost no side products were formed during the reaction, removal of the two geminal chlorine atoms first, followed by distillation, proved to be considerably better.

To obtain 3-(chloromethyl)cyclobutanone, the cyclobutanone **6** was treated with zinc in acetic acid, removing the two α-chlorine atoms reductively without the formation of any side product. Although the first step has a low yield, this short sequence is a major improvement in the synthesis of 3-(chloromethyl)cyclobutanone **2** for its production on a multigram scale. After distillation, the cyclobutanone **2** can be kept in the freezer for months.

Another approach leading to 3-(halomethyl)cyclobutanones was evaluated starting from the known cylcobutanone **7**.[10] Deprotection of the benzyl ether by hydrogenation was not successful and led to a mixture of compounds. Using concentrated hydrochloric acid with zinc(II) chloride as a catalyst, however, **7** could be converted in one step to 3-(chloromethyl)cyclobutanone (yield = 48%).

SCHEME 3[a]



[a] Reagents: (a)1.2 equiv of NH_4Cl, 1.2 equiv of KCN, MeOH/H_2O, Δ overnight, 33%.

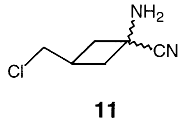


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FIGURE 2.

3-(Bromomethyl)cyclobutanone **8** could also be prepared when using concentrated hydrobromic acid. Some side products were formed during the reaction, and the reaction mixture had to be purified by flash chromatography.

In an initial experiment to construct the 2-aza[2.1.1]-hexane skeleton, as present in 2,4-methanoproline, cyclobutanone **2** was treated with ammonium chloride and potassium cyanide, but the cyclobutanone proved not to be stable in basic media and the cyclopentanone **10** was obtained in 33% yield.

This reaction proceeds most probably via the bicyclic intermediate **9** (Scheme 3), which undergoes a ring expansion due to the release of ring strain. Using an excess of ammonium chloride, a small amount of adduct **11** (Figure 2) could be isolated (29% yield).

This procedure was difficult to reproduce, and the resulting compound **11** proved to be very unstable. To overcome this problem, the corresponding imines were prepared using the current procedures, i.e., reaction of cyclobutanone **2** with primary amines in the presence of stoichiometric amounts of titanium(IV) chloride, in very good yields.[9] The addition of cyanide onto the imines was then evaluated with the *N*-isopropyl derivative **12a** but led to a similar result, producing cyclopentylidene amines **13** (72% yield) (Scheme 4).

Attempts to isolate the bicyclic intermediate in the absence of a nucleophile failed and also failed using bases such as sodium hydride and lithium hexamethyldisilazide.

It was clear that the cyclobutanone could only be used in neutral or acidic medium. The addition of hydrogen cyanide gas onto the imine proved to be the methodology of choice to introduce a cyano group and to prevent side reactions. Imine **12a** was treated with an access of

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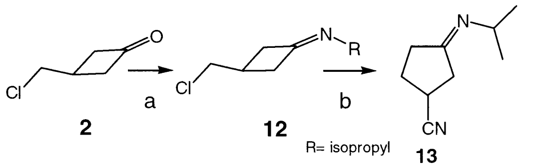
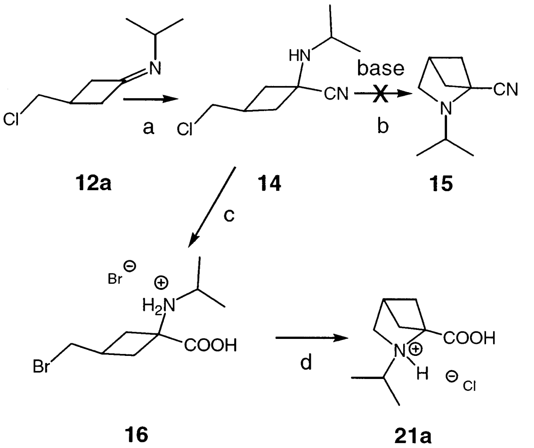
SCHEME 4[a]



[a] Reagents: (a) RNH$_2$, TiCl$_4$, Et$_2$O, rt overnight; **12a** R = isopropyl, 80%; **12b** R = *sec*-butyl, 77%; **12c** R = allyl, 89%; **12d** R = *tert*-butyl, 76%; **12e** R = *n*-propyl, 95%; **12f** R = benzyl, 89%; (b) 1.1 equiv of KCN/MeOH, Δ 1 d.

SCHEME 5[a]



[a] Reagents: (a) 5 equiv HCN; (b) 5 h, rt, 98%; (c) concentrated HBr/Δ overnight, 76%; (d) 3 equiv of NaOH/H$_2$O, Δ 1.5 h, HCl, 48%.

hydrogen cyanide gas, and the adduct **14** was obtained as a 3/1 mixture of *cis/trans* isomers (yield 98%).

It is important to notice that only the *cis* isomer can lead to the desired end product. Treatment of compound **14** with base led to the formation of a complex reaction mixture without any end product. Deprotonation of the amino group will lead to expulsion of cyanide leading to side reactions, subsequently. To avoid this, the cyano group was first hydrolyzed in acidic medium. Refluxing the adduct **14** with concentrated hydrobromic acid did not lead only to the amino acid, but the chloro atom was also substituted by a bromo atom. This does not pose a problem since a better leaving group facilitates subsequent ring closure. Indeed, refluxing the amino acid for 1 h in a sodium hydroxide solution leads to the desired amino acid salt **21a** (Scheme 5).

The disadvantage of this reaction, however, is that only the *cis* isomer leads to the desired 2,4-methanoproline derivative, explaining the relatively low yield.

From previous experiments, it is known that the introduced cyano group can be eliminated in basic conditions. However, to avoid the formation of the *trans* isomer, reaction conditions were required allowing isomerization, followed by ring closure in a one-pot procedure. This was achieved using acetone cyanohydrine as hydrogen cyanide source and performing the reaction in refluxing methanol for 5 days.

If the reaction is stopped after 1 h of reflux, the imine is almost completely converted to the adduct **18** (Scheme 6) and only traces of bicyclic end product can be observed. If the reaction is prolonged to 2 or 3 days, the end product is formed almost completely, but still some adduct **18** (ca. 10−20%, depending on the R-group) is present in an almost constant *cis/trans* ratio of 3:1. The nearly constant ratio of the cis/trans adducts indicates that the isomerization is relatively fast compared to the ring closure (Table 1).

After 5 days of reflux, the reaction was complete and the end product was isolated as the only compound. The obtained bicyclic products **19** can be purified by two methods in order to remove the eventual excess of acetone cyanohydrine. The first method consists of a purification by flash chromatography, which has the disadvantage that the polar silica binds the end product very strongly, leading to low yields. This is in agreement with previous work on 2-azabicylo[2.1.1]hexanes.[9] A more convenient method to remove the acetone cyanohydrine consists of an acid−base extraction. This method is less time-consuming, and the yields after purification are significantly better.

The bicyclic compounds **19** are stable, and the cyano group also offers the possibility to further elaborate the chemistry making a series of derivatives.

The cyano group can, for example, be easily reduced to the corresponding aminomethyl group using lithium aluminum hydride in very good yield and without the formation of any side products (Scheme 7).

In Scheme 8, the synthesis of methanoproline analogues and methanoproline itself is depicted. In Scheme 5 the disadvantage was the formation of the less useful *trans* isomer. Using the acetone cyanohydrine methodology, this can be avoided by hydrolysis of the cyano group of **19**. The bicyclic skeleton proved to be stable in acidic medium, and the 2,4-methanoproline derivatives could be obtained in relatively good yields. Using this procedure, a series of *N*-alkyl derivatives of methanoproline were synthesized.

The benzyl group of **21e** was removed by hydrogenation to obtain the deprotected 2,4-methanoproline which can be used in peptide synthesis (yield = 99%).

Conclusions

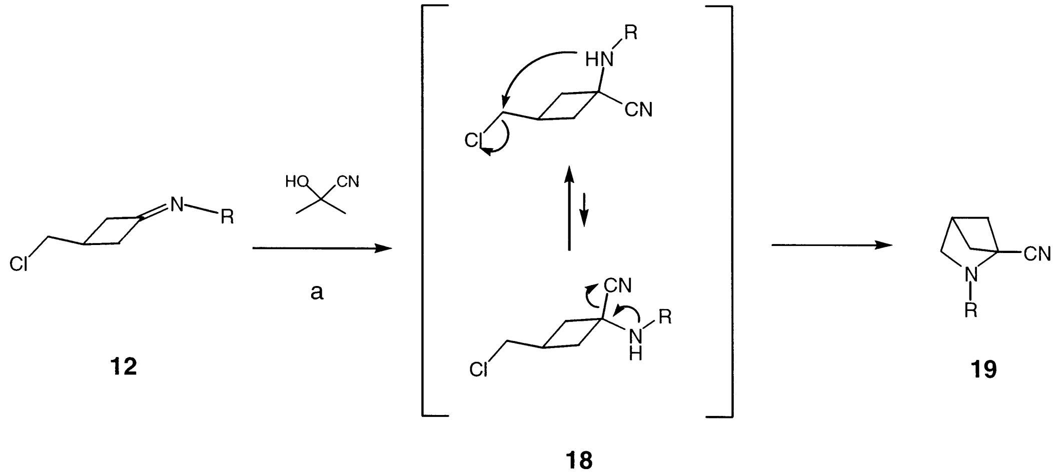
The results described clearly show the usefulness of 3-(chloromethyl)cyclobutanone to construct the 2-azabicyclo[2.1.1]hexane skeleton. 3-(Chloromethyl)cyclobutanone is prepared by a two-step methodology in a way that allows a multigram synthesis. Because of this short sequence, it forms an ideal precursor for the synthesis of 2,4-methanoproline and analogues in only four steps.

Experimental Section

^{1}H NMR spectra were recorded at 270 MHz with CDCl$_3$ as solvent (unless otherwise stated) and tetramethylsilane (TMS) as internal standard. ^{13}C NMR-spectra were recorded at 67.8 MHz. Diethyl ether and THF were dried and distilled over sodium (benzophenone ketyl control). Dichloromethane was dried and distilled over calcium hydride.

3-(Chloromethyl)-2,2-dichlorocyclobutanone (6). In an oven-dried three-necked flask of 500 mL was cooled to 0 °C a solution of 26.7 g of allyl chloride and 14 g of a Zn−Cu couple in 180 mL of dry ether under a nitrogen atmosphere. Over a period of 30 min, a solution of 19.5 mL of trichloroacetyl chloride and 25 mL of POCl$_3$ in 140 mL of dry ether was added. After the reaction mixture refluxed for 1 day (under a N$_2$

SCHEME 6[a]

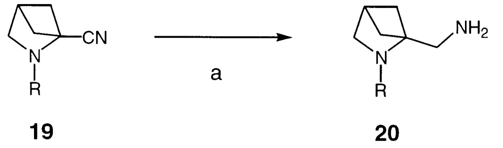


[a] Reagents: (a) 3 equiv of acetone cyanohydrine/Δ 5 d, MeOH.

TABLE 1.

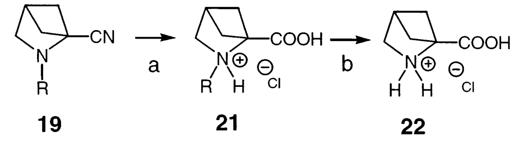
	yield (%) after chromatography	yield (%) after acid−base extraction
19a R = isopropyl	50	68
19b R = *sec*-butyl	56	74
19c R = allyl	55	78
19d R = *tert*-butyl	40	50
19e R = *n*-propyl	58	67
19f R = benzyl		73

SCHEME 7[a]



[a] Reagents: (a) 1.5 equiv of $LiAlH_4$, Et_2O, overnight, rt, **20a** R = isopropyl, 78%, **20b** R = *sec*-butyl, 84%, **20c** R = allyl, 82%, **20d** R = *tert*-butyl, 92%, **20e** R = *n*-propyl, 91%.

SCHEME 8[a]



[a] Reagents: (a) 6 N HCl/Δ overnight, **21a** R = isopropyl, 78%, **21b** R = *sec*-butyl, 82%, **21c** R = *tert*-butyl, 68%, **21d** R = *n*-propyl, 85%, **21e** R = benzyl, 88%; (b) H_2−Pd/C, overnight, **22,** 99%.

atmosphere), the solution was filtered over Celite and washed with ether. The filtrate was evaporated to 200 mL. This solution was extracted with 3 × 150 mL of petroleum ether. The clear yellow upper solution was decanted from the brown residue into a separatory funnel of 1000 mL. The organic layer was washed with 3 × 100 mL of water and 1 × 100 mL of a saturated NaCl solution. After the organic layer was dried with $MgSO_4$, evaporation of the solvent lead to 11.96 g (63.76 mmol) of 3-(chloromethyl)-2,2-dichlorocyclobutanone **6** (bp 45 °C/0.5 mm Hg): ^1H NMR (270 MHz, $CDCl_3$) δ 3.21 (1H, dd, $J = 16.8$ Hz; $J = 8.2$ Hz), 3.3−3.4 (1H, m), 3.52 (1H, dd, $J = 16.8$ Hz; $J = 9.2$ Hz), 3.77 (1H, dd, $J = 11.6$ Hz; $J = 6.9$ Hz), 3.95 (1H, dd, $J = 11.6$ Hz, $J = 7.2$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 42.93, 46.77, 46.85, 86.86, 191.08; IR (NaCl) 1810 cm^{-1} (C=O); MS 186/188/190/192 (M^+, 1), 151/153/155 (8), 146 (26), 144 (27), 111 (65), 109 (100), 87 (13), 73 (9), 51 (14). Anal. Calcd for $C_5H_5Cl_3O$: C, 32.04; H, 2.69. Found: C, 32.24; H, 2.76.

3-(Chloromethyl)cyclobutanone (2). (See also ref 9.) A solution of 23.77 g of 2,2-dichloro-3-(chloromethyl)cyclobutanone **6** in 20 mL of acetic acid (glacial) was slowly added to a vigorously stirred solution of 54 g of zinc in 200 mL of glacial acetic acid. During the addition, the solution started to reflux and refluxing was maintained for an additional 4 h. After cooling, the mixture was filtered over Celite and washed with dichloromethane. The filtrate was poured into a separatory funnel of 1000 mL containing 200 mL of dichloromethane. The solution was washed with 100 mL of water and afterward with a saturated $NaHCO_3$ solution until basic. The organic phase was dried with $MgSO_4$, filtered, and evaporated. Distillation of the crude product lead to the isolation of 12.76 g of 3-(chloromethyl)cyclobutanone (yield 85%, bp 65 °C/4.5 mmHg). For spectral data see ref 9 or Supporting Information.

3-(Bromomethyl)cyclobutanone (8). A solution of 5.0 g (26.3 mmol) of cyclobutanone **7** in 50 mL of concentrated hydrobromic acid (48% solution in water) was refluxed for 7 h. Subsequently, 100 mL of dichloromethane was added, and the reaction mixture was washed with 100 mL of water and 100 mL of a saturated $NaHCO_3$ solution. The organic phase was dried with $MgSO_4$. After filtration and evaporation of the solvent, the brown liquid was purified by flash chromatography (Hex/EtOAc 80/20; $R_f = 0.25$), and 2.3 g (14.1 mmol, 54%) of 3-(bromomethyl)cyclobutanone **8** was obtained: ^1H NMR (270 MHz, $CDCl_3$) δ 2.86−2.97 (3H, m), 3.14−3.27 (2H, m), 3.64 (2H, d, $J = 6.3$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.4, 37.9, 52.0, 205.1; IR (NaCl) 1788 cm^{-1}; MS 165/163 (M^+, 2), 84 (63), 55 (100). Anal. Calcd for C_5H_7BrO: C, 36.84; H, 4.33. Found: C, 36.50; H, 4.01.

Synthesis of *N*-[3-(Chloromethyl)-1-cyclobutylidene]amines (12). To a solution of 2.2 g (18.6 mmol) of 3-(chloromethyl)cyclobutanone (**2**) in 25 mL of dry ether was added 74.4 mmol (4 equiv) of primary amine, followed by dropwise addition of 0.6 equiv of titanium(IV) chloride in 5 mL of pentane at 0 °C. The reaction mixture was stirred overnight at room temperature, filtered, poured into 20 mL of sodium hydroxide (1 N), and extracted with diethyl ether. After drying ($MgSO_4$), filtration, and evaporation of the solvent, γ-chloroimines **12** were obtained as oils with a purity sufficient for further use (>95% purity). For the spectral data of **12a** and **12d** see ref 9. The benzyl derivative **12f** was prepared using only 3 equiv of benzylamine and 0.5 equiv of titanium(IV) chloride. The reaction was stirred for 4 h at 0 °C followed by the described workup. Spectral data are available in Supporting Information.

3-(Chloromethyl)-1-[(1-methylethyl)amino]cyclobutanecarbonitrile (14). Hydrogen cyanide gas was generated by adding a concentrated hydrochloric acid solution to potassium cyanide (2.4 g, 5 equiv) in a well-ventilated hood (**caution!**). The gas was passed through a tube containing $CaCl_2$ and an empty wash bottle and was then bubbled into a solution of 1.18 g of imine **12a** (7.4 mmol) dissolved in 50 mL of dry ether. The reaction mixture was stirred at 0 °C for 5 h while a nitrogen flow was used as HCN gas carrier through the setup. The exhaust of gas was passed again through an empty wash bottle and twice through a 6 N solution of sodium hydroxide (wash bottle) to trap the excess of hydrogen cyanide gas. After 5 h, the ether was evaporated, and 1.35 g of pure 3-(chloromethyl)-1-[(1-methylethyl)amino]cyclobutanecarbonitrile **14** was obtained as a mixture of *cis*/*trans* isomers (3/1; 98% yield): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.08 (6H, d, $J = 6.3$ Hz, major), 1.11 (6H, d, $J = 6.3$ Hz, minor), 2.01−2.09 (2H, m, major), 2.29−2.42 (4H, m, minor), 2.67−2.91 (3H, m, major and minor), 3.13 (1H, sept, $J = 6.3$ Hz, major and minor), 3.59 (2H, d, $J = 6.3$ Hz, major), 3.65 (2H, d, $J = 6.3$ Hz, minor); ^{13}C NMR (68 MHz, $CDCl_3$) δ major 23.40, 30.53, 39.33, 46.85, 48.21, 49.70, 122.17; minor 23.68, 31.68, 37.90, 47.01, 48.37, 50.73, 121.92; IR (NaCl) 2219 cm^{-1}; MS (*cis*, the *trans* derivative forms **19a** during GC-analysis) no M$^+$, 173/171 (14), 95 (51), 83 (78), 43 (55), 41 (100). Anal. Calcd for $C_9H_{15}ClN_2$: C, 57.90; H, 8.10. Found: C, 58.13; H, 8.28.

3-(Bromomethyl)-1-[(1-methylethyl)amino]cyclobutanecarboxylic Acid Hydrobromide (16). A solution of 0.52 g (12.8 mmol) of 3-(chloromethyl)-1-[(1-methylethyl)amino]cyclobutanecarbonitrile **14** in 13 mL of concentrated hydrobromic acid (48% solution in water) was refluxed overnight. After cooling of the reaction mixture, 10 mL of distilled water was added, and the mixture was filtered over a paper filter and washed with water. Evaporation of the solvent and recrystallization from a water/methanol mixture (1/1) gave 0.7 g (2.1 mmol, 76%) of the amino acid **16**: ^{1}H NMR (270 MHz, D_2O) δ 1.23 (6H, d, $J = 6.6$ Hz), 2.25−2.34 (2H, m), 2.67−2.77 (2H, m), 2.85 (1H, sept, $J = 7.6$ Hz), 3.49 (2H, d, 6.6 Hz), 3.54 (1H, sept, $J = 6.2$ Hz); ^{13}C NMR (68 MHz, D_2O) δ 20.34, 31.37, 36.44, 38.32, 51.24, 58.54, 173.65; IR (KBr) 1737 cm^{-1}; MS (methyl ester, after treatment with diazomethane) 263/265 (M$^+$, 2), 248/250 (2), 204/206 (26), 143 (44), 128 (100), 82 (22). Anal. Calcd for $C_9H_{17}Br_2NO_2$: C, 32.65; H, 5.18. Found: C, 32.76; H, 5.11.

General Procedure for the Synthesis of 2-Alkyl-2-azabicyclo[2.1.1]hexane-1-carbonitriles (19). To a solution of 16.6 mmol *N*-[3-(chloromethyl)-1-cyclobutylidene]amines **12** in 30 mL of dry methanol was added 3 equiv. of acetone cyanohydrine, and the reaction mixture was refluxed under a nitrogen atmosphere for 5 days. Purification could be performed by two means. The first way was by flash chromatography. After removal of the solvent (MeOH) under vacuum, 30 mL of dichloromethane was added together with 3−4 g of silica, and the solvent was again evaporated. The product was then purified by flash chromatography, which has the disadvantages of being time-consuming and leading to a lower yield. The second way was more convenient and consisted of an acid base extraction. After removal of the solvent under vacuum, 20 mL of a 2 N HCl solution was added. The solution was extracted with diethyl ether to remove the access of acetone cyanohydrine (3 × 40 mL). A concentrated K_2CO_3 solution was added to the water layer until basic, followed by an extraction of the water layer with dichloromethane (3 × 50 mL). After drying the organic layer with $MgSO_4$, filtration and evaporation of the solvent lead to the end products with a significant higher yield. Spectral data are available in Supporting Information.

General Procedure for the Synthesis of (2-Alkyl-2-azabicyclo[2.1.1]hex-1-yl)methylamine (20). A solution of 0.2 g (1.4 mmol) 2-alkyl-2-azabicyclo[2.1.1]hexane-1-carbonitrile **19** in 10 mL of dry ether was slowly added to a solution of 1.5 equiv of $LiAlH_4$ in 1 mL of dry ether at 0 °C. The reaction is stirred overnight at room temperature, followed by careful addition of water to neutralize the excess of lithium aluminum hydride. The mixture is filtered over Celite and washed with ether. The filtrate was dried overnight on magnesium sulfate, filtered, and evaporated to give the pure (2-alkyl-2-azabicyclo-[2.1.1]hex-1-yl)methylamine **20** (purity >97%). Spectral data are available in Supporting Information.

General Procedure for the Synthesis of 2-Alkyl-2-azabicyclo[2.1.1]hexane-1-carboxylic Acid Hydrochlorides (21). An amount of 0.2 g of 2-alkyl-2-azabicyclo[2.1.1]-hexane-1-carbonitrile **19** was dissolved in 3 mL of a 6 N hydrochloric acid solution. The reaction mixture was refluxed overnight and evaporated under reduced pressure. Distilled water was added and evaporated again. The amino acids were crystallized from water and methanol (1/1). To obtain mass spectra, the amino acids were derivatized to the corresponding methyl esters using diazomethane under standard conditions.

2-(1-Methylethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic Acid Hydrochloride (21a). There were two ways to synthesize compound **21a**: (a) The first started from compound **19a** and is described above. (b) To a solution of 0.11 g of sodium hydroxide in 5 mL of distilled water was 0.3 g (0.91 mmol) of amino acid **16**, and the mixture was heated until reflux. After 1.5 h the reaction mixture was evaporated and 5 mL of 6 N hydrogen chloride solution was added. After evaporation of the solution under vacuum, the crystals obtained were extracted with acetone and subsequently recrystallized from acetone giving 88 mg (0.44 mmol) of 2-(1-methylethyl)-2-azabicyclo-[2.1.1]hexane-1-carboxylic acid hydrochloride **21a** (yield 48%): ^{1}H NMR (270 MHz, D_2O) δ 1.30 (6H, d, $J = 6.6$ Hz), 1.92−2.04 (2H, m), 2.34−2.40 (2H, m), 2.88 (1H, br s), 3.44 (1H, d, $J = 9.9$ Hz), 3.71 (1H, d, $J = 9.9$ Hz), 3.84 (1H, sept, $J = 6.6$ Hz); ^{13}C NMR (68 MHz, D_2O) δ 18.41, 19.33, 35.61, 36.28, 45.42, 56.94, 57.14, 75.99, 169.84; IR (KBr): 1728 cm^{-1}; MS (methyl ester, from the reaction with diazomethane) 183 (M$^+$, 34), 168 (81), 124 (22), 108 (26), 82 (100). Anal. Calcd for $C_9H_{16}ClNO_2$: C, 52.56; H, 7.84. Found: C, 52.99; H, 7.63. The other spectral data are available in Supporting Information.

2,4-Methanoproline Hydrochloride 22. A suspention of 0.05 g (0.197 mmol) of **21e** and 0.02 g of Pd/C (0.1 equiv; 10% Pd/C)in 1 mL of dry methanol was stirred at room temperature in a H_2-bottle (5 bar H_2). After stirring overnight, the suspention was filtered over Celite, and 0.03 g of **22** was obtained (99%). Removal of the hydrochloride using Dowex 50 (H$^+$ form) gave the natural 2,4-methanoproline. For spectral data see ref 1.

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Supporting Information Available: Spectral and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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