A New Entry into 2-Azabicyclo[2.1.1]hexanes via 3-(Chloromethyl)cyclobutanone

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2-Azabicyclo[2.1.1]hexanes, which possess the skeleton of 2,4-methanoproline (a naturally occurring insect antifeedant), were synthesized by imination of the previously unknown 3-(chloromethyl)-cyclobutanone and subsequent reductive cyclization. The precursor of the latter, 3-oxocyclobutane carboxylic acid, was prepared by two pathways in multigram quantities.

Introduction

During our research concerning the synthesis of bioactive compounds with potential use in agrochemistry, the structure of 2,4-methanoproline (**1**) as well as its biological activity rose to our attention. Methanoproline is a non-protein amino acid isolated from the seeds of *Ateleia* herbert smithii Pittier, a plant growing on the coasts of Costa Rica.[1] It is well known for its strong antifeedant activity and protects the seeds of the plant against a wide variety of seed predators. The scarce information in the literature on the skeleton of methanoproline and its structural isomer L-*exo*-*cis*-3,4-methanoproline (**2**) (Scheme 1), isolated from *Aesculus parviflora*,[2] initiated our research for a new entry into the 2-azabicyclo[2.1.1]hexane skeleton.

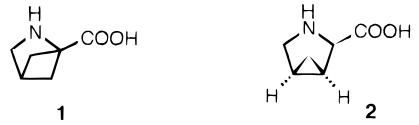
The 2-azabicyclo[2.1.1]hexane skeleton has been synthesized by [2 + 2] cycloaddition of appropriate protected amino acids under the influence of UV light[3] or by cyclization of a protected 1-amino-3-[(methanesulfonyloxy)methyl]cyclobutane-1-carboxamide.[4] Our approach consisted of the use of a suitable γ-haloimine derivative which could furnish the named bicyclic skeleton after hydride-induced intramolecular nucleophilic substitution.

Results and Discussion

From our experience with the earlier developed ω-haloimine chemistry,[5] an approach to the 2-azabicyclo[2.1.1]-hexane skeleton was deduced (Scheme 2). The idea consisted of the addition of a suitable nucleophile onto the carbon−nitrogen double bond of a *N*-[3-(chloromethyl)-1-cyclobutylidene]amine (**4**) in order to construct an adduct **5** containing the right stereochemistry for the intramolecular displacement of the chloride anion during cyclization.

This hypothesis prompted us to search for a suitable entry for the unknown 3-(chloromethyl)cyclobutanone (**3**), the precursor of *N*-[3-(chloromethyl)-1-cyclobutylidene]-

Scheme 1



1 **2**

amines (**4**). Four viable routes were found in the literature and were evaluated for the multigram preparation of the desired cyclobutanone **3**.

(1) Condensation of a malonate ester with 1-bromo-3-chloro-2-propyl benzyl ether[6] was not used because of the multistep procedure for the preparation of the starting materials.

(2) Chlorocarbonylation of cyclobutanone by oxalyl chloride under UV irradiation followed by methanolysis[7] gave results that were difficult to reproduce and could only be performed on a small scale.

(3) [2 + 2] Cycloaddition of allene and acrylonitrile[8] under pressure at 220 °C led to 3-methylenecyclobutylcarbonitrile which was further hydrolyzed to 3-methylenecyclobutanecarboxylic acid (**8**) (Scheme 3).

The poor yield of both reactions was due to the high solubility of the products in water and the tar formation in the first step. Ozonolysis of the methylene function at low temperature yielded 3-oxocyclobutane carboxylic acid **9** in 50% yield. The overall yield for carboxylic acid **9** from allene was only 4%.

(4) The most straightforward synthesis of **3** which could be performed on a large scale (∼30 g) consisted of the base-induced cyclocondensation of 1,3-dibromo-2,2-dimethoxypropane (**10**) and diisopropyl malonate which was then hydrolyzed to 3-oxocyclobutane-1-carboxylic acid (**9**) in 33% overall yield (Scheme 4).[9]

The base-induced condensation of the bromo acetal **10** with Meldrum's acid did not lead to the production of the corresponding cyclobutane derivative, while an attempt to perform the hydrolysis under Krapcho conditions (NaCl, DMSO, H_2O) did not produce any decarboxylated product.

The isolation of 3-oxocyclobutane-1-carboxylic acid (**9**) required a continuous extraction with diethyl ether. After drying of the ethereal layers ($MgSO_4$), diethyl ether was evaporated, replaced by dichloromethane, and dried again ($MgSO_4$). This additional drying procedure was necessary in order to get a complete esterification and acetalization in the next step. Incomplete reactions gave

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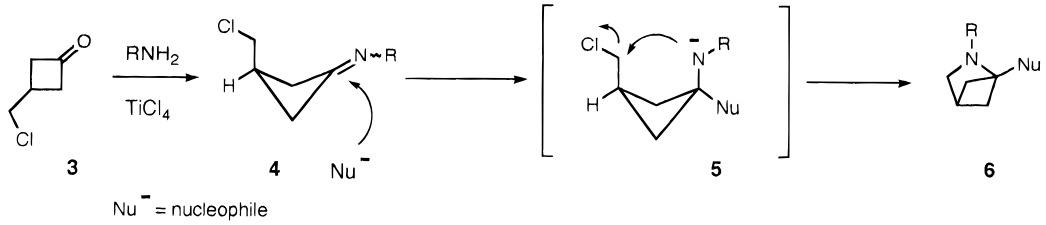
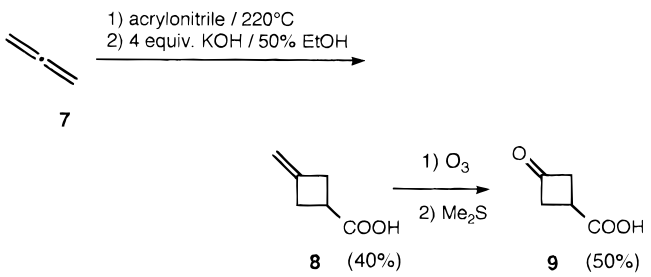
Scheme 2



Scheme 3



varying amounts of 3-(methoxycarbonyl)cyclobutanone together with the corresponding acetal **11**. Reduction of **11** with lithium aluminum hydride in diethyl ether yielded 86% of the alcohol **12**. The cyclobutanone derivative **3** was now available by a straightforward tosylation of the alcohol, substitution of the tosyl group by chloride using lithium chloride in DMF, and immediate hydrolysis (without isolation) of the acetal.

3-(Chloromethyl)cyclobutanone (**3**) was obtained in 9.7% overall yield, starting from the acetal **10** and diisopropyl malonate. The long reaction pathway for the synthesis of the 2-azabicyclo[2.1.1]hexane skeleton is due to the lack of an easy entry in the class of the 3-substituted cyclobutanones.

3-(Chloromethyl)cyclobutanone (**3**) was then treated with 3.5 equiv of a primary amine in diethyl ether in the presence of 0.6 equiv of titanium(IV) chloride as a dehydrating agent (Scheme 5). Although competing reactions such as 1,2-dehydrochlorination, 1,3-dehydrochlorination, or nucleophilic substitution could occur, the imination proceeded readily and the corresponding novel γ-chloroimines **4** were isolated in 72−87% yield.

Because of the lability of the γ-chloroimines **4**, they were not purified but used as such. Spectroscopically, no side products in the synthesis of **4** were detected (purity ≥96%), except for the *N*-ethyl derivative for which the purity was estimated at 94%.

The *N*-[(3-chloromethyl)-1-cyclobutylidene]amines were then treated with lithium aluminum hydride in an ethereal solvent. Treatment of the *N*-isopropylimine **4a** with lithium aluminum hydride in diethyl ether under reflux led to the reduced compound **13** as a single stereoisomer, but no ring closure was observed. Executing the reduction of **4a** with lithium aluminum hydride in tetrahydrofuran under reflux led to ring closure, resulting in the synthesis of 2-isopropyl-2-azabicyclo-[2.1.1]hexane (**14a**).

For the *N*-cyclohexyl and the *N*-ethyl derivatives **4b**,**c**, the reaction was performed in diethyl ether because the use of THF as solvent resulted in complex reaction mixtures. Using diethyl ether, the reaction mixtures leading to **14b** and **14c** were only contaminated with small amounts of the corresponding 3-(chloromethyl)-cyclobutylamine (**13**) (yield: 89% for **14b** and 57% for **14c**). However, purification of the 2-azabicyclo[2.1.1]-hexanes **14b**,**c** by column chromatography (see Experimental Section) resulted in severe losses of end products. The removal of the cyclobutylamines decreased the yields to 26% for **14b** and 18% for **14c**. These losses were accounted for by the high binding affinity of the azabicyclic compounds to the silica gel. The compounds could only be recovered from the silica gel by desorption using CH_2Cl_2/MeOH (1/1) after elution of the contaminating compounds with EtOAc/MeOH (9/1) during flash chromatography.

The synthesis of 2-*sec*-butyl-2-azabicyclo[2.1.1]hexane (**14d**) in tetrahydrofuran went smoothly in 72% yield. The yield was calculated from the ^{1}H-NMR spectrum because not all the solvent could be removed due to the volatility of the product. Flash chromatography using ethyl acetate/methanol (9/1) as eluent (R_f = 0.04) led to the isolation of **14d** in 50% yield with a purity of 85%. A pure sample of 2-*sec*-butyl-2-azabicyclo[2.1.1]hexane could be obtained by preparative gas chromatography (column temperature: 100 °C).

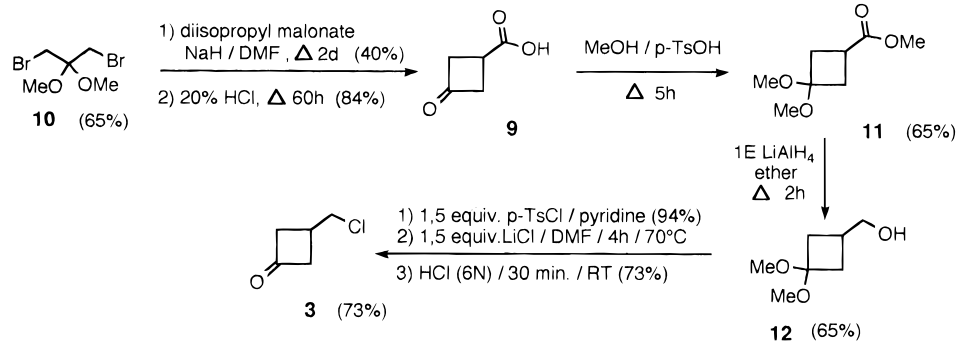
Treatment of the *N*-*tert*-butylimine **4e** with lithium aluminum hydride in diethyl ether did not give the corresponding 2-azabicyclo[2.1.1]hexane derivative **14** (*R* = *t*-Bu) but resulted in the isolation of *N*-*tert*-butyl-*N*-(3-methyl-1-cyclobutyl)amine (**16**). Apparently, after reduction of the imino function in **4e** further reduction of the chloromethyl substituent takes place. The steric requirements of the bulky *N*-*tert*-butyl substituent probably inhibit the ring closure so that further dechlorination can occur. However, the stereochemistry of compound **16**, obtained as one stereoisomer, could not be determined by NMR spectroscopy. It is assured to have the cis stereochemistry, based on accepted concepts of cyclobutanone attack (vide infra).

The predominant attack of hydride at the exo side of the γ-chloroimines **4** can be explained by steric interactions of the chloromethyl group (Scheme 6). Due to the folded nature of the cyclobutane derivatives, attack of the nucleophile will be favored from the exo side in either case **17** or **18**.

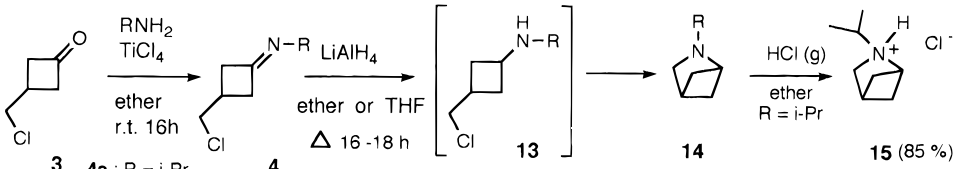
Neither NOE experiments nor 2D-NMR experiments on *N*-cyclohexyl-(3-chloromethyl)-1-cyclobutylamine (**13b**) could prove unequivocally the cis configuration of the protons at the 1- and 3-positions of the cyclobutyl ring because no considerable NOE effects could be observed during the various NMR irradiation experiments.

The spectral identification of the free amines **14** by ^{1}H-NMR was problematic because of the considerable overlap of most of the signals. Therefore, in order to fully unravel the structure of the 2-azabicyclo[2.1.1]hexane skeleton, the 2-azabicyclo[2.1.1]hexane **14a** was treated with gaseous hydrogen chloride in diethyl ether in order to prepare the hydrochloride salt. Unfortunately, it was only possible to prepare the hydrochloride of **14a**, since **14b**, **14c**, and **14d** formed sticky gums upon treatment with gaseous hydrogen chloride. The advantage of preparing the hydrochloride of **14a** was the resolution of the signals in the ^{1}H-NMR spectrum. All the coupling constants (Chart 1) could be measured by running several

Scheme 4

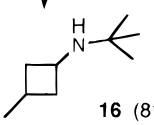


Scheme 5



4a : R = i-Pr
4b : R = c-Hex
4c : R = Et
4d : R = s-Bu
4e : R = t-Bu

R = t-Bu
1 equiv.LiAlH4 / THF
Δ 16 h



16 (81%)

	R	Crude Yield	Purity	Yield after Purification
14a	i-Pr	86%	>97%	80%
14b	c-Hex	89%	85%	26%
14c	Et	57%	70%	18%
14d	s-Bu	72%	85%	50%

Scheme 6

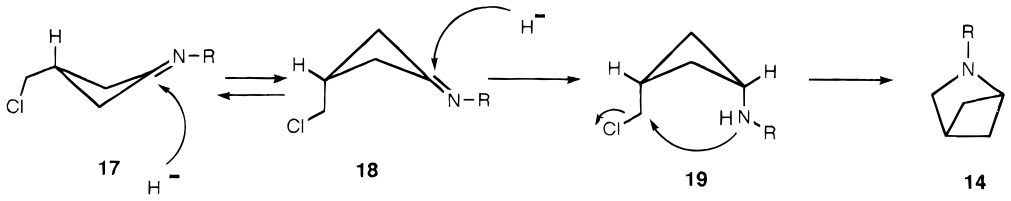
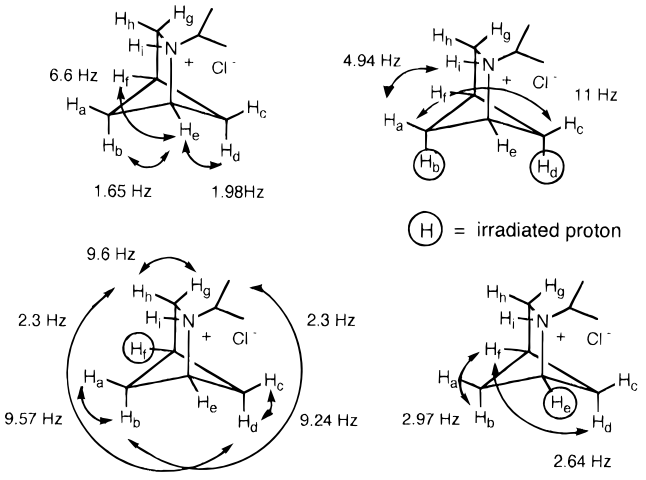


Chart 1. Coupling Constants of 2-Aza-2-isopropylbicyclo[2.1.1]hexane Hydrochloride (15) Obtained by ^{1}H-NMR Experiments (D_2O)



irradiation experiments and *J*-resolved spectra on the hydrochloride **15** in D_2O. From the normal ^{1}H-NMR spectrum, the diagnostic coupling constant H_e-H_f for 2-azabicyclo[2.1.1]hexanes **14** was determined as 6.6 Hz which is typical for the coupling of bridgehead protons. This diagnostic value is in agreement with literature data of 2-oxabicyclo[2.1.1]hexane.[9] The coupling constants H_e-H_a, H_e-H_c and H_f-H_a, H_f-H_c are ≈ 0 due to a dihedral angle which is close to 90°. The coupling constant of H_e-H_b and H_e-H_d, however, is 1.65 and 1.98 Hz, respectively. All of the remaining coupling constants had to be measured by irradiation experiments. Irradiation of proton H_f revealed the coupling constants H_h-H_g (9.6 Hz), H_d-H_h (2.3 Hz), and H_b-H_g (2.3 Hz). The coupling constants H_d-H_h and H_b-H_g are remarkably large (coupling over five bonds) because of a well-shaped W-form. Irradiation of proton H_f also gave the coupling constants H_a-H_b (9.57 Hz), H_c-H_d (9.24 Hz), and H_f-H_h (≈0 Hz) and H_f-H_g (≈0 Hz). Irradiation of proton H_e resulted in the measurement of the coupling constants H_b-H_f (2.97 Hz) and H_d-H_f (2.64 Hz). Finally, irradiation of protons H_b and H_d, which overlap, led to the coupling constants H_a-H_c (~11 Hz) and H_a-H_i (4.94 Hz). Also characteristic is the large coupling constant of about 11 Hz between H_a and H_c due to the W-shape of the C-skeleton. This is also in agreement with similar coupling constants found in methanoproline (**1**) itself (14.7 Hz)[3a] and in 2-oxabicyclo[2.1.1]hexane (10.8 Hz).[10]

The spectrum of the free bicyclic amine is considerably different because of the overlapping of the signals and

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because of the symmetry of the molecule resulting in the fact that several coupling constants become equal or close to zero.

In the free bicyclic amine **14a**, the geminal coupling of H_h-H_g becomes 0 Hz instead of 9.6 Hz in the hydrochloride **15**. The sharp singlet observed in the ^{1}H-spectrum for H_f and H_g does not give any coupling in the COSY-spectrum which was also observed for the oxygen analogue.[10] Also, the geminal coupling of H_a-H_b and H_c-H_d decreases considerably to 4.6 Hz.

Further experiments using nucleophiles other than hydride did not lead to promising results but are currently under investigation. The use of cyanide as nucleophile would open an interesting way to 2,4-methanoproline (**1**).

In conclusion, the synthesis of 3-(chloromethyl)cyclobutanone (**3**) was evaluated using two methodologies. This functionalized cyclobutanone **3** was further used as precursor for *N*-[3-(chloromethyl)-1-cyclobutylidene]-amines which were converted into 2-azabicyclo[2.1.1]-hexanes by hydride-induced intramolecular cyclization.

Experimental Section

General Methods. ^{1}H-NMR spectra (δ) were recorded at 60, 270, and 500 MHz with $CDCl_3$ as solvent (unless otherwise stated) and tetramethylsilane (TMS) as internal standard. ^{13}C-NMR spectra (δ) were recorded at 67.8 MHz. For the preparation of 3-oxocyclobutanecarboxylic acid (**9**),[9] the recipe was modified for a large scale procedure. After drying of the ethereal solution of **9** with $MgSO_4$ in diethyl ether, diethyl ether was evaporated, replaced by dichloromethane, and dried once more with $MgSO_4$.

The reported peak assignments were derived from DEPT or 2D NMR experiments (COSY and HETCOR).

Synthesis of Methyl 3,3-Dimethoxycyclobutane-1-carboxylate (11). To a solution of 31.23 g (274 mmol) of 3-oxocyclobutane-1-carboxylic acid (**9**) in 320 mL of dry methanol was added 0.8 g (6 mmol) of *p*-toluenesulfonic acid, and the mixture was refluxed for 8 h. After cooling, methanol was evaporated to about 20% of its volume, and the reaction mixture was then poured into water and extracted three times with dichloromethane. After drying ($MgSO_4$), evaporation of the solvent afforded the crude ester. Distillation under reduced pressure (bp 80−83 °C/8 mmHg) yielded 30.9 g (65%) of methyl 3,3-dimethoxycyclobutane-1-carboxylate. Sometimes, traces of methyl 3-oxocyclobutanecarboxylate could be detected by GC−MS coupling due to an incomplete conversion, which arises from insufficiently dried starting material **9** (see above).

^{1}H-NMR: 2.3−2.5 (4H, m); 2.89 (1H, quint, J = 8.6 Hz); 3.14 (3H, s); 3.17 (3H, s); 3.69 (3H, s). ^{13}C-NMR: 28.62 (d); 35.51 (t); 48.42 (q); 48.71 (q); 51.91 (q); 99.76 (s); 175.25 (s). IR (NaCl): 1738 cm^{-1} (C=O); 2835 cm^{-1} (OMe). MS *m*/*z*: no M$^+$ 159 (0.7, M$^+$ − Me); 143 (39); 142 (25); 115 (7); 111 (11); 88 (100); 83 (89); 68 (25); 58 (29); 55 (18); 43 (32). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.30; H, 8.02.

Synthesis of (3,3-Dimethoxy-1-cyclobutyl)methanol (12). To 1.50 g (40 mmol) of lithium aluminum hydride in 60 mL of dry ether was added dropwise at 0 °C 7.07 g (40 mmol) of methyl 3,3-dimethoxycyclobutane-1-carboxylate **11**, dissolved in 15 mL of dry ether. The mixture was then refluxed for 2 h. After cooling, 3 g of water was added carefully and the resulting aluminum salts were filtered and washed with ether. After drying of the ethereal layer ($MgSO_4$), the solvent was evaporated, yielding 5.78 g (86%) of pure (3,3-dimethoxy-1-cyclobutyl)methanol (**12**).

^{1}H-NMR: 1.0−1.3 (1H, m); 1.8−2.6 (4H, m); 3.19 (3H, s); 3.21 (3H, s); 3.5−3.8 (2H, m). ^{13}C-NMR: 26.60 (d); 34.16 (t); 48.21 (q); 48.50 (q); 66.60 (t); 100.82 (s). IR (NaCl): 3400 (br) (OH). MS *m*/*z*: no M$^+$; 114 (12, M$^+$ − CH_2O); 96 (11); 88 (67); 83 (100); 68 (39); 58 (39); 55 (44); 53 (22). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.66; H, 9.52.

Synthesis of (3,3-Dimethoxy-1-cyclobutyl)methyl *p*-Toluenesulfonate. To a solution of 5.78 g (40 mmol) of (3,3-dimethoxy-1-cyclobutyl)methanol (**12**) in 60 mL of pyridine was added portionwise 11.28 g (1.5 equiv) of *p*-toluenesulfonyl chloride. The mixture was stirred for 1 h at room temperature and was then kept for 16 h at 5 °C. After filtration of the precipitate, the filtrate was poured into water and extracted three times with diethyl ether (3 × 40 mL). The ethereal solution was washed with 6 N hydrochloric acid and dried (K_2CO_3/$MgSO_4$). Filtration and evaporation of the solvent yielded 11.13 g (94%) of pure (3,3-dimethoxy-1-cyclobutyl)methyl *p*-toluenesulfonate. ^{1}H-NMR: 1.76−1.83 (2H, m); 2.19−2.25 (2H, m); 2.3−2.4 (1H, m); 2.45 (3H, s); 3.06 (3H, s); 3.11 (3H, s); 4.03 (2H, d, J = 6.9 Hz); 7.35 (2H, d, J = 8.8 Hz); 7.78 (2H, d, J = 8.6 Hz). ^{13}C-NMR: 21.65 (d); 24.00 (q); 34.19 (t); 48.21 (q); 48.50 (q); 73.69 (t); 100.21 (s); 127.90 (d); 129.86 (d); 133.10 (s); 144.77 (s). IR (NaCl) ν_{max}: 1600 cm^{-1}; 1360 cm^{-1}; 1280 cm^{-1} (OMe); 1180 cm^{-1}. The mass spectrum could not be obtained. Anal. Calcd for $C_{14}H_{20}O_5S$: C, 55.98; H, 6.71. Found: C, 56.08; H, 6.80.

Synthesis of 3-(Chloromethyl)cyclobutanone (3). A solution of 27.34 g (91 mmol) of (3,3-dimethoxy-1-cyclobutyl)-methyl *p*-toluenesulfonate in 120 mL of dry dimethylformamide was treated with 5.74 g (136 mmol) of lithium chloride. The mixture was then heated for 16 h in an oil bath of 70 °C. Afterwards, 135 mL of concentrated hydrochloric acid (12 N) was added, and the mixture was stirred for 3 h and was then extracted three times with ether. After drying ($MgSO_4$), filtration, and evaporation of the solvent, the resulting oil still contained some dimethylformamide. Flash chromatography of the oil on silica gel with hexane/ethyl acetate (80:20) as eluent led to the isolation of 6.75 g (63%) of pure 3-(chloromethyl)cyclobutanone (**3**). ^{1}H-NMR: 2.80−2.90 (1H, m); 2.92−2.99 (2H, m); 3.16−3.22 (2H, m); 3.75 (2H, d, J = 6.6 Hz). ^{13}C-NMR: 26.08 (d); 48.29 (t); 50.85 (t); 205.11 (s). IR (NaCl): 1785 cm^{-1} (C=O). MS *m*/*z*: 159/61 (4, M$^+$); 144/46 (2); 108 (4); 83 (58); 82 (10); 68 (6); 55 (18); 43 (38); 41 (100); 40 (28). Anal. Calcd for C_5H_7ClO: C, 50.65; H, 5.95; Cl, 29.90. Found: C, 50.52; H, 6.05; Cl, 29.72.

Synthesis of *N*-[3-(Chloromethyl)-1-cyclobutylidene]-amines 4. General Procedure. To a solution of 2.2 g (18.6 mmol) of 3-(chloromethyl)cyclobutanone (**3**) in 25 mL of dry ether was added 74.4 mmol (4 equiv) of the primary amine and afterwards dropwise 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 ($MgSO_4$/K_2CO_3), filtration, and evaporation of the solvent, the labile γ-chloroimines **4** were obtained as oils with a sufficient purity (>92%) for further use without additional purification. For the *N*-ethyl derivative, more ethylamine (4 equiv) was added after 2 and 4 h of stirring.

***N*-[3-(chloromethyl)-1-cyclobutylidene)isopropylamine (4a).** Yield: 80%. ^{1}H-NMR: 1.12 (3H, d, J = 6.3 Hz, Me); 1.13 (3H, d, J = 6.3 Hz, Me); 2.0−2.2 (1H, m, C*H*CH_2Cl); 2.1−2.2 (1H, m, CH); 2.25−2.4 (1H, m, CH); 2.49 (1H, ddt, J_1 = 16.5 Hz, J_2 = 8.3 Hz, J_3 = 2.6 Hz, CH); 2.68 (1H, ddt, J_1 = 16.6 Hz, J_2 = 8.3 Hz, J_3 = 2.3 Hz, CH); 2.98 (1H, d, J = 6.9 Hz, C*H*Cl); 3.00 (1H, d, J = 6.3 Hz, C*H*Cl); 3.23 (1H, quint, J = 6.3 Hz, C*H*Me_2). ^{13}C-NMR: 23.88 (Me); 23.91 (Me); 29.49 (*C*HCH_2Cl); 37.93 (CH_2); 41.47 (CH_2); 48.76 (CH_2Cl); 52.27 ($CHMe_2$); 162.47 (C=N). IR (NaCl): 1712 cm^{-1} (C=N). MS *m*/*z*: 159/61 (M$^+$, 4); 144/46 (2); 108 (4); 83 (58); 82 (10); 68 (6); 55 (18); 43 (38); 41 (100); 40 (28).

***N*-[3-(Chloromethyl)-1-cyclobutylidene]cyclohexylamine (4b).** Yield: 72%. ^{1}H-NMR: 1.1−1.5 (6H, m, 3 × CH_2); 1.5−1.8 (4H, m, 2 × CH_2); 2.5−2.8 (3H, m, 3 × CH); 2.9−3.1 (3H, m, 3 × CH); 3.63 (2H, d, J = 6.6 Hz, CH_2Cl); ^{13}C-NMR: 24.76 (2 × CH_2); 25.57 (CH_2); 29.40 (*C*HCH_2Cl); 33.67 (2 × CH_2); 38.26 (*C*H_2CN); 41.60 (*C*H_2CN); 48.88 (CH_2Cl); 60.45 (N*C*H); 164.60 (C=N). IR (NaCl): 1718 cm^{-1} (C=N). MS *m*/*z*: 199 (3, M$^+$); 123 (36); 84 (10); 83 (100); 82 (16); 55 (67); 42 (11); 41 (69).

***N*-[3-(Chloromethyl)-1-cyclobutylidene]ethylamine (4c).** Yield: 87% (purity ~95%). ^{1}H-NMR: 1.19 (3H, t, J = 7.3 Hz, Me); 2.5−2.9 (3H, m, 3 × CH); 2.95−3.1 (2H, m, 2 × CH); 3.23 (2H, q, J = 7.3 Hz; NCH_2); 3.65 (2H, dd, J_1 = 6.6 Hz, J_2 = 6.2

Hz, CH_2Cl). ^{13}C-NMR 15.70 (Me); 29.27 (CH); 38.18 (CH_2); 41.51 (CH_2); 46.47 (CH_2); 48.82 (CH_2); 166.45 (C=N). IR (NaCl): 1715 cm^{-1} (C=N). MS *m/z*: 145 (M^+, 2); 96 (2); 69 (84); 68 (5); 55 (3); 54 (3); 53 (4); 42 (7); 41 (100).

***N*-[3-(Chloromethyl)-1-cyclobutylidene]-*sec*-butylamine (4d).** Yield: 77%. ^{1}H-NMR: 0.82 (3H, t, J = 7.2 Hz, Me); 1.09 (3H, d, J = 6.3 Hz, Me); 1.45−1.55 (2H, m, NCHCH_2); 2.6−2.8 (3H, m, 2 × CH + C$H$$CH_2Cl$); 2.9−3.2 (3H, m, 2 × C$H$ + CHN); 3.65 (2H, t, J = 6.3 Hz, CH_2Cl). ^{13}C-NMR: 11.03 (Me); 21.54 (Me); 29.49 (*C*HCH_2Cl); 30.69 (CH_2); 38.47 (CH_2); 41.44 (CH_2); 48.86 (CH_2Cl); 58.24 (NCH); 164.45 (C=N). IR (NaCl): 1710 cm^{-1} (C=N). MS *m/z*: 173 (M^+, 3); 97 (40); 91 (4); 82 (13); 81 (4); 68 (7); 57 (56); 56 (5); 55 (19); 54 (3); 44 (9); 43 (4).

***N*-[3-(Chloromethyl)-1-cyclobutylidene]-*tert*-butylamine (4e).** Yield: 76%. ^{1}H-NMR: 1.23 (9H, s, *t*-Bu); 2.6−2.8 (2H, m, 2 × CH); 2.8−2.9 (1H, m, CH); 3.0−3.1 (1H, m, CH); 3.15−3.30 (1H, m, CH); 3.65 (2H, dd, J_1 = 7.3 Hz, J_2 = 6.6 Hz, CH_2Cl). ^{13}C-NMR: 29.67 (CH); 29.97 (*t*-Bu); 42.42 (CH_2); 43.32 (CH_2); 48.93 (CH_2Cl); 56.49 ($C_{quat.}$); 163.27 (s, C=N). IR (NaCl): 1710 cm^{-1} (C=N). MS *m/z*: 173 (M^+, 1); 158 (1); 122 (2); 97 (8); 82 (5); 57 (100); 41 (44).

Synthesis of 2-Isopropyl-2-azabicyclo[2.1.1]hexane (14a). To 0.17 g (4.5 mmol) of lithium aluminum hydride in 10 mL of dry THF was added dropwise 0.72 g (4.5 mmol) of imine **4a**, dissolved in 2 mL of dry THF. The reaction mixture was refluxed for 18 h, and after cooling, 20 mL of ether was added followed by 2 mL of sodium hydroxide (2 N). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed by distillation using a Vigreux column. 2-Isopropyl-2-azabicyclo[2.1.1]hexane (**14a**) was obtained as an oil (0.48 g) in 86% yield. An analytical sample was obtained by preparative gas chromatography (3 m column, GE SE-30 (7%), internal diameter 0.4 cm). The crude mixture could also be purified by conversion of **14a** to the hydrochloride **15** upon treatment with dry hydrogen chloride in ether. The melting point of the hydrochloride could not be measured due to decomposition of the product. ^{1}H-NMR (500 MHz): 1.09 (6H, d, J = 6.1 Hz, CH*M*e_2); 1.41 (2H, dd, J_1 = 4.5 Hz, J_2 = 1.9 Hz, 2 × CH); 1.61 (2H, m, 2 × CH); 2.47 (1H, sept, J = 6.1 Hz, C*H*Me_2); 2.68 (2H, brs, CH_2N); 2.70 (1H, m, $CH_{bridgehead}$); 3.63 (1H, dt, J_1 = 6.4 Hz, J_2 = 1.9 Hz, $CH_{bridgehead}$). ^{13}C-NMR: 22.03 (Me); 36.73 (CH_2); 39.82 (CH); 52.76 (*C*HMe_2); 54.93 (CH_2N); 61.17 (*C*HN). IR (NaCl) ν_{max}: 1585, 1385, 1315, 1182 cm^{-1}. MS *m/z*: 125 (M^+, 55); 110 (100); 84 (25); 83 (33); 82 (60); 70 (21); 69 (16); 68 (66); 67 (35); 56 (85); 55 (93); 44 (47); 43 (54); 42 (63); 41 (87). Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.07; N, 11.19. Found C, 76.69; H, 12.13; N, 11.06.

Synthesis of 2-Cyclohexyl-2-azabicyclo[2.1.1]hexane (14b). To 0.12 g (2.7 mmol) of lithium aluminum hydride in 20 mL of diethyl ether was added dropwise 0.55 g (2.7 mmol) of *N*-[(3-chloromethyl)-1-cyclobutylidene]cyclohexylamine (**4b**) in 3 mL of dry ether, and the mixture was refluxed for 16 h. After cooling, the reaction mixture was poured into 5 mL of sodium hydroxide (2 N) and extracted with ether (3 × 20 mL). After drying ($MgSO_4$), filtration, and evaporation of the solvent, 0.4 g of crude product was obtained (^{1}H-NMR; GC; purity: 85%). Further purification could be done by flash chromatography but led to a considerable loss of product. The impurities were therefore first eluted from the silica gel using ethyl acetate/methanol (9:1) followed by desorption of the bicyclo[2.1.1]hexane derivative using dichloromethane/methanol (1:1). After evaporation of the solvent, pure 2-cyclohexyl-2-azabicyclo[2.1.1]hexane (**14b**) was obtained (yield: 26%). ^{1}H-NMR: 1.0−1.3 (4H, m, 4 × HC*H*); 1.3−1.45 (2H, m, 2 × HC*H*); 1.61 (4H, brs, CH_2, CH_2); 1.73−1.77 (2H, brs, 2 × HC*H*); 1.91−1.95 (2H, m, 2 × HC*H*); 2.0−2.14 (1H, m, C*H*N); 2.69 (3H, s, CH_2N, C$H_{bridgehead}$; complete overlap of signals); 3.69 (1H, dt, J_1 = 6.9 Hz, J_2 = 2.0 Hz, $CH_{bridgehead}$). ^{1}H-NMR (C_6D_6): 1.0−1.45 (10 H, m); 1.65−1.77 (2H, m, 2 × C*H*); 1.80−1.85 (2H, m, 2 × C*H*); 2.04−2.13 (1H, m, C*H*N); 2.45−2.50 (1H, m, C$H_{bridgehead}$); 2.58 (2H, s, CH_2N); 3.58 (1H, d × t, J_1 = 6.59 Hz, J_2 = 1.65 Hz, C$H_{bridgehead}$). ^{13}C-NMR: 25.17 (2 × CH_2); 26.18 (CH_2); 32.09 (2 × CH_2); 36.66 (2 × CH_2); 39.48 ($CH_{bridgehead}$); 54.48 (CH_2N); 60.04 ($CH_{bridgehead}N$); 61.53 (CHN). IR (NaCl) ν_{max}: 2940, 2860, 1455, 1218 cm^{-1}. MS *m/z*: 165 (M^+, 27); 150 (23); 124 (15); 123 (16); 122 (55); 108 (15); 84 (100); 83 (23); 82 (48); 81 (16); 80 (16); 68 (44); 67 (27); 56 (21); 55 (62); 54 (20); 42 (32); 41 (53). Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found: C, 80.10; H, 11.44; N, 8.32.

Synthesis of 2-Ethyl-2-azabicyclo[2.1.1]hexane (14c). To 0.14 g (3.7 mmol) of lithium aluminum hydride in 20 mL of dry ether was added dropwise 0.37 g (2.5 mmol) of *N*-ethylimine **4c** at room temperature, and the mixture was refluxed for 16 h. After cooling, 0.3 g of water and 30 mL of ether were added carefully to the mixture, and the aluminum salts were filtered off afterwards. After drying ($MgSO_4$), the solvent was distilled off to give 0.23 g of crude 2-ethyl-2-azabicyclo[2.1.1]hexane (**14c**) as an oil (yield 57%; purity 70%). Further purification of this compound could be done by flash chromatography. Elution of the impurities was performed on silica gel using ethyl acetate/dichloromethane (9:1), followed by desorption of the product using dichloromethane/methanol (1:1) as eluent. Evaporation of the solvent yielded 0.05 g (18%) of pure 2-ethyl-2-azabicyclo[2.1.1]hexane (**14c**). ^{1}H-NMR: 1.54 (3H, t, J = 7.3 Hz, Me); 2.13 (4H, ∼d, J = 6.6 Hz, 2 × CH_2); 2.73 (1H, brs, NCH); 2.94−2.99 (1H, m, $CH_{bridgehead}$); 3.22 (2H, ∼q, J = 6.9 Hz, NCH_2Me); 3.8−3.9 (1H, brs, NCH); 4.15 (1H, d, J = 6.3 Hz,, NCH). ^{13}C-NMR: 10.76 (CH_3); 36.0 very broad signal for 2 × $CH_{2\ bridge}$; 38.65 ($CH_{bridgehead}$); 48.10 (NCH_2Me); 55.11 (CH_2N); 65.35 ($CH_{bridgehead}$). IR (NaCl) ν_{max}: 1470, 1450, 1395, 910 cm^{-1}. MS *m/z*: 111 (M^+, 5); 110 (28); 96 (57); 84 (26); 82 (29); 70 (12); 69 (37); 68 (41); 67 (22); 56 (54); 55 (43); 54 (26); 42 (100).

Synthesis of 2-*sec*-Butyl-2-azabicyclo[2.1.1]hexane (14d). To a suspension of 0.182 g (4.7 mmol) of lithium aluminum hydride in 20 mL of dry THF was added dropwise 0.83 g (4.7 mmol) of *N*-*sec*-butylimine **4d** at room temperature. The reaction mixture was refluxed during 16 h followed by addition of 0.36 g of water in 5 mL of diethyl ether. The mixture was then extracted three times with ether, dried ($MgSO_4$), and filtered. After careful evaporation of the solvent 0.7 g of the crude mixture (containing ±30% of THF) was obtained (yield of **14d**: 72%). The mixture was further purified by flash chromatography using CH_2Cl_2: MeOH (1:1) as eluent (R_f = 0.04). Due to the lability of the product, the purity was not better than 90% after chromatography. Attempts to purify **14d** by treatment with gaseous hydrogen chloride in dry diethyl ether failed. ^{1}H-NMR: 0.90 (3H, t, J = 7.3 Hz, Me); 1.08 (3H, d, J = 6.3 Hz,Me); 1.2−1.4 (2H, m, CH_2); 1.39−1.41 (2H, m, 2 × CH); 1.45−1.68 (2H, m, 2 × CH); 2.2−2.3 (1H, m, CHN); 2.63−2.76 (3H, m, CH_2N + CH_{bridge}); 3.65 (1H, d × t, J_1 = 6.6 Hz, J_2 = 1.65 Hz, CH_{bridge}). ^{13}C-NMR: 10.33 (Me); 17.99 (Me); 28.03 (CH_2); 36.06 (CH_2); 37.12 (CH_2); 39.66 (CH_{bridge}); 55.24 (CH_2); 59.26 (CHN); 60.81 (CH_{bridge}). IR (NaCl) ν_{max}: 2940, 1460, 1375, 1050 cm^{-1}. MS *m/z*: 139 (M^+, 39); 124 (61); 111 (33); 110 (100); 84 (65); 82 (60); 70 (35); 69 (41); 68 (58); 67 (53); 57 (42); 56 (88); 55 (81); 54 (37); 44 (76).

Synthesis of *N*-(3-Methylcyclobutyl)-*tert*-butylamine (16). To a solution of 88 mg (2.3 mmol) of lithium aluminum hydride in 10 mL of dry THF was added dropwise 0.4 g (2.3 mmol) of γ-chloroimine **4e**, and the mixture was refluxed for 8 h. After cooling, 0.8 g of water was added and the mixture was filtered. The filtrate was dried ($MgSO_4$) and filtered, and after evaporation of the solvent, 0.32 g (81%) of crude *N*-(3-methylcyclobutyl)-*tert*-butylamine (**16**) was obtained (GC; purity 95%). An analytical sample was obtained by preparative gas chromatography. ^{1}H-NMR: 1.02 (3H, d, J = 6.6 Hz, Me); 1.07 (9H, s, *tert*-Bu); 1.24 (2H, m, 2 × CH); 1.93 (1H, m, C*H*Me); 2.40 (2H, m, 2 × CH); 3.15 (1H, m, C*H*N). ^{13}C-NMR: 21.94 (Me); 23.95 (CH); 29.99 (*tert*-Bu); 42.53 (2 × CH_2); 45.12 (CH); 50.82 ($C_{quat.}$). IR (NaCl) ν_{max}: 2960, 2870, 1455, 1360, 1265 cm^{-1}. MS *m/z*: 141 (M^+, 2); 126 (3); 99 (38); 84 (80); 57 (32); 44 (37); 43 (100). Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.91. Found: C, 76.40; H, 13.59; N, 9.87.

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