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Novel synthesis of indolizidines and quinolizidines

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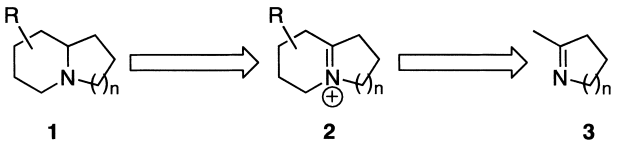
Abstract—A very short synthesis of indolizidines, quinolizidines and some higher homologues was developed by alkylation of 2-methyl-1-pyrroline or 6-methyl-2,3,4,5-tetrahydropyridine with 1,3- or 1,4-dihaloalkanes, followed by reduction of the intermediate iminium salts, resulting in the desired 1-azabicyclo[*m.n*.0]alkanes in good yields.

1. Introduction

In the past three decades, a whole range of biological active alkaloids has been isolated from amphibian skin. Especially frogs from the Dendrobatidae,[1] Mantellinae,[2] Myobatrachidae and Bufonidae[3] families contain a wide variety of lipophilic skin alkaloids. These compounds consist mainly of bicyclic and also tricyclic structures bearing a single nitrogen atom. Among others, pyrrolizidines, di- and trisubstituted indolizidines and disubstituted quinolizidines have been characterized. Many of these compounds, e.g. pumiliotoxins, have caught the attention of the medical world due to their potential physiological activities.[4–7] Furthermore, interesting alkaloids were isolated from plants, e.g. ajmaline found in the roots of *Rauwolfia serpentina*,[8] and also from micro-organisms, e.g. the broad-spectrum antibiotic lemonomycin produced by *Streptomyces candidus*.[9]

The synthetic strategies towards 1-azabicyclo[*m.n*.0]-alkanes are in general either long and inefficient, or rather expensive due to the use of some less common reagents. Many synthetic designs presented in the past made use of a radical[10–15] or a reductive cyclization method.[16–19] Also cycloaddition[20–22] and metathesis reactions[23,24] have been explored. One remarkable example of a bicyclic enamine synthesis is known in the literature, in which deprotonation of 6-methyl-2,3,4,5-tetrahydropyridine and alkylation with 1-chloro-3-iodopropane resulted in the corresponding bicyclic enamine.[25,26] However, in this case, the intermediate iminium salt was not trapped but in situ converted into the enamine by treatment with base. Finally, aza-annulation of cyclic enamines, stabilized by electron-withdrawing groups, with acryloyl chloride was developed as a synthesis of 1-azabicyclo[4.3.1]nonanes.[27]

In the present report, a very short, reliable and efficient synthesis of alkyl substituted indolizidines, quinolizidines and also larger bicyclic ring systems is presented. The general strategy consists of deprotonation at the α-position of a cyclic imine, such as 2-methyl-1-pyrroline and 6-methyl-2,3,4,5-tetrahydropyridine, followed by reaction with a ω,ω′-dihaloalkane. The resulting bicyclic iminium salt is then further transformed into the desired 1-azabicyclo[*m.n*.0]alkane by reduction (Scheme 1).



Scheme 1.

The numbering and nomenclature of indolizidines and quinolizidines was performed according to the literature (Fig. 1).[28] In substituted indolizidines and quinolizidines the descriptors *cis* and *trans* are related to the relative position of the hydrogen atom on the carbon atom 8a and 9a (for indolizidines and quinolizidines, respectively) with respect to the hydrogen atom on the substituted carbon atom.

Figure 1.

Keywords: iminium salts; reduction; indolizidines.

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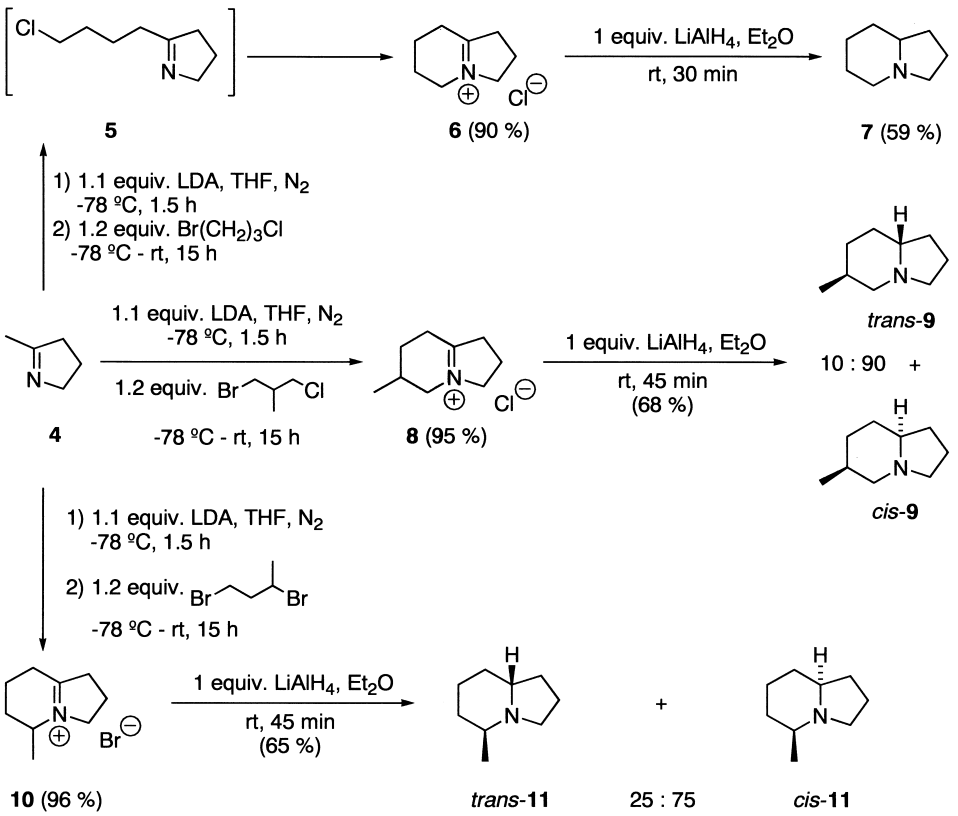


Scheme 2.

2. Results and discussion

Kinetic deprotonation of 2-methyl-1-pyrroline **4** with LDA at −78°C and consecutive reaction with 1-bromo-3-chloropropane resulted in a bicyclic iminium salt **6**, which was characterized spectroscopically (^{1}H NMR, ^{13}C NMR, IR). This stable salt was formed after work-up, upon prolonged evaporation of the solvent. Apparently the intermediate 2-(4-chlorobutyl)-1-pyrroline **5**, which was not isolated, is transformed quickly into the indolizidinium salt. After reduction of this salt with lithium aluminum hydride in diethyl ether, δ-coniceïne **7** was isolated (Scheme 2). This bicyclic compound is a frequent target in indolizidine chemistry.[29–49]

The outlined method is also applicable for the preparation of methyl substituted indolizidines. For this purpose, the alkylation was performed with 1-bromo-3-chloro-2-methylpropane and 1,3-dibromobutane. In both cases an intermediate iminium salt was isolated, which was reduced with $LiAlH_4$. In this way two diastereomeric isomers were formed, in a ratio of 10:90 for *trans*- and *cis*-6-methylindolizidine **9** and 25:75 for *trans*- and *cis*-5-methylindolizidine **11**, as determined by gas chromatography. These isomers could not be separated by flash chromatograpy (silica gel). Fortunately, analytical pure samples of

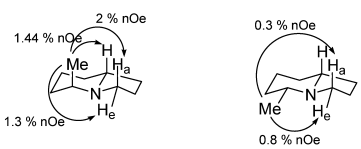


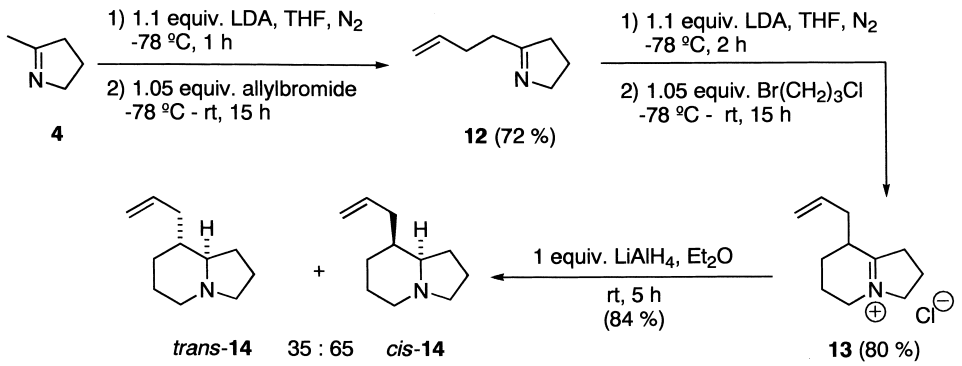
Figure 2.

cis- and *trans*-5-methylindolizidine **11** could be obtained by means of preparative gas chromatography (Scheme 2).

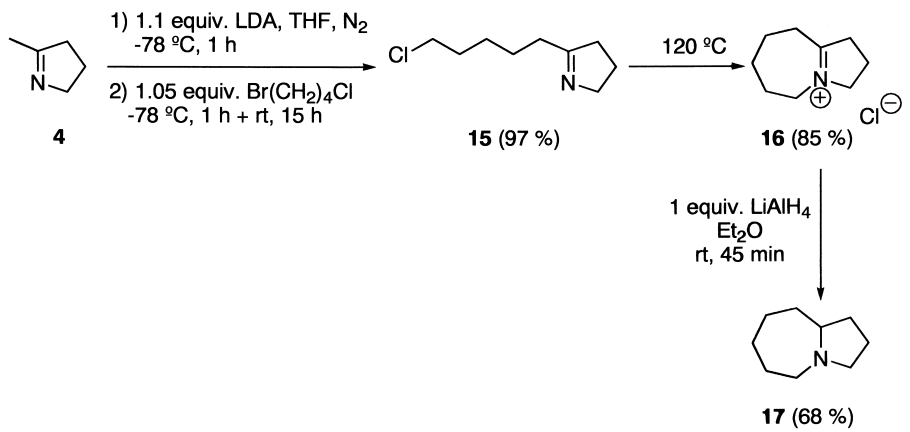
The relative stereochemistry of indolizidine **11** was unequivocally determined using nOe experiments (Fig. 2). In the infrared spectra the typical 'Bohlmann bands' appeared at 2770 and 2795 cm^{-1} for the *cis*- and *trans*-isomer, respectively, indicating that the bicyclic structures were *trans*-fused.[50–52] The appearance of a triplet×doublet (at 3.24 and 2.81 ppm for *cis*- ($3H_a$) and *trans*-**11** ($3H_e$), respectively) and a quadruplet (at 1.97 and 2.54 ppm for *cis*-($3H_e$) and *trans*-**11** ($3H_a$), respectively) in ^{1}H NMR ($CDCl_3$) also indicates a *trans*-fused system, in accordance with the literature.[53] The reported data of *cis*- and *trans*-5-methylindolizidine **11**, prepared from *trans*-5-cyanoindolizidine, correspond well with the data obtained here.[54]

The synthesis of 8-substituted indolizidines was realized starting from 2-methyl-1-pyrroline **4** by two consecutive alkylations. The first time allylbromide was used as an electrophile, resulting in 2-(3-butenyl)-1-pyrroline **12**. After a second deprotonation with LDA, followed by reaction with 1-bromo-3-chloropropane, a salt was formed during work-up. Spectral analysis confirmed the structure of this 8-allylindolizidinium chloride **13**. Hydride reduction gave rise to two diastereomers *trans*-**14** and *cis*-**14**, in a ratio of 35:65, which could be separated by preparative gas chromatography (Scheme 3).

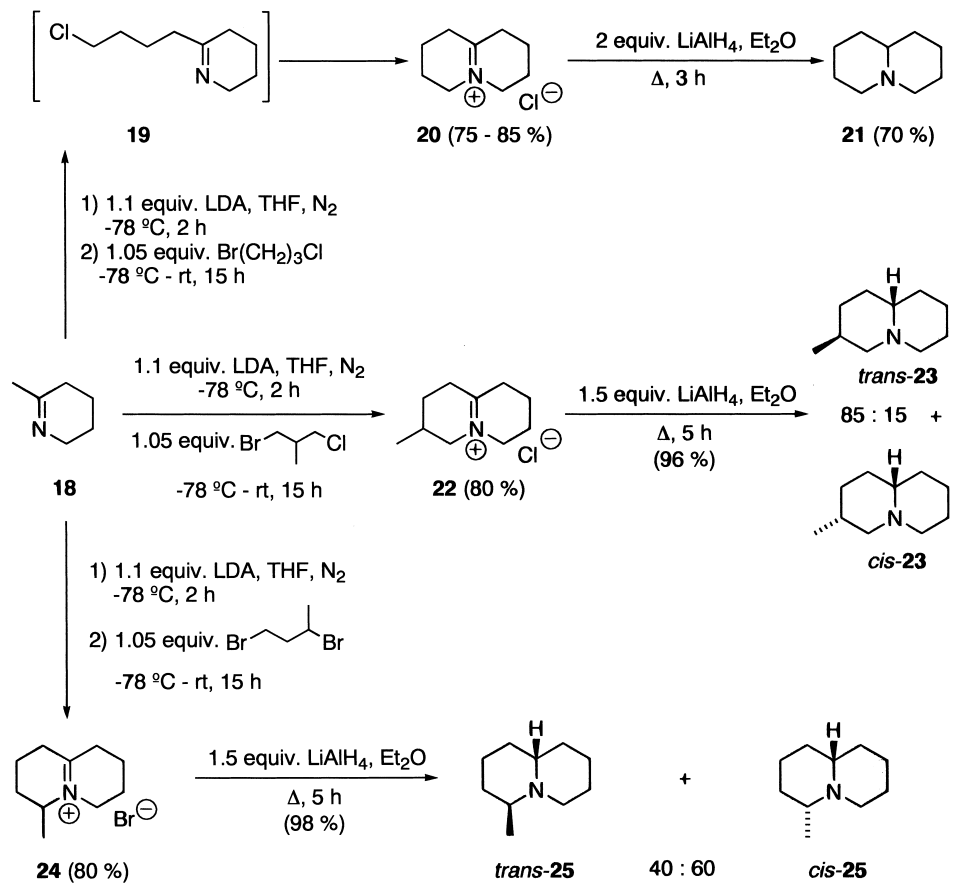
Besides substituted indolizidines also larger ring systems become accessible by variation of the alkylating reagent, as illustrated by using 1-bromo-4-chlorobutane. In this case the intermediate 2-(5-chloropentyl)-1-pyrroline **15** was



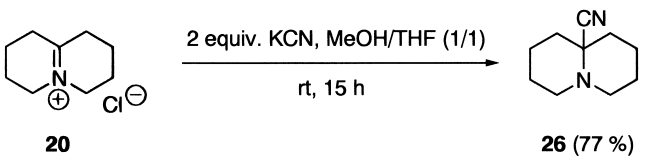
Scheme 3.



Scheme 4.



Scheme 5.



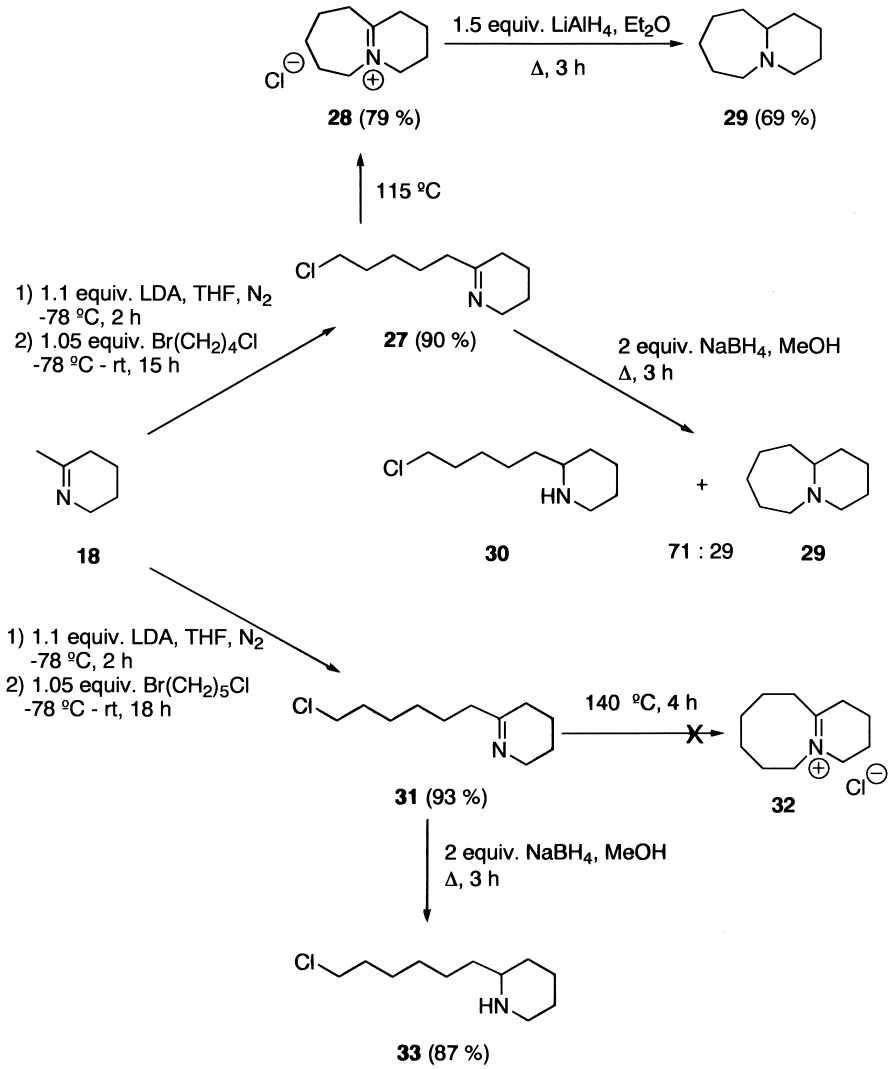
Scheme 6.

isolated, which showed to be remarkably stable. Attempted distillation of this 1-substituted pyrroline (120°C/0.05 mm Hg) resulted in an iminium salt **16**, which was reduced to the desired 1-azabicyclo[5.3.0]decane **17** (Scheme 4). This azabicyclic skeleton is found as a structural unit in the alkaloids stemoamide and stenine, isolated from the roots of *Stemona tuberosa*.[55]

Extension of this general method towards the synthesis of quinolizidines was performed using 6-methyl-2,3,4,5-tetrahydropyridine **18**. This cyclic imine was prepared from 2-methylpiperidine according to a known procedure.[56] Alkylation with 1-bromo-3-chloropropane and reduction of the obtained quinolizidinium salt **20** with $LiAlH_4$ resulted in 1-azabicyclo[4.4.0]decane **21** (Scheme 5). When the quinolizidinium salt **20** was reacted with potassium cyanide in methanol/THF (1:1), the bicyclic α-aminonitril 6-cyano-1-azabicyclo[4.4.0]decane **26** was isolated, which can be useful for further elaboration (Scheme 6).

Methyl-substituted quinolizidines were synthesized using 1-bromo-3-chloro-2-methylpropane and 1,3-dibromobutane, after deprotonation of 6-methyl-2,3,4,5-tetrahydropyridine with LDA. In both cases reduction of the quinolizidinium salts yielded two diastereomers, in a ratio of 85:15 for *trans*-**23** and *cis*-**23** and 40:60 for *trans*-**25** and *cis*-**25**. By means of preparative gas chromatography, analytical pure samples of *cis*-**23** and *trans*-**25** were isolated (Scheme 5).

In the literature, spectrometric data (^1H NMR and ^{13}C NMR) of the methyl-doublet of **23** are reported.[28,57] For *cis*- and *trans*-3-methylquinolizidine **23** the spectrometric data of the methyl-doublet both were in accordance with the literature. For *cis*- and *trans*-4-methylquinolizidine **25**, however, the reported coupling constants[28,57] were the opposite of the experimentally obtained data; the reported value for the *cis*-isomer corresponds with the data obtained here for the *trans*-isomer and vice versa. Infrared spectroscopy indicated that all quinolizidines were



Scheme 7.

trans-fused,[28] as can be derived from the following absorbances: 2799 cm^{-1} and 2763 cm^{-1} for *cis*- and *trans*-3-methylquinolizidine **23**; 2784 and 2745 cm^{-1} for *cis*- and *trans*-4-methylquinolizidine **25** and 2817 and 2768 cm^{-1} for 6-cyano-1-azabicyclo[4.4.0]decane **26**.

Although bicyclic structures with a seven-membered ring annelated to a six-membered ring frequently occur in alkaloids, for example in lemonomycin,[9] very little synthetic strategies towards these alkaloids are known. In one article a rather long synthesis of such a type of iminium salt is reported starting from a N-functionalised δ-lactam, in a low yield.[58] The alkylation of 6-methyl-2,3,4,5-tetrahydropyridine **18** with 1-bromo-4-chlorobutane offers an excellent alternative. The intermediate 6-(5-chloropentyl)-2,3,4,5-tetrahydropyridine **27** was isolated in 90% yield. After heating this imine at 115°C for 4 h (neat), an iminium salt **28** was obtained, which was transformed into 1-azabicyclo[5.4.0]undecane **29** by reduction with $LiAlH_4$. Treatment of the intermediate 6-substituted tetrahydropyridine **27** with hydride resulted in a mixture of 29% 1-azabicyclo[5.4.0]undecane **29** and 71% 2-(5-chloropentyl)piperidine **30** (Scheme 7). This proves that the preparation of the bicyclic amine is far more efficient using the iminium salt method instead of direct reductive cyclization of a ω-chloroimine. Finally, 1-bromo-5-chloropentane was used as an electrophile. The resulting ω-chloroimine **31** was isolated and heated to 140°C for 4 h (neat). Although the product was partially decomposed, a signal in ^{13}C NMR (210 ppm (C=N^+); DMSO) indicated the presence of the desired iminium salt **32**. Direct reduction of the alkylated tetrahydropyridine yielded the corresponding piperidine derivative **33** exclusively, without any cyclization to the bicyclic amine (Scheme 7).

3. Experimental

^1H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer (VARIAN MAT 112, 70 eV) using a GC-MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). IR spectra were measured with a Perkin–Elmer 1310 spectrophotometer or a Spectrum One FT-IR. Dichloromethane was dried over calcium hydride. Methanol was dried by distillation over magnesium, while diethyl ether and THF were dried by distillation over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

3.1. General procedure for the alkylation of 2-methyl-1-pyrroline 4 and 6-methyl-2,3,4,5-tetrahydropyridine 18

As an example, the synthesis of 2-(3-butenyl)-1-pyrroline **12** is described. To a solution of 2.23 g (0.022 mol) diisopropylamine in 20 mL of dry THF at 0°C was added slowly via a septum 8.8 mL of n-butyllithium (0.022 mol, 2.5 M in hexane) under nitrogen atmosphere. After 5 minutes this solution was cooled to −78°C and 1.66 g (0.02 mol) of 2-methyl-1-pyrroline **4**, dissolved in 20 mL of dry THF, was added dropwise. The reaction mixture was then stirred at −78°C for 2 h. Finally a solution of 2.56 g (0.021 mol) of allylbromide in 20 mL of dry THF was added slowly, after which the reaction mixture was stirred for 16 h at room temperature. Work-up was carried out by pouring the reaction mixture in 75 mL of a 0.5 M sodium hydroxide solution, followed by extraction with ether (2×75 mL, 1×50 mL). After drying of the organic phase with K_2CO_3 and filtration of the drying agent, the solvent was removed in vacuo. Distillation (69–77°C/40 mm Hg) yielded 1.77 g (72%) of compound **12** as a light-yellow liquid. Compounds **6**, **8**, **10**, **13**, **20**, **22** and **24** were obtained as solids upon in vacuo evaporation of the ethereal extract, followed by removal of final traces of solvent under high vacuum (0.01 mm Hg). Because of the extreme hygroscopicity of these salts, it was irrelevant to measure the melting points (broad melting point range). The purity of these salts was sufficiently high (>95%) to use them as such in the next step.

3.1.1. 2-(3-Butenyl)-1-pyrroline 12. ^1H NMR (270 MHz, $CDCl_3$): δ 1.86 (2H, quint, J=7.84 Hz, CH_2CH_2N); 2.26–2.52 (6H, m, CH_2(CH_2)$_2$N and (CH_2)$_2$CH=CH_2); 3.72–3.85 (2H, m, CH_2N); 4.99 (1H, d×d, J=10.23, 0.66 Hz, CH=(HCH_{cis})); 5.04 (1H, d, J=17.16 Hz, geminal coupling not visible, CH=(H_{trans}CH)); 5.79–5.93 (1H, m, CH=CH$_2$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.55 (*C*H$_2$CH$_2$N); 30.40 and 32.99 ((*C*H$_2$)$_2$CH=CH$_2$); 37.29 (*C*H$_2$(CH$_2$)$_2$N); 60.77 (CH$_2$N); 114.95 (CH=*C*H$_2$); 137.73 (*C*H=CH$_2$); 177.66 (C=N). IR (NaCl, cm^{-1}): 1639 ($\nu_{C=N}$); 3077 ($\nu_{C=HCH}$). MS (70 eV): m/z (%): 123 (M^+, 24); 122 (100); 120 (8); 108 (26); 96 (14); 95 (14); 94 (19); 83 (6); 82 (8); 80 (7); 68 (5); 67 (16); 55 (11); 54 (12). Anal. calcd for $C_8H_{13}N$: C 77.99%; H 10.64%; N 11.37%. Found: C 77.85%; H 10.86%; N 11.29%.

3.1.2. 2,3,5,6,7,8-Hexahydro-1*H*-indolizinylium chloride 6. Yield 90%, yellow–orange salt. ^1H NMR (270 MHz, $CDCl_3$): δ 2.00–2.15 (4H, m, CH$_2$(CH_2)$_2$CH$_2$N$^+$); 2.34 (2H, quintet, J=7.90 Hz, CH$_2$CH_2CH$_2$C=N$^+$); 2.95 (2H, broad s, CH$_2$C=N$^+$); 3.36 (2H, t, J=7.92 Hz, CH$_2$C=N$^+$); 3.84 (2H, broad s, CH$_2$N$^+$); 4.30 (2 H, t, J=7.60 Hz, CH$_2$N$^+$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.74 and 19.37 (CH$_2$(*C*H$_2$)$_2$CH$_2$N$^+$); 17.11 (CH$_2$*C*H$_2$CH$_2$C=N$^+$); 26.97 (*C*H$_2$C=N$^+$); 38.04 (*C*H$_2$C=N$^+$); 47.21 (CH$_2$N$^+$); 59.79 (CH$_2$N$^+$); 189.24 (C=N$^+$). IR (NaCl, cm^{-1}): 1650 ($\nu_{C=N^+}$).

3.1.3. 2,3,5,6,7,8-Hexahydro-6-methyl-1*H*-indolizinylium chloride 8. Yield 95%, yellow–orange salt. ^1H NMR (270 MHz, $CDCl_3$): δ 1.72 (3H, d, J=6.27 Hz, Me); 1.70–1.92 (6H, m, CH_2CH$_2$N$^+$ and (CH_2)$_2$CH$_2$C=N$^+$); 2.28–2.53 (4H, m, 2×CH$_2$C=N$^+$); 2.68–2.84 (2H, m, CH$_2$N$^+$); 3.06–3.22 (1H, m, MeC*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.29; 18.06; 28.27 (*C*H$_2$CH$_2$N$^+$ and (*C*H$_2$)$_2$-CH$_2$C=N$^+$); 18.42 (Me); 28.73 (*C*H$_2$C=N$^+$); 39.78 (*C*H$_2$C=N$^+$); 54.93 (CH$_2$N$^+$); 58.58 (Me*C*H); 191.25 (C=N$^+$). IR (NaCl, cm^{-1}): 1672 ($\nu_{C=N^+}$).

3.1.4. 2,3,5,6,7,8-Hexahydro-5-methyl-1*H*-indolizinylium bromide 10. Yield 96%, yellow–orange salt. ^1H NMR (270 MHz, $CDCl_3$): δ 1.09 (3H, d, J=6.93 Hz, *Me*CH); 1.47–1.67 (1H, m); 1.75–1.92 (4H, m);

2.31–2.41 (2H, m); 2.33–2.52 (2H, m); 3.44–3.53 (2H, m, CH_2N^+); 3.72–3.84 (2H, m, CH_2N^+). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.01 (Me); 18.38; 25.00; 26.76; 28.07; 38.72 (4×CH_2 and CH); 54.03 and 60.65 (2×CH_2N^+). IR (NaCl, cm^{-1}): 1685 ($\nu_{C=N^+}$).

3.1.5. 2,3,5,6,7,8-Hexahydro-8-(2-propenyl)-1*H*-indolizinylium chloride 13. Yield 80%, yellow–orange salt. ^1H NMR (270 MHz, $CDCl_3$): δ 1.63–1.79 (1H, m, CH(*H*CH)$(CH_2)_2N^+$); 1.95–2.18 (3H, m, CH(HC*H*)CH_2-CH_2N^+); 1.21–2.50 (3H, m, $CH_2CH_2CH_2N^+$ and CH(*H*CH)CH=CH_2); 2.58–2.71 (1H, m, CH(HC*H*)CH=CH_2); 3.06–3.21 (1H, m, C*H*CH_2CH=CH_2); 3.29–3.48 (2H, m, C$H_2(CH_2)_2N^+$); 3.80–3.94 (2H, m, CH$(CH_2)_2$-CH_2N^+); 4.36 (2H, t, J=7.59 Hz, $(CH_2)_2CH_2N^+$); 5.17 (1H, d×d, J=9.08, 1.22 Hz, CH=(HCH_{cis})); 5.19 (1H, d×d, J=16.50, 1.22 Hz, CH=(H_{trans}CH)); 5.69–5.86 (1H, m, C*H*=CH_2). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.20 (CH_2-*C*$H_2CH_2N^+$); 19.26 ($CHCH_2$*C*$H_2CH_2N^+$); 22.21 (CH*C*H_2-$(CH_2)_2N^+$); 35.60 (*C*H_2CH=CH_2); 37.75 (*C*H_2C=N^+); 37.90 (*C*HC=N^+); 48.73 ($CH(CH_2)_2$*C*H_2N^+); 61.26 ($(CH_2)_2$*C*H_2N^+); 119.01 (CH=*C*H_2); 133.80 (*C*H=CH_2); 192.16 (C=N^+). IR (NaCl, cm^{-1}): 1679 ($\nu_{C=N^+}$); 3079 ($\nu_{=C-H}$).

3.1.6. 2-(5-Chloropentyl)-1-pyrroline 15. Yield 97%, colorless liquid. ^1H NMR (270 MHz, $CDCl_3$): δ 1.42–1.58 (2H, m, $Cl(CH_2)_2CH_2$); 1.59–1.70 (2H, m, $ClCH_2$-CH_2); 1.75–1.92 (4H, m, CH_2CH_2N and $Cl(CH_2)_3CH_2$); 2.35 (2H, t, J=7.25 Hz, CH_2C=N); 2.47 (2H, t, J=7.40 Hz, CH_2C=N); 3.54 (2H, t, J=6.80 Hz, CH_2Cl); 3.80 (2H, t×t, J=7.26. 1.65 Hz, CH_2N). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.53 ($Cl(CH_2)_3$*C*H_2); 25.59 ($ClCH_2$*C*H_2); 26.72 ($Cl(CH_2)_2$*C*H_2); 32.38 (*C*H_2CH_2N); 33.51 (*C*H_2C=N); 37.29 (*C*H_2C=N); 44.87 (CH_2Cl); 60.68 (CH_2N); 178.18 (C=N). IR (NaCl, cm^{-1}): 1640 ($\nu_{C=N}$). MS (70 eV): *m*/*z* (%): no M^+; 138 (M^+-Cl, 10); 122 (5); 110 (11); 108 (3); 96 (18); 94 (2); 84 (9); 83 (100); 82 (26); 81 (7); 69 (4); 68 (6); 67 (5); 55 (16); 54 (7); 44 (2); 43 (2); 42 (16); 41 (26). Anal. calcd for $C_9H_{16}ClN$: C 62.24%; H 9.29%; N 8.06%. Found: C 62.08%; H 9.37%; N 8.16%.

3.1.7. 1,2,3,5,6,7,8,9-Octahydro-1*H*-pyrrolo[1,2-*a*]azepinylium chloride 16. By heating of compound **15** at 120°C (oil bath), the initial liquid solidified after 1 h. The solid was washed with dry diethyl ether in order to remove the impurities and the yellow-orange residue was placed under high vacuum (0.01 mm Hg) in order to remove trace amounts of solvent. Yield 85%. ^1H NMR (270 MHz, $CDCl_3$): δ 1.7–2.00 (6H, m, $(CH_2)_3CH_2C$=N^+); 2.37 (2H, quintet, J=7.92 Hz, C$H_2CH_2N^+$); 3.08–3.12 (2H, m, CH_2C=N^+); 3.51 (2H, t, J=7.30 Hz, CH_2CH_2C=N^+); 4.10–4.13 (2H, m, CH_2N^+); 4.49 (2H, t, J=7.92 Hz, $CH_2CH_2N^+$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.14 (CH_2-*C*H_2CH_2C=N^+); 21.40; 24.19 and 28.79 ((*C*$H_2)_3CH_2$-C=N^+); 31.23 (*C*H_2C=N^+); 42.23 ($(CH_2)_4CH_2C$=N^+); 52.88 (CH_2N^+); 63.93 ($(CH_2)_4$*C*H_2N^+). IR (NaCl, cm^{-1}): 1675 ($\nu_{C=N^+}$).

3.1.8. 1,2,3,4,6,7,8,9-Octahydro-quinolizinylium chloride 20. Yield 85%, yellow–orange salt. ^1H NMR (270 MHz, $CDCl_3$): δ 1.88–1.97 (4H, m, 2×CH_2CH_2C=N^+); 2.04–2.12 (4H, m, 2×C$H_2CH_2N^+$=C); 2.79–3.03 (4H, m, 2×CH_2C=N^+); 3.79–3.94 (4H, m, 2×CH_2N^+). ^{13}C NMR (68 MHz, $CDCl_3$): δ 16.86 (2×*C*H_2CH_2C=N^+); 20.74 (2×*C*$H_2CH_2N^+$); 33.06 (2×*C*H_2C=N^+); 54.30 (2×CH_2N^+); 187.02 (C=N^+). IR (NaCl, cm^{-1}): 1686 ($\nu_{C=N^+}$).

3.1.9. 1,2,3,4,6,7,8,9-Octahydro-3-methylquinolizinylium chloride 22. Yield 80%, yellow–orange salt. ^1H NMR (270 MHz, $CDCl_3$): δ 1.06 (3H, d, J=6.60 Hz, CH_3); 1.57–1.74 (2H, m, CHCH_2CH_2C=N^+); 1.83–2.01 (2H, m, CH_2CH_2C=N^+); 2.03–2.13 (2H, m, C$H_2(CH_2)_2C$=N^+); 2.22–2.48 (1H, m, CH); 2.86–3.02 (4H, m, 2×CH_2C=N^+); 3.39–3.53 (1H, m, CH(*H*CH)N^+); 3.68–3.88 (3H, m, CH(HC*H*)N^+ and $CH_2CH_2N^+$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 16.93 (*C*H_2CH_2C=N^+); 18.17 (CH_3); 20.75 (*C*$H_2(CH_2)_2C$=N^+); 25.05 (*C*H_2CH_2C=N^+); 26.81 (CH); 32.96 and 33.67 (2×*C*H_2C=N^+); 54.39 ($CH_2CH_2N^+$); 60.38 (CH*C*H_2N^+); 186.95 (C=N^+). IR (NaCl, cm^{-1}): 1688 ($\nu_{C=N^+}$).

3.1.10. 1,2,3,4,6,7,8,9-Octahydro-4-methyl-quinolizinylium bromide 24. Yield 80%, yellow–orange salt. ^1H NMR (270 MHz, $CDCl_3$): δ 1.54 (3H, d, J=6.93 Hz, CH_3); 1.76–2.08 (6H, m, CH_2(*H*CH)CH(Me)N^+ and CH_2-(*H*CH)CH_2N^+); 2.09–2.22 (1H, m, (HC*H*)CH_2N^+); 2.31–2.46 (1H, m, (HC*H*)CH(Me)N^+); 2.98 (4H, broad s, 2×CH_2C=N^+); 3.88 (2H, broad s, CH_2N^+); 4.04 (1H, broad s, CH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.78 (*C*$H_2CH_2CHN^+$); 17.09 (*C*$H_2(CH_2)_2N^+$); 18.60 (CH_3); 21.11 (*C*$H_2CH_2N^+$); 27.53 (*C*H_2CH(Me)N^+); 33.64 and 33.69 (2×*C*H_2C=N^+); 52.69 (C=N^+*C*H_2); 59.89 (CH); 187.90 (C=N^+). IR (NaCl, cm^{-1}): 1672 ($\nu_{C=N^+}$).

3.1.11. 6-(5-Chloropentyl)-2,3,4,5-tetrahydropyridine 27. Yield 90%, colorless liquid. ^1H NMR (270 MHz, $CDCl_3$): δ 1.41–1.72 (8H, m, $ClCH_2(CH_2)_2$ and $NCH_2(CH_2)_2$); 1.79–1.86 (2H, quint, J=6.93 Hz, $Cl(CH_2)_3$-CH_2); 2.06–2.20 (4H, m, 2×CH_2C=N); 3.51–3.60 (4H, m, CH_2Cl and CH_2N). ^{13}C NMR (68 MHz, internal standard $CDCl_3$): δ 19.34; 21.67; 25.30 and 26.42 ($NCH_2(CH_2)_2$ and $ClCH_2(CH_2)_2$); 28.93 (*C*H_2C=N); 32.18 ($Cl(CH_2)_3CH_2$); 40.43 (*C*H_2C=N); 44.71 (CH_2Cl); 48.92 (CH_2N); 170.87 (C=N). IR (NaCl, cm^{-1}): 1662 ($\nu_{C=N}$). MS (70 eV): *m*/*z* (%): 187 (M^+, 1); 152 (17); 138 (2); 124 (8); 110 (15); 97 (100); 96 (26); 82 (7); 70 (11); 55 (10). Anal. calcd for $C_{10}H_{18}ClN$: C 63.99%; H 9.67%; N 7.46%. Found: C 64.12%; H 9.79%; N 7.37%.

3.1.12. 2,3,4,6,7,8,9,10-Octahydro-1*H*-pyrido[1,2-*a*]azepinylium chloride 28. By heating compound **27** at 115°C (oil bath) during 1 h a dark solid was obtained, which, after washing with dry diethyl ether, yielded an orange salt, that was further dried under high vacuum (0.01 mm Hg). Yield 79%. ^1H NMR (270 MHz, $CDCl_3$): δ 1.68–1.80 (2H, m, $CH_2CH_2(CH_2)_3N^+$); 1.81–1.99 (6H, m, $CH_2(CH_2)_2CH_2N^+$ and $(CH_2)_2CH_2(CH_2)_2N^+$); 2.00–2.11 (2H, m, $(CH_2)_3$-C$H_2CH_2N^+$); 3.00–3.14 (4H, m, 2×CH_2C=N^+); 3.94–4.04 (2H, m, $(CH_2)_4CH_2N^+$); 4.15–4.25 (2H, m, $(CH_2)_3$-CH_2N^+). ^{13}C NMR (68 MHz, $CDCl_3$): δ 16.84 (*C*$H_2(CH_2)_3$-N^+); 20.92 ($(CH_2)_3CH_2CH_2N^+$); 21.51 ($(CH_2)_2CH_2(CH_2)_2$-N^+); 23.90 ($(CH_2)_2CH_2CH_2N^+$); 28.75 ($CH_2CH_2(CH_2)_2$-N^+); 35.09 (*C*$H_2(CH_2)_3N^+$); 37.39 (*C*$H_2(CH_2)_4N^+$); 55.56 ($(CH_2)_4CH_2N^+$); 59.71 ($(CH_2)_3CH_2N^+$); 193.56 (C=N^+). IR (NaCl, cm^{-1}): 1675 ($\nu_{C=N^+}$).

3.1.13. 6-(6-Chlorohexyl)-2,3,4,5-tetrahydropyridine 31. Yield 93%, colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28–1.61 (8H, m, $Cl(CH_2)_2(CH_2)_3$ and NCH_2CH_2); 1.62–1.73 (2H, m, $N(CH_2)_2CH_2$); 1.78 (2H, quint, J=7.42 Hz, $ClCH_2CH_2$); 2.07–2.19 (4H, m, 2×CH_2C=N); 3.49–3.59 (4H, m, $ClCH_2$ and NCH_2). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.57; 21.89; 26.20 and 28.68 ($NCH_2(CH_2)_2$ and $Cl(CH_2)_3(CH_2)_2$); 26.70 ($Cl(CH_2)_2CH_2$); 29.09 (CH_2C=N); 32.49 ($ClCH_2CH_2$); 40.83 (CH_2C=N); 45.07 ($ClCH_2$); 49.09 (NCH_2); 171.19 (C=N). IR (NaCl, cm^{-1}): 1663 ($\nu_{C=N}$). MS (70 eV): *m/z* (%): 201/3 (M^+, 3); 166 (17); 152 (2); 138 (3); 124 (8); 110 (19); 98 (12); 97 (100); 96 (23); 82 (7); 69 (6); 55 (8). Purity: 99% (GC). Anal. calcd for $C_{11}H_{20}ClN$: C 65.49%; H 9.99%; N 6.94%. Found: C 65.62%; H 10.08%; N 7.03%.

3.2. General procedure for the reduction of iminium salts

As an example the reduction of 1,2,3,4,6,7,8,9-octahydroquinolizinylium chloride **20** is given. To 1.74 g (0.01 mol) of quinolizidinium chloride **20**, suspended in 20 mL of dry diethyl ether, was added slowly at 0°C 0.76 g (0.02 mol) of $LiAlH_4$. After heating 3 h under reflux water (3 mL) was added at 0°C in order to neutralize the excess of $LiAlH_4$. The mixture was stirred for 10 min after which the grey suspension was filtered over K_2CO_3 and celite. The filter cake was then washed thoroughly with dry ether (3×25 mL). After removal of the solvent in vacuo, the colorless quinolizidine **21** was obtained in 70% yield (purity >97%, GC).

3.2.1. 1-Azabicyclo[4.4.0]decane 21. Spectral data are in accordance with the literature, but are annotated in more detail.[17] ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.12–1.36 (4H, m, 2×$NCH_2CH_2CH_2$); 1.44–1.81 (9H, m, 2×NCH_2CH_2, 2×$CHCH_2$, NCH); 1.88–2.06 (2H, m, 2×NHC(H)); 2.72–2.84 (2H, m, 2×NHC(H)). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.64 (2×$CH_2CH_2CH_2$); 25.89 (2×NCH_2CH_2); 33.46 (2×CH_2CH); 56.66 (2×CH_2N); 63.00 (CHN). IR (NaCl, cm^{-1}): ν=3359. MS (70 eV): *m/z* (%): 139 (M^+, 48); 138 (100); 124 (12); 111 (15); 110 (43); 98 (10); 97 (68); 96 (16); 83 (57); 82 (16); 69 (7); 56 (5); 55 (22); 54 (6); 42 (7); 41 (11).

3.2.2. δ-Coniceïne 7. Yield 59%, colorless liquid. The spectrometric data of indolizidine are in accordance with the literature data.[36,47] ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.15–1.33 (2H, m); 1.34–1.52 (1H, m); 1.53–1.88 (8H, m); 1.90–2.10 (2H, m); 3.00–3.11 (2H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.70; 24.64; 25.62; 30.58; 31.21 (5×CH_2); 53.15 and 54.38 (2×CH_2N); 64.42 (CHN).

3.2.3. 6-Methylindolizidine 9. Yield 68%, colorless liquid. Bp (mixture of *cis* and *trans*) 61–68°C/12 mm Hg. An analytical pure sample of one diastereomer could be obtained by preparative gas chromatography (temperature column 110°C, *cis*/*trans* 10/90 or vice versa). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (3H, d, J=6.27 Hz, *Me*CH); 1.14–1.94 (11H, m); 2.04 (1H, q, J=8.91 Hz, (H)C*H*N); 2.99–3.07 (2H, m, 2×(*H*)CHN). Other isomer (recognizable signals): 1.10 (d, J=7.26 Hz, *Me*CH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.55 (Me); 21.11; 30.22; 30.85; 31.27; 33.69 (5×CH_2); 54.09 (CH_2N); 60.79 (CH_2N); 64.15 (CHN). Other isomer (recognizable signals): 18.80; 20.74; 26.47; 28.54; 30.37; 54.81; 59.12; 65.05. IR (NaCl, cm^{-1}): ν_{max}=2850; 2730; 1615; 1425; 1360; 1323; 1252; 1105; 998; 807. MS (70 eV): *m/z* (%): 139 (M^+, 45); 138 (100); 124 (17); 111 (34); 110 (27); 97 (16); 96 (20); 84 (13); 83 (40); 82 (12); 70 (19); 69 (17); 68 (9); 55 (14); 43 (9); 41 (25). Anal. calcd for $C_9H_{17}N$: C 77.63%; H 12.31%; N 10.06%. Found: C 77.51%; H 12.39%; N 10.13%.

3.2.4. *cis*- and *trans*-5-Methylindolizidine 11. Yield 68%, colorless liquid. Bp (mixture of *cis* and *trans*) 62–67°C/13 mm Hg. Both diastereomers were separated by preparative gas chromatography (temperature column 110°C, *cis*/*trans* 75/25). Spectral data are in accordance with the literature.[54] *cis*-**11**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.11 (3H, d, J=6.27 Hz, Me); 1.17–1.87 (10H, m); 1.80–1.85 (1H, overlap, m, CHN); 1.97 (1H, q, J=8.91 Hz, (H_e)CH_aN); 1.96–2.03 (1H, overlap, m, MeC*H*); 3.24 (1H, t×d, J=8.58, 1.98 Hz, (H_e)CH_aN). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.23; 24.73; 30.57; 31.05; 34.30 (5×CH_2); 21.13 (Me); 51.77 (CH_2N); 58.92 (Me*C*H); 64.80 (CHN). IR (NaCl, cm^{-1}): ν_{max}=2930; 2770; 2700; 2593; 1451; 1370; 1329; 1318; 1230; 1182; 1131; 1070. MS (70 eV): *m/z* (%): 139 (M^+, 22); 138 (17); 124 (100); 111 (15); 110 (20); 96 (35); 70 (17); 49 (20); 42 (20); 41 (29); 40 (84). *trans*-**11**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.97 (3H, d, J=6.60 Hz, Me); 1.09–1.86 (10H, m); 2.38–2.49 (1H, m, CHN); 2.54 (1H, q, J=8.8 Hz, (H_e)CH_aN); 2.81 (1H, t×d, J=8.7, 2.97 Hz, (H_e)CH_aN); 3.19–3.30 (1H, m, MeC*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 9.28 (Me); 19.32; 20.81; 30.55; 31.46; 31.57 (5×CH_2); 49.15 (CH_2N); 49.97 (Me*C*H); 54.52 (CHN). IR (NaCl, cm^{-1}): ν_{max}=2925; 2793; 1460; 1370; 1339; 1262; 1172; 1151; 1092; 1077; 1022; 992; 840. MS (70 eV): *m/z* (%): 139 (M^+, 22); 138 (16); 125 (14); 96 (20); 88 (20); 86 (43); 84 (64); 51 (20); 49 (76); 44 (15); 41 (24); 40 (100).

3.2.5. *cis*- and *trans*-8-(2-Propenyl)indolizidine 14. Yield 84% (mixture of *cis* and *trans*), yellow liquid. Both diastereomers were separated by preparative gas chromatography (temperature column 110°C, *cis*/*trans* 35/65 or vice versa). *cis*- or *trans*-**14**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.80 (1H, q×d, J=12.26, 5.07 Hz, NCH(*H*CH) or NCHCH(*H*CH)); 1.16–2.18 (13H, m, N(*H*CH)CH_2-(HC*H*)C*H*(CH_2CH=CH_2) and NC*H*(CH_2)$_2$(*H*CH) or N(*H*CH)(CH_2)$_2$C*H*(CH_2CH=CH_2) and NC*H*(HC*H*)CH_2-(*H*CH)); 2.92–3.03 (2H, m, 2×N(HC*H*)); 4.85–4.97 (2H, m, CH_2=CH); 5.61–5.78 (1H, m, CH_2=C*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.78; 24.78; 28.36; 29.34 and 37.25 ($NCH_2(CH_2)_2CH(CH_2CH$=$CH_2)$ and $NCH_2(CH_2)_2CH$); 40.90 ($N(CH_2)_3CH(CH_2CH$=$CH_2)$); 52.00 and 53.75 (2×NCH_2); 68.37 (NCH); 115.02 (CH_2=CH); 136.06 (CH_2=C*H*). IR (NaCl, cm^{-1}): ν_{max}=3076; 2961; 2929; 2781; 2719. MS (70 eV): *m/z* (%): 165 (M^+, 16); 164 (27); 136 (76); 124 (32); 123 (100); 122 (55); 97 (30); 96 (52); 84 (21); 83 (25); 69 (28). *trans*- or *cis*-**17**: ^{1}H NMR (270 MHz, $CDCl_3$): recognizable signals from a mixture of *cis* and *trans*: δ 2.61–2.68 (m) and 2.81–2.89 (m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.96; 20.31; 24.71; 26.65 and 30.35 ($NCH_2(CH_2)_2CH(CH_2CH$=$CH_2)$ and $NCH_2(CH_2)_2CH$); 34.23 ($N(CH_2)_3CH(CH_2CH$=$CH_2)$); 52.85 and 54.27 (2×NCH_2); 66.22 (NCH); 114.46 (CH_2=CH); 137.73 (CH_2=C*H*). MS (70 eV): *m/z* (%): 165 (M^+, 16); 164

(24); 136 (68); 124 (32); 123 (100); 122 (51); 97 (36); 96 (61); 84 (24); 83 (26); 69 (33). Anal. calcd for $C_{11}H_{19}N$: C 79.94%; H 11.59%; N 8.47%. Found: C 79.77%; H 11.51%; N 8.62%.

3.2.6. 1-Azabicyclo[5.3.0]decane 17. Yield 78%, colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.2–2.1 (12H, m, 6×CH_2); 2.2–2.4 (4H, m, 2×CH_2N); 2.9–3.1 (1H, m, CHN). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.89; 26.01; 26.27; 28.37; 33.60; 35.17 (6×CH_2); 55.63 (CH_2N); 57.88 (CH_2H); 65.39 (CHN). IR (NaCl, cm^{-1}): ν_{max}=2793; 2697; 1417; 1362; 1325; 1280; 1205; 775; 757. MS (70 eV): *m*/*z* (%): 139 (M^+, 33); 138 (25); 124 (8); 111 (10); 110 (40); 97 (39); 96 (100); 84 (15); 83 (61); 82 (15); 70 (12); 69 (12); 67 (6); 56 (6); 55 (26); 54 (8); 42 (18). Anal. calcd for $C_9H_{17}N$: C 77.63%; H 12.31%; N 10.06%. Found: C 77.79%; H 12.45%; N 9.96%.

3.2.7. *cis*- and *trans*-4-Methylquinolizidine 25. Yield 96% (mixture of *cis* and *trans*), yellow liquid. The *trans*-diastereomer was separated by preparative gas chromatography (temperature column 110°C, *cis*/*trans* 15/85). *trans*-**25**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.84 (3H, d, *J*=5.93 Hz, CH_3); 1.17–1.37 and 1.49–1.81 (13H, 2×m, N(*H*CH)C*H*(Me)(CH_2)$_2$C*H*(CH_2)$_3$); 1.89–2.03 (1H, m, N(*H*CH)CH_2); 2.68–2.84 (2H, m, N(HC*H*)CH_2 and N(HC*H*)CH(Me)). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.77 (CH_3); 24.69; 25.86 and 33.35 (N(CH_2)$_2$(*C*H$_2$)CH*C*H$_2$); 31.23 (*C*H(Me)); 33.21 and 33.49 (NCH_2CH(Me)*C*H$_2$ and NCH_2*C*H$_2$); 56.59 (N*C*H$_2$CH$_2$); 62.50 (CHN); 64.46 (N*C*H$_2$CH(Me)). IR (NaCl, cm^{-1}): ν_{max}=2929; 2865; 2853; 2799; 2763; 1456; 1375; 1122. MS (70 eV): *m*/*z* (%): 153 (M^+, 44); 152 (100); 138 (16); 124 (33); 111 (30); 110 (13); 98 (10); 97 (44); 96 (15); 84 (12); 83 (31); 82 (15); 69 (5); 55 (18). Anal. calcd for $C_{10}H_{19}N$: C 78.37%; H 12.50%; N 9.14%. Found: C 78.22%; H 12.61%; N 9.24%. *cis*-**25**: ^{1}H NMR (270 MHz, $CDCl_3$): recognizable signals from a mixture of *cis* and *trans*: δ 1.11 (3H, d, *J*=7.26 Hz, CH_3); 2.09–2.16 (1H, m); 2.50–2.56 (1H, m); 2.63–2.68 (1H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.29 (CH_3); 25.59; 28.41; 28.55; 30.04; 30.94 and 32.85 (NCH_2(*C*H$_2$)$_3$-CH(*C*H$_2$)$_2$*C*H(Me)CH_2); 56.96 (N*C*H$_2$CH(Me)); 61.99 (CHN); 63.43 (N*C*H$_2$CH$_2$). MS (70 eV): *m*/*z* (%): 153 (M^+, 41); 152 (100); 138 (21); 125 (12); 124 (35); 111 (35); 110 (17); 98 (10); 97 (45); 96 (15); 86 (34); 84 (58); 83 (33); 82 (20); 69 (7); 55 (21); 49 (26).

3.2.8. *cis*- and *trans*-3-Methylquinolizidine 23. Yield 97% (mixture of *cis* and *trans*), yellow liquid. The *cis*-diastereomer was separated by preparative gas chromatography (temperature column 110°C, *cis*/*trans* 60/40). *cis*-**23**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.10 (3H, d, *J*=6.27 Hz, CH_3); 1.18–1.82 and 1.87–2.05 (14H, 2×m, NCH(Me)-(CH_2)$_3$C*H*(CH_2)$_3$(*H*CH)); 1.87–2.05 (1H, m, NC*H*(Me)); 3.20–3.31 (1H, m, N(HC*H*)). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.74 (CH_3); 24.53; 24.67; 26.29; 33.84; 34.05 and 35.31 (NCH_2(*C*H$_2$)$_3$ and NCH(Me)(*C*H$_2$)$_3$); 51.77 (CH_2N); 59.07 (N*C*H(Me)); 63.05 (CHN). IR (NaCl, cm^{-1}): ν_{max}=2961; 2928; 2857; 2784; 2745; 1644; 1444. MS (70 eV): *m*/*z* (%): 153 (M^+, 12); 152 (14); 138 (100); 124 (6); 110 (14); 97 (7); 96 (5); 83 (9); 55 (10). Anal. calcd for $C_{10}H_{19}N$: C 78.37%; H 12.50%; N 9.14%. Found: C 78.24%; H 12.58%; N 9.08%. *trans*-**23**: ^{1}H NMR (270 MHz, $CDCl_3$): recognizable signals from a mixture of *cis* and *trans*: δ 1.00 (3H, d, *J*=6.60 Hz, CH_3). MS (70 eV): *m*/*z* (%): 153 (M^+, 13); 152 (11); 138 (100); 124 (5); 110 (12); 97 (7); 96 (5); 83 (7); 55 (7).

3.2.9. 1-Azabicyclo[5.4.0]undecane 29. Yield 69%, yellow liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.17–1.88 (14H, m, NCH_2(CH_2)$_4$CH(CH_2)$_3$CH_2); 1.91–2.02 (1H, m, CH); 2.17–2.28 (1H, m, N(*H*CH)); 2.38–2.52 (1H, m, N(HC*H*)); 2.66–2.76 (1H, m, N(*H*CH)); 2.78–2.87 (1H, m, N(HC*H*)). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.60; 24.94; 26.13; 26.85 and 27.15 (NCH_2(*C*H$_2$)$_3$CH_2CHCH_2(*C*H$_2$)$_2$-CH_2); 34.48 and 35.47 (2×NCH*C*H$_2$); 57.45 and 57.50 (2×NCH_2); 65.66 (CH). IR (NaCl, cm^{-1}): ν_{max}=2934; 2858; 2808; 1445; 908. MS (70 eV): *m*/*z* (%): 153 (M^+, 41); 152 (29); 124 (63); 111 (34); 110 (100); 97 (53); 96 (27); 83 (30); 69 (16); 55 (20). Anal. calcd for $C_{10}H_{19}N$: C 78.37%; H 12.50%; N 9.14%. Found: C 78.57%; H 12.59%; N 9.07%.

3.3. General procedure for the reduction of cyclic imines

As an example, the reduction of imine **27** is described. To a solution of 0.19 g (0.001 mol) of 6-(5-chloropentyl)-2,3,4,5-tetrahydropyridine **27** in 5 mL of methanol was added 0.08 g (0.002 mol) of $NaBH_4$ at 0°C. After heating 4 h at reflux the reaction mixture was poured into 20 mL of 0.5 M NaOH solution. Extraction with diethyl ether (2×30 mL, 1×20 mL), drying with K_2CO_3 and evaporation of the solvent yielded 0.17 g of a colorless liquid in which 71% piperidine **30** and 29% bicyclic amine **29** was present (GC-MS).

3.3.1. 2-(5-Chloropentyl)piperidine 30. Colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.96–1.13 (1H, m, (*H*CH)(CH_2)$_4$Cl); 1.23–1.71 (11H, m, (CH_2)$_3$CH_2N and (HC*H*)(CH_2)$_2$(CH_2)$_2$Cl); 1.77 (2H, quint, *J*=6.85 Hz, CH_2-CH_2Cl); 2.37–2.50 (1H, m, CH); 2.62 (1H, t×d, *J*=11.71, 2.86 Hz, (*H*CH)N); 3.01–3.11 (1H, m, (HC*H*)N); 3.53 (2H, t, *J*=6.77 Hz, CH_2Cl). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.87; 25.16; 26.65; 27.06 and 37.30 ((*C*H$_2$)$_3$CH_2N and CH_2(*C*H$_2$)$_2$(CH_2)$_2$Cl); 32.52 (*C*H$_2$CH$_2$Cl); 32.97 (*C*H$_2$-(CH_2)$_4$Cl); 45.03 (CH_2Cl); 47.22 (CH_2N); 56.75 (CH). IR (NaCl, cm^{-1}): 3276 (ν_{NH}); ν_{max}=2930; 2855; 2797; 1443. MS (70 eV): *m*/*z* (%): 189 (M^+, 1); 154 (3); 153 (3); 125 (4); 110 (7); 86 (14); 84 (100); 57 (5); 56 (7); 55 (5); 51 (5); 49 (16).

3.3.2. 2-(6-Chlorohexyl)piperidine 33. Yield 87%, colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.96–1.70 (14H, m, Cl(CH_2)$_2$(CH_2)$_4$ and CH(CH_2)$_3$CH_2N); 1.77 (2H, quint, *J*=7.09 Hz, ClCH_2CH_2); 2.36–2.48 (1H, m, CHN); 2.62 (1H, t×d, *J*=11.63, 2.86 Hz, (*H*CH)N); 3.01–3.11 (1H, m, (HC*H*)N); 3.53 (2H, t, *J*=6.77 Hz, CH_2Cl); NH invisible. ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.91; 25.73; 26.65; 26.83; 29.09; 32.99 and 37.38 ((*C*H$_2$)$_3$CH_2N and (*C*H$_2$)$_4$(CH_2)$_2$Cl); 32.58 (*C*H$_2$CH$_2$Cl); 45.10 (CH_2Cl); 47.24 (CH_2N); 56.82 (CH). IR (NaCl, cm^{-1}): 2928 (ν_{NH}); ν_{max}=2855; 2797; 2737; 1443; 1328; 1310; 1122. MS (70 eV): *m*/*z* (%): 203/5 (M^+, 5); 168 (3); 140 (2); 112 (2); 85 (17); 84 (100); 56 (12); 49 (6). Purity: 99% (GC).

3.4. Synthesis of quinolizidine-9a-carbonitrile 26

To 0.45 g (26 mmol) of quinolizidinium chloride **20**, dissolved in 10 mL of a 1:1 mixture of methanol:

tetrahydrofuran, was added at room temperature 0.34 g (52 mmol) of potassium cyanide. This mixture was stirred during 15 h at room temperature after which it was poured in 15 mL of water and extracted with diethyl ether (3×20 mL). Drying of the organic phase ($MgSO_4$) and removal of the solvent in vacuo afforded 0.33 g (77%) of compound **26** as a light-yellow liquid.

3.4.1. 6-Cyano-1-azabicyclo[4.4.0]decane 26. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.43–1.78 (10H, m, 2×NCH_2-(CH_2)$_2$(HCH)); 1.79–1.91 (2H, m, 2×(HC*H*)CCN); 2.28–2.43 (2H, m, 2×(*H*CH)N); 2.62–2.73 (2H, m, 2×(HC*H*)N). ^{13}C NMR (68 MHz, internal standard $CDCl_3$): δ 20.88 and 24.46 (2×NCH_2(CH_2)$_2$); 36.28 (2×CH_2CCN); 51.79 (2×CH_2N); 60.49 (*C*CN); 117.27 (CN). IR (NaCl, cm^{-1}): 2216 (ν_{CN}); ν_{max}=2935; 2863; 2817; 2768; 1642; 1446; 1355; 1291; 1117. It was not possible to obtain a correct mass spectrum of this compound due to its lability.

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