



## Rearrangement of $\alpha,\delta$ -Dichloroaldimines to 2-Formylpyrrolidines : $\alpha,\alpha$ -Azacyclobisalkylation of Aldehydes

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*Key words* : Aldimines; pyrrolidines; alkylation; aldehydes; rearrangement.

*Abstract* : Treatment of  $\alpha,\delta$ -dichloroaldimines, prepared via  $\alpha$ -chlorination with *N*-chlorosuccinimide of the corresponding  $\delta$ -chloroaldimines, with potassium carbonate in methanol led to the formation of 1-alkyl-2-(dimethoxymethyl)pyrrolidines in good yields. The reaction mechanism involved a skeletal rearrangement of the  $\alpha,\delta$ -dichloroaldimines to give bicyclic aziridinium intermediates which suffered ring opening to form 1-alkyl-2-(dimethoxymethyl)pyrrolidines. The latter were hydrolyzed in acid medium to give novel 1-alkyl-2-formylpyrrolidines. The overall pathway involves an  $\alpha,\alpha$ -azacyclobisalkylation of aldehydes.

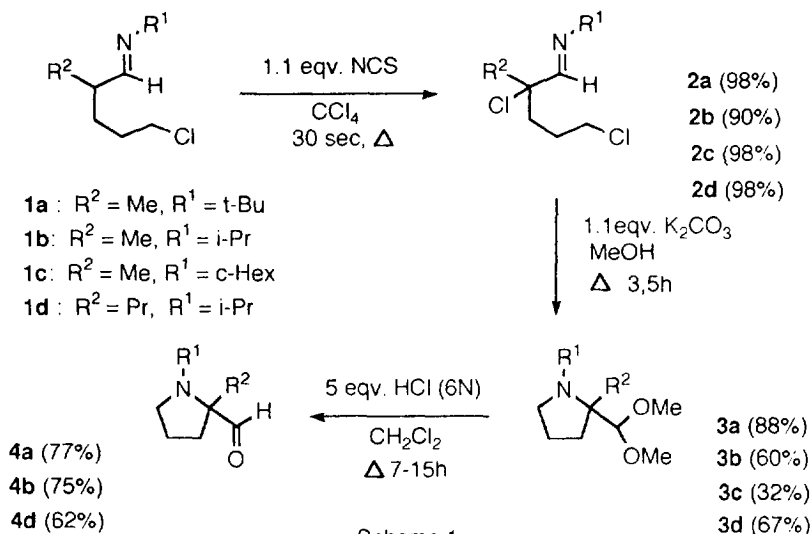
### INTRODUCTION

During our ongoing research on the synthesis of building blocks for natural products and on the reactivity of halogenated imines, i.e.  $\omega$ -halogenated imines,<sup>1</sup> our interest was drawn to the novel class of  $\alpha,\omega$ -dihalogenated imines and their use for the synthesis of azaheterocyclic skeletons, especially pyrrolidines and piperidines. The presence of three reactive centers in one small molecule was thought to reveal new reaction pathways when the reaction centers could be controlled separately. In the present report, a straightforward synthesis of functionalized pyrrolidines via cyclization of  $\alpha,\delta$ -dichloroaldimines and subsequent ring contraction is reported.

### RESULTS AND DISCUSSION

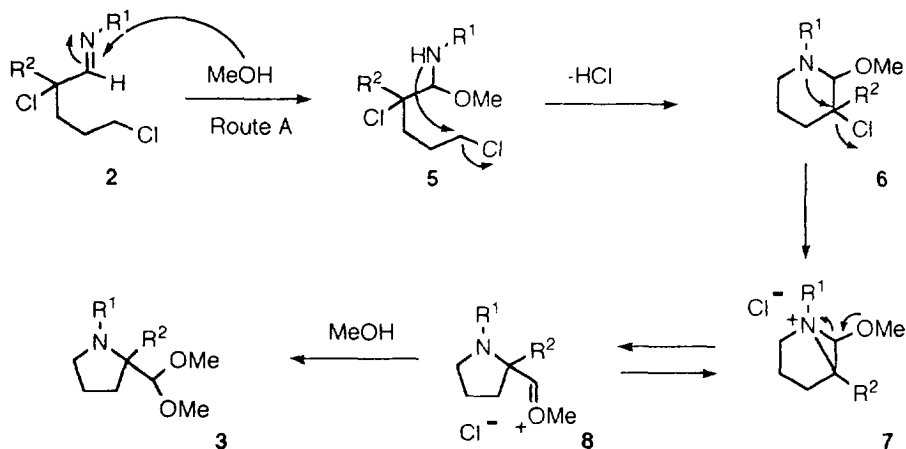
Imines have been used for a long time as nonisolated intermediates in natural product synthesis. The possibility to isolate these thermolabile and moisture sensitive compounds now leads to new transformations and alternative reaction pathways. Earlier work on the  $\omega$ -haloalkylation of imines led to a convenient synthesis of  $\delta$ -halogenated imines.<sup>2</sup> From these  $\delta$ -halogenated imines **1**, the synthesis of the novel

$\alpha,\delta$ -dichlorinated imines was straightforward. The  $\delta$ -halogenated imines **1** were treated with N-chlorosuccinimide (NCS) in carbon tetrachloride resulting in  $\alpha$ -halogenation via the intermediate enamine form. Refluxing the  $\delta$ -halogenated imines **1** with NCS for 30 seconds led to a complete conversion and the end products could be simply isolated by evaporation of the solvent after filtration of succinimide at 0°C (Scheme 1). The  $\alpha,\delta$ -dichlorinated imines **2** showed a satisfactory purity by spectroscopic means (purity > 97%) and



were mostly used as such, since some of them were unstable upon purification by distillation or column chromatography. The  $\alpha,\delta$ -dichloroaldimines could, however, be stored at -20°C for several weeks.

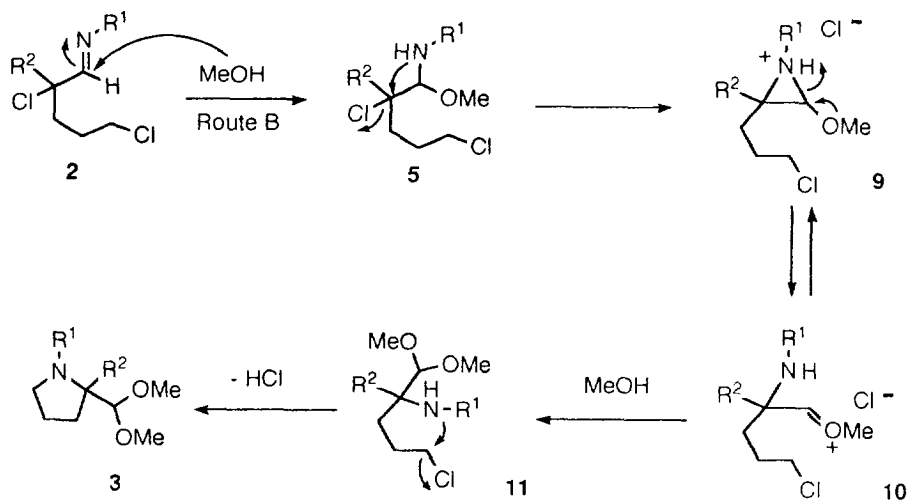
Treatment of imines **2** with a variety of bases (RONa, RLi, ...) mostly lead to tar formation or extremely complex reaction mixtures which were not analyzed further. The use of potassium carbonate in methanol under reflux, however, led to the formation of 1,2-dialkyl-2-(1,1-dimethoxymethyl)pyrrolidines **3**



as the only product in the reaction mixture. High vacuum distillation gave the pure pyrrolidines **3** in acceptable yields, except for the cyclohexyl derivative **3c**, which decomposed partially upon distillation (the yield before distillation was 65%; after distillation : 32%).

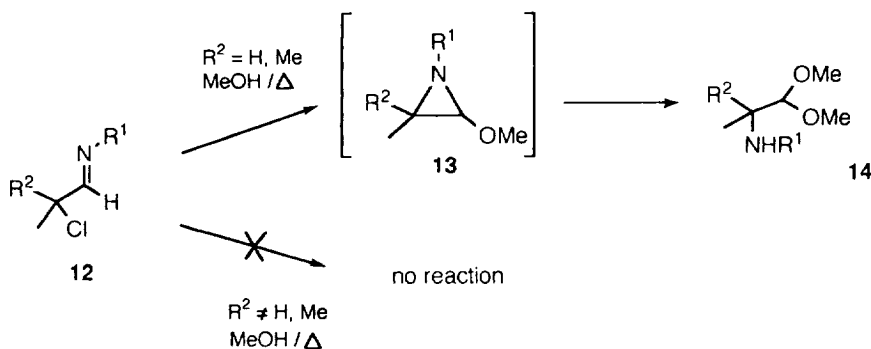
The mechanism of this rearrangement could be postulated considering two potential pathways for the formation of the pyrrolidines **3**. The first pathway (route A) is based on the higher reactivity of the primary  $\omega$ -chlorine compared to the tertiary  $\alpha$ -chlorine atom. Therefore, attack of methanol across the imino function leads to piperidine **6** via an intramolecular nucleophilic substitution of adduct **5** (Scheme 2). This reactive 3-chloro-2-methoxypiperidine **6** does not survive the reaction conditions and suffers further transformation. The nitrogen lone pair displaces the chlorine atom at the 3-position with formation of the bicyclic piperidinium salt **7**,<sup>3</sup> which subsequently undergoes ring opening by the solvent. The opening of the bicyclic piperidinium salt brings about the conversion of **6** into the pyrrolidine **3** via the stabilized cation **8**.

A second possible pathway (route B) is based on a presumed higher reactivity of the  $\alpha$ -chlorine compared to the  $\omega$ -chlorine atom due to the influence of the imino function. After addition of methanol across the carbon-nitrogen double bond, the adduct **5** leads to the aziridinium ion **9**, which suffers similar solvolysis to give  $\alpha$ -amino acetal **11**. Intramolecular nucleophilic substitution of this transient  $\delta$ -chloroamine **11** leads then to the pyrrolidines **3** (Scheme 3).



Scheme 3

This second pathway (route B) could be rejected on the ground of the reactivity of very similar  $\alpha$ -halogenated aldimines in alcohols in the presence or absence of bases. It is known that treatment of  $\alpha$ -chloroaldimines **12** ( $R^2=H, Me$ ) with methanol gave  $\alpha$ -aminoacetals **14** in good yields via the intermediacy of 2-methoxyaziridines **13**.<sup>4,5</sup> However, this type of reaction was never observed with  $\alpha$ -chloroaldimines derived from higher aldehydes ( $R^2 \neq H, Me$ ). In this case, only elimination was observed while no rearranged products were obtained.<sup>4</sup> This reaction showed the importance of steric bulk at the  $\alpha$ -carbon of  $\alpha$ -haloimines. Surpassing the level of gem. dimethyl substitution blocked the aziridine formation completely. Therefore,

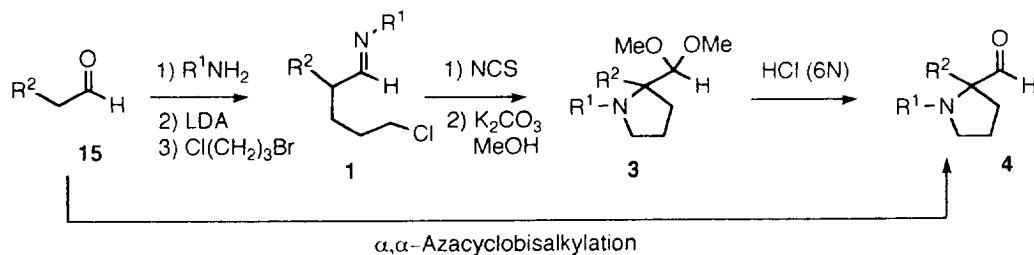


Scheme 4

the rearrangement of  $\alpha,\delta$ -dichloroaldimines **2** is believed to proceed according to the first pathway (Route A) described, i.e. initial piperidine formation and ring contraction.<sup>3</sup>

The 2-(1,1-dimethoxymethyl)pyrrolidines **3** could be further hydrolyzed to the corresponding 2-formylpyrrolidines **4** which are interesting substrates for further elaboration. The hydrolysis was performed using 5 equivalents of hydrochloric acid (6N) in a two phase system under reflux, which resulted in a good procedure for the obtention of 2-formylpyrrolidines **4**.

When the synthesis of the initial  $\delta$ -chloroimines **1** is considered as well (starting from aldehydes following imination and  $\omega$ -chloroalkylation), the overall sequence consists of the introduction of a pyrrolidine ring at the  $\alpha$ -position of an aldehyde. In analogy with our previously published  $\alpha,\alpha$ -cyclobisalkylation of aldehydes via imines,<sup>6</sup> the complete transformation of **15** to **4** can be formulated as an  $\alpha,\alpha$ -azacyclobisalkylation of aldehydes. The overall yield for the  $\alpha,\alpha$ -azacyclobisalkylation of the aldehydes ranges from 28-58%.

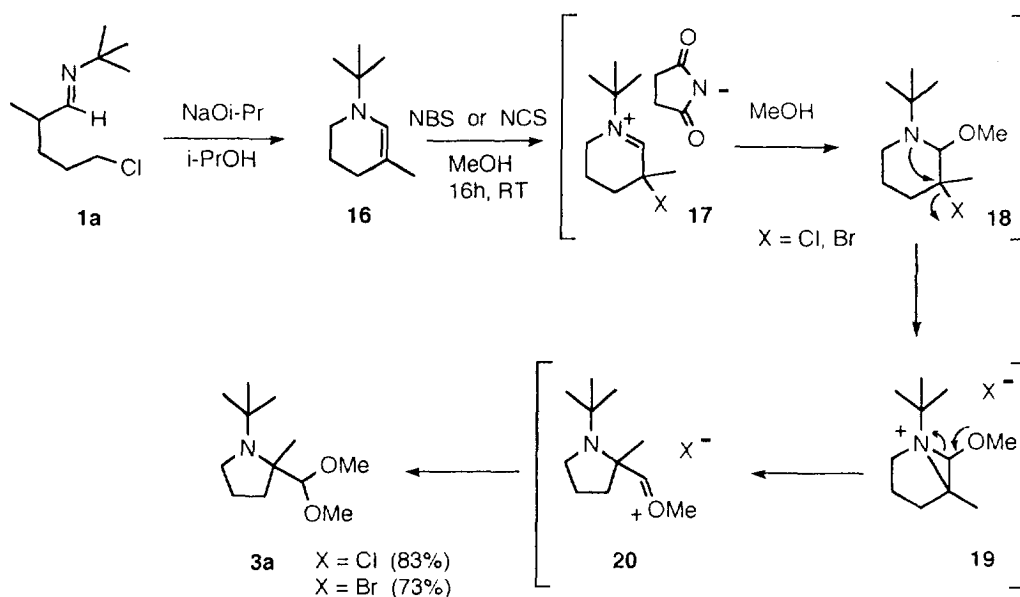


Scheme 5

A second pathway to 2-formylpyrrolidines **4** from  $\delta$ -chloroimines **1** could be elaborated from our earlier described synthesis of endocyclic enamines.<sup>2</sup>  $\delta$ -Halogenated imines undergo base-promoted cyclization to form 1,2,3,4-tetrahydropyridines **16** which reacted with N-bromosuccinimide or N-chlorosuccinimide in methanol at room temperature to provide good access to 2-(1,1-dimethoxymethyl)pyrrolidines **3** in good yield (73-83% crude yield; purity > 95%). Again, the reaction passes along transient 3-halopiperidines **18**,

formed by addition of methanol across the intermediate iminium salt **17**. The subsequent ring contraction of the piperidine **18** into the pyrrolidine **3** occurs in an analogous way as described above. This type of ring-contraction from tetrahydropyridine **16** into pyrrolidine **3** was documented previously in the literature although the halogenating agent used was always bromine and the enamine mostly needed to be activated by a phenyl substituent at the 2-position or an electron-withdrawing group at the 3-position.<sup>7-12</sup> In the present report, we were able to induce a contraction of the endocyclic enamine **16** with a 3-alkyl substituent into the corresponding pyrrolidine **3a** using a N-halosuccinimide as halogenating agent which adds to the scope of the reaction.

In conclusion, a convenient synthesis of 2-formylpyrrolidines (and protected derivatives) was developed from simple aldehydes via ring closure and rearrangement of  $\alpha,\delta$ -dihaloimines. The overall sequence consists of the introduction of a pyrrolidine ring at the  $\alpha$ -position of an aldehyde.



Scheme 6

## EXPERIMENTAL PART

### General Methods

<sup>1</sup>H-NMR spectra were recorded at 60 MHz or 270 MHz with CDCl<sub>3</sub> as solvent. <sup>13</sup>C-NMR spectra were recorded at 20 or 67.5 MHz. All solvents were dried extensively over sodium (ether), sodium/benzophenone-ketyl (THF) or CaH (CH<sub>2</sub>Cl<sub>2</sub>). The alkylation experiments of imines were performed under N<sub>2</sub>.

### General Procedure for the Synthesis of $\delta$ -Chloroaldimines 1

To a solution of 0.6 mol diisopropylamine in dry tetrahydrofuran was added dropwise 0.65 mol of *n*-butyllithium at 0°C and subsequently 0.5 mol *N*-(alkylidene)alkylamine in dry THF. After 2 h at 0°C, 0.5 mol of 1-bromo-3-chloropropane was added and the reaction mixture was stirred for 6 h at room temperature and poured into an aqueous solution of sodium hydroxide (1N) afterwards. The alkylated imine was extracted with ether, dried (MgSO<sub>4</sub>) and the solvent was evaporated to give the crude alkylated imines.

The purification of imines 1 was performed by high vacuum distillation.

#### *N*-(5-Chloro-2-methylpentylidene)*t*-butylamine 1a

Yield : 77%. <sup>1</sup>H-NMR : 1.05 (3H, d, J=6.5 Hz, Me); 1.16 (9H, s, *t*-Bu); 1.4-2.0 (4H, m, CH<sub>2</sub>CH<sub>2</sub>); 2.1-2.5 (1H, m, MeCH); 3.4-3.9 (2H, m, CH<sub>2</sub>Cl); 7.41 (1H, d, J=6 Hz, CH=N). <sup>13</sup>C-NMR : 17.23 (q, CH<sub>3</sub>CH); 29.69 (q, CCH<sub>3</sub>); 30.34 (t, MeCHCH<sub>2</sub>); 31.43 (t, CH<sub>2</sub>); 39.18 (d, MeCH); 44.71 (t, CH<sub>2</sub>Cl); 56.34 (s, CMe<sub>3</sub>); 161.99 (d, C=N). IR (NaCl) : 1668 cm<sup>-1</sup> (C=N). MS *m/z* (%) : 189/91 (1, M<sup>+</sup>); 174/76(9); 154(21); 138(3); 134(9); 126(16); 113(25); 98(25); 81(6); 70(15); 58(60); 57(90); 43(100); 42(16); 41(34); 39(10). Anal. Calcd. for C<sub>10</sub>H<sub>19</sub>ClN : C 63.64%, H 10.15%; Found C 63.44%; H 10.23%.

#### *N*-(5-Chloro-2-methylpentylidene)isopropylamine 1b

Yield : 90%. Bp. 25-35°C/0.1 mmHg. <sup>1</sup>H-NMR : 1.06 (3H, d, J=6.5 Hz, CHCH<sub>3</sub>); 1.13 (6H, d, J=6.5 Hz, CH(CH<sub>3</sub>)<sub>2</sub>); 1.4-2.0 (4H, m, CH<sub>2</sub>CH<sub>2</sub>); 2.0-2.5 (1H, m, MeCH); 3.26 (1H, sept., J=6.5 Hz, Me<sub>2</sub>CH); 3.53 (2H, t, J=6.5 Hz, CH<sub>2</sub>Cl); 7.46 (1H, d, J=6 Hz, CH=N). <sup>13</sup>C-NMR (C<sub>6</sub>D<sub>6</sub>) : 17.41 (q, Me); 24.38 (q, CH(CH<sub>3</sub>)<sub>2</sub>); 24.44 (q, CH(CH<sub>3</sub>)<sub>2</sub>); 30.48 (t, CH<sub>2</sub>); 31.31 (t, CH<sub>2</sub>); 38.38 (d, CHMe); 44.70 (t, CH<sub>2</sub>Cl); 61.39 (d, CHMe<sub>2</sub>); 163.91 (d, C=N). IR (NaCl) : 1670 cm<sup>-1</sup> (C=N). MS *m/z* (%) : 175/77 (0.7, M<sup>+</sup>); 174/76(1); 160/62(10); 140(71); 112(19); 99(45); 98(17); 84(24); 82(10); 70(38); 69(12); 58(10); 56(10); 55(12); 44(19); 43(100); 42(19); 41(36). Anal. Calcd. for C<sub>9</sub>H<sub>17</sub>ClN : C 61.88%; H 9.81%. Found C 62.06%; H 9.72%.

#### *N*-(5-Chloro-2-methylpentylidene)cyclohexylamine 1c

Yield : 93% crude yield; unstable upon purification. <sup>1</sup>H-NMR : 1.05 (3H, d, J=6.5 Hz, CH<sub>3</sub>); 1.1-2.0 (15H, m, C<sub>6</sub>H<sub>11</sub>, CH<sub>2</sub>CH<sub>2</sub>); 2.93 (1H, m, CH); 3.4-3.8 (2H, m, CH<sub>2</sub>Cl); 7.48 (1H, d, J=6 Hz, CH=N). <sup>13</sup>C-NMR (C<sub>6</sub>D<sub>6</sub>) : 17.51 (q, Me); 24.84 (t, CH<sub>2</sub>); 26.11 (t, CH<sub>2</sub>); 30.47 (t, CH<sub>2</sub>); 31.35 (t, CH<sub>2</sub>); 34.79 (t, CH<sub>2</sub>); 34.88 (t, CH<sub>2</sub>); 38.45 (d, CHMe); 44.71 (t, CH<sub>2</sub>Cl); 69.40 (d, CHN); 164.32 (d, C=N). IR (NaCl) : 1668 cm<sup>-1</sup> (C=N). MS *m/z* (%) : 215/17 (3, M<sup>+</sup>); 180(83); 152(17); 139(58); 110(50); 98(33); 96(25); 83(67); 82(17); 81(25); 70(17); 69(8); 68(17); 67(25); 58(25); 56(33); 55(100); 54(25); 41(100); 39(25).

#### *N*-(5-Chloro-2-propylpentylidene)isopropylamine 1d

Yield : 90%. Bp. : 48-52°C/0.02 mmHg. <sup>1</sup>H-NMR : 0.90 (3H, t, J=6.9 Hz, CH<sub>3</sub>CH<sub>2</sub>); 1.15 (6H, d, J=6.3 Hz, (CH<sub>3</sub>)<sub>2</sub>CH); 1.2-1.8 (8H, m, (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>); 2.1-2.3 (1H, m, CHCH=N); 3.26 (1H, sept., J=6.3 Hz, CH(CH<sub>3</sub>)<sub>2</sub>); 3.53 (2H, t, J=6.6 Hz, CH<sub>2</sub>Cl); 7.36 (1H, d, J=7.3 Hz, HC=N). <sup>13</sup>C-NMR : 14.16 (q, CH<sub>3</sub>); 20.23 (t, CH<sub>2</sub>CH<sub>3</sub>); 24.24 (q, (CH<sub>3</sub>)<sub>2</sub>CH); 29.70 (t, CH<sub>2</sub>); 30.22 (t, CH<sub>2</sub>); 34.99 (t, CH<sub>2</sub>); 44.41

(d,  $\underline{\text{C}}\text{HCH}=\text{N}$ ); 44.85 (t,  $\text{CH}_2\text{Cl}$ ); 61.49 (d,  $\underline{\text{C}}\text{HMe}_2$ ); 165.21 (d,  $\underline{\text{C}}\text{H}=\text{N}$ ). IR (NaCl) : 1667  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ ).  
Anal. Calcd. for  $\text{C}_{11}\text{H}_{22}\text{ClN}$  : C 64.84% ; H 10.88%. Found C 64.93% ; H 11.06%.

### General Procedure for the $\alpha$ -Chlorination of $\delta$ -Chloroimines

To a solution of 0.05 mol of  $\delta$ -chloroimine **1** in carbon tetrachloride (10% solution) was added portionwise 0.055 mol of N-chlorosuccinimide at room temperature. After the complete addition, the reaction mixture was refluxed for one minute. The reaction mixture was then cooled to  $0^\circ\text{C}$  and filtered. Afterwards, the filtrate was kept three hours at  $-20^\circ\text{C}$  and filtered again to remove the last traces of succinimide. Evaporation of the carbon tetrachloride yielded the crude  $\alpha,\delta$ -dichloroaldimines in excellent yield (purity > 97%). The  $\alpha,\delta$ -dichloroimines **2** had a satisfactory purity to be used as such in the next synthesis.

#### N-(2,5-Dichloro-2-methylpentylidene)t-butylamine 2a

Yield : 98%. Bp.  $41-43^\circ\text{C}/0.1$  mmHg.  $^1\text{H-NMR}$  : 1.18 (9H, s, t-Bu); 1.65 (3H, s, Me); 1.8-2.2 (4H, m,  $\text{CH}_2\text{CH}_2$ ); 3.4-3.7 (2H, m,  $\text{CH}_2\text{Cl}$ ); 7.60 (1H, s,  $\text{CH}=\text{N}$ ).  $^{13}\text{C-NMR}$  : 27.40 (q, Me); 28.16 (t,  $\text{CH}_2$ ); 29.36 (q,  $\text{CMe}_3$ ); 39.11 (t,  $\text{CH}_2$ ); 44.63 (t,  $\text{CH}_2\text{Cl}$ ); 56.68 (s,  $\underline{\text{C}}\text{Me}_3$ ); 71.92 (s,  $\text{Me}\underline{\text{C}}\text{Cl}$ ); 158.37 (d,  $\text{C}=\text{N}$ ). IR (NaCl)  $1660\text{ cm}^{-1}$  ( $\text{C}=\text{N}$ ). MS m/z (%) : 208/10/12 (4;  $\text{M}^+-\text{Me}$ ); 188/90(9); 147/49(7); 132/34(9); 112(4); 96(4); 91(4); 84(9); 58(11); 57(100); 56(7); 41(21). Anal. Calcd. for  $\text{C}_{10}\text{H}_{19}\text{Cl}_2\text{N}$  : C 53.58% ; H 8.54%. Found : C 53.84% , H 8.63%.

#### N-(2,5-Dichloro-2-methylpentylidene)isopropylamine 2b

Yield : 90%. Bp.  $91-95^\circ\text{C}/5$  mmHg.  $^1\text{H-NMR}$  : 1.15 (6H, d,  $J=6$  Hz,  $\text{CH}(\underline{\text{Me}})_2$ ); 1.66 (3H, s, Me); 1.8-2.3 (4H, m,  $\text{CH}_2\text{CH}_2$ ); 3.40 (1H, sept.,  $\underline{\text{C}}\text{HMe}_2$ ); 3.4-3.7 (2H, m,  $\text{CH}_2\text{Cl}$ ); 7.66 (1H, s,  $\text{CH}=\text{N}$ ).  $^{13}\text{C-NMR}$  : 23.73 (q, Me); 23.80 (t,  $\text{CH}_2$ ); 27.36 (q,  $\text{CHMe}_2$ ); 28.08 (q,  $\text{CHMe}_2$ ); 39.11 (t,  $\text{CH}_2$ ); 44.65 (t,  $\text{CH}_2\text{Cl}$ ); 60.30 (d,  $\underline{\text{C}}\text{HMe}_2$ ); 71.19 (s,  $\underline{\text{C}}\text{ClIme}$ ); 161.53 (d,  $\text{C}=\text{N}$ ). IR (NaCl) :  $1665\text{ cm}^{-1}$  ( $\text{C}=\text{N}$ ). MS m/z (%) : 209/11/13 (0.2,  $\text{M}^+$ ); 194/96/98(1); 174/76(9); 133(9); 70(68); 43(100); 41(30). Anal. Calcd. for  $\text{C}_9\text{H}_{17}\text{Cl}_2\text{N}$  : C 51.44% ; H 8.15%. Found C 51.62% , H 8.24%.

#### N-(2,5-Dichloro-2-methylpentylidene)cyclohexylamine 2c

Yield : 98%; not distillable.  $^1\text{H-NMR}$  : 1.0-2.4 (14H, m,  $\text{C}_6\text{H}_{10}$ ,  $\text{CH}_2\text{CH}_2$ ); 1.65 (3H, s, Me); 2.8-3.4 (1H, m,  $\text{CHN}$ ); 3.4-3.7 (2H, m,  $\text{CH}_2\text{Cl}$ ); 7.66 (1H, s,  $\text{CH}=\text{N}$ ).  $^{13}\text{C-NMR}$  : 24.43 (t,  $2\times\text{CH}_2$ ); 25.65 (t,  $\text{CH}_2$ ); 27.41 (q, Me); 28.12 (t,  $\text{CH}_2$ ); 34.08 (t,  $2\times\text{CH}_2$ ); 39.11 (t,  $\underline{\text{C}}\text{H}_2\text{C}_{\text{quat}}$ ); 44.67 (t,  $\text{CH}_2\text{Cl}$ ); 68.17 (d,  $\text{CHN}$ ); 71.32 (s,  $\text{C}_{\text{quat}}$ ); 161.76 (d,  $\text{C}=\text{N}$ ). IR (NaCl) :  $1668\text{ cm}^{-1}$  ( $\text{C}=\text{N}$ ). MS m/z (%) : 249/51/53 (0.3,  $\text{M}^+$ ); 214/16(19); 206/08(2); 178(7); 173/75(12); 138(7); 132/34(14); 110(19); 96(7); 83(100); 67(12); 55(55); 41(38).

#### N-(2,5-Dichloro-2-propylpentylidene)isopropylamine 2d

Yield : 98%; not distillable.  $^1\text{H-NMR}$  : 0.93 (3H, t,  $J=7.3$  Hz,  $\text{CH}_3$ ); 1.16 (6H, d,  $J=6.3$  Hz,  $(\underline{\text{CH}}_3)_2\text{CH}$ ); 1.4 (2H, m,  $\underline{\text{C}}\text{H}_2\text{CH}_3$ ); 1.8-2.2 (6H, m,  $(\underline{\text{C}}\text{H}_2)_2\text{CClCH}_2$ ); 3.39 (1H, sept.,  $J=6.3$  Hz,  $\text{CH}$ ); 3.58 (2H, t,  $J=6.3$  Hz,  $\underline{\text{C}}\text{H}_2\text{Cl}$ ); 7.62 (1H, s,  $\underline{\text{H}}\text{C}=\text{N}$ ).  $^{13}\text{C-NMR}$  : 14.17 (q, Me); 17.57 (t,  $\text{CH}_2$ ); 23.83 (q,  $\text{Me}(2\times)$ );

27.83 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{Cl}$ ); 36.55 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CH}_3$ ); 42.50 (t,  $\underline{\text{C}}\text{H}_2(\text{CH}_2)_2\text{Cl}$ ); 44.72 (t,  $\text{CH}_2\text{Cl}$ ); 60.73 (d, CH); 75.04 (s, CCl); 161.43 (d, CH=N). IR (NaCl) : 1667  $\text{cm}^{-1}$  (C=N). MS m/z (%) : no  $\text{M}^+$ ; 195/7/9 ( $\text{M}^+$ - $\text{CH}_2=\text{CHMe}$ , 5); 150/2/4(4); 138(10); 124(4); 99(28); 98(10); 96(9); 95(7); 91(6); 90(5); 85(6); 83(6); 82(6); 81(6); 80(6); 71(7); 70(61); 68(9); 56(6); 55(15); 54(6); 53(10); 44(13); 43(100); 41(30).

### General Procedure for the Synthesis of 1-Alkyl-2-(dimethoxymethyl)pyrrolidines 3

To a solution of 0.05 moles of  $\alpha,\delta$ -dichloroaldimines **2** in 100 ml of dry methanol was added under stirring 0.055 moles (1.1 equivalent) of potassium carbonate. The reaction mixture was refluxed for 3.5 h after which the reaction mixture was evaporated to a quarter of its original volume and poured afterwards in 200 ml of aqueous sodium hydroxide (1N). The mixture was then extracted with dichloromethane (3x50 ml). The organic layers were dried ( $\text{MgSO}_4$ ), filtered and the solvent evaporated under vacuo. High vacuum distillation yielded the pure pyrrolidines.

#### 2-(Dimethoxymethyl)-2-methyl-1-t-butylpyrrolidine 3a

Yield : 88%; Bp. 44°C/0.1 mmHg.  $^1\text{H-NMR}$  : 1.10 (3H, s, Me); 1.20 (9H, s, t-Bu); 1.3-2.0 (2H, m,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{N}$ ); 2.0-2.4 (2H, m,  $\underline{\text{C}}\text{H}_2\text{CMe}$ ); 2.8-3.2 (2H, m,  $\text{CH}_2\text{N}$ ); 3.41 (3H, s, OMe); 3.55 (3H, s, OMe); 4.20 (1H, s,  $\underline{\text{C}}\text{H}(\text{OMe})_2$ ).  $^{13}\text{C-NMR}$  : 22.85 (t,  $\text{CH}_2$ ); 24.74 (q, Me); 30.10 (q,  $\text{CMe}_3$ ); 37.50 (t,  $\underline{\text{C}}\text{H}_2\text{CMe}$ ); 47.99 (t,  $\text{CH}_2\text{N}$ ); 53.63 (s,  $\underline{\text{C}}\text{Me}_3$ ); 57.17 (q, OMe); 58.13 (q, OMe); 67.24 (s,  $\underline{\text{C}}_{\text{quat}}$ ); 112.00 (d,  $\underline{\text{C}}\text{H}(\text{OMe})_2$ ). IR (NaCl) : 2830  $\text{cm}^{-1}$  (OMe). MS m/z (%) : 215 (0.6;  $\text{M}^+$ ); 184(2); 140(30); 128(80); 96(8); 84(100); 58(10); 57(15); 43(21); 42(10); 41(13). Anal. Calcd. for  $\text{C}_{12}\text{H}_{25}\text{NO}_2$  : C 66.93%; H 11.70%. Found : C 66.78%; H 11.65%.

#### 2-(Dimethoxymethyl)-1-isopropyl-2-methylpyrrolidine 3b

Yield : 60%; Bp. 67-72/2 mmHg.  $^1\text{H-NMR}$  : 0.9-1.2 (6H, m,  $\text{CHMe}_2$ ); 1.03 (3H, s, Me); 1.3-2.0 (4H, m,  $\text{CH}_2\text{CH}_2$ ); 2.7-3.0 (2H, m,  $\text{CH}_2\text{N}$ ); 3.30 (1H, sept.,  $J=6.8$  Hz,  $\underline{\text{C}}\text{HMe}_2$ ); 3.50 (6H, s,  $(\text{OMe})_2$ ); 3.90 (1H, s,  $\underline{\text{C}}\text{H}(\text{OMe})_2$ ).  $^{13}\text{C-NMR}$  : 19.35 (q, Me); 20.81 (q,  $\text{CHMe}_2$ ); 22.76 (t,  $\text{CH}_2$ ); 23.43 (q,  $\text{CHMe}_2$ ); 36.08 (t,  $\text{CH}_2$ ); 43.98 (t,  $\text{CH}_2\text{N}$ ); 45.36 (d,  $\underline{\text{C}}\text{HMe}_2$ ); 57.92 (q,  $(\text{OMe})_2$ ); 65.73 (s,  $\underline{\text{C}}_{\text{quat}}$ ); 112.99 (d,  $\underline{\text{C}}\text{H}(\text{OMe})_2$ ). IR (NaCl) : 2830  $\text{cm}^{-1}$  (OMe). MS m/z (%) : 201 (1,  $\text{M}^+$ ); 186(1); 170(15); 127(11); 126(100); 96(11); 84(65); 53(12); 52(19); 51(13). Anal. Calcd. for  $\text{C}_{11}\text{H}_{23}\text{NO}_2$  : C 65.63%; H 11.52%. Found C 65.70%; H 11.62%.

#### 1-Cyclohexyl-2-(dimethoxymethyl)-2-methylpyrrolidine 3c

Yield : 65% (crude mixture); 32% (after distillation); Bp. 80-85°C/0.1 mmHg.  $^1\text{H-NMR}$  : 1.03 (3H, s, Me); 1.1-2.3 (14H, m,  $(\text{CH}_2)_6$ ,  $\text{CH}_2\text{CH}_2$ ); 2.7-3.1 (3H, t,  $\text{CH}_2\text{N}$ , CHN); 3.48 (6H, s, 2xOMe); 3.92 (1H, s,  $\underline{\text{C}}\text{H}(\text{OMe})_2$ ).  $^{13}\text{C-NMR}$  : 19.60 (q, Me); 23.01 (t,  $\text{CH}_2$ ); 26.42 (t,  $\text{CH}_2$ ); 26.57 (t,  $\text{CH}_2$ ); 27.01 (t,  $\text{CH}_2$ ); 32.51 (t,  $\text{CH}_2$ ); 34.33 (t,  $\text{CH}_2$ ); 36.01 (t,  $\underline{\text{C}}\text{H}_2$   $\underline{\text{C}}_{\text{quat}}$ ); 45.27 (t,  $\text{CH}_2\text{N}$ ); 54.41 (d, CHN); 57.86 (q, OMe); 65.69 (s,  $\underline{\text{C}}_{\text{quat}}$ ); 112.92 (d,  $\underline{\text{C}}\text{H}(\text{OMe})_2$ ). IR (NaCl) :  $\nu_{\text{max}}$  : 2940  $\text{cm}^{-1}$ , 2830  $\text{cm}^{-1}$ , 1450  $\text{cm}^{-1}$ , 1110  $\text{cm}^{-1}$ , 1072  $\text{cm}^{-1}$ . MS m/z (%) : 241 (2,  $\text{M}^+$ ); 226(1); 210(11); 178(4); 166(100); 132(5); 128(7); 110(9); 96(9); 84(87); 83(24); 82(7); 75(5); 68(4); 67(9); 55(35); 54(7); 53(5); 42(16); 41(35). Anal. Calcd. for  $\text{C}_{14}\text{H}_{27}\text{NO}_2$  : C 69.66%; H 11.28%. Found : C 69.72%; H 11.31%.



**2-(Dimethoxymethyl)-1-isopropyl-2-propylpyrrolidine 3d**

Yield (67%; Bp. 49-50°C/0.01 mmHg).  $^1\text{H-NMR}$  : 0.89 (3H, t,  $J=6.9$  Hz, Me); 1.02 (6H, d,  $J=6.3$  Hz, Me(2x)); 1.1-2.0 (8H, m,  $(\text{CH}_2)_2\text{C}(\text{CH}_2)_2$ ); 2.85 (2H,  $\sim$ t,  $J=6.3$  Hz,  $\text{NCH}_2$ ); 3.23 (1H, sept.,  $J=6.3$  Hz,  $\text{NCHMe}_2$ ); 3.45 (3H, s, MeO); 3.50 (3H, s, MeO); 3.96 (1H, s,  $\text{CH}(\text{OMe})_2$ ).  $^{13}\text{C-NMR}$  : 15.09 (q, Me); 17.09 (t,  $\text{CH}_2$ ); 20.93 and 22.59 (q,  $(\text{Me})_2\text{CH}$ ); 22.98 (t,  $\text{CH}_2$ ); 31.46 and 35.94 (t,  $\text{NCH}_2(\text{CH}_2)_2$ ); 43.81 (d,  $\text{NCH}$ ); 43.92 (t,  $\text{CH}_2\text{N}$ ); 57.23 and 58.45 (q, 2xOMe); 68.16 (s,  $\text{C}_{\text{quat}}$ ); 112.95 (d,  $\text{CH}(\text{OMe})_2$ ). IR (NaCl) :  $\nu_{\text{max}}$  : 2828  $\text{cm}^{-1}$ , 1460  $\text{cm}^{-1}$ , 1385  $\text{cm}^{-1}$ , 1359  $\text{cm}^{-1}$ , 1205  $\text{cm}^{-1}$ . MS  $m/z$  (%) : 229 (0.4,  $\text{M}^+$ ); 214(0.6); 198(11); 154(100); 138(4); 124(5); 112(35); 98(13); 70(4); 43(6). Anal. Calcd. for  $\text{C}_{13}\text{H}_{27}\text{NO}_2$  : C 68.08%; H 11.86%. Found : C 68.13%; H 12.01%.

**General Procedure for the Hydrolysis of the 2-(Dimethoxymethyl)pyrrolidines 3**

To a solution of 0.02 mol 2-(dimethoxymethyl)pyrrolidine 3 in 50 ml of dichloromethane was added 33 ml of 6N hydrochloric acid (10 equiv.). The two phase system was refluxed for 7-15 h while stirring vigorously. After cooling, the reaction mixture was made alkaline by addition of 40%-sodium hydroxide solution and was then extracted with dichloromethane (3x50 ml). The combined organic layers were dried on magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude 2-formylpyrrolidines 4 could be additionally purified by high vacuum distillation.

**2-Formyl-2-methyl-1-t-butylpyrrolidine 4a**

Reflux time for the hydrolysis : 7 h. Yield : 77%; Bp. 25°C/0.1 mmHg.  $^1\text{H-NMR}$  : 1.10 (9H, s, t-Bu); 1.20 (3H, s, Me); 1.6-2.1 (4H, m,  $\text{CH}_2\text{CH}_2$ ); 2.9-3.3 (2H, m,  $\text{CH}_2\text{N}$ ); 9.30 (1H, s, CHO).  $^{13}\text{C-NMR}$  : 18.10 (q, Me); 22.85 (t,  $\text{CH}_2\text{CH}_2\text{N}$ ); 29.15 (q, t-Bu); 36.78 (t,  $\text{CH}_2$   $\text{C}_{\text{quat}}$ ); 46.27 (t,  $\text{CH}_2\text{N}$ ); 53.47 (s,  $\text{CMe}_3$ ); 69.78 (s,  $\text{C}_{\text{quat}}$ ); 204.26 (d, CHO). IR (NaCl) : 1730  $\text{cm}^{-1}$  (CHO). MS  $m/z$  (%) : 140 (18,  $\text{M}^+$ -CHO); 118(4); 84(100); 82(5); 57(8); 55(4); 42(14). Anal. Calcd. for  $\text{C}_{10}\text{H}_{19}\text{NO}$  : C 70.96%; H 11.31%. Found C 70.82%; H 11.21%.

**2-Formyl-1-isopropyl-2-methylpyrrolidine 4b**

Reflux time for the hydrolysis : 15 h. Yield : 75%; Bp. 48-50°C/1 mmHg.  $^1\text{H-NMR}$  : 0.93 (3H, d,  $J=6.8$  Hz,  $\text{CHMe}$ ); 1.06 (3H, d,  $J=6.8$  Hz,  $\text{CHMe}$ ); 1.06 (3H, s, Me); 1.2-2.1 (4H, m,  $\text{CH}_2\text{CH}_2$ ); 2.6-2.9 (2H, m,  $\text{CH}_2\text{N}$ ); 2.9-3.4 (1H, m,  $\text{CHMe}_2$ ); 9.35 (1H, s, CHO).  $^{13}\text{C-NMR}$  : 13.64 (q, Me); 22.50 (t,  $\text{CH}_2$ ); 22.65 (q,  $\text{CHMe}$ ); 23.41 (q,  $\text{CHMe}$ ); 35.14 (t,  $\text{CH}_2$   $\text{C}_{\text{quat}}$ ); 48.54 (t,  $\text{CH}_2\text{N}$ ); 48.58 (d,  $\text{CHMe}_2$ ); 62.92 (s,  $\text{C}_{\text{quat}}$ ); 203.70 (d, CHO). IR (NaCl) : 1728  $\text{cm}^{-1}$  (CHO). MS  $m/z$  (%) : 126 (69,  $\text{M}^+$ -CHO); 84(100); 82(6); 70(4); 55(8); 43(10); 42(27); 41(16). Anal. Calcd. for  $\text{C}_9\text{H}_{17}\text{NO}$  : C 69.63%; H 11.04%. Found C 69.42%; H 11.22%.

**2-Formyl-1-isopropyl-2-propylpyrrolidine 4d**

Reflux time for the hydrolysis : 15 h. Yield : 62%.  $^1\text{H-NMR}$  : 0.94 (3H, t,  $J=7.3$  Hz, Me); 1.02 (3H, d,  $J=6.4$  Hz, Me); 1.07 (3H, d,  $J=6.4$  Hz, Me); 1.2-2.0 (8H, m,  $\text{CH}_3(\text{CH}_2)_2\text{C}(\text{CH}_2)_2$ ); 2.9 (1H, m,  $\text{CHMe}_2$ ); 3.0 (2H, m,  $\text{CH}_2\text{N}$ ); 9.28 (1H, s, CHO);  $^{13}\text{C-NMR}$  : 14.99 (q, Me); 17.84 (t,  $\text{CH}_2$ ); 22.48 (t,  $\text{CH}_2$ ); 23.13

(q, Me); 31.28 (t, CH<sub>2</sub>); 32.96 (t, CH<sub>2</sub>); 45.59 (d, CH); 45.86 (t, CH<sub>2</sub>N); 71.30 (s, C<sub>quat.</sub>); 201.56 (s, CHO). IR (NaCl) : 1722 cm<sup>-1</sup> (CHO). MS m/z (%) : 154 (50, M<sup>+</sup>-CHO); 140(4); 113(7); 112(81); 98(4); 83(5); 70(6); 55(5); 44(9); 43(9); 42(5); 41(12).

#### General Procedure for the synthesis of 1-t-Butyl-2-(dimethoxymethyl)pyrrolidines **3a** from Endocyclic Enamine **16**

To a solution of 1.6 mmol of endocyclic enamine **16** in 10 ml of dry methanol was added 1.8 mmol of N-halosuccinimide and the solution was stirred 16 h at room temperature. The reaction mixture was then poured into 10 ml of aqueous sodium hydroxide (1N), extracted with dichloromethane (3x15 ml), dried (MgSO<sub>4</sub>) and filtered. After evaporation of the solvent, 1-t-butyl-2-(dimethoxymethyl)pyrrolidine **3a** was obtained either in 73% yield (using NBS) or in 83% yield (using NCS) (purity > 95%).

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