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Syntheses of the Principal Bread Flavor Component, 6-Acetyl-1,2,3,4-tetrahydropyridine, and Acetal Protected Precursors

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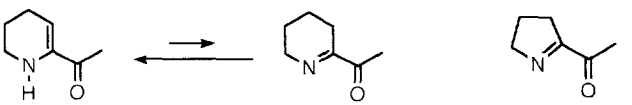
Abstract : Various synthetic approaches towards the principle bread flavor component, 6-acetyl-1,2,3,4-tetrahydropyridine, and some of its more stable acetal and enol ether derivatives have been developed by elaboration and ring closure of appropriately functionalized imines. The aza-Wittig type cyclization of functionalized δ-azido ketones, carrying an acetal function at the α'-position, proved to be the most successful route. The synthetic scheme leading to the labile bread flavor component incorporates (1) a regioselective acetalization of a nonsymmetric α-dione and (2) an entry into stable protected acetal derivatives. An alternative to the required δ-chloroketone, carrying an acetal function at the α'-position, consisted of selective hydrolysis of the corresponding δ-chloro-imine. In addition, some N-alkylated analogues of the Maillard flavor compound have been synthe-sized. Alternative approaches towards acetal protected 2-acetyltetrahydropyridines involved initial azidation of δ-chloroimines, selective hydrolysis of the imino function in the presence of an acetal moiety and intramolecular aza-Wittig type formation of cyclic imines.

INTRODUCTION

The Maillard reaction, i.e. the nonenzymatic browning reaction between reducing sugars and α-ami-no acids, is a very important process for the generation of flavor compounds during cooking, baking and even during preservation of foodstuffs.[1,2] This reaction becomes more important at higher temperatures and delivers a whole range of heterocyclic flavor compounds. Some of these heterocyclic compounds display a pronounced cracker like flavor, contributing extensively to the flavor of baked goods. Among the heterocyclic Maillard compounds, 6-acetyl-1,2,3,4-tetrahydropyridine **1** is considered to be the most important bread flavor component. This potent cracker-like flavor occurs in solution as a tautomeric equilibrium between the enamine **1** and the imine **2** (Scheme 1). Major features of this compound are the lability and the extremely low odor threshold value of 1.4 ppb (measured in water).[3] A similar cracker-like flavor is 2-acetyl-1-pyrroline **3**, which has even more powerful flavor characteristics, and which is considered as the most important flavor compound of cooked rice.[4]



1 2 3

SCHEME 1

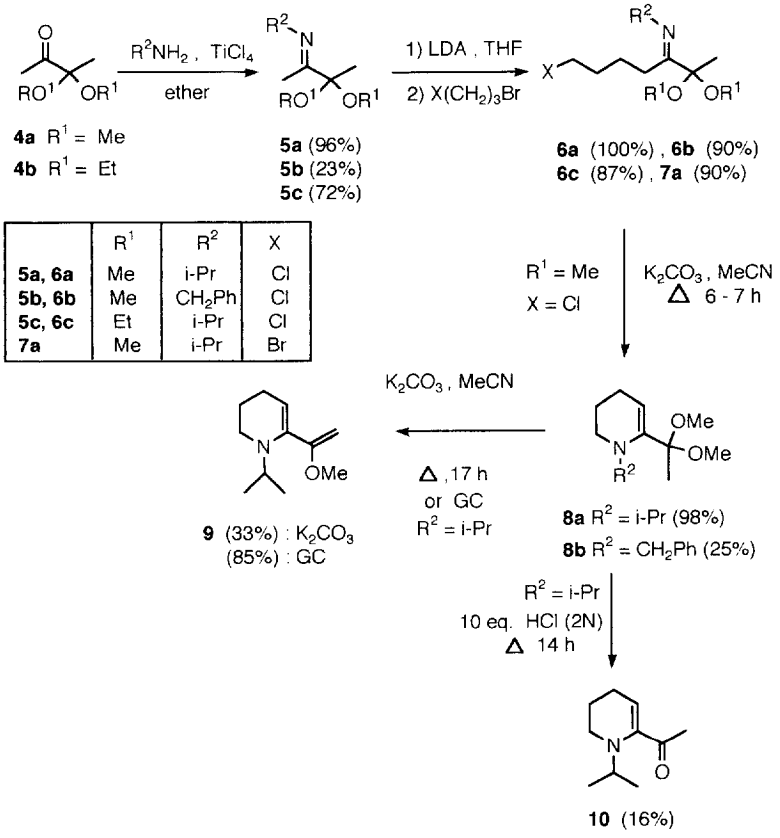
6-Acetyl-1,2,3,4-tetrahydropyridine **1** is a natural flavor compound which has been identified in freshly baked bread.[5-7] The synthesis of this labile tetrahydropyridine has been described in the literature (1) in an unspecified way by thermal condensation of proline with 1,3-dihydroxy-2-propanone,[5,8,9] (2) by rhodium-catalyzed hydrogenation of 2-acetylpyridine and subsequent oxidation of the resulting amino alcohol with a large excess of silver salts,[10] and (3) by oxidation of 2-cyanopiperidine to 2-cyano-1-piperideine and subsequent addition of methylmagnesium iodide to the latter imidoylcyanide.[11,12] A very recently disclosed patent[13] on the synthesis of the bread flavor component by construction of the piperideine ring by ring closure of 7-azidoheptane-2,3-dione urged us to present our own results of an alternative synthesis of 6-acetyl-1,2,3,4-tetrahydropyridine **1**.

RESULTS AND DISCUSSION

Based on our previous experience in piperidine syntheses,[14,15] δ-halo imines **6** and **7**, carrying a protected carbonyl function at the α'-position, were selected as key substrates in the synthesis of the bread flavor compound **1**. N-(3,3-Dialkoxy-2-butylidene)amines **5** were prepared from butane-2,3-dione mono-acetals **4** by reaction with primary amines in the presence of titanium(IV) chloride. N-Isopropyl imines **5a,c** were synthesized without difficulty but the N-benzyl imine **5b** proved to be a rather labile substance as it decomposed partially upon high vacuum distillation. Alkylation of the α,α-dialkoxyimines **5** to afford δ-haloimines **6** and **7** was performed smoothly via generation of the corresponding 1-azaenolate by interaction of lithium diisopropylamide and subsequent reaction with either 1-bromo-3-chloropropane or 1,3-dibromopropane. These alkoxylated δ-haloimines **6** and **7** were obtained in excellent yields with only traces of impurities (purity more than 96%). These functionalized imines can be kept at -20°C in an inert atmosphere for several days. However, complete decomposition occurred during high vacuum distillation. In addition, column chromatography over silica gel resulted in hydrolysis and decomposition of these compounds. Accordingly, these imines **6** and **7** were prepared freshly and utilized immediately in further elaborations.

In order to verify the feasability of δ-haloimines, carrying the bulky 1,1-dialkoxyethyl group at the imino carbon, for the synthesis of functionalized piperidines, compounds **6a,b** were cyclized with potassium carbonate in acetonitrile under reflux for 6-7h into analogues of the target flavor compound, i.e. 1-substituted 6-(1,1-dimethoxyethyl)-1,2,3,4-tetrahydropyridines **8a,b** (Scheme 2). Again here, the N-isopropyl derivative gave no side reactions while the N-benzyl imine **6b** gave only about 25% of the cyclized compound **8b** besides a whole variety of unidentified compounds. When the reaction of **6a** with potassium carbonate in acetonitrile was prolonged to 17h, the cyclic enamine **8a** underwent loss of the elements of methanol to afford the heterocyclic 2,3-difunctionalized 1,3-butadiene **9**. A similar elimination of methanol was observed during

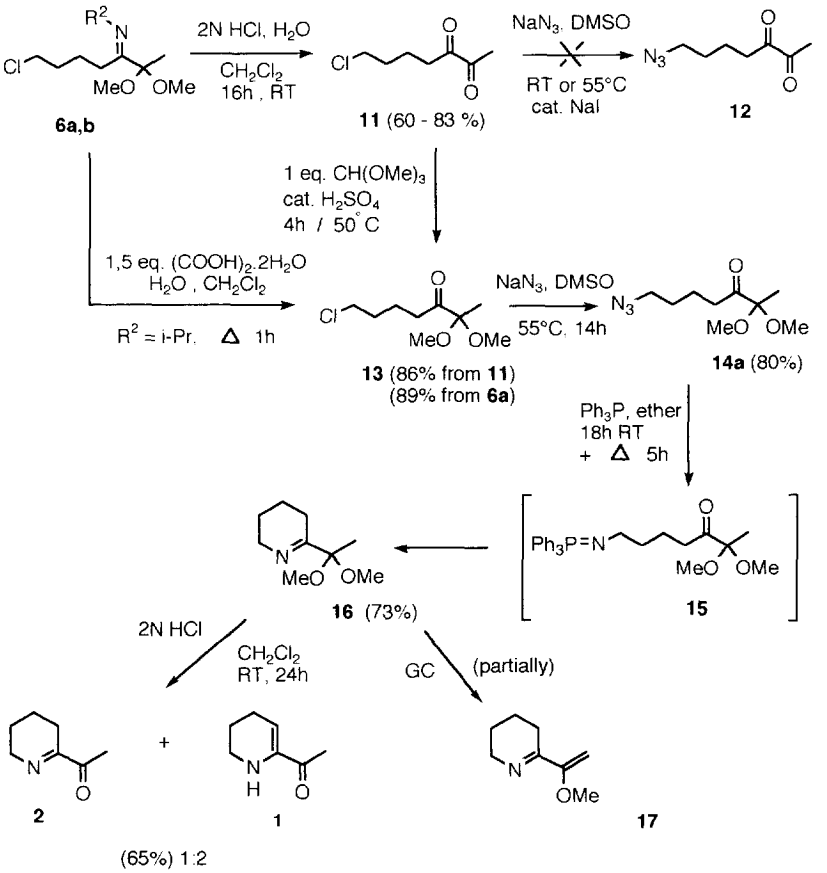
preparative gas chromatography. Acidic hydrolysis of the functionalized tetrahydropyridine **8a** with aqueous hydrogen chloride afforded 6-acetyl-1-isopropyl-1,2,3,4-tetrahydropyridine **10** in an unoptimized yield of 16%. This is a N-alkyl derivative of the natural bread flavor component.



	R^1	R^2	X
5a, 6a	Me	i-Pr	Cl
5b, 6b	Me	CH_2Ph	Cl
5c, 6c	Et	i-Pr	Cl
7a	Me	i-Pr	Br

SCHEME 2

Next, efforts were undertaken to prepare the natural bread flavor component **1** (Scheme 3). Hydrolysis of dialkoxylated δ-chloroimines **6** with aqueous hydrogen chloride in a two-phase system with dichloromethane produced 7-chloroheptane-2,3-dione **11**, which could not be converted into the corresponding azide **12** by reaction with sodium azide in dimethyl sulfoxide in the presence of catalytic amounts of sodium iodide.[16] The ω-azido-α-dione **12** was already used as a precursor to 6-acetyl-1,2,3,4-tetrahydropyridine **1** but the synthesis of the starting material **12** followed a very elaborate procedure, i.e. (a) trimethylsilylcyanation of 2-methylcinnamaldehyde, (b) deprotonation and alkylation of the resulting α-hydroxy nitrile trimethylsilyl ether with 3-bromopropylazide, (c) tetrabutylammonium fluoride induced desilylation and decyanation and (d) ozonolysis in methanol-dichloromethane at -78°C.[13] After reaction of the ω-chloro-α-dione **11** with sodium azide in dimethyl sulfoxide at 55°C for 15h or at room temperature for 15h, no trace of a ω-azido-α-dione component was present. Therefore, the α-dione **11** was regioselectively acetalized into 7-chloro-2,2-dime-



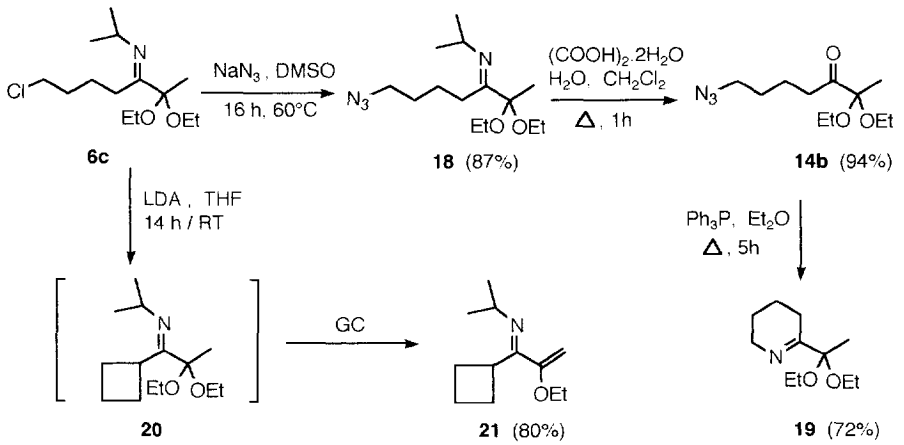
SCHEME 3

thoxy-3-heptanone **13** utilizing trimethyl orthoformate and a catalytic amount of sulfuric acid. Compound **13** was obtained in 96% yield with a purity of 90%. A better procedure for the preparation of this compound **13** consisted of the selective hydrolysis of the imino function of compound **6a** in the presence of an acetal function, a conversion which could easily be performed using aqueous oxalic acid in a two-phase system with dichloromethane. In this way, α-ketoacetal **13** was obtained in 89% yield without interference of any side product. Azidation of the chloro compound **13** under classical conditions,[16] i.e. reaction with sodium azide in DMSO at 55°C for an overnight period, gave access to the azide **14a**, which underwent a smooth intramolecular aza-Wittig reaction via the intermediacy of an iminophosphorane **15**.[17] After separation of triphenylphosphine oxide, the acetal **16**, derived from the bread flavor component, was obtained in 73% yield. This compound lost partially the elements of methanol under preparative gas chromatographic conditions to give the enol ether **17**. Upon acidic hydrolysis of the acetal **16** by means of aqueous hydrogen chloride at room temperature for 24h, the bread flavor component **1**, occurring in tautomeric equilibrium with its imino isomer **2**, was obtained in 65% yield (Scheme 3). A longer reaction time resulted in substantial decomposition while

shorter reaction times resulted in incomplete hydrolysis.

An alternative procedure leading to the acetal-protected flavor compound **19** was worked out by azidation of δ-chloroimine **6c** to afford δ-azidoimine **18** and subsequent selective hydrolysis of the imino function in the presence of the acetal function. As described above, this conversion is most conveniently executed by aqueous oxalic acid. The resulting azide **14b** was cyclized with triphenylphosphine in ether, according to the aza-Wittig reaction[17,18] to afford 6-(1,1-diethoxyethyl)-2,3,4,5-tetrahydropyridine **19** in 72% yield.

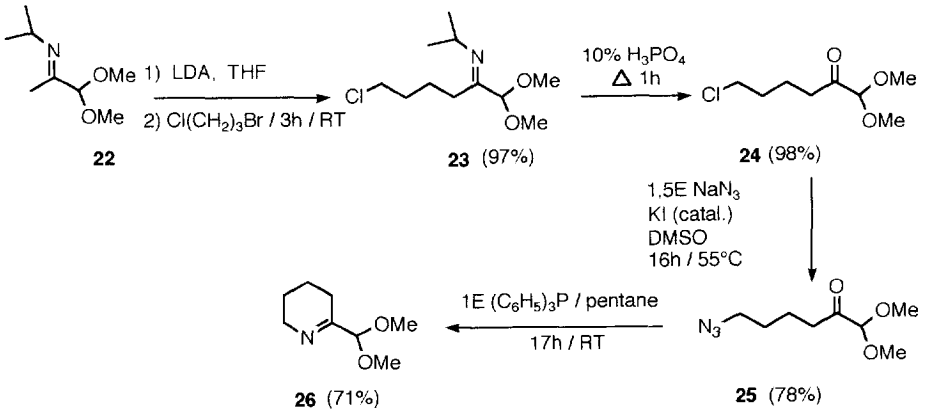
Treatment of δ-chloroketimine **6c** with lithium diisopropylamide in THF did not result in the formation of a cyclic enamine but afforded the cyclobutane derivative **20**, which was not isolated but which, upon purification by preparative gas chromatography, expelled ethanol to form the functionalized enol ether **21** (Scheme 4).



SCHEME 4

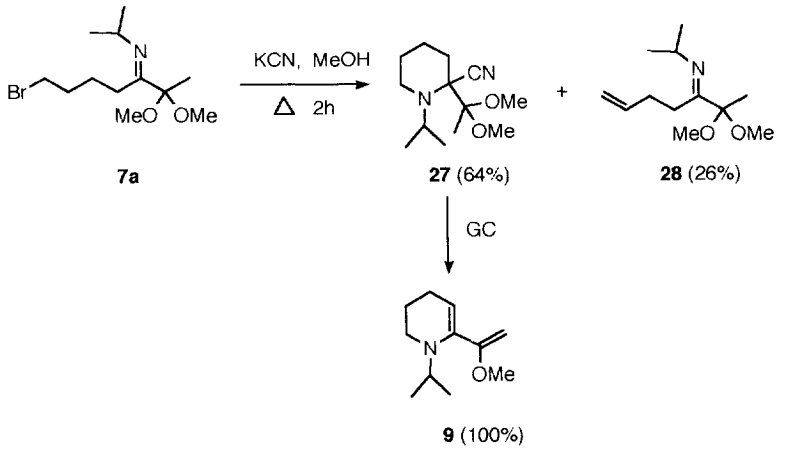
The flexibility of the synthetic procedure leading to acetal-protected 2-acyltetrahydropyridines (*vide supra* for the synthesis of the bread flavor compound **1** and azaheterocycle **19**) was demonstrated by the synthesis of 2-(dimethoxymethyl)-1-piperideine **26**. 3-Chloropropylation of 1,1-dimethoxyacetone imine **22** afforded δ-chloroketimine **23** which was selectively hydrolyzed into the α-ketoacetal **24**, both steps proceeding in nearly quantitative yields. Azidation and aza-Wittig reaction were the final steps which concluded this synthetic procedure leading to 2-(dimethoxymethyl)-1-piperideine **26** (Scheme 5).

It was worthwhile to evaluate the use of δ-bromoimines in these piperideine syntheses, because it could lead to milder reaction conditions or faster ring closure reactions with respect to the chloro analogues. However, the limited shelf life of δ-bromoketimines, e.g. **7a**, is a major drawback for their general use. The reaction of δ-bromoketimine **7a** with potassium carbonate in acetonitrile under reflux for 2h led to 1-isopropyl-6-(1,1-dimethoxyethyl)-1,2,3,4-tetrahydropyridine **8a** (60% yield) but this azaheterocycle was contaminated with unidentified compounds, making this procedure via brominated substrates less attractive. The azidation of δ-bromoketimine **7a** with sodium azide in acetone for 2h under reflux afforded the corresponding δ-azidoimine (about 50%), but cyclization to tetrahydropyridine **8a** (15%) underwent competition with side



SCHEME 5

reactions. The presence of several side products rendered this route via the bromo compounds again less attractive.



SCHEME 6

On the other hand, the reaction of δ-bromoketimine **7a** with potassium cyanide in methanol under reflux provided a good access to 2-cyanopiperidine **27**. However, this reaction suffered also from a 1,2-dehydrobromination leading to the alkenylimine **28**. Both compounds were separated by preparative gas chromatography during which 2-cyano-2-(1,1-dimethoxyethyl)-1-isopropylpiperidine **27** underwent a quantitative elimination of methanol and hydrogen cyanide to give tetrahydropyridine **9**.

In conclusion, various synthetic approaches towards acetal-protected 2-acetyltetrahydropyridines have been developed. These syntheses of functionalized tetrahydropyridines were applied to the synthesis of the principal bread flavor component, 6-acetyl-1,2,3,4-tetrahydropyridine.

EXPERIMENTAL PART

^{1}H NMR spectra were recorded with Varian T-60 (60 MHz), Jeol PMX60 si (60 MHz) and Jeol JNM-EX 270 (270 MHz) NMR spectrometers, while ^{13}C NMR spectra were obtained from a Varian FT-80 (20 MHz) and a Jeol JNM-EX 270 (67 MHz) NMR spectrometer. IR spectra were measured with a Perkin Elmer model 1310 spectrophotometer. Mass spectra were recorded with a Varian-MAT 112 mass spectrometer (70 eV). 3,3-Dialkoxy-2-butanones **4** were prepared by mono-acetalyzation of diacetyl.[19-21]

Synthesis of α,α-Dialkoxyimines **5**

The synthesis of N-(3,3-dimethoxy-2-butylidene)isopropylamine **5a** is representative of all other preparations of imines **5**.

An ice-cooled and vigorously stirred solution of 13,2 g (0.1 mol) of 3,3-dimethoxy-2-butanone **4a** and 23.6 g (0.4 mol) of isopropylamine in 150 ml of dry diethyl ether was treated portionwise with 11.4 g (0.06 mol) of titanium(IV) chloride, dissolved in 10 ml of pentane. The reaction mixture was then stirred for 30 min at room temperature after which it was poured into 100 ml of 0,5 N sodium hydroxide, covered by 50 ml of ether. The layers were shaken vigorously and the organic layer was isolated. The aqueous layer was further extracted twice with ether. The combined organic layers were dried with potassium carbonate, filtered and evaporated in vacuo. The residual liquid was distilled in vacuo to afford 16.5 g (96%) of imine **5a**. Bp. 60-63°C/11 mmHg. ^{1}H NMR ($CDCl_3$) : 1.16 (6H, d, J=6Hz, Me_2); 1.88 (3H, s, MeC=N); 1.41 (3H, s, MeC$(OMe)_2$); 3.26 (6H, s, $(OMe)_2$); 3.75 (1H, septet, J=6Hz, NCH). ^{13}C NMR ($CDCl_3$) : 13.00 (q, MeC=N); 20.99 (q, MeC$(OMe)_2$); 23.20 (q, Me_2); 49.16 (q, $(OMe)_2$); 50.92 (d, NCH); 102.42 (s, C$(OMe)_2$); 165.55 (s, C=N). IR (NaCl) : 2850 cm^{-1} (OMe); 1670 cm^{-1} (C=N). Mass spectrum m/z (%) : no M^+; 142 (8; M^+-OMe); 89(84); 84(27); 58(13); 43(54); 42(100); 41(21).

Elemental analysis : Calcd. : C 62.34%, H 11.05%, N 8.08%
Found : C 62.45%, H 11.00%, N 8.21%

N-(3,3-dimethyl-2-butylidene)benzylamine **5b**

Bp. 104-107°C/0.05 mmHg.

^{1}H NMR ($CDCl_3$) : 1.42 (3H, s, MeC$(OMe)_2$); 1.87 (3H, s, broadened, MeC=N); 3.23 (6H, s, $(OMe)_2$); 4.60 (2H, s, broadened, NCH_2); 7.2-7.4 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) : 13.85 (q, MeC=N); 20.67 (q, MeC$(OMe)_2$); 55.12 (t, NCH_2); 49.32 (q, $(OMe)_2$); 102.55 (s, C$(OMe)_2$); 126.48 (d, CH=para); 127.57 and 128.27 (each d, 2xCH=CH meta and ortho); 139.90,(s, NCH_2C=C); 170.08 (s, C=N). IR (NaCl) : 2830 cm^{-1} (OMe); 1670 cm^{-1} (C=N). Mass spectrum m/z (%) : no M^+; 190 (4; M^+-OMe); 132(4); 91(64); 89(100); 65(11); 43(42).

Elemental analysis : Calcd. : C 70.56%, H 8.65%, N 6.33%
Found : C 70.71%, H 8.60%, N 6.52%

N-(3,3-diethoxy-2-butylidene)isopropylamine **5c**

^{1}H NMR ($CDCl_3$) : 1.10 (6H, d, J=6.5Hz, $CH(Me)_2$); 1.16 (6H, t, J=6.5Hz, $MeCH_2$); 1.38 (3H, s, J=6.5Hz, MeC$(OEt)_2$); 1.85 (3H, s, MeC=N); 3.48 (4H, q, J=6.5Hz, $(OCH_2Me)_2$); 3.3-3.8 (1H, m,

$C\underline{H}(Me)_2$). ^{13}C NMR ($CDCl_3$) : 12.84 (q, $\underline{C}H_3C=N$); 15.58 (q, $\underline{C}H_3CH_2$); 21.84 (q, Me_2); 23.32 (q, $\underline{C}H_3$ C_{quat}); 50.75 (d, $\underline{C}HMe_2$); 57.00 (t, $\underline{C}H_2Me$); 102.53 (s, $\underline{C}(OEt)_2$); 166.28 (s, C=N). IR (NaCl) : 1670 cm^{-1} (C=N). Mass spectrum m/z (%) : no M^+; 156 (18, M^+-OEt); 117(78); 105(82); 89(33); 84(25); 77(39); 61(71); 58(24); 51(20); 43(100); 42(92).

Elemental analysis : Calcd. : C 65.63%, H 11.52%, N 6.96%
Found : C 65.83%, H 11.42%, N 7.05%

Synthesis of N-(2,2-dialkoxy-7-halo-3-heptylidene)amines **6** and **7**

The preparation of N-(7-chloro-2,2-dimethoxy-3-heptylidene)isopropylamine **6a** is representative of all other preparations of functionalized imines **6** and **7**.

A solution of lithium diisopropylamide (0.012 mol) was prepared by addition of 7.2 ml of a 1.65 M butyllithium (0.012 mol) in hexane to a solution of 1.31 g (0.013 mol) of diisopropylamine in 20 ml of dry tetrahydrofuran (0°C, magnetic stirring, nitrogen atmosphere). After 15 minutes, this cold solution was treated dropwise by syringe with a 1.73 g (0.01 mol) of N-(3,3-dimethoxy-2-butylidene)isopropylamine **5a**, dissolved in 2 ml of dry tetrahydrofuran. The mixture was stirred for 2-3h at 0°C after which 1.83 g (0.012 mol) of 1-bromo-3-chloropropane was added dropwise by syringe. This solution was stirred for 20h during which the temperature came to ambient temperature. The reaction mixture was poured in 100 ml of 0.05 N sodium hydroxide and extracted three times with ether. The combined organic extracts were dried (K_2CO_3), filtered and evaporated to afford 2.50 g (100%) of a clear oil consisting of pure δ-chloroketimine **6a**. Due to the labile nature of δ-chloroketimines **6a-c** and δ-bromoketimine **7a**, they were neither distilled in vacuo (partial or complete decomposition) nor submitted to flash chromatography (hydrolysis and decomposition). These compounds were used as such in further experiments.

N-(7-chloro-2,2-dimethoxy-3-heptylidene)isopropylamine **6a**

^1H NMR ($CDCl_3$) : 1.16 (6H, d, J=6Hz, Me_2); 1.40 (3H, s, Me); 3.20 (6H, s, $(OMe)_2$); 1.5-2.0 (4H, m, CH_2CH_2); 2.2-2.5 (2H, m, $CH_2C=N$); 3.57 (2H, t, J=6.5Hz, CH_2Cl); 3.70 (1H, septet, J=6Hz, NCH). ^{13}C NMR ($CDCl_3$) : 22.15 (q, $\underline{Me}C(OMe)_2$); 23.62 (q, Me_2); 24.83 and 26.73 (each t, CH_2CH_2); 32.98 (t, $\underline{C}H_2C=N$); 44.33 (t, CH_2Cl); 48.90 (q, $(OMe)_2$); 50.59 (d, NCH); 102.74 (s, $\underline{C}(OMe)_2$); 168.54 (s, C=N). IR (NaCl) : 2830 cm^{-1} (OMe); 1660 cm^{-1} (C=N). Mass spectrum m/z (%) : no M^+; 218/220 (8, M^+-OMe); 160/162(16); 118/120(37); 89(100); 82(18); 58(8); 55(10); 43(37); 41(11).

N-(7-Chloro-2,2-dimethoxy-3-heptylidene)benzylamine **6b**

Yellow oil (90%). This labile compound contained some impurities, probably due to partial isomerization into the N-benzylidene derivative. This compound is stable at -20°C but decomposed in $CDCl_3$ at room temperature for an overnight period. ^1H NMR ($CDCl_3$) : 1.48 (3H, s, $\underline{Me}C(OMe)_2$); 3.24 (6H, s, $(OMe)_2$); 1.5-2.2 (4H, m, CH_2CH_2); 2.2-2.6 (2H, m, $CH_2C=N$); 3.6 (2H, t, J=6.5Hz, CH_2Cl); 4.70 (2H, s, $C\underline{H}_2Ph$); 7.1-7.4 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) : 21.66 (q, Me); 23.91 and 27.20 (each t, CH_2CH_2); 32.84 (t, $CH_2C=N$); 44.30 (t, CH_2Cl); 49.28 (q, $(OMe)_2$); 54.65 (t, NCH_2); 102.98 (s, $\underline{C}(OMe)_2$); 127.54 and 128.30 (each d, =CH's ortho and meta); 162.70 (s, $NCH_2\underline{C}=$); 172.96 (s, C=N); the para =CH signal was difficult to attribute due to the presence of some signals of impurities.

N-(7-Chloro-2,2-diethoxy-3-heptylidene)isopropylamine **6c**

The compound could be distilled on a small scale (bp. : 73-75°C/0.05 mmHg). Distillation on a larger scale led to decomposition of the product.

Yellow oil (87%). ^{1}H-NMR ($CDCl_3$) 1.0-1.3 (6H, d, J=6.5Hz, CMe_2); 1.18 (6H, t, J=6.5Hz, $(OEt)_2$); 1.40 (3H, s, Me C_{quat}); 1.5-2.0 (4H, m, CH_2CH_2); 2.2-2.5 (2H, m, CH_2CN); 3.48 (4H, q, J=6.5Hz, $(OEt)_2$); 3.4-3.8 (2H, m, CH_2Cl); 3.5-4.0 (1H, quint., J=6.5Hz, $CHMe_2$). ^{13}C NMR ($CDCl_3$) : 15.52 (q, $MeCH_2$); 22.97 (q, Me C_{quat}); 23.80 (q, Me_2); 25.05 (t, CH_2); 26.71 (t, CH_2CH_2Cl); 33.91 (t, CH_2C=N); 44.24 (t, CH_2Cl); 50.53 (d, $CHMe_2$); 56.76 (t, CH_2O); 102.69 (s, $C(OEt)_2$); 169.03 (s, C=N). IR (NaCl) : 1662 cm^{-1} (C=N). Mass spectrum m/z (%) : no M^+, 233/35 (12, M^+-OEt); 160/62(12); 118/20(40); 117(100); 89(24); 82(17); 61(38); 55(12); 43(45).

N-(7-Bromo-2,2-dimethoxy-3-heptylidene)isopropylamine **7a**

^{1}H NMR ($CDCl_3$) : 1.13 (6H, d, J=6Hz, Me_2); 1.38 (3H, s, $MeC(OMe)_2$); 1.5-2.2 (4H, m, CH_2CH_2); 2.1-2.5 (2H, m, CH_2C=N); 3.40 (2H, ~t, CH_2Br); 3.80 (1H, septet, J=6Hz, NCH); 3.17 (6H, s, $(OMe)_2$). ^{13}C NMR ($CDCl_3$) : 22.18 (q, $MeC(OMe)_2$); 23.63 (q, Me_2); 26.03 and 26.56 (each t, CH_2CH_2); 32.93 (t, CH_2C=N); 33.11 (t, CH_2Br); 50.55 (d, NCH); 48.48 (q, $(OMe)_2$); 102.70 (s, $(OMe)_2$); 168.34 (s, C=N). IR (NaCl) : 2830 cm^{-1} (OMe); 1665 cm^{-1} (C=N). Mass spectrum m/z (%) : 293/295 (M^+; 0.1); 278/280 (0.2); 262/264 (4); 204/206(9); 162/164(17); 89(100); 82(25); 58(8); 55(9); 43(38); 41(23). This labile compound should be kept at -20°C under a nitrogen atmosphere or should be preferably used immediately for further elaboration. This δ-bromoketimine **7a** decomposed in $CDCl_3$ at room temperature overnight.

Synthesis of 1-substituted 6-(1,1-dimethoxyethyl)-1,2,3,4-tetrahydropyridines **8**

A stirred solution of 0,001 mol of N-(7-chloro-2,2-dimethoxy-3-heptylidene)amines **6a** or **6b** in 6 ml of acetonitrile was treated with 0,002 mol of potassium carbonate and refluxed for 6-7h after which it was poured into 50 ml of ether. The reaction mixture was stirred for 15 min, filtered and evaporated to give tetrahydropyridines **8**. Compound **8a** was obtained in 98% yield without interference of impurities (GC, ^{1}H NMR). An analytical sample was obtained by preparative gas chromatography but most of this compound (85%) was converted into enol ether **9**. The latter compound was obtained as well by refluxing tetrahydropyridine **8a** with potassium carbonate in acetonitrile for an extended period of time (17h), resulting in a quantitative conversion into a reaction mixture containing compound **8a** and **9** in a 2:1 ratio. The reaction of δ-chloroketimine **6b** with potassium carbonate in acetonitrile afforded a reaction mixture which contained only 25% of tetrahydropyridine **8b**. No efforts were made to isolate compound **8b** from this complex reaction mixture.

6-(1,1-Dimethoxyethyl)-1-isopropyl-1,2,3,4-tetrahydropyridine **8a**

^{1}H NMR (CCl_4) : 1.02 (6H, d, J=7Hz, Me_2); 1.32 (3H, s, $MeC(OMe)_2$); 1.4-1.7 (2H, m, CH_2); 1.8-2.2 (2H, m, CH_2); 2.8-3.1 (2H, m, NCH_2); 3.10 (6H, s, $(OMe)_2$); 4.02 (1H, septet, J=7Hz, NCH); 5.06 (1H, t, J=3.5Hz, CH=C). ^{13}C NMR ($CDCl_3$) : 20.45 (q, Me_2); 22.73 and 23.04 (each t, CH_2CH_2); 23.59 (q, $MeC(OMe)_2$); 41.56 (t, NCH_2); 48.03 (d, NCH); 48.85 (q, $(OMe)_2$); 101.13 (s, $C(OMe)_2$); 103.88 (d, CH=C). IR (NaCl) : 2830 cm^{-1} (OMe); 1630 cm^{-1} (C=C). Mass spectrum m/z (%) : 213 (M^+; 13); 183(10); 182(14); 168(14); 166(15); 150(10); 140(13); 124(14); 112(22); 110(24); 89(100); 82(19); 69(12);

57(61); 43(51); 42(20); 41(43).

Elemental analysis : Calcd. : C 67.56%, H 10.87%, N 6.56%
Found : C 67.68%, H 10.78%, N 6.71%

6-(1-Methoxyethenyl)-1-isopropyl-1,2,3,4-tetrahydropyridine **9**

^{1}H NMR ($CDCl_3$) : 1.06 (6H, d, J=6.7Hz, Me_2); 1.5-2.2 (4H, m, CH_2CH_2); 2.9-3.2 (2H, m, NCH_2); 3.5 (1H, septet, J=6.7Hz, NCH); 3.63 (3H, s, OMe); 4.06 and 4.32 (each d, AB, J=3Hz, $C=CH_2$); 4.93 (1H, t, J=4Hz, CH=C). ^{13}C NMR ($CDCl_3$) : 19.95 (q, Me_2); 22.53 and 22.93 (each t, CH_2CH_2); 40.65 (t, NCH_2); 43.44 (d, NCH); 54.93 (q, OMe); 84.08 (t, $C=\underline{C}H_2$); 103.76 (d, $\underline{C}H=C$); 143.44 (s, $CH=\underline{C}$-N); 161.80 (s, MeO-$\underline{C}=C$). IR (NaCl) : 1620 cm^{-1} (broad, C=C-C=C). Mass spectrum m/z (%) : 181 (77; M^+); 166(100); 151(13); 138(18); 136(32); 134(39); 124(17); 82(24); 55(29); 54(29); 43(28); 42(21); 41(45).

Elemental analysis : Calcd. : C 72.88%, H 10.56%, N 7.72%
Found : C 72.98%, H 10.70%, N 7.61%

Hydrolysis of Acetal **8a** into Tetrahydropyridine **10**

To a mixture of 3.14 g (0.014 mol) of 6-(1,1-dimethoxyethyl)-1-isopropyl-1,2,3,4-tetrahydropyridine **8a** in 50 ml dichloromethane was added 0.14 mol (10 equiv.) of aqueous hydrochloric acid (2N). The mixture was refluxed for 14 h and, after cooling, extracted with dichloromethane and dried ($MgSO_4$). After filtration, evaporation of the solvent and distillation, 0.4 g (16%) of the tetrahydropyridine **10** was obtained. B.p. 50-53°C/ 0.05 mmHg.

^{1}H NMR ($CDCl_3$) : 1.06 (6H, d, J=6.5Hz, CMe_2); 1.5-1.9 (2H, m, CH_2); 2.0-2.4 (2H, m, CH_2-C=); 2.25 (3H, s, MeC=O); 2.8-3.2 (2H, m, CH_2N); 3.45 (1H, quint, J=6.5Hz, $C\underline{H}Me_2$); 5.61 (1H, t, J=4Hz, CH=). ^{13}C NMR ($CDCl_3$) : 19.95 (q, $CHMe_2$); 21.60 (t, CH_2); 23.21 (t, CH_2); 27.15 (t, CH_2); 40.81 (t, CH_2N); 50.62 (d, $CHMe_2$); 114.74 (d, CH=); 147.80 (s, =C-N); 199.64 (s, C=O). IR (NaCl) : 1680 cm^{-1} (C=O); 1603 cm^{-1} (C=C). Mass spectrum m/z (%) : 167 (M^+, 45); 152(100); 134(30); 124(28); 82(43); 54(41); 43(77).

Elemental analysis : Calcd. : C 71.81%, H 10.24%, N 8.37%
Found : C 71.50%, H 10.41%, N 8.51%

Synthesis of 7-Chloroheptane-2,3-dione **11**

A solution of 12.47 g (0.05 mol) of δ-chloroketimine **6a** in 40 ml of dichloromethane was treated with 250 ml of 2N aqueous hydrogen chloride. Both layers were vigorously stirred for 16 h at room temperature after which the organic layer was isolated. The aqueous layer was extracted again with dichloromethane. Both organic extracts were dried ($MgSO_4$) and evaporated to afford 7.16 g (87%) of almost pure 7-chloroheptane-2,3-dione **11** (GC, NMR). Distillation in vacuo gave 6.8 g (83%) of the pure α-dione as a yellow oil, bp. 98-110°C/11 mmHg.

^{1}H NMR ($CDCl_3$) : 1.6-1.9 (4H, m, CH_2CH_2); 2.34 (3H, s, CH_3CO); 2.81 (2H, ~t, J=6.5Hz); 3.57 (2H, ~t, J=6Hz, CH_2Cl). ^{13}C NMR ($CDCl_3$) : 20.32 (q, Me); 23.63 (t, CH_2); 31.78 (t, CH_2); 34.78 (t, CH_2); 44.56 (t, CH_2); 197.32 (s, C=O); 198.65 (s, C=O). IR (NaCl) : 1715-1727 cm^{-1} (C=O). Mass spectrum m/z (%) : 162 (M^+, 8); 121(22); 119(54); 93(20); 91(48); 63(12); 56(11); 55(100); 44(14); 43(87).

Elemental analysis : Calcd. : C 51.70%, H 6.82%, Cl 21.80%
Found : C 51.91%, H 7.00%, Cl 21.98%

In similar way as described above, δ-chloroketimine **6b** (0.001 mol scale) was hydrolyzed to 7-chloroheptane-2,3-dione **11** in 60% yield (GC, ^{1}H NMR). The final product was contaminated by about 10% benzaldehyde (isolated by preparative GC). Therefore, the preparation of α-dione **11** via N-benzyl δ-chloroketimine **6b** is less recommended as compared to the synthesis via the N-isopropyl δ-chloroketimine **6a**.

Reaction of 7-Chloroheptane-2,3-dione **11** with sodium Azide

A solution of 0.81 g (0.005 mol) of α-dione **11** in 8 ml of dimethyl sulfoxide was treated with 0.49 g (0.0075 mol) of sodium azide and 75 mg (0.0005 mol) of sodium iodide. The mixture was stirred at 55°C for 15h. Aqueous work up and extraction with ether gave a viscous reaction which did not contain 7-azido-heptane-2,3-dione **12**. The same reaction at room temperature gave a similar result. Also the reaction of α-dione **11** with sodium azide in acetone under reflux did not give dione **12**.

Regioselective Acetalyzation of 7-Chloroheptane-2,3-dione **11**

A mixture of 0.40 g (0.0025 mol) of 7-chloroheptane-2,3-dione **11**, 0.26 g (0.0025 mol) of trimethyl orthoformate and 1 drop of concentrated sulfuric acid was stirred at 50°C for 4h. The reaction mixture was poured in aqueous sodium hydroxide (0.5 N) and extracted three times with dichloromethane. The combined extracts were washed with brine, dried (K_2CO_3) and evaporated to give 0.50 g of a reaction mixture containing 90% of α-ketoacetal **13** (GC, ^{1}H NMR).

^{1}H NMR (CCl_4) : 1.26 (3H, s, Me); 1.5-1.9 (4H, m, CH_2CH_2); 2.57 (2H, ~t, CH_2C=O); 3.18 (6H, s, $(OMe)_2$); 3.52 (2H, ~t, CH_2Cl). ^{13}C NMR ($CDCl_3$) : 19.71 (q, Me); 20.81 (t, CH_2); 32.20 (t, CH_2); 37.10 (t, CH_2); 44.62 (t, CH_2Cl); 49.56 (q, OMe); 102.67 (s, $C(OMe)_2$); 208.14 (s, C=O). IR (NaCl) : 2835 cm^{-1} (OMe); 1730 cm^{-1} (C=O). Mass spectrum m/z (%) : 194 (0.6); 177/79(8); 89(79); 58(29); 43(100).

Elemental analysis : Calcd. : C 51.80%, H 8.21%, Cl 16.99%
Found : C 51.84%, H 7.99%, Cl 17.04%

An improved procedure for the synthesis of α-ketoacetal **13** is given in the next experiment.

Selective hydrolysis of N-(7-chloro-2,2-dimethoxy-3-heptylidene)isopropylamine **6a** to 7-Chloro-2,2-dimethoxy-3-heptanone **13**

To a solution of (11.97 g) 0.048 mol of iminoacetal **6a** in 120 ml of dichloromethane was added 9.07 g (0.072 mol) oxalic acid dihydrate in 100 ml of water. The mixture was refluxed for 1h and extracted three times with dichloromethane. After drying ($MgSO_4$), filtration and evaporation of the solvent, the resulting oil was distilled under high vacuum (bp. 58-60°C/0.05 mmHg) giving 8.89 g (89%) of ketoacetal **13** as a yellow oil.

Azidation of 7-Chloro-2,2-dimethoxy-3-heptanone **13**

A solution of 0.206 g (0.001 mol) α-ketoacetal **13** in 6 ml of DMSO was treated with 0.097 g (0.0015 mol) of sodium azide. The mixture was heated at 55°C overnight after which it was poured in water, extracted with ether, dried (K_2CO_3) and evaporated to give 0.172 g (80%) of a clear oil which consisted of pure

δ-azidoketone **14a** (GC, ^{1}H NMR).

^{1}H NMR ($CDCl_3$) : 1.36 (3H, s, Me); 1.5-1.8 (4H, m, CH_2CH_2); 2.65 (2H, ~t, CH_2CO); 3.24 (6H, s, $(OMe)_2$); 3.3 (2H, covered, CH_2N_3). ^{13}C NMR ($CDCl_3$) : 19.73 (q, Me); 20.71 (t, $\underline{C}H_2CH_2CO$); 28.61 (t, $\underline{C}H_2CH_2N_3$); 37.41 (t, $\underline{C}H_2CO$); 49.54 (q, $(OMe)_2$); 51.46 (t, $\underline{C}H_2N_3$); 102.76 (s, $\underline{C}(OMe)_2$); 208.06 (s, C=O). IR (NaCl) : 2100 cm^{-1} (N_3); 1733 cm^{-1} (C=O). Mass spectrum m/z (%) no M^+; 89(100); 82(6); 58(8); 57(3); 56(3); 55(5); 47(6); 43(55); 42(5).

Aza-Wittig Cyclization of α-ketoacetal **14a** with Triphenylphosphine

A solution of 0.645 g (0.003 mol) of α-ketoacetal **14a** in 70 ml of dry ether was treated with 0.786 g (0.003 mol) of triphenylphosphine. After stirring for 18h at ambient temperature, ^{1}H NMR monitoring revealed that only 50% conversion into the cyclic imine **16** had taken place. The reaction mixture was additionally refluxed under stirring for 5h, after which the solvent was evaporated in vacuo. The solid residue was extracted three times with pentane. The combined extracts were evaporated to give 0.38 g (73%) of a colorless oil, consisting of pure 6-(1,1-dimethoxy)ethyl-2,3,4,5-tetrahydropyridine **16** (GC, ^{1}H NMR; purity > 97%). This compound was used as such in the next hydrolysis experiment.

^{1}H NMR ($CDCl_3$) : 1.42 (3H, s, Me); 1.4-1.8 (4H, m, CH_2CH_2); 2.0-2.3 (2H, m, CH_2C=N); 3.25 (6H, s, $(OMe)_2$); 3.6-3.9 (2H, m, NCH_2). ^{13}C NMR ($CDCl_3$) : 21.05 (q, Me); 19.29, 21.87 and 25.08 (each t, $CH_2CH_2CH_2$); 49.30 (t, NCH_2); 49.16 (q, $(OMe)_2$); 101.86 (s, $\underline{C}(OMe)_2$); 169.87 (s, C=N). Mass spectrum m/z (%) : 171 (M^+; 4); 156(11); 140(33); 139(12); 126(6); 124(9); 109(9); 108(12); 101(48); 89(100); 73(12); 55(36); 43(36); 42(18); 41(24).

Elemental analysis : Calcd. : C 63.13%, H 10.01%, N 8.18%
Found : C 63.02%, H 10.36%, N 7.97%

Preparative gas chromatographic analysis of cyclic imine **16** caused partial loss (about 15%) of methanol resulting in 6-(2-methoxy)ethenyl-2,3,4,5-tetrahydropyridine **17**.

Mass spectrum of enol ether **17** : m/z (%) 139 (M^+; 87); 124(30); 109(100); 108(90); 85(51); 83(84); 82(36); 81(36); 55(51); 54(63); 51(39); 49(84); 43(60); 42(60); 41(96); 40(93).

Hydrolysis of Acetal **16** into 6-Acetyl-1,2,3,4-tetrahydropyridine **1**

A solution of 0.38 g (0.0022 mol) acetal **16** in 10 ml dichloromethane was treated under stirring with 11 ml of 2N hydrogen chloride (0.022 mol). Stirring was continued for 24h at room temperature after which the reaction mixture was made alkaline with 4N sodium hydroxide. The organic layer was isolated and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford 0,18 g (65%) of pure 6-acetyl-1,2,3,4-tetrahydropyridine **1** (GC, ^{1}H NMR; purity > 96%). The freshly prepared compound **1** occurred in solution as a mixture of enamine **1** and imine **2** in a 2:1 ratio (^{1}H NMR; $CDCl_3$). The spectral data of compounds **1** and **2** matched in all aspects with those previously reported.[11]

Azidation of δ-Chloroketimine **6c**

A solution of 6,94 g (0.025 mol) of δ-chloroketimine **6c** was treated with 2,44 g (0.037 mol) of sodium azide in DMSO. The reaction mixture was stirred for 16h at 60°C, subsequently poured into aqueous sodium hydroxide (1N) and extracted with ether. After drying (K_2CO_3 + $MgSO_4$) and filtration, the solvent was removed in vacuo. The resulting azide (6.2 g; 87%) was sufficiently pure (purity > 97%) to use as such in the next step.

^{1}H NMR ($CDCl_3$) : 1.10 (6H, d, J=6.5Hz, $CHMe_2$); 1.16 (6H, t, J=6.5Hz, $(OEt)_2$); 1.40 (3H, s, Me C_{quat}); 1.2-1.8 (4H, m, CH_2CH_2); 2.1-2.5 (2H, m, $C\underline{H}_2C{=}N$); 3.1-3.6 (2H, m, CH_2N_3); 3.46 (4H, q, J=6.5Hz, $(OC\underline{H}_2CH_3)_2$); 3.63 (1H, ~quint., J=6.5Hz, $C\underline{H}Me_2$). ^{13}C NMR ($CDCl_3$) : 15.50 (q, $(OEt)_2$); 23.01 (q, Me C_{quat}); 23.79 (q, $CHMe_2$); 25.03 (t, CH_2); 27.02 (t, CH_2); 29.47 (t, CH_2); 50.59 (d, $CHMe_2$); 51.20 (t, CH_2N_3); 56.81 (t, $(O\underline{C}H_2CH_3)_2$); 102.77 (s, C_{quat}); 169.06 (s, C=N). IR (NaCl) : 2090 cm^{-1} (N_3); 1668 cm^{-1} (C=N).

Selective Hydrolysis of δ-Azidoketimine **18**

A solution of 5,48 g (0.019 mol) of δ-azidoketimine **18** in 50 ml dichloromethane was treated with 3.64 g (0.028 mol) of oxalic acid dihydrate, dissolved in 40 ml of water. Both phases were vigorously stirred at reflux temperature for 1h. The mixture was then extracted with dichloromethane and the combined organic layers dried (K_2CO_3 + $MgSO_4$). After filtration and evaporation of the solvent, 4.44 g of δ-azidoketimine **18** was isolated (yield : 94%).

^{1}H NMR ($CDCl_3$) : 1.20 (6H, t, J=7Hz, $(C\underline{H}_3CH_2O)_2$); 1.36 (3H, s, Me C_{quat}); 1.4-1.8 (4H, m, CH_2CH_2); 2.5-2.9 (2H, m, $CH_2C{=}O$); 3.41 (2H, m, CH_2N_3); 3.2-3.7 (4H, m, $(OC\underline{H}_2CH_3)_2$). ^{13}C NMR ($CDCl_3$) : 15.41 (q, $(OCH_2\underline{C}H_3)_2$); 20.72 (q, Me C_{quat}); 20.72 (t, $\underline{C}H_2$); 28.54 (t, CH_2); 37.23 (t, $\underline{C}H_2C{=}O$); 51.42 (t, CH_2N_3); 57.67 (t, $(O\underline{C}H_2CH_3)_2$); 102.44 (s, C_{quat}); 208.85 (s, C=O). IR (NaCl) = 2095 cm^{-1} (N_3); 1730 cm^{-1} (C=O).

Aza-Wittig Cyclization of δ-Azidoketimine **14b** with Triphenylphosphine

The aza-Wittig cyclization of **14b** in cyclic imine **19** was performed in analogous way as described for the synthesis of compound **16**. The imino acetal **19** was obtained as a colorless oil in 72% yield (purity > 97%; GC) (bp. : 38-42°C/0.1 mmHg).

^{1}H NMR ($CDCl_3$) : 1.18 (6H, t, J=7Hz, $(OCH_2\underline{C}H_3)_2$); 1.40 (3H, s, Me C_{quat}); 1.4-1.8 (4H, m, CH_2CH_2); 2.0-2.4 (m, $CH_2C{=}$); 3.46 (4H, q, J=7Hz, $(O\underline{C}H_2CH_3)_2$); 3.4-3.9 (2H, m, CH_2N). ^{13}C NMR ($CDCl_3$) : 15.48 (q, $OCH_2\underline{C}H_3$); 19.54 (t, CH_2); 22.08 (t, CH_2); 22.13 (q, Me C_{quat}); 25.25 (t, $CH_2C{=}N$); 49.33 (t, CH_2N); 56.95 (t, $O\underline{C}H_2CH_3$); 101.94 (s, C_{quat}); 170.97 (s, C=N). IR (NaCl) : 1670 cm^{-1} (C=N); 2880 cm^{-1} (OCH_2). Mass spectrum m/z (%) : 199 (3, M^+); 154 (32, M^+-OEt); 126(32); 117(69); 109(32); 89(53); 61(100); 43(47).

Elemental analysis : Calcd. : C 66.29%, H 10.62%, N 7.03%
Found : C 66.06%, H 10.48%, N 7.13%

Cyclization of δ-Chloroketimine **6c** in Cyclobutylketimine **20**

A solution of freshly prepared LDA (0.039 mol; from 1,8 ml 2.5 N butyllithium in hexane and 0.41 g (0.039 mol) diisopropylamine, dissolved in 50 ml of THF) was treated with 0.86 g (0.003 mol) of δ-chloroketimine **6c**, dissolved in 10 ml of THF at 0°C (N_2 atmosphere). The reaction mixture was stirred for 14 h at room temperature, then poured into 100 ml of aqueous sodium hydroxide (1N) and extracted three times with ether. After drying ($MgSO_4$), the solvent was evaporated leaving 0.57 g of crude cyclobutylketimine **20** as an unstable oil. Upon preparative gas chromatography, compound **20** lost methanol to afford enol ether **21**.

^{1}H NMR ($CDCl_3$) : 1.08 (6H, d, J=6Hz, $CHMe_2$); 1.28 (3H, t, J=7Hz, CH_2CH_3); 1.6-2.4 (7H, m, $CH_2CH_2CH_2CH$); 2.9-3.3 (1H, m, $CHMe_2$); 3.4-4.0 (2H, m, OCH_2CH_3); 4.0-4.3 (2H, m, CH_2=). ^{13}C NMR ($CDCl_3$) 14.44 (q, CH_2CH_3); 17.99 (t, CH_2); 24.10 (q, $CHMe_2$); 26.08 (t, CH_2); 42.84 (d, CH); 52.77 (d, $CHMe_2$); 62.58 (t, OCH_2CH_3); 83.74 (t, CH_2=); 156.54 (s, CH_2=C); 166.37 (s, C=N). IR (NaCl) : 1645 cm^{-1} (C=N); 1605 cm^{-1} (C=C). Mass spectrum m/z (%) : 195 (M^+, 3); 180(13); 166(20); 138(13); 124(23); 108(13); 98(38); 82(100); 55(35); 54(20); 43(35).

Elemental analysis : Calcd. : C 73.79%, H 10.84%, N 7.17%
Found : C 73.70%, H 10.98%, N 7.28%

Synthesis of N-(6-Chloro-1,1-dimethoxy-2-hexylidene)isopropylamine **23**

N-(1,1-Dimethoxy-2-propylidene)isopropylamine **22** was converted into δ-chloroketimine **23** in 97% yield, according to an analogous procedure described above for the synthesis of compounds **6**.

^{1}H NMR ($CDCl_3$) : 1.16 (6H, d, J=6.4Hz, $CHMe_2$); 1.5-2.0 (4H, m, CH_2CH_2); 2.1-2.5 (2H, m, CH_2); 3.40 (6H, s, OMe); 3.45 (2H, t, CH_2Cl); 3.83 (1H, quint., J=6.4Hz, $CHMe_2$); 4.46 (1H, s, $CH(OMe)_2$). ^{13}C NMR ($CDCl_3$) : 23.92 (q, $CHMe_2$); 25.05 (t, CH_2); 25.64 (t, CH_2); 33.10 (t, CH_2); 44.25 (t, CH_2Cl); 50.15 (d, $CHMe_2$); 54.90 (q, OMe); 109.48 (d, $CH(OMe)_2$); 165.31 (s, C=N). IR (NaCl) : 1662 cm^{-1} (C=N); 2830 cm^{-1} (OMe). Mass spectrum m/z (%) : 235/37 (0.5, M^+); 160/62(42); 118/20(100); 82(53); 75(39); 58(11); 55(22); 47(11); 43(28); 42(11); 41(25).

Elemental analysis : Calcd. : C 56.04%, H 9.40%, N 5.94%
Found : C 55.90%, H 9.58%, N 6.07%

Synthesis of 6-Chloro-1,1-dimethoxy-2-hexanone **24**, 6-Azido-1,1-dimethoxy-2-hexanone **25** and 6-(Dimethoxymethyl)-2,3,4,5-tetrahydropyridine **26**

Compounds **24**, **25** and **26** were prepared according to procedures described above for the synthesis of compounds **13**, **14a** and **16**.

6-Chloro-1,1-dimethoxy-2-hexanone **24**

^{1}H NMR ($CDCl_3$) : 1.5-2.0 (4H, m, CH_2CH_2); 2.5-2.8 (2H, m, CH_2C=O); 3.3-3.6 (2H, m, CH_2Cl); 3.46 (6H, s, OMe); 4.52 (1H, s, $CH(OMe)_2$). ^{13}C NMR ($CDCl_3$) : 20.48 (t, CH_2); 32.11 (t, CH_2); 36.21 (t, CH_2); 44.52 (t, CH_2Cl); 54.93 (q, OMe); 104.61 (d, $CH(OMe)_2$); 204.90 (s, C=O). IR (NaCl) : 1730 cm^{-1} (C=O). Mass spectrum m/z (%) : 163 (2, M^+-OMe); 75(100); 55(9); 47(24); 45(14).

Elemental analysis : Calcd. : C 49.36%, H 7.76%, 18.21%

Found : C 49.30%, H 7.91%, 18.04%

6-Azido-1,1-dimethoxy-2-hexanone **25**

^{1}H NMR ($CDCl_3$) : 1.5-1.9 (4H, m, CH_2CH_2); 2.4-2.8 (2H, m, CH_2CO); 3.1-3.5 (2H, m, CH_2N_3); 3.46 (6H, s, OMe); 4.48 (1H, s, $CH(OMe)_2$). ^{13}C NMR ($CDCl_3$) : 20.36 (t, CH_2); 28.51 (t, CH_2); 36.44 (t, CH_2); 51.35 (t, CH_2N_3); 54.91 (q, OMe); 104.75 (d, $CH(OMe)_2$); 204.83 (s, C=O). IR (NaCl) : 2098 cm^{-1} (N_3); 1730 cm^{-1} (C=O).

6-(Dimethoxymethyl)-2,3,4,5-tetrahydropyridine **26**

^{1}H NMR ($CDCl_3$) : 1.5-1.8 (4H, m, CH_2CH_2); 2.0-2.3 (2H, m, CH_2-C=); 3.31 (6H, s, OMe); 3.4-3.8 (2H, m, CH_2N); 4.37 (1H, s, $CH(OMe)_2$). ^{13}C NMR ($CDCl_3$) : 19.07 (t, CH_2); 22.39 (t, CH_2); 23.40 (t, CH_2); 49.18 (t, CH_2N); 54.64 (q, OMe); 107.84 (d, $CH(OMe)_2$); 167.75 (s, C=N). IR (NaCl) : 1670 cm^{-1} (C=N). Mass spectrum m/z (%) 157 (1.6, M^+); 127(13); 126(13); 112(13); 75(100); 55(23); 47(23); 44(13); 41(16). bp. 28°C/0.02 mmHg.

Elemental analysis : Calcd. : C 61.12%, H 9.62%, N 8.91%
Found : C 61.20%, H 9.51%, N 8.79%

Cyanation of δ-Bromoketimine **7a**

A mixture of 0.6 g (0.002 mol) of δ-bromoketimine **7a** and 0.26 g (0.004 mol) of potassium cyanide 10 ml methanol was stirred under reflux for 2h. The reaction mixture was poured in water and was extracted three times with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to afford a colorless reaction mixture (0.42 g), whose ^{1}H NMR spectrum revealed the presence of the labile piperidine derivative **27** and the 1,2-dehydrobromination product **28**. Preparative GC gave a complete conversion into tetrahydropyridine **9** (64%) (see spectral data given above) and homoallylketimine **28** (26%).

N-(2,2-Dimethoxy-6-hepten-3-ylidene)isopropylamine **28**

^{1}H NMR ($CDCl_3$) : 1.16 (6H, d, J=6Hz, Me_2); 1.40 (3H, s, $MeC(OMe)_2$); 2.0-2.4 (4H, m, CH_2CH_2); 3.18 (6H, s, $(OMe)_2$); 3.75 (1H, septet, J=6Hz, NCH); 4.7-6.0 (3H, m, $CH=CH_2$). IR (NaCl) : 1640-1660 cm^{-1} (C=N, C=C). Mass spectrum m/z (%) : no M^+; 198 (M^+-Me; 1); 182(6); 166(15); 124(30); 89(95); 82(100); 55(21); 43(60); 41(30).

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