Diastereoselective Synthesis of *Cis*-3- and 3,5-Alkylpyrrolizidines

Olivier Provot

Faculté de Pharmacie, Laboratoire de Chimie Organique, URA BIOCIS 1843,
Rue J. B. Clément, 92296 Châtenay-Malabry, France

Jean-Pierre Célérier and Gérard Lhommet*

Université Pierre et Marie Curie, Laboratoire de Chimie des Hétérocycles, URA 408,
4 Place Jussieu, 75252 Paris cedex 05, France

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Cis-3 and 3,5-substituted pyrrolizidines can be prepared from β-enaminolactones. Substituted pyrrolidinoketones lead to these compounds by an amino reductive annelation with a low diastereomeric excess, but a best access to these azabicycles consists in preparing *cis*-2,5-disubstituted pyrrolidines which are then transformed into the expected heterocycles.

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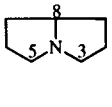
Numerous alkaloids have a common structural moiety in the pyrrolizidine skeletal unit **1**. Among others, 3,5-disubstituted pyrrolizidines **3** are produced by ants in the genera *Monomorium* or *Solenopsis* [1], substituents are either alkyl or alkenyl groups. However, monosubstituted derivatives **2** could also be interesting for their synthetic potential.



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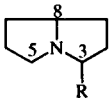

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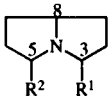

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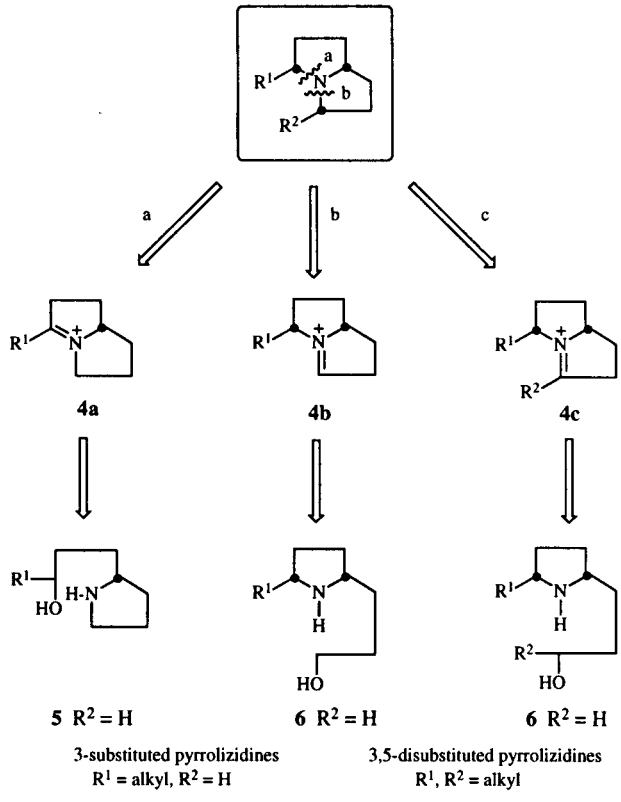
Although a variety of syntheses of natural compounds **3** have been described [2], it is worthwhile to explore new accesses to *cis*-3-mono- and 3,5-dialkylated pyrrolizidines and to establish a general strategy to prepare mono and disubstituted pyrrolizidines.

A disconnective analysis shows that all these compounds can be prepared *via* iminium intermediates **4** obtained by cyclization of cyclic aminocarbonyl compounds. An interesting access to mono-substituted pyrrolizidines **2** needs the preliminary diastereoselective synthesis of a *cis*-pyrrolidine primary alcohol **6** (route b).

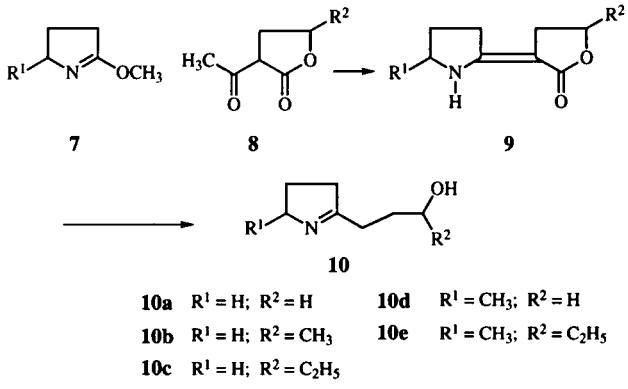
Another interesting and more general approach consists in the synthesis of amino secondary alcohols **5** bearing the alkyl substituent R^1, followed by an intramolecular and diastereo controlled amino reductive cyclization (route a). For the synthesis of disubstituted pyrrolizidines **3**, the aminoalcohol precursor **6** must also have a *cis* relative stereochemistry.

These three retrosynthetic pathways involve cyclic aminoalcohols precursors which all can be prepared from cyclic β-enaminolactones. In this paper we present these three strategies which lead to such bicyclic heterocycles.



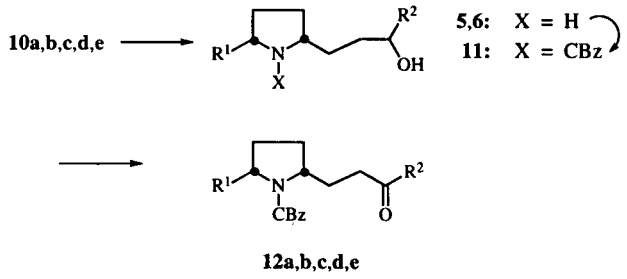
We have recently described the preparation of β-enaminolactones **9** by condensation of lactim ethers **7**, derived from lactams, with acetylbutyrolactones **8** [3]. Compounds **9** were easily hydrolyzed with aqueous hydrochloric acid [2c] and led to cyclic iminoalcohols **10**.

Reduction of the primary iminoalcohols **10a-c** and chemical transformations of the hydroxy function led to bicycles and the stereochemistry of the pyrrolizidine was fixed during the last reaction step. For compounds **10d,e** a catalytic reduction led diastereospecifically to *cis*-2,5-disubstituted pyrrolidines **6d,e**. For disubstituted pyrrolizi-



dines, only the third stereogenic center is obtained at the end of the sequence.

In all cases, the hydroxy group of the aminoalcohols **5** and **6** was transformed into a carbonyl group with pyridinium chlorochromate.

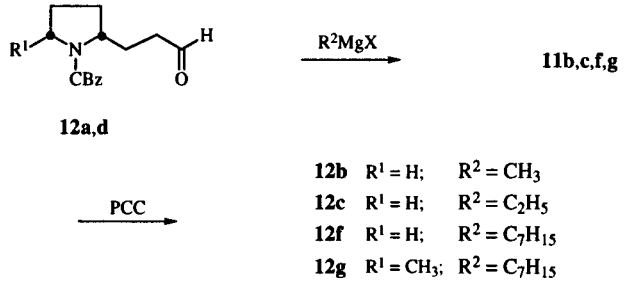


Secondary aminoalcohols **5** and **6** (R^2 = H) could directly be obtained (Method A) by hydrolysis of enaminolactones **9** followed by the reduction of iminoalcohols **10**. However, the yields observed by condensation of lactim ethers **7** and acetylbutyrolactones **8** were rapidily decreasing with the length of the side chain R^1 or R^2 [3].

Another route to secondary aminoalcohols consisted in introducing the substituent R^1 or R^2 during the last steps (Method B) by Grignard condensation with protected amino aldehydes **12a** led to secondary protected alcohols **11b,c,f** or **12d** led to **11g**. All these aminoalcohols were at least oxidized. This second method permitted to prepare aminoalcohols **11f,g** bearing an heptyl substituent often present in natural alkaloids.

The pyrrolizidine skeleton is formed during the last step with three consecutive chemical transformations: fast debenzylation of pyrrolidine **12a** [4], iminium formation and then reduction of the intermediate **4**.

Monosubstituted 3-alkylpyrrolizidines **2** could be prepared two ways: route a: from 2-substituted pyrrolidines **5**; route b: from 2,5-disubstituted pyrrolidines **6** (R^2 = H).



Obviously, route b is totally stereospecific for the formation of the two stereogenic centers which have been introduced early during the reduction of the imine **10**. In contrast, with route a the diastereoselection is not efficient due to the quasi-planar structure of the iminium intermediate.

3,5-Disubstituted pyrrolizidines **3** are also obtained from 2,5-disubstituted pyrrolidines **6** (route b or c) with a high diastereoselectivity (up to 98%).

In conclusion, the syntheses of 3-alkyl and 3,5-dialkylpyrrolizidines require in all cases the preliminary syntheses of 2,5-disubstituted pyrrolidines in order to observe the best selectivity during the formation of the second ring of the pyrrolizidinic skeleton.

EXPERIMENTAL

The ir spectra were recorded on a Philips PU 9700 spectrometer. The ^{1}H nmr and ^{13}C nmr spectra were measured with a Bruker WP 80 (80 MHz), and Bruker AC 200 (200 MHz). The ^{1}H nmr chemical shifts are reported in ppm from an internal standard tetramethylsilane, or of residual chloroform. The ^{13}C nmr chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.1 ppm). Analytical tlc was performed on Merck precoated silica gel 60F plates.

General Procedure for the Preparation of Iminoalcohols **10a-e**.

A solution of 20 mmoles of β-enaminolactone **9a-e** [3] in 3*N* hydrochloric acid (30 ml) was stirred at 60° for 12 hours. After cooling and neutralization with potassium carbonate, the mixture was extracted with chloroform (3 x 30 ml). The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*.

2-[Hydroxypropyl]-3,4-dihydro-5*H*-pyrrole **10a**.

This compound was obtained in 90% yield as a colorless oil, bp 134° (25 mm Hg); ir (neat): 3600-3200, 1640 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.90-4.70 (m, 1H), 3.80-3.75 (m, 2H), 3.65 (t, 2H, J = 6.5 Hz), 2.50-2.40 (m, 4H), 1.90-1.80 (m, 4H); ^{13}C nmr (deuteriochloroform): δ 179.3, 62.6, 60.3, 38.0, 32.0, 28.7, 22.6.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.40; H, 10.50; N, 10.37.

2-[2-Hydroxybutyl]-3,4-dihydro-5*H*-pyrrole **10b**.

This compound was obtained in 90% yield as a colorless oil, bp 131° (25 mm Hg); ir (neat): 3600-3200, 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.30-5.10 (m, 1H), 3.80-3.60 (m, 3H), 2.55-2.35 (m, 4H), 1.60-1.00 (m, 4H), 1.05 (d, 3H, J = 6 Hz); ^{13}C nmr (deuteriochloroform): δ 179.2, 67.0, 60.1, 37.6, 34.8, 30.4, 23.4, 22.7.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.91; H, 10.48; N, 10.22.

2-[3-Hydroxypentyl]-3,4-dihydro-5*H*-pyrrole **10c**.

This compound was obtained in 89% yield as a colorless oil, bp 136° (25 mm Hg); ir (neat): 3600-3200, 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.30-5.10 (m, 1H), 3.85-3.75 (m, 2H), 3.60-3.45 (m, 1H), 2.60-2.40 (m, 4H), 1.90-1.70 (m, 4H), 1.55-1.40 (m, 2H), 0.95 (t, 3H, J = 6 Hz); ^{13}C nmr (deuteriochloroform): δ 179.4, 72.6, 60.1, 37.8, 32.6, 30.7, 30.3, 22.4, 10.0.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.40; H, 10.99; N, 8.97.

2-[1-Hydroxypropyl]-5-methyl-3,4-dihydro-5*H*-pyrrole **10d**.

This compound was obtained in 92% yield as a colorless oil, bp 134° (25 mm Hg); ir (neat): 3600-3200, 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.25-5.10 (m, 1H), 3.95-3.75 (m, 1H), 3.50 (t, 2H, J = 6 Hz), 2.50-2.25 (m, 4H), 2.05-1.85 (m, 1H), 1.70 (q, 2H, J = 6 Hz), 1.35-1.15 (m, 1H), 1.05 (d, 3H, J = 6.5 Hz); ^{13}C nmr (deuteriochloroform): δ 177.8, 67.2, 62.2, 37.9, 31.7, 30.5, 28.7, 21.8.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.02; H, 10.70; N, 9.83.

2-[3-Hydroxypentyl]-5-methyl-3,4-dihydro-5*H*-pyrrole **10e**.

This compound was obtained in 92% yield as a colorless oil, bp 140° (25 mm Hg); ir (neat): 3600-3200, 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.40-5.25 (m, 1H), 4.00-3.75 (m, 1H), 3.50-3.25 (m, 1H), 2.50-2.20 (m, 4H), 2.10-1.85 (m, 1H), 1.70-1.55 (m, 2H), 1.50-1.20 (m, 3H), 1.10 (t, 3H, J = 6 Hz), 0.85 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 178.0, 72.5, 67.2, 37.9, 32.6, 30.4(2), 30.3(2), 21.7(2), 9.9(2).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.18. Found: C, 71.02; H, 11.11; N, 8.29.

General Procedure for the Preparation of Aminoalcohols **5a-c** and **6d,e**.

Method A.

Chemical Reduction of **10a-c**.

Sodium borohydride (30 mmoles) was added by small portions to a solution of **10a-c** in ethanol (10 ml) with stirring for 48 hours. The solution was acidified with 6*N* hydrochloric acid until *p*H = 1. Ethanol was removed under reduced pressure and the resulting solution was saturated with potassium carbonate. Extraction of the latter was achieved with chloroform. Organic layers were then dried over sodium sulfate and concentrated *in vacuo* affording **5a-c**.

2-[1-Hydroxypropyl]pyrrolidine **5a**.

This compound was obtained in 90% yield as a colorless oil, bp 102° (0.05 mm Hg) [lit [5] bp 112-113° (5 mm Hg)]; ir (neat): 3600-3200 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.10-3.90 (m, 2H), 3.80-3.55 (m, 2H), 3.15-2.85 (m, 3H), 2.05-1.25 (m, 8H); ^{13}C nmr (deuteriochloroform): δ 62.2, 59.0, 46.0, 33.4, 31.7, 30.5, 25.4.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.45; H, 11.60; N, 10.80.

2-[2-Hydroxybutyl]pyrrolidine **5b**.

This product was obtained as a mixture of two diastereomers in 76% yield as a colorless oil, bp 134° (25 mm Hg) [lit [5] bp 129-130° (15 mm Hg)]; ir (neat): 3600-3200 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.10-3.90 (m, 2H), 3.50-3.30 (m, 1H), 3.20-2.90 (m, 3H), 1.90-1.20 (m, 8H), 1.10 (d, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 67.2, 66.8, 59.7, 58.2, 46.0, 45.8, 35.9, 33.4, 32.3, 31.6, 30.9, 25.5, 23.7, 23.3.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.10; H, 11.61; N, 9.49.

2-[3-Hydroxypentyl]pyrrolidine **5c**.

This product was obtained as a mixture of two diastereomers in 80% yield as a colorless oil, bp 102° (0.2 mm Hg); ir (neat): 3600-3200 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.10-3.85 (m, 2H), 3.50-3.35 (m, 1H), 3.20-2.95 (m, 1H), 2.90 (t, 2H, J = 7 Hz), 1.95-1.25 (m, 10H), 0.90 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 71.3, 71.1, 58.9, 58.7, 47.8, 45.9, 34.7, 34.4, 32.3, 32.1, 31.5, 30.0, 29.9, 25.1, 10.1.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.24; H, 12.11; N, 8.90.

Catalytic Reduction of **10d,e**.

Ten mmoles of **10d,e** and 20 mmoles of hydrochloric acid were stirred in 60 ml of methanol under hydrogen (140 bars) with a catalytic amount of Raney Ni for 5 hours. After filtration and distillation of the solvent under reduced pressure, the residue was diluted in water. The resulting aqueous solution was saturated with potassium carbonate and extracted with chloroform (5 x 50 ml). The organic layers were dried over sodium sulfate and concentrated *in vacuo*.

Cis-2-[1-Hydroxypropyl]-5-methylpyrrolidine **6d**.

This compound was obtained in 85% yield as a colorless oil, bp 138° (25 mm Hg); ir (neat): 3600-3200 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.05-3.80 (m, 2H), 3.60-3.40 (m, 2H), 3.20-2.90 (m, 2H), 2.00-1.15 (m, 8H), 1.15 (d, 3H, J = 6.5 Hz); ^{13}C nmr (deuteriochloroform): δ 62.3, 59.0, 54.5, 33.8, 33.1, 31.3, 30.2, 21.1.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.13; H, 11.91; N, 9.81.

Cis-2-[3-Hydroxypentyl]-5-methylpyrrolidine **6e**.

This compound was obtained in 90% yield as a colorless oil, bp 137° (25 mm Hg); ir (neat): 3600-3100 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.30-4.00 (m, 2H), 3.55-3.00 (m, 3H), 2.05-1.30 (m, 10H), 1.20 (d, 3H, J = 6 Hz), 0.90 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 73.0, 72.8, 58.3, 54.9, 35.2, 33.8, 33.3, 33.2, 33.0, 32.6, 32.3, 30.5, 30.1, 21.3, 21.1, 10.2.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.37; N, 8.18. Found: C, 70.13; H, 12.04; N, 8.29.

General Procedure for the Preparation of Carbamate Alcohols **11a,e**.

Method A.

Benzyl chloroformate (10 mmoles, 1.705 g) was added slowly at 0° to an aqueous solution (17 ml) of **5a-c** or **6d,e** (10 mmoles) and sodium bicarbonate (10 mmoles). The solution was stirred 30 minutes at 0° for 1.5 hours at room temperature and extracted with chloroform (3 x 20 ml). The organic layers were dried over sodium sulfate and concentrated *in vacuo*.

1-Carbobenzyloxy-2-[hydroxypropyl]pyrrolidine **11a**.

This compound was obtained in 65% yield as a colorless oil, bp 203° (0.3 mm Hg); ir (neat): 3600-3200, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.25 (br s, 5H), 5.10 (s, 2H), 3.90 (s, 1H), 3.70-3.30 (m, 4H), 2.80-1.30 (m, 9H); ^{13}C nmr (deuteriochloroform): δ 155.1, 136.9, 128.4, 127.8, 66.6, 62.3, 57.3, 46.4, 30.6, 30.3, 29.1(2), 23.4.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.24; H, 8.06; N, 5.36.

1-Carbobenzyloxy-2-[2-hydroxybutyl]pyrrolidine **11b**.

This product was obtained as a mixture of two diastereomers in 72% yield as a colorless oil, bp 183° (0.05 mm Hg); ir (neat): 3600-3200, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30 (br s, 5H), 5.20-5.00 (s, 2H), 3.95-3.20 (m, 4H), 2.15-1.20 (m, 9H), 1.15 (d, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 155.4, 128.4, 127.9, 68.1, 66.6, 57.3, 46.5, 35.5, 30.5(2), 23.6, 23.5, 23.3, 21.5.

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.09; H, 8.24; N, 4.98.

1-Carbobenzyloxy-2-[3-hydroxypentyl]pyrrolidine **11c**.

This compound was obtained in 82% yield as a colorless oil, bp 170° (0.05 mm Hg); ir (neat): 3600-3300, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.35 (br s, 5H), 5.10 (s, 2H), 4.00-3.30 (m, 5H), 2.00-1.20 (m, 10H), 0.85 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 155.4, 137.1, 128.5, 127.9, 73.3, 73.0, 66.6, 59.0, 58.7, 54.3, 33.3, 32.2, 31.9, 31.7, 30.4, 30.0, 29.7, 22.0, 10.0.

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.42; H, 9.02; N, 4.79.

Cis-1-Carbobenzyloxy-2-[hydroxypropyl]-5-methylpyrrolidine **11d**.

This compound was obtained in 92% yield as a colorless oil, bp 180° (0.5 mm Hg); ir (neat): 3600-3200, 1670 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30 (br s, 5H), 5.15 (s, 2H), 4.05-3.80 (m, 2H), 3.70-3.50 (m, 2H), 2.15 (s, 1H), 2.10-1.35 (m, 8H), 1.20 (d, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 155.3, 136.9, 128.4, 127.8, 66.5, 62.4, 58.7, 54.1, 33.3, 32.0(2), 29.4, 29.2, 22.0.

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.09; H, 8.37; N, 5.24.

Cis-1-Carbobenzyloxy-2-[3-hydroxypentyl]-5-methylpyrrolidine **11e**.

This product was obtained as a mixture of two diastereomers in 82% yield as a colorless oil, bp 170° (0.05 mm Hg); ir (neat): 3600-3300, 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.25 (br s, 5H), 5.20 (s, 2H), 4.00-3.65 (m, 2H), 3.75-3.35 (m, 1H), 2.10-1.30 (m, 11H), 1.50 (d, 3H, J = 6.5 Hz), 0.85 (t, 3H, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 155.4, 137.1, 128.5, 127.9, 73.3, 73.0, 66.6, 59.0, 58.7, 54.3, 33.3, 32.2, 31.9, 31.7, 30.4, 30.0, 29.7, 22.0, 10.0.

Anal. Calcd. for $C_{18}H_{27}NO_3$: C, 70.70; H, 8.91; N, 4.59. Found: C, 70.52; H, 9.02; N, 4.79.

Preparation of Carbamates Alcohols **11b,c,f,g** from Aldehydes **12a,d**.

Method B.

Eleven mmoles of alkyl bromide was slowly added to 12 mmoles of magnesium in 25 ml of anhydrous ether. The resulting Grignard reagent was then added to 10 mmoles of the corresponding aldehyde **12a,d** (see below) in 10 ml of dry ether. After 3 hours, the resulting mixture was poured on a saturated ammonium chloride solution and extracted with ether (3 x 10 ml). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*.

1-Carbobenzyloxy-2-[2-hydroxybutyl]pyrrolidine **11b**.

This compound was obtained from methylmagnesium bromide and aldehyde **12a** in 91% yield and described in this paper.

1-Carbobenzyloxy-2-[3-hydroxypentyl]pyrrolidine **11c**.

This compound was obtained from ethylmagnesium bromide and aldehyde **12a** in 89% yield and described in this paper.

1-Carbobenzyloxy-2-[3-hydroxydecyl]pyrrolidine **11f**.

This compound was obtained from heptylmagnesium bromide and aldehyde **12a** in 65% yield as a colorless oil, bp 200° (0.7 mm Hg); ir (neat): 3600-3200, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.25 (br s, 5H), 5.20 (s, 2H), 4.00-3.35 (m, 4H), 2.00-1.10 (m, 21H), 0.85 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 154.9, 136.8, 128.3, 127.7, 71.7, 71.3, 70.9, 66.4, 57.2, 46.1, 37.6, 37.1, 33.5, 31.7, 30.5, 30.3, 30.0, 29.6, 29.2, 25.5, 23.5, 22.9.

Anal. Calcd. for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.21; H, 9.94; N, 4.02.

Cis-1-Carbobenzyloxy-2-[3-hydroxydecyl]-5-methylpyrrolidine **11g**.

This compound was obtained from heptylmagnesium bromide and aldehyde **12d** in 62% yield as a colorless oil, bp 204° (0.1 mm Hg); ir (neat): 3600-3200, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30 (br s, 5H), 5.15 (s, 2H), 4.10-3.45 (m, 3H), 2.70-2.50 (m, 1H), 2.05-1.10 (m, 23H), 0.85 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 155.4, 137.0, 128.4, 127.8, 72.0, 71.6, 66.6, 58.6, 54.2, 37.7, 33.7, 37.2, 32.1, 31.9, 31.8, 29.6, 29.3, 25.7, 22.6, 21.9, 14.1.

Anal. Calcd. for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.20; H, 10.00; N, 3.71.

General Procedure for the Corey-Suggs Oxidation [6].

At 0°, 10 mmoles of the alcohol **11a-g** in 30 ml of anhydrous dichloromethane was slowly added to a solution of 16 mmoles of pyridinium chlorochromate in 40 ml of anhydrous dichloromethane. After 30 minutes, the resulting mixture was still stirred for 3 hours at room temperature. The dark solution was filtred over Celite and silica gel and the residue was triturated with ether (5 x 50 ml). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*.

1-Carbobenzyloxy-2-[1-oxopropyl]pyrrolidine **12a**.

This compound was obtained in 86% yield as a colorless oil. An analytical sample was distillated, bp 163° (0.1 mm Hg); ir (neat): 1720, 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.75-9.50 (m, 1H), 7.30 (br s, 5H), 5.15 (s, 2H), 4.10-3.75 (m, 1H), 3.60-3.20 (m, 2H), 2.60-2.20 (m, 2H), 2.20-1.50 (m, 6H);

^{13}C nmr (deuteriochloroform): δ 201.8, 155.8, 137.0, 128.6, 128.0, 66.8, 56.9, 46.6, 40.8, 30.6, 27.0, 23.5.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.56; H, 7.37; N, 5.31.

1-Carbobenzyloxy-2-[2-oxobutyl]pyrrolidine **12b**.

This compound was obtained in 81% yield as a colorless oil, bp 185° (1 mm Hg); ir (neat): 1720, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30 (br s, 5H), 5.10 (s, 2H), 3.95-3.20 (m, 3H), 2.55-2.20 (m, 2H), 2.20-1.50 (m, 9H); ^{13}C nmr (deuteriochloroform): δ 208.3, 155.2, 137.0, 128.4, 127.9, 66.7, 57.0, 46.4, 40.5, 30.5, 29.7, 28.6, 23.4.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.48; H, 7.21; N, 4.93.

1-Carbobenzyloxy-2-[3-oxopentyl]pyrrolidine **12c**.

This compound was obtained in 83% yield as a colorless oil, bp 190° (1 mm Hg); ir (neat): 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30 (br s, 5H), 5.20-5.00 (s, 2H), 3.90-3.75 (m, 1H), 3.50-3.20 (m, 2H), 2.50-2.20 (m, 4H), 2.00-1.50 (m, 6H), 0.95 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 211.0, 155.1, 136.9, 128.4, 127.9, 66.6, 57.1, 46.3, 39.1, 35.6, 30.4, 28.6, 23.4, 7.9.

Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.37; H, 8.07; N, 4.97.

Cis-1-Carbobenzyloxy-2-[1-oxopropyl]-5-methylpyrrolidine **12d**.

This compound was obtained in 82% yield as a colorless oil. An analytical sample was distillated, bp 220° (0.1 mm Hg); ir (neat): 1715, 1685 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.80-9.50 (m, 1H), 7.30 (br s, 5H), 5.15 (m, 2H), 4.00-3.75 (m, 2H), 2.60-2.20 (m, 2H), 2.10-1.40 (m, 6H), 1.15 (d, 3H, J = 6.5 Hz); ^{13}C nmr (deuteriochloroform): δ 202.0, 155.2, 136.8, 128.4, 127.9, 66.7, 58.3, 54.4, 40.7, 31.8, 29.7, 27.9, 22.1.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.01; H, 7.79; N, 5.10.

Cis-1-Carbobenzyloxy-2-[3-oxopentyl]-5-methylpyrrolidine **12e**.

This compound was obtained in 84% yield as a colorless oil, bp 170° (0.1 mm Hg); ir (neat): 3600-3300, 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.35-7.15 (br s, 5H), 5.15 (s, 2H), 3.95-3.75 (m, 2H), 2.55-2.30 (m, 4H), 2.20-1.50 (m, 6H), 1.20 (d, 3H, J = 7 Hz), 0.95 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 211.1, 155.2, 137.1, 128.5, 127.9, 66.7, 58.3, 54.5, 39.3, 35.7, 31.9, 29.9(2), 22.2, 7.9.

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.12; H, 8.38; N, 4.85.

1-Carbobenzyloxy-2-[3-oxodecyl]pyrrolidine **12f**.

This compound was obtained in 82% yield as a colorless oil, bp 170° (0.1 mm Hg); ir (neat): 1695 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.25 (br s, 5H), 5.20 (s, 2H), 3.85-3.55 (m, 1H), 3.50-3.25 (m, 2H), 2.50-2.20 (m, 4H), 2.05-1.20 (m, 16H), 0.85 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 210.4, 155.1, 136.9, 128.3, 127.8, 66.5, 57.0, 46.3, 42.5, 39.4, 31.6, 30.5, 29.1, 29.0, 28.5, 23.7, 23.3, 22.5, 13.9.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.29; H, 9.11; N, 3.84.

Cis-1-Carbobenzyloxy-2-[3-oxodecyl]-5-methylpyrrolidine **12g**.

This compound was obtained in 60% yield as a colorless oil, bp 200° (1 mm Hg); ir (neat): 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30 (br s, 5H), 5.15 (s, 2H), 4.00-3.80 (m, 2H), 2.50-2.20 (m, 4H), 2.10-1.10 (m, 19H), 0.85 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 211.0, 155.3, 137.0, 128.4, 127.9, 66.6, 58.2, 54.3, 42.7, 39.6, 31.6(2), 29.7, 29.2, 29.1(2), 23.8, 22.6, 22.1, 14.1.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.78; H, 9.48; N, 3.91.

Preparation of **1** and **2b** from Aldehydes **12a,d**.

Compounds **12a,d** (2.68 mmoles) were stirred under reflux with 13 mmoles of ammonium formate and 0.75 g of Pd/C in 25 ml of methanol [4]. After 30 minutes, the mixture was filtered over Celite and concentrated *in vacuo*. The residue was washed with 15 ml of 1*N* sodium hydroxide and extracted with ether (6 x 20 ml). The etheral layers were dried over sodium sulfate and concentrated *in vacuo*.

1*H*-Pyrrolizidine **1**.

This compound was obtained in 55% yield as a colorless oil, bp 92° (45 mm Hg) [lit [7] bp 140-143° (148 mm Hg)]; ir (neat): 2860 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.60-3.45 (m, 1H), 3.15-3.00 (m, 2H), 2.60-2.45 (m, 2H), 2.05-1.70 (m, 6H), 1.50-1.30 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 64.3, 55.0, 32.4, 26.0.

Anal. Calcd. for $C_7H_{13}N$: C, 75.62; H, 11.79; N, 12.60. Found: C, 75.08; H, 11.56; N, 12.40.

Cis-3-Methylpyrrolizidine **2b**.

This compound was obtained in 60% yield as a colorless oil, bp 100° (45 mm Hg); ir (neat): 2860, 2800 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.70-3.50 (m, 1H), 3.30-3.10 (m, 1H), 3.00-2.80 (m, 1H), 2.65-2.45 (m, 1H), 2.20-1.25 (m, 8H), 1.20 (d, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 64.4, 57.7, 46.1, 32.9, 32.3, 30.6, 26.2, 16.6.

Anal. Calcd. for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.82; H, 11.81; N, 11.04.

In a similar procedure, ketone **12b** gave **2b** (R = Me) as a diastereoisomeric mixture (*cis*/*trans*) = (70/30) in 60% overall yield.

Preparation of 3-Ethylpyrrolizidine **2c** and 3-Heptylpyrrolizidine **2f**.

Two mmoles of ketone **12c,f** in acetic acid (20 ml) was hydrogenated at atmospheric pressure over Pd/C (20 mg). When 2 equivalents of hydrogen were absorbed, the solution was filtered over Celite and concentrated *in vacuo*. The residue was dissolved in 1*N* sodium hydroxide (30 ml) and extracted with ether (6 x 20 ml). The organic layers were dried over sodium sulfate and concentrated *in vacuo*, affording a mixture (50/50) of *cis* and *trans* isomers.

3-Ethylpyrrolizidine **2c**.

This product was obtained as a mixture of two diastereomers in 60% yield as a colorless oil, bp 120° (50 mm Hg); ir (neat): 2860, 2790 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.65-3.40 (m, 1H), 2.95-2.30 (m, 3H), 2.15-1.15 (m, 10H), 0.90 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 69.5, 65.2, 65.1, 64.5, 54.5, 45.9, 33.5, 32.5, 32.3, 31.8, 29.5, 28.3, 25.9, 25.8, 24.6(2), 12.5, 11.6.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.95; H, 11.77; N, 9.78.

3-Heptylpyrrolizidine **2f**.

This product was obtained as a mixture of two diastereomers in 84% yield as a colorless oil, bp 190° (25 mm Hg); ir (neat): 2830, 2760 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.40-4.20 (m, 1H), 3.60-3.25 (m, 1.5H), 2.90-2.55 (m, 1.5H), 2.35-1.05 (m, 20H), 0.80 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 67.8, 65.1, 64.2, 63.2, 54.4, 45.8, 36.9, 33.9, 32.4, 31.8, 31.6, 29.9, 29.3, 29.2, 28.5, 28.0, 27.3, 25.8, 22.6, 14.1.

Anal. Calcd. for $C_{14}H_{27}N$: C, 80.31; H, 13.00; N, 6.63. Found: C, 80.52; H, 12.84; N, 6.61.

Preparation of 3-Ethyl-5-methylpyrrolizidine **3e**.

Two mmoles of **12e** in methanol was hydrogenated at atmospheric pressure over Pd/C (20 mg). When 2 equivalents of hydrogen were absorbed, the solution was filtered over Celite and concentrated *in vacuo*.

Cis-3-Ethyl-5-methylpyrrolizidine **3e**.

This compound was obtained in 62% yield as a colorless oil, bp 100° (18 mm Hg); ir (neat): 2860, 2790, 2700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.60-2.40 (m, 1H), 2.35-2.05 (m, 2H), 2.00-1.20 (m, 10H), 1.15 (d, 3H, J = 6 Hz), 0.85 (t, 3H, J = 8 Hz); ^{13}C nmr (deuteriochloroform): δ 72.4, 62.3, 55.7, 38.2, 35.1, 28.1, 25.5(2), 21.5, 10.9.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.15; H, 12.41; N, 9.01.

Preparation of 3-Heptyl-5-methylpyrrolizidine **3g**.

Two mmoles of ketone **12g** in acetic acid (20 ml) was hydrogenated at atmospheric pressure over Pd/C (20 mg). When 2 equivalents of hydrogen were absorbed, the solution was filtered over Celite and concentrated *in vacuo*. The residue was dissolved in 1*N* sodium hydroxide (30 ml) and extracted with ether (6 x 20 ml). The organic layers were dried over sodium sulfate and concentrated *in vacuo*.

Cis-3-Heptyl-5-methylpyrrolizidine **3g**.

This compound was obtained in 67% yield as a colorless oil, bp 190° (25 mm Hg); ir (neat): 2860, 2790, 2700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.60-2.40 (m, 1H), 2.40-2.05 (m, 2H), 1.85-1.05 (m, 20H), 1.15 (d, 3H, J = 7 Hz), 0.85 (t, 3H, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 72.3, 60.9, 55.7, 38.2, 35.6(2), 31.8, 29.9, 29.3, 26.8, 25.5(2), 22.6, 21.3, 14.1.

Anal. Calcd. for $C_{15}H_{29}N$: C, 80.64; H, 13.09; N, 6.27. Found: C, 80.63; H, 13.00; N, 6.19.

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