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The Use of the ß-Amino-Alcohol-N-Oxide Derivatives in the Synthesis of 2,3 or 4-Alkyl Substituted NH Pyrrolidines[1]

Georges Roussi* and Jidong Zhang
Institut de Chimie des Substances Naturelles, C.N.R.S.,
91198 Gif sur Yvette, France

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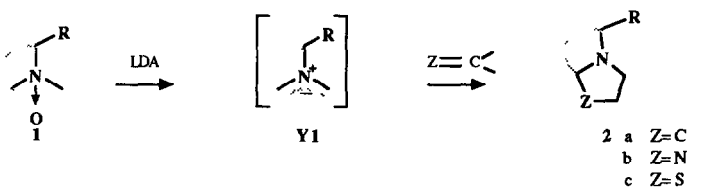
Nonstabilized azomethine ylides generated from the various ß-amino alcohols N-oxides **13, 17, 23** and **24** undergo [3+2] cycloaddition reactions with **unactivated** alkenes to afford the corresponding pyrrolidines **14a-g, 18a-g, 25** and **27** in moderate to good yields. These compounds are precursors of NH pyrrolidines substituted in position 2, 3 or 4.

We have discovered an efficient access to **nonstabilized** azomethine ylides Y_1 by lithium base deprotonation of tertiary amine N-oxides.[2a] These entities are so reactive that they undergo 3+2 intermolecular cycloaddition reaction to **unactivated** olefins leading to the corresponding N-alkylated pyrrolidines **2a** in 60-70% yields.[2] By using acetylenic derivatives, imines or thiones as dipolarophiles, pyrroles or pyrrolines, imidazolidines **2b** and thiazolidines **2c** were respectively obtained (Scheme 1).[2b]



Scheme 1

Because it is possible to build complex systems from the NH fonction and because some NH pyrrolidines are important derivatives from a biological point of view[3], we report here various attempts to reach these compounds by the N-oxide deprotonation route

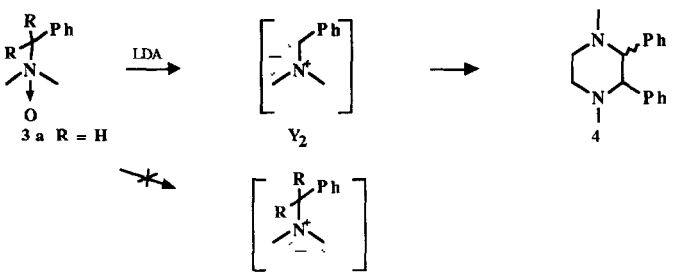
Attempts from N-alkylated pyrrolidines.

Several methods to N-demethylate tertiary amines or piperidines are repowhich rted (Polonovski and von Braun type reactions, $KMnO_4$ oxidation, for exemple)[4] and we tested them, since no specific method could be found in the literature, for N-demethylation of N-methyl pyrrolidines. In no case did we obtain the expected derivative, and we could only caracterise trace amounts of compounds resulting from ring opening. This

fundamentally different behaviour from the piperidine one has already been often encountered in the course of other reactions.[5]

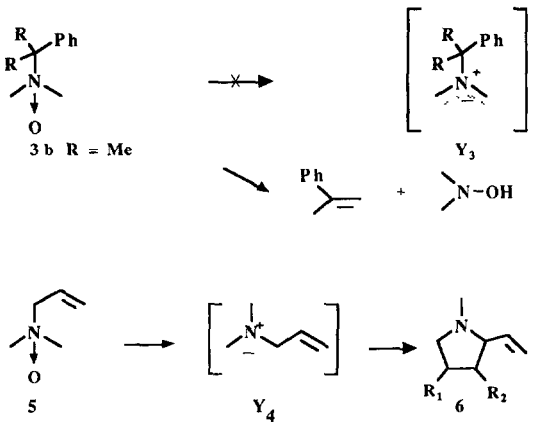
Attempts from benzylic or allylic N-oxides.

A straightforward access could be considered from the N-oxides **3a** and **5** bearing, respectively, a benzyl and an allyl group easily removable after cycloaddition. We knew, from our previous studies,[2a] that deprotonation of N-oxide **3a** involves exclusively the benzylic position, leading to the ylide $\mathbf{Y_2}$ which ultimately dimerises into piperazine **4** (Scheme 2). We then reacted the α,α' dimethylated benzylic N-oxide **3b** which was designed to give specifically the ylide $\mathbf{Y_3}$. Unfortunately, this compound happened to be unstable and to undergo



Scheme 2

spontaneous Cope elimination at 0°C. The easily prepared allylic N-oxide **5** was similarly deprotonated at the most acidic center, like **3a**, but an important difference was nevertheless observed, since 3+2 cycloaddition reaction occured to give the pyrrolidine **6**, *via* the conjugated ylide **Y4** (Scheme 3).



Scheme 3

Attempts from specially devised tertiary amine N-oxides.

We then decided to design an N-oxide which would meet the following requirements:

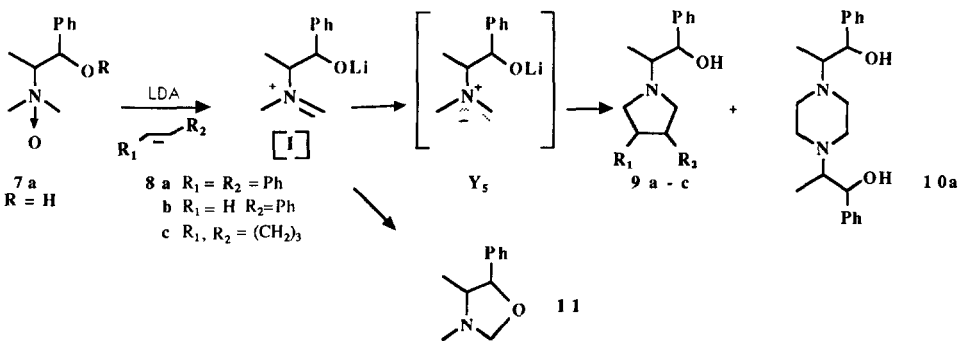
i Easy access
ii Stability and easy handling
iii Regiospecific ylide formation and efficient 3+2 cycloaddition reaction to the olefin
iv Quantitative dealkylation

We first chose N-oxides bearing a β-hydroxy group which are easily accessible from the commercially available corresponding β-amino-alcohols and for which different N-C bond cleavage methods exist.[6] Moreover, it is easy to find derivatives bearing an α substituent which could *a priori* prevent the deprotonation on this site and thus allow regospecific formation of the ylide, at difference to unsubstituted N-oxides.[2c]

RESULTS AND DISCUSSION

I. Access to 3 and/or 4-alkyl substituted NH pyrrolidines.

When methyl-ephedrine N-oxide **7a** is treated in THF with LDA in the presence of *trans* stilbene **8a** the ylide Y_5 is regiospecifically generated, as shown by the exclusive formation of the expected diastereomeric pyrrolidines **9a** obtained in a 67:33 ratio.[7] However, this entity appears to be of low reactivity in 3+2 cycloaddition as revealed by the presence of large amounts of piperazine **10a** resulting from its competitive dimerization Another competitive reaction takes place, due to the 5-endo-trig intramolecular trapping of the imonium **I** by the lithium alkoxide, leading to the oxazolidine **11** (Scheme 4).



Scheme 4

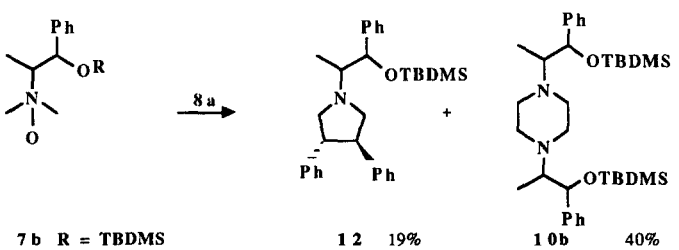
Numerous experiments have been performed under various conditions in order to favour the cycloaddition reaction and thus increase pyrrolidine formation.The results are summarized in the Table I.

	Reaction Conditions				Products		
Entry	T°C	LDA /7a	Adjuvant	8a /7a	9a	10a	11
					Yields %		
1	-78	4.5	_	1 1	20	_	_
2	-78	4 5	_	3	28	32	11
3	0	4.5	_	1.1	40	20	20
4	0	4 5	_	3	33	38	10
5	0	6.5	_	1.1	39	20	24
6	0	4 5	_	1.1	_	_	_
7	0	4 5	P_2O_5	1 1	10.5	_	_
8	0	4 5	$Zn(AcO)_2$	1 1	10	_	_
9	0	4 5	$PdCl_2$/ Pd	1 1	_	_	_

Table I. Reaction between methylephedrine N-oxide **7a** and *trans* -stilbene **8a**

The oxazolidine **11** and pyrrolidine **9a** formation was decreased at low temperature (entries 1-2). The relative values of the LDA / **7a** ratio had no effect (entries 3 and 5) while a large excess of *trans* stilbene diminished the oxazolidine formation and increased piperazine yields (entries 2 and 4). The addition of P_2O_5 (entry 7) or metallic salts (entries 8 and 9) gave a complex mixture of products, among them small quantities of pyrrolidines **9a** could be isolated.

In order to prevent the unwanted oxazolidine formation, the hydroxyl function was protected by a *t*-butyl-dimethyl-silyl (TBDMS) group. The decreased reactivity of **7b**, resulting in a 40% yield formation of piperazine **10b** and 19% of the expected pyrrolidine **14** can be attributed to stabilization of the intermediate ylide by the vacant d orbitals of the silicon atom (Scheme 5).[8]



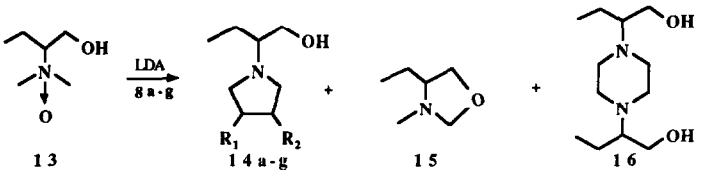
7b R = TBDMS 12 19% 10b 40%

Scheme 5

The results obtained with styrene **8b** and cyclopentene **8c** as dipolarophiles confirmed the lack of reactivity of the ylide Y_5 since it led to the corresponding pyrrolidines **9b,c** in 20 and 10% yields respectively.

All these facts, put together, suggest that interaction with the β-phenyl group could stabilize the methyl-ephedrine N-oxide derived ylide.

This led us to prepare the N-oxide **13**, devoid of phenyl group but bearing an alkyl substituent on the carbon β to the hydroxy function, in order to avoid the deprotonation on this site (Scheme 6).



.Scheme 6

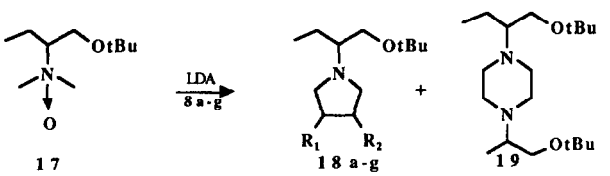
In the presence of LDA **13**, and the various nonactivated olefins **8a-g**, yielded the expected pyrrolidines **14a-g** as a mixture of diastereoisomers.[7] The yields were modest and the balance could not be established because of volatility of the oxazolidine **15** and solubility of the piperazine **16** in water. The results are summarized in the table II.

	Olefins 8 a-g		Products			
	R_1	R_2	14a-g		15	16
			Yields % *	de %		
a	Ph	Ph	34	36	–	–
b	H	Ph	47	20	–	–
c		$(CH_2)_3$	54		–	–
d		$(CH_2)_6$	38		–	–
e	H	Butyl	48		–	–
f	H	CH_2OH	15	30	–	–
g	H	CH_3CH_2OH	9	30	–	–

* Calculated upon N-oxide 13

Table II. Reaction between the N-oxide **13** and various olefins **8a-g.**

It was finally postulated that the ylide would not be stabilized if the hydroxy group were substituted by a *t*-butyloxy group instead of TBDMS (Scheme 7).[9a]



Scheme 7

Thus, the resulting N-oxide **17**, treated with LDA at 0°C in the presence of the olefins **8a-g** led regiospecifically to the expected pyrrolidines **18a-g** in diastereomeric form. The results are summarized in the table III. The yields ranging between 22% to 63% are then significantly higher than those obtained from the free hydroxy derivative **13**. The diastereomeric excess was determined in the course of the reaction with allylic alcohol **8f**. It is much smaller (de=6%) than in the case of the unprotected N-oxide **13** (de=30%). The yields of the piperazine **19** were highly decreased, in accordance with the very high reactivity of the ylide so generated.

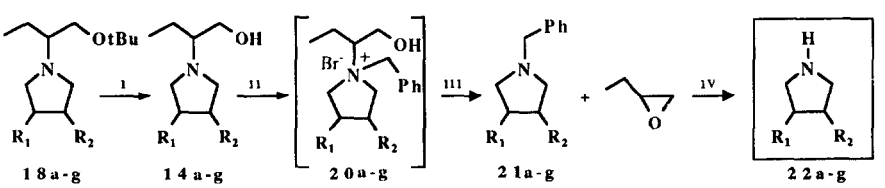
	Olefins 8 a-g		18a-g	19
	R_1	R_2	Yields %*	Yields %
a	Ph	Ph	63 (70)**	-
b	H	Ph	48 -	-
c	$(CH_2)_3$		52 (70) **	21
d	$(CH_2)_6$		52 (58) **	21
e	H	Butyl	64 -	-
f	H	CH_2OH	35 (37) **	43
g	H	CH_3CH_2OH	22 -	67

* Calculated upon N-oxide 17

** Determined, by NMR spectroscopy, after acidic extraction

Table III. Pyrrolidines **18a-g** from reaction between the N-oxide **17** and various olefins **8a-g.**

The oxidative[6a] and dehydrating[6b] methods used to cleave the N-C bond of ß-amino alcohols failed in the case of the pyrrolidine ring system. We turned then towards the Hofmann elimination reaction[10] applied to the quaternary ammonium salts **20a-g** prepared from the corresponding deprotected pyrrolidines **14a-g.**[9b] Up to now this reaction has essentially been used in the formation of epoxides, and few exemples have been described for the tertiary amine preparation (Scheme 8) [11]



i Me_3SiI/CCl_4 , ii $PhCH_2Br/MeOH$, iii *t* BuOK/tBuOH , iv $HCOONH_4/Pd$

Scheme 8

In the presence of $NaHCO_3$ benzyl bromide exclusively reacted with the nitrogen atom. The resulting ammonium salts **20** were not isolated but simply heated with *t*-BuOK to lead, quantitatively, to the benzyl derivatives **21**. Hydrogenolysis of the latter compounds was achieved by ammonium formate in methanol in the presence of Pd on charcoal.[12]

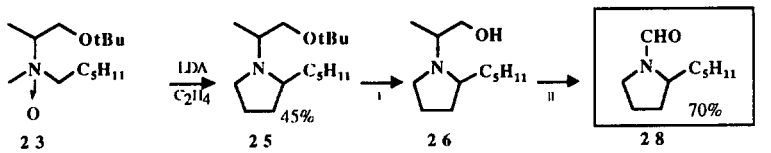
The results are summarized in the Table IV which shows that the sequence is highly efficient and constitutes a novel pathway to N-H pyrrolidines **22a-g** from non activated double bonds.

	14a-g	**21a-g** yields %	**22a-g**	**17** ⟶ **22a-g** overall yields %
a	100	96	99	60
b	99	90	91	39
c	97	85	98	42
d	98	85	95	41
f	94	89	99	29

Table IV. The various yields of the deprotection sequence

II. Access to alkyl-2-pyrrolidines

We extended this methodology to N-oxides **23** and **24**, N-alkylated by a β-amino alcohol chain, and unsymmetrically substituted (at difference to **7a,b**, **13**, **17**) in order to explore an access to 2-alkyl pyrrolidine derivatives **26** and **27**, the latter compound being a precursor of several natural products such as Hygroline, Dehydrodarline and Ruspolinone (Scheme 9).[3]



Scheme 9

We tested the reactivity of the two N-oxides **23** and **24** when treated by LDA in the presence of ethylene. The results show the efficiency of the 3+2 cycloaddition reaction which gave **25** and **27** in 45 and 40% yields respectively as a mixture of diastereoisomers.

Dealkylation of pyrrolidine 26

Another dealkylation method was tested here.[13] Treatment of the easily accessible ß-hydroxy pyrrolidine **26** with NaOH (50%) in $CHCl_3$ in presence of phase transfer agent gave **28** in 70% yields. This method is shorter than the previous one depicted in scheme 8 but is less general, because the intermediate carbene $:CCl_2$ is not compatible with aromatic ring or double bonds.

CONCLUSION

We have shown in this work that the 1,3-dipolar cycloaddition reaction between nonactivated olefins **8a-g** and azomethine ylides generated from protected ß-amino-alcohol N-oxides **17, 23, 24** gave the corresponding pyrrolidines **18a-g, 25** and **27** in good yields. These compounds can easily be transformed into N-H pyrrolidines substituted on position 2, 3 or 4.

This methodology is promissing in natural product synthesis. Further works are in progress.

EXPERIMENTAL SECTION

General Low resolution mass spectra (MS) were obtained on a AEI MS 50 spectrometer, chemical ionisation mass spectra (CIMS) on a spectrometer AEI-MS-9 and exact masses (HRMS) were determined by high-resolution mass specroscopy on a Kratos MS-50. ^{1}H NMR spectra in $CDCl_3$ were recorded on a Perkin-Elmer R12 (60 MHz), and Bruker WP 200-54 (200MHz). Chemical shifts from TMS are given in δ Purifications were achieved by column chromatography, preparative thin layer chromatography (TLC, elution). Analytical analysis were performed on TLC or gas liquid chromatography (GLC).

Materials. Amine N-oxides were prepared by H_2O_2 oxidation of the corresponding amines.

General procedures. The amine N-oxide (1 equiv) was dried just before use by heating under vacuum at 30°C in a three-neck flask for 1h The dipolarophile (1.1 equiv.) in anhydrous THF (50ml) was then added via a syringe through a rubber septum under stirring, and the suspension was cooled to the chosen temperature before LDA (3.5 equiv.) was introduced. The reaction was monitored by GLC and TLC

(1'-t-butyldimethylsilyloxy-1'-phenyl-2'-propyl)-dimethyl-amine-N-oxide 7b. N-Oxide **7a** (0.83 g, 4,3 mmol) in CH_2Cl_2 was added to *t*-butyl-dimethyl-silyl-chloride (0.72g, 4.74 mmol) and DBU (0.76 mL, 5.12 mmol) in CH_2Cl_2 (8 mL).[14] **7b** (0.87 g, 2 84 mmol, 66%) are obtained pure. ^{1}H NMR (200MHz) δ 0 33 (s, 3H), 0.49 (s, 3H), 1.30 (s, 9H), 1.63 (d, 3 H, J = 7 8 Hz), 3.50 (s, 6 H), 3.80-4.30 (m, 1 H), 6 62 (s, 1 H), 7.5-8.1 (m, 5H); MS m/e 309, 291, CIMS MH^+ 310, 294, 292.

***trans*-3,4-Diphenyl-N-(1'-hydroxy-1'-phenyl-2'-propyl)-pyrrolidine 9a; N,N-di-(1'-hydroxy-1'-phenyl-2'-propyl)-piperazine 10 and 4-phenyl 5-methyl-N-methyl oxazolidine 11.** N-Oxide **7a** (0.48 g, 2.46 mmol) and *trans* stilbene (0.48 g, 2.71 mmol) were treated with LDA at 0°C A crude mixture (0,88 g) was obtained after workup. Column chromatography yielded **9a** as a diastereomeric mixture formed in a 67 33 ratio (0.34 g, 39% CH_2Cl_2/MeOH 97·3), **10a** (0.087 g, 0 21 mmol, 20% CH_2Cl_2/MeOH 80·20) and **11** (0.103 g, 0 59 mmol, 24% CH_2Cl_2/MeOH 97 3)

9a . ^{1}H NMR (200 MHz) d 0 91 (d, 3 H, J = 7 0 Hz), 2 69-2.83 (m, 1 H),

9a : ^{1}H NMR (200 MHz) d 0.91 (d, 3 H, J = 7 0 Hz), 2 69-2.83 (m, 1 H), 3.03-3.20 (m, 2 H), 3.35-3.57 (m, 4 H), 4.15 (bs, 1 H), 5 07 and 5.8 (2d, 1 H, J = 3.0 Hz), 7 10-7 79 (m, 15 H), MS m/e 357, 340, 211; HRMS Calcd for $C_{21}H_{27}NO$ 357,2092, found 357,1704.

10a ^{1}H NMR (200 MHz) δ 0.96 (d, 6 H, J = 7 0 Hz), 2.63 (s, 4 H), 2.92-3.53 (m, 2 H), 3 83-4 32 (4 H), 5 08 (d, 2 H, J = 3.0 Hz), 7 55-7 92 (bs, 10H); MS m/e 354

11 Identical with authentic sample.[15]

3-Phenyl-N-(1'-hydroxy-1'-phenyl-2'-propyl)pyrrolidine 9b. N-Oxide **7a** (0.18 g, 1.12 mmol) and styrene **8b** (0 77 mL, 1 5 mmol) were treated with LDA at 0°C A crude mixture (0.14 g) was obtained after workup, containing **9b** as a 60:40 diastereomeric mixture determined by ^{1}H NMR (0.067 g, 0 24 mmol, 17% , CH_2Cl_2/MeOH 97:3), **10a** and **11.**

9b: ^{1}H NMR (200 MHz) δ 0.87 (d, 3 H, J = 7.0 Hz), 1.89-2.23 (m, 1 H), 2,39-2.63 (m, 1 H), 2.65-2.83 (m, 1 H), 2.83-3.46 (m, 4 H), 3.46-3.86 (m, 2 H), 5.23 and 5.27 (2d, 1 H, J = 4 Hz) 7.46-8.03 (m, 10 H); CIMS 282 (MH^+), 264; HRMS, Calcd for $C_{14}H_{23}NO$ 281.1779, found 281.1776.

***trans*-3,4-Diphenyl-N-(1'-*t*-butyldimethylsilyloxy-1'-phenyl-2'-propyl)-pyrrolidine 12 and N,N-di-(1'-*t*-butyl-dimethylsililoxy-1'-phenyl-2'-propyl)-piperazine 10b.** N-Oxide **7b** (0.309 g, 1.0 mmol) and *trans* stilbene **8a** (0 17 g, 1.2 mmol) were treated with LDA at 0°C. A crude mixture (0.540 g) was obtained after workup. Column chromatography yielded **12** (0.090 g, 0.14 mmol, 14%), CH_2Cl_2/MeOH 98:2) and **10b** (0.120 g, 0.20 mmol, 40%, CH_2Cl_2/MeOH 85:15).

12: ^{1}H NMR (200 MHz) δ 0.28 (s, 6 H), 1.11 (s, 9 H), 1.3 (d, 3 H, J = 7.3 Hz), 2.92-3.15 (m, 3 H), 3.28-3.56 (m, 4 H), 4.97 (d, 1 H, J = 3.0), 7.17-7.90 (m, 15 H); MS m/e 471, 457, 412, 340; CIMS MH^+ 472.

10b · ^{1}H NMR (200 MHz) δ 0.38 (d, 12H, J = 2.0 Hz), 1.20-1.35 (s + m, 24H), 2.58-2.70 (m, 8H), 3.10 (m, 2H), 5.0 (m, 2H), 7.60 (m, 10H); MS m/e 582, 361.

1-Hydroxy-2-butyl-dimethylamine-N-oxide 8. Obtained in 94% yield by oxidation of the corresponding amine, ^{1}H NMR (200 MHz) δ 1.8 (t, 3 H, J = 7 5 Hz), 1.46-1.76 (m, 1 H), 1.76-1.99 (m, 1 H), 3.3 (d, 6 H, J = 8 3 Hz), 3 86-4 16 (m, 2 H), 7.36-7 73 (bs, 1 H); MS m/e 84, 116.

3,4-Diphenyl-*trans*-N-(1'-hydroxy-2'-butyl)-pyrrolidine 14a. N-Oxide **8** (0.106 g. 0.80 mmol) and *trans* stilbene **8a** (0.43g, 2 4 mmol) were treated with LDA at 0°C Acid-base extraction yielded a 68 32 diastereomeric mixture of **14a** determined by GLC (0.080g, 0.27 mmol, 34%); ^{1}H NMR (200 MHz), δ 1.0 (t, 3 H, J = 7.5 Hz), 1.43-1.66 (m, 1 H), 1.66-1.99 (m, 1H), 2.69-2.86 (M, 1H), 3 03-3 33 (m, 2 H), 3.33-3.62 (m, 4 H), 3.62-3.73 (m, 1H), 3.73-3.89 (m, 1 H), 4.89-5.53 (bs, 1 H), 6 99-7 72 (m, 10 H); MS m/e 295, 278, 264; CIMS MH^+ 296; HRMS Calcd for $C_{20}H_{21}NO$ 295.1435, found 295.1426

3-Phenyl-N-(1'-hydroxy-2'-butyl)-pyrrolidine 14b. N-Oxide **8** (1 33g, 10 mmol) and styrene **8b** (5.7 ml, 50 mmol) were treated with LDA at 0°C. Acid-base extraction yielded a 60:40 diastereomeric mixture of **14b** determined by GLC (1.01g, 4 7 mmol, 47%). ^{1}H NMR (200 MHz) δ 0.98 (t, 3 H, J = 7 5 Hz), 1.36-1 59 (m, 1 H), 1.59-1.83 (m, 1H), 1 83-2 06 (m, 1H), 2 14-2 49 (m, 1 H), 2.49-2 73 (m, 1 H), 2.73-3 29 (m, 5 H), 3.29-3.56 (m, 1 H), 3.69-3.89 (m, 1H),7 26-7 53 (m, 5 H), MS m/e 179, 187; CIMS MH^+180, HRMS, Calcd for $C_{14}H_{17}NO$, 179.1623, found, 179.1629.

N-(1'-Hydroxy-2'-butyl)-2-aza-3,3,0-bicyclooctane 14c N-Oxide **8** (0.230 g, 1.73 mmol) and cyclopentene **8c** (0.46 mL, 5.2 mmol) were treated with LDA at 0°C. Acid-base extraction with CH_2Cl_2 yielded **14c** (0.170 g, 0.93 mmol, 54%). ^{1}H NMR (200 MHz) δ 0.93 (t, 3 H, J = 7.5 Hz), 1.30-1 62 (m, 8 H), 2.8-2.43 (m, 2 H), 2 43-2.66 (m, 1 H), 2.66-2.93 (m, 2H), 2.93-3.23 (bs, 1 H), 3.23-3.49 (m, 2 H), 3.35-3.70 (dd, 2 H, J = 4.5 Hz), CIMS MH^+ 184.

N-(1'-Hydroxy-2'-butyl)-2-aza-6,3,0-bicycloundecane 14d. N-Oxide **8** (0.85 g, 2.50 mmol) and cyclooctene **8d** (1.0 mL, 7.5 mmol) were treated with LDA at 0°C Acid-base extraction with CH_2Cl_2 and column chromatography yielded **14d** (0.17 g, 0 75 mmol, 30%) ^{1}H NMR (200 MHz) δ 0.93 (t, 3 H, J = 7.5 Hz), 1.23-1.93 (m, 14 H), 1.93-2.37 (m, 4 H), 2 37-2.63 (m, 1 H), 3 10-3.37 (m, 1 H), 3.37-3 57 and 3 70-4.07 (2 dd, 2 H, J = 3 0 Hz), 3.90 (bs, 1 H); MS m/e 184, 208, 144, CIMS, MH^+ 186, 208, 144

3-Butyl-N-(1'-hydroxy-2'-butyl)-pyrrolidine 14e. N-Oxide **8** (0 245 g, 1.84 mmol) and 1-hexene **8e** (1.14 mL, 9 mmol) yielded **14e** in the same conditions (0 174 g, 0 88 mmol, 48%) ^{1}HNMR (200 MHz) δ 1 07 (t, 3H, J = 7 2 Hz), 1.23 (t, 3H, J = 7.0 Hz), 1 26-2 05 (m, 11 H) , 2.55-3.10 (m, 5 H), 3.43-3.56 (dd, 2H, J = 7Hz) 3.43-3.56 (bs, 1 H); CIMS MH^+ 200.

3-Hydroxymethyl-N-(1'-hydroxy-2'-butyl)-pyrrolidine 14f N-Oxide **8** (0 294 g, 2.17 mmol) and allyl alcohol **8f** (0 450 mL, 6 63 mmol) yielded after column chromatography a 65:35 diastereomeric mixture of **14f** determined by GLC (0 057 g, 0 33 mmol, 15%)· ^{1}H NMR (200 MHz) δ 0.92 (t, 3 H, J = 7 5 Hz), 1.34-1.67 (m, 3 H), 1 83-2 09 (m, 1 H), 2 23-2.56 (m, 2 H), 2 60-2 81 (m, 4 H), 3.03-3.29 (bs, 2 H), 3.40-3 73 (m, 4 H); MS m/e 173, 156, 142, CIMS MH^+ 174; HRMS Calcd for $C_9H_{14}NO_2$ 173 1415, found 173.1427.

3-Hydroxy-ethyl-N-(1'-hydroxy-2'-butyl)-pyrrolidine 14g. N-Oxide **8** (0.264 g, 1 98 mmol) and homoallyl alcohol **8g** (0 5 mL, 5.9 mmol) yielded after column chromatography a 65·35 diastereomeric mixture of **14g** determined by GLC (0 034 g, 0.18 mmol, 9%): ^{1}H NMR (200 MHz) δ 0.95 (t, 3 H, J = 7.5 Hz), 1.48-1.74 (m, 5 H), 1.96-2.16 (m, 1 H), 2,21-2,46 (m, 1 H), 2 46-2 66 (m, 2 H), 2.68-3.16 (m, 3 H), 3.46-3.86 (m, 4 H), 4.06-4.46 (bs, 2 H); MS m/e 187, 186, 170, 156; HRMS, Calcd for $C_{10}H_{17}NO_2$ 187.1571 , found 187.1566

1-*t*-Butoxy-2-butyl-dimethylamine-N-oxide 17. Obtained in 90% yield by oxidation of the corresponding tertiary amine ^{1}H NMR (200 MHz) δ 1.05 (t, 3 H, J = 7 6 Hz), 1.23 (s, 9 H), 1.79-2.24 (m, 2 H), 3.09-3 36 (m, 1 H), 3 18 (s, 3 H), 3.26

(s, 3 H), 3.36-3.66 (dd, 1 H, J = 10 8, 4.60 Hz), 3.93-4.8 (d, 1 H, J = 10.8 Hz); ^{13}C NMR δ 11.29, 18 49, 27.12, 56.17, 57.07, 76.49; MS m/e 189, 172, 128; CIMS MH^+ 190.

3,4-Diphenyl-*trans*-N-(1'-*t*butoxy-2'-butyl)-pyrrolidine 18a. N-Oxide **17** (0.523 g, 2.77 mmol) and *trans* stilbene **8a** (1.5 g, 8.3 mmol) were treated with LDA at 0°C. Acid-base extraction with CH_2Cl_2 yielded crude product (0.684 g). Column chromatography afforded **18a** (0.616 g, 1.75 mmol, 63%, CH_2Cl_2/MeOH 99:1): ^{1}H NMR (200 Hz) δ 1.0 (t, 3 H, J = 7.5 Hz), 1 17 (s, 9 H), 1.59-1.79 (m, 2 H), 2.53-2.69 (m, 1 H), 2.96-3.14 (bs, 2 H) 3.20-3.43 (bs, 4 H), 3.46-3.58 (m, 2 H), 7.8-7.46 (m, 10 H); CIMS MH^+ 352. HRMS , Calcd for $C_{24}H_{33}NO$ 351.5895, found 351.5890.

3-Phenyl-N-(1'-*t*butoxy-2'-butyl)-pyrrolidine 18b. N-Oxide **17** (0.531 g, 2.81 mmol) and styrene **8b** (0.96 mL, 5.43 mmol) yielded **18b** (0.372 g, 1.35 mmol, 48%, CH_2Cl_2-MeOH 95:5): ^{1}H NMR δ 1.03 (t, 3 H, J = 7.5 Hz), 1.21 (s, 9 H), 1 79-2 03 (m, 2 H), 2.03-2.29 (m, 1 H), 2.43-2.63 (m, 1 H), 3.01-3.16 (m, 1 H), 3.16-3.39 (m, 1 H), 3.39-3.63 (m, 2H), 3.63-3.96 (m, 3 H) , 7 43-7.73 (m, 5H); MS m/e 275, 274; CIMS MH^+ 276; HRMS, Calcd for $C_{18}H_{29}NO$ 275.1849, found 275.1842.

N-(1'-*t*-butoxy-2'-butyl)-2-aza[3,3,0]bicycloctane 18c and N,N-di-(1'-*t*butoxy-2'-butyl)-piperazine 14. N-Oxide **17** (0.144 g, 0.76 mmol) and cyclopentene **8c** (0.34 mL, 3.8 mmol) were treated with LDA at 0°C. A crude mixture (0.154 g) was obtained after workup Column chromatography yielded **18c** (0 054 g, 0 41 mmol), 52%, CH_2Cl_2/MeOH 95 5) and **14** (0 027 g, 0.08 mmol, 17%, CH_2Cl_2/MeOH 95:5)

18c : ^{1}H NMR (400 MHz), δ 0.93 (t, 3 H, J = 7.5 Hz), 1 27 (s, 9 H), 1.42-1.56 (m, 2 H), 1.56-1.83 (m, 6 H), 2 12-2.32 (m, 2 H), 2 39-2.61 (m, 1 H), 2 71-2.90 (m, 2 H), 3.21-3 65 (m, 2 H), 3.66-3.73 (dd, 1 H, J = 5, 10 Hz), 3.79-3.82 (dd, J=5, 10 Hz), MS m/e 239, 152, HRMS, Calcd for $C_{15}H_{29}NO$ 239 1848, found 239.1854.

14. ^{1}H NMR (200 MHz) δ 0.93 (t, 6 H, J = 7.5 Hz), 1.14 (s, 18 H), 1 43-1 66 (m, 4H), 2.43-2 63 (m, 2H), 2 63-3.06 (m, 8 H), 3.23-3.56 (m, 4 H), MS m/e, 342, 327, 269, 215, CIMS MH^+ 343; HRMS, Calcd for $C_{20}H_{42}N_2O_2$, 342.3246, found 342 3210

N-(1'-*t*Butoxy-2'-butyl)-2-aza[6,3,0]bicycloundecane 18d. N-Oxide **17** (0 149 g, 1.05 mmol) and cyclooctene **8d** (0 67 mL, 5.2 mmol) yielded **18d** after purification on column chromatography (0 153 g, 0.55 mmol, 52 % CH_2Cl_2/MeOH 75:25) and **14** (0.038 g, 0 11 mmol, 17%, CH_2Cl_2/MeOH 75 25)

18d: ^{1}H NMR (200 MHz) δ 0.96 (t, 3 H, J = 7.5 Hz), 1 26 (s, 9 H), 1.40-1.77 (m, 14 H), 2 03-2.33 (m, 4 H), 2.33-2.63 (m, 1 H), 3.33-3.53 (m, 2 H), 3.52-3.66 (dd, 2 H, J = 3.8, 1.5 Hz); MS m/e 281, 280, 210, 208, 144, HRMS, Calcd for $C_{18}H_{35}NO$ 281 2718, found 281.2718.

3-Butyl-N-(1'-*t*butoxy-2'-butyl)-pyrrolidine 18e. N-Oxide **17** (0.30 g, 1.59 mmol) and 1-hexene **8d** (0.92 mL, 7.8 mmol) yielded **18e** after column chromatography (0.262 g, 1 02 mmol, 64%; CH_2Cl_2/MeOH 97:3): ^{1}H NMR (200 MHz) δ 0.92 (t, 3 H, J = 6 0 Hz), 1.05 (t, 3 H, J = 7.5 Hz), 1.23 (s, 9 H), 1.28-1.60 (m, 6H), 1.60-2.03 (m, 2H), 2.03-2.36 (m, 2H), 2.36-2.86 (m, 1 H), 2 86-3 14 (m, 2 H), 3.14-3.59 (m, 1 H) 3 68-3.73 (m, 2H), 3.73-3 93 (m, 2 H); MS m/e 215, 186, 168.; CIMS MH^+216; HRMS, Calcd for $C_{16}H_{33}NO$, 215.2153 found 215 2159

3-Hydroxymethyl-N-(1'-*t*butoxy-2'-butyl)-pyrrolidine 18f. N-oxide **17** (0 140 g, 1 0 mmol) and allyl alcohol **8f** (0 186 mL, 2 mmol) yielded **18f** (0 070 g, 0.35 mmol, 34,5%, CH_2Cl_2/MeOH 93 7) and **14** (0 074 g, 0 18 mmol, 43%, CH_2Cl_2/MeOH 95.5).

18f ^{1}H NMR (200 MHz) δ 0.88 (t, 3 H, J = 7.5 Hz), 1.08 (s, 9H), 1.59-1 89 (m, 3 H), 1 89-2 8 (m, 1 H), 2 36-2.53 (m, 1 H), 2 66-2 85 (m, 1 H), 2.85-2.99 (m, 1 H), 2.99-3 26 (m, 3 H), 3 47 (d, 2 H, J = 5.0 Hz), 3.50-3.61 (m, 2 H), 4.36-5.01 (bs, 1 H); MS m/e 229, 199, 156, 142; CIMS MH^+230

3-Hydroxyethyl-N-(1'-*t*butoxy-2'-butyl)-pyrrolidine 18g N-Oxide **17** (0.207 g, 1.10 mmol) and homoallyl alcohol **8g** (0 118 mL, 1 38 mmol) yielded **18g** (0 059 g , 0 24 mmol, 18%, CH_2Cl_2/MeOH 95·5) and **14** (0.114 g, 0 35 mmol, 67% CH_2Cl_2/MeOH 95 5).,

18g . ^{1}H NMR (200 MHz) δ 0.93 (t, 3 H, J = 7 5 Hz), 1.20 (s, 9 H), 1 65-1 75 (m, 5 H), 2 00-2 10 (m, 1 H), 2 35-2.45 (m, 1 H), 2.75-2.95 (m, 3 H), 3 05-3 21 (m, 2 H), 3 52-3 62 (m, 4 H), 5.62-5.85 (bs, 1 H), MS m/e 243, 172, 170, 156, 87

3,4-Diphenyl-*trans*-N-benzyl-pyrrolidine 21a. Pyrrolidine **14a** (0.114 g, 0.39 mmol) in MeOH (10mL) was treated with benzyl bromide (0.230 mL, 1.85 mmol) at 20°C in the presence of $NaHCO_3$. After complete consumption of the starting product, MeOH was distilled of *t*-BuOK (0 180 g, 1 8 mmol) in *t*-BuOH (7 mL) was added and the mixture was heated to reflux Usual workup yielded **21a** (0.117 g, 0 37 mmol, 96%) ^{1}H NMR (200 MHz) δ 2.79-2.99 (dd, 2 H, J = 8, 10 Hz), 2 99-3.36 (dd, 2 H, J = 8, 10 Hz), 3.36-3.56 (m, 2 H), 3.69-3 96 (d, 2 H, J = 8 Hz), 7 09-7.83 (m, 15 H); CIMS MH^+ 314

3-Phenyl-N-benzyl-pyrrolidine 21b. Pyrrolidine **14b** (0.086 g, 0.33 mmol) successively treated with benzyl bromide (0.116 mL, 1.0 mmol) *t*BuOK (0.089 g, 10.80 mmol) yielded **21b** (0.082 g, 0.30 mmol, 90%); ^{1}H NMR (200 MHz) δ 1.84-1.98 (m, 1 H), 2.28-2.39 (m, 1 H), 2.46-2.56 (dd, 1 H, J = 9.4, 4 7 Hz), 2.64-2.73 (m, 1 H), 2.84-2.96 (m, 1 H), 3.01-3 14 (dd, 1H, J = 9.4, 4 7 Hz) 3.29-3 46 (m, 1 H), 3 63-3.81 (s, 2 H), 7.09-7.56 (m, 10 H); MSCI MH$^+$ 238. Picrate F = 171-173°C; Lit.[16] 172-173°C

N-Benzyl-2-aza[3.3.0]bicyclooctane 21c. Pyrrolidine **14c** (0.051 g, 0.17 mmol) successively treated with benzyl bromide (0.103 mL, 0.87 mmol) then *t*-BuOK (0.162 g, 1.5 mmol) yielded **21c** (0.050 g, 0.18 mmol, 85%); ^{1}H NMR (200 MHz) δ 1.33-1.58 (m, 6 H), 1.96-2.14 (m, 2 H), 2.49-2.76 (m, 2H), 2.76-2.96 (m, 2 H), 3.54 (s, 2 H), 7 8-7 43 (m, 5 H), MS m/e 201, 200, 110; CIMS MH$^+$ 202; HRMS, Calcd for $C_{14}H_{14}N$ 201.1517, found 201.1510.

N-Benzyl-10-aza[6.3.0]bicycloundecane 21d. Pyrrolidine **14d** (0.033 g, 0.18 mmol) successively treated with benzyl bromide (0.064 mL, 0.4 mmol) then *t*BuOK (0.080 g, 0.75 mmol) yielded **21d** (0.031 g, 0.15 mmol, 85%) ^{1}H NMR (200 MHz) δ 1.17-1 70 (m, 12 H), 1 73-1 93 (dd, 2 H, J = 11, 10 Hz), 2.09-2.36 (m, 2 H), 3.03-3.26 (dd, 2 H, J = 11, 10 Hz), 3.57 (s, 2 H), 7 14-7.49 (m, 5 H); CIMS MH$^+$ 244; HRMS, Calcd for $C_{17}H_{21}N$ 243.2014, found 243.208

3-Hydroxymethyl-N-benzyl-pyrrolidine 21f. Pyrrolidine **14f** (0 107 g, 0 62 mmol) successively treated with benzyl bromide (0.360 mL, 3 mmol) then *t*BuOK (0 090 g, 0.8 mmol) yielded **21f** (0.105 g, 0.55 mmol, 89%), ^{1}H NMR (200 MHz) δ 1 55-1 75 (m, 1 H), 1 86-2 07 (m, 1 H), 2 26-2.44 (m, 2 H), 2.44-2.65 (m, 1 H), 2.65-2.83 (m, 1 H), 3.40-3.50 (m, 1 H), 3.51 (s, 2 H), 3 51-3.73 (m, 3 H), 6.98-7 35 (m, 5H); MS m/e 191, 176, CIMS MH$^+$ 192; HRMS, Calcd for $C_{12}H_{17}NO$ 191 811, found 191 820

3,4-Diphenyl-*trans*-pyrrolidine 22a. Pyrrolidine **21a** (0.082 g, 0.20 mmol) in MeOH treated with amonium formate (0 041 g, 0.65 mmol) in the presence of Pd 10% on charcoal[12] yielded **22a** (0.054 g, 0.26 mmol 100%) identical with an authentic sample;[16] ^{1}H NMR (200 MHz) δ 2 49 (s, 1H), 2.96 (dd, 2 H, J = 14, 9.0 Hz), 3 17 (dd, 2H, J = 14, 90 Hz), 3.37 (m, 2H) 6.90-7 40 (m, 10 H), MS m/e 223.

3-Phenyl pyrrolidine 22b Pyrrolidine **21b** (0.054 g, 0 23 mmol) treated in the same conditions yielded **22b** (0 031 g, 0 17 mmol, 91 %), ^{1}H NMR (400 MHz) δ 2 08-2 23 (m, 1 H), 2 23-2 44 (m, 1 H), 2.83 (s, 1 H), 3 17-3 92 (m, 4 H), 7.16-7 66 (m, 5 H); MS m/e 147. Picrate: mp 156-157°C (EtOH), lit[17] 155°C.

3-Aza[3.3.0]bicyclooctane 22c. Pyrrolidine **21c** (0.016 g, 0.08 mmol) treated in the same conditions yielded **22c** (0 009 g, 0.08 mmol, 98%); ^{1}H NMR (200 MHz) δ 1 49-1.75 (m, 6 H), 2.81-3.03 (m, 4 H), 3.44-3.57 (m, 2 H), CIMS MH$^+$ 112.[18]

10-Aza[6.3.0.]bicycloundecane 22d Pyrrolidine **21d** (0.020 g, 0 08 mmol) yielded **22d** (0 012 g, 0.08 mmol, 97%), ^{1}H NMR (200 MHz) δ 1.12-1.52 (m, 12 H), 2.21-2 49 (m, 2 H) 2.69 (s, 1 H), 2.67-2.89 (m, 1 H), 3.23-3.46 (m, 1 H), 3.46-3.73 (m, 2 H); CIMS MH$^+$ 154

3-Hydroxymethyl pyrrolidine 22f. Pyrrolidine **21f** (0.034 g, 0 18 mmol) yielded **22f** (0.016 g, 0 10 mmol, 89%); ^{1}H NMR (200 MHz) δ 1.43-1 76 (m, 1 H), 1 76-2 8 (m, 1 H), 2 23-2 49 (m, 1 H), 2.83-3.33 (m, 2 H), 3.46-3.70 (m, 2 H), 3.70-4 29 (m, 4 H), MS m/e 101, 83; CIMS MH$^+$ 102

(1'-*t*Butoxy-2'-propyl)-methyl-hexylamine-N-oxide 23 The oxidation of the corresponding amine (1 6 g, 7.0 mmol) yielded **23** (1 7 g, 6 94 mmol, 99%), ^{1}H NMR (200MHz) δ 0.85 (t, 3 H, J = 5 0 Hz), 1 20 (s, 9 H), 1 20-1.52 (m + 2d, 11 H, J = 7.0 Hz), 1.66-1.99 (m, 2 H), 3.2 (d, 3 H, J = 2.0 Hz), 3.31-3 57 (m, 3 H), 3.63-3.89 (m, 2 H); CIMS (MH$^+$ -O) 230

(1'-*t*Butoxy-2'-butyl)-(1,1'-diethoxy-3'-propyl)-methylamine-N-oxide 24 The oxidation of (1'-*t*butoxy-2'-butyl)-(1',1'-diethoxy-3'-propyl)-methylamine[19] (2 5 g, 8.7 mmol) yielded **24** (2.6 g, 8.3 mmol, 95%). ^{1}H NMR (200 MHz) δ 1.0 (m, 6 H), 1.18 (m +s, 12 H), 1.29-1 42 (m, 1 H), 1.69-1 81 (m, 2 H), 2.18-2.36 (m, 1 H), 3.8 (m + s, 5 H), 3.18-3 48 (m, 1 H), 3 51-3 73 (m, 6 H), 4 73 (t, 1 H, J = 5 0 Hz); CIMS (MH$^+$ - O) 290.

2-Pentyl-N-(1'-*t*butoxy-2'-propyl)-pyrrolidine 25. N-Oxide **23** (0.383 g, 1 56 mmol) was treated with LDA at -78°C under ethylene bubbling. Usual workup yielded **25** after column chromatography (0 178 g, 0.70 mmol, 45%, CH_2Cl_2/MeOH 95 5), ^{1}H NMR (200 MHz) δ 0.93 (t, 3 H, J = 4 0 Hz), 1.02 (d, 3 H, J = 7.0 Hz), 1 20 (s, 9 H), 1.20-1.38 (m, 8 H), 1 62-1 93 (m, 4 H), 2.43-2 90 (m, 2 H), 3.05-3.35 (m, 2 H), 3 20-3.40 (m, 2 H), MS m/e 255, 184, 168, HRMS, Calcd for $C_{16}H_{33}NO$ 255 2162, found 255.2153.

2-(1',1'-Diethoxy-ethyl)-N-(1'*t*butoxy-2'-butyl)-pyrrolidine 27. N-Oxide **24** (0.210 g, 0 82 mmol) was treated with LDA at -20°C under ethylene bubbling. Usual workup and column chromatography yielded **27** (0.104 g, 0 33 mmol, 40%); ^{1}H

NMR (200 MHz) δ 0.77-1.07 (m, 9 H), 1.20 (s, 9 H), 1.29-1.59 (m, 3 H), 1.59-1.95 (m, 3 H), 2.51-3.02 (m, 4 H), 3.03-3.29 (m, 2 H), 3 29-3.73 (m, 6 H), 4.49-4.67 (m, 1H); MS m/e 315, 286, 242; CIMS MH^+ 316.

2-Pentyl-N-formyl-pyrrolidine 28. Pyrrolidine **25** (0.064 g, 0.25 mmol) was treated with NaI (0.076 g, 0.50 mmol) and trimethylsilyl chloride (0.065 mL, 0.50 mmol) in CH_3CN (2.5 mL).[9b] Usual workup yielded **26** (0.047 g, 0.24 mmol, 94%) which was treated with NaOH 50% (0 5 ml in $CHCl_3$ in the presence of TBABr (0.001 g).[14]

Pyrrolidine **28** was obtained after column chromatography (0.030 g, 0.18 mmol, 70%, CH_2Cl_2/MeOH 98:2): ^1H NMR (200MHz) δ 0.90 (t, 3 H, J = 3.0 Hz), 1.15-1.49 (m, 8 H), 1.52-1.70 (m, 2 H), 1.75-2.10 (m, 2 H), 3.18-3.82 (m, 3H), 8.3 (s, 1 H); MS m/e 169, 140; CIMS MH^+ 170; HRMS, Calcd for $C_{10}H_{14}NO$ 169.1466, found 169.1460.

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