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Reaction of the lithio-derivative of methoxyallene with hydrazones. Part 2: Formation of 3-pyrrolines and azetidines; synthetic and mechanistic aspects

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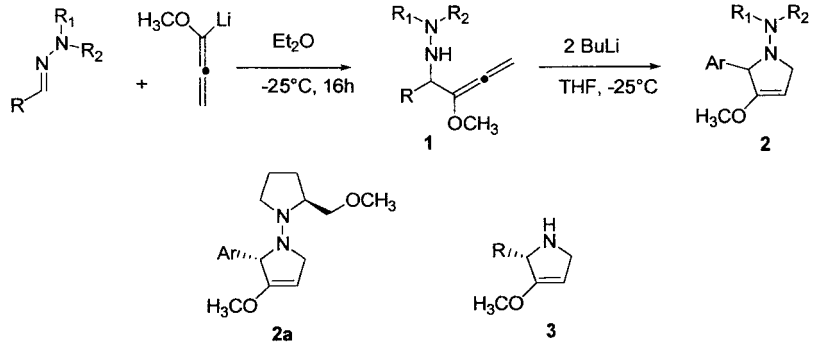
Abstract—The reaction of α-lithiomethoxyallene with aromatic hydrazones leads to 3-pyrrolines when run in THF. In the case of SAMP-hydrazones, this reaction occurs with almost complete stereodifferentiation. With other hydrazones (dimethyl, piperidinyl, morpholinyl), the 3-pyrrolines are accompanied by azetidines. However, formation of the latter compounds is reversible, since they are transformed to 3-pyrrolines when the time and temperature of the reaction are increased, but the rate of this transformation depends on the substituents of the terminal nitrogen. A reaction mechanism is proposed which involves intermolecular or intramolecular electron transfers from the lithium amide leading to hydrazinyl radicals. The relative stabilities of these intermediates may then explain the role of the substituents of the terminal nitrogen in the formation of azetidines by a 4-*exo-dig* radical process.

In the preceding paper,[1] we have shown that the reaction of the lithio-derivative of methoxyallene with aldehyde hydrazones leads, when the solvent *is ether*, to α-allenic hydrazines **1**. These compounds, when treated in THF with 2 equiv. of butyllithium, are cleanly transformed in the case of aromatic hydrazines (R=phenyl, naphthyl, etc.) to *N*-dialkylaminopyrrolines **2**. The cyclization process appears to be particularly easy in the case of SAMP-hydrazines which are transformed to **2a**, regardless of the aliphatic or aromatic nature of R. Still more interesting is the almost complete diastereoselection observed in the case of these SAMP-hydrazones which permits, after hydrogenolysis of the N–N bond, the 3-pyrrolines **3** to be obtained with high enantiomeric purity (Scheme 1).

In this paper, we will provide evidence to show that the same reaction of hydrazones with the lithio-derivative of methoxyallene leads, in many cases, directly to the *N*-dialkylaminopyrrolines **2** when run in THF. We will discuss the influence of structural and experimental factors, which favour cyclization and finally propose a reaction mechanism based on the intermediate formation of a hydrazinyl radical.



Scheme 1.

Keywords: allenes; pyrrolines; azetidines; radical cyclizations; hydrazinyl radicals.
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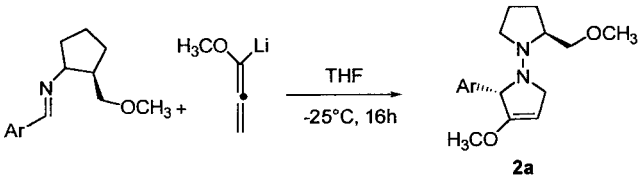
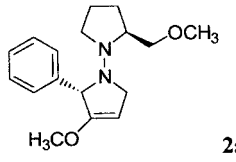
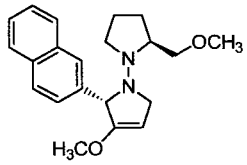
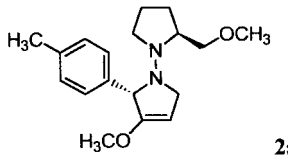
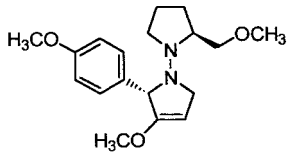
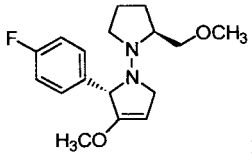
Table 1.



2a

Hydrazone	Product	Yield (%)[a]	D.e. (%)
Ar=Ph	 **2a$_1$**	88	>99
Ar=β-naphthyl	 **2a$_2$**	76	>99
Ar=*p*-CH_3Ph	 **2a$_3$**	79	>99[b]
Ar=*p*-CH_3OPh		75	>99
Ar=*p*-FPh	 **2a$_5$**	69	>99

[a] Yields were determined by comparing the amount of **2a** isolated by flash chromatography to that of the starting aldehydes ArCHO.

1. Results

1.1. Reaction in THF at −25°C

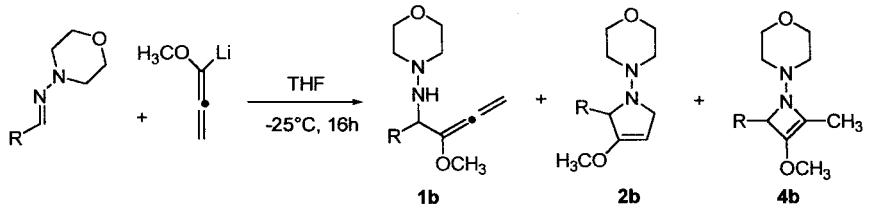
The first reactions were made by adding, at −78°C, the preformed lithio-derivative[2] in THF to a solution of the hydrazone in the same solvent. After 2 h at −78°C, the temperature was raised to −25°C and maintained at that temperature for 16 h. After work up, the pyrrolines **2** were isolated by flash chromatography; the allenic hydrazines **1** are fairly unstable under these chromatographic conditions, but the crude product is generally of good purity as shown by ^{1}H and ^{13}C NMR spectroscopy.

Under these conditions, only the reactions involving SAMP-hydrazones lead to the *N*-dialkylamino pyrrolines **2a** and cyclization appears to be limited to aryl-hydrazones. The results of these reactions, listed in Table 1, show that the yields, based on the starting aromatic aldehydes, are generally good and that the diastereoselection is complete in all cases, as analysed by GC–MS, ^{1}H and ^{13}C spectroscopy. The only exception was **2a$_3$**, for which GC–MS analysis revealed the presence of 0.4% of the other diastereomer. Based on the model proposed by Enders et al. as well as on our previous results[1] (X-ray analysis of **2a$_1$**), the *S* configuration was assigned to the stereogenic carbon.

All the reactions carried out with other hydrazones, under the same conditions, lead to the corresponding α-allenyl hydrazines **1** or to a mixture of them with cyclized products.

Aliphatic SAMP-hydrazones are uniformly converted to **1** with modest yield [R=Et: 38%; R=nC$_5$H$_{11}$: 30%; R=*iso*Pr: 60%; R=*t*-But: 50%] but with d.e. >95%.

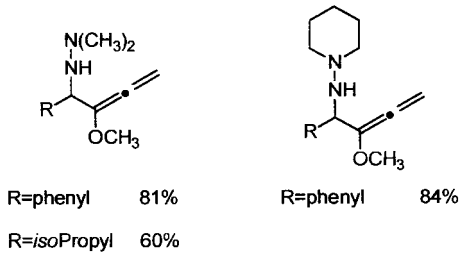
The behaviour of *morpholinyl hydrazones* is more complex since they lead, for the aromatic ones, to a mixture of the allenylhydrazines **1b**, of the *N*-morpholinyl pyrrolines **2b** and of *N*-morpholinyl azetidines **4b** (Scheme 2). As found for SAMP-hydrazones, the aliphatic morpholinyl hydrazones are converted to the α-allenyl hydrazines [R=Et: 85%; R=*iso*Pr: 85%; R=*t*Bu: 75%]. It is noteworthy that, in this series, when the reaction was run with cyclohexanone hydrazone, the corresponding hydrazine was obtained with a 60% yield (the corresponding SAMP-hydrazone is almost inert under similar conditions).



1b **2b** **4b**

R=Phenyl	10%	40%	22%
R=β-naphthyl	16%	51%	10%

Scheme 2.



Scheme 3.

The *dimethylhydrazones* as well as their *piperidinyl homologues* are converted only into the allenyl hydrazines **1**, regardless of the nature of R (Scheme 3).

The results of these reactions, run at −25°C, show that two factors facilitate the cyclization: the nature of the hydrazino group (SAMP-hydrazones are by far the best substrates for obtaining the pyrrolines **2**) and the aromatic nature of R. The formation of the azetidine **4b** in the case of aromatic morpholinyl hydrazones has also to be underlined.

1.2. Reaction in THF at higher temperatures

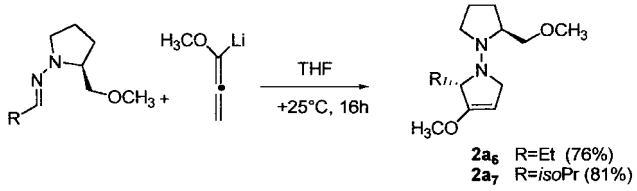
To try to obtain the *N*-dialkylamino-3-pyrrolines **2** preferentially, experiments were repeated at higher temperatures.

Aliphatic SAMP-hydrazones were converted to the corresponding **2a** when treated in THF with 6 equiv. of α-lithiomethoxyallene for 16 h at 25°C (Scheme 4). As was found in the case of their aromatic counterparts, the yield are good and the diastereoselection is high.

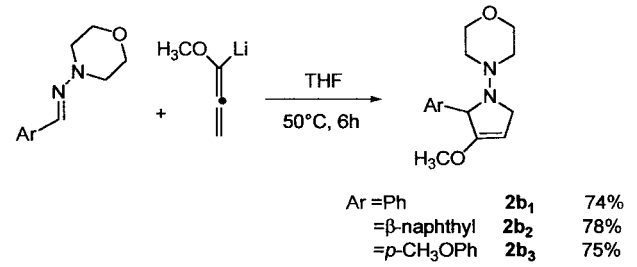
These results show that, in this series, the pyrrolines **2a** are generally obtained. Consequently, the parent 3-pyrrolines **3** can probably be formed with a high enantiomeric excess (≥95%), after hydrogenolysis of the N–N bond.[1]

In the *morpholinyl series*, the reaction run at room temperature still leads to a mixture of the allenyl hydrazine **1b**, of the *N*-morpholinyl pyrroline **2b** and of the *N*-morpholinyl azetidine **4b** (see Scheme 2) with small variations in composition, compared to the products obtained in the reaction run at −25°C. For example, in the case of the phenylhydrazone, the reaction at room temperature for 16 h produces $\mathbf{1b_1}$ (5%), $\mathbf{2b_1}$(66%) and $\mathbf{4b_1}$ (10%). If the reaction time is increased to 96 h the allenyl hydrazine $\mathbf{1b_1}$ is no longer observed and the product is composed of $\mathbf{2b_1}$ (59%) and $\mathbf{4b_1}$ (15%). However, the increase of the temperature to 50°C has a more spectacular effect since $\mathbf{2b_1}$ is obtained exclusively. The same conditions were applied to other aromatic hydrazones, leading to morpholinyl pyrrolines **2b** (Scheme 5).

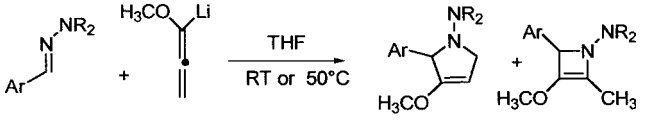
On the contrary, the increase in temperature has no effect when aliphatic hydrazones are used: the α-allenylhydrazine



Scheme 4.



Scheme 5.



R=CH_3, Ar=Ph	RT, 16h	53% $\mathbf{2c_1}$	22% $\mathbf{4c_1}$
	id + 50°C, 6h	46%	26%
Ar=β-naphthyl	RT, 16h	77% $\mathbf{2c_2}$	-
Ar=*p*-CH_3Ph	RT, 16h[a]	45% $\mathbf{2c_3}$	35% $\mathbf{4c_3}$
Ar=*p*-CH_3OPh	RT, 16h	35% $\mathbf{2c_4}$	38% $\mathbf{4c_4}$
R=-$(CH_2)_5$-, Ar=Ph	RT, 16h	46% $\mathbf{2d_1}$	28% $\mathbf{4d_1}$
	id + 50°C, 6h	55%	16%
Ar= β-naphthyl	RT, 16h[b]	78% $\mathbf{2d_2}$	4% $\mathbf{4d_2}$
Ar=*p*-CH_3Ph	RT, 16h	43% $\mathbf{2d_3}$	38% $\mathbf{4d_3}$
Ar=*p*-CH_3OPh	RT, 16h	38% $\mathbf{2d_4}$	38% $\mathbf{4d_4}$

α-allenylhydrazine **1** : a 8%, b 3%.

Scheme 6.

1b is the only reaction product formed at room temperature as well as at 50°C.

The results of the reactions of *dimethylhydrazones* as well as *piperidinyl hydrazones* are slightly different, except for alkyl hydrazones which are transformed only to α-allenyl hydrazines **1** regardless of the temperature (−25 to 50°C).

In both the cases, with aromatic hydrazones, a mixture of pyrrolines **2** and azetidines **4** is obtained at room temperature as well as at 50°C. The proportions of these compounds are only slightly influenced by the increase of temperature. Unfortunately, it was impossible to obtain pure **2** by increasing the reaction time at 50°C. If the ratio **2**:**4** is increased, when longer times are used (see below), there is a parallel formation of tars which complicates the purification of **2** and decreases the yield of the process.

High selectivity was observed only with β-naphthyl hydrazones which are converted at 50°C (almost) exclusively to *N*-dimethylamino- or *N*-piperidinyl-3-pyrrolines **2** (Scheme 6).

2. Discussion

In this paper, and as previously reported,[1] the reaction of α-lithiomethoxyallene with hydrazones can produce, depending on the conditions, either the expected α-allenyl hydrazines **1** or cyclized products *N*-dialkylamino-3-pyrrolines **2** or even *N*-dialkylamino azetidines **4**. We have also shown that **1** is converted to the cyclized products **2** in certain cases and, eventually, **4** when treated in THF by 2 equiv. of *n*-butyllithium. This last result proves that the lithium hydrazinide **5** is able to cyclize only in THF; it is stable in Et_2O at −25°C, where its hydrolysis produces the hydrazines **1**.

Even in THF, the cyclization is not general and its behaviour is influenced by temperature and mainly by two structural factors: the substituents of the terminal nitrogen of the hydrazine and the nature, aromatic or aliphatic, of the starting aldehyde. From the presented results, it appears that cyclization, essentially to **2**, is easier when SAMP-hydrazones of aromatic aldehydes are involved.

Hence, it would appear that cyclization is favoured by a partial or total dissociation of the N–Li bond of **5**, giving the anion **6** (Fig. 1). This dissociation, as expected, takes place more readily in THF than in ether and is probably much easier in the case of SAMP-hydrazinide, where the lithium can be coordinated intramolecularly by the methoxy group of the SMP moiety.

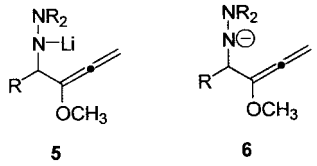


Figure 1.

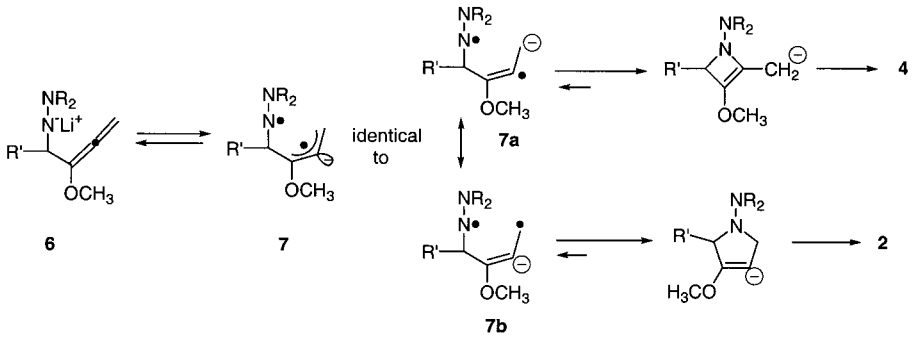
The problem remains, however, of determining the mode of cyclization of **6** to **2** and eventually to **4**. If we take Baldwin's rules[3] into consideration, a concerted 4-*exo-dig* process can be postulated for the formation of **4** from **6**. On the contrary a concerted *5-endo-trig* process for the transformation of **6** to **2** has to be disregarded. Generally, this cyclization of allenyl amines or homologues to nitrogen heterocycles (aziridines to piperidines) is promoted by electrophilic species (H^+, Ag^+, Cu^+) or by palladium complexes. In the first case an intermediate, allylic cation, is generally proposed which is transformed into 5- or 6-membered rings by apparent *exo-trig*[4] or *endo-trig*[5] processes.

Similarly, the cyclization catalysed by palladium (II) complexes has, depending on the substrate and on the complex involved, either a π-allylpalladium[5] or a σ-vinylpalladium[6,7] intermediate which can be converted, apparently by *endo-dig* or *exo-trig* processes, into 3- to 6-membered rings.

The only cyclization of an amide formed by the reaction of a base with an α-allenyl amine has only very recently been described: it leads cleanly to pyrrolines or pyrroles depending on the conditions.[8] This cyclization, which appears to be closely related to the transformation **1**→**2**, has not been explained from a mechanistic point of view.

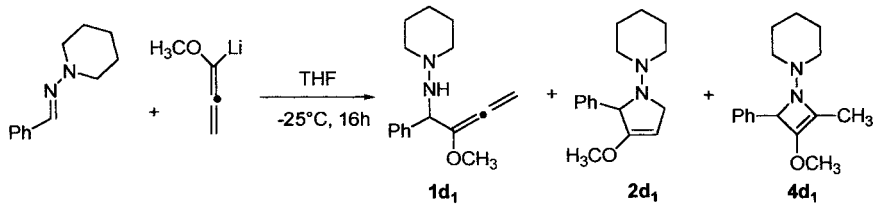
On the contrary, the cyclization of α-allenic alcohols to dihydrofuranes and/or epoxides has been described by Magnus et al.[9] It occurs only in DMSO and was explained by electron and hydrogen transfers between the substrate and the solvent.

In spite of some differences (we never observed aziridines,



Scheme 7.

Table 2.



1d$_1$ **2d$_1$** **4d$_1$**

Time (h)	*T* (°C)	**1d$_1$**	**2d$_1$**	**4d$_1$**
12	−25	100%	–	–
24	25	25%	45%	30%
60	25	ϵ	50%	50%
6	50	–	50%	50%
20	50	–	68%	32%
45	50	–	85%	15%

and Magnus et al. did not obtain 4-membered rings), it may be possible to propose, for the cyclization **5**→**2**+**4**, a similar mechanism with a single electron transfer from the nitrogen to the allenyl moiety (Scheme 7).

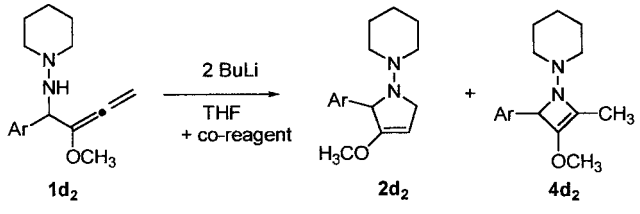
This proposal seems to agree with the formation of the 5-membered ring, but is less appropriate with that of the 4-membered ring. On one hand, the canonical form **7b**, which is evidently more stable than **7a**, is probably more representative of the structure of **7** and, on the other hand, **2** is favoured to **4** by 21–34 kcal/mol depending on the substituents R of the terminal nitrogen (hyperchem software): such a mechanism would lead essentially to the pyrrolines **2**. Consequently, two questions remain concerning (i) the mechanism for the formation of **4** and (ii) the nature of the electron transfer agent which was supposed to be DMSO in the Magnus mechanism.

In an attempt to answer these two questions, two sets of additional reactions were undertaken.

The influence of experimental conditions (time and temperature) was more carefully determined by following the reaction by GC. For this experiment, the reaction of the piperidinyl hydrazone of benzaldehyde with 6 equiv. of α-lithiomethoxyallene in THF was chosen since it gives rise, depending on the conditions, to three possible products **1d$_1$**, **2d$_1$** and **4d$_1$**. The results, given in Table 2, show the percentages of **1d**, **2d** and **4d**, formed at different reaction times and temperatures in the same reaction mixture. Samples were analysed by GC using dodecane as internal reference and the proportions of each product were determined after standardization with purified compounds. The evolution of the composition shows clearly that (i) lithium allenyl hydrazide **6** is completely transformed to the cyclized products **2d$_1$** and **4d$_1$** with the increase in time and temperature, and (ii) transformation of **4d$_1$** to **2d$_1$** is observed when these two factors are increased, thus showing the reversibility of the formation of the 4-membered ring.

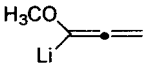
As it appears that the cyclization is favoured in the direct reaction of lithioallene with hydrazones in THF, compared to that of *n*-butyllithium with hydrazines **1** in the same solvent, the question of the role of the excess lithioallene in the cyclization process had to be addressed. To determine this effect, the reaction of *n*-BuLi with the piperidinyl

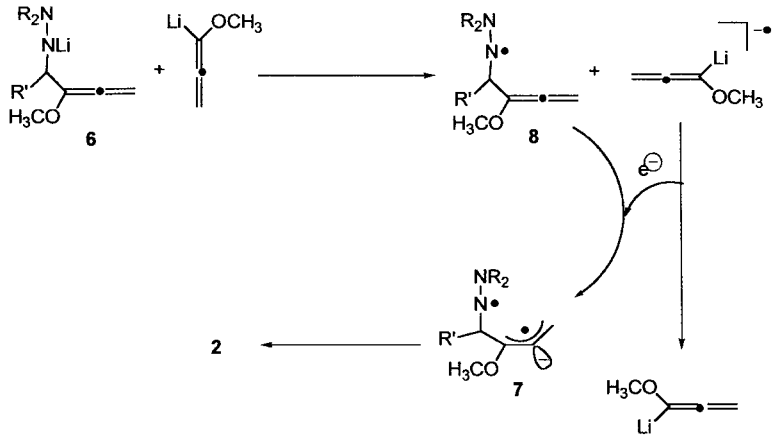
Table 3.



1d$_2$ **2d$_2$** **4d$_2$**

Ar=β-naphthyl

Co-reagent	Time (h)	*T* (°C)	**1d$_2$**	**2d$_2$**	**4d$_2$**
–	60	25	100%	–	–
					
2 equiv.	16	−25	100%	–	–
	16	25	–	66%	34%
	6	50	–	97%	3%
id 6 equiv.	16	25	–	100%	–
$CuCl_2$ 10%	16	25	–	89%	11%



Scheme 8.

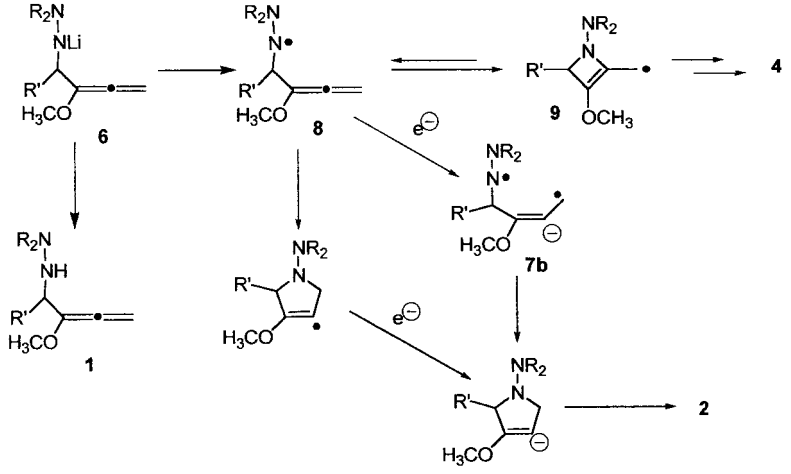
naphthylhydrazine $\mathbf{1d_2}$ was run under different conditions as depicted in Table 3.

The results show that the α-lithiomethoxyallene plays a role in the cyclization process, which evolves with the increase of temperature and eventually with that of time, leading to the formation of the pyrroline $\mathbf{2d_2}$ only. As a catalytic quantity of cupric chloride exerts the same influence, it appears that the allenic organometallic is probably an electron transfer agent in the cyclization process, transforming first the amide **6** to the hydrazinyl radical **8**, which is then reduced to **7** which then cyclizes preferentially to **2** (Scheme 8).

Even if the formation of the radical anion of α-lithiomethoxyallene is surprising, it is supported by the formation of a $C_3H_2Li_2$ species by treatment of allene with 2 equiv. of *n*-BuLi, one possible structure for the species being *bis* lithioallene.[10] If the methoxyallene moiety is able to accommodate two negative charges, it is reasonable to suppose that a three-electron species has also a certain stability.

As mentioned before, the cyclization of **7** would lead preferentially to the pyrroline **2**, but its evolution to the azetidine **4** is far less probable. In comparison, a radical cyclization of β-allenyl hydrazinyl radical **8** can be envisaged. These hydrazinyl radicals are not well-known species, and it is only recently that they were mentioned in the literature.[11] Comparatively, the cyclization of carbon radicals by a reversible 4 *exo-trig* process is known.[12] Indeed, it has been shown that the radical cyclization of *N*-vinyl α-halogeno amides leads to β-lactams at room temperature while it gives γ-lactams in refluxing toluene.[13] This result has been explained by a kinetic 4-*exo* process which reverses at higher temperature leading to the more stable 5-membered ring isomer. Lastly, the cyclization of the β-allenyl carbon radical was described and it gives vinylcyclopropane[14] in low yield. Comparatively, the cyclization of 3,4-pentadien-1-yllithium gives exclusively α-methyl-lithiocyclobutene while the corresponding Grignard reagent is transformed to its vinylcyclopropyl isomer.[15] It is noteworthy that the formation of cyclopentene was not described in the reports of Crandall et al.

In spite of these two lines of evidence (the chemistry of hydrazinyl radicals is not well known and the cyclization of β-allenyl radicals or organometallics gives troublesome results), we make the hypothesis that the azetidines **4** come from a reversible 4-*exo-dig* cyclization of the intermediate **8**. Then, depending on the nature of the R and R′ substituents, the reversibility of the process can operate at



Scheme 9.

different rates depending on the stability of **8**. It can give the pyrrolines **2**, either by a disfavoured 5-*endo* process, or more probably via **7** due to a double electron transfer (Scheme 9).

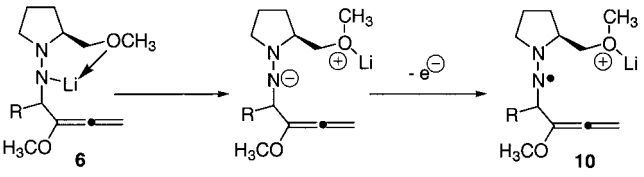
In this hypothesis, the relative proportions of **2** and **4** at a given temperature would reflect the relative stability of the radicals **8** and **9**. Since the stability of **9** seems to be independent of the substituents R and R′, the main factor governing these proportions and the rate of ring opening of **9** would be the stability of the hydrazinyl radical **8**, which can be influenced by the following two factors.

The aliphatic or aromatic nature of R′. In the case of an aromatic substituent, the nitrogen radical can be stabilized by homoconjugation, due to its homobenzylic character.[16] Hence, cyclizations are easier in the case of the reaction of aromatic hydrazones since the transformation of **2** is favoured for a β-naphthyl substituent compared to a phenyl substituent (see Scheme 6). The increase of the stability of **7** and **8** can then explain either the easier formation of **7** from **6** or the faster reversibility of the 4-*exo-dig* process **8**→**9**.

The nature of the R substituent can also influence the stability of the nitrogen radical of **7** and **8** by varying the electron donating ability of the terminal nitrogen. The stability of α-amino carbon radicals is governed by the substituents of amino groups: it is known that the dimethylamino group stabilizes a vicinal radical by about 10 kcal/mol compared to an NH_2 group.[17] It is reasonable to think that the same effect can be obtained with a hydrazinyl radical which would be better stabilized by a more basic terminal nitrogen. In our case, large differences in the behaviour of the cyclization process were observed depending on the nature of the starting hydrazones:

- in order to observe cyclization with dimethyl and piperidinyl hydrazones, the reaction must be run at room temperature where it gives rise to a mixture of **2** and **4**, with a slow evolution at higher temperature and longer time towards the preferential formation of **2** (Scheme 6 and Tables 2 and 3).
- with aromatic morpholinyl hydrazones, the cyclization is partially observed at −25°C giving both **2** and **4**, but the reaction at 50°C leads only to **2**.
- with SAMP-hydrazones, the cyclization only to pyrrolines **2** is easier since it occurs at −25° with aromatic hydrazones (Table 1) and at room temperature with their aliphatic counterparts. In this series, the azetidine **4** was never observed.

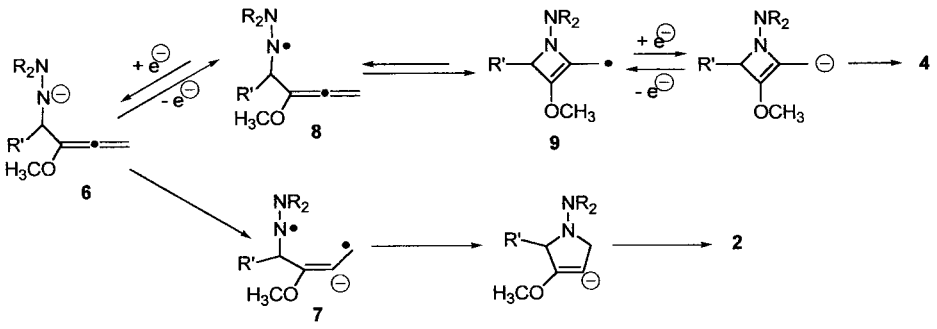
These different behaviours can probably be related to the basicity of the NR_2 group. From literature data,[18] it appears that, if dimethylamine and piperidine have about the same basicity constants, morpholine is, depending on the solvent and temperature, 10^2–10^3 times less basic. This loss of basicity is probably due to the electron withdrawing character of the β-carbon–oxygen bond since (2-methoxyethyl)methylamine has a basicity of the same magnitude as morpholine. It is consequently reasonable to think that SMP, which also has a β-carbon–oxygen bond, has a basicity in the same range as that of morpholine. On this basis, it appears that cyclization, particularly cyclization to **2**, is favoured by a less basic terminal nitrogen. The difference between SAMP-hydrazones and morphinyl hydrazones could be the consequence of the coordination of the lithium cation by the methoxymethyl group which favours the dissociation of the N–Li bond of **6** giving **10**, where the basicity of the pyrroline nitrogen is decreased by the electron-withdrawing effect of the coordinated ether functionality (Scheme 10).



Scheme 10.

With these considerations, one explanation for all the experimental results would be that the amide **6** has, in THF, two possibilities: it can give rise, directly by intramolecular electron-transfer, to the bis-radical anion **7** which rapidly cyclizes to the 5-membered ring or it can transfer the electron to α-lithiomethoxyallene (see Scheme 9) giving the allenyl hydrazinyl radical which cyclizes reversibly to the 4-membered ring (Scheme 11).

As mentioned before, both processes are favoured when R′ is aromatic but it seems that **8** is more stable when it is substituted by a basic nitrogen and it is only in that case that the 4-*exo-dig* process can be observed. In other words, for the intermolecular electron transfer between **6** and α-lithiomethoxyallene to take place, the centred nitrogen radical has to be well stabilized by the terminal amino group. In other cases, the intramolecular electron transfer giving **7** is favoured to a large extent.



Scheme 11.

3. Conclusion

The results presented here and in our previous report[1] show that the reaction of α-lithiomethoxyallene with hydrazones constitutes an easy entry in the preparation of 5-membered nitrogen heterocycles since the nucleophilic addition can be followed by the cyclization of the lithium amide on the allenic linkage. The main interest from a synthetic point of view relies on its almost complete diastereoselectivity when SAMP-hydrazones are used, allowing then the formation of enantiopure 3-pyrrolines.

The study of the cyclization process with variations of the substituents on the hydrazones has shown that a second mode of cyclization is possible, leading to azetidines by a reversible radical 4-*exo-dig* process. The evolution of the reaction has been explained by intramolecular or intermolecular electron transfers, developing hydrazinyl radicals which are relatively new reaction intermediates.

4. Experimental

4.1. General procedure

See preceding paper.

4.1.1. Preparation of *N*-dialkylamino-3-pyrrolines 2. Only compounds not already described in the preceding paper[1] are described herein.

α-Lithiomethoxyallene was synthetized in situ by addition of an equivalent of *n*-butyllithium (2.5 M hexane solution) to a solution of 5 mmol methoxyallene in THF (5 ml) at −40°C. The solution was chilled to −78°C. After 20 min, a solution of hydrazone (0.833 mmol in 2 ml of THF) was added dropwise to the α-lithiomethoxyallene solution. The mixture was warmed to −20°C and, after 16 h at this temperature, it was quenched with 5 ml of water and extracted with ether (2×5 ml). The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified by FC on neutral alumina gel (Merck 90 type II–III: 0.063–0.20 mm) with a mixture of petroleum ether EP/AcOEt as a solvent to give pure **2** and/or **4** as an oil. Its purity was controlled by TLC on alumina using phosphomolybdic acid as chemical tracer.

4.1.2. *N*-(−)-(*S*)-2-Methoxymethylpyrrolidinyl-(*S*)-2-(*p*-methoxyphenyl)-3-methoxy-2,5-dihydropyrrole (2a$_4$). Yield: 75%, R_f=0.11 (97/3 EP/AcOEt), $[\alpha]_D^{20}$=+132 (c=1.55, $CHCl_3$). IR (film): ν=3020, 2980–2810, 1660, 1610, 1460. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.21, 1.56 (2m, 2H), 1.66 (m, 2H), 2.65 (m, 1H), 2.88 (m, 2H), 3.21 (s, 3H), 3.26–3.34 (m, 2H), 3.52 (s, 3H), 3.71–3.89 (m, 2H), 3.78 (s, 3H), 4.59 (m, 1H), 4.93 (m, 1H), 6.82–6.86 (m, 2H), 7.30–7.34 (m, 2H). ^{13}C NMR (50 MHz): δ=21.08 (CH_2), 26.04 (CH_2), 43.81 (CH_2), 55.0 (CH_2), 56.5 (CH_3), 59.0 (CH_3), 59.6 (CH), 63.6 (CH), 74.4 (CH_2), 90.1 (CH), 113.6 (2CH), 129.1 (2CH), 134.8 (C), 157.5 (C), 158.9 (C). EI MS *m*/*z* (%): 318 (100), 273 (84), 190 (22), 175 (15), 159 (49), 91 (6), 71 (43). $C_{18}H_{26}N_2O_3$ (318.4): calculated C 67.9, H 8.2, N 8.8; found C 68.37, H 8.23, N 8.14.

4.1.3. *N*-(−)-(*S*)-2-Methoxymethylpyrrolidinyl-(*S*)-2-(*p*-fluorophenyl)-3-methoxy-2,5-dihydropyrrole (2a$_5$). Yield: 69%, R_f=0.27 (95/5 EP/AcOEt), $[\alpha]_D^{20}$=+112 (c=1.55, $CHCl_3$). IR (film): ν=3020, 2990–2910, 1660, 1610, 1450. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.25, 1.51–1.61 (m, 2H), 1.64–1.69 (m, 2H), 2.64 (m, 1H), 2.78–2.93 (m, 2H), 3.21 (s, 3H), 3.23–3.37 (m, 2H), 3.51 (s, 3H), 3.68–3.95 (m, 2H), 4.59 (m, 1H), 4.95 (m, 1H), 6.95–7.01 (m, 2H), 7.34–7.39 (m, 2H). ^{13}C NMR (50 MHz): δ=21.07 (CH_2), 26.2 (CH_2), 44.25 (CH_2), 54.7 (CH_2), 56.6 (CH_3), 59.5 (CH), 63.8 (CH), 74.4 (CH_2), 90.3 (CH), 114.8 (CH), 115.1 (CH), 129.5 (CH), 129.6 (CH), 138.6 (C), 138.7 (C), 157.0 (C). EI MS *m*/*z* (%): 306 (8), 190 (14), 177 (32), 147 (20), 109 (12), 95 (6), 71 (100), 45 (44), 28 (12). $C_{17}H_{23}N_2O_2F$ (306.4): calculated C 66.6, H 7.6, N 9.1; found C 66.82, H 7.66, N 9.22.

4.1.4. *N*-Morpholino-2-(*p*-methoxyphenyl)-3-methoxy-2,5-dihydropyrrole (2b$_2$). Yield: 74%, R_f=0.33 (85/15 EP/AcOEt). IR (film): ν=3030, 2980–2820, 1660, 1450. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.69 (m, 4H), 3.51 (s, 3H), 3.67 (m, 4H), 3.79 (s, 3H), 4.56 (m, 1H), 4.87 (m, 1H), 6.84–6.88 (m, 2H), 7.30–7.34 (m, 2H). ^{13}C NMR (50 MHz): δ=50.0 (CH_2), 50.2 (CH_2), 55.2 (CH_3), 56.6 (CH_3), 64.5 (CH), 67.3 (CH_2), 89.7 (CH), 113.5 (CH), 129.1 (CH), 134.5 (C), 157.4 (C), 159.9 (C). EI MS; *m*/*z* (%): 290 (32), 190 (100), 159 (57), 147 (10), 115 (10), 91 (13), 56 (17), 43 (34), 28 (21). HRMS EI: theoretical: 290.16304; measured: 290.16301.

4.1.5. *N*-Dimethylamino-2-*p*-methylphenyl-3-methoxy-2,5-dihydropyrrole (2c$_3$). Yield: 43%, R_f=0.29 (93/7 EP/AcOEt). IR (film): ν=3040, 2960–2780, 1660, 1450. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.34 (s, 3H), 2.36 (s, 6H), 3.53 (s, 3H), 3.76 (m, 2H), 4.55 (m, 1H), 4.78 (m, 1H), 7.15 (m, 2H), 7.30 (m, 2H). ^{13}C NMR (50 MHz): δ=22.6 (CH_3), 40.8 (CH_3), 48.2 (CH_2), 60.4 (CH_3), 65.5 (CH), 89.4 (CH), 127.9 (CH), 128.9 (CH), 136.7 (C), 139.4 (C), 157.5 (C). EI MS; *m*/*z* (%): 174 (39), 159 (81), 144 (28), 115 (27), 105 (12), 91 (37), 77 (19), 43 (100), 27 (20). HRMS EI: theoretical: 232.15756; measured: 232.15760.

4.1.6. *N*-Dimethylamino-2-(*p*-methoxyphenyl)-3-methoxy-2,5-dihydropyrrole (2c$_4$). Yield: 35%, R_f=0.36 (85/15 EP/AcOEt). IR (film): ν=3030, 2970–2760, 1660, 1450. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.38 (s, 6H), 3.52 (s, 3H), 3.78 (s, 3H), 4.54 (m, 1H), 4.77 (m, 1H), 6.86 (m, 2H), 7.35 (m, 2H). ^{13}C NMR (50 MHz): δ=40.8 (CH_3), 47.9 (CH_2), 55.2 (CH_3), 56.6 (CH_3), 65.3 (CH), 89.3 (CH), 113.66 (CH), 129.0 (CH), 134.5 (C), 157.5 (C), 158.9 (C). EI MS *m*/*z* (%): 248 (100), 190 (68), 175 (37), 59 (40), 147 (24), 43 (20). HRMS EI: theoretical: 248.15247; measured: 248.15243.

4.1.7. *N*-Piperidino-2-β-naphthyl-3-methoxy-2,5-dihydropyrrole (2d$_2$). Yield: 78%, R_f=0.48 (90/10 EP/AcOEt). IR (film): ν=3030, 2930–2820, 1660, 1450. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.30 (m, 2H), 1.55 (m, 4H), 2.68 (m, 4H), 3.54 (s, 3H), 4.63 (m, 1H), 5.18 (m, 1H), 7.45 (m, 2H), 7.66 (s, 1H), 7.84 (m, 4H). ^{13}C NMR (50 MHz): δ=24.4 (CH_2), 26.4 (CH_2), 51.0 (CH_2), 56.6 (CH_3), 64.6 (CH), 90.1 (CH), 125.4 (CH), 125.7 (CH), 126.4 (CH), 126.9 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 133.1 (C), 133.4 (C),

140.9 (C), 157.3 (C). EI MS *m/z* (%): 308 (41), 209 (29), 179 (41), 165 (31), 127 (7), 98 (8), 70 (17), 42 (100). HRMS CI: theoretical: 309.19663; measured: 309.19675.

4.1.8. *N*-Piperidino-2-(*p*-methylphenyl)-3-methoxy-2,5-dihydropyrrole (2d$_3$). Yield: 43%, R_f=0.58 (96/4 EP/AcOEt). IR (film): ν=3030, 2950–2760, 1660, 1460. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.52 (m, 2H), 2.34 (s, 3H), 2.60 (m, 4H), 2.81 (m, 4H), 3.51 (s, 3H), 3.75–3.92 (m, 2H), 4.55 (m, 1H), 4.95 (m, 1H), 7.13 (m, 2H), 7.32 (m, 2H). ^{13}C NMR (50 MHz): δ=21.6 (CH_3), 24.7 (CH_2), 26.7 (CH_2), 51.7 (CH_2), 56.6 (CH_2), 57.0 (CH_3), 64.4 (CH), 90.2 (CH), 128.4 (CH), 129.0 (CH), 132.7 (C), 137.6 (C), 157.9 (C). EI MS *m/z* (%): 272 (25), 174 (9), 159 (24), 143 (11), 115 (10), 91 (13), 70 (23), 55 (48), 42 (100). HRMS EI: theoretical: 272.18886; measured: 272.18875.

4.1.9. *N*-Piperidino-2-(*p*-methoxyphenyl)-3-methoxy-2,5-dihydropyrrole (2d$_4$). Yield: 38%, R_f=0.39 (90/10 EP/AcOEt). IR (film): ν=3030, 2920–2730, 1660, 1460. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.55 (m, 2H), 1.72 (m, 2H), 2.75 (t, 2H, *J*=5.18 Hz), 3.55 (s, 3H), 3.78 (s, 3H), 3.82 (m, 2H), 4.56 (m, 1H), 4.92 (m, 1H), 6.87 (m, 2H), 7.32 (m, 2H). ^{13}C NMR (50 MHz): δ=23.9 (CH_2), 25.4 (CH_2), 51.2 (CH_2), 55.2 (CH_3), 56.6 (CH_3), 56.8 (CH_2), 63.8 (CH), 89.8 (CH), 113.8 (CH), 129.1 (CH), 135.3 (C), 157.4 (C), 158.8 (C). EI MS *m/z* (%): 288 (53), 190 (51), 159 (40), 91 (11), 70 (15), 55 (44), 42 (100). HRMS EI: theoretical: 288.18378; measured: 288.18384.

Compounds **4** obtained were mixed with compounds **2**. They were isolated when possible; in the other cases (**4d$_3$** and **4d$_4$**), they were fully characterized by use of ^{2}D NMR: COSY, HSQC and HMBC techniques from the mixture **4d$_3$**+**2d$_3$** and **4d$_4$**+**2d$_4$**.

4.1.10. *N*-Morpholino-2-phenyl-3-methoxy-4-methyl-azacyclobut-3-ene (4b$_1$). Yield: 22%, R_f=0.24 (97/3 EP/AcOEt). IR (film): ν=3020, 2960–2810, 1610, 1440. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.18 (s, 3H), 2.88 (t, 4H, *J*=4.41 Hz), 3.69 (s, 3H), 3.85 (t, 4H), 6.24 (s, 1H), 7.30 (m, 3H), 7.68 (m, 2H). ^{13}C NMR (50 MHz): δ=14.99 (CH_3), 55.18 (CH_2), 58.55 (CH_3), 66.36 (CH_2), 117.44 (CH), 127.52 (CH), 128.41 (CH), 134.92 (C), 157.4 (C), 154.48 (C), 160.59 (C). EI MS *m/z* (%): 260 (12), 245 (6), 201 (4), 188 (5), 176 (100), 118 (25), 90 (23), 77 (3), 56 (17), 28 (13). HRMS CI: theoretical: 261.160303; measured: 261.161252.

4.1.11. *N*-Dimethylamino-(2-*p*-methylphenyl)-3-methoxy-4-methyl-azacyclobut-3-ene (4c$_3$). Yield: 35%, R_f=0.39 (93/7 EP/AcOEt). IR (film): ν=3030, 2970–2790, 1510, 1470. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.15 (s, 3H), 2.34 (s, 3H), 2.60 (s, 6H), 3.53 (s, 3H), 6.18 (s, 1H), 7.13 (m, 2H), 7.60 (m, 2H). ^{13}C NMR (50 MHz): δ=14.83 (CH_3), 21.33 (CH_3), 47.31 (CH_3), 58.37 (CH_3), 116.85 (CH), 129.11 (CH), 129.31 (CH), 129.32 (CH), 132.28 (C), 137.21 (C), 154.11 (C), 159.17 (C). EI MS *m/z* (%): 232 (3), 217 (4), 187 (2), 148 (100), 132 (6), 115 (4), 104 (7), 78 (9), 42 (12), 28 (6). HRMS EI: theoretical: 232.15756; measured: 232.15762.

4.1.12. *N*-Dimethylamino-(2-*p*-methoxyphenyl)-3-methoxy-4-methyl-azacyclobut-3-ene (4c$_4$). Yield: 38%, R_f=0.42 (85/15 EP/AcOEt). IR (film): ν=3290, 3020–2790, 1605, 1505, 1450. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.15 (s, 3H), 2.60 (s, 6H), 3.65 (s, 3H), 3.83 (s, 3H), 6.17 (s, 1H), 6.87 (m, 2H), 7.66 (m, 2H). ^{13}C NMR (50 MHz): δ=14.74 (CH_3), 47.33 (CH_3), 55.24 (CH_3), 58.32 (CH_3), 113.83 (CH), 116.67 (CH), 127.89 (C), 130.75 (CH), 153.20 (C), 158.88 (C), 159.25 (C). EI MS *m/z* (%): 248 (41), 233 (33), 178 (11), 164 (100), 148 (14), 121 (10), 91 (7), 77 (7), 44 (16). HRMS EI: theoretical: 248.15247; measured: 248.15166.

4.1.13. *N*-Piperidino-(2-*p*-methylphenyl)-3-methoxy-4-methyl-azacyclobut-3-ene (4d$_3$). Yield: 38%, R_f=0.64 (96/4 EP/AcOEt). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.30 (m, 2H), 1.58–1.72 (m, 2H), 2.16 (s, 3H), 2.33 (s, 3H), 3.69 (s, 3H), 6.19 (s, 1H), 7.13 (m, 2H), 7.60 (m, 2H). ^{13}C NMR (50 MHz): δ=15.30 (CH_3), 21.62 (CH_3), 23.34 (CH_2), 25.65 (CH_2), 51.18 (CH_2), 58.74 (CH_3), 117.35 (CH), 128.98 (C), 129.14 (CH), 136.89 (C), 140.59 (C), 154.62 (C), 159.79 (C). EI MS *m/z* (%): 272 (8), 257 (5), 188 (100), 167 (5), 132 (13), 105 (8), 78 (10), 55 (13), 42 (26). HRMS EI: theoretical: 272.18886; measured: 272.18899.

4.1.14. *N*-Piperidino-(2-*p*-methoxyphenyl)-3-methoxy-4-methyl-azacyclobut-3-ene (4d$_4$). Yield: 38%, R_f=0.44 (90/10 EP/AcOEt). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.32 (m, 2H), 1.55 (m, 2H), 2.17 (s, 3H), 2.61 (m, 2H), 3.68 (s, 3H), 3.88 (s, 3H), 6.18 (s, 1H), 6.88 (m, 2H), 7.69 (m, 2H). ^{13}C NMR (50 MHz): δ=14.84 (CH_3), 24.4 (CH_2), 26.38 (CH_2), 50.84 (CH_2), 55.23 (CH_3), 58.31 (CH_3), 113.82 (CH), 116.72 (CH), 127.96 (C), 130.75 (CH), 153.35 (C), 158.72 (C), 159.45 (C). EI MS *m/z* (%): 288 (3), 204 (100), 167 (8), 148 (8), 121 (11), 91 (11), 55 (9), 42 (18). HRMS EI: theoretical: 288.18378; measured: 288.18384.

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