

# Synthesis of Pentasubstituted Pyridines

## II—NMR Study of the Addition Products of 1-(*N,N*-Diethylamine)prop-1-yne to Methyl 2-Isothiocyanato-3-phenylpropenoate

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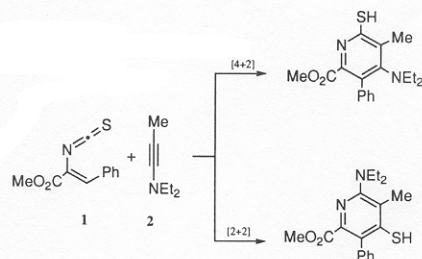
The structure of the pentasubstituted pyridines obtained in the reaction of methyl 2-isothiocyanato-3-phenylpropenoate with 1-(*N,N*-diethylamine)prop-1-yne were assigned based on 2D heteronuclear correlation experiments and NOE measurements. At 0 °C a 2-azabicyclo[2.2.2]octa-2,7-diene intermediate was isolated and spectroscopically characterized.

KEY WORDS NMR <sup>1</sup>H-NMR <sup>13</sup>C-NMR HMBC NOESY Pyridines Diels–Alder reaction

### INTRODUCTION

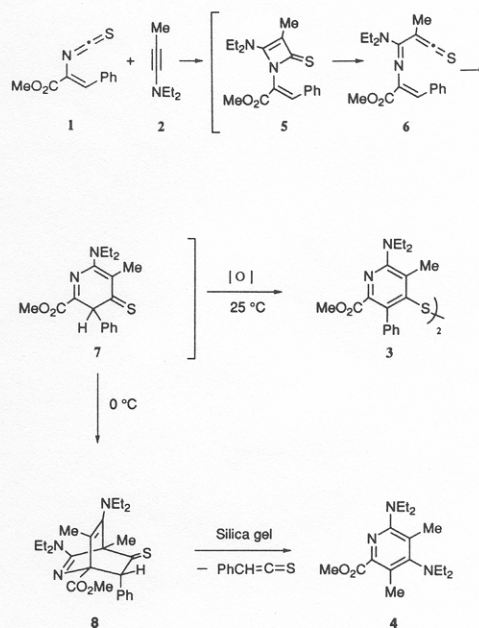
Numerous methods for the synthesis of a wide variety of substituted pyridines have been described.<sup>1</sup> They can be grouped in two main strategies: modification of a preformed pyridine nucleus or pyridine ring formation from suitably chosen synthons. In the latter approach, 2-azabutadienes have proved to be very useful starting materials<sup>2</sup> owing to their ability to participate in Diels–Alder reactions<sup>3</sup> with a large selection of dienophiles. However, there remain important limitations to the access of polysubstituted derivatives containing several functionalities.<sup>4</sup>

When the 2-azadienic framework is part of a heterocumulenic system, two cycloaddition modes are possible, 4 + 2 *vs.* 2 + 2, affording different pyridine regioisomers (Scheme 1). This regiochemical flexibility becomes a major problem because of the formation of



Scheme 1

mixtures of isomers usually in low yields.<sup>5</sup> Recently we have reported the regioselective synthesis of pentasubstituted polyfunctionalized pyridines<sup>6</sup> through the addition of *N*-vinylisothiocyanate (1) to the ynamine 2 (Scheme 2). We showed that two different domino reactions<sup>7</sup> could take place in a temperature range of 25 °C, and pyridines 3 or 4 were obtained in almost quantitative yields. Moreover, the intermediate azabicyclonornadiene derivative 8 was also isolated as a single diastereomer. This compound is stable at room



Scheme 2

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temperature but transforms quantitatively into **3** by column chromatography on silica gel.

In this paper, we present the spectroscopic evidence which allowed the assignment of the structure and stereochemistry of compounds **3**, **4** and **8**. The assignments are based on the information derived from the 2D HMQC,<sup>8</sup> HMBC<sup>9</sup> and nuclear Overhauser effect (NOE) difference spectra. The stereochemical elucidation of **8** was based on a 2D NOESY<sup>10</sup> spectrum because of the extensive overlap of multiplets in the 1D <sup>1</sup>H NMR spectrum.

## RESULTS AND DISCUSSION

As stated above, two pyridine regioisomers could be formed in the reaction between vinylheterocumulene **1** and ynamine **2**; they are shown in Scheme 1. When a 1:1 stoichiometry was used and the reaction was carried out in chloroform at room temperature for 24 h, solvent evaporation yielded a single product **3** (95%) (Scheme 2). The mass spectrum showed a very small peak at *m/z* 658 (*M*<sup>+</sup> < 1%) and the base peak at *m/z* 329. If the peak at *m/z* 658 corresponded to the molecular ion, it would mean that in the formation of **3** two molecules of **1** have reacted with two molecules of the ynamine and a molecule of hydrogen has been lost in this process. Therefore, a molecular formula of C<sub>36</sub>H<sub>42</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> would be obtained for **3**. Since the experimental intensities of the isotopic cluster of *m/z* 658 matched those calculated<sup>11</sup> for a compound with the proposed formula, it was assumed to be the correct one.

Compound **3** showed very simple <sup>1</sup>H and <sup>13</sup>C NMR spectra, with half the number of signals expected from its molecular formula, i.e. **3** is highly symmetric. Conventional chemical shift analysis of these spectra (see Table 1) enabled signals for one phenyl ring, one

**Table 1. Partial <sup>1</sup>H NMR assignments for compounds **3**<sup>a</sup>, **4**<sup>b</sup> and **8**<sup>c</sup> [ $\delta$ (ppm)]**

	<b>3</b>	<b>4</b>	<b>8</b>
H-6	—	—	4.21
H-8	3.51	3.91	—
H-9	3.21	3.17	—
H-10	1.14	1.09	3.62
H-11	2.24	2.17	—
H-12	—	3.14	—
H-13	—	1.02	—
H-14	—	2.28	—
H-15	—	—	1.81
H-16	—	—	1.74
H-18	—	—	1.05
H-20	—	—	0.75 and 0.93

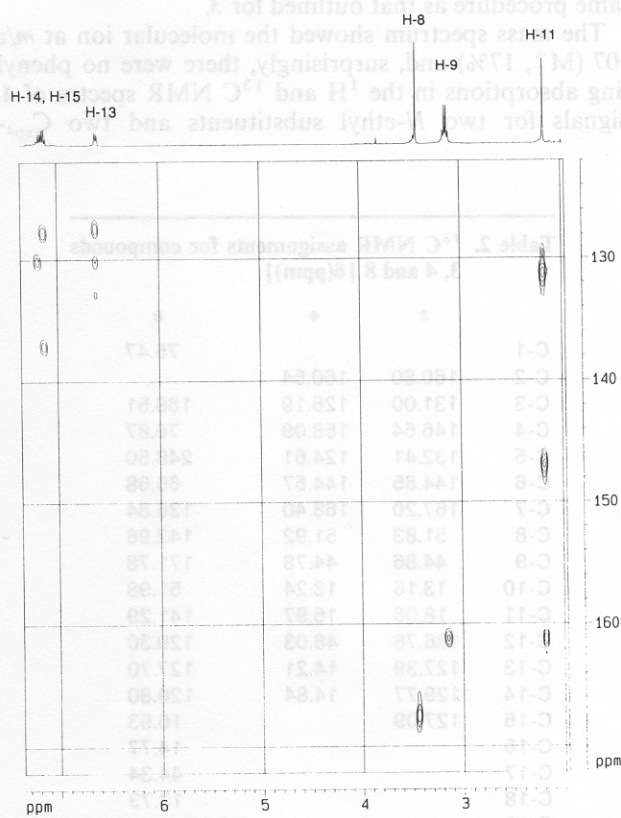
<sup>a</sup> Bis(6-*N,N*-diethylamine-2-methoxycarbonyl-5-methyl-3-phenyl-4-pyridyl)disulphide.

<sup>b</sup> 2,4-Bis(6-*N,N*-diethylamine-2-methoxycarbonyl-3,5-dimethylpyridine).

<sup>c</sup> Methyl *endo*-4,8-bis(*N,N*-diethylamino)-4,7-dimethyl-6-phenyl-5-thioxo-2-azabicyclo-[2.2.2]octa-2,7-diene-1-carboxylate.

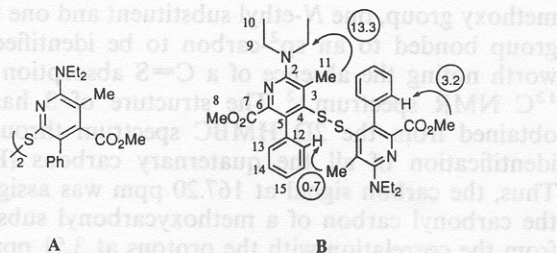
methoxy group, one *N*-ethyl substituent and one methyl group bonded to an sp<sup>2</sup>-carbon to be identified. It is worth noting the absence of a C=S absorption in the <sup>13</sup>C NMR spectrum.<sup>12</sup> The structure of **3** has been obtained from the 2D HMBC spectrum through the identification of all the quaternary carbons (Fig. 1). Thus, the carbon signal at 167.20 ppm was assigned to the carbonyl carbon of a methoxycarbonyl substituent from the correlation with the protons at 3.51 ppm. The *C-ipso* of the phenyl ring (136.76 ppm) and the carbon directly bonded to it (132.41 ppm) were easily identified through their connection with the 3-*meta* and 2-*ortho* protons, respectively. Finally, the methyl protons at 2.24 ppm show three cross peaks at 131.0, 146.54 and 160.80 ppm. Clearly, the signal at 131.0 ppm corresponds to the carbon bearing the methyl group. On the other hand, the carbon at 160.80 ppm is further correlated with the methylene protons of the *N,N*-diethyl moiety. The large  $\delta$  value suggests that this carbon must be sp<sup>2</sup>-hybridized and bonded to an additional heteroatom. The only reasonable atom in agreement with the molecular formula would be nitrogen. Therefore, only two quaternary carbons remained unassigned, those at 144.85 and 146.54 ppm. Both are sp<sup>2</sup>-hybridized and one of them must be connected to the methoxycarbonyl group while the other must be bonded to a sulphur atom.

These fragments contribute half the molecular weight of **3**. Since a C=S moiety has been ruled out and no absorption for an SH group was observed in either the IR or the <sup>1</sup>H NMR spectrum, it follows that **3** must be



**Figure 1.** Section of the 400 MHz proton detected HMBC spectrum in CDCl<sub>3</sub> for **3**.





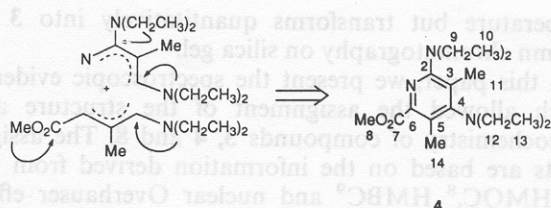
**Figure 2.** Possible structures for **3**. Selected NOEs are indicated by arrows and circled numbers show the percentage of enhancement. The numbering scheme used in the assignment is included.

a dimer with a sulphur-sulphur bridge. The information available is consistent with two isomeric structures, **A** and **B** for **3** (Fig. 2).

Structure **A** can be discarded based on the known reaction pathways for *N*-vinylheterocumulenes<sup>3,5</sup> and steady-state NOE experiments confirmed the assignment of structure **B** to **3**. Selected NOEs for **3** are shown in Fig. 2. Clearly, the 0.7% enhancement observed for the *ortho* protons while presaturating the methyl group at 2.24 ppm is only compatible with the structure **B** and confirms the dimeric nature of **3**. As a corollary, the quaternary carbons at 144.85 and 146.54 ppm can be assigned to C-6 and C-4, respectively (Table 2).

An increase in the reaction temperature to 100 °C shortens the reaction time<sup>6</sup> but at the cost of a small decrease in yield (83%). However, if the reaction is carried out at 0 °C, a new compound (**4**) is isolated. The structural assignment of **4** was performed following the same procedure as that outlined for **3**.

The mass spectrum showed the molecular ion at *m/z* 307 ( $M^+$ , 17%) and, surprisingly, there were no phenyl ring absorptions in the <sup>1</sup>H and <sup>13</sup>C NMR spectra of **4**. Signals for two *N*-ethyl substituents and two C<sub>sp<sup>2</sup></sub>-



**Figure 3.** Structural fragments identified in the HMBC spectrum of **4** and final structure including the numbering scheme used.

methyl and one methoxycarbonyl group were observed instead. There was no signal from a C=S bond in the <sup>13</sup>C NMR spectrum. These data suggested that two ynamine units were incorporated in the structure of **4**, while only half of the heterocumulenic system was retained. As a consequence, the reaction was repeated using a 1:2 stoichiometry of heterocumulene to ynamine and **4** was isolated in quantitative yield. The structural elucidation was straightforward from the HMBC spectrum. The key entries were the methyl groups at 2.17 and 2.28 ppm. Each showed three correlations, some of which further correlate with methylene protons of the *N*-ethyl substituents (arrows in Fig. 3). The ester carbonyl at 168.40 ppm was again identified through the long-range correlation with the methoxy protons at 3.91 ppm. The three molecular fragments thus obtained could be linked in one way only, affording **4**.

The formation of pyridines **3** and **4** can be explained by a regioselective 2 + 2 cycloaddition of the ynamine **1** to the vinylheterocumulene **2**, affording the 2-azetin-4-one **5**. Ring opening of the four-membered ring followed by electrocyclic ring closure of the heterocumulene **6** would give the pyridine-4-thione **7**. At 25 °C this intermediate would be oxidized<sup>13</sup> to the dipyridine disulphide **3**, whereas at 0 °C the 4 + 2 addition of a second molecule of ynamine is favoured, yielding the 2-azabicyclo[2.2.2]octa-2,7-diene derivative **8**, which by a subsequent retro-Diels-Alder reaction finally yields the pyridine **4** (Scheme 2).

The dramatic change in reactivity promoted by a small temperature decrease, from room temperature to 0 °C, prompted us to try to identify some of the intermediates postulated in Scheme 2. Therefore, the progress of the reaction between **1** and **2** was followed by NMR, starting at -20 °C, in deuteriochloroform. After 3 h of reaction no significant changes were observed in the proton spectrum. The temperature was then gradually increased to 0 °C. At this temperature, the reaction occurred smoothly and was completed in 12 h, affording a crude product which contained a new compound **8** (92%). However, all attempts to purify **8** failed and the pyridine **4** was isolated instead. Therefore, the structural assignment of **8** was carried out on the crude reaction product using HMBC and 2D NOESY experiments.

A preliminary analysis of the 1D spectra enabled us to identify molecular fragments derived from one diene molecule plus two ynamine molecules. The ynamine subunits were situated in chemically different environments with four non-equivalent *N*-ethyl groups. At this point it could not be said whether the origin of the non-equivalence was due to steric constraints or to the exis-

**Table 2.** <sup>13</sup>C NMR assignments for compounds **3**, **4** and **8** [ $\delta$ (ppm)]

	<b>3</b>	<b>4</b>	<b>8</b>
C-1			75.47
C-2	160.80	160.54	
C-3	131.00	125.19	168.51
C-4	146.54	158.09	76.87
C-5	132.41	124.61	248.50
C-6	144.85	144.57	66.68
C-7	167.20	168.40	136.84
C-8	51.83	51.92	142.96
C-9	44.86	44.78	171.78
C-10	13.16	13.24	51.98
C-11	18.06	15.97	141.29
C-12	136.76	46.03	129.30
C-13	127.39	14.21	127.70
C-14	129.77	14.84	126.80
C-15	127.09		16.53
C-16			14.77
C-17			44.34
C-18			13.73
C-19			46.28 and 47.23
C-20			13.22 and 14.67

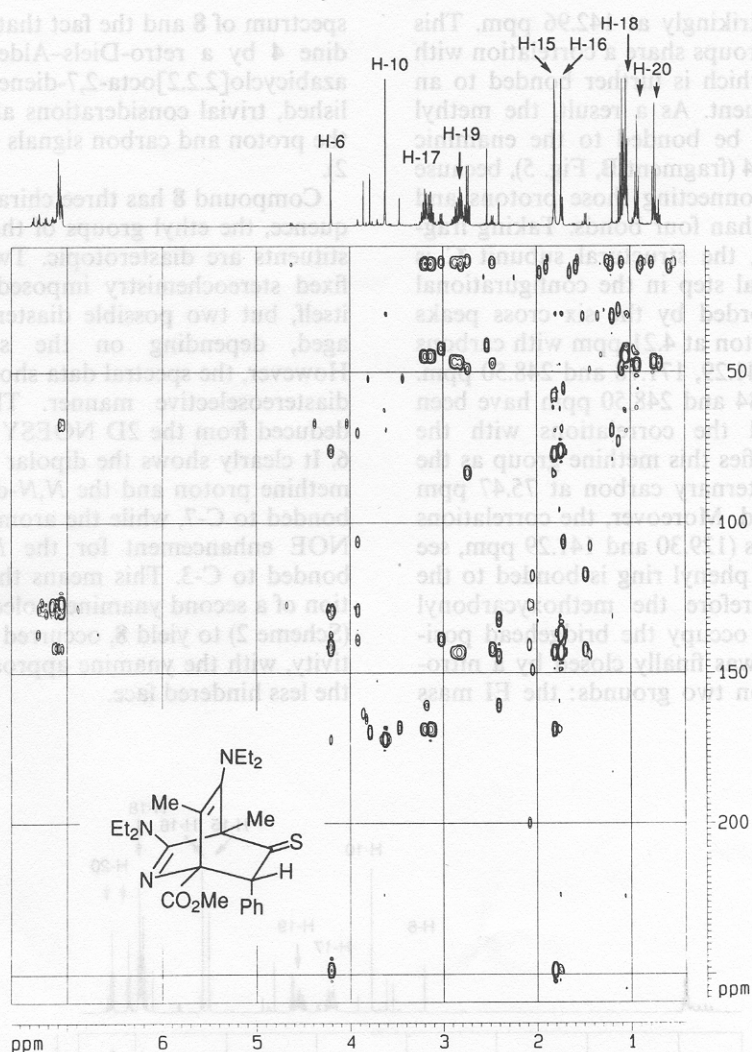


Figure 4. 400 MHz proton detected HMBC spectrum in  $\text{CDCl}_3$  for **8**

tence of some chiral element. Another interesting point was a one-proton singlet at 4.21 ppm. The  $^{13}\text{C}$  NMR signal at 248.50 ppm clearly represents a thiocarbonyl group. Standard DEPT-edition<sup>14</sup> techniques readily identified the signal at 66.68 ppm as a CH, while those at 75.47 and 76.87 ppm were due to quaternary carbons.

Some relevant expansions of the HMBC spectrum are shown in Fig. 4. The entry points for its analysis were the correlations observed for the methyl protons at 1.74 and 1.81 ppm. The methyl signal at 1.81 ppm showed four cross peaks with carbons at 76.87, 142.96, 168.51 and 248.50 ppm. This requires that the methyl group is bonded to an  $\text{sp}^3$ -hybridized quaternary carbon, i.e. the carbon resonating at 76.87 ppm. The highly deshielded carbon at 248.5 ppm can be assigned to the  $\text{C}=\text{S}$  group, whereas the signals at 142.96 and 168.51 ppm were identified as  $\text{sp}^2$ -carbons linked to two different  $N,N$ -diethylamine substituent, based on the  $^3J_{\text{CH}}$  correlations of the methylene protons. Therefore, compound **8** must contain the structural fragment A depicted in Fig. 5.

Looking at the methyl protons at 1.74 ppm, three correlations were observed with the carbon nuclei at

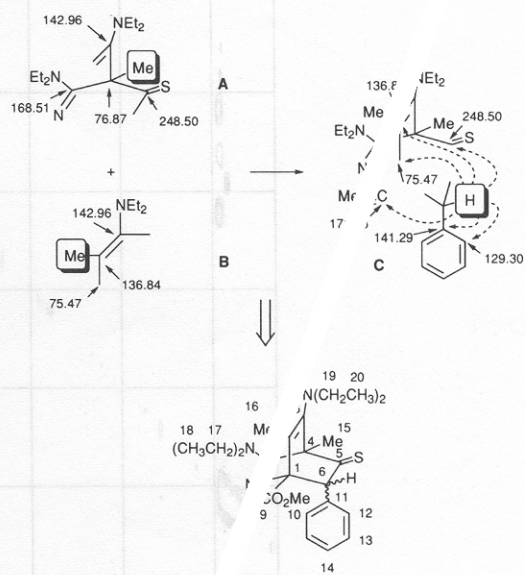


Figure 5. Structural fragments and final structure for **8** obtained from the analysis of its  $^1\text{H}$  NMR spectrum. Numbering scheme is included.



75.47, 136.84 and most strikingly at 142.96 ppm. This means that both methyl groups share a correlation with the same carbon atom, which is further bonded to an *N,N*-diethylamine substituent. As a result, the methyl group at 1.74 ppm must be bonded to the enaminic carbon absorbing at 136.84 (fragment **B**, Fig. 5), because this is the only way of connecting those protons and this carbon through less than four bonds. Taking fragments **A** and **B** together, the structural subunit **C** is obtained (Fig. 5). The final step in the configurational assignment of **8** was afforded by the six cross peaks shown by the methine proton at 4.21 ppm with carbons at 75.47, 129.30, 136.84, 141.29, 171.78 and 248.50 ppm. The signals at 75.47, 136.84 and 248.50 ppm have been previously identified and the correlations with the proton at 4.21 ppm identifies this methine group as the link between the  $sp^3$  quaternary carbon at 75.47 ppm and the C=S double bond. Moreover, the correlations with two aromatic carbons (129.30 and 141.29 ppm, see Table 2) indicate that the phenyl ring is bonded to the methine carbon and therefore the methoxycarbonyl group (171.78 ppm) must occupy the bridgehead position. The bicyclic system was finally closed by a nitrogen atom (Fig. 5) based on two grounds: the EI mass

spectrum of **8** and the fact that it is converted into pyridine **4** by a retro-Diels–Alder reaction. Once the 2-azabicyclo[2.2.2]octa-2,7-diene skeleton of **8** was established, trivial considerations allowed the assignment of the proton and carbon signals of the substituents (Table 2).

Compound **8** has three chiral centres and, as a consequence, the ethyl groups of the *N,N*-diethylamino substituents are diastereotopic. Two of the centres have a fixed stereochemistry imposed by the bicyclic system itself, but two possible diastereoisomers can be envisaged, depending on the stereochemistry of C-6. However, the spectral data showed that **8** is formed in a diastereoselective manner. The stereochemistry was deduced from the 2D NOESY spectrum plotted in Fig. 6. It clearly shows the dipolar relationship between the methine proton and the *N,N*-diethylamino substituents bonded to C-7, while the aromatic ring protons display NOE enhancement for the *N,N*-diethylamino group bonded to C-3. This means that the Diels–Alder addition of a second ynamine molecule to the intermediate **7** (Scheme 2) to yield **8**, occurred with complete face selectivity, with the ynamine approaching the diene through the less hindered face.

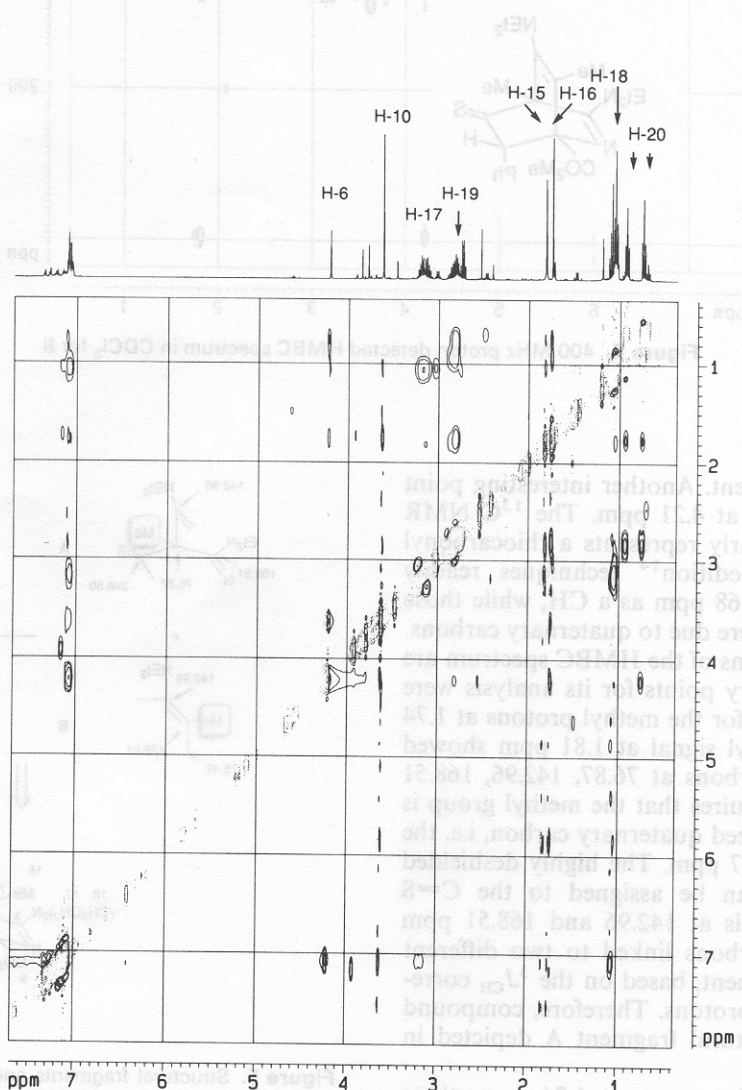


Figure 6. 400 MHz NOESY spectrum in  $CDCl_3$  for **8**. Antiphase diagonal peaks are plotted with dotted lines.

## CONCLUSIONS

The products obtained in the reaction of the vinyl-heterocumulene **1** with the ynamine **2** have been fully characterized by a combination of 2D heteronuclear correlation data and steady-state NOE enhancements. Following the reaction, evolution at 0°C allowed the isolation and identification of the bicyclic intermediate **8** involved in the formation of pyridine **4**, which supports the proposed reaction mechanism. Compound **8** was formed as a single diastereoisomer and the stereochemistry was assigned based on the 2D NOESY spectrum.

## EXPERIMENTAL

The synthesis of the compounds studied has been reported previously.<sup>6</sup> Infrared spectra were recorded on a Mattson 3020 Fourier transform IR spectrophotometer. Mass spectra were obtained on a Hewlett-Packard 5987 A instrument.

### NMR spectroscopy

NMR spectra were recorded on a Bruker AMX 400 spectrometer operating at 400.13 and 100.61 MHz for

<sup>1</sup>H and <sup>13</sup>C, respectively, using a 5 mm broadband inverse probe. CDCl<sub>3</sub> was used as solvent and chemical shifts were referenced internally to TMS. Relevant parameters were as follows: pulse widths 4.8 μs (45°, <sup>1</sup>H) and 5.1 μs (45°, <sup>13</sup>C) at an attenuation level of 3 dB in both cases, sweep width 4 kHz (<sup>1</sup>H) and 20–27 kHz (<sup>13</sup>C), number of scans 16 (<sup>1</sup>H) and 512 (<sup>13</sup>C) and computer memory 32K. NOE experiments were performed on samples degassed by several freeze–thaw cycles. Each line of the target multiplet was included in a frequency list and individually pre-irradiated during 0.2 s at the minimum power level available. The process was repeated cyclically to afford a total saturation of 7 s. A 90° read pulse yielded the FID which was weighted with an exponential function of line broadening factor of 0.3 Hz. Two-dimensional NMR spectra were measured with the standard pulse sequences. Heteronuclear correlations: 2048 × 256 data set, HMQC [pulse delay = 2 s, (2 × <sup>1</sup>J<sub>CH</sub>)<sup>-1</sup> = 3.45 ms], number of scans 48, TPPI mode<sup>15</sup> and GARP decoupling<sup>16</sup> during acquisition; HMBC spectroscopy [pulse delay = 2 s, (2 × <sup>1</sup>J<sub>CH</sub>)<sup>-1</sup> = 3.45 ms], (2 × <sup>n</sup>J<sub>CH</sub>)<sup>-1</sup> = 60 ms, 96 scans. Data processing using zero filling in the F<sub>1</sub> domain and shifted sinus-bell apodization of factor 0 in both dimensions. The phase-sensitive (TPPI)<sup>15</sup> NOESY spectrum was recorded with a mixing time of 1.5 s, 130 increments, 2048 × 1024 final matrix after zero filling and sine squared apodization of factor 2 in both dimensions.

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