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^{1}H and ^{13}C NMR spectral data of bioactive cage-like polycyclic compounds

Roberta C. Salles,[a] Valdemar Lacerda Jr,[a]* Adilson Beatriz,[b] Felicia M. Ito,[b] Reginaldo B. dos Santos,[a] Sandro J. Greco,[a] Eustáquio V. R. de Castro[a] and Dênis P. de Lima[b]

Bioactive cage-like polycyclic compounds have attracted the attention of several research groups because of their unique appearance and their biological activities. Their structures were established on the basis of ^{1}H NMR and ^{13}C NMR spectroscopic data. The ^{1}H and ^{13}C signal assignments and most homonuclear hydrogen coupling constants were assigned by use of techniques such as 1D ^{1}H and ^{13}C NMR and 2D gCOSY, non-edited gHSQC and gHMBC. The gNOESY experiments proved the endo-stereochemistry. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: ^{1}H ^{13}C NMR; gCOSY; gHSQC; gHMBC; gNOESY; cage-like compounds

Introduction

Since 1930, cage-like compounds have attracted the attention of several research groups due to their unique appearance and their biological activities. The milestone in the study of these compounds was the classical synthesis of Cookson's diketone in 1928.[1] In the synthesis proposed by Cookson, a pentacyclodiketone (**1a**) (Scheme 1), which contains an important cycle of four members was formed through an intramolecular reaction photocyclization adduct **1**, obtained from a Diels–Alder reaction.

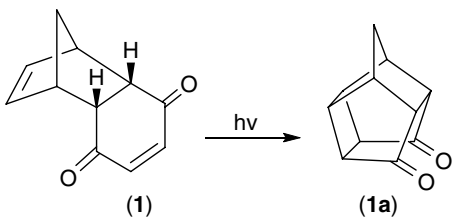
The biological activity of cage-like compounds was only discovered in 1964 by Davies *et al*.[2] It was demonstrated in their study that amantadine has antiviral activity. Later, in 1969, Schwab *et al*.[3] showed that amantadine is also beneficial for patients with Parkinson's disease.

From this work, other cage-like compounds were synthesized and new biological activities were studied.[4–8] The studies show that the cage-like structures are useful in specific interaction with biological receptors and/or competitive inhibition or non-competitive with smaller chemical species in their inside.[9]

These rigid structures enhance lipophilicity through cell membranes, increasing their affinity for lipophilic regions in the recipients, and providing metabolic stability, which may prolong the pharmacological effect, thereby reducing the dosage.[10,11]

An important factor in the study of these compounds is the correct knowledge of their structure since they can interact in highly specific way with a biological receptor. However, no detailed NMR study of these compounds could be found in the relevant literature.

In this study, we present a detailed assignment of NMR data for the bioactive cage-like polycyclic compounds **1**–**6**, including the measurement of most homonuclear hydrogen coupling constants and a complete assignment of NMR signals. The 2D NMR (gCOSY,[12] gHSQC,[13] gHMBC[14] and gNOESY[15]) data are also presented. The availability of reliable NMR data for this class of compounds can provide easier and faster identification of both current cage-like compounds and new ones.



Scheme 1. Intramolecular cyclization of the Diels–Alder adduct **1**.

Experimental

Materials

The bioactive cage-like polycyclic compounds used in this present study were prepared from cyclopentadiene and *p*-benzoquinone as described in the relevant literature and shown in Schemes 2 and 3.[16]

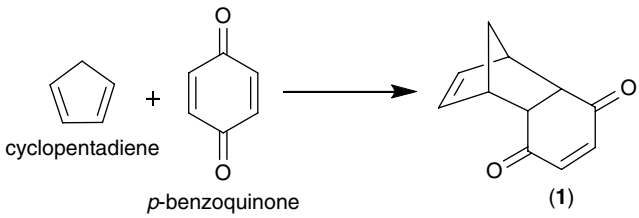
NMR measurements

^{1}H NMR, ^{13}C NMR, ^{13}C{^{1}H}, DEPT, gCOSY, gNOESY, gHSQC and gHMBC experiments were performed on a Bruker Avance DPX 300 spectrometer equipped with a 5-mm direct probe with z-gradient field. ^{1}H and ^{13}C NMR spectra (at 300 and 75 MHz, respectively) were measured at a temperature of 300 K, using

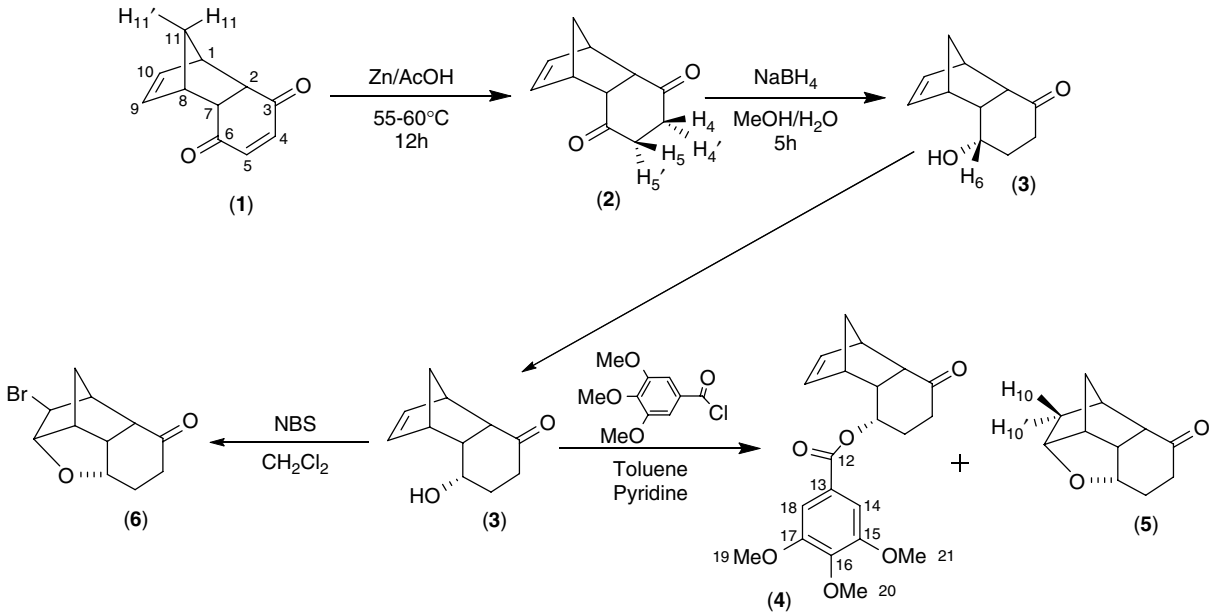
* *Correspondence to: Valdemar Lacerda Jr, Departamento de Química, Centro de Ciências Exatas da Universidade Federal do Espirito Santo, Av. Fernando Ferrari 514, 29.075-910 Vitória, ES, Brazil. E-mail: vljuniorqui@gmail.com*

a *Departamento de Química, Centro de Ciências Exatas da Universidade Federal do Espirito Santo, Av. Fernando Ferrari 514, 29.075-910 Vitória, ES, Brazil*

b *Departamento de Química, Centro de Ciências Exatas e Tecnologia da Universidade Federal do Mato Grosso do Sul, Av. Senador Filinto Müler 1555, 79.074-460, Campo Grande MS, Brazil*



Scheme 2. Preparation of the adduct **1** from the Diels–Alder reaction.



Scheme 3. Preparation of the compounds studied.

10 mg ml^{-1} in $CDCl_3$ as solvent. Tetramethylsilane was used as an internal reference. Chemical shifts are given on the δ scale. The experiments were performed through standard pulse sequences, as suggested by the equipment manufacturer. Typical parameters were as follows.

For ^{1}H NMR analysis, 16 transients were acquired with a 1-s relaxation delay using 64 K data points. The 90° pulse was 8.0 µs with a spectral width of 3612 Hz. ^{13}C{^{1}H} and DEPT spectra were obtained for a spectral width of 23 809 Hz, collecting 64 K data points. The 90° pulse was 14.5 µs. Overall, 1024 transients were acquired for ^{13}C{^{1}H} and 512 transients for DEPT with a relaxation delay of 2 s.

The number of scans for the gCOSY, gNOESY, gHSQC and gHMBC was 16, 16, 32 and 64, respectively. The gNOESY experiments were performed on degassed samples with a mixing time of 800 ms. Recording parameters were take from standard Bruker microprograms.

Results and Discussion

Compounds **1–6** were prepared from a Diels–Alder reaction between cyclopentadiene and *p*-benzoquinone (Scheme 2).

From the adduct of Diels–Alder adduct **1,** the studied compounds were synthesized, as shown in Scheme 3.[16]

Table 1. ^{1}H and ^{13}C NMR chemical shifts, δ (ppm), multiplicities and coupling constants J(^{1}H,^{1}H) (Hz), ^{1}H–^{1}H and ^{1}H–^{13}C correlations in gCOSY and gHMBC spectra for compound **1**[a]

C	δ (^{13}C)	δ (^{1}H)	Coupling constants (Hz)	Multiplicity	gCOSY	gHMBC
1/8	48.2	3.49 (2H)	1.7	sept	H2; H7; H9; H10; H11; H11′	C2; C7; C11
2/7	48.7	3.18 (2H)	1.7	t	H1; H8	C9; C10; C3; C6; C1; C8
3/6	199.3	–	–	–	–	–
4/5	141.9	6.52 (2H)	–	s	–	C3; C6; C2; C7
9/10	135.2	6.01 (2H)	1.7	t	H1; H8	C2; C7; C11
11	48.6	H_{11} – 1.39 (1H)	8.2; 1.7	dt	H11′; H1; H8	C9; C10
		$H_{11'}$ – 1.48 (1H)	8.2; 1.7	dt	H11; H1; H8	C9; C10; C1; C8

[a] In $CDCl_3$ solution, all these assignments are in agreement with the gCOSY, gHSQC and gHMBC spectra.

Table 2. ^{1}H and ^{13}C NMR chemical shifts, δ (ppm), multiplicities and coupling constants $J(^{1}H,^{1}H)$ (Hz), $^{1}H-^{1}H$ and $^{1}H-^{13}C$ correlations in gCOSY and gHMBC spectra for compound **2**[a]

C	δ (^{13}C)	δ (^{1}H)	Coupling constants (Hz)	Multiplicity	gCOSY	gHMBC
1/8	47.4	3.40 (2H)	1.7	sept	H2; H7; H9 e H10; H11; H11′	C2; C7
2/7	51.8	3.17 (2H)	1.7	t	H1; H8	C3; C6; C9; C10; C11
3/6	209.6	–	–	–	–	–
4	37.8	H_4 – 2.59 (1H)	–	m	H4′; H5′	C3; C6; C5
		H_4' – 2.26 (1H)			H4; H5	
5	37.8	H_5 – 2.59 (1H)	–	m	H4′; H5′	C3; C6; C4
		H_5' – 2.26 (1H)			H4; H5	
9/10	136.5	6.13 (2H)	1.7	t	H1; H8	C1; C8
11	48.7	H_{11} – 1.31 (1H)	8.6; 1.7	dt	H11′; H1; H8	C1; C8; C9; C10
		H_{11}' – 1.43(1H)	8.6; 1.7	dt	H11; H1; H8	C2; C7; C3; C6; C9; C10

[a] In $CDCl_3$ solution, all these assignments are in agreement with the gCOSY, gHSQC and gHMBC spectra.

Table 3. ^{1}H and ^{13}C NMR chemical shifts, δ (ppm), multiplicities and coupling constants $J(^{1}H,^{1}H)$ (Hz), $^{1}H-^{1}H$ and $^{1}H-^{13}C$ correlations in gCOSY, gHMBC and gNOESY spectra for compound **3**[a]

C	δ (^{13}C)	δ (^{1}H)	Coupling constants (Hz)	Multiplicity	gCOSY	gHMBC	GNOESY
1	45.7	3.16 (1H)	–	br.s	H2; H10; H11; H11′	–	H9; H10; H11; H11′
2	51.3	2.79 (1H)	10.1; 4.1	dd	H7; H1	C1; C3; C7; C10	H11
3	213.7	–	–	–	–	–	–
4	35.9	H_4 – 2.09 (1H)	–	m	H5; H5′	C3; C5; C6	–
		H_4' – 2.09 (1H)					
5	27.6	H_5 – 1.72 (1H)	–	m	H4; H4′; H6	C3; C4; C6; C7	–
		H_5' – 1.72 (1H)					
6	67.4	4.22 (1H)	–	m	H5; H5′; H7	C2; C7	–
7	45.6	2.76 (1H)	10.1; 4.1	td	H2; H6; H8	C2; C3; C8	H11
8	44.9	2.99 (1H)	–	br.s	H7; H9; H11; H11′	C2; C7	H11
9	135.1	6.11 (1H)	5.5; 3.0	dd	H10; H8	C7; C8; C10; C11	H1
10	136.4	6.03 (1H)	5.5; 3.0	dd	H9; H1	C1; C11	H1
11	49.8	H_{11} – 1.25 (1H)	8.2; 1.4	dt	H11′; H1; H8	C1; C2; C7; C8; C9; C10	H1; H2; H7; H8
		H_{11}' – 1.31 (1H)	8.2; 1.4	dt	H11; H1; H8		H1

[a] In $CDCl_3$ solution, all these assignments are in agreement with the gCOSY, gHSQC, gHMBC and gNOESY spectra.

Table 4. ^{1}H and ^{13}C NMR chemical shifts, δ (ppm), multiplicities and coupling constants $J(^{1}H,^{1}H)$ (Hz), $^{1}H-^{1}H$ and $^{1}H-^{13}C$ correlations in gCOSY, gHMBC and gNOESY spectra for compound **4**[a]

C	δ (^{13}C)	δ (^{1}H)	Coupling constants (Hz)	Multiplicity	gCOSY	gHMBC	gNOESY
1	45.4	2.99 (1H)	–	m	H2; H10; H11; H11′	C3	H10
2	51.7	3.04 (1H)	5.4; 2.7	dd	H7; H1	C8	H4; H6; H11
3	211.5	–	–	–	–	–	–
4	35.6	H_4 – 2.25 (1H)	–	m	H4′; H5; H5′	C3; C5; C6	H2; H5; H6
		H_4' – 2.31 (1H)	–	m	H4; H5; H5′		H5′
5	25.6	H_5 – 2.01 (1H)	–	m	H4; H4′; H5′; H6	C3; C6; C7	H4; H6; H7
		H_5' – 2.09 (1H)	–	m	H4; H4′; H5; H6		H4′
6	70.0	5.58 (1H)	7.4; 5.4; 2.9	ddd	H5; H5′; H7	–	H2; H4; H5
7	44.4	3.07 (1H)	5.4; 2.9	dd	H2; H6	C2; C9	H5; H11
8	45.0	3.30 (1H)	–	br.s	H9; H11; H11′	–	H9; H11; H11′
9	135.8	6.18 (1H)	5.6; 2.7	dd	H10; H8	C8	H8
10	135.4	6.00 (1H)	5.6; 2.7	dd	H9; H1	C8	H1
11	49.7	H_{11} – 1.31 (1H)	8.4; 2.7	dt	H11; H8; H1	C9	H2; H7; H8
		H_{11}' – 1.43 (1H)	8.4; 2.7	dt	H11′; H8; H1	C2; C8; C9	H8

Table 4. (*Continued*)

C	δ (^{13}C)	δ (^{1}H)	Coupling constants (Hz)	Multiplicity	gCOSY	gHMBC	gNOESY
12	165.1	–	–	–	–	–	–
13	125.0	–	–	–	–	–	–
14	106.8	7.14 (2H)	–	s	–	C12; C13; C15; C16	–
15	152.9	–	–	–	–	–	–
16	142.2	–	–	–	–	–	–
19/21	56.2	3.88 (6H)	–	s	–	C16	–
20	60.9	3.88 (3H)	–	s	–	C15	–

[a] In $CDCl_3$ solution, all these assignments are in agreement with the gCOSY, gHSQC, gHMBC and gNOESY spectra.

Table 5. ^{1}H and ^{13}C NMR chemical shifts, δ (ppm), multiplicities and coupling constants $J(^{1}H,^{1}H)$ (Hz), ^{1}H–^{1}H and ^{1}H–^{13}C correlations in gCOSY, gHMBC and gNOESY spectra for compound **5**[a]

C	δ (^{13}C)	δ (^{1}H)	Coupling constants (Hz)	Multiplicity	gCOSY	gHMBC	gNOESY
1	39.3	2.43 (1H)	–	m	H2; H10; H10′; H11; H11′	–	H10
2	51.2	2.60 (1H)	–	m	H1; H10′	–	–
3	214.0	–	–	–	–	–	–
4	35.1	H_4 – 2.49 (1H)	–	m	H4′; H5; H5′	C3; C5; C6	H6
		H_4' – 2.30 (1H)	–	m	H4; H5; H5′		–
5	26.5	H_5 – 2.20 (1H)	–	m	H4; H4′; H5′; H6	C3; C4; C6; C7	H6
		H_5' – 1.87 (1H)	–	m	H4; H4′; H5; H6	C4	–
6	74.4	4.26 (1H)	3.7; 1.6	td	H7; H5; H5′	C2; C4	H4; H5
7	43.5	2.54 (1H)	3.7	t	H6; H8	C2; C3; C5; C6; C9	H11
8	49.1	2.93 (1H)	–	m	H7; H9; H11; H11′	C2; C11	H10
9	79.6	4.44 (1H)	6.2	t	H10; H8	C10	H10
10	37.2	H_{10} – 1.40 (1H)	–	m	H1; H9; H10′	C2; C9	H1; H8; H9
		H_{10}' – 1.48 (1H)	7.1; 3.0; 1.8	ddd	H10; H1; H2	C2; C8; C9; C11	–
11	37.4	H_{11} – 1.55 (1H)	10.6; 1.5	dt	H11′; H1; H8	C10	H7
		H_{11}' – 1.34 (1H)	10.6; 1.5	dt	H11; H1; H8	C2; C7; C8; C10	–

[a] In $CDCl_3$ solution, all these assignments are in agreement with the gCOSY, gHSQC, gHMBC and gNOESY spectra.

Table 6. ^{1}H and ^{13}C NMR chemical shifts, δ (ppm), multiplicities and coupling constants $J(^{1}H,^{1}H)$ (Hz), ^{1}H–^{1}H and ^{1}H–^{13}C correlations in gCOSY, gHMBC and gNOESY spectra for compound **6**[a]

C	δ (^{13}C)	δ (^{1}H)	Coupling constants (Hz)	Multiplicity	gCOSY	gHMBC	gNOESY
1	46.9	2.71 (1H)	–	Br.s	H2; H11; H11′	C3; C7; C10	H10; H11
2	49.8	2.75 (1H)	4.0	t	H1; H7	C1; C7	–
3	211.7	–	–	–	–	–	–
4	35.0	H_4 – 2.34 (1H)	–	m	H4′; H5; H5′	C3; C5; C6	H6
		H_4' – 2.37 (1H)	–	m	H4; H5; H5′		–
5	25.8	H_5 – 1.89 (1H)	13.8; 11.0; 6.9; 2.0; 0.6	ddddd	H5′; H4; H4′; H6	C4	H6
		H_5' – 2.26 (1H)	13.8; 6.9; 4.0	ddd	H5; H4; H4′; H6		–
6	75.2	4.27 (1H)	4.0; 2.0	td	H7; H5′; H5	C2; C4	H4; H5; H7; H8
7	42.2	2.57 (1H)	10.2; 4.0	dt	H2; H6; H8	C2; C4	H6; H11
8	48.5	2.99 (1H)	–	m	H7; H9	C2	H6; H9; H11; H11′
9	88.4	4.58 (1H)	5.2	d	H8	–	H8; H10; H11′
10	55.0	3.71 (1H)	2.1	d	H11	C8; C9; C11	H1
11	34.8	H_{11} – 1.65 (1H)	–	m	H1; H8; H10; H11′	–	H1; H7; H8
		H_{11}' – 2.18 (1H)	–	m	H1; H8; H11		H8; H9

[a] In $CDCl_3$ solution. All these assignments are in agreement with the gCOSY, gHSQC, gHMBC and gNOESY spectra.

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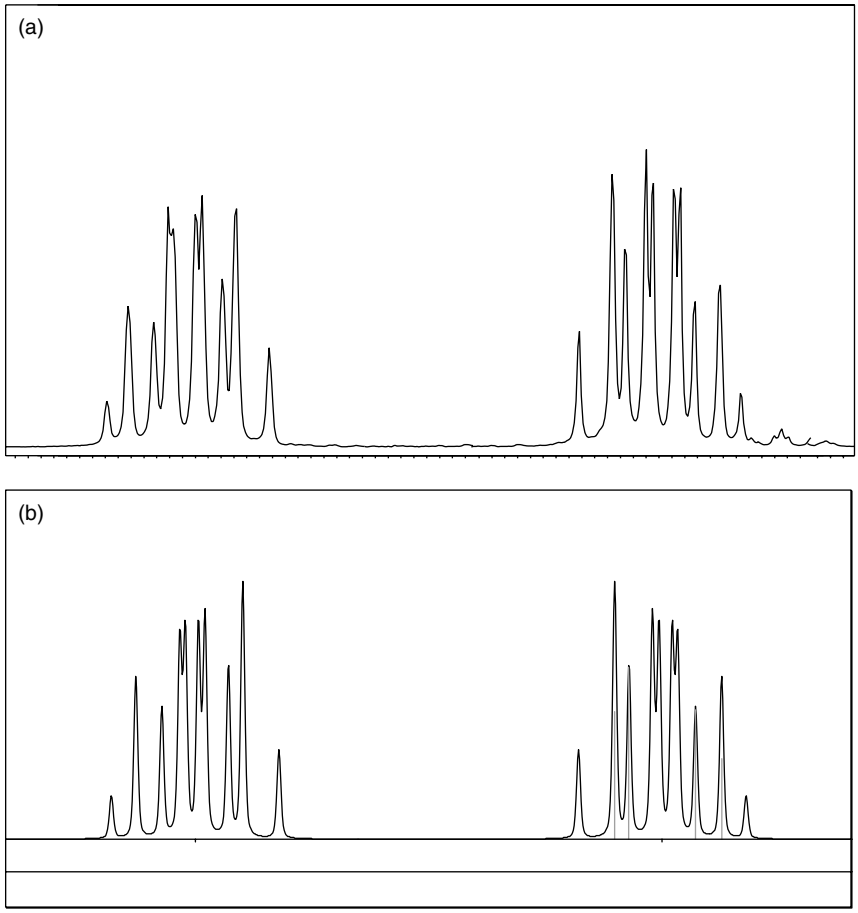

Figure 1. Experimental (a) and simulated (b) second-order coupling pattern signals of hydrogens 4 and 5 of compound **2**.

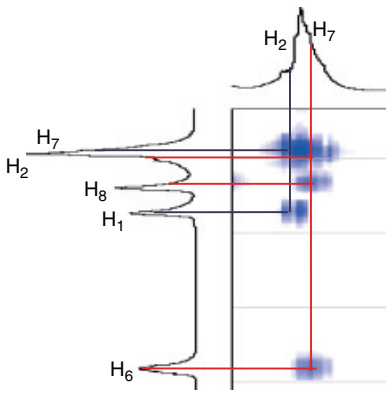

Figure 2. Expansion of 2D NMR spectrum (^{1}H, ^{1}H-COSY) of compound **3**.

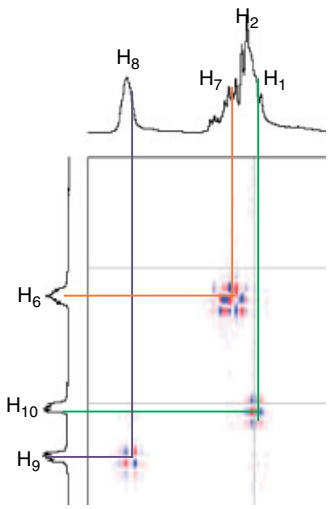

Figure 3. Expansion of 2D NMR spectrum (^{1}H, ^{1}H-COSY) of compound **4**.

The unequivocal assignment of ^{1}H and ^{13}C NMR signals of compounds **1–6** is listed in Tables 1–6.

The signals of hydrogens 4 and 5 of compound**2** are multiplets and have a second-order coupling pattern. They were simulated in the SimEsp_NMR software,[17] in which a great deal of similarity to the experimental spectrum was observed (Fig. 1).

The distinction between hydrogens H_2 and H_7 of **3** was confirmed by analyzing the 2D gCOSY spectrum (Fig. 2) where the H_7 couples with H_8 and H_6 ($\delta = 2.76$ ppm) and H_2 ($\delta = 2.79$ ppm) with H_1. From the HMBC experiment, it was possible to assign the signals of C_9 and C_{10} and from the HSQC experiment those of H_9 and H_{10}. The bridge hydrogens (H_{11} and H_{11}') were assigned by the 2D gNOESY NMR spectrum in which the signal of H_{11}' was attributed to the larger chemical shift value. The determination of the endo/exo stereochemistry was done in a trustworthy way based upon the observed coupling between the bridge hydrogen H_{11} and hydrogens H_2 and H_7 in the 2D NOESY NMR spectrum. This attribution is possible only in endo configuration.

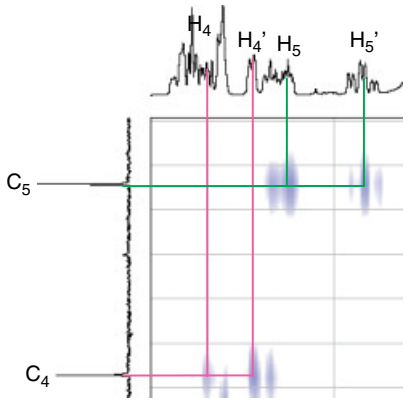

Figure 4. Expansion of 2D NMR spectrum (^{1}H, DEPT-HSQC) of compound **5**.

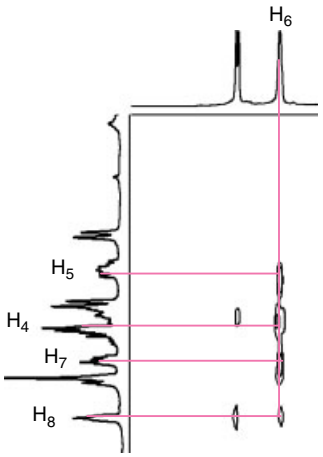

Figure 5. Expansion of 2D NMR spectrum (^{1}H, ^{1}H-NOESY) of compound **6**.

In the ^{1}H NMR spectrum of **4**, the distinction between the hydrogens H_1 ($\delta = 2.99$ ppm), H_2 ($\delta = 3.04$ ppm), H_7 ($\delta = 3.07$ ppm) and H_8 ($\delta = 3.30$ ppm) was made with the aid of 2D gCOSY and gHMBC NMR spectra in which the couplings between hydrogens H_8 and H_9, H_7 and H_6 as well as between H_1 and H_{10} can be observed (Fig. 3). With these assignments and using a gHSQC spectrum, it was possible to assign the signals of C_1 ($\delta = 45.4$ ppm), C_2 ($\delta = 51.7$ ppm), C_7 ($\delta = 44.4$ ppm) and C_8 ($\delta = 45.0$ ppm). With the gNOESY spectrum, it was possible to assign the signals of hydrogens H_{11} and $H_{11'}$ and the stereochemistry as described for **3**.

The signals of the hydrogens 5, 5′ and 7 of **5** were attributed on the basis of the 2D gCOSY and gHMBC spectra. With these assignments, it was possible to make a distinction between carbons C4 and C5 through the gHSQC spectrum (Fig. 4).

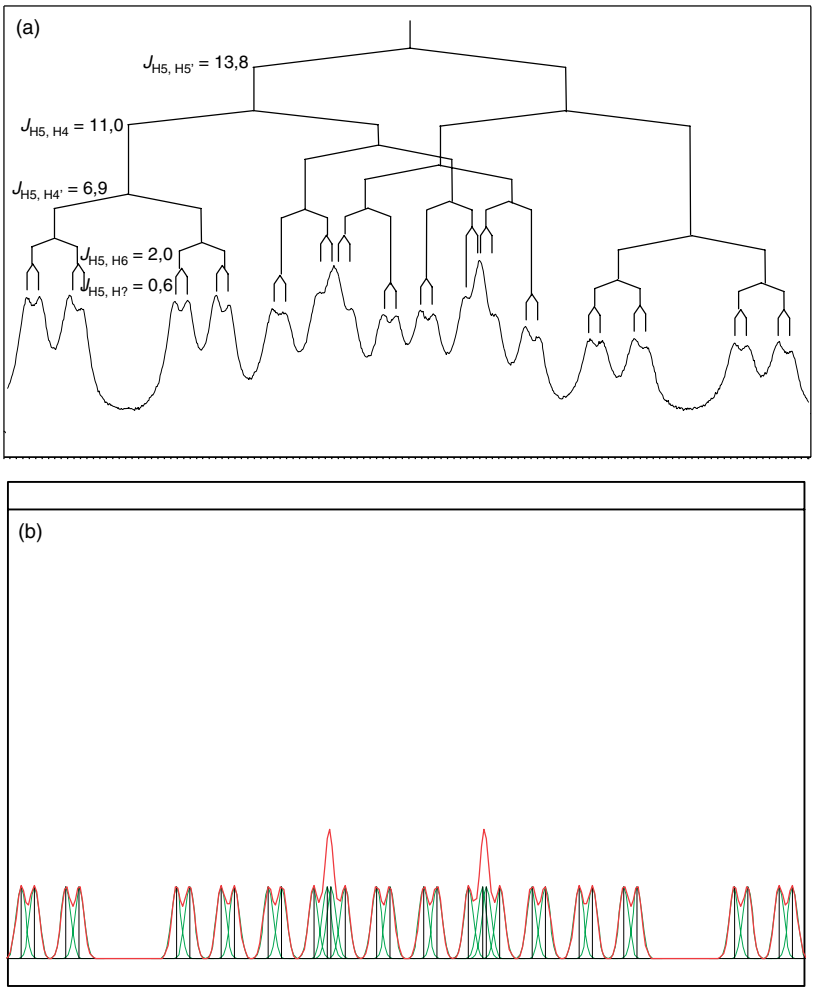

Figure 6. Experimental (a) and simulated (b) signals of hydrogen H_5 of compound **6**.

The assignments of the hydrogens H_4, H_4', H_5 and H_5' of **6** were performed with the aid of 2D gNOESY spectrum, in which it is possible to observe contacts of hydrogens H_4 and H_5 with H_6 (Fig. 5). In this spectrum, we can also see the spatial proximity of H_2 and H_{11} and assign the bridge hydrogens H_{11} ($\delta = 1.65$ ppm) and H_{11}' ($\delta = 2.18$ ppm).

In order to confirm the coupling constants for hydrogen H_5 of compound **6**, a simulation in the FOMSC3 program[17] was performed. From the simulated spectrum (Fig. 6(b)), it is possible to observe a great deal of similarity to the experimental spectrum (Fig. 6(a)). This confirms the multiplicity attributed to H_5.

Acknowledgements

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