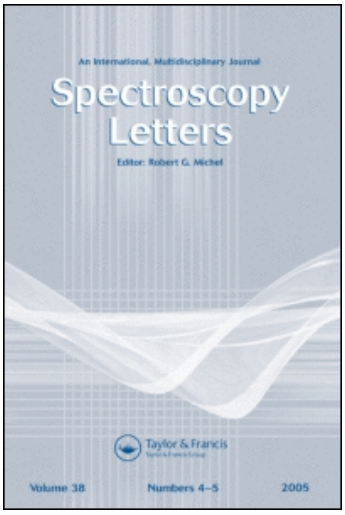

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

^{1}H and ^{13}C NMR Determination of 1-Naphtyl-Polymethoxylated Diphenylwiethanes

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To cite this Article Waterlot, Christophe , Legrand, Anne , Rigo, Benoit and Couturier, Daniel(2000) '^{1}H and ^{13}C NMR Determination of 1-Naphtyl-Polymethoxylated Diphenylwiethanes', Spectroscopy Letters, 33: 2, 211 — 226
To link to this Article: DOI: 10.1080/00387010009350071
URL: http://dx.doi.org/10.1080/00387010009350071

SPECTROSCOPY LETTERS, 33(2), 211–226 (2000)

^{1}H AND ^{13}C NMR DETERMINATION OF 1-NAPHTYL-POLYMETHOXYLATED DIPHENYLMETHANES

KEY WORDS:

1-[Chloro-(3,4,5-trimethoxyphenyl)methyl]naphtalene ; 1-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)methyl]naphtalene ; 1-[(2,5-Dimethoxyphenyl)-(3,4,5-trimethoxyphenyl)methyl]naphtalene ; Benzofluorene ; Lewis acid ; Cation ; ^{1}H and ^{13}C NMR ; 2D NMR.

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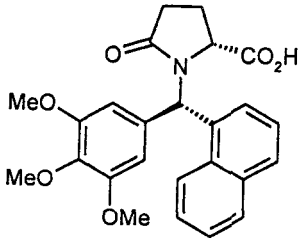
ABSTRACT

The complete structural analysis of 1-[(4-methoxyphenyl)-(3,4,5-trimethoxyphe- nyl)methyl]naphtalene **5a** and 1-[(2,5-dimethoxyphenyl)-(3,4,5-



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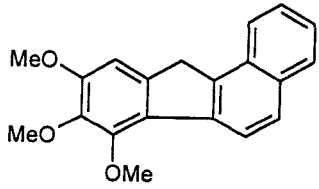

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FIG. 1. Structure of N-(1-naphtyl-(3,4,5-trimethoxyphenyl)methyl)pyroglutamic acid **1** and benzofluorene **2**

trimethoxyphenyl) methyl]naphtalene **5b**, prepared by alkylation of 1-[chloro-(3,4,5-trimethoxyphenyl) methyl]naphtalene without by-products such as benzofluorene **2**, may be accurately determined by ^{1}H, ^{13}C NMR and 2D NMR analysis.

INTRODUCTION

One of our research projects concerns the synthesis of compounds whose structure shows some similarities with anticancer agents azatoxin [1] and podophyllotoxin [2]. We recently described a new way of synthesis for them by cyclization of N-(1-naphtyl-(3,4,5-trimethoxyphenyl)methyl)pyroglutamic acid **1** [3] (FIG. 1). The result of ^{1}H NMR and irradiation studies showed that the structure of benzofluorene 2 (FIG. 1), isolated in low yield (2%) was possible for the aromatic by-product formed during the cyclization of acid **1** (FIG. 1).

The structure of benzofluorene **2** (FIG. 2) was explained by formation of cation **3** (FIG. 2).

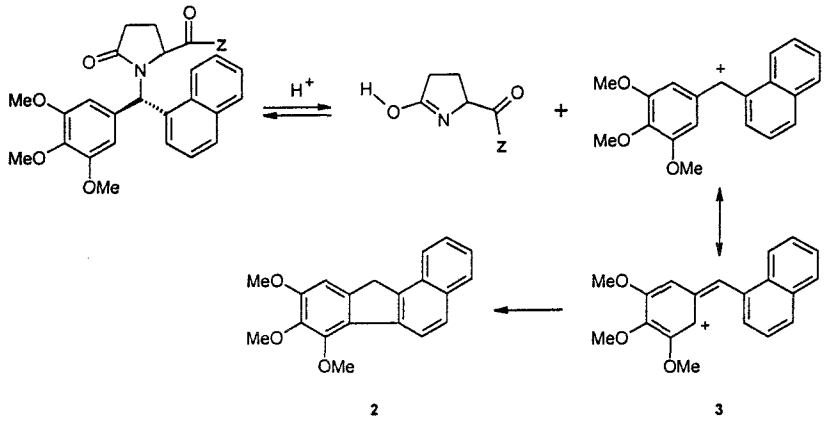

FIG. 2. Cyclization of the cation **3** to the benzofluorene **2**

Starting from chloride **4** (FIG. 3) it is possible to obtain cation **3** (FIG. 2); it was thus interesting to explore the reactivity of this cation, mainly to ascertain if its cyclization into fluorene **2** (FIG. 2) is easy, or if its intermolecular reaction with other compounds would be favored. In that way we performed the Friedel-Crafts reaction of chloride **4** (FIG. 3) with aromatic products.

In this paper we describe these syntheses ; very good yields in compounds **5a** and **5b** were obtained and the ^{1}H and ^{13}C NMR analysis of the crude reaction mixture shows that benzofluorene **2** was never formed within the conditions studied (Table 1).

We report here the results of the spectrum analysis of the purified substituted naphtalenes **5** (FIG. 3) obtained and the complete assignment of all chemical shifts of protons and carbons in this type of triaryl methanes.

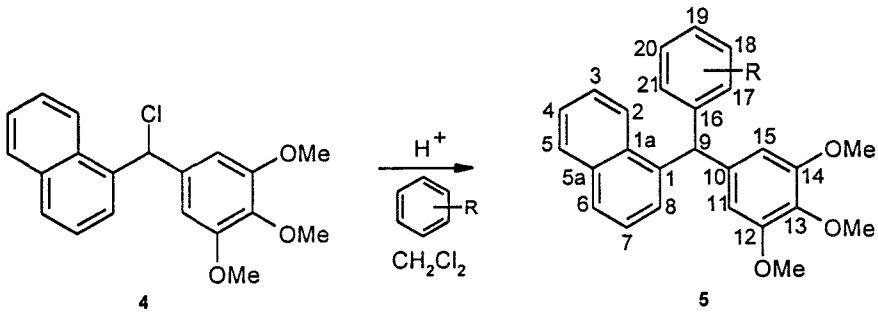

FIG. 3. Reaction scheme

TABLE 1

Results of Friedel-Crafts reactions between **4** and anisole or *p*-dimethoxybenzene

Entry	N° products		Lewis Acid	Time hours	**2** (%)[c]	**5** (%)[c]	Others products (%)[c, e]
1	**5a**	Anisole	$AlCl_3$	48	0	60	40
2	**5a**	Anisole	$ZnCl_2$	48	0	100	0
3	**5a**	Anisole	$AlCl_3$	25	0	75	25
4	**5a**	Anisole	$ZnCl_2$	25	0	100	0
5[d]	**5a**	Anisole	$AlCl_3$	0.25	0	100 (93)[d]	0
6[b]	**5b**	*p*-dimethoxy-benzene	$AlCl_3$	0.25	0	100 (82)[d]	0

[a]Reaction conditions : compound 4, 1.5 mmol ; Lewis acid, 1.5 mmol ; CH_2Cl_2, 40 mL ; 25°C. [b]*p*-dimethoxybenzene was added 10 min. after the beginning of the reaction. [c]Yields were determined by ^1H and ^{13}C NMR or HPLC [4]. [d]Isolated yield. [e]Nature of the others products forms in the reaction was not elucidated.

EXPERIMENTAL

IR spectra were recorded in the solid state (KBr pellets) on a Brücker IFS 48 spectrometer, wavenumbers are expressed in cm^{-1}. The structure of all products were determined by ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$ on a Brücker AC 300 spectrometer operating respectively at 300.133 MHz and 75.469 MHz, using a 5 mm dual ^{1}H / ^{13}C probehead at 25°C (Service RMN - Université Lille I, France).

Chemical shifts are expressed downfield from TMS (0 ppm). The complete assignments of ^{1}H and ^{13}C NMR signals were performed by 2D experiments. Homonuclear chemical shift correlation, 2D experiments [5] and heteronuclear shift correlated NMR spectra [6] were obtained by using the pulse sequence described in the Brücker program COSY.AU, NOESY.AU, COSYRCT.AU, XHCORR.AU, COLOC.AU. Others spectral data are listed in Table 2.

Mass spectra were recorded on a Nermag R10-10H (Argenteuil). Melting points were determined with a Metler FP1 and are uncorrected. Elemental analyses were performed by the "Service Central de Microanalyses" of CNRS, in Vernaison, France. Analytical HPLC was carried out with a LKB 2249 metering pump model. The detection was performed by a HP 1040 Photodiode Array Spectrophotometer connected to a HP 9000 S300 Computer.

Procedure for the synthesis of 1-[chloro-(3,4,5-trimethoxyphenyl)methyl] naphtalene 4.

Trimethylsilyl chloride (10.58 mL, 83.3 mmol) was added dropwise to a stirred solution of 1-naphtyl-(3,4,5-trimethoxyphenyl) carbinol [3] (13.5 g, 41.2 mmol) in dichloromethane (40 mL). The mixture was cooled down to 5°C and stirred for 60 min. A solution of 1N Na_2CO_3 (50 mL) was added and the mixture was stirred for 15

TABLE 2

Spectral data for each NMR technique used

Program	Number of scan	Number of increments	Spectral width F_2 (^{13}C)	F_1 (^1H)
COSY.AU	8	128	--------	2551
NOESY.AU	16	128	--------	2551
COSYRCT.AU	8	128	--------	2551
XHCORR.AU	8	128	12075	2551
COLOC.AU	64	128	12075	2551

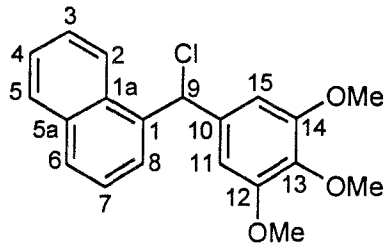

FIG. 4. Chemical Structure of Compound **4**

min. The reaction mixture was extracted with dichloromethane (2×20 mL) and dried over $CaCl_2$. The solvent was evaporated under *vacuum* to give a solid product which was recrystallized from diethyl oxide - petroleum ether (2:8) yielding 11.4 g (80%) of **4** (FIG. 4.) as a brown solid. Compound **4** displayed the following $\nu_{max.}$ (KBr) : 2996, 2927, 2829 (C-H) 1592, 1509, 1455 (C=C) 1233 (C-O) 779 (C Cl) cm^{-1} ; m/z 342.5 (M^+, 22.3%) 307 (M^+-Cl, 100%) ; mp 140°C ; Anal. Calcd. for $C_{20}H_{19}ClO_3$: C 70.07, H 5.59, O 14.00. Found : C 70.41, H 5.52, O 13.69.

The ^1H and ^{13}C NMR data for **4** are listed in Tables 3 and 4. Comparison with other substituted naphtalene, such as 1-naphtyl-(3,4,5-trimethoxyphenyl) carbinol [3, 7] allowed us to assign the chemical shifts of some protons and carbons : δ_H(300 MHz, $CDCl_3$) 3.80 (6H, s, 12-OMe, 14-OMe), 3.88 (3H, s, 13-OMe), 6.74 (2H, s, H11 and H15), 6.87 (1H, s, H9) ; δ_c(75 MHz, $CDCl_3$) 56.2 (12-OMe, 14-OMe), 60.9 (13-OMe), 61.9 (C9), 105.4 (C11 and C15) ; 153.2 (C12 and C14).

Procedure for the synthesis of 1-[(4-methoxyphenyl)-(3,4,5-trimethoxyphenyl)methyl]naphtalene 5a.

Aluminium chloride (1.4 g, 10.2 mmol) was added (10min) to a solution of 1-[chloro-(3,4,5-trimethoxyphenyl)methyl]naphtalene (3.5 g, 10.2 mmol) and anisole (1.33 mL, 12.2 mmol) in dichloromethane (500 mL) under stirring. The reaction was continued for 10 additional minutes. Then the mixture was acidified with diluted HCl, extracted with dichloromethane (2×20 mL) and dried over $CaCl_2$. The solvent was evaporated under *vacuum* yielding a solid which was washed with diethyl oxide - petroleum ether (2:8) mixture, thus giving 3.9 g (93%) of **5a** (FIG. 5.) as a white solid. Compound **5a** displayed the following $\nu_{max.}$ (KBr) : 2996, 2931, 2832 (C-H) 1592, 1507, 1457 (C=C) 1241-1046 (C-O) cm^{-1} ; m/z 414 ($M^{+\cdot}$, 100%) 383 (M^+-$2CH_3$, 29.7%) ; mp 145°C ; Anal. Calcd. for $C_{27}H_{26}O_4$: C 78.24, H 6.32. Found : C 78.25, H 6.45.

The ^1H and ^{13}C NMR data for **5a** are listed in Tables 5 and 6. We can assign the chemical shifts of five protons and seven carbons by comparison with another substituted naphtalene [3] : δ_H(300 MHz, $CDCl_3$) 3.69 (6H, s, 12-OMe, 14-OMe), 6.15 (3H, s, H9), 6.32 (2H, s, H11, H15) ; δ_c(75 MHz, $CDCl_3$) 52.5 (C9), 56.0 (12-OMe, 14-OMe), 106.9 (C11, C15) ; 153.1 (C12, C14).

TABLE 3

ctral data (p.p.m. form $SiMe_4$ in $CDCl_3$ as solvent at 300 MHz) for compound **4**

13-OMe	H(11) H(15)	H(9)	H(7)	H(4)	H(3)	H(8)	H(6)	H(5)
3.88	6.74	6.87	7.45	7.50	7.57	7.60	7.85	7.90
3H	2H	2H	1H	1H	1H	1H	1H	1H
(s)	(s)	(s)	(m)	(m)	(m)	(d)	(d)	(dd)
						J=7.5	J=8.2	J=8.4 J=2.0

TABLE 4

ectral data (p.p.m. form $SiMe_4$ in $CDCl_3$ as solvent at 75 MHz) for compound **4**

13-OMe	C(9)	C(11) C(15)	C(2)	C(7)	C(4)	C(3)	C(8)	C(5)	C(6)	C(1a)	C(5a)	C(10)	C(1)	C(13)
60.9	61.9	105.4	123.6	125.2	125.9	126.6	126.7	128.9	129.4	130.5	133.9	135.8	136.0	137.8

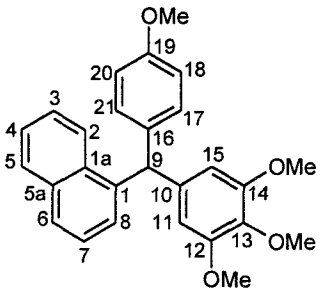

FIG. 5. Chemical Structure of Compound **5a**

Procedure for the synthesis of 1-[(2,5-dimethoxyphenyl)-(3,4,5-trimethoxyphenyl)methyl]naphtalene 5b.

Aluminium chloride (1.4 g, 10.2 mmol) was slowly added to a solution of 1-[chloro-(3,4,5-trimethoxyphenyl)methyl]naphtalene (3.5 g, 10.2 mmol), 1,4-dimethoxybenzene (1.69 g, 12.2 mmol) in dichloromethane (350 mL) under stirring. Work-up was done for 1-[(4-methoxyphenyl)-(3,4,5-trimethoxyphenyl)methyl]naphtalene **5a**. The crude product was washed with the following solvent system : diethyl ether / petroleum ether (5:5) yielding 3.7 g (81%) of **5b** (FIG. 6.). Compound **5b** displayed the following $\nu_{max.}$ (KBr) : 3000, 2940, 2832 (C-H) 1588, 1498, 1459 (C=C) 1231 (C-O) cm^{-1} ; m/z 444 ($M^{+\cdot}$, 100%) 413 (M^{+}-$2CH_3$, 28.6%) ; mp 160°C ; Anal. Calcd. for $C_{28}H_{28}O_5$: C 75.66, H 6.35. Found : C 75.35, H 6.31.

The ^1H and ^{13}C NMR data for **5b** are listed in Tables 5 and 7. The following assignments were performed by comparison of the known chemical shift of similar products [3, 4] : δ_H(300 MHz, $CDCl_3$) 3.68 (9H, s, 12-OMe, 14-OMe and 17-OMe or 20-OMe), 6.34 (2H, s, H11, H15), 6.40 (1H, dd, J1819=8.5 and J2119=2.9, H19),

TABLE 5

tral data (p.p.m. form $SiMe_4$ in $CDCl_3$ as solvent at 300 MHz) for compound **5**

OMe OMe	19-OMe	13-OMe	H(9)	H(11) H(15)	H(18) H(20)		H(8)	H(17) H(21)	H(7)	H(3) H(4)	H(6)	H(2)
69	3.78	3.94	6.15	6.32	6.82		6.98	7.04	7.36	7.42	7.75	7.85
3H	3H	3H	1H	2H	2H		1H	2H	1H	2H	1H	1H
(s)	(s)	(s)	(s)	(s)	(d)		(d)	(d)	(d)	(m)	(d)	(d)
					J=8.6		J=7.0	J=8.6	J=7.0		J=8.2	J=7.1
OMe	12-OMe 14-OMe 17-OMe	13-OMe	H(9)	H(11) H(15)	H(21)	H(19)	H(8)	H(18)	H(7)	H(3) H(4)	H(6)	H(2)
62	3.68	3.84	6.52	6.34	6.40	6.73	6.98	6.85	7.37	7.39	7.73	7.84
3H	9H	3H	1H	2H	1H	1H	1H	1H	1H	2H	1H	1H
(s)	(s)	(s)	(s)	(s)	(d)	(dd)	(d)	(d)	(d)	(m)	(d)	(d)
					J=2.9	J=8.5 J=2.9	J=7.8	J=8.5	J=7.8		J=7.8	J=8.1
		30	-111	-6			0		-3	9	6	3

d as a change in shift from A to B ($\delta A - \delta B$) and is expressed in Hz.
d = doublet ; dd = double doublet ; m = multiplet

TABLE 6

ectral data (p.p.m. form $SiMe_4$ in $CDCl_3$ as solvent at 75 MHz) for compound **5a**

19-OMe	12-OMe 14-OMe	13-OMe	C(11) C(15)	C(18) C(20)	C(5)	C(7)	C(4)	C(3)
55.2	56.0	60.9	106.7	113.8	124.3	125.3	125.5	126.1

C(17) C(21)	C(16)	C(1a)	C(5a)	C(13)	C(10)	C(1)	C(12) C(14)	C(19)
130.5	131.9	133.9	135.7	136.4	139.9	140.2	153.1	158.8

TABLE 7

ctral data (p.p.m. form $SiMe_4$ in $CDCl_3$ as solvent at 75 MHz) for compound **5b**

20-OMe	12-OMe 14-OMe	17-OMe	13-OMe	C(11) C(15)	C(19)	C(18)	C(21)	C(2)	C(7)	C(4)
55.5	56.0	56.4	60.9	106.8	111.0	111.7	117.6	124.3	125.2	125.4

C(6)	C(5)	C(1a)	C(16)	C(5a)	C(13)	C(10)	C(1)	C(20)	C(12) C(14)	C(17)
127.2	128.6	132.0	133.6	133.9	136.3	139.1	140.0	151.3	153.0	153.4

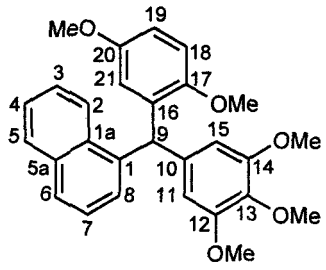

FIG. 6. Chemical Structure of Compound **5b**

6.52 (1H, s, H9), 6.73 (1H, d, J1921=2.9, H21), 6.85 (1H, d, J1918=8.5, H18) ; δ_c(75 MHz, $CDCl_3$) 46.2 (C9), 56.0 (12-OMe, 14-OMe), 106.8 (C11, C15) ; 153.0 (C12, C14).

RESULTS AND DISCUSSION

We used various NMR techniques for the determination of protons and carbons chemical shifts of 1-naphtyl polymethoxylated diphenylmethanes **4**, **5a** and **5b**. In this paper, these methods are correlated for the assignment of naphtalene atoms.

In the first approach, two groups of protons were formed by analyzing the COSY H - H spectra of compound **4**. The first one is formed by: H2, H3, H4, H5 and the second one by: H6, H7, H8. This result was confirmed from the lack of NOESY correlation between the protons of the first group with the other protons. The ambiguous assignments between the H2, H5 and H3, H4 protons were resolved by using the COSYRCT.AU technique (FIG. 7.).

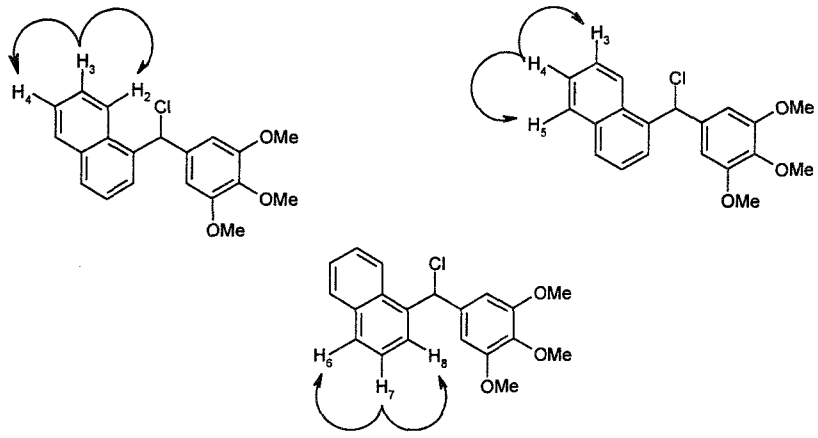

FIG. 7. RELAYED COSY Correlation observed for the Naphtalenic Protons of **4**

The C2, C3, C4, C5, C6, C7, and C8 positions were then obtained from the COSY correlation between these carbons and the corresponding hydrogens.

The HETCOR (FIG. 8.) and Relayed COSY results allowed us to attribute C1a, C5a, C1 and C13 (FIG. 8. ; Tables 3 and 4).

These different NMR techniques were also used to assign protons chemical shift of compounds **5a** and **5b** (FIG. 9.). Spectroscopy data are summarized in Tables 5, 6 and 7. It appears that the presence of *p*-methoxyphenyl or 2,5-dimethoxyphenyl does not change the mean shift value to the naphtalenic protons (5a8, 5b8 : δ=6.98, 6.98 ; 5a7, 5b7 : δ=7.36, 7.37 ; 5a6, 5b6 : δ=7.75, 7.73 ; 5a2, 5b2 : δ=7.85, 7.84 ; 5a3, 5b3 : δ=7.42, 7.39 ; 5a4, 5b4 : δ=7.42, 7.39 ; 5a5, 5b5 : δ=7.99, 7.98). On the other hand, proton H9 (FIG. 9) of the two products **5a** and **5b** near the chiral center substituted by the *p*-methoxyphenyl or 2,5-dimethoxyphenyl group shows a significant difference (5a9, 5b9 : 6.15, 6.52).

FIG. 8. HETCOR correlation observed for the compound **4**

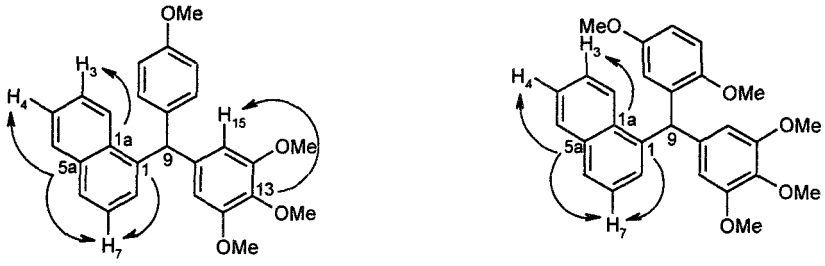

FIG. 9. HETCOR correlation observed for compound **5a** and **5b**

For the substituted naphtalenes **5a** and **5b**, both chemical shifts of the carbons were obtained by using the XHCORR.AU and COLOC.AU techniques. Because the H3 and H4 chemical shift of each of the molecules are the same : 7.42 (**5a)** and 7.41 (**5b**), we thought that it could be interesting to perform HETCOR measurements (J=7Hz) to determine the C1a and C5a positions.

Results show that C5a is correlated with H4 and H7 and that C1a is correlated with H3 (FIG. 9.). Thus it was obvious to deduce the C1a and C5a shifts of **5a** and **5b**.

In conclusion the chemical shifts of all protons and carbons of compounds **5a** and **5b**, which were obtained by alkylation of 1-[chloro-(3,4,5-trimethoxyphenyl)-methyl)naphtalene **4** without by-products, such as, benzofluorene **2**, were assigned by NMR spectroscopy.

REFERENCES

[1] a) F. Leteurtre, J. Madalengoitia, A. Orr, T. J. Cuzi, E. Lehnert, T. McDonald, and Y. Pommier, *Cancer Res.*, **52** (1992) 4478. b) E. K. Lehnert, K. E. Miller, J. S. Madalengoitia, T. J. Cuzi and T. McDonald, *Bioorg. Med. Chem. Letters*, **4** (1994) 2411. c) F. Leteurtre, D. L. Sackett, J. S. Madalengoitia, G. Kohlhagen, T. McDonald, E. Hamel, K. D. Paull and Y. Pommier, *Biochem. Pharmacol.*, **49** (1995) 1283. d) Y. Pommier, T. McDonald and J. S. Madalengoitia, US patent 5,622,960 (1997) ; *Chem. abstr.*, **126** (1997) 343431j.

[2] a) L. Wilson and M. Friedkin, *Biochemisyty*, **6** (1967) 3126. b) L. Wilson and J. Brian, *Adv. Cell Mol. Biol.*, **3** (1974) 21. c) J. D. Loike, C. F. Brewer, H. Sternlicht, W. J. Gensler and S. B. Horwitz, *Cancer Res.*, **38** (1978) 2688.

[3] A. Legrand, B Rigo, J. P. Hénichart B. Norberg, F. Camus, F. Durant and D. Couturier, *J. Heterocyclic. Chem.*, **in Press (1999)**.

[4] The composition of the solution was obtained by HPLC analysis (C_{18} column, 80/20 acetonitrile/water as the mobile phase, flow 1.3 mL/min) : 4.0 min (**5a**) ; 4.4 min (**5b**).

[5] A. Bax, R. Freeman and G. A. Morris, *J. Magn. Reson.*, **42** (1981) 169.

[6] J. A. Wilde and P. H. Bolton, *J. Magn. Reson.*, **59** (1984) 343.

[7] P. Gautret, S. Ghammarti, A. Legrand, D. Couturier and B. Rigo, *Synth. Commun.*, **29** (1996) 707.

Date Received: June 15, 1999
Date Accepted: September 1, 1999