Reference Data

^{13}C NMR Data for 7- and/or 9-Aza-Substituted Naphthalenecyclolignans

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^{13}C NMR assignments are provided for 45 7- and/or 9-aza-substituted naphthalenecyclolignans. © 1997 John Wiley & Sons, Ltd.

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INTRODUCTION

Cyclolignans are natural products that include compounds, such as podophyllotoxin, with important antineoplastic and antiviral properties. In recent years they have been the subject of numerous studies, focused on obtaining more potent and less toxic anticancer agents, which have resulted in the clinical introduction of etoposide and teniposide.[1]

One of the research lines followed by our group in the past few years is to perform structural modifications of cyclolignans obtained from easily available natural sources, such as podophyllotoxin or deoxypodophyllotoxin. During that time we have prepared a large number of cyclolignan derivatives. Some of them were the subject of a previous compilation of ^{13}C NMR data,[2] which complemented previously published work by Agrawal and Thakur.[3] The analysis of the ^{13}C NMR data for different lignans has been very useful for the recognition of the various skeletal types of lignans, neolignans and oxyneolignans and also for the determination of the substitution pattern of side-chains.[4]

Owing to the great utility that these data could have for the scientific community working in the lignan field, we have now collected NMR data for another group of cyclolignans, prepared in our laboratory, which have in common the presence of heteroatom substitutions at the C-7 and C-9 positions of the cyclolignan skeleton. In order to elucidate the influence of heteroatoms at these two positions, we have included ^{13}C NMR data for some compounds reported previously.[5,6]

In this paper, 45 semisynthetic cyclolignans have been included. They have been classified, according to their structural characteristics, into the following groups: (1) pyrazolignans, those having a pyrazole or pyrazoline moiety fused to the lignan at positions 7, 8 and 9; (2) isoxazolignans, those having an isoxazole or isoxazoline ring; and (3) hydrazones and oximes at positions 7 or 9.

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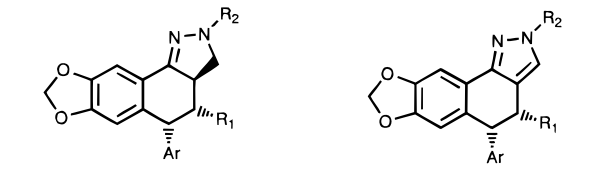
RESULTS

Pyrazolignans

This group includes compounds **1**–**17** (Fig. 1) which were obtained by condensation of podophyllotoxone with substituted hydrazines, followed by simple chemical transformations of the resultant hydroxy acids.[4] One-bond and long-range two-dimensional heteronuclear H–C spectra were obtained for the methyl esters **2** and **14** as representative compounds with an aryl and alkyl substituent, respectively, on the pyrazoline ring. The correlations observed for both compounds are summarized in Tables 1 and 2.

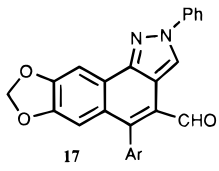
Isoxazolignans

In this group, compounds **18**–**24** are included (Fig. 2). They were prepared by condensation of podophyllotoxone with hydroxylamine and further transformations of the carboxylic group.[7] Compound **18** was chosen for performing the 2D NMR experiments and the results are summarized in Table 3.



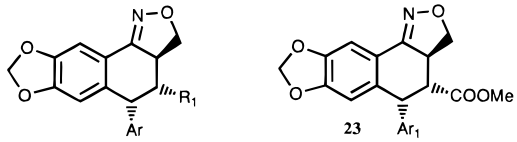
	R_1	R_2
1	COOH	Ph
2	COOMe	Ph
3	CH_2OH	Ph
4	CH_2OAc	Ph
5	COOH	*m*-NO_2Ph
6	COOMe	*m*-NO_2Ph
7	COOMe	*p*-MePh
8	COOMe	$COCH_3$
9	COOH	Me
10	COOMe	Me
11	COOH	$CONH_2$
12	COOMe	$CONH_2$
13	COOH	CH_2CF_3
14	COOMe	CH_2CF_3

	R_1	R_2
15	CH_2OH	Ph
16	CH_2OAc	Ph

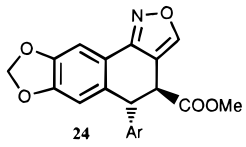


(Ar = 3,4,5-trimethoxyphenyl)

Figure 1. Structures of pyrazolignans.



	R_1
18	COOH
19	COOMe
20	CH_2OH
21	CH_2OAc
22	CHO



Ar = 3,4,5-trimethoxyphenyl; Ar_1 = 4-hydroxy-3,5-dimethoxyphenyl

Figure 2. Structures of isoxazolignans.

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Reference Data

Table 1. 2D heteronuclear correlations for compound 2 ($CDCl_3$, δ ppm; reference TMS)

δ_C	Type[a]	Coupled H δ_H	Long-range coupled H δ_H	Assignment[b]
40.6	CH	3.84 m		8
48.0	CH	4.60 d		7′
50.5	CH	3.23 dd		8′
51.6	CH_3	3.71 s		$COOCH_3$
55.1	CH_2	3.11 dd		9
		4.38 t		
56.3	CH_3	3.75 s		MeO-3′,5′
60.8	CH_3	3.81 s		MeO-4′
101.5	CH_2	5.98 s		OCH_2O
103.1	CH	7.54 s		2
107.1	CH	6.19 s	4.60 d	2′,6′
109.2	CH	6.52 s		5
113.5	CH	7.12 s		2″,6″
119.6	CH	6.86 t	7.12 d	4″
122.5	C		3.84 m	1
			4.60 d	
			6.52 s	
129.1	CH	7.28 t	6.86 t	3″,5″
133.5	C		4.60 d	6
			7.54 d	
135.7	C		3.23 dd	1′
			6.19 s	
137.9	C			4′
146.0	C		7.28 t	1″
146.6	C		6.25 s	3
			7.54 s	
149.3	C		6.52 s	4,7
			7.54 s	
153.1	C		3.75 s	3′,5′
			3.81 s	
171.9	C			9′

[a] From DEPT experiments.
[b] Positions marked with double primes correspond to carbons atoms of substituents placed at the pyrazolic nitrogen.

Hydrazones and oximes

Compounds **25**–**45** are included in this group (Fig. 3). They were prepared by condensation of the corresponding carbonyl derivatives at the C-7 or C-9 position with differently substituted hydrazines or hydroxylamines.[8] Results of one-bond and long-range 2D heteronuclear correlations for compound **41** are shown in Table 4.

Chemical shifts

^{13}C chemical shifts of the cyclolignans studied are listed in Table 5. The numbering adopted (Fig. 4) is uniform for all the compounds and is that proposed by Ayres and Loike.[1]

The ^{13}C NMR data in Table 5 are divided into groups according to the classification given above. Structures are given for all the compounds. References containing published data for particular compounds are included in the table.

EXPERIMENTAL

^{13}C NMR spectra were recorded on a Bruker WP 200 SY spectrometer operating in the pulsed Fourier transform (FT) mode at 50.3 MHz. All of the compounds were examined at 25 °C as $CDCl_3$ solutions containing a small amount of TMS as internal standard, unless stated otherwise.

Heteronuclear H/C 2D-NMR experiments

Typical long-range H/C experiments (200/50.3 MHz) were performed as follows: 128 FIDs of 500–900 scans each, with a 1 s recycle delay and incrementing t_1 from 5 μs to 64 ms, were acquired, using the DEPT-COSY sequence,[9] on a *ca.* 0.6 M $CDCl_3$ solution of the lignan derivative. The spectral width in F_2 was 8800 Hz (digital resolution $DR = 15.5$ Hz per point) whereas the F_1 carrier and width (*ca.* 1000 Hz, $DR = 4.2$ Hz per point) were selected to avoid folding. The *J*-focusing delay was tuned for a value of $^nJ(CH) = 8.3$ Hz. FT was performed after sine-bell multiplication in both domains and applying one degree of zero-filling in F_1.

One-bond 2D NMR experiments were performed similarly except for $SW_2 = 4032$ Hz, number of scans = 160 and the focusing delay selected for $^1J(CH) = 135$ Hz.

Reference Data

Table 2. 2D heteronuclear correlations for compound 14 ($CDCl_3$, δ ppm; reference TMS)

δ_C	Type[a]	Coupled H δ_H	Long-range coupled H δ_H	Assignment
42.2	CH	3.60 m	2.52 dd	8
			3.17 dd	
			4.57 d	
47.9	CH	4.57 d	3.17 dd	7′
			6.13 s	
			6.53 s	
50.4	CH	3.17 dd	2.52 dd	8′
			4.57 d	
51.7	CH_3	3.65 s		$COOCH_3$
56.4	CH_3	3.72 s		MeO-3′,5′
57.9 c	CH_2	3.25 m		CH_2CF_3
(128 Hz)		4.20 m		
60.7	CH_3	3.79 s		MeO-4′
61.7	CH_2	2.52 dd	3.25 m	9
		4.07 t	4.20 m	
101.4	CH_2	5.96 s		OCH_2O
103.4	CH	7.39 s		2
107.3	CH	6.13 s	4.57 d	2′,6′
109.2	CH	6.53 s	4.57 d	5
121.6	C		4.57 d	1
			6.53 s	
124.0 c	C		3.25 m	CF_3
(668 Hz)			4.20 m	
134.0	C		4.57 d	6
			7.39 s	
135.4	C		3.17 dd	1′
			4.57 d	
138.1	C		3.79 s	4′
			6.13 s	
147.6	C		5.96 s	3
			6.53 s	
149.7	C		5.96 s	4
			6.53 s	
151.8	C		4.07 t	7
153.2	C		3.72 s	3′,5′
			6.13 s	
171.7	C		3.17 dd	9′
			3.60 m	

[a] From DEPT experiments.

Reference Data

Table 3. 2D heteronuclear correlations for compound 18 ($CDCl_3$, δ ppm; reference TMS)

δ_C	Type[a]	Coupled H δ_H	Long-range coupled H δ_H	Assignment
46.0	CH	3.80 m		8
49.0	CH	4.67 d	6.20 s	7′
53.8	CH	3.23 dd		8′
56.6	CH_3	3.66 s		MeO-3′,5′
61.0	CH_3	3.76 s		MeO-4′
76.2	CH_2	3.90 t		9
		4.84 t		
103.1	CH_2	5.99 s		OCH_2O
104.2	CH	7.43 s	3.80 m	2
109.2	CH	6.20 s		2′,6′
110.4	CH	6.56 s		5
120.2	C		6.56 s	1
138.0	C		3.66 s	4′
			3.76 s	
			6.20 s	
138.2	C		3.66 s	1′
			3.76 s	
			6.20 s	
138.5	C		7.43 s	6
148.8	C		3.74 s	3
			5.99 s	
			6.56 s	
151.9	C		3.74 s	4
			5.99 s	
			6.56 s	
154.0	C		3.66 s	3′,5′
			3.76 s	
			6.20 s	
159.5	C			7
178.8	C			9′

[a] From DEPT experiments.

Reference Data

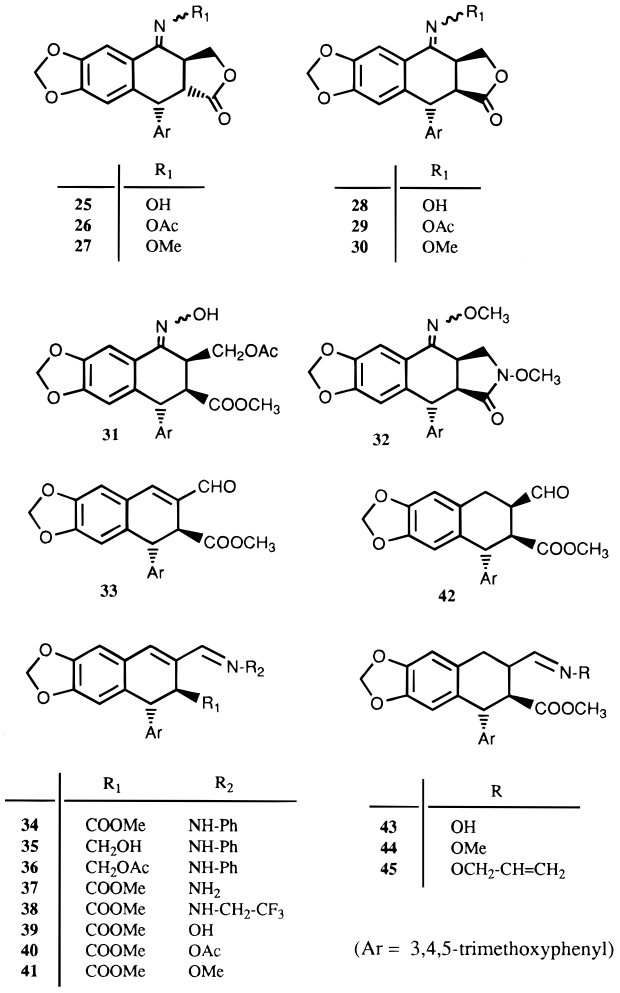

Figure 3. Structures of hydrazone and oxime derivatives.

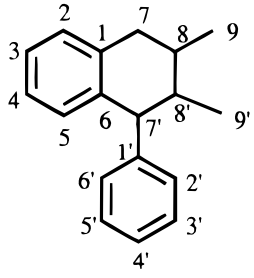

Figure 4. Numbering of cyclolignans.

Table 4. 2D Heteronuclear correlations for compound 41 ($CDCl_3$, δ ppm; reference TMS)

δ_C	Type[a]	Coupled H δ_H	Long-range coupled H δ_H	Assignment
46.3	CH	4.06 d	4.48 d	8′
			6.62 s	
			7.79 s	
46.7	CH	4.48 d	4.06 d	7′
			6.29 s	
			6.65 s	
52.2	CH_3	3.61 s		$COOCH_3$
56.2	CH_3	3.72 s		MeO-3′,5′
60.7	CH_3	3.76 s		MeO-4′
61.9	CH_3	3.80 s		N-OCH_3
101.3	CH_2	5.90 s		OCH_2O
		5.91 s		
105.3	CH	6.29 s	4.48 d	2′,6′
107.8	CH	6.69 s	6.65 d	2
109.7	CH	6.62 s	4.48 d	5
126.6	C		6.62 s	1
			7.79 s	
127.1	C		4.06 d	8
			4.48 d	
131.1	C		4.06 d	6
			4.48 d	
			6.65 s	
			6.69 s	
132.6	CH	6.65 s	4.06 d	7
			6.69 s	
			7.79 s	
137.5	C		3.76 s	4′
			6.29 s	
138.2	C		4.06 d	1′
			4.48 d	
147.1	C		6.62 s	3
148.2	C		5.90 s	4
			5.91 s	
			6.69 s	
149.6	CH	7.79 s	6.65 s	9
153.2	C		3.72 s	3′,5′
			3.76 s	
			6.29 s	
172.5	C		3.61 s	9′
			4.06 d	
			4.06 d	

[a] From DEPT experiments.

Table 5. ^{13}C chemical shifts of cyclolignans (δ ppm, $CDCl_3$ as solvent and TMS as internal reference)

	Carbon																											
No.	1	2	3	4	5	6	7	8	9	OCH_2O	1′	2′,6′	3′,5′	4′	7′	8′	9′	MeO-3′,5′	MeO-4′	1′	2″	3″	4″	5″	6″	$COOCH_3$	OAc	Other	Ref.
Pyrrazolingnans																													
1	122.4	103.2	147.7	149.0	109.2	133.3	149.3	40.5	55.1	101.5	135.5	107.2	153.1	137.7	47.8	50.0	178.8	56.3	60.7	146.5	113.5	129.1	119.7	129.1	113.5				5
2	122.5	103.1	146.6	149.3	109.2	133.5	149.3	40.6	55.1	101.5	135.7	107.1	153.1	137.9	48.0	50.5	171.9	56.3	60.8	146.0	113.5	129.1	119.6	129.1	113.5	51.6			5
3	122.4	103.2	147.3	149.3	109.6	135.2	151.1	41.5	54.4	101.3	136.2	107.6	153.2	137.5	45.2	47.6	63.5	56.4	60.6	146.9	113.6	129.1	119.6	129.1	113.6				5
4	122.2	103.2	147.4	149.4	109.5	134.7	150.2	41.8	54.3	101.3	135.5	107.6	153.2	137.9	41.9	47.8	65.1	56.3	60.7	146.8	113.6	129.1	119.7	129.1	113.6		170.4 20.8		5
5	121.7	103.3	146.9	147.8	109.3	134.0	150.8	40.8	54.6	101.6	135.1	107.5	153.2	139.0	47.8	50.2	176.2	56.4	60.7	149.9	107.8	149.4	113.6	129.7	118.8				5
6	121.7	103.3	146.9	147.8	109.3	134.2	151.1	40.9	54.5	101.6	135.3	107.2	153.2	137.8	47.9	50.4	171.8	56.3	60.7	149.9	107.5	149.4	113.6	129.7	118.7	51.6			5
7	122.6	103.1	149.0	149.2	109.2	133.3	147.6	40.7	55.6	101.4	135.8	107.1	153.1	144.6	48.0	50.5	172.0	56.3	60.8	–[a]	113.6	129.6	118.9	129.6	113.6	51.8		20.5	5
8	121.5	103.4	147.8	150.6	109.4	135.0	155.0	40.2	50.2	101.7	135.5	107.2	153.2	–	47.8	50.4	171.2	56.3	60.8							51.9		169.3 21.3	5
9	122.1	103.4	147.6	149.6	109.2	133.9	152.8	41.9	62.7	101.5	135.5	107.1	153.0	137.6	47.9	50.3	178.0	56.2	60.7									43.7	5
10	122.5	103.2	147.5	149.3	109.2	133.6	151.6	42.0	62.8	101.3	135.8	107.2	153.1	137.6	48.1	50.5	171.9	56.3	60.7							51.6		43.8	5
11	126.4	106.4	148.6	150.3	108.9	133.3	154.4	43.5	75.8	102.5	138.1	107.2	153.3	140.3	43.5	53.2	174.6	56.3	60.8									194.3	5
12	126.4	106.4	148.6	148.6	108.9	133.2	154.1	43.5	75.8	102.5	138.2	107.5	153.4	140.4	43.5	53.1	174.3	56.4	60.8							51.9		194.2	
13	121.7	103.4	147.7	149.8	109.2	133.9	151.8	42.0	61.6	101.5	135.2	107.4	153.1	137.9	47.7	50.2	176.2	56.3	60.6									57.8c 125.0c	
14	121.6	103.4	147.6	149.7	109.2	134.0	151.8	42.2	61.7	101.4	135.4	107.3	153.2	138.1	47.9	50.4	171.7	56.4	60.7							51.7		57.9c 124.0c	
15	123.0	103.6	147.4	148.0	109.5	134.4	150.5	118.0	125.9	101.2	136.0	106.2	153.1	137.5	39.6	48.7	63.3	56.1	60.8	140.7	118.9	129.5	124.4	129.5	118.9				5
16	122.8	103.6	147.5	148.0	109.5	134.0	150.3	117.2	126.1	101.2	135.1	106.0	153.0	–	36.4	48.6	64.8	56.0	60.7	140.5	118.0	129.5	124.0	129.5	118.0		170.0 20.9		5
17	125.5	101.4	145.9	148.4	106.8	131.4	150.2	114.8	127.6	101.8	138.5	108.8	153.3	140.6	128.0	129.6	192.6	56.4	61.0	147.1	120.6	129.6	123.5	129.6	120.6				5
Isoxazolignans																													
18[b]	120.2	104.2	151.9	110.4	148.8	138.5	159.5	46.0	76.2	103.1	138.2	109.2	154.0	138.0	49.0	53.8	178.8	56.6	61.0										5
19	119.1	104.1	147.7	150.5	109.2	138.1	156.4	43.6	74.5	101.9	135.1	107.2	153.2	134.9	48.1	50.1	171.4	56.3	60.7							51.9			
20	119.0	103.9	147.4	150.5	109.5	137.7	157.6	44.6	73.9	101.6	136.6	107.6	153.2	135.6	44.8	47.8	63.7	56.4	60.8										
21	118.9	104.1	147.6	150.6	109.4	138.0	156.9	41.5	73.7	101.6	136.0	107.5	153.4	134.9	44.6	48.2	65.4	56.4	60.8								170.3 20.7		
22	119.2	104.0	147.8	150.6	109.2	138.1	156.2	42.2	74.1	101.7	135.0	106.9	153.5	134.4	46.5	56.1	199.5	56.4	60.7										
23	119.1	104.0	147.7	150.6	109.2	135.1	156.3	43.6	74.5	101.7	134.8	106.9	147.2	130.7	48.0	52.2	171.4	56.5								51.8			
24	118.5	104.4	147.7	150.0	109.8	133.5	157.4	111.3	154.7	101.6	137.4	105.7	153.6	137.8	43.9	48.2	171.5	56.3	60.7							52.5			

Hydrazones and oximes																												
25	133.2	105.0	148.0	150.1	108.7	124.7	152.4	36.8	71.4	101.8	133.9	106.5	153.1	137.4	45.2	45.2	176.6	56.1	60.9									
26	133.4	106.2	148.3	151.6	108.7	123.1	158.2	37.8	70.3	102.0	135.5	107.0	153.4	138.2	44.9	44.9	175.1	56.3	60.8								167.5 19.6	
27	133.7	104.2	147.8	149.8	109.5	124.8	153.4	36.8	70.1	101.7	134.8	108.1	153.1	137.9	43.9	46.8	173.2	56.4	60.7									62.4
28	132.7	104.7	148.1	150.2	109.5	123.9	154.6	33.7	71.0	101.7	135.1	105.1	153.7	137.7	44.8	45.7	176.3	56.3	60.8									
29	133.4	105.0	148.3	151.6	109.6	123.1	158.2	37.8	70.3	102.0	135.0	106.0	153.4	138.2	44.9	44.9	175.1	56.3	60.8								167.5 19.0	
30	132.5	105.0	148.1	150.1	109.4	124.1	153.2	34.1	71.1	101.5	137.8	105.0	153.7	137.5	44.8	45.8	176.3	56.2	60.9									62.5
31	134.9	105.1	145.5	149.8	109.2	133.5	153.8	33.6	61.3	101.3	139.1	107.1	153.4	137.9	43.9	49.4	171.9	56.4	60.8							51.8	171.9 20.7	
32	132.4	104.8	148.2	150.2	109.5	124.5	154.9	28.4	49.5	101.4	138.1	105.1	153.6	137.4	44.4	45.8	169.0	56.1	60.7									61.9 62.4
33	133.9	108.9	147.5	150.5	110.1	133.3	145.3	125.2	191.0	101.8	137.3	105.4	153.4	137.8	46.4	44.5	172.0	56.3	60.7							52.4		
34	130.5	107.4	147.0	147.5	109.7	130.5	138.7	127.3	144.7	101.2	138.5	105.2	153.2	137.0	47.0	46.8	173.4	56.3	60.7	–	112.8	129.2	120.0	129.2	112.8	52.2		
35	133.4	107.2	146.7	147.6	110.5	130.0	139.9	127.2	144.6	101.1	140.0	105.4	153.1	137.1	45.3	44.0	64.6	56.3	60.7	140.2	112.8	129.3	120.1	129.3	112.8			
36	130.5	107.4	147.0	147.6	109.7	130.5	138.7	127.3	144.7	101.1	138.5	105.5	153.3	137.0	47.1	46.8	64.2	56.3	60.7	–	112.8	129.8	120.1	129.8	112.8		173.4 20.1	
37	132.0	108.1	147.2	109.9	129.9	137.0	126.7	161.6	101.4	138.1	105.4	153.3	137.5	46.7	46.6	172.7	56.3	60.7							52.3		51.6c	
38	130.6	107.4	147.1	147.8	109.8	130.0	129.8	127.1	141.3	101.2	138.6	105.4	153.2	137.1	46.7	46.4	172.9	56.2	60.6							52.0		
39	131.1	107.8	147.1	148.3	109.6	126.8	133.2	126.4	151.4	101.3	138.2	105.3	153.3	137.6	46.5	172.5	56.3	60.7							52.3			
40	131.7	107.3	147.1	148.6	109.8	126.8	133.3	126.4	151.5	101.2	138.3	105.1	153.5	137.7	46.6	46.6	172.4	56.7	60.7					52.8		52.8	170.5 20.7	
41	131.1	107.8	147.1	148.2	109.7	127.1	132.6	126.6	149.6	101.3	138.2	105.3	153.2	137.5	46.7	46.3	172.5	56.2	60.7							52.2		61.9
42	127.5	108.3	146.6	147.0	109.8	128.6	26.6	33.0	201.9	100.9	140.3	106.6	153.4	138.3	46.4	48.1	172.1	56.3	60.7							52.0		
43	127.3	108.2	146.6	109.7	129.4	31.6	34.5	152.2	100.8	140.3	106.8	153.3	137.4	45.6	51.0	172.7	56.4	60.8							51.7			
44	127.4	108.2	146.5	146.6	109.7	129.4	31.7	34.4	150.7	100.8	140.4	106.9	153.3	137.5	45.9	51.0	172.7	56.4	60.8							51.6	61.3	
45	127.4	108.2	146.6	146.6	109.7	129.4	31.9	34.6	150.9	100.8	140.5	106.6	153.3	137.5	45.8	51.0	172.7	56.4	60.7							51.7		74.5 134.2 117.3

[a] Dashes indicate signals not observed.
[b] Spectrum measured in MeOH-d_4.

Reference Data

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