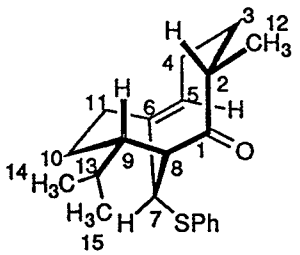
JOC The Journal of Organic Chemistry

J. Org. Chem., 1997, 62(23), 8155-8161, DOI:10.1021/jo971244d

Structure, Stereochemistry, and Conformation of 2. ^{1}H and ^{13}C show the presence of a ketone carbonyl, a trisubstituted double bond, and a phenyl substituent; the aliphatic regions show three secondary methyls, four methylenes, and five methines. The ^{1}H NMR spectrum is well resolved and can be readily assigned from a DQF-COSY spectrum, that also allows tracing of the connectivity of the molecule as follows:

- the presence of $CH_3CHCH_2CH_2CH=$ } and $(CH_3)_2CHCHCH_2CH_2$ fragments are obvious from a corresponding network of vicinal and geminal correlations.
- an allylic coupling (J = 3 Hz) between H-5/H-11' establishes a connection between these two fragments.
- a homoallylic coupling between H-4' and a downfield methine (δ 4.33 br s) shows that the latter occupies the remaining position at the double bond, and this is H-7.
- weak vicinal coupling of the remaining methine (δ 2.86 br s) with both H-7 and H-9 identify the former as H-8.
- the remaining SPh and C=O fragments are connected to H-7 and to H-2/H-8, respectively, based on their chemical shifts.

The structure of **2** is therefore as shown below. The indicated relative stereochemistry and preferred conformation is derived from examination of the magnitudes of vicinal coupling constants and interpretation of long-range couplings, and is further confirmed by the results of several NOE experiments (see below). The ^{1}H NMR data and assignments for **2** are found in Table 1.



- The strong H-5/H-11 allylic coupling (3 Hz), the much weaker H-5/H-11 allylic coupling (1 Hz), and the large vicinal coupling involving one of the C-10 methylene protons with H-11 (12 Hz) and H-9 (11.5 Hz) define a chair-like conformation in the left half of the ten-membered ring, with axial H-11 and H-9 and equatorial H-11' and *i*-Pr group.
- The H-4/H-7 homoallylic coupling indicates an extended W-coupling arrangement, and combines with the large H-3/H-4 (12 Hz) and H-3/H-2 (11.5 Hz) vicinal couplings to define the crown-like conformation of the 8-membered ring, with equatorial H-4', H-3' and methyl group, axial H-4, H-3, and H-2, and endo-oriented H-5 and SPh group.
- The following NOE enhancements are fully consistent with the above assignments:

↓ Ph-H^{o} → Ph-H^{m} (~4%), H-5 (~1%), H-7 (~4%), H-8 (~0.5%), and H-11' (~0.5%).

↓ H-2 → H-3' (~2.5%), H-4 (~2%), H-9 (~13%), and H-12 (~1.5%).

↓ H-5 → H-3 (~2.5%), H-4' (~4%), H-7 (~0.5%), and Ph-H^{o} (~ -1.5%). This last NOE is negative at 400 MHz; at 300 MHz a weaker, positive NOE (~1%) is observed.

↓ H-7 → H-5 (<0.5%), H-8 (~2%), H-10 (~5.5%), H-11' (~1%), H-13 (~1%), H-14 (<0.5%), H-15 (<0.5%), and Ph-H^{o} (~3%).

↓ H-12 → H-2 (~7.5%), H-3 (~2.5%), H-3' (~4.5%), H-8 (~1%), and H-9 (~2.5%).

Table 1. ^{1}H NMR of **2** (400 MHz, C_6D_6).

pos.	δ	mult.	*J* [Hz]
H-2	2.59	ddq (br)	11.5, 1.5, 7
H-3	2.02	dddd	13, 12, 11.5, 4.5
H-3'	*		
H-4	2.20	dddd	12.5, 12.5, 12, 4.5
H-4'	1.82	ddd (br)	12.5, 4.5, 4
H-5	6.21	ddd (br)	12, 4, 3
H-7	4.33	s (br)	
H-8	2.86	s (br)	
H-9	1.76	ddd (br)	11.5, 7.5, 6.5
H-10	*		
H-10'	*		
H-11	2.73	dddd	17, 12, 7.5, 1
H-11'	2.04	m (br)	
H-12	0.81	d (3 H)	7
H-13	1.18	dqq	6.5, 6.5, 6.5
H-14/	0.60	d (3 H)	6.5
H-15	0.59	d (3 H)	6.5
Ph-H^o	7.46	m (2 H)	
Ph-H^m	7.02	m (2 H)	
Ph-H^p	6.91	m	

* 1.51-1.32 m (3 H)

Structure and Stereochemistry of 12. Most resonances in the ^{1}H NMR spectrum of **12** (400 MHz, C_6D_6) appear broad and extensively overlapped. Besides a few other distinct resonances, only an olefinic proton (δ 5.59), a downfield proton (δ 3.20) probably representing the methine of a secondary alcohol, and three secondary methyl groups (δ 0.91, 0.87, 0.84) are immediately obvious from inspection. This situation is due to slow conformational exchange, as it improves partially upon warming to 65 °C, although several resonances still remain featureless at this temperature. A 400 MHz DQF-COSY spectrum run at 65 °C provided some assignment information, but due to resonance overlap did not allow tracing of the connectivity within the entire molecule.

The ^{1}H NMR spectra in DMSO-d_6 (400 MHz, 25 °C and 65 °C) revealed an exchangeable proton coupled to the downfield methine, thus verifying the presence of a secondary alcohol. Although a somewhat different pattern of chemical shifts is realized in the DMSO-d_6 spectra, the DQF-COSY spectrum (400 MHz, 65 °C) did not provide sufficient additional information to allow for full assignment of resonances and connectivity. For this purpose, additional assignment information from a one-bond ^{1}H,^{13}C-shift correlation was definitely required.

Unfortunately, the ^{13}C NMR spectrum of **12** (C_6D_6 or DMSO-d_6, 100 MHz, 25 °C) does also show numerous extremely broad resonances. This situation improves only moderately upon warming to 65 °C in either solvent. Careful examination of these spectra allows only 14 out of the expected 15 resonances to be defined, and multiplicity-assignment via DEPT succeeded only for the sufficiently sharp resonances. Nevertheless, with the exception of a trisubstituted double bond and an alcohol methine, all remaining resonances appeared to be purely aliphatic. However, the spectrum is unsuitable for the recording of a conventional ^{13}C-detected one-bond ^{1}H,^{13}C-correlation map.

This problem could be overcome and full assignments of ^{13}C shifts and multiplicities as well as the essential one-bond $^{1}H,^{13}C$-shift correlation information could be obtained, by recording a $^{1}H,^{13}C$-HMQC spectrum at *ambient temperature* (400 MHz, DMSO-d_6, 25 °C). It is at this point important to note the following: since HMQC is a proton-detected technique, the line widths (and resulting intensities) of the 2D-crosspeaks correlating ^{13}C with directly connected ^{1}H nuclei depend mainly on the T1 relaxation time of a respective *proton* rather than the corresponding carbon. Therefore, strong crosspeaks for $^{13}C/^{1}H$ pairs are observed when the respective ^{1}H-resonance is sharp (long T1), even when the corresponding ^{13}C-resonance is approaching coalescence and can hardly be localized in the ^{13}C spectrum. The same applies vice versa, i.e., a weak correlation will result for a broad (short T1) ^{1}H-resonance even though the corresponding ^{13}C-resonance may be sharp.

By combining the information about the location of geminal pairs of methylene vs methine protons contained n the HMQC spectra with the $^{1}H,^{1}H$-coupling information contained in the DQF-COSY spectra, it was possible to trace the connectivity of **12** as shown below. Besides identification of obvious vicinal coupling relationships, it was crucial to recognize weak H-7/H-11 and H-7/H-11' allylic, and unresolved H-9/H-10, H-10/H-11, H-10/H-1, and H-1/H-2 vicinal couplings in the DQF-COSY spectra. The ^{1}H and ^{13}C assignments derived from the HMQC and DQF-COSY spectra are summarized in the following tables.

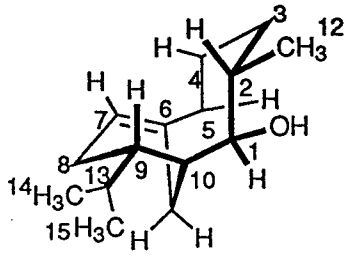


Table 2. ^{13}C Chemical Shifts and Multiplicities for **12** as Extracted from a $^{1}H,^{13}C$ HMQC Spectrum[a] (400 MHz, DMSO-d_6, 25 ° C).

pos.	δ	mult.(1)
C-1	78.0	d (vbr)
C-2	33.4	d (vbr)
C-3	28.4	t (br)
C-4	30.8	t (vbr)
C-5	35.6	t
C-6	142.4	s
C-7	121.4	d
C-8	26.0	t
C-9	43.1	d
C-10	44.1	d (vbr)
C-11	27.9	t (br)
C-12	25.6	9 (vbr)(2)
C-13	32.5	d
C-14/	20.4	q
C-15	19.7	q

[a] Chemical shifts for those resonances that are sufficiently sharp at 25 or 65 °C are taken from the regular ^{13}C spectrum for better accuracy. Chemical shifts for the broader resonances are ±0.2 ppm due to the limited resolution of the HMQC-experiment in the ^{13}C dimensions (F1).

(1) br - broad, vbr - very broad in a regular ^{13}C spectrum at 25 °C.

(2) this signal is near coalescence at 25 °C and 65 °C and can not be recognized in a regular ^{13}C spectrum.

Table 3. ^{1}H NMR (400 MHz) of **12** in C_6D_6[a] and DMSO-d_6.

	C_6D_6/65 °C			DMSO-d_6/25 °C		
pos.	δ	mult.	*J* [Hz]	δ	mult.	*J* [Hz]
1-OH	0.81	br s		4.36	br s	
H-1	3.22	br s		3.11	br dd	3.5, 3
H-2	1.86	m		(2)		
H-3	1.95	m		(1)		
H-3'	1.11	br m		(4)		
H-4	1.89	m		(1)		
H-4'	1.39	m		1.32	m	
H-5	2.24	ddd	12.5, 5, 4.5	2.17	m	
H-5'	1.96	m		(1)		
H-7	5.57	m		5.55	m	
H-8	1.99	ddd	14, 7.5, 6	2.02	ddd	14, 7.5, 6
H-8'	1.62	m		(3)		
H-9	0.92	m		(4)		
H-10	1.74	m		(2)		
H-11	2.44	br d	12.5	2.41	br d	12.5
H-11'	1.76	m		1.65	m	
H-12	0.90	d	7	0.82	d	7
H-13	1.49	dqq	6.5, 6.5, 6.5	(3)		
H-14/	0.87	d	6.5	0.88	d	6.5
H-15	0.84	d	6.5	0.85	d	6.5

[a] Chemical shifts of overlapping resonances have been extracted from DQF-COSY spectra.

(1) 2.03-1.83 brm (3 H)

(2) 1.79-1.68 m (2 H)

(3) 1.60-1.47 m (2 H)

(4) 0.95-0.78 brm (2 H)

Assignment of the relative stereochemistry shown below to **12** follows from observation of the listed NOE enhancements (DMSO-d_6, 400 MHz, 25 °C):

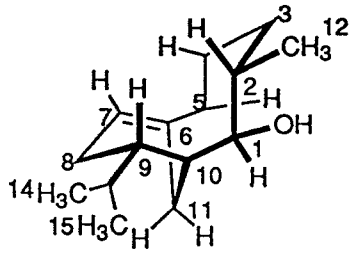
↓H-7 → H-2 (~1%), H-4'$_\beta$ (~0.5%), H-5$_\beta$ (~3.5%), and H-8$_\beta$ (~4%).

↓1-OH → H-1 (~8%), H-10 (~4.5%), and H-12 (<0.5%).

↓H-1 → 1-OH (~6%), H-10 (~7%), H-12 (~2%), H-13 (~2%), H-14 (~1%), H-15 (~1%), and H-9 (this NOE is masked by overlap of H-9 with the methyl groups H-12, H-14, and H-15).

↓H-11 → 1-OH (~0.5%), H-10 (~5%), and H-11' (~23%).

↓H-5 → H-4' (~1.5%), H-4 and H-5' (overlapped, Σ ~21%), and H-7 (~8.5%).



Structure and Stereochemistry of 13. Comparison of the ^1H NMR spectra of **13** (300 MHz/$CDCl_3$ and 400 MHz/$CDCl_3$) and of salsolene oxide (400 MHz/$CDCl_3$) clearly shows that the two compounds are *not* identical. The close similarity of their ^{13}C NMR spectra, however, indicates that they are closely related structurally.

The connectivitiy of **13** can be identified by careful examination of its COSY spectrum that indicates the epoxide-proton (H-7) to be the terminus of a $(CH_3)_2CHCHCH_2CH$ fragment. A CH_2CH fragment representing the bridge and bridgehead of the molecule shows connectivity with the internal methine of the first fragment (H-9) as well as with the olefinic proton of the trisubstituted double bond (H-1). Finally, a $(CH_2)_3$ fragment can be recognized that shows allylic coupling with the olefinic proton. From this information, the structure shown below can be derived.

(*Z*)-geometry of the double bond can be assigned based on a strong NOE (~8.5%) observed at the olefinic proton (H-1) upon preirradiation of the olefinic methyl group (H-12).

Relative stereochemistry at C-9 and C-10 can be inferred from the precursor molecules, while that at C-6 and C-7 is determined by epoxidation occurring from the less hindered face of the precursor molecule, as becomes clear upon inspection of a model. These assignments are confirmed in this region of the molecule: close to zero coupling between H-7/H-8, H-8/H-9 and H-9/H-10, and the sizes of the syn-vicinal couplings between H-7/H-8' (3.5 Hz) and H-8'/H-9 (7.5 Hz), indicate a boat-like conformation of the six-membered ring with 4 equatorial H-7, H-8, H-9, and H-10, and with pseudoaxial orientation of H-8', C-1 (ring substituent) and C-13 (*i*-Pr group). This assignment is further supported by observation of a H-9/H-11 W-coupling. This W-coupling also makes possible the stereochemical assignment of H-11 (4 equatorial) and H-11' (4 axial; syn the *i*-Pr and epoxide-oxygen).

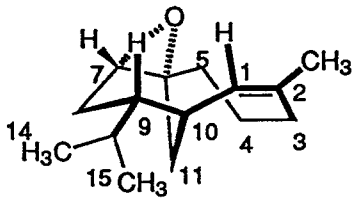


Table 4. ^{1}H NMR of **13** (300 MHz/$CDCl_3$).

pos.	δ	mult.	*J* [Hz]
H-1	4.96	br s	
H-3	2.66	br dd	12.5, 12
H-3'	1.89	m	
H-4	2.05	m	
H-4'/H-5	1.42-1.25	m (2 H)	
H-5'$_\beta$	1.20	br dd	12.5, 5
H-7$_\beta$	2.72	br d	3.5
H-8$_\alpha$	2.00	br d	16
H-8'$_\beta$	1.82	ddd	16, 7.5, 3.5
H-9$_\beta$	0.99	m	
H-10$_\alpha$	2.41	br s	
H-11$_\beta$	2.36	br dd	15.5, 3
H-11$_\alpha$	1.86	br dd	15.5, 3
H-12	1.75	dd (3 H)	2, 1
H-13	1.68	dqq	10.5, 6.5, 6.5
H-14/	0.91	d (3 H)	6.5
H-15	0.80	d (3 H)	6.5

Structure and Stereochemistry of 18. The ^1H NMR spectrum ($CDCl_3$, 25 °C) exhibits considerable overlap, and the broad appearance of several resonances indicates that some sort of slow conformational exchange may be operating. Two downfield protons (δ 5.40 and 5.14) and a methyl singlet (δ 2.00) are consistent with the expected trisubstituted double bond and a secondary acetate. Three secondary methyl groups (δ 1.13, 0.94, and 0.91) are also observed as expected. Integration is consistent with a total proton count of 28, but only two of the remaining protons show resolved resonances (δ 2.64 and 2.32) that are immediately obvious from inspection. The proton connectivities observed in a DQF-COSY spectrum are partially ambiguous due to resonance overlap, and the constitution of the molecule cannot be derived from this information along.

Several resonances in the DEPT-135 ^{13}C NMR spectrum ($CDCl_3$, 25 °C) are very broad and the number of resonances observed is less than expected for a H_{28} compound. This is a further indication of slow conformational exchange, leading to extreme broadening of, and failure to observe, several resonances that are near coalescence. However, all of the ^{13}C resonances could be localized in proton-detected HMQC (one-bond) and HMBC (multiple-bond) $^1H,^{13}C$ shift-correlation spectra obtained at 25 °C (*cf.* remarks in the writeup for **12** as to why this is possible even though several resonances are "missing" from the regular ^{13}C spectrum due to coalescence). The shift-correlation information contained in these spectra, in conjunction with the DQF-COSY spectrum, allowed the complete derivation of ^1H and ^{13}C assignments and confirmation of the constitution of the acetoxyalkene to be as shown.

A ^1H NMR spectrum recorded in DMSO-d_6 at 25 °C was very similar to that in $CDCl_3$ with respect to chemical shifts but showed even more severe overlap, and was therefore not further analyzed in detail. However, variable temperature ^1H NMR spectra in DMSO-d_6 (75, 100, and 125 °C) served to confirm that the various broad

resonances observed at 25 °C in both $CDCl_3$ and DMSO-d_6 are due to slow chemical exchange since significant line narrowing of the broad resonances was observed at the higher temperatures. It was furthermore possible to directly observe all 17 carbon resonances in a ^{13}C NMR spectrum recorded in DMSO-d_6 at 125 °C. Most resonance assignments for this spectrum are obvious from comparison with the previously assigned ^{13}C NMR spectrum in $CDCl_3$ at 125 °C. Tables 5 and 6 summarize the ^{13}C and ^{1}H assignments, including proton-proton coupling and NOE information from which olefin geometry and relative configuration of the chiral centers can be derived as follows.

The double bond geometry is defined as *Z* primarily because of the observation of a strong NOE between one of the allylic protons (H-4, δ 2.32) and one of the protons of the methylene bridge (H-7, δ 2.64), while the olefinic proton (H-5, δ 5.40) shows NOE to the complementary allylic proton (H-4', δ 1.82).

Assignment of relative stereochemistry at C-1 and C-2 followed from NOE's between the methyl group (H-12, δ 1.13) and both H-4 and H-7, and between the acetate methine (H-1, δ 5.14) and H-4', and is consistent with the coupling constants between H-1/H-7 (9 Hz) and H-1/H-2 (<2 Hz). Although the NOE pattern defines olefin geometry and relative stereochemistry unambiguously, it also reflects the fact that the left-hand portion of the ten-membered ring does not adopt a single preferred conformation. In particular, the significant NOE's between H-1 and H-4' on one hand, and between H-12 and H-4 on the other, require that multiple conformations are assumed in solution. This is also consistent with the observation of broad resonances for H-1, H-3/3' and H-12 in the ^{1}H NMR, and for C-2, C-3, C-4 and C-12 in the ^{13}C NMR spectra.

Assignment of relative stereochemistry at C-9 follows from a number of observations including long-range couplings between H-7/H-9 and H-7/H-11', allylic coupling between H-5/H-11, and NOE between H-1/H-9. These data are consistent

with adoption of a half-chair conformation by the six-membered ring such that W-alignment of H-7/H-9 and H-7/H-11' is realized, and H-11 (syn to bridge) is positioned perpendicular to the double-bond plane. However, the observation of broad resonances for H-9 and H-10/10' in the ^{1}H NMR, and for C-9, C-10 and C-13 in the ^{13}C NMR spectra indicates conformational flexibility of the six-membered ring as well. The structure of the acetoxyalkene can therefore be represented as shown below.

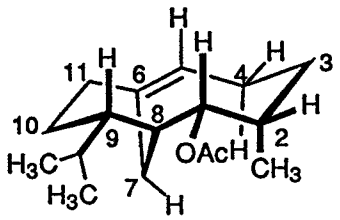


Table 5. ^{13}C Chemical Shifts(2) and Multiplicities for **18.**

pos.	δ ($CDCl_3$, 25 °C)[a]	mult.(1)	δ (DMSO-d_6, 125 °C)	mult.(1)
C-1	78.5	d	77.5	d
C-2	38.7 (±0.5)	d (coal.)	36.1	d (br)
C-3	35.5	t (br)	34.3	t
C-4	22.7	t (br)	22.0	t
C-5	121.1	d	120.3	d
C-6	140.8 (±0.5)	s	139.6	s
C-7	26.1	t	25.0	t
C-8	42.6	d	41.7	d
C-9	42.7	d (br)	41.6	d
C-10	27.0	t (br)	25.7	t
C-11	32.1	t	31.2	t
C-12	12.1 (±0.5)	q (coal.)	13.7	q (br)
C-13	27.4	d (br)	27.1	d
C-14	21.4	q	20.4	q
C-15	21.3	q	20.5	q
OAc	21.3	q	20.2	q
	171.0 (±0.5)	s	169.3	s

[a] Chemical shifts for protonated resonances that are sufficiently sharp at 25 °C are taken from a regular DEPT-135 ^{13}C NMR spectrum. Chemical shifts of those protonated carbons that are not observed in the regular ^{13}C NMR spectrum due to coalescence (C-2 and C-12), and chemical shifts of the quaternary carbons (C-6 and acetate C=O), were extracted from HMQC and HMBC spectra ($CDCl_3$, 25 °C), respectively.

(1) q, t, d, s - quartet (CH_3), triplet (CH_2), doublet (CH), singlet (4 °C); br - broad; coal. - not observed in regular ^{13}C NMR spectrum due to coalescence.

(2) Internally referenced to $CDCl_3$ (δ_C 77.0) and DMSO-d_6 (δ_C 39.5), respectively.

Table 6. ^{1}H NMR Data(1) (400 MHz, $CDCl_3$, 25 °C) of **18**.

pos.	δ	mult.(2)	*J* [Hz]	J_{LR}(3)	relevant NOE's(4)
H-1	5.14	br d	(w/H-8)	H-9, H-11'	H-2 (4.5), H-4' (5), H-8 (1), H-9 (2.5), H-12 (0.2)
H-2	2.07	m			
H-3	1.74	br m			
H-3'	1.67	br m			
H-4(α)	2.32	dddd	14,13,8,2.5		H-4' (8.5), H-7 (9), H-12 (0.5)
H-4'(β)	1.82	m			
H-5	5.40	br dd	8,7	H-11	H-4' (5.5), H-11' (2.5)
H-7	2.64	br d	12.5	H-9,H-11'	H-4 (9), H-7' (19), H-8 (3), H-12 (2.5)
H-7'	1.82	dd(5)	12.5, 4		
H-8	2.14	m			
H-9	0.94	m		H-7	
H-10 H-10'	1.78	AB-m			
H-11(α)	2.10	m		H-5	
H-11'(β)	1.99	dddd	12,4.5,4,2	H-7	
H-12	1.13	br d(3H)	7.5		H-1 (1), H-2 (7), H-4 (2), H-7 (6.5), H-8 (4)
H-13	1.86	dqq	9.5,6.5,6.5		
H-14	0.94	d (3H)	6.5		
H-15	0.91	d (3H)	6.5		
OAc	2.00	s (3H)			

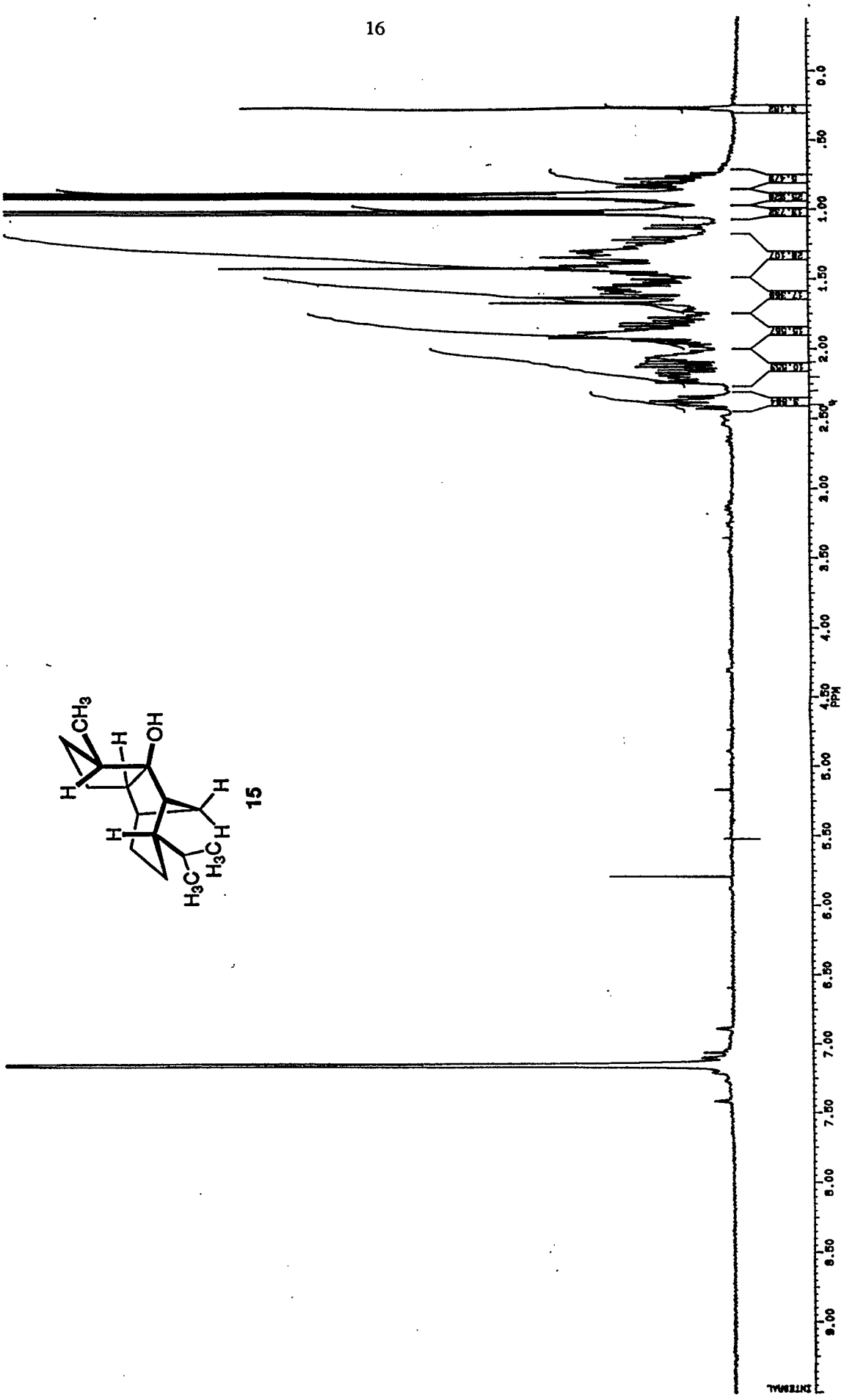
(1) Referenced to internal TMS (δ_H 0.0).

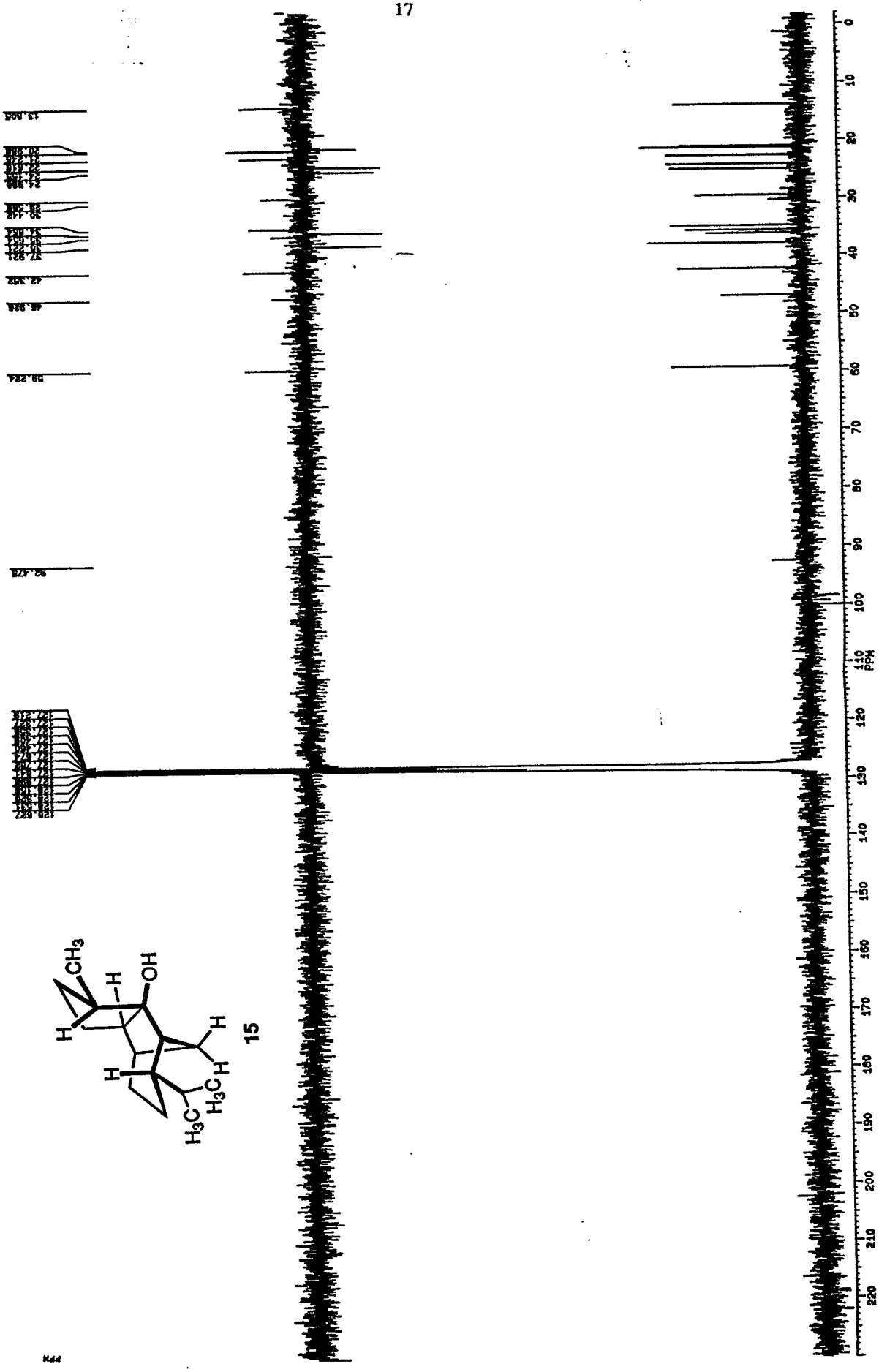
(2) Chemical shifts of overlapping resonances (m) have been extracted from a DQF-COSY spectrum.

(3) Long-range couplings (allylic ^4J; W-type ^5J) observed in DQF-COSY spectrum.

(4) Enhanced resonances (% NOE) observed upon pre-irradiation of the respective target resonance (6 sec., field strength γ-$B_2/2\pi$ = ca. 2 Hz).

(5) Chemical shift and coupling constants extracted from NOE spectrum (↓ H-7).





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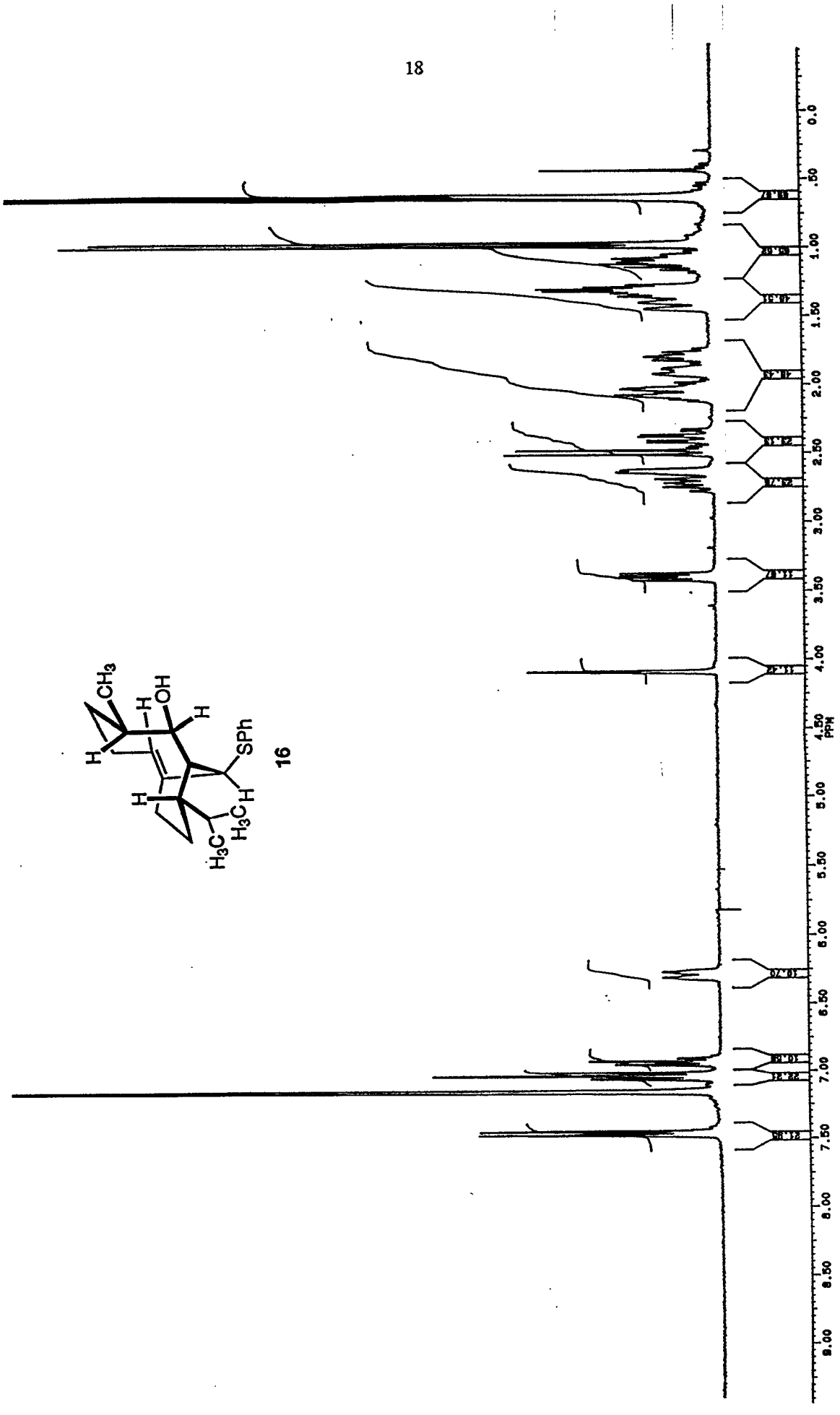

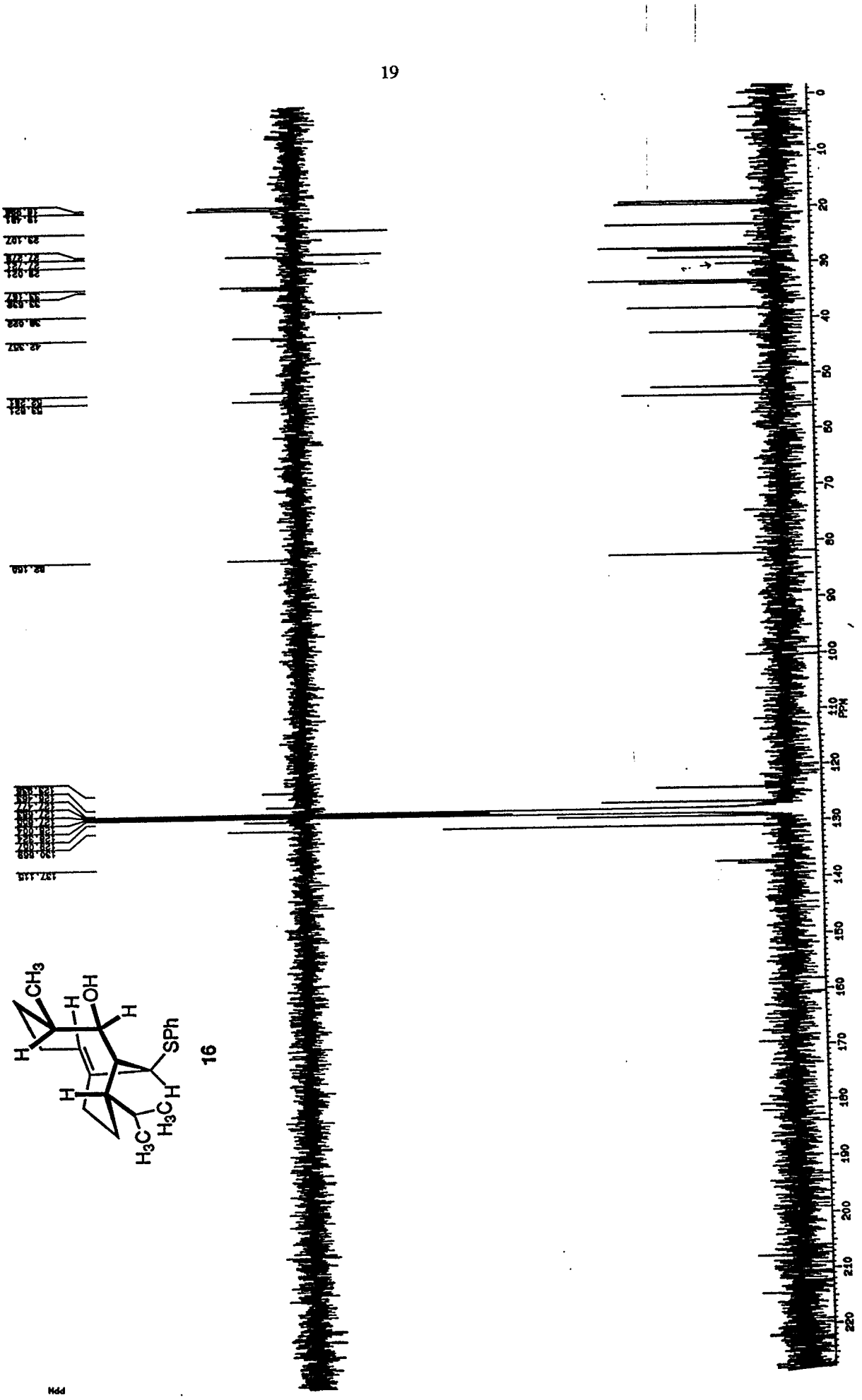

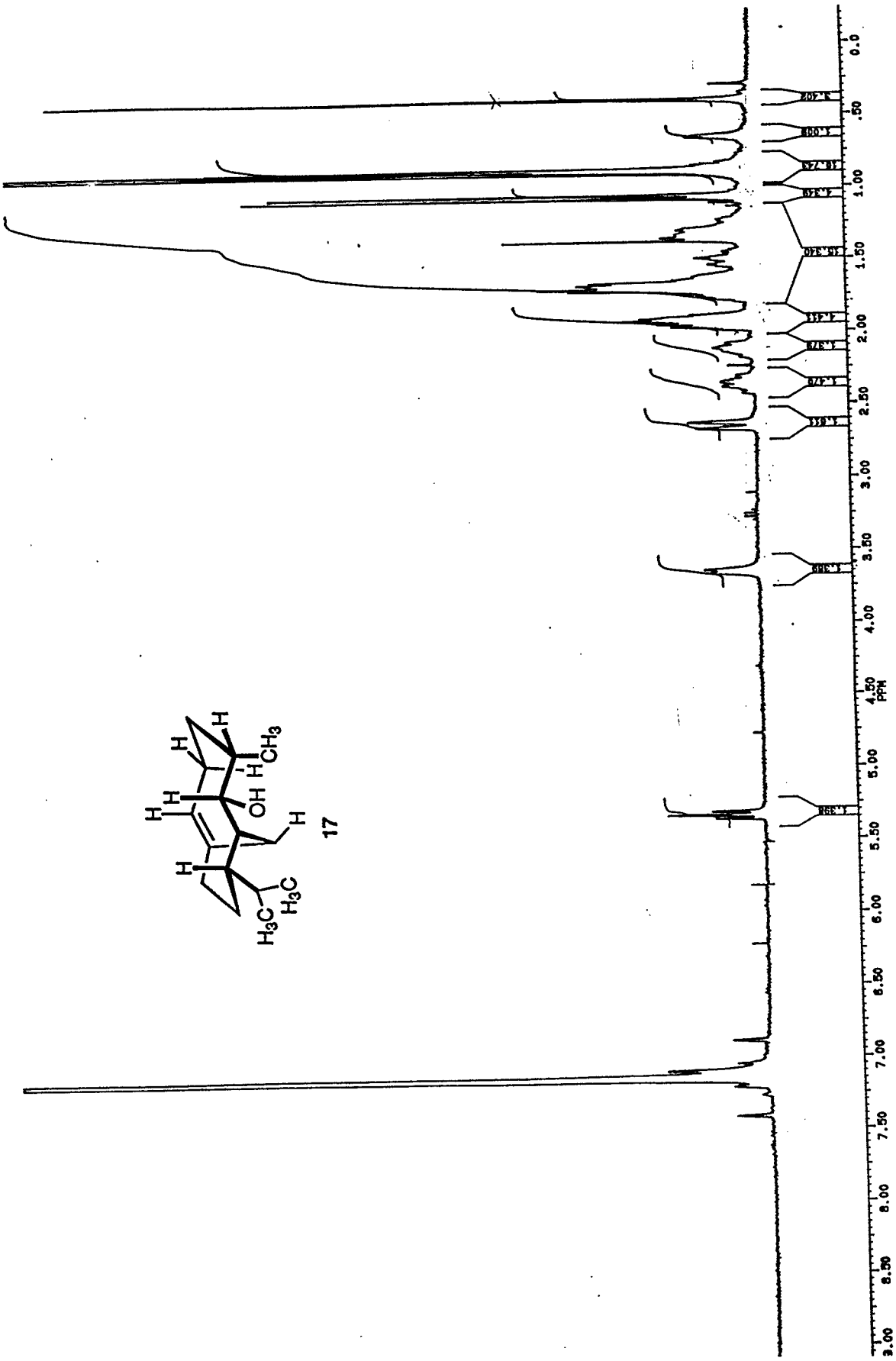

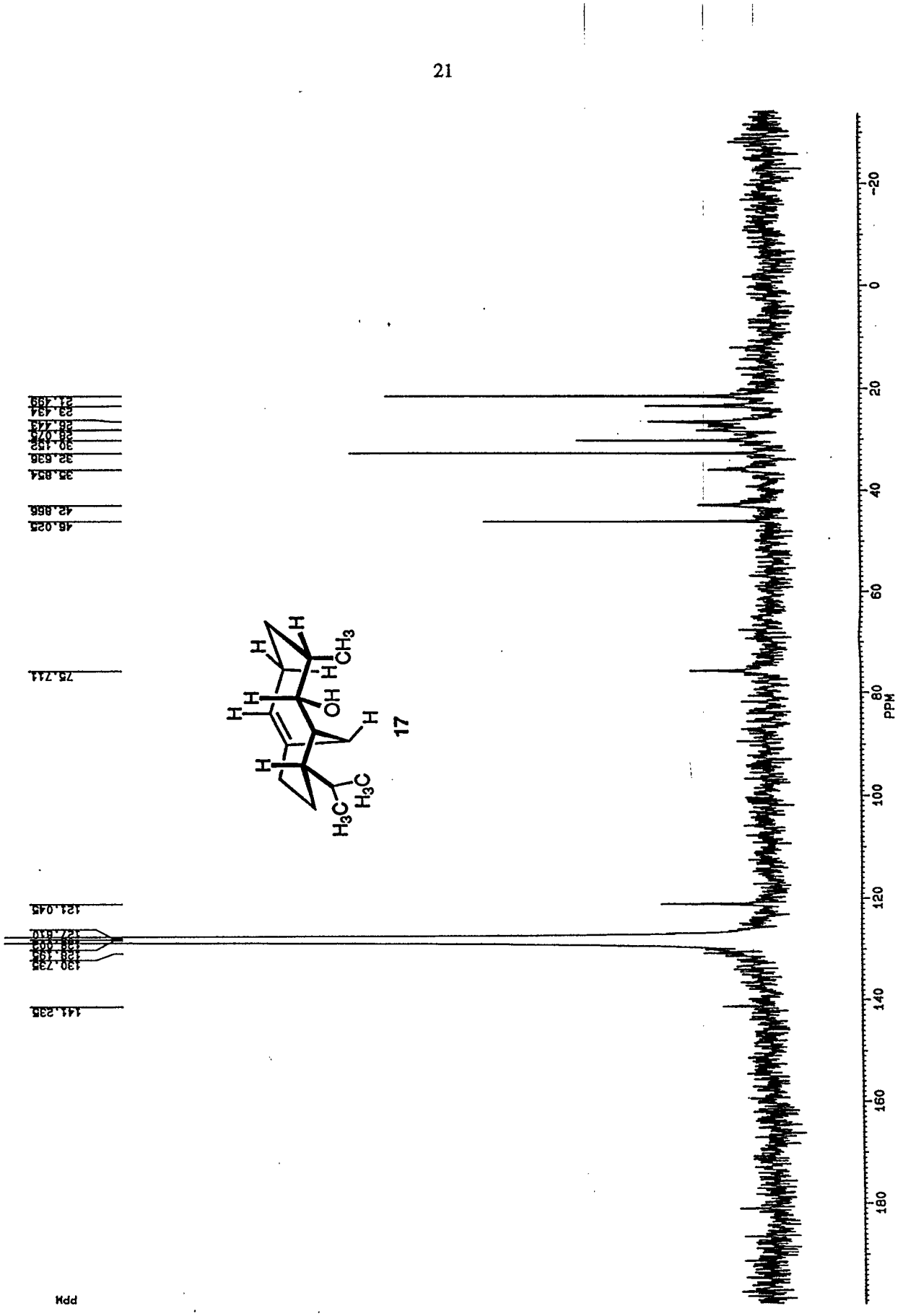

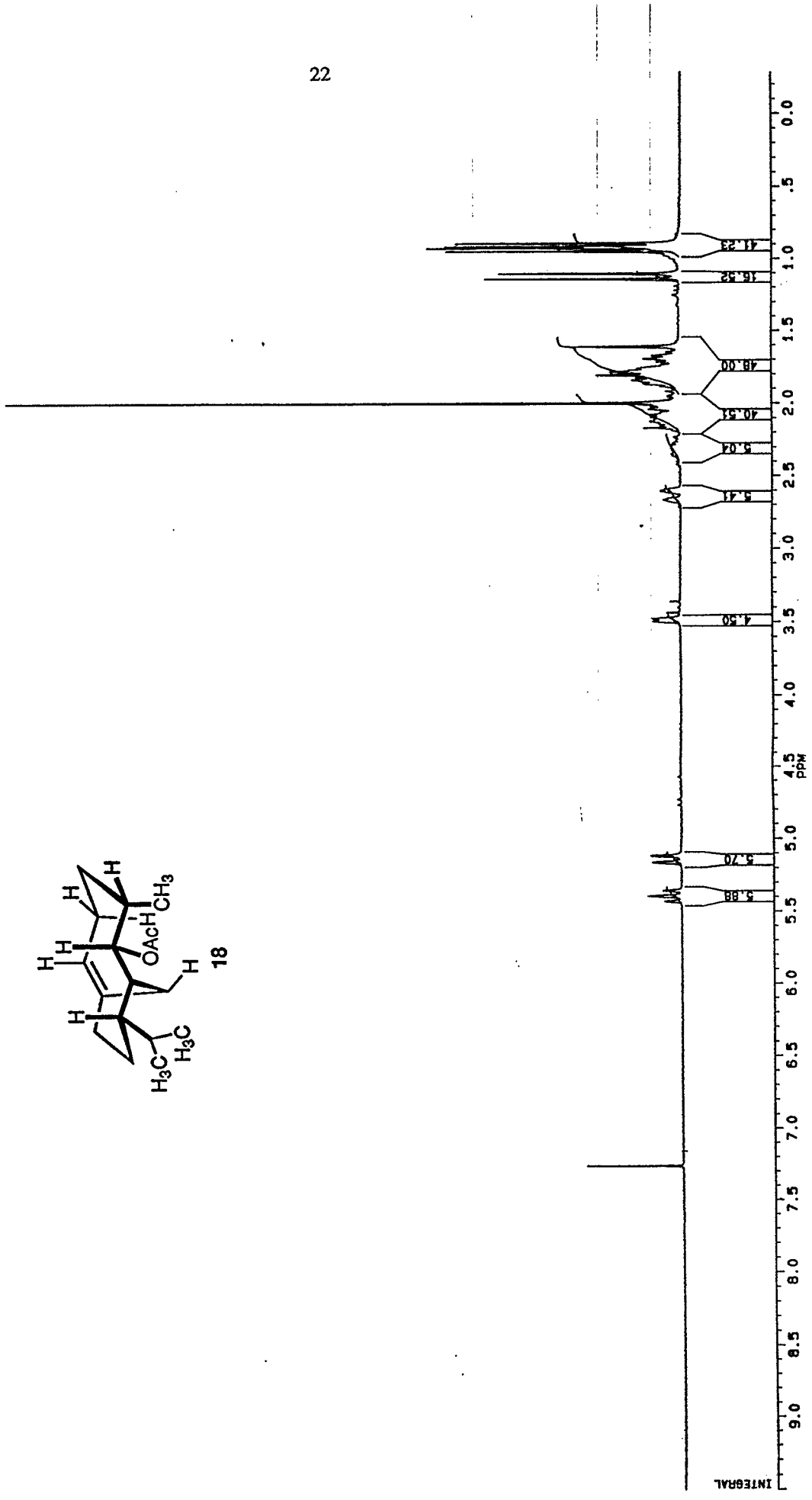

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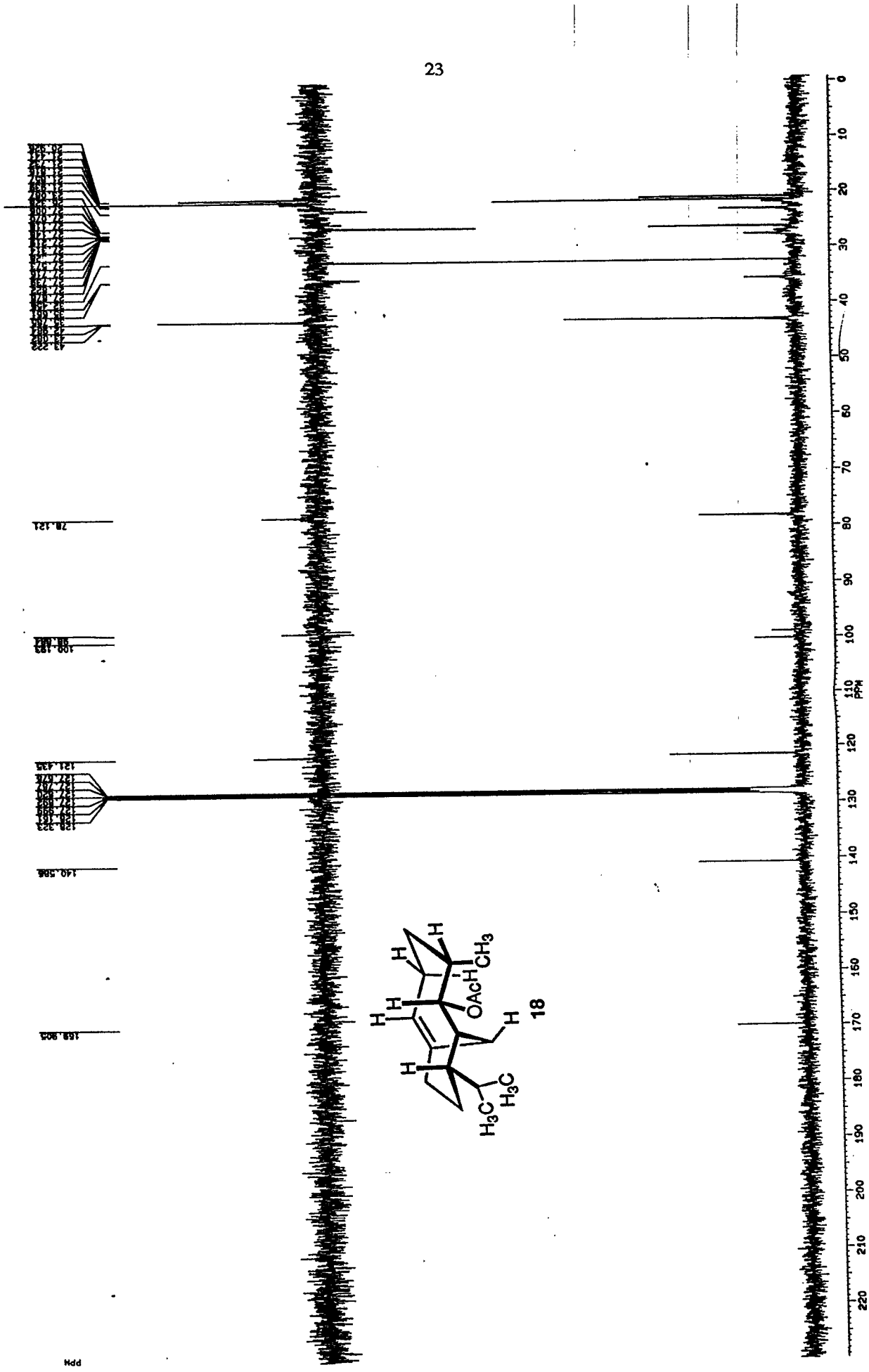

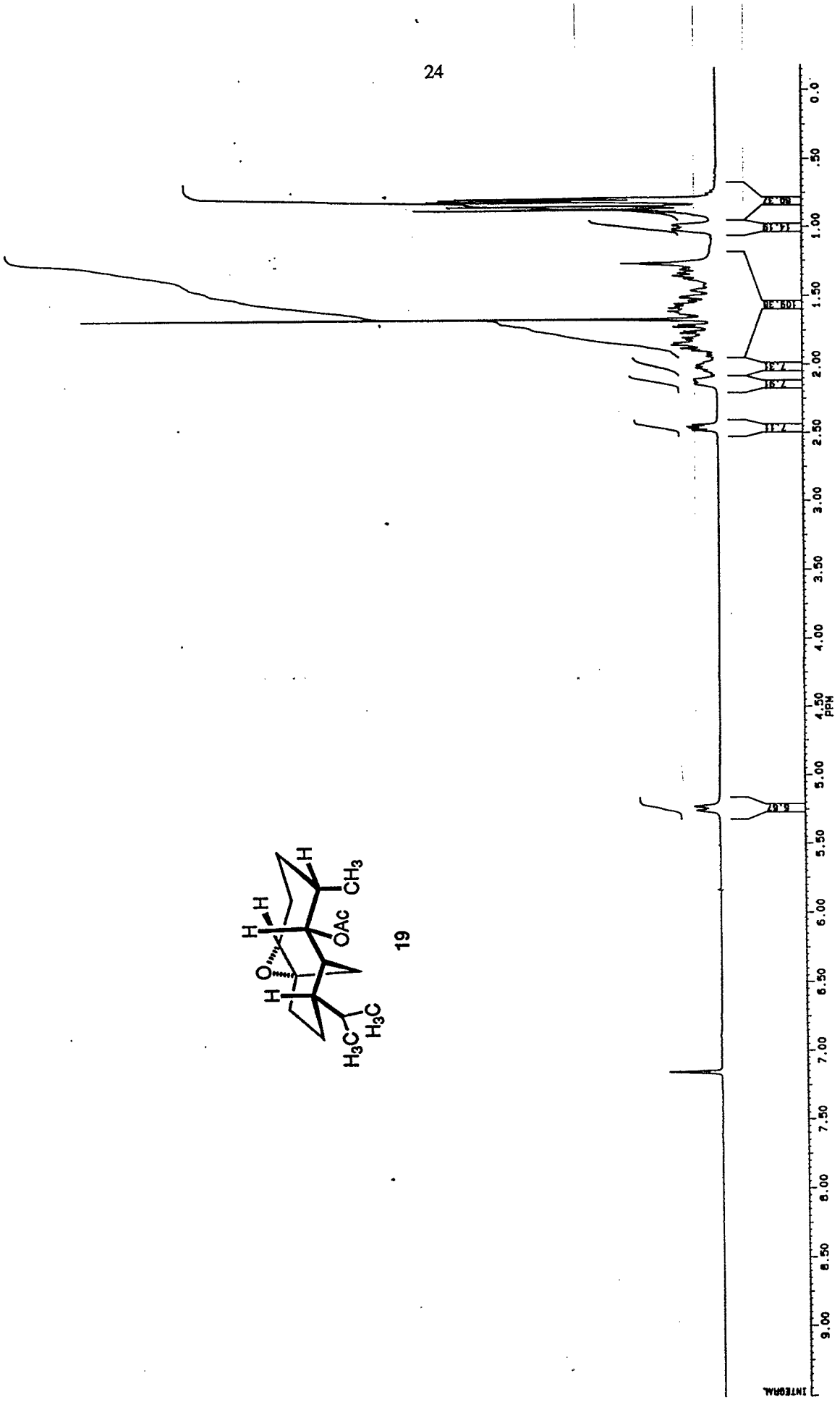

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