

22aD'. The deuterium content of both **22aD** and **22aD'** and the deuterium redistribution upon going from **22aD** to **22aD'** are outlined in Table III.

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74-3; 20, 77903-75-4; 21a, 77903-77-6; 21b, 77903-79-8; 21c, 77903-81-2; 21d, 77903-83-4; *cis*-22a, 77903-84-5; *trans*-22a, 77903-85-6; *cis*-22b, 77903-86-7; *trans*-22b, 77903-87-8; *cis*-22c, 77903-88-9; *trans*-22c, 77903-89-0; 23a, 77903-90-3; 23b, 77903-92-5; *cis*-27, 77903-93-6; *trans*-27, 77903-94-7; 28, 77924-77-7; 29, 77924-77-7; 22aD, 77924-78-8; 23aD, 77903-95-8; 3-(2-hydroxyethyl)-1H-indole-2-carboxylic acid, 77903-96-9; 2-ethyl-3-(2-hydroxyethyl)-1H-indole, 76507-86-3; [1-[3-(2-hydroxyethyl)-1H-indol-2-yl]ethyl]trimethylammonium iodide, 77903-97-0; dimethyl 2,6-dideuteriopyridine-3,5-dicarboxylate, 77903-98-1; dimethyl 3,5-pyridinedicarboxylate, 4591-55-3; methyl 3-pyridinecarboxylate, 93-60-7; 3-cyanopyridine, 100-54-9; 3-ethylpyridine, 536-78-7.

Structure of Nepetalic Acid in the Solid State and in Solution by X-ray Diffraction and Nuclear Magnetic Resonance Analysis

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Single-crystal X-ray analysis of nepetalic acid (**1c**, mp 75 °C) from *Nepeta cataria* shows that the six-membered ring adopts a half-boat conformation with near planarity of the lactone (C-C(O)O-C) moiety, the absolute configuration of the chiral centers being 3*S*, 4*R*, 4*aR*, 7*S*, and 7*aR* as determined by the Bijvoet method. The crystals are monoclinic: $P2_1$, $a = 6.625$ (3) Å, $b = 8.885$ (3) Å, $c = 8.408$ (3) Å, $\beta = 95.06$ (3)°. The structure was solved by direct methods and refined by block-diagonal least-squares methods to an R value of 0.030 for 1073 reflections. Solution studies by ¹H and ¹³C NMR established the presence of two epimers at C(3) (CHOH) with axial and equatorial OH, respectively, in a ratio of (77 ± 3):(23 ± 3) in the -15 to -25 °C temperature range and (79 ± 2):(21 ± 2) in the -40 to -70 °C temperature range ($\Delta G^\circ = 0.60 \pm 0.05$ kcal/mol). The coalescence temperatures of the pertinent signals in ¹³C NMR lead to an activation energy of 14.8 kcal/mol for interconversion of the epimers.

(+)-Nepetalic acid (**1a-c**; mp 75 °C) and nepetalactone (**2**) were the first of the methylcyclopentane monoterpenoids to have their constitution^{2a-c} and their absolute configuration^{3a} elucidated. The structures of **1** and **2** are correlated as shown in Scheme I. Because of its biological activity as a feline attractant, **2** is usually the focus of attention.^{2e} However, **1** is chemically more significant since it was the source of the intermediate nepetalinic acids^{2a} (**5** is one example), the nepetonic acids,^{2a,c} and the nepetic acids^{2c,d} which served as important reference compounds for constitution and configurational correlation to the iridomyrmecins^{2g} and other iridoids,^{4,5a,b} the methylcyclo-

pentane sesquiterpenes,^{6a} and the skytanthine related methylcyclopentane monoterpenoid alkaloids as they were discovered.^{5c,6b,c} These earlier studies established, through chemical correlation to (+)-pulegone, the absolute configuration^{3a} of C(7) of **1a** and **2** and the relative configuration at other centers with the exception of C(3) of **1**. Recent ¹H and ¹³C NMR studies have confirmed these earlier relative configurational assignments^{3b} to **2**.

The tautomeric relationship of **1a-c** was known,^{2a} and the reactions of Scheme I along with formation of carbonyl derivatives of **1b** support the aldehyde acid structure **1b**. However, nepetalic acid also displays chemical evidence of the lactol structures **1a/1c**: formation of an acetate,^{2e} conversion to nepetalic anhydride, a diether,^{2e,f} and thermal dehydration^{2a,e,f} as well as remarkable resistance to air oxidation, in contrast to rapid air oxidation once the lactol structure is disrupted, as shown in the facile conversion^{2a} of **3** to **4**. Unfortunately, these observations do not reveal whether the aldehyde acid (**1b**) or lactol (**1a,c**) structure predominates since any of the reactions may occur through minuscule amounts of a minor tautomer, nor do they allow assignment of configuration (**1a** or **1c**) to the lactol, if nepetalic acid is, in fact, partially or entirely in the lactol

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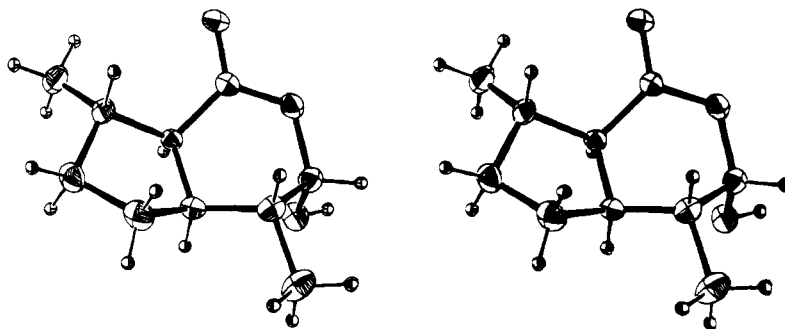


Figure 1. Stereoview of nepetalic acid (1c).

form. More conclusive evidence in favor of a predominant lactol structure is provided by the infrared spectrum which shows a relatively narrow OH band in the 3250–3300-cm⁻¹ region (in contrast to the broad CO₂H band in the 2600–3100-cm⁻¹ region displayed by 5).^{6d} The object of the present study was to examine the extent of preponderance of 1a/1c over 1b, to determine the ratio of 1a/1c in nepetalic acid solutions, to assess the barrier to their interconversion, to establish the structure as well as the absolute configuration in the solid state, and finally to compare the conformation of the lactone ring in the crystal state and in solution. These objectives were sought through proton and ¹³C NMR spectroscopy and single-crystal X-ray diffraction studies.

The equilibrium 1a ⇌ 1b ⇌ 1c is reached rapidly on the laboratory time scale. The proton NMR spectrum shows a single carbinol (CHOH) proton (along with an OH and a mass of protons at higher field); it displays no evidence whatsoever for the aldehydo acid form 1b since no signal was detected below 6 ppm. The room-temperature ¹³C NMR spectrum (Table I, 1a ⇌ 1c) shows 10 peaks of which at least two (corresponding to the lactone C=O and the CHOH) were quite broad, suggesting incipient coalescence. Indeed, at -20 °C, the C=O and CHOH peaks and several other peaks were completely decoalesced, and it was quite evident that equilibration of 1a and 1c had become slow on the NMR scale.

From the ratio of ¹³C peak areas [C(1), C(3), C(7a)] the presence of 23 ± 3% of the minor isomer in the temperature range -15 to -25 °C was computed, with a mean -ΔG° of 0.62 ± 0.04 kcal/mol. The carbonyl peak of the minor isomer is upfield of that of the major one, but the CHOH peak was downfield. From the latter evidence it may be inferred that the minor isomer 1a has an equatorial OH, leading to downfield position of the adjacent C(3) (α_e effect of OH > α_a effect)⁷⁻⁹ as well as of the β-carbon C(4) (β_e effect of OH > β_a effect)⁷⁻⁹ and of the γ-carbon C(4a) (absence of the upfield-shielding γ_a effect).⁷⁻⁹ The other isomer, 1c, is thus the one with an axial OH group.

The above inference is supported by the low-temperature proton spectrum. The peak at 5.55 ppm in the room-temperature spectrum is resolved on cooling of the sample to -40 °C into a minor, broad peak at 5.35 ppm and a major, narrower peak at 5.57 ppm. The half-width (~20 Hz) and coupling constant (8.2 Hz) of the former suggests it represents an axial or near-axial proton (equatorial OH) whereas the latter (half-width about 10 Hz) is more characteristic of an equatorial or near-equatorial proton. The ratio of the two signals in the -40 to -70 °C temperature interval ranges from 77:23 to 81:19

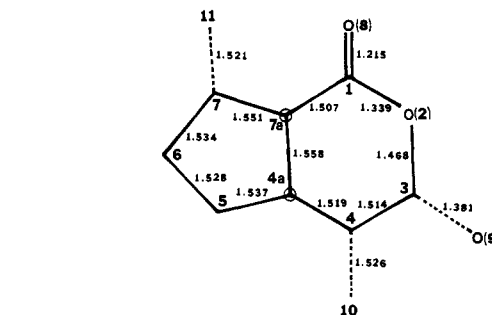


Figure 2. Bond lengths and numbering scheme for nepetalic acid (1c). Standard deviations vary from 0.002 to 0.003 Å.

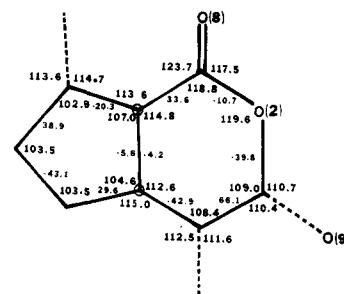


Figure 3. Bond angles and torsional angles of nepetalic acid (1c). Standard deviations are 0.1° for bond angles and 0.2° for torsional angles.

with an average -ΔG° of 0.58 ± 0.06 kcal/mol. Again the evidence is that the isomer with axial OH (equatorial H) predominates.

As expected, nepetalic acid crystallizes as the major configurational isomer 1c which was subjected to single-crystal X-ray analysis. The results of this analysis are shown as a stereoview in Figure 1 with the numbering scheme, bond lengths, bond angles, and torsional angles shown in Figures 2 and 3.

There is some strain in the fused ring system, which is reflected in the long C(4a)-C(7a) distance (1.558 Å). The difference in bond distance for the two C-O distances of the δ-lactone ring C(1)-O(2) (1.339 Å) and C(3)-O(2) (1.468 Å) is the commonly observed feature for lactone rings.¹⁰ The observed absolute configuration, shown in all figures, corresponds to that previously established through chemical correlation to (+)-pulegone.^{3a} The five- and six-membered rings are cis fused, as is the case in iridomyrmecin and iso-iridomyrmecin,^{11,12} but in the present compound the six-membered ring is fused by means of the α-

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Table I. ^{13}C NMR Chemical Shifts^a

compd	C(1)	C(3)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(7a)	C(10)	C(11)
1a \rightleftharpoons 1c ^b	176.00	99.20	(30.23)	(38.90)	31.88	34.48	38.46	(49.26)	15.09	20.44
1a ^{c,d}	175.82	101.36	(41.30)	(40.83)	31.71	34.53	38.21	(48.98)	14.94	20.60
1c ^{c,e}	177.46	98.97	(39.14)	(38.53)	32.41	34.53	38.21	(48.21)	15.50	20.60

compd	C(6)	C(9)	C(7)	C(2)	C(3)	C(4)	C(5)	C(1)	C(8)	C(10)
3 ^f	175.41	203.41	48.01	42.79	29.87	33.46	38.67	53.38	13.04	20.94
4 ^g	175.52	181.88	44.79	41.21	29.81	33.59	38.46	53.43	17.26	21.00
5	(182.47)	(183.43)	44.20	41.77	30.55	34.11	39.48	54.63	17.12	18.91

^a In parts per million downfield from Me₄Si in CDCl₃. Parenthesized assignments in horizontal rows may need to be interchanged. For the numbering see Scheme I; the numbering scheme of compound 1b is used for 3-5. ^b At room temperature. ^c At -50 °C. ^d Minor isomer. ^e Major isomer. ^f Also OCH₃ at 51.11 ppm. ^g Also OCH₃ at 51.01 ppm.

and β -carbon atoms rather than the β - and γ -carbon atoms of the δ -lactone ring. The lactone group C-C(O)O-C is only approximately planar with a mean deviation of 0.038 Å and a maximum deviation of 0.077 Å (O(2)). That the planarity is not ideal can also be seen in the nonzero torsional angle of C(1)-O(2) (-10.7°). The β - and γ -carbon atoms, however, are on the same side of the least-squares plane (distances: C(4a), 0.662 Å; C(4), 1.134 Å), which gives the δ -lactone ring a half-boat conformation. This also can be deduced from the torsional angles in Figure 3. This observation is in general agreement with the conclusions of Cheung, Overton, and Sim,¹⁰ that δ -lactone rings normally adopt the half-chair conformation but that the boat conformation arises in response to special circumstances, as in this case the cis-fused α - and β -carbon atoms. Atom O(9) donates a hydrogen bond to O(8) ($2 - x, 1/2 + y, 1 - z$) with the following dimensions: O...O, 2.817 Å; H...O, 1.932 Å; O-H...O, 168.7°. Associated with this hydrogen bond is a short C(1)...H(9) distance of 2.623 Å, giving a C(1)-O(8)...H(9) angle of 135.4°. There are no other short van der Waals contacts.

Whether the conformation of 1c in solution is the same as that in the solid state and whether the conformation of 1a corresponds to that of 1c cannot be unequivocally deduced from the NMR spectra. The half-width of the anomeric proton signal (CHOH) in 1c, 10 Hz, and the coupling constant, ca. 2 Hz, are compatible (though not uniquely so) with the H(3)-C(3)-C(4)-H(4) torsional angle of 68.4° (Table X¹⁹) of the half-boat conformation in the solid state. However, a deformed-chair structure is more in accord with the 20-Hz half-width and 8.2-Hz coupling constant of the anomeric proton signal seen in the spectrum of 1a, for which, of course, no X-ray data are available.

The coalescence temperature of the carbinol carbons ($\Delta\nu = 43.2$ Hz) is 238 K. Using the formulas¹³ $k(\text{coal}) = 1/2 \cdot 2^{1/2} \pi \Delta\nu$ and $k_e = n_e k$, $k_a = n_a k$ [where n_e and n_a are the mole fractions of the equatorial OH (1a) and axial OH (1c) isomers, respectively, and k_e and k_a are the rates of interconversion of 1a and 1c, respectively], one calculates $\Delta G^\ddagger = 14.6$ kcal/mol ($\Delta G^\ddagger = RT \ln(kh/k_B T)$, where h is Planck's constant, k_B Boltzmann's constant, and T the absolute temperature at coalescence).

The ^{13}C spectra of compounds 3-5 are recorded in Table I, along with those of 1a and 1c. Table IV provides data of relative signal intensities below the coalescence temperature. Coalescence temperatures [and activation energies for epimerization at C(3) derived therefrom] for various carbon signals are shown in Table V.

Experimental Section

Compounds 1-5. These were available from previous work.^{3b}

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Table II. Crystallographic Data

formula	C ₁₀ H ₁₆ O ₃	space group	P2 ₁
mol wt	184.24	Z	2
parameter ^a	at -135 °C	at 25 °C	
a, Å	6.6252 (26)	6.7264 (9)	
b, Å	8.8850 (27)	9.0766 (9)	
c, Å	8.4083 (33)	8.4085 (10)	
β , deg	95.06 (3)	96.58 (1)	
V, Å ³	493.02	509.98	
d_{calcd} , g/cm ³		1.200	
d_{obsd} , g/cm ³ b		1.201	

^a Cell dimensions were determined by a least-squares fit to the $+2\theta$ and -2θ values of 48 reflections taken from all octants of reciprocal space by using Cu K α_1 radiations ($\lambda = 1.54051$ Å). ^b The density was measured by the flotation method with an aqueous solution of sodium potassium tartrate.

Single-Crystal X-ray Analysis. A single crystal (0.36 \times 0.22 \times 0.18 mm) of nepetalic acid, obtained by crystallization from petroleum ether, was chosen for data collection. The crystal system is monoclinic, space group P2₁, with two molecules in the unit cell. Unit cell data (Table II) and intensity data were measured at -135 °C on a CAD-4 automatic diffractometer equipped with Enraf-Nonius cold-stream cooling device. Intensities of all 1073 unique reflections with $2\theta \leq 150^\circ$ for Cu K α radiations ($\lambda = 1.5418$ Å) were measured by using the θ - 2θ scan technique. A variable scan width of $1.25 + 0.14 \tan \theta$ degrees and a variable horizontal aperture width of $4.2 + 0.86 \tan \theta$ mm were used. A maximum of 60 s was spent on each reflection (40 s for measuring the peak and 10 s for measuring each of the left and right backgrounds). The intensities of three monitor reflections, measured after every 3000 s of X-ray exposure, showed a maximum variation of $\pm 3\%$ for which appropriate scaling corrections were made. The orientation matrix was checked after every 300 measurements. Eighteen reflections were considered indistinguishable from background on the basis that the net count was less than $2\sigma(I)$. Lorentz and polarization corrections were applied to the data, and an experimental weight, based on counting statistics,¹⁴ was assigned to each structure amplitude.

Structure Determination and Refinement. The structure was solved by direct methods, and all nonhydrogen atoms were located from the E map by using the computer program MULTAN.¹⁵ The structure was refined by using a block-diagonal least-squares program initially with isotropic thermal parameters for the C and O atoms and, after a few cycles of refinement, with anisotropic thermal parameters. After several more cycles of refinement all hydrogen atoms were located from a difference Fourier map and were refined isotropically. The R factor, defined as in eq 1, based

$$R = \frac{\sum ||kF_o| - |F_c||}{\sum |kF_o|} \quad (1)$$

on final parameters (Table III, VI, and VIII) was 0.0295 for 1052

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Table III. Positional Parameters ($\times 10^5$) of Carbon and Oxygen Atoms^a

atom	x	y	z
C(1)	92 069 (21)	51 322 (19)	70 876 (17)
O(2)	87 815 (16)	55 508 (15)	55 646 (12)
C(3)	71 959 (24)	66 766 (20)	51 662 (18)
C(4)	54 457 (24)	63 864 (19)	61 670 (20)
C(4a)	61 642 (22)	66 782 (19)	79 059 (18)
C(5)	48 188 (25)	60 029 (24)	91 229 (21)
C(6)	62 822 (27)	57 774 (22)	106 131 (20)
C(7)	81 796 (25)	51 223 (20)	99 502 (19)
C(7a)	83 117 (22)	60 197 (18)	83 811 (17)
O(8)	103 613 (17)	40 808 (16)	73 474 (14)
O(9)	79 450 (18)	81 135 (15)	54 354 (14)
C(10)	35 914 (27)	73 247 (26)	55 990 (24)
C(11)	100 667 (29)	52 063 (23)	111 169 (21)

^a Estimated standard deviations for the last digits are given in parentheses.

Table IV. Integrated Intensities of Proton and Carbon-13 Signals^a for 1c/1a

signal	temp, °C						
	-15	-20	-25	-40	-50	-60	-70
H(3)				80	77	81	79
C(1)	81	75	78				
C(3)	78	78	80				
C(7a)	75	74	75				

^a Expressed as percentage of the major signal. The relative intensity of signals of the minor conformer is 100 minus the figure in the Table.

Table V. Coalescence Temperature of Carbon Signals and Activation Energies for 1c \rightleftharpoons 1a

	C(1)	C(3)	C(5)	C(7a)	Me(10)
coalesec temp, °C	10	10	0	2	-5
ΔG^\ddagger , kcal/mol	14.8	14.6	15.0	15.0	14.7

reflections (0.030 for all reflections). All reflections were used in calculating the standard deviations, and at the final stage of refinement all shifts were less than 0.25σ . A final difference Fourier map showed a maximum residual electron density of $0.2 \text{ e } \text{Å}^{-3}$. The scattering factors for C and O atoms were taken from the literature,¹⁶ and those for H atoms were taken from Stewart, Davidson and Simpson.¹⁷

Determination of the Absolute Configuration. Because of the close agreement between the observed and calculated structure factors, an attempt was made to determine the absolute configuration of nepetalic acid by using the anomalous contribution of the oxygen atoms. Twenty-four pairs of reflections which were most sensitive to the choice of enantiomer were selected for the purpose. The reflections chosen for the experiment were those with the largest sensitivity factor,¹⁴ that is, those reflections which showed the largest calculated values of $(F_+^2 - F_-^2)/\sigma(F_+^2)$. The values of F_+^2 and F_-^2 were calculated according to the method of James.¹⁸ Intensities $I(hkl)$ and $I(\bar{h}\bar{k}\bar{l})$ for the 24 pairs were measured 15 times each. The results are summarized in Table VII.¹⁹ Of the 24 pairs of reflections, 19 reflections indicated the absolute configuration for nepetalic acid structure as shown in the figures, 4 reflections showed opposite absolute configuration, and 1 reflection did not show any indication. $I(hkl)$ and $I(\bar{h}\bar{k}\bar{l})$ were measured by using Cu K α radiation.

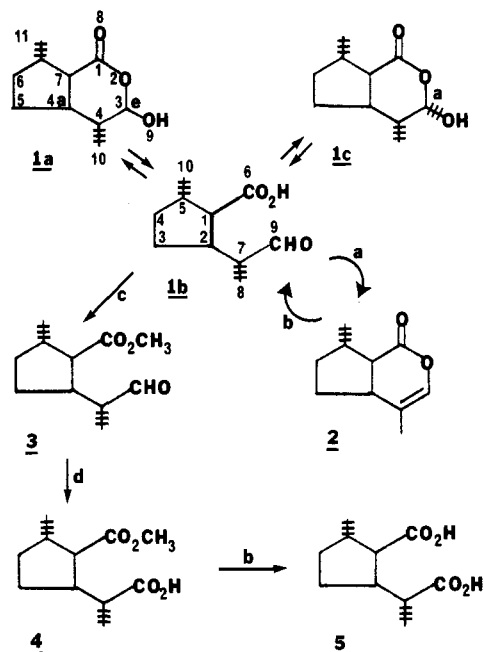
The experiment was repeated with 23 pairs of enantiomorph-

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(19) These data are part of the Supplementary Material which includes the following: Table VI, positional parameters ($\times 10^3$) and isotropic thermal parameters for hydrogen atoms; Table VII, comparison of observed and calculated Bijvoet differences (Cu K α radiation); Table VIII, anisotropic thermal parameters ($\times 10^4$) for C and O atoms; Table IX, structure factors; Table X, exocyclic torsion angles.

Scheme I^a

^a a, Δ ; b, OH^- , H_3^+O^+ ; c, CH_2N_2 ; d, O_2 , C_6H_6 .

sensitive reflections, this time using the anomalous contribution of oxygen atoms for Cu K α radiations. The results were very similar to the results obtained in the previous experiment. The fact that in both experiments, where $I(hkl)$ and $I(\bar{h}\bar{k}\bar{l})$ were measured 15 times each, one absolute configuration has been consistently favored led us to assign the present absolute configuration to nepetalic acid. The anomalous scattering factors for the oxygen atoms were those of Cromer and Liberman,²⁰ and the method employed for the determination of absolute configuration was that of Bijvoet.²¹

NMR Analysis. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 Fourier transform nuclear magnetic resonance spectrometer equipped with a Varian 620/L computer and a Diablo Model 31 disk accessory. The FT software used was a Varian disk FT PN 994120-B. For ^1H NMR spectra the general running conditions were as follows: pulse flip angle, 23° ($90^\circ = 27 \mu\text{s}$), acquisition time, 4 s; pulse delay, 0 s; sweep width, 200 Hz; number of pulses, 20; weighting time constant, -4. For ^{13}C NMR spectra the conditions were as follows: pulse flip angle, 29° ($90^\circ = 50 \mu\text{s}$), acquisition time, 0.8 s; pulse delay, 0° ; sweep width, 2500 or 500 Hz; number of pulses, 400-1000; weighting time constant, -0.8; the data length was doubled by zero filling. A high-field single sideband filter was used for both ^1H and ^{13}C spectra in the receiver. The observed frequency for ^1H spectra was 100.06 MHz, and that for the ^{13}C spectra was 25.16 MHz. Me_4Si was used as an internal standard. ^1H peak positions were measured from a calibrated chart, and the ^{13}C peak positions were measured from a computer line list. The temperatures were measured by insertion of a calibrated 5-mm thermometer (Wilma Glass Co. catalogue No. T-811) into the NMR probe. The temperature stability was $\pm 1^\circ\text{C}$ and the accuracy $\pm 3^\circ\text{C}$.

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Supplementary Material Available: Tables VI-X¹⁹ (11 pages). Ordering information is given on any current masthead page.

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