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Complete Assignment of ^1H and ^{13}C NMR Spectra of *trans*- and *cis*-Myrtanol

Kye-Young Kim and Sueg-Geun Lee*
Chemical Analysis Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusung, Taejeon 305-606, Korea

The proton and carbon spectra of the title compounds were completely assigned by the use of 2D NMR techniques including 2D INADEQUATE. Contradictory assignments from the literature were clarified and incomplete data completed. The validity of the assignments of proton spectra was checked by computer simulation. © 1997 by John Wiley & Sons, Ltd.

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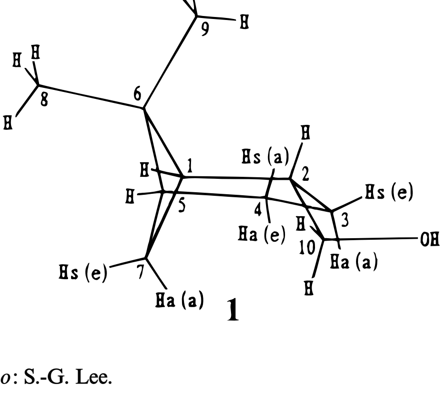
INTRODUCTION

The unique structure of bicyclo[3.1.1]heptane and its derivatives is of great interest, because their geometries are ideal for the study of the relationship between dihedral angle and the magnitude of NMR parameters.[1–3] However, this system presents several particularly troublesome spectroscopic problems. The most obvious of these is that of spectral overlap, which is severe even with 750 MHz NMR.[4] Furthermore, the strong coupling between the spins makes first-order spectral analysis invalid, and the spreading of NOE enhancements led by extended spin systems between the protons gives misleading NOE results. ^1H NMR studies of highly substituted derivatives under the influence of a chemical shift reagent[2,5] allowed the partial assignment of coupling constants.[2] ^{13}C NMR studies also have been used to determine the conformations of bicyclic[3.1.1] derivatives.[6] Numerous NMR approaches, including substituent effects, DEPT, COSY, HETCOR, deuterium isotope shift and ^{13}C–^1H coupling constant studies, have been used to assign the carbon skeleton of these molecules.[1,7–10] However, these indirect approaches resulted in chemical shift assignments that were either completely wrong or, at best, ambiguous, because the proton spectra did not exhibit well resolved signals. In the course of our work on the revision of the ^{13}C chemical shifts of bicyclo[3.1.1]heptane derivatives,[11] we became interested in the analysis of the ^1H NMR spectra of these molecules. Thus, the proton–proton molecular conformation of this system can be established quantitatively by the use of exact coupling constants. In addition, new examples of coupling constants for dihedral angles larger than about 120° can be determined. Here we report the conclusive ^{13}C and ^1H assignments of *trans*-myrtanol (**1**) and *cis*-myrtanol (**2**), representative bicyclic[3.1.1] derivatives, by the combined use of 1D and 2D NMR experiments including 2D INADEQUATE and spectral simulation.



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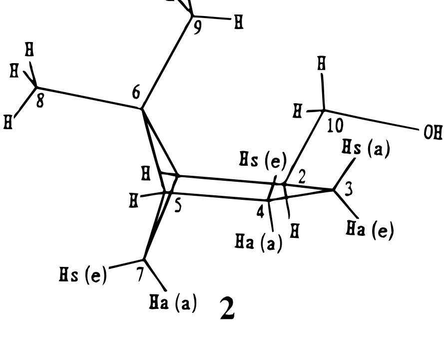

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EXPERIMENTAL

Compounds **1** and **2** were commercially available and used without purification. All NMR spectra were recorded on a Bruker AMX-500 spectrometer. In all cases, a 5 mm Willmad NMR tube was used, and 0.3, 1.0 and 5 M solutions in $CDCl_3$ were used at an ambient probe temperature of *ca.* 21–22 °C. All proton and

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[*] *Correspondence to*: S.-G. Lee.

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carbon spectra were recorded at 500.13 and 125.76 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS, but were measured against the central solvent peaks at 7.24 and 77.00 ppm, respectively. The ^{1}H spectra were collected as 16K data points over a 2000 Hz spectral width using a 30° pulse. The proton decoupled ^{13}C spectra with 30° pulse and DEPT spectra were collected as 16K data points over 7800 Hz (*trans*) and 8600 Hz (*cis*) spectral widths (1.5 and 1.9 s repetition times). Data were processed using exponential multiplication with a 1.5 Hz line broadening.

The ^{1}H–^{1}H COSY[12] spectra were obtained using a COSY-45 pulse sequence. The spectral widths were both set at 1700 Hz. An initial matrix of 1K × 512 data points were zero-filled to give 1K × 1K points and then processed by sinusoidal multiplication in each dimension followed by symmetrization of the final matrix. Four transients with a 1 s delay were accumulated for each of the 512 increments.

In the heteronuclear correlation (HETCOR)[13] experiments, the spectral widths were 7800 Hz in F_2 and 1700 Hz in F_1. The initial matrix of 1K × 256 points was zero-filled to 1K × 512 points. For each increment, 4–16 transients were accumulated with an average $^1J_{CH}$ of 140 Hz and a 1 s relaxation delay.

The 2D INADEQUATE[14] experiments were carried out on 5 M solutions. The spectral width of the F_1 dimension was half that of $F_2 = 7000$ Hz to increase the digital resolution of the F_1 dimension. The initial matrix of 2K × 64 data points was zero-filled to 2K × 512 points and then processed by exponential multiplication (LB = 2.5) in the F_2 dimension and $\pi/2$ shifted sine-bell window in the F_1 dimension to give the final spectrum. For each increment, 64 transients were accumulated; the relaxation delay was 2 s, and the ^{13}C–^{13}C coupling constant was set to 40 Hz (6.25 ms).

For the NOE experiments,[15] two standard spectrometer software (Bruker UXNMR) pulse sequences, noedif and selno, were used. The 1D-NOESY (selno) spectra were obtained using a Gaussian-shaped pulse.[16]

Molecular mechanics calculations were carried out using SYBYL 6.0 (Tripos) and the ^{1}H spectra were simulated using the nine spin version of the NUMARIT program (courtesy of Professor K. Marat, Department of Chemistry, University of Manitoba), which was run on a Bruker X-32 computer.

RESULTS AND DISCUSSION

The ^{13}C 2D INADEQUATE spectrum of *trans*-myrtanol (**1**) is shown in the Fig. 1. All assignments of the 2D ^{13}C spectra were achieved by choosing their characteristic shifts from DEPT spectra as the starting points. That is, the carbon 10 (66.25 ppm) in compound **1** has a correlation peak with the methine carbon at 38.12 ppm which is carbon 2. The methine carbon has correlation peaks with one methine (42.87 ppm) and one methylene carbon (18.79 ppm) which are carbons 1 and 3, respectively. Since this method gives direct proof of the C–C connectivities, we can assign the complete and self-consistent structure unambiguously except for

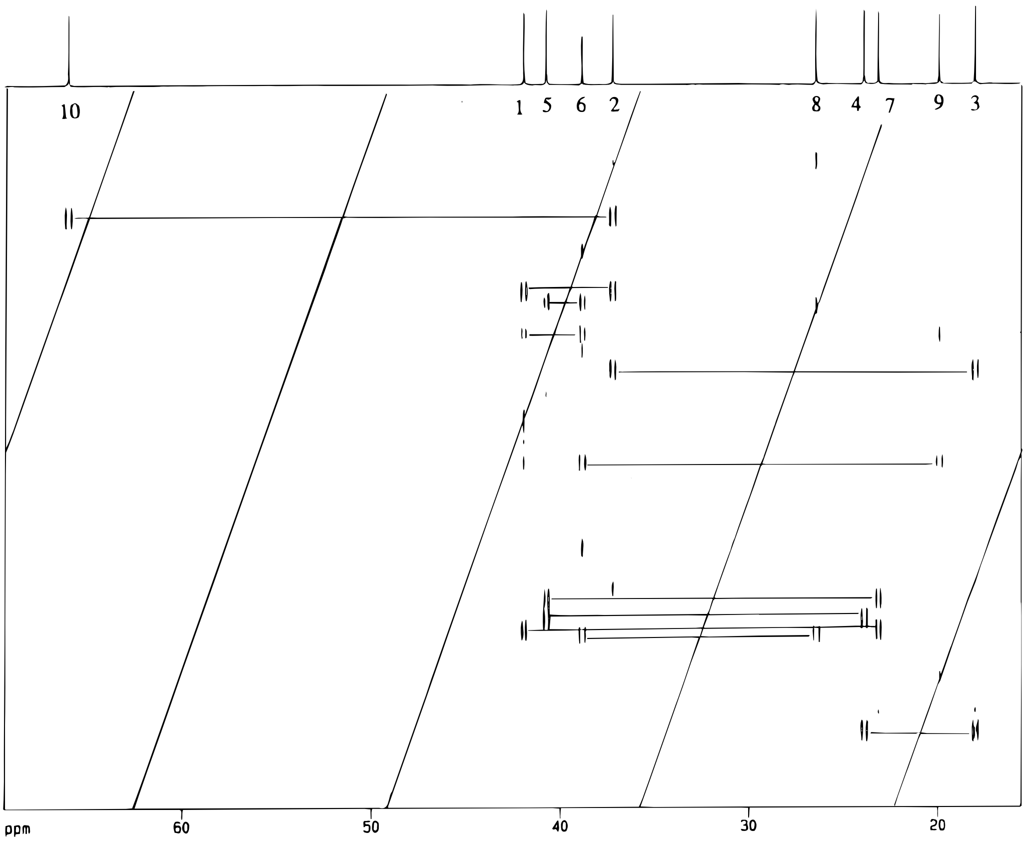

Figure 1. 2D-INADEQUATE spectrum of *trans*-myrtanol (**1**) in CDCl$_3$.

carbons 8 and 9. The assignment of carbons 8 and 9 was accomplished by the use of 2D C–H correlation and NOE experiments (observing NOEs between the 9-methyl and protons of 2 and 4s in *trans*-**1** and between the 9-methyl and protons of 3s and 10 in *cis*-**2**). More dilute concentrations (0.3 and 1.0 M) of sample were also studied to check the sequence of carbon signals by 2D C–H correlation experiments. These experiments showed that the signal sequence in the ^{13}C spectra was not changed with the sample concentrations. The ^{13}C chemical shifts of **1** and **2** in 1 M solutions are shown in Tables 1 and 2. These data support the introductory statements concerning various erroneous assignments in the literature. These results show that some of the earlier spectroscopic inferences are qualitatively usable, for example, the chemical shift differences between the carbon 6 and 7 for the bridged-chair or bridged-boat conformation.[6,8,10] However, the assignments of carbons 1 and 5 and carbons 3 and 4 are reversed in most publications,[1,6] which has led to completely wrong ^{13}C–^{1}H coupling constants and proton chemical shifts from the 2D C–H correlation experiments.

Table 1. ^{13}C and ^{1}H NMR data for compound 1

Atom	^{13}C (δ, ppm)	^{1}H (δ, ppm)	^{1}H–^{1}H coupling constants (Hz)	
1	42.87	1.84	J(1–2) 1.2	J(4s–5) 1.5
2	38.12	2.10	J(1–5) 5.5	J(4s–7s) 1.3
3	18.79	a 1.18	J(1–7s) 5.8	J(4s–4a) 13.5
		s 1.56	J(2–3a) 8.9	J(5–7s) 5.8
4	24.74	a 1.69	J(2–3s) 8.6	J(7a–7s) 10.1
		s 1.77	J(2–7s) 1.5	J(10–10′) 10.4
5	41.58	1.82	J(2–10) 6.5	
6	39.48		J(2–10′) 7.5	
7	23.81	a 1.26	J(3a–4a) 10.2	
		s 1.99	J(3a–4s) 8.9	
8	27.02	1.17	J(3a–3s) 14.6	
9	20.45	0.80	J(3s–4a) 1.3	
10	66.25	3.37	J(3s–4s) 9.0	
		3.34	J(4a–5) 4.5	

Table 2. ^{13}C and ^{1}H NMR data for compound 2

Atom	^{13}C (δ, ppm)	^{1}H (δ, ppm)	^{1}H–^{1}H coupling constants (Hz)	
1	42.79	1.96	J(1–2) 2.0	J(4s–5) 1.0
2	44.26	2.17	J(1–5) 5.1	J(4s–7s) 2.0
3	18.70	a 1.86	J(1–7s) 6.5	J(4s–4a) 13.6
		s 1.39	J(2–3a) 10.0	J(5–7s) 6.4
4	25.91	a 1.82	J(2–3s) 7.0	J(7a–7s) 9.5
		s 1.89	J(2–7s) 0.0	J(10–10′) 10.4
5	41.37	1.85	J(2–10) 7.7	
6	38.52		J(2–10′) 7.6	
7	33.05	a 0.88	J(3a–4a) 10.5	
		s 2.34	J(3a–4s) 3.0	
8	27.87	1.13	J(3a–3s) 14.8	
9	23.23	0.92	J(3s–4a) 5.6	
10	67.53	3.49	J(3s–4s) 11.4	
		3.45	J(4a–5) 5.7	

Except for the chemical shifts of protons 10 and the coupling constants $J_{10,10'}$, $J_{2,10}$ and $J_{2,10'}$, accurate determinations of chemical shifts and coupling constants were impossible on the 1D spectra owing to spectral overlap, the presence of second-order effects and unresolved long-range coupling constants. However, the combination of the information from COSY and HETCOR spectra with 2D INADEQUATE results readily gave the positions of each proton on the carbon skeleton. Then NOE difference spectra were used to distinguish protons 7a and 7s upon saturation of the signal of the methyl protons 8 in both compounds. In compound **1**, proton 1, which is overlapped with protons 4s and 5, was isolated from the overlapped region in the benzene and acetone solvents. Therefore, these spectra were used to determine the coupling constants to give an independent confirmation of the correctness of the corresponding values obtained in $CDCl_3$. However, for **2** the highly overlapped region δ 1.76–1.91, corresponding to protons, 3a, 4a, 4s and 5, was too poorly dispersed for determination of coupling constants in the other solvents. However, the chemical shift and coupling constants of protons 3a, 4a, 4s and 5 in compound **2** were obtained from the 1D slice spectra corresponding column of carbons 3, 4 and 5 taken from the 2D C–H shift correlation matrix. Additionally, homodecoupling experiments were also used to obtain some coupling constants between protons. The NOE difference experiment and the 1D-NOESY spectrum, obtained by Gausian shaped pulse excitation of the methyl protons 9, clearly differentiated protons 4a and 4s in compound **1**. Protons 4a and 4s in *cis*-**2** were distinguished by the coupling constants with 3a and 3s in the 1D slice spectrum of carbon 4 with the aid of the respective dihedral angles H3a—C—C—H4a and H3a—C—C—H4s (10.4° and 105.9°) and H3s—C—C—H4a and H3s—C–C—H4s (123.1° and 6.7°, respectively) calculated by an MM2 molecular mechanics calculation. It has been shown that the coupling constants between the protons on the plane formed by the rather flexible three-carbon bridge in this bicyclic system can be obtained from the dihedral angle by using the Karplus equation.[17] In our case, the experimental vicinal coupling constants are not in good agreement with the calculated coupling constants obtained by MM2 calculations and the Karplus equation modified by the cyclohexane system.[18–20] However, the difference of the coupling constants $J_{3a,4a}$ (10.5 Hz) and $J_{3a,4s}$ (3.0 Hz) obtained from the 1D slice spectrum of carbon 4 was large enough to distinguish the protons 4a and 4s in *cis*-**2** with the aid of the respective dihedral angles (see above). Using all of these observed values, each spectrum was simulated by means of the nine-spin version of the NUMARIT program. The coupled spin system, which consists of 11 spins, is still too large to be handled by this simulation software. Therefore, for *trans*-**1**, the substituted methylene protons were excluded in the simulation. However, the final analysis of the spectrum could be performed, because the other protons, 1, 3a and 3s, gave the coupling constants with proton 2. In *cis*-**2**, the chemical shifts of the protons, 5, 3a, 4a and 4s, and the coupling constants, $J_{3a,4a}$, $J_{3a,4s}$ and $J_{4a,4s}$, were not iterated in the simulation because the change of 1–2 Hz in the chemical shifts and 0.1–0.2 Hz in the coupling constants, obtained from the slice spectrum of the C–H 2D correlation, severely changed the shape of this overlapped spectrum. On the other hand, additional simulations, including complete simulation of proton 2 and simulation with variation of the chemical shifts of 4a and 4s, were done to check the validity of the other values. The agreement between the experimental and simulated spectra of **1** and **2** was excellent.

The chemical shifts and coupling constants of compounds **1** and **2** are given in Tables 1 and 2, respectively. All the final assignments of the chemical shifts of the *syn*(s) and *anti*(a) protons, which belong to equatorial or axial protons of cyclohexane depending on position, are generally valid for the relationship, $\delta H_a < \delta H_e$. However, in compound **1**, the chemical shift of 4a, which is equivalent to the equatorial proton, resonates at higher field than that of the axial proton 4s. This chemical shift order indeed appears to be an anomaly in view of the several reports in the literature along with the chemical shift data for **1** and **2** that are in accord with what is normally found for protons attached to cyclohexane rings.[1]

In summary, this study has shown that the use of high-field NMR with modern pulse techniques, including 2D INADEQUATE along with a simulation program (NUMARIT), leads to the complete and unambiguous analysis of the bicyclic rings of **1** and **2** without the use of chemical shift reagents. It is also evident that some of the spectroscopic inferences made for the bicyclic compounds in previous studies should be reinvestigated.

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