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RE-INVESTIGATION OF THE CONFORMATION OF LAURENOBIOLIDE, A TEN-MEMBERED RING SESQUITERPENE LACTONE BY VARIABLE-TEMPERATURE CARBON-13 NMR SPECTROSCOPY. EVIDENCE FOR THE PRESENCE OF FOUR CONFORMATIONAL ISOMERS IN SOLUTION

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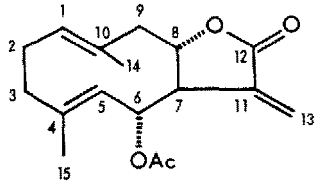
During our research program[1] of seeking for a ten-membered ring sesquiterpene which would provide evidence for the presence of more than two conformational isomers in solution, we found as the first example, that laurenobiolide (1), a ten-membered ring sesquiterpene lactone isolated from Laurus nobilis L.,[2] exists as all four possible conformational isomers of the ten-membered ring in solution suggested by an examination of Dreiding models (see FIG. 1).† Based on variable-temperature 100-MHz ^{1}H NMR spectroscopy, we reported previously that this compound 1 exists in solution as a 8 : 2 mixture of conformations A and B shown in FIG. 1 at low temperatures.[3] However, a recent re-examination of the 220-MHz ^{1}H NMR spectra of 1 suggested that it exists as more than two conformations. Therefore, we studied variable-temperature ^{13}C FT NMR spectra of 1 to find clear evidence for the co-existence of all four conformations.

The ^{1}H-noise-decoupled natural-abundance ^{13}C FT NMR spectrum of 1 in $CDCl_3$ shows merely



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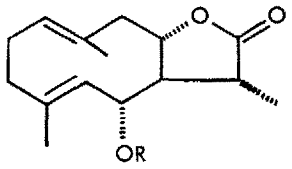

2, R = Ac
3, R = H

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† Five out of eight possible conformational isomers of 3,3-difluoro-trans-cyclodecene were detected earlier by ^{19}F NMR spectroscopy at -152°.[4]

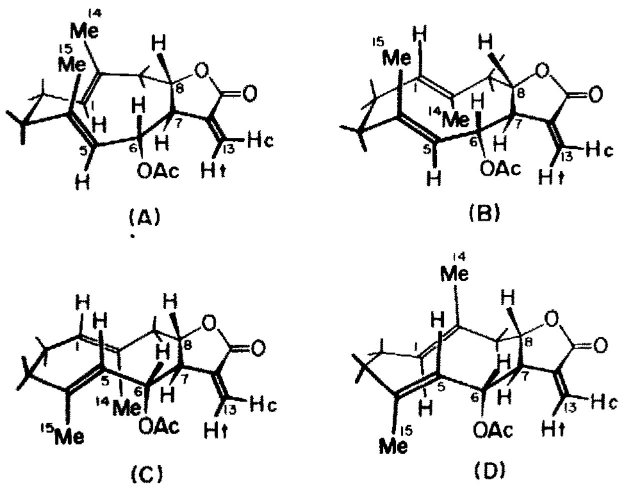

FIG. 1. The four possible conformations of laurenobiolide (1).

broadened signals at ambient probe temperatures. However, these developed into sharper peaks at elevated temperatures (ca. 100°), corresponding to the seventeen carbons in the molecule. At temperatures lower than ca. -15°, each of these signals separated into four sharp peaks with an intensity ratio of about 5 : 4 : 3 : 1 (see FIG. 2). This suggested that each of the four peaks arose from the four major conformations shown in FIG. 1.

Variable-temperature ^{1}H NMR spectra of 1 were further examined in the presence of different amounts of Eu(fod)$_3$-d$_{27}$.[5] With an increase in molar ratio of Eu(fod)$_3$-d$_{27}$ to substrate 1, some signals, each corresponding to one proton at high temperatures, separated into four (or less) signals each corresponding to one proton of each isomer at low temperatures. The intensity ratios of these isomeric signals almost agreed with those obtained from the ^{13}C NMR spectra. Re-examination of various ^{1}H NMR spectra revealed the J values for the major two isomers to be almost equal to those reported,[3] and the J values for the third isomer to be $J_{5,6}$ 5.7, $J_{6,7}$ 10.5, $J_{7,8}$ 5.8, $J_{8,9\alpha}$ 11.5, and $J_{8,9\beta}$ 3.0: J ±0.2 Hz; the signals due to the least abundant isomer were too small to allow estimation of the J values. From the above J values as well as the nuclear-Overhauser-effect results obtained previously,[3] the conformations in the above order were inferred to have forms A, B, C, and D, respectively. The ratio for conformation A previously reported[3] might include C and probably D.

^{13}C NMR spectra of dihydrolaurenobiolide (2) showed two sets of signals, each set corresponding to one conformation in an intensity ratio of about 12 : 1 at room temperature. These sets coalesced at elevated temperatures and collapsed into one set of sharp singlets at 115°. As reported previously,[3] variable-temperature 100-MHz ^{1}H NMR spectra of 2 did not show such a dramatic change in the range

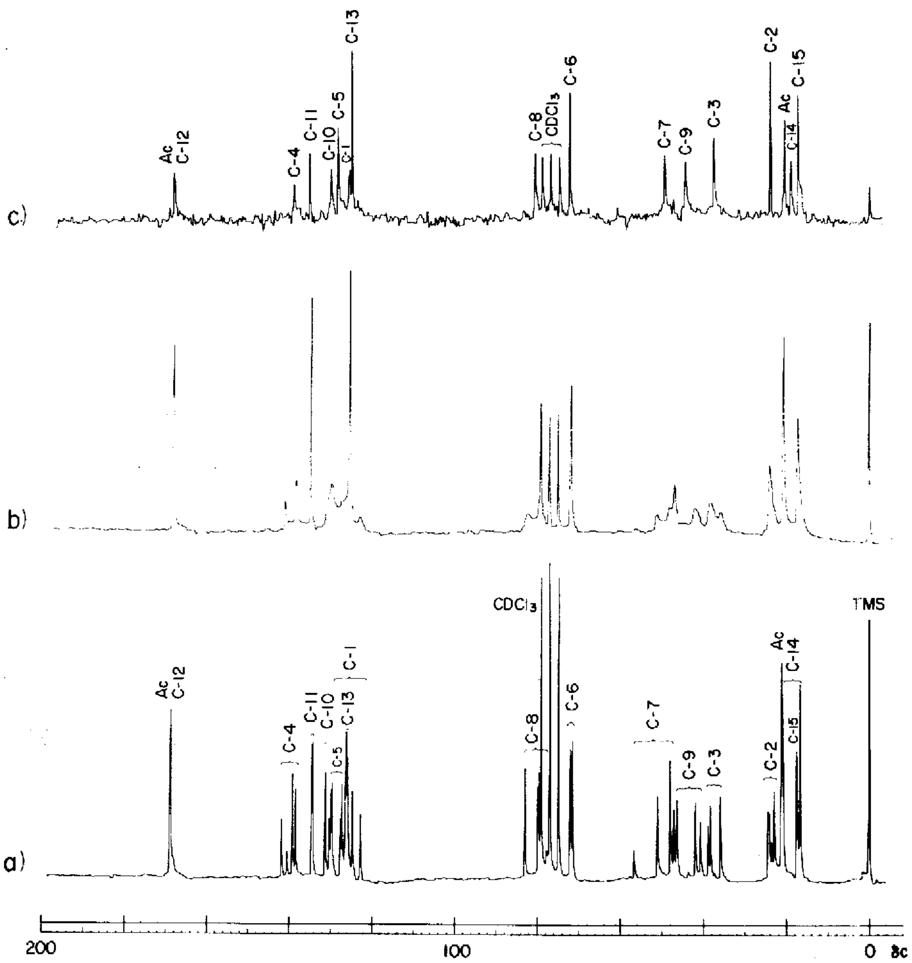

FIG. 2. Variable-temperature ^{13}C NMR spectra of laurenobiolide (1) in $CDCl_3$ at 15.087 MHz. (a) -15°, number of transients, 63,000; (b) 30°, 20,000; and (c) 110°, 18,000.

from -37° to +115° probably because of small chemical shift differences between the corresponding protons in the two conformations. These major and minor isomers seem to correspond respectively to conformations A and B shown in FIG. 1 according to a variable-temperature CD spectral study with application of the exciton theory.[3]

TABLE. ^{13}C Chemical Shift Data, δ_C,[a] and Signal Assignments[b]

Carbon			**1**				**2**			**3**	
No.	A	B	C	D	Av.[c]	A	B	Av.[c]	A	B	Av.[c]
C-1	126.6[d]	125.2	123.2	n	126.2	130.5	125.6[i]	129.7	130.5	125.4	129.3
C-2	22.2	24.4	24.2	23.6	24.1	25.1	23.1	24.8	25.0	22.8	24.4
C-3	36.0	38.3	38.9	n	37.8	38.7	36.3	38.4	38.5	36.2	38.1
C-4	139.8	138.3	142.3	140.9	139.6	138.3	139.3	138.7	135.1	135.8	135.5
C-5	129.9	127.6	128.9	n	128.9	128.3	125.1[i]	127.7	132.6	129.4	131.7
C-6	72.2[e]	71.7[e]	72.2[e]	71.7[e]	72.5	73.1	75.0	73.9	70.8	72.3	71.5
C-7	48.1	51.1	47.2	57.0	49.7	40.8	40.1	40.7	41.1	40.5	40.7
C-8	83.3	80.0	80.1	78.1	81.0	79.4	82.7	80.2	80.0	83.7	80.3
C-9	46.6	42.1	40.9	n	44.7	47.7	43.6	47.2	47.7	43.6	46.9
C-10	131.7	130.3	130.7	n	130.7	130.7	131.9	130.9	130.7	132.3	130.9
C-11	135.0	134.6	135.0[f]	134.6[f]	135.8	57.0	54.2	56.8	59.1	56.2	58.5
C-12	169.4	169.4	169.4	169.4	168.9	177.4	177.4	177.1	179.6	179.6	178.6
C-13	126.6[d]	126.2[d]	126.6[g]	126.2[g]	125.6	17.2	17.2	17.1	17.7	17.7	17.7
C-14	16.7	16.7	20.7	n	19.1	16.6	17.9[j]	17.1[k]	16.6	21.1[l]	17.7[m]
C-15	17.5	17.4	17.5[h]	17.4[h]	17.5	16.9	16.9[j]	17.5[k]	16.6	16.6[l]	16.6[m]
$\underline{C}O\text{-}CH_3$	169.4	169.4	169.4	169.4	168.9	169.2	169.2	169.2	-	-	-
$\overline{C}O\text{-}\underline{C}H_3$	21.1	21.1	21.1	21.1	20.7	20.9	20.9	20.8	-	-	-

[a] ^{13}C NMR spectra were recorded on a Varian NV-14 FT NMR spectrometer at 15.087 MHz using about 1-mmol cm^{-3} solutions in $CDCl_3$ and 8-mm spinning tubes; errors of δ_C (from internal TMS) are about ±0.1. The ^1H NMR spectra were taken with Varian HR-220, HA-100, and A-60A spectrometers in $CDCl_3$ and toluene-$\underline{d}_8$.

[b] ^{13}C signals were assigned using known chemical-shift rules,[6] the ^1H-single-frequency off-resonance decoupling technique,[6] and Eu(fod)$_3$-induced shift method for **2** at 30°;[7] residual indirect $^{13}C,^1H$ coupling patterns in the off-resonance spectra[8] were quite useful. The spectrum of **2** was also compared with that of the deacetyl-derivative (**3**) for assignment purposes;[9] the isomer ratio was ca. 5 : 1 at 10°.

[c] Averaged signal positions in rapid inversion of the ten-membered ring at elevated temperatures.

[d-m] These assignments may be interchanged.

[n] Not determinable.

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