Conformational Isomers of Laurenobiolide, a New Ten-membered-ring Sesquiterpene Lactone

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Summary The ^{1}H n m r and c d spectra of two conformational isomers of laurenobiolide (I) at various temperatures have been examined to determine the conformations and Gibbs' free energy difference of the conformers

THE ^{1}H n m r spectra of a new sesquiterpene lactone, laurenobiolide (I),[1] showed rather broad signals in several solvents at ordinary probe temperature,† variable-temperature n m r studies revealed that this compound exists as two conformational isomers, distinguishable by n m r , in a ratio of *ca* 8 : 2 at low temperatures At temperatures higher than *ca* 100 °C, its spectra show one set of sharp signals implying that (I) has a rapidly inverting ten-membered ring, while at temperatures lower than *ca* −20 °C they exhibit two sets of sharp signals, one set corresponding to each isomer of (I) (see Figure 1), as already reported for isabelin (II)[2] and neolinderalactone (III) [3]

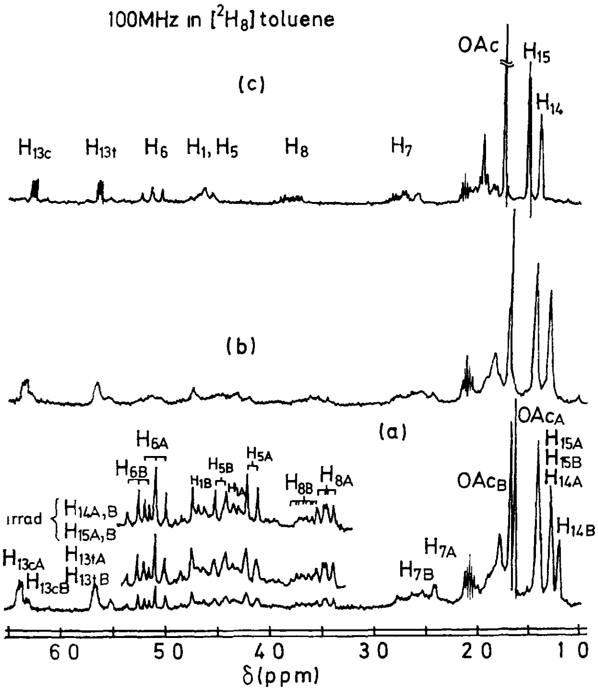
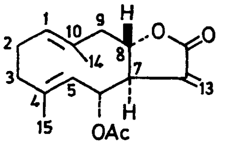
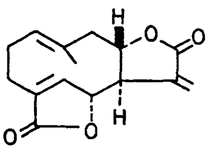


FIGURE 1 *Variable temperature* ^{1}H *n m r of laurenobiolide* (I) *in* [^{2}H$_8$]*toluene at* 100 *MHz* (a) −27 °C, (b) 43 °C, *and* (c) 115 °C

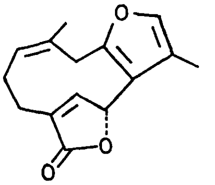
In order to ascertain the conformation of the two conformers (A) and (B) from the four possible isomers predicted from examination of Dreiding models, the double-resonance spectra in [^{2}H$_8$]toluene at −27 °C were examined, the differences in proton chemical shifts between the conformers (A) and (B) being larger in toluene than in several other solvents examined



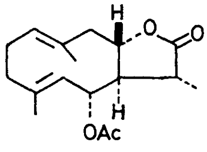
(I)



(II)



(III)



(IV)

The isolated signals due to 1-, 5-, 6-, 7-, 8-, 13c-, and 13t-H of each isomer were assigned by the double and triple resonance experiments Double irradiation of a singlet at δ 1 15 p p m caused an apparent increase in the 5B-H signal area without any decoupling, but caused decoupling of the 1B-H signal without any increase in its area Irradiation of a singlet at δ 1·27 p p m caused a significant increase in the 8A-H signal area (8%) without any decoupling, but caused the decoupling of the 1A-H signal without any increase in its area Therefore, the former and the latter singlet signals irradiated were assigned to 14B-H and 14A-H, respectively On double irradiation at δ 1 41 p p m , distinct increases in signal areas of 1B-, 6A-, 6B-, 8A-, and 8B-H occurred without any appreciable decouplings, while only decouplings were observed for both 5A- and 5B-H signals Thus, the signals at δ 1·41 and 1 40 p p m were assigned to 15A- and 15B-H, respectively The fact that no N O E s were observed between 14- and 1-H or between 15- and 5-H indicates that the two double bonds of (I) are both in *trans*-configuration The triple resonance spectra irradiated at δ 1·22 and 1 41 p p m are shown in Fig 1(a)

The chemical shifts, *J*-values, and intramolecular N O E s[4] obtained for each conformer are listed in the Table The *J* (5,6), *J* (6,7), and *J* (8,9) values and the N O E values determined the conformations (A) and (B) as shown in Figure 2

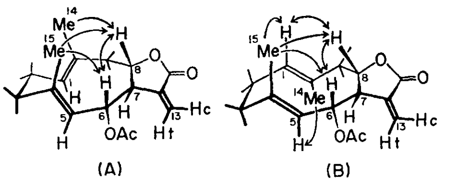


FIGURE 2 *The conformations of laurenobiolide* (A) *major isomer,* (B) *minor isomer Arrows indicate the observations of positive* N O E s

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† There are *J*-values for structural determination were unobtainable

TABLE

Chemical shifts (δ*/p.p.m. downfield from* $\mathrm{Me_4Si}$), *coupling constants* (J*/Hz*), *and nuclear Overhauser effects* (%) *obtained for the major* (A) *and minor* (B) *conformers of laurenobiolide* (I) *in* $[^2\mathrm{H}_8]$*toluene at* −27 °C *and in* $\mathrm{CDCl_3}$ *at* −37 °C (*in parentheses*)[a]

		Signal									
		1-H	5-H	6-H	7-H	8-H	13c-H	13t-H	14-H	15-H	OAc
Conformer (A)	δ	4·35 (4·85)	4·19 (4·73)	5·11 (5·24)	2·48	3·49 (4·05)	6·41 (6·39)	5·68 (5·95)	1·27 (~1·68)	1·41 (~1·68)	1·64 (2·09)
	N.O.E.[b]	c	9 [7-H]	[8-H] 11 [15-H]		10 [6-H] 8 [14-H] 5 [15-H]					
	$\lvert J \rvert$	(5,6) = 10·2, (6,7) = 10·2, (7,8) = 7·0, (8,9α) = 9·2, (8,9β) = 0·5, (7,13c) = 3·0, (7,13t) = 2·7, (13c,13t) = 1·5									
Conformer (B)	δ	4·67 (4·90)	4·50 (4·71)	5·28 (5·36)	2·70	3·71 (3·98)	6·34 (6·39)	5·54 (5·97)	1·15 (~1·68)	1·40 (~1·68)	1·68 (2·12)
	N.O.E.[b]	c [8-H] [15-H]	c [14-H] [7-H]	8 [8-H] 11 [15-H]		c [1-H] [6-H] 5 [15-H]					
	$\lvert J \rvert$	(5,6) = 10·2, (6,7) = 10·2, (7,8) = 5·0, (8,9α) = 11·2, (8,9β) = 4·4									

[a] The spectra were recorded on a Varian HA-100 spectrometer in the frequency-swept and $\mathrm{C_6H_6}$- or $\mathrm{Me_4Si}$-locked mode using about 8% (w/v) carefully degassed solutions containing 1% $\mathrm{Me_4Si}$ as internal reference. [b] For the N.O.E. measurements, see ref. 2c. Proton signals saturated are shown in square brackets. [c] Positive N.O.E. was clearly observed, but exact figures were undeterminable owing to the overlapping of signals.

Variable-temperature c.d. data should provide information about the Gibbs' free-energy difference of the conformers.[5] The c.d. curves of (I) in ethanol and dioxan show a negative maximum $\{[\theta]_{253} - 5660$ (EtOH) and $[\theta]_{258} - 4790$ (dioxan)$\}$ associated with the n-π^* transition of the unsaturated lactone and a positive maximum $\{[\theta]_{208} + 43{,}800$ (EtOH)$\}$ in the region of the π-π^* transition. Examination of the temperature dependence of the negative part of the c.d. curve at 255 nm in ether–pentane–ethanol–($R_0^{+24°} = -3{\cdot}76 \times 10^{-40}$, $R_0^{-68°} = -4{\cdot}45 \times 10^{-40}$, and $R_0^{-190°} = -5{\cdot}52 \times 10^{-40}$ c.g.s.) permits calculation of the free-energy difference between the two conformers on the assumption that they are the only preferred forms. The energy difference proved to be 0·74 kcal mol^{-1}, and thus the stable conformer represents *ca.* 80% of the mixture at 25 °C. This finding is consistent with the n.m.r. result.

Application of the exciton theory to the conformers (A) and (B) suggests that they would respectively give a markedly positive and a negative c.d. band associated with a lower energy π-π^* transition. Therefore, the observed positive c.d. band at 208 nm suggests that the conformation (A) is more stable than (B). This suggestion is supported by the examination of the temperature dependence of the positive c.d. band near 216 nm of dihydrolaurenobiolide (IV, $[\theta]_{217\cdot5}^{24°} + 129{,}000$, $[\theta]_{216\cdot5}^{-68°} + 162{,}000$, and $[\theta]_{215\cdot5}^{-190°} + 209{,}000$ in ether–pentane–ethanol); the result leads to a value of 0·72 kcal mol^{-1} for the free-energy difference between the two conformers assumed for (IV), which is similar to those for (I). The variable-temperature 100 MHz ^{1}H n.m.r. spectra of (IV) in several solvents showed no significant changes in signal shapes down to −37 °C; from this fact, its ten-membered ring is inferred to be rapidly inverted on the n.m.r. time scale.

The potential barrier to inversion of the ring of (I) could not be determined because none of the 100 MHz ^{1}H n.m.r. spectra in several solvents have suitable signals; in $[^2\mathrm{H}_8]$-toluene, unfavourable chemical shift changes due to interaction with the solvent[6] also interfere with determination of the potential barrier.

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