Tetrahedron Letters No. 19, pp 1753 - 1756, 1974. Pergamon Press. Printed in Great Britain.

ABSOLUTE CONFIGURATION AND CONFORMATION OF CONFERTOLIDE, A GERMACRANOLIDE ISOLATED FROM VERNONIA CONFERTA

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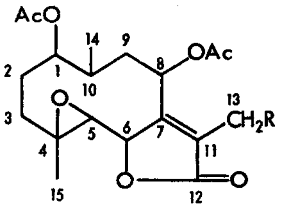
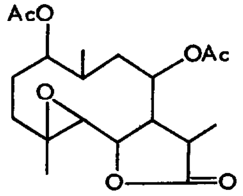
(Received in Japan 23 March 1974; received in UK for publication 1 April 1974)

Recently,[1] we have reported the structure elucidation of a new germacranolide, confertolide (**1**), isolated from Vernonia conferta,[2] on the bases of chemical and spectroscopic evidence. We wish to report here the absolute configuration and the conformation of **1** determined by intramolecular internuclear Overhauser effect (NOE)[3] and CD spectroscopic measurements. The stereostructures of 13-deacetoxyconfertolide (**2**)[1] and its dihydro derivative (**3**)[1] are also described.



(**1**, R = OAc)
(**2**, R = H)



(**3**)

The 100 MHz ^1H NMR spectrum of **1** in $CDCl_3$ shows isolated signals due to H-1, H-5, H-6, H-8, H-13, H-14, H-15, and OAc (see the Table). On double irradiation of the H-15 singlet, integrated intensities of the H-1 multiplet and the H-6 doublet signals were increased by 10 and 18%, respectively, whereas no changes in the other isolated signals were observed. Saturation of the H-5 doublet causes a collapsing of the H-6 doublet and vice versa, but with no increase in its intensity. When the H-14 signal

Table

Chemical Shift (δ) Data in $CDCl_3$[a]

Compound	H-1	H-5	H-6	H-7	H-8	H-10	H-11	H-13	H-14	H-15	OAc
1	5.24m	2.77d	4.90d	---	5.29d	2.06m	---	4.87s	0.93d	1.77s	2.06s 2.08s 2.08s
2	5.26m	2.72d	4.82d-q	---	5.26d	~2.2m	---	1.95d	0.93d	1.78s	2.08s 2.11s
3	4.93m	3.65d	4.21q	2.64m	5.14m		2.79d-q	1.14d	1.04d	1.45s	2.02s 2.04s

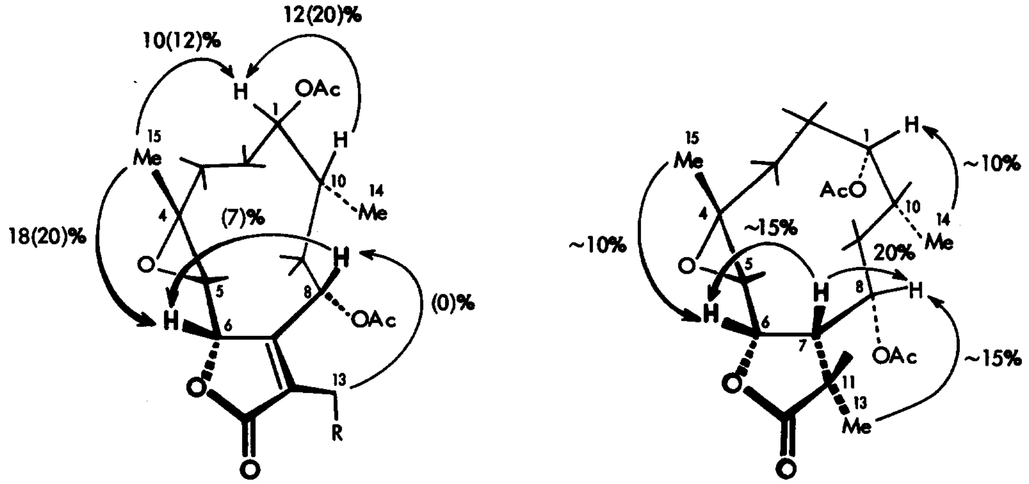
[a] The ^{1}H NMR spectra were taken with a Varian HA-100 spectrometer operating at 100 MHz in the frequency-swept and internal-Me_4Si-locked mode. NOE experiments were carried out as described previously.[4] Accuracies of chemical shifts (δ), coupling constants (J in Hz), and NOE enhancements (%) are about ±0.01 ppm, ±0.1 Hz, and ±2% (±5% in the case of **3**, owing to its small sample quantity), respectively.

was irradiated, no changes in the isolated signals were found, but the approximate position (δ 2.06) of the H-10 signal was revealed. Thus, irradiation at δ 2.06 was found to cause a 12% increase in the H-1 signal intensity.

On the basis of these NOE experiments and from the J-values shown by these signals, one reasonable conformation for the molecule of **1** can be depicted as shown in FIG. (A), by examining Dreiding models.[†] However, even though the axial nature of H-8 could be assumed from the absence of long-range coupling between H-8 and H-6 signals,[5] the stereochemistry around C-8 is still ambiguous since NOE experiments cannot be done owing to the mutually close positions of the H-6, H-8, and H-13 signals. Examination of the spectrum of **1** in a C_6D_6 solution was also of little help in this problem.

The spectrum of the deacetoxy derivative **2** was therefore examined (see the Table). In this case, besides several results similar to those obtained with **1**, the following confirmatory evidence for the stereostructures was provided by NOE experiments. Double irradiation of the H-8 signal caused a 7% enhancement in the H-6 signal intensity. On the other hand, no NOE was observed on the H-8 signal on saturation of the H-13 signal. Here, the large long-range ^4J value[5] (2.0 Hz) was found between the H-6 and H-13 signals. As a result, molecules **1** and **2** are best suggested to adopt conformations (A) and (B) (see the FIGURE), respectively, in solution.

[†] Configurations of OAc at C-1 and Me at C-10 have tentatively been assigned from the NOE results only.



(A) R = OAc

(B) R = H (values are given in parentheses)

$J_{5,6} = 9.5$ (9.6); $|J_{6,13}| = (2.0)$; $|J_{6,8}| \approx (0.1)$;

$J_{8\beta,9\alpha} = 8.0$ (8.0); $J_{8\beta,9\beta} \approx 0$ (0) Hz

(C)

$J_{5,6} = 9.0$; $J_{6,7} = 4.3$; $J_{7,8} = 3.0$;

$J_{7,11} = 7.0$; $J_{11,13} = 7.0$; $|J_{6,8}| = 0.2$ Hz

FIGURE. The conformations, NOE values, and J values for **1**, **2**, and **3**.

It can be expected that reduction of the C-7 : C-11 double bond of **2** may cause a considerable change in the conformation of its ten-membered ring. Several NOE measurements on the spectrum of **3** in $CDCl_3$ (see the TABLE) have thus been carried out to elucidate the stereostructure as well as the conformation of this molecule. The NOE enhancements observed on the H-6 quartet (~15%) and the H-8 multiplet (~20%) on double irradiation of the H-7 signal, that observed on the H-8 signal (~15%) by saturating the H-13 doublet, and J-values concerning the H-7 signal [see FIG. (C)] gave conclusive evidence for the stereochemistry around the lactone ring. Moreover, in this case, saturation of the H-14 resonance caused an increase in the signal intensity of the H-1 by about 10%, whereas no increase in its signal intensity was caused by irradiating the H-15 signal. Thus, an examination of Dreiding models on the basis of these results suggested that the molecule of **3** has the stereostructure as represented in FIG. (C).†

Incidentally, comparison of the chemical shifts of the compounds listed in the Table shows a large downfield shift of the H-5 signal and a considerable upfield shift of the H-15 signal on going from **1** or **2** to **3**. This fact is compatible with difference in molecular structure between **1** or **2** and **3**, the chemical shift changes resulting mainly from the presence or absence of anisotropic shielding effects exerted by the C-7:C-11 double bond.[6] Since the oxirane ring anisotropy[7] has a different effect upon H-1 in **1** or **2** from that in **3**, the upfield shift of the H-1 signal is also explained by the models.

Evidence for the absolute configuration of **1** may now be provided by CD data on **1** or **2**, in which an αβ unsaturated γ lactone is fused through C_β and C_γ to a ten-membered ring. The CD spectra of **1** ($[\theta]_{249}$ +2,420 and $[\theta]_{222}$ -15,676 in MeOH) and **2** ($[\theta]_{248}$ +2,910 and $[\theta]_{215}$ -25,460 in isooctane) thus indicate[8] the absolute configuration for **1** as well as the preferred conformation as represented in FIG. (A).

Acknowledgement. We thank Dr. G. Lukacs of this Institute for his stimulating discussion.

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