

## THE CONFIGURATION AND CONFORMATION OF ISOGERMACRONE. THE SIGNIFICANCE OF CROSSED CONFORMATIONS IN OLEFINIC CYCLISATIONS

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**Abstract**—The 9,10-double bond of isogermacrone was assigned the *Z* configuration based on  $^1\text{H}$  NMR nOe measurements and the  $^{13}\text{C}$  NMR shifts of the methyl groups. An X-ray crystal structure determination verified this conclusion and the structure of isogermacrone was shown to be (2*Z*,7*E*)-3,7-dimethyl-10(1-methylethylidene)-2,7-cyclodecadien-1-one (1). The molecule crystallised in an *anti* conformation, which according to  $^1\text{H}$  NMR is the predominant conformation in solution at room temperature.  $^1\text{H}$  NMR spectroscopy revealed the presence of *syn* and *anti* conformers in the ratio 1:2 at about  $-60^\circ$ . The stereochemistry of the base-induced formation of isogermacrone (1) from germacrone (2) and that of the transannular cyclisation of isogermacrone are discussed.

Isogermacrone (1) is formed by base isomerisation of germacrone (2),<sup>1-3</sup> and it has also been reported to be a naturally occurring constituent of *Geranium macrorrhizum* L.<sup>4</sup> It has been used as a suitable model for studies of transannular cyclisations of cyclodeca-1,6-diene systems.<sup>1</sup> Isogermacrone has been inferred as a biogenetic precursor of the tricyclic sesquiterpene ketone germazone.<sup>5</sup> The photolysis of isogermacrone has also been studied with the objective of obtaining germazone.<sup>4,6,7</sup>

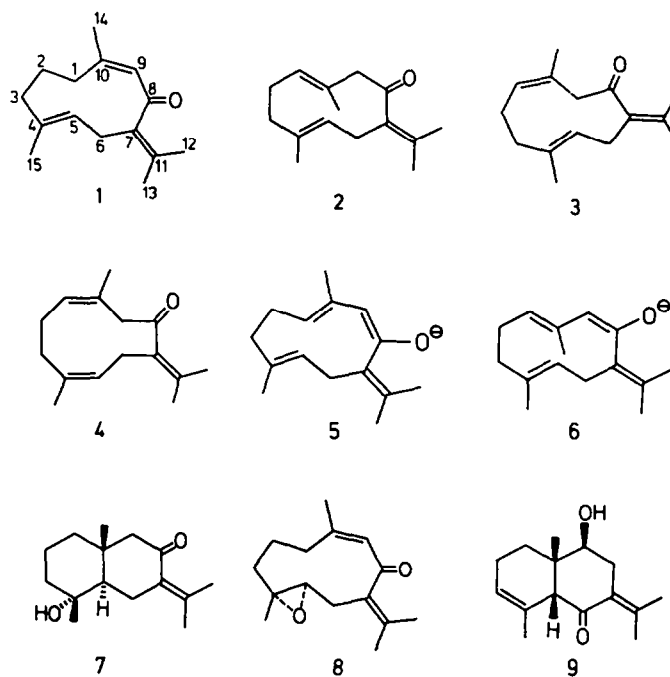
A correct assignment of the configurations of the olefinic bonds in isogermacrone is of particular importance for the interpretation of cyclisation mechanisms. The *E* configuration of the 4,5-bond follows from the formation of isogermacrone (1) from germacrone (2), which has the *E,E* configuration.<sup>8</sup> However, the configuration of the 9,10-bond has not been firmly established. A *9E* configuration has tentatively been proposed based on allylic  $^1\text{H}$ - $^1\text{H}$  couplings, which are difficult to interpret. Herein we present conclusive evidence for the structure of isogermacrone and NMR studies provide information about its conformations. Previous results of metal-assisted cyclisations of isogermacrone will also be discussed in view of this structural information.

The nuclear Overhauser effect (nOe) is a powerful tool for the assignment of the configuration of trisubstituted double bonds and this technique has frequently been used effectively on terpenoids.<sup>3,9</sup> The 14% enhancement of the C(9) proton when the C(10) methyl protons were irradiated in comparison with a nOe of 2% of the C(5) proton when the C(4) methyl protons were irradiated clearly establishes the *Z* relationship of the 9,10-double bond of isogermacrone (1). Further evidence for the 4*E*,9*Z* configuration of isogermacrone (1) followed from a comparison of the  $^{13}\text{C}$ -data with that of various *E* and *Z* isomers of the related germa-

crones 2,<sup>10</sup> 3, and 4.<sup>11,12</sup> (Table 1). A methyl carbon on a trisubstituted double bond of an *E* configuration appears in the range of 15–18 ppm, while the methyl carbon in a *Z* relationship appears at about 20–26 ppm.<sup>13</sup> The shift values of 14.9 and 22.9 ppm for isogermacrone (1) are in accordance with the 4*E*,9*Z* configuration.

Conclusive evidence for the 4*E*,9*Z* configuration of isogermacrone (1) was obtained using X-ray diffraction technique. The structure of isogermacrone is depicted in Fig. 1. Bond lengths and angles were found to be normal (data deposited at Cambridge Crystallographic Data Centre). The torsion angle C(3)–C(4)–C(5)–C(6) is  $163^\circ$  indicating a strained 4*E* double bond in accordance with previous observations on germacradienes. In the solid state the molecule adopts an *anti* orientation of the methyl groups at C(4) and C(10). A similar conformation of the cyclodecadiene was found in tuliranol acetate, which is a 4*E*,9*Z*-germacranolide.<sup>14</sup> Molecular mechanics calculations on *E,Z*-cyclodeca-1,6-diene have also shown that this conformer is of low enthalpy.<sup>15</sup> In contrast, *E,E*-germacra-1,5-dienes crystallised with the C(4) and C(10) methyl groups in the *syn* orientation.<sup>16</sup>

The ring system of isogermacrone (1) in solution is flexible. At room temperature the  $^1\text{H}$  NMR spectrum of isogermacrone (1) reflects a rapid equilibrium between various conformers. When recorded at temperatures below  $-60^\circ$  the spectrum exhibits contributions from two separate conformations in the ratio of 2:1, which is clearly shown by the duplications of the signals of the olefinic protons. The significant nOe (6%) at room temperature on the olefinic C(5) proton upon irradiation at the frequency of the C(10) methyl protons indicates that the predominant conformer is the one with the C(4) and C(10) methyl groups in an *anti* relationship (Fig. 2, 1A). The *syn* conformer (Fig. 2, 1B)



appears to be responsible for the minor signals in the low temperature  $^1\text{H}$  NMR spectrum.

Isogermacrone (1) is readily formed in a high yield by base-induced isomerisation of germacrone (2).<sup>1,2</sup> The isomerisation must proceed *via* an anion species that has a conformation with the C(4) and C(10) methyl groups in an *anti* relationship which schematically can be represented by 5. This intermediate provides the correct steric arrangement for the formation of the 9*Z* double bond of isogermacrone (1). The formation of a 9*E* isomer must proceed *via* an arrangement represented by 6 which is sterically unfavoured.

The previously studied<sup>1</sup> transannular mercuric acetate induced cyclisation of isogermacrone to a *trans* decalin derivative 7 must have taken place from the lower populated *syn* conformation where the endocyclic double bonds are in a crossed arrangement.

It is interesting to note that the acid catalysed cyclisation of the isogermacrone epoxide 8 also proceeds *via* a *syn* conformer to yield the *cis* eudesmane derivative 9.<sup>17</sup>

A crossed arrangement of carbon-carbon double bonds in concerted electrophile-induced cyclisations of

olefins appears to be a general feature in olefinic cyclisations. This stereoelectronic factor may also govern the stereochemistry of many terpenoids during biosynthesis.

#### EXPERIMENTAL

**NMR Data.** NMR spectra were recorded in  $\text{CDCl}_3$  on a Bruker WP 200 instrument. The  $^1\text{H}$  NMR data has been reported earlier.<sup>1</sup> The sample for the nOe measurements was treated several times by the freeze-pump-thaw cycle before vacuum-sealing the tube. The nOe difference technique was used as described by Hall and Sanders<sup>18</sup> and the spectra were collected with the decoupler turned off during pulse and acquisition preceded by 10 s of irradiation either in or out of resonance.

The olefinic protons appeared at 5.16 and 6.01 ppm at 21°. The separation of these peaks started to be visible at -60° and at -70° the signals resolved at 5.05, 5.23, 6.02, and 6.18 ppm.  $^{13}\text{C}$  NMR data are presented in Table 1.

**Crystal data.** Isogermacrone (1) was recrystallised from EtOH (95%). A crystal fragment measuring  $0.22 \times 0.16 \times 0.08$  mm was mounted in a glass capillary. The diffraction data were collected at room temperature by a Syntex P2<sub>1</sub> four-circle computer controlled diffractometer using  $\text{MoK}_\alpha$  radiation ( $\lambda$  0.71069 Å). Cell parameters were determined from a

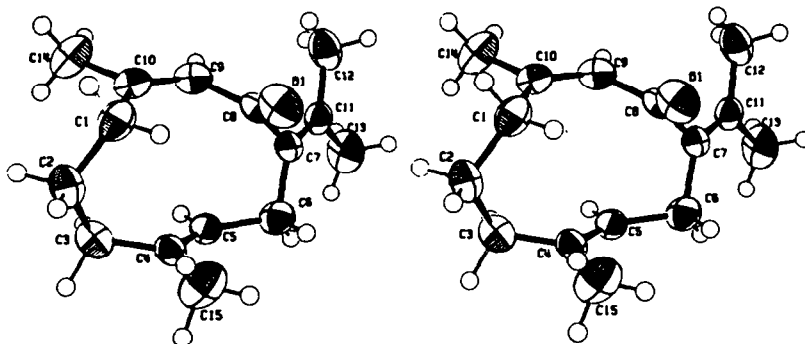


Fig. 1. An ORTEP<sup>20</sup> stereoscopic view of isogermacrone. The hydrogen atoms have been given a *B* value of 1 Å<sup>2</sup>.

Table 1.  $^{13}\text{C}$  NMR data of compounds 1, 2, 3 and 4. The chemical shifts are reported in ppm

	$\lambda^a$	$\lambda^b$	$\lambda^c$	$\lambda^c$
C1	30.2t <sup>e</sup>	132.5d		
C2	21.2t	24.1t	29.2	30.0
C3	39.9t <sup>e</sup>	38.1t	38.2	31.4
C4	135.9s <sup>f</sup>	137.4s		
C5	123.0d	125.4d		
C6	28.0t <sup>d</sup>	29.2t	29.4	25.8
C7	128.6s <sup>f</sup>	129.1s		
C8	204.4s	207.1s	209.4	208.2
C9	130.6d	55.8t	48.3	
C10	149.4s <sup>f</sup>	126.6s		
C11	135.3s <sup>f</sup>	134.7s		
C12	19.5q <sup>g</sup>	19.8q	20.0 <sup>e</sup>	22.1 <sup>e</sup>
C13	21.7q <sup>g</sup>	22.3q	25.6 <sup>e</sup>	23.5 <sup>e</sup>
C14	22.9q <sup>d</sup>	16.7q <sup>e</sup>	26.3	26.5
C15	14.9q <sup>d</sup>	15.6q <sup>e</sup>	18.1	24.9

<sup>a</sup>Recorded at 50.3 MHz in  $\text{CDCl}_3$  with TMS as internal standard. Multiplicities were determined by off resonance decoupling. <sup>b</sup>Ref. 10a (cf. also Ref. 10b). <sup>c</sup>Ref. 12. <sup>d</sup>Assigned by single frequency decoupling. <sup>e,f,g</sup>Assignments are interchangeable.

least-squares fit of 18 reflections. The intensity data were measured by the  $\omega$ -scan mode with variable scan speed, minimum  $0.49^\circ \text{ min}^{-1}$ . During data collection four check reflections were measured every 50 reflections and their intensities varied by 3% without a trend. The number of reflections with  $I > 1.96(I)$  was 1120, 1208 reflections were unobserved.

Fig. 2. Schematic stereodrawings of the *anti* (1A) and the *syn* (1B) conformations of isogermacrone.

Isogermacrone,  $\text{C}_{15}\text{H}_{22}\text{O}$ ,  $M = 218.33$ , monoclinic, space group  $P2_1/n$ ,  $a = 6.499(4)$ ,  $b = 7.908$ ,  $c = 25.750(8)$  Å,  $\beta = 89.73^\circ$ ,  $V = 1323$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.10 \text{ g cm}^{-3}$ ,  $D_m$  (floatation)  $= 1.1 \text{ g cm}^{-3}$ ,  $\mu = 0.7 \text{ cm}^{-1}$ . The structure was solved by direct methods using the program MULTAN.<sup>19</sup> E-Maps were calculated from 142 reflections with  $E > 1.75$ . The solution with the highest figure of merit gave the positions of all non-hydrogen atoms. The structure was refined by full-matrix least-squares method. All the hydrogen atoms were found from Fourier difference maps and were included in the refinement. The final agreement factor  $R$  was 0.046 using a restricted data set of 839 reflections with  $\sin \Theta/\lambda < 0.48$ . With the complete data set of 1120 reflections, an  $R$  value of 0.067 was obtained. The function minimised in the least-squares calculations was  $\sum w_i(|F_o| - |F_c|)^2$ . The weights  $w_i$  were calculated from  $1/\sigma^2(F_o) + (0.01/F_o)^2$ . The goodness-of-fit  $(\sum (F_o - F_c)^2/(m - s))^{1/2}$ , where  $m$  is the number of observations and  $s$  is the number of parameters, was 1.78 and 1.76 for the full data set. All parameter shifts in the last cycle were less than 1% of  $\sigma$ , and a final difference map showed no peak larger than  $0.12 \text{ e Å}^{-3}$ . The final atomic coordinates are deposited with Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, U.K.

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