Tetrahedron. Vol. 29, pp. 271 to 274. Pergamon Press 1973. Printed in Great Britain

CONFORMATIONS OF 10-MEMBERED RINGS IN BICYCLOGERMACRENE AND ISOBICYCLOGERMACRENE

K. NISHIMURA
The Central Research Institute, Suntory Ltd., Dojimanaka, Kita-ku, Osaka, 530 Japan

and

I. HORIBE and K. TORI*
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553 Japan

(*Received in Japan* 3 *August* 1972; *Received in the UK for publication* 6 *October* 1972)

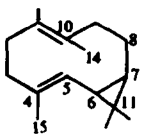
Abstract—The configurations of the endocyclic double bonds and the conformations of 10-membered rings in bicyclogermacrene (1) and isobicyclogermacrene (3), sesquiterpenes containing a fused 1,1′-dimethylcyclopropane ring, have been elucidated in solution by the use of intramolecular nuclear Overhauser effects. Compounds 1 and 3 adopt conformations A and C, respectively; the double bonds of the former have *trans,trans*-orientation, and those of the latter *trans,cis*-orientation.

In a previous paper, the structure of bicyclogermacrene (1), a sesquiterpene isolated from the cold-pressed peel oil of *Citrus junos*, was reported.[1] On being heated at 200°, 1 afforded a mixture of 1, bicycloelemene (2),[2-5] and isobicyclogermacrene (3) in ratios of 4:5:1 after the first 30 min, and 1:1:8 after 2 hr, respectively; 2 was also changed, in a similar manner, into a mixture of 1, 2, and 3 in ratios of 4:3:3 after 30 min, and 1:1:8 after 2 hr, respectively, but 3 was quite stable on thermal treatment. Thus, the double bonds in 1 were concluded to be *trans*, *trans*, and 3 was proposed as the corresponding *cis*,*trans*- or *cis*,*cis*-cyclodeca-1,5-diene derivative.[1]

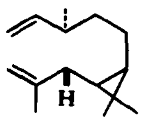
Further, the conformation of 1 has been inferred to be represented by the stereostructure A having both double bonds in *trans*-configuration,[5] by applying an empirical rule[6] proposed for the stereochemistry of the Cope rearrangement to the absolute configuration of 2 elucidated recently.[5]

A number of workers[1,7] have postulated that 1 and 3 are the biogenetically common precursors of other sesquiterpenes containing a fused 1,1′-dimethylcyclopropane ring, such as maaliane-, aristolane-, and aromadendrane-derivatives, which may be expected to be derived from 1 or 3 depending upon the conformations of their 10-membered rings.

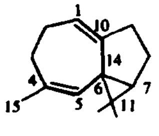
It is, therefore, of key importance to determine the configurations of the double bonds and the conformations of 10-membered rings in 1 and 3. In this paper, the stereochemistry of 1 and 3 are elucidated by the use of intramolecular nuclear Overhauser effect (NOE).[8]



1



2



3

The 100 MHz NMR spectrum of 1 was measured in acetone-d_6 because most of the important signals appear clearly separated in this solvent (Fig 1a). No appreciable changes in spectral features were observed from 70° down to −40°. Therefore, the following experiments were carried out at ordinary probe temperature (35°). The assignments of the isolated signals due to 1-H, 5-H, 6-H, 7-H, 4-Me, 10-Me, and 11-Me_2 were confirmed by double- and triple-resonance techniques. The NMR parameters obtained are listed in Table 1.

Saturation of the 10-Me and the 4-Me signals by double irradiation caused no increases in the integrated intensities of the 1-H and 5-H signals, respectively; this fact demonstrates that the Me group and the hydrogen on both trisubstituted-ethylenic double-bonds in 1 are in *trans* relationships,[9] as previously concluded.[1,5]

Hence, examination of Dreiding models suggests the two major conformations A and B shown in Fig 2 for the 10-membered ring in 1. Other conformations seem highly improbable in view of steric hindrance. Among several NOE's expected to be observable for each conformation, the most im-

---

*Correspondence should be addressed to this author.

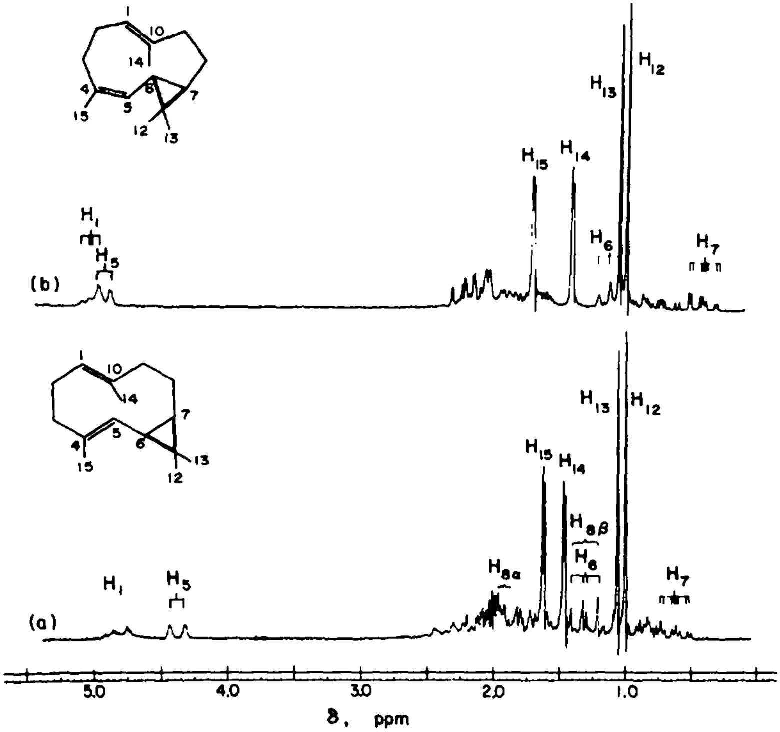
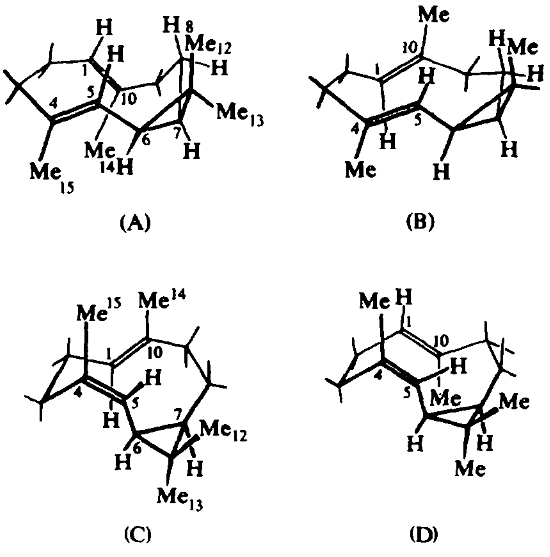


Fig 1. NMR spectra of (a) bicyclogermacrene (1) in acetone-d_6 and (b) isobicyclogermacrene (3) in $CDCl_3$ at 100 MHz.


(A) (B)

(C) (D)

Fig 2. Possible molecular conformations for 1 and 3.

portant are those between the 1-H and 8β-H signals for conformation A, and between the 10-Me and 8β-H signals for conformation B; NOE's between the 5-H and 8β-H signals, and between the 11β-Me and 5-H signals should be observed for both conformations. Therefore, assignment of the 8β-H signal becomes necessary.

Several peaks of multiplet signals due to 8α-H and 8β-H, though overlapped by other proton signals (Fig 3), were assigned on the basis of several partial decoupling experiments with double irradiation at frequencies of some peaks of the octet signal due to 7α-H (δ 0·62 ppm). Model examination shows that the half-height width of the 8β-H signal must be broader than that of the 8α-H signal, whichever conformation shown in Fig 2 is preferred. Therefore, the multiplet at a higher field ($\delta \sim 1{\cdot}28$ ppm) was assigned to the 8β-H signal (Fig 3).

An apparent increase in the height of several peaks of the 8β-H signal was observed when the 1-H signal was saturated. This increase was measured as about 5% (Fig 4). Although enhancement in the integrated intensity area could not be observed, the increase in the peak height must result from an NOE because long-range spin-coupling between these two protons can hardly be detected. Further, NOE's between the 5-H and 8β-H signals, and between the 11β-Me and 5-H signals were observed, as expected (Table 1); the latter NOE determined the assignments of 11α- and 11β-Me signals. Therefore, the conformation for 1 was assigned to the structure A, which has a *crossed* orientation of the double bonds in the 10-membered

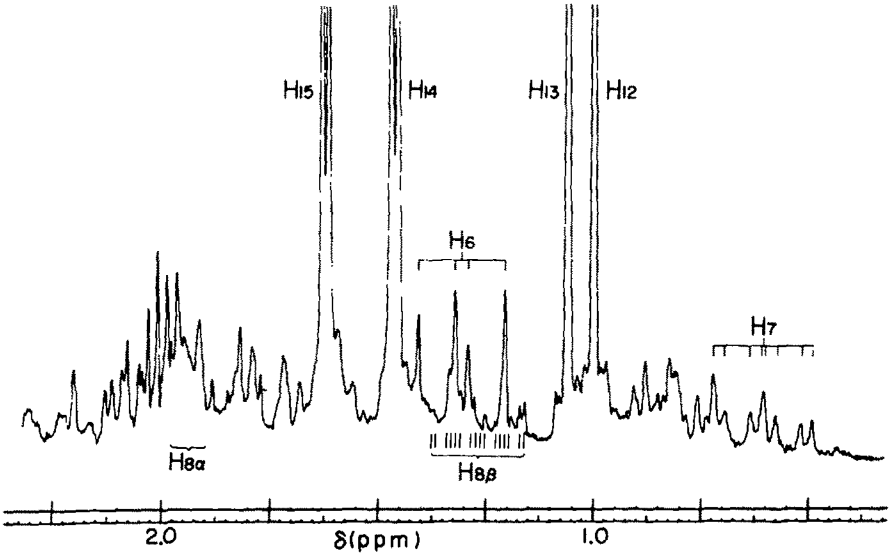


Fig 3. Expanded high-field portion of the NMR spectrum of 1 in acetone-d_6.

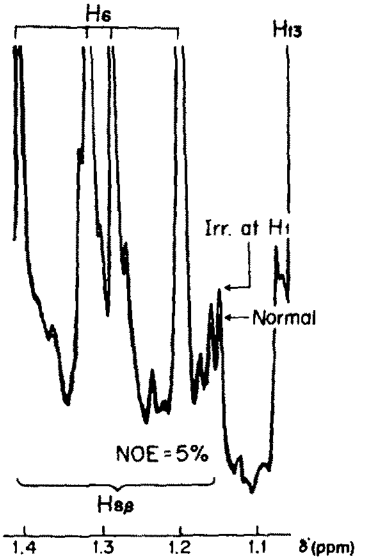


Fig 4. An NOE experiment on the 8β-H signal in 1.

ring. The J-values obtained for 1 can reasonably be explained by this conformation.

The present result offers an additional support for the empirical rule[6] proposed for the stereochemistry of the Cope rearrangement.

The 100 MHz NMR spectrum of 3 was taken in $CDCl_3$ (Fig 1b) and in C_6D_6 at 35°. The assignment of isolated signals in these spectra were confirmed by spin-decoupling experiments. Table 2 summarizes the NOE results together with the other NMR parameters obtained.

The signals due to 1-H and 5-H are mutually overlapped in both solvents. However, it was found that cautious saturation of the 4-Me signal caused a considerable increase only in the signal area of the 5-H signal (Table 2), while saturation of the 10-Me signal caused no increases. These NOE results demonstrate that the olefinic Me and the hydrogen on the C-1 : C-10 and C-4 : C-5 double bonds are in a *trans* and a *cis* relationship, respectively.

Examination of Dreiding models suggests the two major conformations C and D shown in Fig 2

Table 1. NMR data on bicyclogermacrene (1) in acetone-d_6[a]

Proton	1-H	5-H	6-H	7-H	8β-H	12-H	13-H	14-H	15-H
δ	4·83 m	4·38 m	1·31 d-d	0·62 m	~ 1·28 m	1·00 s	1·06 s	1·47 d	1·62 d
NOE[b]	0[12-H]	10[12-H]	0[1-H][c]	0[1-H]	~ 5[1-H][c]				
	0[13-H]	0[13-H]		0[5-H]	~ 6[5-H][c]				
	0[14-H]	0[14-H]			$\sim 9\left[\begin{matrix}\text{1-H}\\ \text{5-H}\end{matrix}\right]^{c}$				
	0[15-H]	0[15-H]							

$J_{1,2\alpha} = 10{\cdot}0$; $J_{1,2\beta} = 5{\cdot}5$; $J_{1,14} = 1{\cdot}5$; $J_{5,6\alpha} = 11{\cdot}5$; $J_{5,15} = 1{\cdot}5$; $J_{6\alpha,7\alpha} = 8{\cdot}5$; $J_{7\alpha,8\beta} = 11{\cdot}5$; $J_{7\alpha,8\alpha} = 2{\cdot}5$

[a] Chemical shifts are expressed in δ in ppm downfield from internal TMS (±0·01 ppm) and coupling constants are in Hz (J, ±0·1 Hz).

[b] NOE's are shown by increases in signal areas in % (±1%). Saturated signals are shown in square brackets.

[c] Enhancement in signal heights (±1%).

Table 2. NMR data on isobicyclogermacrene (3) in $CDCl_3$ and C_6D_6 (in parentheses)[a]

Proton	1-H	5-H	6-H	7-H	12-H	13-H	14-H	15-H
δ	5·03 m	4·95 m	1·11 d-d	0·41 m	0·99 s	1·05 s	1·41 d	1·70 d-d
	(5·05) m	(5·02) m	(1·12) d-d	(0·33) m	(0·99) s	(1·05) s	(1·42) d	(1·68) d-d
NOE[b]	6[7-H] 0[12-H] 0[13-H] 0 (0)[14-H] 0 (0)[15-H]	0[7-H] 11 (14)[12-H] 0[14-H] 15 (13)[15-H]	0[1-H]	8[1-H] 0[14-H]				

$J_{1,14} = 1·4$; $J_{1,2\beta} = 9·6$; $J_{1,2\alpha} = 5·5$; $J_{5,15} = 0·9$; $J_{5,6\alpha} = 8·2$; $J_{6\alpha,7\alpha} = 8·6$; $J_{7\alpha,8\beta} = 11·7$; $J_{7\alpha,8\alpha} = 1·7$; $J_{15,4} = 1·5$

[a] Chemical shifts are expressed in δ in ppm downfield from internal TMS (±0·01 ppm) and coupling constants are in Hz (J, ±0·1 Hz)

[b] NOE's are shown by increases in signal areas in % (±1% in $CDCl_3$ and ±2% in C_6D_6). Saturated signals are shown in square brackets.

for the 10-membered ring in 3. For conformations C and D, we can expect to observe NOE's between the 1-H and 7α-H signals and between the 10-Me and 7α-H signals, respectively; NOE's between the 11β-Me and 5-H signals should be observed for both conformations. As can be seen from Table 2, NOE's between the 1-H and 7α-H signals, and between the 11β-Me and 5-H signals were observed. These results confirm that 3 mainly adopts conformation C with a *crossed* orientation of the two double bonds.

EXPERIMENTAL

The 100-MHz NMR spectra were taken with a Varian HA-100 spectrometer in the frequency-swept and internal C_6H_6-locked mode. The carefully degassed solutions were *ca* 5% (w/v) in acetone-d_6, $CDCl_3$, and(or) C_6D_6 with 1% TMS as an internal reference. Calibration of the charts was carried out by direct readings of resonance frequencies using a Hewlett-Packard HP-5212A electronic counter with accuracies to ±0·1 Hz. NMDR and NMTR experiments were performed using the spectrometer and two Hewlett-Packard HP-200ABR audio-oscillators. NOE experiments were made by measuring, more than four times, the integrated intensities of signal with and without irradiation of the second rf-field at the resonance frequency of another signal, with a sweep rate of 0·4 Hz/sec. Caution was exercised not to overload the audio phase-sensitive detector of the spectrometer in the NOE experiments.[8] The enhancement is expressed in %.

Acknowledgements—We thank Drs. K. Takeda, H. Minato (Shionogi Research Laboratory), and Y. Hirose (The Institute of Food Chemistry) for their advice to this work.

REFERENCES

[1] K. Nishimura, N. Shinoda and Y. Hirose, *Tetrahedron Letters* 3097 (1969).
[2] R. Vlahov, M. Holub, I. Ognjanov, and V. Herout, *Coll. Czech. Chem. Comm.* 32, 808 (1967).
[3] I. Ognjanov and R. Vlahov, *Riechstoff u. Aromen* 17[8], 315 (1967).
[4] N. Shinoda, M. Shiga and K. Nishimura, *Agric. and Biol. Chem. Japan* 34, 234 (1970).
[5] K. Takeda, I. Horibe and H. Minato, *Chem. Comm.* 308 (1971).
[6] K. Takeda, K. Tori, I. Horibe, M. Ohtsuru and H. Minato, *J. Chem. Soc.* C 2697 (1970).
[7] J. Streith, P. Pesnelle and G. Ourisson, *Bull. Soc. Chim. Fr* 518 (1968), and refs therein.
[8] J. H. Noggle and R. E. Schirmer, *The Nuclear Overhauser Effect: Chemical Applications*. Academic Press, New York, N.Y. (1971); G. E. Bachers and T. Schaefer, *Chem. Rev.* 71, 617 (1971).
[9] K. Takeda, K. Tori, I. Horibe, H. Minato, N. Hayashi, S. Hayashi and T. Matsuura, *J. Chem. Soc.* C 985 (1970) and refs therein.