

CONFORMATION OF A NEW TEN-MEMBERED-RING SESQUITERPENE ALCOHOL ISOLATED  
FROM ASARUM CAULESCENS. CAUTION FOR APPLICATION OF N.O.E.  
TO A RING SYSTEM IN SLOW INVERSION

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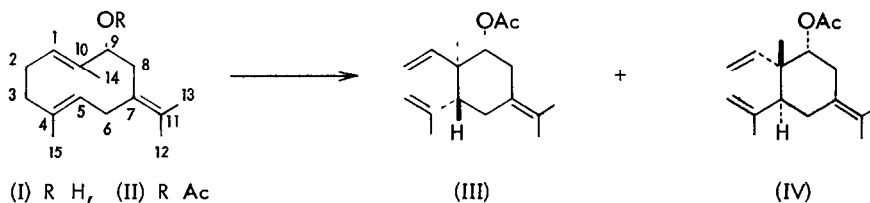
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One of our groups has recently reported the structural elucidation of germacra-1(10),4,7(11)-triene-9 $\alpha$ -ol (I) isolated from a volatile oil in the subterranean part of Asarum caulescens Maxim. (Aristolochiaceae) and the Cope rearrangement of its acetate II (1). On being heated at 220° for 30 min, compound II gave a mixture of III and IV in a ratio of 5 : 3, which have a normal and an antipodal element-type skeleton, respectively. This fact prompted us to determine the conformation of the ten-membered ring in II, since we previously proposed that the stereochemistry of the Cope-rearrangement product of a cyclo-deca-1,5-diene derivative is controlled by the conformation of its ten-membered ring (2). We report here



NMR spectroscopic evidence for the conformation of this new sesquiterpene alcohol acetate II in solution. This is the first example of the determination of conformation of a germacrane-type ten-membered ring in solution, although crystal and molecular structures of silver nitrate adducts of germacratratriene (3),

germacrone (4), and pregeijerene (5) have already been reported

Variable-temperature 100-MHz NMR studies of II in various solvents showed that this compound exists as two NMR-distinguishable conformational isomers in a ratio of about 92 : 8 at temperatures lower than ordinary probe temperature (30°C) (FIG. 1d), and that rapid inversion of the ten-membered ring occurs at temperatures higher than about 105°C (FIG. 1a). Similar phenomena have already been reported for neolinderactone (6), isabelin (7), laurenbiolide (8), and sericenin (9).

The spectrum of II in toluene- $d_8$  at ordinary probe temperature exhibits rather sharp signals, each conformer of the ring seeming to be frozen on the NMR time scale (FIG. 1c). While the conformation of

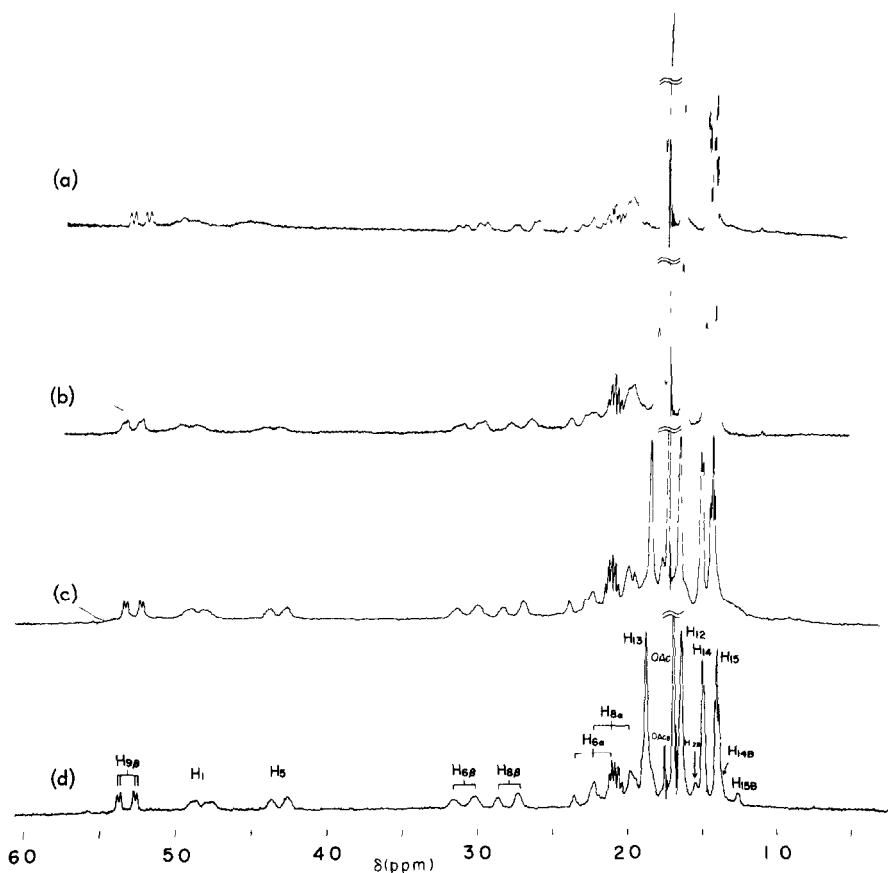


FIG. 1. Variable-temperature 100 MHz NMR spectra of II in toluene- $d_8$ . (a) 105°C, (b) 60°C, (c) 30°C, and (d) -8°C.

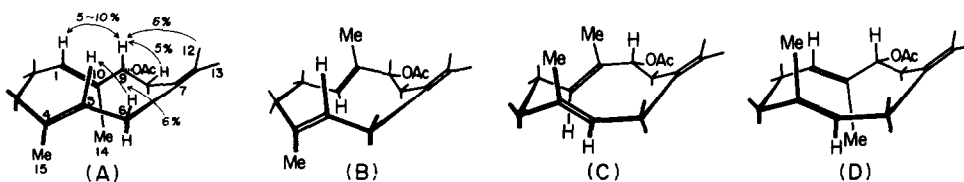


FIG. 2. Possible molecular conformations for II.

the minor conformer seemed undeterminable because of its insufficient population, the major conformer was examined by use of the intramolecular nuclear Overhauser effect (N.O.E.). The NMR spectral experiments were carried out with a Varian HA-100 spectrometer in the frequency-swept and  $C_6H_6$ -locked mode. The assignments of isolated signals were confirmed by double- and triple-resonance techniques. Chemical shifts of 1-H, 5-H, 6 $\alpha$ -H, 6 $\beta$ -H, 8 $\alpha$ -H, 8 $\beta$ -H, 9 $\beta$ -H, 12-H, 13-H, 14-H, 15-H, and OAc are  $\delta$  4.80, 4.29, 2.22, 3.08, 2.11, 2.79, 5.29, 1.87, 1.63, 1.49, 1.40, and 1.69 p.p.m. downfield from TMS, respectively

Saturation of the 10-Me and 4-Me signals by double irradiation caused no increases in the integrated intensities of the 1-H and the 5-H signals, respectively. The methyl and the hydrogen on both endocyclic double bonds in II should then be trans, because saturation of the methyl signal usually causes an increase of more than 15% in the area of the vinyl proton signal when a methyl group is cis to a hydrogen in a trisubstituted ethylenic double-bond as previously reported (6,9). Thus, examination of Dreiding models suggests that there are eight major conformations, (A)-(D) and their mirror images against the axially oriented acetoxy group, for the ten-membered ring in II (see FIG. 2).

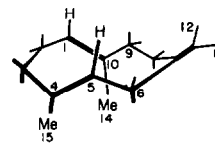
The observed N.O.E.'s,\* [1-H]  $\rightarrow$  9 $\beta$ -H (12%), [5-H]  $\rightarrow$  6 $\beta$ -H (9%), [6 $\alpha$ -H]  $\rightarrow$  5-H (12%), [8 $\alpha$ -H]  $\rightarrow$  1-H and 5-H (14-20%), [12-H]  $\rightarrow$  9 $\beta$ -H (7%), [10-Me]  $\rightarrow$  9 $\beta$ -H (6%), [4-Me]  $\rightarrow$  6 $\beta$ -H (8%), [OAc]  $\rightarrow$  9 $\beta$ -H (9%), clearly show the presence of more than one conformational isomer, this fact implies that the ten-membered ring in II is still slowly inverting on the NMR time scale. Furthermore, saturation of the 1-H signal caused a marked decrease in the intensity of the 5-H signal. It is reasonable to suggest that a considerably broadened signal corresponding to the 5-H of a minor conformer is overlapped with the 1-H signal of the major conformer. In a chemically exchanging system where the exchange rate is such that

\* [1-H]  $\rightarrow$  9 $\beta$ -H represents that an N.O.E. was observed for the 9 $\beta$ -H signal when the 1-H signal was irradiated. \*

separate NMR signals are observed for the exchanging nuclei in two different sites, irradiation of a signal corresponding to one of the sites causes a decrease in intensity of the signal corresponding to the other site, if the relaxation rate of the observed nucleus is slower than the exchange rate (10)

N.O.E. experiments were therefore carried out at  $-8^{\circ}\text{C}$ , at which temperature inversion of the ten-membered ring seems not to occur; no N.O.E.'s due to the contributions of conformational isomers other than the major one were observed. The N.O.E.'s observed between 1-H and  $9\beta\text{-H}$  (5-10%), and between 5-H and  $6\beta\text{-H}$  (6%) indicate that the major conformation of the ten-membered ring in II is such that both the relationship between 1-H and  $9\beta\text{-H}$ , and that between 5-H and  $6\beta\text{-H}$  are syn

Further, the spin coupling constants obtained ( $J_{5,\alpha} = 10.5$ ,  $J_{5,\beta} = 2.7$ ,  $J_{8\alpha,9\beta} = 10.5$ , and  $J_{6\beta,9\beta} = 2.2$  Hz) unambiguously determine the major conformation of II as shown in FIG. 2(A). This conformation closely resembles conformation (E) in a crystal of germacatriene 1:1 adduct with



(E)

silver nitrate (3). Thus, it can be considered that III is obtained from the major conformation of II by the Cope rearrangement

The variable-temperature N.O.E. study of *N,N*-dimethylformamide is well known (11). However, such a study on a more complex molecule has not so far been reported. Thus, it should again be emphasized that much caution is necessary in the application of N.O.E. to a system undergoing slow chemical exchange, when the relationships between N.O.E.'s observed and the chemical structure are discussed.

Further work on the minor conformer of II is now in progress.

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