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STRUCTURAL ELUCIDATION OF MARINE HALOGENATED MONOTERPENES BY 2D-NMR AND NOE DIFFERENCE SPECTROSCOPY. A STEREOCHEMICAL CORRECTION

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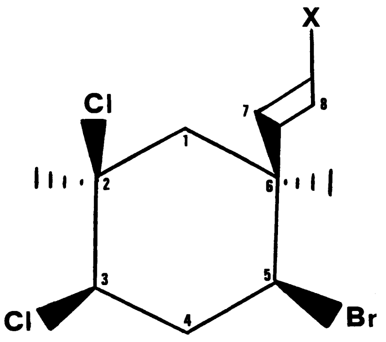
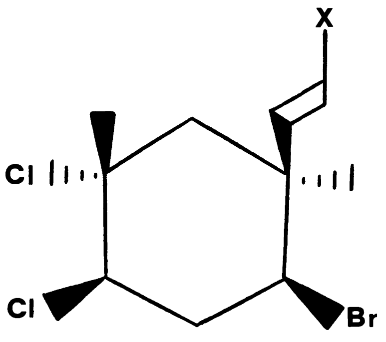
A new methodology for structural elucidation of polyhalogenated monoterpenes is presented. It makes extensive use of correlated 2D-NMR and NOEDS and shows that the structures of coccinene and its bromovinyl analog must be corrected to their C-2 epimers.

We have recently isolated from Plocamium coccineum several polyhalogenated monoterpenes.1) Their structures were proposed by comparison of their spectral data with those previously reported for known compounds.2) In view of the considerable confusion existing in this area, in which it is not unusual for molecules to be corrected twice within a few months,3) we decided to reanalyse our compounds making extensive use of the latest NMR techniques, such as two-dimensional NMR and NOE difference spectroscopy (NOEDS).4) This has allowed us to correct the structures of compound 1, previously isolated from another Plocamium species,5) and of coccinene6) (2), to 3 and 4 respectively, which have the epimeric configuration at C-2.



1 X=Br
2 X=Cl



3 X=Br
4 X=Cl

The NMR analysis of compound 1 will illustrate the general approach used. The connectivities depicted in the COSY-90 spectrum (Fig. 1) clearly show that the molecule has a dimethylvinylcyclohexane skeleton. There exist four groups of protons in the molecule: an isolated methylene group (protons C,E), an ABXY system ($J_{xy} \simeq 0$ Hz) (protons D,F,G,H), two quaternary methyl groups (A and B) and an isolated vinyl group (protons I,J). The gross structure inferred from these data is depicted in Fig. 1.

The methyl groups are inferred to be attached to different quaternary carbons from the long range COSY-90 spectrum (Fig. 2), as each methyl is coupled to a proton of a different -CHX- group. These data refine the structure proposed to the point shown in Fig. 2.

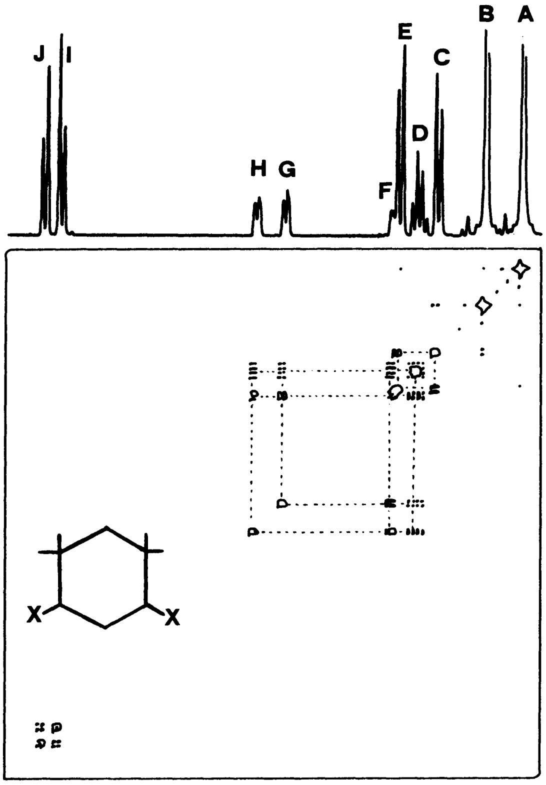


Fig. 1. COSY-90 spectrum of 1.

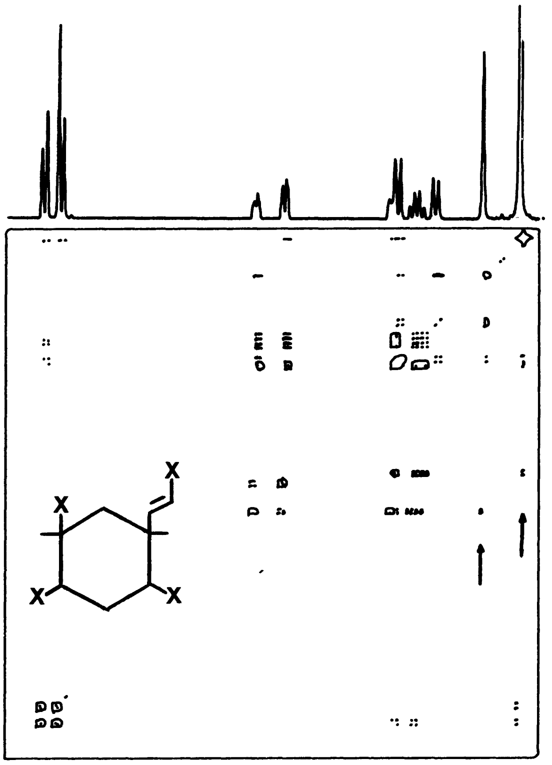


Fig. 2. Long range COSY-90 of 1.

The relative stereochemistry of the four chiral centres of the molecule is obtained from the NOED spectra. The coupling constants of the protons of the -CHX- groups show that those protons are in a diaxial arrangement. Irradiation of the methyl signal at 1.26 ppm (A), induced NOE's on protons C,E,G,I, and J. When the methyl signal at 1.67 ppm (B) was irradiated, NOE was observed for protons D,E,I, and J (Fig. 3). The only structure compatible with our data is that depicted in Fig. 3.

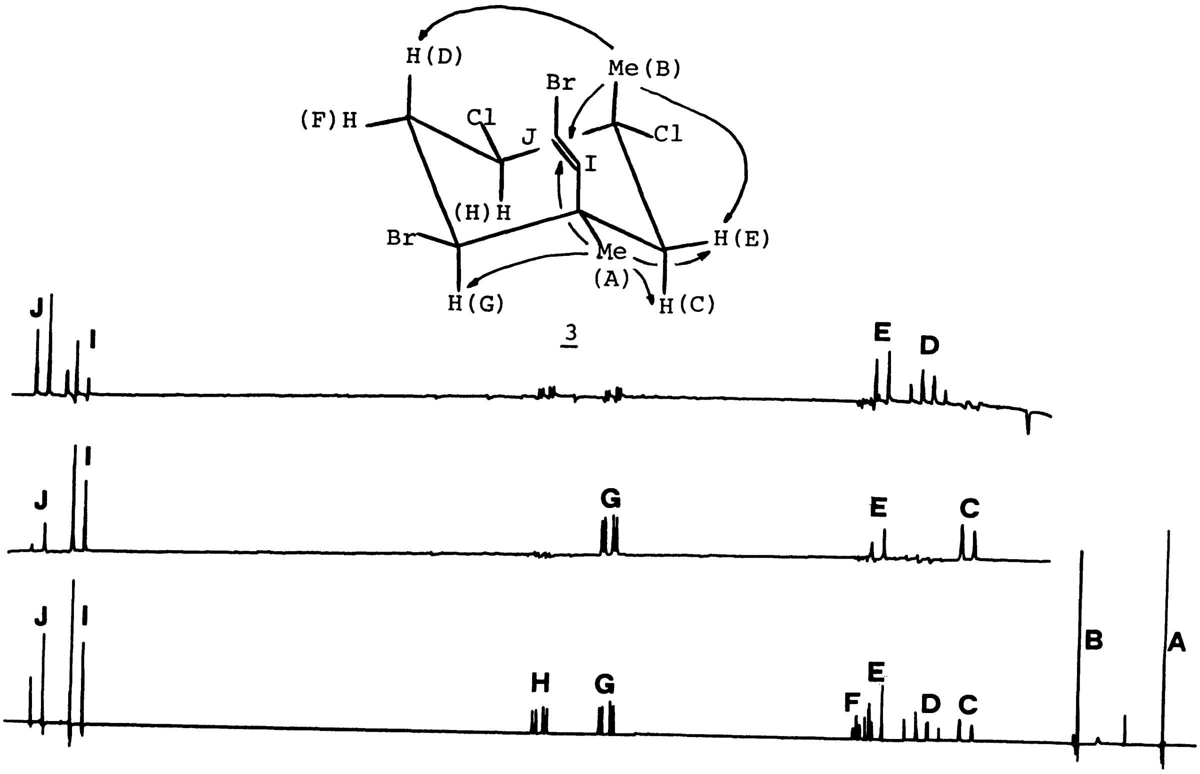


Fig. 3. Lower trace: normal (resolution enhanced) spectrum of 3.[9)]
Middle trace: NOED spectrum with irradiation at 1.26 ppm.
Upper trace: NOED spectrum with irradiation at 1.67 ppm.

The exact location of the halogen atoms was determined from a ^{1}H-^{13}C correlated spectrum which showed that C-3 resonates at 66.8 ppm and that C-5 resonates at 56.4 ppm, proving that a bromine atom[8)] is attached to C-5.

The earlier structural assignement of 1 had been based on X-Ray diffraction,[5)] but it is known that crystals of polyhalogenated monoterpenes undergo considerable damage upon X-Ray irradiation[3c,5)] and this might have been the origin of mistaken conclusions.[7)] In fact the reported final agreement factor for 1 was 9.2%.

It should be remarked that this is the first time that a trans dimethyl arrangement has been proposed for this kind of marine metabolites. This might have important bearing regarding the biosynthesis of polyhalogenated monoterpenes of marine origin.

The methodology described here constitutes a powerful method for structural elucidation of halogenated monoterpenes without resorting to other techniques which might involve a risk of molecular damage.

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3) For instance, mertensene has been reassigned twice:
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6) Coccinene has been correlated to a degradation product of 1.[1]
7) A low temperature X-Ray analysis of compound 3 is in progress. Further crystallographic details will be published elsewhere.
8) The molecule possesses two chlorine and two bromine atoms, one of which is located at the terminal vinyl position, as can be easily deduced from its ^{13}C-NMR spectrum.[5]
9) 3: NMR ($CDCl_3$, 250 MHz) δ 1.26 (s, A), 1.67 (s, B), 2.19 (d, J=14.4 Hz, C), 2.39 (m, J=14.0, 12.9, 12.5 Hz, D), 2.60 (d, J=14.4 Hz, E), 2.66 (dt, J=14.0, 4.3, 4.0 Hz, F), 3.84 (dd, J=12.9, 4.0 Hz, G), 4.15 (dd, J=12.5, 4.3 Hz, H), 6.30 (d, J=14.1 Hz, I), 6.48 (d, J=14.1 Hz, J).

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