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Geometry and Halogen Regiochemistry Determination of Vicinal Vinyl Dihalides by ^{1}H and ^{13}C NMR. Application to the Structure Elucidation of Prefuroplocamioid, an Unusual Marine Monoterpene

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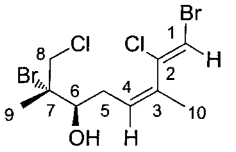
ABSTRACT



Empirical rules based on ^{13}C and ^{1}H NMR spectroscopy to determine the regiochemistry and geometry of the 1,2-bromochloro vinyl portion of naturally occurring or synthetic compounds containing this functionality are proposed. The key feature of the method comes from the comparison of the spectral data of the new monoterpene metabolite, prefuroplocamioid, isolated from *Plocamium cartilagineum,* with those of other marine monoterpenes, as well as with some model compounds found in the literature.

The red alga *Plocamium cartilagineum* is a rich source of halogenated monoterpenes of cyclic, acyclic,[1−2] and oxacyclic[3−5] skeletons. It is common in species of genus *Plocamium* metabolites to find a high degree of halogen incorporation, usually up to 5 halogens, in a skeleton having only 10 carbon atoms. Determining the locations of the halogen atoms in the structural elucidation of these metabolites has been difficult. The structures of many halogenated monoterpenes have been determined by spectroscopic methods and empirical rules.

^{13}C NMR spectroscopy has played an important role in the assignments of the halogen regiochemistry, differentiating sp^3 carbons bearing chlorine or bromine and also halogen-bearing carbons of a 1-vinyl halide group.[6] However, with the recent isolation[7] of polyhalogenated monoterpenes with 1,2-dihalovinyl features, new structural elucidation problems have arisen, such as the geometry of the olefin and the halogen regiochemistry on the olefinic carbons, challenging the power of ^{13}C NMR spectroscopy.

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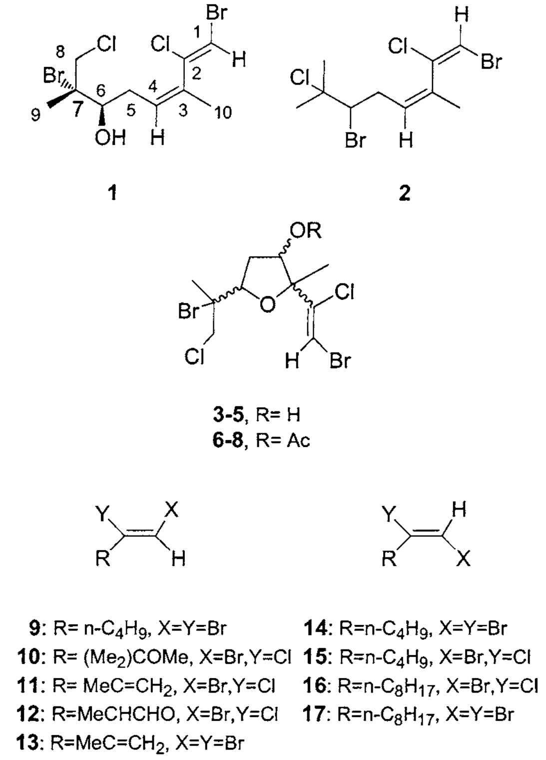

Figure 1.

In this communication, we report empirical rules based on ^{13}C and ^{1}H NMR spectroscopy that allow us to determine the regiochemistry and geometry of the 1,2-bromochloro vinyl portion of any naturally occurring or synthetic compound containing this functionality. The key feature of the method stems from the comparison of the spectral data of the new metabolite **1** with those of the known[8] compound **2**, both isolated from *P. cartilagineum*, other marine compounds **3**−**8** reported by us,[7] and some model compounds **9**−**17** found in the literature[9−15] (Figure 1). Compounds **1**−**5** are the only naturally occurring metabolites having a 1,2-bromochloro vinyl system.

Previously, we established[7] that in 1,2-dihalovinyl-substituted compounds such as furoplocamioids A−C (**3**−**5**, respectively), it is possible to distinguish C-1 chlorovinyl (δ_C ~120 ppm) from C-1 bromovinyl (δ_C ~106 ppm) because the α effect determines the chemical shift of C-1 independently of the *Z*/*E* orientation of the halogen at C-2. However, ^{13}C NMR spectroscopy was unable to establish the double-bond geometry. Now with the possibility of comparing the spectral data of compounds **1** and **2**, whose right half moieties differ only in the geometry of the terminal double bond, additional rules based on the ^{13}C chemical shift of C-1 can be established.

Table 1 shows regular chemical shifts around δ_C ~106 ppm for C-1 bromovinyl in a (*Z*)-geometry of the olefin (compounds **1**, **3**−**9**, and **12**−**13**), whereas in an (*E*)-geometry, these values are around δ_C ~101 ppm (compounds **2** and **14**−**17**). Thus, a ^{13}C chemical shift difference of the order of 5 ppm is large enough to distinguish (*Z*)-1,2-bromochloro (δ_C ~106 ppm) from (*E*)-1,2-bromochloro vinyl systems (δ_C ~101 ppm). Also, H-1 chemical shifts show significant differences (compounds **1** and **3**−**13**) being δ_H ~6.70 ppm for (*Z*)-vinyl dihalides and δ_H ~6.20 ppm for (*E*)-vinyl dihalides (compounds **2** and **14**−**17**). The combination of both gave trustworthy information to discriminate whether the vicinal 1,2-bromochloro vinyl is *Z* or *E*. Because of the wide variety of alkyl substituents on the vinyl system, these criteria appear to be of general application for 1,2-bromochloro dihaloalkenes and also for vicinal 1,2-dibromo vinyl systems (compounds **9**, **13**, **14**, and **17**). This rule confirms the assigned (*Z*)-geometry for the C-1−C-2 olefin of furoplocamioids A−C.

Table 1. ^{1}H and ^{13}C Chemical Shifts for (*Z*)- (**1** and **3**−**13**) and (*E*)- (**2** and **14**−**17**) 1,2-Dihaloalkenes in $CDCl_3$ (δ, ppm)

(*Z*)-1,2-dihaloalkenes			(*E*)-1,2-dihaloalkenes		
compd	C_1	H_1	compd	C_1	H_1
1	105.4	6.63	**2**	100.2	6.28
3	106.1	6.96	**14**	102.1	6.33
4	104.6	6.79	**15**	101.6	6.16
5	106.2	7.08	**16**	101.1	6.25
6	105.0	6.88	**17**	102.1	6.40
7	105.2	6.86			
8	107.5	7.18			
9	105.4	6.58			
10		6.44			
11		6.50			
12	106.8	6.67			
13	109.9	6.81			

Prefuroplocamioid **1** was isolated[16] from *P. cartilagineum* (L.) Dixon (Plocamiaceae), collected along the coast of Chile, after flash chromatography of the crude extract, followed by gel filtration and successive HPLC. The EIMS spectrum showed peaks at *m/z* 378/380/382/384 with relative intensities suggestive of two bromine and two chlorine atoms that correspond to the empirical formula $C_{10}H_{14}OBr_2Cl_2$ $[M]^+$ (HRMS). The hydroxyl group was observed at 3474 cm^{-1}

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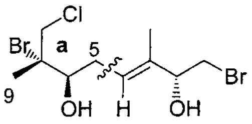
[16] Unstable colorless oil: $[\alpha]^{25}_D$ +34 (*c* 0.6, $CHCl_3$); IR ν_{max} (film) 3474, 2925, 1381, 1046 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 2; EIMS *m/z* 378/380/382/384 $[M]^+$ (4, 10, 8, 3), 183/185/187 $[C_4H_5OBrCl]^+$ (6, 8, 1); HREIMS $[M]^+$ 377.8761 (calcd for $C_{10}H_{14}O_4{}^{79}Br_2{}^{35}Cl_2$, 377.8788), $[C_4H_7OBrCl]^+$ 182.9208 (calcd for $C_4H_5O^{35}Cl^{79}Br$, 182.9212).

Table 2. ^1H and ^{13}C NMR Data of Compounds **1** and **17**−**18** [500 MHz, δ ppm, J (Hz), $CDCl_3$]

	1^a		17		18	
entry	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	6.63 s	105.4	3.52, 3.46	37.7	3.55, 3.50	38.2
2		140.3	4.28	76.2	4.29	75.5
3		132.7		137.1		137.1
4	6.25 t (7.0)	128.8	5.70	123.9	5.70	123.5
5	2.44 m	32.7	2.44	31.7	2.41	30.4
6	3.66 t (7.0)	72.4	3.63	72.9	3.93	73.3
7		73.3		73.3		74.6
8	3.77d (10.7)	51.1	3.80	51.2	3.60	
	4.27d (10.7)		4.28		4.04	39.7
9	1.80 s	26.1	1.82	25.9	1.68	25.5
10	1.88 s	14.9	1.60	12.4	1.69	12.6

[a] Spectrum was taken at −20 °C.

in the IR spectrum. The ^{13}C NMR spectrum[17] of **1** (Table 2) showed signals for 10 carbons. Multiplicities of the carbon signals were determined from the DEPT spectrum: two methyls (one on a double bond), two methylenes (one bearing a halogen), three methines (one bearing oxygen, and two olefinic), and three nonprotonated carbons (one olefinic). The ^1H NMR spectrum of **1** (Table 2) showed signals corresponding to two olefinic protons at δ 6.63 (1H, s) and 6.25 (1H, t, $J = 7.0$) and a triplet at δ 3.66 (1H, t, $J = 7.0$) attributed to a methine geminal to oxygen. A methylene multiplet appeared at δ 2.44 (2H, m), while two doublets corresponding to the protons of the chloromethylene group at δ 3.77 (1H, d, $J = 10.7$) and 4.27 (1H, d, $J = 10.7$) were observed. At high field, the signals at δ 1.80 (3H, s) and 1.88 (3H, s) correspond to two methyl groups, geminal to halogen and on a double bond, respectively. The presence of only two methyl groups suggested that the third methyl group, corresponding to a monoterpene skeleton, was oxidized as halomethylene.



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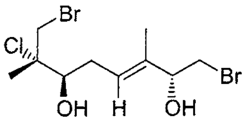

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Comparison of the ^1H and ^{13}C NMR spectra of **1** with that of the plocamenols A and B [18] (**17** and **18**, respectively) suggested that the left half moiety of **1** is identical to that of plocamenol A (**17**) as can be seen by the similarities of the NMR signals of both protons and carbons of the C-5−C-9 portion (Table 2).

The ^1H−^1H COSY NMR spectrum revealed coupling between H-4−H-6, and HMBC data were used to establish the connectivity of this fragment with the rest of the carbons of the molecule. Fragment C-1−C-3 was secured by the correlations between H-1 and C-2, C-3. The position of Me-10 was established by the correlation between H-10 and C-2, C-3 and the C-3/C-4 linkage was evidenced by the correlation between H-4 and C-2, C-3, C-10. The linkage C-7/C-8 was determined by the correlation between H-8 and C-7, C-9. HRMS indicated that the peaks at m/z 185/187/189 (40, 53, 13) correspond to a fragment with the formula of C_4H_7OBrCl, which confirmed the connectivity C-6−C-9. The correlation of H-6 with C-7 and C-9 suggested the overall planar structure **1**, with the requisite of two degree unsaturations.

The (Z)-geometry of the C-1−C-2 double bond was deduced by the NOE between H-1 with Me-10 in a NOESY experiment, Figure 2. The (Z)-geometry of this double bond as well as the regiochemistry for C-1 was also confirmed by the rules mentioned above. The (Z)-geometry of the C-3−C-4 double bond was determined from the ^{13}C chemical shift for C-10 (δ 14.9 ppm), which is very similar to that of compound **2** (δ 14.7 ppm). If the geometry of the double bond were E, an upfield shift of about 5 ppm should be expected for that carbon due to a γ effect from C-4 in a (Z)-relationship.[8,18−20]

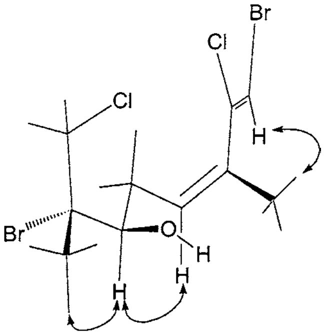

Figure 2. Selected NOE for prefuroplocamioid **1**.

The relative stereochemistry of C-6 was reinforced by 2D NOESY experiments. Clear NOE effects between H-4 with H-6 and also between H-6 with Me-9 were observed, suggesting a relative (R*)-configuration for the C-6 chiral center (Figure 2).

The (S*)-configuration at C-7 in compound **1** was assigned on the basis of the similarities of the chemical shifts of the C-9 methyl group (δ_C ~25.7) compared with the data reported for C-7 (Me-9 δ_C ~25.3) in a series of related monoterpenes whose stereochemistries have been determined[8,21] by X-ray crystallography.

We were unsuccessful in preparing Mosher esters of **1** at −20 °C to establish the absolute configuration. The compound proved to be unstable under the reaction conditions.

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[17] One- and two-dimensional NMR spectra were taken at −20 °C.

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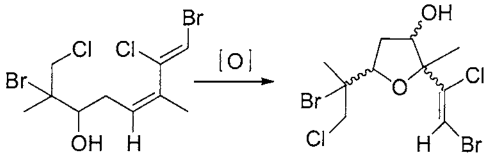
Prefuroplocamioid **1** is also interesting from the biogenetic point of view. It can be considered to be the precursor of furoplocamioids **3**−**5** by oxonium-induced intramolecular cyclization of the hydroxylic function, suggesting that the biosynthesis of the 1,2-bromochloro vinyl system occurs prior to the oxetane ring formation of furoplocamioids (Scheme 1).

Scheme 1



We believe that the proposed rules enhance the power of the ^{13}C and ^{1}H NMR techniques to assign the regiochemistry and geometry of vicinal vinyl bromochloro system-containing compounds and should be an aid to the structural elucidation of polyhalogenated marine compounds.

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Supporting Information Available: Spectral data for compound **1** and a detailed experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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