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HALOGEN CHEMISTRY OF THE RED ALGA *BONNEMAISONIA*

OLIVER J. MCCONNELL* and WILLIAM FENICAL
Institute of Marine Resources, Scripps Institution of Oceanography, La Jolla, CA 92093, U.S.A.

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Key Word Index—*Bonnemaisonia nootkana*; *B. asparagoides*; *B. hamifera*; *Trailliella intricata*; Bonnemaisoniaceae; Rhodophyta; algae; halogenated C_7–C_9 compounds; biological halogenation.

Abstract—Complete accounts of the natural products chemistry of *Bonnemaisonia nootkana, B. asparagoides, B. hamifera* and *Trailliella intricata* are described. In contrast to the chemistry of the closely related alga *Asparagopsis*, *Bonnemaisonia* spp. do not produce halomethanes, but instead an array of C_7–C_9 halogen-containing ketones, alcohols and carboxylic acids. Biomimetic syntheses of these compounds suggest they are precursors and products of *in vivo* Favorsky rearrangements.

INTRODUCTION

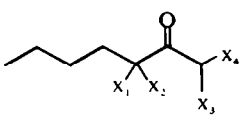
Recent chemical investigations of members of the family of red algae Bonnemaisoniaceae (Rhodophyta) have revealed an array of halogenated organic compounds apparently derived from acetate. Over one hundred halogenated molecules, ranging from one to four carbons, have been identified by us [1–3] and others [4–8] in several *Asparagopsis* species, and in the alternate heteromorphic tetrasporophyte phase *Falkenbergia* [3, 9]. The structures include halomethanes, haloacetaldehydes, haloacetones, halobutenones, and haloacetic and haloacrylic acids. Collections of *Delisea fimbriata* Lemour, from Australian and Antarctic waters, and *Ptilonia australasica*, from Australian waters, have yielded a series of halogenated nine-carbon lactones [10, 11], 1-octen-3-ones [12], and γ-pyrones [13]. Unlike these algae, *Bonnemaisonia hamifera* contains halogenated 2-heptanones [14]. Subsequently, we have found that *Bonnemaisonia* species and the alternate heteromorphic tetrasporophyte phase *Trailliella* contain not only halogenated 2-heptanones, but also brominated 2-nonanones, 2-heptanols, and 2-nonanols, *trans*-1,3,3-tribromo-1-heptene oxide, the presumed *in vivo* Favorsky rearrangement products of 1,1,3-tribromo- and 1,1,3,3-tetrabromo-2-hepta- and 2-nonanone (namely, *E*- and *Z*-3-bromo-2-heptenoic and 2-nonenoic acids, and 2-*n*-butyl- and 2-*n*-hexyl-3,3-dibromoacrylic acids), and polyhalogenated 1-octen-3-ones. Most of these compounds show significant antimicrobial activity [15, 16], and appear to be stored in highly specialized (vesicular) cells which may function in a chemical defense capacity. We report here details of our chemical studies of the genus *Bonnemaisonia*, including *B. hamifera* from the Gulf of California and from Woods Hole, Massachusetts, *B. nootkana* (Esp.) Silva from Monterey [17], *B. asparagoides* from La Escala, Spain [18], and *Trailliella intricata* from northern Europe. Evidence is also presented to support our proposals regarding the cellular location and ecological functions of these compounds [2].

Chemistry of Bonnemaisonia *species*

Bonnemaisonia hamifera, from the Gulf of California, was the first *Bonnemaisonia* species to be examined chemically. Of the many marine organisms sampled from the Gulf of California, *B. hamifera* contained the highest percentage of organobromine to total halogen content [19]. The major halogenated metabolite, isolated from the ethanol extract of the algae by silica gel chromatography, was 1,1,3,3-tetrabromo-2-heptanone (**1**) (0.01% wet weight) [14]. Four additional polyhalogenated 2-heptanones, including 3,3-dibromo-1-iodo-2-heptanone (**5**), were also characterized (Table 1).

Bonnemaisonia nootkana. We began our studies with *Bonnemaisonia asparagoides* and *B. nootkana*. Similar to *Asparagopsis* and *Falkenbergia* species [2, 3], *Bonnemaisonia* and *Trailliella* species are cosmopolitan in distribution [20–22]. They are usually epiphytic and are found in deeper waters than *Asparagopsis* species. *B. nootkana*, a fine, filamentous red alga, was collected at a depth of 70–90 feet one quarter mile off Monestary Beach, Carmel, California, and immediately stored in ethanol. The chloroform–ethanol extract contained mainly *trans*-1,3,3-tribromo-1-heptene oxide (**6**) (Fig. 2), but also *Z*-3-bromo-2-heptenoic acid (**7**), *Z*-3-bromo-2-nonenoic acid (**8**), 2-*n*-butyl-3,3-dibromoacrylic acid (**9**), 2-*n*-hexyl-3,3-dibromoacrylic acid (**10**), 1,1,3,3-tetrabromo-2-nonanone (**11**), 1,1,3,3-tetrabromo-2-heptanol

Table 1. Polyhalogenated 2-heptanones from *Bonnemaisonia hamifera*



	X_1	X_2	X_3	X_4
1	Br	Br	Br	Br
2	H	Br	H	Br
3	H	Br	Br	Br
4	Br	Br	Br	H
5	Br	Br	H	I

* Present address: Skidaway Institute of Oceanography, P.O. Box 13687, Savannah, GA 31406, U.S.A.

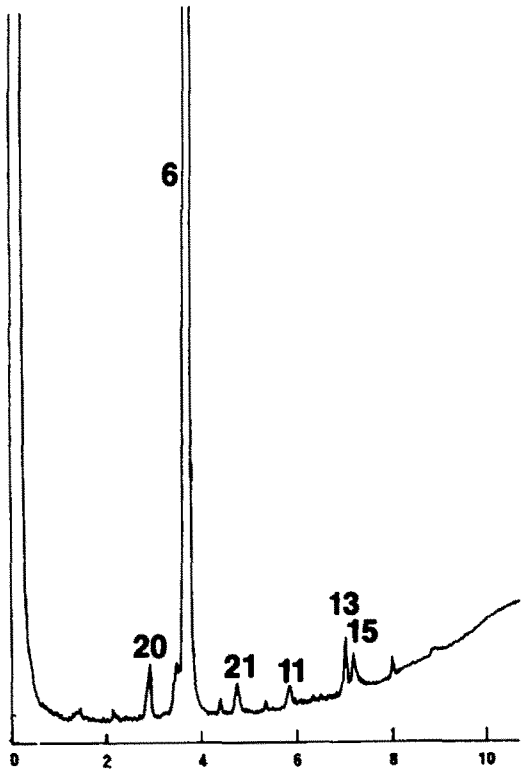


Fig. 1. Gas chromatographic analysis of the pentane extract of *Bonnemaisonia nootkana* from Monterey, Calif. Numbers refer to compounds (see text).

Table 2. ^1H and ^{13}C NMR data for *trans*-1,3,3-tribromo-1-heptene oxide

^1H NMR δ $CDCl_3$ (C_6D_6)	H	Mult.	Carbon	^{13}C NMR δ C_6D_6 ($CDCl_3$)	Mult
5.34 (4.51)	1	*d*, *J* = 3	1	60.2 (56.0)	*d*
3.88 (3.33)	1	*d*, *J* = 3	2	63.5 (59.4)	*d*
2.42 (2.32)	1	*m*	3	68.2 (64.2)	*s*
2.62 (2.50)	1	*m*	4	45.8 (41.8)	*t*
1.80 (1.75)	2	*d*, *d*, *t*; *J* = 7, 7, 7	5	30.0 (25.8)	*t*
1.43 (1.14)	2	*q*, *t*; *J* = 7, 7	6	22.1 (18.0)	*t*
0.95 (0.79)	3	*t*, *J* = 7	7	13.9 (9.8)	*q*

(**12**), 1,1,3,3-tetrabromo-2-nonanol (**13**), 1,1,1,3-tetrabromo-2-heptanol (**14**), and 1,1,1,3-tetrabromo-2-nonanol (**15**). A gas chromatogram of a pentane extract of a decanted ethanol solution of *B. nootkana* (Fig. 1) reveals a preponderant amount of the epoxide **6**. The acids were analysed as their ethyl esters because the algae were stored in ethanol. Structures were confirmed by biomimetric synthesis via Favorsky rearrangements of the appropriately brominated methyl ketone precursors.

As briefly reported in an earlier communication [17], the structures of these compounds were elucidated by spectral analysis, chemical degradation, and synthesis. The gross structure of the epoxide **6** was determined by analysis of the spectral data (Table 2). The location of the epoxide functionally at C-1/C-2, and not at C-2/C-3, was established by reacting **6** with lithium aluminum hydride to provide *E*-3-bromo-2-hepten-1-ol (**16**), and with two equivalents of *n*-butyl lithium in tetrahydrofuran at −78° to yield *E*-7-bromo-6-undecen-5-ol (**17**) (Fig. 2). (The geometry of the olefin in **17** was assigned

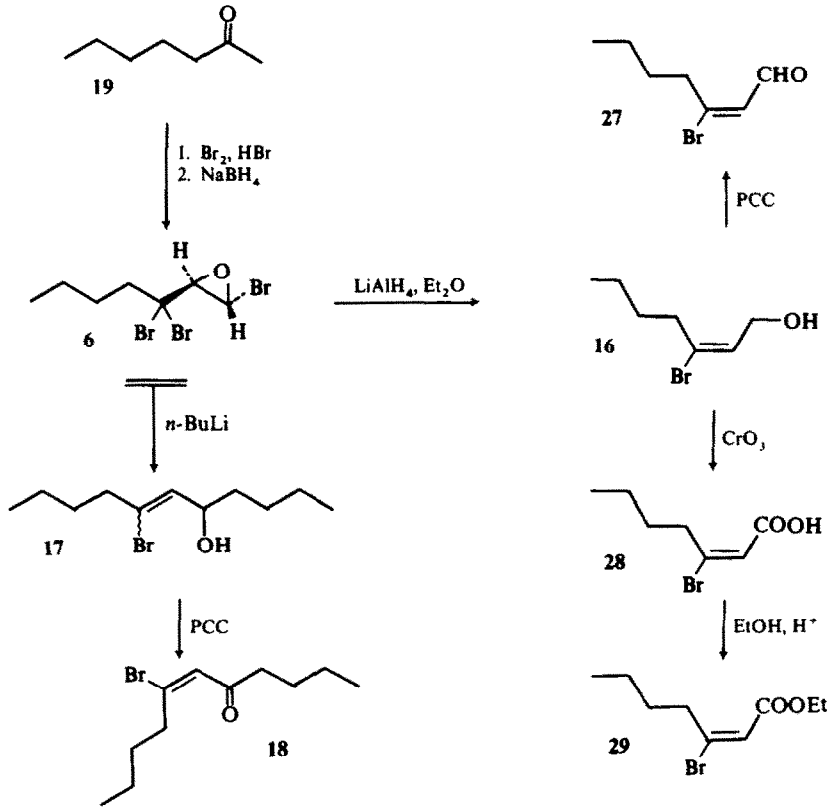
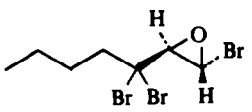
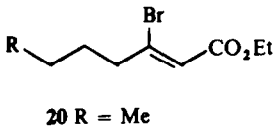


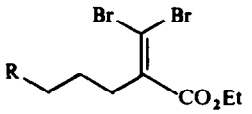
Fig. 2. Synthesis and transformations of *trans*-1,3,3-tribromo-1-heptene oxide (**6**). PCC is pyridinium chlorochromate.



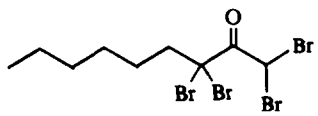
6



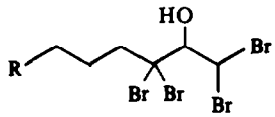
20 R = Me
21 R = CH_2CH_2Me



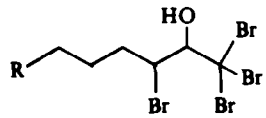
22 R = Me
23 R = CH_2CH_2Me



11



12 R = Me
13 R = CH_2CH_2Me



14 R = Me
15 R = CH_2CH_2Me

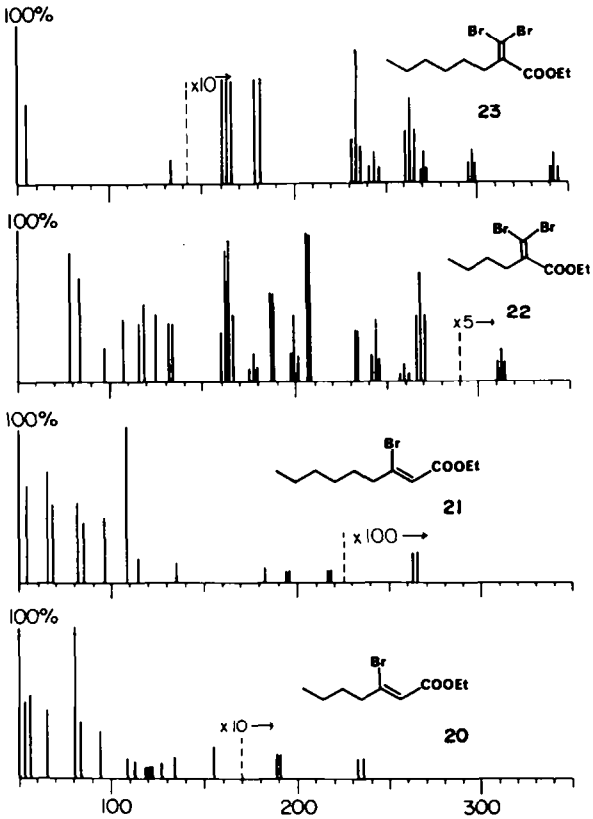


Fig. 3. Mass spectra (EI) of ethyl *Z*-3-bromo-2-heptenoate (**20**), ethyl *Z*-3-bromo-2-nonenoate (**21**), ethyl 2-*n*-butyl-3,3-dibromoacrylate (**22**) and ethyl 2-*n*-hexyl-3,3-dibromoacrylate (**23**).

from the chemical shift of the C-8 protons in the oxidation product, *E*-7-bromo-6-undecen-5-one (**18**) *vide infra*.) Synthesis of (±)-*trans*-1,3,3-tribromo-1-heptene oxide (**6**) from 2-heptanone (**19**) by bromination (Br_2, HBr) [23] and reduction (excess $NaBH_4$, MeOH) established that **6** contained three bromine atoms. The parent isotope cluster in the mass spectrum of **6** was not observable, but the fragment ion corresponding to $M^+ - Br$ was.

The homologous acids (**7** and **8**, and **9** and **10**) were converted to the ethyl esters (ethyl *Z*-3-bromo-2-heptenoate (**20**), ethyl *Z*-3-bromo-2-nonenoate (**21**), ethyl 2-*n*-butyl-3,3-dibromoacrylate (**22**), and ethyl 2-*n*-hexyl-3,3-dibromoacrylate (**23**)) during storage of the algae in ethanol. The structures were initially assigned from their MS (Fig. 3), and confirmed by biomimetic synthesis via Favorsky rearrangement reactions following the modified procedures of Rappe [24, 25] (Fig. 4). A comparison of the MS and GLC retention times of **22** and **23** with those of synthetic ethyl *E*- and *Z*-2,3-dibromo-2-heptenoate (**24**) and 2-nonenoate (**25**) verified that the branched systems are produced in the synthesis of the acids **9** and **10**.

Stereochemical assignments of *Z*-3-bromo-2-heptenoic acid (**7**) and *Z*-3-bromo-2-nonenoic acid (**8**) as the *Z* isomers are proposed based on chemical shift data of the olefin and C-4 protons of the ethyl esters **20** and **21**, the corresponding acids, **7** and **8**, and *Z*-3-bromo-2-hepten-1-ol (**26**), with the *E* isomers, *E*-3-bromo-2-hepten-1-ol (**16**), *E*-3-bromo-2-heptenal (**27**), *E*-3-bromo-2-heptenoic acid (**28**). and ethyl *E*-3-bromo-2-heptenoate (**29**) (Fig. 2), and Rappe's values [24]. The olefin and the allylic methylene protons were observed downfield in the *E* isomers relative to these protons in the *Z* isomers at the higher oxidation levels (see Experimental for chemical shifts).

1,1,3,3-Tetrabromo-2-nonanone (**11**) and the brominated alcohols **12**, **13**, **14**, and **15** were initially recognized by GC–MS in complex mixtures from column chromatography fractions. 1,1,3,3-Tetrabromo-2-nonanol (**13**) was present in large enough quantities to be characterized by ^1H NMR, ^{13}C NMR, and IR after further purification by silica gel chromatography (Table 3). The low resolution MS (50 eV) of **13** did not exhibit a molecular ion, but did reveal an $M^+ - HBr$ fragment ion at *m/e* 376 (0.4%, Br_3). In addition, two α-cleavage fragments were observed at *m/e* 205 (6.4%, Br) and 175 (2.6%, Br).

Reduction (lithium aluminum hydride in ether or sodium borohydride in dimethoxyethane) of synthetic 1,1,3,3-tetrabromo-2-heptanone (**1**) and 1,1,3,3-tetrabromo-2-nonanone (**11**), the only presumed Favorsky

Table 3. ^1H and ^{13}C NMR data for 1,1,3,3-tetrabromo-2-nonanol

	^{13}C NMR (20 MHz) 13		^1H NMR (220 MHz) 13		
Carbon	δ ($CDCl_3$)	Mult. (off-resonance)	δ ($CDCl_3$)	#H	Mult.
1	45.4	*d*	6.55	1	*d*, *J* = 0.25
2	83.5	*d*	4.39	1	*bd*, *J* = 9
3	77.7	*s*	3.27	1	*bd*, *J* = 9(D_2O exchang.)
4	46.6	*t*			
5	31.5	*t*	2.36	2	*m*
6	28.5	*t*	1.70	2	*m*
7	27.3	*t*	1.23	6	*m*
8	22.5	*t*	0.87	3	*t*, *J* = 6
9	14.0	*q*			

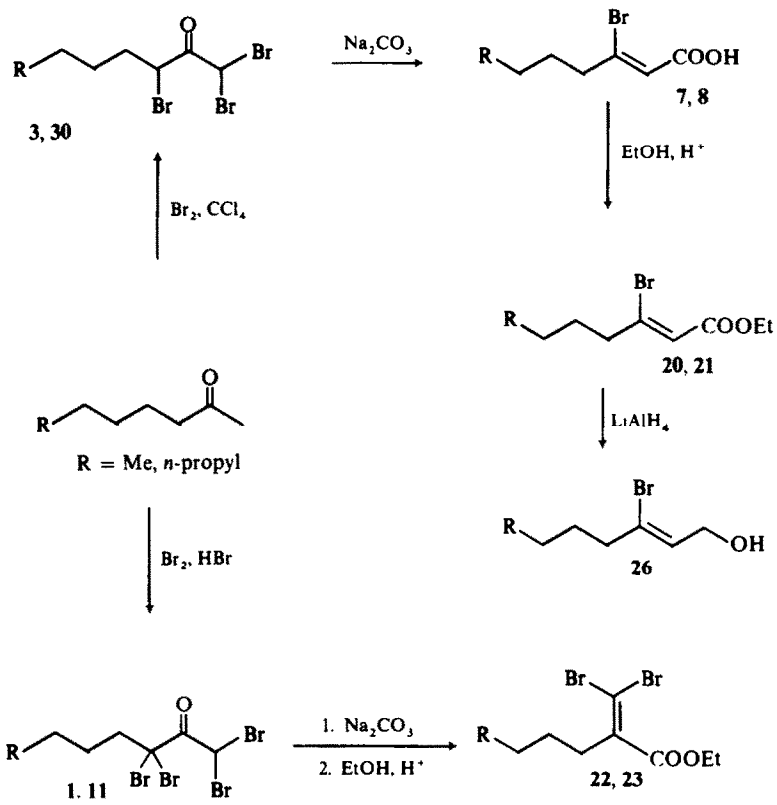


Fig. 4. Synthetic scheme for the production of the linear and branched esters from *Bonnemaisonia* spp. via Favorsky rearrangements of polyhalogenated 2-heptanone and 2-nonanone.

precursor detected which had an identical GLC retention time and MS to naturally-occurring **11**, gave 1,1,3,3-tetrabromo-2-heptanol (**12**) and **13**, respectively, which were identical (MS, GLC) to the natural products.

1,1,1,3-Tetrabromo-2-heptanol (**14**) and 1,1,1,3-tetrabromo-2-nonanol (**15**) were identified from their GLC retention times and MS characteristics. Both **14** and **15** were eluted during gas chromatography (3% SP-2401) immediately before **12** and **13**, respectively. Both **14** and **15** exhibited facile losses of HBr to provide fragment ions of *m/e* 348 and 376. Unlike the tetrabromo-alcohols **12** and **13**, these alcohols lose HBr between C-1 and C-2 to give the ionized analogs of 1,1,3-tribromo-2-heptanone (**3**) and 2-nonanone (**30**). The lower mass ranges in the MS of both alcohols were dominated by fragment ions arising from loss of *m/e* 171 ($^{+}CHBr_2$) and at *m/e* 171 ($+CHBr_2$) just as in the MS of **3** and **30**. In addition, an intense fragment ion containing bromine was observed at *m/e* 135 in the MS of both alcohols.

Bonnemaisonia hamifera. The results of chemical investigations of *B. hamifera* collected in the Gulf of California have already been reported [14]. The major constituent found was 1,1,3,3-tetrabromo-2-heptanone (**1**) (Table 1). In the light of our results with *B. nootkana* and *A. taxiformis*, with respect to the esterification of carboxylic acids by storage of the fresh algae in alcohol, we examined *B. hamifera* from Bahia Los Angeles, Gulf of California, Mexico, after storage in ethanol, and also *B. hamifera* collected in the drift in the Atlantic Ocean. The concentrated pentane extracts of the decanted ethanol solutions were examined by GLC (FID) and GC–MS as before.

B. hamifera contained, in order of abundance, *Z*-3-bromo-2-heptenoic acid (**7**) (ethyl ester = **20**), *E*-3-bromo-2-heptenoic acid (**28**) (ethyl ester = 29), 1,1,3,3-tetrabromo-2-heptanone (**1**), and 1,1,3-tribromo-2-heptanone (**3**) (Fig. 5). The acids were detected, as before, as their ethyl esters and were characterized by comparison (GLC, GC–MS) with the synthetic compounds and degradation standards used in the structure elucidation of the halogenated metabolites from *B. nootkana*. The co-occurrence of the *E* and *Z* isomers of 3-bromo-2-heptenoic acid was somewhat surprising since they do not readily interconvert by acid catalysis (conditions employed in the esterification of the acids **7** and **28** with sulfuric acid in ethanol) and since only the *Z* isomer was found in *B. nootkana*.

Our results contrast greatly with those reported earlier [14]. The presumed *in vivo* Favorsky rearrangement product of 1,1,3-tribromo-2-heptanone, the acid **7**, and the isomeric acid **28**, are in much greater abundance than 1,1,3,3-tetrabromo-2-heptanone (**1**). This pentane extract from *B. hamifera* is also quite different from that obtained from *B. nootkana*.

The pentane residue obtained from *B. hamifera* collected in the Atlantic was also shown to contain poly-

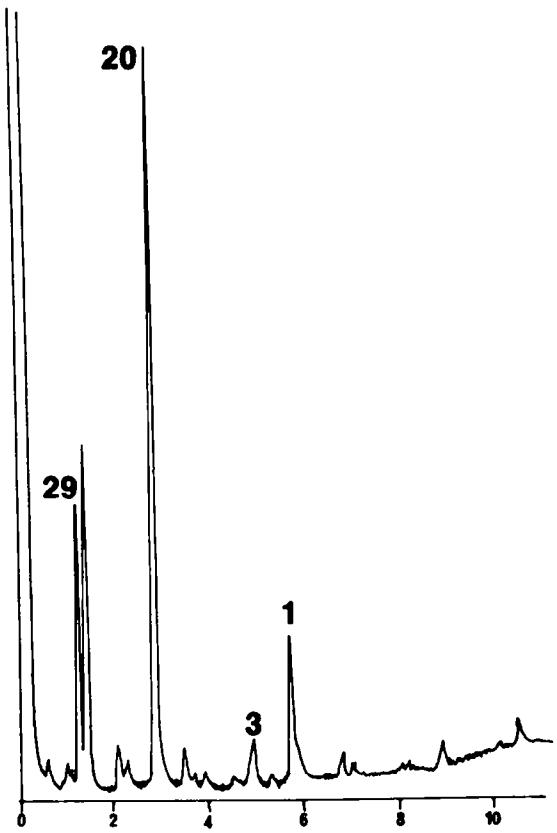


Fig. 5. Gas chromatographic analysis of the pentane extract of *Bonnemaisonia hamifera* from the Gulf of California.

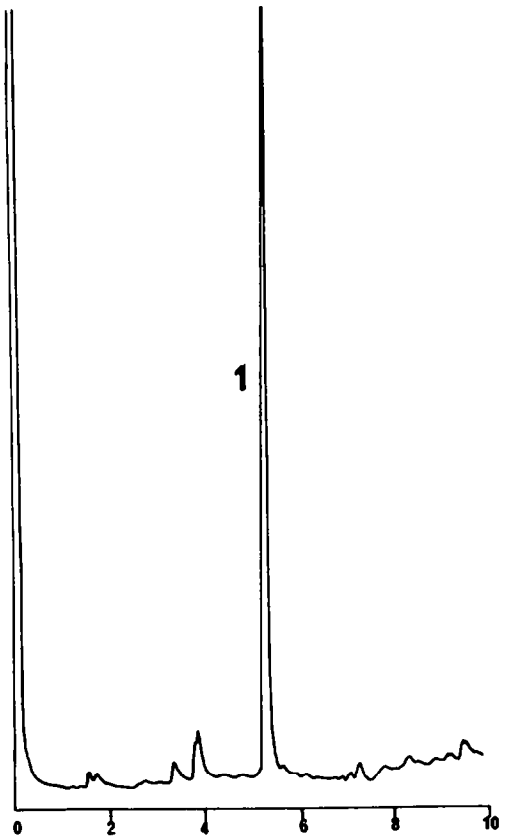


Fig. 7. Gas chromatographic analysis of the pentane extract of *Trailliella intricata* from the North Atlantic ocean.

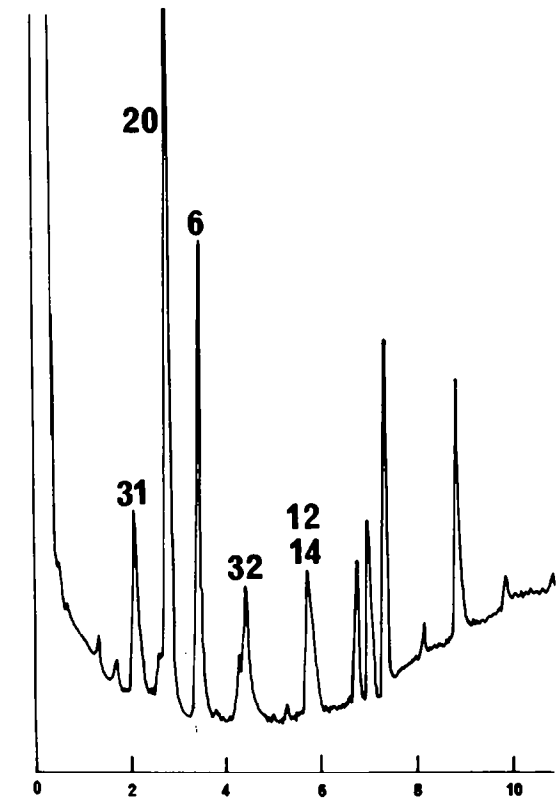


Fig. 6. Gas chromatographic analysis of the pentane extract of *Bonnemaisonia hamifera* from Woods Hole, Mass.

halogenated seven- and nine-carbon compounds as expected. This alga contained *Z*-3-bromo-2-heptenoic acid (**7**) as the major halogenated component (Fig. 6). It was detected as its ethyl ester (**20**). Comparison of the GLC retention times and MS from GC–MS of components from this residue with that of the $LiAlH_4$ and $NaBH_4$ reduction products of 1,1,3,3-tetrabromo-2-heptanone (**1**), resulted in the identification of 1,1-dibromo- (**31**), 1,1,3-tribromo- (**32**), 1,1,1,3-tetrabromo- (**14**), and 1,1,3,3-tetrabromo-2-heptanol (**12**). Also present was *trans*-1,3,3-tribromo-1-heptene oxide (**6**). In addition, another brominated compound was detected which appeared to be a dioxygenated C_9 compound based on its low resolution MS fragmentation pattern.

Trailliella intricata. *Trailliella intricata* is considered the alternate heteromorphic tetrasporophyte phase of both *Bonnemaisonia hamifera* and *B. nootkana* [20]. A collection of this alga, stored in alcohol, was kindly provided by Dr. M. Pederson. Examination of the pentane extract of the decanted alcohol solution by GLC, GC–MS, and ^1H NMR revealed that 1,1,3,3-tetrabromo-2-heptanone (**1**) was by far the major halogenated component (Fig. 7). This component had an identical GLC retention and MS with that of synthetic **1**. In addition, the ^1H NMR of the concentrated extract revealed a characteristic singlet at δ 6.75 (CCl_4) as found in synthetic **1**.

The presence of **1** in *T. intricata* in such large relative amounts is interesting. Like *Falkenbergia* [3, 9], *T. intricata* maintains the ability to synthesize the halogenated compounds found in the gametophyte, although

Table 4. Polyhalogenated 1-octen-3-ones from *B. asparagoides*

	X_1	X_2	X_3	%	*E/Z*
38	H	Cl	Br	7.8	1.0
39	Cl	Cl	Br	66.5	20.0
40	Br	Br	Cl	5.7	—
41	Cl	Br	Br	17.1	*E*
42	Br	Br	Br	1.0	*E*

in both cases its morphology and habitats are significantly different.

Recently, the tetrasporophyte of *B. hamifera* Har. (presumably *T. intricata*, collected near Aarhus, Denmark) has been shown by GC–MS to contain **1–5**, (Table 1) **12**, **22**, **29**, and **32** as well as 1,1-dibromo-2-heptanone (**33**), 1,1,3,3-tetrabromo- (**34**), 1,3,3-tribromo- (**35**), and 1,1,3-tribromo-2-acetoxyheptane (**36**), and 1,3,3-tribromo-2-heptanol (**37**) [26]. The *trans*-epoxide **6** was also claimed to be present, although the evidence provided was insufficient to differentiate this compound from either *cis*- or *trans*-1,1,3-tribromo-2-heptene oxide. It was clearly different from that found by us in *B. nootkana*.

Bonnemaisonia asparagoides. We found that *B. asparagoides* contains five closely related bromine- and chlorine-containing 1-octen-3-ones, **38–42**, instead of compounds similar to those observed in other *Bonnemaisonia* species (Table 4). As mentioned earlier, related compounds have recently been isolated from *Delisea fimbriata* [12] and *Ptilonia australasica* [10, 13].

From a small collection of *B. asparagoides* (collected near La Escala, Spain and immediately stored in 95% ethanol), a residue (10 mg) was obtained and examined by GC–MS. Five major halogen-containing compounds were eluted in the order of **38–42** (Table 4) as the most volatile components of the extract (Fig. 8). The structures of these compounds were tentatively assigned after interpretation of their MS fragmentation patterns [27]

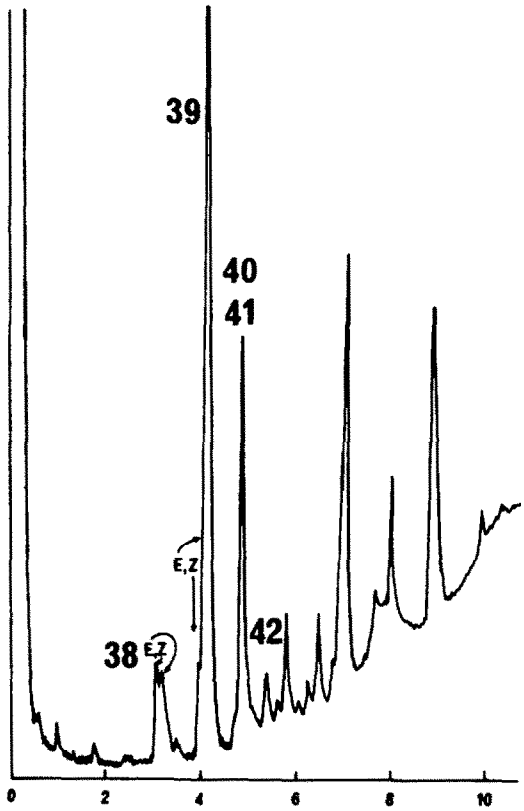


Fig. 8. Gas chromatographic analysis of the pentane extract of *Bonnemaisonia asparagoides* from the Mediterranean Sea.

which included fragment ions corresponding to McLafferty rearrangement, α-cleavage products, and loss of halogen. Subsequently, the total structures and stereochemistry were confirmed by synthesis [18] (Fig. 9).

The mixtures, *E,Z*-1-bromo-1,2-dichloro-1-octen-3-one (**38**) and *E,Z*-1-bromo-1,2,4-trichloro-1-octen-3-one

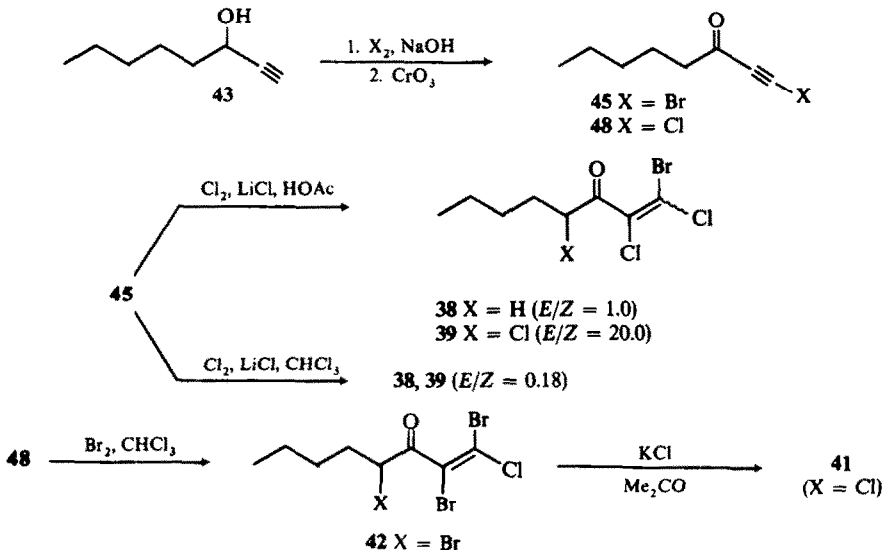


Fig. 9. Synthesis of polyhalogenated octenones found in *Bonnemaisonia asparagoides*.

(**39**) were synthesized from 1-octyn-3-ol (**43**) via bromination to yield 1-bromo-1-octyne-3-ol (**44**), followed by oxidation with Jones' reagent to provide 1-bromo-1-octyn-3-one (**45**), and then chlorination with chlorine in acetic acid with a trace of sulfuric acid to obtain a 1:1 mixture of **45** and 4-chloro-1-bromo-1-octyn-3-one (**46**). This mixture was again chlorinated but with lithium chloride and under two conditions—in chloroform to obtain predominantly the *Z* isomers of **38** and **39**, and in acetic acid to obtain predominantly the *E* isomers. *Z*-1-Bromo-1,2,3-trichloro-1-octen-3-one was isomerized to the *E* isomer (**39**) by treatment with bromine in acetic and sulfuric acids.

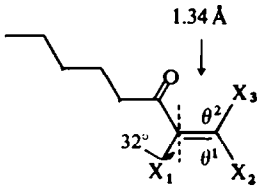
E-1-Chloro-1,2,4-tribromo-1-octen-3-one (**42**) was synthesized from 1-octyn-3-ol (**43**) by terminal chlorination with chlorine in basic aqueous methanol to yield 1-chloro-1-octyn-3-ol (**47**), oxidation with Jones' reagent to yield 1-chloro-1-octyn-3-one (**48**), and then bromination with bromine in chloroform. *E*-1,2-Dibromo-1,4-dichloro-1-octen-3-one (**41**) was obtained by treating **42** with potassium chloride in acetone. Both of the synthetic ketones were identical (GLC, MS) with the naturally-occurring compounds.

The structure of the remaining octenone, 2,4-dibromo-1,1-dichloro-1-octen-3-one (**40**), was assigned by comparing the GLC retention time and MS of 1,4-dibromo-2,3-dichloro-1-octen-3-one (**49**), which was obtained by substitution of a bromine for a chlorine at C-4 in **39** with sodium bromide in acetone, with that of the naturally-occurring compound. Although this compound exhibits characteristic MS fragments which clearly relate it to **40**, they are not identical. Since the differences (retention time and MS relative abundances) could not be accounted for by the C-1/C-2 geometrical isomer, **40** was assigned as 2,4-dibromo-1,1-dichloro-1-octen-3-one.

Assignment of *E* and *Z* isomers in these trihalo-olefin systems is a significant problem, since one cannot resort to the interpretation of chemical shifts and coupling constants in their ^{1}H NMR spectra. Analogy with vicinal dihalo-olefins reveals that if the precursor acetylene is treated with a halide ion and molecular halogen, a greater proportion of the isomer with the *trans*-oriented halogens is obtained than if the halide ion is excluded from the reaction medium [28–30]. This follows from the nucleophilic attack of the halide ion on the intermediate **50** to give a *trans* product (Fig. 10). In these cases, though, simple phenyl acetylenes were used.

Calculations were made using the van der Waals radii of the halogens in the polyhalogenated 1-octen-3-ones to determine the most stable arrangement of the olefin, *E* or *Z*, after the following considerations. IR and UV data from the synthetic mixtures of the polyhalogenated 1-octen-3-ones, and from the compounds obtained from *D. fimbriata* [12], indicated that in order to alleviate the steric repulsions between the carbonyl and *Z*-(*β*)-halogen, the carbonyl rotates out of coplanarity. In the IR spectra of **38**, **39**, and 1,1,2-tribromo-1-octen-3-one [12], the carbonyl stretching frequency ($\nu_{C=O}$) is observed at 1710–1745 cm^{-1}, instead of lower, anticipated values of 1675–1695 cm^{-1} [31]. Higher values in the range 1710–1745 cm^{-1} correspond to the compounds with a halogen at C-4. That the *α*,*β*-unsaturated ketones are not in the *s-cis* conformation is revealed by the UV data. Predicted values for the *n*-*π** transitions are at least 300 nm [32] whereas the observed values are ≤283 nm for these same compounds. In addition, it was not expected that the combined van der Waals radii of two halogens in the same molecule would be as great as that between molecules since the radii for chlorine is 1.80 Å (bromine—1.95 Å), but the distance between chlorine atoms in 1,1-dichloroethylene is 2.9 Å [33–37].

Table 5. *Bonnemaisonia asparagoides*—calculations—steric interactions—polyhalogenated octenones



		X_1	X_2	X_3	θ_1	θ_2	$X_1 - X_3(\Delta)$	$X_2 - X_3(\Delta)$	$\Sigma\Delta$
1.	(*E*)	Cl	Cl	Br	120	116	3.11 (0.49)	3.13 (0.62)	1.11
2.		Cl	Cl	Br	119	118	3.09 (0.51)	3.12 (0.63)	1.14
3.	(*Z*)	Cl	Br	Cl	120	116	3.17 (0.58)	3.13 (0.62)	1.20
4.		Cl	Br	Cl	119	118	3.14 (0.61)	3.12 (0.63)	1.24
5.	(*E*)	Br	Cl	Br	120	116	3.17 (0.58)	3.13 (0.62)	1.20
6.		Br	Cl	Br	119	119	3.14 (0.61)	3.10 (0.65)	1.26
7.	(*Z*)	Br	Br	Cl	120	116	3.23 (0.67)	3.13 (0.62)	1.29
8.		Br	Br	Cl	119	118	3.20 (0.70)	3.12 (0.63)	1.33

Δ = distances below expected van der Waals radii.

Of the various bond angles and bond lengths used for the calculations [33–37], the two listed for each isomer gave the minimum deviations from expected van der Waals radii (Table 5). The *E* isomer consistently showed less deviation than the *Z* isomer and hence was determined to be the thermodynamically more stable isomer.

Biogenesis of halogenated metabolites in Bonnemaisonia

All halogenated compounds found in members of the red algal family Bonnemaisoniaceae appear, on structural grounds, to be derived via acetate through a fatty acid or polyketide biosynthetic pathway. The halogenated secondary metabolites characterized from *B. hamifera*, *B. nootkana*, and *T. intricata* are biogenetically interesting because of their apparent origin from 2-heptanone and 2-nonanone. Both of these latter compounds have been found in plants, insects, and dairy products [38], and 2-heptanone has been shown to function as a pheromone in bees and ants [38]. 2-Heptanone and 2-nonanone, both constituents of Cheddar cheese, have also been shown to attract cheese mites [39].

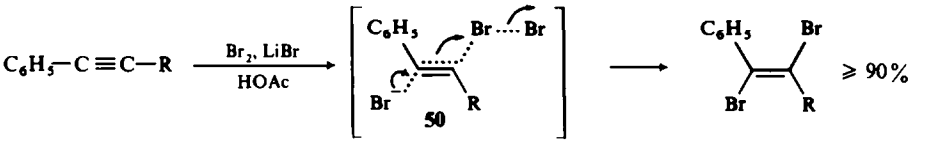


Fig. 10. Synthesis of *trans*-isomers of dihalo-olefins.

Most evidence strongly suggests that naturally-occurring methyl ketones are biosynthesized by decarboxylation of β-keto acids formed during the process of β-oxidation of fatty acids [38, 40]. However, the production of methyl ketones from anabolic fatty acid biosynthesis has also been demonstrated [41]. Also, most 2-alkanols are generally thought to be biosynthesized from the corresponding methyl ketones [38]. We have been able to incorporate both sodium acetate -[2-^{14}C] and sodium palmitate-U-[^{14}C] into *trans*-1,3,3-tribromo-1-heptene oxide (**6**) using freshly collected and intact *B. nootkana* (McConnell, O. J., Young, D. N. and Fenical, W., manuscript in preparation). We were not able to differentiate between an anabolic or catabolic biosynthetic pathway, but we did provide evidence to support the claim of a fatty acid pathway being involved in the biosynthesis of **6** (Fig. 11).

Bromination at activated carbons, reduction, base-rearrangement (Favorsky), and elimination appear to comprise the enzymatic reactions which result in the halogenated metabolites observed in *Bonnemaisonia* species. Hager, who has extensively studied the halogenating enzyme, chloroperoxidase [42–46], isolated from *Caldariomyces fumago*, has recently isolated and partially purified a bromoperoxidase from *B. hamifera* collected in the Gulf of California [47]. Enzymatic bromination of 3-ketooctanoic acid resulted in 1-bromo-, 1,1-dibromo-, and 1,1,1-tribromo-2-heptanone and other, uncharacterized, products. Thus, the transformation from 3-ketooctanoic acid or 2-heptanone to polyhalogenated 2-heptanones has already been verified.

Many of the halogenated organic compounds detected and identified in extracts of *Asparagopsis* and *Bonnemaisonia* species appear to be derived by *in vivo* Favorsky type rearrangements [48–50]. These halogenated compounds include the halogenated acrylic acids in *Asparagopsis* species [2], and *Z*-3-bromo-2-heptenoic (**7**) and 2-nonenoic acids (**8**), and 2-*n*-butyl- and 2-*n*-hexyl-3,3-dibromoacrylic acids (**9**, **10**) in *Bonnemaisonia* species. Presumed precursors to the rearrangement products are 1,1,3-tribromo- and 1,1,3,3-tetrabromo-2-ketones, which are also found in the organic extracts of these algae.

It is generally accepted that the Favorsky rearrangement proceeds by one of two mechanisms depending on the structure of the α-halogenated ketone. A 'semibenzilic' acid mechanism is favored when the α′ position has a non-acidic, hindered, or otherwise inaccessible hydrogen atom [48]. Otherwise, compounds may rearrange by a path involving a cyclopropanone intermediate formed by loss of both α-halogen and α′-hydrogen atoms. In general, acyclic α-halogenated ketones undergo Favorsky rearrangement via the cyclopropanone intermediate [49]. The direction of base-induced ring-opening is a function of the structure of the cyclopropanone and to a lesser extent of the structure of the attacking base. In most cases, the major product may be predicted from ring-opening of the cyclopropanone to give the more stable carbanion (primary > secondary > tertiary). However, if there are bulky substituents attached to the cyclopropanone intermediate, bond cleavage to relieve steric interactions may result in the less stable carbanion. The latter factor appears to predominate in the Favorsky rearrangement reactions of 1,1,3-tribromo-2-hepta- (**3**) and 2-nonanone (**30**), and 1,1,3,3-tetrabromo-2-hepta- (**1**) and 2-nonanone (**11**).

The linear seven- and nine-carbon polyhalogenated ketones, alcohols, epoxide, and the presumed *in vivo* Favorsky rearrangement products, the linear and branched acids, appear to be derived from an intermediate such as 3-ketooctanoic or 3-ketodecanoic acid. The biogeneses of the eight- and nine-carbon halogenated compounds in *B. asparagoides*, *D. fimbriata*, and *P. australasica*, however, do not appear to be as simple. The polyhalogenated 1-octen-3-ones could be derived from 3-ketooctanoic acid via a multistep reduction, dehydration, and halogenation similar to that proposed for the halobutenones [2]. On the other hand, the polyhalogenated nine-carbon lactones (the γ-pyrones) and the 1-octen-3-ones could be derived from polyhalogenated 2,4-nonadiones (with hydroxylation at C-6 for some of

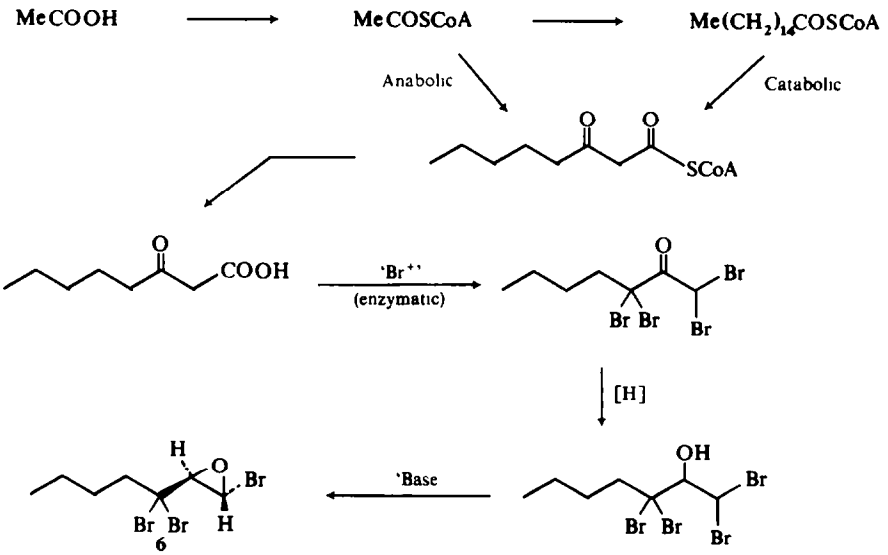


Fig. 11. Biosynthesis of *trans*-1,3,3-tribromo-1-heptene oxide.

the lactones or polybrominated 2,4,6-nonatriones for the γ-pyrones) via Favorsky reactions (Fig. 12). Base reaction, involving the C-2 carbonyl, could ultimately yield the halo-1-octen-3-ones and γ-pyrones. Reactions involving the C-4 carbonyl could yield the C-4 carboxylate substituted *n*-octane skeleton which, through enolization of the remaining carbonyl toward C-1, could cyclize to give the *Delisea* lactones.

Conclusions

The most intriguing aspects of the chemical investigations presented above are the relationship between the numerous halogenated organic compounds and vesicular cells in *Bonnemaisonia* species, and the functions of these compounds and cells in the algae. Vesicular cells are morphologically distinct and highly specialized vegetative cells characteristic of the Bonnemaisoniaceae [51, 52]. These cells were demonstrated by early European investigators to liberate molecular iodine under a variety of conditions, all of which resulted in the death of the cells [53–56]. Recently, Wolk has shown by X-ray fluorescence microprobe spectroscopy that vesicular cells contain thirty times the amount of bromine, three times the amount of iodine, and only half the amount of chlorine as the adjacent vegetative cells, but in unknown form [57]. Wolk showed that bromine, and not iodine, is the predominant halogen in these cells. We believe that the halogenated (mainly brominated) organic compounds we have characterized are stored in the vesicular cells due to the evidence provided by Wolk and to the fact that most of these compounds are strong alkylating agents [58] which require isolation from the numerous reactive functionalities found in biochemically important molecules.

Several lines of evidence suggest that both halogenated organic compounds and vesicular cells function in a chemical defense capacity. Most of the compounds we have characterized are quite toxic to microorganisms [15, 16]—minimum inhibitory concentrations of the tetrabrominated ketones **1** and **11** against *Staphylococcus aureus* are 37 and 0.05 μg/ml, respectively, and against *Candida albicans* are 25 and 0.05 μg/ml, respectively. We have not observed signs of predation during numerous field observations when collecting *Bonnemaisonia*. In

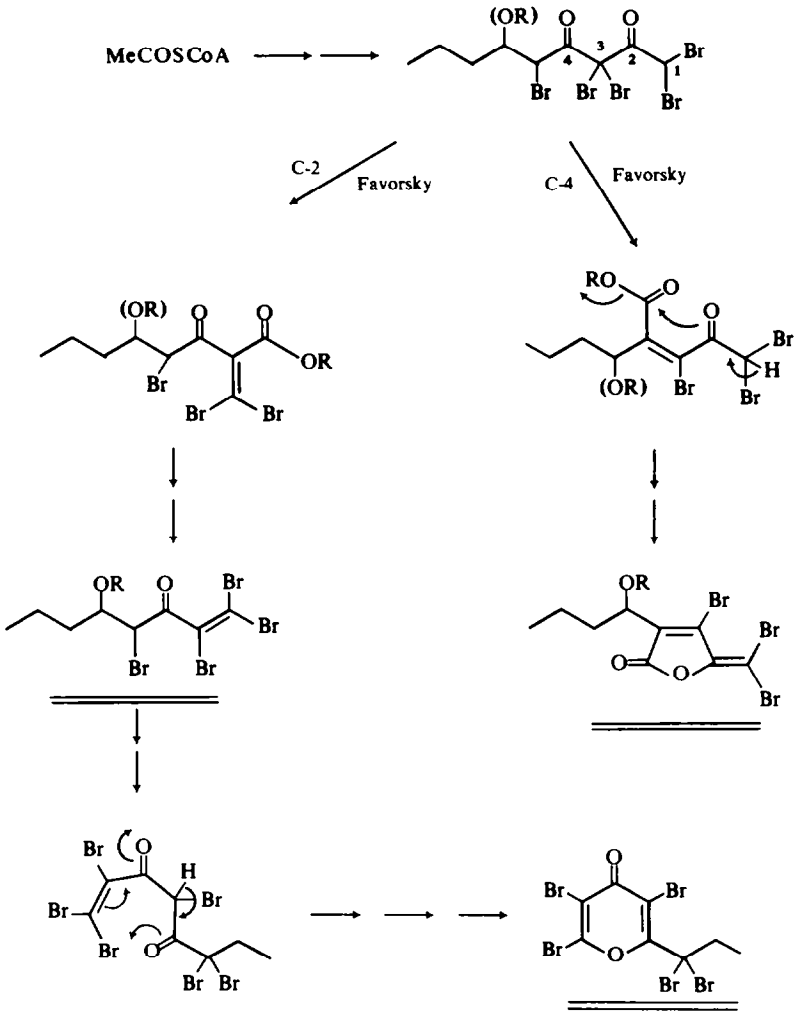


Fig. 12. Proposed biogenesis of *Delisea*, *Ptilonia*, and *Bonnemaisonia*-derived compounds involving Favorsky rearrangements.

addition, these algae have a strong odor of halogenated compounds when freshly collected. This seems to reflect the fact that these compounds are actively exuded from the vesicular cells which, in *Bonnemaisonia* species, are located evenly over the entire thallus amongst the outer cortical cells [51, 52]. Most plant chemical defenses can afford to be passive and portions of the plant are eaten before the anti-feedent effect is realized. *Bonnemaisonia* species appear to have localized defensive compounds in the vesicular cells to discourage predators.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Varian HR-220 and Varian EM 360 spectrometers. The Varian HR-220 spectrometer has computerized Fourier transform and spin-decoupling capabilities. ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer. Chemical shifts are expressed as δ values in ppm relative to TMS = 0. Low resolution GC–MS were obtained using a Hewlett–Packard 5930A mass spectrometer interfaced with a Hewlett–Packard 5910 gas chromatograph and using an LKB 9000 GC–MS system. High resolution mass measurements were supplied by Dr. K. Fang, Department of Chemistry, U.C.L.A. Gas chromatograms (FID) and GC–MS were obtained by temp. programming; *Bonnemaisonia* and *Trailliella* species—120 to 250° at 16°/min with 2 min delay. For all gas chromatograms, a 2 m × 2 mm glass column packed with 3% SP-2401 was used with He as the carrier gas at 60 ml/min. Acid = 5% HCl (aq.). Base = satd $NaHCO_3$ soln. Brine = satd NaCl soln.

Bonnemaisonia nootkana—*collection and work-up.* A collection of this alga was made 0.25 mile off Monestary Beach, Carmel, California, at a depth of 70–90 ft on 14 August 1975. The algae were immediately stored in 95% EtOH. Subsequently, the algae were homogenized and heated to reflux for 2 hr in 95% EtOH–$CHCl_3$ (1:1). The filtrate was reduced in vol. *in vacuo* and the residue was taken up in Et_2O. Before the major extraction, a portion of the EtOH soln was extracted with purified pentane and the reduced pentane was investigated by GLC (Fig. 1) and GC–MS. The extract (7.5 g) was obtained from *ca* 900 g of fresh wet algae (0.83% extract, fr. wt).

Structure elucidation—Trans-1,3,3-*tribromo*-1-*heptene oxide* (**6**). The organic extract (7.0 g) was chromatographed on Si gel (2.5 × 100 cm). The first compound, which was eluted with 100% petrol, was the straight chain hydrocarbon *n*-heptadecane, as determined by NMR and GC–MS. Increasing the polarity of the solvent system to 1–2% Et_2O in petrol eluted 1.86 g of the major component (26.6% crude extract, 0.22% wet wt), *trans*-1,3,3-tribromo-1-heptene oxide (**6**). Compound **6** provided the following data: $[\alpha]_D^{23}$ +78.6 (*c* 6, $CHCl_3$) $M^+ - Br = C_7H_{11}O^{79}Br_2$ (obs. 268.919, calc. 268.918); ^{1}H NMR ($CDCl_3$ (C_6D_6)): δ 0.95 (3H, 7, J = 7 (0.79)), 1.43 (2H, *q*, *t*, J = 7, 7 (1.14)), 1.80 (2H, *d*, *d*, *t*, J = 7, 7, 7 (1.75)), 2.42 (1H, *m* (2.32)), 2.62 (1H, *m* (2.50)), 3.88 (1H, *d*, J = 3 (3.33)), 5.34 (1H, *d*, J = 3 (4.51)); 20 MHz ^{13}C NMR (C_6D_6 ($CDCl_3$)): C-1, δ 60.2 (56.0) (*d*); C-2, 63.5 (59.4) (*d*); C-3, 68.2 (64.2) (*s*); C-4, 45.8 (41.8) (*t*); C-5, 30.0 (25.8) (*t*); C-6, 22.1 (18.0) (*t*); C-7, 13.9 (9.8) (*q*); low resolution MS (50 eV): 269 (2.0, Br_2), 268 (0.8, Br_2), 240 (0.2, Br_2), 239 (0.2, Br_2), 227 (0.03, Br_2), 226 (0.02, Br_2), 211 (0.03, Br_2), 199 (0.7, Br_2), 198 (0.4, Br_2), 189 (1.5, Br), 173 (0.2, Br), 171 (0.3, Br), 161 (0.5, Br), 159 (0.7, Br), 147 (0.8, Br), 133 (2.5, Br), 131 (0.9, Br), 119 (7.5, Br), 81 (100), 67 (6.5), 55 (26.7), 53 (14.2), 41 (13.3), 39 (15.0).

Synthesis of (±)-trans-1,3,3-*tribromo*-1-*heptene oxide*, (**6**). To 2-heptanone (**19**) (7.7 g, 0.068 mol), cooled to 0°, was added, with stirring, 5 ml 48% HBr (aq.). After 5 min, Br_2 (37.8 g. 0.239 mol, 12.1 ml) was added dropwise and the reaction mixture was stirred for 10 days at room temp. Brine (50 ml) was added and the mixture was extracted with 3 × 50 ml Et_2O. The combined Et_2O layers were washed with 2 × 30 ml brine, dried, and reduced *in vacuo* to yield 22 g 99% pure (GLC, NMR) 1,1,3,3-tetrabromo-2-heptanone, (**1**) (76% yield): IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1736; ^{1}H NMR (60 MHz, CCl_4): δ 6.75 (1H, *s*), 2.4–2.7 (2H, *m*), 1.3–1.8 (4H, *m*), 0.98 (3H, *t*, J = 7); ^{13}C NMR (20 MHz, $CDCl_3$): δ 33.8 (*d*, C-1), 185.9 (*s*, C-2), 64.6 (*s*, C-3), 44.3 (*t*, C-4), 29.1 (*t*, C-5), 21.8 (*t*, C-6), 13.8 (*q*, C-7); low resolution MS (50 eV): 370 (3.0, Br_4), 347 (0.4, Br_3), 305 (0.7, Br_3), 291 (0.7, Br_3), 267 (1.4, Br_2), 255 (2.1, Br_2), 227 (7.4, Br_2), 199 (3.0, Br_2), 171 (11.1, Br_2), 147 (21.1, Br), 120 (7.4, Br), 114 (8.7, Br), 67 (81.5), 55 (18.5), 53 (16.7), 51 (13.7), 43 (40.7), 41 (100), 39 (85.2).

Trans-1,3,3-tribromo-1-heptene oxide (**6**), was synthesized by adding excess $NaBH_4$ to **1** (6 g, 14.1 mmol) in 100 ml MeOH at room temp. with stirring until no further reaction occurred. The mixture was stirred for 18 hr at room temp. and then worked up by adding acid and brine, extracting with Et_2O, washing the combined Et_2O layers with brine, drying, and reducing *in vacuo* to yield 3.5 g of a complex mixture containing six major components by GLC. One of these components was identical (GLC retention time, MS; 15% yield—GLC) to naturally-occurring **6**.

E-3-*Bromo*-2-*hepten*-1-*ol* (**16**). $LiAlH_4$ (*ca* 0.02 g, 0.5 mmol) was added in one portion with stirring to **6** (0.185 g, 0.53 mmol) in 50 ml dry Et_2O at 0° under N_2. The ice bath was removed after 5 min and the reaction mixture was stirred for 1.5 hr. Water was cautiously added dropwise until no more reaction occurred. A pinch of $MgSO_4$ was stirred in and after several min the Et_2O soln was filtered and reduced *in vacuo* to yield 0.08 g of pure *E*-3-bromo-2-hepten-1-ol (**16**) (79% yield): IR (CCl_4) cm^{-1}: ν_{O-H} 3215 (strong), $\nu_{C=C}$ 1640 (med.); ^{1}H NMR (220 MHz ($CDCl_3$) (60 MHz, CCl_4)): δ 6.15 (1H, *t*, J = 7) (6.05), 4.11 (2H, *d*, J = 7) (4.00), 2.50 (2H, *t*, J = 8) (2.49), 1.57 (2H, *m*), 1.33 (2H, *m*), 0.93 (3H, *t*, J = 7) (0.96); low resolution MS (50 eV): 192 [M^+] (0.9, Br), 113 (10.7), 95 (21.4).

E-3-*Bromo*-2-*heptenal* (**27**). To pyridinium chlorochromate (0.127 g, 0.59 mmol) in 2 ml CH_2Cl_2 was added *E*-3-bromo-2-hepten-1-ol (**16**) (0.051 g, 0.26 mmol), with stirring, in 2 ml CH_2Cl_2. After stirring for 2 hr at room temp., the reaction mixture was diluted with Et_2O, filtered and then passed through a Si gel column (0.5 × 5.0 cm) with 100% Et_2O to obtain 0.03 g pure *E*-3-bromo-2-heptenal (**27**) (61% yield): IR (CCl_4) $\nu_{C=O}$ 1681 cm^{-1} (strong), $\nu_{C=C}$ 1613 cm^{-1} (med.); ^{1}H NMR (60 MHz, CCl_4) δ 9.7 (1H, *d*, J = 6), 6.5 (1H, *d*, J = 6), 3.0 (2H, *t*, J = 6), 1.2–1.8 (4H, *m*), 0.9 (3H, *t*, J = 6).

E-3-*Bromo*-2-*heptenoic acid* (**28**). To *E*-3-bromo-2-hepten-1-ol, (**16**) (0.146 g, 0.77 mmol) in 20 ml Me_2CO was added Jones' reagent dropwise, with stirring, at room temp until an orange color persisted. The mixture was stirred for 2 hr at room temp, 50 ml brine was added, and the mixture was extracted with 3 × 40 ml Et_2O. The combined Et_2O layers were washed with 30 ml base, 2 × 30 ml brine, dried ($MgSO_4$) and reduced *in vacuo* to give 0.11 g material. Pure *E*-3-bromo-2-heptenoic acid (0.09 g, 57% yield) was eluted with 75% Et_2O in petrol from Si gel chromatography: IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1695 (strong), $\nu_{C=C}$ 1620 (med.); ^{1}H NMR (60 MHz, CCl_4); δ 11.2 (1H, *s*), 6.40 (1H, *s*), 3.13 (2H, *t*, J = 6.5), 1.2–1.8 (4H, *m*), 0.95 (3H, *t*, J = 6); low resolution MS (50 eV): 206 (0.9, Br), 177 (1.3, Br), 127 (34.8), 109 (7.8), 97 (9.1), 85 (39.1), 81 (60.9), 55 (47.8), 43 (91.3), 41 (100), 39 (91.3).

Ethyl E-3-*Bromo*-2-*heptenoate* (**29**). *E*-3-Bromo-2-heptenoic acid, (**28**) (0.031 g, 0.15 mmol), was esterified with 95% EtOH (3.0 ml) and H_2SO_4 (0.5 ml) by stirring at room temp. for 6 hr and at reflux for 1 hr. After work-up, 0.027 g of the ester **29** was

obtained pure (77%): ^{1}H NMR (60 MHz, CCl_4): δ 6.30 (1H, *s*), 4.15 (2H, *q*, J = 7), 3.13 (2H, *t*, J = 7), 1.1–1.8 (7H, *m*), 0.95 (3H, *t*, J = 6); low resolution MS (50 eV): 234 [M^+] (1.3, Br), 205 (1.0, Br), 189 (8.3, Br), 177 (1.0, Br), 155 (70.7), 127 (19.0), 113 (11.0), 109 (20.7), 85 (24.4), 81 (100.0), 69 (19.5), 67 (25.6), 55 (43.9), 53 (29.3), 43 (51.2), 41 (53.7), 39 (43.9).

E-7-*Bromo*-6-*undecen*-5-*ol* (**17**). *Trans*-1,3,3-tribromo-1-heptene oxide, (**6**) (0.187 g, 0.54 mmol), in 15 ml dry THF was cooled to −78° with a dry ice–acetone bath under argon. *n*-Butyllithium (0.23 ml 2.3 M soln, 1.00 mmol) was delivered by syringe into this soln with stirring and this mixture was stirred for 2 hr at −78°. The reaction was quenched by cautious addition of 1.5 ml H_2O. The reaction soln was diluted with 75 ml petrol. The organic phase was washed with 2 × 10 ml brine, dried, and reduced *in vacuo* to yield 0.1 g of pure *E*-7-bromo-6-undec-5-ol (**17**) (75% yield): ^{1}H NMR (220 MHz, C_6D_6): δ 5.91 (1H, *d*, J = 8.5), 4.07 (1H, *m*), 2.32 (2H, *t*, J = 7), 1.14–1.73 (10H, *m*), 1.05 (6H, *t*, J = 8); IR (CCl_4) cm^{-1}: ν_{O-H} 3472 (weak, sharp) and 3279, $\nu_{C=C}$ 1650; low resolution MS (50 eV): 191 (10.3, Br), 169 (11.3), 135 (6.5, Br), 127 (19.4), 113 (11.3), 111 (16.1), 93 (32.3), 85 (54.8), 69 (41.9), 67 (35.5), 57 (77.4), 55 (64.5), 43 (77.4), 41 (100), 39 (32.3); GLC retention time = 5.2 min from temp. programming 120–250°, 2 min delay, 16°/min (3%SP-2401).

E-7-*Bromo*-6-*undecen*-5-*one* (**18**). Pyridinium chlorochromate was used to oxidize *E*-7-bromo-6-undecen-5-ol, (**17**) (see *E*-3-bromo-2-heptenal for procedure). A 50% yield of **18** resulted from 0.064 g **17** (0.26 mmol) after prep. Si gel TLC. ^{1}H NMR (60 MHz, CCl_4): δ 6.6 (1H, *s*), 3.05 (2H, *t*, J = 7), 2.40 (2H, *t*, J = 7); IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1690 (med.), $\nu_{C=C}$ 1600 (med.–str.); low resolution MS (50 eV): 246 [M^+] (1.5, Br), 217 (0.5, Br), 189 (4.6, Br), 167 (12.1), 137 (10.3), 125 (6.4), 109 (9.0), 95 (9.5), 85 (100), 81 (30.8), 67 (16.7), 57 (89.7), 55 (23.1), 53 (19.2), 43 (24.4), 41 (61.5), 39 (26.9).

Structure elucidation of ethyl Z-3-*bromo*-2-*heptenoate* (**20**) *and ethyl* Z-3-*bromo*-2-*nonenoate* (**21**). Both ethyl *Z*-3-bromo-2-heptenoate (**20**), and ethyl *Z*-3-bromo-2-nonenoate (**21**) were eluted with 5–10% Et_2O in petrol from Si gel column chromatography, but in minor amounts (1 and 0.9% crude extract, respectively), and in complex mixtures. The structures of these compounds were initially determined from their low resolution MS (50 eV): **20**—234 [M^+] (0.8, Br), 189 (1.0, Br), 155 (25.0), 127 (12.5), 120 (5.8, Br), 119 (5.8, Br), 113 (16.7), 109 (16.7), 95 (16.7), 85 (29.2), 81 (100), 67 (33.3), 55 (41.7), 53 (33.3), 43 (50.0), 41 (58.3), 39 (50.0); **21**—262 [M^+] (0.1, Br), 217 (7.2, Br), 193 (7.8, Br), 183 (22.2), 155 (10.0), 137 (23.9), 113 (24.4), 109 (100), 95 (62.7), 85 (42.7), 81 (52.4), 69 (52.4), 67 (87.8), 55 (67.1), 43 (95.1), 41 (97.6), 39 (48.8). Both of these compounds were synthesized.

Synthesis of ethyl Z-3-*bromo*-2-*heptenoate* (**20**). To 2-heptanone (1.14 g, 0.01 mol) in 100 ml CCl_4 was added, with stirring and at room temp., excess Br_2 (11.9 g, 0.075 mol, 3.8 ml). The mixture was stirred for 18 hr at room temp. Excess $MgSO_4$ was added with stirring. The soln was filtered and reduced *in vacuo*. The residue was taken up in Et_2O and passed over Si gel (0.5 × 5.0 cm). The Et_2O solution was again reduced to yield 3.44 g which, by GLC and GC–MS, contained 1,1,3-tribromo-2-heptanone (**3**) of 76% purity (1,3-dibromo-2-heptanone and 3,3-dibromo-2-heptanone were the only other components present). IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1725 (strong); ^{1}H NMR (60 MHz, CCl_4): δ 6.28 (1H, *s*), 4.77 (1H, *t*, J = 6.5), 2.0–2.6 (2H, *m*), 1.3–1.7 (4H, *m*), 0.95 (3H, *t*, J = 6); low resolution MS (50 eV): 292 (1.0, Br_3), 269 (0.6, Br_2), 227 (1.6, Br_2), 177 (8.4, Br), 171 (5.0, Br_2), 149 (4.4, Br), 147 (3.0, Br), 120 (6.6, Br), 119 (6.6, Br), 69 (90.0), 55 (28.0), 41 (100), 39 (58).

Without further purification, the mixture containing 1,1,3-tribromo-2-heptanone (**30**) (1.3 g) was dissolved in 30 ml H_2O and MeOH (4:1) and treated with $NaHCO_3$ (1.4 g, 0.013 mol) at room temp. for 22 hr. Brine (50 ml) was added and the mixture was extracted with 50 ml Et_2O. The aq. layer was acidified to 4 < pH < 7 and then extracted with 2 × 50 ml Et_2O. The combined Et_2O layers were washed with 2 × 30 ml brine, dried, and reduced to yield 0.9 g of a mixture of products. Pure *Z*-3-bromo-2-heptenoic acid (**7**) (0.12 g, 20% yield) was obtained from Si gel chromatography by elution with 40% Et_2O in petrol. IR (CCl_4) cm^{-1}: $\nu_{O=H}$ 2600–3200 (broad), $\nu_{C=O}$ 1705 (strong), $\nu_{C=C}$ 1630 (med.); ^{1}H NMR (60 MHz, CCl_4): δ 9.5 (1H, *bs*), 6.31 (1H, *s*), 2.65 (2H, *t*, J = 7), 1.2–1.7 (4H, *m*), 0.95 (3H, *t*, J = 6).

Z-3-bromo-2-heptenoic acid (**7**) (0.1 g, 0.49 mmol) was added to 3 ml 95% EtOH and 0.5 ml H_2SO_4 and heated under reflux 1 hr. The reaction soln was taken up in 80 ml petrol, which was washed with 2 × 20 ml brine. After drying and removing the solvent *in vacuo*, 0.09 g of ethyl *Z*-3-bromo-2-heptenoate (**20**) was obtained (78% yield). IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1730 (strong), $\nu_{C=C}$ 1635; ^{1}H NMR (60 MHz, CCl_4): δ 6.22 (1H, *s*), 4.2 (2H, *q*, J = 7), 2.58 (2H, *t*, J = 7), 1.2–1.7 (7H, *m*), 0.95 (3H, *t*, J = 6); low resolution MS and GLC retention identical with naturally-occurring **20**.

Z-3-bromo-2-hepten-1-ol was also synthesized. To ethyl *Z*-3-bromo-2-heptenoate (**20**) (0.09 g, 0.38 mmol) in 30 ml dry Et_2O, cooled to 0° in an ice-bath, was added with stirring, excess $LiAlH_4$ and the mixture was stirred for 15 min. After work-up, 0.04 g of *Z*-3-bromo-2-hepten-1-ol was obtained (55% yield). ^{1}H NMR (60 MHz, CCl_4): δ 5.89 (1H, *t*, J = 5), 4.21 (2H, *d*, J = 5), 2.48 (1H, *t*, J = 7), 1.2–1.7 (4H, *m*), 0.95 (3H, *t*, J = 6).

Synthesis of ethyl Z-3-*bromo*-2-*nonenoate* (**21**). Br_2 (14.2 g, 0.09 mol, 4.55 ml) was added dropwise, with stirring, to 2-nonanone (2.0 g, 0.014 mol) in 125 ml CCl_4. The mixture was stirred for 26 hr at room temp. After work-up, 5.23 g was obtained which, by GLC and GC–MS, contained 1,1,3-tribromo-2-nonanone (**30**) of *ca* 60% purity (the other components were 1,3-dibromo-2-nonanone (20%) and 3,3-dibromo-2-nonanone (20%)). ^{1}H NMR (60 MHz, CCl_4): δ 6.33 (1H, *s*), 4.81 (1H, *t*, J = 6), 1.9–2.6 (2H, *m*), 1.2–1.8 (8H, *m*), 0.93 (3H, *t*, J = 6); low resolution MS (50 eV): 292 (1.0, Br), 205 (5.1, Br), 171 (4.4, Br), 133 (1.7, Br), 135 (3.4, Br), 121 (6.1, Br), 97 (39.0), 95 (19.7), 69 (13.6), 67 (10.2), 55 (100), 43 (50.8), 41 (74.6), 39 (44.1).

Na_2CO_3 (8.5 g, 0.081 mol) was added with stirring to this mixture (5.13 g) in 75 ml H_2O and MeOH (2:1). The mixture was stirred for 21 hr at room temp. After work-up, 3.0 g of material was obtained and was chromatographed over Si gel. *Z*-3-Bromo-2-nonenoic acid (**8**) (0.364 g, 19% yield) was eluted pure with 25% Et_2O in petrol. ^{1}H NMR (60 MHz, CCl_4): δ 6.31 (1H, *s*), 2.65 (2H, *t*, J = 7), 1.2–1.7 (8H, *m*), 0.95 (3H, *t*, J = 6).

2 ml 95% EtOH and 0.1 g H_2SO_4 were combined with *Z*-3-bromo-2-nonenoic acid (0.09 g, 0.38 mmol), heated to 60° for 0.5 hr with stirring, stirred at room temp. for 0.5 hr, and then worked up. Ethyl *Z*-3-bromo-2-nonenoate (**21**) was obtained in 80% yield. ^{1}H NMR (60 MHz, CCl_4): δ 6.2 (1H, *s*), 4.19 (2H, *q*, J = 7), 2.55 (2H, *t*, J = 7), 1.2–1.8 (11H, *m*), 0.9 (3H, *t*, J = 6); low resolution MS and GLC retention time were identical to naturally-occurring **21**.

Structure elucidation of ethyl 2-n-*butyl*-3,3-*dibromoacrylate* (**22**) *and ethyl* 2-n-*hexyl*-3,3-*dibromoacrylate* (**23**). Both ethyl 2-*n*-butyl-3,3-dibromoacrylate (**22**) and ethyl *n*-hexyl-3,3-dibromoacrylate (**23**) were eluted from Si gel chromatography with 5% Et_2O in petrol, before **20** and **21**. They were found in a complex mixture by GC–MS and in very minor amounts (0.4 and 0.2% crude extract, respectively). The structures of these compounds were initially determined from their low resolution MS (50 eV): **22**—312 [M^+] (6.0, Br_2), 270 (1.0, Br_2), 267 (26.0, Br_2), 257 (8.0, Br_2), 242 (16.0, Br_2), 233 (42.0, Br), 205 (100, Br), 197 (44.0, Br), 187 (60.0, Br), 175 (12.0, Br_2), 163 (46.0, Br), 161

(50.0, Br), 159 (29.2, Br), 131 (36.0, Br), 125 (40.0), 119 (50.0), 117 (40.0), 107 (40.0), 97 (20.0), 83 (60.0), 79 (80.0), 43 (82.0), 41 (100), 39 (60.0); **23**—340 [M^+] (0.6, Br_2), 295 (1.5, Br_2), 270 (1.5, Br_2), 261 (4.2, Br), 242 (2.3, Br_2), 233 (6.5, Br), 179 (5.0, Br), 163 (5.0, Br), 161 (5.0), 135 (17.3), 67 (21.2), 55 (42.3), 43 (100), 41 (76.9), 39 (32.7). Both of these compounds were synthesized.

Synthesis of ethyl 2-n-*butyl*-3,3-*dibromoacrylate* (**22**). Na_2CO_3 (8.4 g, 0.08 mol) was added to 1,1,3,3-tetrabromo-2-heptanone (**1**) (4.26 g, 0.01 mol) in 100 ml H_2O and MeOH (3:1). The mixture was refluxed for 22 hr and then worked up by adding acid and extracting the aq. layer with 3 × 150 ml Et_2O. The combined Et_2O layers were washed with 2 × 100 ml brine, dried, and reduced *in vacuo* to yield 1.26 g 95% pure 2-*n*-butyl-3,3-dibromoacrylic acid (**9**) (42% yield). IR (CCl_4) cm^{-1}: ν_{O-H} 2600–3200 (broad), $\nu_{C=O}$ 1700 (strong); ^1H NMR (60 MHz, CCl_4): δ 12.0 (1H, *s*), 2.53 (2H, *t*, J = 7), 1.2–1.7 (4H, *m*), 0.95 (3H, *t*, J = 6); ^{13}C NMR (20 MHz, $CDCl_3$): δ 171.8 (*s*), 139.5 (*s*), 96.9 (*s*), 35.6 (*t*), 29.3 (*t*), 22.3 (*t*), 13.7 (*q*); low resolution MS (50 eV): 284 [M^+] (19.1, Br_2), 242 (34.5, Br_2), 229 (59.1, Br_2), 205 (70.9, Br), 187 (61.8, Br), 165 (63.6), 163 (89.1), 161 (38.2), 159 (15.5), 125 (36.4), 119 (36.4), 117 (31.8), 107 (29.1), 97 (23.6), 83 (81.8), 79 (50.0), 55 (50.0), 51 (43.6), 43 (100), 41 (90.9), 39 (59.1). 2-*n*-Butyl-3,3-dibromoacrylic acid (0.1 g, 0.35 mmol) was combined with 2 ml 95% EtOH and 0.1 g H_2SO_4 and refluxed for 1.5 hr. After work-up, 0.1 g ethyl 2-*n*-butyl-3,3-dibromoacrylate (**22**) was obtained. This compound had an identical MS and GLC retention time as naturally-occurring **22**.

Synthesis of ethyl 2-n-*hexyl*-3,3-*dibromoacrylate* (**23**). Br_2 (7.2 g, 0.045 mol, 2.3 ml) was added dropwise to an ice-cooled solution of 2-nonanone (1.42 g, 0.01 mol) and 1 ml 48% HBr. The soln was stirred for 10 days at room temp. After work-up, 3.65 g 1,1,3,3-tetrabromo-2-nonanone (**11**) was obtained which, by NMR and GLC, was 99% pure (80% yield). IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1736 (strong); ^1H NMR (60 MHz, CCl_4): δ 6.78 (1H, *s*), 2.3–2.6 (2H, *m*), 1.2–1.8 (8H, *m*), 0.9 (3H, *t*, J = 6); ^{13}C NMR (20 MHz, $CDCl_3$): δ 33.8 (*d*), 186.2 (*s*), 64.7 (*s*), 44.7 (*t*), 31.5 (*t*), 28.4 (*t*), 27.0 (*t*), 22.5 (*t*), 14.0 (*q*); low resolution MS (50 eV): 370 (2.5, Br_4), 299 (0.7), 297 (1.4), 295 (1.3), 293 (1.1), 291 (0.4), 215 (1.8, Br_2), 203 (1.8), 201 (3.0), 199 (3.4), 197 (2.0), 175 (7.5, Br), 171 (10.4, Br_2), 133 (8.6, Br), 120 (6.1, Br), 119 (5.0, Br), 109 (2.1), 107 (7.9), 105 (4.6), 95 (100), 69 (16.1), 67 (30.4), 55 (66.1), 53 (21.4), 43 (69.6), 41 (100), 39 (60.7).

Na_2CO_3 (7.7 g, 0.073 mol) was added to 1,1,3,3-tetrabromo-2-nonanone (4.0 g, 8.8 mmol) in 100 ml H_2O and MeOH (2:1), and the mixture was refluxed for 22 hr. After work-up, 1.51 g was obtained which contained 2-*n*-hexyl-3,3-dibromoacrylic acid (**10**) of 80% purity (NMR, TLC). ^1H NMR (60 MHz, CCl_4): δ 9.7 (1H, *bs*), 2.53 (2H, *t*, J = 7), 1.2–1.7 (8H, *m*), 0.9 (3H, *t*, J = 6).

Esterification of 2-*n*-hexyl-3,3-dibromoacrylic acid with 95% EtOH and H_2SO_4 provided ethyl 2-*n*-hexyl-3,3-dibromoacrylate (**23**) in 80% yield which had the same MS and GLC retention time as naturally-occurring **23**.

Synthesis of ethyl 2,3-*dibromo*-2-*heptenoate* (**24**) *and ethyl* 2,3-*dibromo*-2-*nonenoate* (**25**). To 2-heptynoic acid (1.26 g, 0.01 mol) (Farchan Chemical Co.) in 3 ml 95% EtOH was added 0.25 g H_2SO_4 (conc.). The mixture was stirred for 14 hr at room temp. and heated under reflux for 1.5 hr. The reaction mixture was worked up by adding 200 ml Et_2O and 50 ml brine. After shaking, the aq. layer was discarded. The organic layer was washed with 2 × 30 ml base, 1 × 30 ml brine, dried, and reduced *in vacuo* to yield 1.37 g ethyl 2-heptynoate (89% yield). ^1H NMR (60 MHz, CCl_4): δ 4.2 (2H, *q*, J = 7), 2.36 (2H, *t*, J = 7), 1.3–1.7 (4H, *m*), 1.3 (3H, *t*, J = 7), 0.95 (3H, *t*, J = 6).

2-Nonynoic acid (1.54 g, 0.01 mol) was treated in an identical fashion to yield 1.54 g ethyl 2-nonynoate (85% yield). ^1H NMR (60 MHz, CCl_4): δ 4.2 (2H, *q*, J = 7), 2.35 (2H, *t*, J = 7), 1.2–1.7 (8H, *m*), 1.3 (3H, *q*, J = 7), 0.92 (3H, *t*, J = 5).

To ethyl 2-heptynoate (0.56 g, 3.6 mmol) and NaBr (0.37 g, 3.6 mmol) in 50 ml CCl_4 was added Br_2 (0.21 ml, 0.65 g, 4.1 mmol) dropwise, with stirring, at room temp. The reaction mixture was stirred for 23 hr at room temp., filtered, and reduced *in vacuo* to yield ethyl *E,Z*-2,3-dibromo-2-heptenoate (**24**) and ethyl *E,Z*-2,2,3-tribromo-3-heptenoate. Ethyl *E,Z*-2,3-dibromo-2-heptenoate: ^1H NMR (60 MHz, CCl_4)—allylic protons—δ 2.85; low resolution MS (50 eV): 312 [M^+] (3.9, Br_2), 267 (3.5, Br_2), 233 (21.7, Br), 205 (13.0, Br), 187 (8.7, Br), 163 (20.9, Br), 159 (13.0, Br), 125 (34.8), 107 (29.6), 97 (34.8), 81 (71.1), 79 (100), 67 (26.1), 55 (26.1), 53 (39.1), 51 (39.1), 43 (91.3), 41 (82.6), 39 (60.9). The geometrical isomers were present in 1:1 ratios and had identical MS. The GLC retention times and MS were quite different from **22**. Ethyl *E,Z*-2,2,3-tribromo-3-hepenoate: ^1H NMR—δ 5.2, 5.6—triplets (J = 6); low resolution MS (50 eV); 390 [M^+] (Br_3).

Ethyl 2-nonynoate (0.47 g, 2.6 mmol) was treated in an identical fashion to yield ethyl *E,Z*,-2,3-dibromo-2-nonenoate (**25**) and ethyl *E,Z*-2,2,3-tribromo-3-nonenoate. Ethyl *E,Z*-2,3-dibromo-2-nonenoate: ^1H NMR (60 MHz, CCl_4)—allylic protons—δ 2.85; low resolution MS (50 eV): 340 [M^+] (2.3, Br_2), 295 (1.7, Br_2), 261 (13.0, Br), 233 (3.4, Br), 177 (9.9, Br), 153 (16.9), 135 (28.1), 107 (100), 95 (20.3), 79 (41.0), 69 (23.4), 67 (39.0), 57 (23.4), 55 (42.9), 43 (94.0), 41 (93.5), 39 (42.9). The geometrical isomers were also present in 1:1 ratios and had identical MS. The GLC retention times and MS were quite different from **23**. Ethyl *E,Z*-2,2,3-tribromo-3-nonenoate: ^1H NMR—δ 5.2, 5.6—triplets (J = 6); low resolution MS (50 eV): 418 [M^+] (Br_3).

1,1,3,3-*Tetrabromo*-2-*nonanone* (**11**). 1,1,3,3-Tetrabromo-2-nonanone (**11**) was eluted in fractions from Si gel chromatography with 1–5% Et_2O–petrol, but in quite minor amounts (0.5% crude extract). It was identified by its characteristic MS and GLC retention time (see section on synthesis of ethyl 3,3-dibromo-*n*-hexylacrylate for details of MS of **11**).

Structure elucidation of 1,1,3,3-*tetrabromo*-2-*heptanol* (**12**) *and* 1,1,3,3-*tetrabromo*-2-*nonanol* (**13**). 1,1,3,3-Tetrabromo-2-heptanol (**12**) (1% crude extract) and 1,1,3,3-tetrabromo-2-nonanol (**13**) (2.5% crude extract) were both eluted from Si gel chromatography with 5–10% Et_2O–petrol. 1,1,3,3-Tetrabromo-2-heptanol was identified by its MS (low resolution, 50 eV): 349 (1.8, Br_3), 331 (2.5, Br_3), 269 (10, Br_2), 257 (2.7, Br_2), 251 (2.7, Br_2), 227 (9.1, Br_2), 226 (10.0, Br_2), 201 (14.5, Br_2), 177 (18.2, Br), 175 (7.3), 173 (18), 171 (13.2), 149 (9.1, Br), 147 (23.6, Br), 135 (36.4, Br), 122 (59.1, Br), 69 (68.2), 67 (86.4), 55 (72.7), 43 (63.6), 41 (100), 39 (63.6). 1,1,3,3-Tetrabromo-2-nonanol (**13**) was identified by ^1H NMR, IR, ^{13}C NMR, and MS data since it comprised 75% of a fraction (fraction exhibited $[\alpha]_D^{23}$ +5.8° (*c* 4, $CHCl_3$)). **13** could not be further purified by column chromatography or HPLC using μ-porasil as the support. IR (CCl_4) cm^{-1}; ν_{O-H} 3370 (sharp-broader peak centred at same value); ^1H NMR (220 MHz, $CDCl_3$): δ 6.55 (1H, *d*, J = 0.25), 4.39 (1H, *bd*, J = 9), 3.27 (1H, *bd*, J = 9, D_2O exchangeable), 2.36 (2H, *m*), 1.70 (2H, *m*), 1.23 (6H, *m*), 0.87 (3H, *t*, J = 6); ^{13}C NMR (20 MHz, $CDCl_3$): δ 45.5 (*d*), 83.5 (*d*), 77.7 (*s*), 46.6 (*t*), 31.5 (*t*), 28.5 (*t*), 27.3 (*t*), 22.5 (*t*), 14.0 (*q*); low resolution MS (50 eV): 376 (0.4, Br_3), 297 (0.9, Br_3), 279 (1.3, Br_3), 255 (2.0, Br_3), 205 (6.9, Br), 199 (5.2, Br_2), 175 (2.8, Br), 171 (6.1, Br_2), 135 (15.2, Br), 119 (17.4), 107 (17.4), 95 (40.0), 69 (19.6), 67 (32.6), 57 (21.7), 55 (73.9), 53 (23.9), 43 (73.9), 41 (100), 39 (56.5). Both of these compounds were synthesized.

Synthesis of 1,1,3,3-*tetrabromo*-2-*heptanol* (**12**). $LiAlH_4$ (0.286 g, 7.5 mmol) was added in portions with stirring to an ice-cooled Et_2O soln (50 ml) containing 1,1,3,3-tetrabromo-2-heptanone (**1**) (3.18 g, 7.5 mmol). The mixture was stirred under N_2 for

20 hr as the ice bath warmed to room temp. After work-up, 2.66 g of a mixture was obtained which, by GLC and GC–MS, contained **12** as the predominant component (73% mixture). (The other major component was determined to be 1,1,3-tribromo-2-heptanol by its MS.) A similar product ratio was obtained by treatment of **1** (0.52 g, 1.2 mmol) in 1,2-dimethoxyethane (25 ml) with $NaBH_4$ (0.046 g, 1.2 mmol) for 1.5 hr from 0° to room temp. (0.47 g material obtained after work-up). Synthetic 1,1,3,3-tetrabromo-2-heptanol (**12**) had an identical GLC retention time and MS to naturally-occurring **12**. ^1H NMR (60 MHz, CCl_4): δ 6.52 (1H, *d*, J = 0.25), 4.32 (1H, *bd*, J = 8), 3.23 (1H, *bd*, J = 8), 2.4 (2H, *m*), 1.3–1.9 (4H, *m*), 0.97 (3H, *t*, J = 6); IR (CCl_4) cm^{-1}: ν_{O-H} 3400 (sharp-centered on broad peak).

Synthesis of 1,1,3,3-*tetrabromo*-2-*nonanol* (**13**). $LiAlH_4$ (0.135 g, 3.5 mmol) was added, all at once, to an ice-cooled Et_2O (50 ml) soln containing 1,1,3,3-tetrabromo-2-nonanone (**11**) (1.6 g, 3.6 mmol). The reaction mixture was stirred for 3 hr under N_2 as the ice bath warmed to room temp. After work-up, 1.06 g was obtained. Elution with 5% Et_2O–petrol from Si gel chromatography afforded 0.757 g **13** (47% yield). Synthetic 1,1,3,3-tetrabromo-2-nonanol (**13**) was identical in GLC retention time and MS to naturally-occurring **13**.

Structure elucidation of 1,1,1,3-*tetrabromo*-2-*heptanol* (**14**) *and* 1,1,1,3-*tetrabromo*-2-*nonanol* (**15**). These two alcohols, 1,1,1,3-tetrabromo-2-heptanol (**14**) and 1,1,1,3-tetrabromo-2-nonanol (**15**), were also eluted with 5–10% Et_2O–petrol from Si gel chromatography. Their structures were deduced from their MS characteristics and by comparison of their GLC retention times with **12** and **13**. Low resolution MS (50 eV): 1,1,1,3-tetrabromo-2-heptanol (**14**): 348 (1.4, Br_3), 177 (39.3, Br), 171 (6.4, Br_2), 135 (71.4, Br), 69 (50), 57 (78.6), 55 (64.3), 43 (97.9), 41 (100), 39 (64.3); 1,1,1,3-tetrabromo-2-nonanol (**15**): 376 (3.0, Br_3), 205 (79.0, Br), 171 (9.5, Br_2), 135 (78.6, Br), 107 (87.5), 97 (41.2), 95 (47.1), 81 (82.4), 69 (76.5), 57 (64.7), 55 (94.1), 43 (88.2), 41 (100), 39 (58.8). 1,1,1,3-Tetrabromo-2-heptanol (**14**) eluted immediately (nearly co-eluted) before 1,1,3,3-tetrabromo-2-heptanol (**12**) by GLC and similarly, 1,1,1,3-tetrabromo-2-nonanol (**15**) eluted immediately before 1,1,3,3-tetrabromo-2-nonanol (**13**) (GLC conditions: temp. programming, 120–250°, 2 min delay, 16°/min, 3% SP-2401, He flow = 60 ml/min).

Bonnemaisonia hamifera—*Gulf of California*. A collection of this alga was made at Bahia Los Angeles, Gulf of California, Mexico, in April 1977, and immediately stored in 95% EtOH. Pentane extracts of the decanted EtOH solution were examined by GLC (Fig. 5) and GC–MS. Ethyl *Z*-3-bromo-2-heptenoate (**20**), ethyl *E*-3-bromo-2-heptenoate (**29**), 1,1,3,3-tetrabromo-2-heptanone (**1**), and 1,1,3-tribromo-2-heptanone (**3**) were identified by their characteristic MS and GLC retention times.

Bonnemaisonia hamifera—*Atlantic* (*Woods Hole*). *Bonnemaisonia hamifera* was collected by Dr. Richard Searles (Duke University) in May 1976. It was stored and sent in *ca* 500 ml 95% EtOH. The EtOH decant was extracted with purified pentane and, as before, the conc pentane soln was examined by GLC (Fig. 6), and GC–MS. The only new halogenated compounds detected were 1,1-dibromo- (**31**) and 1,1,3-tribromo-2-heptanol (**32**), and a compound which appeared to be a dioxygenated C_9 compound, based upon its MS (50 eV): 391 (2.1, Br_3), 331 (1.1, Br_3), 311 (0.4, Br_2), 299 (0.7, Br_2), 269 (1.4, Br_2), 251 (4.1, Br_2), 243 (3.4, Br_2), 197 (0.9, Br_2), 189 (0.9, Br_2), 171 (8.6, Br), 149 (4.7), 93 (10.0), 92 (8.6), 91 (8.6), 57 (12.9), 55 (20.0), 43 (100), 41 (31.4), 39 (17.1). Compounds **31** and **32** were previously detected in the hydride reduction product mixtures of 1,1,3,3-tetrabromo-2-heptanone (**1**). Synthesis thus confirmed these structures. Low resolution MS data (50 eV): 1,1-dibromo-2-heptanol (**31**): 201 (1.1, Br_2), 191 (2.9, Br), 171 (2.9, Br_2), 135 (3.7, Br), 133 (2.3, Br), 101 (54.3), 83 (91.4), 69 (51.4), 55 (100), 43 (48.6), 41 (77.1), 39 (31.4); 1,1,3-tribromo-2-heptanol (**32**): 271 (0.6, Br_2), 253 (1.2, Br_2), 227 (3.5, Br_2), 201 (4.1, Br_2), 191 (3.2, Br), 179 (23.5, Br), 171 (8.8, Br), 161 (10.3, Br), 149 (6.5, Br), 147 (6.5, Br), 135 (15.6, Br), 123 (50.0, Br), 93 (32.4), 81 (73.5), 69 (44.1), 67 (38.2), 57 (44.1), 55 (70.6), 43 (88.2), 41 (100), 39 (58.8).

Bonnemaisonia asparagoides—*collection and work-up*. A collection of this alga was made on 30 June 1975, at La Escala, Spain (along the Mediterranean coast) and the few small plants that could be found were placed in a 1 pint container which was then filled with 95% EtOH. The decanted EtOH soln was repeatedly extracted with purified pentane. The combined pentane phases were carefully reduced in vol. by distillation, yielding 10 mg residue which was examined by GLC (Fig. 8) and GC–MS. Five major halogen-containing compounds were eluted in the order **38–42** as the most volatile components of the extract.

Bonnemaisonia asparagoides—*mass spectra of the polyhalogenated* 1-*octen*-3-*ones*, **38–42**. The low resolution MS of the polyhalogenated 1-octen-3-ones, **38–42**, provided the following (50 eV): *E,Z*-1-bromo-1,2-dichloro-1-octen-3-one (**38**): 237 (4.0, BrCl), 216 (32.0, $BrCl_2$), 210 (20.0, $BrCl_2$), 193 (12.8, Cl_2), 173 (14.0, $BrCl_2$), 99 (21.4), 71 (28.6), 57 (10.7), 55 (25.0), 43 (100), 41 (39.3), 39 (21.4); *E,Z*-1-bromo-1,2,4-trichloro-1-octen-3-one (**39**): 271 (1.0, $BrCl_2$), 250 (9.8, $BrCl_2$), 210 (100, $BrCl_2$), 173 (13.7, $BrCl_2$), 69 (39.1), 55 (43.5), 43 (48.3), 41 (100), 39 (47.8); 2,4-dibromo-1,1-dichloro-1-octen-3-one (**40**): 315 (2.8, Br_2Cl), 294 (13.8, Br_2Cl_2), 201 (41, $BrCl_2$), 173 (9.6, $BrCl_2$), 69 (42.6), 55 (47.0), 43 (41.2), 41 (100), 39 (47.1); *E*-1,2-dibromo-1,4-dichloro-1-octen-3-one (**41**): 294 (3.1, Br_2Cl_2), 271 (2.0, $BrCl_2$), 245 (47.9, Br_2Cl), 217 (9.0, Br_2Cl), 69 (51.0), 55 (91.8), 43 (61.2), 41 (100), 39 (56.1); *E*-1-chloro-1,2,4-tribromo-1-octen-3-one (**42**): 338 (4.0, Br_3Cl), 315 (2.5, Br_2Cl), 245 (33.8, Br_2Cl), 217 (5.1, Br_2Cl), 69 (23.3), 57 (20.0), 55 (53.3), 43 (100), 41 (55.0), 39 (25.0).

Synthesis of the polyhalogenated 1-*octen*-3-*ones* (**38–42**). E,Z-1-*Bromo*-1,2-*dichloro*-1-*octen*-3-*one* (**38**) *and* E,Z-1-*Bromo*-1,2,4-*trichloro*-1-*octen*-3-*one* (**39**). 1-Octyn-3-ol (**43**) (commercially available from Aldrich Chemical Co.) (8.82 g, 0.07 mol) was dissolved in 150 ml H_2O–MeOH (1:1), and the soln was cooled to below 10° by an ice–water bath. NaOH (16.8 g, 0.42 mol) was added with stirring. After the NaOH had dissolved, Br_2 (16.8 g, 5.4 ml, 0.11 mol) was added dropwise. Additional ice was added to the bath to keep the temp. of the reaction soln below 15–20°. After stirring for 2–3 hr, *ca* 100 ml brine was added and the aq. phase was extracted with 3 × 150 ml Et_2O. The combined Et_2O layers were washed with 50 ml acid, 2 × 30 ml brine, dried ($MgSO_4$), and reduced *in vacuo* to yield 12.3 g of crude material. Distillation (bp 86–88°/1.4 mm (McLeod gauge)) yielded 8.1 g pure 1-bromo-1-octyn-3-ol (**44**) (57% yield) which exhibited the following IR and ^1H NMR absorptions: IR (CCl_4) cm^{-1}: ν_{O-H} 3425 (sharp, med.) and 3155 (br., strong); ^1H NMR (60 MHz, CCl_4): δ 4.3 (1H, *t*, J = 5), 3.47 (1H, *s*), 1.3–1.7 (8H, *m*), 0.93 (3H, *t*, J = 5).

Oxidation of **44** (8.5 g, 0.042 mol) in 50 ml Me_2CO with excess Jones' reagent (50 ml) overnight at room temp. yielded, after work-up, 1-bromo-1-octyn-3-one (**45**) in 70% isolated yield (6.0 g, 0.03 mol) with the following spectral data: IR (CCl_4) cm^{-1}: $\nu_{C\equiv C}$ 2150 (sharp, strong), $\nu_{C=O}$ 1695 (str.); ^1H NMR (60 MHz, CCl_4): δ 2.53 (2H, *t*, J = 7), 1.3–1.8 (6H, *m*), 0.92 (3H, *t*, J = 5). Retention time = 5.5 min with temp. programming—80–230°, 2 min delay, 16°/min (He flow = 60 ml/min)—using 3% SP-2401 as the support.

To **45** (0.47 g, 2.3 mmol) in 40 ml glacial HOAc was added, with stirring, 3.3 equivs. Cl_2 (0.53 g, 7.6 mmol) in 16 ml HOAc and 0.5 ml H_2SO_4. After stirring 15 hr at room temp., 50 ml brine was added and the mixture was extracted with 3 × 50 ml Et_2O. The combined Et_2O layers were washed with 4 × 30 ml

base, 1 × 30 ml acid, and 2 × 30 ml brine, dried, and reduced *in vacuo* to yield 0.59 g of a 1:1 mixture of unreacted **45** and 1-bromo-4-chloro-1-octyn-3-one, (**46**): IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1739 and 1695; ^1H NMR (CCl_4): δ 4.19 (*t*, J = 6) and 2.5 (*t*, J = 7); GLC retention times—4.5 min, **45**, and 5.5 min, **46**—from temp. programming of 85–250°, 2 min delay, 16°/min (3% SP-4201).

This mixture was chlorinated under several conditions. To this mixture (0.23 g) in 30 ml glacial HOAc was added, with stirring and at room temp., LiCl (1.36 g, 0.032 mol) and Cl_2 (0.192 g, 2.7 mmol) in 7 ml HOAc. After stirring 28 hr, the reaction was worked up as above to yield 0.3 g of a mixture which, by GLC (coinjection with the naturally-occurring mixture of *B. asparagoides*) and GC–MS, contained components identical to naturally-occurring **38** and **39** and with the same peak ratios corresponding to the *E* and *Z* isomers. IR (CCl_4) cm^{-1}: $\nu_{C=O}$ 1740 and 1710; ^1H NMR (60 MHz, CCl_4): δ 2.73 (*t*, J = 6), 4.0–4.2 (envelope of several peaks); UV λ_{max}^{MeOH} nm: 262–264 (ε 2000).

This mixture of **45** and **46** (0.15 g/40 ml $CHCl_3$) was again treated with Cl_2 (0.136 g/3 ml $CHCl_3$) and LiCl (1.01 g, 0.024 mol), but in $CHCl_3$ instead, for 28 hr at room temp. to yield 0.33 g of a mixture of **38** and **39** as determined by GLC (coinjection) and GC–MS. The ratio of GLC peak areas of **39** was 0.191 (area of peak from compound eluted last/area of peak from compound eluted first) under these reaction conditions rather than 20.0, which was the ratio obtained from the previous chlorination reaction.

Treatment of this latter chlorination reaction mixture of **38** and **39** (0.08 g/25 ml glacial HOAc) with Br_2 (0.144 g, 0.91 mmol, 0.046 ml) and H_2SO_4 (5 drops) at room temp. for 24 hr in an attempt to brominate C-4 in **38** led to a reversal of GLC peak ratios from 0.181 to 20.0 of **39**—the same as in naturally-occurring **39**.

E-1,2-*Dibromo*-1,4-*dichloro*-1-*octen*-3-*one* (**41**) *and* E-1-*chloro*-1,2,4-*tribromo*-1-*octen*-3-*one* (**42**). 1-Octyn-3-ol (**43**) (13.0 g, 0.103 mol) and NaOH (44 g, 1.1 mol) were added to 150 ml H_2O–MeOH (1:1) with stirring and cooled to below 10° by an ice–water bath. Excess Cl_2 gas was bubbled into the soln. The mixture was stirred for 2 hr as the ice bath warmed up. The reaction was worked up as for **44**. Distillation (bp 66–67°/0.6 mm) yielded 3.57 g (22% yield) of 1-chloro-1-octyn-3-ol (**47**); IR (CCl_4) cm^{-1}: ν_{O-H} (weak, sharp) and 3200 (strong, br.), $\nu_{C\equiv C}$ 2183 (med., sharp), ^1H NMR (MHz, CCl_4): δ 5.1 (1H, *s*), 4.35 (1H, *t*, J = 6), 1.2–1.8 (8H, *m*), 0.93 (3H, *t*, J = 6).

1-Chloro-1-octyn-3-ol (**47**; 1.4 g, 8.75 mmol) was oxidized with Jones' reagent at room temp. for 4 hr to yield 1.1 g 1-chloro-1-octyn-3-one (**48**) (80% yield); IR (CCl_4) cm^{-1}; $\nu_{C\equiv C}$ 2150 and $\nu_{C=O}$ 1710; ^1H NMR (60 MHz, CCl_4): δ 2.52 (2H, *t*, J = 6), 1.2–1.8 (8H, *m*), 0.9 (3H, *t*, J = 6); GLC retention time = 3.6 min with temp. programming—90–200°, 2 min delay, 16°/min (3% SP-2401).

Bromination of 1-chloro-1-octyn-3-one (**48**) (0.255 g, 1.6 mmol) in $CHCl_3$ (30 ml) was affected by addition of Br_2 (0.53 g, 3.4 mmol, 0.17 ml) with stirring at room temp. for 12 hr. The reaction was worked up by adding a pinch of $MgSO_4$ with stirring, filtering, reducing *in vacuo*, and passing the residue over Si gel (0.5 × 5.0 cm) with 100% Et_2O to yield 0.5 g of a mixture which was comprised of **42** and 1-chloro-1,2-dibromo-1-octen-3-one (3:1) by GLC (coinjection with the naturally-occurring mixture from *B. asparagoides*) and GC–MS analysis.

The 4-chloro analogue of **42**, *E*-1,2-dibromo-1,4-dichloro-1-octen-3-one (**41**), was obtained by reacting **42** (0.144 g of this mixture) in 50 ml Me_2CO with excess KCl (1.084 g, 14.6 mmol) at 40° for 15 hr. The reaction mixture was worked up by simply filtering off the KBr and excess KCl and reducing *in vacuo*. An 80% conversion of **42** to **41** occurred as evidenced by GLC. Synthetic **41** was shown to be identical to naturally-occurring **41** by GLC (coinjection) and GC–MS.

Synthesis of E-1,4-*Dibromo*-1,2-*dichloro*-1-*octen*-3-*one* (**49**). To the mixture of **38** and **39** (0.173 g, obtained from chlorination of **45** and **46** in $CHCl_3$) in 30 ml Me_2CO was added NaBr (1.04 g, 10.2 mmol), and the reaction mixture was stirred for 10 hr at 40°. By GLC, a 93% conversion from **39** to *E*-1,4-dibromo-1,2-dichloro-1-octen-3-one (**49**) occurred. By coinjection of **48** and the pentane extract of *B. asparagoides*, there was a significant difference in retention times (3%, Fig. 8) between **49** and **40** and the MS of **49** was similar, but not identical, to **40**. Therefore, the structure of **40** was assigned as 2,4-dibromo-1,1-dichloro-1-octen-3-one. Low resolution MS of *E*-1,4-dibromo-1,2-dichloro-1-octen-3-one (**49**) (50 eV): 315 (1.3, Br_2Cl), 294 (11.0, Br_2Cl_2), 271 (3.3, $BrCl_2$), 201 (100, $BrCl_2$), 173 (19.4, $BrCl_2$), 69 (74.2), 55 (77.4), 43 (22.6), 41 (77.4), 39 (38.7).

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