Registry No.—**5b** (R = Me), 50896-84-9; **8**, 28309-53-7; **9**, 4105-38-8; acetyl chloride, 75-36-5; valeric anhydride, 2082-59-9; isovaleric anhydride, 1468-39-9; *sec*-valeryl chloride, 5856-79-1; pivaloyl chloride, 3282-30-2; pivalic anhydride, 1538-75-6; pivalic acid, 75-98-9; decanoyl chloride, 112-13-0; margaroyl chloride, 40480-10-2; margaric acid, 506-12-7; lignoceroyl chloride, 58576-73-1; cyclopropanecarboxylic anhydride, 33993-24-7; 1-adamantanecarboxylic anhydride, 42601-02-5; 1-adamantoyl chloride, 2094-72-6; crotonic anhydride, 623-68-7; benzoic anhydride, 93-97-0; γ-phenylbutyric anhydride, 1940-02-9; cinnamic anhydride, 538-56-7; acetic anhydride, 108-24-7; cytidine, 65-46-3; boron trifluoride, 7637-07-2; benzoyl chloride, 98-88-4; 2′,3′,5′-tri-*O*-benzoylcytidine, 31652-74-1; benzoic acid, 65-85-0; uridine, 58-96-8.

References and Notes

(1) See, e.g., (a) R. B. Livingston and S. K. Carter, *Cancer Chemother. Rep., Part 3*, **1**, 179 (1968); (b) J. J. Wang, O. S. Selawry, T. J. Vietti, and G. P. Bodey, *Cancer*, **25**, 1 (1970); (c) R. R. Ellison et al., *Blood*, **32**, 507 (1968); (d) E. Frei, J. N. Bickers, J. S. Hewlett, M. Lane, W. V. Leary, and R. W. Talley, *Cancer Res.*, **29**, 1325 (1969); (e) R. L. Momparler, *ibid.*, **34**, 1775 (1974).

(2) See, e.g., (a) G. D. Gray, M. M. Mickelson, and J. A. Crim, *Transplantation*, **6**, 805 (1968); (b) R. O. Gordon, M. E. Wade, and M. S. Mitchell, *J. Immunol.*, **103**, 233 (1969).

(3) See, e.g., (a) D. A. Buthala, *Proc. Soc. Exp. Biol. Med.*, **115**, 69 (1964); (b) H. N. Prince, E. Grunberg, M. Buck, and R. Cleeland, *ibid.*, **130**, 180 (1969).

(4) See, e.g., (a) A. Hoshi, F. Kanzawa, and K. Kuretani, *Gann*, **63**, 353 (1972); (b) J. M. Venditti, M. C. Baratta, N. H. Greenberg, B. J. Abott, and I. Kline, *Cancer Chemother. Rep., Part 1*, **56**, 483 (1972).

(5) E. K. Hamamura, M. Prystasz, J. P. Verheyden, J. G. Moffatt, K. Yamaguchi, N. Uchida, K. Sato, A. Nomura, O. Shiratori, S. Takase, and K. Katagiri, *J. Med. Chem.*, **19**, 663 (1976).

(6) K. Kondo, T. Adachi, and I. Inoue, *J. Org. Chem.*, **41**, 2955 (1976).

(7) See, e.g., (a) E. R. Walwick, W. K. Roberts, and C. A. Dekker, *Proc. Chem. Soc., London*, 84 (1959); (b) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967).

(8) J. Beránek and J. Pitha, *Collect. Czech. Chem. Commun.*, **29**, 625 (1964).

(9) See, e.g., H. S. Booth and D. R. Martin, "Boron Trifluoride and Its Derivatives", Wiley, New York, N.Y., 1949, p 72.

(10) (a) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Justus Liebigs Ann. Chem.*, **632**, 38 (1960); (b) T. C. Jain, I. D. Jenkins, A. F. Russell, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **39**, 30 (1974).

(11) A. Holý, *Collect. Czech. Chem. Commun.*, **38**, 423 (1973).

(12) R. Marumoto and M. Honjo, *Chem. Pharm. Bull.*, **22**, 128 (1974).

(13) (a) P. K. Kadaba, M. Carr, M. Tribo, J. Triplett, and A. C. Glasser, *J. Pharm. Sci.*, **58**, 1422 (1969); (b) J. L. Marshall, K. C. Erickson, and T. K. Folsom, *Tetrahedron Lett.*, 4011 (1970); (c) P. K. Kadaba, *Synthesis*, 317 (1971); *J. Pharm. Sci.*, **63**, 1333 (1974).

(14) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 28 (1963).

Acyclic Polyhalogenated Monoterpenes from the Red Alga *Plocamium violaceum*

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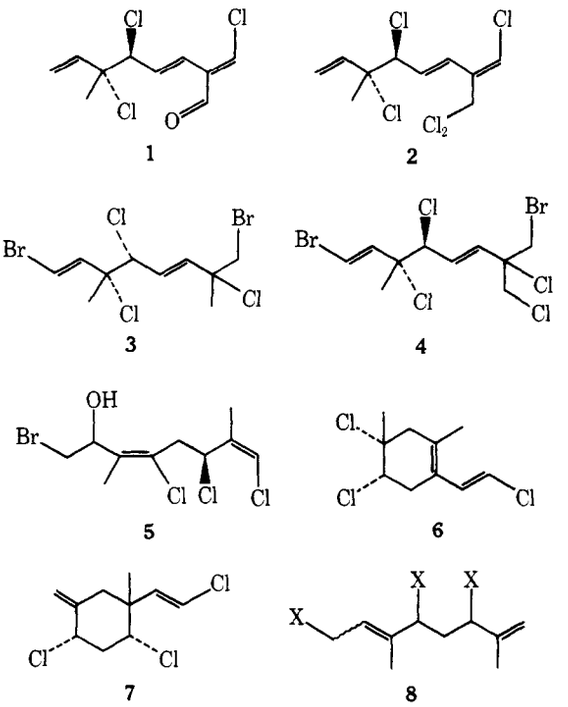
Several new acyclic 1,4,6-trichloro-3,7-dimethyl-2,7-octadiene monoterpenes are reported from the red marine alga *Plocamium violaceum* (Dixon) collected along a narrow coastal region of Monterey County, Calif. Both the gross structures and all of the stereochemical features of these halocarbons were established by extensive analysis of their ^1H and ^{13}C NMR data in comparison to data from numerous model compounds.

Our recent study of the natural products from the marine algae of the Plocamiaceae has revealed a fascinating array of halogenated monoterpenes. Without exception, every Plocamiaceae species that we have examined has been rich in one or more of these natural products.[1] For example, *Plocamium cartilagineum* (Dixon) contains several 2,7-dimethyl-1,5,7-octatrienes such as cartilagineal **1**[2] or **2**.[3] Other unusual acyclic monoterpenes including **3** and **4** can be isolated from *Plocamium oregonum* (Doty),[4] and costatol (**5**) is found in *Plocamium costatum* (C. Ag.).[5] By contrast, *Plocamium violaceum* (Farlow) has been a source for a number of alicyclic monoterpenes[6,7] such as plocamene B (**6**) and plocamene D (**7**).

Our past work upon the monocyclic constituents from *P. violaceum* has involved specimens toxic to both fish and insects which are collected from a broad area north of Santa Cruz, Calif. (Santa Cruz and San Mateo Counties). Concurrent work by others has shown that *P. violaceum* from San Diego County, Calif., contains additional examples of cyclic monoterpenes.[8] Not long ago we had occasion to collect samples of *P. violaceum* from a narrow coastal region of Monterey County just south of Santa Cruz, Calif. These seaweeds displayed no alicyclic monoterpenes and instead yielded several new acyclic monoterpenes. Reported below are the structures of these interesting new compounds.

Collections of *P. violaceum* from Pescadero Point, Point Joe, and Asilomar Beach (all in Monterey County, Calif.) gave crude oils, from $CHCl_3$ extraction of fresh plants, having fairly



a, X = $ClBr_2$

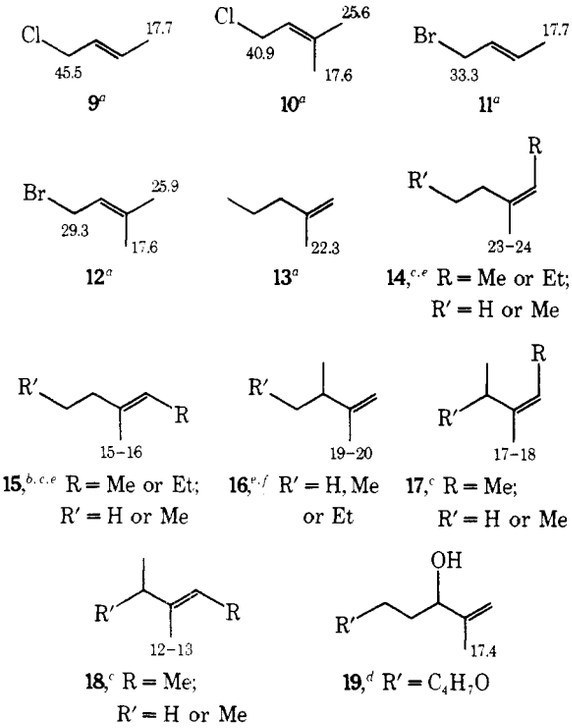
b, c, X = Cl_3

different GC/MS profiles. The Point Joe oil contained a single major component, which was easily purified, of molecular formula $C_{10}H_{15}ClBr_2$ to which we assigned a gross structure **8a**. While its UV was blank above 200 nm and the IR showed only halocarbon functionality, both the mass spectrum (weak M^+ cluster at *m/e* 328/330/332) and the ^{13}C NMR spectrum (Table I) provided information about the total formula. In addition, the ^{13}C NMR exhibited two double bonds thereby revealing, in combination with the molecular formula, an acyclic constitution. The relative atom connectivities were solved from the ^1H NMR spectra ($CDCl_3$, 100 MHz). The 15 H's were distributed among six multiplet clusters divisible into four subgroups: (a) two vinyl CH_3's δ 1.87 (A = 6) singlet (as two singlets δ 1.67 and 1.77 in 1:1 $CDCl_3$–Bz-d_6); (b) $XCHCH_2CHX$ δ 2.42 (A = 2) triplet (J = 7.2 Hz), δ 4.66 and 4.69 (A = 1, 1) overlapping triplets (J = 7.2 Hz), collapsible to a single triplet at δ 4.61 (A = 2) in 1:1 $CDCl_3$–Bz-d_6 or collapsible to two singlets by irradiation at δ 2.42; (c) $>C{=}CH_2$ δ 4.95 and 5.11 (A = 1, 1) br singlets; and (d) $XCH_2CH{=}C<$ δ 4.07 (A = 2) doublet (J = 7.4 Hz), δ 5.80 (A = 1) br triplet (J = 7.4 Hz). These four fragments could be pieced together in only one way as shown by structure **8a**.

The remaining details unsolved for the total structure of **8a** included the geometry about the C_2–C_3 trisubstituted double bond, the absolute halogen regiochemistry, and the relative stereochemistry of the halogens at C_4 and C_6. Each of these assignments was unambiguously established below by employing several types of NMR data.

The ^{13}C shift assignments for **8a** (Table I) were made based upon the J_{CH} data[6] and reference to chemical shift data for several model compounds (Scheme I). That ^{13}C shifts for

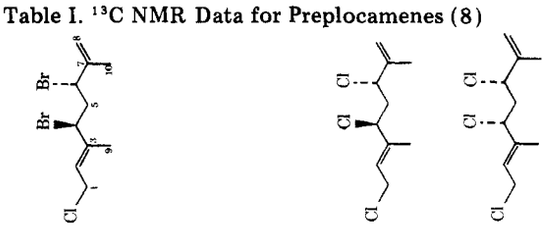
Scheme I. ^{13}C NMR Chemical Shifts of Model Compounds



[a] This work. [b] Reference 9. [c] Reference 10. [d] Reference 11. [e] Reference 12. [f] Reference 13.

halogenated carbons in an isostructural environment are quite dependent upon the type of halogen substituent is illustrated in Scheme I. Thus, a $-CH_2Br$ appears 12 ppm higher than a $-CH_2Cl$ in models **9** and **10** vs. **11** and **12**. Of the three halogenated carbons in **8a** which occur at δ 39.8, 56.5, and 57.9, it

Table I. ^{13}C NMR Data for Preplocamenes (8)



Carbon	δ	Mult	J_{CH}	δ	δ
1	39.7	t	151	39.5	40.4
2	124.6	d	156	125.3	124.7
3	139.9[a]	s		142.7	
4	56.2[b]	d	159	62.8[b]	63.1[b]
5	43.4	t	131	42.7	43.0
6	57.6[b]	d	159	63.9[b]	64.4[b]
7	143.7	s		142.7	
8	114.8	t	156	115.5	114.8
9	12.7	q	127	11.5	11.9
10	18.4	q	127	16.9	17.7

[a,b] The assignments of these close-lying peaks could be reversed.

was possible to assign the Cl to the peak at δ 39.8 attached at C_1 because of the similarity in shift between that carbon and the $-CH_2Cl$ in **10** (δ 41.3). The remaining two Br's could then be placed at C_4 and C_6 which was consistent with closeness of their δ's.

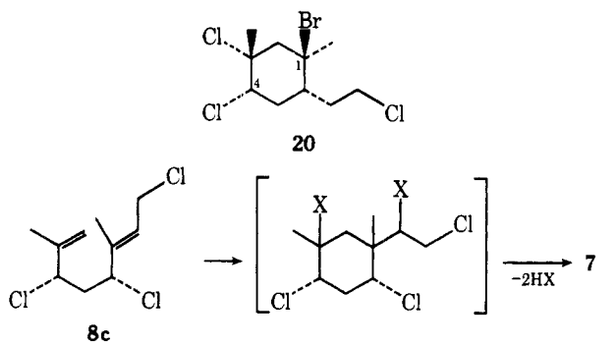
Turning to the vinyl methyl carbons, by comparison to Scheme I, it was possible to assign the **8a** C_7 CH_3 to the peak at 18.4 ppm and the 12.7 ppm absorption to the C_3 CH_3. In addition arguments which follow indicated that this latter methyl must be oriented cis to the $-CH_2Cl$ unit. The pattern of methyl shifts from the trisubstituted olefins in Scheme I reveals, in agreement with past observations,[14] that the chemical shift of a methyl cis to an alkyl chain is shielded by about 5–8 ppm relative to a trans methyl. The base shift value for a methyl which is geminal to a straight alkyl chain and either on a 1,1-disubstituted alkene or trans to another alkyl appears at δ 22–24 (i.e., **13** and **14**) while the base value for a methyl which is geminal to an alkyl chain and cis to another alkyl appears upfield at δ 15–16 (i.e., **15**). Comparison of the data for compound sets **13** and **16**, **14** and **17**, and **15** and **18** shows that a γ-alkyl substituent on the alkyl chain imparts a 3–6 ppm upfield shift upon the geminal methyl.[15] The methyl shifts for the series, **13**, **16**, and **19** are also informative and indicate that the γ shift of a polar group is about 2 ppm larger than for a γ-alkyl substituent. Applying these collective insights to the data of **8a** led to the methyl shift and double bond geometry assignments shown in Table I.

The seven-carbon constellation in **8a** from C_2 to C_8 has a symmetry element at C_5. Within this fragment the Br's at C_4 and C_6 can adopt either a relative C_s or C_2 type arrangement, which will then impart a distereotopic or homotopic relationship, respectively, for the protons on C_5. An extension of this analysis to the mildly unsymmetrical C_1–C_8 piece is enticing and a relative C_2-like Br stereochemistry is indicated based upon the observation that the methylene protons appear as a sharp triplet and maintain their chemical shift equivalence even at 360 MHz in both benzene-d_6 and $CDCl_3$.

Mixtures of two isomers **8b** and **8c** of formula $C_{10}H_{15}Cl_3$ (*m/e* 240/242/244) were isolated from *P. violaceum* from Pescadero Point and Asilomar Beach Calif., but they could not be separated by either normal or reverse phase preparative HPLC or by preparative GLC. However, the purified isomer mixtures were found to be enriched in **8b** (70%) or **8c** (60%) from the collections at these different sites. A comparison of

the GC/MS and magnetic resonance data for these enriched mixtures enabled specific NMR peak assignments for each isomer. Most of the ^1H NMR signals (100 MHz, $CDCl_3$) of these two components had identical chemical shifts which were similar to that of **8a** for the peaks at δ 1.79 (A = 6), singlet; 4.98 and 5.09 (A = 1, 1), br singlets; 4.08 (A = 2), doublet, J = 7.4 Hz; and 5.74 (A = 1), br triplets, J = 7.4 Hz; but different than **8a** for the resonances due to the $XCHCH_2CHX$ unit at δ 2.22 (A = 2), overlapping triplet and multiplet, and 4.41 and 4.61 (A = 2), br triplet, J = 7.3 Hz. These data along with the molecular formula indicated that gross structure **8** was also appropriate for **8b** and **8c**. This was further supported by the vinyl carbons observable in the ^{13}C spectra of the **8b** and **8c** mixtures. The specific assignments shown in Table I for **8b** and **8c** were made by comparison to the data for **8a** and the model compounds in Scheme I. In agreement with arguments above, the ^{13}C shifts of C_1 in **8b** and **8c** of 39.7 and 40.6 ppm were ascribable to a $-CH_2Cl$ cis to another alkyl chain or methyl. As expected the shift positions for C_4 and C_6 in both isomers were quite similar. The diagnostic shift positions of the C_3 methyl peaks (**8b** δ 11.5, **8c** δ 11.9) were consistent only with a cis geometry of the methyl and $-CH_2Cl$ unit. Having the C_2–C_3 double bond of identical geometry for **8b** and **8c** then required the halogens at C_4 and C_6 to be respectively C_s-like and C_2-like for the two diastereomers. This could be further confirmed by analogy to the case for **8a** in that the ^1H NMR at 360 MHz of the isomer mixture showed a triplet resonance (J = 7.3 Hz) ascribable to the C_5 methylene protons of isomer **8b** and two sets of ddd (J = 14.5, 8, 6 Hz) for the C_5 methylene protons of the isomer assigned as **8c**.

Scheme II



Several pairs of erimeric acyclic distereomers have been isolated from both *Plocamium cartilagineum*[3] and *Plocamium oregonum*[4] and they all have adjacent chiral centers. In contrast, the epimeric diastereomers **8b** and **8c** contain chiral centers which are separated by two bonds. This same structural feature is also present in a few of the monocyclic terpenes from *Plocamium*. Thus, structural frame **8** provides a logical biogenetic relay to the cyclic series of *Plocamium* compounds. For example, addition of X_2 to **8c** accompanied by olefin-assisted cyclization followed by loss of 2HX could produce a 1,1,5-trialkylcyclohexane ring skeleton such as **7**. In view of this potential relationship we have given the trivial name of preplocamene to the skeleton of **8**. Recently, the x-ray structure of **20** was reported by Mynderse et al.[16] Owing to the striking relationship between the S–C_4 in **20** and C_6 in **8c**,[17] it is tempting to propose an S stereochemistry for this latter center, and in view of the relative C_6 and C_4 (**8c**) symmetry deduced above, an R arrangement at C_4 in **8c**.

Experimental Section

The NMR spectra were recorded on a JEOL PS 100 pulsed FT spectrometer operating at 100 MHz for ^1H and 25.1 MHz for ^{13}C. The 360-MHz ^1H spectra were recorded at the Stanford Magnetic Resonance Laboratory. Optical rotations were measured on a Perkin-Elmer 141 polarimeter with a 1-dm cell (5 mL). GC/MS data were recorded on a Finnigan 4000 system equipped with a 6 ft × 0.125 in. glass column packed with 3% OV-17 on Chromosorb G and temperature programmed 115–225 °C at 5 °C/min. Routine low-resolution mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer and UV data were recorded on a Cary 14 spectrometer. Infrared data were recorded on a Perkin-Elmer 237 B spectrophotometer. High-performance liquid chromatography (HPLC) was done on a Waters ALC 201 instrument fitted with Porasil columns (8 ft × 0.375 in.) for normal phase and C-18 Corasil columns (4 ft × 0.375 in.) for reverse phase. All solvents were reagent grade and distilled prior to HPLC use. Spectral grade solvents were used for NMR (Me_4Si standard), UV, and optical rotation measurements. Low-boiling petroleum ether was used in all instances.

Collections and Extractions. *Plocamium violaceum* was collected intertidally from three locations (wet weight and yield of extract) including the following: Point Joe, Dec 3, 1975 and Dec 20, 1975 (2.38 kg, 3.65 g, 0.15%); Pescadero Point, June 29, 1976 and July 27, 1976 (3.65 kg, 4.23 g, 0.12%); and Asilomar Beach, July 15, 1976 (0.34 kg, 0.43 g, 0.13%), all within a 10-mile range in Monterey County, Calif.

The freshly collected algae were either directly extracted or frozen until extraction. All samples were extracted first with $CHCl_3$ for ca. 3 days and then with EtOH for ca. 3 days in a Soxhlet apparatus. The combined extracts were then chromatographed through silica gel (Grace Co. grade 62, 60–200 mesh, activated) using petroleum ether. The resulting semipurified oil was then subjected to HPLC using petroleum ether–benzene (95:5).

Isolations. Following the procedure above, compounds **8a** and mixtures of **8b** and **8c** were isolated.

1-Chloro-4,6-dibromo-3,7-dimethyl-2,7-octadiene (8a) was isolated as a clear, mobile oil, HPLC fractions 10–14 (20-mL fractions, 116 mg oil) from the collections made at Point Joe. Its ^1H and ^{13}C NMR are described in the text and in Table I and at 360 MHz (benzene-d_6), H_{5a} and H_{5b} are seen as a dt at δ 2.40 (J = 7.5, 2.3 Hz) and H_{1a} as dd at δ 3.65 and 3.75 (J = 11.3, 7.5 Hz). It displayed an $[\alpha]^{20}_D$ −35° (c 1.43, $CHCl_3$); IR 1430, 1380, 1260, 910 cm^{-1}; MS m/e 328, 330, 332 (M^+); 293, 295, 297 ($M^+ - Cl$); 249, 251, 253 ($M^+ - Br$); 213, 215 ($M^+ - HBr, Cl$); 169, 171 ($M^+ - HBr, Br$); 133 base ($C_{10}H_{13}$).

Ozonolysis of 8a. Several attempts were made to ozonize **8a** (10 mg) in CH_2Cl_2 at −78 °C with a stream of ozone generated by a Welsbach T-408 apparatus. The crude ozonide from above was worked up with several reagents including $(Ph)_3P$ and $(CH_3)_2S$ and in each case an unstable product was obtained whose spectral properties indicated oxygen formation (i.e., IR peak at 1720 cm^{-1}). Attempts to purify this material (i.e., distillation, chromatography, or DNPH formation) yielded only intractable material.

Hydride Reduction of 8a. Attempts to displace a bromine in **8a** by $Li(Et)_3BH$ were also unsuccessful. Following a good literature analogy,[18] **8a** (10 mg) in 2 mL of HF (anhydrous) was reacted with 1 equiv of $Li(Et)_3BH$ in THF solution (1 M) at 0 °C for 15 min which resulted in only recovery of starting material. Prolonged reaction at higher temperatures yielded only decomposed products.

1,4,6-Trichloro-3,7-dimethyl-2,7-octadienes (8b and 8c) were isolated as a mixture of diastereomers in varying relative percents from two locations. Neither preparative HPLC (Porasil A or Corasil C_{18}) or preparative GC afforded separation of the mixture. Analytical GLC did show two separate peaks for **8b** and **8c**, t_r 18.3 and 19.0 min. The collections made at Pescadero Point yielded pure **8b** and **8c** (180 mg) as an oil after reverse phase HPLC (CH_3CN–H_2O solvent, 60:40), ten recycles. The ratio of **8b**:**8c**, 69:31, was determined by integration of the –CHCl– region in the ^1H NMR (100 MHz, $CDCl_3$) where **8b** signals (δ 4.41, triplet, J = 7.3 Hz) were clearly separable from **8c** signals (δ 4.61, triplet, J = 7.3 Hz) and by rough intensity comparisons to the C_5 methylene region in which a triplet at δ 2.28 (J = 7.3 Hz) (**8b**) and multiplet at δ 2.32 (J = 14.5 and 7.3 Hz) (**8c**) were observed. These upfield resonances along with the added detail observable at 360 MHz added strength to our specific ^1H NMR assignments of **8b** and **8c** (Table I). At 360 MHz in benzene-d_6 **8b** displayed –CH(Cl)– δ 4.23 (t), J = 7.3 Hz, and 4.36 (t), J = 7.3 Hz; H_5 δ 1.98 (t), J = 7.3 Hz, while **8c** displayed –CH(Cl)– δ 4.49 (dd), J = 8.4, 5.7 Hz, and 4.58 (dd), J = 8.4, 5.7 Hz; H_{5a} δ 1.97 (ddd), J = 14.5, 8, 6 Hz, and H_{5b} 2.26 (ddd), J = 14.5, 8, 6 Hz. The ratio of **8b**:**8c** was also determined by GC/MS and ^{13}C NMR data as 70:30 and 71:29, respectively. Another collection from Asilomar Beach (22 mg) afforded the opposite enrichment as determined by GC/MS (**8b**:**8c** 40:60). The mixture of **8b** and **8c** displayed IR 1430, 1260, 910, 800 cm^{-1}, and MS at each GC peak m/e 240, 242, 244 (M^+); 225, 227, 229 ($M^+ - CH_3$); 205, 207, 209 ($M^+ - Cl$); 170, 172 ($M^+ - Cl_2$); 81 base (C_6H_4).

^{13}C NMR of Model Compounds. Compounds **9**, **11**, and **13** were

purchased from Aldrich Chemical Co. and **10** and **12** were prepared according to the literature.[19] ^{13}C NMR data were obtained with 50% solutions in $CDCl_3$. ^{13}C NMR data (Me_4Si standard) not in Scheme I; 1-chloro-*trans*-2-butene (**9**), C_2 127.5, C_3 130.7; 1-chloro-3-methyl-2-butene (**10**), C_2 121.0, C_3 139.0; 1-bromo-*trans*-2-butene (**11**), C_2 127.8, C_3 131.0; 1-bromo-3-methyl-2-butene (**12**), C_2 121.0, C_3 139.5; 2-methyl-1-pentene (**13**), C_1 110.1 (t), C_2 145.7 (s), C_3 40.6 (t), C_4 21.2 (t), C_5 13.9 ppm (q).

Acknowledgment. We thank Professor I. A. Abbott (Hopkins Marine Station) for guidance in alga identification. We also thank the NOAA office of Sea Grant and UCSC Committee on Research for support of this research, and the NSF Chemical Instrumentation Program for their financial assistance in the purchase of a GC/MS apparatus.

Registry No.—**8a**, 62743-07-1; **8b**, 62743-08-2; **8c**, 62743-09-3; **9**, 4894-61-5; **10**, 503-60-6; **11**, 29576-14-5; **12**, 870-63-3; **13**, 763-29-1.

References and Notes

(1) P. Crews in "NATO Conference on Marine Natural Products", D. J. Faulkner and W. Fenical, Ed., Plenum Press, New York, N.Y., 1977, pp 211–223.
(2) P. Crews and E. Kho, *J. Org. Chem.* **39**, 3303 (1974).
(3) J. S. Mynderse and D. J. Faulkner, *Tetrahedron*, **31**, 1963 (1975).
(4) P. Crews, *J. Org. Chem.*, in press.
(5) R. Kazlauskas, P. T. Murphy, R. J. Quinn, and R. J. Wells, *Tetrahedron Lett.*, 4451 (1976).
(6) P. Crews and E. Kho, *J. Org. Chem.*, **40**, 2568 (1975).
(7) P. Crews and E. Kho-Wiseman, Abstracts, 31st Northwest Regional Meeting of the American Chemical Society, June 1976, No. G122.
(8) J. S. Mynderse and D. J. Faulkner, *J. Am. Chem. Soc.*, **96**, 6771 (1974).
(9) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971).
(10) J. W. de Haan, and L. J. M. van de Ven, *Org. Magn. Reson.*, **5**, 147 (1973).
(11) F. Bohlmann, R. Zeisberg, and E. Klein, *Org. Magn. Reson.*, **7**, 426 (1975).
(12) P. A. Couperus, A. D. H. Clague, and J. P. C. M. van Dongen, *Org. Magn. Reson.*, **8**, 426 (1976).
(13) J. W. de Haan, L. J. M. van de Ven, A. R. N. Wilson, A. E. van der Hout-Ludder, C. Altona, and D. H. Faber, *Org. Magn. Reson.*, **8** 477 (1976).
(14) J. W. de Haan and L. J. M. van de Ven, *Tetrahedron Lett.*, 3965 (1971).
(15) For a discussion of ^{13}C NMR γ effects in acyclic systems see (a) G. C. Levy and G. R. Nelson, "Carbon-13 Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, Chapter 3; (b) G. J. Martin, M. L. Martin, and S. Odiot, *Org. Magn. Reson.*, **7**, 2 (1975), and references cited therein.
(16) J. S. Mynderse, D. J. Faulkner, J. Finer, and J. Clardy, *Tetrahedron Lett.*, 2175 (1975).
(17) See Scheme II and the discussion in ref 6.
(18) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **95**, 1669 (1973).
(19) S. Julia, M. Julia, and G. Linsturmelle, *Bull. Soc. Chim. Fr.*, 3499 (1966).

Majusculamides A and B, Two Epimeric Lipodipeptides from *Lyngbya majuscula* Gomont

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Majusculamides A and B are major lipophilic constituents of the blue-green alga *Lyngbya majuscula* Gomont. Detailed spectral analysis, chemcial degradation, and x-ray crystallographic studies show that majusculamide A is *N*-[(2*R*)-2-methyl-3-oxodecanoyl]-D-*N*,*O*-dimethyltyrosyl-L-*N*-methylvalinamide (**6a**) and that majusculamide B is *N*-[(2*S*)-2-methyl-3-oxodecanoyl]-D-*N*,O-dimethyltyrosyl-L-*N*-methylvalinamide (**6b**). Majusculamide B is epimerized into a mixture of majusculamides A and B and then degraded into D-*N*,O-dimethyltyrosyl-L-*N*-methylvaline lactam (**2**) and racemic 2-methyl-3-oxodecanoic amide (**1**) at 140 °C in anhydrous dimethyl sulfoxide.

The blue-green alga *Lyngbya majuscula* Gomont is responsible for sporadic outbreaks of a contact dermatitis known in Hawaii as "swimmers' itch".[2] Not all varieties of this seaweed show dermonecrotic activity. *L. majuscula* from Laie Bay, Oahu, however, is frequently dermatitis-producing during the summer months. The causative agent, which is found in the lipid extract of the seaweed, may be debromoaplysiatoxin,[3] a poisonous substance that was first isolated from the digestive tract of the gastropod mollusk *Stylocheilus longicauda*.[4]

We have found that *L. majuscula* is characterized chemotaxonomically by the presence of two major lipophilic constituents which we have named majusculamides A and B. Majusculamides A and B are constituents of both the dermatitis- and nondermatitis-producing varities, but are not found in *L. gracilis*.[5a] In this report we describe the structure determination of these two nontoxic[5b] compounds.

Isolation. The alga was collected in shallow water (0.5–2 m) from several points around the island of Oahu, but mainly from Kahala Beach for the structure work. Extraction of the wet seaweed with methanol and chloroform or the freeze-dried seaweed with chloroform gave an oily extract which after chromatography and gel filtration resulted in a crystalline mixture of majusculamides A and B. Separation of the two epimeric compounds was readily achieved by high-pressure liquid chromatography.

Structure Determination. Majusculamides A and B both crystallized from aqueous methanol and analyzed for $C_{28}H_{45}N_3O_5 \cdot H_2O$. Molecular ions could not be observed in their electron-impact (EI) mass spectra, but fragment ions appeared at *m/e* 486 and 487 for loss of NH_3 and NH_2 from the molecular ions and high-resolution mass measurements gave elemental compositions of $C_{28}H_{42}N_2O_5$ for the *m/e* 486 peaks. Molecular ions, however, were easily seen at *m/e* 503 in the field desorption (FD) mass spectra. The loss of NH_3 and NH_2 from the molecular ions in the EI mass spectra suggested that the majusculamides were primary amides and this was confirmed by IR and ^1H NMR.

The ^1H NMR spectra of majusculamides A and B in chloroform-*d* and dimethyl-d_6 sulfoxide at room temperature were rather complex due to the presence of two slowly interconverting conformers for each compound. At 140 °C in anhydrous dimethyl-d_6 sulfoxide, however, the ^1H NMR spectra were greatly simplified and each one clearly showed the presence of a para-substituted anisole ring, two *N*-methyl groups, three secondary methyl groups, two adjacent methine