

quenched (-78 °C) with dry pyridine (three drops). The solutions were processed with saturated NaHCO₃, ether, water, brine, and drying agent as described above (method A). The resulting crude reaction mixtures were purified and analyzed as described below.

Ketone 1 (Table IV, Entry 1). Method A. Ketone 1 (139 mg, 1.0 mmol) afforded, after flash chromatography (silica gel, 20 cm × 1 cm, 1.9 ether/hexane), ketal 8 (85 mg, 47%) and ketone 1 (39 mg, 28%).

Ketone 2 (Table IV, Entries 2 and 3). Method A. Ketone 2 (152 mg, 1.0 mmol) yielded only recovered camphor 2 (150 mg, 98%). **Method B.** Ketone 2 (152 mg, 1.0 mmol) afforded, after chromatography (HPLC, 1:19 ethyl acetate/hexane), starting material 2 (152 mg, 100%).

Ketone 3 (Table IV, Entries 4 and 5). Method A. Fenchone 3 (152 mg, 1.0 mmol) afforded after distillation only recovered fenchone 3 (147 mg, 97%). **Method B.** Ketone 3 (152 mg, 1.0 mmol) yielded, after chromatography (HPLC, 1:19 ethyl acetate/hexane), recovered fenchone 3 (152 mg, 100%).

Ketone 5 (Table IV, Entries 6 and 7). Method A. Enone 5 (178 mg, 1.0 mmol) provided, after chromatography (HPLC, 1.0:1.86 ethyl acetate/hexane) ketal 13 (51 mg, 23%) and recovered enone 5 (62 mg, 35%). The formation of ketal 11a was not

detected (HPLC, ¹H NMR). **Method B.** Enone 5 (178 mg, 1.0 mmol) yielded, after chromatography (HPLC, 1.0:1.86 ethyl acetate/hexane), only recovered ketone 5 (178 mg, 100%).

Ketone 6 (Table IV, Entry 8). Enone 6 (84 mg, 0.38 mmol) afforded, after chromatography (HPLC, 1.0:1.86 ethyl acetate/hexane), only recovered starting material 6 (73 mg, 87%).

Ketone 7 (Table IV, Entry 9). Enone 7 (110 mg, 1.0 mmol) yielded, after flash chromatography (silica gel, 1:1 ether/hexane), the dimer 18 (87 mg, 57%) and recovered enone 7 (39 mg, 35%).

Registry No. 1, 2408-37-9; 2, 76-22-2; 3, 1195-79-5; 4, 105018-93-7; 5, 878-55-7; 6, 105018-96-0; 7, 1193-18-6; 8, 71018-58-1; 9, 18501-53-6; 10, 105018-92-6; 11a, 105018-94-8; 11b, 105087-93-2; 12, 105018-95-9; 13, 65898-56-8; 14, 105087-94-3; 15, 105018-99-3; 16, 105018-97-1; 18, 105018-98-2; ethylene glycol, 107-21-1; 1,2-bis[(trimethylsilyl)oxy]ethane, 7381-30-8.

Supplementary Material Available: Experimental details for the crossover experiments, 1-bar control experiments referred to in Tables I and II, the effect of solvent in the formation of ketal 10, and 15-kbar experiments using triethyl orthoformate at 20 °C (7 pages). Ordering information is given on any current masthead page.

Complete Structural Analysis of Cyclic Polyhalogenated Monoterpenes. A Force Field 2D NMR Study

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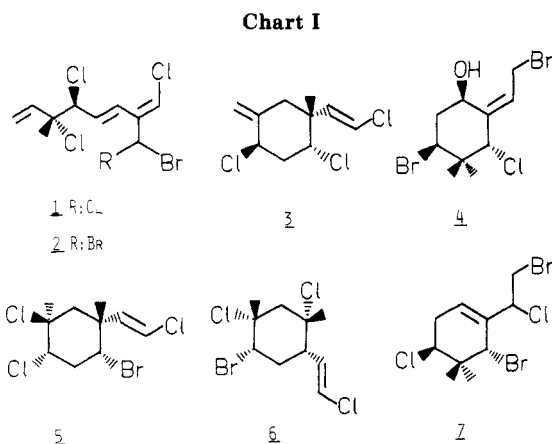
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The information obtained from two-dimensional NMR and NOED spectroscopy led to the complete structural analysis of five cyclic monoterpenes of marine origin. Correlated 2D spectra allowed the establishment of the gross structural features, the final stereochemical assignments being made by NOEDS. The use of ¹³C NMR shifts in defining the regio- and stereochemistry of monoterpenes 17-21 is criticized in terms of the inappropriateness of the models used. Force field calculations show that models 8-16 do not accurately reproduce the structural features of the cyclic terpenes 17-21, thus precluding the straightforward application of ¹³C additive effects. The calculated minimum energy conformers of 17-21 agree well with the geometries deduced experimentally by using a generalized Karplus equation.

The complete structural analysis of natural products is a topic of continuing interest among chemists. One of the important characteristics of the molecules obtained from natural sources is the wide variety of the structures exhibited by them, which has served as a permanent stimulus for the development of spectroscopic techniques of increasing power and sophistication.

The analysis of ¹³C shift data in terms of substituent effects has led to the structural elucidation of many natural products.^{1,2} The approach used is to determine a series of additive substituent shift effects from the study of suitable model compounds and to apply them to the molecules of interest. This technique has been extensively used in the field of marine natural products, a recent example of this being represented by the excellent work of P. Crews and co-workers³ who identified the structures of three newly isolated polyhalogenated monoterpenes 1-3 and proposed corrected structures for the other four compounds 4-7 (Chart I) by using additive effects taken from simple models (Chart II).

Unsuspectedly, a few months later the proposed structure 5 was revised as its epimer 19 by a low-temperature



X-ray analysis.⁴ This finding prompted us to investigate this issue further and to develop a more reliable spectro-

(1) Maciel, G. E. *Topics in C-13 NMR Spectroscopy*; Levy, G. C., Ed.; Wiley: New York, 1974; Vol. I, p 53.

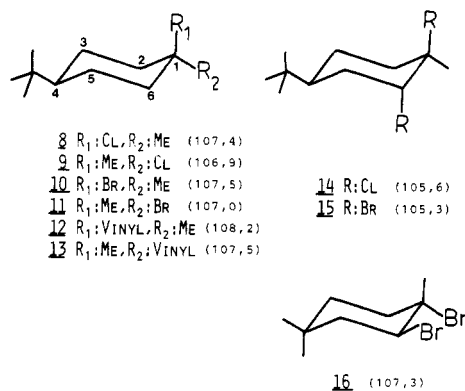
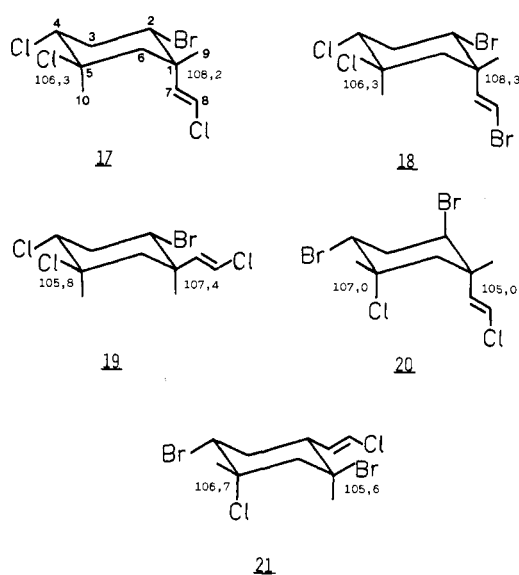
(2) (a) Wenkert, E.; Buckwalter, B. L.; Burfit, I. R.; Gasic, M. J.; Gottlieb, H. E.; Hagaman, E. W.; Schell, F. M.; Wovkulich, P. M. *Topics in C-13 NMR Spectroscopy*; Levy, G. C., Ed.; Wiley: New York, 1976; Vol. II, p 81. (b) Wehrli, F. W.; Nishida, T. *Prog. Chem. Org. Nat. Prod.* 1979, 36, 1.

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Table I. Force Field Calculated Torsion Angles for Models 8-16 and Terpenes 17-21 (X-ray Data for Mertensene (19) Shown in Parentheses)

angle	compounds													
	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1-2-3-4	56.0	56.4	55.8	56.5	56.3	56.6	56.3	54.7	55.9	56.9	56.9	57.6 (59.8)	55.9	57.6
2-3-4-5	52.2	54.3	55.0	54.1	54.1	54.4	53.7	53.1	51.9	56.4	56.4	57.0 (60.2)	55.5	57.4
3-4-5-6	55.2	54.3	55.0	54.1	55.8	54.2	53.9	53.6	51.8	53.3	53.2	52.0 (53.3)	50.5	51.2
4-5-6-1	56.0	56.4	55.8	56.5	59.6	56.4	54.4	54.2	55.2	53.9	53.8	50.7 (55.9)	50.5	49.4
5-6-1-2	52.6	54.6	52.0	54.8	56.7	53.3	51.5	51.1	54.2	53.6	53.3	50.4 (52.9)	51.8	50.2
6-1-2-3	52.6	54.6	52.0	54.8	55.2	53.5	52.5	52.0	54.7	53.4	53.3	52.0 (57.0)	52.2	52.2

Chart II**Chart III**

scopic technique for the structural analysis of polyhalogenated monoterpenes and in particular for compounds 17-21 that we have recently isolated from a *Plocamium*⁵ species. Chart III shows the structures of these compounds as corrected on the basis of the work reported on this paper.⁶

Results and Discussion

Molecular Distortions and ¹³C NMR. The ¹³C additive effects approach is based on the assumption that the effects deduced from the models embrace all the structural factors influencing ¹³C chemical shifts and that they are rigorously additive. The aforementioned X-ray result cast some doubts on the validity of the method in that case, and consequently we tried first to find out whether or not those models are appropriate to study compounds 17-21.

We reasoned that models 8-16 might not be appropriate for two reasons: First, it is known that ¹³C shifts are profoundly modified by geometric changes (molecular distortions)¹ and it is reasonable to suppose that such heavily substituted molecules as those depicted in Charts I and III must depart significantly from the ideal cyclohexane chair in order to accommodate steric and dipolar repulsions among the substituents. It is not clear that the models account for such deformations. Second, steric

factors are known to influence ¹³C shifts,⁷ and the models do not account for such important effects as 1,3-diaxial interactions that are always present in the cyclic polyhalogenated terpenes.

In order to clarify whether the models do reliably reproduce the structural features of our molecules, we carried out detailed molecular mechanics calculations (Allinger's MM II program)⁸ for both the models 8-16 and the compounds 17-21. The geometries of the most stable conformers are represented in Chart III, the alternative chair and boat forms having considerable higher energies (3-5 kcal·mol⁻¹). There is good agreement between the X-ray data for 19 and the calculated bond angles and distances (root mean square deviation 1.82° and 0.036 Å). Charts II and III include the values of the exocyclic angles at C₁ of the models and at C-1 and C-5 of the terpenes.

For its part, the most significant torsion angles for the calculated structures of 8-21 and the crystalline structure of 19 are listed in Table I. It can be readily seen that both models and monoterpenes are rather distorted, the departure from the ideal geometry being more pronounced in monoterpenes 17-21 than in the models. This is particularly so for compounds 19, 20, and especially 21, which

(3) Crews, P.; Naylor, S.; Hanke, F. J.; Hogue, E. R.; Kho, E.; Braslau, R. *J. Org. Chem.* 1984, 49, 1.

(4) Capon, R. J.; Engelhardt, L. M.; Ghisalberti, E. L.; Jefferies, P. R.; Patrick, V. A.; White, A. H. *Aust. J. Chem.* 1984, 37, 537.

(5) Castedo, L.; García, M. L.; Quiñoá, E.; Riguera, R. *J. Nat. Prod.* 1984, 47, 724.

(6) (a) A preliminary account of this work including the structural revision of 17 and 18 has already been published: Sardina, F. J.; Quiñoá, E.; Castedo, L.; Riguera, R. *Chem. Lett.* 1985, 697. (b) Structure 17 in Chart III represents a three-dimensional view of structure 5 (Chart I) that had been previously assigned to mertensene (19).^{3,4}

(7) (a) Dalling, D. K.; Grant, D. M.; Paul, E. G. *J. Am. Chem. Soc.* 1973, 95, 3718. (b) Seidman, K.; Maciel, G. E. *J. Am. Chem. Soc.* 1977, 99, 659. (c) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* 1967, 89, 5315. (d) Engelhardt, G.; Jancke, H.; Zeigan, D. *Org. Magn. Reson.* 1977, 9, 528. (e) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* 1976, 54, 917. (f) Duddeck, H. *Org. Magn. Reson.* 1975, 7, 151. (g) Cheney, B. V.; Grant, D. M. *J. Am. Chem. Soc.* 1967, 89, 5319.

(8) Burkert, U.; Allinger, N. L. *ACS Monogr.* 1982, No. 177.

Table II. Proton NMR Data for Monoterpenes 17–21 (Vicinal Coupling Constants Calculated according to the Generalized Karplus Equation¹⁰ in Parentheses)

proton	compound 17			compound 18			compound 19			compound 20			compound 21		
	δ	mult	J , Hz	δ	mult	J , Hz	δ	mult	J , Hz	δ	mult	J , Hz	δ	mult	J , Hz
H-6 _{ax}	2.20	d	14.4	2.19	d	14.4	2.25	d	14.4	2.13	d	15.2	2.71	d	15.0
H-6 _{eq}	2.58	d	14.4	2.60	d	14.4	2.43	d	14.4	2.18	d	15.2	3.02	d	15.0
H-4	4.15	dd	4.3 (4.1) 12.5 (11.5)	4.15	dd	4.3 (4.1) 12.5 (11.5)	4.16	dd	4.4 (4.1) 12.6 (11.5)	4.60	dd	3.6 (3.8) 12.0 (11.7)	4.07	dd	4.2 (4.2) 12.0 (11.6)
H-3 _{ax}	2.38	m	12.5 (11.5) 12.9 (11.8) 14.0	2.39	m	12.5 (11.5) 12.9 (11.8) 14.0	2.38	m	12.6 (11.5) 12.7 (11.8) 14.0	2.93	m	2.6 (3.2) 12.0 (11.7) 14.8	2.29	m	12.0 (11.6) 12.0 (12.1) 13.8
H-3 _{eq}	2.65	dt	4.0 (3.9) 4.3 (4.1) 14.0	2.66	dt	4.0 (3.9) 4.3 (4.1) 14.0	2.65	dt	4.1 (3.9) 4.4 (4.1) 14.0	2.48	dt	3.6 (3.8) 3.7 (3.7) 14.7	2.14	dt	4.2 (4.2) 4.2 (4.6) 13.8
H-2	3.84	dd	4.0 (3.9) 12.9 (11.8)	3.84	dd	4.0 (3.9) 12.9 (11.8)	3.94	dd	4.1 (3.9) 12.7 (11.8)	4.42	bs	2.6 (3.2) 3.7 (3.7)	2.88	m	0.7 4.2 (4.6) 12.0 (12.1) 7.5
H-7	6.15	d	13.8	6.30	d	14.1	5.84	d	13.6	5.97	d	13.9	6.03	dt	7.5 13.4
H-8	6.21	d	13.8	6.48	d	14.1	6.07	d	13.6	6.48	d	13.9	6.16	dd	13.4 0.7
Me-9	1.26	s		1.26	d		1.28	s		1.20	s		1.95	s	
Me-10	1.67	s		1.67	s		1.77	s		1.71	s		1.68	s	

presents deviations up to 10° from the ideal value, but as can be deduced from Table I, even the less distorted terpenes (e.g., 17 and 19) depart clearly from the ideal geometry.

The causes for the deformation of 19–21 are different for each compound, but all of them have similar stereochemical origin. In mertensene (19), there exists a strong interaction between the two axial methyl groups (the shortest calculated H–H distance is 2.09 Å). This leads to a closing of the C1–C5–CH₃ and the CH₃–C1–vinyl bond angles and to the overall flattening of the ring. In compound 20 the axial Br atom exerts a strong pressure on the CH₃ at C-1 causing the CH₃–C1–vinyl bond angle to close (Chart III).

As for compound 21 it is worth noting that it possesses a skeleton that differs from that of 17–20, and although this point has not been studied in detail, the deformations calculated for 21 suggest that the 1,5-dimethyl-2-ethenylcyclohexane skeleton is more prone to flattening than that of 1,5-dimethyl-1-ethenylcyclohexane, as no strong steric interactions similar to those found in 19 or 20 are present in 21.

The geometrical features of compounds 17–21 may also be derived from the observed vicinal H–H coupling constants, since the later are related to the interproton torsion angles via the generalized Karplus equation.⁹ On the other side, starting from the MM II calculated torsion angles, the expected coupling constants can be obtained,¹⁰ and this can be used as a further check of the goodness of the calculated geometries. The calculated and the actual vicinal coupling constants for 17–21 are shown in Table II. There exists a very good agreement for the ax–eq and eq–eq coupling constants, but the calculated ax–ax ones fall in all cases short of the actual values. This systematic deviation is not surprising since it is known that the calculated J 's ax–ax in chloro- and bromocyclohexanes turn to be on the low side.⁹ In spite of this, the correspondence between the calculated and the actual J 's is excellent, thus supporting the goodness of the computed geometries. In conclusion, the force field calculations clearly show that the geometries of the natural monoterpenes 17–21 differ

significantly from those of the models used in ref 3. Furthermore, the strong 1,3-diaxial interactions revealed by the calculations for the monoterpenes are not accounted for by the models, so that the results of applying ¹³C shift effects should be regarded with caution.

2D NMR and NOEDS. For the above reasons we decided to apply the more reliable 2D NMR^{11a} and NOEDS^{11b} techniques to the problem of the structural elucidation of 17–21. From the COSY-90^{11a} and the "long-range" COSY-90^{11a} spectra, we obtained the connectivities of the coupled nuclei (¹H in this case), and this allowed the establishment of the gross structure of the molecule. The final stereochemical assignment came from the analysis of the coupling constants and NOED^{11b} spectra. In order to test the technique we chose mertensene (19) as the first compound to be studied, since the structure of this terpene has been rigorously established by low-temperature X-ray diffraction. The COSY-90 spectrum of terpene 19 shows that there are four groups of protons in the molecule producing an ABXY ($J_{xy} = 0$) system made up by protons at 2.38, 2.65, 3.94, and 4.16 ppm; an AB system originated by the protons at 2.25 and 2.43 ppm; two quaternary methyl groups at 1.28 and 1.77 ppm; and another AB system due to a trans-substituted vinyl group (5.84, 6.07 ppm). These data strongly suggest a dimethylvinylcyclohexane skeleton for mertensene, as depicted in Chart III. The ABXY system has its origin in the protons attached to carbons 2, 3, and 4; the isolated AB system comes from the methylene group at carbon 6 and the rest of the signals are self-explanatory. It is interesting to note here the existence of a long-range coupling between one of the protons of the methylene at C-6 and both of the methyl groups. We shall discuss the stereochemical implications of this later.

The complete regiochemical elucidation came from the analysis of the long-range COSY-90^{11a} spectrum, in which both methyl groups are shown to be coupled to the α -halogenated protons at C-2 and C-4, the most revealing fact being that the methyl at 1.28 ppm is coupled to the proton at 3.94 ppm only and that the methyl at 1.77 ppm is coupled to the proton at 4.16 ppm only. This serves to indicate that the two methyl groups are not bonded to the

(9) Hasnoot, C. A. G.; De Leeuw, F. A. A.; Altona, C. *Tetrahedron* 1980, 36, 2783.

(10) Sedee, A. C. J.; Beijersbergen, G. M. J.; Guijt, W.; Haasnoot, C. A. G. *J. Org. Chem.* 1985, 50, 4182.

(11) (a) Benn, R.; Günter, H. *Angew. Chem., Int. Ed. Engl.* 1983, 22, 350. (b) Noggle, J. H.; Shirmer, R. E. *The Nuclear Overhauser Effect; Chemical Applications*; Academic: New York, 1971.

same carbon. Mertensene thus possesses structure 19 (without stereochemical assignment at this point).

The splittings exhibited by H-2, H-3_{ax}, H-3_{eq}, and H-4 (Table II) are clear indicators that the halogens at C-2 and C-4 are both equatorial; H-3_{ax} presents three large couplings of about 14 Hz that are due to a geminal coupling (to H-3_{eq}) and two diaxial couplings (to H-2 and H-4). For its part, H-3_{eq} has a large geminal coupling (14 Hz) and two ax-eq couplings (4.4 Hz to H-4 and 4.1 Hz to H-2).

The stereochemistry of the two remaining centers, C-1 and C-5, was obtained by NOEDS.^{11b} Irradiation of the methyl at 1.28 ppm gave observable NOE with the H-3_{ax} and the 2.43 ppm signals and with those of the other methyl group and both vinylic protons. These enhancements are only possible if the methyl at 1.28 ppm is in an axial position and on the same carbon as the vinyl function.

For its part, the methyl at 1.77 ppm gave NOE with the signals of the other methyl H-3_{ax} and the doublet at 2.43 ppm. Again, these data agree with an axial configuration of the irradiated methyl group at 1.77 ppm. The doublet at 2.43 ppm must thus be due to H-6_{eq}. The origin of the coupling between the methyl groups and H-6_{ax} is now clear, as there is a *W* path between those protons, so long as both methyl substituents are in an axial position. The chair form 19 shown in Chart III is the only structure compatible with all these data.

Having successfully applied this methodology to mertensene (19), we turned our attention to the rest of the monoterpenes isolated from our *Plocamium coccineum*.

The structural elucidation of 17, 18, 20, and 21 is straightforward although there are certain special features of interest, in particular those related to the stereochemical results obtained for coccinene (17) and for 18. For these compounds, the observed nuclear Overhauser effects are in conflict with the structures previously given to them in the literature.^{5,6} In this way, the irradiation in both compounds of the methyl signal at 1.27 ppm induced NOE's on the C-6 methylene group, on H-2_{ax}, and on the vinyl protons, indicating that this methyl is equatorial and on the same carbon as the vinyl group. For its part, irradiation of the methyl at 1.66 ppm induced NOE's on H-3_{ax}, on H-6_{eq}, and on the vinyl group, demonstrating that this methyl is axial and not equatorial as previously believed.^{12,6a} The appearance in the COSY-90 spectra of 17 and 18 of a long-range coupling between H-6_{ax} and the CH₃ group at C-5 gives further support to the axial configuration of that methyl.

The analysis of compounds 20 and 21 leads to the confirmation of the structures that had been proposed.^{12,13} Our data indicate that 20 has the conformation shown in Chart III with an axial vinyl group in accordance with the result of a LIS analysis.¹³

The combined use of ¹H correlation spectroscopy and NOEDS has allowed us to unequivocally assign all the proton resonances of monoterpenes 17-21. In order to get some complementary data we decided to analyze the carbon-proton correlated spectra of these polyhalogenated

compounds. Unfortunately this could only be carried out for 17, 18, and 21 as very limited amounts of 19 and 20 were available. The inspection of the aliphatic part of the correlated spectra of 17 and 18 proved that the resonances assigned in the literature¹⁴ for the methyl carbons should be reversed. Most importantly, it confirmed the halogen regiochemistry of those molecules since C-2 resonates at 56.4 ppm (typical of a carbon bonded to bromine) while C-4 resonates at 66.8 ppm (typical of a carbon bonded to chlorine). The carbon-proton correlated spectrum of 21 confirms the assignments given in ref 12.

Conclusion

The results presented here show that two-dimensional and NOED spectroscopy complemented by molecular mechanics calculations provide a reliable method for the structural analysis of cyclic polyhalogenated monoterpenes. The use of ¹³C shift data in terms of supposedly additive effects deduced from models should be viewed with caution since simple models do not accurately reproduce all the stereochemical features of these monoterpenes. Furthermore, our force field calculations show that the large number of substituents, and in particular the halogen atoms, produces important deviations from the ideal conformation in the compounds studied.

Experimental Section

¹H and ¹³C NMR spectra were recorded at room temperature as CDCl₃ solutions on a Bruker WM-250 spectrometer operating at 250.13 MHz for proton and at 62.83 MHz for carbon. Chemical shifts given in δ values were measured with respect to Me₄Si (¹H) and to the central line of CDCl₃ (δ 77 for ¹³C). NOE difference experiments were run automatically by a microprogram developed according to Neuhaus et al.¹⁵ Two-dimensional spectra were obtained with the standard Bruker software.

The structures of compounds 8-21 were calculated by means of general valence force field methods using the MM II¹⁶ computer program. The minimum energy conformers were localized by optimization of different entry geometries corresponding to the chair and boat conformations; the obtained geometries were further refined by rotation of the vinyl and methyl groups in every case. The parameters not included in the standard MM II program were estimated from similar situations.¹⁷ Samples of terpenes 17-21 were isolated from *P. coccineum*.⁵

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Registry No. 8, 25276-09-9; 9, 25276-10-2; 10, 25276-11-3; 11, 25276-12-4; 12, 41498-78-6; 13, 51197-94-5; 14, 20237-25-6; 15, 20237-26-7; 16, 20245-25-4; 17, 95044-70-5; 18, 105016-85-1; 19, 66389-40-0; 20, 105017-62-7; 21, 89254-84-2.

(14) Naylor, S.; Hanke, M. J.; Manes, L. V.; Crews, P. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 189.

(15) Neuhaus, D.; Sheppard, R. N.; Bick, R. C. *J. Am. Chem. Soc.* **1983**, *105*, 5996.

(16) Allinger, N. L.; Yuh, Y. Y. *Quantum Chemistry Program Exchange*; Indiana University: Bloomington, IN; No. 395.

(17) The following parameters not included in the standard MMII program have been used. Stretching, K_s (mdyn/Å), L_0 (Å): C(sp²)-Cl, 2.970, 1.834; C(sp²)-Br, 2.970, 1.834. Bending, K_b (mdyn·Å/rad²), angle (deg): C(sp²)-C(sp²)-Cl, 0.400, 120.500; C(sp²)-C(sp²)-Br, 0.400, 120.500. Torsion, V_1 (kcal/mol), V_2 (kcal/mol), V_3 (kcal/mol): C(sp²)-C(sp²)-C(sp²)-Cl, 0.0, 15.000, 0.0; C(sp²)-C(sp²)-C(sp²)-Br, 0.0, 15.000, 0.0; H-C(sp²)-C(sp²)-Cl, 0.0, 15.000, 0.0; H-C(sp²)-C(sp²)-Br, 0.0, 15.000, 0.0; C(sp²)-C(sp²)-C(sp²)-Cl, 0.0, -0.250, 0.550; C(sp²)-C(sp²)-C(sp²)-Br, 0.0, -0.410, 1.060.

(12) Gonzalez, A. G.; Arteaga, J. M.; Martin, J. D.; Rodriguez, M. L.; Fayos, J.; Martinez-Ripolls, M. *Phytochemistry* **1978**, *17*, 947.

(13) Higgs, M. D.; Vanderah, D. J.; Faulkner, D. J. *Tetrahedron* **1977**, *33*, 2775.