Halogen Regiochemistry and Substituent Stereochemistry Determination in Marine Monoterpenes by ^{13}C NMR

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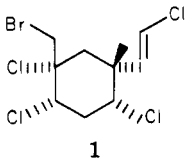
The use of ^{13}C NMR shifts in defining halogen regiochemistry or six-membered ring substituent stereochemistry in marine monoterpenes is considered in detail. New additivity parameters and model compound ^{13}C NMR shift data are presented. Structures are proposed for three new red seaweed monoterpenes (**3**, **4**, and **5**), and revisions are suggested for four other published structures (**6**, **7**, **8**, and **9**). Our approach can be extended to certain marine sesquiterpenes such as the chamigrane class. Comparisons between calculated and experimental chamigrane shifts are explored, followed by discussion of structures which contain ambiguities.

Many would consider complete structure analysis of a monoterpene to be straightforward given the well-developed strategies of organic spectroscopy, especially ^{13}C NMR.[1] Recent structure and stereochemical determinations for novel terrestrial plant monoterpenes such as the neptalactones[2a] or rothrockene[2b] certainly illustrate this. However, monoterpenes isolated from marine organisms usually contain multiple halogens,[3] Br and Cl, and they appear to test the limits of a spectroscopic approach for determining halogen regiochemistry or for establishing the stereochemistry of substituents in close proximity to halogens. A dramatic illustration of this problem, are recent revisions by X-ray crystallography, to the structures of such seminal marine monoterpenes as violacene (**1**)[4] and chondrocole A (**2**).[5] In both cases incorrect halogen assignments were based upon chemical and/or spectroscopic arguments. Some have felt that an alternative strategy of using ^{13}C (or ^{1}H) T_1 measurements[6] might resolve such difficulties, but ambiguities have been noted.[7] A computerized correlation of ^{13}C NMR shift assignments represents another interesting approach, but to date such efforts have been limited to just a few compound types and they utilize limited data bases.[8]



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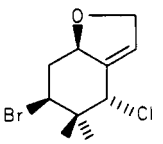

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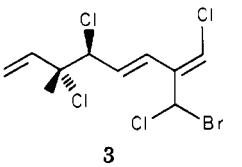
The use of ^{13}C data to determine halogen regiochemistry and substituent stereochemistry ought to be profitable,[9] but suitable model compound data or critical tests of such an approach have been fragmentary. Previously, we have demonstrated the use of ^{13}C NMR chemical shift analysis in unraveling Br/Cl regiochemistry[10a] or >C(CH$_3$)X stereochemistry,[10b,11] We have extended this rationale and now wish to demonstrate its use in characterizing new compounds and in correcting errors in published structures. Three new seaweed monoterpenes are described: 7-(bromochloromethyl)-3(*R**),4(*S**),8-trichloro-3-methyl-1,5(*E*),7(*E*)-octatriene (**3**) from *Plocamium cartilagineum*, *epi*-plocamene D (**4**) from *Plocamium violaceum*, and 1,6(*S**)-dibromo-8(*S**)-chloro-2(*Z*)-ochtodene (**5**) from *Ochtodes secundiramea*. Revisions are also suggested for four other structures: 7-(dibromomethyl)-3(*R**),4(*S**),8-trichloro-3-methyl-1,5(*E*),7(*E*)-octatriene (**6**) (rather than **6a**),[12] mertensene (**7**) (rather than **7a**),[7] 4(*S**)-bromo-1-



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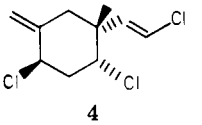

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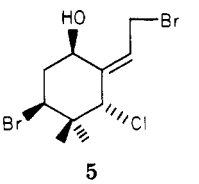

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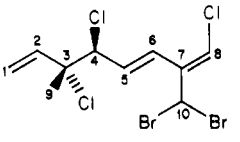

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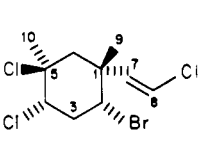

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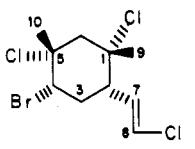

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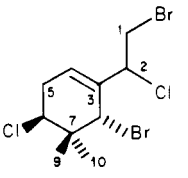

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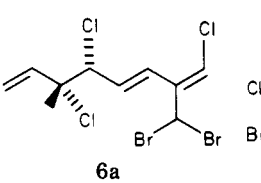
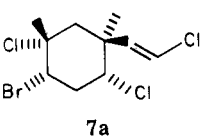
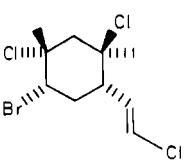


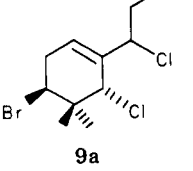
6a



7a



8a



9a

(1) Werhli, F. W.; Nishida, T. *Prog. Chem. Org. Nat. Prod.* **1979**, *36*, 1.

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(10) (a) Crews, P.; Kho-Wiseman, E. *J. Org. Chem.* **1977**, *42*, 2812. (b) Crews, P.; Kho-Wiseman, E. *Tetrahedron Lett.* **1978**, 2483.

(11) Crews, P. *J. Org. Chem.* **1977**, *42*, 2634.

(12) Imperato, F.; Minale, L.; Riccio, R. *Experientia* **1977**, *33*, 1273.

0022-3263/84/1949-1371$01.50/0

Table I. ^{13}C Alkane Increment Constants[14]

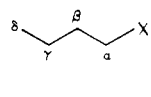
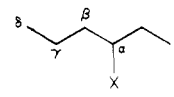
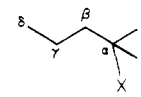
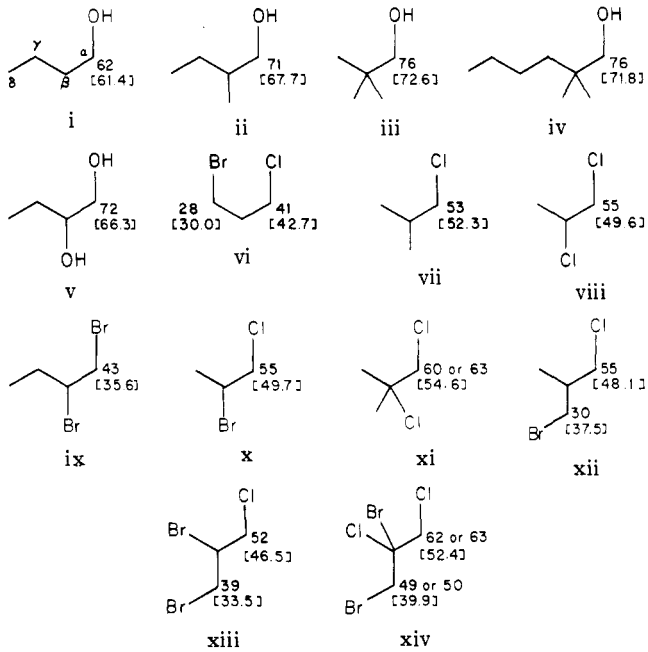
	X	α	β	γ	δ	α	β	γ	δ	α	β	γ	δ
													
base value	H	13.1	24.9	24.9	13.1	32.1	32.1	23.0	14.2	27.6	41.6	20.5	14.0
	CH_3	9	8	−1	−1	5	9	−4	−1	2	5	−3	−1
	OH	49	10	−4	−1	42	10	−4	−1	38	5	−3	0
	Cl	31	10	−4	−1	36	11	−2	0	41	10	−2	
	Br	19	10	−3	−2	28	11	−3	−1	38	11	−1	
	I	−8	10	−1	0	4	12	−2	−1				

Chart I. Calculated[a] vs. [Experimental][14] ^{13}C Shifts (ppm) for Acyclics



[a] Sample calculation (ix). Data from Table I.

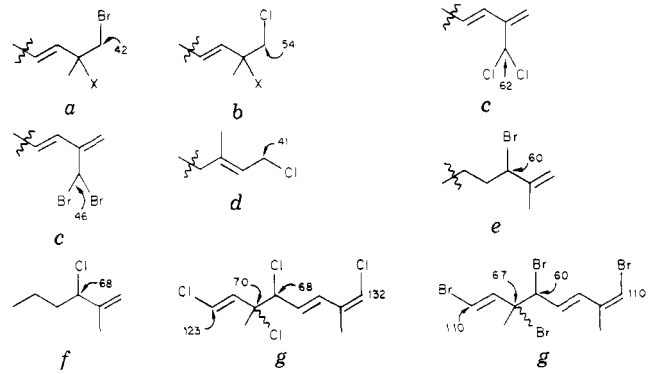
base value for C_α	13
primary Br @ C_α	19
secondary Br @ C_β	11
total	43

(*S**),5(*R**)-dichloro-2(*S**)(*E*)-(chlorovinyl)-1,5-dimethylcyclohexane (**8**) (rather than **8a**),[7b] and 1,8(*R**)-dibromo-2,6(*S**)-dichloro-3-ochtodene (**9**),[5b] which cannot be distinguished from **9a**.[9a] Interestingly, this group of structures spans all the marine monoterpene carbon skeleton types isolated to date.[3]

Results and Discussions

Halogen Regiochemistry in Acyclics. Substituent additivity constants, used to calculate a ^{13}C shift, provide an effective way to correlate observed spectral lines to specific carbons in acyclic molecules.[13] Surprisingly, no increment constants are available to calculate ^{13}C shifts of tertiary halogenated carbons though this is a common structural feature in marine natural products.[3] Presented in Table I are a set of new increment constants for the halogens, OH, and CH_3 in tertiary as well as secondary and primary environments.[14] Several interesting observations

Table II. Base Value Shifts for Acyclic Models



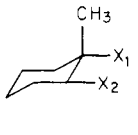
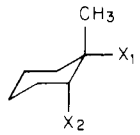
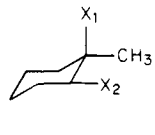
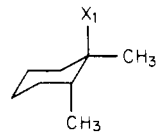
[a] Reference 11. [b] Reference 11 and Table I increments. [c] Compound 1, ref 12, and Table I increments. [d] Reference 10a. [e] Compound 8a, from ref 10a, and Table I increments. [f] Compounds 8b and 8c from ref 10a, and Table I increments. [g] Combined consideration of compounds 1 and 6, from ref 11, data in ref 12 and Table I increments.

can be made after perusal of this data. Good agreement is expected and can be realized between calculated and observed shifts in simple acyclics such as i, ii, vi, vii, or xii (Chart I). Sims[9a] found, however, that a good match between a calculated and experimental value for a methine or methylene carbon which is attached to a polar group and vicinal to another polar group could only be achieved after a correction factor of −6 ppm was applied. This same correction factor must also be used to calculate the shift of a carbon α to a polar group and flanked also by at least two nonpolar β-substituents. This is shown by data in Chart I for compounds iii and iv. Additional limitations in the use of simple substituent additivity constants can be seen in compounds v, viii–xi, and xiii in Chart I. Each of these compounds has a polar substituent on the C β to the carbon shift being calculated and each gives a 5–8 ppm difference between the calculated and experimental ^{13}C shift. These examples clearly illustrate that standard additivity values cannot be used in ^{13}C shift analysis of molecules with vicinal polar substituents.

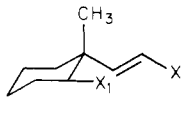
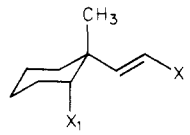
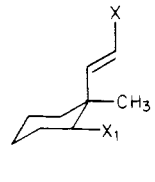
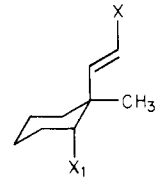
It has been possible to distinguish between C–Br and C–Cl by ^{13}C NMR[10] because α-substituent effects are large. Table I shows that the α ^{13}C shift difference between –C–Br and –C–Cl decreases markedly in going from a primary (12 ppm), to a secondary (8 ppm), to a tertiary (3 ppm) environment. Thus a primary C–X type offers the most, *and tertiary the least*, reliable setting wherein Br can be distinguished from Cl. Sims[9a] also observed that the absolute shift difference of 11–12 ppm for $-CH_2Br$ vs. $-CH_2Cl$ is conserved even when adjacent groups vary considerably. Compound xiv in Chart I illustrates that this absolute shift difference is also maintained when there is extensive C_β polar substitution. However, the calculated vs. observed shift difference at CH_2Cl of 10 ppm is almost as large as

(13) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: New York, 1976.
(14) (a) Spectra from the Catalog of ^{13}C NMR Spectra, Sadtler Research Laboratories, 1982, Philadelphia, PA 19104, served as a source for much of the data in Table I. (b) Breitmaier, E.; Haas, G.; Voelter, W. "Atlas of Carbon-13 NMR Data"; Heyden: Philadelphia, PA, 1979.

Table III. Base Value Shifts for Cyclic Models[a]

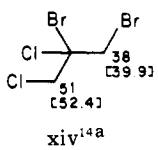
X_1	X_2	CH_3	C-X_1	C-X_2	CH_3	C-X_1	C-X_2	CH_3	C-X_1	C-X_2	CH_3	C-X_1	C-X_2
Cl	Cl	24	71	66	26	71	66	32	71	66	33	71	66
Cl	Br	24	70	61	26	70	61	32	70	61	33	70	61
Br	Cl	26	70	66	28	70	66	34	70	66	35	70	66
Br	Br	26	70	61	28	70	61	34	70	61	35	70	61

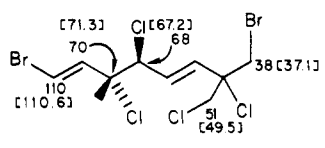
X_1	CH_3	C-X_1	CH_3	C-X_1	CH_3	C-X_1	CH_3	C-X_1
Cl	18	65	21	65	26	65	27	65
Br	18	56	21	56	26	56	27	56

[a] Estimated via data from compounds 11-23 in Charts III and IV and appropriate compounds in ref 10b, with more weight given to empirical data from compounds of unambiguous structure.

Chart II. Calculated[a] vs. [Experimental] ^{13}C Shifts for Acyclics



xiv[14a]



10[11]

[a] Base values from Table II with β, γ, or δ increments from Table I. Sample calculation (C_8, 10): base value

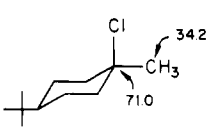
base value (a)	42
primary Cl C_γ	−4
total	38

that expected for $-CH_2Br$ vs. $-CH_2Cl$. (Note that a difference of 28 ppm can be observed for the experimental shifts of $-CH_2Br$ vs. $-CH_2Cl$ in compounds **29** and **30** in Chart VI. Finally, the shifts of compound xiv illustrate how an incorrect halogen regiochemical assignment might arise. Specifically, if only the experimental value for $-CH_2Cl$, 52.4 ppm, was available, it would best compare to the calculated value (Table I) for $-CH_2Br$, 49 ppm, and not $-CH_2Cl$, 62 ppm.

The disagreement in the calculated vs. experimental values for compounds iii–v, viii–xi, xiii, and xiv arises because the α effect is almost always overestimated. In order to avoid this difficulty we considered using appropriate model compounds where only increments of β, γ, and δ effects need be added. This approach actually provides a much better fit. A set of acyclic model base values are collected in Table II. When these are used with β, γ, or δ increments from Table I, the agreement between calculated and experimental is usually *less than 5 ppm* (without the need of a 6 ppm correction factor). When xiv (Chart II) or the natural product **10** was used as an example, the agreement of calculated vs. [experimental] shifts for $-CH_2-X$ sites are excellent (see Chart II).

Stereochemistry and Halogen Regiochemistry in Alicyclics. We have previously shown that ^{13}C shift effects on methyl groups from α-, β-, and γ-substituents can be used to solve side chain stereochemistry problems in six-membered ring natural products.[10b] In the absence of ring heteroatoms,[15] axial methyls occur 6–8 ppm upfield

Chart III. Experimental ^{13}C Shifts for Synthetic Models



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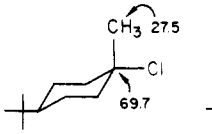

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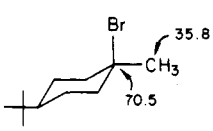
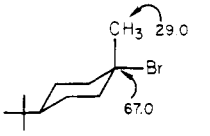
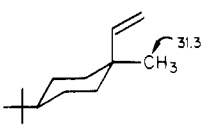


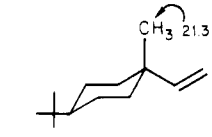
13



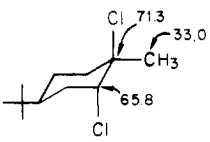
14



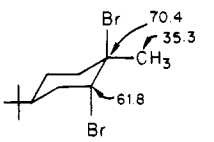
15[16]



16[16]



17



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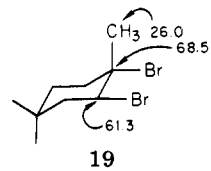


19

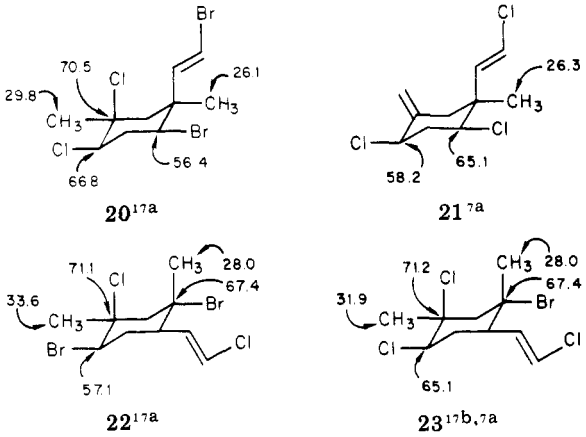
from equatorial ones as illustrated by synthetic compounds **11–16** in Chart III. That γ effects do not change this net difference is shown by compounds **17–19** in Chart III and arguments stated in ref 10b. Adding the appropriate γ shift increment[10b] to the model compound base value from Chart III accurately reproduces the observed methyl shifts for various natural products such as **20–23** (Chart IV), whose structures and stereochemistries are unambiguously known from either X-ray analysis or chemical correlation to a compound studied by X-ray. In order to apply these results to problem solving, we used the data in Charts III

(15) (a) Vierhapper, F. W.; Eliel, E. L.; Zuniga, G. *J. Org. Chem.* **1980**, *45*, 4844. (b) Eliel, E. L.; Pietrusiewicz, K. M. In "Topics in C-13 NMR Spectra"; Levy, G., Ed.; Wiley-Interscience: New York, 1979; Vol. 3, p 171.

(16) Buckwalter, B. L.; Burfitt, I. R.; Felkin, H.; Joly-Goudket, M.; Naemura, K.; Salomon, M. F.; Wenkert, E.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 6445.

(17) (a) Gonzalez, A. G.; Arteaga, J. M.; Martin, J. D.; Rodriguez, M. L.; Fayos, J.; Martinez-Ripoll, M. *Phytochemistry* **1978**, *17*, 947. (b) Mynderse, J. S.; Faulkner, D. J.; Finer, J.; Clardy, J. *Tetrahedron Lett.* **1975**, 2175.

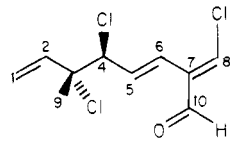
Chart IV. Experimental ^{13}C Shifts for Natural Product Models



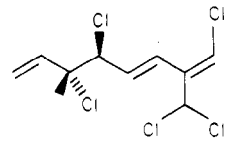
and IV to generate a set of diagnostic methyl shifts summarized in Table III.

We pointed out above that success in solving halogen regiochemistry (Cl vs. Br) in acyclics is dependent upon the magnitude of their relative α effects. Unfortunately these relative effects are quenched in going from acyclics to alicyclics. As illustration, consider the experimental ring ^{13}C shifts for synthetic compounds **11–14** and **17–19**, and natural products **20–23**. Differences in ^{13}C experimental shifts between the tertiary and secondary C–Br vs. C–Cl are respectively 1 and 4 ppm. This is about a factor of two less than would have been predicted based upon alicyclic models (see Table I). The miniscule α effect difference at these tertiary halogenated carbons severely limits this data for making ring regiochemical assignments.

Application of Empirical Schemes to Structure Analysis. Collections of *Plocamium cartilagineum* from Davenport Landing (Santa Cruz County, CA.) yielded halocarbon **3** ($C_{10}H_{11}Cl_4Br$, M^+ 350, 352, 354, 356). Prominent mass spectral features such as the M^+ cluster and fragment ion peaks at 89/91 (C_4H_6Cl)[7a] along with 6 sp^2 ^{13}C NMR peaks (Table VI) and the near identity of 7 ^{13}C line positions to those in cartilagineal (**24**)[11] supported



24

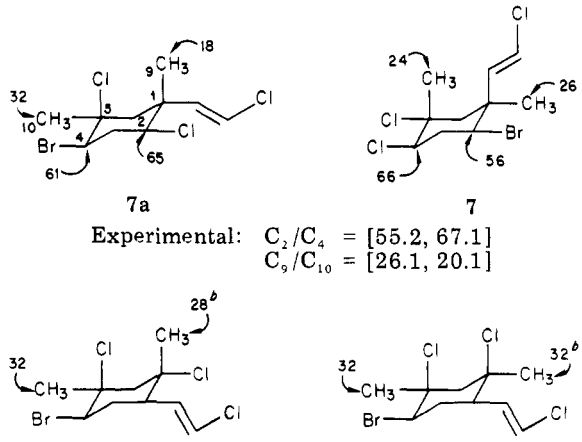


25

the gross structure shown for **3**. Reference to the shift data in Table II made it easy to unambiguously assign the halogens as follows: C_3–Cl (δ 71.7), C_4–Cl (δ 69.4), C_8–Cl (δ 131.9), and by default the remaining Cl and Br must both be located at C_{10}. Comparison of the H_6 δ 6.57 ($CDCl_3$) to that observed by Faulkner for **25**, δ 6.56 ($CDCl_3$),[18] supports the *E* stereochemistry shown across C_7=C_8. The 3(*R**)4(*S**) relative vicinal dichloride stereochemistry shown in **3** is based upon the observed characteristic ^{13}C Me_9 shift of δ 25 (vs. expected values for 3(*R**)4(*S**) = δ 25 and 3(*R**)4(*R**) = δ 28). Minale[12] also observed a ^{13}C Me_9 shift of δ 25.1 for **6a** but used the observed ^1H Me_9 shift of δ 1.78 to assign the relative C_3–C_4 stereochemistry as *RR* (with his assignment based upon ^1H NMR values expected for 3(*R**)4(*R**) = δ 1.79 and 3(*R**)4(*S**) = δ 1.73).[18] We have previously emphasized that ^{13}C shifts rather than ^1H shifts provide a more reliable index for

(18) Mynderse, J. S.; Faulkner, D. J. *Tetrahedron* **1975**, *31*, 1963.

Chart V. Calculated[a] and [Experimental] ^{13}C Shifts for Mertensenes (7)[7b] and (8)[7b]

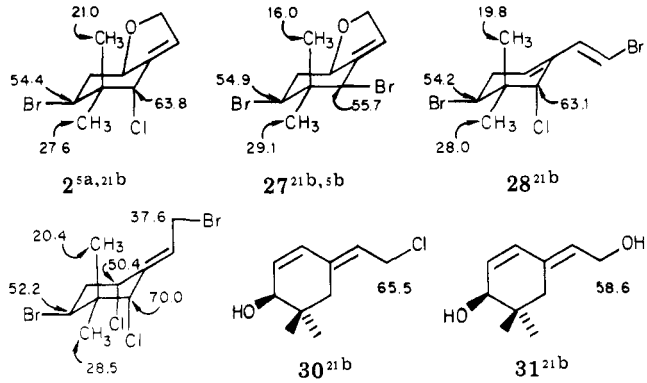


Experimental: C_2/C_4 = [55.2, 67.1]
C_9/C_{10} = [26.1, 20.1]

Experimental: C_9/C_{10} = [32.7, 34.0]

[a] Values from Table III. [b] Calculated values from compounds 22 and 23 and increments from Tables I and III and ref 10b.

Chart VI. Experimental Shifts for the Ochtodane Skeleton[a]



[a] The variation in the C_8 shift of **2** (δ 63.8) or **28** (δ 63.1) vs. **29** (δ 70.0) is due to the increased deshielding caused by an axial Cl at C_4.

making such assignments.[11] We therefore suggest the stereochemistry of **6a** be revised to 3(*R**)4(*S**) as shown for **6**.

A collection of *Plocamium violaceum* from Patrick's Point (Humboldt Count, CA) yielded *epi*-plocamene D (**4**) ($C_{10}H_{13}Cl_3$, M^+ 238, 240, 242, 244). The spectral properties of **4** (Table V, VI) were nearly identical with those of plocamene D (**21**)[7a] excepting a broad ^1H triplet J = 4, 4 Hz at δ 4.74 for an equatorial H_4. The placement of Cl's at C_2, C_4, and C_8 and an equatorial C_1–Me are all solidly justified by comparison of observed ^{13}C shifts to model values in Table III (see also Charts III and IV). After our work was completed,[19a] Sims[19b] also reported **4** as a component of *Plocamium cartilagineum* from Antarctica.

Two additional monocyclic compounds **7a** and **8a** from an Australian *Plocamium*[7b] have been reported but their ^{13}C NMR data are not congruent with the published structures. This discrepancy is analyzed in Chart V. Specifically, the **7a** Me_9 δ 26.1 (expt) is characteristic of

(19) (a) Kho-Wiseman, E., Ph.D. Thesis, University of California at Santa Cruz, 1978. (b) Stierle, D. B.; Sims, J. J. *Tetrahedron* **1979**, *35*, 1261.

Table IV.[22] Base Value Shifts for Ochtodanes[a]

X_1	X_2	CH_3 (a)	CH_3 (e)	C-X_1	C-X_2
Br (e)	Br (e)	18	29	56	55
Cl (e)	Cl (e)	18	29	63	61
Br (a) Br (e)	Br (e) Br (a)	20	30	56	55
Cl (a) Cl (e)	Cl (e) Cl (a)	20	30	63	61
Br (a)	Br (a)	23	30	56	55
Cl (a)	Cl (a)	23	30	63	61

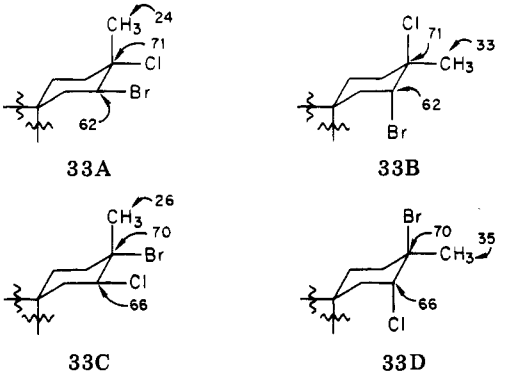
[a] Estimated by using increments from ref 10b to calculate Me shifts, data from **27**, and a cyclic >C(H)X average difference of Br vs. Cl of 7 ppm (see text and data for **17–23**).

an equatorial and not an axial methyl at that site as is detailed in Chart V and by comparison with other experimental data, **20** Me_9 (δ 26.1) and **21** Me_9 (δ 26.3) in Charts III and IV. Similarly, the **7a** Me_{10} δ 20 (expt) is also incompatible with an equatorial methyl as proposed by Norton.[7b] Rather, the methyl stereochemistry must be as in **7** and shift assignments are Me_9 = δ 26.1 (expt) vs. δ 26 (calcd) and Me_{10} = δ 20.1 (expt) vs. δ 24 (calcd). An analysis of the shift pattern at C_2 and C_4 also shows that the halogen arrangement in **7** is preferred to that of **7a** (Chart V).[20] Finally, an error appears evident for the Me_9 stereochemical assignment in **8a**. The experimental[7b] Me shifts of δ 32.7 and 34.0 are close to a calculated shift of δ 32 for both Me_9 and Me_{10} in an equatorial arrangement as seen in Chart V. Thus **8** seems a better description than **8a**.

A collection of *Ochtodes secundiramea* from the Hog Islands (Honduras, Central America) yielded compound **5** ($C_{10}H_{15}Br_2ClO$, *m/e*, 309/311/313, M^+ – Cl). The gross skeleton of **5** could be identified by comparison of its ^{13}C shifts, including C_1, C_2, C_5, C_6, C_8, C_9, and C_{10}, with those in ochtodene (**29**),[21a] and chondrocole A (**2**)[21b] (Chart VI). The C_4–OH and its stereochemistry could be identified from the ^{13}C doublet, δ 73.6, and a ^1H ddd, δ 4.47, J = 11.6, 7.4, 1.8 Hz. The $^4J_{2,4}$ = 2 Hz in **5** is identical with that observed in **2**[5] and supports their identical (*E*) C_2=C_3 geometry. Also in agreement with this is the $^4J_{2,8}$ = 0 Hz observed for both **5** and **2**.[5] Comparing shifts in **5** at C_6 = δ 54.9 and C_8 = δ 68.8 to corresponding values in **29** and other compounds in Chart VI (and in Table IV) suggested the halogenated placement of C_6–Br and C_8–Cl as in **5**. The experimental ^{13}C shifts for $-CH_2X$ in **5** at δ 39.6 compared to δ 37.6 for **29**[21] vs. δ 65.5 for **30**[21b] and δ 58.6 for **31**[21b] suggest a $-CH_2Br$. Assignment of the C_6–Br stereochemistry was based upon the characteristic J's = 11.9 and 4.9 Hz for H_6. The use of ^{13}C experimental vs. calculated shifts for different side chain stereochemical possibilities was applied to assign the C_8–Cl. Table IV summarizes several calculated values, and verifies that variation in the calculated axial *gem*-dimethyl ^{13}C shifts are the most sensitive to stereochemical changes of adjacent halogens.[22] The experimental **5** Me_9 shift of δ 21.5 closely matches the Table IV $X_{2(e)}X_{1(a)}$ calculated value of δ 20 which completes the proof of all the features of structure **5**.

Two isomeric structures, **9**[5b] and **9a**,[9a] are in the literature for the same ochtodane derivative. Neither are supported by unequivocal spectral or chemical arguments.

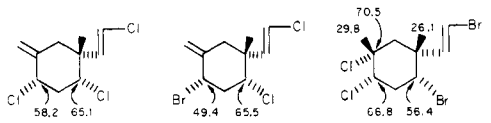
Chart VII. Calculated ^{13}C Shifts for the B Ring Chamigrane Skeleton[a]



33A 33B 33C 33D

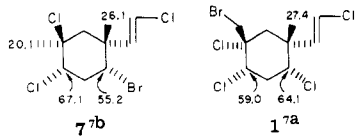
[a] Shifts estimated from data in Table III and Charts III and IV.

(20) Revision of the mertensene structure from **7a** to **7** can also be justified by comparing ^{13}C NMR shifts of mertensene to those of similar compounds. The chemical shifts shown below for natural products **26a** and **26b** illustrate the magnitude of shift variation between –CHBr– and



26a[7a] **26b**[7a] **20**[17a]

–CHCl– of 0.2 ppm for ^1H and 7 ppm for ^{13}C. Significantly, the ^{13}C NMR shifts of mertensene (**7**) at C_2 and C_4 are nearly identical with those of

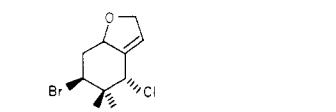


7[7b] **1**[7a]

20 (structure established by X-ray analysis). Furthermore, the CH_3 shifts in the series **7**, **1**, and **20** clearly correlate with the Me_9 and Me_{10} stereochemistries shown. It should be pointed out, however, that approaching the Me_9/Me_{10} stereochemical problem in **7** (or **20**) by using data from Table III could be slightly misleading. Specifically, shifts of 18 and 32 ppm are calculated respectively for a β-Me_9/α-Me_{10} vs. 18 and 24 ppm respectively for β-Me_9/β-Me_{10}. But, by analogy to the Me_9 shift of **1** and **20** we find the assignment of the **7** Me_9 at 26.1 ppm to be compelling and thus incompatible with these latter predicted shifts.

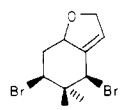
(21) (a) McConnell, O. J.; Fenical, W. *J. Org. Chem.* **1978**, *44*, 4238. (b) Paul, V. J.; McConnell, O. J.; Fenical, W. *Ibid.* **1980**, *45*, 3401.

(22) We find axial, rather than equatorial, methyl shifts to be useable in evaluating the stereochemistry of C_6 or C_8 halogen (or oxygen substituents) for the ochtodane skeleton. The experimental and calculated shifts along with data in Table IV for **2** and **27** illustrate that the Me(e)



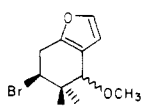
expt	21.0	27.6
calcd	20	30

2[21b]



	16.0	29.1
	18	29

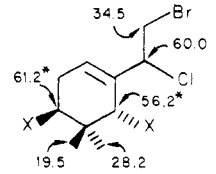
27[5b]



	20.4	28.2
Br (e), OCH_3 (a)	17	28
Br (e), OCH_3 (e)	15	27

32[9a]

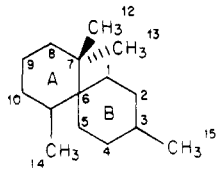
shift is not sensitive to stereochemical changes of C_6 and/or C_8 substituents. Likewise, focusing upon experimental vs. calculated Me(a) shifts in furan **32** indicates the previously unassigned $-OCH_3$ stereochemistry must be axial.



9, C_6-X = Cl; C_8-X = Br
9a, C_6-X = Br; C_8-X = Cl
* can be switched

Unfortunately, a choice cannot be made between them based upon ^{13}C shifts, as can be seen by comparison of experimental data[23a] to shifts calculated using Chart VI and Table IV for a >CHX in an $-C_6HX-C(Me)_2-C_8HX-$ array where X = Br, C_6 = δ 55, C_8 = δ 56; X = Cl, C_6 = δ 63, C_8 = δ 64–69.[23b]

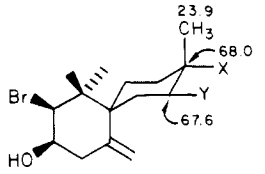
Our empirical approach can be expanded to other natural product classes. The seaweed chamigrane sesquiterpenes provide an excellent example, because distinguishing between four isomeric ring B possibilities (**33A–33D**) has been troublesome.[24] On the basis of preceeding



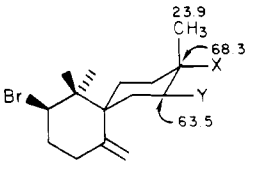
33

arguments (eg., compounds **17–19** and data in Table III), we can calculate ^{13}C shifts, as shown in Charts VII and VIII, for the different B ring types. These shift variations clearly indicate that a choice can be made between a secondary Br or Cl and that methyl stereochemistry can be established for a B ring $-C(CH_3)X-$ unit. That these calculated shifts accurately reproduce experimental trends can be seen by the following comparisons: calculated shifts in **33A** match those of kylinone (**34**)[25] or 4,10-dibromo-3-chloro-7,8-epoxychamigrane (**35**); calculated shifts in **33C** match those of obtusane (**36**);[26] and calculated shifts in **33D** match those of isofurocaspitane (**37**)[26] all of which are in Charts VII and VIII.

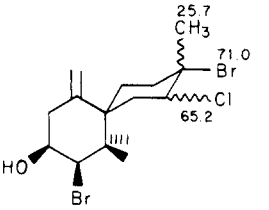
The structure of the obtusol B ring was revised from **38b** to **38a** by X-ray crystallography.[24c] Inspection of the ^{13}C shifts of **38** would have directly led to the same conclusion, in light of data in Charts VII and VIII. The two possibilities, **39a**[27a] and **39b**[27b] have been suggested at different times, but unfortunately the correlations presented here cannot be applied because the experimental –CHX– shift in **39** of δ 63.5 is midway between the calculated values of X = Br (δ 62) and X = Cl (δ 66). Finally, an ambiguity exists for the *solution structure* of isoobtusol (**40**). A diaxial C_3Br-C_4Cl subunit with Me_{15} equatorial, **40b**, has been suggested for isoobtusol by X-ray crystallography,[24a,26] but this is clearly inconsistent with its experimental Me_{15}



obtusol (**38**)[26]
38a, X = Br; Y = Cl
b, X = Cl; Y = Br



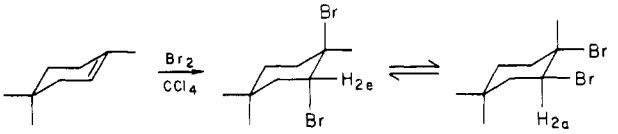
nidificine (**39**)[9]
39a, X = Cl; Y = Br
b, X = Br; Y = Cl



isoobtusol (**40**)[26]
40a, CH_3-β; Cl-β
b, CH_3-α; Cl-α

shift of δ 26 which resembles the experimental δ 24–26 for axial methyls in **19** and **34–36** and differs significantly from the experimental δ 33–35 for equatorial methyls in **17**, **18**, and **37**. By this comparison, the stereochemistry of **40a** is clearly favored.[28]

An additional observation indicating that conformation **40a** is preferred over **40b** is that compound **19**, prepared



19b **19a**

by transbromination of 1,4,4-trimethylcyclohexene, has **19a** as the preferred conformation (^1H NMR, benzene-d_6, δ 4.25, dd, J = 11, 5 Hz, H_{2a}).

Experimental Section

Our general analytical, chemical, and chromatographic methods have been described previously.[25] Algal collections were as follows: *Plocamium cartilagineum* (net weight 6.68 kg), intertidal from Davenport Landing (Santa Cruz County, CA), June, 1980; *Plocamium violaceum* (net weight 0.19 kg), intertidal from Patrick's Point (Humboldt County, CA), July, 1977; *Ochtodes secundiramea* (net weight 0.050 kg), subtidal from Hog Island (Honduras, Central America), March, 1978. The freshly collected algae were either directly extracted or frozen until extracted. Extractions were carried out in CH_2Cl_2 or $CHCl_3$ upon wet algae in a Soxhlet apparatus. Concentration of the extract gave an oil which was purified by flash chromatography using a hexane–ether–ethyl acetate gradient. Purified compounds were obtained after HPLC using hexane–ethyl acetate mixtures (97:3 is representative).

7-(Bromochloromethyl)-3(*R),4(*S**),8-trichloro-3-methyl-1,5(*E*),7(*E*)-octatriene (3).** The crude *P. cartilagineum* extract gave 3.93 g of crude oil. A GC/MS run[29] showed cartilagineal (**14**)[11] (M^+ 252) and violacene (**1**)[7a] (M^+ 352) as major components and **3** (m/e 306) as a very minor component. HPLC (97:3 hexane/ethyl acetate) of fractions 7–9 from gradient elution flash chromatography gave fractions 6 (0.006 g) and 7 (0.015 g) which were respectively semipure and pure **3** (0.002% combined yield): ^1H and ^{13}C NMR in Tables V and VI; MS, m/z 350, 352,

(23) (a) Curiously, the ^{13}C shift for $-CH_2Br$ reported by Sims[9] does not agree with that reported by Burreson. (b) We favor structure **9** based upon comparison of ^{13}C NMR data to other compounds we have isolated: Crews, P.; Myers, B.; Naylor, S.; Clason, E. L.; Jacobs, R. S.; Staal, G. *Phytochemistry*, in press.

(24) (a) Gonzalez, A. G.; Martin, J. D.; Martin, V. S.; Martinez-Ripoll, M.; Fayos, J. *Tetrahedron Lett.* **1979**, 2717. (b) Waraszkiewicz, S. M.; Erickson, K. L.; Finer, J.; Clardy, J. *Tetrahedron Lett.* **1977**, 2311. (c) Gonzalez, A. G.; Darias, J.; Martin, J. D.; Perez, C. *Tetrahedron Lett.* **1974**, 1249.

(25) Selover, S. J.; Crews, P. *J. Org. Chem.* **1980**, *45*, 69.

(26) We only partially agree with some analogous summary shift values suggested by: Gonzalez, A. G.; Martin, J. D.; Martin, V. S.; Norte, M. *Tetrahedron Lett.* **1979**, 2719.

(27) (a) Waraszkiewicz, S. M.; Erickson, K. L. *Tetrahedron Lett.* **1974**, 2003. (b) Reference 9a, p 339.

(28) Our analysis of a ^1H NMR (220 MHz, $CDCl_3$, so kindly provided by Professor Bruce Howard, San Francisco State University) of isoobtusol acetate (**40**–OAc) shows the following important peaks: H_4, δ 4.44, br t (non-first-order pattern) J (4, 5a + 4, 5e) = 15 ± 2 Hz; H_9, 4.80, dt, J = 16, 5, 5,; H_8, 4.44 d, J = 5 (for numbering see **33**).

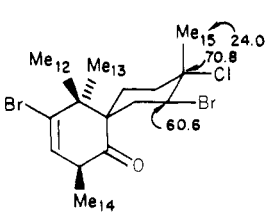
(29) For examples of GC/MS traces see: Crews, P. In: "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum Press: New York, 1977; p 214.

Table V. ^{1}H NMR Data

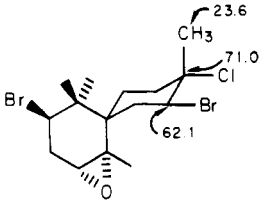
H	chemical shift, δ (pattern, J, Hz) 3[a]	4[b]	5[a]
1	4.90 (d, 10.8) 5.11 (d, 17.1)		4.3 (m)
2	5.85 (dd, 10.8, 17.1)	4.33 (dd, 12, 4)	5.30 (dt, 6.7, 6.7, 1.8)
3		2.2-2.3 (m)	
4	4.13 (d, 9.0)	4.74 (br t, 4, 4)	4.47 (d,d,d, 11.6, 7.4, 1.8)
5	6.58 (dd, 9.0, 16.2)		1.92 (d,d,d, 12, 7, 5) 1.86 (q, 12)
6	6.44 (d, 16.2)	2.35 (d, 14.7) 2.65 (d, 14.7)	4.17 (d,d, 11.9, 4.9)
7		5.92 (d, 12)	
8	5.58 (s)	6.08 (d, 12)	3.85 (s)
9	1.52 (s)	1.26 (s)	
			0.78 (s)
10	5.80 (s)	4.93 (br s) 5.18 (br s)	1.0 (s)

[a] Bz-d_6, 360 MHz. [b] $CDCl_3$, 100 MHz.

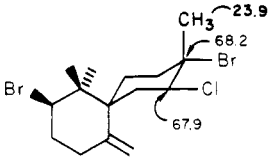
Chart VIII. Experimental ^{13}C Shifts for the B Ring Chamigrane Skeleton



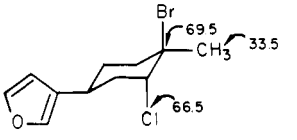
kylinone 34[25]



35



obtusane 36[26]



isofurocaspitane 37[26]

354, 356 (M^+, 1.3:3.1:2.5:1.0); 315, 317, 319, 321 (2.7: 10:6:2, M^+ - 35); 306, 308, 310, 312 (3.2:5.1:3.2:1.0); 271, 273, 275 (1.6:2.1:1.0); 89, 91 (1.4:1, base peak).

***epi*-Plocamene D (4).** The crude *P. violaceum* extract gave 0.5 g of crude oil. A GC/MS run on this oil showed a mixture of 4 and plocamene-D[7a] in a ratio of 53:47. HPLC (95:5, petroleum ether/benzene) of a semipurified oil from flash chromatography gave fractions 9–10 (0.100 g, 0.05%): ^{1}H and ^{13}C NMR in Tables V and VI; MS, *m/z* 238, 240, 242, 244 (M^+); 223, 225 ($M^+ - CH_3$); 203, 205, 207 (M^+ - Cl); 167, 165 (M^+ - Cl, HCl); 131 (M^+ - Cl, HCl, HCl); 91 (base peak).

1,6(*S)-Dibromo-8(*S**)-chloro-2(*Z*)-ochtodene (5).** The crude *Ochtodes secundiramea* extract gave 0.35 g of oil. The two crude oil major components included chondrocole A (2) (MS, *m/z* 264, 266, 268 (M^+, 5:6.6:1)) and 5 (MS, *m/z* 309, 311, 313 (M^+ - 35)) in a ratio of 1.6:1.0 by GC or 3.4:1.0 by 360 MHz ^{1}H NMR. Flash chromatography using a solvent gradient (hexane/benzene) gave 5 as a pure oil (0.010 g) from fraction 10 (1:1 hexane/benzene): ^{1}H and ^{13}C NMR in Tables V and VI; MS, *m/z* 309, 311, 313 (1:1.8:1, M^+ - Cl); 285, 287, 289 (1.4:2.2:1.0); 265, 267, 269 (3:4:1, M^+ - Br); 185, 187 (2.9:1, M^+ - HBr, Br, base peak).

Carbon NMR of Model Compounds. *trans*-1,2-Dichloro-4-*tert*-butyl-1-methylcyclohexane (17) was prepared by adding Cl_2 (saturated C_2H_5OH) at 0 °C to 1-methyl-4-*tert*-butyl-1-cyclohexene: ^{13}C NMR shifts (ppm) 71.3 (s) C_1, 65.8 (d) C_2, 30.7 (t) C_3, 39.5 (d) C_4, 21.5 (t) C_5, 28.6 (t) C_6, 31.6 (s) and 27.2 (q) $C(CH_3)_3$, 33.0 (q) CH_3.

trans-1,2-Dibromo-4-*tert*-butyl-1-methylcyclohexane (18) was prepared by adding Br_2 in CCl_4 at 0 °C to 1-methyl-4-*tert*-butyl-1-cyclohexene: ^{13}C NMR shifts (ppm) 70.4 (s) C_1, 61.8 (d) C_2, 33.0 (t) C_3, 44.0 (d) C_4, 23.6 (t) C_5, 36.6 (t) C_6, 31.7 (s) and 27.4 (q) $C(CH_3)_3$, 35.3 (q) CH_3.

Table VI. ^{13}C NMR Data ($CDCl_3$, 25 MHz) Chemical Shift

C	3	4	5
1	116.6	43.3	39.6
2	139.4	63.0	125.0
3	71.7	40.9	
4	69.4	61.2	73.6
5	124.2[a]	142.2	42.6
6	123.8[a]	41.1	54.9
7	136.0	134.0	
8	131.9	120.3	68.8
9	25.1	26.2	21.5
10	69.4	115.2	26.6

[a] Can be switched; note assignments based upon proper off resonance multiples.

trans-1,2-Dibromo-1,4,4-trimethylcyclohexane (19) was prepared by adding Br_2 in CCl_4 at 0 °C to 1,4,4-trimethyl-1-cyclohexene: ^{13}C NMR shifts ($CDCl_3$, ppm) 68.5 (s) C_1, 61.3 (d) C_2, 47.4 (d) C_3, 33.1 (s) C_4, 36.0 (d) C_5, 40.1 (d) C_6, and 31.5 (q) C_4–Me(e), 25.1 (q) and 26.0 (q) C_1–Me(a) and C_4–Me(a). The methyl assignments were confirmed by single frequency ^{1}H decoupling (SFD) in benzene-d_6 at δ 1.64 (Me_1).

Compound 35 was provided by Prof. W. Fenical (S.I.O.): ^{13}C NMR shifts ($CDCl_3$, ppm) 25.9 (t) C_1, 38.0 (t) C_2, 71.0 (s) C_3, 62.1 (d) C_4, 40.2 (t) C_5, 44.3 (s) C_6, 62.0 (s) C_7, 57.4 (d) C_8, 32.5 (t) C_9, 61.8 (d) C_{10}, 42.0 (s) C_{11}, 26.9 (q); Me_{12} by SFD at δ 1.13 (s, C_{12}), 21.2 (q); Me_{13} by SFD at δ 1.23 (s, C_{13}), 25.5 (q); Me_{14} by SFD at δ 1.55 (s, C_{14}), 26.9 (q); Me_{15} at SFD at δ 1.80 (s, C_{15}).

Compounds 11–14 were prepared by adding HX to 1-methyl-4-*tert*-butyl-1-cyclohexene. ^{13}C shifts ($CDCl_3$, ppm): 11 71.0 (s) C_1, 41.8 (t) C_2 and C_6, 23.2 (t) C_3 and C_5, 47.3 (d) C_4, 32.3 (s) C_7, 34.2 (q) C_1–CH_3; 12 69.7 (s) C_1, 43.2 (t) C_2 and C_6, 25.2 (t) C_3 and C_5, 47.3 (d) C_4, 32.1 (s) C_7, 27.5 (q) C_1–CH_3; 13 70.5 (s) C_1, 43.2 (t) C_2 and C_6, 24.0 (t) C_3 and C_5, 47.1 (d) C_4, 32.2 (s) C_7, 35.8 (q) C_1–CH_3; 14 67.0 (s) C_1, 44.6 (t) C_2 and C_6, 25.5 (t) C_3 and C_5, 47.1 (d) C_4, 32.2 (s) C_7, 29.0 (q) C_1–CH_3.

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