

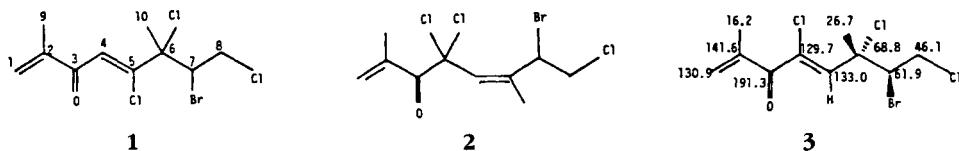
C-13 SUBSTITUENT EFFECTS IN MULTIFUNCTIONAL
MARINE NATURAL PRODUCTS

S. NAYLOR, L. V. MANES, and P. CREWS*

*Thimann Laboratories and Center for Marine Studies,
University of California, Santa Cruz, California 95064*

ABSTRACT.—Analysis of ^{13}C -nmr data using newly developed substituent constants reveals structures **1** and **2** previously assigned for the marine monoterpene plocamenone are incorrect, and structure **3** is now proposed.

Recently, we demonstrated how substituent regiochemistry can be readily elucidated in halogenated marine natural products by use of ^{13}C -nmr additivity constants (1,2). This strategy employs α , β , and γ increments, which are applied according to the degree of substitution at the carbon of interest. Unfortunately, α -effects are always overestimated in compounds containing vicinal polar substituents (2). To overcome this limitation, we have developed new substituent values, which appear in Table 1. The analysis of $\text{C}=\text{O}$ shifts also represents an unexplored strategy which we have tested by generating a set of polar vicinal β increment values collected in Table 2. Many experimental chemical shifts can now be accurately reproduced via Tables 1 or 2, and to illustrate their use, we have examined two past structures **1** (4) and **2** (5) proposed for plocamenone. After comparing available spectroscopic data (1,3-5) to calculated ^{13}C -nmr shifts along with other arguments, we conclude that structures **1** and **2** are in error and suggest **3** as a corrected structure.



Analyzing the ^{13}C shifts of some 80 vicinal dipolar compounds, the $\text{C}=\text{O}$ shifts of 40 α haloketones, and shifts of more than 50 alkyl and 20 alkenyl ketones provided the increments in Tables 1 and 2. One example of the excellent agreement between experimental shifts and those calculated from these tables comes from inspection of the $\text{C}=\text{O}$ shifts for three poly α -substituted ketones **4** (6) (calc=188 ppm, expt=190.9), **5** (7) (calc=186 ppm, expt=186.2) and **6** (8) (calc=189 ppm, expt=188.3).¹ By contrast, a substantial difference of 5 ppm in the calculated vs. experimental $\text{C}=\text{O}$ shift exists for plocamenone (**1**) (calc=196) while perfect agreement is observed for its recently revised structure **2** (5) (calc=191, expt=191.3).¹ In spite of this, we were still uncertain about the placement of the halogens at C-4, C-5, and C-6. In particular, assignment of Cl at C-4 as shown by **3** also provided a perfect match of its calculated $\text{C}=\text{O}$ shift (190) vs. the experimental.

Consideration of other ^{13}C data revealed serious inconsistencies between reported chemical shifts and structure **2**. First, a calculated value of 88 ppm is obtained for C-4² using increments from Table 1, and it along with experimental shifts of 85-95 ppm for tal vs. expected ^{13}C shift is also apparent for the C-6 methyl. Based upon analogy to the α chloro ketones **iii**, **ix**, and **xiv** (Table 3) are vastly different compared to δ 69 previously assigned at C-4 in structure **2** (5). Next, a substantial difference in the experimen-

¹ $\text{C}=\text{O}$ shifts were calculated by adding appropriate increments from Table 2 to the following base values: **1-3**=214 ppm (2-methyl-3-hexanone); **4, 5**=211 ppm (3-hexanone); **6**=209 ppm (2-hexanone).

²We calculate C-4=88 ppm for 4,4-dichloro-3-decanone by using a base value of C-4=43 ppm for 3-decanone (9) and adding appropriate increments from Table 1.

TABLE 1. α Additivity Values for X Vicinal to a Polar Substituent

X				
CH ₃	5	3	3	3
Cl	20±2	25±1	20±1	—
Br	11±1	16±1	13	—
OH	35±1	—	26	35

Y=ClorBr				
X	5	—	4	—
CH ₃	26	30	24	40
Cl	18	28	18	30
Br	—	31	—	—

X		
X	2	—
CH ₃	30	X _a 39
OH	—	X _{eq} 36

^aModel compound data from Ref. 9, 12, or Table 3;

^bRef. 2, 9, 13, 14, or Table 3; ^cRef. 9;

^dRef. 1, 2, 9, 15; ^eRef. 1, 9; ^fRef. 16;

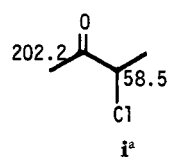
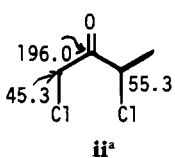
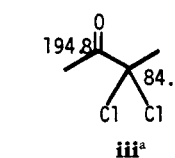
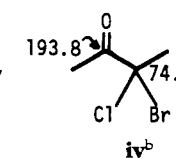
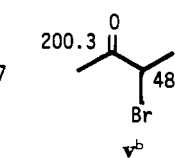
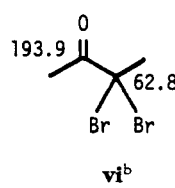
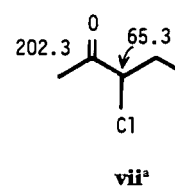
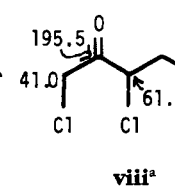
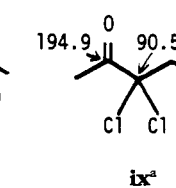
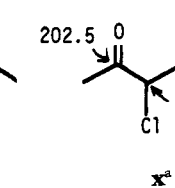
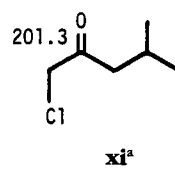
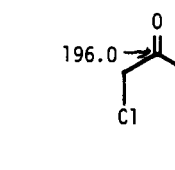
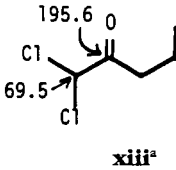
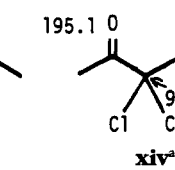
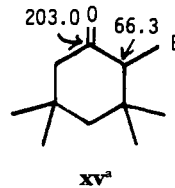
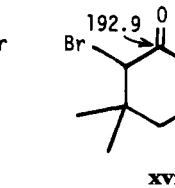
^gValue refers to addition of a second X at α position.

TABLE 2. β Substituent Effect^a of X on C=O

X	Increment per X	
CH ₃	2.5	2.5 ^b
Cl	-6	-7 ^b
Br	-7	-6 ^b
OH	3	—
=C (adding conj only)	-10 ^c	-8 ^{b,d}

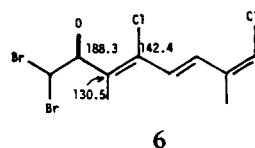
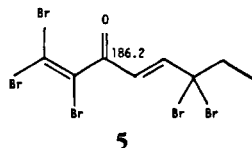
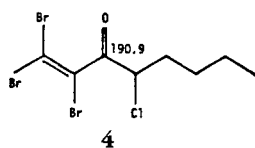
^aData from Table 3, Refs. 9, 11, or 12; ^bValue refers to addition of a second X at α position; ^cRefers to changing from $-\text{CR}_3$ to $=\text{CR}_2$ [eg. $\text{R}-\text{C}(=\text{O})\text{C}=\text{C}$]; ^dRefers to $\text{C}=\text{C}-\text{C}(=\text{O})-\text{C}=\text{C}$.

TABLE 3. Chemical Shifts of α -Substituted Carbonyls.

 i^a	 ii^a	 iii^a	 iv^b	 v^b
 vi^b	 vii^a	 viii^a	 ix^a	 x^a
 xi^a	 xii^a	 xiii^a	 xiv^a	
 xv^a	 xvi^a			

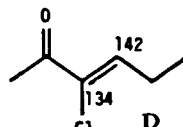
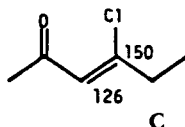
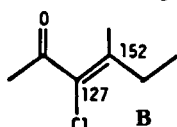
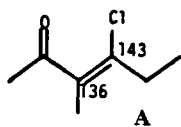
^aThis work^bRef. 12

tal vs. expected ^{13}C shift is also apparent for the C-6 methyl. Based upon analogy to the prelocamenes and arguments presented therein (10), a *Z* or *E* C-6 methyl should occur at 18 or 13 ppm, respectively, neither of which is close to its reported shift of 26.7 ppm.



The revisions suggested by structure **3** provide a uniform match of all the experimental nmr data and observed chemical degradation results. Specifically, assignment of the 69 ppm singlet at C-6 is within 1 ppm of its expected shift (2). Additional justification for the Cl at C-4 is provided by the observed ^{13}C singlet at δ 129.7 compared to a calculated value of δ 134 which is quite different vs. a calculated shift of δ 150 for Cl at C-5 in **1**.³ Similarly, the Cl at C-4 is consistent with a coupled INEPT double-double-

³Experimental data from Ref. 11 of: *trans*-hex-3-ene-2-one C-3 = 131 ppm, C-4 = 147 ppm gave base values to which were added C=C increments: Cl (C- α = 3.3, C- β = -5.4) Me (C- α = 10.3, C- β = -7.8) to yield calculated values shown below. Better agreement is observed between data for **6** and **A** vs. **B**.



quartet observed by Brownlee for plocamenone at Me-10 (4). Also of importance are the ^{13}C and ^1H C-4 methyl shifts (δ 26.7, δ 1.74) which agree with a -C(Me)Cl-C(H)Br-constellation and a relative R*,S* stereochemistry (1). Unfortunately, attempts to employ calculated ^1H shifts at C-5 to resolve the double bond stereochemistry were not fruitful.⁴ Lastly, base catalyzed rearrangement of either **2** or **3** by Stierle's mechanism predicts *identical* degradation products.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Nmr spectra were recorded on a JEOL FX-100 PFT spectrometer operating at 25.0 MHz for ^{13}C and 100 MHz for ^1H . Gc-ms data were obtained on a Finnigan 4000 system equipped with a $\frac{1}{8}$ in x 6 ft glass column packed with 3% OV-17 on Chromosorb Q and temperature programmed in the range of 130-225° at either 5 or 10° min⁻¹. ^{13}C nmr peak multiplicities were determined by obtaining SEFT spectra, (17) using a standard delay time of 8 ms. The sources of samples used in this work to obtain the data in Table 3 are as follows. Compounds **i-iii**, **vii-xiv** were prepared as described by Wyman and Kaufman, (18) using the appropriate alkyl ketone with sulfonyl chloride. Product mixtures were separated by hplc or characterized by gc/ms. The bromo ketones **xv** and **xvi** were prepared according to the literature (19).

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⁴Trisubstituted double bonds with attached groups including: C=O, OR, CHX or CHX₂ usually show greater than an 0.5 ppm difference between expt. and calc. proton shifts: (a) S.W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969); (b) S. Naylor, unpublished results, UCSC, 1984.