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STEREOCHEMICAL ASSIGNMENTS IN MARINE NATURAL PRODUCTS BY ^{13}C NMR γ EFFECTS

Phillip Crews* and Ernest Kho-Wiseman
Thimann Laboratories
University of California-Santa Cruz
Santa Cruz, California 95064

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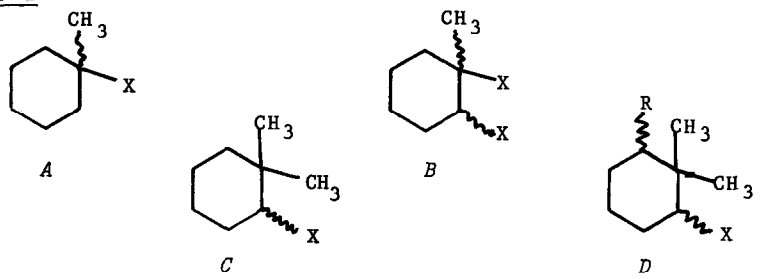
The net shielding experienced by a carbon γ gauche to a newly introduced first or second row substituent has been examined in some detail recently.[1-3] The contrasting deshielding caused by some γ anti substituents[1,2] or γ effects observed in ^{31}P and ^{19}F NMR[3] suggests that the mechanism of this phenomenon is more complex than initially envisioned.[4] In spite of this uncertainty, the γ shielding effect is often employed in making preliminary carbon shift assignments,[4a] and it has been utilized to study a variety of stereochemical relationships.[5]

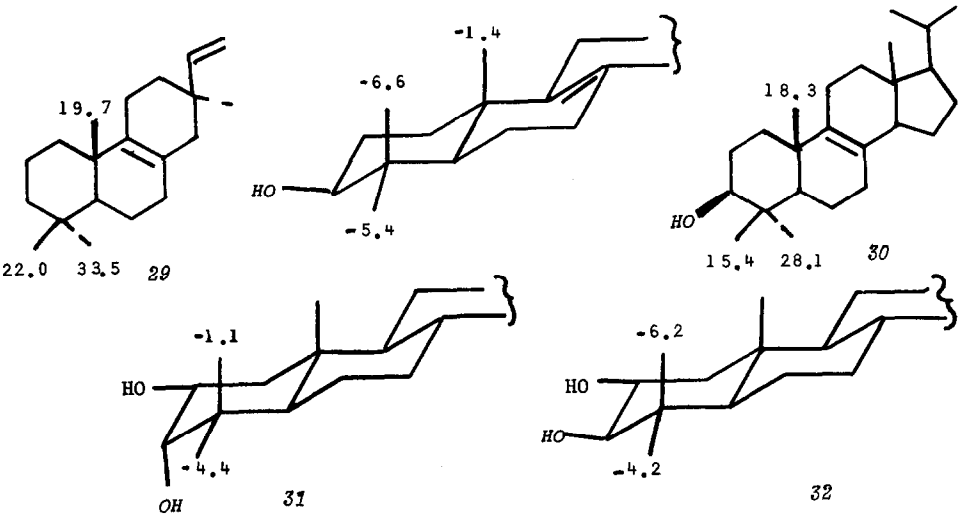
We have found that γ shift correlations can be useful for making certain stereostructural assignments in acyclic marine natural products.[6] Described in this communication is a generalized scheme to yield stereochemical information in six-membered rings based upon quantitative γ-effect analysis.

Large differences in ^{13}C shift vs. stereochemistry can be observed for secondary or quaternary methyls in simple and polyfunctional conformationally fixed six-membered rings. In addition, the shifts of such methyls are also diagnostically sensitive to the relative stereochemistry of adjacent substituents. For example, comparing the diols *12, 13, 16, 17* (Table 1) reveals that the shift of an equatorial methyl gauche to a γ OH (27.2 or 27.5 ppm) is quite different compared to an axial methyl gauche to an equatorial γ OH (18.8) or an axial methyl anti to an axial γ OH (24.2). Building upon this, we have compiled a set of reference methyl shifts (Tables 1-2) to enable a determination of the stereochemistry of a secondary or quaternary methyl on a cyclohexane ring (Type *A* & *B*, Scheme I), and more powerfully the stereochemistry of substituents adjacent to an axial methyl or adjacent to a gem dimethyl (Type *B-D*). These various situations represent often encountered terpene substructures and are summarized in Scheme I.

Scheme I



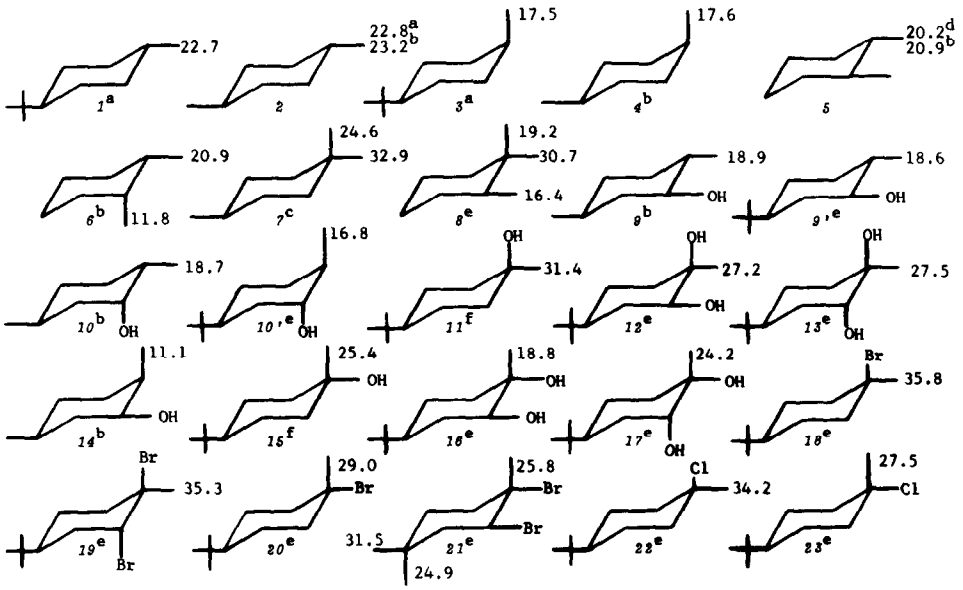
A set of γ substituent increments has been calculated, Table 3, based upon the model compounds in Tables 1-2 and literature data.[12] These shift increments should be broadly usable because of their consistency with data derivable from polycyclic ring systems. For example, a comparison of the ^{13}C shifts between *29* and *30*[13] reveals that the OH substituent increment at the axial CH_3 (-6.6) and the equatorial CH_3 (-5.4) is in close agreement with that in Table 3. Similarly, after subtracting the δ effect, the calculated γ increment for steroids[14] *31* and *32* is also consistent with that in Table 3.



It is important to note that β substituents attached to a methyl cyclohexane exert parallel shifts regardless of their configuration. Relative to methyl cyclohexane with a $\Delta\delta=\delta_a-\delta_e$ = 5.2ppm comparable Δδ's are observable for added β substituents including: a CH_3 (*7*Δδ=8.3ppm), an OH (*11* vs. *15*Δδ=6.0), a Br (*18* vs. *20*Δδ=6.8), a Cl (*22* vs. *23*Δδ=6.7), and a CO_2H (1-methylcyclohexane-1-carboxylic acid,[10] Δδ=8.7). This regularity illustrates that quaternary methyl stereochemistries can be reliably assigned in model type *A*.

A similar pattern can be seen for model type *B*. Using the monoterpenes *33* and *34* as an example, the shifts of the equatorial methyls are quite similar to that calculated for the isostructural methyl in *B'* (Table 4). By this same methodology, the similarity between the $C(CH_3)Cl$ shift in epoxide *35* to that of *B"* indicates that this methyl must be axial in agreement to the literature assignment based upon a biogenetic analogy.[16a]

Table 1. Carbon Shifts for Cyclohexane Model Compounds



[a]Ref 7; [b]Ref 8; [c]Ref 9a; [d]Ref 9b; [e]This Work; [f]Ref 10

Table 2. Carbon Shifts for Decalin Models[11]

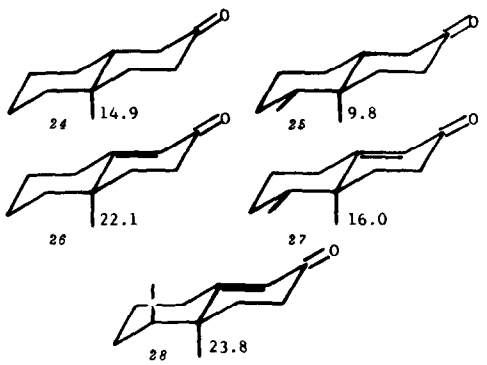
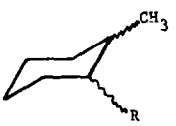


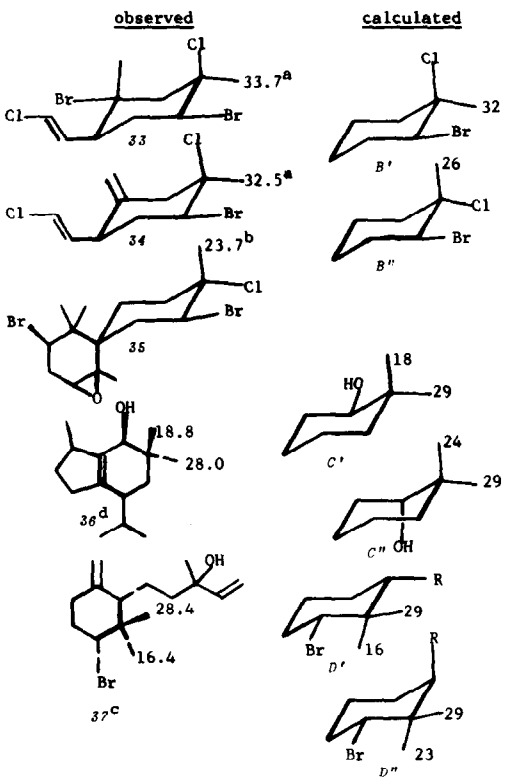
Table 3. Substituent Increments[a]



	CH_3(eq)		CH_3(ax)	
R	R(eq)	R(ax)	R(eq)	R(ax)
CH_3	-2.4±0.6	-2.1±0.3	-5.6±0.5	+1.7
OH	-4.1±0.3	-4.2±0.3	-6.5±0.1	-1.0±0.3
Br	-1.8[b]	-0.5	-3.2	(-1)[c]

[a]Entries with error range based upon multiple observations from Tables 1 & 2; [b]Based upon a comparison of elatol and debromoelatol[12]; [c]Estimate based upon analogy to the OH substituent effect.

Table 4. Comparison of Observed vs. Calculated Carbon Shifts



[a]Ref 15; [b]This Work; [c]Ref 16b; [d]Ref 17

The additional examples in Table 4 provide applications for models *C* and *D*. Fenical and Stallard recently isolated brasilenol (*36*) from a sea hare.[17] They found that the stereochemical assignment of the alcohol group was not straightforward. This assignment can be approached by comparison of the observed gem dimethyl shifts to those calculated for *C'* and C" with the former providing a better fit, implying an equatorial like arrangement for the OH. The lack of J Value information for the side chain methine proton in β-snyderol (*37*),[16b] from the red seaweed *Laurencia*, presented similar difficulties in the assignment of the side chain stereochemistry. As above, a comparison of the observed gem dimethyl shifts of *37* to that calculated for *D'* suggests the side chain stereochemical assignment as shown in *37*.

Additional work is in progress in our lab to expand the increment values presented in Table 3, and to explore the limitations of this method.

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