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ABSOLUTE CONFIGURATIONS OF MARINE DITERPENES POSSESSING A XENICANE SKELETON. AN APPLICATION OF AN ADVANCED MOSHER'S METHOD

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Abstract-- By means of Mosher's method using ^1H NMR spectroscopy at 500 MHz the absolute configurations of marine diterpenes, **7** and **8**, have been elucidated.

Mosher's method using MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] esters is a convenient and important chemical process for determination of the absolute configurations of secondary alcohols.[1,2,3] The most important factor in use of the method is the difference in steric bulkiness of the substituents on two β (next to the carbinyl carbon)-carbons; the steric repulsion between the phenyl group of the MTPA moiety and the β-substituents is essential to bring about the chemical shift difference of the CF_3 (^{19}F) or OMe (^1H) group. Erroneous predictions on absolute configurations have occasionally occurred, however.[4] One reason for this is that certain compounds can exist in a conformation in which β-substituents are placed far from the MTPA moiety, and other substituents (*e.g.*, on γ, δ, or ε-position) may cause a greater steric interaction with the MTPA group.[4] In such case, a simple comparison of the bulkiness between the β-substituents is meaningless.

In a solution, the carbinyl proton, ester carbonyl and trifluoromethyl groups of the MTPA moiety are oriented on the same plane (Figure 1).[1,5] Due to the diamagnetic effect of the benzene ring, H_A of an (*R*)-MTPA ester shows the ^1H NMR signal at upfield relative to that of an (*S*)-MTPA ester. We considered that the anisotropic effect of the benzene ring of the MTPA moiety would affect the chemical shifts of the protons which are even more than 10 nanometer apart from the phenyl group.[6] The (*R*) and (*S*)-MTPA esters of *l*-menthol (**1**) are good examples. The numerical value denoted for each proton is chemical shift difference [$\Delta\delta = \delta_S - \delta_R$;[7] for convenience, Δδ values were given in hertz (500 MHz).] obtained by subtracting the chemical shift (δ_R) of a proton of the (*R*)-MTPA ester from that (δ_S) of the (*S*)-MTPA ester.

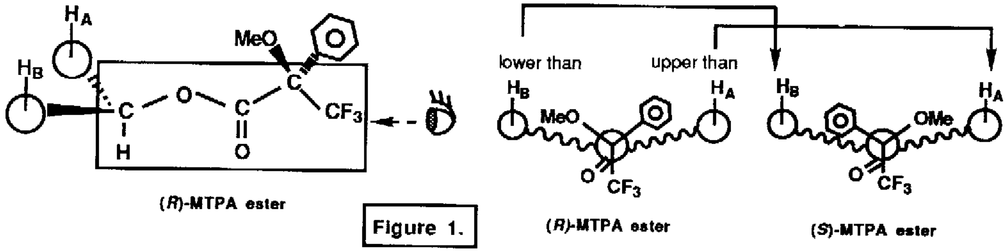
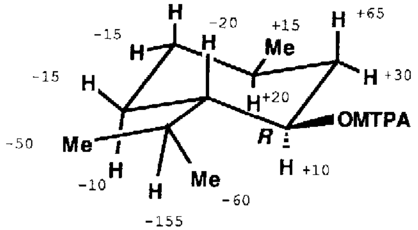


Figure 1.



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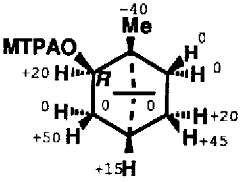

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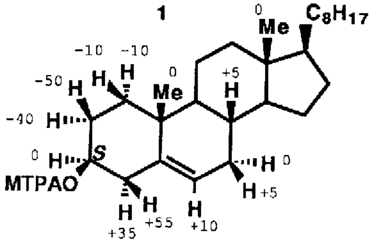

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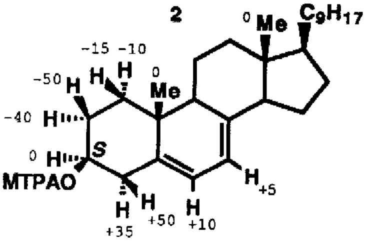

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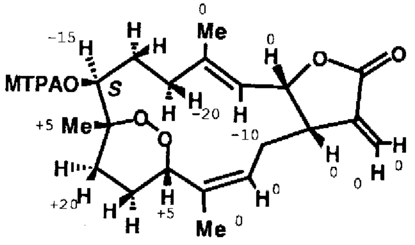

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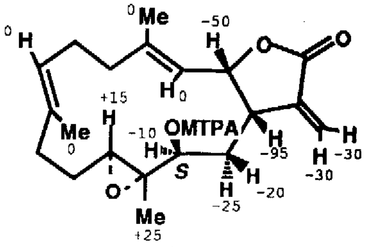

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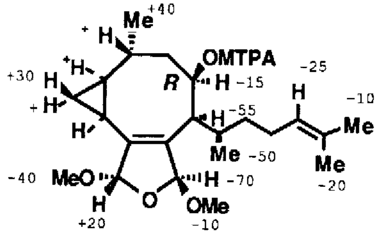

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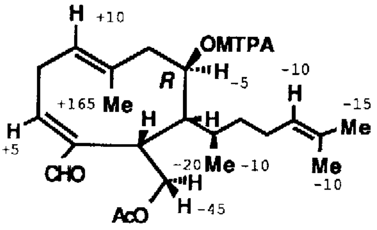

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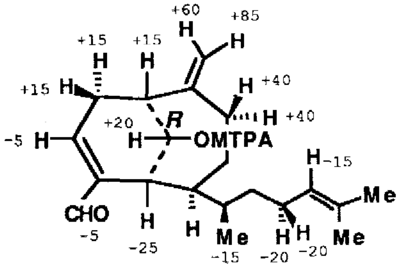

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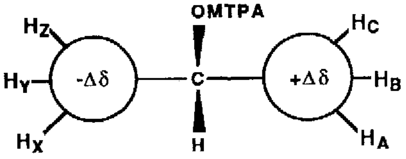

Figure 2. **Model A**

The positive signs show that they have higher chemical shifts (smaller δ) in (*R*)-ester than in (*S*)-ester, that is, these protons are located on the right-hand side of the "MTPA plane" (Figure 1). As shown in **1**, all the protons having positive $\Delta\delta$ values are found on the right-hand side (except for the carbinyl proton), and those having negative $\Delta\delta$ values are on the left-hand side of the plane containing -COO- group of MTPA.

We generalized this method as follows: (1) Assign as many proton signals as possible of (*R*) and (*S*)-MTPA esters. (2) Obtain $\Delta\delta$ values for the protons. (3) Put the protons with positive $\Delta\delta$ on the right-hand side, and those with negative $\Delta\delta$ on the left-hand side of model A (Figure 2). (4) Construct a molecular model of the compound, and confirm that all the assigned protons with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane, respectively. The absolute values of $\Delta\delta$ must be qualitatively proportional to the distance from the MTPA moiety. When these conditions are satisfied, model A will show the correct absolute configuration of the compound.[8]

Compounds **2**-**4** and **5**[4], the absolute configurations of which are known, demonstrate the validity of the method. In all cases, $\Delta\delta$ values are systematically arranged according to this rule. The protons located near the MTPA plane (*e.g.*, 18 and 19-Me's of **3** and **4**) do not show significant differences ($\Delta\delta$ = 0). Also, the protons on the C and D rings and those on the side chains of **3** and **4** are remote from the MTPA group, so that their $\Delta\delta$ values are zero. It should be noted that both of the β-carbons of **3** and **4** are secondary (having the same bulkiness). In such a case, neither of the two conventional methods which use ^{19}F NMR spectroscopy or a lanthanide-shift reagent is applicable.

The present method was applied to elucidate the absolute configurations of marine diterpenes **6**-**9**. Their relative stereochemistry and stable conformations are known. The *S*-configuration at the carbinyl carbon of **6**[4] and the *R*-configurations of **7**,[9] **8**,[10] and **9**,[11,12] respectively, were easily deduced by the $\Delta\delta$ values depicted in the respective structures. It should be emphasized again that the β-carbons of the MTPA ester **9** are both tertiary. Noteworthy is the fact that Mosher's method using ^{19}F NMR spectroscopy gave incorrect predictions about the absolute configurations of **2**,[2] **5**,[4] **6**,[4] and **8**.[13]

It is of biogenetical interest that the absolute configurations of the xenicanes **7** and **8** from the Dictyotaceae algae are opposite to that of xenicin[14] isolated from a soft coral.

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