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Novel *nor*-Sesquiterpenoids in New Zealand Honeys. The Relative and Absolute Stereochemistry of the Kamahines: An Extension of the Mosher Method to Hemiacetals[1]

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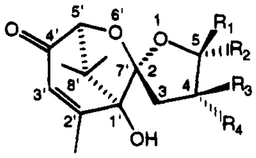
The relative stereochemistries of the diastereoisomeric kamahines A (**1a**) and B (**1b**) were determined by correlation of the NMR-derived NOE and coupling constant data of kamahine A and B acetates (**2a** and **2b**) with those from the previously crystallographically solved kamahine C acetate (**2c**). The kamahines were shown to be C4,C5 epimers of 4,5-dihydro-1′,5-dihydroxy-2′,4,8′,8′-tetramethylspiro[furan-2(*3*)*H*,7′[6′]oxabicyclo[3.2.1]oct[2′]en]-4′-one. Absolute configurations of the kamahines were determined by an NMR and molecular modeling study (MacroModel) of the diastereoisomeric hemiacetal methoxymandelate esters (**6a−c** and **7a−c**). The results of the determination, coupled with a consideration of crystallographically determined hemiacetal ester conformations obtained from a search of the Cambridge Structural Database, suggested that the Mosher−Trost model used for prediction of absolute configuration should be amended to take into account a torsion angle of +25 to +50° between the methine hydrogen and the carbonyl of hemiacetal mandelate esters. The kamahines were shown to have the absolute configurations (1′*R*,2*R*,4*R*,5*S*,5′*S*)-**1a**, (1′*R*,2*R*,4*S*,5*S*,5′*S*)-**1b**, and (1′*R*,2*R*,4*R*,5*R*,5′*S*)-**1c**.

Introduction

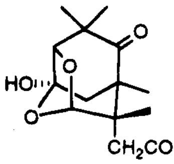
Recently, we reported the isolation and structural characterization of an unusual spiroketal, kamahine C (**1c**), from the honey of the New Zealand native tree *Weinmannia racemosa* (kamahi).[2] Kamahine C was isolated from a mixture of three compounds **1a-c** present in the noncarbohydrate extractives of kamahi honey.[2] These extractives are showing considerable potential as floral source markers, and analysis of these compounds by GLC[3,4] may prove to be a viable replacement for melissopalynology.[5]

While the structures of kamahines A (**1a**) and B (**1b**) were not determined, they were clearly diastereoisomers of **1c**.[2] Kamahine C was initially reported to be a *nor*-carotenoid[2] on the basis of the similarity of its ring substitution to those of the carotenoids such as violaxanthin **3**. Of the noncarbohydrate extractives isolated from honey, the kamahines, and the recently characterized meliracemoic acid **4**,[1] are unique in that they possess a C_{14} skeleton. Most *nor*-carotenoids isolated from plant material are C_{13} or C_{15} compounds; these structures originate from the facile oxidative cleavage of the C7−C8 and C9−C10 double bonds, respectively, in the parent carotenoids.[6] However, another possible source for the kamahines is the sesquiterpenoid abscisic acid **5**, which can itself be derived from a carotenoid such as **3**.[7] It is not yet clear whether the reactions leading to the formation of these compounds are taking place within the honey or are associated with metabolism by the bees themselves.



	R1	R2	R3	R4
1a	H	OH	H	Me
1b	H	OH	Me	H
1c	OH	H	H	Me
2a	H	OAc	H	Me
2b	H	OAc	Me	H
2c	OAc	H	H	Me
6a	H	O-(*S*)-χ	H	Me
6b	H	O-(*S*)-χ	Me	H
6c	O-(*S*)-χ	H	H	Me
7a	H	O-(*R*)-χ	H	Me
7b	H	O-(*R*)-χ	Me	H
7c	O-(*R*)-χ	H	H	Me

(χ = methoxymandelate)



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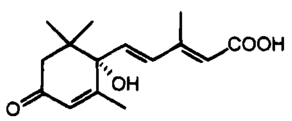

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The determination of the absolute configuration of the kamahines would assist in determining the source of compounds such as **1** and **4**. This paper reports the full structural characterization of compounds **1a−c** and the determination of the absolute configuration of compounds **1a−c**. Owing to the exceedingly small quantities of the

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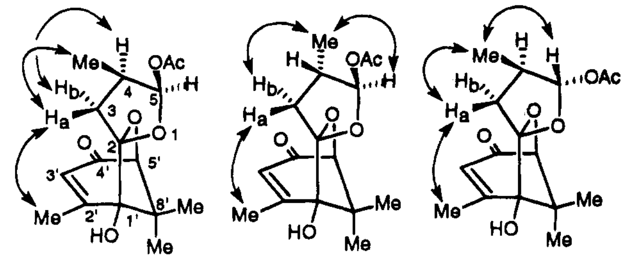

2a **2b** **2c**

Figure 1. Key NOE enhancements observed for **2a–c**.

kamahines available, and the difficulties in obtaining complete separation of their diastereoisomers, analysis of the absolute configuration by optical methods such as CD or ORD was not feasible. The method of choice, therefore, was the synthesis of the corresponding methoxymandelate esters, followed by an analysis of the ^{1}H NMR diamagnetic shielding information, using the model put forward by Mosher[8] and Trost.[9] The correlation of the conformations taken up by the mandelate esters with the diamagnetic shielding was assisted by consideration of the crystallographically determined conformations attained by hemiacetal esters and molecular mechanics calculations on the mandelate esters utilizing converged Monte Carlo torsion angle searches.

Results and Discussion

Isolation and Relative Stereochemistry of Kamahines A–C. The kamahines were obtained from kamahi or rewarewa (*Knightia excelsa*) honey as a mixture of three diastereoisomers. Their separation on a preparative scale was difficult and was complicated by the interconversion of **1a** and **1c**. The initial structural analysis of the kamahines was performed on the acetylated material. Compound **2c** was separated from the acetylated mixture as a pure compound, and its characterization by single-crystal X-ray diffraction and NMR has been reported elsewhere.[2] We were eventually able to partially separate **2a** and **2b** by preparative TLC, and it was clear from 2D ^{1}H–^{1}H and ^{1}H–^{13}C NMR investigations that **2a** and **2b** shared the same skeleton as **2c**. The relative stereochemistries were assigned by comparison of the 1D NOE enhancements and vicinal coupling constants in the spirotetrahydrofuran ring with those from **2c**. The enhancement observed between 2′-Me and H3$_a$ in **2a–c** confirmed that the spirotetrahydrofuran ring orientation was the same in each isomer with the diastereoisomerism arising in epimerization of C4 and C5 in the ring. The NOE from 2′-Me to H3$_a$ also provided the key information required to determine the relative configurations of C4 and C5, by identifying the H3$_a$ resonance in each isomer. In **2a**, irradiation of H3$_a$ led to an enhancement of 4-Me, establishing a *cis* relationship between these substituents. Irradiation of H3$_b$ in **2b** gave an enhancement of 4-Me, suggesting that in **2b**, H3$_a$ and 4-Me were *trans*, while irradiation of H3$_a$ in **2c** enhanced 4-Me, giving a *cis* configuration, as seen in the crystal structure.[2] The key NOE enhancements are shown in Figure 1; these were all consistent with the MM2* (MacroModel[10])-calculated internuclear distances. Full assignments of the ^{1}H NMR spectra are given in Table 1. The MM2*-calculated structures were also utilized for the analysis of the relationship of torsion angles between vicinal hydrogens and the observed ^3J values from protons on the spirotetrahydrofuran ring. The relative configurations were consistent with the observed coupling constants and agreed with those calculated in MacroModel (using the parameters derived from Haasnoot[11]) to better than ±1 Hz.

We were able to ascertain that there was a direct correlation between the structures of acetates **2a–c** and the parent acetals after a microscale multiple-elution TLC separation of **1b**. Acetylation of **1b** in an NMR tube with Ac$_2$O/pyridine led to the formation of **2b**. Additional evidence for the direct correspondence of **1a–c** with **2a–c** was obtained from the observation that the ratio of **1a** and **1c** in the mixture of **1a–c** changed over time, while the amount of **1b** appeared to remain constant. The acetate **2a**, when dissolved in CDCl$_3$, gradually epimerized to **2c**; in d_6-acetone this epimerization was much slower. Presumably the CDCl$_3$ was sufficiently acidic to catalyze epimerization of the hemiacetal. While we could never obtain a complete separation of **1a** and **1c**, it was possible to obtain all the required ^{1}H and ^{13}C NMR data from the mixture of the two compounds.

Absolute Configuration of the Kamahines. The (*S*)-methoxymandelates **6a–c** and (*R*)-methoxymandelates **7a–c** were synthesized by treating the mixture of **1a–c** with either (*S*)-(+)- or (*R*)-(−)-methoxymandelic acid in the presence of dicyclohexylcarbodiimide (DCC).[9b] Analysis of the resulting mixtures by both ^{1}H NMR and GC/MS showed that only three diastereoisomers were present in both cases. There was no evidence of racemization of **1a–c** during the reaction. The ^{1}H signal from H5 was particularly diagnostic, in that the multiplicity and *J* values for this proton in each of **6a–c** and **7a–c** were identical to the corresponding acetates **2a–c**. The observation that only three diastereomers were present in the mixtures also showed that racemization of the methoxymandelate was insignificant under the conditions used for the synthesis. Separation of the mixture by preparative TLC gave sufficient quantities of each isomer for analysis by ^{1}H NMR.

The absolute configurations of a number of natural products containing secondary alcohols have been assigned from the NMR analysis of their methoxymandelate or methoxy(trifluoromethyl)phenyl acetic (MTPA) esters.[12] Only a few examples exist where the absolute configurations were not readily accessible from this analysis.[13] The cornerstone of the technique is the assumption that the carbinyl proton of the secondary alcohol, the ester carbonyl, and the methoxyl oxygen attain a defined conformation. That this conformation, in the case of the methoxymandelate esters, was effectively syn,syn coplanar was shown by a crystal structure of methoxymandelate ester **8**.[9b] To our knowledge,

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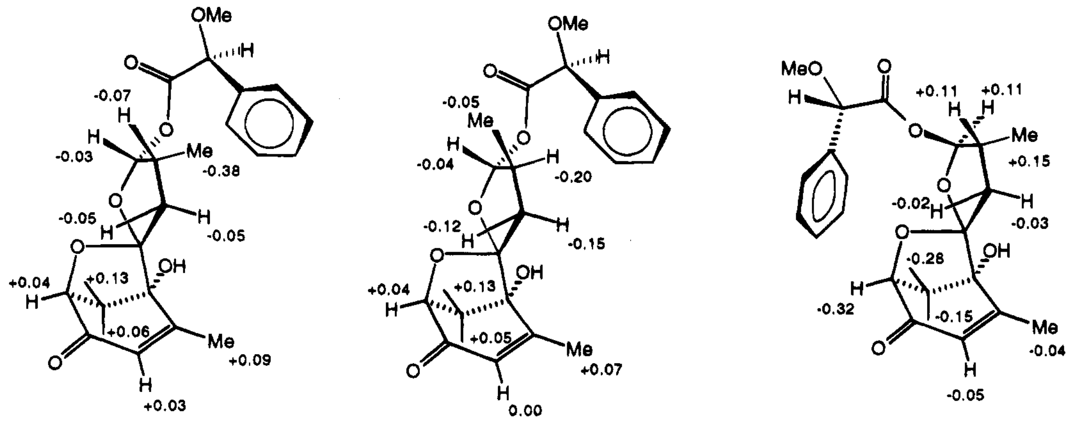


6a **6b** **6c**

Figure 2. ^{1}H $\Delta\delta$ ($\delta S - \delta R$) values (in ppm).

Table 1. ^{1}H and ^{13}C NMR Data for 1a–c and 2a–c

	1a		**1b**		**1c**	
carbon	δ ^{13}C	δ ^{1}H, J (Hz)	$^1\delta$ ^{3}C	δ ^{1}H, J (Hz)	δ ^{13}C	δ ^{1}H, J (Hz)
4-Me	12.3	1.03, d, ^3J 6.8	15.3	1.11, d, ^3J 7.2	15.7	1.09, d, ^3J 6.8
8′-Me$_{ax}$	18.1	0.99, s	18.1	0.99, s	18.2	0.98, s
2′-Me	20.7	2.09, d, ^4J 1.6	20.8	2.09, d, ^4J 1.6	20.4	2.04, d, ^4J 1.4
8′-Me$_{eq}$	21.9	1.30, s	22.0	1.30, s	21.9	1.31, s
3	38.7	H3a, 1.80, dd, ^2J 12.4, ^3J 12.4, H3b, 1.87 dd, ^2J 12.4, ^3J 6.6	38.7	2.31, dd, ^2J 13.3, ^3J 7.6, 1.63, dd, ^2J 13.3, ^3J 1.8	41.3	1.60, dd, ^2J 13.1, ^3J 8.1, 2.03, dd, ^2J 13.1, ^3J 6.9
4	39.2	2.45, m	39.2	2.15, m	39.7	2.25, m
8′	52.0		51.9		52.1	
1′	84.7	3.25, s (broad), 1′-OH	84.9	3.25, s (broad), 1′-OH	84.4	2.97, s (broad), 1′-OH
5′	89.9	3.95, d, ^4J 2.1	90.0	3.96, d, ^4J 2.1	89.6	3.97, d, ^4J 2.0
5	100.5	5.52, d, ^3J 4.8	105.1	5.35, s (broad), 4.18 s (broad), 5-OH	107.1	5.03, t, J 5.9, 3.88, s (broad), 5-OH
7′	115.0		115.9		112.9	
3′	125.1	5.90, dq, ^4J 2.1, ^4J 1.6	125.9	5.90, dq, ^4J 2.1, ^4J 1.6	125.3	5.89, dq, ^4J 2.0, ^4J 1.4
2′	166.6		166.6		165.5	
4′	195.0		195.5		195.7	

	2a		**2b**		**2c**	
	δ ^{13}C	δ ^{1}H, J (Hz)	δ ^{13}C	δ ^{1}H, J (Hz)	δ ^{13}C	δ ^{1}H, J (Hz)
4-Me	12.0	0.98, d, ^3J 6.7	16.8	1.16, d, ^3J 7.6	16.1	1.10, d, ^3J 6.9
8′-Me$_{ax}$	18.0	0.99, s	17.9	0.99 s	18.1	1.00, s
2′-Me	20.5	2.08, d, ^4J 1.6	20.5	2.08, d, ^4J 1.6	20.3	2.06, d, ^4J 1.5
*Me*CO	21.2	2.09, s	21.3	2.06, s	21.3	2.12, s
8′-Me$_{eq}$	21.7	1.27, s	21.7	1.29, s	21.8	1.27, s
4	35.8	2.59, m	38.2	2.25, m	36.8	2.51, m
3	38.5	H3a, 1.80 dd, ^2J 12.6, ^3J 12.6, H3b, 1.88 dd, ^2J 12.6, ^3J 6.7	37.7	2.25, dd, ^2J 12.0, ^3J 7.6, 1.62, d, ^2J 12.0	40.5	1.66, dd, ^2J 13.0, ^3J 9.9, 2.09, dd, ^2J 13.0, ^3J 7.3
8′	51.9		51.7		52.0	
1′	84.4	2.62, s (broad), 1′-OH	84.9	2.66, s (broad), 1′-OH	84.9	2.90, s (broad), OH
5′	89.9	3.94, d, ^4J 2.1	90.1	3.96, d, ^4J 2.2	89.9	3.98, d, ^4J 2.2
5	99.5	6.39, d, ^3J 4.8	104.6	6.09, s	103.6	5.85, d, ^3J 4.8
7′	115.8		117.2		114.6	
3′	125.3	5.89, dq, ^4J 2.1, ^4J 1.6	125.3	5.89, dq, ^4J 2.2, ^4J 1.6	125.4	5.91, dq, ^4J 2.2, ^4J 1.5
2′	165.3		165.3		164.8	
MeCO	169.9		169.8		170.8	
4′	194.5		194.7		194.6	

no such assignments have been attempted on systems such as the kamahines, where the methine carbon involved is actually a hemiacetal carbon. An additional complication in the case of the kamahines is the problem of the geometry of the skeleton—the *spiro*-linkage gives the kamahines a three-dimensional shape which makes visualization of the ester conformations nontrivial.

Analysis of the resulting ^{1}H NMR spectra of **6a–c** and **7a–c** showed that systematic variations in chemical shift had occurred. As a starting point in the interpretation, we used the model building facility in MacroModel to generate the conformations of the mandelate esters for both possible enantiomers of each of **6a–c** as would be predicted by the Mosher rules. Representations of these structures are shown in Figure 2, along with the observed $\Delta\delta$ values ($\delta S - \delta R$) for the ^{1}H resonances.

In each case, the protons with positive and negative $\Delta\delta$ values are on opposite sides of the plane formed between H5 and the ester carbonyl. This result was a good indication that the mandelate group was attaining a conformation similar to that observed in secondary alcohols.[8,9] The shielding interactions are generally

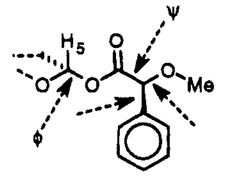
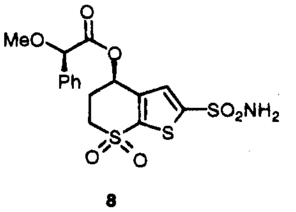


Figure 3. Variable torsion angles used to generate starting conformations: ϕ = H5−C5−O−C=O, ψ = O=C−C−O (arrows point at rotatable bonds).

consistent with the conformations of **6a−c** as shown in Figure 2. Examination of models of the corresponding esters of the opposite enantiomers of **1a−c** showed that $\Delta\delta$ values of opposite signs to those observed would be obtained. The interpretation of the shielding data thus indicates that the kamahines possess the following configurations: (1′*R*,2*R*,4*R*,5*S*,5′*S*)-**1a**, (1′*R*,2*R*,4*S*,5*S*,5′*S*)-**1b**, and (1′*R*,2*R*,4*R*,5*R*,5′*S*)-**1c**.

Conformational Analysis. While the shielding data for compounds **6** and **7** appear to be internally consistent, with respect to the location of positive and negative $\Delta\delta$ values on opposite sides of the ester plane, and consistent with what has been observed for secondary alcohols,[8,9] we were cautious about the extrapolation of the interpretation from esters of secondary alcohols to hemiacetal esters. A more detailed examination of the preferred conformations of acetal esters was undertaken, using molecular mechanics. It has been demonstrated that the most efficient conformational search technique for small organic molecules is the Monte Carlo torsion angle search method[14] —this technique is particularly well implemented in MacroModel. We thus subjected each diastereoisomer to a torsion angle search, starting from an arbitrarily chosen MM2* minimized conformation. The randomly varied torsion angles are shown in Figure 3.

It was immediately clear from the global minima observed in the simulations that the preferred conformation of the mandelate moiety was with the methoxyl oxygen and the ester carbonyl approximately syn coplanar (torsion angle ψ of ca. ±10° and an H5−C5−O−CO torsion angle (ϕ) in the range $-60°\ \phi \leq +60°$—in this case we define the positive angle to represent the carbonyl group being rotated toward O1 in **2**, **6**, and **7**). We performed a similar torsion angle search on compound **8**, which has been used[9b] to help correlate the solution- and solid-state conformations of methoxymandelates (*vide supra*). The simulation produced results similar to those obtained crystallographically:[9b] the conformers of **8** within 4 kJ of the global minimun had average torsion angles of ψ = 9.6° and ϕ = 39.9°. The stereoview shown in Figure 4 could thus represent a partial time-average of the conformational space covered by the freely rotating mandelate group.



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It is interesting to note that analysis of the crystal structure of kamahine C acetate **2c** gives a corresponding torsion angle ϕ between H5 and the acetate carbonyl of 36°. A Monte Carlo torsion angle search of **2c** gave a global minimum with ϕ = 43°. While we were encouraged at the good correlation between $\phi_{\text{cryst struct}}$ and $\phi_{\text{MM2*}}$ in **2c**, we were cautious about overinterpreting the MM2* results obtained for the mandelate esters **6** and **7**. Although Trost et al.[9b] commented on the crystallographically determined value of ψ in **8** of 29° no mention of the ϕ torsion angle was made. A QUEST search and GSTAT analysis[15] of the Cambridge Structural Database (CSD) revealed that ϕ for **8** was 26.05° while for the eight MTPA and two methoxymandelate esters in the CSD the magnitude average $|\phi_{\text{ave}}|$ was 24°. A general search of the CSD revealed that for cyclopentanol esters, $|\phi_{\text{ave}}|$ = 30.9° while $|\phi_{\text{ave}}|$ for esterified 2-hydroxytetrahydrofurans was 35.7°. In the latter case, 16 of the 18 entries in the CSD had torsion angles with the carbonyl group rotated toward the tetrahydrofuran oxygen, with ϕ_{ave} = +36.2°. It was assumed that given the diverse nature of the relevant structures found in the CSD, the effects of crystal packing on the torsion angles would be less significant than the intramolecular stereoelectronic effects associated with the ester structures.

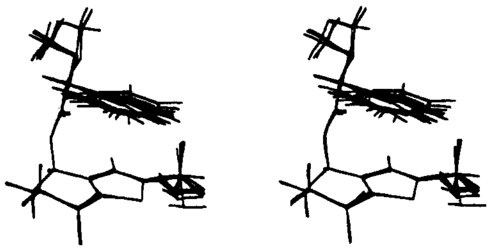

Figure 4. Stereo view of overlayed conformations within 4 kJ/mol of MM2* global minimum of **8**.

The crystallographic data led us to the conclusion that the preferred ϕ angle for acetal esters lies in the range +25 to +40°. While the MM2* global minima we determined for **6a** and **6b** have ϕ = −61° and −47°, respectively, there were a number of conformations within 2−3 kJ/mol of the global minimum with $\phi \sim +40°$. The global minimun for **6c** had ϕ = +47°. These variations are significant for compounds such as the kamahines, where small changes in ϕ could result in significant changes in the magnitude of the observed $\Delta\delta$ values. This result is illustrated in Figure 5a, which shows an overlay of the four lowest energy conformers for **6b**. In both **6a** and **6b** the $\Delta\delta$ values observed are entirely consistent with a conformation with $\phi \sim +40°$ whereas a conformation with $\phi \sim -45°$ could lead to significant changes in the diamagnetic shielding effects to those actually observed. Indeed, even changes in ϕ from 0° as used in the Mosher−Trost predictive model) to ca. +40° can bring more hydrogens into the shielding cone of the phenyl group. This effect is noticeable for compound **6c** (see Figure 5b), where the global minimum (ϕ = 47°) and the model structure (ϕ = 0°) are overlayed. In the global minimum structure, H5′ ($\Delta\delta$ = −0.32 ppm) is deeper into the shielding region of the phenyl group, whereas in the ideal structure 8-Me$_{\text{eq}}$ ($\Delta\delta$ = −0.27 ppm) is closer to the phenyl group. The observed greater shielding of H5′ compared to 8-Me$_{\text{eq}}$ suggests that the

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[15] The CSD QUEST package allows the user to search for a defined structural fragment within the CSD and save the search results in the FDAT format. The GSTAT package takes an input from the QUEST search and allows the user to search for defined structural parameters.

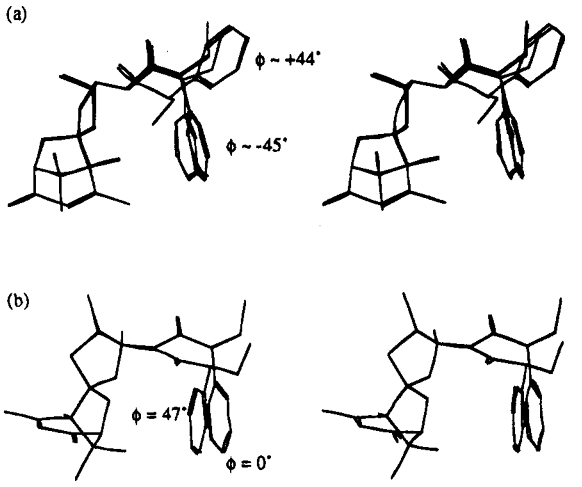

Figure 5. Stereo views of (a) overlay of four lowest minima for **6b**; the conformer with $\phi = +44°$ most closely correlates to the observed $\Delta\delta$ values; and (b) overlay of model structure ($\phi = 0°$ and global minimum ($\phi = +47°$ for **6c**; the global minimum most closely correlates to the observed $\Delta\delta$ values.

MM2*-calculated structure ($\phi = +47°$) more closely represents the time-averaged preferred conformation of the mandelate group in **6c**.

Summary

While the results of the molecular modelling simulations and crystallographic data analyses generally support the use of the model proposed by Mosher and Trost[8,9] for the determination of absolute configurations of hemiacetals such as **1**, in that the phenyl group of the mandelate moiety is in the same relative position in both cases, they also suggest that the Mosher–Trost "rules" should be applied with caution, particularly in cases where the compounds under investigation have structures which may give diamagnetic shielding results sensitive to small conformational changes in the methoxymandelate ester moiety. In the case of hemiacetal methoxymandelates, the crystallographic and MM2* data lead us to the conclusion that the most significant conformation of the ester on the NMR time scale is probably best represented by a ϕ angle of ca. +25–50° and a ψ angle of ±10° rather than the predictive model ϕ of 0°. The preference for a positive value of ϕ, with the ester carbonyl oxygen directed toward O1, suggests that there may be some stabilizing interaction between the two oxygen atoms.

Experimental Section

All NMR spectra were recorded on a Bruker AC300 at a probe temperature of 300 K. Proton–proton connectivities were established with 2D absolute value double-quantum filtered COSY experiments. Proton–carbon connectivities were established by 2D absolute value ^{13}C–^{1}H chemical shift correlation (XHCORR) or in some cases with the inverse-mode ^{1}H–^{13}C HMQC[16] experiment (GARP-1 ^{13}C decoupling was delivered by a Bruker BFX-5 fast-switching amplifier). Long-range proton–carbon connectivities were established by changing the Δ_1 and Δ_2 delays in the XHCORR experiment to 35 and 25 ms, respectively, or by use of the inverse-mode HMBC[17] experiment. The 1D NOE difference experiments were obtained with sequential irradiation of each line in the multiplet.[18]

Molecular modeling was performed on a Silicon Graphics IRIS Indigo XS24 workstation running MacroModel V3.5x.[10] Structural minimization of **2a–c** was performed using the MacroModel-implemented MM2* forcefield with GB/SA chloroform solvent included. Monte Carlo torsion angle searches were performed *in vacuo*. Each search consisted of the generation and minimization of 300 structures,[19] with a conformer being kept if it fell within 50 kJ/mol of the current global minimum and did not duplicate any previously stored conformer. Typically, each run would generate about 120 unique conformers. This process was repeated twice more, each time starting from a conformer chosen arbitrarily from the most recent coordinate set to test for convergence of the simulation. A full search would typically require about 6 h of CPU time.

Isolation of Kamahines. The concentrated extractives obtained from kamahi or rewarewa honey, as described previously,[2] were fractionated by flash chromatography on silica gel using 1:3 diethyl ether:petroleum ether as the solvent system. The fractions were analyzed by GC/MS to identify those containing **1a–c**. Subsequently, these fractions were further purified by preparative TLC using the above solvent system at 1:1 then 1:3. The major band from the TLC plate ($R_f = 0.50$) was extracted with diethyl ether and concentrated under reduced pressure to yield a colorless oil (15 mg) which was confirmed to be the kamahine component by GC/MS analysis. A microscale separation of compound **1b** was achieved by splitting the above band at $R_f = 0.50$ and extracting the removed trailing edge of the band. This gave a fraction which was essentially pure **1b**, and the observed ^{1}H NMR data are given in Table 1. ^{13}C NMR data for the kamahines was taken from the mixture. IR (mixture of three alcohols): 3444 (OH), 2955 and 2877 (CH), 1672 cm^{-1} (C=O, α,β-unsaturated ketone). UV (mixture of three alcohols): (EtOH) λ_{max} 206 (log ε 3.6), 243 nm (log ε 3.7). MS (mixture) EI: 251 (2, $M^{\bullet+} - OH$), 222 (5), 179 (5), 170 (30), 152 (88), 137 (45), 109 (100), 89 (45), 83 (26), 71 (33), 69 (35). CI: 269 (3, $M^{\bullet+} - 1$), 251 (40), 221 (11), 193 (10), 169 (12), 153 (100), 127 (10), 109 (16), 99 (55), 83 (18). High-resolution MS: $M^{\bullet+}$ *m/z* = 268.1307 (calcd *m/z* for $C_{14}H_{20}O_5$ = 268.1311).

Compounds 2a–c. The mixture of **1a–c** (15 mg, 0.06 mmol) was dissolved in an excess of pyridine/acetic anhydride (1:1) and stirred overnight. The reaction mixture was then poured into water (30 mL), extracted with diethyl ether (2 × 15 mL), and washed with 5% H_2SO_4 (2 × 10 mL), water (30 mL), saturated $NaHCO_3$ solution (2 × 30 mL), and saturated brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The resulting oil (10 mg) was plated using 1:2 diethyl ether: petroleum ether to give **2c** and a mixture of **2a** and **2b**. The fraction containing **2a** and **2b** was subjected to further multiple-elution preparative TLC, and a partial separation was obtained which facilitated NMR analysis. For **2c**. IR: 3459 (OH), 2964 and 2922 (CH), 1738 (C=O, ester), 1682 cm^{-1} (C=O, α,β-unsaturated ketone). UV (EtOH): λ_{max} 212 (log ε 3.7), 250 nm (log ε 3.6). MS EI: 251 (8, $M^{\bullet+} - OAc$), 221 (4), 194 (6), 165 (3), 152 (100), 137 (22), 124 (45), 109 (40), 99 (35), 83 (14). For the mixture of **2a** and **2b**. IR: 3502 (OH), 2970 and 2933 (CH), 1734 (C=O, ester), 1683 cm^{-1} (C=O, α,β-unsaturated ketone). UV (EtOH): λ_{max} 194 (log ε 3.7), 230 nm (log ε 3.8). MS EI: 251 (6, $M^{\bullet+} - OAc$), 221 (3), 194 (4), 165 (5), 152 (100), 137 (19), 124 (50), 109 (40), 99 (38), 83 (13).

General Esterification Procedure for Preparation of Methoxymandelates. DCC (11.3 mg, 0.05 mmol) was added to a solution of parent alcohol (10.0 mg, 0.037 mmol), (*S*)- or (*R*)-*O*-methylmandelate (7.1 mg, 0.042 mmol), and 4-(dimethylamino)pyridine (DMAP) (0.5 mg, 0.0037 mmol) in $CDCl_3$ (7 mL), and the reaction mixture was stirred at room temperature for 2 h (quantitative conversion of the parent alcohols to

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[16] Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565.

[17] Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

[18] Kinns, M.; Sanders, J. K. M. *J. Magn. Reson.* **1984**, *56*, 518.

[19] The small number of rotatable bonds resulted in a 3 × 300 stucture array being sufficient to ensure convergence of the search.

the corresponding ester derivatives was evident from TLC). The dicyclohexylurea was removed by filtration, the filter cake washed with 2 × 5 mL of CHCl$_3$, and the combined filtrates were washed with 2 M HCl (2 × 10 mL), saturated sodium bicarbonate (15 mL), and saturated brine (15 mL). The organic phase was dried over MgSO$_4$ and filtered and the solvent removed under vacuum to afford a colorless oil containing some suspended solid (dicyclohexylurea). The crude product was purified by preparative TLC using 1:1 petroleum spirit:diethyl ether, and the resulting bands were extracted with diethyl ether.

Compound 6a. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.54 (3H, d, $J_{4\text{-Me},4}$ = 6.8 Hz, 4-Me), 1.00 (3H, s, 8′-Me$_{ax}$), 1.27 (3H, s, 8′-Me$_{eq}$), 1.55 (1H, t, $J_{3a,3b} = J_{3a,4}$ = 13.0 Hz, H3a), 1.76 (1H, dd, $J_{3b,3a}$ = 13.0, $J_{3b,4}$ = 7.0 Hz, H3b), 2.10 (3H, d, $J_{2'\text{-Me},3'}$ = 1.4 Hz, 2′-Me), 2.50 (1H, m, H4), 2.60 (s (broad), OH), 3.45 (3H, s, OMe), 3.95 (1H, d, $J_{5',3'}$ = 2.2 Hz, H5′), 4.76 (1H, s, OC*H*Ph(OMe)), 5.90 (1H, dq, $J_{3',5'}$ = 2.2, $J_{3',2'\text{-Me}}$ = 1.4 Hz, H3′), 6.36 (1H, d, $J_{5,4}$ = 4.8 Hz, H5), 7.35−7.48 (5H, m, ArH). ^{13}C NMR (75.5MHz) δ: 11.28 (q, 4-Me), 17.97 (q, 8′-Me$_{ax}$), 20.46 (q, 2′-Me), 21.68 (q, 8′-Me$_{eq}$), 36.35 (d, C-4), 38.21 (t, C-3), 51.86 (s, C-8′), 57.43 (s, OMe), 82.40 (d, −CO*C*HPh(OMe)), 84.53 (s, C-1′), 89.99 (d, C-5′), 100.35 (d, C-5), 116.02 (s, C-7′), 125.36 (d, C-3′), 127.33−129.02 (d, 4 × Ar), 136.13 (s, Ar), 165.14 (s, C-2′), 169.29 (s, O*C*OCHPh(OMe)), 194.36 (s, C-4′). IR (Nujol mull, KBr disks): 3488 (OH), 2933 (CH and ArH), 1756 (C=O, ester), 1683 (C=O, α,β-unsaturated ketone). UV (EtOH): λ_{max} 229 nm (log ϵ 3.4). MS: 251 (30, M − 165 (−OCOCHPh(OMe)), 152 (20), 121 (100), 99 (25), 77 (25), 43 (60).

Compound 6b. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.00 (3H, s, 8′-Me$_{ax}$), 1.10 (3H, d, $J_{4\text{-Me},4}$ = 7.2 Hz, 4-Me), 1.28 (3H, s, 8′-Me$_{eq}$), 1.50 (1H, d, $J_{3b,3a}$ = 13.0 Hz, H3b), 1.85 (1H, d, $J_{4,3a}$ = 7.5 Hz, H4), 1.97 (1H, dd $J_{3a,3b}$ = 13.0, $J_{3a,4}$ = 7.5 Hz, H3a), 2.00 (3H, d, $J_{2'\text{-Me},3'}$ = 1.6 Hz, 2′-Me), 2.62 (s (broad), OH), 3.42 (3H, s, OMe), 3.96 (1H, d, $J_{5',3'}$ = 2.2 Hz, H5′), 4.75 (1H, s, OCOC*H*Ph(OMe)), 5.87 (1H, dq, $J_{3',5'}$ = 2.2, $J_{3',2'\text{-Me}}$ = 1.6 Hz, H3′), 6.10 (1H, s, H5), 7.35−7.43 (5H, m, ArH). IR (Nujol mull, KBr disks): 3389 (OH), 2922 (CH), 2856 (ArCH), 1744 (C=O, ester), 1672 (C=O, α,β-unsaturated ketone). UV (EtOH): λ_{max} 217 nm (log ϵ 3.1).

Compound 6c. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.83 (3H, s, 8′-Me$_{ax}$), 0.89 (3H, s, 8′Me$_{eq}$), 1.10 (3H, d, $J_{4\text{-Me},4}$ = 6.9 Hz, 4-Me), 1.58 (1H, dd, $J_{3a,3b}$ = 12.9, $J_{3a,4}$ = 9.5 Hz, H3a), 2.01 (3H, d, $J_{2'\text{-Me},3'}$ = 1.5 Hz, 2′-Me), 2.09 (1H, dd, $J_{3b,3a}$ = 12.9, $J_{3b,4}$ = 7.1 Hz, H3b), 2.55 (1H, m, H4), 2.71 (1H, s (broad), OH), 3.43 (3H, s, O*Me*), 3.60 (1H, d, $J_{5',3'}$ = 2.2 Hz, H5′), 4.80 (1H, s, −C*H*Ph(OMe)), 5.85 (1H, dq, $J_{3',5'}$ = 2.2, $J_{3',2'\text{-Me}}$ = 1.5 Hz, H3′), 5.96 (1H, d, $J_{5,4}$ = 4.1 Hz, H5), 7.34−7.48 (5H, m, ArH). ^{13}C NMR (75.5 MHz) δ: 16.65 (q, 4-Me), 17.99 (q, 8′-Me$_{ax}$), 20.19 (q, 2′-Me), 21.52 (q, 8′-Me$_{eq}$), 36.87 (d, C-4), 40.62 (t, C-3), 51.84 (s, C-8′), 57.39 (s, O*Me*), 82.26 (d, OCO*C*HPh(OMe)), 85.00 (s, C-1′), 89.63 (d, C-5′), 103.82 (d, C-5), 114.67 (s, C-7′), 125.35 (d, C-3′), 127.39−128.74 (d, 4 × Ar), 135.10 (s, Ar), 164.52 (s, C-2′), 170.37 (s, −O*C*OCHPh(OMe)), 194.7 (s, C-4′). IR (Nujol mull, KBr disks): 3466 (OH), 2922 (CH), 1753 (CO ester), 1680 (α,β-unsaturated ketone). UV (EtOH): λ_{max} 214 nm (log ϵ 3.3).

Compound 7a. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.92 (3H, d, $J_{4\text{-Me},4}$ = 6.8 Hz, 4-Me), 0.94 (3H, s, 8′-Me$_{ax}$), 1.14 (3H, s, 8-Me$_{eq}$), 1.60 (1H, t, $J_{3a,3b} = J_{3a,4}$ = 12.6 Hz, H3a), 1.81 (1H, dd, $J_{3b,3a}$ = 12.6, $J_{3b,4}$ = 6.5 Hz, H3b), 2.01 (3H, d, $J_{2'\text{-Me},3'}$ = 1.6 Hz, 2′-Me), 2.57 (1H, m, H4), 3.44 (3H, s, OMe), 3.91 (1H, d, $J_{5'3'}$ = 2.1 Hz, H5′), 4.76 (1H, s, OCOC*H*Ph(OMe)), 5.87 (1H, dq, $J_{3',5'}$ = 2.1, $J_{3',2'\text{-Me}}$ = 1.6 Hz, H3′), 6.39 (1H, d, $J_{5,4}$ = 4.6 Hz, H5), 7.35−7.47 (5H, m, ArH). ^{13}C NMR (75.5 MHz) δ: 11.94 (q, 4-Me), 17.94 (q, 8′-Me$_{ax}$), 20.43 (q, 2′-Me), 21.56 (q, 8′-Me$_{eq}$), 36.03 (d, C-4), 38.27 (t, C-3), 51.80 (s, C-8′), 57.47 (s, OMe), 82.63 (d, OCO*C*HPh(OMe)), 84.29 (s, C-1′), 89.96 (d, C-5′), 100.15 (d, C-5), 115.87 (s, C-7′), 125.26 (d, C-3′), 127.09−129.07 (d, 4 × Ar), 136.01 (s, Ar), 165.50 (s, C-2′), 169.47 (s, O*C*OCHPh(OMe)), 194.60 (s, C-4′). IR (Nujol mull, KBr disks): 3625 (OH), 2934 (CH), 1750 (C=O, ester), 1680 (C=O, α,β-unsaturated ketone). UV (EtOH): λ_{max} 216 nm (log ϵ 3.4), 250 nm (log ϵ 3.5).

Compound 7b. (NMR data taken from mixture) ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.95 (3H, s, 8′-Me$_{ax}$), 1.15 (3H, d, $J_{4\text{-Me},4}$ = 6.8 Hz, 4-Me), 1.15 (3H, s, 8′-Me$_{eq}$), 1.65 (1H, d, $J_{3b,3a}$ = 12.5 Hz, H3b), 2.02 (3H, d, $J_{2'\text{-Me},3'}$ = 1.4 Hz, 2′-Me), 2.15 (1H, d, $J_{4,3a}$ = 7.5 Hz, H4), 2.16 (1H, dd, $J_{3a,3b}$ = 12.6, $J_{3a,4}$ = 7.5 Hz, H3a), 3.44 (3H, s, OMe), 3.92 (1H, d, $J_{5',3'}$ = 1.9 Hz, H5′), 5.23 (1H, s, OCOC*H*Ph(OMe)), 5.87 (1H, dq, $J_{3',5'}$ = 1.9, $J_{3',2'\text{-Me}}$ = 1.4 Hz, H3′), 6.14 (1H, s, H5), 7.35−7.47 (5H, m, ArH). ^{13}C NMR (75.5 MHz) δ: 16.66 (q, 4-Me), 18.00 (q, 8′-Me$_{ax}$), 20.51 (q, 2′-Me), 21.58 (q, 8′-Me$_{eq}$), 37.56 (t, C-3), 38.16 (d, C-4), 51.61 (s, C-8′), 57.52 (s, OMe), 82.70 (d, OCO*C*HPh(OMe)), 84.87 (s, C-1′), 90.10 (d, C-5′), 104.86 (d, C-5), 117.20 (s, C-7′), 125.23 (d, C-3′), 127.50−129.62 (d, 4 × Ar), 136.01 (s, Ar), 165.44 (s, C-2′), 169.50 (s, O*C*OCHPh(OMe)), 194.73 (s, C-4′).

Compound 7c. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.95 (3H, d, $J_{4\text{-Me},4}$ = 6.9 Hz, 4-Me), 0.98 (3H, s, 8′-Me$_{ax}$), 1.17 (3H, s, 8′-Me$_{eq}$), 1.61 (1H, dd, $J_{3a,3b}$ = 13.1, $J_{3a,4}$ = 8.9 Hz, H3a), 2.05 (3H, d, J = 1.5, 2′-Me), 2.09 (1H, dd, $J_{3b,3a}$ = 13.1, $J_{3b,4}$ = 7.5 Hz, H3b), 2.44 (1H, m, H4), 2.76 (s (broad), OH), 3.42 (3H, s, OMe), 3.92 (1H, d, $J_{5',3'}$ = 2.1 Hz, H5′), 4.83 (1H, s, OCOC*H*Ph(OMe)), 5.85 (1H, d, $J_{5,4}$ = 4.2 Hz, H5), 5.90 (1H, dq, $J_{3'5'}$ = 2.1, $J_{3',2'\text{-Me}}$ 1.5 Hz, H3′), 7.32−7.48 (5H, m, ArH). ^{13}C NMR (75.5 MHz) δ: 16.14 (q, 4-Me), 18.09 (q, 8′-Me$_{ax}$), 20.25 (q, 2′-Me), 21.72 (q, 8′-Me$_{eq}$), 36.86 (d, C-4), 40.37 (t, C-3), 51.99 (s, C-8′), 57.38 (s, OMe), 82.48 (d, OCO*C*HPh(OMe)), 84.88 (s, C-1′), 89.90 (d, C-5′), 104.08 (d, C-5), 114.91 (s, C-7′), 125.40 (d, C-3′), 127.33−128.88 (d, 4 × Ar), 135.88 (s, Ar), 164.67 (s, C-2′), 170.45 (s, O*C*OCHPh(OMe)), 194.64 (s, C-4′). IR (Nujol mull, KBr disks): 3464 (OH), 2932 (CH), 2855 (ArH), 1744 (C=O, ester), 1680 (C=O, α,β-unsaturated ketone). UV (EtOH): λ_{max} 198 (log ϵ 6.0), 240 nm (log ϵ 3.4).

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