Identification of Absolute Configuration of Tertiary Alcohols by Combination of Mosher's Method and Conformational Analysis

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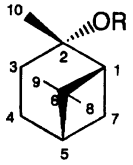
Synopsis. Mosher's method for identification of the absolute configurations of secondary alcohols could be extended to that of tertiary alcohols, such as (1*S*,2*S*,5*R*)- and (1*S*,2*R*,5*R*)-pinan-2-ol, on the basis of its conformational analysis.

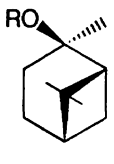
There have been many investigations for the identification of absolute configuration and optical purity of secondary alcohols by Mosher's method.[1—9] However, such an attempt to identify the chiral center of tertiary alcohols has never been reported, because it is difficult to predict the α-methoxy-α-(trifuluoromethyl)-phenylacetyl (MTPA) plane[7—9] in the MTPA ester of tertiary alcohols. We here wish to report a convenient method for identifying the absolute configuration and optical purity of tertiary alcohols by a combination of Mosher's method and conformational analysis.

First, preferred conformations of (*S*)- and (*R*)-MTPA esters of (1*S*,2*S*,5*R*)-pinan-2-ol (**1**) were estimated by the MM2 calculation.[10,11] Due to the absence of torsional parameters for the C(O)CCF, the MM2 calculation was done for the corresponding acetates instead of the MTPA esters. Assuming that the conformation of the pinanyl group was not changed by the substitution of an MTPA group for the acetyl group, the preferred conformations of (*S*)- and (*R*)-MTPA esters (**2** and **3**) of **1** can be estimated[12] as is shown in Fig. 1 (Chart 1).

The preferred conformations of the (*S*)- and (*R*)-MTPA esters (**2** and **3**) were confirmed by measurement of the nuclear Overhauser effect (NOE) in the ^{1}H NMR spectra of the MTPA esters. As shown in Fig. 2 (b), irradiation at the C-10 methyl signal of (*R*)-MTPA ester (**3**) elicited NOE enhancement of the signal for methoxyl proton with significant magnitude, but for the (*S*)-MTPA ester (**2**), no NOE enhancement was observed between the methoxyl proton and the methyl groups of the pinanol moiety (Fig. 2 (a)). These observations supported the preferred conformations, **2** and **3**, in Fig. 1, which were estimated by the MM2 method.



1: R=H
2: R=(*S*)-MTPA
3: R=(*R*)-MTPA



4: R=H
5: R=(*S*)-MTPA
6: R=(*R*)-MTPA

Chart 1.

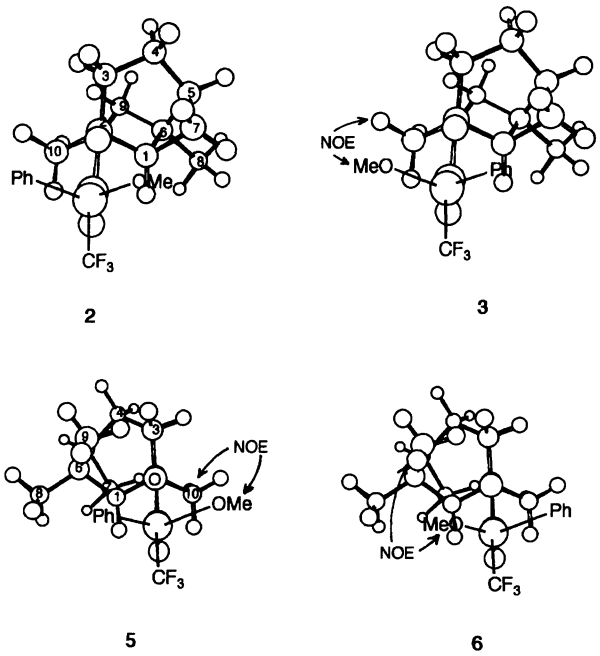


Fig. 1. Perspective views for the predicted conformers of the MTPA esters, **2**, **3**, **5**, and **6**, of pinan-2-ols.

When considering the anisotropic effect of the phenyl group in the preferred conformers (**2** and **3**), it is expected that the C-10 methyl signal in the ^{1}H NMR spectrum of (*S*)-MTPA ester (**2**) will shift to the high field. Therefore, the $\Delta\delta$ value [$\delta_{(S\text{-MTPA ester})} - \delta_{(R\text{-MTPA ester})}$] is estimated to be negative for the C-10 methyl group, as shown in Table 1.

Experimental values for the methyl groups of (*S*)- and (*R*)-MTPA esters (**2** and **3**) of (1*S*,2*S*,5*R*)-pinan-2-ol are shown in Table 1. The $\Delta\delta$ value for the C-10 methyl group was negative (−0.081), but the $\Delta\delta$ values for the C-8 and C-9 methyl groups were nearly zero. This observation agrees with the above expectations on the basis of the conformational analysis.

A similar examination was done in the MTPA esters

Table 1. ^{1}H NMR Chemical Shift of (*S*)- and (*R*)-MTPA Esters (**2** and **3**) of (1*S*,2*S*,5*R*)-Pinan-2-ol (**1**)

Methyl group	Observed chemical shift			Predicted $\Delta\delta$
	(*S*)-MTPA	(*R*)-MTPA	$\Delta\delta$	
C-8	0.927	0.929	−0.002	±
C-9	0.880	0.881	−0.001	±
C-10	0.806	0.887	−0.081	−

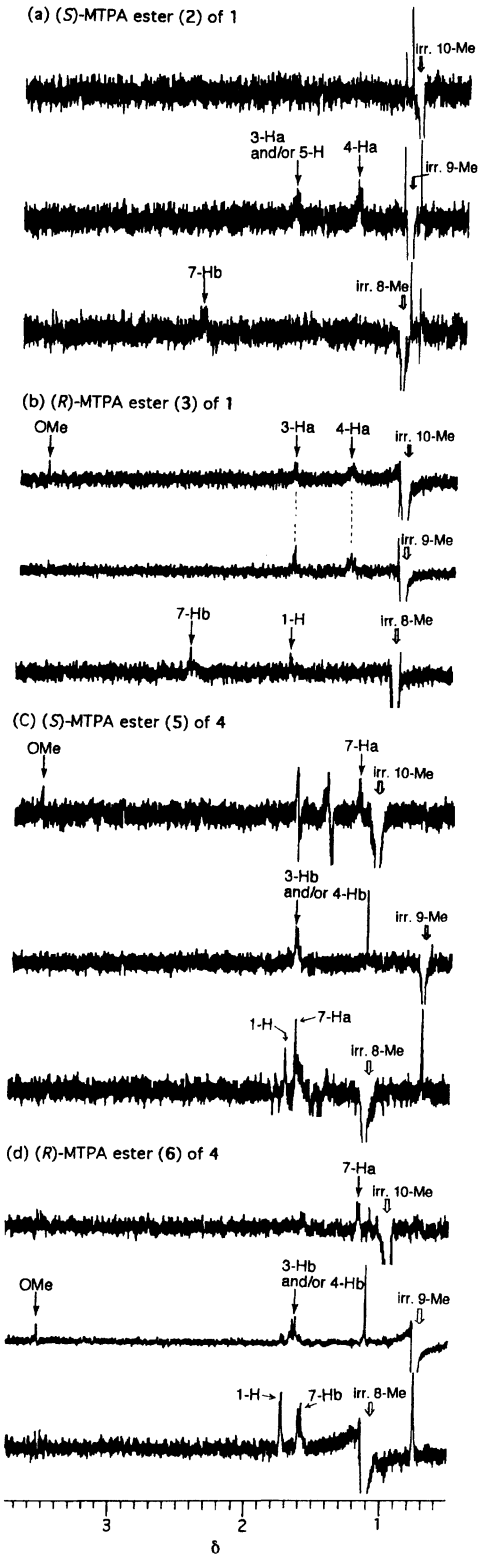


Fig. 2. Differential NOE spectra of (*S*)- and (*R*)-MTPA esters (**2**, **3**, **5**, and **6**) of (1*S*,2*S*,5*R*)- and (1*S*,2*R*,5*R*)-pinan-2-ol (**1** and **4**).

of (1*S*,2*R*,5*R*)-pinan-2-ol (**4**). The preferred conformations of (*S*)- and (*R*)-MTPA esters (**5** and **6**) were estimated by MM2 calculations, as shown in Fig. 1. The preferred conformations were confirmed by the NOE measurement; the NOE enhancements in the methoxyl protons were observed by irradiation of the C-10 methyl group of **5** and the C-9 methyl group of **6** (Fig. 2 (c) and (d)). On the basis of the preferred conformers, the phase of $\Delta\delta$ value of the methyl protons of the (*S*)- and (*R*)-MTPA esters (**5** and **6**) was predicted; the $\Delta\delta$ values of the C-9 and C-10 methyl groups of (1*S*,2*R*,5*R*)-pinan-2-ol are estimated to negative for the C-9 methyl group and positive for the C-10 methyl group. Measurement of ^{1}H NMR spectra shows that the $\Delta\delta$ values of the C-9 and C-10 methyl groups were also in accord with the expectation as shown in Table 2.

Thus, it was demonstrated that Mosher's method can be extended to the estimation of the absolute configuration of tertiary alcohols, if Mosher's method is combined with conformational analysis.

Experimental

Melting points were measured on a Yanagimoto micro melting-point apparatus and are uncorrected. ^{1}H NMR spectra (270 and 500 MHz) were observed with a JEOL GSX-270 and GSX-500 spectrometers using tetramethylsilane as an internal standard in $CDCl_3$. Differential NOE were obtained with 4 s preirradiation and the results are shown in Fig. 2. The estimation of preferred conformations was done with the calculation on the two molecular mechanics programs, MM2(77)[11] and Chem3D Plus.[13]

Materials. (1*S*,2*S*,5*R*)-Pinan-2-ol (**1**) [mp 77—78 °C; (lit,[14] 77—78 °C), $[\alpha]_D^{25}$ −28.3 (*c* 2.00, EtOH); (lit,[14] $[\alpha]_D^{20}$ −29.7 (*c* 2.15, $CHCl_3$))] was prepared from (1*S*,5*R*)-β-pinene via its oxide by the methods similar to those in the literatures.[14,15] (1*S*,2*R*,5*R*)-Pinan-2-ol (**4**) [mp 58—59 °C; (lit,[14] 58—59 °C), $[\alpha]_D^{25}$ −8.3 (*c* 0.80, EtOH); (lit,[14] $[\alpha]_D^{20}$ −8.8 (*c* 2.0, $CHCl_3$))] was prepared from (1*S*,5*R*)-nopinone[15] by the Grignard reaction. The MTPA esters were prepared from the corresponding alcohols by the usual method.[3]

(*S*)-MTPA Ester (2) of 1: IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.806 (3H, s, 10-Me), 0.880 (3H, s, 9-Me), 0.927 (3H, s, 8-Me), 1.105 (1H, dd, $J_{7a,7b}$=13 Hz, $J_{7a,5}$=4 Hz, 7-Ha), 1.211 (1H, ddt, $J_{4a,4b}$=12 Hz, $J_{4a,3a}$=10 Hz, $J_{4a,3b}=J_{4a,5}$=2 Hz, 4-Ha), 1.25—1.39 (2H, m, 3-Hb and 4-Hb), 1.736 (1H, d, $J_{1,7b}$=4 Hz, 1-H), 1.76—1.83 (2H, m, 3-Ha and 5-H), 2.459 (1H, dt, $J_{7b,7a}$=13 Hz, $J=_{7b,5}=J_{7b,1}$=4 Hz, 7-Hb), 3.564 (3H, s, O–Me), 7.41—7.47 (3H, m), and 7.54—7.56 (2H, m).

(*R*)-MTPA Ester (3) of 1: IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.881 (3H, s, 9-Me), 0.887 (3H, s, 10-

Table 2. ^{1}H NMR Chemical Shift of (*S*)- and (*R*)-MTPA Esters (**5** and **6**) of (1*S*,2*R*,5*R*)-Pinan-2-ol (**4**)

Methyl group	Observed chemical shift			Predicted $\Delta\delta$
	(*S*)-MTPA	(*R*)-MTPA	$\Delta\delta$	
C-8	1.147	1.145	+0.002	±
C-9	0.722	0.786	−0.064	−
C-10	1.077	0.982	+0.095	+

Me), 0.929 (3H, s, 8-Me), 1.003 (1H, dd, $J_{7a,7b}=14$ Hz, $J_{7a,5}=4$ Hz, 7-Ha), 1.119 (1H, ddd, $J_{4a,4b}=12$ Hz, $J_{4a,3a}=10$ Hz, $J_{4a,5}=2$ Hz, 4-Ha), 1.26—1.31 (2H, m, 3-Hb and 4-Hb), 1.708 (1H, d, $J_{1,7b}=5$ Hz, 1-H), 1.72—1.76 (1H, m, 5-H), 1.816 (1H, ddd, $J_{3a,3b}=13$ Hz, $J_{3a,4a}=10$ Hz, $J_{3a,3b}=3$ Hz, 3-Ha), 2.453 (1H, dt, $J_{7b,7a}=13$ Hz, $J_{7b,1}=J_{7b,5}=5$ Hz, 7-Hb), 3.553 (3H, s, O–Me), 7.40—7.46 (3H, m), and 7.52—7.53 (2H, m).

(*S*)-MTPA Ester (5) of 4: IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.722 (3H, s, 9-Me), 1.077 (3H, s, 10-Me), 1.085 (1H, tt, $J_{4a,4b}=J_{4a,3a}=11$ Hz, $J_{4a,3b}=J_{4a,5}=2$ Hz, 4-Ha), 1.147 (3H, s, 8-Me), 1.217 (1H, dd, $J_{7a,7b}=10$ Hz, $J_{7a,5}=1$ Hz, 7-Ha), 1.451 (1H, tt, $J_{5,4b}=J_{5,7b}=6$ Hz, $J_{5,4b}=J_{5,7a}=2$ Hz, 5-H), 1.620 (1H, dt, $J_{7b,7a}=10$ Hz, $J_{7b,1}=J_{7b,5}=6$ Hz, 7-Hb), 1.63—1.69 (3H, m, 3-Ha, 3-Hb, and 4-Hb), 1.737 (1H, bd, $J_{1,7b}=6$ Hz, 1-H), 3.564 (3H, s, O–Me), 7.37—7.40 (3H, m), and 7.55—7.56 (2H, m).

(*R*)-MTPA Ester (6) of 4: IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.786 (3H, s, 9-Me), 0.982 (3H, s, 10-Me), 1.077 (1H, tt, $J_{4a,4b}=J_{4a,3a}=11$ Hz, $J_{4a,3b}=J_{4a,5}=2$ Hz, 4-Ha), 1.145 (3H, s, 8-Me), 1.220 (1H, dd, $J_{7a,7b}=11$ Hz, $J_{7a,5}=1$ Hz, 7-Ha), 1.458 (1H, tt, $J_{5,4b}=J_{5,7b}=6$ Hz, $J_{5,4a}=J_{5,7a}=1$ Hz, 5-H), 1.624 (1H, dt, $J_{7b,7a}=11$ Hz, $J_{7b,1}=J_{7b,5}=6$ Hz, 7-Hb), 1.63—1.69 (3H, m), 1.761 (1H, bd, $J_{1,7b}=6$ Hz, 1-H), 3.542 (3H, s, O–Me), 7.40—7.45 (3H, m), and 7.54—7.56 (2H, m).

The measurement of ^1H NMR spectra and the use of Chem3D Plus program were done at Instrument Center for Chemical Analysis, Hiroshima University.

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