Determination of Absolute Configurations of Tertiary Alcohols by NMR Spectroscopy

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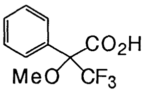
(Received July 28, 1999; CL-990660)

A method has been developed for determining the absolute configurations of acyclic tertiary alcohols using their 2NMA [methoxy-(2-naphthyl)acetic acid] esters. The ^{1}H NMR spectra of (*R*)- and (*S*)-2NMA esters of model compounds were measured, and $\Delta\delta$ values ($\delta_{R\text{-ester}} - \delta_{S\text{-ester}}$) were calculated. The absolute configuration for tertiary hydroxy group is determined based on the sign of $\Delta\delta$ values like that for secondary hydroxy group.

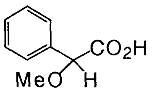
The absolute configurations of chiral secondary alcohols are easily determined by the modified Mosher's method using methoxytrifluoromethylphenylacetic acid (MTPA).[1] It has been reported that 2NMA [methoxy-(2-naphthyl)acetic acid] is a useful NMR reagent for determining the absolute configuration of the chiral center bearing a secondary hydroxy group especially in the case of long C-C chain compounds, owing to the greater anisotropic effect of the 2-naphthyl group compared to the benzene ring of MTPA.[2] The method using 2NMA has been applied to the determination of absolute stereochemistry of β- or γ-substituted secondary alcohols.[3] In the case of tertiary alcohols, however, the method has been very limited to establish their absolute configurations.[4] This paper describes the method for determination of absolute configurations of chiral tertiary alcohols by using 2NMA.

Model alcohols **1-OH~11-OH** were prepared from geraniol as enantiomeric pure compounds[5] by sequential reactions involving Sharpless asymmetric epoxidation. The absolute configurations of the synthetic compounds were confirmed by the datum of optical rotation for the common synthetic intermediate, (*R*)-3,7-dimethyl-6-octene-1,3-diol[6]; $[\alpha]_D^{22}$ -2.6° (*c* 1.75, CHCl$_3$). Compound **1-OH** [(*R*)-1-acetoxy-3,7-dimethyl-6-octen-3-ol] was esterified with MTPA, MPA (methoxyphenylacetic acid) and 2NMA, respectively, using DCC and DMAP in CH$_2$Cl$_2$ in order to select a suitable chiral anisotropic reagent (Figure 1). Corresponding esters were obtained in 12%, 35% and 27% yield, respectively. Unexpectedly, MPA and 2NMA were racemized during esterification, so each ester was obtained as a 1:1 mixture of diastereomers. These diastereomers were fortunately separable by recycling HPLC (MPA ester; 10 times, 2NMA ester; 9 times). The absolute configuration of each diastereomer was distinguishable by the sign of $[\alpha]_D$ value: (*R*)-MPA and (*R*)-2NMA esters showed negative signs, while (*S*)-isomers positive signs. Moreover, these absolute configurations were confirmed by CD spectroscopy.[7]

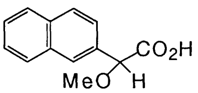
The ^{1}H NMR spectrum of each ester is measured. The $\Delta\delta$ values obtained for these esters of MTPA, MPA and 2NMA are shown in Figure 1 ($\Delta\delta$: MTPA; $\delta_{S\text{-ester}} - \delta_{R\text{-ester}}$, MPA and 2NMA; $\delta_{R\text{-ester}} - \delta_{S\text{-ester}}$). Positive and negative $\Delta\delta$ values are systematically arranged except for β-methylene protons adjacent to the tertiary hydroxy group. Because $|\Delta\delta|$ values of the 2NMA ester are the largest, 2NMA was chosen for further examination.



MTPA



MPA



2NMA

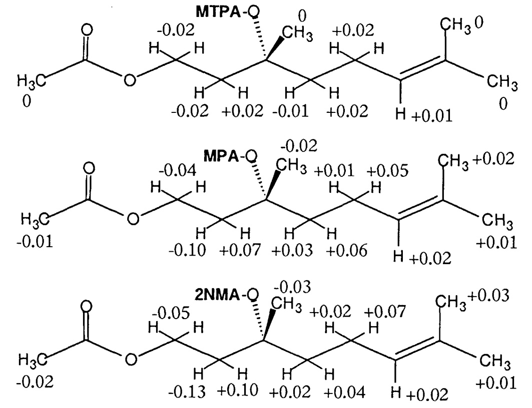


Figure 1. $\Delta\delta$ Values (ppm) of MTPA, MPA and 2NMA esters of **1-OH**.

Model alcohols **2-OH~11-OH** were esterified with racemic 2NMA to give 2NMA esters **2~11**, and then these diastereomers were separated by recycling HPLC. The absolute configurations of the 2NMA moiety were elucidated by the sign of $[\alpha]_D$ value and CD data in the similar manner for the 2NMA ester of **1-OH**. The ^{1}H NMR spectra of (*R*)- and (*S*)-2NMA esters were measured and $\Delta\delta$ values ($\delta_{R\text{-ester}} - \delta_{S\text{-ester}}$) of the corresponding

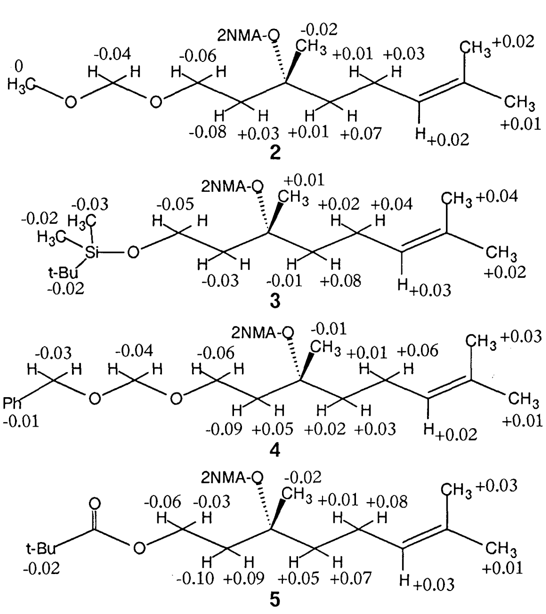


Figure 2. $\Delta\delta$ Values (ppm) of 2NMA esters of **2-OH~5-OH**.

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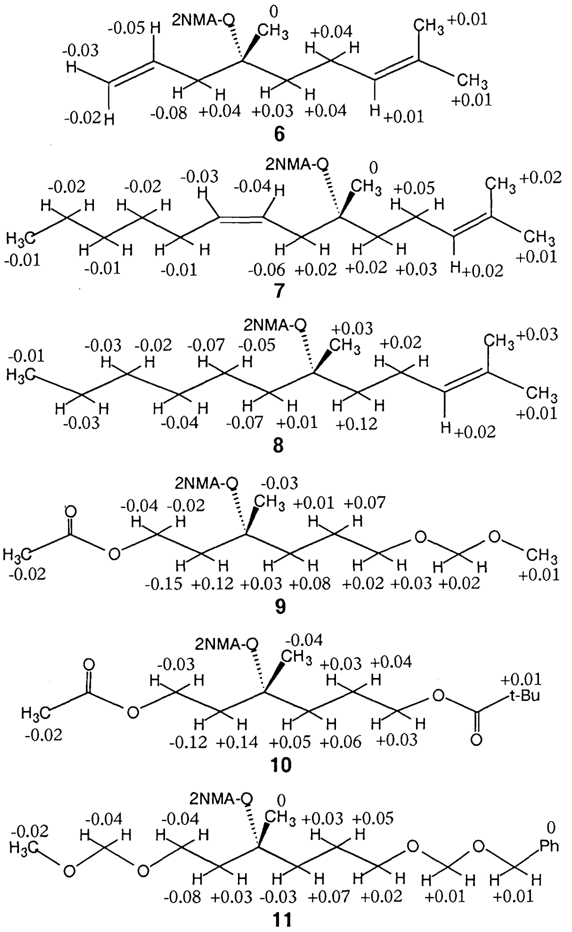

Figure 3. Δδ Values (ppm) of 2NMA esters of **6-OH~11-OH**.

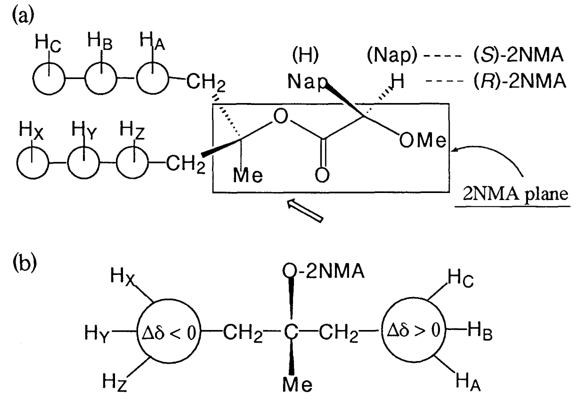

Figure 4. (a) The 2NMA plane of a 2NMA ester is shown. $H_{A, B, C}$ and $H_{X, Y, Z}$ are on the right and left sides of the plane, respectively. (b) A model to determine the absolute configurations of tertiary alcohols is illustrated. This model is a view of the 2NMA ester drawn in (a) from the direction indicated by the outlined arrow.

protons were calculated as summarized in Figures 2 and 3.

In all cases, positive and negative Δδ values are systematically arranged except for the β-methylene protons adjacent to the tertiary hydroxy group. The |Δδ| values of the methyl protons at α-position to the tertiary hydroxy group are smaller than that of each methylene protons at β-positions and are also smaller than those for secondary alcohols (about one fifth).[2] These results indicate that the conformation illustrated in Figure 4a (the methyl group, carbonyloxygen and methoxy group are on the same plane like 2NMA ester of secondary alcohols) is the major component, although other conformations may exist.

In conclusion, the absolute configurations of acyclic α-methyl substituted tertiary alcohols could be determined by NMR spectroscopy based on the method using 2NMA. When Δδ values are calculated by subtracting the proton chemical shifts of (*S*)-2NMA ester from those of (*R*)-2NMA ester in the case of the tertiary alcohol having the absolute configuration as shown in Figure 4b, the protons having positive Δδ values are placed at the right side of 2NMA plane and those having negative Δδ values are placed at the left side of 2NMA plane except for the β-protons.

The authors are grateful to Prof. Takenori Kusumi, Tokushima University, for valuable discussions and encouragement.

References and Notes

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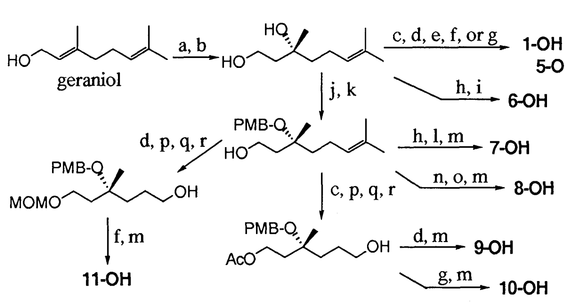
5 Model alcohols **1-OH~11-OH** were prepared from geraniol by the following sequence of reactions.



Reagents and conditions: a) *t*BuOOH, (-)-DIPT, Ti(*i*PrO)$_4$, 4A MS, CH_2Cl_2; b) Red-Al, toluene; c) Ac_2O, pyridine; d) MOMCl, *i*Pr_2-NEt, CH_2ClCH_2Cl; e) TBSCl, DMAP, CH_2Cl_2; f) BOMCl, *i*Pr_2-NEt, CH_2ClCH_2Cl; g) Piv.Cl, DMAP, CH_2Cl_2, pyridine; h) SO_3-Py, NEt_3, DMSO; i) $(Ph_3PCH_3)^+I^-$, BuLi, THF; j) *p*-anisaldehyde dimethyl acetal, cat. TsOH, THF; k) DIBAL, CH_2Cl_2; l) $(Ph_3PC_6H_{11})^+Br^-$, BuLi, THF; m) DDQ, CH_2Cl_2/H_2O (19:1); n) TsCl, pyridine; o) Bu_2CuLi, ether; p) *m*CPBA, Na_2HPO_4, $CHCl_3$; q) H_5IO_6, *t*BuOH, H_2O; r) $NaBH_4$, MeOH.

6 G. Ohloff, W. Giersch, K. H. Schulte-Elte, P. Enggist, and E. Demole, *Helv. Chim. Acta*, **63**, 1582 (1980). In this report (*R*)-3,7-dimethyl-6-octene-1,3-diol was synthesized from (-)-(*R*)-linalool.

7 (*R*)-MPA ester of **1-OH**: $[\alpha]_D^{22}$ -37.7° (*c* 0.48, $CHCl_3$); CD (MeOH) λ_{ext} 228 nm (Δε -8.06). (*S*)-MPA ester of **1-OH**: $[\alpha]_D^{22}$ +32.8° (*c* 0.54, $CHCl_3$); CD (MeOH) λ_{ext} 228 nm (Δε +6.47). (*R*)-2NMA ester of **1-OH**: $[\alpha]_D^{22}$ -36.0° (*c* 0.16, $CHCl_3$); CD (MeOH) λ_{ext} 243 nm (Δε -3.30). (*S*)-2NMA ester of **1-OH**: $[\alpha]_D^{22}$ +35.8° (*c* 0.13, $CHCl_3$); CD (MeOH) λ_{ext} 243 nm (Δε +4.02).