Determination of Absolute Configurations of β– or γ–Methyl Substituted Secondary Alcohols by NMR Spectroscopy

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Abstract

A new method has been developed for determining the absolute configurations of acyclic β– or γ–methyl substituted secondary alcohols using their 2NMA esters. The ^{1}H-NMR spectra of (R)- and (S)-2NMA esters of model compounds were measured, and Δδ values ($\delta_{R\text{-ester}} - \delta_{S\text{-ester}}$) for the corresponding protons were compared between *syn* and *anti* compounds. Threshold values important for judging the relative stereochemistry of the two chiral centers bearing methyl and hydroxy groups were obtained. The absolute configuration of the chiral center bearing a secondary hydroxy group is easily determined based on the sign of Δδ values as in the MTPA method and thus in the present study it was also possible to clearly determine the absolute configuration of the chiral center bearing a methyl group. © 1998 Elsevier Science Ltd. All rights reserved.

*Keywords*: alcohol; configuration; NMR; stereochemistry

The absolute configuration of secondary alcohols is 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 benzene ring of MTPA.[2] However, there has been no good method to establish the stereochemistry of a secondary methyl group present in an aliphatic chain.[3] This paper describes that the absolute configurations of the secondary methyl groups in β– or γ–methyl substituted secondary alcohols could be determined by NMR spectroscopy based on the method using 2NMA.
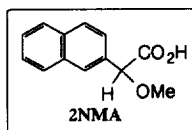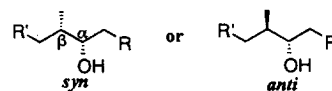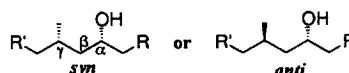
Compounds 1s~5s (*syn*) and 1a~5a (*anti*), model (*R*)- and (*S*)-2NMA esters derived from acyclic β–methyl substituted secondary alcohols, were prepared.[4] The ^{1}H-NMR spectra of (*R*)- and (*S*)-2NMA esters were measured and the Δδ values ($\delta_{R\text{-ester}} - \delta_{S\text{-ester}}$) of the corresponding protons were calculated for both *syn* and *anti* isomers as summarized in Figure 1.[5] Absolute values (|Δδ|) of the Δδ values at γ– and δ–methylene in *syn* isomers are clearly different from those in *anti* isomers as shown in Figure 2: |Δδ| of each proton at γ– and δ–methylene for *syn* isomers exceeds those for *anti* isomers. Threshold values of |Δδ|, which enable *syn* and *anti* isomers to be distinguished, have been established as 0.35 ppm for the γ–position and 0.25 ppm for the δ–position. If these |Δδ| of γ– and δ–protons in β–methyl substituted secondary alcohols are found to be larger than the corresponding threshold values, the relative stereochemistry of the two chiral centers (bearing methyl and hydroxy groups, respectively) can be assigned as *syn*. On the contrary, if |Δδ| is smaller than the threshold values, the relative stereochemistry is *anti*.
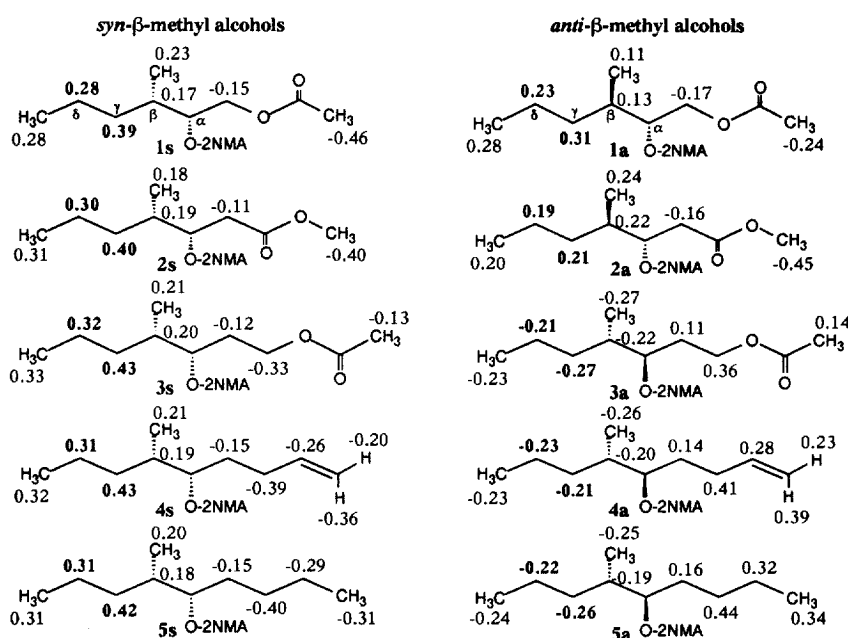

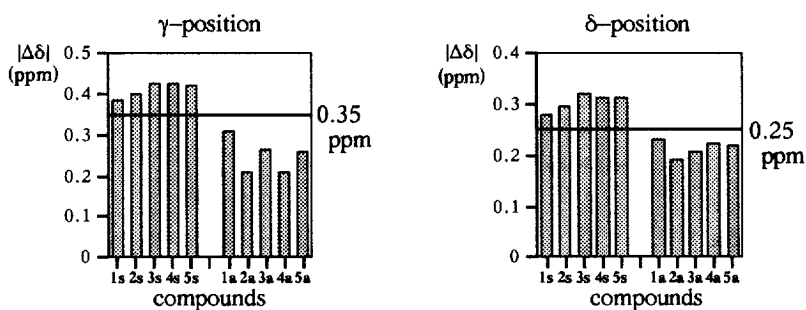**Figure 1.** Δδ Values (ppm) of *syn* and *anti* isomers (1s~5s and 1a~5a)

Figure 2. |Δδ| Values of γ– and δ–protons

Model acyclic γ–methyl substituted secondary alcohols, **6s~10s** (*syn*) and **6a~10a** (*anti*), were prepared,[6] and then esterified with (*R*)- and (*S*)-2NMA. Figures 3 and 4 show
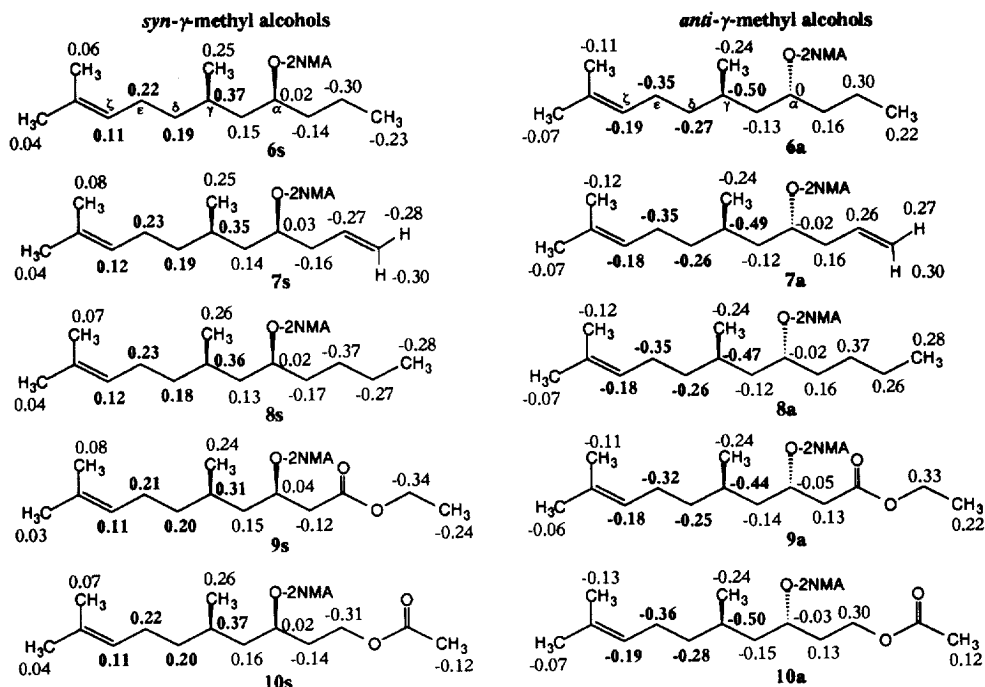

Figure 3. Δδ Values (ppm) of *syn* and *anti* isomers (**6s~10s** and **6a~10a**)

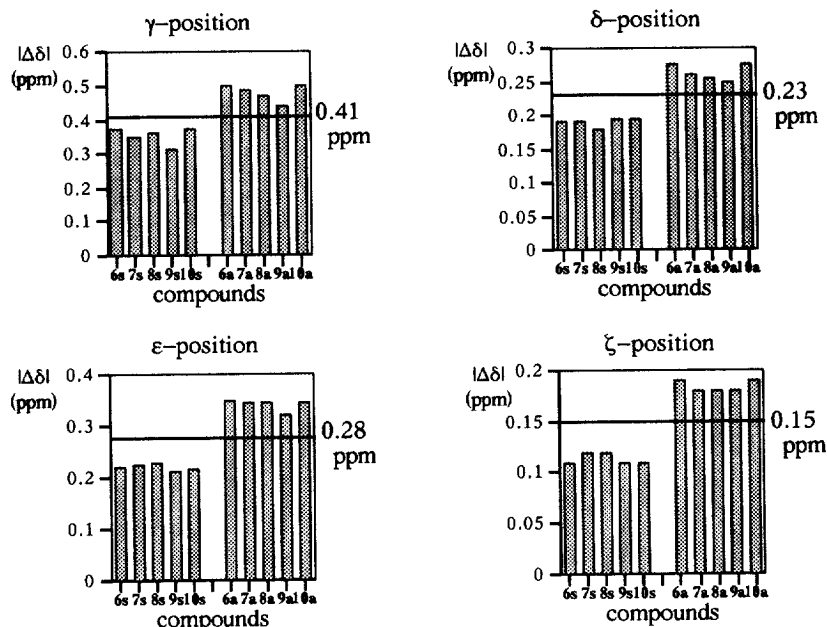**Figure 4.** |Δδ| Values of γ–, δ–, ε– and ζ–positions

$\Delta\delta$ values and $|\Delta\delta|$ of each proton at γ–, δ–, ϵ– and ζ–positions. Threshold values of $|\Delta\delta|$ that can discriminate between *syn* and *anti* have been established as 0.41, 0.23, 0.28 and 0.15 ppm for γ–, δ–, ϵ– and ζ–positions, respectively. In the case of γ–methyl substituted secondary alcohols, when these $|\Delta\delta|$ of protons at γ–, δ–, ϵ– and ζ–positions is larger than the corresponding threshold values, the relative stereochemistry can be determined as *anti*. Smaller $|\Delta\delta|$ than the threshold values shows *syn* stereochemistry.

The absolute configuration of the hydroxy group of β– or γ–methyl substituted secondary alcohols can easily be determined based on the sign of each $\Delta\delta$ value (Figures 1 and 3).[1] Since the relative stereochemistry for two chiral centers bearing hydroxyl and methyl can be determined as described above, the absolute configuration of the methyl group in β– or γ–methyl substituted secondary alcohols can also be established.

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References and Notes

[1] Ohtani I, Kusumi T, Kashman Y, Kakisawa H. *J. Am. Chem. Soc.*, 1991, *113*, 4092-4096.

[2] a) Kusumi T, Takahashi H, Xu P, Fukushima T, Asakawa Y, Hashimoto T, Kan Y, Inouye Y. *Tetrahedron Lett.*, 1994, *35*, 4397-4400. b) Kusumi T, Takahashi H, Hashimoto T, Kan Y, Asakawa Y. *Chem. Lett.*, 1994, 1093-1094.

[3] Recently, an enantiomeric separation of carboxylic acids having a secondary methyl group in their aliphatic chain has been reported; Akasaka K, Meguro H, Ohrui H. *Tetrahedron Lett.*, 1997, *39*, 6853-6856.

[4] *Syn* series of secondary alcohols 1s-OH~4s-OH were prepared from (Z)-2-hexen-1-ol by the following sequence of reactions. Alcohol 5s-OH was prepared by using propylmagnesium bromide in the reaction of i. *Anti* series of secondary alcohols 1a-OH~5a-OH were similarly prepared from (E)-2-hexen-1-ol.
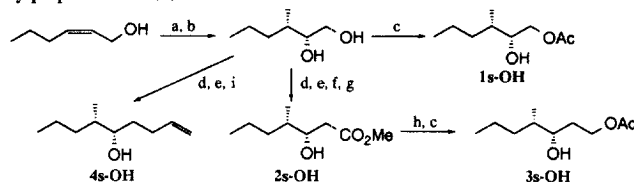
Reagents: a; *t*BuOOH, (+)-DIPT, Ti(*i*PrO)$_4$, CH$_2$Cl$_2$. b; Me$_3$Al, BuLi, pentane. c; Ac$_2$O, pyridine, 0 °C. d; *p*TsCl, DMAP, pyridine. e; NaOMe, MeOH. f; NaCN, 40% EtOH aq, heat. g; CH$_2$N$_2$. h; LAH. i; CH$_2$=CHCH$_2$MgBr, CuI·Bu$_3$P, ether.

[5] $\Delta\delta$ Values of methylene protons were averaged.

[6] γ-Methyl substituted secondary alcohols 6s-OH, 6a-OH, 8s-OH~10s-OH and 8a-OH~10a-OH were prepared from (R)-citronellal by following reactions as a diastereomeric mixture. Alcohols 7s-OH and 7a-OH were prepared using allylmagnesium bromide in the reaction of a. After esterification of a diastereomeric alcohol mixture with (R)- and (S)-2NMA, a diastereomeric ester mixture was subjected to HPLC separation to give each diastereomer as a pure form.
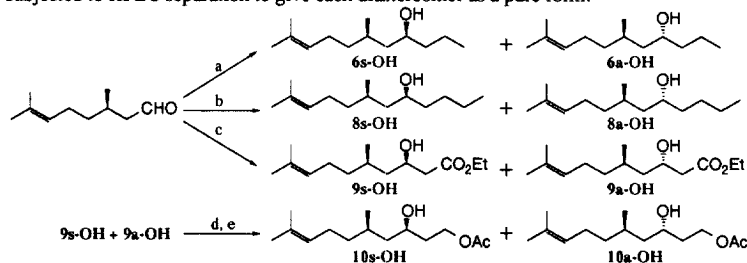
Reagents: a; CH$_3$CH$_2$CH$_2$MgBr, ether. b; BuLi, ether. c; BrCH$_2$CO$_2$Et, Zn, THF. d; LAH. e; AcCl, collidine, CH$_2$Cl$_2$, -78 °C.