

TETRAHEDRON LETTERS

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 ¹H-NMR spectra of (*R*)- and (*S*)-2NMA esters of model compounds were measured, and $\Delta\delta$ values ($\delta_{R-ester} - \delta_{S-ester}$) 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 $\Delta\delta$ 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.

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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.





γ-methyl substituted secondary alcohol



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 ¹H-NMR spectra of (R)- and (S)-2NMA esters were measured and the $\Delta\delta$ values ($\delta_{R-ester} - \delta_{S-ester}$) of the corresponding protons were calculated for both syn and anti isomers as summarized in Figure 1.⁵ Absolute values ($|\Delta\delta|$) of the $\Delta\delta$ values at γ - and δ -methylene in syn isomers are clearly different from those in anti isomers as shown in Figure 2: $|\Delta\delta|$ of each proton at γ - and δ methylene for syn isomers exceeds those for anti isomers. Threshold values of $|\Delta\delta|$, 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 $|\Delta\delta|$ 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 $|\Delta\delta|$ is smaller than the threshold values, the relative stereochemistry is anti.



Figure 1. $\Delta\delta$ Values (ppm) of syn and anti isomers (1s~5s and 1a~5a)



Figure 2. $|\Delta \delta|$ Values of γ - and δ -protons





Figure 4. $|\Delta\delta|$ Values of γ -, δ -, ϵ - and ζ -positions

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

 $\Delta\delta$ 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; tBuOOH, (+)-DIPT, Ti(tPrO)₄, CH₂Cl₂. b; Me₃Al, BuLi, pentane. c; Ac₂O, pyridine, 0 °C. d; pTsCl, DMAP, pyridine. e; NaOMe, MeOH. f; NaCN, 40% EtOH aq, heat. g; CH₂N₂. h; LAH. i; CH₂=CHCH₂MgBr, Cul·Bu₃P, 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; CH₃CH₂CH₂MgBr, ether. b; BuLi, ether. c; BrCH₂CO₂Et, Zn, THF. d; LAH. e; AcCl, collidine, CH₂Cl₂, -78 °C.