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Determination of the absolute configuration of linear secondary alcohols adopting one enantiomer of the chiral anisotropic reagents, methoxy-(1- and 2-naphthyl)acetic acids

Hiroshi Yamase, Takashi Ooi, and Takenori Kusumi*

Faculty of Pharmaceutical Sciences

Tokushima University

Tokushima 770-8505, Japan

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Abstract

The absolute configurations of the aliphatic secondary alcohols can be determined by NMR spectroscopy using only one enantiomer of the chiral anisotropic reagents, 1NMA and 2NMA.

Keywords: Alcohols; Configuration; NMR; Stereochemistry

The modified Mosher's method [1] is now worldwidely used for determination of the absolute configuration of secondary alcohols. In the Mosher's and analogous methods, both (*R*)- and (*S*)-esters are necessary to obtain $\Delta\delta$ values. Recently, as a unique countermeasure for this intricacy, Riguera, et al, has proposed the use of a single methoxyphenylacetic ester derivative, the ^{1}H-NMR spectrum of which was recorded at two different temperatures [2].

We have reported that the chiral anisotropic reagents, 1- and 2-naphthylmethoxyacetic acids (1NMA and 2NMA), show anisotropic effect larger than MTPA [3, 4]. This extremely large anisotropy of 1NMA and 2NMA led us to the idea that a single enantiomer of these reagents would be enough for determining the absolute configuration of secondary alcohols. We at first considered that the absolute configuration could be determined by subtracting chemical shifts of the NMA ester from those of the original alcohol ($\Delta\delta_{OH\text{-}NMA} = \delta_{OH} - \delta_{NMA}$). The $\Delta\delta_{OH\text{-}NMA}$ values obtained[1] for 1NMA and 2NMA esters of (*R*)-2-octanol are shown in Figure 1.

[1] All the NMR spectra (400 MHz) were recorded in $CDCl_3$ at 30 °C. Concentration of the sample was set at 0.1-0.2 *M*.

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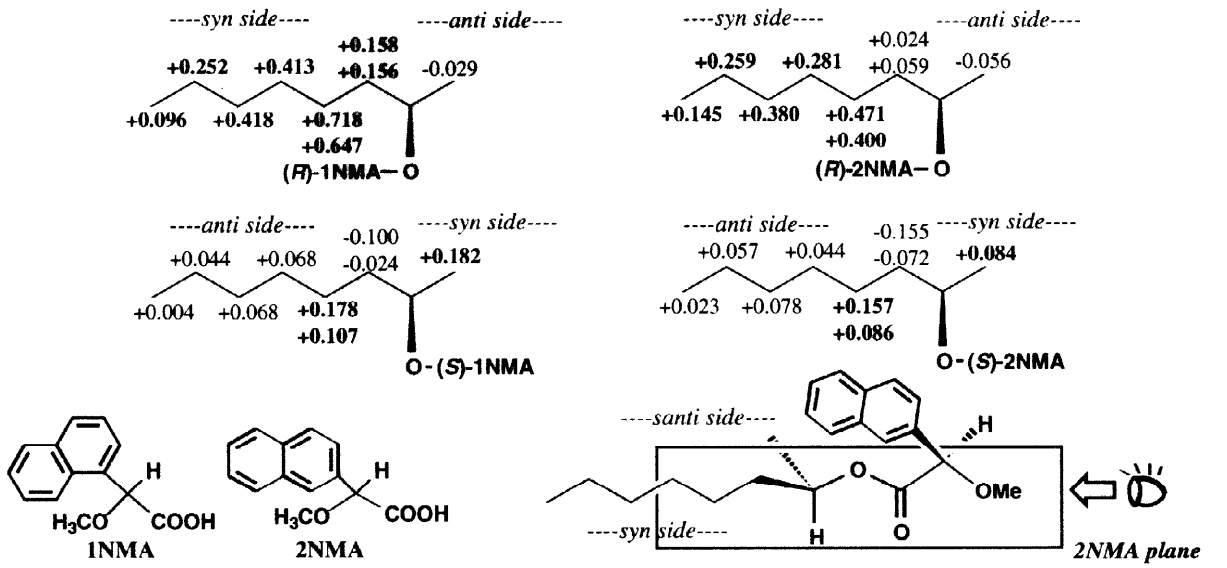

Figure 1. $\Delta\delta_{OH\text{-}NMA}$ values obtained for (*R*)-2-octanol are shown. Values larger than 0.08 ppm are shown in bold. The ideal conformation of the (*R*)-2NMA ester of (*R*)-2-octanol is described on the right bottom. In the ideal conformation, the naphthyl group directed toward the left side of the plane. Such direction of the naphthyl group is shown in the structures of the NMA esters.

In (*R*)-NMA ester, the protons with large $\Delta\delta_{OH\text{-}NMA}$ values (> +0.08 ppm) distribute on the same side (*syn* side) of the naphthyl group of NMA. In the case of (*S*)-NMA ester, however, the protons with large $\Delta\delta_{OH\text{-}NMA}$ values are seen on the opposite side (*anti* side) to the naphthyl group of NMA as well as *syn* side. This conflicting results might be due to ignorance of the electronic effect caused by esterification of the alcohol.

We next intended to compare the chemical shifts of the NMA ester with those of the acetate. The $\Delta\delta_{Ac\text{-}NMA}$ values ($\Delta\delta_{Ac\text{-}NMA} = \delta_{Ac} - \delta_{NMA}$) obtained for (*R*)-2-octanol are shown in Figure 2. When the threshold value was set at 0.08 ppm, the protons over the threshold distribute on only *syn* side of NMA. This indicates that the absolute configuration

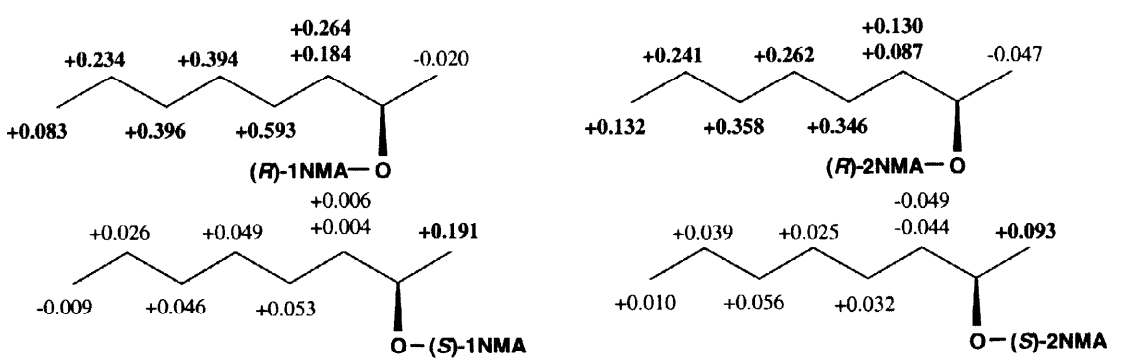

Figure 2. $\Delta\delta_{Ac\text{-}NMA}$ values obtained for (*R*)-2-octanol. The values over the threshold value [0.08 ppm] are shown in bold .

can be determined by $\Delta\delta_{Ac\text{-}NMA}$ values and setting the threshold at 0.08 ppm. However, this methodology needs two derivatization reactions [acetylation and esterification with (*R*)- or (*S*)-NMA], and it does not seem to be more advantageous than the conventional method using e.g. $\Delta\delta = \delta_{(R)\text{-}2NMA} - \delta_{(S)\text{-}2NMA}$.

During our works on the utility of 1NMA and 2NMA, a number of ^{1}H-NMR data of the acetates of linear and cyclic secondary alcohols have been accumulated, and we have noticed that there was a marked tendency about the chemical shifts of the NMA esters. This led us to establishment of the increment parameters shown in Figure 3. The increment parameters were obtained from the average differences between $\delta_{(acetate)}$ and $\delta_{(alcohol)}$ of fifteen linear alcohols including (*S*)-10-nonacosanol [4]. The $\Delta\delta'$ value is defined as [$\Delta\delta' = \delta_{OH} - \delta_{NMA}$ + increment], and an example is shown in Figure 4. The protons with $\Delta\delta'$ values over the threshold(0.08 ppm) distribute only *syn* side of NMA.

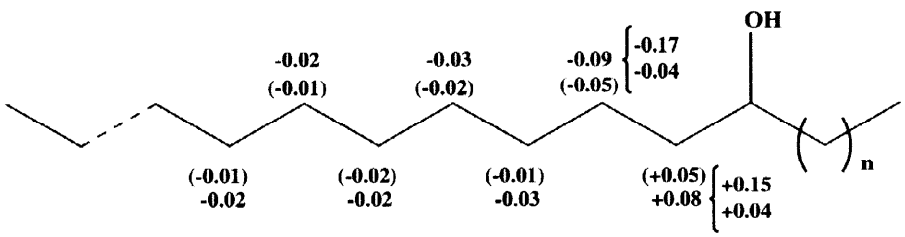

Figure 3. The increment parameter for the linear alcohols. The values in parenthesis is for the methyl group at the position. These parameters should be used for the protons irrespctive of the direction of the naphthyl group. In case that the protons at β- or γ-positions appear as nonequibvalent signals, the upper (lower) value in the half parenthesis is used for the proton with a larger (smaller) $\Delta\delta_{OH\text{-}NMA}$ instead of the average value.

This methodology was applied to other linear alcohols. Figure 5 shows $\Delta\delta'$ values for the 1NMA and 2NMA esters of 2-butanol, 2-pentanol, 2-hexanol and 3-hexanol. $\Delta\delta'$ values over

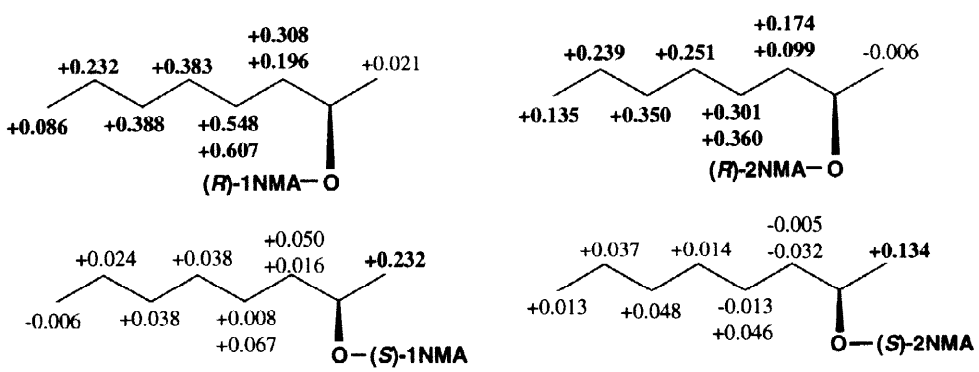

Figure 4. $\Delta\delta'$ values obtained for 1NMA and 2NMA esters of (*R*)-2-octanol. The values over threshold (0.08 ppm) are shown in bold.

threshold (0.08 ppm) in all the compounds are found on *syn* side of the naphthyl group. From these results, we have concluded that the absolute configurations of linear alcohols can be determined by Δδ' values adopting the increment parameters shown in Figure 3.

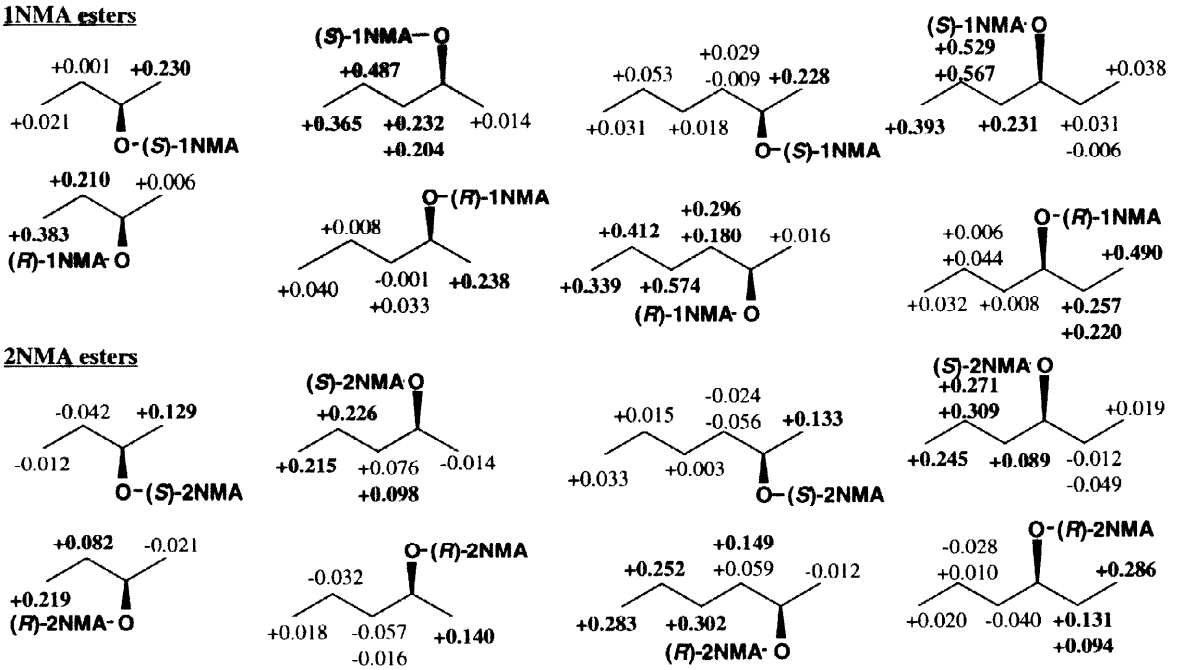

Figure 5. Δδ' values obtained for the 1NMA and 2NMA esters of (*R*)-2-butanol, (*S*)-2-pentanol, (*R*)-2-hexanol and (*S*)-3-hexanol.

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