

New Chiral Anisotropic Reagents, NMR Tools to Elucidate the Absolute Configurations of Long-chain Organic Compounds

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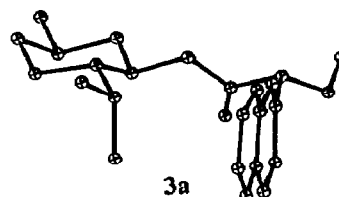
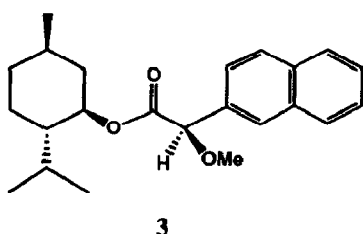
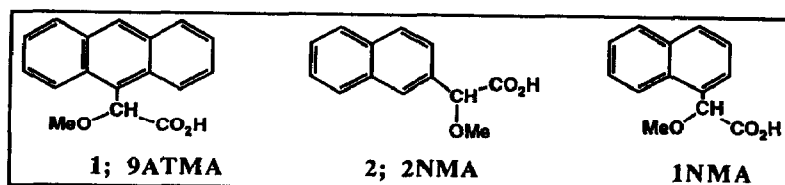
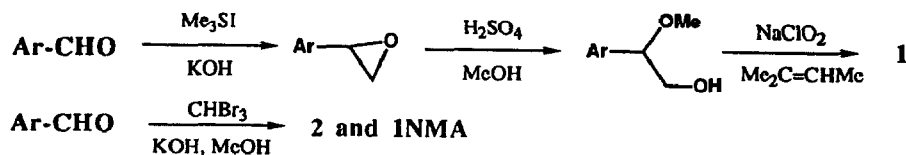
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Abstract: Modified Mosher's method has been extended by use of 9-anthranylmethoxyacetic acid (9ATMA) and 2-naphthylmethoxynaphthylacetic acid (2NMA) instead of MTPA of the conventional method. Anisotropic effects of these reagents are much greater than that of MTPA, and the reagents have been shown to be useful especially to determine the absolute configurations of the secondary alcohols involved in long-chain compounds.

The NMR methods based on the Mosher's idea¹ have become inevitable means to elucidate the absolute configurations of secondary alcohols,^{1,2} and primary amines.^{1,3} Recently we have reported⁴ the synthesis (Scheme 1) as well as the comparison of the anisotropic effects of three Trost-type of compounds, 9-anthranylmethoxyacetic acid (**1**; 9ATMA), 1-naphthylmethoxyacetic acid (1NMA), and 2-naphthylmethoxyacetic acid (**2**; 2NMA), with that of MTPA. We there demonstrated, using (-)-menthol and other compounds, that the upfield shifts due to 9ATMA (**1**) are 6 to 10 times larger than those of MTPA, but the anisotropic effects are short-range, while the shifts caused by 2NMA (**2**) are around 3 times larger than those of MTPA, but the anisotropic effects are long-range, that is, the diamagnetic field of 2-naphthyl group reaches farther than those of the other chiral anisotropic reagents do.⁵ The examples are shown in Figure 1.

We herein report that 2NMA (**2**) is a useful NMR reagent to determine the absolute configuration of a hydroxy group involved in a long-chain compound.

Racemic **2** was resolved into enantiomers by (i) esterification with (*S*)-phenethyl alcohol, (ii) chromatographic separation of the resulting diastereomers, and (iii) acid hydrolysis (HCl/dioxane), giving grams of each enantiomer.⁶ The absolute configuration of (*R*)-2NMA was elucidated by X-ray crystallography on its ester with (-)-menthol (**3**; X-ray structure **3a**), in which the chiral group exists in the conformation as demonstrated by Trost^{2b} (carbinyl proton, carbonyl oxygen, and methoxy group on the same plane), and 2-naphthyl group faces directly on the menthyl group, thus making the diamagnetic field from the



aromatic ring effectively shower on the protons of the menthyl residue.

Versatility of 2NMA is demonstrated when it was applied to a diacetylenic long-chain compound (4a) and methyl 9-hydroxystearate (6a).⁷ 2NMA ester 4b exhibits larger $\Delta\delta$ values than MTPA ester 5b, from which (*S*)-configuration of the hydroxy group is established. In the latter case, $\Delta\delta$ values of the terminal vinyl protons are within experimental errors. Yet the modified Mosher's method is valid to determine the (*S*)-configuration, because the substituents of both sides of the MTPA-oxy group are different, which eases the assignment of the protons of 5b. However, in the case of 6a, the conventional MTPA method is no more available, since the presence of seriously overlapping signals of methylenes makes it impossible to correlate the proton signals at C-8 and 10 to those of C-18 methyl and C-2 methylene, respectively, even by use of HOHAHA spectrum or other proton-relaying 2D techniques. On the contrary, the signals located on the same side of 2-naphthyl group of each 2NMA diastereomer (6b) are separated beautifully as shown in Figure 2; the signals of CH₂-10 in (*R*)-2NMA diastereomer are easily correlated to those of CH₃-18 by use of ordinary COSY spectrum, and the signals of CH₂-8 are correlated to those of CH₂-2, giving $\Delta\delta$ values indicated in 6b, which led to the (*S*)-configuration of 9-hydroxy group. The distribution pattern of the signs of $\Delta\delta$ in 6b suggests the zigzag conformation of this lipid chain.

It should be emphasized here that $\Delta\delta$ values of 9ATMA, 1NMA, and 2NMA esters⁸ are so large that only one enantiomer of the reagents may be needed; by comparison of the proton chemical shifts of one diastereomer with those of the original compound, the absolute configuration of the hydroxy group is predictable.

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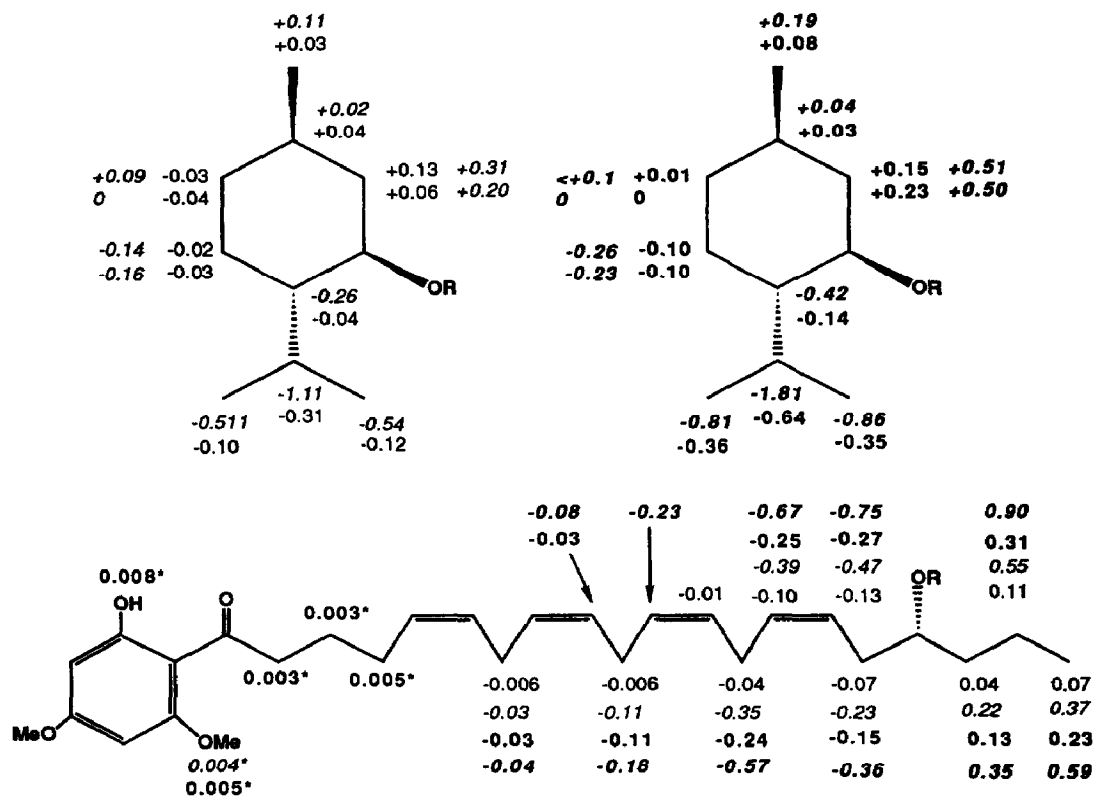
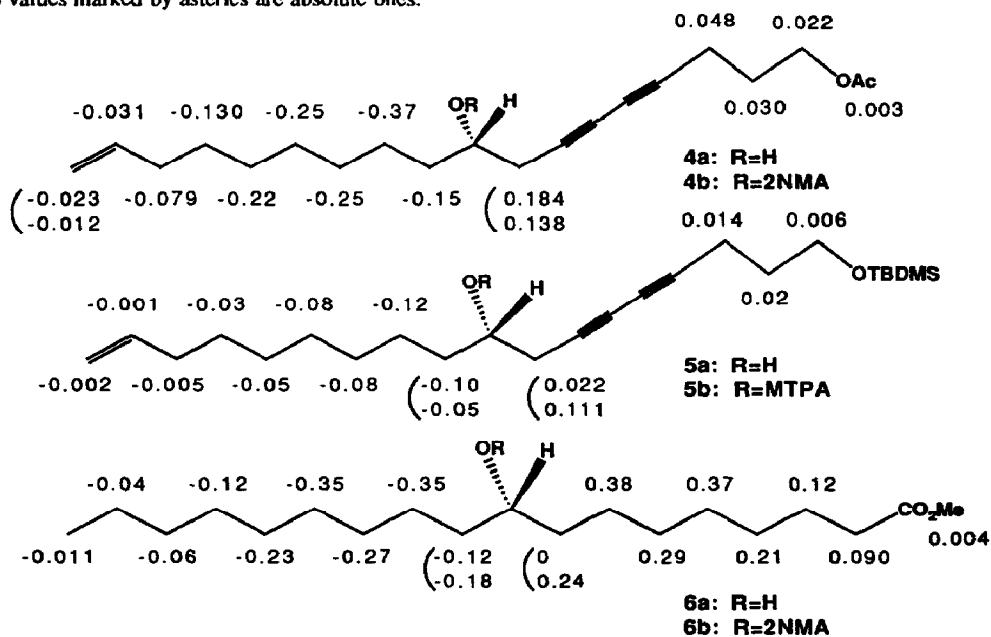


Figure 1 Comparison of $\Delta\delta$ values of MTPA (plain), 1NMA (plain italics), 2NMA (bold), and 9ATMA (bold italics) esters obtained for (-)-menthol and a derivative of an algal product.³ The values smaller than 0.003 ppm are abbreviated. The $\Delta\delta$ values marked by asterisks are absolute ones.



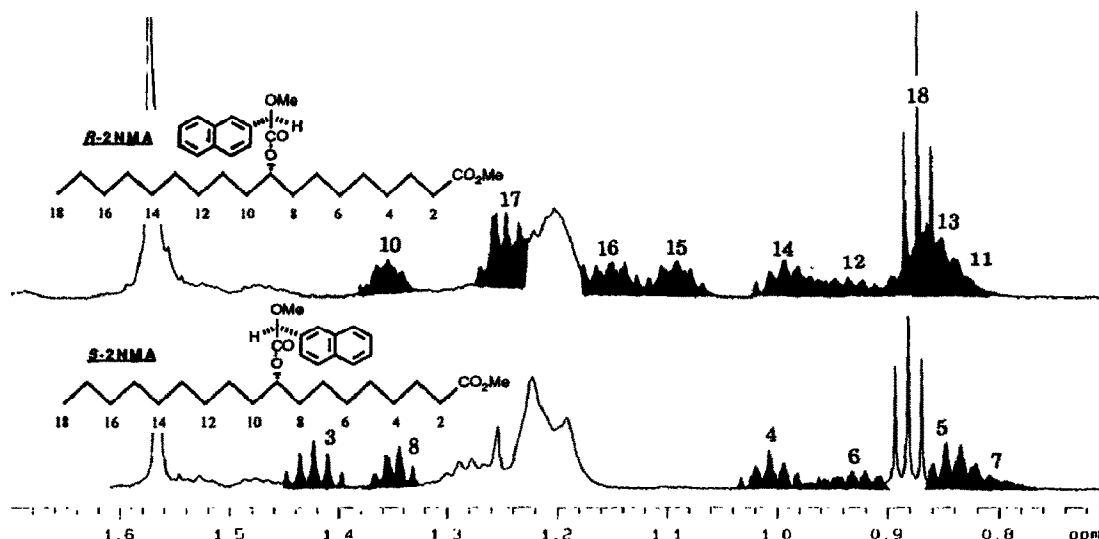


Figure 2 Parts of the 600 MHz $^1\text{H-NMR}$ spectra (CDCl_3) of (*R*)-2NMA (above) and (*S*)-2NMA (below) esters of methyl 9-hydroxystearate (6a). The shadowed signals are those due to the methylene and methyl protons that are located in the same side of the naphthyl group.

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- A few examples are (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.*, **1991**, *113*, 4092.
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- The idea of the reagents such as 1 and 2 is based on Professor Mosher's outstanding discernment on the conformations of MTPA and mandelic acids (See reference 1.). Very recently, similar reagents are prepared on the same background (Fukushi, Y.; Yajima, C.; Mizutani, J. *Tetrahedron Lett.*, **1994**, *35*, 599.), and number of similar reagents will increase in future. The term 'chiral anisotropic reagents' is proposed for the chiral chemicals that are used to determine the absolute configuration of organic compounds in the similar way as proposed by Mosher.
- (*R*)-2; $[\alpha]_{\text{D}}^{25} -138.7^\circ$ ($c = 0.35$, MeOH). (*S*)-2; $[\alpha]_{\text{D}}^{25} +100.5^\circ$ ($c = 0.63$, MeOH).
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