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A NEW METHOD FOR ESTABLISHMENT OF ABSOLUTE CONFIGURATIONS OF SECONDARY ALCOHOLS BY NMR SPECTROSCOPY

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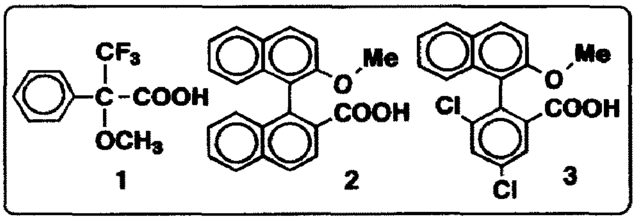
Abstract : Axially chiral 2'-methoxy-1,1'-binaphthyl-2- carboxylic acid (MBNC, **2**) and 2-(2'-methoxy-1'-naphthyl)-3,5-dichlorobenzoic acid (MNCB, **3**) were used as chiral derivatizing agents to determine absolute configurations of secondary alcohols by ^{1}H and ^{13}C NMR spectroscopy.

Recently a number of chiral derivatizing agents have been developed for determining absolute configurations and enantiomeric purities of optically active compounds[1]. Almost all of them possess C-centrochirality, and among of them, Mosher's α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**) has been most widely used[2]. "Modified Mosher's method", a modern variation of Mosher's (^{1}H) method improved by Ohtani *et al.*, is applicable to general secondary alcohols except sterically hindered ones[3]. On the other hand, Miyano *et al.* pointed out the utility of axially chiral 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (MBNC, **2**) as derivatizing agent for discrimination of enantiomeric alcohols and amines by ^{1}H NMR with the aid of Eu(fod)$_3$[4].

We estimated that axially chiral carboxylic acids like **2** and 2-(2'-methoxy-1'-naphthyl)-3,5-dichlorobenzoic acid (MNCB, **3**) would be more versatile agents than MTPA for Mosher's (^{1}H) method. Enantiomers of **2** were prepared by a known method[5]. Racemic **3** was prepared following the procedure of Hotta *et al.*[6], and derivatized into diastereomeric esters of (*S*)-1-phenethol which were separated each other by silica-gel column chromatography. Purified diastereomers were respectively hydrolyzed by alkali to yield (a*R*)- and (a*S*)-**3**[7]. Various secondary alcohols (**4-16**) were esterified with (a*R*)- and (a*S*)[8]-**2**, and (a*R*)- and (a*S*)-**3** by DCC and 4-pyrrolidinopyridine[9]. On the basis of ^{1}H NMR analyses of the respective diastereomers and the X-ray crystallographic data of (a*S*)- **2** ester of (-)-menthol[7], we devised a new method that could predict the absolute configurations of the chiral secondary alcohols including sterically hindered ones. The basic concept of this method is essentially the same as that of "modified Mosher's method".

For explanation of this method, hereinafter MNCB esters are used. The idealized conformation of MNCB esters is depicted in Figure **1A**. 1) The carbinyl proton, ester carbonyl and benzene ring of MNCB moiety lie in the same plane, and the alcohol moiety is near the naphthalene ring. 2) The naphthalene and the benzene rings of MNCB moiety are orthogonal. For convenience, the plane containing the benzene ring and the conformation of the MNCB group are named the CB plane and the ideal conformation, respectively. Due to the diamagnetic effect of the naphthalene ring, the Ha, Ha', Hb and Hb' NMR signals of MNCB ester should appear upfield relative to those of the original alcohol, and also the Ha signal of the (a*R*)-MNCB ester should appear upfield



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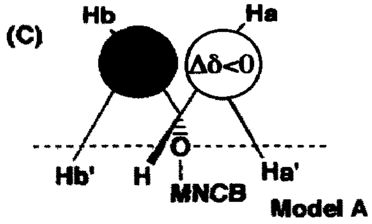

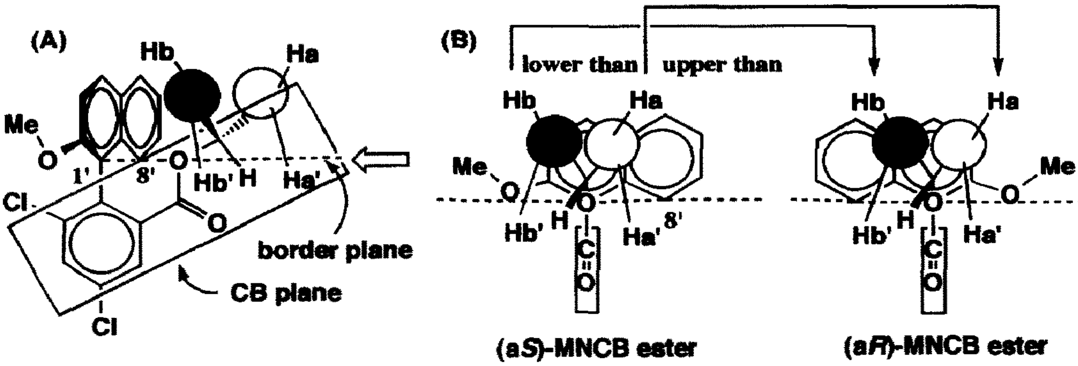

Figure 1. (A) Configurational correlation model for the (a*S*)-MNCB derivatives. CB and border planes are shown. Ha and Hb are on the left and right sides of the CB plane, respectively. Ha', Hb' and carbinyl proton are under the border plane. (**B**) and (**C**) Views of the (a*S*)- and (a*R*)-MNCB esters drawn from the direction shown by the outlined arrow in (**A**).

relative to that of the (a*S*)-MNCB ester. The reverse should hold true for Hb (Figure **1B**). Therefore, when chemical shift difference is defined as $\Delta\delta(\text{ppm}) = \delta aS - \delta aR^{10a}$, protons on the left side of the CB plane must have positive values ($\Delta\delta>0$) and protons on the right side of the plane must have negative values ($\Delta\delta<0$). The principle is illustrated in Figure **1B** and **1C**. The plane, which contains 1' and 8' carbons of the naphthalene ring and the alkoxy oxygen, is drawn with a dotted line in Figure **1A-C**. This plane is named the border plane. Δδ values of the protons under the border plane (Ha', Hb' and the carbinyl) are unpredictable, because these protons are strongly affected by a fine deviation from the ideal conformation. However the signs of Δδ of irregular protons are apt to be the same as that of the carvinyl proton's Δδ. When these conditions are satisfied, model A will indicate the correct absolute configuration of the compound in question.

As an example, (-)-menthol derivatives (**16**) can be used to demonstrate the validity of the present method (Figure 2 and Table 1). It is evident that the individual proton signal of the alcohol moieties of MNCB esters appears in upper field than the corresponding one of the original alcohol except the carbinyl proton. Especially, 2β proton signals of (a*S*)- and (a*R*)-MNCB esters appear at 0.13 and -0.23ppm, respectively. The protons with $\Delta\delta>0$ are located on the left side of the CB plane and the ones with $\Delta\delta<0$ on the right side. Also, Δδ values are influenced by the distance between the protons and the naphthalene ring. C_{10} methyl protons, which may be under the border plane (**16'**), show positive Δδ value but the sign is the same as that of the carbinyl proton. This correlation also holds in MBNC esters (**4**, **9**, **16**) in Figure 2. By comparison between MNCB and MBNC esters of (-)-menthol in ^{1}H MNR (Table 1), the absolute configuration of each enantiomer of MNCB was determined.

Table 1. ^{1}H NMR Data of (-)-Menthol and its MNCB and MBNC Esters (**16**).

Position	1	2α	2β	3	4	5α	5β	6α	6β	7	8	9	10
R=H	1.42	1.96	0.95	3.41	1.11	0.99	1.61	1.66	0.84	0.93	2.17	0.91	0.81
MNCB(a*R*)	1.16	1.26	-0.23	4.40	0.63	0.78	1.43	1.47	0.52	0.64	1.33	0.68	0.42
(a*S*)	1.22	1.48	0.13	4.44	0.41	0.77	1.39	1.49	0.54	0.73	1.11	0.50	0.46
MBNC(a*S*)	1.18	1.34	-0.23	4.48	0.68	0.82	1.44	1.50	0.54	0.64	1.45	0.71	0.49
(a*R*)	1.26	1.62	0.24	4.52	0.44	0.80	1.40	1.53	0.58	0.76	1.12	0.48	0.47

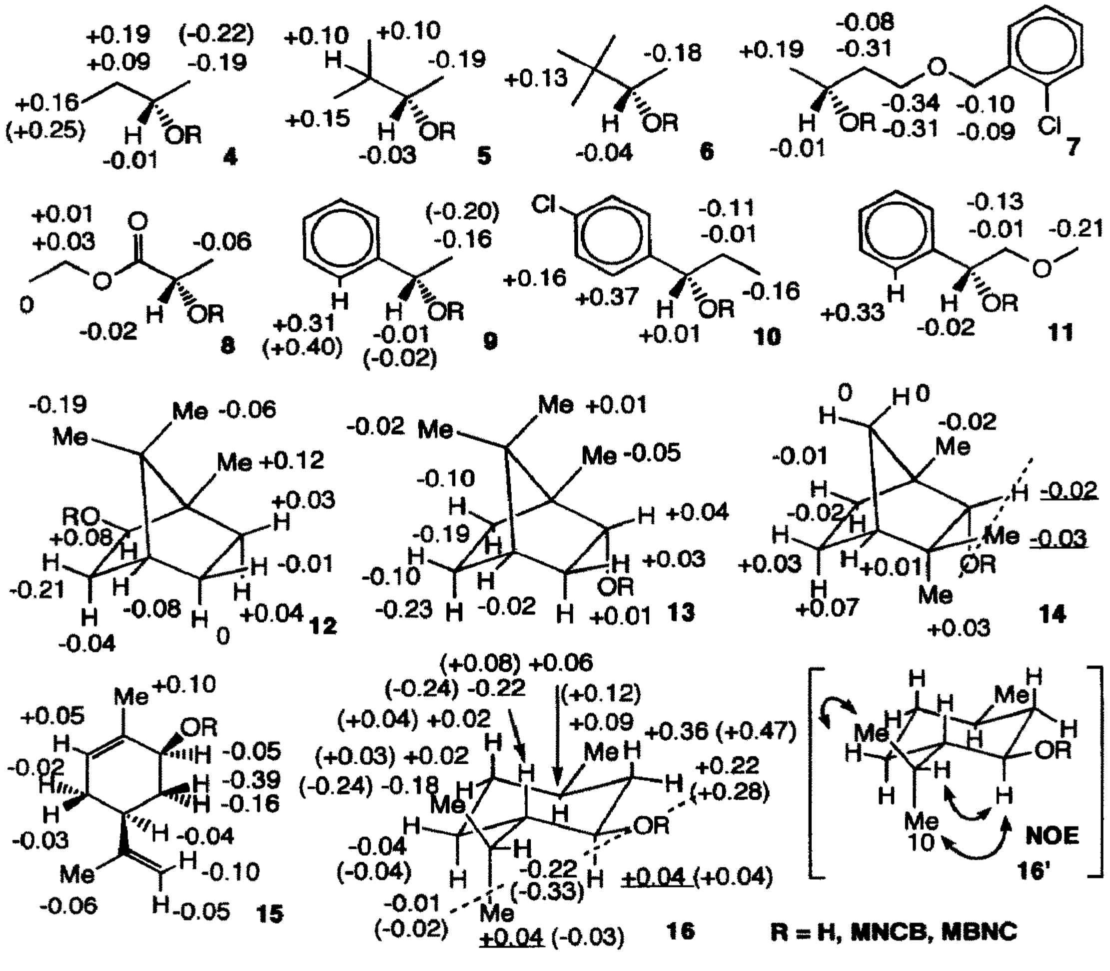

Figure 2 Δδ values in ^{1}H NMR obtained for the MNCB and MBNC esters of secondary alcohols. The values in the parentheses are Δδ of MBNC^{10b} esters. Border planes are shown by dotted lines. For consistency, the results have been transposed to one enantiomer of alcohol (ex. (a*S*, *R*) = (a*R*, *S*)). **16'** shows possible conformations of **16** (R = MNCB and MBNC).

This method is applicable to sterically hindered alcohols (**12**, **14**), and in ^{13}C NMR[11] (Figure 3). The present method may be useful for determination of absolute configurations of various natural products and their derivatives, and preparation of optically active secondary alcohols. Further versatility and limitation of this new method are under study.

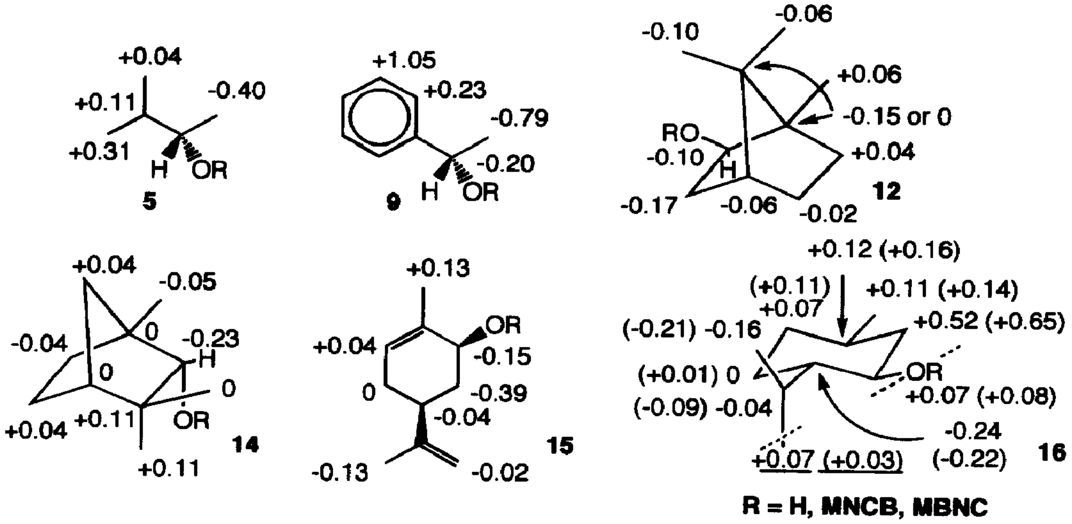

Figure 3. Δδ values in ^{13}C NMR obtained for the MNCB and MBNC esters of some secondary alcohols. The values in the parentheses are Δδ of MBNC^{10b} esters. Border plane is shown by a dotted line.

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