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A New NMR Chiral Derivatizing Reagent for Determining the Absolute Configurations of Carboxylic Acids

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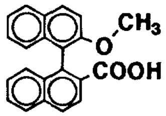
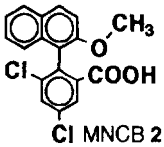
Abstract : Axially chiral 1,1'-binaphthalene-8,8'-diol (BNDO) was used as a chiral derivatizing reagent to determine the absolute configurations of α-chiral carboxylic acids by ^{1}H and ^{13}C NMR spectroscopy. Copyright © 1996 Elsevier Science Ltd

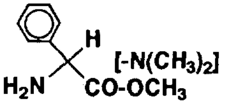
Recently a number of chiral derivatizing agents have been developed for determining absolute configurations and enantiomeric purities of optically active compounds[1]. Miyano *et al.* pointed out the utility of axially chiral 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (MBNC, **1**) as a derivatizing reagent for discrimination of enantiomeric alcohols and amines by ^{1}H NMR with the aid of Eu(fod)$_3$[2a]. We also reported that MBNC (**1**) and 2-(2'-methoxy-1'-naphthyl)-3,5-dichlorobenzoic acid (MNCB, **2**) are versatile reagents for determination of the absolute configurations of chiral secondary alcohols by ^{1}H and ^{13}C NMR spectroscopy[2b]. We herein describe another axially chiral reagent for α-chiral carboxylic acids.



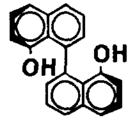
MBNC **1**



MNCB **2**



PGME **3** [PGDA **4**]



(a*R*)-BNDO **5**

Two *C*-centrochiral reagents (**3**, **4**) have been developed to elucidate the absolute configurations of carboxylic acids[3]. We estimated that axially chiral 1,1'-binaphthalene-8,8'-diol (BNDO, **5**) would be also available for the same purpose. Racemic **5** was prepared following the procedure of Artz *et al.*[4]. Methods for resolution of **5** were reported[5]. Here, racemic **5** was derivatized into diastereomeric monoesters of (*R*)-2-phenylpropionic acid (**6**) which were separated each other by silica-gel column chromatography. Purified diastereomers were respectively reduced by LiAlH$_4$ to yield (a*R*)- and (a*S*)-**5**. Several carboxylic acids possessing known absolute configurations were esterified with (a*R*)-, (a*S*)- and/or racemic **5**. On the basis of ^{1}H NMR analyses[6] of the respective diastereomers, we could devise a new method predicting the absolute configurations of α-chiral carboxylic acids.

The idealized conformation of BNDO monoester is depicted in Figure **1A**. 1) The naphthalene rings are orthogonal. 2) The carbonyl moiety and the hydroxyl group are *syn*-conformation[5a]. 3)The α proton locates near the centre of the faced naphthalene ring. Due to the diamagnetic effect of the naphthalene ring, the Ha, Hb and α proton signals of BNDO monoester should appear upfield relative to those of the original carboxylic acid, and also the Ha signal of the (a*R*)-BNDO monoester should appear downfield relative to that of the (a*S*)-BNDO monoester. The reverse should hold true for Hb (Figure 1 **B**). Therefore, when chemical shift difference is defined as $\Delta\delta=\delta\text{a}S-\delta\text{a}R$, in Figure 1 C, protons on the left side must have positive values ($\Delta\delta>0$) and protons on the right side must have negative values ($\Delta\delta<0$). When these conditions are satisfied, model **A** will indicate the correct absolute configuration of the compound in question.

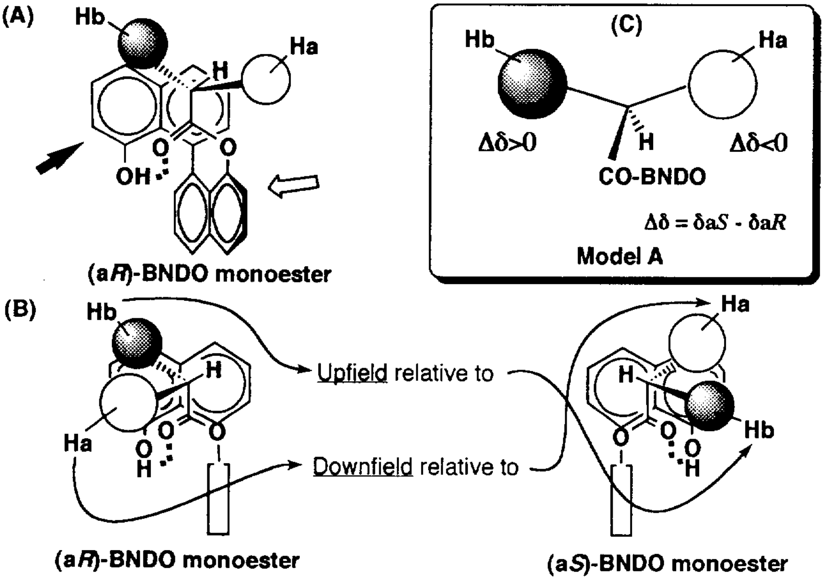
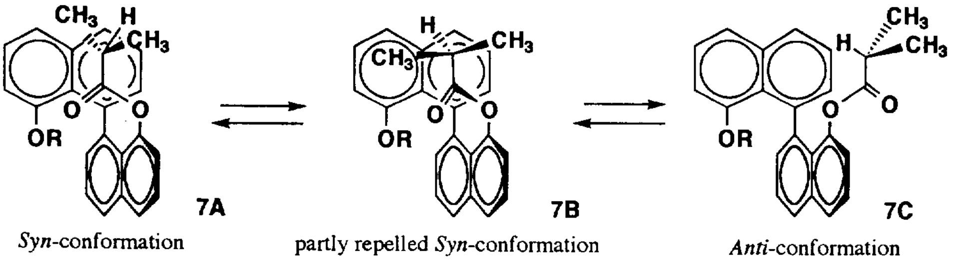


Figure 1. (**A**) Configurational correlation model for the (a*R*)-BNDO monoesters. (**B**) Views of the (a*R*)- and (a*S*)-BNDO monoesters drown from the direction shown by the outlined arrow in (**A**). (**C**) A view of the BNDO monoesters drown from the direction shown by the bold arrow in (**A**).

For demonstration of the presence of the ideal conformation in solution, isobutyric acid (**7a**) and its derivatives (**7b**~**f**) were subjected to ^{1}H NMR analyses (Table 1). It is evident that the signals of acid moieties

Table 1. Chemical shifts of geminal methyl and α protons, and/or ΔδGM (chemical shift difference between the geminal methyl protons) for isobutyric acid (**7a**) and its esters (**7b**~**f**).

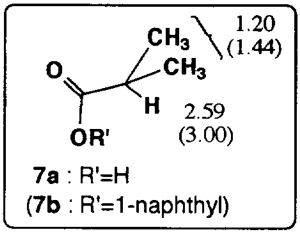


Syn-conformation

partly repelled *Syn*-conformation

Anti-conformation

R	α proton	geminal methyl protons	ΔδGM
7c : H	0.88	0.48, 0.75	0.27
7d : CH_3	0.72	0.49, 0.70	0.21
7e : $COCH(CH_3)_2$	0.70	0.57, 0.67	0.10
7f : $COC(CH_3)_3$	2.32	0.61, 0.69	0.08

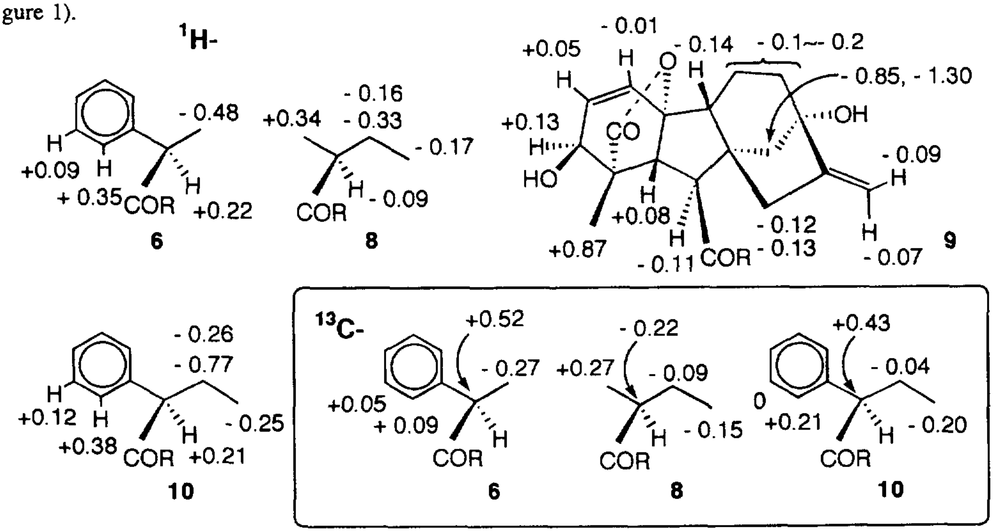


7a : R'=H

(**7b** : R'=1-naphthyl)

for esters (**7c~f**) appear in upper field than the corresponding ones for isobutyric acid (**7a**) and 1-naphthyl isobutyrate (**7b**). The α proton for **7c** appears at 0.88ppm, which indicates that the α proton is close to the centre of the faced naphthalene ring (**7A**). Those for **7d** and **7e** appear at 0.72 and 0.70ppm, respectively. The steric repulsion between OR and C=O may drive the conformations of **7d** and **7e** to that like **7B**. On the other hand, the α proton signal for **7f** (R=COC(CH_3)$_3$) appears very low field (2.32ppm) suggesting that the most abundant conformer of **7f** is like **7C**. In conclusion, the ratios of *syn* (**7A**) / **7B** / *anti* (**7C**) are influenced by the OR groups. Considering from the values of ΔδGM for **7c~f**, BNDO monoesters (R=H) are suitable for stereochemical analyses of carboxylic acids.

The Δδ values in ^1H and ^{13}C NMR obtained for the BNDO monoesters of chiral carboxylic acids (**6**,**8~10**) are summarized in Figure 2. The signs of the Δδ values agree with those predicted from Model **A** (Figure 1).



R=BNDO : Δδ (ppm) = δa*S* - δa*R*

Figure 2. Δδ values in ^1H and ^{13}C NMR obtained for the BNDO monoesters of chiral carboxylic acids.

Diasteromers shown in Figure 2 were well separated on silica-gel thin-layer plates[7]. The developing pattern of a pair of diastereomers may be explained by the steric and electronic interactions between the solutes and silica-gel stationary phase as shown in Figure 3. This method could be useful for preparation of optically active carboxylic acids and their primary-alcoholic derivatives.

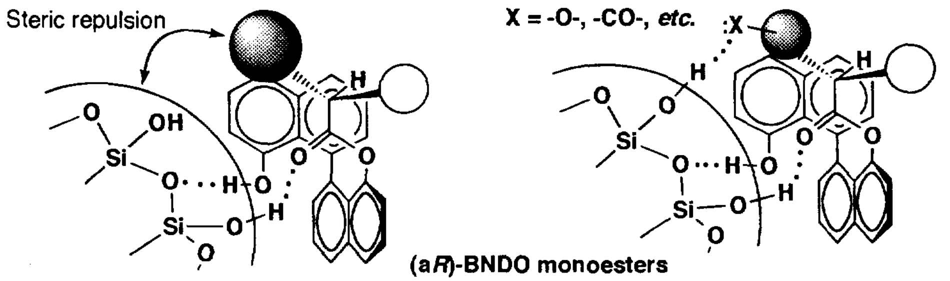


Figure 3. Schematic views of the interaction of (a*R*)-BNDO monoesters with silica-gel stationary phase[8].

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6. A JEOL EX 270 and a Bruker AM 500 spectrometers were used to record ^{1}H and ^{13}C NMR spectra in $CDCl_3$ (ambient temperature). Proton and carbon chemical shifts were determined in δ value relative to TMS and $CDCl_3$, respectively.

7. The *Rf* values for the respective diasteremers on a silica-gel TLC [Kieselgel $60F_{254}$ (Merck)] are summarized as following (a*S*, a*R*, solvent system):
   6: (0.36, 0.49, toluene:EtOAc=20:1), **8**: (0.46, 0.41, toluene:EtOAc=20:1),
   9: (0.43, 0.38, $CHCl_3$:MeOH=10:1), **10**: (0.40, 0.52, toluene:EtOAc=20:1).

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