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2-Methoxy-2-(1-naphthyl)propionic acid, a powerful chiral auxiliary for enantioresolution of alcohols and determination of their absolute configurations by the ^{1}H NMR anisotropy method

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Abstract

Racemic 2-methoxy-2-(1-naphthyl)propionic acid (**1**, MαNP acid) was enantioresolved as its esters derived from various chiral alcohols. For example, a diastereomeric mixture of esters prepared from (±)-**1** and (1*R*,3*R*,4*S*)-(–)-menthol was easily separated by HPLC on silica gel yielding esters (–)-**2a** and (–)-**2b**, the separation factor $\alpha = 1.83$ being unusually large. The ^{1}H NMR chemical shift differences, $\Delta\delta = \delta(R) - \delta(S)$, between diastereomers **2a** and **2b**, are much larger than those of conventional chiral auxiliaries, e.g. Mosher's MTPA and Trost's MPA acids. This acid **1** is therefore very powerful for determining the absolute configuration of chiral alcohols by the ^{1}H NMR anisotropy method. Solvolysis of the separated esters yielded enantiopure acids (*S*)-(+)-**1** and (*R*)-(–)-**1**, which are useful for enantioresolution of racemic alcohols.

Almost two decades ago, (–)-2-methoxy-2-(1-naphthyl)propionic acid (**1**, MαNP acid) was designed as a chiral auxiliary useful for enantioresolution of amines derived from amino acids, although the absolute configuration of (–)-**1** remained undetermined.[1] Recently, we have unambiguously determined the *S* absolute configuration of acid (+)-**1** by X-ray crystallography and chemical correlation (Fig. 1)[2] and also reported the *S* absolute configuration of (+)-2-hydroxy-2-(1-naphthyl)propionic acid (HαNP acid) as determined by the ^{1}H NMR anisotropy method.[3] In those studies, we predicted that the acid **1** would be a promising chiral auxiliary useful for determining the absolute configuration of alcohols by the ^{1}H NMR anisotropy method. In this paper, we report the application of this acid **1** to configurational studies of chiral alcohols,

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emphasizing that the acid **1** is very powerful for both enantioresolution of racemic alcohols and determination of absolute configurations of chiral alcohols including natural products.

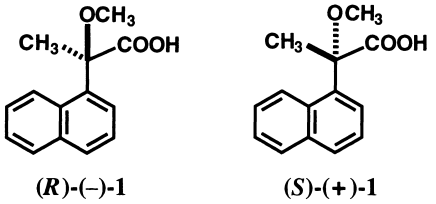
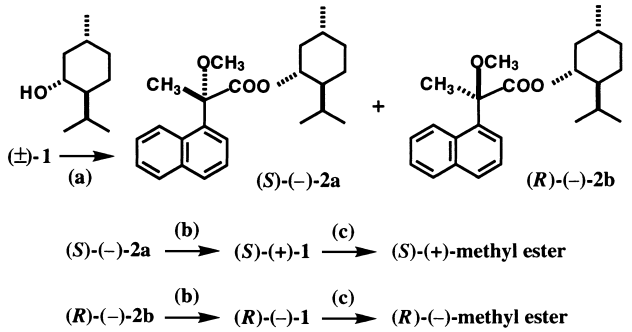


Figure 1. (*R*)-(–)- and (*S*)-(+)-2-Methoxy-2-(1-naphthyl)propionic acids **1**

Racemic acid **1** was routinely prepared according to a slight modification of the scheme previously reported.[2] The acid **1** was condensed with (1*R*,3*R*,4*S*)-(–)-menthol yielding a mixture of diastereomeric esters **2a** and **2b**; a mixture of (±)-**1**, (–)-menthol (1.2 equiv.), 4-dimethylaminopyridine (DMAP, 0.5 equiv.), and 1,3-dicyclohexylcarbodiimide (DCC, 1.7 equiv.) in CH_2Cl_2 was stirred at room temperature overnight, yielding a diastereomeric mixture of esters (Scheme 1). The mixture was easily separated by HPLC on silica gel (hexane:EtOAc 15:1): separation factor $\alpha = 1.83$; resolution factor $Rs = 2.26$. The first-eluted ester (–)-**2a** (49%, $[\alpha]_D^{23}$ –62.5 (*c* 1.346, $CHCl_3$)) and the second one (–)-**2b** (46%, $[\alpha]_D^{23}$ –35.8 (*c* 1.305, $CHCl_3$)) were obtained.



Scheme 1. (a) (–)-Menthol, DCC, DMAP, CH_2Cl_2, (–)-**2a**, 49%; (–)-**2b**, 46%; (b) $NaOCH_3/CH_3OH$ and then H_2O, 87–94%; (c) CH_2N_2/diethyl ether, 99%

Fig. 2(a) shows HPLC separation of two diastereomers **2a** and **2b**. It was quite surprising to find such clean separation of two diastereomeric organic compounds composed of only carbon, hydrogen, and oxygen atoms. Trost's chiral acid,[4] α-methoxyphenylacetic acid (MPA acid), also brings similar separation of diastereomers. For example, diastereomeric esters synthesized from (–)-menthol and (±)-MPA acid were separated by HPLC on silica gel using hexane:EtOAc 20:1: $\alpha = 1.21$, $Rs = 1.19$. However, its separation and resolution factors are smaller than those of esters **2a** and **2b**. On the other hand, Mosher's α-methoxy-α-trifluoromethylphenylacetic acid (MTPA acid)[5] is unsuitable for such diastereomeric separation: $\alpha = 1.28$, $Rs = 0.82$ (hexane:EtOAc 50:1).

The strong power of this acid **1** for diastereomer separation is also demonstrated by the case of 2-butanol. Commercially available (*S*)-(+)-2-butanol was esterified with racemic acid **1**; the obtained mixture of diastereomeric esters **3a** and **3b** was almost base-line separated by HPLC on silica gel (hexane:EtOAc 20:1) as shown in Fig. 2(b): $\alpha = 1.15$, $Rs = 1.18$. The acid **1** thus has a great ability to recognize the small difference between methyl and ethyl groups. It is well known

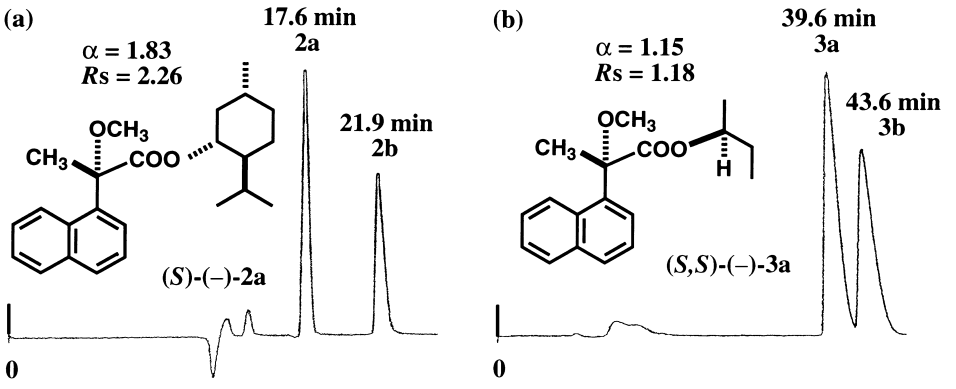


Figure 2. (a) Separation of diastereomers (–)-**2a** and (–)-**2b** by HPLC on silica gel (hexane:EtOAc 15:1); (b) separation of esters **3a** and **3b** (hexane:EtOAc 20:1)

that chiral discrimination between methyl and ethyl groups is the most difficult in enantioresolution and also even in asymmetric reactions. Now we have obtained a facile method to get enantiopure 2-butanol. In fact, using enantiopure acid **1**, racemic 2-butanol was enantioresolved.

To recover the enantiopure carboxylic acid, purified ester (–)-**2a** was treated with $NaOCH_3$ in methanol and then with water, yielding (*S*)-(+)-**1**: $[\alpha]_D^{26}$ +67.4 (*c* 1.39, $CHCl_3$); methyl ester of (*S*)-(+)-**1**, $[\alpha]_D^{24}$ +37.8 (*c* 1.205, $CHCl_3$), CD (EtOH) λ_{ext} 280.0 nm ($\Delta\varepsilon$ –0.51), 226.0 (+9.1). The absolute configuration of acid (+)-**1** was assigned as *S* by comparison with the authentic sample {Ref. 2, methyl ester of (*S*)-(+)-**1**, $[\alpha]_D^{27}$ +34.8 (*c* 2.62, $CHCl_3$)}. In a similar way, solvolysis of ester (–)-**2b** afforded acid (*R*)-(–)-**1**: $[\alpha]_D^{23}$ –67.4 (*c* 1.305, $CHCl_3$); methyl ester of (*R*)-(–)-**1**, $[\alpha]_D^{23}$ –39.4 (*c* 1.12, $CHCl_3$), CD (EtOH) λ_{ext} 280.8 nm ($\Delta\varepsilon$ +0.58), 226.4 (–8.9).

Another great merit of this acid **1** is the strong anisotropy effect in the ^1H NMR spectra of its esters. The chemical shift data of diastereomeric esters (*S*)-(–)-**2a** and (*R*)-(–)-**2b** are listed in Fig. 3(a) together with the $\Delta\delta$ values (ppm): $\Delta\delta = \delta(R) - \delta(S)$. The protons of the *iso*-propyl group are largely up-field shifted by the diamagnetic anisotropy effect of naphthalene moiety in ester **2b**, while the protons at the 2-position are up-field shifted in ester **2a**. Since the absolute configurations of the MαNP acid and (–)-menthol are already known as discussed above, those anisotropy data lead to the preferred conformations of esters **2a** and **2b** as illustrated in Fig. 3(a).

These preferred conformations of esters **2a** and **2b** are supported by the following fact: the chemical shift data of **2a** and **2b** and hence their $\Delta\delta$ values are very similar to those of the corresponding HαNP esters, in which the rotational conformations are fixed by the intramolecular hydrogen bonding between free hydroxyl and ester carbonyl groups[3] as shown in Fig. 3(b). Therefore it is concluded that MαNP esters **2a** and **2b** take conformations similar to HαNP esters. It is well known that the ^1H NMR anisotropy methods using MTPA, MβNA (2-methoxy-2-(2-naphthyl)acetic acid), and MPA acids are very useful for determining the absolute configurations of chiral alcohols including natural products.[4–6] The $\Delta\delta$ values of **2a** and **2b** observed here are much larger than those of the corresponding MTPA, MβNA, and MPA esters (Fig. 3c–e). Therefore, as a chiral auxiliary for the ^1H NMR anisotropy method, MαNP acid **1** is superior to MTPA, MβNA, and MPA acids. Another merit of acid **1** is the point that the α-position of carboxylic acid, a stereogenic center, is fully substituted and therefore it is inert toward racemization. Although MβNA acid has been proposed as a chiral auxiliary giving large $\Delta\delta$ values (Fig. 3d),[5,6] it has a demerit to racemize.

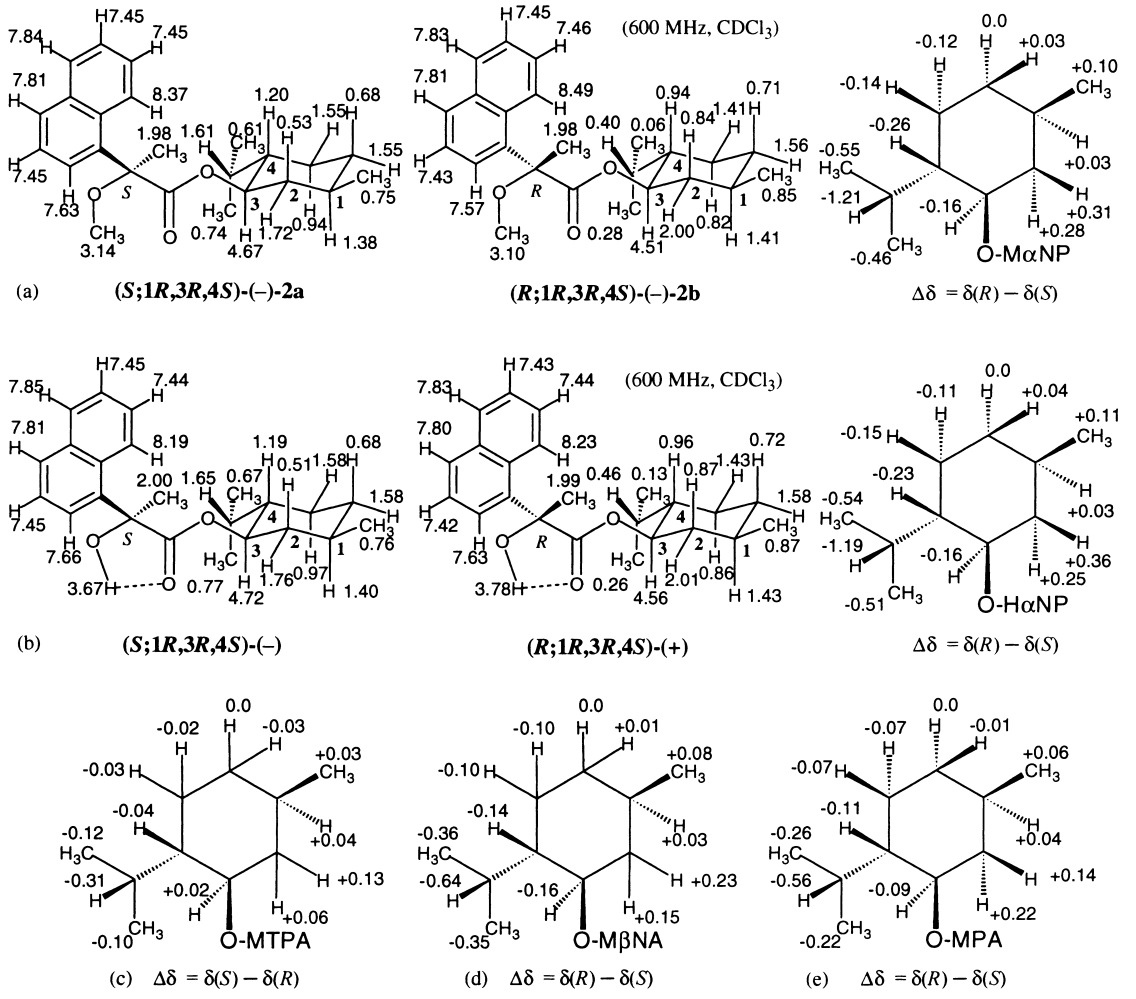


Figure 3. (a) The NMR chemical shift data of esters (–)-**2a** and (–)-**2b** and Δδ values (ppm); (b) the corresponding chemical shift data and Δδ values using HαNP group (Ref. 3); (c) Δδ values of MTPA ester (Ref. 5); (d) MβNA ester (Ref. 5); (e) MPA ester

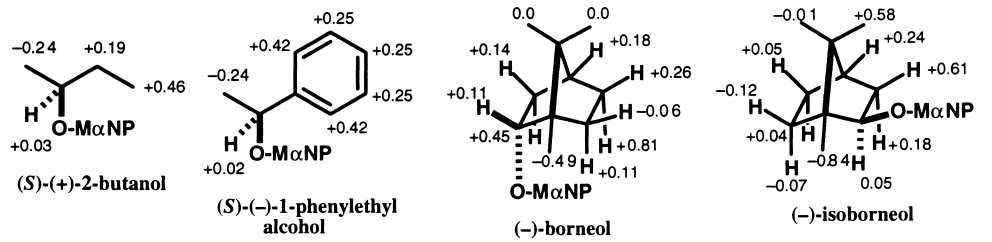


Figure 4. The Δδ values (=δ(*R*)–δ(*S*), ppm) of MαNP ester of chiral alcohols (400 or 600 MHz, $CDCl_3$)

The ^{1}H NMR anisotropy method using MαNP acid was applied to other chiral alcohols, and the Δδ values obtained are listed in Fig. 4. As seen in these data, the Δδ values strongly correlates with the absolute configuration of chiral alcohols. The most striking characteristic of our method is the fact that, in all cases in Fig. 4, racemic acid (±)-**1** could be used, because diastereomeric esters formed were easily separated by HPLC on silica gel. To determine the absolute configuration of the acid part, a small portion of esters separated was converted to MαNP acid methyl ester, the CD spectrum of which was measured. The negative CD Cotton effect at 280 nm corresponds to the *S* configuration of the acid part, the positive one to the *R* configuration. The ^{1}H NMR Δδ values, combined with CD data, thus lead to the determination of the absolute configuration of the alcohol part. In cases where diastereomeric esters are inseparable by HPLC, enantiopure acids (*R*)-**1** and (*S*)-**1** are used to form diastereomeric esters as usual. Extension of this strategy and further application to various alcohols are now in progress.

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