Novel Chiral Molecular Tools for Preparation of Enantiopure Alcohols by Resolution and Simultaneous Determination of Their Absolute Configurations by the $^1$H NMR Anisotropy Method

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Abstract: The development and applications of novel chiral molecular tools, (S)-(−)-2-methoxy-2-(1-naphthyl)propionic acid (MzNP acid (2)) and (S)-(−)-2-methoxy-2-(9-phenanthryl)propionic acid (M9PP acid (3)), useful for preparation of enantiopure secondary alcohols and simultaneous determination of their absolute configurations by the $^1$H NMR anisotropy method are explained. Racemic MzNP acid 2 was enantioresolved with (+)-menthol, and the enantiopure MzNP acid (S)-(+)−2 obtained was allowed to react with racemic alcohols yielding diastereomeric esters, which were easily and clearly separated by HPLC on silica gel. By applying the sector rule of $^1$H NMR anisotropy effect, the absolute configurations of the first-eluted MzNP esters were unambiguously determined. MzNP acid (S)-(+)−2 has thus a great power to discriminate the chirality of various alcohols, especially of aliphatic alcohols, in both HPLC and $^1$H NMR. The solvolysis or reduction of the first-eluted MzNP esters yielded enantiopure alcohols, whose absolute configurations were simultaneously determined. Another chiral molecular tool, M9PP acid (S)-(−)-3, was similarly applied to prepare both enantiomers of sulcatol, an insect pheromone, in enantiopure forms.

1. Introduction

It is well recognized that molecular chirality is essential to life processes, and that most biologically active compounds controlling physiological functions of living organisms are chiral. Hence, in the structural study of biologically active compounds, including natural products, determination of the absolute configuration becomes the first major issue. The second issue is chiral synthesis of natural products and biologically active compounds that become pharmaceutical targets and how efficiently the desired enantiomers can be synthesized with 100% enantiopurity or enantiomeric excess (% ee). Furthermore, studies on chiral functional molecules and molecular machines, such as the light-powered chiral molecular motor developed in our laboratory, has been rapidly progressing in recent years. Therefore, the unambiguous determination of the absolute configuration of chiral compounds as well as their chiral syntheses are of vital importance in the field of material science.

We have recently developed chiral carboxylic acids as novel molecular tools proven to be powerful for enantioresolution and simultaneous determination of the absolute configuration of various alcohols. Those chiral molecular tools are very useful for the facile synthesis of enantiomers with 100% ee and also for the absolute configurational assignment. The methods using these chiral tools have been successfully applied to various compounds, and their methodologies and applications are explained throughout this paper.

2. Methodologies for determining absolute configuration and their evaluations

The methodologies for determining the absolute configurations of chiral compounds are classified into the following two categories.

2.1 Nonempirical methods for determining absolute configurations of chiral compounds:

As the methods in this category, there are the Bijvoet method of X-ray crystallography and the circular dichroism (CD) exciton chirality method. These powerful methods provide nonempirical determination of a target molecule's configuration without knowledge of the absolute configuration of reference compounds. In X-ray crystallography, since the anomalous dispersion effect of heavy atoms can be measured very accurately under proper conditions, the absolute stereosstructure obtained is unambiguous and reliable. In addition, the molecule can be projected as a three-dimensional structure, and, therefore, the method has been employed extensively. However, the X-ray method needs single crystals of suitable size good for X-ray diffraction, and so the critical problem is how to obtain such single crystals. As a consequence, a study using this method often becomes a lengthy trial-and-error search for ideal single crystals.

The CD exciton chirality method is also useful because the absolute configuration can be determined in a nonempirical manner, and it does not require crystallization. Furthermore, chiral chemical and biological reactions are traceable by CD, and even the absolute configurations and conformations of unstable compounds can be obtained by this method. However, because some compounds are not ideal targets for this method, the results must be interpreted carefully.

2.2 Relative and/or empirical methods for determining absolute configuration using an internal reference with known absolute configuration:

Absolute configuration can be obtained by determining the relative configuration at the position of interest against a
reference compound or substituent with known absolute configuration. A typical example is the X-ray crystallography taken after the introduction of a chiral auxiliary with known absolute configuration (Figure 1). In this case, the absolute configuration of the point in question can be automatically determined using the chirality of the auxiliary introduced as an internal reference. Consequently, the samples do not need to contain heavy atoms for anomalous dispersion effect. The result obtained is very clear, even when the final R-value is not small enough due to poor quality of the single crystal. The absolute configuration can be determined with certainty, even if only the relative configuration is obtained. A variety of methods to link an internal reference to the target molecule have been developed. For example, there are ionic bonding such as conventional acid-base salts, covalent bonding such as esters or amides, and the use of recently developed inclusion complexes. These relative X-ray methods are expected to find widespread application.

Recently, the proton nuclear magnetic resonance (1H NMR) anisotropy method has often been employed as the relative method, and it is useful for the study of the absolute configuration of natural products. In particular, the absolute configurations of secondary alcohols are frequently determined using the advanced Mosher method developed by Kusumi et al. In this case, the absolute configurations of chiral auxiliaries, such as Mosher’s reagent [α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)] and Trost’s reagent [α-methoxyphenylacetic acid (MPA)], are known, and the preferred conformation of the esters formed with chiral secondary alcohols and MTPA or MPA acid is rationalized. In addition, the aromatic substituent (phenyl group) generates a magnetic anisotropy effect due to the ring current induced under the external magnetic field, and so the proton NMR signals of the alcohol moiety facing the phenyl group in the preferred conformation are moved to a higher magnetic field (high field shift). By observing the 1H NMR anisotropy effect, the absolute configuration of the alcohol part can be determined. This method is very convenient, since it does not require crystallization of compounds and NMR machines are daily used. One problem of this method is that it is based on the assumption of preferred conformation of molecules in solution. However, it is highly reliable since the method itself has a self-diagnostic function; in some exceptional cases, to which the NMR anisotropy method is not applicable, the observed Δδ values reflecting the anisotropy effect distribute randomly. On the other hand, in the most cases leading to the correct assignment, the Δδ values show a reasonable distribution pattern. Therefore, the applicability of the NMR anisotropy method can be judged from the distribution pattern of the observed Δδ values. Although the method has been widely applied to secondary alcohols, the method would be extended to other kinds of compounds.

The absolute configuration can be determined relatively by chemical correlation or comparison of optical rotation, [α]D, and/or CD spectrum with that of reference compounds with known absolute configuration. Although this method is also frequently employed, a careful selection of reference compounds is necessary for reliable analysis.

3. Methodologies for chiral synthesis and their evaluations

The task after determination of absolute configuration is the synthesis of chiral compounds. The practical methods to synthesize chiral compounds are roughly divided into two categories, each of which is further divided and has advantages and disadvantages as described below. In this paper, “chiral synthesis” includes not only so-called asymmetric synthesis but also enantioresolution. In addition, the method in which covalently bonded diastereomers are formed using a chiral auxiliary, followed by HPLC separation and recovery of the target compound, is also defined as enantioresolution.

3.1 Enantioresolution of racemates:

Type a). In this method, a chiral auxiliary is ionically bonded to racemates as seen in the conventional cases of acid–base combination, and a mixture of the diastereomers formed is subjected to fractional recrystallization to obtain enantiopure compounds. This method is also applicable to inclusion complexes formed by, e.g., hydrogen bonding. The critical point is whether or not the diastereomer can be obtained with 100% enantiopurity through fractional recrystallization. It should be noted that recrystallization does not always afford a 100% enantiopure diastereomer. If this method is successful, it is suitable for the mass preparation of chiral compounds.

Type b). In this method, a chiral auxiliary is covalently bonded to racemates to produce a diastereomeric mixture, which is separated by conventional HPLC on silica gel or other methods to enantiopure diastereomers, and then the chiral auxiliary is cleaved off (Fig. 1). This method can yield an enantiopure compound. The point is whether or not diastereomers can be clearly separated by HPLC. If a clear separation is achieved, each diastereomer obtained is enantiopure, and the target compound after cleavage of the chiral auxiliary is also 100% enantiopure. It is advisable to use a chiral auxiliary that can be cleaved off easily.
Type e). This is an excellent method where racemates are directly enantioseparated by HPLC or GC using columns made of chiral stationary phases, and a number of reports have been published.\(^{14}\) The question is again whether racemates are clearly separated into two enantiomers or not. If a clear separation is achieved, 100% pure enantiomers are obtained by this method as well. The method is convenient and suitable for analytical separation, as it does not require derivatization. In general, chiral columns are expensive and are, therefore, mostly used for analytical purposes. However, in some cases, mass separation is conducted on an industrial scale to obtain chiral compounds such as pharmaceutical materials. Careful analysis is required when determining absolute configuration by the elution order, as there are many exceptions.

Type f). This is a unique method where racemates undergo an enzymatic or asymmetric reaction to yield enantiomers by the kinetic resolution effect. In particular, high stereoselectivity of the enzymatic reaction leads to high enantiopurity.\(^{15}\) However, care should be taken, since the method does not always yield 100% enantiopurity.

3.2 Asymmetric syntheses:

Type a). This is a highly efficient and powerful method to obtain chiral products by the action of a chiral reagent or chiral catalyst on achiral compounds. Being a well-known method, many eminent reviews have been published for these asymmetric syntheses, and so no further explanation is required here. The problem with this method is that the products obtained are not always enantiopure. Furthermore, it is generally difficult to determine the absolute configuration of the products based on the reaction mechanism. Accordingly, an independent determination of the absolute configuration by the methods described above is suggested.

Type b). There is also another method to obtain chiral compounds such as by enzymatic reaction on achiral or meso compounds. The asymmetric reaction of a meso compound by an enzyme is particularly interesting and is defined as the desymmetrization reaction. In this case too, the enantiopurity is not always 100%, and the absolute configuration must be determined separately.

4. Camphorsultam dichlorophthalic acid (CSDP acid \((-)-1\)) useful for enantioresolution of alcohols by HPLC and determination of their absolute configurations by X-ray crystallography.

The authors consider that the most reliable and powerful method for determining the absolute configuration is the X-ray crystallography of compounds containing a chiral auxiliary with known absolute configuration as the internal reference, as described above. Namely, the absolute configuration of the point in question can be unambiguously determined from the ORTEP drawing showing a relative stereochemistry, because the absolute configuration of the chiral auxiliary is already known. Therefore, it is easy to determine the absolute configuration, and there is no possibility of making a mistake in the assignment.

We also consider that a highly efficient method for preparing an appropriate amount of various chiral compounds with 100% enantiopurity in a laboratory scale is the enantioresolution of type 1b), as illustrated in Figs. 1 and 2. In this method, a chiral auxiliary is covalently bonded to racemates, and the obtained diastereomeric mixture can be separated by conventional HPLC or silica gel. If the chromatogram shows a base-line separation, the diastereomers obtained are enantiopure. This method is characterized by a clear and efficient separation even with a small amount of sample, compared to the fractional recrystallization method described in type 1a).

As chiral auxiliaries satisfying these two requirements, we have designed and prepared a chiral molecular tool, camphorsultam dichlorophthalic acid (CSDP acid) \((-)-1\) connecting \((1S,2R,4R)-2,10\)-camphorsultam and 4,5-dichlorophthalic acid, and have applied this chiral tool to various compounds (Figure 2).\(^{16-20,38,44}\) The 2,10-camphorsultam was selected because of its good affinity with silica gel used in HPLC, allowing good separation of two diastereomers. In addition, the sultam amide moiety is effective for providing prismatic single crystals suitable for X-ray diffraction experiment. Furthermore, the \((1S,2R,4R)\) absolute stereochemistry of 2,10-camphorsultam established is useful as the internal reference of absolute configuration. To connect alcohols, an ester bond was chosen, because it could be readily formed and cleaved off. Accordingly, 4,5-dichlorophthalic acid was selected as a linker (Figure 2).\(^{16,17}\) In telephthalic acid and succinic acid, the two chiral moieties are separated spatially. However, in phthalic acid, they are close enough to result in a stronger interaction. So we expected its diastereomeric recognition would be effective in HPLC.

![Figure 2. Design of a chiral molecular tool, CSDP acid containing 2,10-camphorsultam moiety.](image)

The desired molecular tool, CSDP acid \((-)-1\), was synthesized by reacting \((1S,2R,4R)-2,10\)-camphorsultam anion with 4,5-dichlorophthalic anhydride \([-\text{(-)}-1, \text{mp } 221°C \text{ from EtOH}; [\alpha]_D^{20} -101.1 (\text{c } 1.375, \text{ MeOH})]\); Figure 2). Compound 1 should be formally called phthalic acid amide. However, here we adopted its common name, CSDP acid. This carboxylic acid was condensed with alcohol under the conditions of 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).\(^{16,17}\)

The application of the CSDP acid method to various alcohols has been already reviewed in this journal, although it was written in Japanese.\(^{28}\) Therefore, please see it and the references cited therein for details. Here, we show the recent data of fluorinated diphenylmethanol to exemplify a general procedure of this method.\(^{44}\) The CSDP acid \((-)-1\) was allowed to react with \((\pm)-4\)-trifluoromethylphenylphenylmethanol (5) using DCC and DMAP in CH\(_2\)Cl\(_2\) yielding diastereomeric esters, which were separated by HPLC on silica gel: hexane/EtOA = 5:1; \(\alpha = 1.34, R_t = 2.37\) (Figures 3 and 4a)). The first-eluted ester \((\pm)-6a\) obtained was recrystallized from EtOH giving prisms: mp 171°C. A single crystal of 6a was subjected to X-ray analysis affording the ORTEP drawing as shown in Figure 4b), from which the absolute configuration of the alcohol part was determined as \(R\) based...
on the absolute configuration of the camphorsultam moiety used as an internal reference. The $R$ absolute configuration of 6a was also confirmed by the heavy atom effect of two chlorine and sulfur atoms contained. The solvolysis of the first-eluted ester $\text{(R-)(-)}$-6a with K$_2$CO$_3$ in MeOH yielded enantiopure alcohol $\text{(R-)(-)}$-5.

Although the absolute configuration of $\text{(+)}$-5 had previously been estimated as $S$ by the Horeau method, the abnormality of its application had been pointed out. Therefore, the direct and unambiguous determination of its absolute configuration has been desired for a long time. The absolute configuration of (4-trifluoromethylphenyl)phenylmethanol $\text{(R-)(-)}$-5 was thus first determined by X-ray analysis.

Another important example is the case of 2-[(1-naphthyl)propane-1,2-diol (7), which was isolated as a chiral metabolite of 1-isopropynaphthalene in rabbits (Figure 5). The metabolite, however, was not enantiopure and its absolute configuration had been only empirically estimated based on the reaction mechanism. To obtain the enantiopure diol 7 and to determine its absolute configuration in an unambiguous way, the method of CSDP acid was applied to $\text{(±)}$-7. In this case, only the primary alcohol part was esterified, and the diastereomeric mixture obtained was clearly separated by HPLC on silica gel: hexane/EtOAc = 4:1, $\alpha = 1.3$, $R_s = 1.1$. In this HPLC, the presence of a free tertiary hydroxyl group is important, because the protection of the tertiary alcohol group led to poor separation.

Despite repeated recrystallizations, both diastereomers were obtained only as amorphous solids. Therefore, the first-eluted fraction $\text{(-)}$-8a was reduced with LiAlH$_4$ to yield enantiopure glycol $\text{(-)}$-7, which was further converted to 4-bromobenzoate $\text{(S-)(-)}$-9 (Figure 5). By recrystallization from EtOH, $\text{(-)}$-9 gave good single crystals suitable for X-ray analysis, and consequently its absolute configuration was explicitly determined as $S$ by the Bijvoet pair measurement of the anomalous dispersion effect of the bromine atom contained (Figure 5b)).

Furthermore, we have obtained enantiopure 2-methoxy-2-(1-naphthyl)propionic acid (MeNP acid) $\text{(S)-(+)}$-2 via several reactions from diol $\text{(S-)(-)}$-7 (Figure 5c)). We have discovered that this novel carboxylic acid, MeNP acid (2), was also effective for enantioreolution and simultaneous determination of the absolute configuration of various secondary alcohols by the $^1$H NMR anisotropy method. The results obtained by the $^1$H NMR
anisotropy method are, of course, consistent with those by the X-ray method. Therefore, the methods of CSDP and MzNP acids are useful as complementary molecular tools.

5. A novel chiral molecular tool, 2-methoxy-2-(1-naph-thylpropionic acid (MzNP acid (S)-(+)-2), useful for enantioresolution of alcohols and simultaneous determination of their absolute configurations by the $^1$H NMR anisotropy method.

We have discussed above the design and applications of CSDP acid useful for both the synthesis of enantiopure compounds and the unambiguous determination of their absolute configurations by X-ray analysis. The X-ray crystallographic method using the internal reference of absolute configuration thus leads to the unambiguous and reliable determination of absolute configuration. However, the drawback of X-ray crystallography is that the method needs single crystals, and, therefore, it is not applicable to non-crystalline materials. However, in daily experiments, prismatic single crystals suitable for X-ray analysis are not always obtainable. So is there any other method applicable to non-crystalline materials? In addition, the applications of the CSDP method of the X-ray crystallographic method has been mostly limited to aromatic compounds. So, a powerful method applicable to aliphatic compounds has been required.

We have recently discovered that 2-methoxy-2-(1-naph-thylpropionic acid (MzNP acid 2) is remarkably effective in enantioresolution of aliphatic alcohols, especially acyclic aliphatic alcohols. In the $^1$H NMR spectra of the esters formed from MzNP acid 2 and alcohols, the chemical shifts of the protons in the alcohol moiety are strongly affected by the magnetic anisotropy effect induced by the naphthyl group. Therefore, this MzNP acid 2 can be used as the chiral auxiliary of the advanced Mosher method useful for determining the absolute configuration of secondary alcohols. Another advantage of the MzNP acid 2 is that it does not racemize, because the $\alpha$-position of 2 is fully substituted, and, therefore, it is easy to prepare the enantiopure acid 2.

As discussed below, MzNP acid 2 is a very powerful chiral derivatizing agent, which simultaneously enables both enantioresolution of secondary alcohols and determination of their absolute configurations. Namely, the MzNP acid method explained here is very useful for enantioresolution of racemic acids and also for determination of the absolute configurations of natural products and biologically active synthetic chiral compounds, e.g., chiral drugs. In this sense, the chiral MzNP acid 2 is superior to the conventional chiral acids, Mosher’s MTPA acid, Trost’s MPA acid, 1- and 2-NMA acids developed by the Riguer group and Kusumi group.

The following sections describe in detail the principle and applications of this chiral MzNP acid method: a) synthesis of chiral MzNP acid 2, b) determination of its absolute configuration by X-ray and chemical correlation, c) enantioresolution of racemic acid 2 with chiral alcohols, d) absolute configurational and conformational analyses of MzNP acid esters by NMR and CD spectroscopic methods, e) enantioresolution of racemic alcohols and determination of their absolute configuration using chiral MzNP acid 2, f) recovery of chiral alcohols with 100% enantiopurity from the separated diastereomeric esters.

5.1 Facile synthesis of MzNP acid (2) and its extraordinary enantioresolution with natural (-)-menthol

To synthesize a large amount of enantiopure chiral MzNP acid 2, the facile synthesis and enantioresolution of racemic acid 2 were carried out as shown in Figure 7. In general, for enantioresolution of carboxylic acids, chiral synthetic amines or alkaloids have been used. However, we have adopted the following novel strategy to use chiral alcohols. In this method, chiral alcohols are condensed with racemic acid 2 and the diastereomeric esters formed are separated by HPLC on silica gel. The separated esters are then hydrolyzed to yield both enantiomers of the desired carboxylic acids.

As a chiral alcohol, naturally occurring (-)-menthol was selected and esterified with racemic acid 2. It was most surprising that the diastereomeric esters 12a and 12b formed were very easily separated by HPLC on silica gel.
(hexane/EtOAc = 10:1) as illustrated in Figure 8. The separation and resolution factors were extraordinarily high (\(\alpha = 1.83, R_s = 4.55\)), indicating that acid 2 has great ability to recognize the chirality of the alcohols. The efficiency in separation enabled the HPLC of a preparative scale: esters 12a/12b (1.0–1.8 g) were separable in one run using a glass column of silica gel (25 \(\phi \times 400\) mm). The first-eluted ester 12a was subjected to solvolysis to yield chiral acid \((+)-2\), while the second-eluted ester 12b gave acid \((-)-2\). To determine the absolute configurations of chiral acids 2 obtained, they were converted to methyl esters, the CD spectra of which were measured. By comparison of those CD spectra with that of the authentic sample with known absolute configuration established by X-ray analysis and chemical correlation, the absolute configurations of chiral acids 2 were determined as \((S)-(+)\) and \((R)-(+)\), respectively, leading to the assignment of \((S)-(-)-12a\) and \((R)-(-)-12b\) (Figure 7).

5.2 The \(^{1}H\) NMR anisotropy method for determining the absolute configuration of secondary alcohols: the sector rule and applications\(^{[11,41]}\)

As described above, the \(^{1}H\) NMR anisotropy method has been frequently used as a relative and empirical method for determining the absolute configurations of chiral organic compounds.\(^{[10-13]}\) In particular, the advanced Mosher method for chiral secondary alcohols has been successfully employed in the field of natural products. In the cases of Mosher’s MTPA and Trost’s MPA acids, the phenyl group exhibits the magnetic anisotropy effect induced by the aromatic ring current, affecting the chemical shift (\(\delta\)) of protons in the alcohol part. Therefore, the absolute configuration of chiral alcohol can be determined by the difference (\(\Delta\delta\)) in the chemical shifts of esters formed with \((R)\) and \((S)\) carboxylic acids: \(\Delta\delta = \delta(R) - \delta(S)\) or \(\Delta\delta = \delta(S) - \delta(R)\). We have found that MezNP acid 2 is superior to Mosher’s MTPA and Trost’s MPA acids, because the magnetic anisotropy effect of the naphthyl group is much larger than that of a phenyl group and, therefore, larger \(\Delta\delta\) values are obtained. So, the absolute configuration of chiral alcohols can be unambiguously determined, when using MezNP acid 2 as a chiral NMR anisotropy reagent. Moreover, MezNP acid has another advantage in that it does not racemize, because the \(\alpha\)-position of 2 is fully substituted. For these reasons, it is advisable to use MezNP acid 2, rather than other conventional chiral acids, for determining the absolute configuration of chiral alcohols including natural products.

All NMR proton peaks of diastereomeric MezNP esters 12a and 12b were fully assigned by various methods including two-dimensional ones \((\^{1}H, ^{1}H-^{1}H\text{ COSY}, ^{13}C, ^{1}H-^{13}C\text{ COSY, HMBC, Figure 9a})\). The protons of the isopropyl group in ester 12b appeared at much higher fields than in ester 12a. On the other hand, the protons in the 2-position in 12a appeared at higher fields than in ester 12b. Those high field shifts are obviously due to the magnetic anisotropy effect induced by the naphthyl group of the MezNP acid moiety.

To determine the absolute configuration from the \(^{1}H\) NMR anisotropy effect, it is required to determine the preferred conformation of each diastereomer. In esters 12a and 12b, the absolute configurations of MezNP acid and menthol moieties are established as described above, and so the following stable conformations are proposed to satisfy the anisotropy effects observed in the NMR spectra (Figure 9). Namely, the two oxygen atoms of the methoxyl and ester carbonyl groups are synperiplanar (syn) to each other in their stable conformations. In addition, the ester carbonyl oxygen atom is also syn to the alcohol methine proton. Therefore, the methoxyl group, ester group, and alcohol methine proton lie in the same plane, which is called the MezNP plane (Figures 9 and 10). These syn conformations are similar to those proposed for MPA esters. In ester 12a, the naphthyl group and H-2 protons are on the same front side of the MezNP plane, and the H-2 protons are located above the naphthyl plane. Therefore, the H-2 protons feel the magnetic anisotropy effect of high field shift, and so appear at higher field. In ester 12b, the naphthyl group is close to the isopropyl group, and the high field shifts of isopropyl protons are observable.

The predominance of the syn conformations in esters 12a and 12b is also supported by the comparison of the NMR data with those of 2-hydroxy-2-(1-naphthyl)propionic acid (HzNP) menthol esters shown in Figure 9(b). From the
NMR chemical shift and IR data, it is obvious that the tertiary hydroxyl group of HαNP esters is intramolecularly hydrogen-bonded to the oxygen atom of the ester carbonyl group. Namely, the hydroxyl group and the ester carbonyl oxygen atom take a syn conformation. We have found a very interesting fact that the NMR chemical shift data of MαNP acid menthol ester (S;1R,3R,4S)-(-)–12a, especially those of the menthol part, are very similar to those of HαNP acid menthol ester (S;1R,3R,4S)-(-) as shown in Figure 9, (a) and (b). The same is true for the pairs of other diastereomers, (R;1R,3R,4S)-(-)–12b and HαNP acid menthol ester (R;1R,3R,4S)-(-) (Figure 9). These facts indicate that MαNP acid menthol esters take the syn conformation, as HαNP acid menthol esters usually do. This fully explains the observed magnetic anisotropy effects.

By using the NMR anisotropy effect of MαNP esters, the sector rule for determining the absolute configuration of secondary alcohols can be deduced (Figure 10). The basic procedure is as follows; (R)-MαNP and (S)-MαNP acids are separately allowed to react with a chiral alcohol, the absolute configuration of which is defined as X. So, the ester prepared from (R)-MαNP acid has the (R,X) absolute configuration, while the other ester from (S)-MαNP acid has the (S,X) absolute configuration. All NMR proton signals of (R,X)- and (S,X)-esters are fully assigned by careful analysis. If necessary, the use of two-dimensional spectra is suggested. The Δδ values (Δδ = δ(R,X)−δ(S,X)) are calculated for all protons in the alcohol moiety. Figure 10 shows the sector rule for the MαNP ester, where the MαNP group is placed in the down and front side, while the methine proton of the secondary alcohol in the down and rear side. The group L1 with protons exhibiting positive Δδ values is placed in the right side, while the group L2 with protons showing negative Δδ values in the left side. From this projection, the absolute configuration X of chiral alcohol can be determined.

The magnetic anisotropy effect of chiral MαNP acid is much stronger than that of conventional chiral carboxylic acid (Figure 11). For instance, the Δδ values of the MαNP-menthol ester are ca. four times larger than those of Mosher’s MTPA ester (Figure 11(c)); comparable to 1-NMA and 2-NMA esters reported by Riguera11 and Kusumi12 et al. MαNP acid is thus effective for determining the absolute configuration of natural products.

Some application examples of this MαNP acid method to chiral alcohols are shown in Figure 12.

5.3 Enantioresolution of various alcohols using MαNP acid and simultaneous determination of their absolute configurations

Another extraordinary quality of MαNP acid is its excellent ability in chiral recognition. For example, as discussed above, racemic MαNP acid could be successfully enantioresolved as the esters of natural (−)-menthol; the diastereomeric esters formed were clearly separated by HPLC on silica gel.

Figure 13. HPLC separation of diastereomeric esters formed from aliphatic alcohols and (S)-(+)-MαNP acid (silica gel, 22 φ × 300 mm, hexane/EtOAc = 20:1).
ca gel. MeNZNP acid could be also enantioresolved with other chiral alcohols as listed in Figure 12. These facts logically indicate that if enantiopure MeNZNP acid is used, racemic alcohols can be enantioresolved. In fact, we have succeeded in enantioresolution of various alcohols using enantiopure MeNZNP acid (S-)(+)-2 as exemplified in Figure 13.

This novel chiral MeNZNP acid (S-)(+)-2 has thus a remarkable enantioresolving power for alcohols, especially for aliphatic alcohols. For instance, in the case of 2-butanol, the diastereomeric esters can be baseline separated with the separation factor $\alpha = 1.15$ and resolution factor $R_s = 1.18$. In this case, it is obvious that the chiral carboxylic acid 2 recognizes well the slight difference between methyl and ethyl groups. This is an excellent and practical method since the chiral acid 2 exhibits a high resolving power to aliphatic alcohols, to which in general asymmetric syntheses are hardly applicable.

The next question is then how the absolute configuration of the alcohol moiety is determined. The absolute configurations of separated diastereomers can be determined by applying the $^1$H NMR anisotropy method using chiral MeNZNP acid described above. A general scheme is illustrated in Figure 14. Racemic alcohol is esterified with MeNZNP acid (S-)(+)-2 yielding a mixture of diastereomeric esters, which is separated by HPLC on silica gel. The absolute configuration of the first-eluted ester is defined as (S,X), where $S$ denotes the absolute configuration of the MeNZNP acid part, while $X$ denotes that of the alcohol part. So, the absolute configuration of the second-eluted ester is expressed as (S,-X), where $-X$ indicates the opposite absolute configuration of $X$. The original definition of $\Delta\delta$ value is $\Delta\delta = \delta(R,X) - \delta(S,X)$, and so the value of $\delta(R,X)$ is required to calculate the $\Delta\delta$ value. However, the enantiomer (R,X) does not exist in this scheme, and so the original equation of $\Delta\delta$ is not useful here.

To solve the above problem, the following conversion of the equation was performed. Since the ester (S,-X) is the enantiomer of ester (R,X), their NMR data should be identical: $\delta(R,X) = \delta(S,-X)$. Therefore, $\Delta\delta = \delta(R,X) - \delta(S,X) = \delta(S,-X) - \delta(S,X) = \delta(2nd fr.) - \delta(1st fr.)$. So, the absolute configuration $X$ of the first-eluted fraction can be determined from the $\Delta\delta$ value which is obtained by subtracting the chemical shift of the first-eluted fraction from that of the second-eluted fraction (Figure 14). This method has been applied to the esters shown in Figure 13, giving $\Delta\delta$ values and the absolute configurations of the first-eluted esters (Figure 15). The $\Delta\delta$ values are reasonably distributed: positive values at the right, and negative value at the left. The absolute configuration of the first-eluted ester can be thus determined, and the opposite absolute configuration is, of course, assigned to the second-eluted ester. It should be noted that when MeNZNP acid (R)-(-)-2 is used, the $\Delta\delta$ value

![Figure 14. Enantioresolution of racemic alcohol as (S)-MeNZNP esters, and determination of the absolute configuration of the first-eluted fraction by the NMR anisotropy method.](image1)

![Figure 15. Determination of the absolute configurations of the alcoholic part of the first-eluted esters by the NMR anisotropy method using (S)-(+)-MeNZNP acid, and the observed $\Delta\delta$ values.](image2)

![Figure 16. Recovery of enantiopure alcohol and MeNZNP acid.](image3)
is defined as $\Delta \delta = \delta(R,X) - \delta(S,X) = \delta(R,X) - \delta(R,-X) = \delta(1\text{st fr}) - \delta(2\text{nd fr})$.

The next step is the recovery of enantiopure alcohol and chiral MnzNP acid 2. As exemplified in Figure 16, both enantiopure alcohols were readily obtained by the solvolysis of the separated esters. The chiral MnzNP acid 2 was also recovered and could be recycled.

How good is the enantiopurity of the recovered alcohols?

In our method, both diastereomeric esters obtained are enantiopure, if MnzNP acid 2 used is enantiopure, because they are fully separated in HPLC. The MnzNP acid 2 was also recovered and could be recycled.

Table 1. HPLC separation of diastereomeric esters formed from alcohols with MnzNP acid, determination of their absolute configurations by the $^1$H NMR anisotropy method, and absolute configurations of recovered chiral alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Alcohol</th>
<th>Solvent $^b$</th>
<th>$\alpha$</th>
<th>$R_e$</th>
<th>Ester (1st Fr.)</th>
<th>Chiral Alcohol (from 1st Fr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)-2</td>
<td>(±)-20</td>
<td>H/E = 20:1</td>
<td>1.93</td>
<td>3.68</td>
<td>(S,S)-(-)-29a</td>
<td>(S)-(+)-20</td>
</tr>
<tr>
<td>2</td>
<td>(+)-2</td>
<td>(±)-21</td>
<td>H/E = 10:1</td>
<td>1.30</td>
<td>2.38</td>
<td>(S,S)-(-)-30a</td>
<td>(S)-(+)-21</td>
</tr>
<tr>
<td>3</td>
<td>(+)-2</td>
<td>(±)-22</td>
<td>H/E = 20:1</td>
<td>1.88</td>
<td>4.97</td>
<td>(S,1R,2S)-(-)-31a</td>
<td>(1R,2S)-(-)-22</td>
</tr>
<tr>
<td>4</td>
<td>(+)-2</td>
<td>(±)-23</td>
<td>H/E = 20:1</td>
<td>1.21</td>
<td>1.54</td>
<td>(S,1R,2R)-(-)-32a</td>
<td>(1R,2R)-(-)-23</td>
</tr>
<tr>
<td>5</td>
<td>(+)-2</td>
<td>(±)-24</td>
<td>H/E = 2:1</td>
<td>1.35</td>
<td>1.82</td>
<td>(S,1R,2R)-(-)-33a $^c$</td>
<td>(1R,2R)-(-)-24</td>
</tr>
<tr>
<td>6</td>
<td>(+)-2</td>
<td>(±)-25</td>
<td>H/E = 10:1</td>
<td>1.22</td>
<td>1.54</td>
<td>(S,S)-(+)-34a</td>
<td>(S)-(+)-25</td>
</tr>
<tr>
<td>7</td>
<td>(+)-2</td>
<td>(±)-26</td>
<td>H/E = 15:1</td>
<td>1.46</td>
<td>2.77</td>
<td>(S,3R,4S)-(+)-35a $^c$</td>
<td>(3R,4S)-(+)-26</td>
</tr>
<tr>
<td>8</td>
<td>(+)-2</td>
<td>(±)-27</td>
<td>H/E = 15:1</td>
<td>1.12</td>
<td>1.45</td>
<td>(S,R)-(-)-36a</td>
<td>(R)-(-)-27</td>
</tr>
<tr>
<td>9</td>
<td>(+)-2</td>
<td>(±)-28</td>
<td>H/E = 15:1</td>
<td>1.10</td>
<td>1.40</td>
<td>(S,R)-(-)-37a</td>
<td>(R)-(-)-28</td>
</tr>
</tbody>
</table>

$^a$Glass column (22 φ × 300 mm, or 25 φ × 400 mm) of silica gel (particle size 5-10 µm). $^b$H = n-hexane, EA = ethyl acetate. $^c$Separation factor $\alpha = (t_2-t_0)/(t_1-t_0)$ where $t_1$ and $t_2$ are the retention times of the first- and second-eluted fractions, respectively, and $t_0$ is the retention time of an unretained compound (void volume marker). $^d$Resolution factor $R_s = 2(W_1/W_2)/(W_1+W_2)$ where $W_1$ and $W_2$ are the band-widths of the first- and second-eluted fractions at the base-line level, respectively. $^e$Mono-MnzNP ester.

As described here, MnzNP acid has excellent enantioresolving power regardless of its simple molecular structure and the absence of so-called hetero atoms. Besides, the chiral acid 2 is superior to Mosher’s MTPA and Trost’s MPA acids in the magnetic anisotropy effect, and, therefore, further development of this method is expected.

5.4 Recent applications of the MnzNP acid method to various alcohols: large-scale HPLC separation.

The MnzNP acid method has been successfully applied to various racemic alcohols listed in Table 1 for preparation of enantiopure secondary alcohols and simultaneous determination of their absolute configurations. If the separation factor $\alpha$ is as large as in the case of 1-octyn-3-ol 20 (entry 1 in Table 1, $\alpha = 1.93$), a large-scale HPLC separation of diastereomeric MnzNP esters is feasible. For example, in the case of esters 29a and 29b derived from alcohol 20, ca 0.85-1.0 g of the mixture was separable in one run by the HPLC (hexane/EtOAc = 20:1) using a silica gel glass column (22 φ × 300 mm) (Figures 17 and 18).
The HPLC separation data of diastereomeric esters prepared from other racemic alcohols 21-28 with MₙNP acid (S;S)-(+)-2 are listed in Table 1. It should be emphasized that in the cases of most alcohols, their diastereomeric MₙNP esters are clearly separated with α values larger than 1.10. Acetylene alcohol 21 was separable as MₙNP esters 30a/30b (α = 1.30, entry 2). Substituted cyclohexanols 22 and 23 were also effectively separated as MₙNP esters (entries 3 and 4). Especially, the α value of trans-2-isopropylcyclohexanol MₙNP esters 31a/31b is as large as 1.88, which is comparable to that of the menthol case. On the other hand, in the case of trans-2-methylcyclohexanol MₙNP esters 32a/32b, the α value is relatively small, α = 1.21. These results indicate that the combination of a longer and larger alkyl group on one side and a smaller alkyl group on the other side leads to better separation of two diastereomers, as seen in 2-hexadecanol esters 18a/18b (Figure 13) and trans-2-isopropylcyclohexanol MₙNP esters 31a/31b.

Entry 5 is an interesting case, where mono-MₙNP esters 33a/33b of trans-1,2-cyclohexanediol 24 were sufficiently separated, regardless of the existence of a polar hydroxyl group (α = 1.35). In the cases of cyclic naphthalene alcohols 25 and 26, their MₙNP esters were separated well, but the values depend on the neighboring substituent. Namely, the MₙNP esters 35a/35b of trans-alcohol 26 were more efficiently separated (α = 1.46) than those of unsubstituted alcohol 25 (esters 34a/34b, α = 1.22) (entries 6 and 7). The enantioresolution of ortho-substituted diphenylmethanols 27 and 28 was one of the most difficult cases. Namely, we previously applied the CSDP acid method to these alcohols.25,26 However, the diastereomeric CSDP esters of 27 appeared as a single peak in HPLC, indicating no separation at all. However, the MₙNP esters 36a/36b of alcohol 27 were base-line separated (α = 1.12, entry 8). In a similar way, alcohol 28 was also enantioresolved as MₙNP esters 37a/37b (α = 1.10, entry 9).

By applying the ¹H NMR anisotropy method, the absolute configurations of the first-eluted MₙNP esters 29a–37a were determined as illustrated in Figure 19. The observed Δδ values are distributed in a reasonable manner; protons near the MₙNP group show larger Δδ values than remote ones. In the 1-octyn-3-ol MₙNP esters 29a/29b, the acetylene proton showing positive Δδ value (+0.11) is placed on the right side, while the pentyl group having negative Δδ values is on the left side. So, the absolute configuration of (−)-29a was assigned as S. In the phenyl acetylene alcohol esters 30a/30b, the phenyl protons show clearly positive Δδ values, regardless of the long distance from the MₙNP group, while the iso-butyl group shows large negative Δδ values. Therefore, the S absolute configuration was assigned to (−)-30a.

In the cyclic alcohol esters 31a/31b and 32a/32b, the observed Δδ values are similar at the corresponding positions, leading to the (1R,2S)-absolute configuration of (−)-31a and the (1R,2R)-absolute configuration of (−)-32a. The case of vicinal diol mono-MₙNP esters 33a/33b is a unique example; there was some concern that the conformation of the MₙNP group might be deviated from the ideal syn-conformation by the effect of the adjacent polar hydroxyl group. However, the distribution pattern of observed Δδ values is similar to that of esters 31a/31b, although their absolute values are different. So, the (1R,2R) absolute configuration was assigned to (−)-33a.

The naphthalene-cyclic alcohol esters 34a/34b are also interesting cases; the naphthalene moiety contained in the alcohol skeleton also works as a strong ¹H NMR anisotropy-inducing group. Therefore, it was considered that the ¹H NMR anisotropy effect of MₙNP esters 34a/34b might
become complex because of the two naphthalene groups. However, $\Delta \delta$ values observed are reasonably distributed even in the naphthalene region. Furthermore it should be emphasized that the 2-axial proton exhibits a very large negative $\Delta \delta$ value (-1.36 $\sim$ -1.29) as shown in Figure 19. This phenomenon is interpreted as follows; the MeNP ester group takes an axial orientation in both 34a and 34b because of the peri-position of the naphthalene group, and, therefore, in the syn-conformation of 34b, the 2-axial proton is located just below the naphthalene ring of the MeNP moiety, falling in the area of high field shift. From the observed $\Delta \delta$ data, the S absolute configuration was unambiguously assigned to the first-eluted ester (+)-39a.

It should be also noted that the boundary line of $\Delta \delta$ values is tilted to the right side as indicated by the dotted line in 34a (Figure 19). Namely, the MeNP plane dividing the space into two sectors of $\Delta \delta$ is moved from the regular position of the C4-C1 line to that of C4-C10. This phenomenon implies that the MeNP ester moiety declines toward the aliphatic side of C-3, not toward the aromatic side of C-4a, because of steric hindrance. This conformation was in fact proved by the X-ray crystallographic analysis of ester 34a, which indicated that the ester plane was tilted from the alcohol methine proton plane by 41.7° to the methylene side at the C-3 position.31 The $\Delta \delta$ data of trans-methyl alcohol esters 35a/35b are similar to those of esters 34a/34b except that of the methyl group, leading to the (3R,4S) absolute configuration of (+)-35a.

In the case of (2-methylphenyl)phenylmethanol MeNP esters 36a/36b, it is easy to assign the proton signals of two phenyl groups, leading to the R absolute configuration of (−)-36a, which was corroborated by X-ray crystallography. In the 2-methylphenyl group on the left side, the $\Delta \delta$ value of the H-5 proton (-0.45) is larger than that of the H-3 proton (-0.22), indicating that esters 36a/36b take a preferred conformation where the H-5 proton is more shielded by the naphthalenyl group than the H-3 proton. A similar phenomenon was also observed in esters 37a/37b, the $\Delta \delta$ value of the H-5 proton (-0.46) is larger than that of the H-3 proton (-0.14). The absolute configuration of 37a was unambiguously determined as R.

Enantiopure alcohols were recovered from the corresponding diastereomeric MeNP esters: i) by hydrolysis with KOH in EtOH, or ii) by solvolysis with NaOCH$_3$ in MeOH followed by treatment with water, or iii) by reduction with LiAlH$_4$, or iv) by hydrolysis with K$_2$CO$_3$ in EtOH as listed in Table 1. The MeNP acid method is thus very effective for preparation of enantiopure alcohols and also for simultaneous determination of their absolute configurations by the $^1$H NMR anisotropy method. The absolute configurations of alcohols (S)-(−)-21, (3R,4S)-(−)-26, and (R)-(−)-28 were first determined by this method.

6. Another chiral molecular tool, M9PP acid (3), and application to sulcatol, an insect pheromone.42)

We have recently found that 2-methoxy-2-(9-phenanthryl)propionic acid (M9PP acid (3), a 9-phenanthryl analogue of MeNP acid, Figure 1) is also useful for enantioresolution of alcohols and simultaneous determination of their absolute configurations by NMR. Chiral M9PP acid 3 was similarly prepared as in the case of MeNP acid (2), and its absolute configuration was determined by X-ray crystallography as (S)-(−).43 This novel chiral resolving agent, M9PP acid (S)-(−)-2, was applied to the enantioresolution of 6-methyl-5-hepten-2-ol (sulcatol, 38), an aggregation pheromone of the ambrosia beetle Onthophagus taurus. Mori reported the syntheses of both enantiomers of sulcatol starting from (S)-(−) and (R)-(−)-glutamic acids, respectively.43)

To enantioresolve racemic sulcatol, alcohol (±)-38 was esterified with M9PP acid (S)-(−)-3. The diastereomeric esters obtained were readily separated by HPLC on silica gel (hexane/EtOAc 9:1) giving the first-eluted ester (−)-39a (40%, $\left[\alpha\right]_D^{23}$ -4 (c 0.76, EtOH)) and the second one (+)-39b (33%, $\left[\alpha\right]_D^{23}$ +105 (c 0.630, EtOH)); separation factor $\alpha = 1.37$ (Figure 20a)). The $^1$H NMR signals of esters (−)-39a and (+)-39b were fully assigned by DQF COSY, PS NOESY, and HSQC spectra; a positive $\Delta \delta$ value ($\Delta \delta = \delta(2\text{nd fraction}) - \delta(1\text{st fraction})$) was obtained for the methyl group of the 1-position ($\Delta \delta = +0.30$), while negative $\Delta \delta$ values were obtained for the remaining part of the alcohol (Figure 20b). These data clearly indicate that the first-eluted fraction (−)-39a has the (S;R) absolute configuration and the second-eluted fraction (+)-39b the (S,S) configuration.

Ester (S;R)-(−)-39a was next treated with NaOMe/MeOH yielding sulcatol (R)-(−)-38 ($\left[\alpha\right]_D^{20}$ -14 (c 0.12, EtOH)); ref 43, $\left[\alpha\right]_D^{23}$ -14.5 (c 0.74, EtOH)). From the second-eluted fraction (S,S)-(−)-39b, the opposite enantiomer (S)-(−)-38 was obtained: $\left[\alpha\right]_D^{23}$ +14 (c 0.11, EtOH); ref 43, $\left[\alpha\right]_D^{23}$ +14.4 (c 0.998, EtOH). Therefore, the absolute configuration of sulcatol determined by the $^1$H-NMR anisotropy method agrees with the previous assignment. To check the enantiopurity of the sulcatol obtained, (R)-(−)-38 was esterified with M9PP acid (S)-(−)-3 giving the ester
(S;R)-(-)-39a only, and no HPLC peak corresponding to (S,S)-(+)-39b was detected (Figure 20c)). The same was true for the case of sulcatol (S)-(+)-38. The chiral M9PP acid 3 is thus useful also for the study of pheromones.

7. Reliability of the 1H-NMR anisotropy method for determining absolute configurations using MαNP acid.44)

As discussed above, the method of MαNP acid is very useful for preparation of enantiopure secondary alcohols and simultaneous determination of their absolute configurations. However, those absolute configurations were determined by the empirical sector rule, which is based on the magnetic anisotropy of the naphthalene ring and the preferred conformation of the MαNP ester. Therefore, the absolute configurations obtained by this method are of empirical nature. How reliable are those absolute configurations? To evaluate the reliability of the MαNP acid method, we have compared the results by the MαNP acid method with those by the X-ray crystallographic analysis, as described below.

As one of such comparison studies, the case of (4-trifluoromethylphenyl)phenylmethanol 5 is explained as follows. The absolute configuration of alcohol 5 was determined as (R)-(-) by the X-ray crystallographic analysis of its CSDP ester (Figures 3 and 4, and Table 2, entry 1). To apply the MαNP acid method, racemic alcohol (+)-5 was esterified with MαNP acid (S)-(+)-2; the diastereomeric mixture of esters 45a and 45b obtained was separated well by HPLC on silica gel (hexane/EtOAc 8:1): 5, 5.5 = 1.39; Rs = 4.84 (Table 2, entry 4). To determine the absolute configuration by the 1H NMR anisotropy method, all NMR signals were fully assigned by the 1H, 1H-1H COSY, 13C, HMQC, and HMBC methods. In the case of fluorinated diphenylmethanols, the 1H-19F coupling was helpful for assigning 1H NMR signals. The Δδ values of the 1H NMR anisotropy effect of (4-trifluoromethylphenyl)phenylmethanol MαNP esters 45a and 45b were calculated; the phenyl group showed large positive Δδ values (+0.11 ~ +0.43 ppm), while the 4-trifluoromethylphenyl group showed large negative Δδ values (-0.58 ~ -0.37 ppm). By applying the MzNP sector rule, the R absolute configuration was assigned to the first-eluted MzNP ester (R)-(-)-45a.

Chiral fluorinated diphenylmethanols could be recovered by reduction with LiA1H4 from the corresponding diastereomeric MzNP esters. So, the first-eluted MzNP ester 45a was treated with LiA1H4, yielding enantiopure alcohol (R)-(-)-5, which was identical with the authentic sample recovered from the first-eluted CSDP ester (R)-(-)-6a. The R absolute configuration of (4-trifluoromethylphenyl)phenylmethanol (R)-(-)-5 determined by the 1H NMR anisotropy method was thus confirmed by X-ray crystallography (Table 2).

Other fluorinated diphenylmethanols were similarly enantioresolved with CSDP acid (R)-1, and the diastereomeric mixtures obtained were subjected to HPLC on silica gel. As shown in Table 2, diastereomeric CSDP esters of alcohols (3-CF3)-40 and (2,6-F2)-41 were separated well with α-values of more than 1.1. The absolute configurations of esters 43a, 43b, and 44a were determined by X-ray crystallography (entries 2 and 3).

The MzNP method was similarly applied to alcohols 40-42; it was relatively difficult to separate the diastereomeric MzNP esters of (3-CF3)-40 and (2,6-F2)-41, because their α-values were around 1.07-1.08 (entries 5 and 6). The absolute configurations of alcohols (3-CF3)-40 and (2,6-F2)-41 determined by the MzNP method agreed with those obtained by the X-ray method (Table 2). The absolute configuration of alcohol (4-F)-42 was determined by this method (entry 7). The MzNP acid method is thus reliable and powerful as a molecular tool for studying the chirality of various compounds.
7. Conclusion

We have developed chiral molecular tools and successfully applied those CDAs (chiral derivatizing agents) to the preparation of enantiopure alcohols by HPLC separation, and simultaneous determination of their absolute configurations by X-ray crystallography and/or by $^1$H NMR anisotropy method. The X-ray crystallographic method using an internal reference is, of course, the best for determining absolute configuration. However, ideal single crystals are not always obtainable. In such a case, the $^1$H NMR method using MnNP acid, which requires no crystalization, is effective. In enantioreselection, chiral CSDP acid and MnNP acid are thus useful as the complementary molecular tools. If the resolution with one CDA is unsuccessful, the use of the other is suggested. The methods described above are very powerful for preparation of enantiomeric alcohols with 100% enantiopurity and also for simultaneous determination of their absolute configurations.

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References

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