Contribution

Powerful Novel Chiral Acids for Enantioresolution, Determination of Absolute Configuration, and MS Spectral Determination of Enantiomeric Excess

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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 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 apidly progressing in recent years. Therefore, the unambiguous determination of the absolute configuration of a molecule as well as that in the chiral synthesis are of vital importance in the field of material science.

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

2. Methodologies for determining absolute configuration and their evaluations

The methodologies to determine the absolute configurations of the chiral compounds are classified into the following two categories.

(1) Nonempirical methods for determining absolute configurations of chiral compounds:

The methods in this category are the Bijvoet method by X-ray crystallography[1)] and circular dichroism (CD) exciton chirality method.[2)] These powerful methods provide non-empirical determination of a target molecule's configuration without knowing the absolute configuration of corresponding reference compounds. In X-ray crystallography, since the anomalous dispersion effect of heavy atoms can be measured very accurately under proper conditions, the absolute stereostructure obtained is clear and unambiguous. Since the molecule can be projected as a three-dimensional structure, the method has been employed extensively. However, the X-ray method requires a single crystal of suitable size adaptable for X-ray diffraction, and so the critical problem is how to obtain such a single crystal. As a consequence, a study using this method often becomes a lengthy trial and error search for an ideal single crystals.

The CD exciton chirality method[2)] 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) Relative 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 a 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.[3-6)] 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

an 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.[7-9] These relative X-ray methods are expected to find widespread application.

Recently, the proton nuclear magnetic resonance (^{1}H 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.*[10-13] In this case, the absolute configurations of the 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 to the phenyl group in the preferred conformation are moved to a higher magnetic field (high field shift). By observing the ^{1}H NMR anisotropy effect, the absolute configuration of the alcohol component can be determined. This method is very convenient, since it does not require crystallization of compounds and NMR machines are easily available. One drawback 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. Although the method has been widely applied to the secondary alcohols, it is expected to be extended to other kinds of compounds.

The absolute configuration can also be determined relatively by chemical correlation or comparison of optical rotation, $[\alpha]_D$, 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 a reliable analysis.

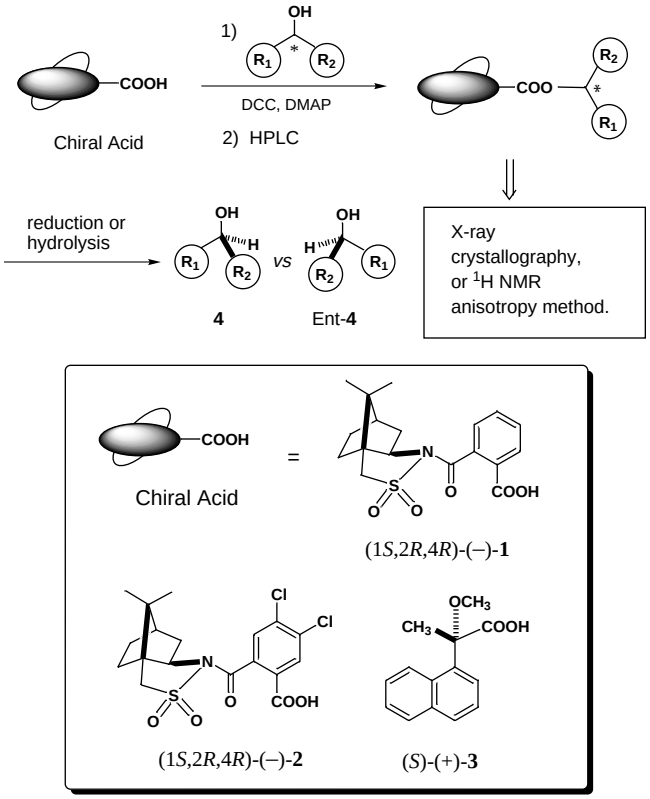


Fig. 1. Enantioresolution and determination of absolute configuration of alcohols using chiral carboxylic acids.

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 the 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 a covalently bonded diastereomer is formed using a chiral auxiliary, followed by HPLC separation and recovery of the target compound, is also defined in a broad sense as enantioresolution.*

(1) Enantioresolution of racemates:

Type a). In this method, a chiral auxiliary is ionically bonded to racemates, and a mixture of 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.[7-9] 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 100% enantiopure diastereomer. If this method is successful, it is suitable for mass preparation of the 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 question 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 c). 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, especially since 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 the absolute configuration by elution order, as there are many exceptions.

Type d). This is a unique method where racemates undergoe enzymatic or asymmetric reactions 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.

(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 synthesss, and so no further explanation is required here. The drawback 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. Chiral auxiliary powerful for HPLC enantioresolution and X-ray crystallography: applications to carboxylic acids

To prepare an appropriate amount of various chiral compounds with 100% enantiopurity on a laboratory scale, enantioresolution **1b)** is considered to be a highly efficient method as illustrated in Fig. 1. In this method, a chiral auxiliary is covalently bonded to racemates, and the obtained diastereomeric mixture is separated by conventional HPLC on 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, compared to the fractional recrystallization method described in type **1a)**.

We have experienced that diastereomers of nitrogen-containing compounds such as hydrazone[16] and amide derivatives[17] can be separated well by HPLC on silica gel. For instance, HPLC on silica gel is very

effective for the separation of diastereomers of amides which are formed with chiral amine and racemic carboxylic acid. However, recovery of the carboxylic acid is the problem to be solved, because amide bonds are not easily hydrolyzed. Accordingly, some extra reactions such as nitrosation prior to hydrolysis are needed.[17)]

We have then discovered that (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam (**5**), a chiral auxiliary employed successfully in asymmetric syntheses, is also very useful for enantioresolution of various carboxylic acids. The obtained diastereomeric mixture of camphorsultam amide is separated well by HPLC on silica gel. In addition, the camphorsultam amide bond of the separated diastereomers can be readily cleaved by $LiAlH_4$ reduction to yield a primary alcohol, and then subsequently converted to an enantiopure carboxylic acid by oxidation.

We have further found that the amides made with 2,10-camphorsultam (**5**) generally have excellent crystallinity to yield the large single crystals necessary for X-ray crystallography in a high probability.[3-6)] In general, a series of trials are required to obtain derivatives that could readily yield single crystals. By this enantioresolution method, two kinds of diastereomers are obtained simultaneously, providing two possibilities to obtain single crystals. If the X-ray analysis of one diastereomer is successful, the absolute configuration of the other is automatically determined.

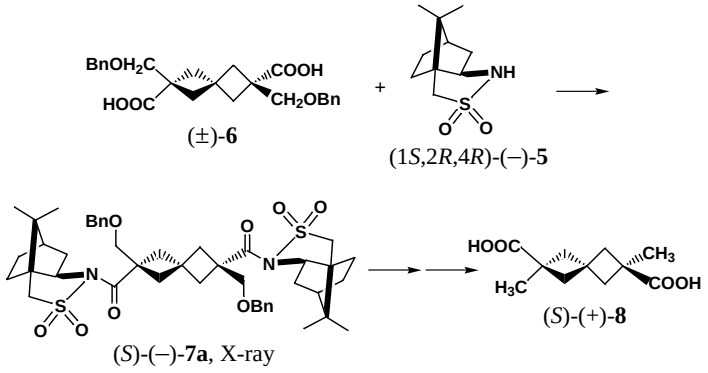


Fig. 2. Enantioresolution of carboxylic acid **6**, determination of its absolute configuration by X-ray crystallography, and synthesis of enantiopure Fecht acid analogue.

The absolute configuration of the chiral auxiliary, (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam (**5**) (available at TCI, Tokyo Kasei Kogyo Co., Ltd.), is known, since it is synthesized from naturally occurring (1*R*,4*R*)-(+)-camphor.[18)] Consequently, it can be used as an internal reference for the determination of the absolute configuration by X-ray crystallography, which leads to the absolute configuration of a carboxylic acid moiety. Moreover, 2,10-camphorsultam (**5**) contains a sulfur atom as the heavy atom, making it possible to determine the absolute configuration by the Bijvoet method. Therefore, the absolute configuration can be determined independently by two methods.

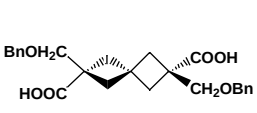
A typical example is illustrated in Fig. 2.[3)] (1*S*,2*R*,4*R*)-(–)-2,10-Camphorsultam (**5**) was treated with NaH to make an anion, which was then allowed to react with the acid chloride of (±)-2,6-bis(benzyloxymethyl)spiro-[3.3]heptane-2,6-dicarboxylic acid (**6**). The resulting two diastereomers **7a** and **7b** showed good separation and appeared as two clear spots (ΔR_f = 0.12) on a 5 cm TLC plate of silica gel. In our experiment, ca. 100 mg was separated by a single HPLC on silica gel ($22\phi \times 300$ mm: benzene/ethyl acetate = 20:1): *R*s =2.9.

The first fraction (–)-**7a** gave prismatic crystals by recrystallization from EtOAc. A single crystal was then analyzed by X-ray crystallography. The absolute configuration was unambiguously determined to be *S* with the camphor moiety as an internal reference. In addition, the absolute configuration determined by the anomalous dispersion effect of the heavy atom was consistent with that by the internal reference method. After reduction of (*S*)-(–)-**7a** with $LiAlH_4$ to cleave the chiral auxiliary, it was converted to (*S*)-(+)-2,6-dimethylspiro[3.3]heptane-2,6-dicarboxylic acid (**8**) using several reactions steps. In this way, we have synthesized non-racemizing and enantiopure Fecht acid analogue **8** and determined its absolute configuration.[3)]

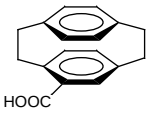
Table. 1. Enantioresolution of carboxylic acids by separation of (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam amides using HPLC on silica gel, and determination of their absolute configurations by X-ray crystallography.

Entry	Solvent[a]	α	*Rs*	X-ray	Abs.Config. First Fr.	Ref.
6	Bz/EA = 20/1	–	2.87	○(1st, Fr.)	*S*	3)
9	H/EA = 5/1	–	1.60	○(1st, 2nd Fr.)	*R*	3,4)
10	H/EA = 5/1	–	0.70	○(1st, Fr.)	*S*	4)
11	H/EA = 5/1	1.20	2.87	○(1st, Fr.)	S	19)
12	H/EA = 4/1	–	–	○(2nd, Fr.)	a*S*	5)
13	H/ET = 2/1	–	–	○(1st, Fr.)	*Psc*	20,22)
14	– (recry.)	–	–	○	–	20,22)
15	– (recry.)	–	–	○	–	20,22)
16	CH_2Cl_2	–	–	○(1st, Fr.)	*Psc*	20.22)
17	H/ET = 1/2	–	–	○(1st, Fr.)	*Msc*	21)

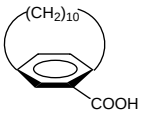
[a] Bz = benzene, EA = ethyl acetate, H = *n*-hexane, ET = diethyl ether.



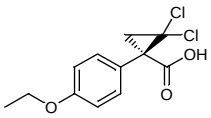
(*S*)-**6**



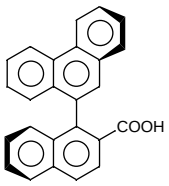
(*R*)-(–)-**9**



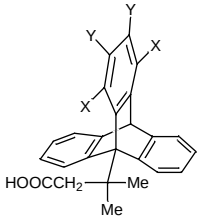
(*S*)-(–)-**10**



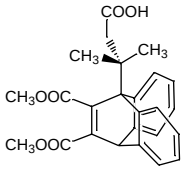
(*S*)-(–)-**11**



(a*S*)-(+)-**12**



13: X=Me, Y=H
14: X=OMe, Y=H
15: X=Y=F
16: X=Y=Cl



(*Msc*)-**17**

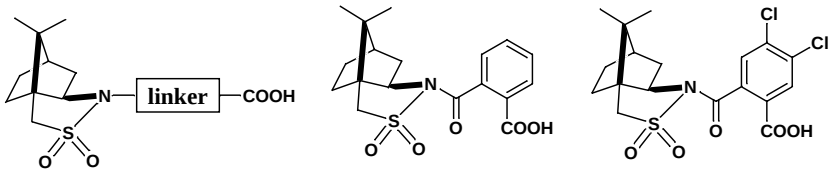
Other application examples are shown in Table 1. This method is, therefore, applicable to the enantioresolution of various carboxylic acids with different structural features, and their absolute configurations can be easily determined by X-ray analysis since they show excellent crystallinity. The absolute configurational studies on the individual compounds listed in Table 1 revealed some interesting facts. For example, the absolute configuration of [8]paracyclophane-10-carboxylic acid had previously been determined as (*S*)-(+) by the chemical correlation to a compound with known absolute configuration. Nevertheless, this configuration was proved wrong by our method[4] and we have concluded that the configurations of compounds **9** and **10** should be revised. Although determination of the absolute configuration by the chemical correlation is considered to be the most reliable one, much care should be taken as such errors could easily occur.

The compounds **13-17**, studied by Toyota *et al*, are also interesting examples of atropisomeric and optically active substances. In general, it is very difficult to determine the absolute configuration of the chiral compounds of atropisomerism based on steric hindrance. However, Toyota *et al.* successfully solved this problem by applying the method described above.[20-22]

5. Molecular design of chiral auxiliaries powerful for enantioresolution of alcohols by HPLC and X-ray crystallographic analysis

The chiral auxiliary, 2,10-camphorsultam (**5**) described above, is useful for the enantioresolution and determination of the absolute configuration of carboxylic acids. However, the demand for the syntheses of chiral alcohols and determination of their absolute configurations is greater than that of the carboxylic acids. The important question is what kind of auxiliary is applicable to the alcohols, while retaining the aforementioned characteristics of chiral auxiliaries.

We approached this problem with the following molecular design. First, introduction of linkers connecting 2,10-camphorsultam and alcohol (Fig. 3)[23] were designed. An amide bond for 2,10-camphorsultam and an ester bond for alcohols to bond with the linker were selected. The amide bond was reserved because of its affinity with HPLC on silica gel, whereas the ester bond was employed for the alcohols as it could be readily formed and cleaved off. Accordingly, phthalic acid was first selected as a linker molecule.[23] In terephthalic acid and succinic acid, the two chiral moieties are separated spatially. However, in phthalic acid, they are close enough and are expected to result in a stronger interaction. We concluded its diastereomeric recognition would be effective in HPLC (Fig. 3).



(1*S*,2*R*,4*R*)-(–)-**1** (1*S*,2*R*,4*R*)-(–)-**2**

Fig. 3. Design of a chiral carboxylic acid containing 2,10-camphorsultam moiety.

The desired chiral phthalic acid (–)-**1** was synthesized by reacting (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam (**5**) anion with phthalic anhydride: mp 184-187 °C from $CHCl_3$; $[\alpha]_D^{20}$ –134.7 (*c* 2.218, MeOH). The compound **1** should be formally called chiral phthalic acid amide. However, here we adopted its common name, chiral phthalic acid. This carboxylic acid was condensed with alcohol under the conditions of DCC and DMAP.[23]

The following exemplifies a general procedure for the preparation. The chiral phthalic acid (–)-**1** was allowed to react with (±)-α-methyl-(4-bromobenzyl)methanol (**18**) (Table 2), followed by separation of the obtained diastereomeric mixture by HPLC on silica gel: hexane/EtOAc = 3:1; α = 1.1, *R*s = 1.3. Chemical components are normally fully separable, if the separation factor α is 1.1 or more. Ester **19b**, eluted as the second fraction, had a good crystallinity, leading to single crystals suitable for X-ray analysis by recrystallization from MeOH. From the ORTEP drawing of X-ray, the absolute configuration of the alcohol part was unambiguously determined to be *S*, by using the 2,10-camphorsultam moiety as an internal reference and also by the heavy atom effect. Enantiopure alcohol (*S*)-(–)-**18** was recovered from diastereomeric ester **19b**.[23]

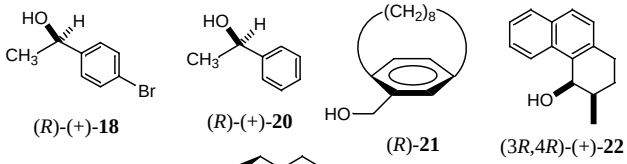
Other examples are shown in Table 2. The successful enantioresolution of various alcohols, determination of their absolute configurations by X-ray analysis, and the recovery of enantiopure alcohols listed in the table proved the effectiveness of this method. In cyanohydrin **27** and amine **28**, the diastereomeric separation and the determination of their absolute configurations were possible. However, there remained a problem in recovering enantiopure compounds **27** and **28**, because the amide bond could not be easily hydrolyzed. Amine **28** was enantioresolved as the salt of (2*R*,3*R*)-(+)-tartaric acid,[19] and its absolute configuration was established as (*S*)-(–) by this method. For compound **29**, its absolute configuration was unambiguously determined by this internal reference method, in spite of the small *R*-value, owing to its poor crystallinity.

In the course of our study, we found that esters of chiral phthalic acid (–)-**1** generally had low solubility, possibly due to its extreme crystallinity, resulting in longer elution time in HPLC on silica gel. In addition, crystals were often obtained in the form of fine needles upon recrystallization, making them unsuitable for X-ray crystallography. Since this indicated that the use of chiral phthalic acid esters with low solubility could be counterproductive, we have explored a variety of compounds in search for other linkers yielding softer esters with higher solubility.

Table 2. Enantioresolution of alcohols by HPLC on silica gel using (1*S*,2*R*,4*R*)-(–)-chiral phthalic acid, and determination of their absolute configurations by X-ray crystallography.

Entry	Solvent[a]	α	*Rs*	X-ray	Abs.Config. First Fr.	Ref.
18	H/EA = 3/1	1.1	1.3	○(2nd, Fr.)	*R*	23)
20	H/EA = 5/1	1.1	1.3	○(1st, Fr.)	*R*	23)
21	H/EA = 4/1	–	0.73	–	*R*	4)
22	H/EA = 7/1	1.1	0.8	–	3*R*,4*R*	24,25)
23	CH_2Cl_2/EA = 50/1	–	–	○(1st, Fr.)	*Msc*	26)
24	H/EA = 2/1	1.2	1.3	–	a*R*,a*R*	27,28)
25	H/EA = 4/1	1.1	1.3	○(1st, Fr.)	*S*	29)
26	H/EA = 5/1	1.1	1.6	○(1st, Fr.)	*R*	29)
27	H/EA = 3/1	1.3	2.8	○(1st, Fr.)	*R*	19)
28	H/EA = 2/1	1.1	1.0	○(1st, Fr.)	*S*	19)
29	H/EA = 3/1	1.1	1.6	○(2nd, Fr.)	*R*	23)

[a] Bz = benzene, EA = ethyl acetate, H = *n*-hexane, ET = diethyl ether.

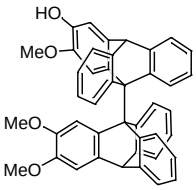


(*R*)-(+)-**18**

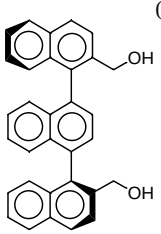
(*R*)-(+)-**20**

(*R*)-**21**

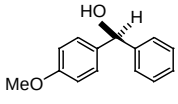
(3*R*,4*R*)-(+)-**22**



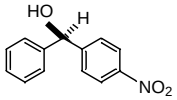
(*Msc*)-**23**



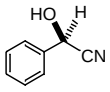
(a*R*,a*R*)-(–)-**24**



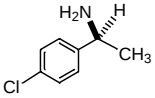
(*S*)-(–)-**25**



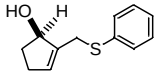
(*R*)-(–)-**26**



(*R*)-**27**



(*S*)-(–)-**28**



(*R*)-[CD(–)282.3]-**29**

6. Chiral dichlorophthalic acid powerful for both HPLC enantioresolution of alcohols and X-ray crystallographic analysis: development and applications

After a series of investigations, we have discovered that chiral dichlorophthalic acid (–)-**2** [mp 221°C from EtOH; $[\alpha]_D^{20}$ –101.1 (*c* 1.375, MeOH); Fig. 3], prepared from 4,5-dichlorophthalic acid as a linker, was effective for solving the problem discussed above. Namely, it has a high solubility and takes a shorter elution time in HPLC. In addition, it tends to provide prismatic crystals suitable for X-ray analysis. As an example, for (±)-*cis*-1,2,3,4-tetrahydro-3-methyl-4-phenanthrenol (**22**) shown in Table 2 and Fig. 4, the elution times of two diastereomers using chiral phthalic acid were 27.6 and 31.0 min, respectively, whereas the times using chiral dichlorophthalic acid under the same conditions were 14.6 and 16.7 min, respectively, almost half of the time required for the chiral phthalic acid. Furthermore, the separation and resolution factors were also improved.[24)]

The chiral auxiliary, dichlorophthalic acid (–)-**2**, is very useful as an internal reference in determining the absolute configuration by X-ray analysis, as in the case of chiral phthalic acid (–)-**1**. Moreover, carboxylic acid **2** contains two chlorine atoms as the heavy atoms in addition to a sulfur atom, thus leading to the efficient determination of the absolute configuration by the anomalous dispersion effect of heavy atoms.

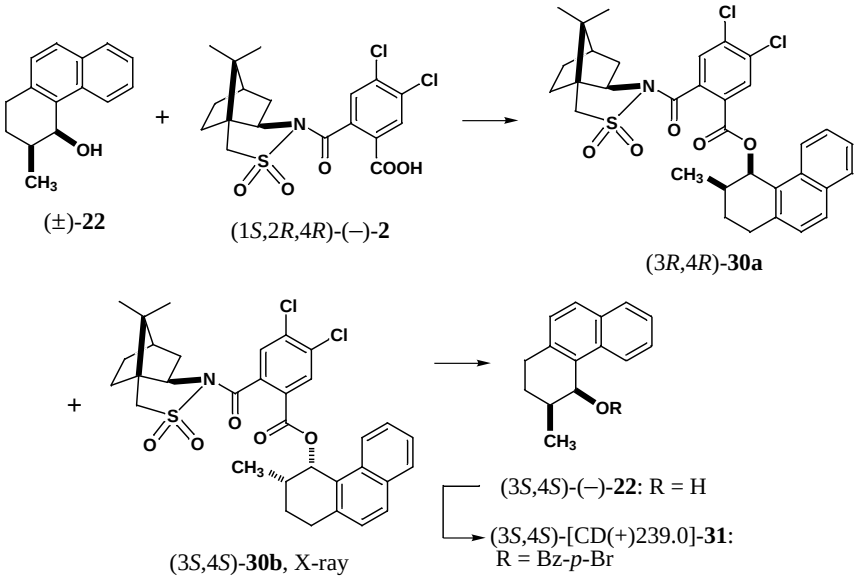


Fig. 4. Enantioresolution of alcohol (**22**) using chiral dichlorophthalic acid (–)-**2** and determination of its absolute configuration by X-ray crystallography.

An example is illustrated in Fig. 4. Alcohol (±)-**22** was condensed with chiral dichlorophthalic acid (–)-**2** in the presence of DCC and DMAP. The diastereomeric mixture of two esters obtained was subjected to HPLC on silica gel: hexane/EtOAc = 7:1, α = 1.18, *R*s = 1.06. While ester **30a** eluted as the first fraction afforded silky and fine needle-like crystals, unsuitable for X-ray analysis when recrystallized from MeOH, the second fraction **30b** gave larger prisms good for X-ray analysis upon recrystallization from EtOAc. The absolute configuration of **30b** was unambiguously determined to be (3*S*,4*S*) using the 2,10-camphorsultam as an internal reference and also the heavy atom effect as well. Ester **30b** was reduced with $LiAlH_4$ to remove the chiral auxiliary, yielding enantiopure alcohol (3*S*,4*S*)-(–)-**22**.[24,25] This absolute configuration was consistent with the result obtained by the CD exciton chirality method applied to the corresponding 4-bromobenzoate (**31**).[24]

Recently we have found that the solvolysis with K_2CO_3/MeOH was very effective to recover enantiopure alcohols from chiral dichlorophthalic acid esters in high yields.

Table 3 lists other application examples. Chiral dichlorophthalic acid esters of *para*-substituted diphenylmethanols **25**, **26**, and **34-38** were clearly separated by HPLC on silica gel, although the *para*-substituents governing the chirality of molecule are apart from the stereogenic center, i.e., the carbon atom with hydroxyl group.[29,30,32] These results indicate that the chiral dichlorophthalic acid easily recognizes the molecular chirality, i.e., the difference between a hydrogen atom and a *para*-substituted functional group.

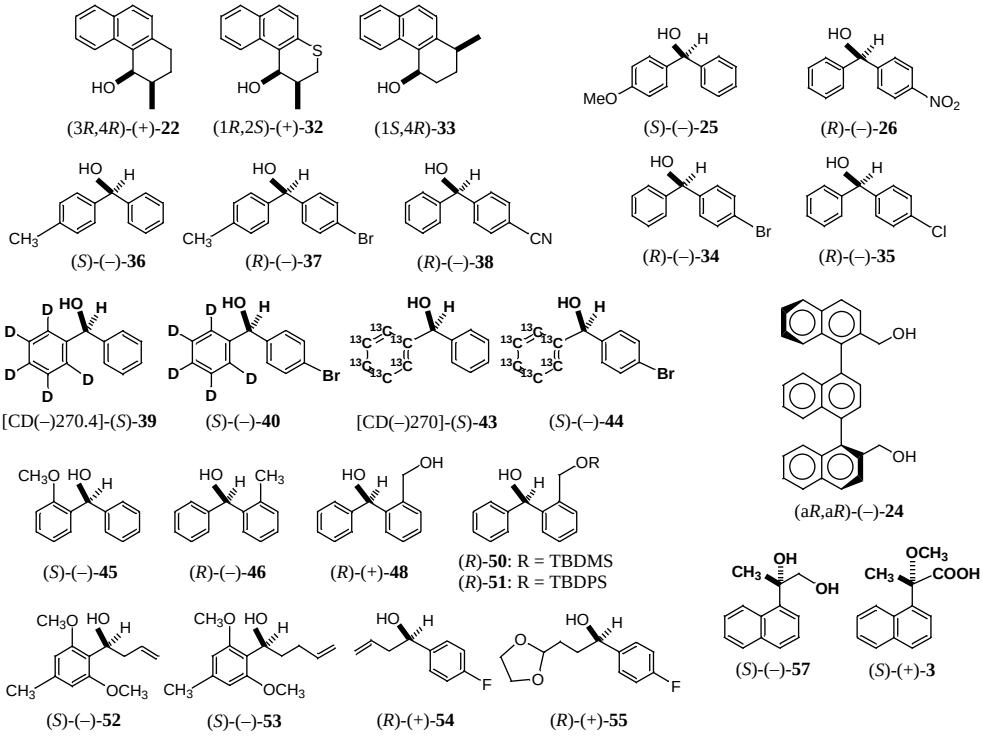
The chirality recognition of the alcohol in (4-methylphenyl)phenylmethanol (**36**) as chiral dichlorophthalic acid ester was impossible. The difference between hydrogen and methyl group constituting the molecular chirality was trivial and its chirality could not be recognized. Therefore, the diastereomeric separation by HPLC on silica gel failed.[29] It was then decided to adopt the following strategy. First, (4-bromophenyl)(4'-methylphenyl)methanol (**37**), selected as the precursor, was well enantioresolved as chiral dichlorophthalates, and then their absolute configurations were determined by X-ray crystallography. The reduction of the bromine atom led to the desired enantiopure alcohol (*S*)-(–)-**36**.[29] This strategy was also useful for the synthesis and determination of the absolute configuration of isotope-substituted chiral diphenylmethanols as described below.

The molecular chirality can also be generated by substitution with isotopes as shown in ^{2}H substituted diphenylmethanol **39** and ^{13}C substituted diphenylmethanol **43**.[32,33] It is almost impossible to directly enantioresolve these isotope-substituted chiral compounds by usual HPLC with chiral stationary phase or by HPLC on silica gel using chiral auxiliary. In such a case, a precursor such as (±)-(4-bromophenyl)(phenyl-2,3,4,5,6-d_5)methanol (**40**) must be selected, and then enantioresolution as chiral dichlorophthalate and determination of the absolute configuration can be carried out. Subsequently, the bromine atom is reduced to yield the desired enantiopure (phenyl-2,3,4,5,6-d_5)phenylmethanol (**39**).[32]

Table 3. Enantioresolution of alcohols by HPLC on silica gel using (1*S*,2*R*,4*R*)-(–)-chiral dichlorophthalic acid, and determination of their absolute configurations by X-ray crystallography.

Entry	Solvent[a]	α	*Rs*	X-ray	Abs.Config. First Fr.	Ref.
22	H/EA = 7/1	1.18	1.06	○ (2nd, Fr.)	3*R*,4*R*	24,25)
32	H/EA = 7/1	1.23	1.27	○ (1st, 2nd, Fr.)	1*R*,2*S*	31)
33	H/EA = 10/1	1.30	1.74	○ (1st, Fr.)	1*S*,4*R*	24)
25	H/EA = 4/1	1.20	0.91	–	*S*	29)
26	H/EA = 5/1	1.26	1.37	–	*R*	29)
34	H/EA = 8/1	1.17	0.80	○ [b]	*R*	32)
35	H/EA = 6/1	1.17	0.95	–	*R*	30)
36	H/EA = 7/1	–	–	–	–	29)
37	H/EA = 8/1	1.18	0.83	○ (1st, Fr.)	*R*	29)
38	H/EA = 4/1	1.1	1.0	–	*R*	30)
40	H/EA = 8/1	1.21	1.07	○ [b]	*S*	32)
44	H/EA = 4/1	1.27	1.20	○ [b]	*S*	33)
45	H/EA = 5/1	1.12	1.01	○ (1st, Fr.)	*S*	34)
48	H/EA = 4/1	1.14	0.91	○ (2nd, Fr.)	*R*	34,35)
50	H/EA = 10/1	1.26	1.03	–	*R*	34)
51	H/EA = 6/1	1.26	1.29	–	*R*	36)
52	H/EA = 5/1	1.16	1.11	○ (1st, Fr.)	*S*	37)
53	H/EA = 5/1	1.12	0.87	○ (1st, Fr.)	*S*	37)
54	H/EA = 2/1	1.11	0.88	–	*R*	37)
55	H/EA = 2/1	1.38	1.19	○ (1st, Fr.)	*R*	37)
24	H/EA = 3/1	1.2	1.6	○ (2nd, Fr.)	a*R*,a*R*	27,28)
57	H/EA = 4/1	1.27	1.14	○ [c]	*S*	38)

[a] H = *n*-hexane, EA = ethyl acetate, [b] X-ray analysis of camphanate ester, [c] X-ray analysis of 4-bromobenzoate.



The preparation of (phenyl-2,3,4,5,6-d_5)phenylmethanol (**39**) was carried out as follows. Racemic alcohol (±)-**40** was condensed with chiral dichlorophthalic acid and then the esters formed were separated by using HPLC on silica gel. Both diastereomeric esters separated gave fine needle-like crystals after a series of recyrstallizations. Accordingly, after recovering the enantiopure alcohol (–)-**40** from the first fraction **41a**, a part of (–)-**40** was converted to ester **42** using (–)-camphanic acid chloride. Ester **42** showed good crystallinity, yielding prismatic crystals suitable for X-ray analysis, and the absolute configuration of the alcohol moiety was determined as *S*, using the absolute configuration of (–)-camphanic acid as an internal reference. Subsequently, alcohol (*S*)-(–)-**40** was reduced with H_2NNH_2/H_2O in the presence of Pd-C to yield the isotope-substituted enantiopure (phenyl-2,3,4,5,6-d_5)phenylmethanol [CD(–)270.4]-(*S*)-**39**, making possible the unambiguous determination of the absolute configuration. The specific rotation $[\alpha]_D$ measured at the wavelength of the sodium D-line (589 nm) is usually used to distinguish enantiomers. However, it was difficult to measure the $[\alpha]_D$ value of the compounds with isotope-substitution chirality. Therefore, we have proposed the new definition method of enantiomers by using CD data, because CD is not only more sensitive than $[\alpha]_D$, but it is also accurately measurable even with a small amount of samples. For example, [CD(–)270.4]-(*S*)-**39** stands for the enantiomer with negative CD at 270.4 nm and *S* absolute configuration.[32)]

It would be even more advantageous if (–)-camphanic acid could be used from the beginning as the chiral auxiliary for enantioresolution. However, the enantioresolution power of (–)-camphanic acid is generally weak. For example, camphanic acid esters of alcohol **40** could not be separated by HPLC on silica gel. Thus, it is sometimes necessary to select two chiral auxiliaries depending on the situation.

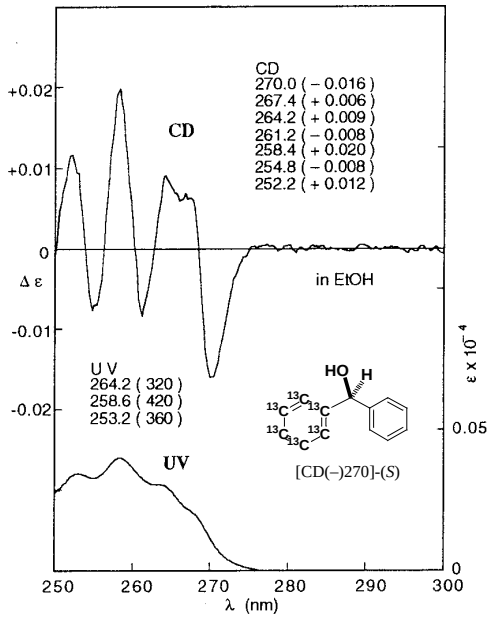


Fig. 5. UV and CD spectra of (phenyl-1,2,3,4,5,6-$^{13}C_6$)phenylmethanol (**43**) in EtOH.

A similar scheme could be applied to synthesize ^{13}C-substituted chiral diphenylmethanol (**43**).[33)] Namely, (4-bromophenyl)(phenyl-1,2,3,4,5,6-$^{13}C_6$)methanol (±)-(**44**) was chosen and then enantioresolution and determination of the absolute configuration were performed in a similar way as described above. Subsequently, the bromine atom was reduced to yield the ^{13}C-substituted chiral (phenyl-1,2,3,4,5,6-$^{13}C_6$)phenylmethanol [CD(–)270]-(*S*)-**43**. Despite the very small molecular chirality due to the slight difference between isotopes ^{12}C and ^{13}C, the CD spectrum of ^{13}C-substituted chiral diphenylmethanol (*S*)-**43** was clearly observable as illustrated in Fig. 5.[33)]

Interesting results were also obtained in the case of *ortho*-substituted diphenylmethanols. Using the method described above, enantiopure (2-methoxyphenyl)phenylmethanol (–)-(**45**) was prepared and its absolute configuration was determined as *S*.[34] Chiral (2-methylphenyl)phenylmethanol (**46**) had previously been synthesized by asymmetric catalytic reaction, and its absolute configuration had been estimated based on the chiral reaction mechanism. But is the absolute configurational assignment based on the reaction mechanism reliable? In such a case, the independent and unambiguous determination of the absolute configuration is necessary. To solve this problem, we have carried out the following experiments. The direct enantioresolution of **46** as chiral dichlorophthalate was unsuccessful, as in the case of *para*-substituted alcohol **36**. It was difficult to discriminate hydrogen atom and methyl group in the *ortho* position. We then attempted the enantioresolution of (4-bromophenyl)(2'-methylphenyl)methanol (**47**). However, the HPLC analysis exhibited only a single peak.

Next we adopted the following indirect method.[34-36] The strategy consisted of enantioresolution of (2-hydroxymethylphenyl)phenylmethanol (**48**) as chiral dichlorophthalate, determination of the absolute configuration by X-ray analysis, and conversion of the enantiopure derivative of **48** obtained to the desired alcohol **46**. Chiral dichlorophthalic acid (–)-**2** (1 eq.) was allowed to react with diol (±)-**48** to yield a diastereomeric mixture of esters, in which the primary alcohol group was selectively esterified. In this case, the chiral auxiliary group bonding to the primary alcohol moiety was remote from the stereogenic center of **48**, but the diastereomeric esters were clearly separated. Single crystals were obtained from the second fraction (–)-**49b**, leading to the determination of its absolute configuration as *S* by X-ray analysis. The first-eluted fraction (*R*)-(–)-**49a** was converted to the desired enantiopure alcohol (*R*)-(–)-**46** through several reaction steps. The result indicated that the absolute configuration of **46** previously assigned on the basis of an asymmetric reaction mechanism was wrong.[35] Since the absolute configurational assignment based on the reaction mechanism sometimes may result in an error, it is advisable to determine the absolute configuration of products independently.

This method is also effective for the preparation of a variety of benzyl alcohols **52-55**,[37] useful as chiral synthons for the total synthesis of natural products because of their unambiguous absolute configurations and 100% enantiopurity.

Atropisomer **24** is a unique chiral compound containing three naphthalene chromophores. Its enantioresolution and determination of the absolute configuration were carried out by the following method.[27,28] Racemic diol, (±)-1,1':4',1''-ternaphthalene-2,2''-dimethanol (**24**), was coupled with chiral dichlorophthalic acid **2** to form a mixture of diesters, which was separated by HPLC on silica gel: hexane/EtOAc = 2:1, α = 1.18. While the first fraction (–)-**56a** yielded fine needle-like crystals by recrystallization from hexane/EtOAc, the second fraction (+)-**56b** yielded large crystals.

In general, single crystals suitable for X-ray analysis have prismatic or columnar forms with definite surfaces and edges, or thick plate-like forms. The ester (+)-**56b** gave odd crystals resembling airplanes with triangular wings upon recrystallization, and they did not look like single crystals. However, after removal of the wings, the body part was subjected to X-ray analysis, which revealed that it was a single crystal. Interestingly, the formula weight of an asymmetric unit estimated from the preliminary lattice constant did not agree with the molecular weight of (+)-**56b**. So, we had initially thought that molecular structure might be incorrect, assuming that the asymmetric unit of **56b** contained one molecule because of the asymmetric structure of chiral dichlorophthalic acid moiety. Careful investigation of the data obtained, however, revealed that a half of the molecule **56b** was equivalent to one asymmetric unit. Namely, ester (+)-**56b** had a C_2 symmetric structure even in crystals, despite the fact that the molecule contained complex chiral dichlorophthalic acid moieties. The absolute configuration, i.e., torsion among three naphthalene chromophores, was unambiguously determined as (a*S*,a*S*) on the basis of the internal reference. The chiral auxiliaries were removed from the ester (a*S*,a*S*)-(+)-**56b** to yield enantiopure diol (a*S*,a*S*)-(+)-**24**. The absolute configuration obtained from this X-ray analysis was consistent with that obtained by application of the CD exciton chirality method to (+)-**24**.[27,28]

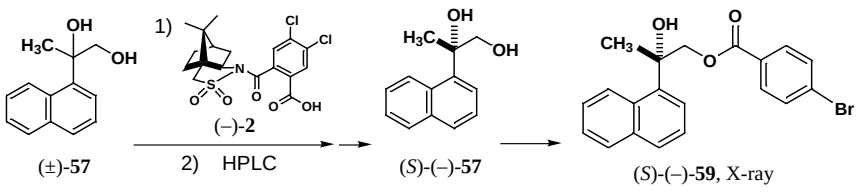


Fig. 6. Enantioresolution and determination of the absolute configuration of 2-(1-naphthyl)propane-1,2-diol (**57**).

The compound, 2-(1-naphthyl)propane-1,2-diol (**57**), was isolated as a chiral metabolite of 1-isopropylnaphthalene in rabbits. 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 **57** and to determine its absolute configuration in an unambiguous way, the method of chiral dichlorophthalic acid was applied to (±)-**57**.[38] In this case, only the primary alcohol part was esterified, and a diastereomeric mixture obtained was clearly separated by HPLC on silica gel: hexane/EtOAc = 4:1, α = 1.3, *R*s = 1.1. In this HPLC, the presence of free tertiary hydroxyl group was important. But the protection of the tertiary alcohol group led to a poor separation.

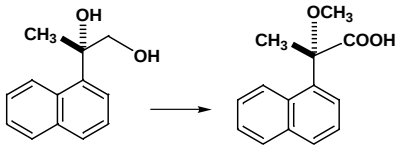
Despite the repeated recrystallizations, both diastereomers were obtained only as amorphous solids. Therefore, the first fraction (–)-**58a** was reduced with $LiAlH_4$ to yield enantiopure glycol (–)-**57**, which was further converted to 4-bromobenzoate (–)-**59** (Fig. 6). Performing recrystallization from EtOH, (–)-**59** 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 from the bromine atom included (Table 4).

Table 4. The Bijvoet pairs of (*S*)-(–)-2-(1-naphthyl)propane-1,2-diol 1-*p*-bromobenzoate (**59**): observed and calculated values of the structural factors for (h,k,l) and (h,k,-l) reflections, and their ratios.

h	k	l	|Fo(hkl)| [|Fc(hkl)|]	|Fo(hk-l)| [|Fc(hk-l)|]	|Fo(hkl)|/|Fo(hk-l)| [|Fc(hkl)|/|Fc(hk-l)|]
1	4	1	39.4 [35.4]	32.1 [27.9]	1.23 [1.26]
1	5	1	39.3 [37.7]	46.2 [42.2]	0.85 [0.89]
2	8	1	78.4 [74.1]	73.8 [68.4]	1.06 [1.08]
4	1	1	102.6 [91.1]	92.8 [84.6]	1.11 [1.08]
5	5	1	10.1 [11.3]	20.2 [19.0]	0.50 [0.59]
2	1	2	162.2 [154.3]	149.3 [143.6]	1.09 [1.07]
4	4	2	83.0 [81.0]	90.7 [87.6]	0.92 [0.92]
5	6	2	71.0 [68.1]	66.4 [62.6]	1.07 [1.09]
1	3	3	76.0 [74.9]	83.6 [79.6]	0.91 [0.94]
2	1	3	75.8 [72.8]	69.5 [66.6]	1.09 [1.09]
2	3	3	89.7 [86.5]	99.6 [94.5]	0.90 [0.90]
2	5	3	80.9 [77.3]	73.8 [69.4]	1.10 [1.11]
3	7	3	66.8 [63.6]	73.2 [69.1]	0.91 [0.92]
5	4	3	40.0 [40.1]	46.4 [45.6]	0.86 [0.88]
2	1	4	104.6 [99.5]	98.0 [92.6]	1.07 [1.07]
2	10	3	49.4 [49.7]	45.0 [43.7]	1.10 [1.07]
7	5	3	42.2 [40.9]	36.3 [35.3]	1.16 [1.16]
4	4	4	80.9 [75.5]	87.0 [80.7]	0.93 [0.94]

[a] Reflections satisfying $|\,|Fo(hkl)| - |Fo(hk\text{–}l)|\,| > 10\,\sigma(Fo)$ were selected, where $\sigma(Fo) = [\sigma count^2 + (0.007\,|Fo|)^2]^{0.5}$.

Furthermore, we have obtained enantiopure (*S*)-(+)-2-methoxy-2-(1-naphthyl)propionic acid (**3**) through several reaction steps from diol (*S*)-(–)-**57** (Fig. 7).[38] As discussed below, we have discovered that this novel carboxylic acid was also powerful for both enantioresolution and determination of the absolute configuration.[39-41] Our application studies of chiral phthalic acid (**1**) and dichlorophthalic acid (**2**) were also accounted for in *J. Synth. Org. Chem. Jpn. (Yuki Gosei Kagaku Kyokaishi)*, written in Japanese.[42]



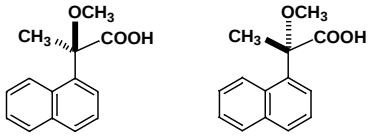
(*S*)-(–)-**57** (*S*)-(+)-**3**

Fig. 7. Synthesis of the novel chiral carboxylic acid, (*S*)-(+)-2-methoxy-2-(1-naphthyl)propionic acid (**3**), and determination of its absolute configuration.

7. A novel chiral carboxylic acid, 2-methoxy-2-(1-naphthyl)propionic acid (MαNP acid), powerful for both enantioresolution of alcohols and determination of their absolute configurations by the ^{1}H NMR anisotropy method: principles and applications

We have discussed the design and applications of chiral phthalic and dichlorophthalic acids useful for both the synthesis of enantiopure compounds and the unambiguous determination of their absolute configurations by X-ray analysis. However, most of the applications listed in Table 2 and 3 are limited to aromatic compounds. Is there then a powerful method applicable to aliphatic compounds?

We have recently discovered that the novel chiral carboxylic acid, 2-methoxy-2-(1-naphthyl)propionic acid (MαNP acid (**3**)), is remarkably effective on enantioresolution of aliphatic alcohols, especially acyclic aliphatic alcohols. In the ^{1}H NMR spectra of the esters formed from MαNP acid **3** 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.[38-41] Therefore, this carboxylic acid **3** can be used as the chiral auxiliary in the advanced Mosher method[10], useful for determining the absolute configuration of secondary alcohols. Another advantage of this acid **3** is that it does not racemize because the α-position of **3** is fully substituted, making the enantiopure acid **3** to be easily prepared. As discussed below, MαNP acid **3** is a very powerful chiral derivatizing agent, simultaneously enabling both enantioresolution of the secondary alcohols and determination of their absolute configurations. The MαNP acid method explained here is very powerful for determining the absolute configurations of natural products and biologically active synthetic chiral compounds, e.g., chiral drugs. In this sense, the chiral MαNP acid **3** is superior to the conventional chiral acids, Mosher's MTPA acid,[10] Trost's MPA acid,[12] 1- and 2-NMA acids developed by Riguera[11] and Kusumi[10] groups.



(*R*)-(–)-**3** (*S*)-(+)-**3**

Fig. 8. Novel chiral MαNP acids with powerful ability to enantioresolve alcohols and strong NMR anisotropy effect.

The following sections describe in detail the bases and the applications of this chiral MαNP acid **3**: synthesis of chiral acid **3**; determination of its absolute configuration by X-ray and chemical correlation; enantioresolution of racemic acid **3** by chiral alcohols and determination of the absolute configuration of the chiral alcohols used; absolute configurational and conformational analyses of MαNP acid esters by NMR and CD spectroscopic methods; enantioresolution and determination of the absolute configurations of the alcohols using chiral MαNP acid; recovery of the chiral alcohols with 100% enantiopurity from the separated diastereomeric esters; and applications of this method to various alcohols.

8. Facile synthesis of MαNP acid (3) and its extraordinary enantioresolution with natural (–)-menthol[40]

To synthesize a large amount of enantiopure chiral MαNP acid (**3**), the facile synthesis and enantioresolution of racemic acid **3** were carried out as shown in Fig. 9. In general, chiral synthetic amines or alkaloids are used for the enantioresolution of carboxylic acids. However, we have adopted the following novel strategy to use chiral alcohols. In this method, the chiral alcohols are condensed with racemic acid **3** 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 **3**. It was much to surprise that the diastereomeric esters **63a** and **63b** formed were easily separated by HPLC on silica gel (hexane/EtOAc =10:1) as illustrated in Fig. 10. The separation and resolution factors were extraordinarily high (α = 1.83, *R*s = 4.55), indicating that acid **3** has a great ability to recognize the chirality of the alcohols. The ester **63a** eluted first was subjected to solvolysis to yield chiral acid (+)-**3**, while the ester **63b** eluted later gave acid (–)-**3**. To determine the absolute configurations of the chiral acids **3** obtained, they were converted to the methyl esters and the CD spectra 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 the chiral acids **3** were determined as (*S*)-(+) and (*R*)-(–), respectively, leading to the assignment of (*S*)-(–)-**63a** and (*R*)-(–)-**63b** (Fig. 9).

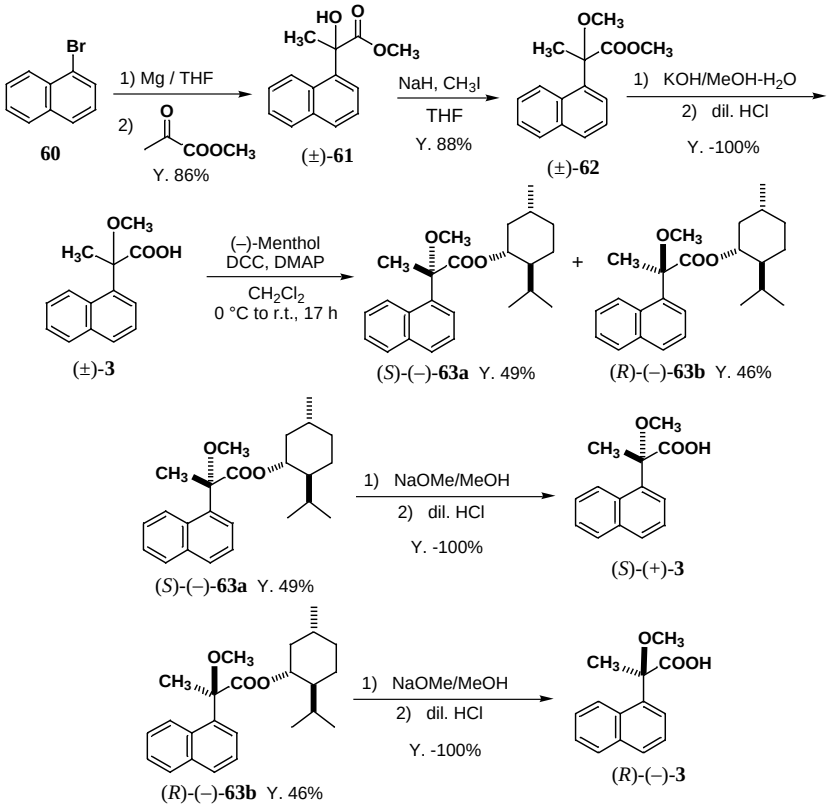


Fig. 9. Facile synthesis and enantioresolution of novel chiral MαNP acid.

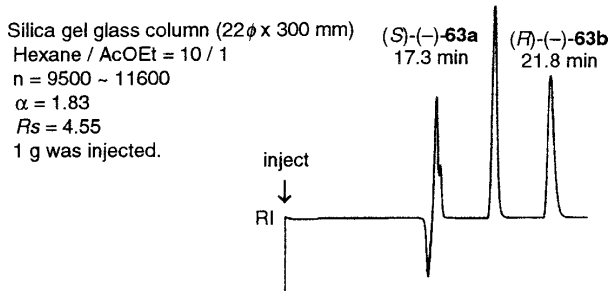


Fig. 10. HPLC separation of MαNP acid menthol esters.

9. The ^{1}H NMR anisotropy method for determining the absolute configuration of secondary alcohols: the sector rule and applications[40,41)]

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 the 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 (δ) of protons in the alcohol part. Therefore, the absolute configuration of the chiral alcohol can be determined by the difference (Δδ) of the chemical shifts of the 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 MαNP acid **3** is superior to the Mosher's MTPA and Trost's MPA acids, because the magnetic anisotropy effect of naphthyl group is much larger than that of phenyl group, therefore resulting larger Δδ values. So, the absolute configuration of the chiral alcohols can be unambiguously determined, when using MαNP acid **3** as a chiral NMR

anisotropy reagent. Moreover, MαNP acid has another advantage that it does not racemize because the α-position of **3** is fully substituted. From these reasons, it is advisable to use MαNP acid **3**, rather than other conventional chiral acids, in determining the absolute configuration of the chiral alcohols including natural products.

All NMR proton peaks of diastereomeric MαNP esters **63a** and **63b** were fully assigned by various methods including two dimensional ones (^{1}H, ^{1}H-^{1}H COSY, ^{13}C, ^{1}H-^{13}C COSY, HMBC, Fig. 11a). The protons of the isopropyl group in ester **63b** appeared at much higher fields than in ester **63a**. On the other hand, the protons in the 2-position in **63a** appeared at higher fields than in ester **63b**. These shifts are obviously due to the magnetic anisotropy effect induced by naphthyl group of MαNP acid moiety.

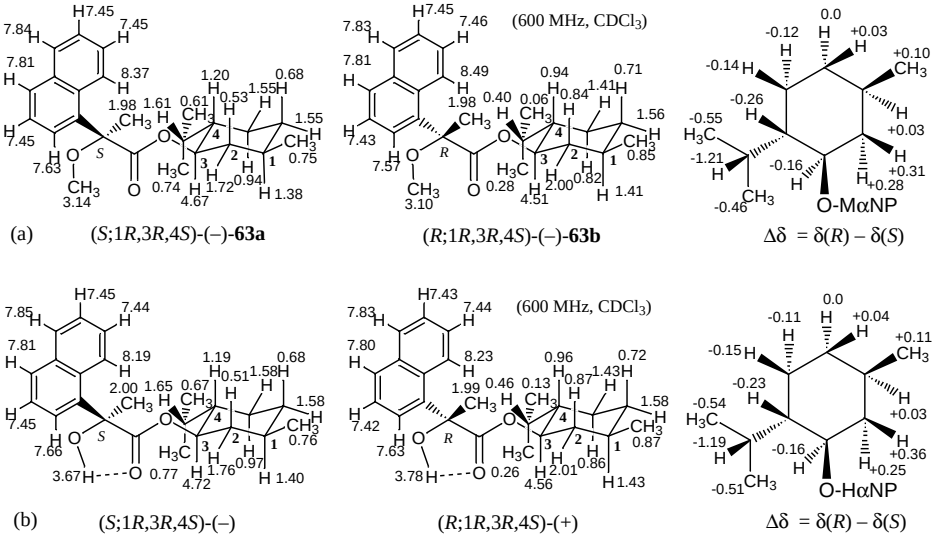


Fig. 11. NMR data of MαNP and HαNP acid menthol esters.

To determine the absolute configuration from the NMR anisotropy effect, it is required to determine the preferred conformation of each diastereomer. In esters **63a** and **63b**, the absolute configurations of MαNP acid and menthol moieties are established as described above, and then the following stable conformations are proposed to satisfy the anisotropy effects observed in the NMR spectra (Fig. 11). Namely, the two oxygen atoms of 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 methane proton. Therefore, the methoxyl group, ester group, and alcohol methane proton lie in the same plane, which is called the MαNP plane (Fig. 11). These *syn* conformations are similar to those proposed for MPA esters. In ester **63a**, the naphthyl group and H-2 protons are on the same front side of the MαNP 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 **63b**, 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 **63a** and **63b** are also supported by the comparison of the NMR data with those of 2-hydroxy-2-(1-naphthyl)propionic acid (HαNP) menthol esters shown in Fig. 11(b). From the NMR chemical shift and IR data, it is obvious that the tertiary hydroxyl group 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*;1*R*,3*R*,4*S*)-(–)-**63a**, especially those of the menthol part, are very similar to those of HαNP acid menthol ester (*S*;1*R*,3*R*,4*S*)-(–) as shown in Fig. 11, (a) and (b). The same is true for the pairs of other diastereomers, (*R*;1*R*,3*R*,4*S*)-(–)-**63b** and HαNP acid menthol ester (*R*;1*R*,3*R*,4*S*)-(–) (Fig. 11). 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 the secondary alcohols can be deduced (Fig. 12). The basic procedure is as follows; (*R*)-MαNP and (*S*)-MαNP acids are separately allowed to react with a chiral alcohol, and their absolute configuration 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 a two dimensional spectra is suggested. The Δδ values (Δδ = δ(*R,X*) – δ(*S,X*)) are calculated for all protons in the alcohol moiety. *Fig. 12 shows the sector rule for MαNP ester, where MαNP group is placed in the down and front side, while methane proton of the secondary alcohol in the down and rear side. The group R_1 with protons exhibiting positive Δδ values is placed in the right side, while the group R_2 with protons showing negative Δδ values in the left side. From this projection, the absolute configuration X of chiral alcohol can be determined.*

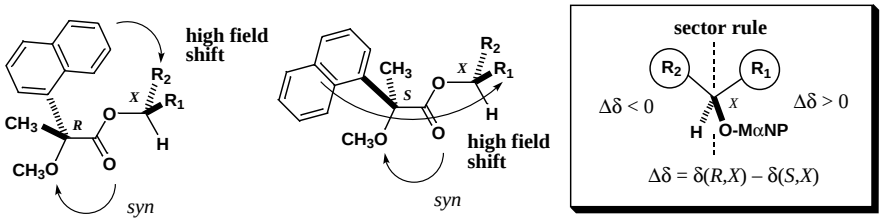
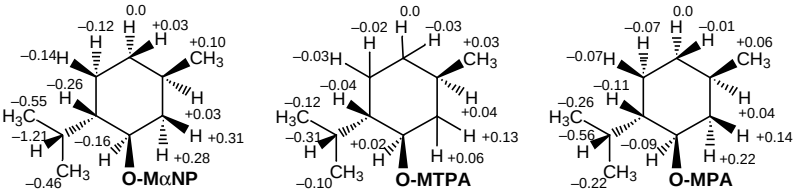


Fig. 12. The preferred conformation of MαNP esters, and the sector rule for determining the absolute configuration of chiral alcohols by use of NMR Δδ values.

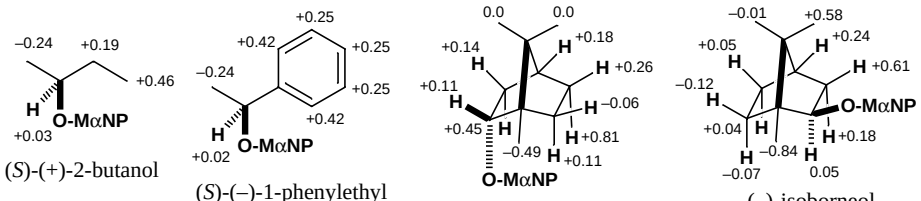
The magnetic anisotropy effect of chiral MαNP acid is much stronger than that of conventional chiral carboxylic acid (Fig. 13). For instance, the Δδ values of MαNP-menthol ester are *ca.* four times larger than those of Mosher's MTPA ester[10] (Fig. 13(b)): twice for Trost's MPA ester[12] (Fig. 13(c)); twice for 2-NMA ester reported by Riguera[11] and Kusumi[10] *et al.* MαNP acid is thus effective for determining the absolute configuration of natural products.



(a) $\Delta\delta = \delta(R) - \delta(S)$ (b) $\Delta\delta = \delta(S) - \delta(R)$ (c) $\Delta\delta = \delta(R) - \delta(S)$

Fig. 13. Comparison of the NMR Δδ values of the menthol esters formed with chiral carboxylic acids.

Some application examples of this MαNP acid method to chiral alcohols are shown in Fig. 14.



(*S*)-(+)-2-butanol (*S*)-(–)-1-phenylethyl alcohol (–)-borneol (–)-isoborneol

Fig. 14. The NMR Δδ values and absolute configurations determined by the MαNP acid method.

10. Enantioresolution of various alcohols using MαNP acid and simultaneous determination of their absolute configurations[41)]

Another extraordinary quality of MαNP acid is its excellent ability in chirality 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. MαNP acid could also be enantioresolved with other chiral alcohols as listed in Fig. 14. These facts logically indicate that, if enantiopure MαNP acid is used, racemic alcohols can be enantioresolved. In fact, we have succeeded in the enantioresolution of various alcohols using enantiopure MαNP acid (*S*)-(+)-**3** as exemplified in Fig. 15.

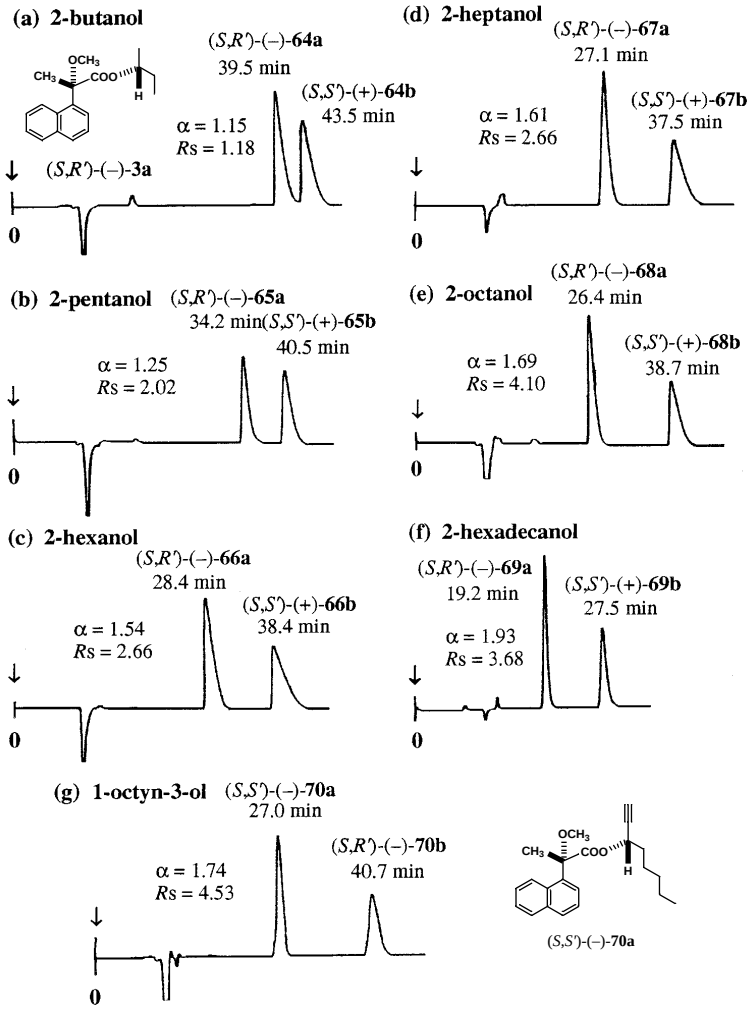


Fig. 15. HPLC separation of diastereomeric esters formed from aliphatic alcohols and (*S*)-(+)-MαNP acid (silica gel, 22$\phi \times$ 300 mm, hexane/EtOAc = 20:1).

This novel chiral MαNP acid (*S*)-(+)-**3** has thus a remarkable enantioresolving power for the alcohols, especially for the aliphatic alcohols. For instance, in the case of 2-butanol, the diastereomeric esters can be baseline separated with the separation factor α = 1.15 and with the resolution factor *R*s = 1.18. In this case, it is obvious that the chiral carboxylic acid **3** recognizes well the slight difference between methyl and ethyl groups. This is an excellent and practical method since the chiral acid **3** exhibits a high resolving power to the aliphatic alcohols, to which in general asymmetric syntheses are hardly applicable.

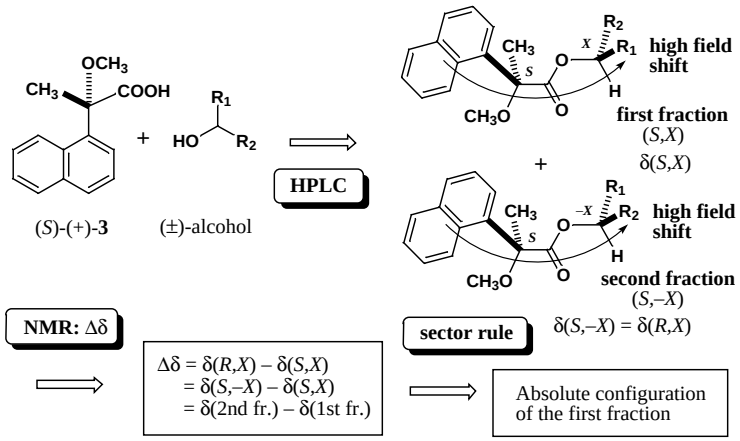


Fig. 16. Enantioresolution of racemic alcohol as (*S*)-MαNP esters, and determination of the first-eluted fraction by the NMR anisotropy method.

The next question is then how the absolute configuration of the alcohol moiety is determined. The absolute configurations of the separated diastereomers can be determined by applying the NMR anisotropy method using chiral MαNP acid as described above. A general scheme is illustrated in Fig. 16. Racemic alcohol is esterified with MαNP acid (*S*)-(+)-**3** 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 MαNP 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 Δδ value is Δδ = δ(*R,X*) – δ(*S,X*), and so the value of δ(*R,X*) is required to calculate the Δδ value. However, the enantiomer (*R,X*) does not exist in this scheme, and so the original equation of Δδ is not useful here.

To solve the above problem, the following conversion to the equation was performed. Since the ester (*S,–X*) is the enantiomer of ester (*R,X*), their NMR data should be identical with each other: δ(*R,X*) = δ(*S,–X*). Therefore, Δδ = δ(*R,X*) – δ(*S,X*) = δ(*S,–X*) – δ(*S,X*) = δ(2nd fr.) – δ(1st fr.). So, the absolute configuration *X* of the first-eluted fraction can be determined from the Δδ value, which is obtained by subtracting the chemical shift of the first-eluted fraction from that of the second-eluted fraction (Fig. 16). This method has been applied to the esters shown in Fig. 15, giving Δδ values and the absolute configurations of the first-eluted esters (Fig. 17). The Δδ 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 assigned to the second-eluted ester. It should be noted that when MαNP acid (*R*)-(–)-**3** is used, the Δδ value is defined as Δδ = δ(*R,X*) – δ(*S,X*) = δ(*R,X*) – δ(*R,–X*) = δ(1st fr.) – δ(2nd fr.).

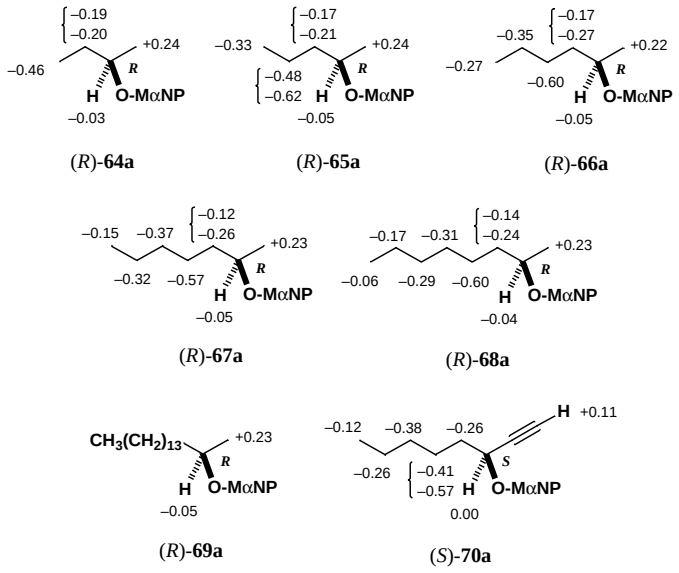


Fig. 17. Determination of the absolute configurations of the alcoholic part of the first-eluted esters by the NMR anisotropy method using (*S*)-(+)-MαNP acid, and the observed Δδ values.

The next step is the recovery of the enantiopure alcohol and the chiral MαNP acid **3**. As exemplified in Fig. 18, both enantiopure alcohols were obtained by the solvolysis of the separated esters. The chiral MαNP acid **3** recovered can be recycled.

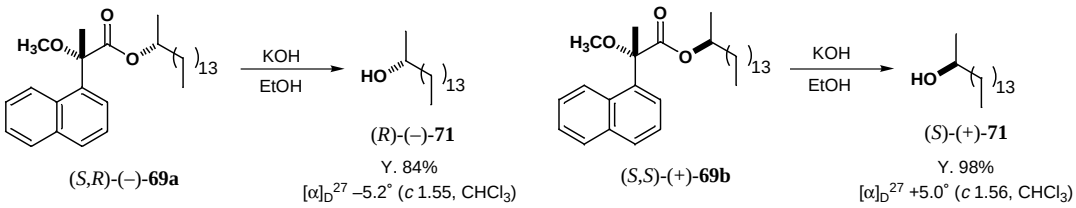


Fig. 18. Recovery of both enantiopure alcohols.

What is the enantiopurity of the recovered alcohols? In our method, both diastereomeric esters obtained are enantiopure, because if MαNP acid **3** used is enantiopure, they can be fully separated in HPLC. The MαNP acid **3** was enantioresolved with natural (–)-menthol, and the enantiopurity was confirmed as 100% by gas chromatography using chiral stationary phase.

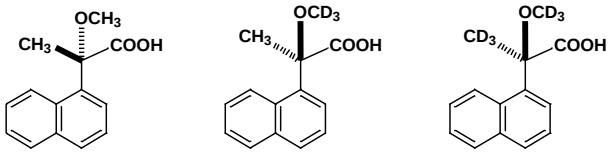
As described above, MαNP acid has excellent enantioresolving power regardless of the simplicity of its molecular structure even with the absence of hetero atoms. Besides, the chiral acid **3** is superior to the Mosher's MTPA and Trost's MPA acids in the magnetic anisotropy effect. However, a further development is expected.

11. Novel diastereomer method for determining enantiomeric excess by ^{1}H NMR and/or MS spectrometry [43)]

How is the enantiomeric excess (% ee) of the chiral compounds obtained by asymmetric syntheses or by enzymatic reactions determined? The novel and exact method for determining % ee is in great demand, since the importance of chiral molecular chemistry is rapidly increasing. The % ee is defined as follows.

$$\% \text{ ee} = 100\{ \mid (R) - (S) \mid \}/\{(R) + (S)\} \qquad (1)$$

As discussed above, we have developed the novel and chiral magnetic anisotropy reagent, MαNP acid **3** (Fig. 19), a powerful reagent for determining the absolute configuration of the chiral alcohols by ^{1}H NMR spectroscopy.[38-41)] Another characteristic of this chiral acid **3** is its great power to enantioresolve racemic alcohols, especially acyclic aliphatic alcohols, by HPLC, as MαNP esters. For instance, racemic 2-hexadecanol (±)-**71** was esterified with MαNP acid (*S*)-(+)-**3**, and the diastereomeric mixture obtained was easily separated by HPLC on silica gel: hexane/EtOAc = 20:1; separation factor α = 1.93 and resolution factors *R*s = 3.68. Both pure enantiomers of 2-hexadecanol **71** were obtained easily by solvolysis of the esters eluted as the first and second fraction. These excellent characteristics of MαNP acid **3** enabled us to develop the novel diastereomer method for determining % ee using ^{1}H NMR and/or mass spectrometry (MS).[43)]



(*S*)-(+)-**3** (*R*)-(–)-**3**-d_3 (*R*)-(–)-**3**-d_6

Fig. 19. MαNP acid and its deuterated enantiomers.

There are a variety of methods in determining % ee of chiral compounds: 1) comparison of $[\alpha]_D$ value or CD intensity with that of enantiopure compound; 2) enantioseparation by HPLC or gas chromatography (GC) using chiral stationary phase;[44)] 3) detection by ^{1}H NMR using chiral organometallic shift reagents;[45)] 4) separation of diastereomers formed with chiral derivatizing agent (CDA) by HPLC or detection by ^{1}H NMR;[46)]

5) detection by MS spectrometry using CDA or chiral host-guest complex;[47-50] 6) method using the scheme of kinetic enantioresolution.[51] These methods all have both advantages and disadvantages. For example, in some cases, data of enantiopure compounds or calibration curves are made using standard samples of known % ee. In other cases, peak broadening disturbs exact determination of peak intensity.

For the diastereomer methods using CDAs, the effect of kinetic resolution is always accompanied, and therefore, the most essential problem is how to evaluate it. If the derivatization reaction proceeds in 100% yield, the term of the kinetic resolution can be excluded. However, the reaction of 100% yield is not practical. On the other hand, the method based on the kinetic resolution effect contains approximations and needs calibration curves. In some extreme cases, the % ee has been determined based on the following rough approximation. Both enantiomers of CDA were allowed to react with a chiral substrate separately and the yields of the products were checked. When the yields were similar to each other, it was simply concluded that the kinetic resolution effect was negligibly small, and the % ee value could be directly calculated without the correcting the kinetic resolution effect. The diastereomer methods for determining % ee have been thus always troubled by the kinetic resolution effect. However, as shown below, we have succeeded in the first development of a novel diastereomer method for determining % ee by ^{1}H NMR and/or MS spectrometry with complete elimination of the kinetic resolution effect.[43] One of the advantages of our method is that the use of MS spectroscopy enables a highly sensitive detection of minor components.

12. Principle and procedure of the novel method for determining % ee: complete removal of the kinetic resolution effect

The principle and procedure of the novel method for determining % ee are explained using 2-hexadecanol **71** as the test sample. As illustrated in Fig. 20, a *ca.* 1:1 mixture of MαNP acid (*S*)-(+)-**3** and deuterium-labeled MαNP acid (*R*)-(–)-**3**-d_3 was allowed to react with chiral alcohol **71** (0-100% ee) to yield a diastereomeric mixture of esters (Fig. 20, R = H, n = 3). .

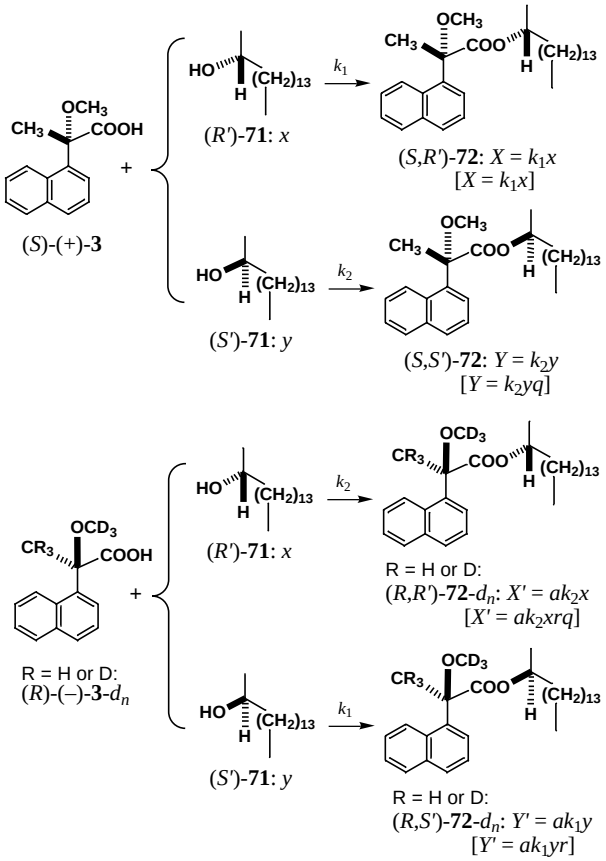


Fig. 20. [a] n = 3 or 6. Parameters k_1 and k_2 are proportional coefficients containing the factors of kinetic resolution. Parameter a is a coefficient reflecting the abundance of labeled (*R*)-(–)-**3**-d_n and isotope effects. The equations in brackets are for MS spectrometry, where q and r are the parameters of ionization efficiency for diastereomer and deuterium labeled isomer, respectively.

The compositions of (*R'*)-**71** and (*S'*)-**71** are defined as x and y, respectively, and $x + y = 1$. Similarly the compositions of the esters formed are defined: ester (*S,R'*)-**72**, X; (*S,S'*)-**72**, Y; (*R,R'*)-**72**-d_3, X'; (*R,S'*)-**72**-d_3, Y'. The amounts of the esters are formulated as $X = k_1x$ and $Y = k_2y$, where k_1 and k_2 are proportional coefficients including the kinetic resolution factor (note that those are not rate constants). Because esters (*S,S'*)-**72** and (*R,R'*)-**72**-d_3 are the enantiomers of each other, the same coefficient k_2 can be used to define the amount of (*R,R'*)-**72**-d_3: $X' = ak_2x$, where a is the coefficient reflecting the abundance of (*R*)-(–)-**3**-d_3 and isotope effects of ester formation. For the remaining ester (*R,S'*)-**72**-d_3, $Y' = ak_1y$. By taking the ratio X/Y', these equations are simplified as shown in equation (1), where k_1, the proportional coefficient including the kinetic resolution factor, is canceled.

$$X/Y' = (k_1x)/(ak_1y) = (1/a)x/y \qquad (2)$$

Similarly k_2 is also canceled.

$$X'/Y = (ak_2x)/(k_2y) = (a)x/y \qquad (3)$$

The product of equations (2) and (3) gives equation (4), where a, the coefficient reflecting the abundance of (*R*)-(–)-**3**-d_3 and isotope effects, is also canceled. Now, the product is equal to the square of the composition ratio of the alcohol (x/y).

$$(X/Y')(X'/Y) = [(1/a)x/y][(a)x/y] = (x/y)^2$$
$$= [(1st,M)/(1st,M+3)][(2nd,M+3)/(2nd,M)] \qquad (4)$$

The mixture of these diastereomeric esters are separated by using HPLC on silica gel (22$\phi \times$ 300 mm, hexane/EtOAc = 20:1) (Fig. 21). The first fraction contains esters (*S,R'*)-**72** and (*R,S'*)-**72**-d_3, and the ratio of components $(X/Y') = [(1st,M)/(1st,M+3)]$ can be determined from the ^{1}H NMR peak intensities of methoxyl and methyl groups of MαNP moiety. Namely, the intensity of the methoxyl group corresponds to X, while that of the methyl group to $X+Y'$. Similar treatment is applicable to the second fraction containing (*S,S'*)-**72** and (*R,R'*)-**72**-d_3. The ratio $(X'/Y) = [(2nd,M+3)/(2nd,M)]$ is obtainable by ^{1}H NMR. By substituting the observed ratio into equation (4), $(x/y)^2$ is calculated, and since $x+y = 1$, the enantiomeric excess (% ee) of alcohol **71** is determined.

13. Practice of the % ee determination by ^{1}H NMR spectroscopy

Deuterium labeled MαNP acid (*R*)-(–)-**3**-d_3 was prepared by methylation of methyl 2-hydroxy-2-(1-naphthyl)propionate with CD_3I (D content >99.5 atom %), followed by hydrolysis and enantioresolution with (–)-menthol. A mixture of (*S*)-(+)-**3** and (*R*)-(–)-**3**-d_3 (ratio, 1:0.987, total 8.1 mg, 0.0349 mmol) was allowed to react with the test sample of chiral 2-hexadecanol (**71**, 9.237 mg, 1.09 × 0.0349 mmol, 60.9% ee calculated by weight) yielding a diastereomeric mixture of esters **72**, which was separated by HPLC on silica gel (hexane/EtOAc 20:1) (Fig. 21).

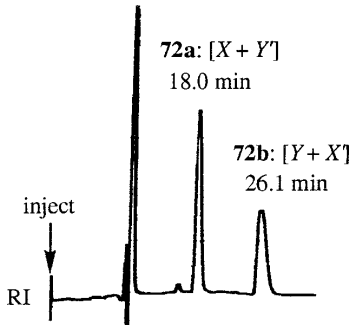


Fig. 21. HPLC separation of diastereomeric esters **72a** and **72b**: silica gel glass column (22$\phi \times$ 300 mm); hexane/EtOAc = 20:1; n = 9,500-11,600; α = 1.96 and *R*s = 4.15.

The compositions of esters (*S,R'*)-**72** and (*R,S'*)-**72**-d_3 were determined from the ^{1}H NMR of the first fraction: X = 1.00, Y' = 0.22, X/Y' = 4.54. Similarly, from the ^{1}H NMR of the second fraction, the compositions of (*S,S'*)-**72** and (*R,R'*)-**72**-d_3 were determined: Y = 1.00, X' = 3.60, X'/Y = 3.60. The product $(X/Y')(X'/Y)$ = 16.3636, and so x/y = 4.045. Since $x+y$ = 1, x = 0.8017 and y = 0.1982, leading to 60.4% ee, which reasonably agrees with 60.9% ee calculated by weight. This method has been applied to 10 test samples **71** with 0-90% ee. As seen in Fig. 22, the % ee values obtained by ^{1}H NMR agree well with those calculated by weight: the average error, ±0.4% ee; maximum error, 1.3% ee. These results clearly verify the scheme and principle of our method for determining % ee. When expanding to 5 test samples with 92-100% ee, however, the deviation became larger: average error, ±1.2% ee; maximum error, 6.3% ee. Such larger deviation may be due to the detection limit in measuring intensity of weak peaks in ^{1}H NMR. To overcome this problem, we then adopted more sensitive MS spectrometry to determine the composition.

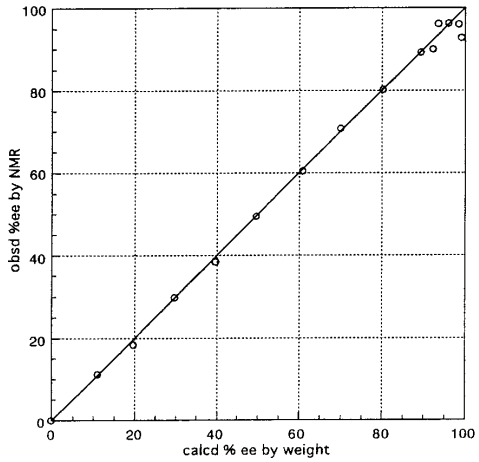


Fig. 22. Comparison of the % ee values determined by ^{1}H NMR with those calculated by weight: (*R*)-2-hexadecanol **71** > (*S*)-**71**.

14. Determination of % ee by MS spectrometry and practice

In the case of MS spectrometry, the ionization efficiency varies between diastereomers (*S,R'*)-**72** and (*S,S'*)-**72**. The same is true for deuterium-substituted ester (*R,S'*)-**72**-d_n and unsubstituted one (*S,R'*)-**72**. Therefore, the factor of the ionization efficiency (*f*) for each isomer was defined as follows: for ester (*S,R'*)-**72**, f = 1 and so $X = k_1x$; for (*S,S'*)-**72**, $f = q$ and $Y = k_2yq$; for (*R,S'*)-**72**-d_n (n = 3 or 6), $f = r$ and $Y' = ak_1yr$; for (*R,R'*)-**72**-d_n (n = 3 or 6), $f = rq$ and $X' = ak_2xrq$, where q is the relative ionization efficiency due to the diastereomeric structure difference, and r is that due to the deuterium substitution. By taking the ratio X/Y', equation (1) is changed to,

$$X/Y' = (k_1x)/(ak_1yr) = (1/ar)x/y \qquad (2')$$

Similarly equation (2) is reformed as,

$$X'/Y = (ak_2xrq)/(k_2yq) = (ar)x/y \qquad (3')$$

Accordingly, equation (3) becomes,

$$(X/Y')(X'/Y) = [(1/ar)x/y][(ar)x/y] = (x/y)^2$$
$$= [(1st,M)/(1st,M+n)][(2nd,M+n)/(2nd,M)] \qquad (4')$$

As the coefficients of the ionization efficiency are all cancelled out, exactly the same scheme for determining % ee is applicable to MS spectrometry.

This % ee determination method by MS spectrometry is essentially applicable to tris-deuterated MαNP acid (*R*)-(–)-**3**-d_3. However, the difference of three *m/z* units (M+3 vs. M) in MS is not enough to avoid the overlap with isotope peaks of natural abundance. Therefore, we needed to make several corrections. After making corrections for the background, overlap with isotope peaks, deuterium content, and racemate (0% ee), a good agreement was obtained in all regions (0-100% ee): average error, ±0.7% ee; maximum error, 1.9% ee. However, these corrections were too complicated for practical use. Therefore, we selected hexa-deuterated MαNP acid (*R*)-(–)-**3**-d_6.

Enantiopure chiral acid (*R*)-(–)-**3**-d_6 was prepared by the Grignard reaction of ethyl 2-(1-naphthyl)-2-oxoacetate using CD_3I (D content >99.5 atom %), followed by methylation with CD_3I (D content >99.5 atom %), hydrolysis, and enantioresolution with (–)-menthol. For this chiral acid (*R*)-(–)-**3**-d_6, the term of overlap with isotope peaks of natural abundance is completely negligible, because of the difference of six *m/z* units (M+6 vs. M).

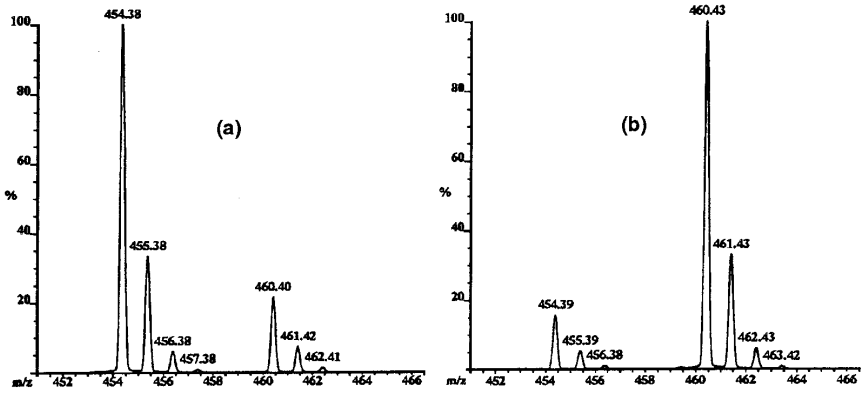


Fig. 23. MS spectra of diastereomeric MαNP esters of 2-hexadecanol (69.77% ee):JEOL, JMS GC mate II, EI 40 eV; (a) the first-eluted **72a** containing (*S,R'*)-**72** and (*R,S'*)-**72**-d_6; (b) the second-eluted **72b** containing (*S,S'*)-**72** and (*R,R'*)-**72**-d_6.

This MS spectrometric method was next checked using the test sample **71** (69.77% ee calculated by weight). A mixture of diastereomeric esters prepared from (*S*)-(+)-**3** and (*R*)-(–)-**3**-d_6 (ratio, 1:0.994) was separated by HPLC on silica gel (hexane/EtOAc 20:1). From the MS of the first fraction shown in Fig. 23(a), the compositions of esters (*S,R'*)-**72** (M^+ *m/z* 454) and (*R,S'*)-**72**-d_6 (M^+ *m/z* 460) were determined with the background correction: $X = 52.284$, $Y' = 11.221$, $X/Y' = 4.6594$. Similarly from the MS data of the second fraction (Fig. 23(b)), the compositions of (*S,S'*)-**72** (M^+ *m/z* 454) and (*R,R'*)-**72**-d_6 (M^+ *m/z* 460) were determined: $Y = 8.607$, $X' = 55.278$, $X'/Y = 6.4224$. The product $(X/Y')(X'/Y) = 29.9245$, and so $x/y = 5.4703$. Since $x+y = 1$, $x = 0.845448$ and $y = 0.154552$, leading to 69.09% ee, which reasonably agreed with 69.77% ee calculated by weight.

The MS spectrometry method has been applied to 15 test samples **71** with 0-100% ee. As shown in Fig. 24, the % ee values obtained by MS agree well with those calculated by weight: the average error, ±1.08% ee; maximum error, 1.79% ee. Unlike the case of ^{1}H NMR, all data points obtained follow a straight line even in the region of 90-100% ee. The MS method, much more sensitive than ^{1}H NMR, is thus applicable to the samples with higher % ee. Although the sample with (*R*)-2-hexadecanol **71** > (*S*)-**71** was treated here, the same scheme would hold for the sample with (*S*)-2-**71** > (*R*)-**71**.

We have, thus, succeeded in developing the novel diastereomer method for determining % ee with complete elimation of the kinetic resolution effect.[43] It should be emphasized that in this method, neither the data of enantiopure compounds nor the preparation of calibration curves using samples with known % ee is necessary. The data of the kinetic resolution effect are not required, either. The excellent properties of this method are purchased at the cost of separating diastereomers by HPLC. Further improvement in accuracy and application to the compounds other than the alcohols is now under investigation. A detailed description of this part has also been reported in Chemistry and Biology (Kagaku to Seibutsu).[52]

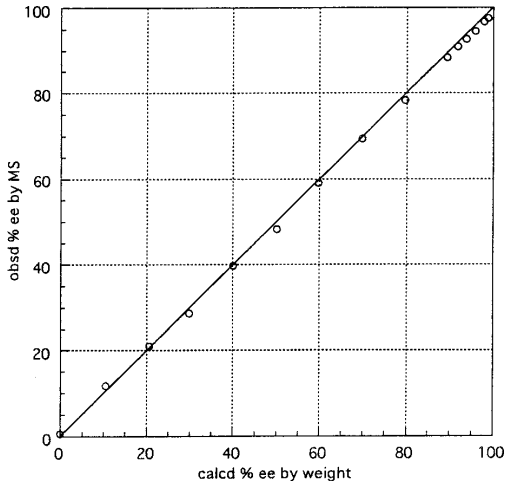


Fig. 24. Comparison of the % ee values determined by MS with those calculated by weight: (*R*)-2-hexadecanol **71** > (*S*)-**71**.

15. Conclusions

We have developed several novel chiral auxiliaries, in particular, chiral carboxylic acids, and *successfully applied these CDAs (chiral derivatizing agents) to the enantioresolution of the alcohols by the diastereomeric HPLC method, the determination of the absolute configuration by X-ray crystallography and/or by ^{1}H NMR anisotropy method, and the determination of % ee (enantiomeric excess) by ^{1}H NMR or MS spectrometry method.* The X-ray crystallographyic method using an internal reference is of course the best for determining absolute configuration. However, ideal single crystals are not always obtained. In such a case, the ^{1}H NMR method using MαNP acid, which requires no crystallization, is effective. In enantioresolution, chiral dichlorophthalic acid and MαNP acid are complementary to each other. When the resolution with one CDA is unsuccessful, the use of the other is suggested. The methods described above are very powerful for the preparation of enantiomeric alcohols with 100% enantiopurity in a laboratory scale and for the simultaneous determination of their absolute configurations. Furthermore, the application of our methods to various compounds, mass production of enantiomers, and improvement of the quantitation in the MS spectral determination of % ee are now in progress. Enantiopure chiral MαNP acids (*S*)-(+)-**3** and (*R*)-(–)-**3** are commercially available from at TCI (Tokyo Kasei Kogyo Co., Ltd.). In addition, their deuterated products are scheduled to be on the market soon.

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Professor Nobuyuki Harada graduated from the Department of Chemistry, Tohoku University (1965) and completed the doctoral course in the Department of Chemistry, Graduate School of Science, Tohoku University, taking D. Sc. (1970). His academic careers are as follows: Research Associate, Chemical Research Institute of Nonaqueous Solutions, Tohoku University (1970-1975); Postdoc, Department of Chemistry, Columbia University, U.S.A. (1973-1975); Associate Professor, Chemical Research Institute of Nonaqueous Solutions, Tohoku University (1975-1991); Adjunct Associate Professor, Institute for Molecular Science, Okazaki National Research Institutes (1980-1982); Visiting Research Scientist, R&D Department, Experimental Station, Du Pont de Nemours & Company, U.S.A. (1987-1987); Associate Professor, Institute for Chemical Reaction Science, Tohoku University (1991-1992); Professor, Institute for Chemical Reaction Science, Tohoku University (1992-2001); Professor, Institute of Multidisciplinary Research for Advanced Materials, Tohoku University (2001-present).

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