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The Modified Mosher's Method and the Sulfoximine Method

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This article describes the application of the modified Mosher's method to a variety of natural products possessing a secondary alcohol for determining their absolute configuration. The method is generally applicable to secondary alcohols with a few exceptions where the hydroxy group is seriously hindered by neighboring substituents. Countermeasures to solve the problems are also described. Recent findings that the modified Mosher's method can be used in solvents other than *deutero*-chloroform are included. Development and application of the sulfoximine method for the determination of the absolute configuration of chiral sulfoxides are also described.

Since the modified Mosher's method was published in 1991,[1] this method has been used world wide as a routine means for determining the absolute configuration of organic, natural, and synthetic compounds. Several methods analogous to the modified Mosher's method have promptly been proposed.[2] The advantages of the modified Mosher's method lie in (i) simple procedures, (ii) usage of an NMR spectrometer, the most familiar analytical instrument for chemists and biologists, and (iii) reliability. MTPA (1-methoxy-1-phenyl-1-trifluoromethylacetic acid) found by Professor Mosher[3] has been used by organic chemists for a long time, and both enantiomers of the reagent are commercially available. Thanks to the remarkable development of modern NMR techniques, sensitivity has been increased so that submilligram samples are enough for measuring ^{1}H NMR spectra. Moreover, assignment of the proton signals has become easier, especially by use of two-dimensional techniques such as COSY, NOESY, HSQC, and HMBC. The tide is running in favor of the modified Mosher's method.

This article is divided into two parts: the first one (Section **1**) dealing with the application of the modified Mosher's method to organic compounds focusing on the works carried out in our laboratory, and the second one (Section **2**) introducing the sulfoximine method developed for the elucidation of the absolute configurations of sulfoxides.

1. The Modified Mosher's Method

Before proceeding further, the reader should keep in mind that (*R*)-MTPA chloride gives (*S*)-MTPA ester, and (*S*)-MTPA chloride affords (*R*)-MTPA ester.

1.1 A Pile of Known Compounds Gave Birth to the Modified Mosher's Method. A natural product chemist who is engaged in isolation is like a miner. When one is lucky enough, one can dig out as much gold as one likes. When the goddess of fortune keeps her back, one only gets rocks and dirt. The latter was the case of a graduate student of Tsukuba University in 1987. Although she was a gifted student, and later achieved a number of remarkable works,[1,4] she was in a melancholy mood at that time, because in spite of her enormous efforts every compound she isolated from several marine organisms was a known compound, which had no value in her laboratory.

She at last found a new compound (**1**) (Fig. 1),[5] a cembranolide, from a soft coral *Sinularia mayi* together with another one with a carbonyl group at C-13. A known cembranolide denticulatolide (**5**)[6] was also isolated from the soft coral. The structure of **1**, whose relative stereochemistry was determined by X-ray analysis, was not unique enough to impress her immediate superior (TK), because a number of similar cembranolides had already been reported (and that is why the compound has had no trivial name until now). So, she was instructed to determine the absolute configuration of **1** before publishing the results.

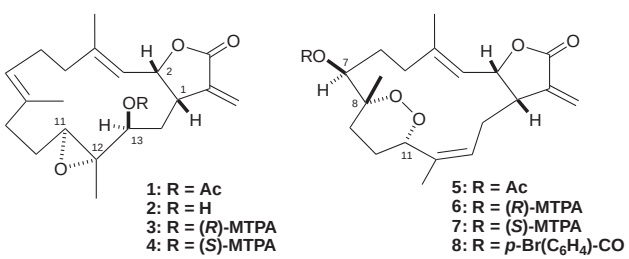

Fig. 1. A new cembranolide (**1**) and denticulatolide (**5**) obtained from a soft coral *Sinularia mayi* and their derivatives that enabled determination of their absolute configurations.

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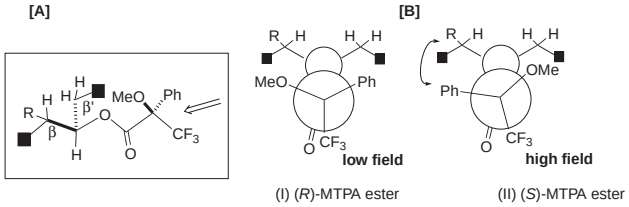


Fig. 2. [A] A preferable conformation of the (*R*)-MTPA ester of a secondary alcohol. [B] Projections of (*R*)- and (*S*)-MTPA esters (I and II) viewed from the direction illustrated in [A].

Initially, the Mosher's method using ^{19}F NMR spectroscopy,[2] which had been most often used as the "Mosher's method" at that period, was applied. In Fig. 2, the principle of the ^{19}F-Mosher's method is interpreted. Mosher proposed that an MTPA ester of a secondary alcohol possesses the conformation shown in [A], which has been later verified by X-ray crystallography and resulted in the modified Mosher's method (vide infra). Note that the degree of substitution at the β- and β'-carbons of the secondary alcohol must be different (e.g. primary vs secondary, primary vs tertiary) when this method is applied. Conformation [A] will be slightly different between (*R*)- and (*S*)-MTPA esters: In the (*R*)-MTPA ester (I in [B]), the steric interaction between substituent R and the methoxy group is less significant than that of the latter (II), in which the bulky phenyl group interacts with substituent R. As a result, the conformation of the MTPA group in II is distorted (rotation around a single bond) so that the phenyl group may be apart from the R group. The CF_3 group in II is closer to the diamagnetic cone of the carbonyl group (upfield anisotropic region). Therefore, ^{19}F-signal will show more upfield chemical shift than that of I. A simple conclusion is that the secondary alcohol has the (*R*)-configuration (such as shown in [A]) when the ^{19}F-signal of its (*S*)-MTPA ester shows a higher chemical shift than that of (*R*)-diastereomer.

The acetate **1** was hydrolyzed to **2**, which was then converted to (*R*)- and (*S*)-MTPA esters **3** and **4** by treatment with (*S*)- and (*R*)-MTPA chlorides, respectively, and their ^{19}F NMR spectra were compared. In these pairs of MTPA esters, the CF_3 of the (*S*)-isomer **4** exhibited a higher chemical shift than that of (*R*)-isomer **3** in the ^{19}F NMR spectroscopy, thus suggesting the 13(*R*)-configuration of **1**. The same experiments were performed on denticulatolide (**5**). Again, the ^{19}F-signal of (*S*)-**7** showed a higher chemical shift than that of (*R*)-**6**, leading to the 7(*R*)-configuration of **5**.

Just before submitting the results to a journal, quite conflicting data was obtained. The X-ray analysis of a single crystal of the *p*-bromobenzoate (**8**) revealed that the absolute stereochemistry of denticulatolide (**5**) was as that shown in Fig. 3. That is, the configuration at C-7 must be *S*. This suggests that the configuration at C-13 of **1** must also be *S* as shown in Fig. 1, considering that both compounds were obtained from the same organism and the β,β-configuration of C-1 and 2 of **5**. There must be something wrong in this ^{19}F NMR method.

Besides the method using ^{19}F NMR, Mosher proposed another one, the "^{1}H-Mosher's method."[7] This method is also based on the conformation [A] in Fig. 2. He assumed that the protons on the same side of the phenyl group of the MTPA

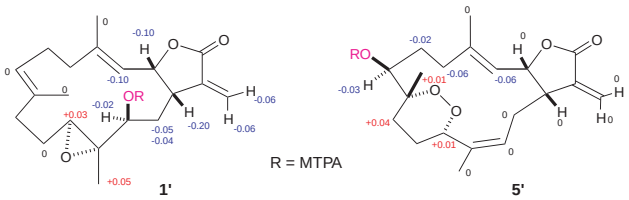


Fig. 3. The values obtained by $\delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}} = (\delta_4 - \delta_3$ and $\delta_7 - \delta_6)$ are assigned to structures **1′** and **5′**.

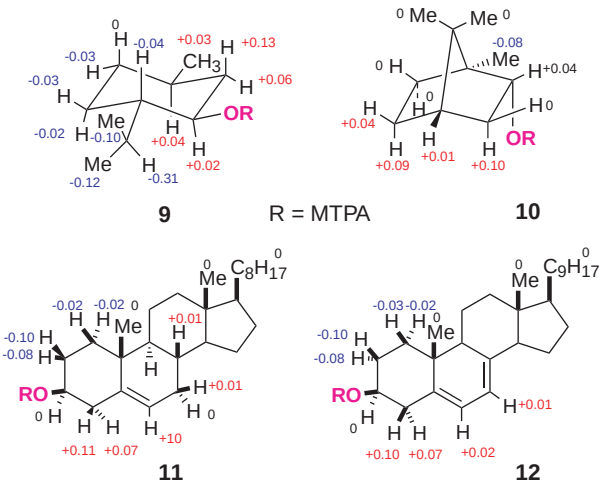


Fig. 4. $\Delta\delta$ values $(\delta_S - \delta_R)$ assigned to the protons of compounds **9**–**12** with known absolute configurations. **9**: (−)-menthol, **10**: (−)-borneol, **11**: cholesterol, and **12**: ergosterol.

moiety were shielded, and by comparing the proton chemical shifts between (*R*)- and (*S*)-MTPA esters, the absolute configuration of the secondary alcohol could be determined. This method had been long forgotten because assignment of the protons in rather complex molecules was extremely difficult in the era when FT-NMR instruments equipped with a superconductive magnet were not available.

By using a 500 MHz NMR instrument, the chemical shifts (in $CDCl_3$) of the protons of **3**, **4**, **6**, and **7** were determined, and the values obtained by subtracting $\delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}}$, that is, the chemical shifts of **4** (**7**) minus those of **3** (**6**). Those values are indicated in structure **1′** and **5′** of Fig. 3.

It can be seen that the positive and negative values are systematically arranged on either side of the MTPA-oxy group in **1′** and **5′**. Based on Mosher's assumption mentioned above, the (*S*)-configuration of the hydroxy groups of **1** and **5** were confirmed. These findings made us conclude that the ^{1}H-Mosher's method was more reliable than the ^{19}F-Mosher's method, and drove us to collect evidence to validate our conclusion.

1.2 Establishment of the Modified Mosher's Method. Since there had been no systematic documents on the ^{1}H-Mosher's method, its validity was examined by use of compounds **9**–**12**, whose absolute configurations were already known. The results are shown in Fig. 4, where $\Delta\delta$ values $[=\delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}}]$ are assigned to the respective structures. Without exception, positive and negative $\Delta\delta$ values are located on the right and left (see Model A in Fig. 5) of the MTPA moiety, and the absolute configurations determined

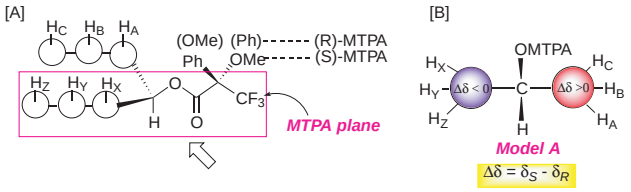


Fig. 5. [A] An ideal conformation of an MTPA ester of a secondary alcohol. MTPA plane is shown. [B] Model A to determine the absolute configurations of secondary alcohols, which is a view of [A] from the arrowed direction.

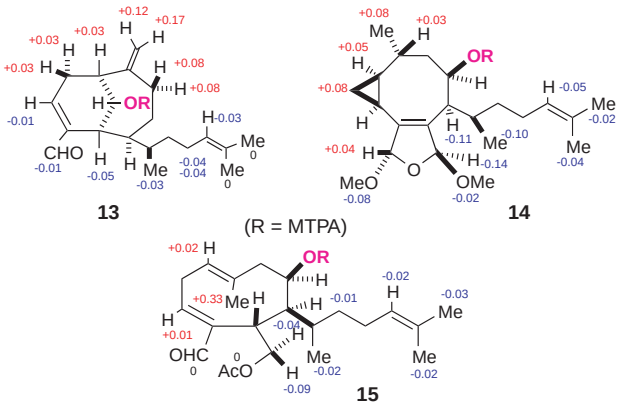


Fig. 6. $\Delta\delta$ values observed for the MTPA esters of marine terpenoids **13**–**15**.

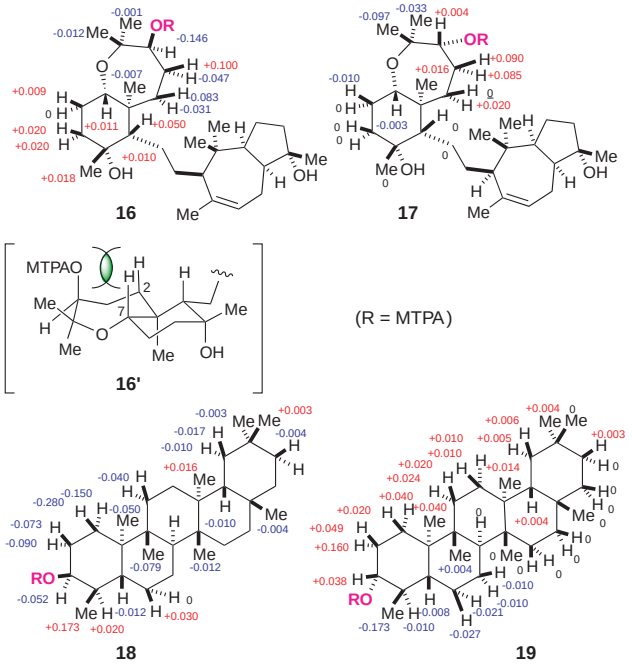


Fig. 7. $\Delta\delta$ values obtained for sipholenol-A (**16**), its diastereomer (**17**), friedelan-3β-ol (**18**), and friedelan-3α-ol (**19**). Partial structure (**16′**) shows the axial orientation of the MTPA-oxy group.

by the $\Delta\delta$ values (Model A) are identical to the known ones.

For convenience, we generalized the ^{1}H-Mosher's method as follows. The most preferable conformation of an MTPA ester of a secondary alcohol is assumed to be as depicted in Fig. 5A. This is called as an ideal conformation. Due to the diamagnetic effect of the benzene ring, $H_{A,B,C,\ldots}$ of the (*R*)-MTPA ester should show the ^{1}H NMR signals upfield relative to those of the (*S*)-MTPA ester. The reverse should hold for $H_{X,Y,Z,\ldots}$. Therefore, when $\Delta\delta = \delta_S - \delta_R$, protons on the right side of the MTPA plane (Fig. 5A) must have positive values ($\Delta\delta > 0$) and protons on the left side of the plane must have negative values ($\Delta\delta < 0$).

Now the Mosher's method can be extended as follows:
(1) Assign as many proton signals as possible with respect to each (*R*)- and (*S*)-MTPA ester.
(2) Obtain $\Delta\delta$ values for the protons.
(3) Put the protons with positive $\Delta\delta$ on the right side, and those with negative $\Delta\delta$ on the left side of Model A (Fig. 5B).
(4) Construct a molecular model of the compound in question, and confirm that all of the assigned protons with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane, respectively. Be sure to view the model so that the MTPA group is up and front, and the oxy methine proton is down and front.

The resurrected ^{1}H-Mosher's method (named as the modified Mosher's method) was applied[1] to three marine diterpenes **13**–**15**[8,9] that had been isolated from brown algae (Fig. 6). The absolute configuration of **13** was confirmed by total synthesis.[10]

1.3 Fate of the ^{19}F NMR Method. The absolute configurations of many natural products had been "determined" by means of the ^{19}F NMR method before we published our results. With ten MTPA esters at hand, we studied whether the ^{19}F NMR method would actually lead to the correct configurations. Astonishingly, it turned out that the ratio of the correct answer derived from the ^{19}F NMR method was 40%.[1] Therefore, the absolute configurations of the natural products determine by the method must all be reexamined. This is particularly important for chemists aiming at total synthesis of natural products. They might end up with the antipode of the true natural product.

1.4 No Rule without Exception. We have encountered several natural products to which the modified Mosher's method is inapplicable. The first example is sipholenol A, a marine triterpene (**16**).[11] The signs of the $\Delta\delta$ values of **16** are irregularly arranged (Fig. 7). The MTPA-oxy group is axially oriented (**16′**), and owing to the steric repulsion from two axial protons at C-2 and -7, the MTPA ester may not take the ideal conformation. When the secondary group of **16** was chemically inverted and the $\Delta\delta$ values were measured for the resulting epimer **17**, the arrangement of positive and negative $\Delta\delta$ values became normal.[1] Therefore, it seemed that the modified Mosher's method might not be applicable to a compound whose secondary hydroxy group is axially oriented. Similar results were obtained for friedelan-3β-ol (**18**) and -3α-ol (**19**). The former with an axial OH group shows irregular signs of $\Delta\delta$ values, and the latter with an equatorial OH exhibits beautifully systematic arrangement of positive and negative $\Delta\delta$ values.

Although such cases might seem to be a drawback of the method, it can be regarded as another advantage of the modified Mosher's method; it has a self-examination mechanism to show whether the observed data can be used or should be abandoned.

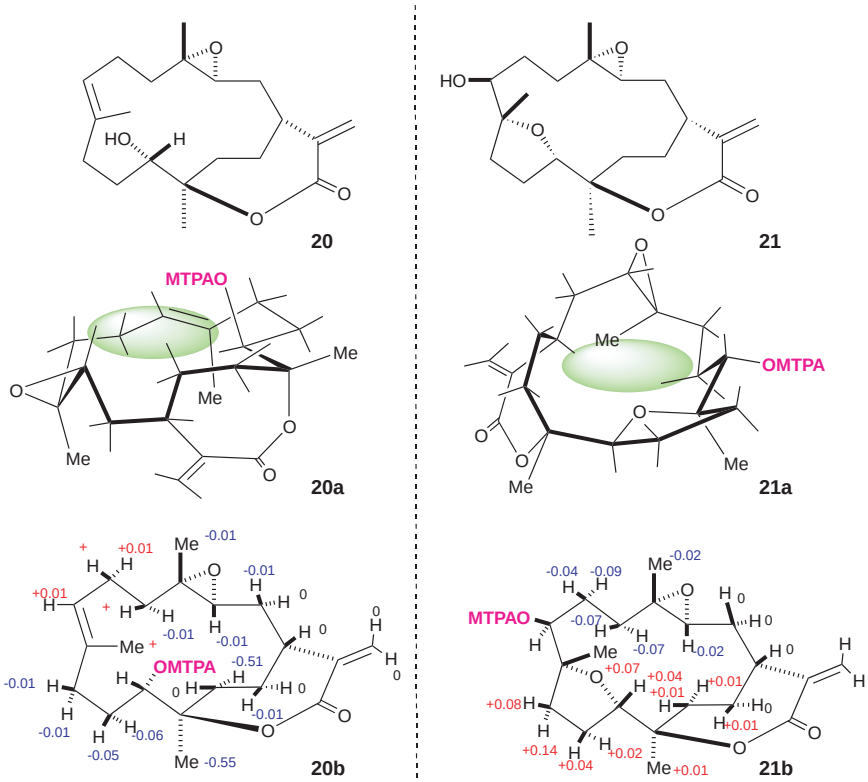


Fig. 8. Structures of two cembranolides **20** and **21**. The stable conformations of the MTPA esters **20a** and **21a** are drawn. $\Delta\delta$ values are assigned in structures **20b** and **21b**. For clarification, H is abbreviated in **20a** and **21b**. In **20b**, + without value means positive $\Delta\delta$ less than 0.01 ppm.

Another example of an anomaly in the modified Mosher's method is shown in Fig. 8. The method was applied to two cembranolides **20** and **21**, which were obtained from an Okinawan soft coral *Sinularia flexibilis* as cytotoxic components.[12] The $\Delta\delta$ values observed for **20** are assigned to **20b**. Although positive and negative values appear in groups, they are indifferent to the position of the MTPA group. Therefore, this result cannot be used for determining the absolute configuration of **20**.

On the contrary, **21b** shows a regular distribution of positive and negative $\Delta\delta$ values, from which the absolute configuration of **21** was established as shown in the structure. The stable conformations of **20a** and **21a** were deduced by detailed analysis of the coupling constants and NOEs in the 2D NMR spectra of **20** and **21**. In **20a**, the MTPA group would be directed toward the inside of the ring if it took the ideal conformation. On the other hand, the hydroxy group of **21** is directed outside of the molecule, and the MTPA group in **21a** takes the ideal conformation.

In cases that the $\Delta\delta$ values show irregular patterns, the authors recommend the following measures to deal with the problem.

(1) Invert the configuration of the OH group by e.g. the Mitsunobu reaction or oxidation to a ketone followed by reduction.

(2) Change the solvent from chloroform-*d* to benzene-d_6, pyridine-d_5, or methanol-d_4 (see Section **1.7**).

In tanabalin (**22**), one of the methylene protons at the β-position of the alcohol (arrowed in Fig. 9) may show an irregular

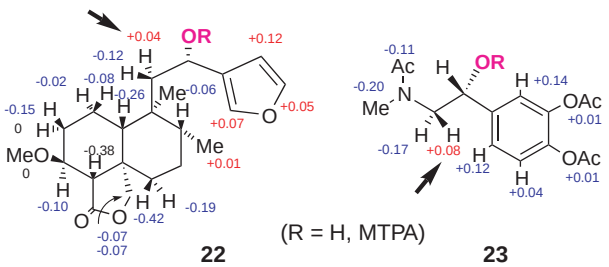
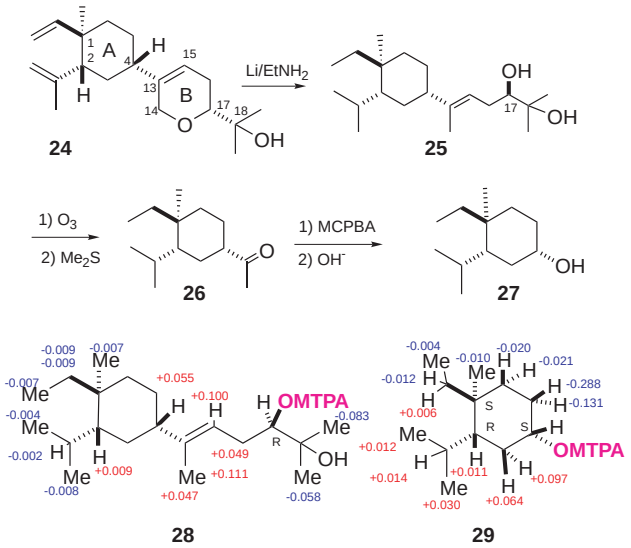


Fig. 9. $\Delta\delta$ values of tanabalin (**22**) and triacetyl L-adrenaline (**23**). Abnormal values are indicated by arrows.

value (Fig. 9).[13] This can be regarded as normal since the corresponding proton of **23** also shows an irregular positive value. Analogous behavior of the methylene protons in several furanyl alcohols is documented.[14] The slight difference in conformations of the aromatic rings (furan and phenyl) between (*S*)- and (*R*)-MTPA esters might cause these irregularities of the $\Delta\delta$ values.

1.5 Application to Natural Products without a Secondary OH Group. A secondary alcohol is created by the combination of organic reactions, and thus the modified Mosher's method can be applied to such compounds that have no secondary hydroxy group.

The absolute configuration of lobatriene (**24**), a marine diterpene isolated from a soft coral, was determined by a series of chemical reactions followed by applying the modified Mosher's method to the products.[15] The relative configuration of the substituents on cyclohexane ring (A) was easily deter-



24 25 26 27 28 29

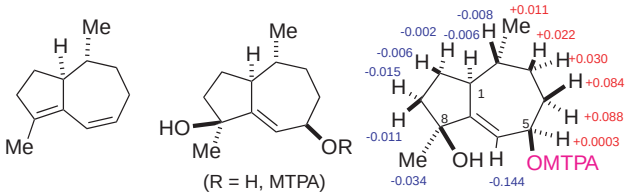
Fig. 10. Chemical transformations of lobatriene (**24**) to **25** and **27**, to which the modified Mosher's method was applied. The $\Delta\delta$ values shown in **28** and **29** led to the absolute configuration of **24**.

mined by analyzing the NMR spectra of **24**. But the stereochemical correlation of the substituents between A and B rings by NMR spectroscopy was impossible because of the rapid rotation around the single bond connecting both rings.

Cleavage of the allylic ether bond and concomitant reduction of the olefinic bonds of the side chains at C-1 and -2 were achieved with lithium in ethylamine and afforded the secondary alcohol **25**. The *R*-configuration at C-17 was deduced by the $\Delta\delta$ values shown in structure **28**. Ozonolysis of **25** gave the methyl ketone **26** (1 mg), which was subjected to the Baeyer–Villigar reaction followed by hydrolysis of the acetate, to give the secondary alcohol **27** (ca. 500 µg). The alcohol was divided into two portions (each 250 µg) and treated with (*R*)- and (*S*)-MTPA chloride. The $\Delta\delta$ are assigned in structure **29**. Systematic arrangement of positive and negative values is observed, confirming the *S*-configuration of the hydroxy group. Because the Baeyer–Villigar rearrangement takes place with retention of the configuration, the absolute configuration at C-4 of **24** must be *S*. Thus, the configuration at the four asymmetric centers of **24** was determined as shown in Fig. 10.

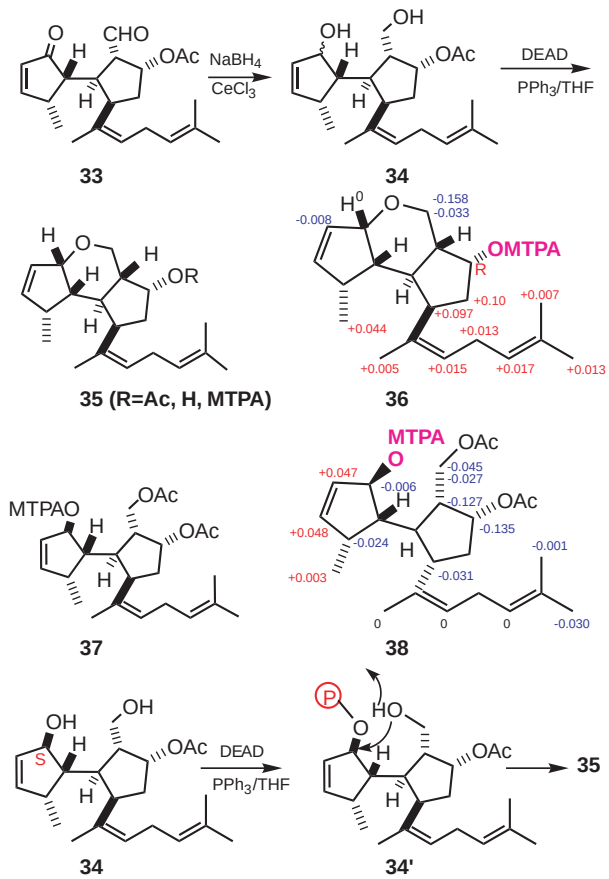
Isoclavukerin A (**30**) is an extremely volatile compound that was isolated from an Okinawan soft coral. After all of the attempts to introduce an oxygen function for use of the modified Mosher's method failed, the compound was kept in a refrigerator for several months. During the storage, **30** changed into a mixture of oxidation products, from which the diol **31** (R = H) was recovered. By applying the modified Mosher's method to this product **32**, the absolute configuration of **30** was established (Fig. 11).[16] Noteworthy is the fact that the benzoate **31** (R = benzoyl) showed no split Cotton effect in the CD spectrum, because the dihedral angle between the benzoyloxy and the olefin groups is almost zero degrees. Even in such a case the modified Mosher's method can be used without a problem.

The last example of the combination of the chemical transformations and the modified Mosher's method is outlined in Fig. 12. Dilokamural (**33**) is a diterpene produced by a brown



30 31 32

Fig. 11. Structures of isoclavukerin A (**30**) and its oxidation product **31**. The $\Delta\delta$ values obtained for **31** are assigned to structure **32**.



33 34 35 (R=Ac, H, MTPA) 36 37 38 34 34' 35

Fig. 12. Conversion of dilokamural (**33**) to the tricyclic compound **35**, to which the modified Mosher's method was applied (**36**). The reaction course of the Mitsunobu reaction (**34** to **35**) is discussed on the basis of the stereochemistry of **38**.

alga, *Dilophus okamurae* Dawson.[17] As in the case of lobatriene (**24**), this diterpene is composed of two separate cyclopentane rings that are connected by a single bond. The relative stereochemistry within each ring can be elucidated by NMR analyses, but both cannot be correlated because of rotation of the rings around the single bond. Such a problem would be solved if the two rings were connected by forming a linkage utilizing substituents on each ring.

Dilokamural (**33**) was reduced with sodium borohydride giving the diol **34**. The stereochemistry of the cyclopentenol moiety of **34** was unknown at this stage, although it was a single product. This diol was subjected to the Mitsunobu reaction,

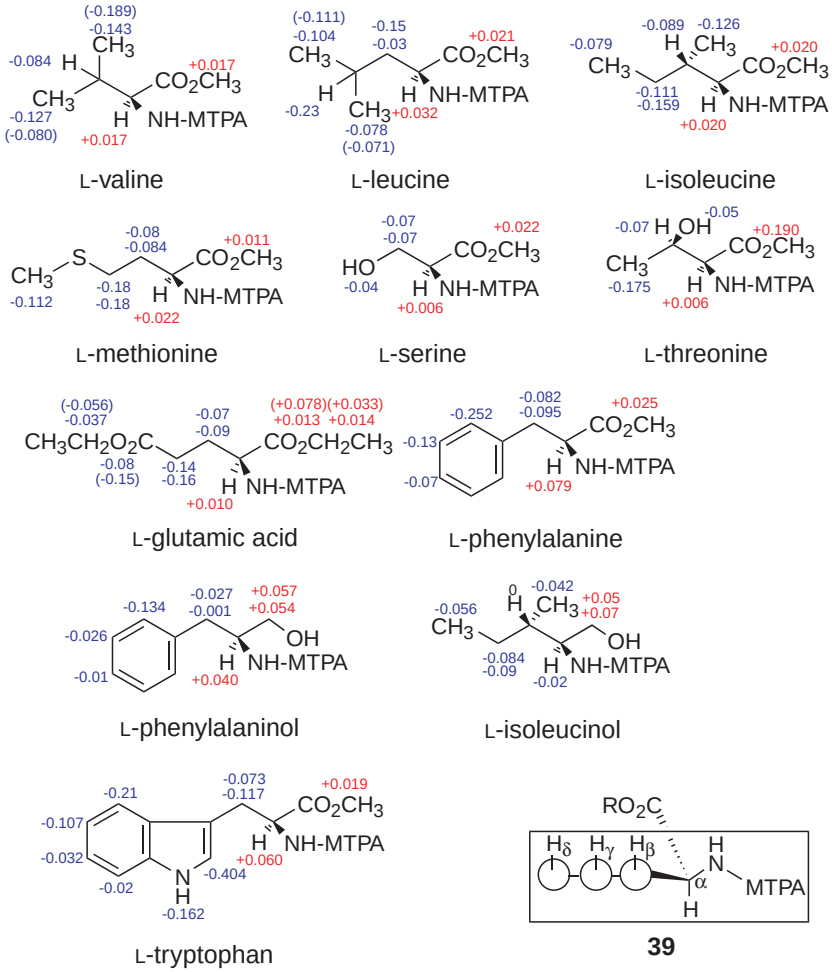


Fig. 13. $\Delta\delta$ values (ppm) obtained for (*R*)- and (*S*)-MTPA amides of eleven L-amino compounds. For the protons that could be interchanged with other protons, two possible values, one in parenthesis, are assigned. Ideal conformation of the amide **39** is shown.

which resulted in the formation of an ether linkage between the primary and secondary alcohols. Because the product **35** (R = Ac) had a rigid tricyclic structure, the relative stereochemistry was determined without difficulty by routine NMR analyses. The acetyl group was then removed by hydrolysis, and the resulting alcohol [**34** (R = H)] was esterified with MTPA. The $\Delta\delta$ values are assigned in structure **36**, which enabled the determination of the absolute configuration of **33** as shown in Fig. 12.

It is worthwhile considering the stereochemical course of the Mitsunobu reaction (**34** to **35**). Our speculation is that (i) the allylic alcohol of **34** had the α-configuration, (ii) the primary alcohol was activated by the Mitsunobu reagent, and (iii) the allyl alcohol attacked at the methylene group to form **35**.

In an attempt to verify the speculation, the modified Mosher's method was applied to the monoacetate of the cyclopentenol **34** to reveal, contrary to our assumption, that the hydroxy group has the β-configuration (**38**). Therefore, it was concluded that in the Mitsunobu reaction the secondary hydroxy group was initially activated, and then the primary OH group attacked from the backside of the allylic OH producing **35**. If the primary OH of **34** were activated and attacked by the secondary OH, a 5-(*trans*,*anti*)-6-(*trans*)-5 ring system would be formed instead of a 5-(*cis*,*anti*)-6-(*trans*)-5 system **35**. A molecular mechanics calculation revealed that the former was highly strained.

1.6 Application to Amines. The modified Mosher's method is also applicable to primary amines connected to a tertiary carbon.[18] As model compounds, eleven amino acid derivatives were chosen, and their MTPA esters were prepared. The $\Delta\delta$ values of these amides are shown in Fig. 13. A noticeable fact is that the arrangement of positive and negative signs is the same as that observed in secondary alcohols. This indicates that the MTPA amide of an amine exists in conformation **39**, and Model A (OMTPA is replaced with NHMTPA) can be used to determine its absolute configuration. The absolute configurations of several amines have been determined by the modified Mosher's method.[19]

1.7 NMR Solvents for the Modified Mosher's Method. In the footnote of the first full paper on the modified Mosher's method,[1] there is a note: The $\Delta\delta$ values are practically independent of the concentration (3–50 mM) of the sample solutions. Use of C_6D_6 instead of $CDCl_3$ resulted in $\Delta\delta$ distribution patterns different from those found in the present method. Therefore, it should be emphasized that the present methodol-

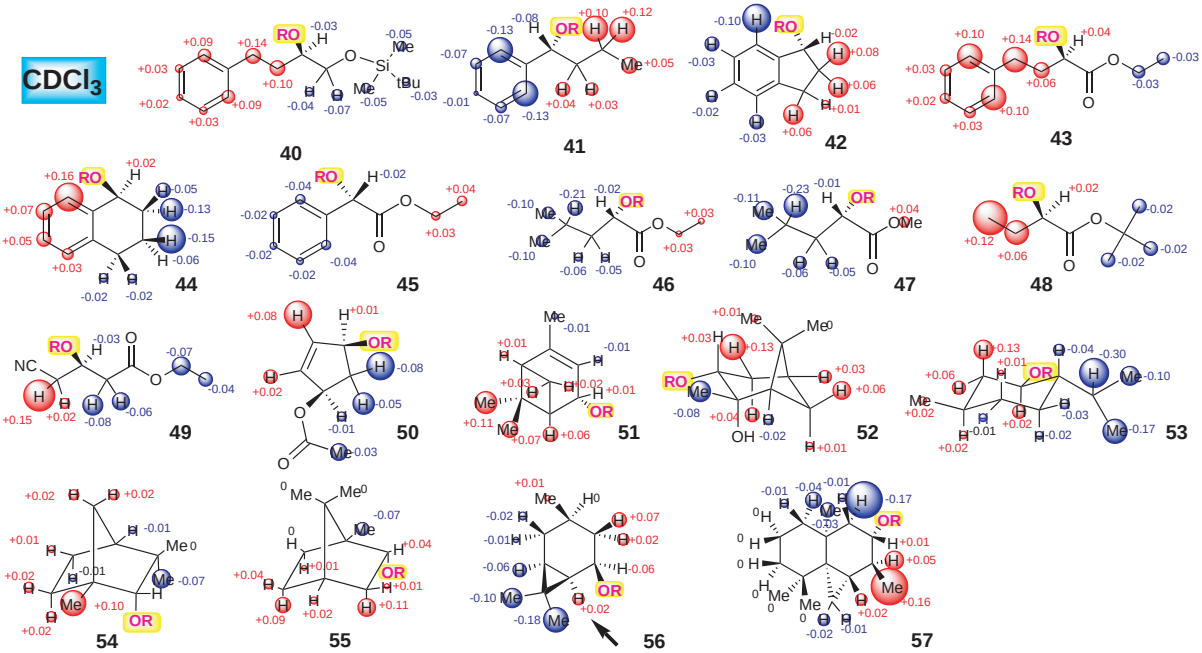


Fig. 14. $\Delta\delta$ value of compounds **40**–**57** obtained by measuring the NMR spectra (400 MHz) in $CDCl_3$. Compounds **55** = **10** and **53** = **9**, and several values are different from those described in Fig. 4. The values in this figure were determined by use of COSY and HSQC, and the values presented here are accurate ones. The arrow in **56** indicates an irregular $\Delta\delta$ value.

ogy is valid only when $CDCl_3$ is used as a solvent. This note was made because all of the date appearing in the article had been obtained by using $CDCl_3$. However, it might have given a groundless belief that no solvents other than $CDCl_3$ are suitable for the modified Mosher's method. A systematic study of the solvent effects on the method is needed.

It should be pointed out that $CDCl_3$, the most frequently used NMR solvent, has a few disadvantageous properties; (1) $CDCl_3$ may produce HCl (or DCl) decomposing acid-fragile substances, and (2) the proton signal due to water dissolved in $CDCl_3$ appears at around δ 1.5 which can obscure sample signals in a dilute solution. Use of C_6D_6, for example, can overcome these problems; C_6D_6 is stable, H_2O in C_6D_6 appears at δ 0.5, and in many cases better separation of signals is obtained in C_6D_6. This section describes the results obtained by the modified Mosher's method using solvents other than $CDCl_3$.[20]

Figure 14 summarizes the structures of compounds **40**–**57** used in the present experiments, together with the $\Delta\delta$ values obtained for $CDCl_3$ solutions. As is obvious from this example, $+\Delta\delta$ and $-\Delta\delta$ values are located systematically on the right and left sides of the MTPA plane. Furthermore, the absolute values of $\Delta\delta$ are proportional to the distance from the MTPA moiety. Therefore, the modified Mosher's method was valid for all the compounds in $CDCl_3$, the only exception being for a β-proton on **56**. It shows a positive value in spite of its position on the left side of the MTPA plane. Because the MTPA group is close to the bulky geminal dimethyl group, either the (*R*)- or (*S*)-MTPA moiety might have a slightly distorted conformation.

Figure 15 summarizes the results obtained for the same compounds in C_6D_6 solutions. There exist several irregularities in the $\Delta\delta$ patterns. The first one is in compound **41**; one of the β-methylene protons shows an anomaly, which has already been interpreted in Section **4**, Fig. 9. One of the geminal methyls of **54** shows a positive value. This may be owing to the fact that the MTPA-oxy group of **54** is in an axial position and under sterically hindered circumstances, which reinforces the contribution of the distorted conformation of the MTPA moiety. The same thing may happen in another sterically hindered alcohol **55**, which shows irregularity in one of the β-protons.

The cases of the cyclopropane-containing compounds **56** and **57** are quite bothersome. Both show irregular distribution of the $\Delta\delta$ patterns, and the modified Mosher's method is inapplicable to these compounds. The factor that causes these irregularities is unknown. However, as a whole, most of the compounds show normal patterns of $\Delta\delta$ values, which indicates that the modified Mosher's method may be valid with a few exceptions where the secondary alcohol is sterically hindered.

Unexpectedly, CD_3OD seems to be a better solvent than C_6D_6 for the modified Mosher's method. Although the number of examples is fewer than those used for $CDCl_3$ and C_6D_6, all of the compounds tested show normal patterns without exception [Fig. 16 (above)]. Even the sterically hindered cyclopropane compound **56** has normal patterns. Furthermore, the average $\Delta\delta$ values are slightly larger than those observed in the former two solvents. This fact may indicate that the population of the ideal conformation of MTPA is larger in CD_3OD than in $CDCl_3$ or C_6D_6.

Figure 16 shows that C_5D_5N is as proper a solvent as $CDCl_3$. It is interesting that the β-proton of **55** shows an irregular sign in a similar way to that seen in the case of $CDCl_3$.

From the experiments described in this section, it has been proved that C_6D_6, CD_3OD, and C_5D_5N can be used as solvents

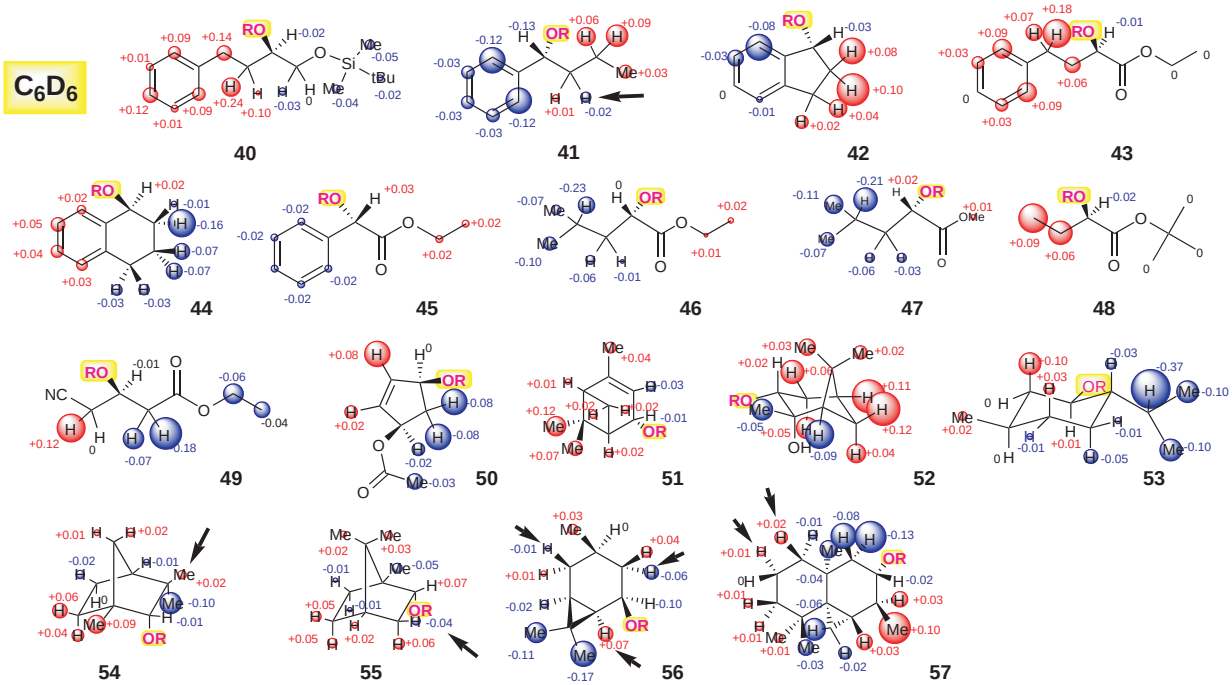


Fig. 15. $\Delta\delta$ values (C_6D_6 at 400 MHz) of compounds **40**–**57**. The arrows show irregular $\Delta\delta$ values.

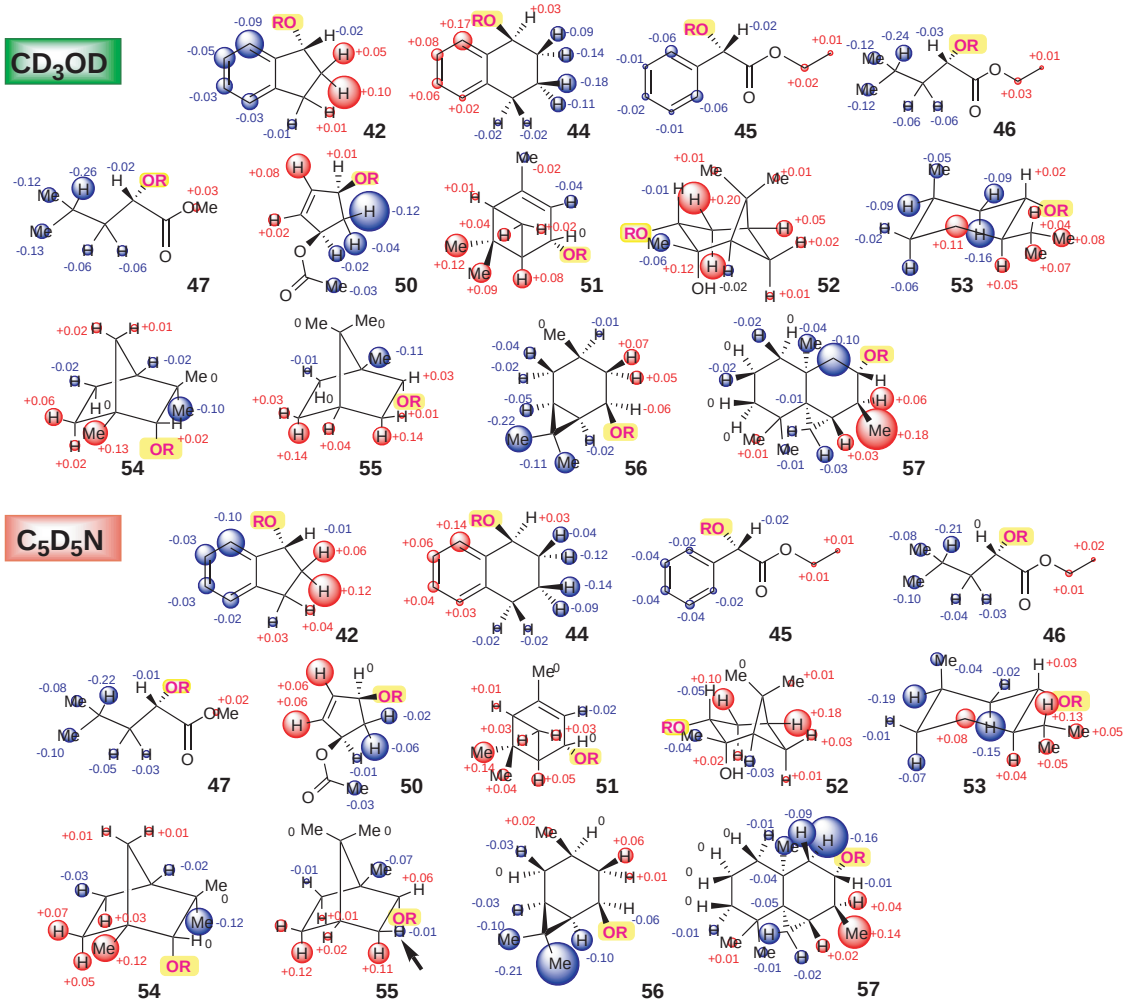


Fig. 16. $\Delta\delta$ values of compounds obtained for CD_3OD (above) and C_5D_5N (below) solutions.

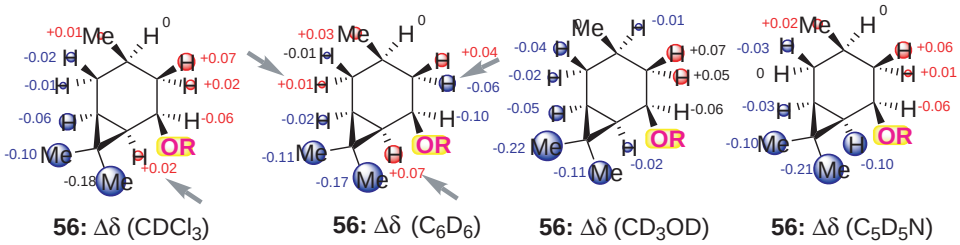


Fig. 17. $\Delta\delta$ values observed for the MTPA ester of *cis*-caran-5-ol (**56**) in different solvents. The arrows show irregular $\Delta\delta$ values.

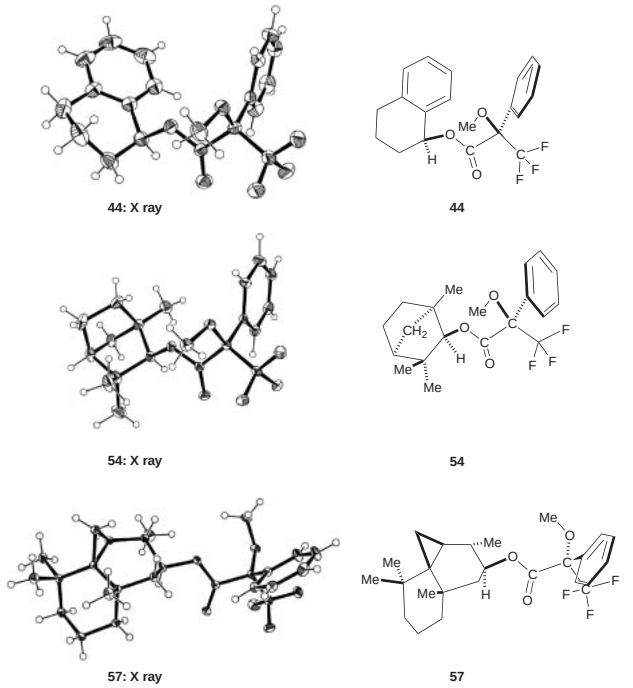


Fig. 18. X-ray structures of (*R*)-MTPA-**44**, (*R*)-MTPA-**54**, (*S*)-MTPA-**57**, and their perspective views.

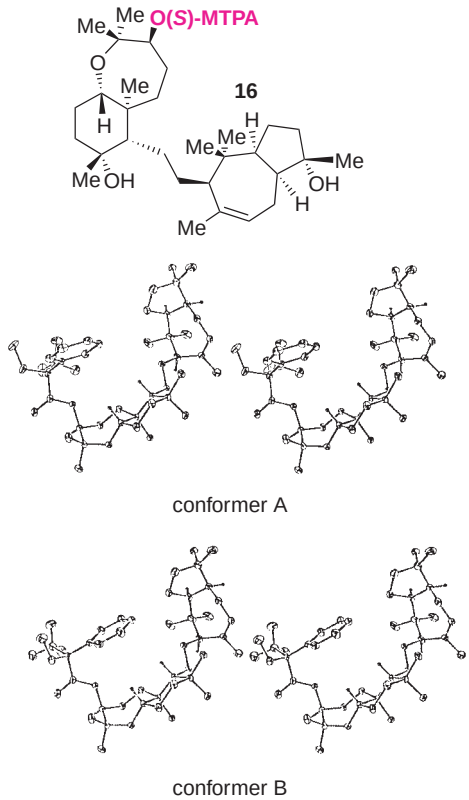


Fig. 19. Stereoview of two conformers A and B observed in the X-ray analysis of (*S*)-MTPA ester of sipholenol A (**16**).

for the modified Mosher's method. This finding gives several advantageous features to the method: When the available proton signal on one side of the MTPA plane is only one singlet (such as **47** and **48**), the NMR spectrum can be measured in either C_6D_6, CD_3OD, or C_5D_5N in addition to $CDCl_3$. If the distribution of $+$ and $-\Delta\delta$ values are normal in more than two solvents, the absolute configuration of the compound can be safely determined.

Another example of benefits is shown in Fig. 17. Compound **56** shows irregular $\Delta\delta$ values in $CDCl_3$ and C_6D_6. In the latter case, the modified Mosher's method cannot be used because of three abnormal $\Delta\delta$ values (arrowed). If one encounters such an anomaly, one can change the solvent, in this particular case, to CD_3OD or C_5D_5N, in which the $\Delta\delta$ patterns are normal.

The present experiments reveals that the modified Mosher's method is applicable to a variety of compounds in C_6D_6, CD_3OD, and C_5D_5N as well as in $CDCl_3$. When the polarity of the compound is high, CD_3OD and C_5D_5N are recommended as solvents. If important signals exist in the aromatic region, $CDCl_3$ and CD_3OD are preferred.

1.8 X-ray Structures of the MTPA Esters. During the course of the experiments, three MTPA esters, (*R*)-MTPA ester of **44**, (*R*)-MTPA ester of **54**, and (*S*)-MTPA ester of **57** gave crystals suitable for X-ray crystallography. ORTEP drawings and perspective views of them are shown in Fig. 18. In each X-ray structure, it can be seen that the MTPA group possesses the ideal conformation, in which the carbinyl proton, carbonyl oxygen, and trifluoromethyl group are on the same plane. These could be the direct proofs of the ideal conformation proposed by Mosher. However, the structure in a crystal is sometimes affected by the surrounding molecules, and actually, we have observed the presence of two conformers in the crystalline (*S*)-MTPA ester of sipholenol A (**16**) (Fig. 19).[21] In conformer B, the MTPA moiety is in the ideal conformation in which the CF_3 is eclipsed by the carbonyl oxygen. In conformer A, the methoxy group is in an eclipsed position to the carbonyl oxygen. Careful examination of the surrounding molecules in the crystal led to the conclusion that a neighboring molecule strongly interacts with the molecule in question, and that this interaction brings about the two conformers of the MTPA group.

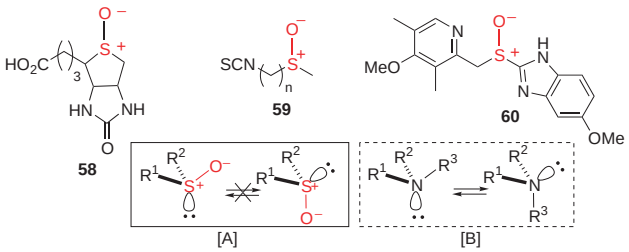


Fig. 20. Structures of naturally occurring sulfoxides: biotin sulfoxide (**58**), iberin (**59**, $n = 3$), sulphoraphan (**59**; $n = 4$), alyssin (**59**; $n = 5$), other sulfoxides (**59**; $n = 6$–10), and an artificial drug, omeprazole (**60**). [A] and [B] are to show inversion of configuration at the chiral centers, S and N, of a sulfoxide and a tertiary amine, respectively.

2. The Sulfoximine Method for Absolute Configuration of Sulfoxides

2.1 A Strategy to the Sulfoximine Method. Sulfur is one of the most important elements that organisms consist of. Among the functional groups containing sulfur, the sulfoxide group is special in that it has a chiral center and naturally occurring sulfoxides (e.g. **58**[22] and **59**[23] in Fig. 20) are usually optically active. The sulfoxide group is extremely important in pharmaceutical industry, because many synthetic drugs, such as omeprazole (**60**),[24] are designed to contain a sulfoxide group that is both lipophilic and hydrophilic.

A sulfoxide can exist as an enantiomer because the activation energy ($\Delta G^{\ddagger}$) of inversion is large (35–42 kcal mol^{-1}) (Fig. 20A). This value is quite a contrast to that of a tertiary amine (5 kcal mol^{-1}) (Fig. 20B), whose configuration at the nitrogen is rapidly inverting and the enantiomers of a tertiary amine cannot be isolated under the ordinary conditions.

Thus far, very few methods to determine the absolute configuration of optically active sulfoxides have been reported. 9-Anthryl-1,1,1-trifluoroethanol,[25] α-methoxyphenylacetic acid,[26] and (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine[27] have been developed as the NMR reagents for deducing the absolute configuration of sulfoxides. These reagents are claimed to form complexes by hydrogen bonds between their acidic OH groups and the oxygen atom of sulfoxide. But, because of the instability of the complexes, the chemical shift differences between the diastereomeric complexes are usually very small or in some cases nonsystematic, which makes these methods somewhat uncertain. Difficulty in assuming the stable conformation of fragile complexes is also an intrinsic drawback of these methods.

Chiral anisotropic reagents, such as MTPA, 2NMA (2-naphthylmethoxyacetic acid),[28] and PGME (phenylglycine methyl ester),[29] must be covalently bonded to alcohol (esterification) or carboxylic acid (amidation) when used. What bothered us most was how to combine a reagent with sulfoxide. Acylation of the oxygen of sulfoxide always brings about a reaction known as Pummerer rearrangement, in which the reaction proceeds through achiral intermediates and the information of the chirality of sulfoxide may be lost (Fig. 21). On the contrary, a sulfone (achiral), an oxidation product of sulfoxide, resists acylation and the Pummerer reaction does not occur. Apparently, the oxygen of sulfone lacks basicity to accept an electrophile.

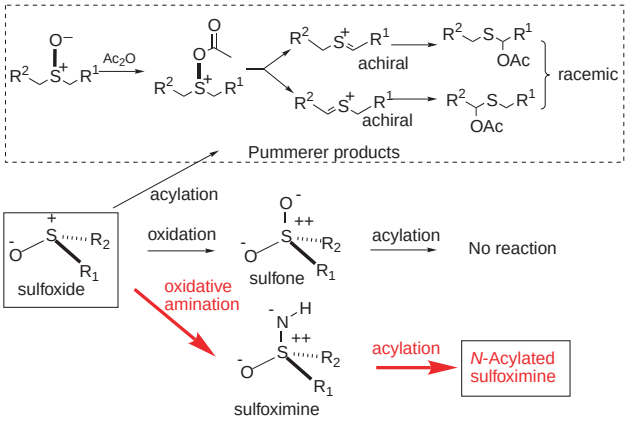


Fig. 21. Consideration leading to development of the sulfoximine method.

Here, we came upon a sulfoximine as a candidate, the nitrogen atom of which is negatively charged. Sulfoximine can easily be acylated with a chiral anisotropic reagent such as MTPA, and by applying the same concept as that of the modified Mosher's method the absolute configuration of the sulfoxide may be determined. The last problem to be solved was how to convert the sulfoxide to a sulfoximine with complete retention or inversion of the chirality at the sulfur atom of the sulfoxide. The stereochemical features of the oxidative amination (Fig. 21) ought to be fully understood.

Finally, we selected *O*-mesitylsulfonylhydroxylamine (**61**: MSH),[30] which can produce a sulfoximine from a sulfoxide with perfect retention of the configuration,[31] and *O*-methylmandelic acid (**62**: MPA)[32] as chiral anisotropic reagents. MPA was preferred to MTPA because the sulfoximine possesses a polar oxygen group besides the acylated nitrogen, and the oxygen may interact with the trifluoromethyl and methoxy groups of MTPA, which would make conformational analysis of the sulfoximide (see Fig. 22) more difficult. The strategy to establish a new method, the sulfoximine method,[33] for determining the absolute configuration of chiral sulfoxides is outlined in Fig. 22.

A chiral sulfoxide (a) is reacted with MSH (**61**) (perchlorate), to give a sulfoximine salt (b), which gives rise to a free sulfoximine (c) by treatment with an alkali. Then, it is converted to the (*S*)- and (*R*)-MPA sulfoximines, (d) and (e), by condensing with the corresponding MPA.

The series of reactions can be done in situ (one-pot reaction): Into a dichloromethane solution (0.5 mL) of (*R*)-ethyl 2-phenylethyl sulfoxide (**68**) (20 mg; 0.11 mmol) was added *O*-mesitylsulfonylhydroxylamine perchlorate (33 mg; 0.15 mmol), and the solution was stirred for 3 h at room temperature. Pyridine (0.1 mL), (*S*)-α-methoxyphenylacetic acid (36 mg; 0.22 mmol), PyBOP (114 mg; 0.22 mmol), and HOBT (30 mg; 0.22 mmol) were added, and the mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with AcOEt and the solution was washed with a 5% HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC, affording **68a** at 61% yield.

The stable conformation of the (*R*)-MPA sulfoximine is sup-

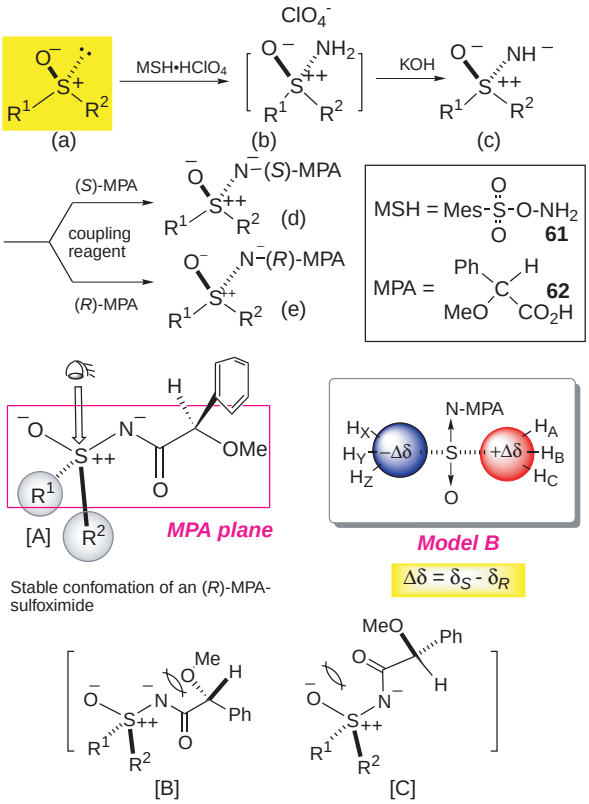


Fig. 22. Outline of the sulfoximine method. A chiral sulfoxide (a) is converted to a sulfoximine (c) with MSH (**61**). Imine (c) is acylated with (*S*)- and (*R*)-MPA (**62**) to yield sulfoximides (d) and (e), respectively. [A] is a presumed to be the stable conformation of the (*R*)-MPA sulfoximide. Conformations [B] and [C] are unstable. Model B is for the determination of the absolute configuration of the sulfoxide (a).

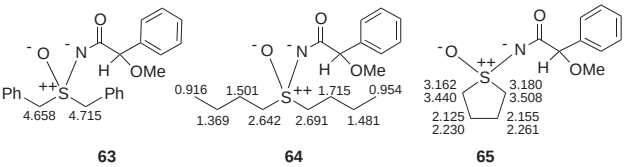


Fig. 23. The ^{1}H NMR chemical shifts of **63**, **64**, and **65** (400 MHz, $CDCl_3$).

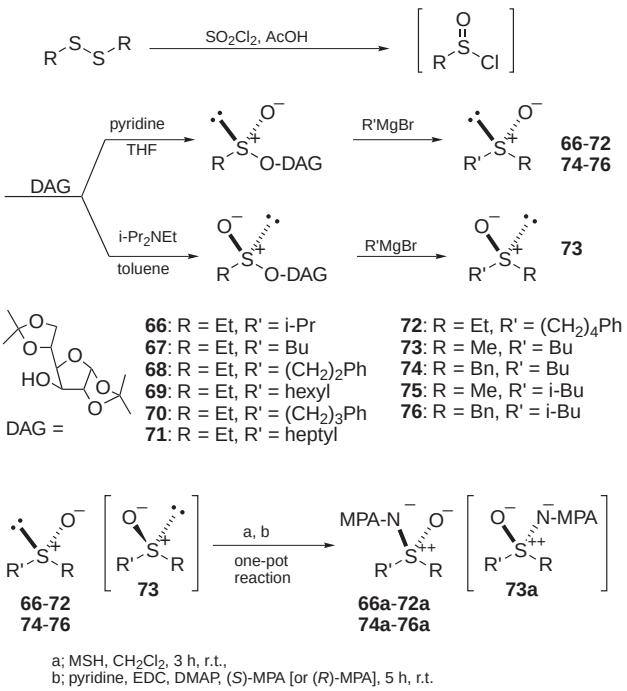


Fig. 24. Synthesis of optically active sulfoxides by the DAG method.

posed to be [A] because other conformers such as [B] and [C] are destablized by electrostatic repulsion between electronegative oxygen and nitrogen atoms. By the same token as discussed for the modified Mosher's method, the absolute configuration of a sulfoxide is determined by Model B ($\Delta\delta = \delta_S - \delta_R$).

2.2 Examination of the Sulfoximine Method Using Achiral Sulfoxides. Optically active sulfoxides are difficult to obtain. Therefore, the validity of the sulfoximine method was at first examined by use of achiral sulfoxides. By reacting MSH with dibenzyl sulfoxide, dibutyl sulfoxide, and tetramethylene sulfoxide, followed by treatment with base and racemic MPA, sulfoximines **63**–**65** were obtained. The proton chemical shifts are assigned in each structure (Fig. 23).

A pair of benzyl proton signals appeared in the ^{1}H NMR spectrum of **63**, the chemical shift difference being 0.057 ppm. This difference may be due to the anisotropic effect from the phenyl group of the MPA (Fig. 22A). In **64**, two kinds of butyl proton signals were observed, and the chemical shift differences of α, β, γ, and δ protons are 0.049, 0.214, 0.112, and 0.038 ppm, respectively. These values are in the same order of those found by the modified Mosher's method, suggesting that the chemical shift differences of the corresponding protons are caused by the anisotropic effect of the phenyl group.

2.3 Application to Chiral Alkyl and Phenylalkyl Sulfoxides. There are few commercially available chiral sulfoxides: therefore, synthesis of chiral sulfoxides was required. The chiral sulfoxides were prepared via Grignard reactions with chiral alkyl sulfinates of diacetone-D-glucose (DAG),[34] the DAG method being shown in Fig. 24. By the DAG method and the subsequent Grignard reaction with inversion of the stereochemistry, the chiral sulfoxides **66**–**76** were synthesized. They were converted to the corresponding *N*-MPA sulfoximines by the one-pot method shown in Fig. 24, affording the *N*-MPA sulfoximines **66a**–**76a** in good yields. The $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$) of each *N*-MPA sulfoximine are assigned to their structures (Fig. 25).

The following noticeable features were found by these experiments.

1) In all of the examples, the positive and negative $\Delta\delta$ values are distributed systematically on the left and right sides of the sulfur atom, respectively. The absolute configurations deduced from the patterns of $\Delta\delta$ values agree with the correct ones without exceptions.

2) The largest $\Delta\delta$ values are observed at β-positions, and the $\Delta\delta$ values observed at β-, δ-, and ζ-positions are larger than those at α-, γ-, and ε-positions. Such a tendency is also observed in the modified Mosher's method applied to acyclic

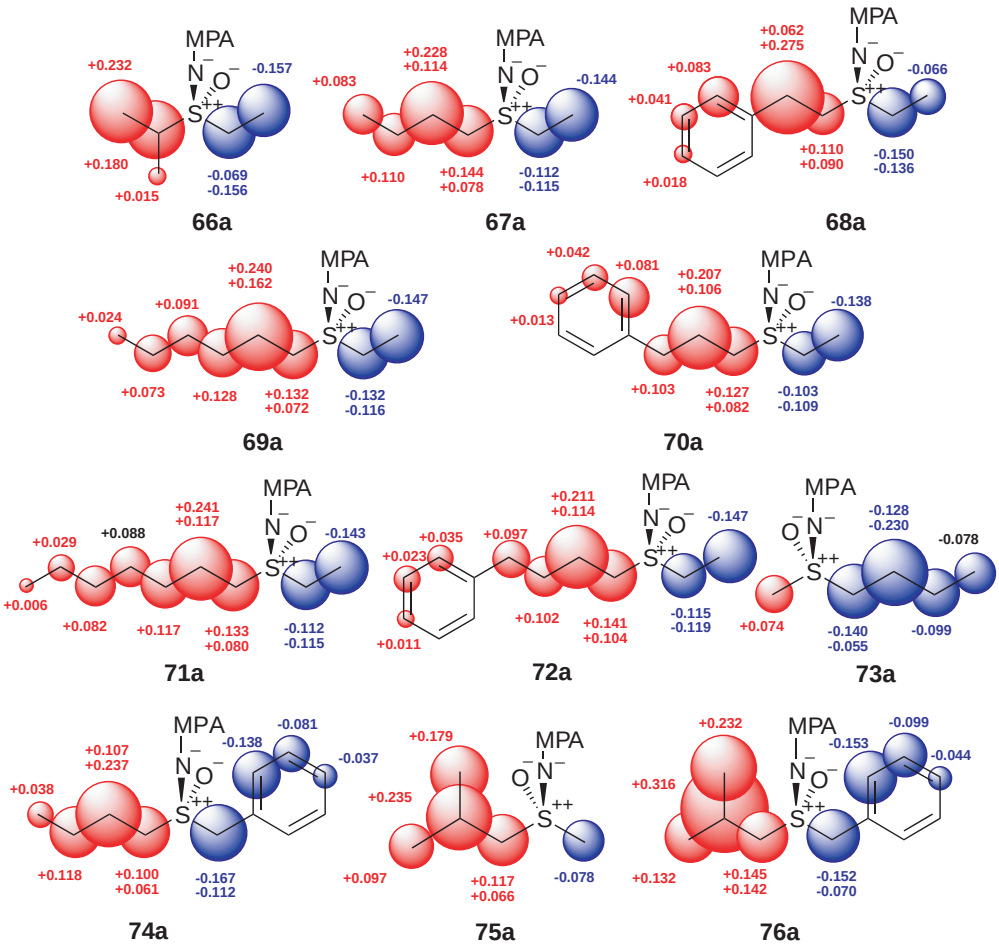


Fig. 25. $\Delta\delta$ values ($\delta_S - \delta_R$) observed for the *N*-MPA sulfoximines **66a**–**76a**. The sizes of the circles are roughly proportional to the $\Delta\delta$ values.

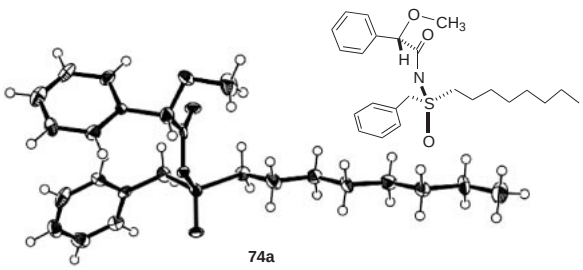


Fig. 26. X-ray structure **74a** and its perspective view.

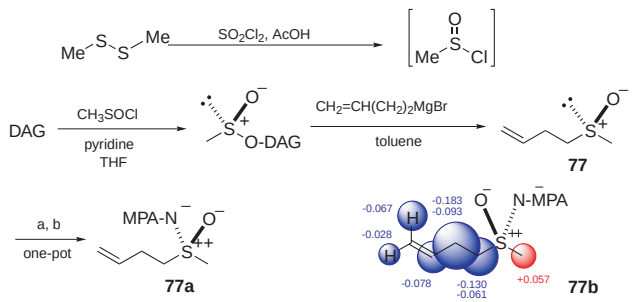


Fig. 27. Synthesis of the butenyl methyl sulfoxide **77** and the *N*-MPA sulfoximine **77a**. $\Delta\delta$ values obtained from **77a** are denoted in **77b**.

secondary alcohols, and it suggests that the alkyl side chains have a zigzag conformation in solutions.

3) The $\Delta\delta$ values observed in this method are larger than those in the modified Mosher's method using MTPA and Trost's method using MPA,[32] both also possessing a phenyl group. It seems that the population of the ideal conformation described in Fig. 22A is larger than those of the other methods.

Of the synthesized MPA sulfoximines, **74a** (racemate) gave a crystal suitable for X-ray analysis (Fig. 26). It is remarkable that the conformation of the (*S*)-MPA sulfoximine moiety is exactly the same as the one predicted in Fig. 22.

2.4 Application to Alkenyl Sulfoxides. Olefinic bonds are generally more reactive than alkyl and aryl groups, and can be oxidized to various types of functional groups such as epoxides, ketones, aldehydes, and carboxylic acids. MSH used in the sulfoximine method is an oxidant. It is possible that this reagent preferentially reacts with the olefinic part of sulfoxides possessing alkenyl groups. In such cases, this method cannot be applied to olefinic sulfoxides. The chiral alkenyl sulfoxide **77** was prepared by using the DAG method (Fig. 27), and the (*S*)- and (*R*)-MPA sulfoximines **77a** were prepared by the one-pot reaction. The result (**77b**) indicates that the sulfoximine method is applicable to an alkenyl sulfoxide without difficulty.

Two alkenyl sulfoxides, **78** and **79**, were coincidentally ob-

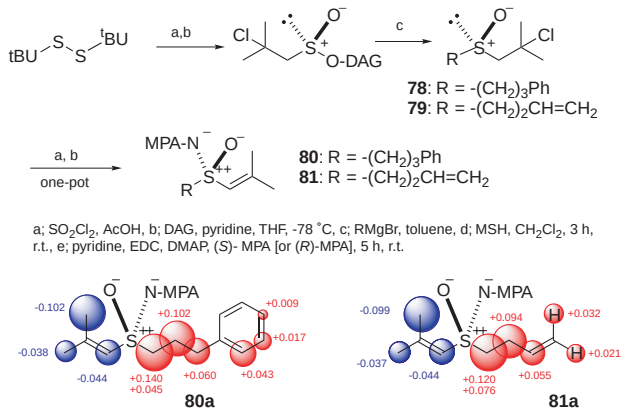


Fig. 28. Formation of the unexpected chlorobutyl sulfoxides **78** and **79**, and their conversion to the *N*-MPA butenyl sulfoximines **80** and **81**. $\Delta\delta$ values are assigned in **80a** and **81a**.

tained during the attempted synthesis of *tert*-butyl alkyl sulfoxides (Fig. 28). Di-*tert*-butyl disulfide was treated with sulfinyl dichloride in acetic acid at $-40\,^{\circ}C$, followed by a DAG reaction. Surprisingly, the only product was (2-chloro-2-methyl)propyl DAG sulfinate, not the expected DAG sulfinate having a *tert*-butyl group. Then, the DAG sulfinate was treated with the Grignard reagents giving the sulfoxides **78** and **79**. When these sulfoxides were treated under the one-pot reaction conditions (Section **2.1**), the products were *N*-MPA amides of the olefinic sulfoximines **80** and **81**, apparently as a result of β-elimination of the chlorine atom. The $\Delta\delta$ values assigned in **80a** and **81a** indicate that the sulfoximine method is applicable to these alkenyl sulfoxides.

2.5 Application to the Sulfoxides with Miscellaneous Functional Groups. 2.5.1 Use of Racemates as Probing Tools: Thus far, the sulfoximine method has proved valid for optically active sulfoxides with alkyl, alkenyl, and phenyl substituents. Without exception, the $\Delta\delta$ values have been systematically arranged, and the absolute configurations determined by the method have been correct. Our major concern now was focused on the utility of the method for sulfoxides possessing other functional groups such as an ester, ether, or amide. If these functional groups were susceptible to the reaction conditions particular to MSH, which is chemically active and has an oxidative potential, the sulfoximine method would be limited to those sulfoxides without active functional groups.

One drawback of the DAG method in obtaining optically active sulfoxide is its usage of a Grignard reaction to convert one of the substituents into a sulfoxide. For example, if a DAG sulfinate (Fig. 24) has an ester group, the Grignard reagent may react with the group as well as the sulfinate, and, therefore, multi-step reactions involving protection and deprotection are needed. Rather than that, we chose racemic sulfoxides having either an ester, amide, or ketone moiety to verify the sulfoximine method.

Figure 29 illustrates a way to determine the absolute configurations of (*S*)-MPA sulfoximines [C] and [D], which are obtained from racemate [A] + [B]. The diastereomers [C] and [D] are supposed to be separable chromatographically. The chemical shifts of (*S*)-MPA sulfoximine [D] [$\delta_{[D]}$ (*S*:*S*)]

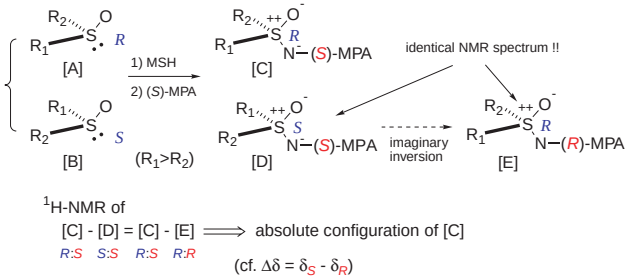


Fig. 29. A method to determine the absolute configurations of the diastereomers [C] and [D] obtained from racemate [A] + [B]. For details, see the text.

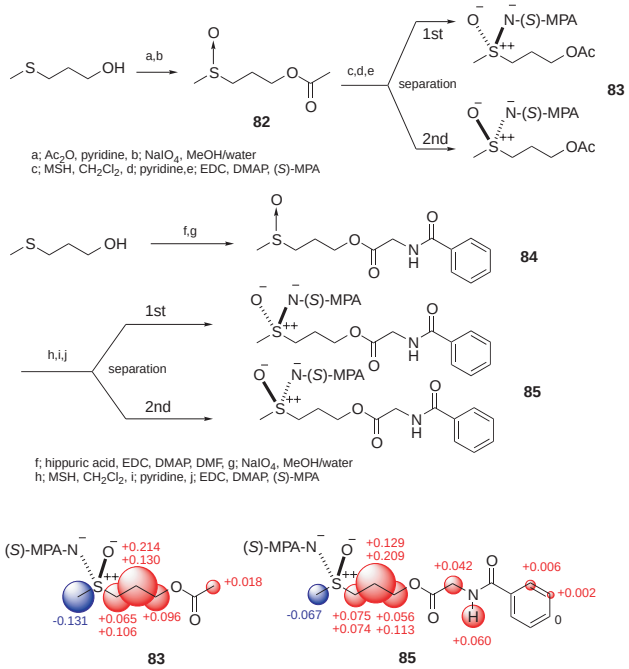


Fig. 30. Preparation of the racemic sulfoxides **82** and **84**, which have oxygen/nitrogen functions, and their (*S*)-MPA sulfoximine derivatives **83** and **85**. These were obtained as diastereomers and were separated by HPLC. $\Delta\delta$ values observed for **83** and **85** are shown. $\Delta\delta = \delta$ (second-eluted isomer) $-$ δ (first-eluted isomer).

are subtracted from those of (*S*)-MPA sulfoximine [C] [$\delta_{[C]}$ (*R*:*S*)]. It should be kept in mind that the ^{1}H NMR spectrum of (*S*)-MPA sulfoximine [D] (*S*:*S*) is identical to that of its enantiomer [E] (*R*:*R*). Therefore, $\delta_{[C]} - \delta_{[D]} = \delta_{[C]} - \delta_{[E]} = \delta(R{:}S) - \delta(R{:}R)$ indicates the absolute configuration (*R*) of diastereomer [C] (Note $\Delta\delta = \delta_S - \delta_R$).

2.5.2 Racemic Sulfoxides with Oxygen and Nitrogen Functional Groups: Sulfoxides composed of an ester **82** and an amide **84** were synthesized, and they were converted to *N*-(*S*)-MPA sulfoximines **83** and **85** (Fig. 30). The resulting mixture of the diastereomers was separated to each component by recycling HPLC, and the NMR spectra of the two diastereomers were measured. The $\Delta\delta$ values produced by subtracting the chemical shifts of a second-eluted diastereomer from those of a first-eluted isomer are illustrated in **83** and **85**. In both cases, the systematic distribution of positive and negative

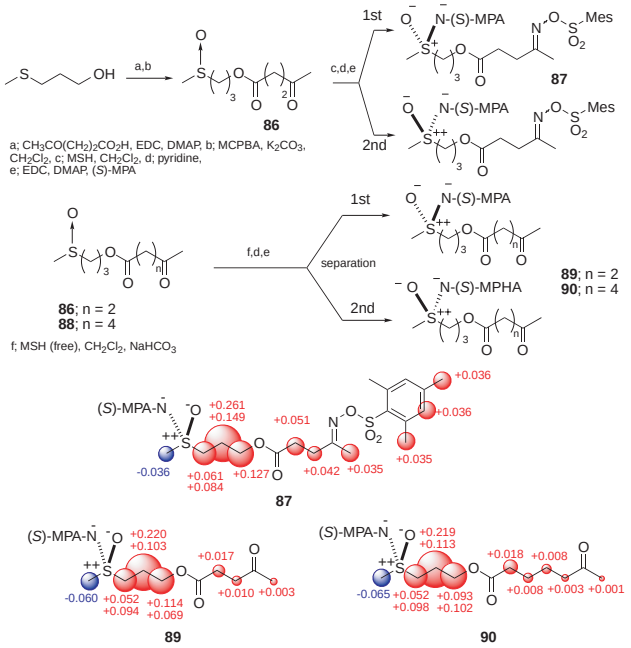


Fig. 31. Preparation of the racemic sulfoxides bearing an ester and a ketone group, **86** and **88**. Diastereomeric oximes **87** are formed during the process required for the sulfoximine method. By the modified method, the ketoester sulfoximines **89** and **90** are obtained. $\Delta\delta$ values of **87**, **89**, and **90** are shown. $\Delta\delta$ (ppm) = δ (second-eluted diastereomer) − δ (first-eluted diastereomer).

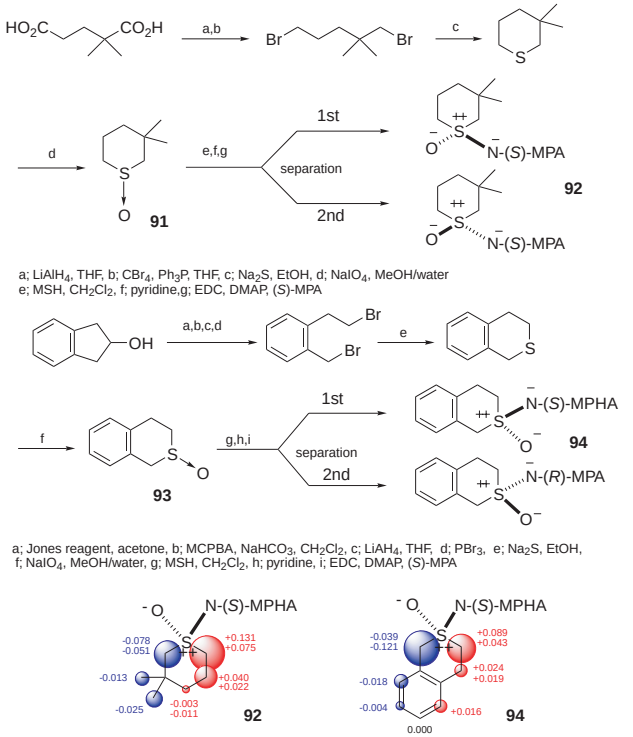


Fig. 32. Preparation of the racemic cyclic sulfoxides **91** and **93**, and their (*S*)-MPA sulfoximines **92** and **94**. $\Delta\delta$ (ppm) = δ (first-eluted diastereomer) − δ (second-eluted diastereomer).

$\Delta\delta$ values is observed. The absolute configurations shown in Fig. 30 correspond to those of the second-eluted diastereomers. It was concluded the sulfoximine method was applicable to sulfoxides having an ester or an amide group and that the functional group remained intact under the reaction conditions.

When the sulfoximine method is applied to a sulfoxide bearing a ketone function, MSH (perchlorate) may form an *O*-mesitylsulfonyl oxime. This actually happened; the sulfoxide having a ketone moiety **86** was prepared by the reactions shown in Fig. 31. When the one-pot sulfoximine method (Section **2.1**) was applied to the racemic sulfoxide **86**, diastereomers of *O*-mesitylsulfonyl oxime **87** were obtained. Interestingly, compound **87** is considerably stable and does not undergo a Beckmann rearrangement at ambient temperature. The mixture was separated into each diastereomer, and their ^{1}H NMR spectra were measured. The $\Delta\delta$ values of compound **87** are illustrated in Fig. 31. Although the positive and negative $\Delta\delta$ values are distributed on each side of the MPA plane regularly, the $\Delta\delta$ values of the mesityl group are noticeably large (0.035, 0.036, and 0.036 ppm). This suggests that the oxime of **87** has the *Z*-configuration and the mesityl protons are close to the MPA phenyl group.

When MSH (perchlorate) was added to a mixture of one equivalent of both acetophenone and phenyl methyl sulfoxide, MSH reacted with acetophenone faster than with phenyl methyl sulfoxide. MSH perchlorate is acidic and, under acidic conditions, oxime formation is accelerated. Use of free MSH instead of the perchlorate salt resulted in production of the desired *N*-MPA sulfoximines **89** and **90** without oxime formation. The respective diastereomers were separated by HPLC, and the $\Delta\delta$ values were calculated [$\Delta\delta$ = δ (second-eluted diastereomer) − δ (first-eluted diastereomer)] (Fig. 31). The configurations of **89** and **90** are those of the second-eluted diastereomers.

2.5.3 Application to Racemic Cyclic Sulfoxides: The racemic cyclic sulfoxides **91** and **93** were synthesized according to the synthetic routes shown in Fig. 32, and the sulfoxides were converted to the corresponding *N*-MPA sulfoximines **92** and **94** by the one-pot reaction. The ^{1}H NMR spectra of both diastereomers of the respective sulfoximines were measured and the $\Delta\delta$ values of the protons were calculated [$\Delta\delta$ = δ (first-eluted diastereomer) − δ (second-eluted diastereomer)]. The $\Delta\delta$ values are systematically arranged, indicating that the sulfoximine method is applicable to cyclic sulfoxides.

3. Conclusion

In this article, we introduced our studies on the development of the modified Mosher's method to elucidate the absolute configuration of secondary alcohols, together with the sulfoximine method for elucidating the absolute configuration of sulfoxides.

The modified Mosher's method is based on the Mosher's method (^{1}H NMR) and, strictly speaking, it can be regarded as a modern version of the Mosher's method. We have generalized the method, discovered cases to which the method was inapplicable, and demonstrated countermeasures to overcome problems. Especially, noteworthy is the fact that there have been no reports on the modified Mosher's method that have led to an incorrect absolute configuration thus far. Our new finding that the modified Mosher's method can be used in var-

ious solvents such as C_6D_6, C_5D_5N, and CD_3OD will be important in cases where the samples are not soluble or labile in $CDCl_3$, and observing the $\Delta\delta$ values in different solvents may become a good indicator to increase the credibility of the results.

The sulfoximine method is a novel method developed for the elucidation of the absolute configuration of chiral sulfoxides. A sulfoximine obtained by the reaction of MSH with a sulfoxide is esterified with (*R*)- and (*S*)-MPA, and the $\Delta\delta$ values are calculated for all of the protons. In that sense, this unique method is similar to the Mosher's method.

The sulfoximine method may be a good example to encourage synthetic chemists to have a common ground with structure-analysis chemists; the former can develop new tools to solve the quandary the latter is in. Modern instrumental analyses are not error free yet. Besides struggling with the absolute configurations of various types of organic compounds, structure analysts are dealing with enormous numbers of difficult compounds such as highly aromatized compounds with few protons and conformationally flexible compounds that do not show sharp NMR signals. By the collaboration of synthetic and analytical chemists, a new scientific field can be developed.

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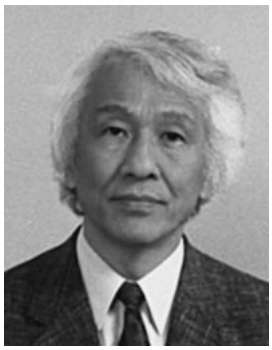

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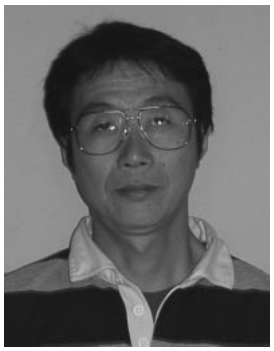

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