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Conformational Analysis of MαNP Esters, Powerful Chiral Resolution and ^{1}H NMR Anisotropy Tools – Aromatic Geometry and Solvent Effects on Δδ Values

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The MαNP acid method is very powerful for the preparation of enantiopure alcohols by resolution and the simultaneous determination of their absolute configurations by the ^{1}H NMR anisotropy effect, where the *syn-syn* conformation is taken as the preferred conformation of MαNP esters. However, the *syn-syn* conformation of MαNP esters looks unstable, because two electronegative oxygen atoms (CH_3O and C=*O*) are close to each other. To solve the problem of why the MαNP esters take such a *syn-syn* conformation, the aromatic geometry and solvent effects on the ^{1}H NMR anisotropy data were studied, leading to the following conclusions: i) the hydrogen-bonding-like interaction among the H-8′ of the naphthyl group, the ester carbonyl oxygen, and the methoxy oxygen supports a triangular intramolecular force to stabilize the *syn-syn* conformation; ii) triangular hydrogen bonding among a hydrogen atom of protic solvents, the ester carbonyl oxygen, and the methoxy oxygen also supports the *syn-syn* conformation. This hydrogen bonding, as the solvation effect implies, suggests that a similar hydrogen bonding between a MαNP ester and a hydroxy group of the silica gel surface would make a dominant contribution to the excellent discrimination of diastereomeric MαNP esters observed in the HPLC on silica gel.

Introduction

It is well known that in 1951, J. M. Bijvoet and coworkers first succeeded in determining the absolute configuration of a chiral compound, sodium rubidium tartrate, using the anomalous dispersion effect of heavy atoms in X-ray crystallography.[1] Since then, the absolute configurations of many compounds containing heavy atoms have been determined by the Bijvoet method. Once the absolute configuration of a compound has been determined by the Bijvoet method, the compound can be used as an internal reference of absolute configuration in the X-ray crystallography of derivatives of the compound. In our opinion, this relative method with the internal reference in X-ray crystallography is the most reliable, because the absolute configuration in question is automatically determined from the stereoview provided by X-ray crystallography. In addition, this method does not need derivatives containing so-called heavy atoms. For example, the absolute configurations of chiral C_{60} fullerene *cis*-3 bisadducts were first established by a combination of this X-ray method and CD spectroscopy.[2] For such internal reference compounds, we have developed the chiral auxiliaries of camphorsultam-phthalic (CSP) and camphorsultam-dichlorophthalic (CSDP) acids,[3–5] which are very powerful for the enantioresolution of racemic alcohols and for the simultaneous determination of their absolute configurations by X-ray crystallography. However, X-ray crystallography has a disadvantage in that it needs single crystals suitable for X-ray diffraction experiments, while such single crystals are not always available.

For non-crystalline compounds, the relative and empirical ^{1}H NMR anisotropy method is useful. For such chiral ^{1}H NMR anisotropy reagents, many chiral acids have been developed for determining the absolute configurations of alcohols and other chiral compounds: α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA),[6] 2-methoxy-2-phenylacetic acid (MPA),[7] 2-methoxy-2-(1-naphthyl)acetic acid (1NMA), 2-methoxy-2-(2-naphthyl)acetic acid (2NMA), 2-(9-anthryl)-2-methoxyacetic acid (9AMA),[8,9] α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA),[10] and other acids.[11] By using these chiral anisotropy reagents, the absolute configurations of many chiral alcohols and natural

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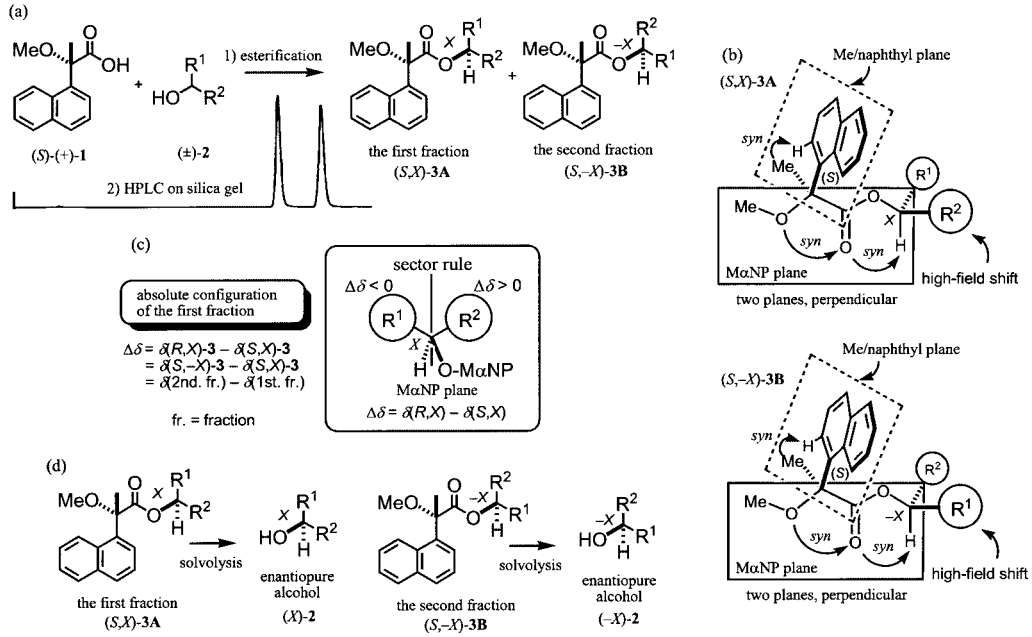


Figure 1. General scheme of enantioresolution and determination of the absolute configuration of the first eluted diastereomeric ester with chiral MαNP acid (*S*)-(+)-**1**.

products have been successfully determined.[8,9] As another chiral ^{1}H NMR anisotropy reagent, we have developed 2-methoxy-2-(1-naphthyl)propionic (MαNP) acid **1**,[12–14] which is also powerful for determining the absolute configurations of chiral secondary alcohols (Figure 1). This chiral ^{1}H NMR anisotropy reagent is unique in the sense that diastereomeric MαNP esters prepared from enantiopure acid (*S*)-(+)-**1** and racemic alcohols are easily separable by HPLC on silica gel. In addition, acid **1** has a chiral quaternary carbon atom, and therefore, does not racemize. Therefore, enantiopure alcohols are easily prepared from separated esters. We have developed a new methodology for the enantioresolution of alcohols and the simultaneous determination of their absolute configurations with MαNP acid **1**.[12–15]

The procedure of the MαNP acid method is outlined in Figure 1 (a). Racemic alcohol (±)-(**2**) is esterified with (*S*)-(+)-MαNP acid **1**, yielding diastereomeric esters, which are easily separable by HPLC on silica gel. The absolute configuration of the first eluted fraction **3A** is designated as (*S*,*X*), where *X* represents the absolute configuration of the alcohol part to be determined, while *S* indicates that of the MαNP acid part. From the logic for the enantioresolution, the absolute configuration of the second eluted fraction **3B** is naturally designated as (*S*,–*X*), where –*X* represents the opposite absolute configuration of *X*. As shown in Figure 1 (b), diastereomeric MαNP esters (*S*,*X*)-**3A** and (*S*,–*X*)-**3B** adopt the preferred conformation, where the terminal methyl group of the propionic acid part is *synperiplanar* to the H-2 of the naphthalene group, which forms the Me/naphthyl plane as shown with dotted lines. On the other hand, the oxygen atom of the methoxyl group is *synperiplanar* to the ester carbonyl oxygen atom, which is also *synperiplanar* to the methine proton of the alcohol moiety, and these three atoms form the MαNP plane as shown in Figure 1 (b). These two planes are perpendicular to each other because of the tetrahedral configuration of the quaternary stereogenic center. In this preferred conformation of the first eluted ester **3A**, the substituent R^2 is in proximity to the plane of the naphthalene moiety, falling in its field of diamagnetic anisotropy and leading to the high-field shifts of R^2 protons. On the other hand, in the second eluted ester **3B**, the substituent R^1 is located above the naphthalene plane, and, therefore, high-field shifts of R^1 protons are observed.

The parameter representing the anisotropy effect is originally defined as $\Delta\delta = \delta(R,X) - \delta(S,X)$. In the case of enantioresolution with the (*S*)-(+)-MαNP acid, this equation is transformed to $\Delta\delta = \delta(S,-X) - \delta(S,X) = \delta$(2nd fraction) – δ(1st fraction).[12,14] From the observed ^{1}H NMR spectroscopic data, the $\Delta\delta$ value of each proton is calculated and plotted according to the sector rule shown in Figure 1 (c), where the substituent R^2 with positive $\Delta\delta$ values is placed on the right side, while the substituent R^1 with negative $\Delta\delta$ values is placed on the left side. By this displacement of substituents, the absolute configuration *X* of the first eluted ester **3A** is determined; it is obvious that the second eluted ester **3B** takes the opposite absolute configuration –*X*. The hydrolysis of esters **3A** and **3B** gives enantiopure alcohols (*X*)-**2** and (–*X*)-**2**, respectively, as shown in Figure 1 (d).

The MαNP acid method has several advantages: (1) in general, diastereomeric esters **3A** and **3B** are clearly separable by HPLC on silica gel indicating that MαNP acid has a great ability to discriminate the chirality of alcohols, (2) the chiral center of MαNP acid is a quaternary carbon atom, and therefore, does not racemize during the derivatization

reaction, the separation by HPLC, and the hydrolysis to recover the alcohol. This is essential for the preparation of an enantiopure alcohol, and (3) although the MαNP acid method for determining the absolute configuration is an empirical rule, we have not encountered any exception during our many studies.[12] This is an important advantage of the MαNP acid method and makes the method reliable. Why has the method no exception? It indicates that in all cases, the conformations shown in Figure 1 (b) are always stable and preferred, leading to the distribution of $\Delta\delta$ values obeying the sector rule. So, the next question is why the conformations depicted in Figure 1 (b) are so stable. At first glance, the conformations look unstable, because the oxygen atom of the methoxyl group is *synperiplanar* to the carbonyl oxygen atom of the ester moiety. Why are two electronegative oxygen atoms close to each other? The objective of these three serial papers[16,17] is to solve these problems.

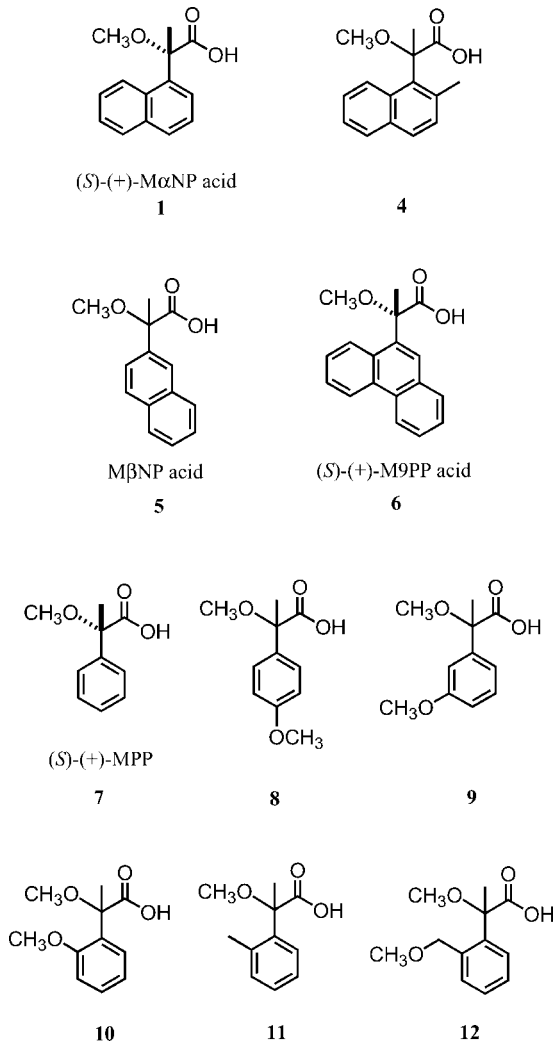
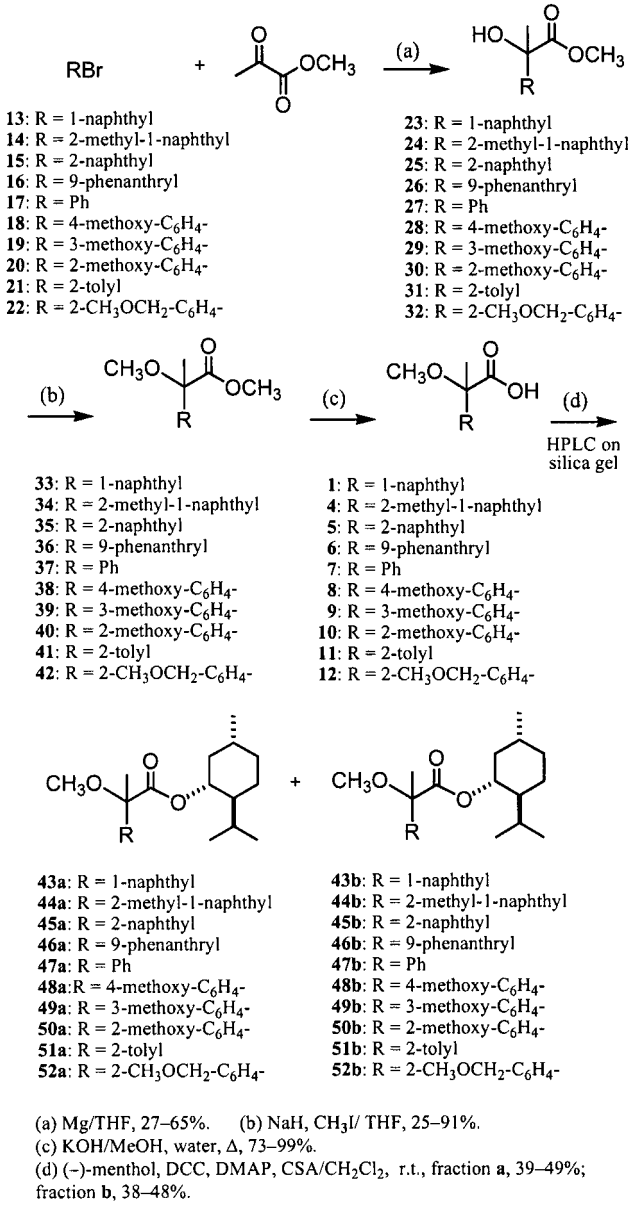


Figure 2. MαNP acid (*S*)-(+)-**1** and related acids.

Results and Discussion

Synthesis of Racemic Carboxylic Acids with Various Aromatic Groups Related to MαNP Acid and Preparation of Their Menthol Esters

To study the dependence of the anisotropy effect, $\Delta\delta$, on the geometry of the aromatic group, carboxylic acids with various aromatic groups were synthesized as shown in Figure 2. The Grignard reagents prepared from aryl bromides (**14**, **15**, **17**–**22**) were allowed to react with methyl pyruvate, yielding methyl 2-aryl-2-hydroxypropionates **24**, **25**, and **27**–**32**, respectively, which were further converted to methyl 2-aryl-2-methoxypropionates **34**, **35**, and **37**–**42**, respectively, by treating with NaH and iodomethane (Scheme 1).



Scheme 1. Preparation of diastereomeric esters from (–)-menthol and racemic carboxylic acids. The preparation of MαNP acid esters **43a**/**43b** and M9PP acid esters **46a**/**46b** has been reported.[12l,19]

Table 1. HPLC separation of diastereomeric esters formed from (–)-menthol with racemic MαNP acid and related acids.[a]

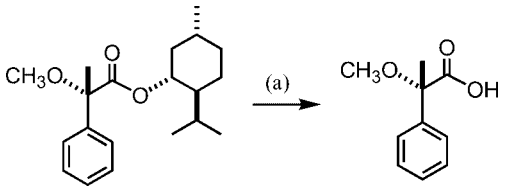
Entry	Acid	Solvent[b]	α	*Rs*	Ester (1st fraction)	Chiral acid recovered from 1st fraction
1[c]	(±)-**1**	H/EA = 10:1	1.83	4.55	(*S*;1*R*,3*R*,4*S*)-(–)-**43a**	(*S*)-(+)-**1**
2	(±)-**4**	H/EA = 20:1	1.93	3.31	**44a**	–
3	(±)-**5**	H/EA = 20:1	1.37	1.86	**45a**	–
4[d]	(±)-**6**	H/EA = 9:1	1.64	–	(*S*;1*R*,3*R*,4*S*)-(+)-**46a**	(*S*)-(+)-**6**
5	(±)-**7**	H/EA = 10:1	1.71	2.55	(–)-**47a**	(*S*)-(+)-**7**
6	(±)-**8**	H/EA = 10:1	1.41	3.30	(–)-**48a**	–
7	(±)-**9**	H/EA = 10:1	1.59	3.97	(–)-**49a**	–
8	(±)-**10**	H/EA = 20:1	1.09	0.90	**50a**	–
9	(±)-**11**	H/EA = 10:1	1.53	1.72	(–)-**51a**	–
10	(±)-**12**	H/EA = 10:1	1.27	1.57	**52a**	–

[a] Glass column (Ø 22 mm × 300 mm, or Ø 25 mm × 400 mm) of silica gel (particle size 5–10 μm). [b] H = *n*-hexane, EA = ethyl acetate. [c] Taken from ref.[12l] [d] Taken from ref.[19]

The methyl esters were hydrolyzed with KOH in methanol, giving 2-aryl-2-methoxypropionic acids **4**, **5**, and **7**–**12**, respectively. The racemic acids obtained were allowed to react with (–)-menthol by stirring with 1,3-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), and 10-camphorsulfonic acid (CSA) in dichloromethane, yielding a mixture of diastereomeric esters **44**, **45**, and **47**–**52**, respectively.

As in the case of menthol MαNP ester **43**, the diastereomeric esters **44**, **45**, and **47**–**52** were subjected to HPLC on silica gel with hexane/EtOAc (10:1 or 20:1); as listed in Table 1, these diastereomeric esters were effectively separated. For example, ester **44** with the 2-methyl-1-naphthyl group was largely separated to **44a** and **44b** with a separation factor α = 1.93. Such a large separation factor enables one to make a separation on a large scale. In the case of 2-methoxyphenyl derivative **50**, the α value was 1.09, which is smaller than in other cases, but it was still possible to make the complete separation.

In the case of menthyl 2-methoxy-2-phenylpropionate **47**, the diastereomeric esters were effectively separated with α = 1.71. The first eluted ester, (–)-**47a**, was hydrolyzed with KOH in methanol, giving (+)-2-methoxy-2-phenylpropionic acid (**7**), the absolute configuration of which was determined as *S* by comparison of the sign of optical rotation with that reported in the literature (Scheme 2).[18]



(*S*)-(–)-**47a** (*S*)-(+)-**7**

(a) KOH/MeOH, water, Δ, 94%

Scheme 2. Recovery of enantiopure carboxylic acid (*S*)-(+)-**7**.

^{1}H NMR Anisotropy Effects of (1*R*,3*R*,4S)-Menthol MαNP Acid Esters and Related Esters

To clarify the dependence of ^{1}H NMR anisotropy effects on the geometry of the aromatic groups, the ^{1}H NMR signals of menthol esters **44a**, **45a**, and **47a**–**52a** were fully assigned with ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, and HMBC spectra. From the observed data, $\Delta\delta$ values were calculated as $\Delta\delta = \delta$(2nd fraction) – δ(1st fraction) for the protons of the menthol moiety; the distribution of $\Delta\delta$ values are shown in Figure 3 together with those of menthol MαNP esters **43a/43b** and menthol 2-methoxy-2-(9-phenanthryl)propionic acid (M9PP acid) **46a/46b**. In the case of menthol MαNP esters **43a/43b**, their absolute configurations are already known, and $\Delta\delta$ {= δ(2nd fraction) – δ(1st fraction)} is equal to $\delta(R,X) - \delta(S,X)$, in agreement with the original definition of $\Delta\delta$ as described in the Introduction. The same is true for the case of M9PP esters **46a/46b**. In the case of esters **44a/44b**, **45a/45b**, and **47a/47b**–**52a/52b**, however, the absolute configurations of carboxylic acid parts are unknown, except for **47a/47b**, and therefore, we have adopted $\Delta\delta$ values as $\Delta\delta = \delta$(2nd fraction) – δ(1st fraction); there is no guarantee that $\Delta\delta = \delta(R,X) - \delta(S,X)$. To evaluate the ^{1}H NMR anisotropy effects here, it is sufficient to use the definition of $\Delta\delta = \delta$(2nd fraction) – δ(1st fraction).

In Figure 3 (a), the $\Delta\delta$ values of menthol MαNP acid esters **43a/43b** are listed as the standard, where $CDCl_3$ was used as the ^{1}H NMR solvent. A new parameter *D* representing the strength of the anisotropy effect is defined as $D = \Delta\delta(\max) - \Delta\delta(\min)$, where $\Delta\delta$(max) indicates the maximum value of $\Delta\delta$ in the alcohol moiety, while $\Delta\delta$(min) indicates the minimum value of $\Delta\delta$ (largest negative value). In the case of menthol esters, $\Delta\delta$(max) was determined by the proton at the 2ax-position, H-2ax, and $\Delta\delta$(min) was determined by H-8′. Therefore $D = \Delta\delta(\max) - \Delta\delta(\min) = \Delta\delta$(H-2ax) – $\Delta\delta$(H-8′); this definition was used for menthol esters **44a/44b**–**52a/52b**. In the case of menthol MαNP acid esters **43a/43b**, $D = +0.31 - (-1.23) = 1.54$.

The observed $\Delta\delta$ values representing anisotropy effects are very sensitive to the geometry of aromatic groups. When

an extra methyl group is placed at the 2-position of the naphthalene group, the observed $\Delta\delta$ values are almost zero as seen in esters **44a/44b** [Figure 3 (a)]; small negative $\Delta\delta$ values are obtained even on the right side. This result indicates that the conformation of esters **44a/44b** is not fixed at some specific position, and therefore, the naphthalene plane is randomly oriented toward the menthol moiety, and hence, no anisotropy effect is observed.

Menthol 2-methoxy-2-(2-naphthyl)propionic (MβNP) acid esters **45a/45b**, containing 2-naphthyl group, also show

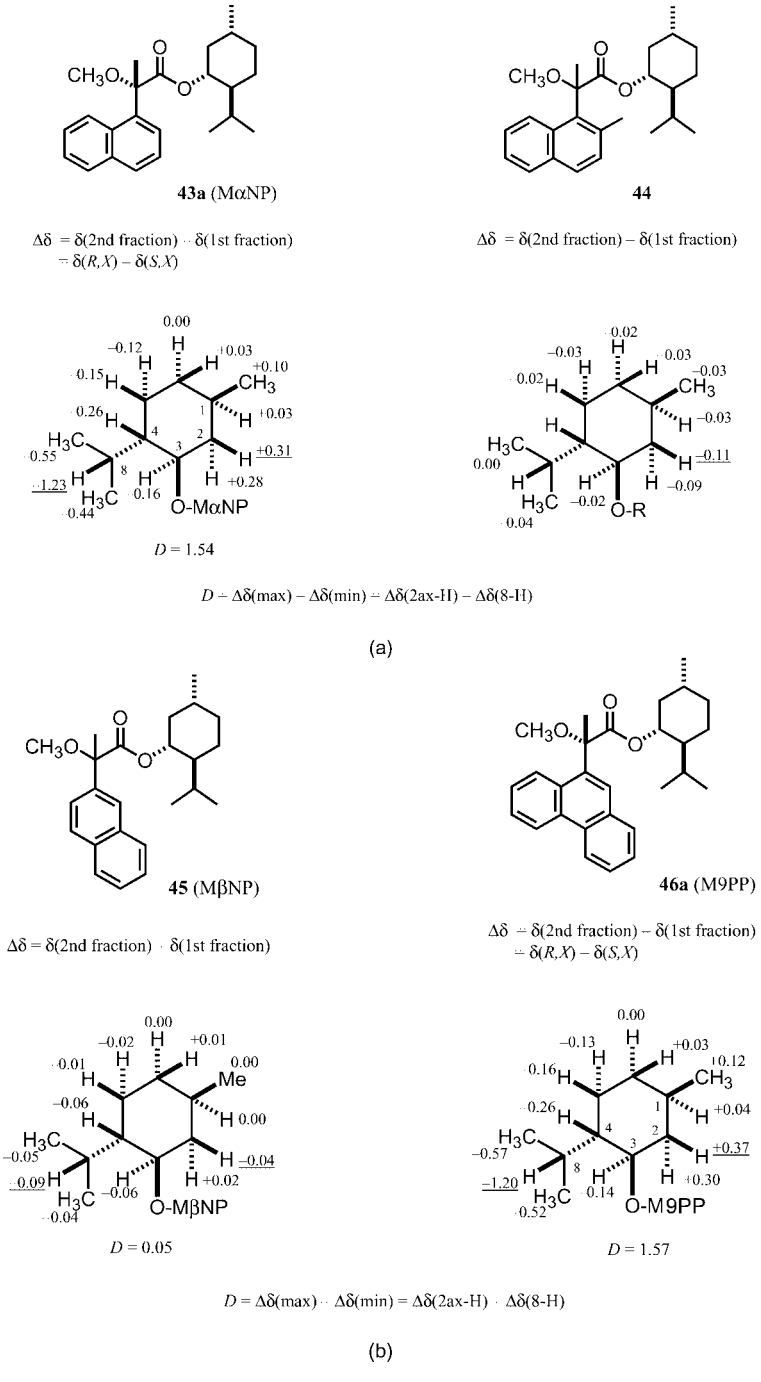


Figure 3. (a) ^{1}H NMR anisotropy effects of (1*R*,3*R*,4*S*)-menthol MαNP acid esters **43a** (first eluted fraction), **43b** (second eluted fraction), and related acid esters **44**. $\Delta\delta$ {= δ(2nd fraction) – δ(1st fraction)} and *D* values are shown in ppm. Spectra were recorded at 600 MHz in $CDCl_3$. For esters **44**, the *D* value was not calculated because of overlap of proton signals. The $\Delta\delta$ values of esters **43a/43b** were taken from ref.[12] (b) ^{1}H NMR anisotropy effects of (1*R*,3*R*,4*S*)-menthol esters **45** and **46**. $\Delta\delta$ {= δ(2nd fraction) – δ(1st fraction)} and *D* values are given in ppm. Spectra were recorded at 600 MHz in $CDCl_3$. The $\Delta\delta$ values of esters **46a/46b** were taken from ref.[19] (c) ^{1}H NMR anisotropy effects of (1*R*,3*R*,4*S*)-menthol esters **47**, **48**, and **49**. $\Delta\delta$ {= δ(2nd fraction) – δ(1st fraction)} and *D* values are given in ppm. Spectra were recorded at 600 MHz in $CDCl_3$. (d) ^{1}H NMR anisotropy effects of (1*R*,3*R*,4*S*)-menthol esters **50**, **51**, and **52**. $\Delta\delta$ {= δ(2nd fraction) – δ(1st fraction)} and *D* values are given in ppm. Spectra were recorded at 600 MHz in $CDCl_3$.

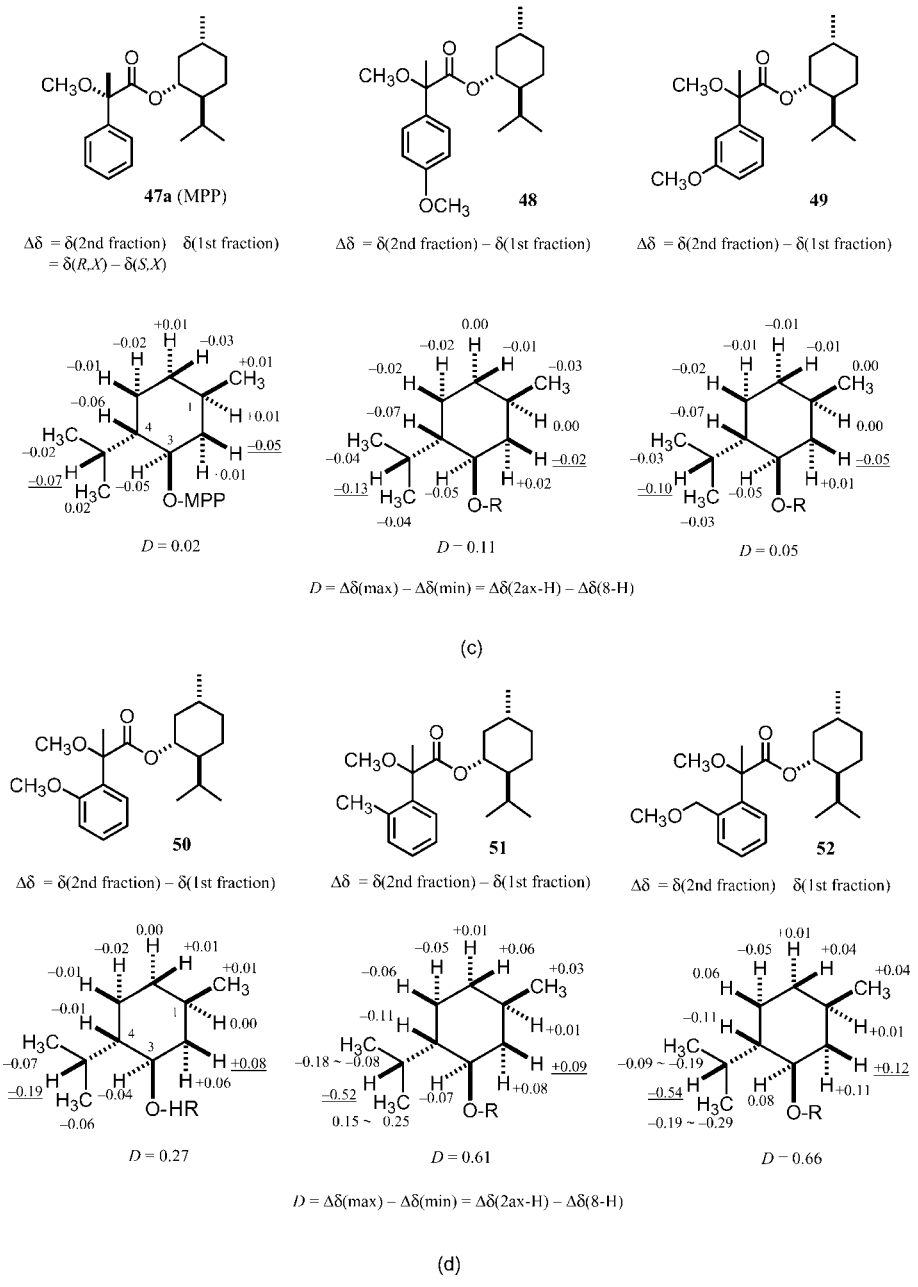


Figure 3. *(continued)*.

nil $\Delta\delta$ values [D = 0.05 in Figure 3 (b)]. This is in strong contrast with the case of menthol 2NMA acid esters, for which moderately large $\Delta\delta$ values were reported;[8b] from the data, the D value was calculated as D = 0.87. Why are the anisotropy effects of menthol MβNP acid esters **45a/45b** and menthol 2NMA acid esters so different? The MβNP esters **45a/45b** are propionic acid derivatives, while 2NMA acid esters are acetic acid derivatives; this difference is solely due to the existence of a methyl group. The data indicate that menthol MβNP acid esters **45a/45b** do not occupy any specific stable conformation leading to large $\Delta\delta$ values. The mechanism of different D values will be discussed below.

It is interesting to compare the behavior of menthol MβNP acid esters **45a/45b** with that of menthol M9PP acid esters **46a/46b** [Figure 3 (b)]. Although esters **46a/46b**, with the 9-phenanthryl group, show large $\Delta\delta$ values (D = 1.57),[19] esters **45a/45b**, with the 2-naphthyl group, give no anisotropy effect (D = 0.05). The shape of the 9-phenanthryl group looks like a hybrid of 1-naphthyl and 2-naphthyl groups, and the results clearly indicate that the 1-naphthyl part is essential for the anisotropy effect.

No anisotropy effect was observed in the cases of menthol esters of 2-methoxy-2-phenylpropionic (MPP) acid **47a/47b**, 2-methoxy-2-(4-methoxyphenyl)propionic acid **48a/48b**, and 2-methoxy-2-(3-methoxyphenyl)propionic

acid **49a/49b** [D = 0.02 for **47a/47b**, D = 0.11 for **48a/48b**, and D = 0.05 for **49a/49b**, Figure 3 (c)]. The result of MPP esters **47a/47b** also contrasts strongly with the menthol esters of MPA acid, which show a moderately large D value of 0.86.[20] The presence of an extra methyl group prevents the appearance of the anisotropy effect, implying that the phenyl group is randomly oriented toward the menthol moiety under the averaged conformations. To study the effect of electron-donating substituents on a phenyl group, 4-methoxyphenyl (**48a/48b**) and 3-methoxyphenyl (**49a/49b**) esters were prepared, and $\Delta\delta$ values were calculated. The results indicate that there is no effect of the electron-donating substituents on $\Delta\delta$ values.

The studies were further continued. In the case of 2-methoxyphenyl esters **50a/50b**, the distribution pattern of $\Delta\delta$ values matches with the sector rule shown in Figure 1 (c), although the observed $\Delta\delta$ values are small (D = 0.27); the right half of the menthol moiety gives positive $\Delta\delta$ values, while the left half gives negative $\Delta\delta$ values [Figure 3 (d)]. This is a good indication of the effect of the substituent at the 2-position. We next checked 2-methylphenyl esters **51a/51b**; it was surprising to find that the distribution of $\Delta\delta$ values obeys the sector rule despite the nonpolar substituent, and the observed anisotropy effect (D = 0.61) was much larger than the case of 2-methoxyphenyl esters **50a/50b**. This result implies that the hydrogens of a methyl group may participate in the stabilization of the conformation matching the sector rule [i.e. the *syn-syn* conformation shown in Figure 1 (b)]. We next studied the case of 2-(methoxymethyl)phenyl esters **52a/52b**, which also showed a similar anisotropy effect (D = 0.66), suggesting the contribution of hydrogen atoms to the stabilization of the *syn-syn* conformer.

The Solvent Dependency of the ^{1}H NMR Anisotropy of (1*R*,3*R*,4*S*)-Menthol MαNP Acid Esters

To clarify the solvent dependency of anisotropy effects, ^{1}H NMR spectra of menthol MαNP acid esters **43a/43b** were measured with various solvents as shown in Figure 4. In all cases, the distribution of $\Delta\delta$ values obeys the sector rule; even in nonpolar solvents such as [D_{12}]cyclohexane and [D_6]benzene, small but non-zero and moderately large D values were obtained, respectively [Figure 4 (a), D = 0.43 in C_6D_{12} and D = 0.83 in C_6D_6]. These results indicate that molecules **43a/43b** have, to some extent, an intramolecular force to stabilize the *syn-syn* conformation depicted in Figure 1 (b). With polar solvents, such as [D_5]pyridine, [D_6]-acetone, [D_3]acetonitrile, and [D_6]DMSO, the $\Delta\delta$ value becomes larger in the order of solvent polarity {D = 1.14 in [D_5]pyridine, D = 1.18 in [D_6]acetone, D = 1.36 in [D_3]acetonitrile, and D = 1.36 in [D_6]DMSO}. However, the D value in [D_6]DMSO is equal to that in [D_3]acetonitrile, although the dielectric constants and dipole moments of DMSO are larger than those of acetonitrile. These data indicate that the solvent polarity also contributes to the stabilization of the *syn-syn* conformation, but it is not the major factor.

It was surprising to find that less polar solvents such as [D_2]dichloromethane and [D]chloroform gave larger D values than [D_6]DMSO as shown in Figure 4 (b) {D = 1.38 in [D_2]dichloromethane and D = 1.54 in [D]chloroform}. These results indicate that the anisotropy effect ($\Delta\delta$) is not proportional to the solvent polarity. A plausible interpretation of these results is that the hydrogen of halomethane molecules may stabilize the *syn-syn* conformation by a hydrogen-bonding-like interaction. This mechanism was supported by the data with protic solvents, such as [D_4]acetic acid, [D_4]methanol, and [D_3]-2,2,2-trifluoroethanol, as shown in Figure 4 (b) {D = 1.57 in [D_4]acetic acid, D = 1.85 in [D_4]methanol, and D = 2.07 in 2,2,2-[D_3]-trifluoroethanol}. These $\Delta\delta$ values are much larger than those with [D_6]DMSO. It is now clear that the proton of protic solvents effectively stabilizes the *syn-syn* conformation by its participation in hydrogen bonding. This is discussed below in detail.

The [D_4]methanol solvent gives a larger D value than that of [D]chloroform, and therefore, when $\Delta\delta$ values observed in [D]chloroform are small, it is advised to use [D_4]-methanol. However, in our opinion, the $\Delta\delta$ values observed in [D]chloroform are large enough for absolute configurational assignment, and therefore, the use of [D]chloroform, in which most compounds are easily soluble, is recommended.

Intramolecular Hydrogen-Bonding-Like Interaction Stabilizing the *syn-syn* Conformation

What kind of mechanism for stabilizing the *syn-syn* conformation can be deduced from the data described above? In the case of 2-hydroxy-2-(1-naphthyl)propionic acid ester shown in Figure 5 (a), the intramolecular hydrogen bonding between the hydroxy proton and the ester carbonyl oxygen makes the *syn-syn* conformation stable. Similarly, we had first considered that the proton of the methoxyl group participates in an intramolecular hydrogen-bonding-like interaction as shown in Figure 5 (b). However, this mechanism is easily ruled out, because the anisotropy effect ($\Delta\delta$ value) sharply depends on the geometry of the aromatic moiety; only MαNP esters **43a/43b**, M9PP esters **46a/46b**, and 2-methoxy-(2-substituted phenyl)propionic acid esters, **50a/50b**, **51a/51b**, and **52a/52b**, gave non-zero and meaningful $\Delta\delta$ values.

We next considered the intramolecular hydrogen-bonding-like interaction among H-8′ of the naphthalene group, the methoxy oxygen (O-7), and the ester carbonyl oxygen (O-6) as shown in Figure 5 (c). Namely, these three atoms could form a triangular hydrogen-bonding-like interaction, where H-8′ is partially positively charged and interacts with the lone pair orbitals of O-6 and O-7. Such interaction stabilizes the *syn-syn* conformation as shown. This mechanism is supported by the ^{1}H NMR spectroscopic data of esters **43a**, **43b**, and related compounds listed in Table 2. In MαNP acid ester **43a**, the H-8′ signal (δ = 8.37 ppm) is shifted downfield compared to those of H-4′ (δ = 7.81 ppm)

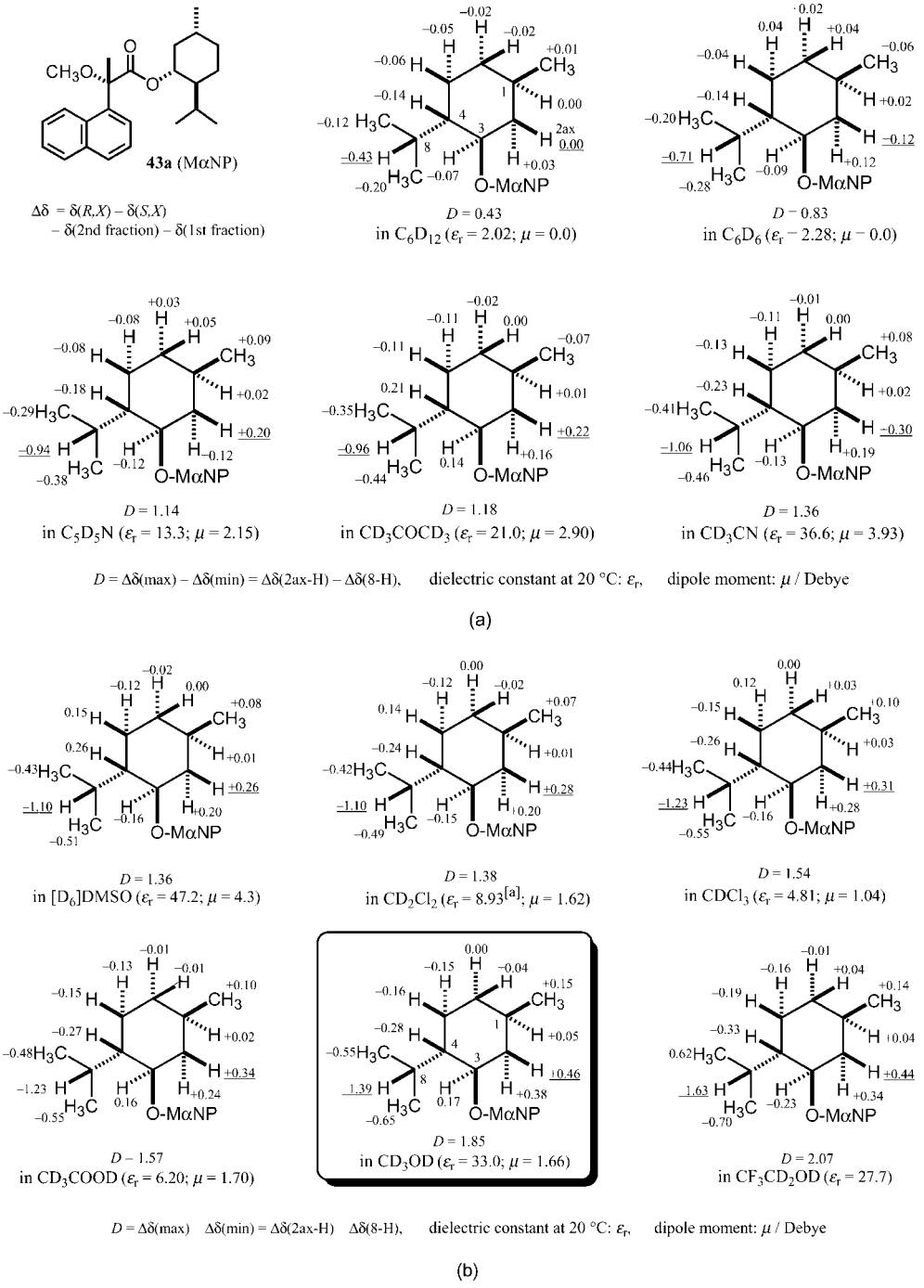


Figure 4. (a) Solvent effect on the ^{1}H NMR anisotropy data of (1*R*,3*R*,4*S*)-menthol MαNP acid esters **43a** and **43b**. $\Delta\delta$ {= δ(2nd fraction) – δ(1st fraction)} and *D* values are given in ppm. Spectra were recorded at 600 MHz. (b) Solvent effect on the ^{1}H NMR anisotropy data of (1*R*,3*R*,4*S*)-menthol MαNP acid esters **43a** and **43b**. $\Delta\delta$ {= δ(2nd fraction) – δ(1st fraction)} and *D* values are given in ppm. Spectra were recorded at 600 MHz. [a] Dielectric constant at 25 °C. The $\Delta\delta$ values in [D]chloroform were taken from ref.[12l]

and H-5′ (δ = 7.84 ppm), indicating that H-8′ is more positively charged by the hydrogen-bonding-like interaction. Similar phenomena were observed in the case of menthol MαNP acid ester **43b** and methyl MαNP acid ester **33**. On the other hand, in the case of methyl 2-(1-naphthyl)propionic acid ester **53**, which lacks a methoxyl group, the H-8′ signal (δ = 8.07 ppm) is shifted upfield, while those of H-4′ (δ = 7.77 ppm) and H-5′ (δ = 7.86 ppm) remained near their original positions. The ^{1}H NMR chemical shift data thus support the triangular hydrogen-bonding-like interaction stabilizing the *syn-syn* conformation.

This mechanism is strongly supported by comparing the $\Delta\delta$ data of menthol MβNP acid esters **45a**/**45b** with those of menthol M9PP acid esters **46a**/**46b**. As described above, esters **46a**/**46b** show large $\Delta\delta$ values (*D* = 1.57), while esters **45a**/**45b** show no anisotropy effect (*D* = 0.05). H-8′ of the

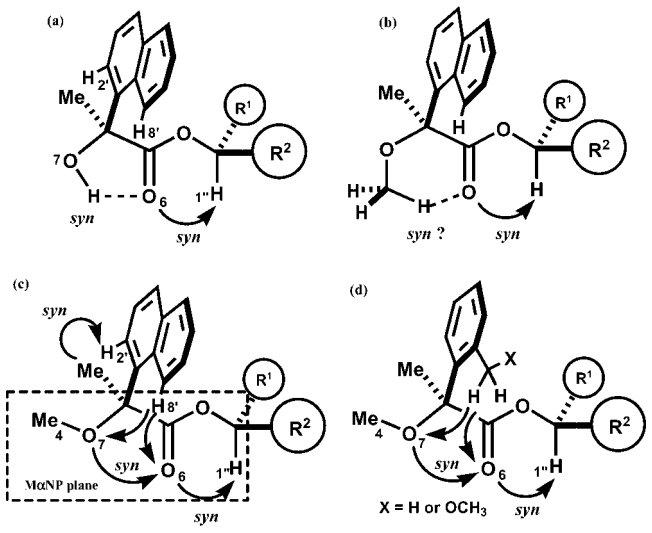
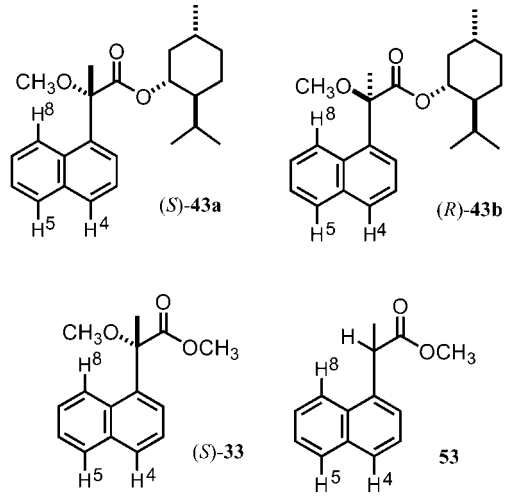


Figure 5. The possible conformers of MαNP and related acid esters stabilizing the *syn-syn* conformation.

Table 2. ^{1}H NMR chemical shift data (600 MHz, $CDCl_3$) for the naphthalene protons of MαNP and related esters.



	δ values (ppm) for compounds			
Naphthyl-H	(*S*)-**43a**	(*R*)-**43b**	(*S*)-**33**	**53**
4-H	7.81	7.81	7.84	7.77
5-H	7.84	7.83	7.86	7.86
8-H	8.37	8.49	8.35	8.07

9-phenanthryl group is close to O-6 and O-7, and therefore, participates in the triangular intramolecular hydrogen-bonding-like interaction, stabilizing the *syn-syn* conformation. On the other hand, MβNP esters **45a/45b** have no proton in such a position, and hence, no anisotropy effect was observed.

The mechanism can be extended to the cases of 2-methoxy-(2-methylphenyl)propionic acid esters **51a/51b** and 2-methoxy-(2-methoxymethylphenyl)propionic acid esters **52a/52b**, where the proton of the methyl group or methoxymethyl group can participate in the triangular hydrogen-bonding-like interaction stabilizing the *syn-syn* conformation. The polarization of the C–H bond in this case is smaller than that in the case of MαNP ester, because in esters **51a/51b** and **52a/52b**, the relevant C is sp^3-hybridized, while in MαNP esters **43a/43b**, the relevant C is sp^2 hybridized. Therefore, the $\Delta\delta$ values observed for esters **51a/51b** and **52a/52b**, are smaller than those of MαNP esters **43a/43b**.

Interpretation of the ^{1}H NMR Anisotropy Difference Between 2-Methoxy-2-arylpropionates and 2-Methoxy-2-arylacetates

As shown above, the ^{1}H NMR anisotropy effects of menthol MβNP acid esters **45a/45b** are nil (D = 0.05), while menthol 2NMA acid esters give moderate anisotropy effects (D = 0.87). Similarly, menthol MPP acid esters **47a/47b** give no anisotropy effects (D = 0.02), while menthol MPA acid esters show a moderate D value (D = 0.86). Although propionic acid esters give no anisotropy effect, acetic acid esters show moderate D values. Why are their anisotropy effects so much different? At the moment, we interpret the phenomena as follows: propionic acid esters are sterically more hindered because of the extra methyl group, and therefore, the aromatic group cannot take any specific orientation causing anisotropy effects. On the other hand, acetic acid esters are less hindered, and therefore, aromatic groups can take an orientation generating anisotropy effects.

On the contrary, in the case of esters with the 1-naphthyl group, both propionic and acetic acid esters show larger $\Delta\delta$ values. Menthol 1NMA acid esters give larger $\Delta\delta$ values,[8b] from which a D value was calculated (D = 1.42). Menthol MαNP esters **43a/43b** show a similar D value as described above (1.54). In these cases, the triangular hydrogen-bonding-like interaction among H-8′, the methoxy oxygen, and the ester carbonyl oxygen stabilizes the *syn-syn* conformation despite the existence of the extra methyl group. So, large anisotropy effects are observable for esters with a 1-naphthyl group.

Trianglular Hydrogen Bonding with Protic Solvents Stabilizing the *syn-syn* Conformation

In the study of the solvent effect on the $\Delta\delta$ value, it was found that protic solvents such as [D_4]methanol give larger $\Delta\delta$ values, indicating more stabilization of the *syn-syn* conformation. This is easily understandable by invoking the triangular hydrogen bonding among O-6/alcoholic D/O-7 as shown in Figure 6 (a). Therefore, the *syn-syn* conformation is stabilized. The triangular hydrogen bonding among O-6/alcoholic proton/O-7 was proved by X-ray crystallography of MαNP ester with a tertiary alcohol as described in part 2 of this series.[16]

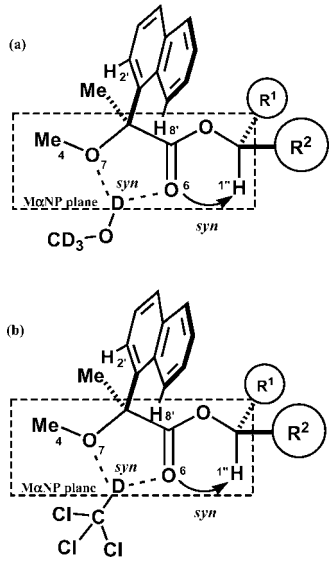


Figure 6. The possible *syn-syn* conformation of MαNP esters stabilized by solvation: hydrogen bonding or hydrogen-bonding-like interaction.

How about the case of [D]chloroform? Here we propose an O-6/D(CCl_3)/O-7 triangular hydrogen-bonding-like interaction, where the D atom of [D]chloroform is also partially positively charged because of the strong electron-withdrawing nature of the CCl_3 moiety, and therefore, the D participates in the hydrogen-bonding-like interaction as an electron accepter. A similar mechanism is applicable to the case of [D_2]dichloromethane. By this mechanism, the *syn-syn* conformation is stabilized in [D]chloroform and [D_2]-dichloromethane, and larger $\Delta\delta$ values are observable.

The Easy Separation of Diastereomeric MαNP Esters by HPLC on Silica Gel

In general, it is hard to separate diastereomeric esters prepared from a racemic alcohol and a chiral organic acid by HPLC on silica gel. However, as reported in our earlier papers,[12–14] most diastereomeric MαNP esters such as **43a/43b** are easily separable by HPLC on silica gel. This is a great advantage of the MαNP acid compared to other chiral anisotropy reagents. Why are MαNP acid esters so easily separable? We propose a plausible mechanism in Figure 7. In the holes of silica gel, hydroxy groups at the surface participate in triangular hydrogen bonding with MαNP esters, which fixes the molecular conformations. Therefore diastereomeric esters take different shapes and are adsorbed on silica gel in a different manner, leading to large separations by HPLC on silica gel.

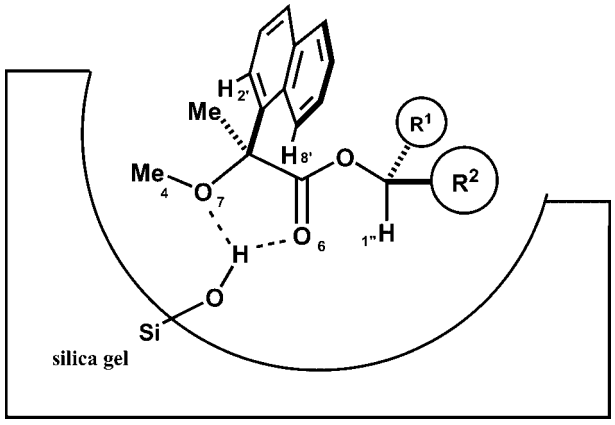


Figure 7. The plausible mechanism of the diastereomeric discrimination of MαNP esters in the holes of silica gel, where ester molecules are adsorbed by hydrogen bonding.

Conclusions

To clarify the mechanism of the anisotropy effect of MαNP acid esters, we studied their ^{1}H NMR spectra and those of related carboxylic acid esters and found that the observed $\Delta\delta$ values are very sensitive to the geometry of the aromatic groups. These results indicate that the *syn-syn* conformation generating larger $\Delta\delta$ values is stabilized by a triangular hydrogen-bonding-like interaction among O-6/H-8′/O-7 [Figure 5 (c)]. Larger $\Delta\delta$ values are also observable in protic solvents such as [D_4]methanol. These results suggest that the *syn-syn* conformation is also stabilized by triangular hydrogen bonding among O-6/proton of a protic solvent/O-7 [Figure 6 (a)]. This mechanism can be extended to the case of halomethane solvents such as [D]chloroform. The mechanisms stabilizing the *syn-syn* conformation discussed here are further supported by the X-ray crystallography of many MαNP acid esters as reported in the following part 2,[16] and also by the ab initio calculations of the conformational energy surface of MαNP acid ester as described in part 3.[17]

Experimental Section

General Methods: Melting points were uncorrected. IR spectra were obtained as neat liquids, as a film on KBr, or as KBr disks with a Jasco FT/IR-410 spectrophotometer. ^{1}H NMR spectra were recorded with a Jeol JNM-LA400 (400 MHz) and/or a Jeol JNM-LA600 (600 MHz) spectrometer. ^{13}C NMR spectra were obtained on a Jeol JNM-LA400 (100 MHz) and/or a Jeol JNM-LA600 (150 MHz) spectrometer. All NMR spectroscopic data of [D]chloroform, [D_{12}]cyclohexane, [D_6]benzene, [D_5]pyridine, [D_6]acetone, [D_3]acetonitrile, [D_6]DMSO, [D_2]dichloromethane, [D_4]acetic acid, [D_4]methanol, and 1,1,1-[D_3]trifluoroethanol solutions are reported in ppm (δ) downfield from TMS. Optical rotations {$[\alpha]_D$} were measured with a Jasco DIP-1000 spectropolarimeter. Silica gel 60 F_{254} precoated plates on glass from Merck Ltd. were used for thin-layer chromatography (TLC). HPLC separation and purification were performed with a prepacked glass column (Ø 22 mm × 300 mm, or Ø 25 mm × 400 mm) of silica gel (particle size 5–10 μm) from Kusano Co., Ltd, and a UV/RI detector (Shimamura YRU-880). The purities of the title compounds were shown to be ≥99% by ^{1}H NMR, TLC, HPLC, and/or elemental analysis.

Preparation of Methyl 2-Aryl-2-hydroxypropionates 24, 25, and 27–32 by Grignard Reaction: For example, to a mixture of magnesium (0.486 g, 20.0 mmol) and a catalytic amount of iodine in dried THF (50 mL), 1-bromo-2-methylnaphthalene (**14**, 4.422 g, 20.0 mmol) was added dropwise, and the mixture was stirred at room tempera-

ture for a few hours. To a solution of methyl pyruvate (2.25 g, 22.0 mmol) in THF (50 mL), cooled to 0 °C, was added dropwise the mixture of the Grignard reagent formed above, and the reaction mixture was stirred at room temperature overnight. After the addition of aqueous NH_4Cl at 0 °C and removal of the organic solvent under reduced pressure, the mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and the solvent was evaporated to dryness. The oily residue was purified by HPLC on silica gel (hexane/EtOAc = 5:1), yielding hydroxy ester **24** as a colorless solid.

Methyl 2-Hydroxy-2-(2-methyl-1-naphthyl)propionate (24): Yield 1.58 g, 32%. IR (KBr): $\tilde{\nu}$ = 3471, 3049, 2993, 2949, 1732, 1253, 1119, 1089, 813, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 2.54 (s, 3 H), 2.89 (s, 1 H), 3.71 (s, 3 H), 3.93 (s, 1 H), 7.22 (d, J = 8.6 Hz, 1 H), 7.37–7.44 (m, 2 H), 7.67 (d, J = 8.6 Hz, 1 H), 7.76–7.81 (m, 1 H), 8.38–8.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 24.8, 52.7, 79.5, 124.6, 124.8, 125.7, 128.3, 128.7, 130.8, 131.2, 133.0, 135.6, 175.5 ppm.

Methyl 2-Hydroxy-2-(2-naphthyl)propionate (25): Yield 47%. IR (neat): $\tilde{\nu}$ = 3501, 3058, 2984, 2952, 1733, 1599, 1507, 1436, 1374, 1246, 1212, 1184, 1139, 1094, 1064, 1017, 976, 934, 904, 860, 822, 752, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (s, 3 H), 3.77 (s, 3 H), 3.93 (s, 1 H), 7.44–7.51 (m, 2 H), 7.64 (dd, J = 8.6, 1.7 Hz, 1 H), 7.82 (br. d, J = 8.6 Hz, 1 H), 7.78–7.87 (m, 2 H), 8.02 (br. d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6, 53.3, 75.9, 123.3, 124.0, 126.2, 127.5, 128.1, 128.3, 132.8, 132.9, 139.9, 176.0 ppm.

Methyl 2-Hydroxy-2-phenylpropionate (27): Yield 29%, colorless oil. IR (neat): $\tilde{\nu}$ = 3500, 3061, 3027, 2986, 2954, 1731, 1600, 1494, 1447, 1374, 1256, 1213, 1148, 1097, 1071, 976, 941, 784, 699, 657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (s, 3 H), 3.78 (s, 3 H), 7.25–7.38 (m, 3 H), 7.53–7.56 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 53.2, 75.7, 125.1, 127.8, 128.3, 142.6, 176.1 ppm. $C_{10}H_{12}O_3$ (180.20): calcd. C 66.65, H 6.71; found C 66.85, H 6.68.

Methyl 2-Hydroxy-2-(4-methoxyphenyl)propionate (28): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 3 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 6.87–6.91 (m, 2 H), 7.44–7.47 (m, 2 H) ppm.

Methyl 2-Hydroxy-2-(3-methoxyphenyl)propionate (29): Yield 65%, colorless oil. IR (neat): $\tilde{\nu}$ = 3502, 2954, 1734, 1602, 1489, 1435, 1259, 1146, 1045, 792, 735, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (s, 3 H), 3.74 (s, 1 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 6.84 (ddd, J = 8.3, 2.4, 1.0 Hz, 1 H), 7.10–7.13 (m, 2 H), 7.27 (dd, J = 8.3, 8.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 53.3, 55.3, 75.7, 111.1, 113.1, 117.5, 129.4, 144.4, 159.6, 176.0 ppm.

Methyl 2-Hydroxy-2-(2-methoxyphenyl)propionate (30): Yield 53%, colorless needles. M.p. 89–90 °C. IR (KBr): $\tilde{\nu}$ = 3482, 2995, 2951, 2840, 1740, 1602, 1587, 1492, 1464, 1437, 1370, 1243, 1134, 1057, 1025, 982, 930, 803, 757, 654 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (d, J = 0.7 Hz, 3 H), 3.71 (s, 3 H), 3.82 (s, 3 H), 4.02 (q, J = 0.7 Hz, 1 H), 6.90 (dd, J = 8.2, 1.0 Hz, 1 H), 7.00 (ddd, J = 7.6, 7.6, 1.0 Hz, 1 H), 7.32 (ddd, J = 8.2, 7.6, 1.6 Hz, 1 H), 7.45 (dd, J = 7.6, 1.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 52.6, 55.5, 74.1, 111.1, 120.9, 126.3, 129.5, 131.0, 156.6, 176.6 ppm. $C_{11}H_{14}O_4$ (210.23): calcd. C 62.85, H 6.71; found C 62.68, H 6.62.

Methyl 2-Hydroxy-2-(2-tolyl)propionate (31): Yield 42%, colorless solid. IR (KBr): $\tilde{\nu}$ = 3491, 2993, 2952, 1732, 1458, 1437, 1291, 1259, 1214, 1190, 1128, 1093, 779, 767, 745, 726 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3 H), 2.31 (s, 3 H), 3.48 (s, 1 H), 3.75 (s, 3 H), 7.14–7.24 (m, 3 H), 7.45–7.47 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2, 26.9, 53.2, 75.8, 125.7, 126.0, 128.2, 131.9, 136.9, 139.1, 177.5 ppm. $C_{11}H_{14}O_3$ (194.23): calcd. C 68.02, H 7.27; found C 67.82, H 7.22.

Methyl 2-Hydroxy-2-(2-methoxymethylphenyl)propionate (32): Yield 27%, colorless oil. IR (neat): $\tilde{\nu}$ = 3468, 3391, 2987, 2950, 2894, 2827, 1736, 1452, 1370, 1254, 1191, 1133, 1099, 977, 933, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 3 H), 3.37 (s, 3 H), 3.73 (s, 3 H), 4.48 (d, J = 11.7 Hz, 1 H), 4.54 (d, J = 11.7 Hz, 1 H), 5.00 (s, 1 H), 7.29–7.38 (m, 3 H), 7.50–7.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8, 52.8, 58.0, 73.9, 76.1, 126.8, 128.2, 128.5, 131.5, 135.2, 141.1, 176.8 ppm.

Preparation of Methyl Ethers 34, 35, and 37–42: For example, to a mixture of hydroxy ester **24** (1.037 g, 4.25 mmol) and iodomethane (0.40 mL, 6.37 mmol) in dried THF (21 mL), sodium hydride (60% dispersion in mineral oil, 0.204 g, 5.09 mmol) was added portionwise, and the mixture was stirred at room temperature overnight. After addition of aqueous NH_4Cl and removal of the organic solvent under reduced pressure, the mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and the solvent was evaporated to dryness. The oily residue was purified by HPLC on silica gel (hexane/EtOAc = 5:1), yielding methyl ether **34** as a yellow oil.

Methyl 2-Methoxy-2-(2-methyl-1-naphthyl)propionate (34): Yield 0.741 g, 68%. IR (neat): $\tilde{\nu}$ = 2992, 2943, 2831, 1733, 1509, 1437, 1371, 1255, 1116, 953, 813, 784, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.53 (s, 3 H), 3.26 (s, 3 H), 3.70 (s, 3 H), 7.23 (d, J = 8.3 Hz, 1 H), 7.35–7.42 (m, 2 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.74–7.79 (m, 1 H), 8.23–8.27 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 22.9, 51.9, 52.3, 83.9, 124.4, 124.6, 125.6, 128.2, 128.6, 131.0, 131.6, 132.8, 133.7, 134.4, 172.9 ppm.

Methyl 2-Methoxy-2-(2-naphthyl)propionate (35): Yield 78%. IR (neat): $\tilde{\nu}$ = 3057, 2989, 2951, 2831, 1734, 1600, 1507, 1436, 1372, 1255, 1185, 1131, 1078, 1050, 978, 952, 897, 858, 821, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3 H), 3.31 (s, 3 H), 3.73 (s, 3 H), 7.45–7.52 (m, 2 H), 7.59 (dd, J = 8.8, 1.9 Hz, 1 H), 7.84 (br. d, J = 8.8 Hz, 1 H), 7.80–7.87 (m, 2 H), 7.95 (br. d, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 52.0, 52.6, 81.8, 123.8, 125.1, 126.2, 126.3, 127.5, 128.2, 128.3, 132.9, 133.0, 138.0, 173.5 ppm.

Methyl 2-Methoxy-2-phenylpropionate (37): Yield 75%, colorless oil. IR (neat): $\tilde{\nu}$ = 2990, 2951, 2831, 1735, 1494, 1448, 1372, 1258, 1196, 1116, 1076, 1049, 976, 864, 770, 729, 699, 645, 559, 519 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (s, 3 H), 3.28 (s, 3 H), 3.72 (s, 3 H), 7.26–7.38 (m, 3 H), 7.46–7.52 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 51.9, 52.5, 81.6, 125.8, 127.9, 128.3, 140.6, 173.5 ppm.

Methyl 2-Methoxy-2-(4-methoxyphenyl)propionate (38): Total yield from **18**: 25%, colorless oil. IR (neat): $\tilde{\nu}$ = 2989, 2952, 2834, 1734, 1610, 1583, 1510, 1457, 1372, 1302, 1252, 1179, 1111, 1031, 978, 833, 803, 608, 509 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (s, 3 H), 3.25 (s, 3 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 51.7, 52.5, 55.2, 81.2, 113.7, 127.3, 132.5, 159.2, 173.7 ppm. $C_{12}H_{16}O_4$ (224.26): calcd. C 64.27, H 7.19; found C 64.04, H 7.14.

Methyl 2-Methoxy-2-(3-methoxyphenyl)propionate (39): Colorless oil. IR (neat): $\tilde{\nu}$ = 2993, 2952, 2834, 1736, 1600, 1585, 1489, 1453, 1434, 1372, 1261, 1194, 1135, 1116, 1046, 979, 878, 827, 788, 727, 697, 542, 451 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (s, 3 H), 3.28 (s, 3 H), 3.73 (s, 3 H), 3.81 (s, 3 H), 6.84 (ddd, J = 7.9, 2.4, 1.0 Hz, 1 H), 7.04 (m, 2 H), 7.27 (ddd, J = 7.9, 7.9, 0.5 Hz, 1 H)

ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 51.9, 52.5, 55.2, 81.6, 111.6, 113.4, 118.2, 129.3, 142.3, 159.6, 173.4 ppm.

Methyl 2-Methoxy-2-(2-methoxyphenyl)propionate (40): Colorless oil. IR (neat): $\tilde{\nu}$ = 2993, 2949, 2835, 1740, 1602, 1587, 1491, 1463, 1437, 1367, 1290, 1256, 1192, 1119, 1104, 1078, 1047, 1026, 982, 873, 802, 757, 643, 592, 504, 458, 427 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 3 H), 3.28 (s, 3 H), 3.71 (s, 3 H), 3.77 (s, 3 H), 6.88 (dd, J = 8.3, 1.2 Hz, 1 H), 7.01 (ddd, J = 7.6, 7.6, 1.2 Hz, 1 H), 7.29 (ddd, J = 8.3, 7.6, 1.7 Hz, 1 H), 7.56 (dd, J = 7.6, 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 51.7, 52.0, 55.4, 79.0, 111.0, 120.6, 126.3, 128.9, 130.3, 155.9, 173.1 ppm.

Methyl 2-Methoxy-2-(2-tolyl)propionate (41): Yield 88%, colorless oil. IR (neat): $\tilde{\nu}$ = 3062, 2991, 2949, 2830, 1735, 1487, 1456, 1435, 1368, 1294, 1256, 1228, 1190, 1128, 1068, 1048, 977, 874, 803, 764, 743, 661, 643 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3 H), 2.30 (s, 3 H), 3.10 (s, 3 H), 3.73 (s, 3 H), 7.15–7.26 (m, 3 H), 7.40–7.43 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 21.6, 50.7, 52.5, 81.3, 125.6, 127.1, 128.2, 131.8, 137.1, 137.4, 174.2 ppm.

Methyl 2-Methoxy-2-(2-methoxymethylphenyl)propionate (42): Yield 82%, colorless oil. IR (neat): $\tilde{\nu}$ = 2949, 1737, 1451, 1255, 1193, 1132, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 3 H), 3.10 (s, 3 H), 3.36 (s, 3 H), 3.70 (s, 3 H), 4.48 (d, J = 12.4 Hz, 1 H), 4.58 (d, J = 12.4 Hz, 1 H), 7.31 (ddd, J = 7.6, 7.6, 1.7 Hz, 1 H), 7.36 (ddd, J = 7.6, 7.6, 1.4 Hz, 1 H), 7.42 (dd, J = 7.6, 1.7 Hz, 1 H), 7.52 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 50.8, 52.5, 58.4, 71.6, 81.3, 127.3, 127.4, 128.5, 129.5, 137.0, 137.4, 174.0 ppm.

Preparation of 2-Aryl-2-methoxypropionic Acids 4, 5, and 7–12: For example, to a solution of ester **34** (0.590 g, 2.28 mmol) in methanol (21 mL), was added a solution of KOH (1.40 g, 25.0 mmol) in water (2.3 mL), and the mixture was gently refluxed for 1–2 d. After removal of the organic solvent under reduced pressure, the mixture was extracted with diethyl ether. The remaining aqueous layer was acidified with 6 M HCl at 0 °C, giving a precipitate, which was extracted with EtOAc three times. The combined EtOAc layers were washed with brine, dried with anhydrous $MgSO_4$, and the solvent was evaporated to dryness, yielding carboxylic acid **4** as a colorless solid.

2-Methoxy-2-(2-methyl-1-naphthyl)propionic Acid (4): Yield 0.512 g, 92%. IR (KBr): $\tilde{\nu}$ = 3851, 2939, 1708, 1131, 1096, 1051, 812, 785, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.59 (s, 3 H), 3.26 (s, 3 H), 7.23 (d, J = 8.3 Hz, 1 H), 7.38–7.44 (m, 2 H), 7.69 (d, J = 8.3 Hz, 1 H), 7.76–7.80 (m, 1 H), 8.34–8.37 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 23.5, 52.0, 83.9, 124.7, 124.8, 125.9, 128.7, 131.0, 132.2, 132.9, 135.0, 176.4 ppm. $C_{15}H_{16}O_3$ (244.29): calcd. C 73.75, H 6.60; found C 73.58, H 6.61.

2-Methoxy-2-(2-naphthyl)propionic Acid (5): Yield 98%, faintly yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 3 H), 3.30 (s, 3 H), 7.47–7.52 (m, 2 H), 7.55 (dd, J = 8.8, 2.0 Hz, 1 H), 7.85 (br. d, J = 8.8 Hz, 1 H), 7.80–7.88 (m, 2 H), 7.95 (br. d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 51.8, 81.4, 123.7, 125.8, 126.4, 126.6, 127.5, 128.3, 128.5, 133.0, 133.1, 136.2, 175.6 ppm.

2-Methoxy-2-phenylpropionic Acid (7): Yield 96%, pale yellow oil. IR (neat): $\tilde{\nu}$ = 3183, 3062, 2989, 2942, 2834, 1716, 1600, 1495, 1448, 1373, 1339, 1223, 1196, 1142, 1123, 1075, 1047, 889, 770, 721, 699, 658, 638, 430 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3 H), 3.27 (s, 3 H), 7.31–7.40 (m, 3 H), 7.47–7.49 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 51.7, 81.3, 126.2, 128.4, 128.6, 138.9 ppm.

2-Methoxy-2-(4-methoxyphenyl)propionic Acid (8): Yield 99%, colorless solid. IR (KBr): $\tilde{\nu}$ = 3467, 3401, 2996, 2962, 2908, 2837, 1704, 1610, 1511, 1457, 1371, 1298, 1254, 1179, 1145, 1097, 1025, 874, 831, 736, 603, 523 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3 H), 3.24 (s, 3 H), 3.81 (s, 3 H), 6.91 (d, J = 8.8 Hz, 2 H), 7.38 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 51.4, 55.3, 81.0, 114.0, 127.6, 130.5, 159.7, 175.0 ppm.

2-Methoxy-2-(3-methoxyphenyl)propionic Acid (9): Yield 93%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3 H), 3.28 (s, 3 H), 3.81 (s, 3 H), 6.87 (ddd, J = 8.3, 2.7, 1.0 Hz, 1 H), 7.02 (dd, J = 2.7, 1.7 Hz, 1 H), 7.05 (ddd, J = 7.8, 1.7, 1.0 Hz, 1 H), 7.30 (dd, J = 8.3, 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 51.7, 55.3, 81.2, 112.2, 113.7, 118.6, 129.6, 140.4, 159.8, 175.1 ppm.

2-Methoxy-2-(2-methoxyphenyl)propionic Acid (10): Yield 73%, colorless crystals. M.p. 91–92 °C. IR (KBr): $\tilde{\nu}$ = 3164, 2942, 2837, 1715, 1602, 1492, 1463, 1438, 1252, 1125, 1101, 1075, 1047, 1025, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (s, 3 H), 3.12 (s, 3 H), 3.80 (s, 3 H), 6.92 (dd, J = 8.3, 1.0 Hz, 1 H), 7.00 (ddd, J = 7.5, 7.5, 1.0 Hz, 1 H), 7.36 (ddd, J = 8.3, 7.5, 1.7 Hz, 1 H), 7.44 (dd, J = 7.5, 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 51.2, 55.6, 78.9, 111.8, 120.5, 126.1, 128.2, 130.4, 157.3, 175.4 ppm. $C_{11}H_{14}O_4$ (210.23): calcd. C 62.85, H 6.71; found C 62.86, H 6.67.

2-Methoxy-2-(2-tolyl)propionic Acid (11): Yield 99%, colorless prisms from hexane/EtOAc. M.p. 96.5–97.5 °C. IR (KBr): $\tilde{\nu}$ = 2989, 1721, 1231, 1143, 1130, 1097, 1065, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (s, 3 H), 2.34 (s, 3 H), 3.10 (s, 3 H), 7.17–7.29 (m, 3 H), 7.40–7.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2, 21.4, 50.7, 81.3, 125.8, 128.1, 129.0, 132.0, 135.0, 137.4, 174.9 ppm.

2-Methoxy-2-(2-methoxymethylphenyl)propionic Acid (12): Yield 90%, colorless oil. IR (KBr): $\tilde{\nu}$ = 3502, 3065, 2988, 2938, 2830, 1731, 1453, 1373, 1228, 1193, 1141, 1096, 1065, 1046, 894, 754, 662 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (s, 3 H), 3.17 (s, 3 H), 3.35 (s, 3 H), 4.43 (d, J = 12.2 Hz, 1 H), 4.78 (d, J = 12.2 Hz, 1 H), 7.30–7.37 (m, 2 H), 7.42–7.48 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 51.1, 58.0, 72.8, 82.0, 127.9, 128.1, 128.7, 130.1, 136.2, 136.6, 175.2 ppm.

Preparation of Diastereomeric (1*R*,3*R*,4*S*)-Menthyl 2-Aryl-2-methoxypropionates 44, 45, and 47–52: For example, a solution of racemic acid (±)-**4** (0.101 g, 0.411 mmol), (1*R*,3*R*,4*S*)-(–)-menthol (0.071 g, 0.45 mmol), 1,3-dicyclohexylcarbodiimide (DCC, 0.102 g, 0.49 mmol), 4-(dimethylamino)pyridine (DMAP, 0.025 g, 0.21 mmol), and 10-camphorsulfonic acid (CSA, 0.010 g, 0.041 mmol) in dichloromethane (0.4 mL) was stirred at room temperature for 1 d. After the addition of a small amount of water, stirring for 1 h, and the addition of diethyl ether and anhydrous $MgSO_4$, the mixture was filtered with Celite, which was washed with EtOAc. The combined organic layers were evaporated under reduced pressure, and the residue was subjected to a short column of silica gel (hexane/EtOAc = 20:1). The crude diastereomeric esters obtained were separated by HPLC on silica gel (Ø 25 mm × 300 mm column, Table 1), giving the first eluted ester **44a** and the second eluted one **44b**.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-methyl-1-naphthyl)propionate (44a): Yield 0.085 g, 49%; colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.57 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.65 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.79 (dddd, J = 13.0, 12.8, 11.9, 3.2 Hz, 1 H, 6ax-H), 0.88 (d, J = 6.6 Hz, 3 H, 1-CH_3), 0.90 (ddd, J = 11.9, 11.9, 11.0 Hz, 1 H, 2ax-H), 0.98 (dddd, J = 13.0, 13.0, 12.8, 3.5 Hz, 1

H, 5ax-H), 1.23–1.39 (m, 2 H, 4-H, *i*Pr CH), 1.47 (m, 1 H, 1-H), 1.58 (dddd, *J* = 13.4, 3.3, 3.3, 3.2 Hz, 1 H, 5eq-H), 1.63 (dddd, *J* = 13.0, 5.3, 3.3, 3.3 Hz, 1 H, 6eq-H), 1.99 (s, 3 H, CH_3), 2.07 (dddd, *J* = 11.9, 4.2, 3.7, 2.0 Hz, 1 H, 2eq-H), 2.57 (s, 3 H, aromatic CH_3), 3.25 (s, 3 H, OCH_3), 4.66 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 7.22 (d, *J* = 8.2 Hz, 1 H, 3′-H), 7.33–7.38 (m, 2 H, 6′-H, 7′-H), 7.64 (d, *J* = 8.2 Hz, 1 H, 4′-H), 7.73–7.76 (m, 1 H, 5′-H), 8.23–8.26 (m, 1 H, 8′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.0, 20.7, 22.0, 23.0, 23.5, 25.2, 31.3, 34.1, 40.1, 46.6, 51.7, 75.4, 84.3, 124.3, 124.7, 125.6, 127.9, 128.5, 131.1, 131.7, 132.7, 133.9, 134.6, 171.4 ppm.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-methyl-1-naphthyl)propionate (44b): Yield 0.066 g, 42%; colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.53 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.65 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.76 (dddd, *J* = 13.0, 12.8, 11.9, 3.2 Hz, 1 H, 6ax-H), 0.79 (ddd, *J* = 11.9, 11.9, 11.0 Hz, 1 H, 2ax-H), 0.85 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 0.95 (dddd, *J* = 13.0, 13.0, 12.8, 3.5 Hz, 1 H, 5ax-H), 1.20 (m, 1 H, 4-H), 1.34 (sept.d, *J* = 7.0, 2.8 Hz, 1 H, *i*Pr CH), 1.44 (m, 1 H, 1-H), 1.56 (dddd, *J* = 13.4, 3.3, 3.3, 3.2 Hz, 1 H, 5eq-H), 1.61 (dddd, *J* = 13.0, 5.3, 3.3, 3.3 Hz, 1 H, 6eq-H), 1.98 (dddd, *J* = 11.9, 4.2, 3.7, 2.0 Hz, 1 H, 2eq-H), 2.01 (s, 3 H, CH_3), 2.61 (s, 3 H, aromatic CH_3), 3.21 (s, 3 H, OCH_3), 4.65 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 7.21 (d, *J* = 8.2 Hz, 1 H, 3′-H), 7.34–7.39 (m, 2 H, 6′-H, 7′-H), 7.64 (d, *J* = 8.2 Hz, 1 H, 4′-H), 7.73–7.76 (m, 1 H, 5′-H), 8.34–8.36 (m, 1 H, 8′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.6, 22.0, 23.0, 23.9, 23.9, 25.4, 31.3, 34.1, 40.1, 46.8, 51.4, 75.2, 84.1, 124.4, 125.3, 125.7, 128.1, 128.4, 131.2, 132.2, 132.8, 133.2, 134.9, 172.0 ppm.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-naphthyl)propionate (45a): Yield 49%, colorless oil. IR (neat): ṽ = 2954, 2870, 1725, 1507, 1456, 1371, 1254, 1184, 1119, 962, 897, 858, 819, 749, 477 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.56 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.64 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.80 (dddd, *J* = 12.8, 12.8, 11.9, 3.5 Hz, 1 H, 6ax-H), 0.86 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 0.95 (ddd, *J* = 11.9, 11.9, 11.2 Hz, 1 H, 2ax-H), 0.98 (dddd, *J* = 13.4, 12.8, 12.8, 3.3 Hz, 1 H, 5ax-H), 1.33 (dddd, *J* = 12.8, 11.0, 3.5, 3.3 Hz, 1 H, 4-H), 1.46 (ddqdd, *J* = 12.8, 11.9, 6.6, 3.4, 3.4 Hz, 1 H, 1-H), 1.47 (sept.d, *J* = 7.0, 3.3 Hz, 1 H, *i*Pr CH), 1.59 (dddd, *J* = 13.4, 6.8, 3.5, 3.5 Hz, 1 H, 5eq-H), 1.63 (ddddd, *J* = 12.8, 6.8, 3.3, 3.3, 1.5 Hz, 1 H, 6eq-H), 1.86 (s, 3 H, CH_3), 1.94 (dddd, *J* = 11.9, 4.2, 3.4, 1.5 Hz, 1 H, 2eq-H), 3.35 (s, 3 H, OCH_3), 4.74 (ddd, *J* = 11.2, 11.0, 4.2 Hz, 1 H, 3-H), 7.45–7.49 (m, 2 H, 6′-H, 7′-H), 7.56 (dd, *J* = 8.6, 1.9 Hz, 1 H, 3′-H), 7.81 (d, *J* = 8.6 Hz, 1 H, 4′-H), 7.80–7.84 (m, 2 H, 5′-H, 8′-H), 7.95 (d, *J* = 1.9 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.6, 22.0, 22.1, 22.9, 25.6, 31.4, 34.1, 40.4, 46.8, 52.1, 75.4, 82.0, 123.7, 126.1, 126.1, 127.5, 127.9, 128.3, 132.8, 133.0, 138.7, 172.5 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 275.2 (5,530), 224.4 (80,340) nm. CD (EtOH): λ (Δε, L mol^{-1} cm^{-1}) = 239.0 (–6.7), 222.0 (+18.6) nm.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-naphthyl)propionate (45b): Yield 42%, colorless oil. IR (neat): ṽ = 2954, 1725, 1507, 1456, 1371, 1251, 1184, 1114, 961, 819, 749 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.52 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.59 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.79 (dddd, *J* = 13.0, 13.0, 11.8, 3.5 Hz, 1 H, 6ax-H), 0.86 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 0.91 (ddd, *J* = 12.0, 12.0, 11.0 Hz, 1 H, 2ax-H), 0.96 (dddd, *J* = 13.4, 13.0, 12.8, 3.5 Hz, 1 H, 5ax-H), 1.27 (dddd, *J* = 12.8, 10.8, 3.5, 2.8 Hz, 1 H, 4-H), 1.38 (sept.d, *J* = 7.0, 2.8 Hz, 1 H, *i*Pr CH), 1.46 (ddqdd, *J* = 12.0, 11.8, 6.6, 3.7, 3.5 Hz, 1 H, 1-H), 1.57 (dddd, *J* = 13.4, 6.8, 3.5, 3.5 Hz, 1 H, 5eq-H), 1.63 (ddddd, *J* = 13.0, 6.8, 3.5, 3.5, 1.6 Hz, 1 H, 6eq-H), 1.89 (s, 3 H, CH_3), 1.96 (dddd, *J* = 12.0, 4.4, 3.7, 1.6 Hz, 1 H, 2eq-H), 3.31 (s, 3 H, OCH_3), 4.68 (ddd, *J* = 11.0, 10.8, 4.4 Hz, 1 H, 3-H), 7.38–7.49 (m, 2 H, 6′-H, 7′-H), 7.58 (dd, *J* = 8.5, 2.0 Hz, 1 H, 3′-H), 7.82 (d, *J* = 8.5 Hz, 1 H, 4′-H), 7.80–7.84 (m, 2 H, 5′-H, 8′-H), 7.93 (d, *J* = 2.0 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.6, 20.5, 21.6, 22.0, 22.9, 25.6, 31.3, 34.1, 40.4, 46.9, 52.0, 75.4, 81.7, 124.0, 125.3, 126.1, 127.5, 127.9, 128.2, 132.9, 133.0, 138.2, 172.6 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 275.4 (5,470), 267.8 (5,220), 224.8 (78,710) nm. CD (EtOH): λ (Δε, L mol^{-1} cm^{-1}) = 286.2 (–1.3), 276.4 (–2.2), 266.8 (–2.0), 230.4 (–21.2), 217.2 (+22.1) nm.

(1*R*,3*R*,4*S*:*S*)-(–)-Menthyl 2-Methoxy-2-phenylpropionate (47a): Yield 43%, colorless oil. $[\alpha]_D^{22}$ = –84.0 (*c* = 1.26, $CHCl_3$). IR (neat): ṽ = 2954, 2932, 2870, 1725, 1493, 1449, 1371, 1253, 1195, 1118, 1077, 1050, 982, 962, 917, 843, 773, 726, 698, 647, 543 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.58 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.73 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.84 (dddd, *J* = 13.0, 13.0, 11.9, 3.5 Hz, 1 H, 6ax-H), 0.88 (d, *J* = 6.4 Hz, 3 H, 1-CH_3), 0.95 (ddd, *J* = 12.1, 12.1, 11.0 Hz, 1 H, 2ax-H), 0.99 (dddd, *J* = 13.4, 13.0, 12.5, 3.3 Hz, 1 H, 5ax-H), 1.35 (dddd, *J* = 12.5, 11.0, 3.3, 2.9 Hz, 1 H, 4-H), 1.46 (ddqdd, *J* = 12.1, 11.9, 6.4, 3.7, 3.3 Hz, 1 H, 1-H), 1.48 (sept.d, *J* = 7.0, 2.9 Hz, 1 H, *i*Pr CH), 1.61 (dddd, *J* = 13.4, 3.5, 3.3, 3.3 Hz, 1 H, 5eq-H), 1.65 (ddddd, *J* = 13.0, 3.3, 3.3, 3.1, 2.0 Hz, 1 H, 6eq-H), 1.77 (s, 3 H, CH_3), 1.93 (dddd, *J* = 12.1, 4.4, 3.7, 2.0 Hz, 1 H, 2eq-H), 3.31 (s, 3 H, OCH_3), 4.70 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 7.26–7.28 (m, 1 H, 4′-H), 7.31–7.35 (m, 2 H, 3′-H), 7.46–7.48 (m, 2 H, 2′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.6, 22.0, 22.1, 23.0, 25.6, 31.4, 34.2, 40.4, 46.9, 52.1, 75.3, 81.9, 125.6, 126.1, 127.7, 128.1, 141.3, 172.5 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 263.6 (170), 258.2 (210) nm. CD (EtOH): λ (Δε, L mol^{-1} cm^{-1}) = 238.4 (–2.7), 213.8 (+2.6) nm. $C_{20}H_{30}O_3$ (318.46): calcd. C 75.43, H 9.50; found C 75.46, H 9.34.

(1*R*,3*R*,4*S*:*R*)-(–)-Menthyl 2-Methoxy-2-phenylpropionate (47b): Yield 43%, colorless oil. $[\alpha]_D^{23}$ = –68.5 (*c* = 1.26, $CHCl_3$). IR (neat): ṽ = 2955, 2870, 1725, 1495, 1450, 1371, 1253, 1195, 1138, 1116, 1078, 1050, 982, 962, 916, 846, 773, 727, 699, 646, 569, 508 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.56 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.71 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.81 (dddd, *J* = 13.0, 12.8, 12.4, 3.5 Hz, 1 H, 6ax-H), 0.87 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 0.90 (ddd, *J* = 12.1, 11.0, 11.0 Hz, 1 H, 2ax-H), 0.97 (dddd, *J* = 12.8, 12.8, 12.8, 3.5 Hz, 1 H, 5ax-H), 1.29 (dddd, *J* = 12.8, 11.0, 3.2, 2.9 Hz, 1 H, 4-H), 1.41 (sept.d, *J* = 7.0, 2.9 Hz, 1 H, *i*Pr CH), 1.47 (ddqdd, *J* = 12.4, 11.0, 7.0, 3.7, 3.3 Hz, 1 H, 1-H), 1.60 (dddd, *J* = 12.8, 3.5, 3.2, 3.2 Hz, 1 H, 5eq-H), 1.64 (ddddd, *J* = 13.0, 3.5, 3.3, 3.2, 2.0 Hz, 1 H, 6eq-H), 1.79 (s, 3 H, CH_3), 1.94 (dddd, *J* = 12.1, 4.4, 3.7, 2.0 Hz, 1 H, 2eq-H), 3.27 (s, 3 H, OCH_3), 4.65 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 7.26–7.29 (m, 1 H, 4′-H), 7.32–7.35 (m, 2 H, 3′-H), 7.45–7.47 (m, 2 H, 2′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.7, 21.4, 22.0, 23.0, 25.6, 31.3, 34.2, 40.4, 46.9, 51.9, 75.3, 81.5, 126.1, 127.8, 128.1, 140.8, 172.6 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 263.8 (160), 258.2 (200) nm. CD (EtOH): λ (Δε, L mol^{-1} cm^{-1}) = 269.2 (+0.05), 263.6 (+0.07), 243.8 (+0.57), 224.4 (–3.78), 215.4 (–3.29) nm. $C_{20}H_{30}O_3$ (318.46): calcd. C 75.43, H 9.50; found C 75.26, H 9.41.

(1*R*,3*R*,4*S*)-(–)-Menthyl 2-Methoxy-2-(4-methoxyphenyl)propionate (48a): Yield 41%, colorless solid. $[\alpha]_D^{22}$ = –65.1 (*c* = 1.20, $CHCl_3$). IR (KBr): ṽ = 2954, 2870, 2833, 1725, 1611, 1583, 1510, 1456, 1370, 1302, 1249, 1178, 1118, 1079, 1051, 1035, 1009, 981, 962, 918, 885, 833, 808, 791, 740, 614, 545 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.61 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.76 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.82 (dddd, *J* = 13.0, 12.7, 12.5, 3.3 Hz, 1 H, 6ax-H), 0.87 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 0.93 (ddd, *J* = 12.1, 12.1, 11.0 Hz, 1 H, 2ax-H), 1.00 (dddd, *J* = 13.4, 12.7, 12.3, 3.2 Hz, 1 H, 5ax-H), 1.36 (dddd, *J* = 12.3, 11.0, 3.4, 2.9 Hz, 1 H, 4-H), 1.47 (ddqdd, *J*

= 12.5, 12.1, 6.6, 3.7, 3.2 Hz, 1 H, 1-H), 1.56 (sept.d, *J* = 7.0, 2.9 Hz, 1 H, *i*Pr CH), 1.62 (dddd, *J* = 13.4, 3.3, 3.3, 3.3 Hz, 1 H, 5eq-H), 1.65 (ddddd, *J* = 13.0, 3.3, 3.2, 3.2, 2.0 Hz, 1 H, 6eq-H), 1.75 (s, 3 H, CH_3), 1.92 (dddd, *J* = 12.1, 4.4, 3.7, 2.0 Hz, 1 H, 2eq-H), 3.28 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.70 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 6.85–6.88 (m, 2 H, 3′-H), 7.37 (m, 2 H, 2′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.7, 22.0, 22.0, 23.0, 25.7, 31.4, 34.2, 40.4, 46.9, 51.9, 55.3, 75.2, 81.4, 113.5, 127.1, 133.3, 159.1, 172.7 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 280.8 (1,300), 274.0 (1,500), 229.8 (10,100) nm. CD (EtOH): λ ($\Delta\varepsilon$, L mol^{-1} cm^{-1}) = 246.4 (–2.62), 225.2 (+4.36), 208.0 (+2.49) nm. $C_{21}H_{32}O_4$ (348.48): calcd. C 72.38, H 9.26; found C 72.45, H 9.26.

(1*R*,3*R*,4*S*)-(–)-Menthyl 2-Methoxy-2-(4-methoxyphenyl)propionate (48b): Yield 40%, colorless oil. $[\alpha]_D^{24}$ = –65.8 (*c* = 0.88, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2954, 2870, 1725, 1610, 1510, 1455, 1370, 1302, 1249, 1179, 1115, 1035, 962, 833, 539 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.57 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.72 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.81 (dddd, *J* = 13.2, 13.0, 11.9, 3.5 Hz, 1 H, 6ax-H), 0.84 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 0.91 (ddd, *J* = 12.1, 12.1, 11.0 Hz, 1 H, 2ax-H), 0.98 (dddd, *J* = 13.3, 13.2, 12.6, 3.5 Hz, 1 H, 5ax-H), 1.29 (dddd, *J* = 12.6, 11.0, 3.3, 2.8 Hz, 1 H, 4-H), 1.43 (sept.d, *J* = 7.0, 2.9 Hz, 1 H, *i*Pr CH), 1.47 (ddqdd, *J* = 12.1, 11.9, 6.6, 3.5, 3.3 Hz, 1 H, 1-H), 1.60 (dddd, *J* = 13.3, 3.5, 3.3, 3.3 Hz, 1 H, 5eq-H), 1.65 (ddddd, *J* = 13.0, 3.5, 3.3, 3.3, 2.0 Hz, 1 H, 6eq-H), 1.77 (s, 3 H, CH_3), 1.94 (dddd, *J* = 12.1, 4.4, 3.5, 2.0 Hz, 1 H, 2eq-H), 3.24 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.65 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 6.85–6.88 (m, 2 H, 3′-H), 7.37–7.39 (m, 2 H, 2′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.7, 21.3, 22.0, 23.0, 25.6, 31.3, 34.2, 40.5, 46.9, 51.7, 55.3, 75.2, 81.0, 113.5, 127.5, 132.8, 159.2, 172.8 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 281.0 (1,500), 274.2 (1,700), 231.0 (10,900) nm. CD (EtOH): λ ($\Delta\varepsilon$, L mol^{-1} cm^{-1}) = 281.8 (–0.49), 273.8 (–0.59), 249.6 (+0.41), 234.6 (–5.01), 219.6 (+0.31), 207.0 (–2.97) nm. $C_{21}H_{32}O_4$ (348.48): calcd. C 72.38, H 9.26; found C 72.43, H 9.31.

(1*R*,3*R*,4*S*)-(–)-Menthyl 2-Methoxy-2-(3-methoxyphenyl)propionate (49a): Yield 43%, colorless oil. $[\alpha]_D^{25}$ = –82.7 (*c* = 1.22, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2954, 2870, 1725, 1600, 1488, 1455, 1371, 1255, 1179, 1117, 1045, 962, 913, 783, 725, 696 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.59 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.74 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.82 (dddd, *J* = 13.0, 13.0, 11.9, 3.5 Hz, 1 H, 6ax-H), 0.88 (d, *J* = 6.4 Hz, 3 H, 1-CH_3), 0.96 (ddd, *J* = 12.1, 11.9, 11.0 Hz, 1 H, 2ax-H), 0.99 (dddd, *J* = 13.1, 13.0, 12.3, 3.5 Hz, 1 H, 5ax-H), 1.36 (dddd, *J* = 12.3, 11.0, 3.3, 2.9 Hz, 1 H, 4-H), 1.47 (ddqdd, *J* = 12.1, 11.9, 6.4, 4.2, 3.5 Hz, 1 H, 1-H), 1.51 (sept.d, *J* = 7.0, 2.9 Hz, 1 H, *i*Pr CH), 1.62 (dddd, *J* = 13.1, 3.5, 3.3, 3.3 Hz, 1 H, 5eq-H), 1.65 (ddddd, *J* = 13.0, 3.5, 3.5, 3.3, 2.0 Hz, 1 H, 6eq-H), 1.75 (s, 3 H, CH_3), 1.94 (dddd, *J* = 11.9, 4.4, 4.2, 2.0 Hz, 1 H, 2eq-H), 3.31 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.70 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 6.82 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1 H, 4′-H), 7.03 (ddd, *J* = 8.0, 1.7, 1.0 Hz, 1 H, 6′-H), 7.05 (dd, *J* = 2.4, 1.7 Hz, 1 H, 2′-H), 7.24 (dd, *J* = 8.0, 8.0 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.7, 22.0, 22.2, 23.0, 25.6, 31.4, 34.2, 40.5, 46.9, 52.1, 55.2, 75.4, 81.8, 111.2, 113.5, 118.0, 129.1, 143.0, 159.6, 172.4 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 274.8 (1,700), 219.2 (6,400) nm. CD (EtOH): λ ($\Delta\varepsilon$, L mol^{-1} cm^{-1}) = 286.0 (–0.14), 264.0 (+0.02), 239.8 (–2.62), 230.0 (–1.12), 223.6 (–2.11), 201.2 (+3.84) nm. $C_{21}H_{32}O_4$ (348.48): calcd. C 72.38, H 9.26; found C 72.29, H 9.12.

(1*R*,3*R*,4*S*)-(–)-Menthyl 2-Methoxy-2-(3-methoxyphenyl)propionate (49b): Yield 39%, colorless oil. $[\alpha]_D^{25}$ = –56.0 (*c* = 1.02, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.56 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.71 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.81 (dddd, *J* = 13.0, 13.0, 11.9, 3.5 Hz, 1 H, 6ax-H), 0.88 (d, *J* = 6.5 Hz, 3 H, 1-CH_3), 0.91 (ddd, *J* = 12.1, 12.1, 11.0 Hz, 1 H, 2ax-H), 0.98 (dddd, *J* = 13.0, 12.8, 12.4, 3.3 Hz, 1 H, 5ax-H), 1.29 (dddd, *J* = 12.4, 11.0, 3.3, 2.8 Hz, 1 H, 4-H), 1.41 (sept.d, *J* = 7.0, 2.8 Hz, 1 H, *i*Pr CH), 1.47 (ddqdd, *J* = 12.1, 11.9, 6.5, 3.6, 3.1 Hz, 1 H, 1-H), 1.60 (dddd, *J* = 12.8, 3.5, 3.3, 3.1 Hz, 1 H, 5eq-H), 1.64 (ddddd, *J* = 13.0, 3.3, 3.1, 3.1, 2.0 Hz, 1 H, 6eq-H), 1.77 (s, 3 H, CH_3), 1.95 (dddd, *J* = 12.1, 4.4, 3.6, 2.0 Hz, 1 H, 2eq-H), 3.27 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.65 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 6.82–6.84 (m, 1 H, 4′-H), 7.02–7.03 (m, 1 H, 6′-H), 7.03–7.04 (m, 1 H, 2′-H), 7.23–7.26 (m, 1 H, 5′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.7, 20.7, 21.3, 22.0, 23.0, 25.6, 31.3, 34.2, 40.5, 46.9, 51.8, 55.3, 75.3, 81.4, 111.7, 113.6, 118.5, 129.1, 142.4, 159.6, 172.4 ppm. UV (EtOH): λ (ε, L mol^{-1} cm^{-1}) = 276.0 (2,400), 218.0 (8,700) nm. CD (EtOH): λ ($\Delta\varepsilon$, L mol^{-1} cm^{-1}) = 245.6 (+0.42), 229.8 (–4.94), 202.4 (+9.05) nm. $C_{21}H_{32}O_4$ (348.48): calcd. C 72.38, H 9.26; found C 72.33, H 9.22.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-methoxyphenyl)propionate (50a): Colorless crystal. M.p. 97–98 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.74 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.81 (dddd, *J* = 13.0, 12.1, 12.1, 3.5 Hz, 1 H, 6ax-H), 0.89 (d, *J* = 6.5 Hz, 3 H, 1-CH_3), 0.93 (ddd, *J* = 12.1, 12.1, 10.8 Hz, 1 H, 2ax-H), 1.01 (dddd, *J* = 13.0, 13.0, 12.7, 3.3 Hz, 1 H, 5ax-H), 1.29 (dddd, *J* = 12.7, 10.9, 3.1, 3.1 Hz, 1 H, 4-H), 1.49 (ddqdd, *J* = 12.1, 12.1, 6.5, 3.5, 3.3 Hz, 1 H, 1-H), 1.61 (dddd, *J* = 13.0, 3.5, 3.3, 3.1 Hz, 1 H, 5eq-H), 1.63 (sept.d, *J* = 7.0, 3.1 Hz, 1 H, *i*Pr CH), 1.65 (ddddd, *J* = 12.1, 3.3, 3.3, 3.3, 2.0 Hz, 1 H, 6eq-H), 1.67 (s, 3 H, CH_3), 2.10 (dddd, *J* = 12.1, 4.4, 3.5, 2.0 Hz, 1 H, 2eq-H), 3.30 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.66 (ddd, *J* = 10.9, 10.8, 4.4 Hz, 1 H, 3-H), 6.82 (dd, *J* = 8.2, 1.1 Hz, 1 H, 3′-H), 6.98 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1 H, 5′-H), 7.27 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1 H, 4′-H), 7.58 (dd, *J* = 7.5, 1.6 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.9, 20.7, 21.1, 22.1, 23.0, 25.5, 31.3, 34.2, 40.4, 46.5, 51.5, 54.9, 75.0, 79.4, 110.1, 120.4, 126.4, 126.4, 128.7, 130.4, 155.8, 171.8 ppm.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-methoxyphenyl)propionate (50b): Colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.9 Hz, 3 H, *i*Pr CH_3), 0.80 (m, 1 H, 6ax-H), 0.81 (d, *J* = 6.9 Hz, 3 H, *i*Pr CH_3), 0.85 (ddd, *J* = 12.1, 11.9, 10.8 Hz, 1 H, 2ax-H), 0.88 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 1.03 (dddd, *J* = 13.5, 13.0, 12.5, 3.3 Hz, 1 H, 5ax-H), 1.30 (dddd, *J* = 12.5, 11.0, 3.1, 3.1 Hz, 1 H, 4-H), 1.49 (m, 1 H, 1-H), 1.62 (dddd, *J* = 13.0, 3.3, 3.3, 3.1 Hz, 1 H, 5eq-H), 1.65 (m, 1 H, 6eq-H), 1.67 (s, 3 H, CH_3), 1.82 (sept.d, *J* = 6.9, 2.8 Hz, 1 H, *i*Pr CH), 2.04 (dddd, *J* = 11.9, 4.4, 3.7, 2.0 Hz, 1 H, 2eq-H), 3.26 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.70 (ddd, *J* = 10.8, 10.8, 4.4 Hz, 1 H, 3-H), 6.84 (dd, *J* = 8.3, 1.0 Hz, 1 H, 3′-H), 6.98 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1 H, 5′-H), 7.27 (ddd, *J* = 8.3, 7.7, 1.6 Hz, 1 H, 4′-H), 7.53 (dd, *J* = 7.7, 1.6 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.1, 20.7, 21.3, 22.1, 23.2, 25.7, 31.3, 40.3, 46.6, 51.5, 54.9, 74.7, 79.5, 110.3, 120.3, 126.7, 128.7, 130.3, 156.0, 171.9 ppm.

(1*R*,3*R*,4*S*)-(–)-Menthyl 2-Methoxy-2-(2-methylphenyl)propionate (51a): Yield 49%, colorless oil. $[\alpha]_D^{24}$ = –28.4 (*c* = 1.07, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2955, 2870, 1726, 1455, 1386, 1369, 1252, 1187, 1129, 1049, 982, 962, 918, 889, 845, 761, 740, 644, 593 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.79 (dddd, *J* = 13.9, 13.9, 11.9, 4.3 Hz, 1 H, 6ax-H), 0.82 (d, *J* = 7.0 Hz, 3 H, *i*Pr CH_3), 0.83 (ddd, *J* = 12.1, 12.1, 11.0 Hz, 1 H, 2ax-H), 0.86 (d, *J* = 6.6 Hz, 3 H, 1-CH_3), 1.01 (dddd, *J* = 13.9, 13.1, 12.4, 3.3 Hz, 1 H, 5ax-H), 1.31 (dddd, *J* = 12.4, 11.0, 3.1, 2.9 Hz, 1 H, 4-H), 1.47 (ddqdd, *J* = 12.1, 11.9, 6.6, 3.5, 3.1 Hz, 1 H, 1-H), 1.62 (dddd, *J* = 13.1, 4.3, 3.1, 3.1 Hz, 1 H, 5eq-H), 1.64 (ddddd, *J* = 13.9, 3.3, 3.1, 3.1, 1.8 Hz, 1 H, 6eq-H), 1.77 (sept.d, *J* = 7.0, 2.9 Hz,

1 H, *i*Pr CH), 1.81 (s, 3 H, CH_3), 1.96 (dddd, J = 12.1, 4.4, 3.5, 1.8 Hz, 1 H, 2eq-H), 2.34 (s, 3 H, CH_3), 3.10 (s, 3 H, OCH_3), 4.71 (ddd, J = 11.0, 11.0, 4.4 Hz, 1 H, 3-H), 7.14 (m, 1 H), 7.18 (m, 1 H), 7.21 (ddd, J = 7.0, 7.0, 1.6 Hz, 1 H), 7.39 (dd, J = 7.5, 1.6 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.8, 20.2, 20.8, 21.4, 22.0, 22.9, 25.8, 31.3, 34.1, 40.1, 46.6, 50.7, 75.2, 81.6, 125.4, 127.2, 127.9, 131.6, 137.0, 137.7, 173.1 ppm. UV (EtOH): λ (ε, $L\,mol^{-1}\,cm^{-1}$) = 272.2 (260), 265.2 (310), 209.6sh (7,800) nm. CD (EtOH): λ ($\Delta\varepsilon$, $L\,mol^{-1}\,cm^{-1}$) = 272.8 (–0.26), 266.6 (–0.29), 242.8 (–0.41), 216.0 (+5.35) nm. $C_{21}H_{32}O_3$ (332.48): calcd. C 75.86, H 9.70; found C 75.71, H 9.70.

(1*R*,3*R*,4*S*)-(–)-Menthyl 2-Methoxy-2-(2-methylphenyl)propionate (51b): Yield 48%, colorless oil. $[\alpha]_D^{24}$ = –83.2 (c = 1.04, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2954, 2870, 1747, 1455, 1386, 1369, 1250, 1189, 1134, 1098, 1039, 982, 963, 918, 889, 844, 761, 740, 664 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.57 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.64 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.80 (dddd, J = 13.2, 13.0, 11.9, 3.5 Hz, 1 H, 6ax-H), 0.89 (d, J = 6.6 Hz, 3 H, 1-CH_3), 0.92 (ddd, J = 12.1, 12.1, 10.8 Hz, 1 H, 2ax-H), 0.96 (dddd, J = 13.3, 13.0, 12.4, 3.5 Hz, 1 H, 5ax-H), 1.20 (dddd, J = 12.4, 10.8, 2.9, 2.8 Hz, 1 H, 4-H), 1.25 (sept.d, J = 7.0, 2.8 Hz, 1 H, *i*Pr CH), 1.48 (ddqdd, J = 12.1, 11.9, 6.6, 3.7, 3.3 Hz, 1 H, 1-H), 1.57 (dddd, J = 13.3, 3.5, 3.5, 2.9 Hz, 1 H, 5eq-H), 1.64 (ddddd, J = 13.2, 3.5, 3.5, 3.3, 2.0 Hz, 1 H, 6eq-H), 1.83 (s, 3 H, CH_3), 2.04 (dddd, J = 12.1, 4.4, 3.7, 2.0 Hz, 1 H, 2eq-H), 2.34 (s, 3 H, CH_3), 3.10 (s, 3 H, OCH_3), 4.64 (ddd, J = 10.8, 10.8, 4.4 Hz, 1 H, 3-H), 7.12–7.13 (m, 1 H), 7.16–7.19 (m, 1 H), 7.20 (ddd, J = 7.1, 7.1, 1.5 Hz, 1 H), 7.35–7.37 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.8, 20.2, 20.5, 21.4, 22.0, 23.0, 25.4, 31.3, 34.2, 40.3, 46.8, 50.5, 75.1, 81.3, 125.4, 127.5, 127.9, 131.6, 137.3, 137.5, 172.9 ppm. UV (EtOH): λ (ε, $L\,mol^{-1}\,cm^{-1}$) = 272.4 (320), 265.2 (380), 208.6sh (9,500) nm. CD (EtOH): λ ($\Delta\varepsilon$, $L\,mol^{-1}\,cm^{-1}$) = 273.0 (+0.64), 266.2 (+0.68), 227.2 (–5.40), 215.4 (–8.81) nm. $C_{21}H_{32}O_3$ (332.48): calcd. C 75.86, H 9.70; found C 75.64, H 9.70.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-methoxymethylphenyl)propionate (52a): Yield 39%, colorless oil. IR (neat): $\tilde{\nu}$ = 2955, 2870, 2829, 1726, 1455, 1371, 1250, 1192, 1132, 1097, 1068, 962, 918, 844, 748 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.73 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.78 (m, 1 H, 6ax-H), 0.81 (ddd, J = 12.1, 12.1, 10.9 Hz, 1 H, 2ax-H), 0.83 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.85 (d, J = 6.6 Hz, 3 H, 1-CH_3), 1.01 (dddd, J = 12.8, 12.8, 12.5, 3.3 Hz, 1 H, 5ax-H), 1.31 (dddd, J = 12.5, 10.9, 3.1, 2.9 Hz, 1 H, 4-H), 1.46 (m, 1 H, 1-H), 1.61–1.65 (m, 2 H, 5eq-H, 6eq-H), 1.77 (sept.d, J = 7.0, 2.9 Hz, 1 H, *i*Pr CH), 1.83 (s, 3 H, CH_3), 1.92 (dddd, J = 12.1, 4.4, 3.5, 1.9 Hz, 1 H, 2eq-H), 3.12 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 4.52 (d, J = 13.0 Hz, 1 H, OCH), 4.63 (d, J = 13.0 Hz, 1 H, OCH), 4.70 (ddd, J = 10.9, 10.9, 4.4 Hz, 1 H, 3-H), 7.26 (ddd, J = 8.0, 7.5, 1.4 Hz, 1 H), 7.34 (ddd, J = 7.5, 7.5, 1.3 Hz, 1 H), 7.36 (dd, J = 8.0, 1.3 Hz, 1 H), 7.57 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.8, 20.7, 21.8, 21.9, 23.0, 25.9, 31.3, 34.1, 40.1, 46.6, 50.8, 58.4, 71.4, 75.5, 81.8, 126.9, 127.2, 128.2, 128.5, 136.9, 137.7, 172.9 ppm. UV (EtOH): λ (ε, $L\,mol^{-1}\,cm^{-1}$) = 264.6 (270), 210.6sh (8,100) nm. CD (EtOH): λ ($\Delta\varepsilon$, $L\,mol^{-1}\,cm^{-1}$) = 272.4 (–0.25), 265.2 (–0.29), 242.8 (–0.67), 227.8 (+1.65), 215.0 (+5.95) nm.

(1*R*,3*R*,4*S*)-Menthyl 2-Methoxy-2-(2-methoxymethylphenyl)propionate (52b): Yield 38%, colorless oil. IR (neat): $\tilde{\nu}$ = 2954, 2870, 2829, 1745, 1454, 1370, 1248, 1192, 1134, 1098, 1067, 1039, 963, 918, 747 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.54 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.64 (d, J = 7.0 Hz, 3 H, *i*Pr CH_3), 0.80 (dddd, J = 12.8, 12.8, 11.9, 3.5 Hz, 1 H, 6ax-H), 0.89 (d, J = 6.6 Hz, 3 H, 1-CH_3), 0.93 (ddd, J = 12.1, 12.1, 10.8 Hz, 1 H, 2ax-H), 0.96 (dddd, J = 13.2, 12.8, 12.6, 3.5 Hz, 1 H, 5ax-H), 1.20 (dddd, J = 12.6, 10.8, 3.1, 2.7 Hz, 1 H, 4-H), 1.23 (sept.d, J = 7.0, 2.7 Hz, 1 H, *i*Pr CH), 1.47 (ddqdd, J = 12.1, 11.9, 6.6, 3.7, 3.3 Hz, 1 H, 1-H), 1.57 (dddd, J = 13.2, 3.5, 3.3, 3.1 Hz, 1 H, 5eq-H), 1.64 (ddddd, J = 12.8, 3.5, 3.3, 3.3, 2.0 Hz, 1 H, 6eq-H), 1.84 (s, 3 H, CH_3), 2.03 (dddd, J = 11.9, 4.4, 3.7, 2.0 Hz, 1 H, 2eq-H), 3.13 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 4.48 (d, J = 13.2 Hz, 1 H, OCH), 4.62 (ddd, J = 10.8, 10.8, 4.4 Hz, 1 H, 3-H), 4.66 (d, J = 13.2 Hz, 1 H, OCH), 7.26 (m, 1 H), 7.32 (ddd, J = 7.8, 7.8, 1.3 Hz, 1 H), 7.35 (dd, J = 7.8, 1.3 Hz, 1 H), 7.57 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.0, 20.7, 21.9, 22.2, 23.3, 25.7, 31.5, 34.4, 40.5, 47.0, 51.0, 58.7, 71.6, 75.6, 81.7, 127.0, 127.7, 128.3, 128.4, 136.6, 138.2, 172.9 ppm. UV (EtOH): λ (ε, $L\,mol^{-1}\,cm^{-1}$) = 264.6 (370), 210.2sh (9,600) nm. CD (EtOH): λ ($\Delta\varepsilon$, $L\,mol^{-1}\,cm^{-1}$) = 272.4 (+0.41), 265.8 (+0.48), 229.8 (–3.23), 215.8 (–8.68) nm.

Recovery of Enantiopure Carboxylate: For example, to a solution of ester (–)-**47a** (0.0253 g, 0.0794 mmol) in MeOH (1.2 mL) was added a solution of KOH (0.201 g, 3.58 mmol) in water (0.3 mL), and the mixture was gently refluxed for 27 h. After the addition of water, the mixture was extracted with diethyl ether, and the aqueous layer was acidified with 2 M HCl at 0 °C and then extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and the solvent was evaporated to dryness, yielding carboxylic acid (*S*)-(+)-**7** as a colorless syrup.

(*S*)-(+)-2-Methoxy-2-phenylpropionic Acid (7): Yield 0.0135 g, 94%. $[\alpha]_D^{27}$ = +51.1 (c = 0.68, $CHCl_3$); ref.[18a] $[\alpha]_D$ = +31.5 (neat, 0.1 dm) and $[\alpha]_D$ = +25 (c = 1, MeOH); ref.[18b] methyl ester, α_D^{25} = +50 (neat, 1 dm). Other spectroscopic data agreed with those of carboxylic acid (±)-**7**.

(*R*)-(–)-2-Methoxy-2-phenylpropionic Acid (7): From ester (–)-**47b**, yield 85%, colorless syrup. $[\alpha]_D^{27}$ –50.6 (c = 0.82, $CHCl_3$); ref.[18a] $[\alpha]_D$ = –32.5 (neat, 0.1 dm) and $[\alpha]_D$ = –26 (c = 1, MeOH); ref.[18b] methyl ester, α_D^{24} = –52.2 (neat, 1 dm). Other spectroscopic data agreed with those of carboxylic acid (±)-**7**.

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