รายงานวิจัยฉบับสมบูรณ์

โครงการการออกแบบและสังเคราะห์สารเตรียมอนุพันธ์ไครัลชนิดใหม่

Design and Synthesis of New Chiral Derivatizing Agents

ผศ.ดร.เทียนทอง ทองพันชั่ง

มกราคม 2553

สัญญาเลขที่ RMU4980021

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มหาวิทยาลัยมหิดล

สนับสนุนโดยสำนักงานคณะกรรมการการอุดมศึกษา

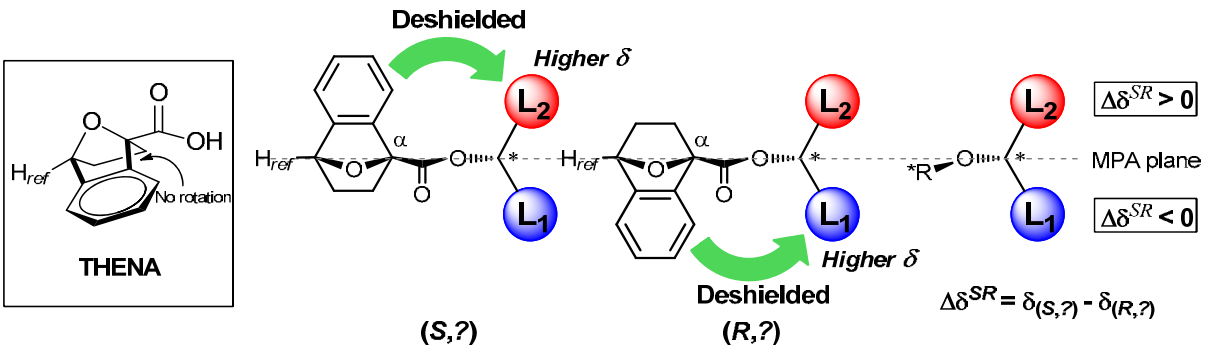
และสำนักงานกองทุนสนับสนุนการวิจัย

บทคัดย่อ

โครงการวิจัยนี้ เป็นการออกแบบ สังเคราะห์และพัฒนาสารอนุพันธ์ไครัลชนิดใหม่ (THENA) เพื่อใช้ศึกษาคอน-ฟิกุเรชันสัมบูรณ์ของสารไครัลอัลกอฮอล์อย่างมีประสิทธิภาพและมีความถูกต้องแม่นยำในการแปลผล ซึ่งการออกแบบโครงสร้างของสารอนุพันธ์ไครัลชนิดใหม่นั้น จำลองจากการจัดตัวของเอสเทอร์ของกรดแมนเดลิก ซึ่งจัดให้ RO-C-C_a-C(O)-O-C*-H อยู่ในระนาบเดียวกันแบบ *syn*-periplanar โดยในสารอนุพันธ์ไครัลชนิดใหม่นี้ จะมีระนาบดังกล่าวเป็นส่วนหนึ่งของระบบไบไซคลิก ซึ่งจะยึดให้วงอะโรมาติกไม่สามารถหมุนได้ เมื่อประกอบกับการที่มีโปรตอนอ้างอิง (H_{ref}) ภายในโมเลกุลเพื่อช่วยในการเปรียบเทียบสเปกตรัมแล้ว การระบุค่าความต่างของ ^{1}H NMR chemical shift จะมีความแม่นยำ ทำให้การระบุค่าคอนฟิกุเรชันสัมบูรณ์มีความถูกต้องยิ่งขึ้น

สารอนุพันธ์ไครัลชนิดใหม่นี้ เมื่อนำมาทำปฏิกิริยากับสารไครัลอัลกอฮอล์ที่สนใจก็จะได้สารประกอบที่เป็นคู่อิแนนทิโอเมอร์ซึ่งจะให้สเปกตรัมของ ^{1}H NMR ที่ต่างกัน ซึ่งเมื่อนำผลต่างของค่า chemical shifts ดังกล่าวมาวิเคราะห์คู่กับแบบจำลองความสัมพันธ์ระหว่างค่าความแตกต่างของ chemical shifts กับค่าคอนฟิกุเรชันสัมบูรณ์ ก็สามารถบอกค่าคอนฟิกุเรชันสัมบูรณ์ของสารไครัลอัลกอฮอล์ชนิดทุติยภูมิได้อย่างถูกต้องและมีประสิทธิภาพ นอกจากนี้ สารอนุพันธ์ไครัลที่เตรียมขึ้นสามารถใช้ในการแยกเรโซลูชันของสารในกลุ่มไบแนพธอลได้อย่างมีประสิทธิภาพอีกด้วย

การปรับปรุงโครงสร้างของสารอนุพันธ์ไครัล (THENA) โดยการขยายวงอะโรมาติกให้ยาวขึ้นเพื่อเพิ่มผลของ anisotropic effect และการเติมหมู่อิพอกไซด์เข้าไปเพื่อลดความซับซ้อนของการอ่านสปกตรัมของ ^{1}H NMR ทำให้การใช้สารอนุพันธ์ไครัลดังกล่าวในการระบุค่าคอนฟิกุเรชันสัมบูรณ์ทำได้สะดวกมากขึ้น

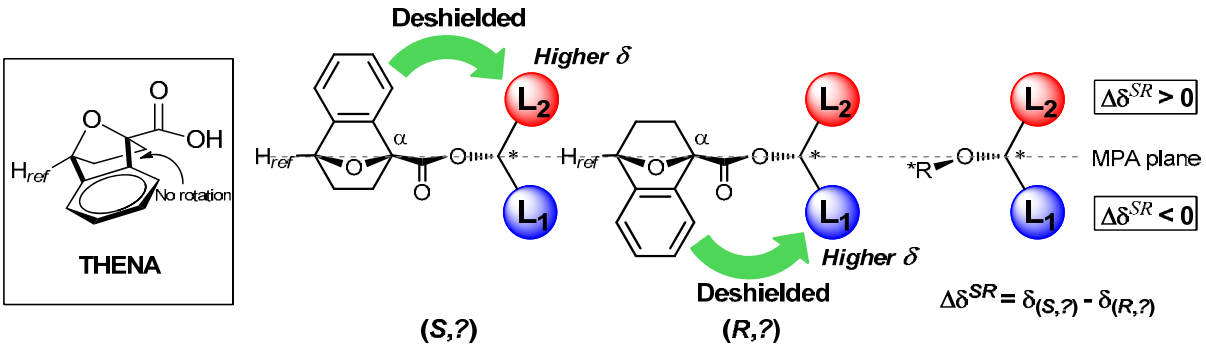


Abstract

This research focuses on the design, synthesis and development of a new chiral derivatizing agent (THENA) for the determination of the absolute configuration of chiral secondary alcohols, with high efficiency and reliable accuracy. The design was based on the preferred conformation of the mandelate ester with the *syn*-periplanar orientation of RO-C-C_a-C(O)-O-C*-H. This plane now becomes a part of the bicyclic system in order to constrain the rotational degree of freedom of the aromatic group. With the presence of an internal reference proton (H_{ref}) which can facilitate the spectral alignment, the determination of the chemical shift difference could be done unambiguously, leading to an accurate absolute configuration.

A diastereomeric pair from the reaction between the new chiral derivatizing agents and the chiral alcohol of interest would give ^{1}H NMR spectra with different chemical shifts. The correlation between the model derived from the chemical shift differences and the absolute configuration of the compound of interest would then lead to the absolute configuration of the chiral alcohol. In addition, it was found that THENA could also be used to resolved binaphthol derivatives.

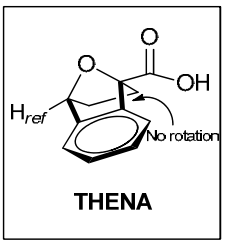
Modification of THENA by extending the aromatic group as well as by installing an epoxide subunit led to a less complicated ^{1}H NMR spectra, making the determination of the absolute configuration more convenient.



Executive summary

Research in the field of bioactive natural products, especially those with chiral centers, is of great significance since it can provide new potential pharmaceutical leads. Accordingly the simple and efficient tools to determine the absolute configuration of the chiral molecules are in high demand and this has led to the development of chiral derivatizing agents and the NMR shift difference method.

This research focuses on the development of a new chiral derivatizing agent (THENA) for the determination of the absolute configuration of chiral alcohols. The key features of THENA design include *i)* the analogous MPA plane as a part of bicyclic system, to limit the rotational degree of freedom of the aromatic moiety *ii)* the observed anisotropic deshielding effect on the substituents, due to the bicyclic tether *iii)* the presence of an internal reference proton (H_{ref}) to facilitate the spectra alignment *iv)* readily accessible at low cost *via* a straightforward synthesis.



THENA

Enantiomers of THENA were synthesized and then applied to determine the absolute configuration of chiral secondary alcohols with known absolute configuration. The correlation between the model derived from the chemical shift differences and the absolute configuration of the compound of interest was constructed. In all cases, the absolute configurations derived from the experimental data were satisfactorily in good agreement with the known configuration. The application of THENA in the resolution of binaphthol derivatives was also realized.

Modification of THENA by extending the aromatic moiety as well as an addition of an epoxide subunit onto the bicyclic skeleton provided a new chiral derivatizing agent with much less complicated ^{1}H NMR spectra. This modified THENA could also be used successfully in the determination of the absolute configuration of the chiral alcohols.

At present, almost all of the chiral derivatizing agents being used in Thailand are imported. The success of this work thus provided an opportunity to implement the domestic

research and development through collaboration with natural product chemists who are interested to use this chiral derivatizing agent in their research.

Design and Synthesis of New Chiral Derivatizing Agents

Part I. Design of new chiral derivatizing agent THENA

Introduction

Research on the complex bioactive natural products which requires structure elucidation and the emerging of asymmetric synthesis in chemical and pharmaceutical areas have stimulated the development of simple, reliable and inexpensive methods to determine the absolute configuration of chiral centers.[1]

At present, there are several methods for determining the absolute configuration of a chiral compound. The most widely known is X-ray crystallography[2] which can be used to assign the absolute configuration of an optically pure compound and is often used to confirm the hypotheses used for stereochemical assignment. However, there are some inconveniences and limitations. Related to the equipment, the technique is very specific to the method and requires special training for operation. Related to the sample, the X-ray diffraction analysis (XRD) requires single crystals of good quality which is frequently not obtainable. The other methods, such as optical rotation study,[3] have also been applied with great convenience. However, the technique which is based on the rotation of plane-polarized light by the sample can be reliable only if the rotation of the pure compound is accurately known. This is impractical for a newly prepared material or a newly discovered natural product.

The utility of NMR spectroscopy then becomes the solution as one of the most convenient ways of detecting and analyzing the diastereomeric products. As exemplified in Figure 1, the difference in NMR spectra can be observed as a result of the difference in the physical properties of diastereomers derived from the covalent or noncovalent complex formation between the chiral molecules with unknown configurational chiral center and another chiral reagent with known absolute stereochemistry, the chiral derivatizing agents (CDAs).[4] The changes in the chemical shifts of the substituents of the asymmetric carbon of the substrate (L_1 and L_2) in the two derivatives can then be considered. These differences in the chemical shifts are represented by $\Delta\delta$, and the sign of this parameter (+ or –) provides the information about the configuration. For a particular substituent (e.g., L_1), $\Delta\delta$ is defined as the difference of chemical shifts of a given signal of the substituent (δL_1) in the two spectra

under consideration. The sign of the chemical shift differences of the substituents attached to the asymmetric carbon can then be correlated with the absolute configuration by using an empirical model.

a)

b)

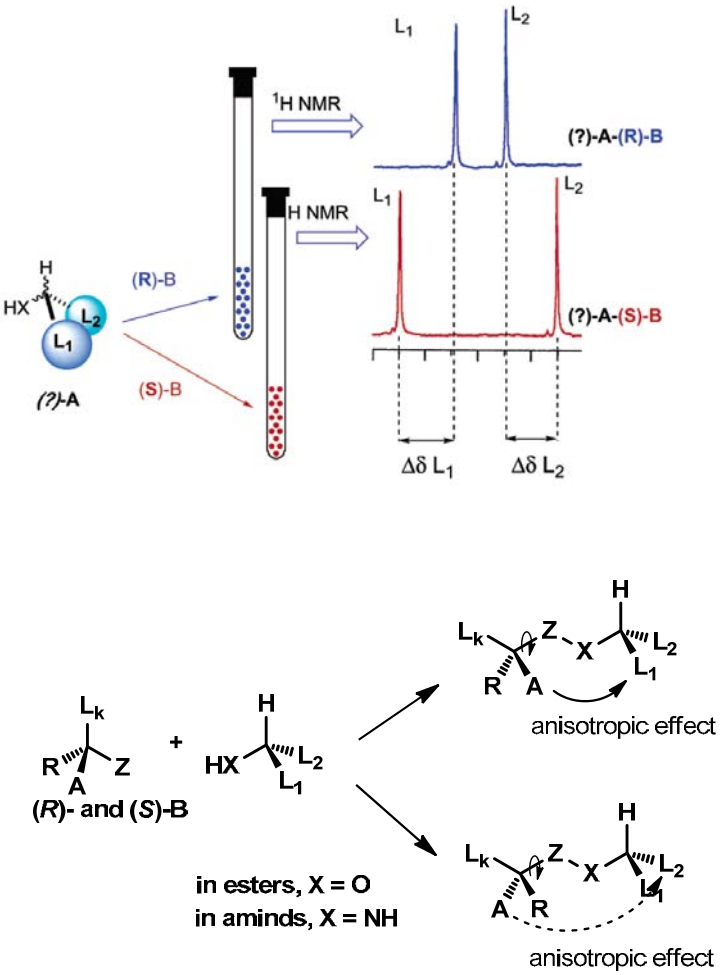


Figure 1. a) Representative protocol for the CDA-NMR shift difference method.[4]; b) General structure of CDA and the anisotropic effect of the corresponding esters.

Furthermore, the difference in the physical properties of the diastereomers provides the basis of chemical and physical separation processes. The process of the resolution is the separation of a diastereomeric mixture produced by the reaction of a racemic mixture with a pure enantiomer of a second reagent, the resolving agent. Since the two resulting products will be diastereomers, they can be separated. The separated diastereomers can then be converted to the pure enantiomers by reversing the initial chemical transformation, *i.e.* the hydrolysis reaction.

1.1. Procedure

The procedure to correlate the NMR chemical shift differences with the absolute configuration assignment can be described comprehensibly as follows. The chiral substrate (*i.e.* a secondary alcohol or amine) of unknown absolute stereochemistry (*?*)-A is separately esterified with the (*R*)- and (*S*)- enantiomers of an auxiliary reagent B of which the molecule possesses an aromatic functional group (*e.g.* a phenyl group) to provide the anisotropic effect. The NMR spectra of the two resulting diastereomers (*?*)-A-(*R*)-B and (*?*)-A-(*S*)-B are compared (Figure 1). The different anisotropic influence from the phenyl group of the chiral auxiliary on the substituents in each diastereoisomer then causes of chemical shift differences and thus the two spectra should be different and the assignment of configuration is based on the existence of a certain association between the absolute stereochemistry at the chiral centre of the auxiliary reagent B, and the chemical shifts of L_1/L_2 in the two derivatives.

For this relationship to exist, some characteristics and conditions of CDA have to be fulfilled:

a) have a polar or bulky group (L_k) (*e.g.* OMe) to fix a particular conformation which should be the same in the two diasteroisomeric derivatives and independent of the nature of substituents L_1 and L_2 of A.
b) have a functional group (Z) (*e.g.* carboxylic acid) that provides a site for covalent attachment of the substrate.
c) have anisotropic group Y (*e.g.* phenyl) which should be able to affect in a selective and recognized way the chemical shifts of substituents L_1/L_2 at the substrate part and strong enough to ensure that the chemical shifts of L_1 and L_2 are different in the two species, and
d) there should exist in both derivatives a significantly more populated conformer where group Y acts strongly on L_1/L_2.

1.2. Common CDA

1.2.1. α-Methoxy-α-phenylacetic acid (MPA)

α-Methoxy-*α*-phenylacetic acid (MPA) or mandelic acid (MA) **1** (Figure 2a) represents a facile approach for analyzing the absolute configuration of chiral secondary

alcohols. The model proposed by Dale and Mosher[5] correlated NMR shifts and absolute stereochemistry of the mandelate ester derivatives of chiral alcohols. It is assumed that the representative conformer in terms of NMR is the one in which the methoxy, carbonyl, and C(1')H groups are situated in the same plane (Figure 2b). In this way, the NMR chemical shift of the substituent which eclipsed the phenyl ring then always appeared upfield, presumably as a result of the shielding effect from the phenyl ring. Derivative (*S*)-MPA ester should show its L_2-proton shift more upfield than that of the corresponding signal in (*R*)-MPA ester and the reverse should be true for the incident of L_1 group (Figure 2b). Consequently, the comparison of both spectra leads to $\Delta\delta^{RS}$ $L_1 < 0$ and $\Delta\delta^{RS}L_2 > 0$ (Figure 2c).

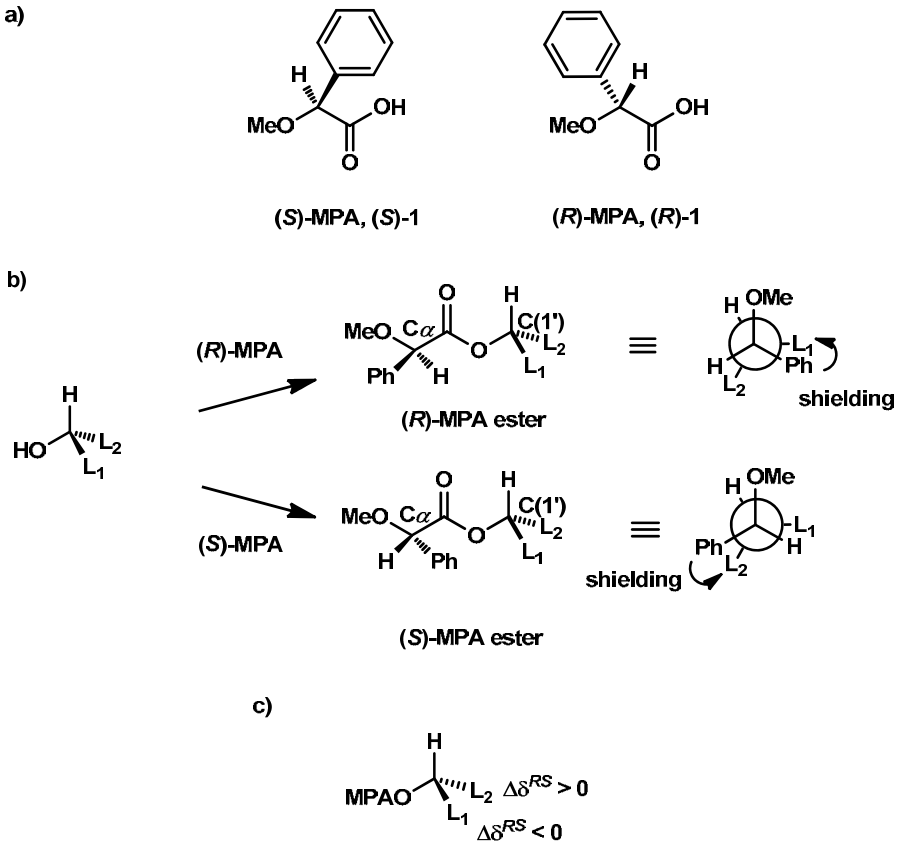
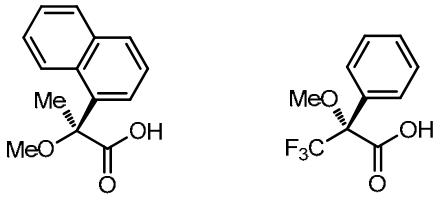


Figure 2. a) *α*-Methoxy-*α*-phenylacetic acid (MPA) or mandalic acid **1**; b) the model for determining of absolute configuration of secondary alcohol; c) the expected signs of $\Delta\delta^{RS}$.

Because of the potential problem with racemization found during esterification,[4] the *α*-methoxy-*α*-phenylacetic acid (MPA) **1** has been less used. This factor led to the design of

new resolving agent to avoid this problem such as methoxy-2-(1-naphthyl)propionic (M*α*NP) acid **2** and Mosher's acid (MTPA) **3** (Figure 3).



M*α*NP; 2 **MTPA; 3**

Figure 3. The chemical structures of methoxy-2-(1-naphthyl)propionic (M*α*NP) acid **2** and Mosher's acid (MTPA) **3**.

1.2.2. Methoxy-2-(1-naphthyl)propionic (MαNP) acid

Methoxy-2-(1-naphthyl)propionic (M*α*NP) acid **2** is also a powerful tool for determining the absolute configuration of chiral secondary alcohols.[6] This chiral ^{1}H NMR anisotropy reagent is unique in the sense that the diastereomeric M*α*NP esters prepared from enantiopure acid (*S*)-(+)-M*α*NP and racemic alcohols are easily separable by HPLC. In addition, the M*α*NP acid **2** has a chiral quaternary carbon atom, and therefore, does not racemize.

In the (*R*)-M*α*NP ester of the alcohol shown in Figure 4a, substituent L_1 experiences a shielding influence from the naphthyl group, whereas, in the (*S*)-M*α*NP ester, the shielded group is substituent L_2. Therefore, substituent L_1 results in a negative $\Delta\delta^{RS}$ value and substituent L_2 yields a positive $\Delta\delta^{RS}$ value (Figure 4b).

To explain the anisotropy effect of M*α*NP acid esters, the studies of their ^{1}H NMR spectra and those of related carboxylic acid esters suggested that the observed $\Delta\delta$ values are very sensitive to the geometry of the aromatic groups. These results indicate that the *syn-syn* conformation generates a larger $\Delta\delta$ value which is stabilized by a triangular hydrogen-bonding interaction among O-6/ H-8/ O-7 (Figure 4c).

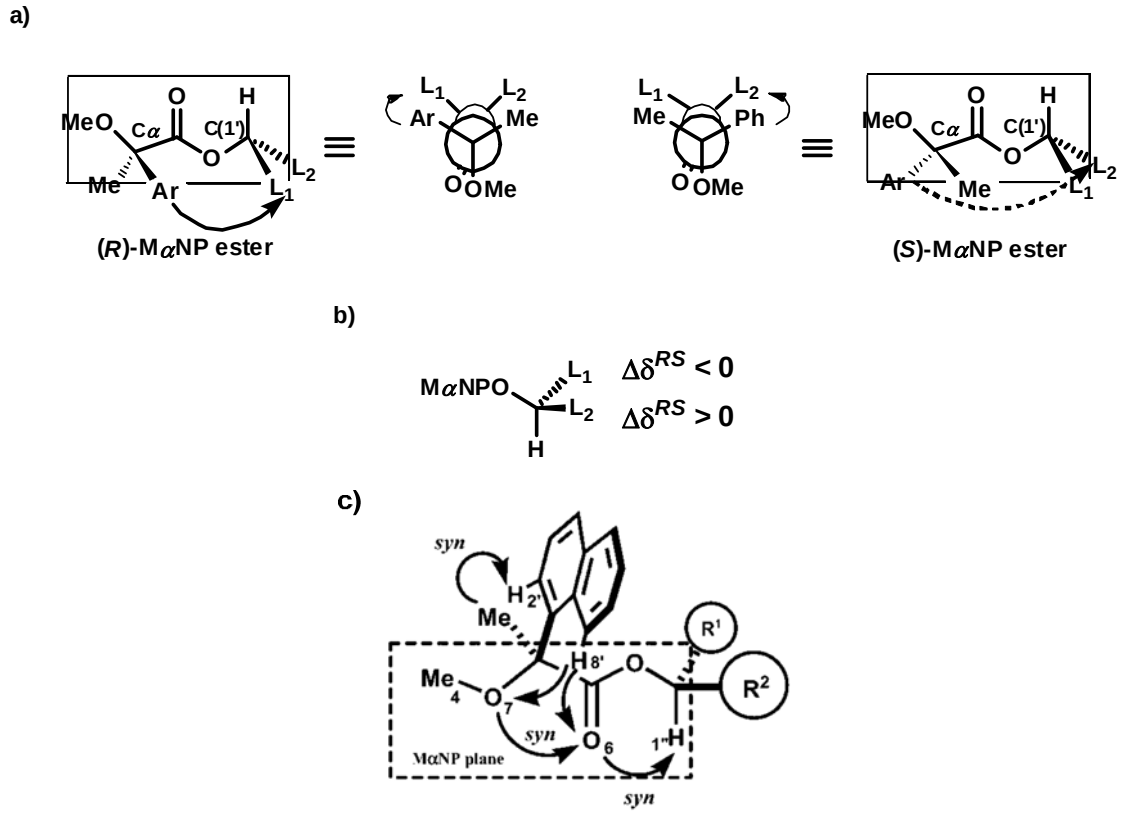


Figure 4. a) Model of methoxy-2-(1-naphthyl)propionic (MαNP) acid **2** for determining of the absolute configuration of secondary alcohols; b) the expected signs of $\Delta\delta^{RS}$; c) the proposed conformation of MαNP acid esters.

1.2.3. Mosher's acid

In 1991, Kakisawa *et al.*[7] reported the high-field NMR application of Mosher's method[5] to assign the absolute configurations of secondary alcohols. The model was proposed that, in solution, the carbinyl proton, ester carbonyl and the trifluoromethyl group of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) moiety lie in the same plane, called MTPA plane (Figure 5a). Similar to the *O*-methylmandelate or MPA's model, due to the diamagnetic effect of the benzene ring, L_2-protons NMR signals of the (*R*)-MTPA ester should appear upfield relative to those of the (*S*)-MTPA ester. The reverse should hold true for L_1-protons. Therefore, when $\Delta\delta^{SR} = \delta_S - \delta_R$, protons on the L_2's side of the MTPA plane must have negative values ($\Delta\delta^{SR}$ $L_2 < 0$) and protons on the L_1's side of the plane must have positive values ($\Delta\delta^{SR}$ $L_1 > 0$) (Figure 5b). Moreover, the values of $\Delta\delta$ must be proportional to the distance from the anisotropic group of MTPA moiety.

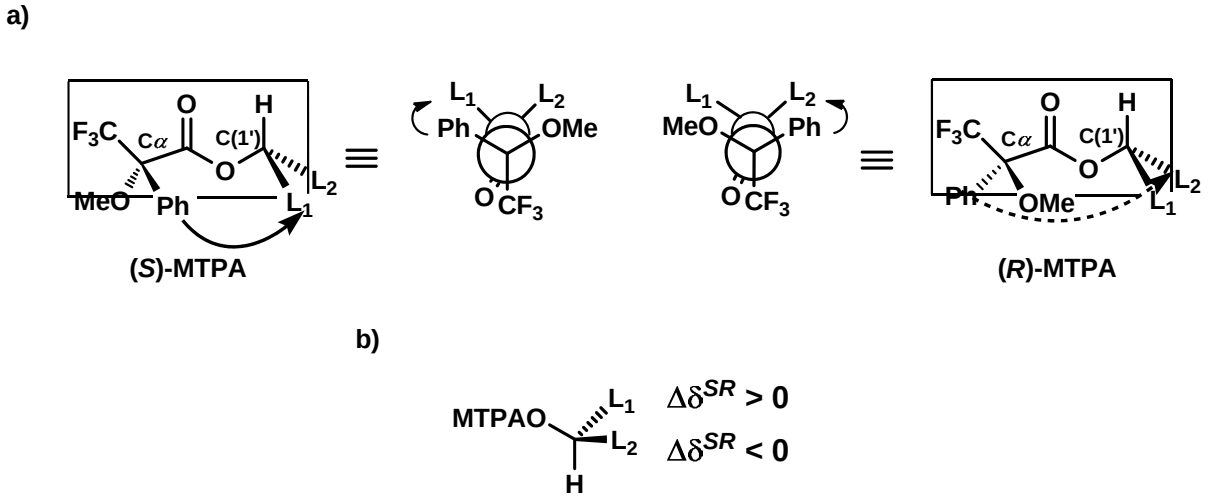


Figure 5. a) Models of MTPA-ester for the assignment of the absolute configuration by ^{1}H NMR and b) the expected sign of Δ^{SR}.

Although MTPA is widely used in determining the absolute configuration of chiral alcohols and amines, its application is sometimes restricted by the conformational limits imposed by the reagent.[8] Three conformations of similar population are presented in Figure 6.[7] Conformer *ap*$_1$ is the most stable conformer and has the CF_3 group anti-periplanar, with respect to the carbonyl group; its phenyl ring produces a deshielding effect on the substituent of the alcohol. The next conformer, in terms of energy, is *sp*$_1$; it has the CF_3 and carbonyl groups in a *syn*-periplanar disposition, as in the empirical Mosher's model, and its phenyl ring produces a shielding effect on the alcohol part. The third conformer is *sp*$_2$, and this conformer also has a *syn*-periplanar disposition that results in deshielding on the alcohol's substituent. The contribution of the three main conformers affects the chemical shift, resulting in the origin of the two most important limitations of this reagent: 1) the small $\Delta\delta^{SR}$ values and 2) irregular sign distributions.

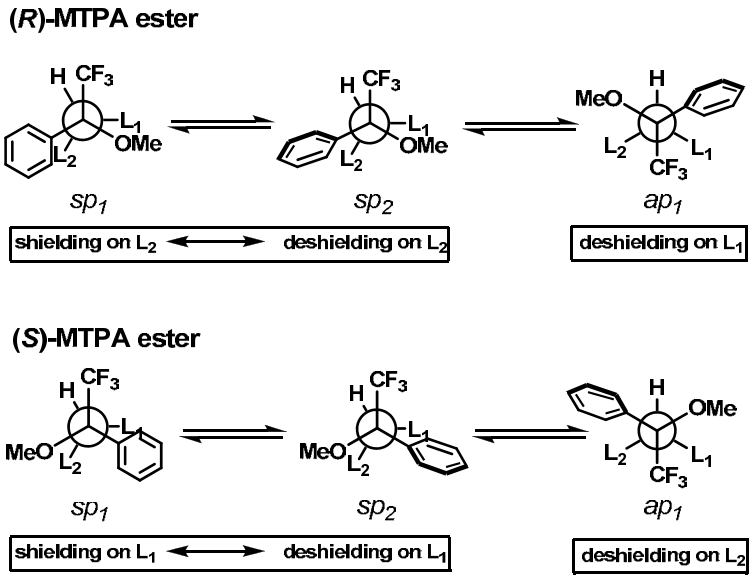


Figure 6. Shielding/deshielding effects in the three most representative conformers of the MTPA esters.

In contrast to the case of MTPA esters, the MPA esters present a simpler conformational composition with only two conformers (*sp*/*ap*) and a clearer preference for one of those (*sp*) (Figure 7), which, in turn, transmits a shielding effect to the substituents to give higher $\Delta\delta^{RS}$ values that are more reliable and with the same trend of sign distribution.

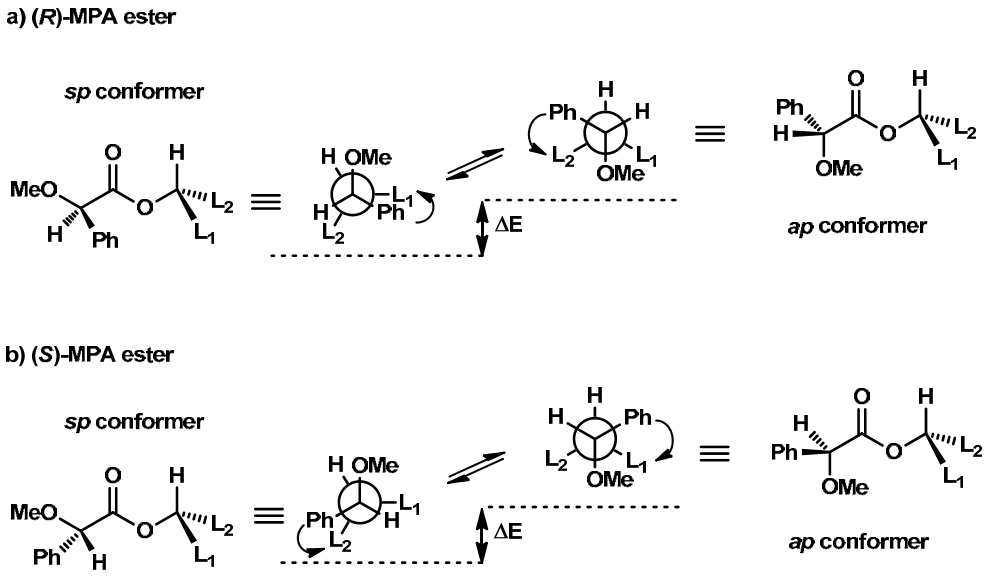
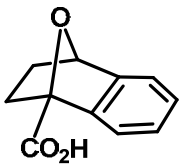


Figure 7. Conformational composition of MPA esters.

To overcome the ambiguousness of those methods concerning the flexible conformation of the anisotropic aromatic group, the design aimed to limit the rotational degree of freedom of the aromatic moiety was conducted through a new CDA for determination of the absolute configuration of chiral secondary alcohols, tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid (THENA) **4** (Figure 8). THENA has the analogous MPA plane as a part of rigid bicyclic system with the merit of chiral quaternary carbon atom to avoid racemization. Moreover, the availability of a proton in the structure which is not influenced by the diastereotopic environment should serve as an internal reference for spectra alignment. Such conformation constraint, along with an internal reference proton, should provide an unambiguous determination of the sign of NMR chemical shift difference, leading to an explicit assignment of the absolute configuration.

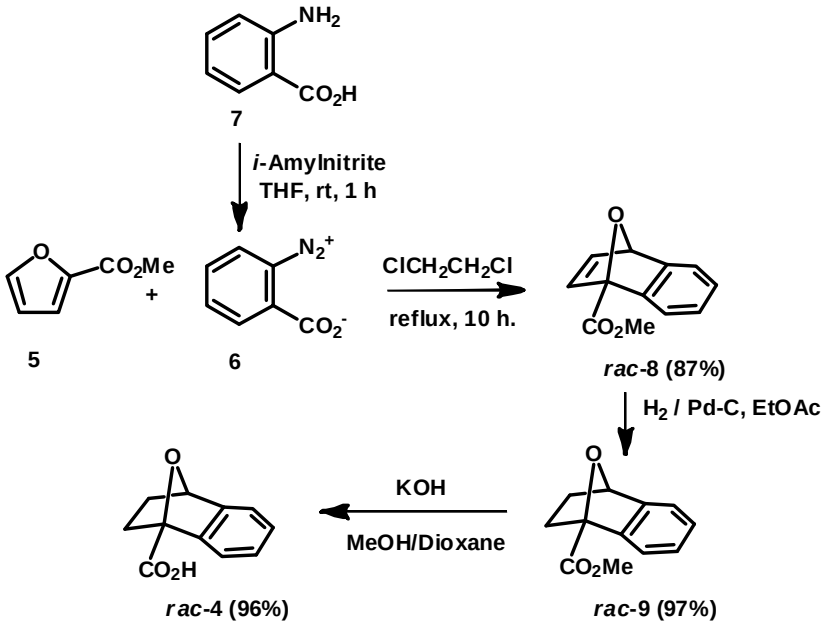


4

Figure 8. Tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid (THENA) **4**.

Results

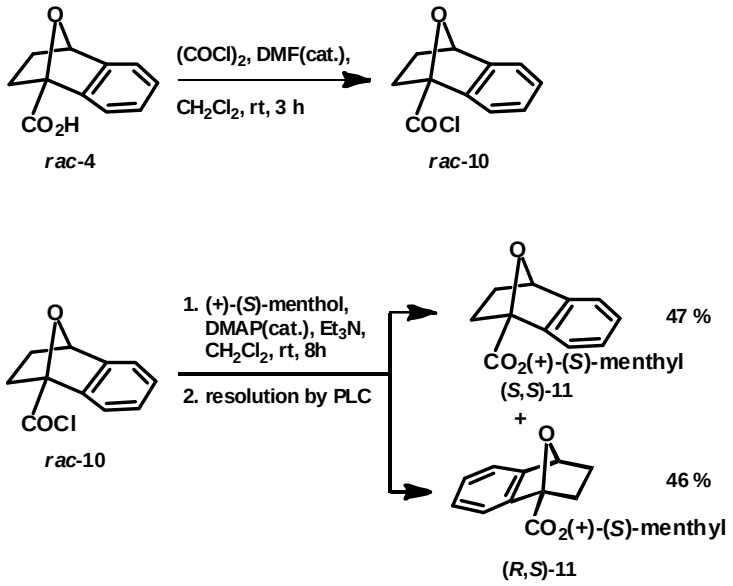
(±)-Tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid **4** could be synthesized from commercially available and low cost starting materials following a modified Best and Wege's method.[9] The key step for the preparation of **4** was the Diels-Alder reaction of methyl furan-2-carboxylate **5** with benzenediazonium-2-carboxylate **6**, generated from the reaction between anthranilic acid **7** and *iso*-amylnitrite, in boiling dichloroethane to yield (±)-methyl 1,4-dihydro-1,4-epoxynaphthalene-1-carboxylate **8**. The ester **8** was then subjected to hydrogenation and hydrolysis to yield (±)-methyl 1,2,3,4-tetrahydro-1,4-epoxynaphthalene-1-carboxylate **9** and (±)-tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid **4,** respectively. The overall synthetic scheme is shown in Scheme 1.



Scheme 1. Preparation of (±)-tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid ***rac* 4**.

The resolution of ***rac*-4** could be affected as follows. Treatment of ***rac*-4** with oxalyl chloride and DMF in dichloromethane at room temperature for 3 h gave acid chloride ***rac*-10** which was then reacted with *D*-(+)-menthol and DMAP (as a catalyst) and then triethylamine in dichloromethane to give the mixture of diasteromers **(*S*,*S*)-11** and **(*R*,*S*)-11** (the absolute configuration assignment derived from the X-ray data as discussed later). The mixture was separated by PLC (Hexane:EtOAc 98:2). The first-eluted ester **(*S*,*S*)-11** (47 %, $[\alpha]_D$ +43.54

(c = 3.85 w/v %, $CHCl_3$) and the second one **(*R*,*S*)-11** (46 %, $[\alpha]_D$ +22.11 (c = 3.99 w/v %, $CHCl_3$) were obtained (Scheme 2).



Scheme 2. Resolution of diastereomers **(*S*,*S*)-11** and **(*R*,*S*)-11**.

Because the conformation of the aromatic group was locked by the bicyclic structure, the substituent proton of *D*-(+)-menthol which eclipsed the phenyl ring would be affected by the deshielding anisotropic effect. Therefore, presumably, the *iso*-propyl group situated close to aromatic group should be lower-field shifted than the analogous protons in the other diastereomer. From the ^{1}H NMR spectra of diastereomeric esters **(*S*,*S*)-11** and **(*R*,*S*)-11** (Figure 10), it was found that the protons of *iso*-propyl group in ester **(*S*,*S*)-11** were lower-field shifted than the analogous protons in **(*R*,*S*)-11**. The key ^{1}H NMR chemical shifts of both diastereomers are listed in Figure 9.

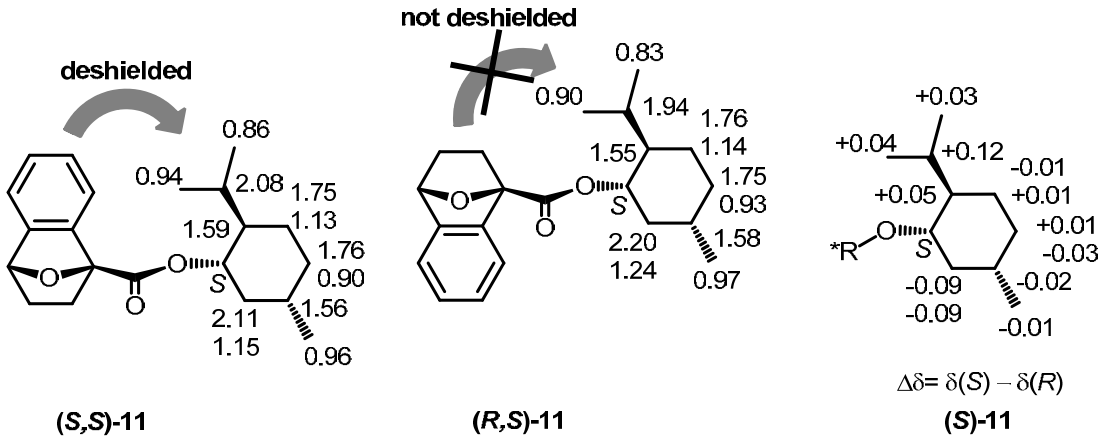


Figure 9. ^{1}H NMR chemical shift data of esters **(*S*,*S*)-11** and **(*R*,*S*)-11** and Δδ values.

Theoretically, THENA **4** should prefer the conformation that the C–O bond, the ester carbonyl and the C(1')H all are in the same plane like *sp* conformer of MPA (Figure 10). It could be postulated that, due to the electronic effect, the σ–π* interaction between the electron rich sigma C–C bond, rather than the C–O bond, and the electron poor π* orbital of the carbonyl carbon stabilize this conformation.

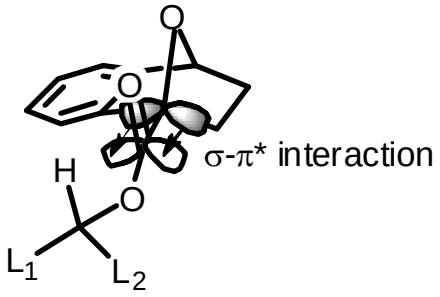


Figure 10. The stable conformation of THENA ester.

The X-ray data (Figure 11)[11] revealed the structure of diastereomeric ester **(*R*,*S*)-11**. The absolute configuration of the THENA moiety could be assigned as '*R*'. The X-ray structure also showed the analogous MPA plan (dotted plane), confirming the preferred confirmation of the THENA moiety as the *syn*-periplanar conformation.

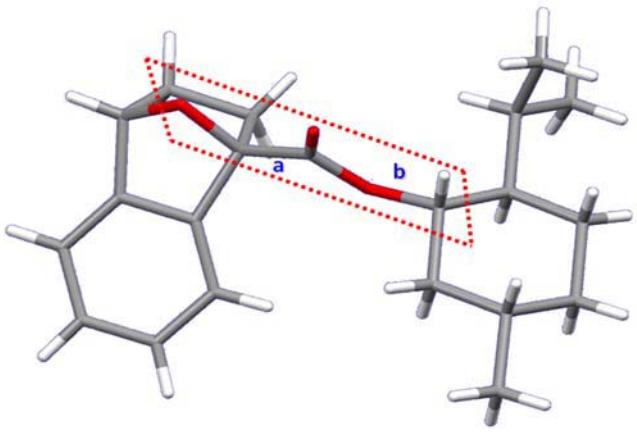


Figure 11. X-ray structure of compound **(*R*,*S*)-11** ; angle **a** is 10° and **b** is 20°.

Finally, (+)-2,3-dihydro-1,4-epoxynaphthalene-1(2H)-carboxylic acid **(*S*)-(+)-4** could be obtained by the hydrolysis of **(*S*,*S*)-11** and (–)-2,3-dihydro-1,4-epoxynaphthalene-1(2H)-carboxylic acid **(*R*)-(–)-4** could be obtained by the hydrolysis of **(*R*,*S*)-11**.

The model for determination of the absolute configuration of chiral secondary alcohols

Due to the diamagnetic deshielding effect of the benzene ring, L^1 's ^{1}H NMR signals of the (*R*)-acid ester should appear downfield relative to those of the (*S*)-acid ester. The reverse should hold true for L^2 's H. Therefore, a model for determining the absolute configuration of chiral secondary alcohols is presented in Figure 12. When $\Delta\delta^{SR} = \delta_S - \delta_R$, protons on the right side of the model should have positive values ($\Delta\delta^{SR} > 0$) and protons on the left side of the model should have negative values ($\Delta\delta^{SR} < 0$). The absolute values of $\Delta\delta$ will be proportional to the distance of the substituents from the aromatic moiety of the CDA. When these conditions were satisfied, the model in Figure 12 would indicate the correct absolute configuration of the compound.

Importantly, the presence of H_{ref} (Figure 10) which is not influenced by the diasteretopic environment should serve as an internal reference for spectra alignment.

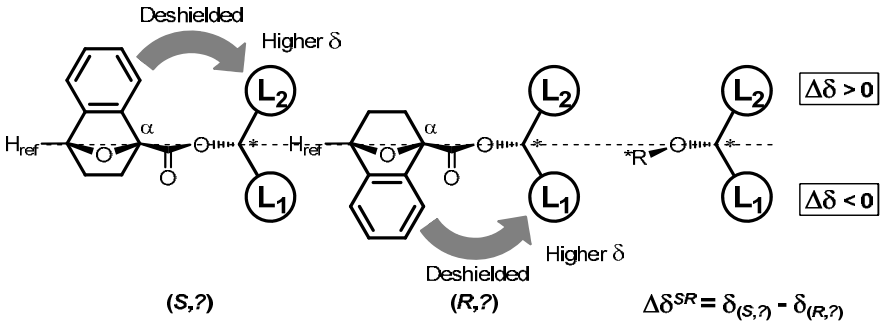


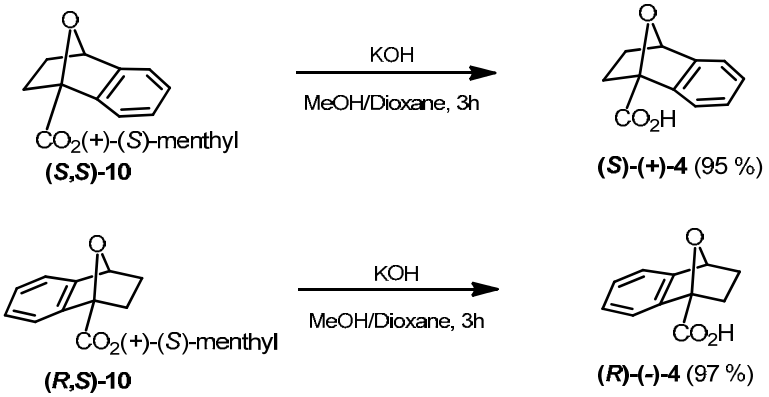
Figure 12. Model for the absolute configuration assignment of chiral secondary alcohols.

Based on the anisotropic data and the proposed model, the chirality of menthol could be reconstructed and was identical to the known absolute configuration of *D*-(+)-menthol. This result implied that each enantiomer of THENA **4** could be used for esterification of chiral alcohol, as a chiral auxiliary, to determine the absolute configuration of alcohols by using ^{1}H NMR anisotropic data.

*The validation of THENA **4** with a variety of chiral secondary alcohols*

The validation of THENA **4** as a chiral derivatizing agent with other cases of chiral secondary alcohols must be performed to assure its reliability.

Firstly, to recover the optically active acids **(*S*)-(+)-4** and **(*R*)-(–)-4**, compounds **(*S*,*S*)-11** and **(*R*,*S*)-11** were subjected to hydrolysis with KOH in 1:1 MeOH : dioxane at room temperature for 3 h to give **(*S*)-(+)-4** and **(*R*)-(–)-4** in 95% yield and 97% yields, respectively (Scheme 3).



Scheme 3. Preparation of optically active acids (*S*)-(+)-THENA **4** and (*R*)-(–)-THENA **4**.

Then, optically active acids **(*S*)-(+)-4** and **(*R*)-(–)-4** were tested with a varieties of chiral secondary alcohols **12**–**21** of which absolute configuration has already known, as shown in Figure 13.

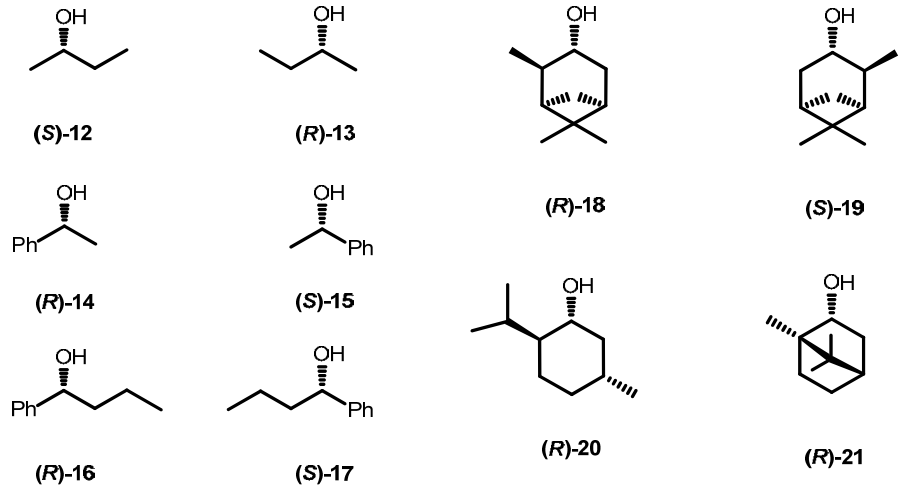
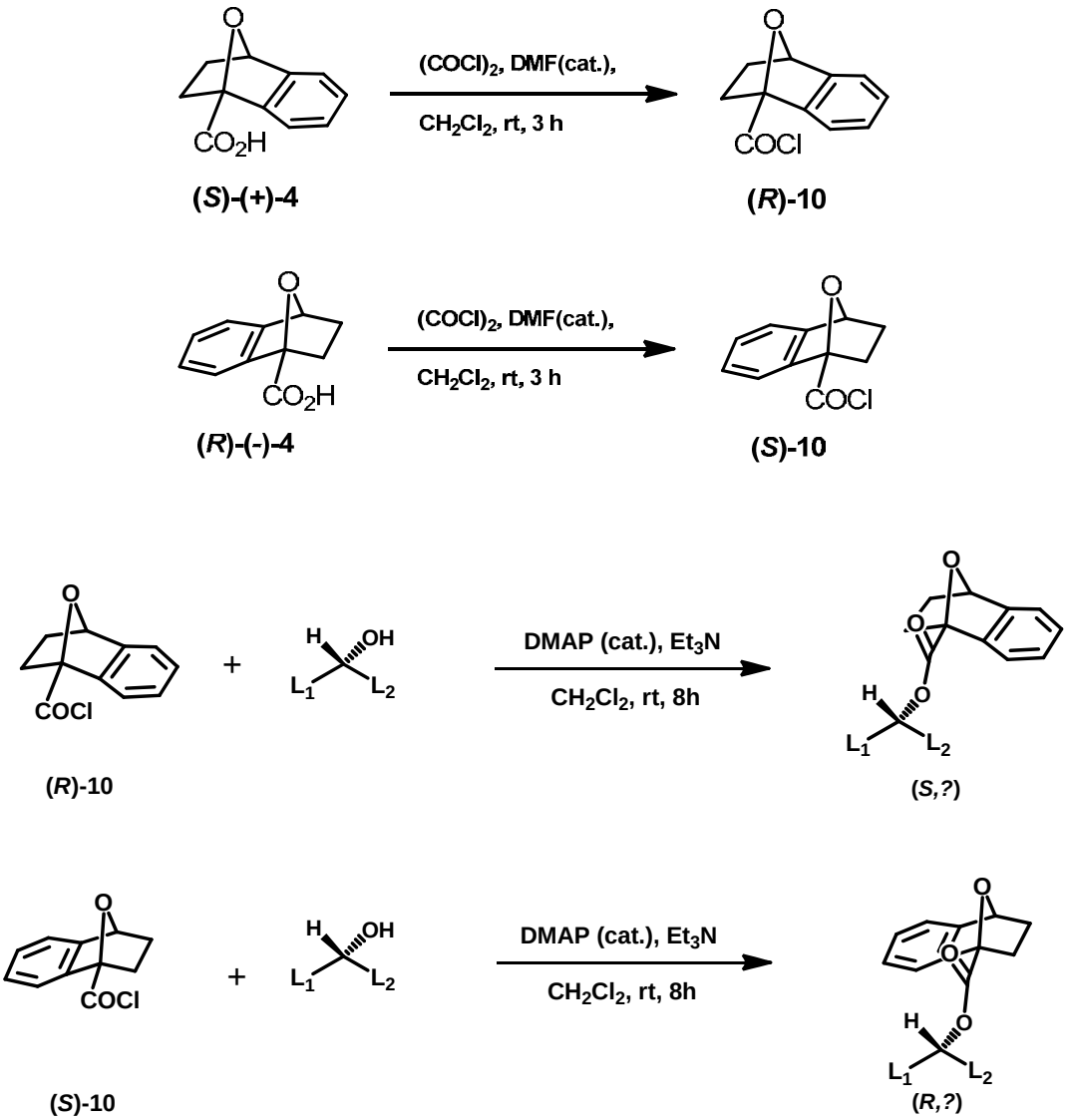
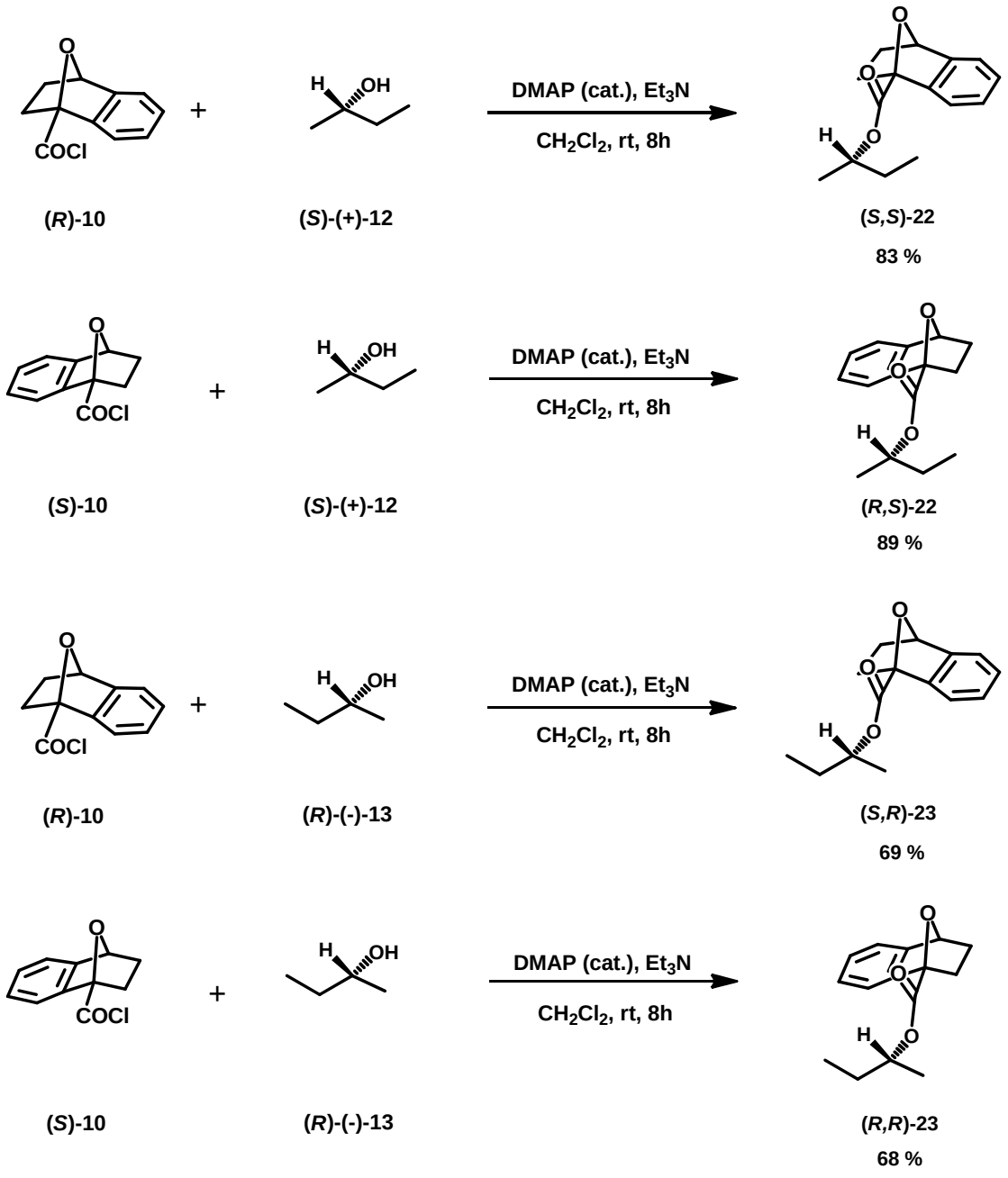


Figure 13. The optically chiral alcohols which are used for tested the anisotropy effect of acid.

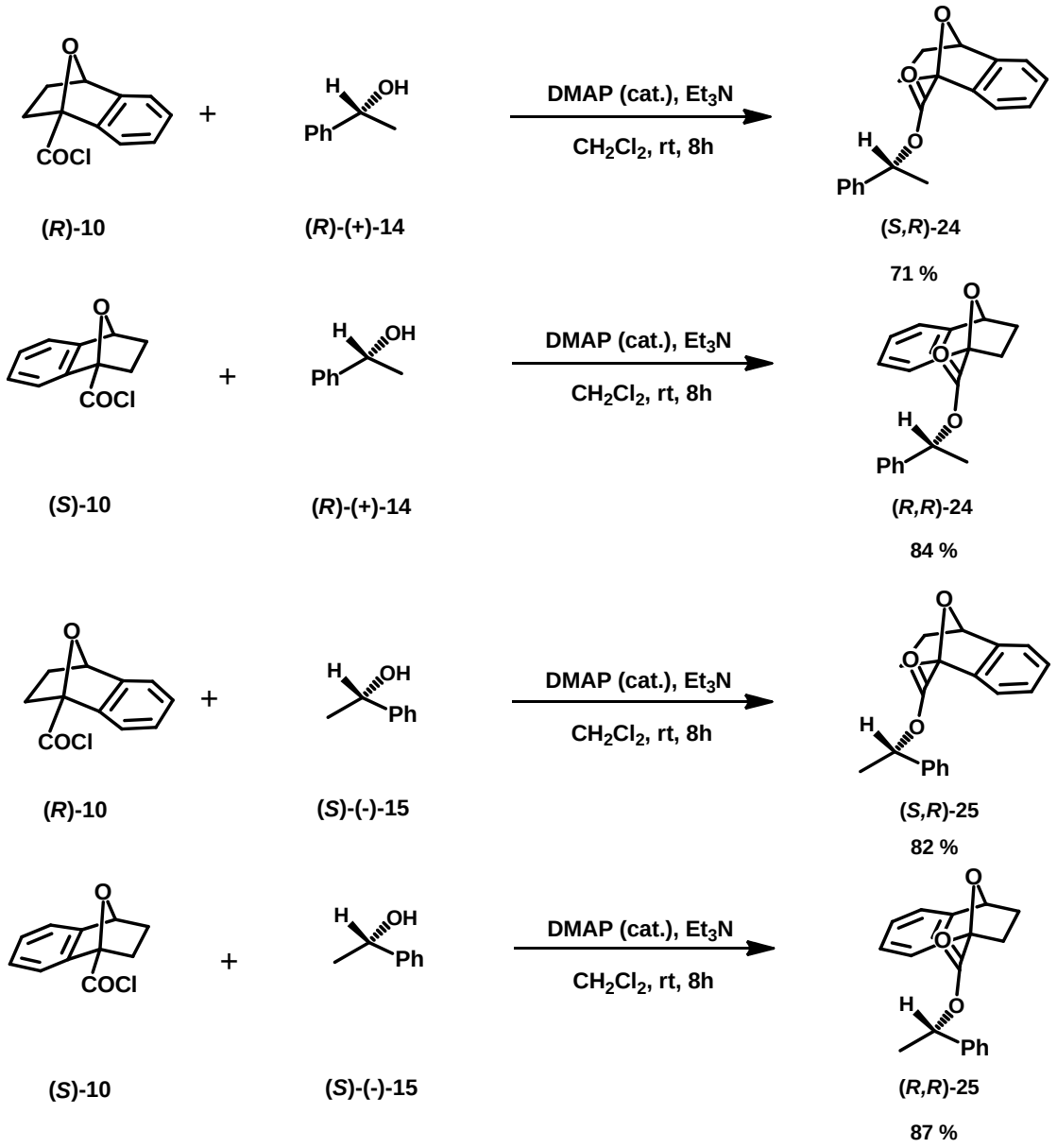
Diastereomeric esters of **(*S*)-(+)-4** and **(*R*)-(–)-4** with the optically active alcohols could be prepared as follows. Treatment of optically active acids **(*S*)-(+)-4** and **(*R*)-(–)-4** with oxalyl chloride and DMF (as a catalyst) at room temperature in dichloromethane generated acid chlorides **(*R*)-10** and **(*S*)-10**, respectively. Then, in a separate reaction, both acid chlorides, **(*R*)-10** and **(*S*)-10**, were reacted with the alcohols with DMAP (as a catalyst) at room temperature in CH_2Cl_2 and then triethylamine to give the corresponding diastereomeric pairs which were separated by PLC (Hexane:EtOAc 95:5–90:10) (Scheme 4).



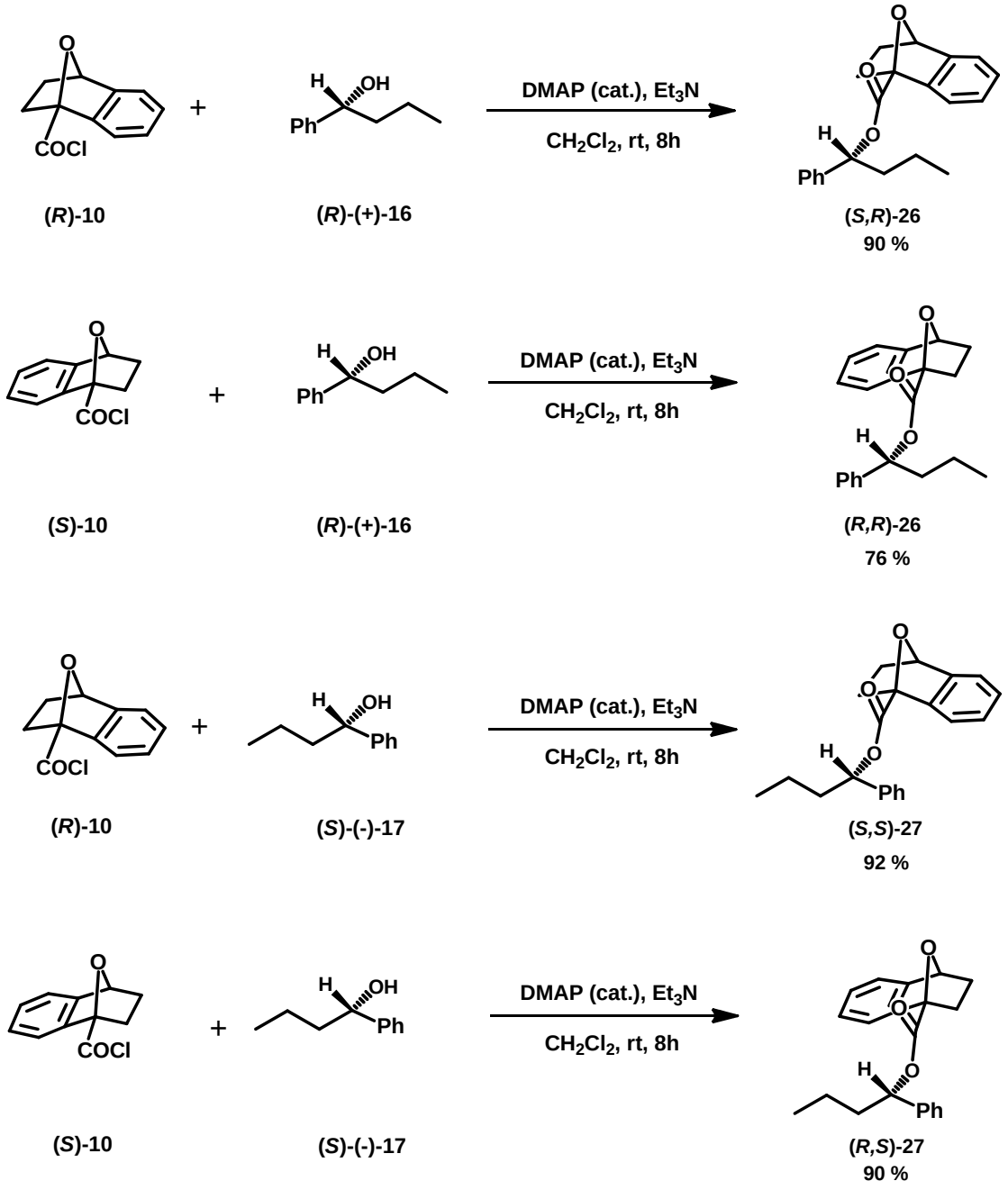
Scheme 4. Preparation of diastereomeric esters of **(*S*)-(+)-4** and **(*R*)-(–)-4** with the optically active alcohols.



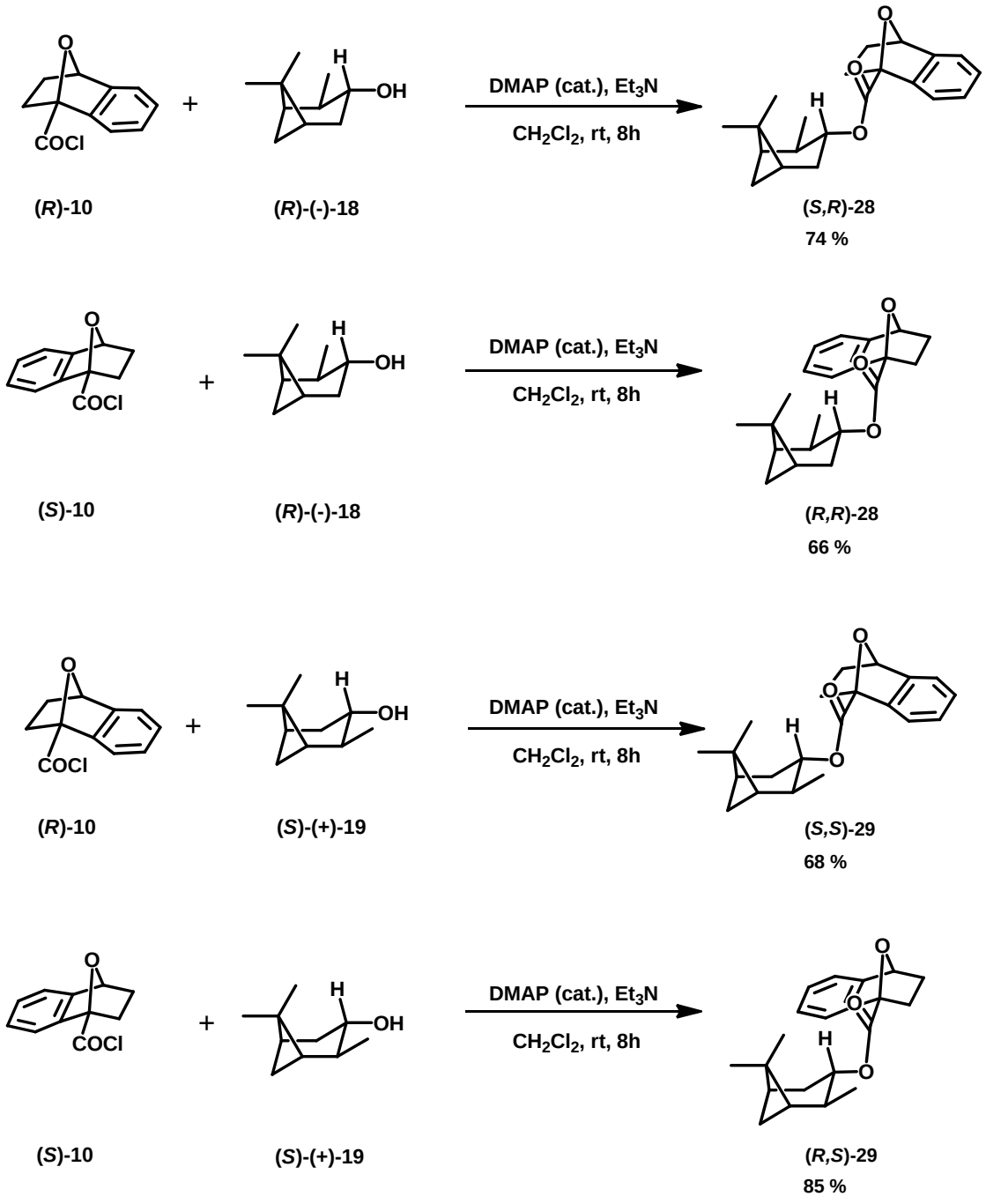
Scheme 4. Preparation of diastereomeric esters of **(*S*)-(+)-4** and **(*R*)-(–)-4** with the optically active alcohols (continued).



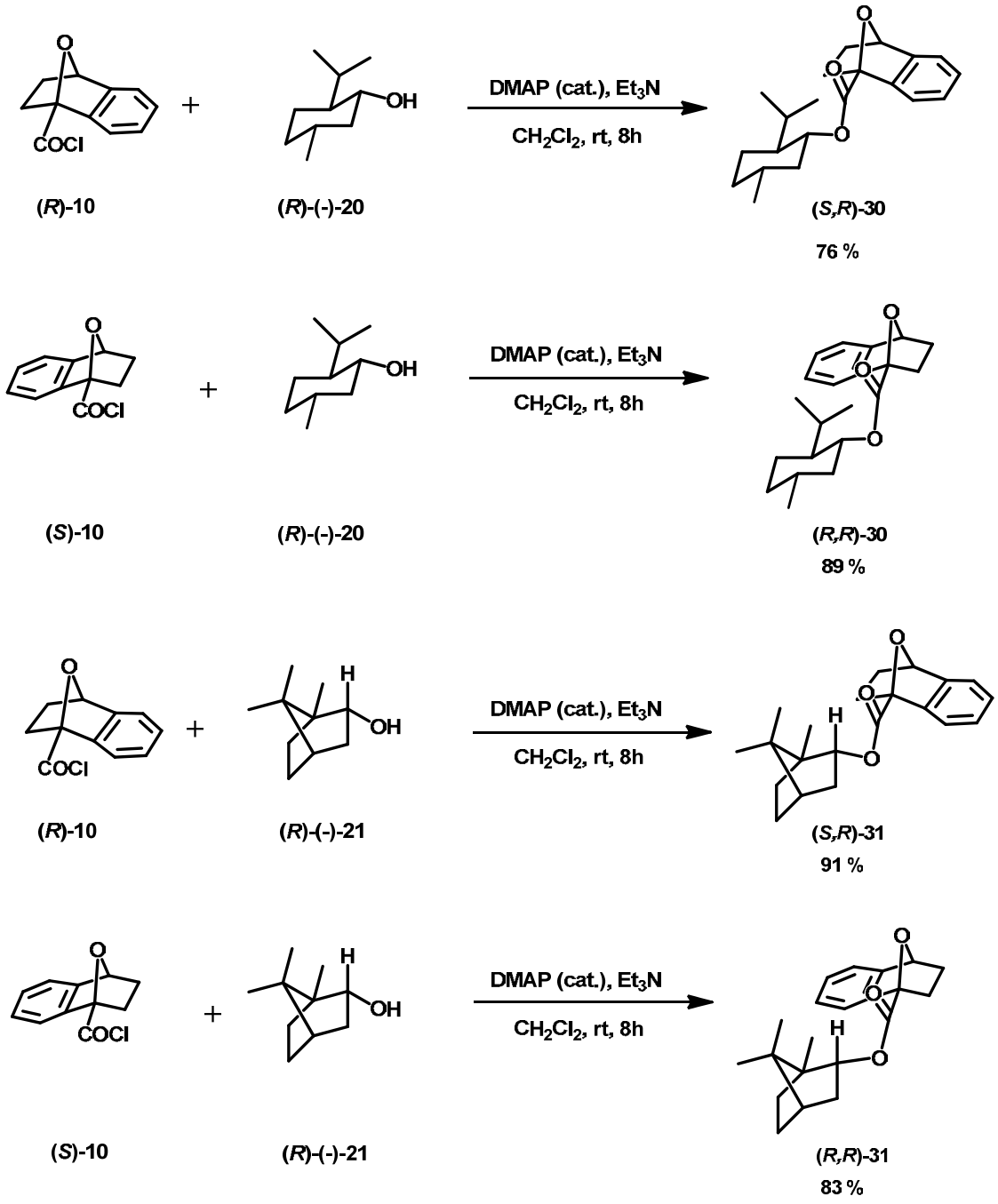
Scheme 4. Preparation of diastereomeric esters of **(*S*)-(+)-4** and **(*R*)-(–)-4** with the optically active alcohols (continued).



Scheme 4. Preparation of diastereomeric esters of **(*S*)-(+)-4** and **(*R*)-(–)-4** with the optically active alcohols (continued).



Scheme 4. Preparation of diastereomeric esters of **(*S*)-(+)-4** and **(*R*)-(–)-4** with the optically active alcohols (continued).



Scheme 4. Preparation of diastereomeric esters of **(*S*)-(+)-4** and **(*R*)-(–)-4** with the optically active alcohols (continued).

The anisotropic effect was observed in all diastereomeric esters **22**–**31**. The chemical shift data of the diastereomeric esters **11**, **22**–**31** were listed in Figure 14 together with the Δδ values (ppm): $\Delta\delta^{SR} = \delta(S) - \delta(R)$ and the results of the Δδ values were concluded in Figure 14. It was found that protons of the alkyl group which were close to aromatic side of acid were downfield shifted by the anisotropy effect of aromatic moiety while the protons of

the alkyl group which were far away from the aromatic ring were not affected. The absolute configuration derived from the experiments all matched well with the known values.

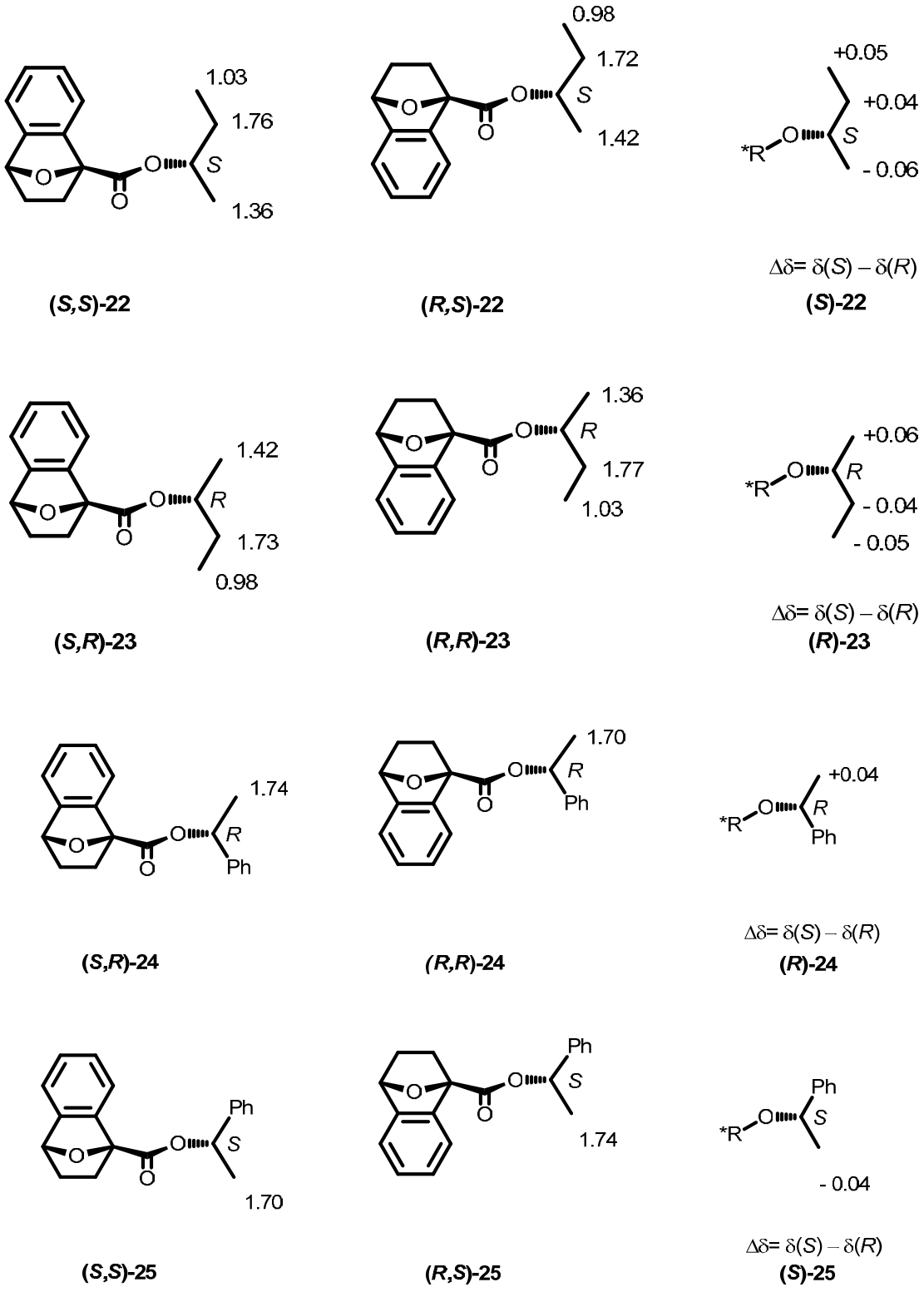


Figure 14. ^{1}H NMR chemical shift data of esters **11**, **22**–**31** and $\Delta\delta^{SR}$ values.

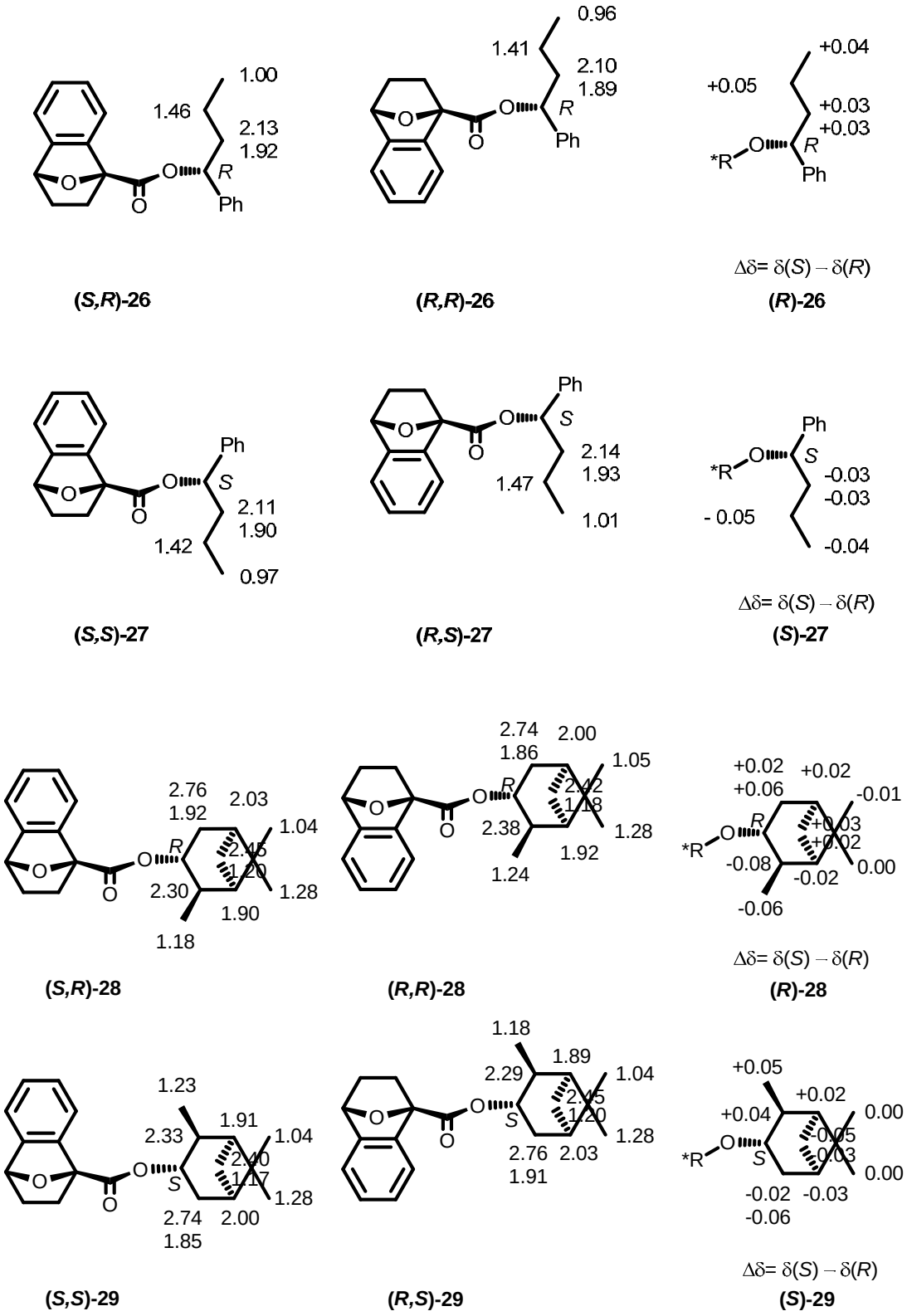


Figure 14. ^{1}H NMR chemical shift data of esters **11**, **22**–**31** and $\Delta\delta^{SR}$ values (continued).

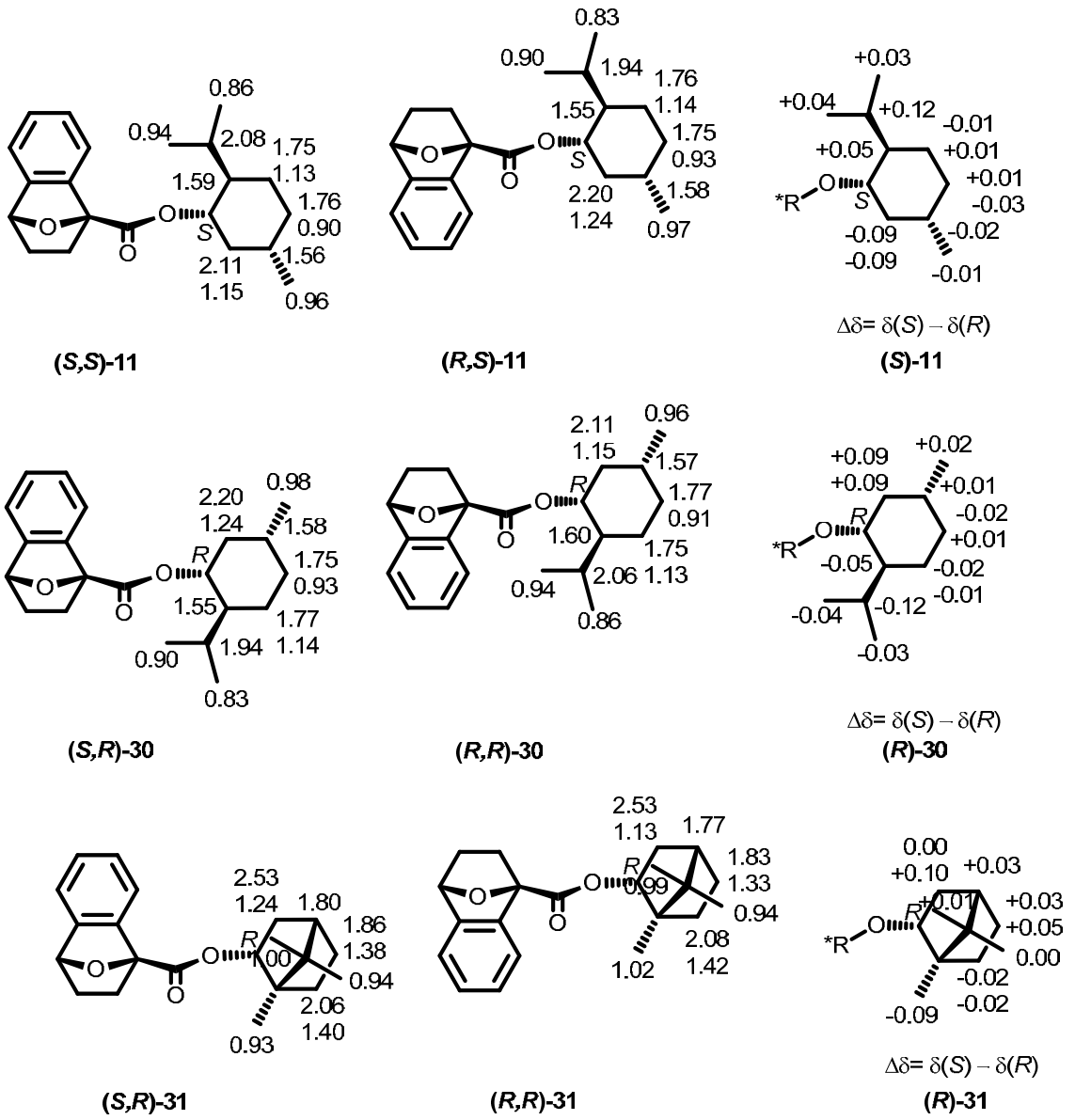


Figure 14. ^{1}H NMR chemical shift data of esters **11**, **22–31** and $\Delta\delta^{SR}$ values (continued).

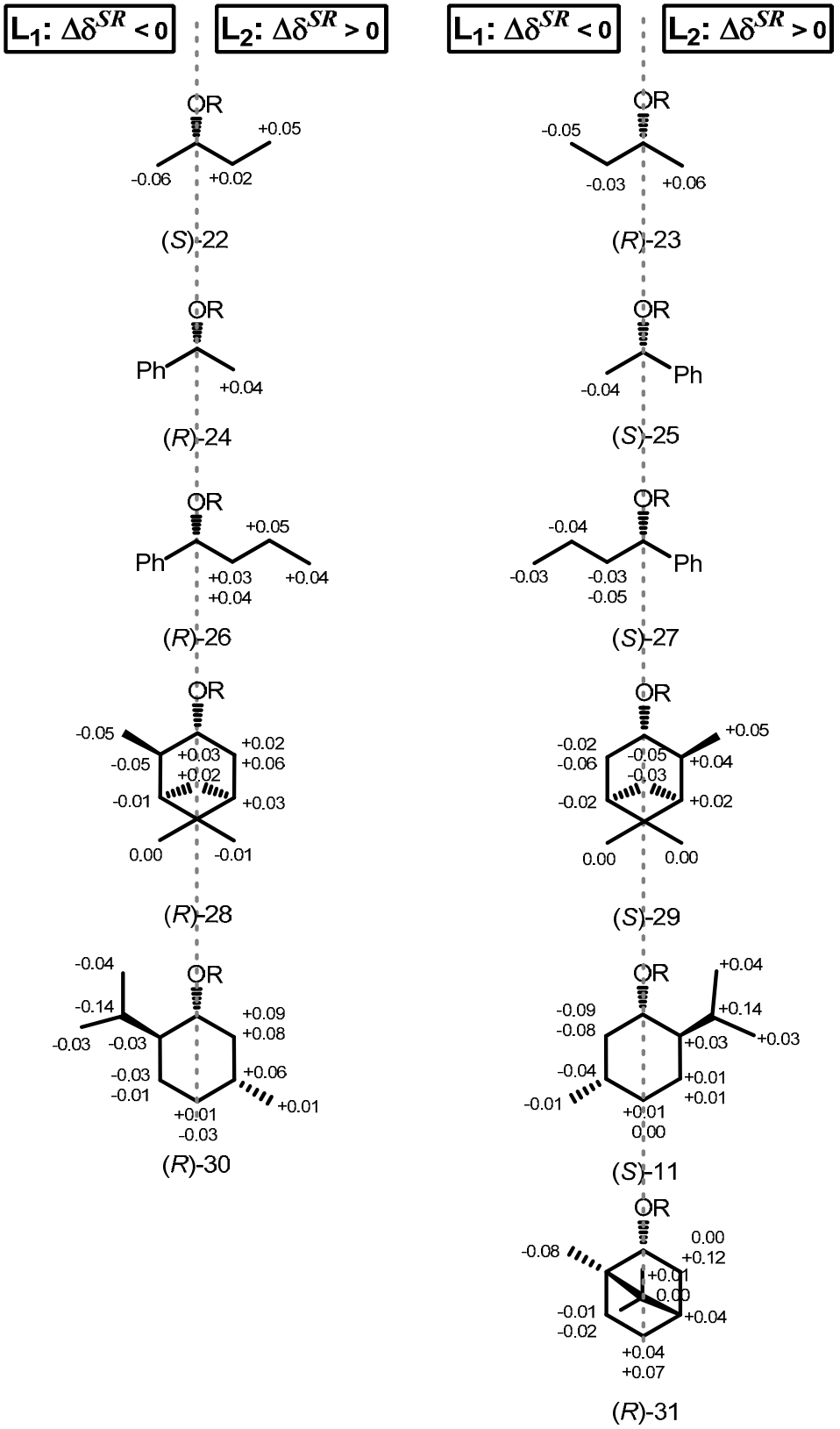
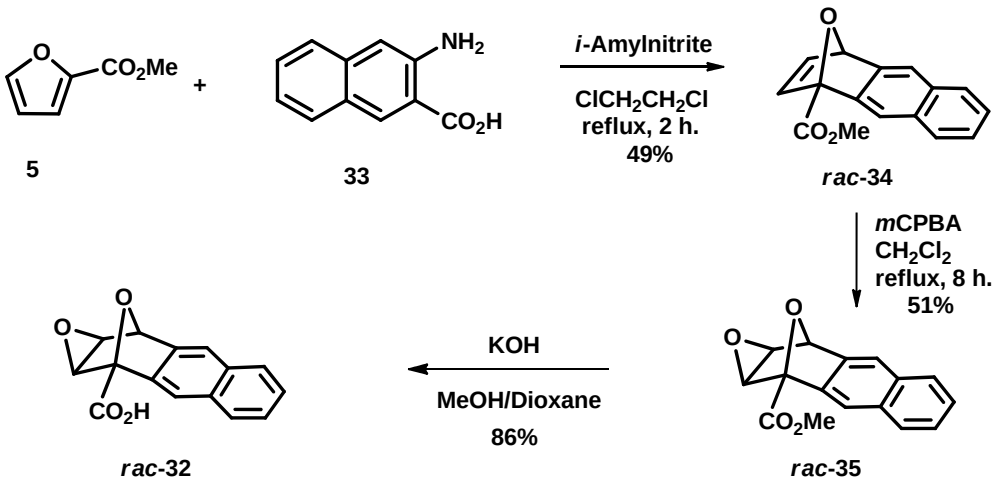


Figure 15. The chemical shift difference values ($\Delta\delta^{SR}$) of tested chiral alcohols with known absolute configuration (dashed line represents the plane).

Further study to improve the effectiveness and convenience in using the bicyclic acid as a chiral derivatizing agent was conducted. The aim was to extend the aromatic moiety to enhance the deshielding effect which would increase the chemical shift difference. Moreover, the methylene group of which the ^{1}H NMR signals were very complicated should be modified to appear with less complicated signals and in the region that did not interfere with other signals.

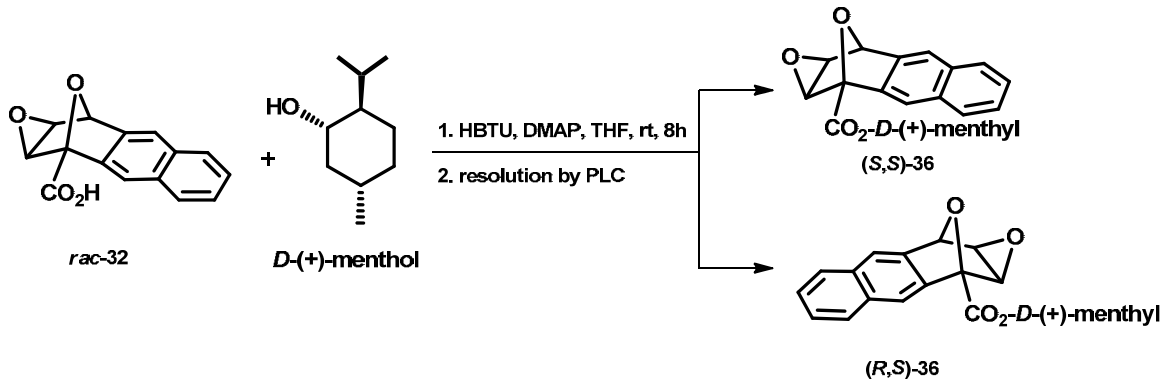
The α-alkoxa bicyclic acid **32** was then proposed. The naphthalene moiety should provide an extended anisotropic effect while the epoxide should provide a less complicated signal as well as its appearance at lower field which did not interfere much with aliphatic signals. The synthesis of **32** could be accomplished as described in Scheme 5. The Diels-Alder reaction of methyl furan-2-carboxylate **6** with naphthyne, generated from 3-amino-2-naphthoic acid **33** and *i*so-pentylnitrite, provided (±)-methyl 1,4-dihydro-1,4-epoxyanthracene-1-carboxylate ***rac*-34**. The adduct ***rac*-34** was epoxidized to yield compound ***rac*-35**. Then, compound ***rac*-35** was further subjected to hydrolysis to yield (±)-1*a*,2,9,9*a*-tetrahydro-2,9-epoxyanthra[2,3-*b*]oxirene-2-carboxylic acid (±)**-32**.



Scheme 5. Preparation of (±)-1*a*,2,9,9*a*-tetrahydro-2,9-epoxyanthra[2,3-*b*]oxirene-2 carboxylic acid ***rac*-32**.

Resolution of ***rac*-32** could be affected as follows. Treatment of ***rac*-32** with *D*-(+)-menthol and DMAP at room temperature in CH_2Cl_2 and then reacted with HBTU, following Pon's method,[12] gave diasteromers **(*S,S*)-36** and **(*R,S*)-36**. The mixture was separated by PLC

(Hexane:EtOAc 91:9). The first-eluted ester **(*S*,*S*)-36** and the second one **(*R*,*S*)-36** were obtained, respectively (Scheme 6).



Scheme 6. Preparation of diastereomers **(*S*,*S*)-36** and **(*R*,*S*)-36**.

Similar to the benzene analog, it was proposed that the σ–π^* interaction stabilized the conformation of the acid **32** in which the C−O bond, the ester carbonyl and C(1')H are situated in the same plane like *sp* conformer of MPA (Figure 16).

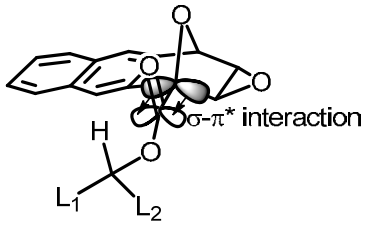


Figure 16. The stable conformation of the ester of compound **5**.

The anisotropic effect in the ^{1}H NMR spectra of diastereomeric esters **(*S*,*S*)-36** and **(*R*,*S*)-36** (Figure 17) showed that the protons of *iso*-propyl group in ester **(*S*,*S*)-36** were lower-field shifted than the analogous protons in **(*R*,*S*)-36**. As a result, the conformation of ester **(*S*,*S*)-36** should align in the way that was *iso*-propyl group situated close to the aromatic group. On the other hand, the *iso*-propyl group of ester **(*R*,*S*)-36** should place away from the aromatic group.

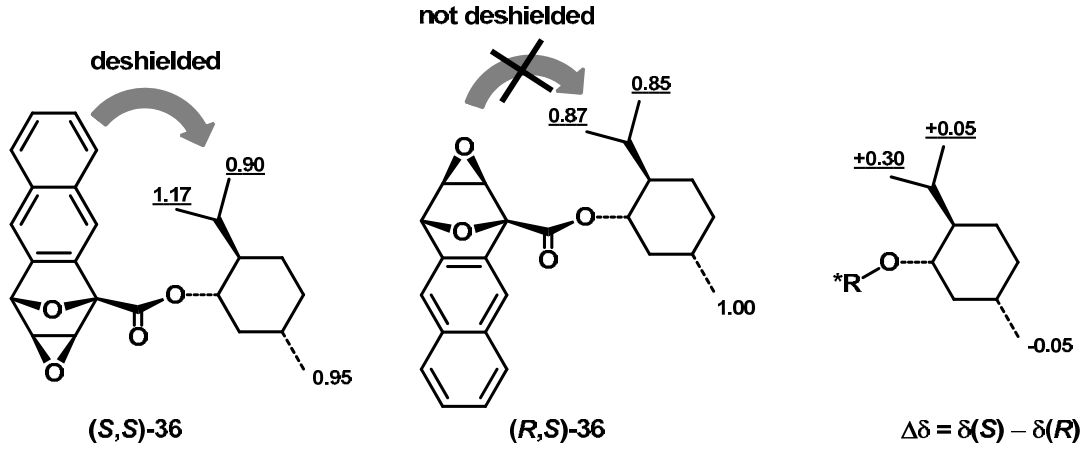
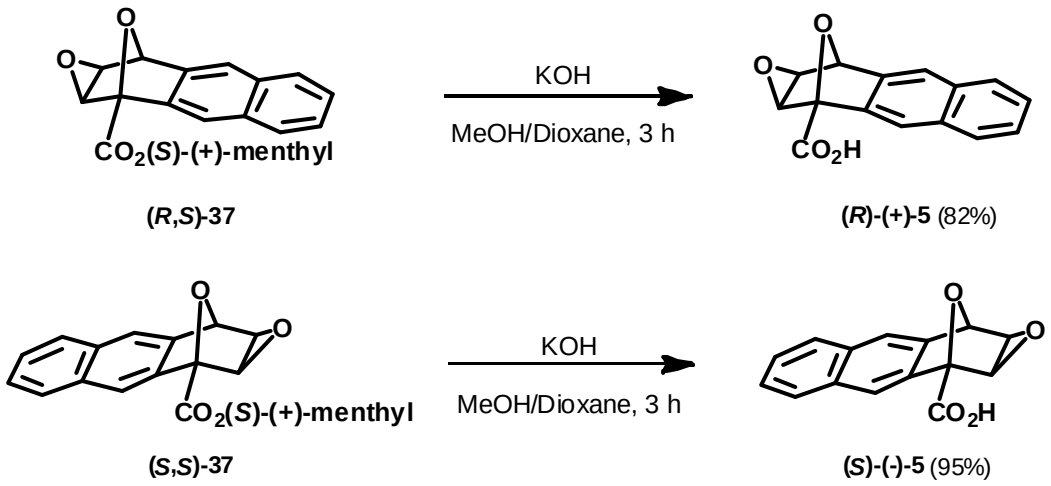


Figure 17. ^{1}H NMR chemical shift data of esters **(*S*,*S*)-36** and **(*R*,*S*)-36** and Δδ values.

Finally, (+)-2,3-dihydro-1,4-epoxynaphthalene-1(2H)-carboxylic acid **(*S*)-(+)-32** could be obtained from the hydrolysis of **(*S*,*S*)-36** while (–)-2,3-dihydro-1,4-epoxynaphthalene-1(2H)-carboxylic acid **(*R*)-(–)-32** could be obtained from the hydrolysis of **(*R*,*S*)-36**.

*The validation of acid **5** with a variety of chiral secondary alcohols*

To obtain optically active acid **(*R*)-(+)-5** and **(*S*)-(–)-5**, compound **(*R*,*S*)-37** and **(*S*,*S*)-37** were subjected to hydrolysis with KOH in 1:1 MeOH:Dioxane at room temperature for 3 h to give **(*R*)-(+)-5** and **(*S*)-(–)-5** in 82% and 95% yields, respectively (Scheme 7).



Scheme 7. Preparation of optically active acids **(*R*)-(+)-5** and **(*S*)-(–)-5**.

Then, optically active acids **(*R*)-(+)-5** and **(*S*)-(–)-5** would be tested with a variety of chiral secondary alcohols, **(*S*)-(+)-14, (*R*)-(–)-15, (*S*)-(–)-19, (*R*)-(–)-22** and **(*R*)-(–)-23** of which the absolute configurations were already known, as shown in Figure 18.

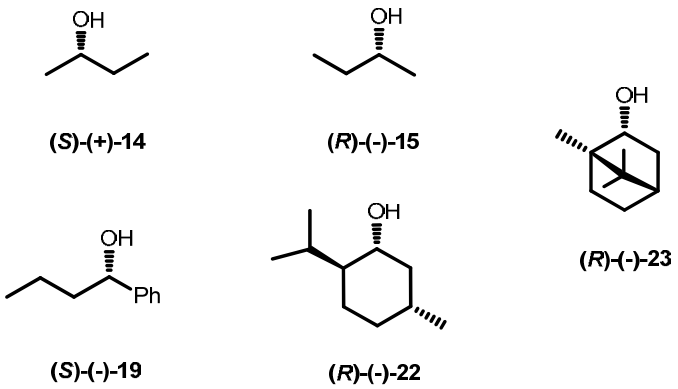
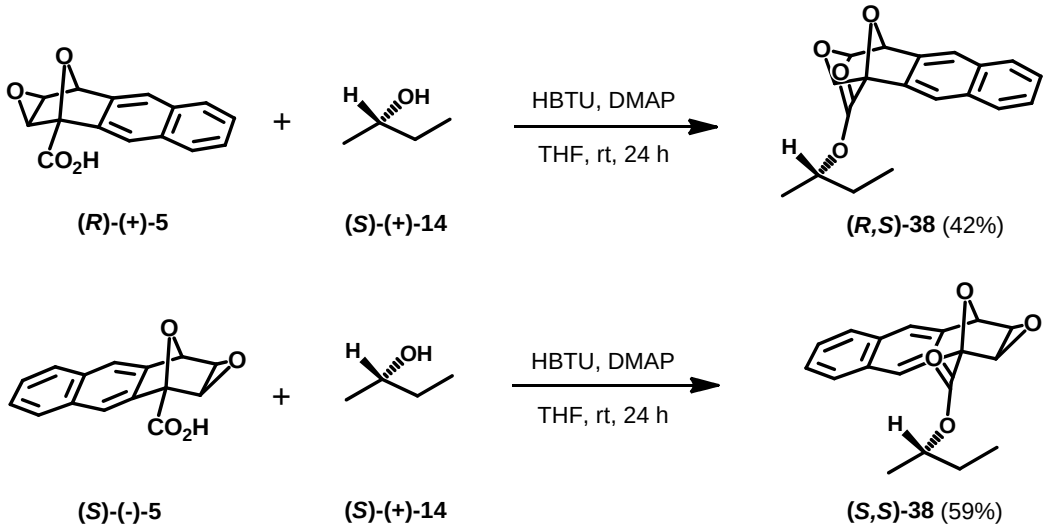
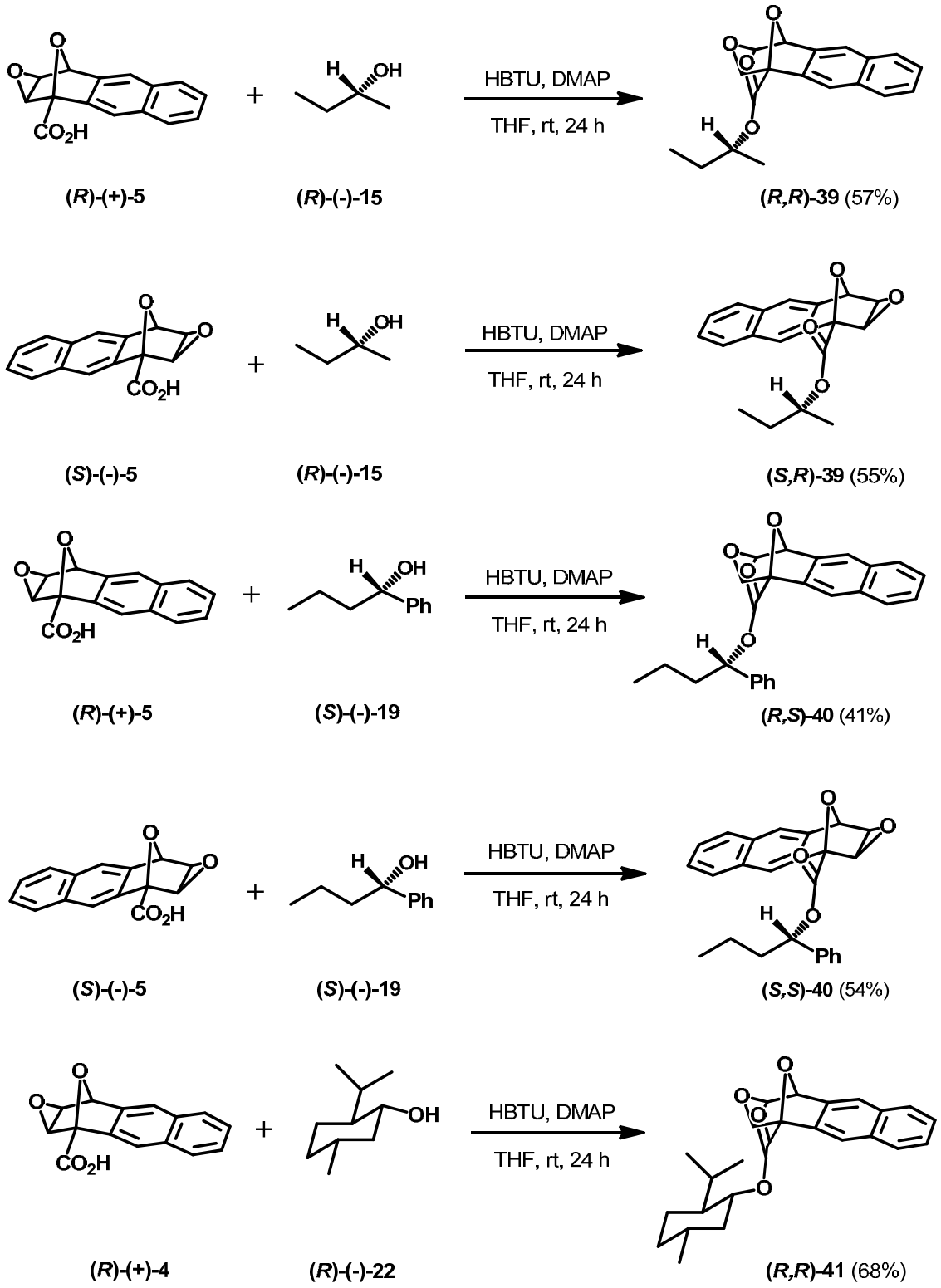


Figure 18. The optically chiral alcohols used for tested the anisotropic effect of acid **5**.

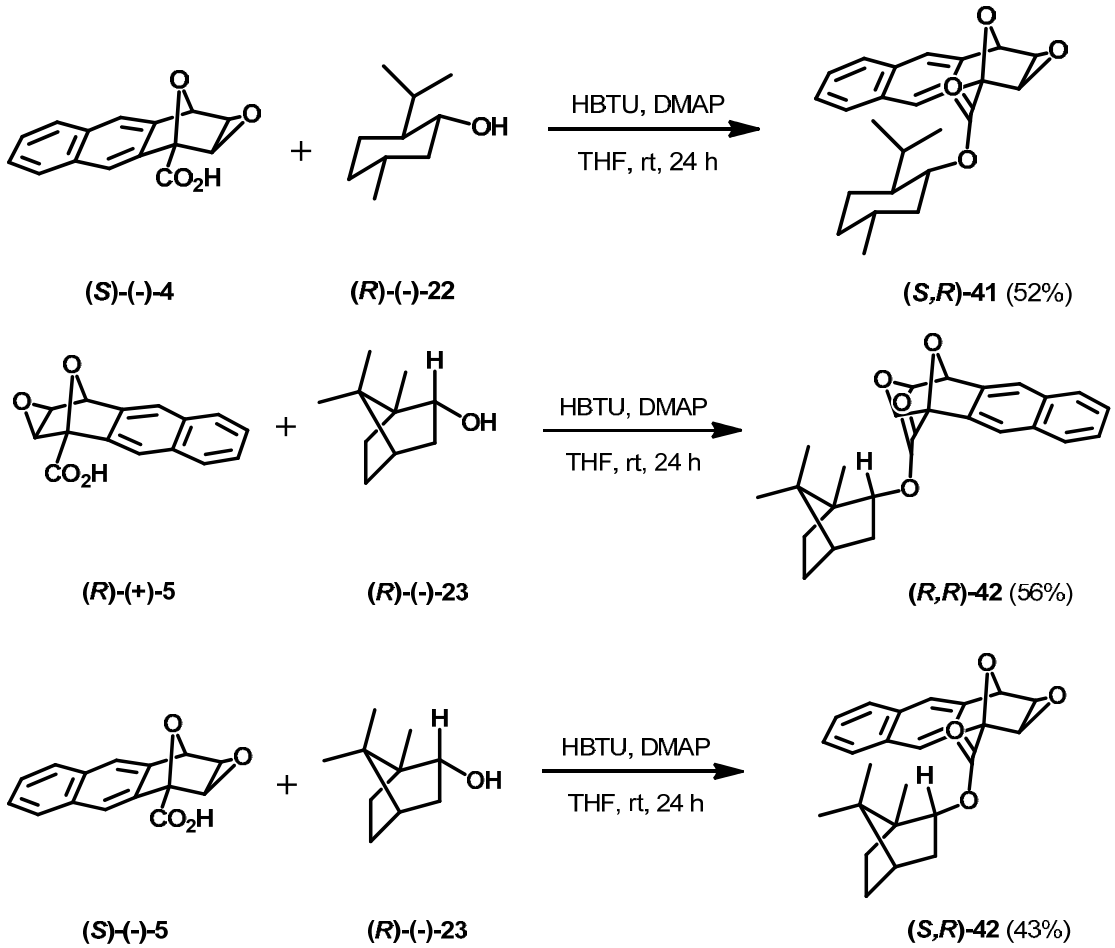
Diastereomeric esters of **(*R*)-(+)-5** and **(*S*)-(–)-5** with the optically active alcohols could be prepared as follows. Treatment of the optically active acids **(*R*)-(+)-5** and **(*S*)-(–)-5** separately with the optically active alcohol of interest and DMAP at room temperature in CH_2Cl_2 and then HBTU gave the corresponding diastereomeric pairs. The products were separated by PLC (Hexane:EtOAc = 95:5–90:10) (Scheme 8).



Scheme 8. Preparation of diastereomeric esters of optically active acid **5** with the tested alcohols.



Scheme 8. Preparation of diastereomeric esters of optically active acid **5** with the tested alcohols (continued).



Scheme 8. Preparation of diastereomeric esters of optically active acid **5** with the tested alcohols (continued).

The chemical shift difference data of the diastereomeric esters of the optically active acid **5** with the tested alcohols were listed in Figure 19, and the $\Delta\delta^{RS}$ values (ppm): $\Delta\delta^{RS} = \delta(R) - \delta(S)$ are summarized in Figure 20. Similar to the benzene derivative, it was found that protons of the alkyl group which were close to the aromatic side of the acid residue were downfield shifted by the anisotropic effect while the protons of the alkyl group which were far away from aromatic ring of the acid were not shifted. The resulting signs of $\Delta\delta^{RS}$ values correlated with the model could determine the absolute configuration and all found to be identical to the known configuration of the tested alcohols.

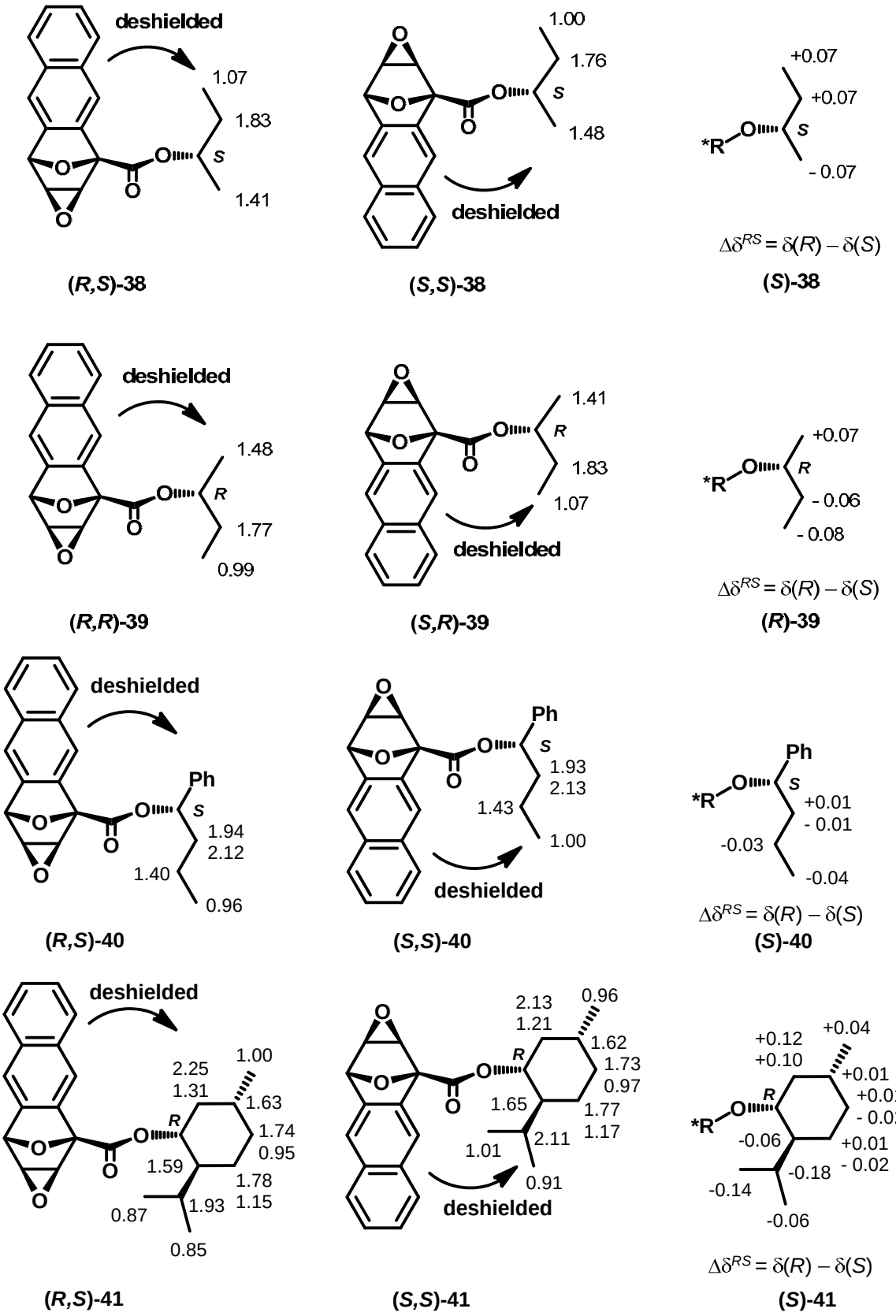


Figure 19. ^{1}H NMR chemical shift data of the esters of optically active acid **5** with the tested alcohols and the corresponding $\Delta\delta^{RS}$ values.

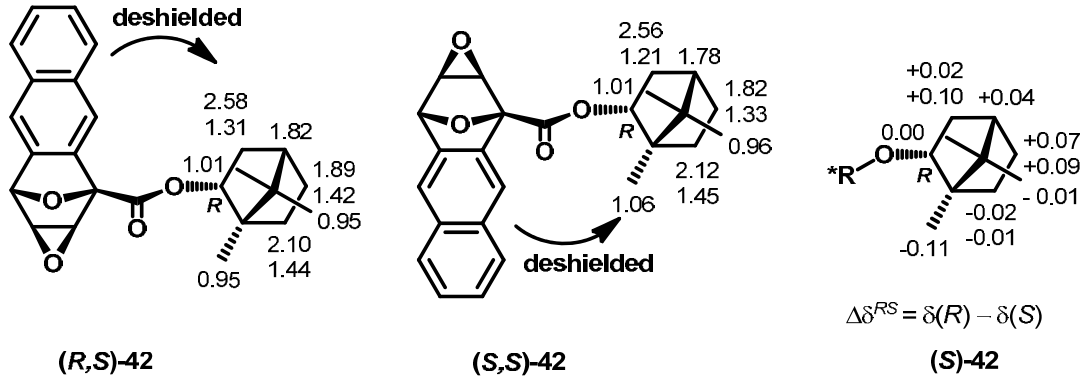


Figure 19. [1]H NMR chemical shift data of the esters of optically active acid **5** with the tested alcohols and the corresponding $\Delta\delta^{RS}$ values (continue).

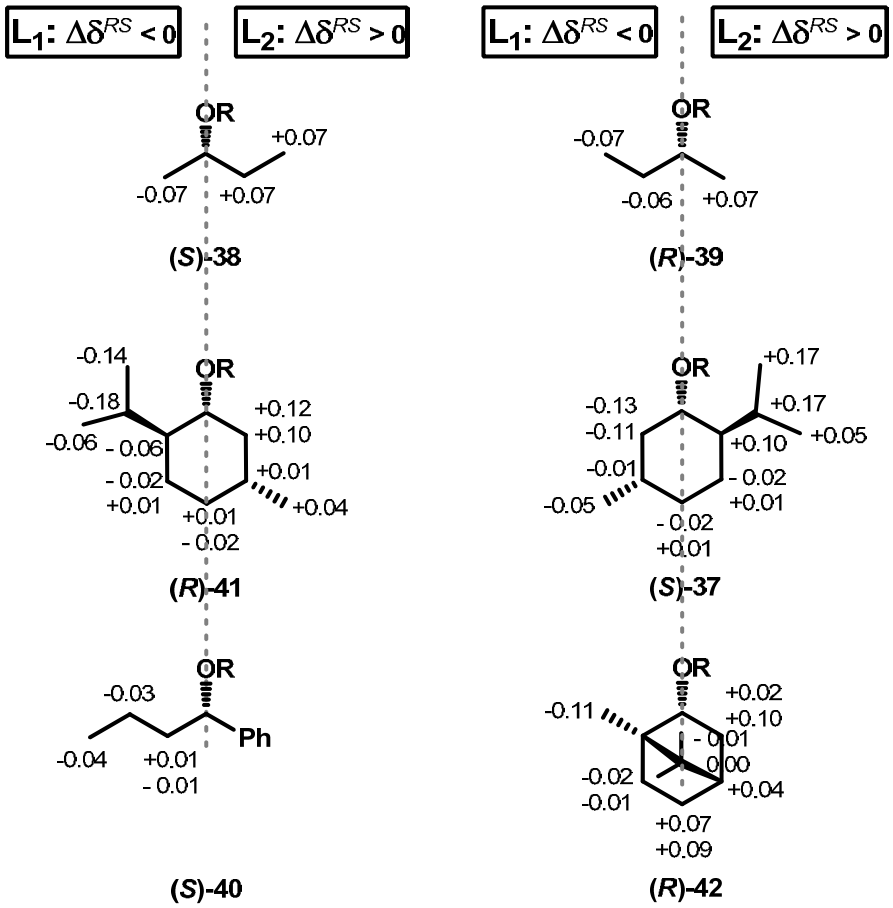


Figure 20. Chemical shift difference values ($\Delta\delta^{RS}$) of tested chiral alcohols with known absolute configuration (dashed line represents the plane).

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APPENDIX

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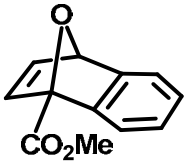


rac-9

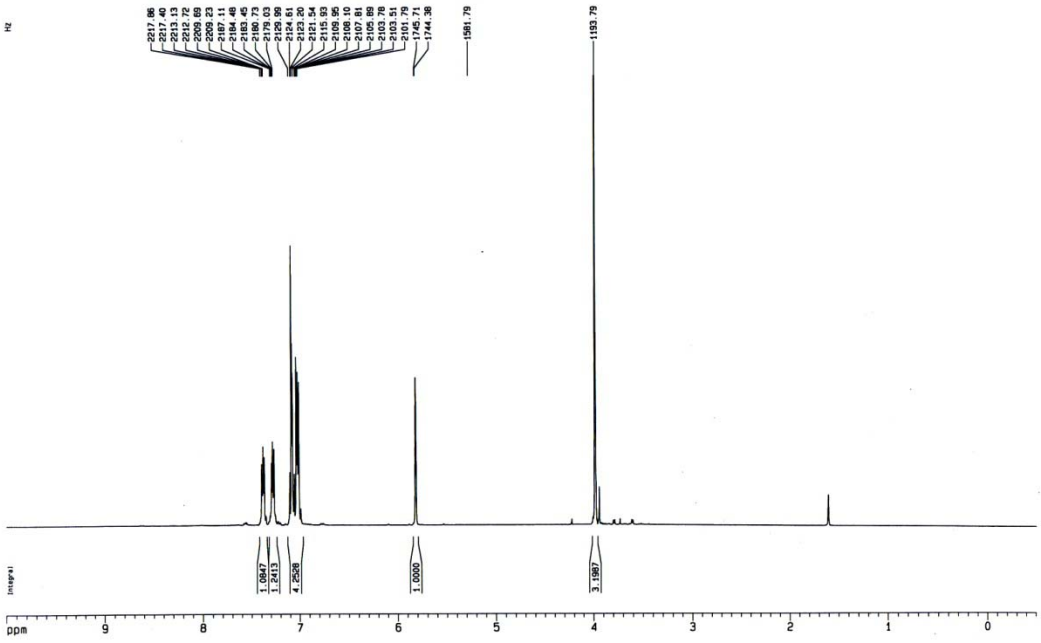


Figure A1. ^{1}H NMR spectrum of compound ***rac*-9.**

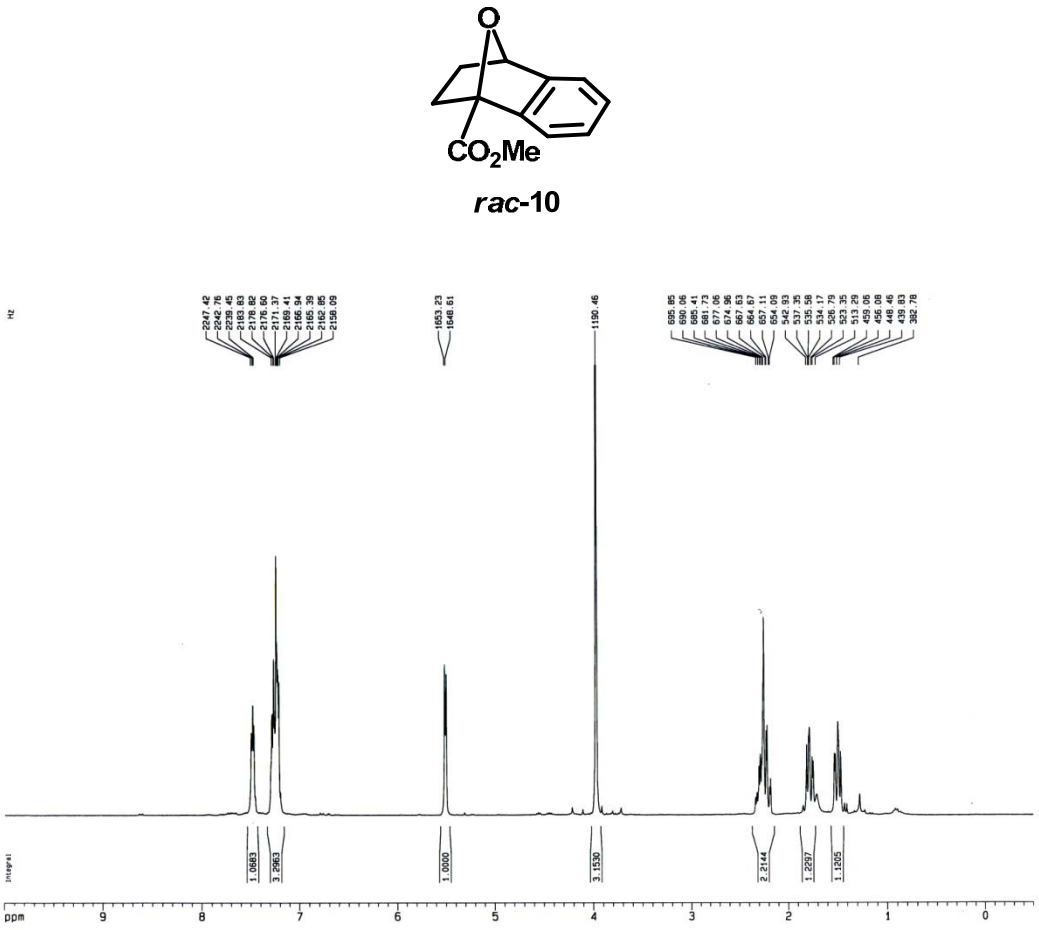
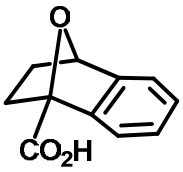


Figure A1. ^{1}H NMR spectrum of compound ***rac*-10**.



rac-4

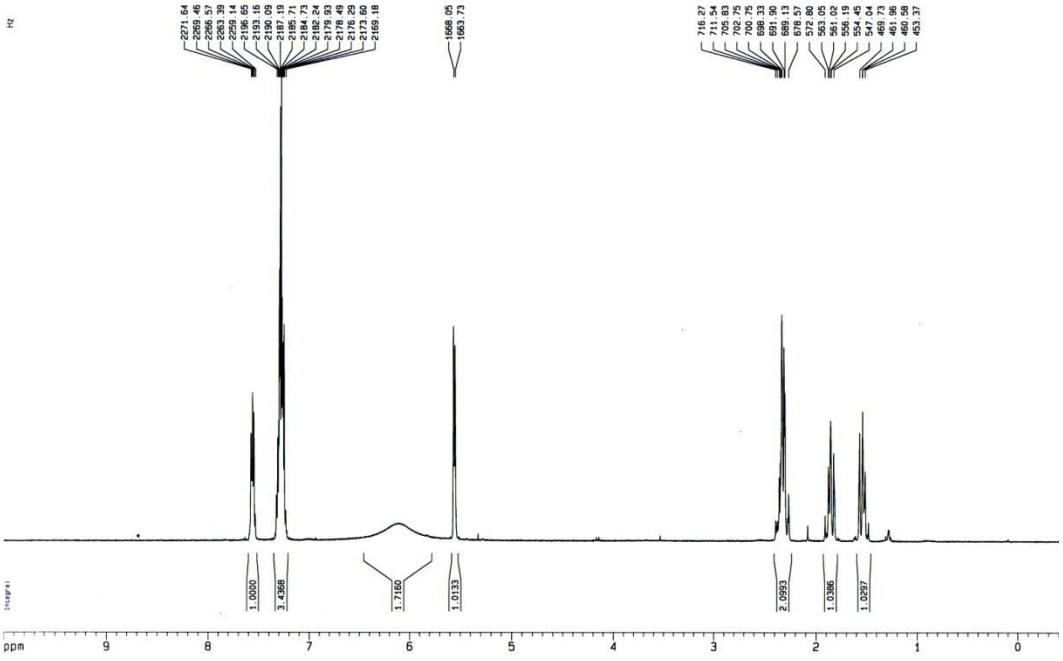


Figure A3. ^{1}H NMR spectrum of compound ***rac*-4**.

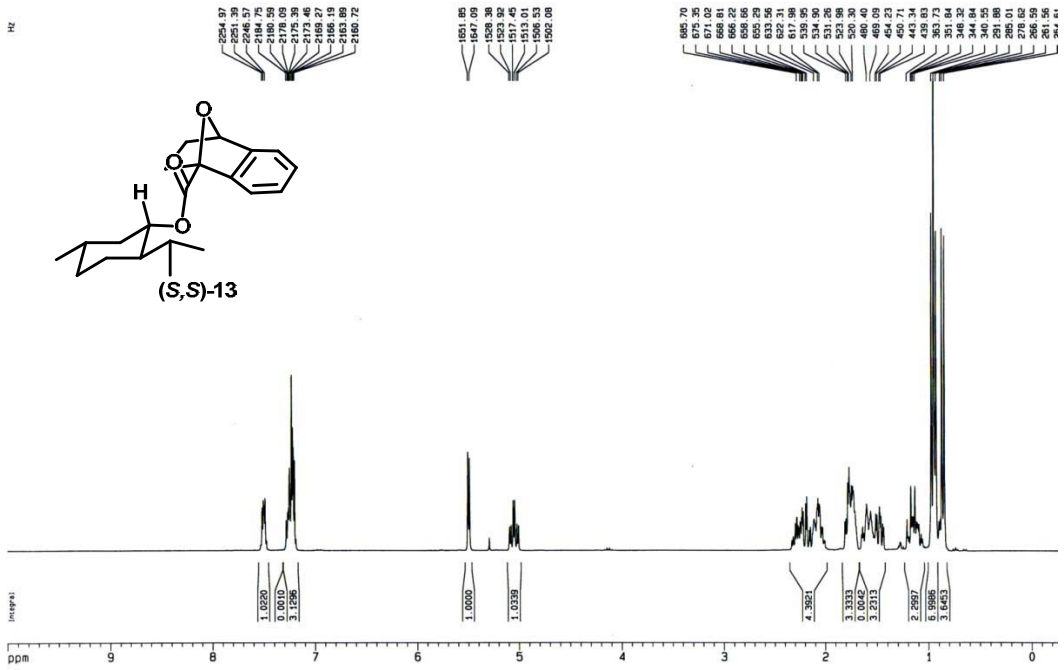


Figure A4. ^{1}H NMR spectrum of compound **(*S*,*S*)-13**.

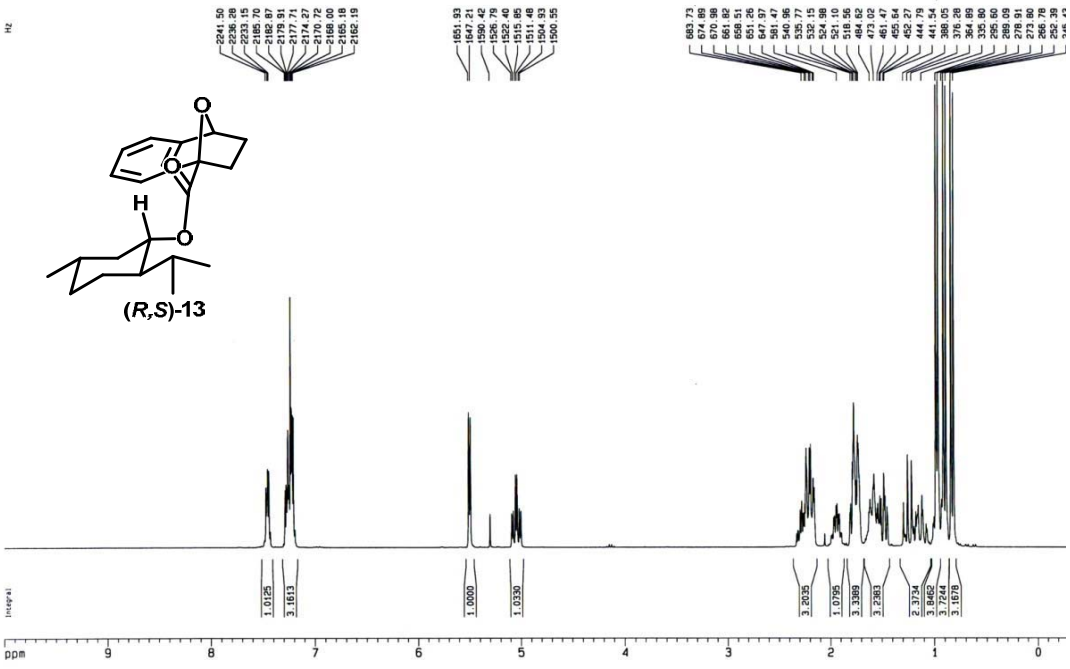


Figure A5. ^{1}H NMR spectrum of compound **(*R*,*S*)-13**.

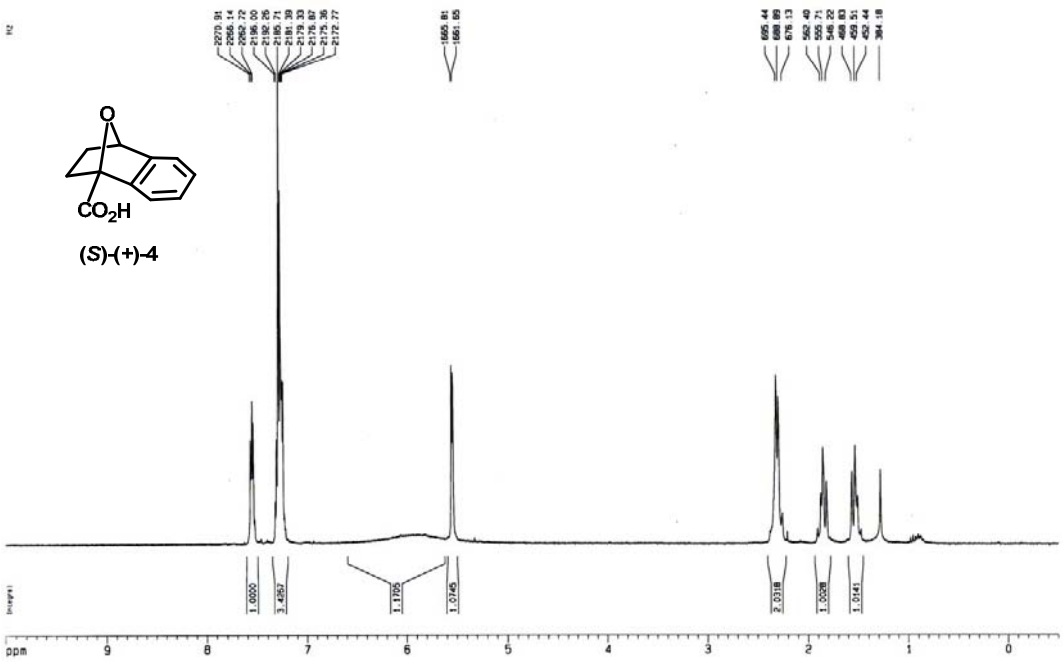


Figure A6. ^{1}H NMR spectrum of compound **(*S*)-(+)-4**.

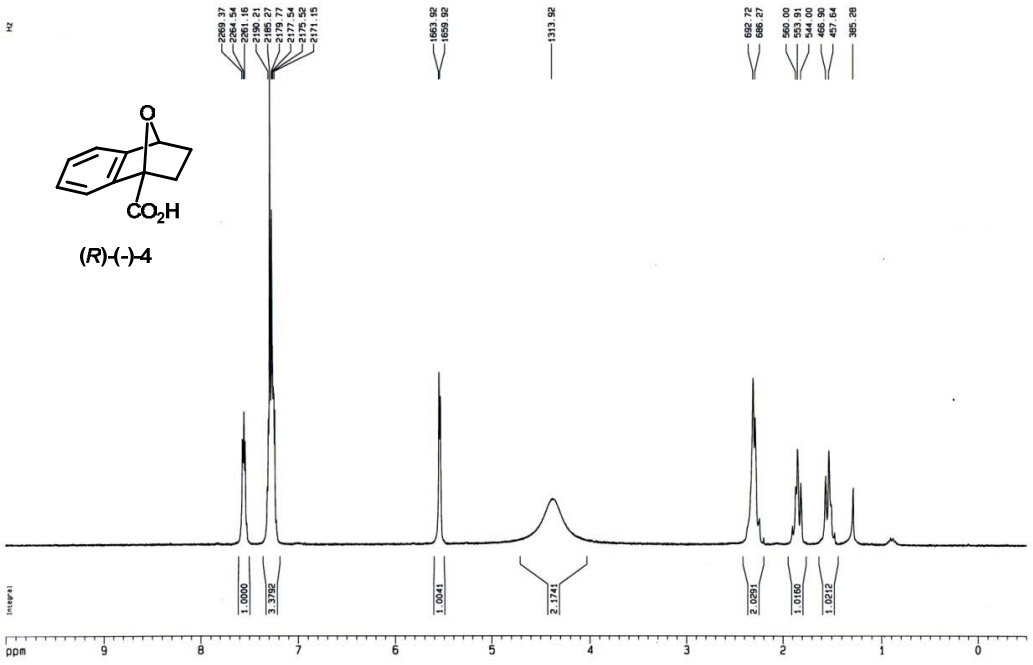


Figure A7. ^{1}H NMR spectrum of compound **(*R*)-(–)-4**.

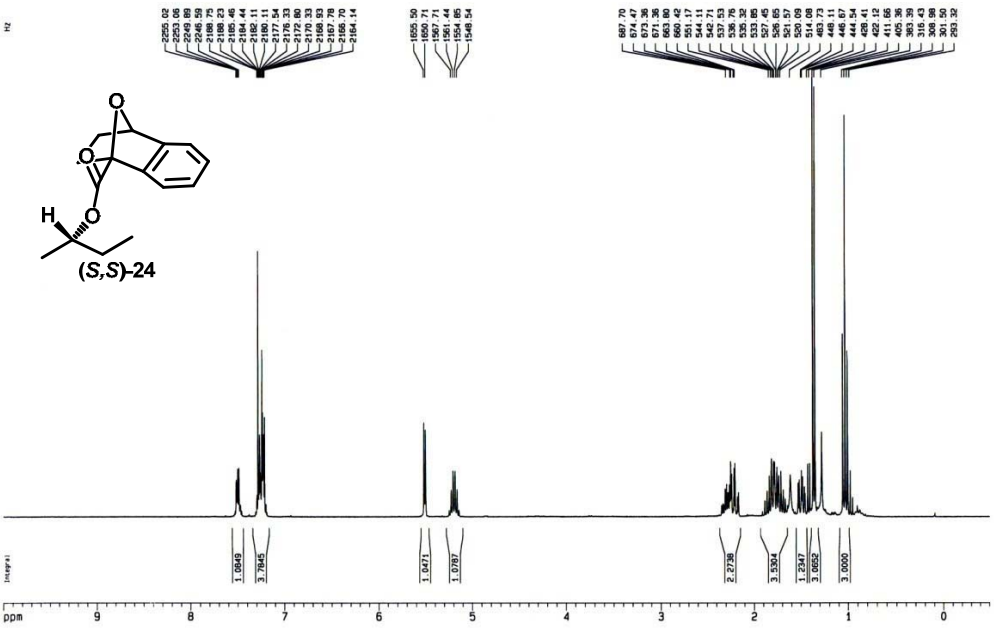


Figure A8. ^{1}H NMR spectrum of compound **(*S*,*S*)-24**.

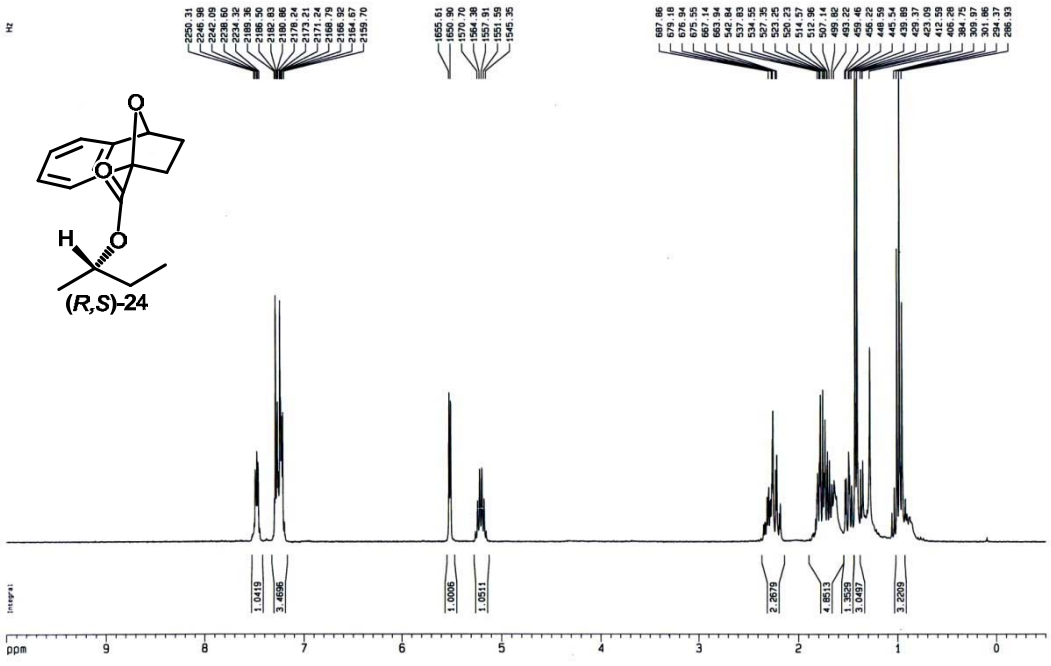


Figure A9. ^{1}H NMR spectrum of compound **(*R*,*S*)-24**.

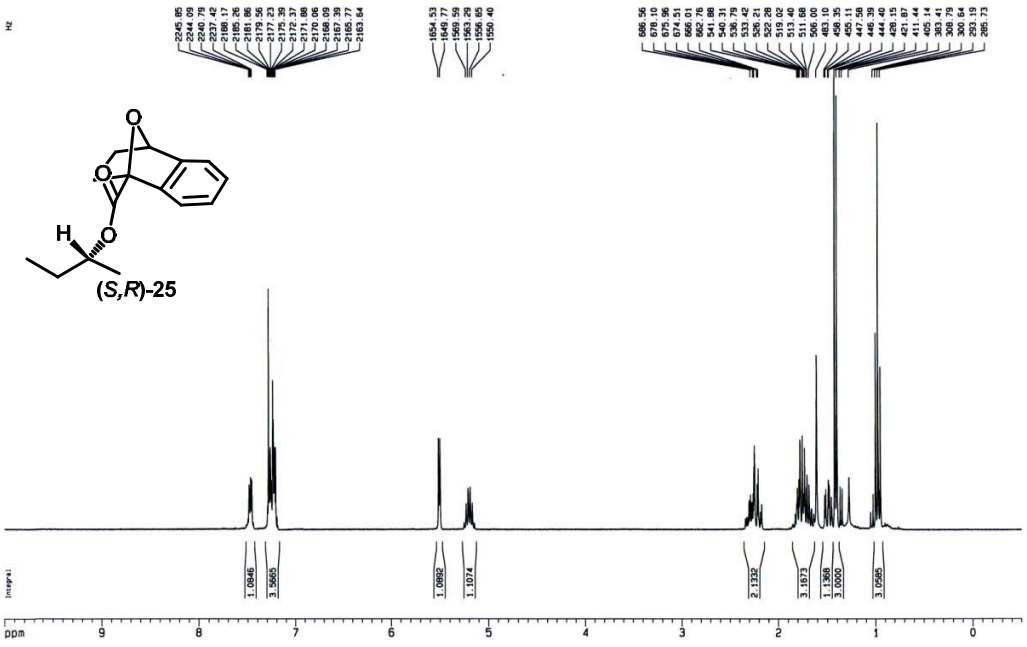


Figure A10. ^{1}H NMR spectrum of compound **(*S*,*R*)-25**.

^{1}H NMR in $CDCl_3$

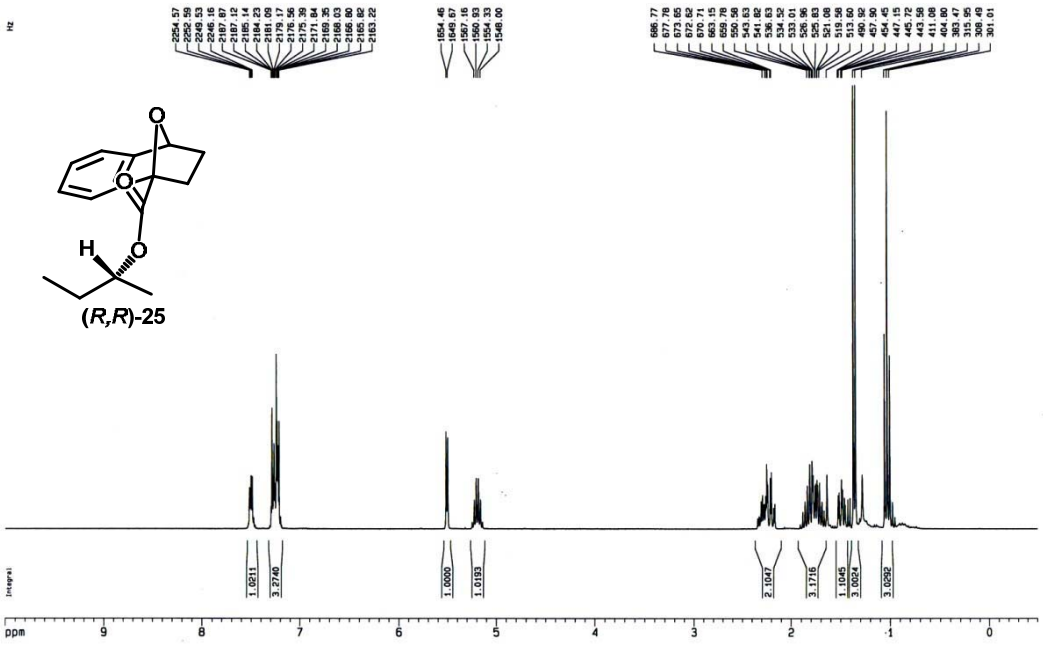


Figure A11. ^{1}H NMR spectrum of compound **(*R*,*R*)-25**.

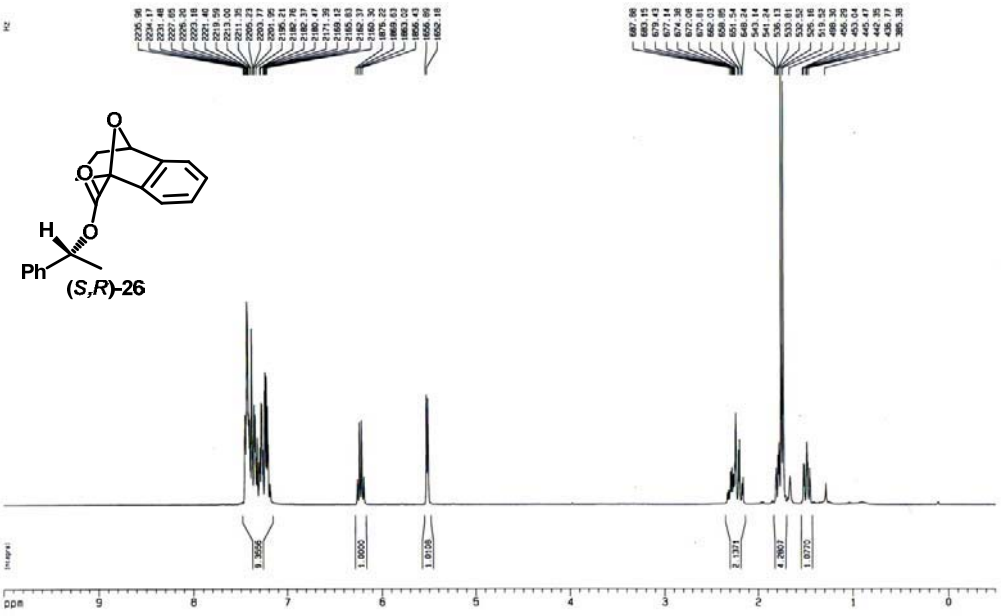


Figure A12. ^{1}H NMR spectrum of compound **(*S*,*R*)-26**.

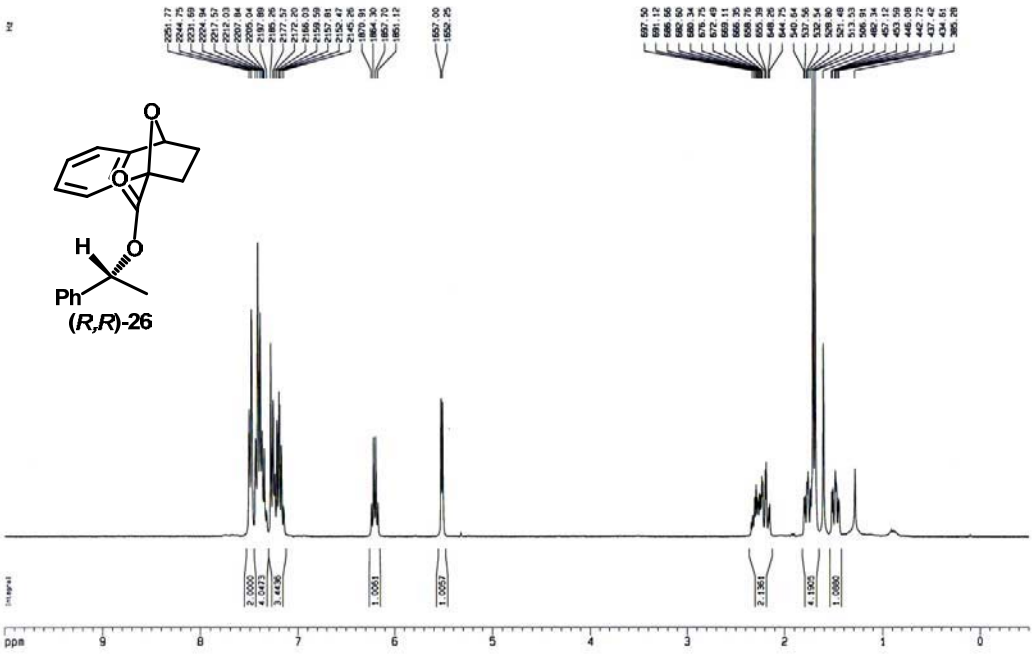


Figure A13. ^{1}H NMR spectrum of compound **(*R*,*R*)-26**.

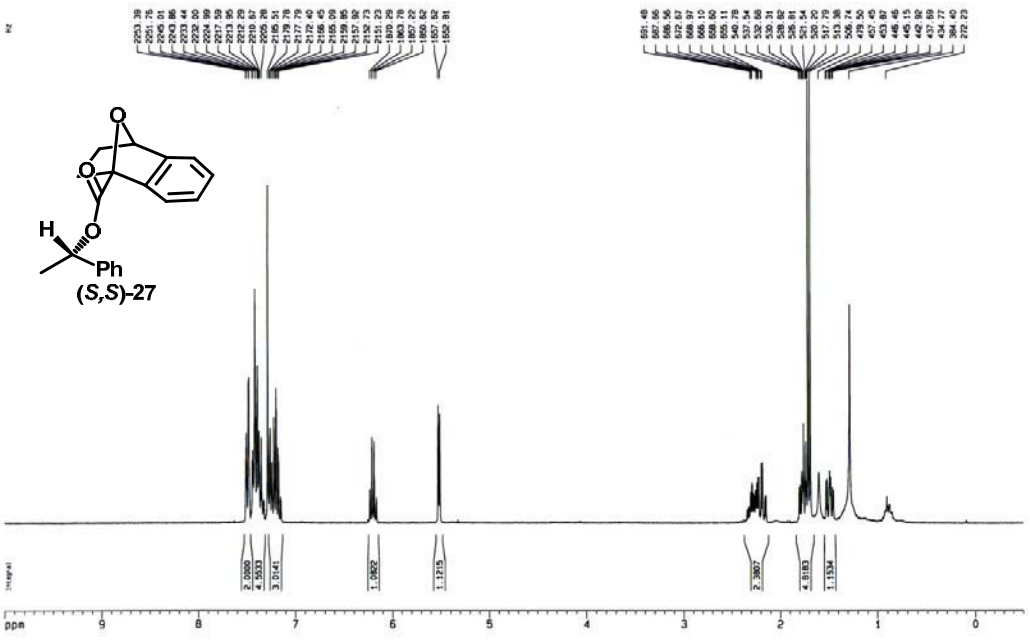


Figure A14. ^{1}H NMR spectrum of compound **(*S*,*S*)-27**.

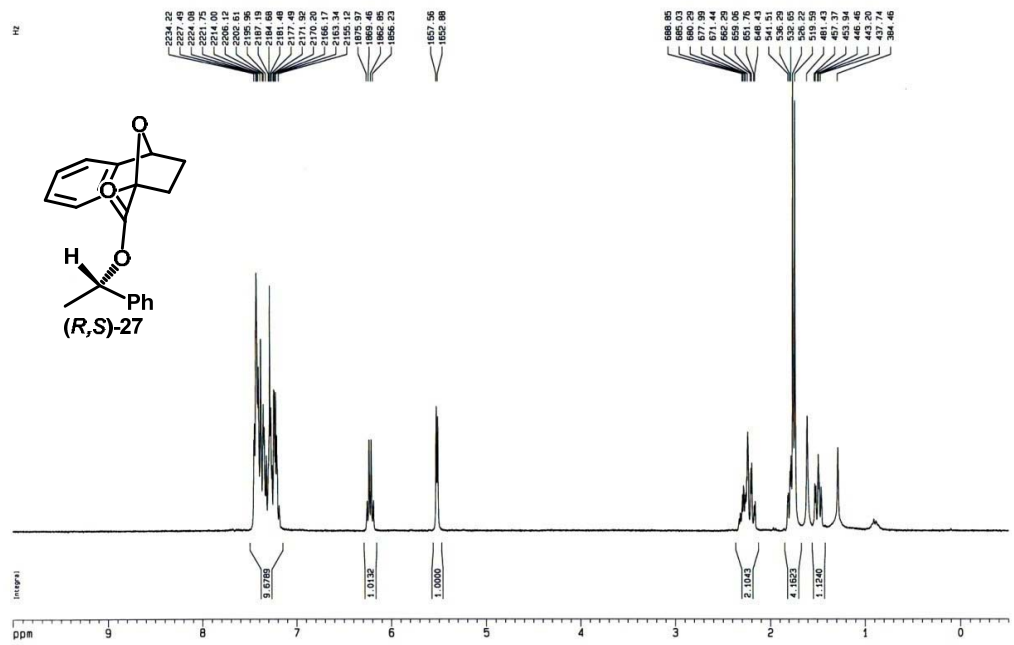


Figure A15. ^{1}H NMR spectrum of compound **(*R*,*S*)-27**.

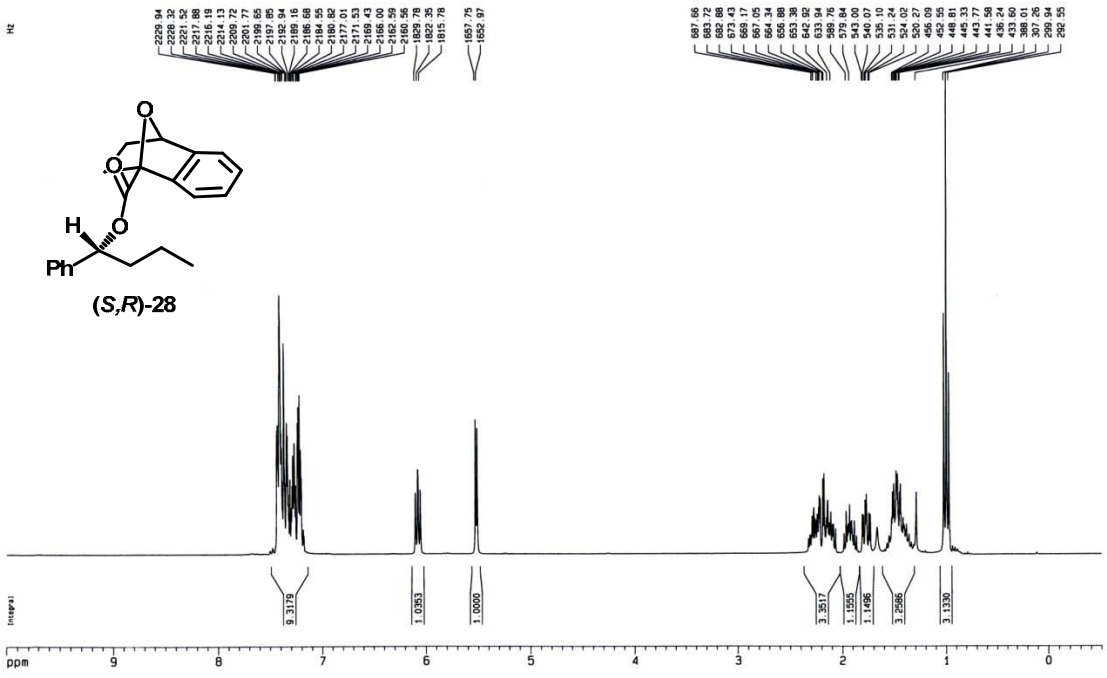


Figure A16. ^{1}H NMR spectrum of compound **(*S*,*R*)-28**.

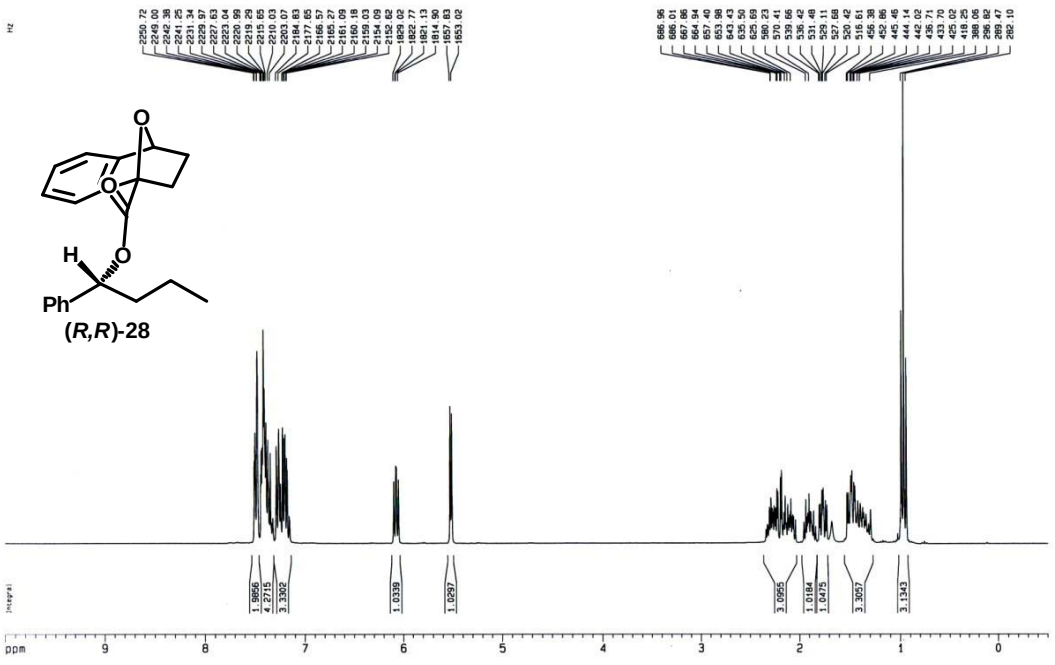


Figure A17. ^{1}H NMR spectrum of compound **(*R*,*R*)-28**.

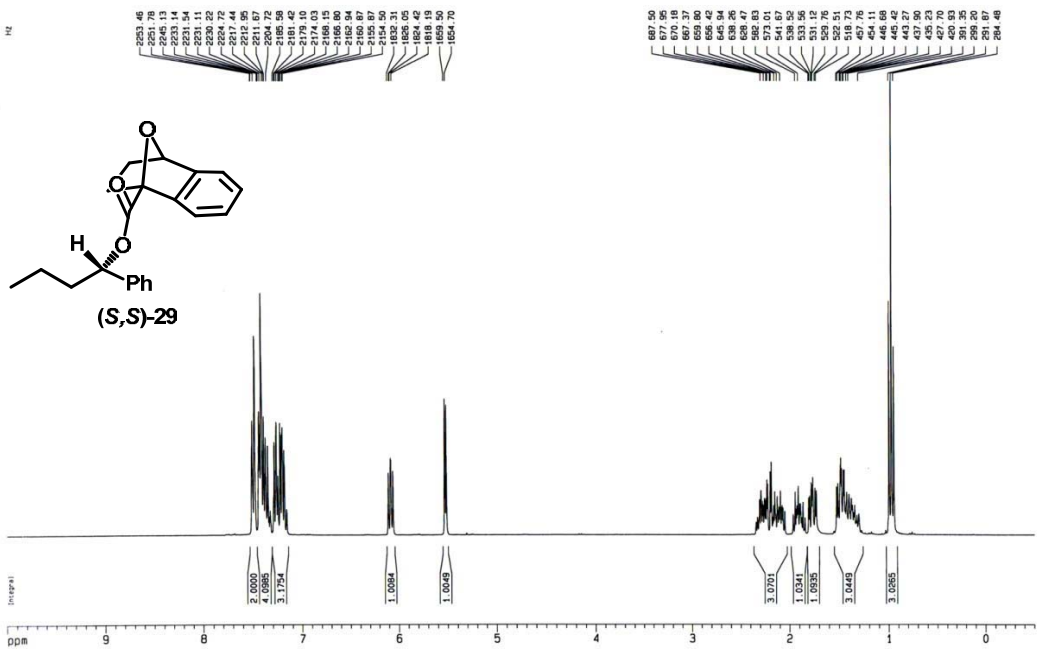


Figure A18. ^{1}H NMR spectrum of compound **(*S*,*S*)-29**.

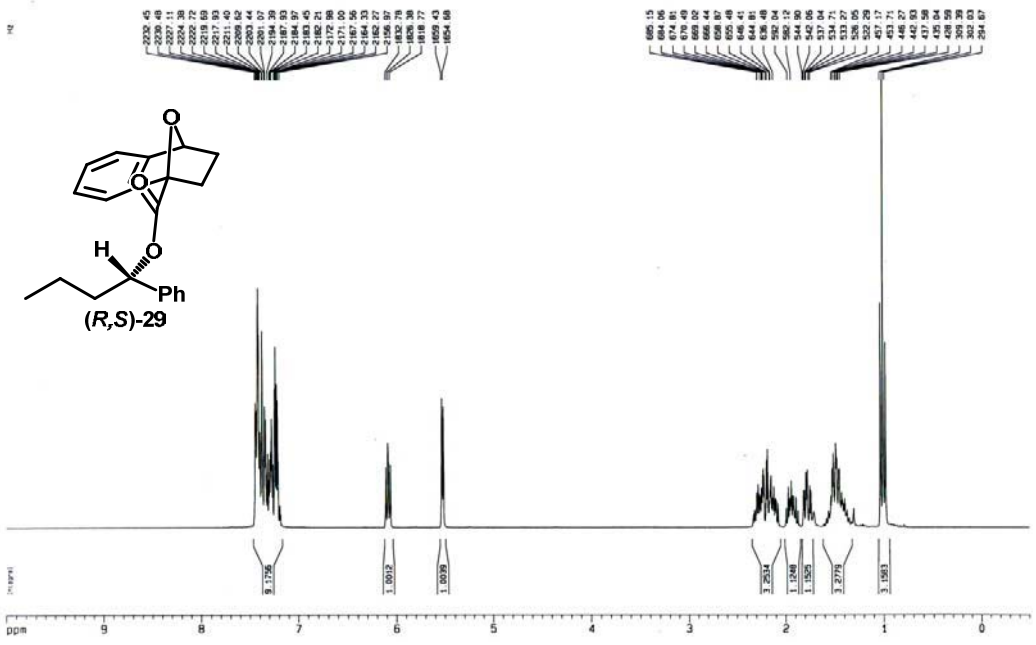


Figure A19. ^{1}H NMR spectrum of compound **(*R*,*S*)-29**.

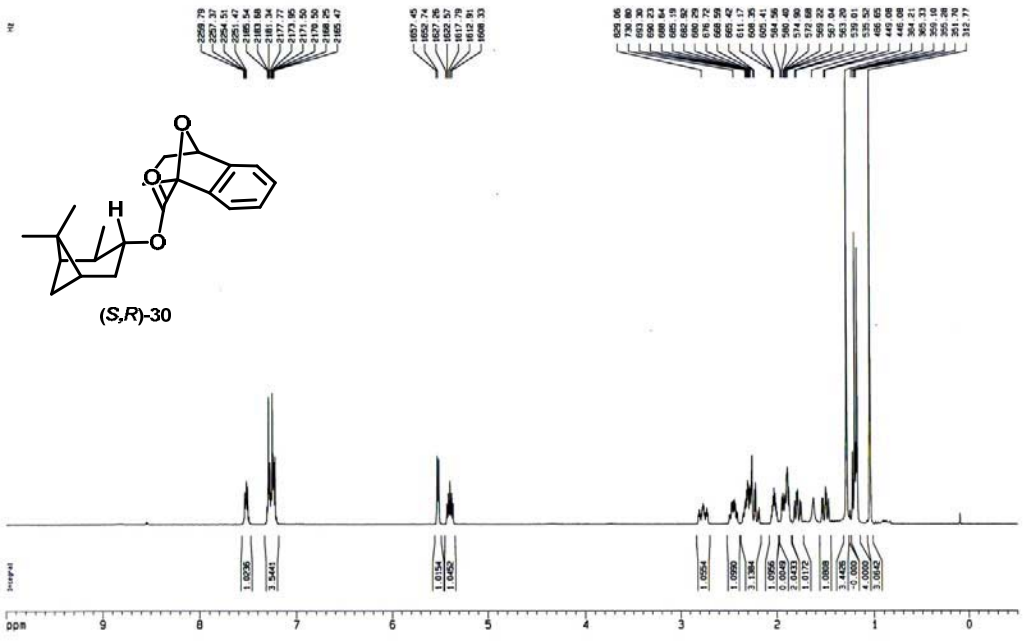


Figure A20. ^{1}H NMR spectrum of compound **(*S*,*R*)-30**.

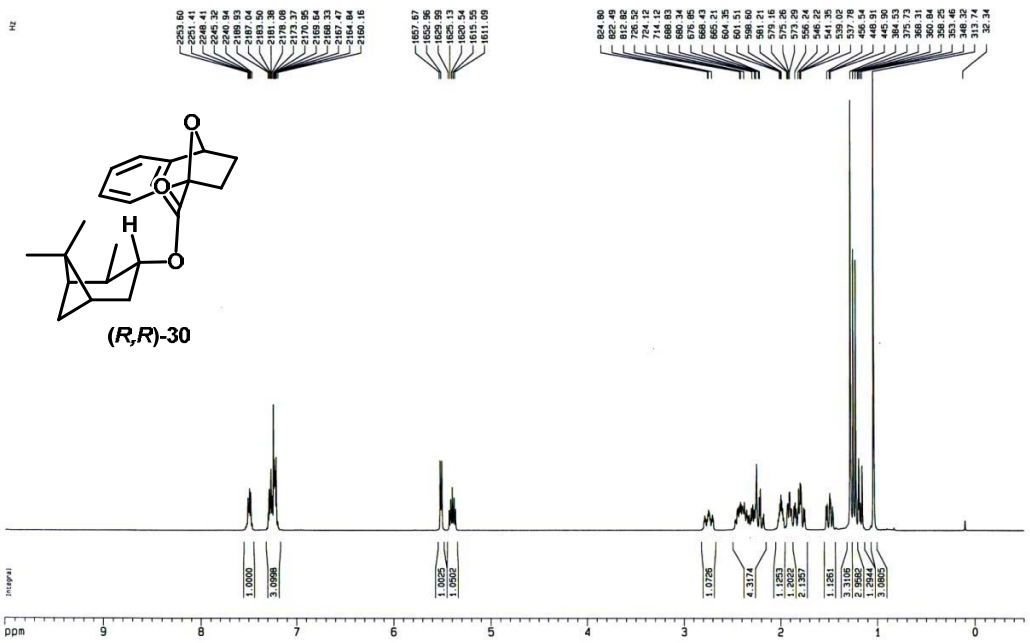


Figure A21. ^{1}H NMR spectrum of compound **(*R*,*R*)-30**.

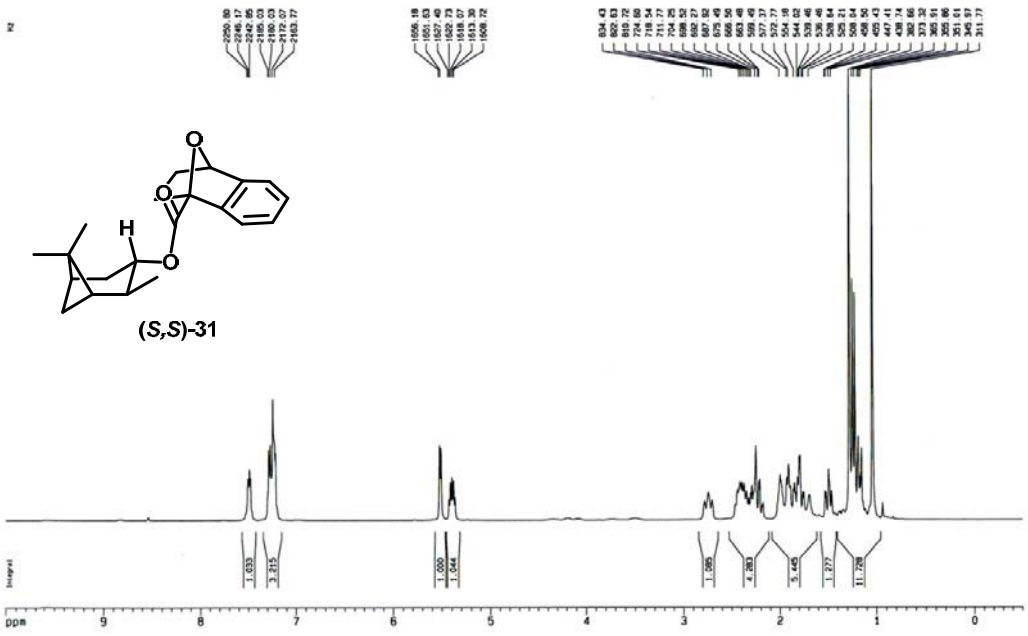


Figure A22. ^{1}H NMR spectrum of compound **(*S*,*S*)-31**.

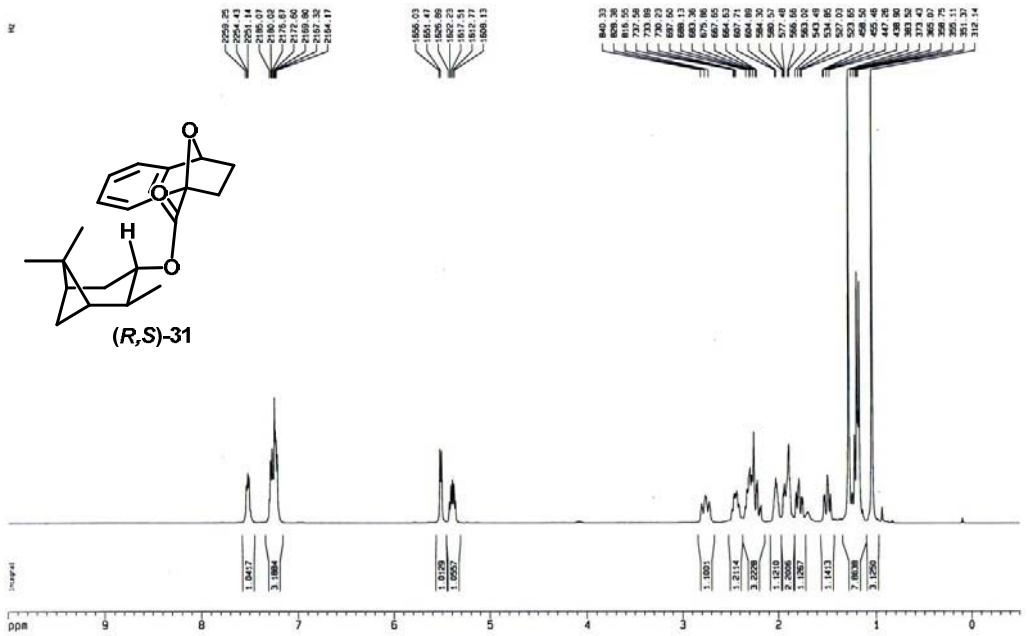


Figure A23. ^{1}H NMR spectrum of compound **(*R*,*S*)-31**.

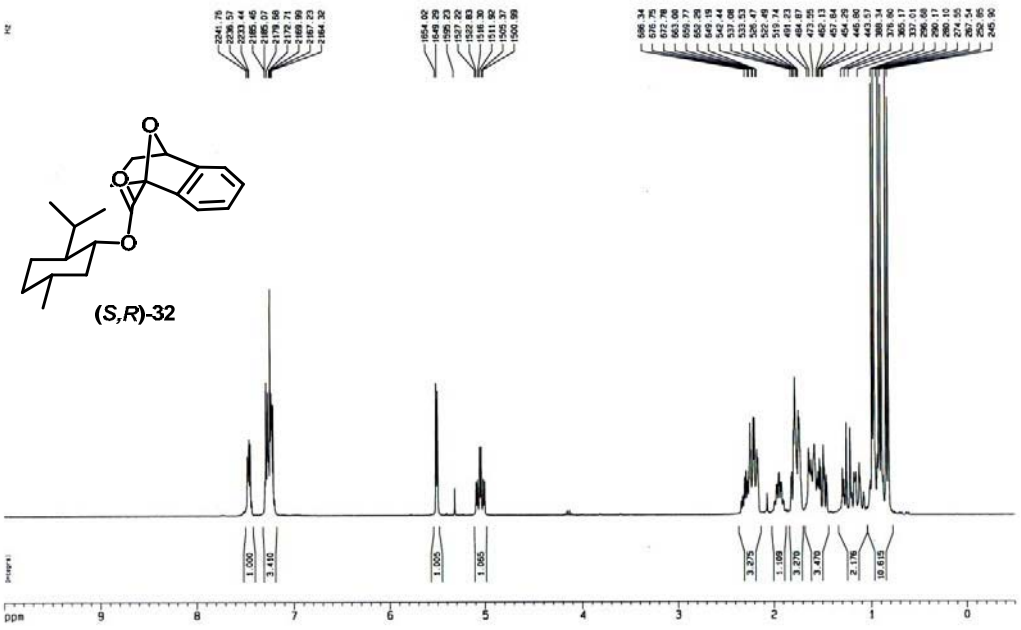


Figure A24. ^{1}H NMR spectrum of compound **(*S*,*R*)-32**.

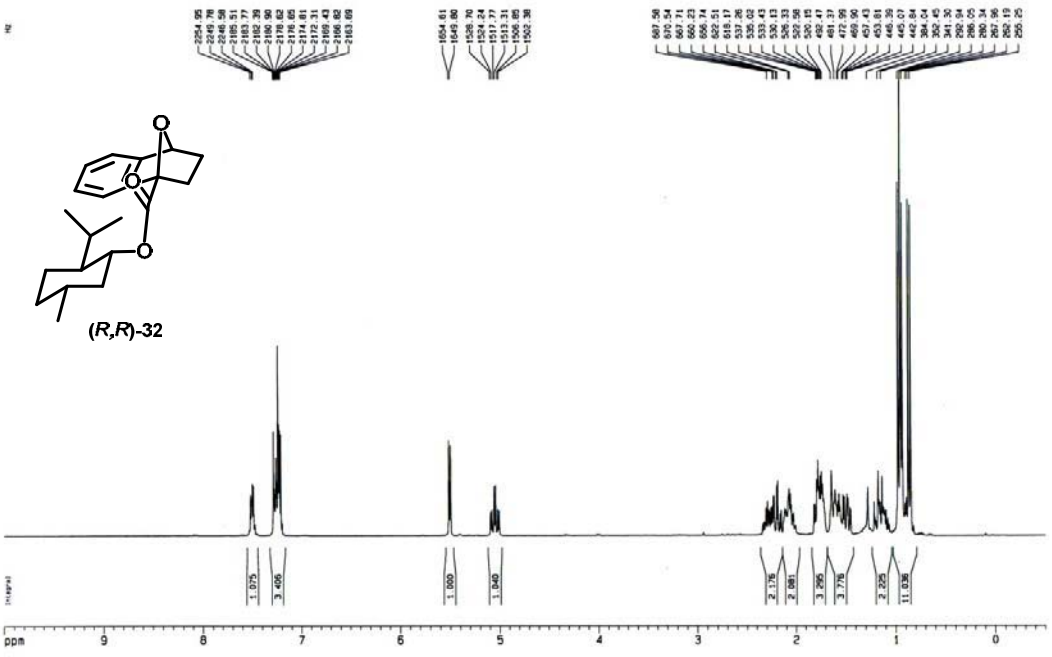


Figure A25. ^{1}H NMR spectrum of compound **(*R*,*R*)-32**.

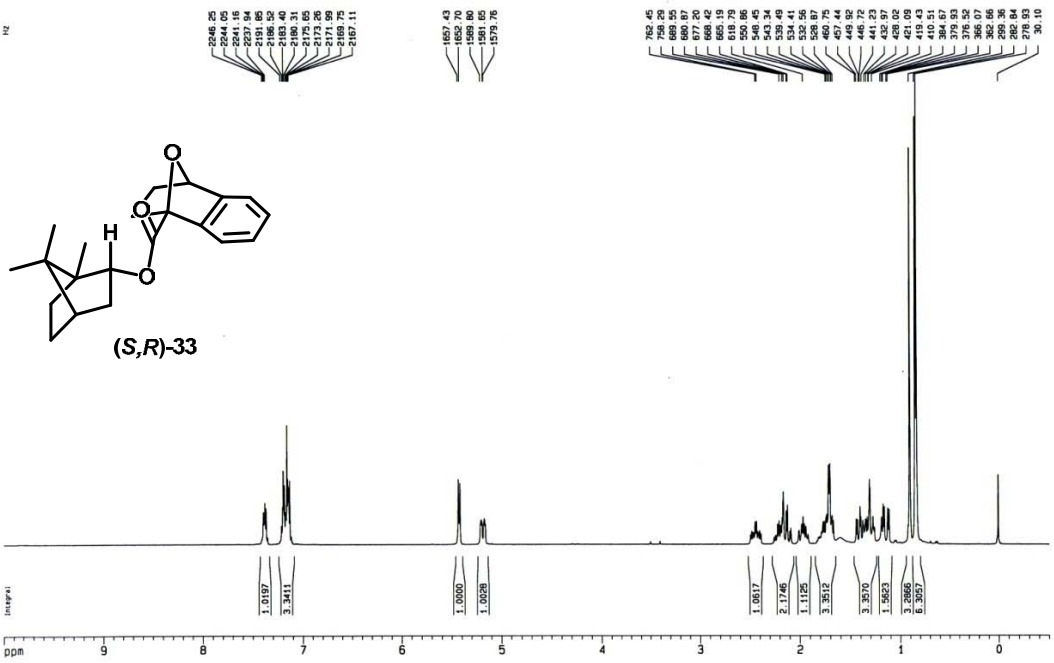


Figure A26. ^{1}H NMR spectrum of compound **(*S*,*R*)-33**.

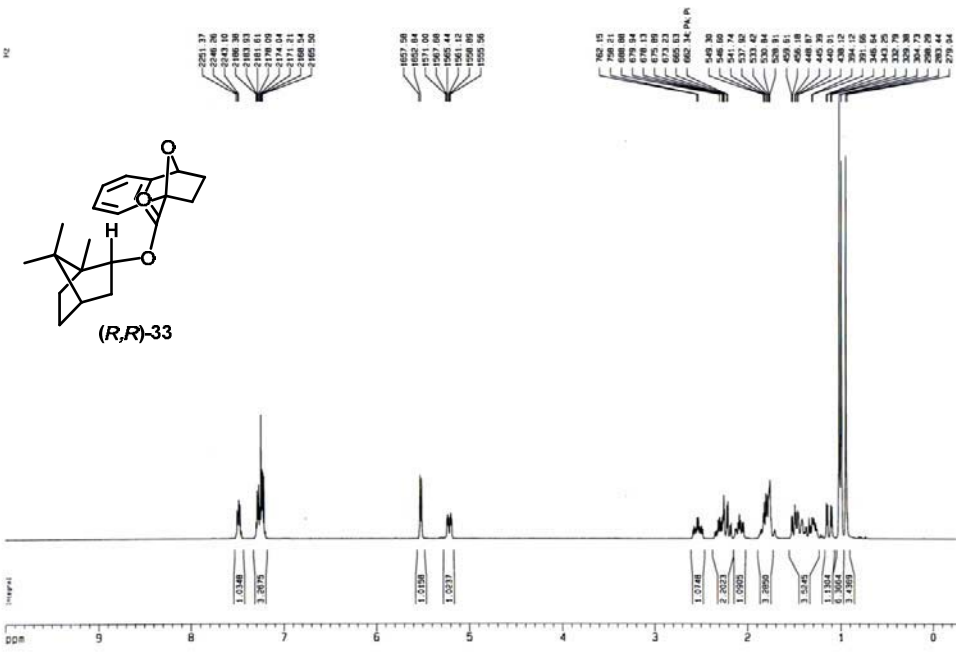


Figure A27. ^{1}H NMR spectrum of compound **(*R*,*R*)-33**.

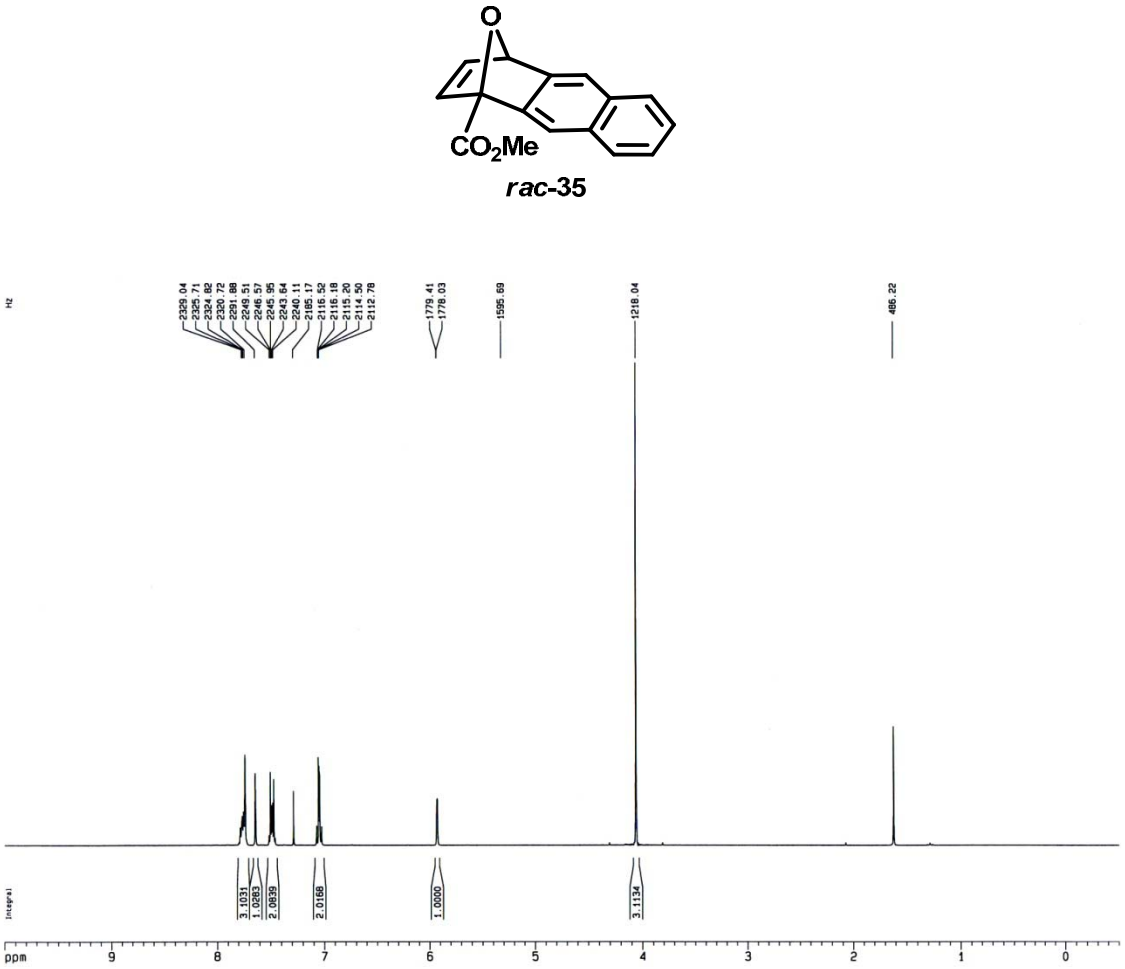
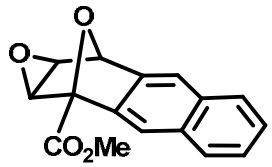


Figure A27. ^{1}H NMR spectrum of compound ***rac*-35**.



rac-36

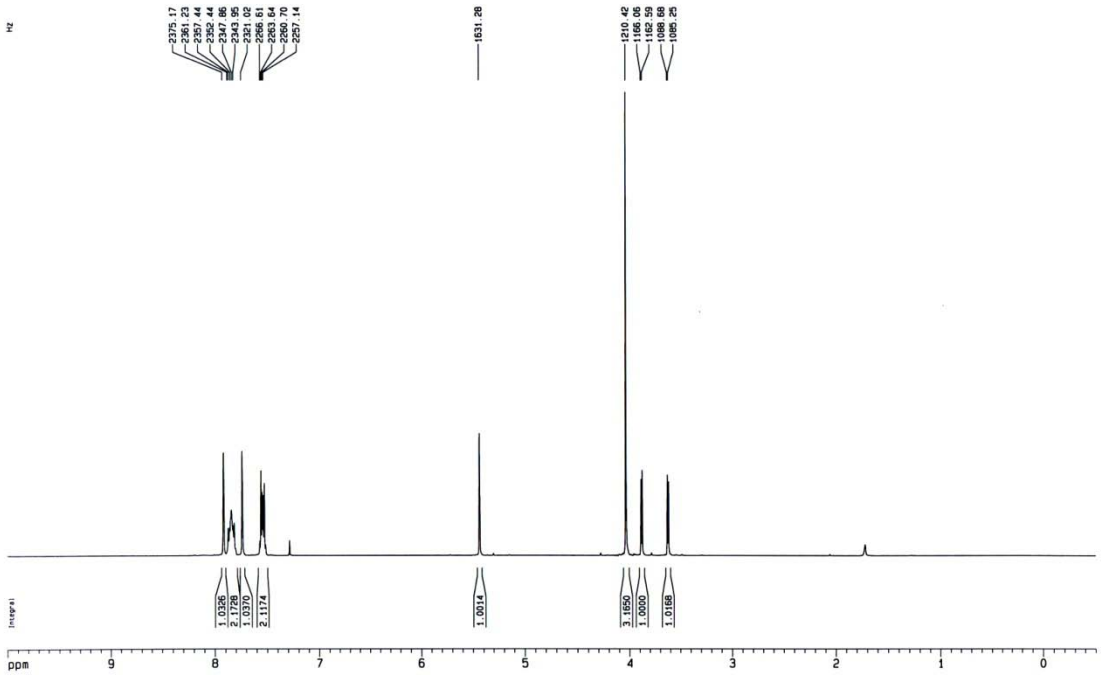
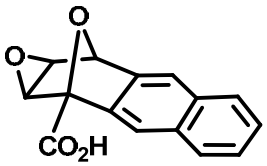


Figure A28. ^{1}H NMR spectrum of compound ***rac*-36**.



rac-5

^{1}H NMR in Acetone-D_6

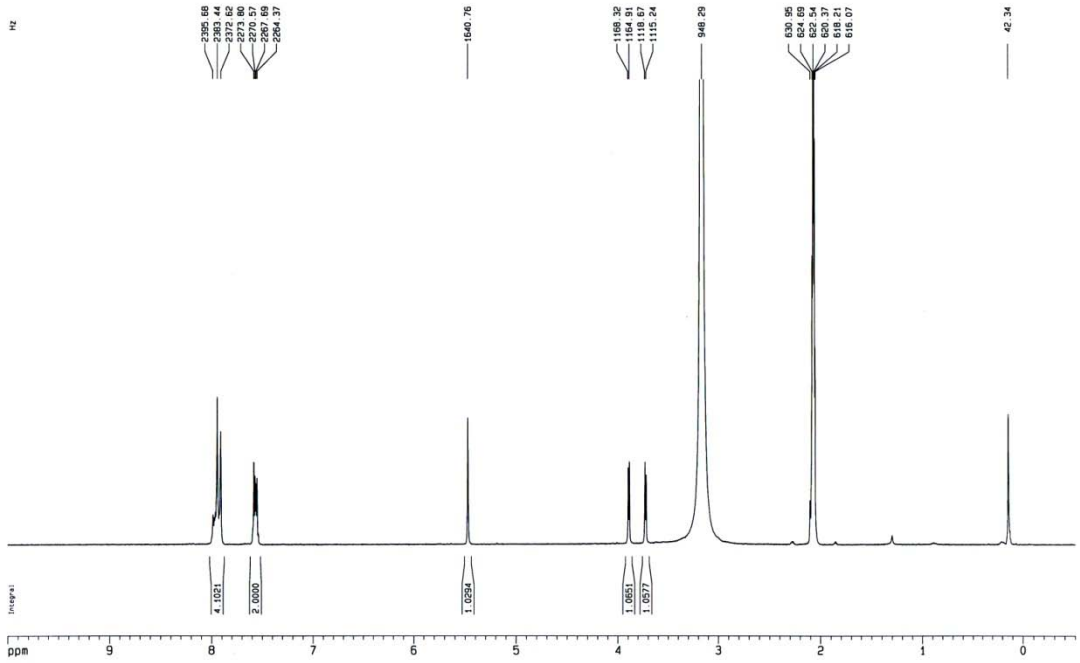


Figure A29. ^{1}H NMR spectrum of compound ***rac*-5**.

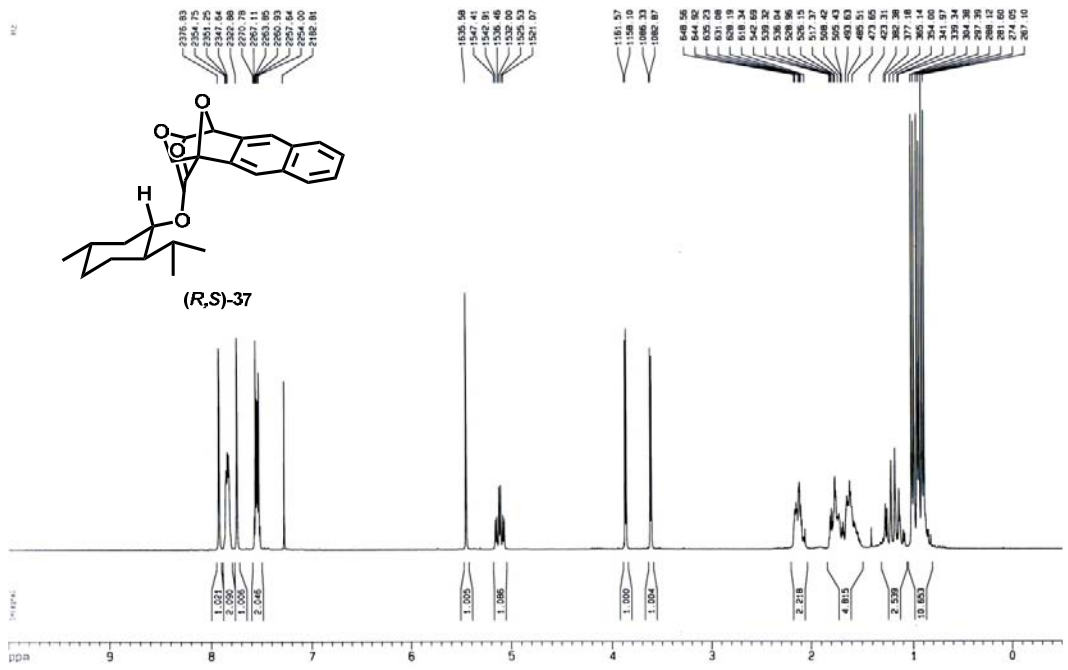


Figure A30. ^{1}H NMR spectrum of compound **(*R*,*S*)-37**.

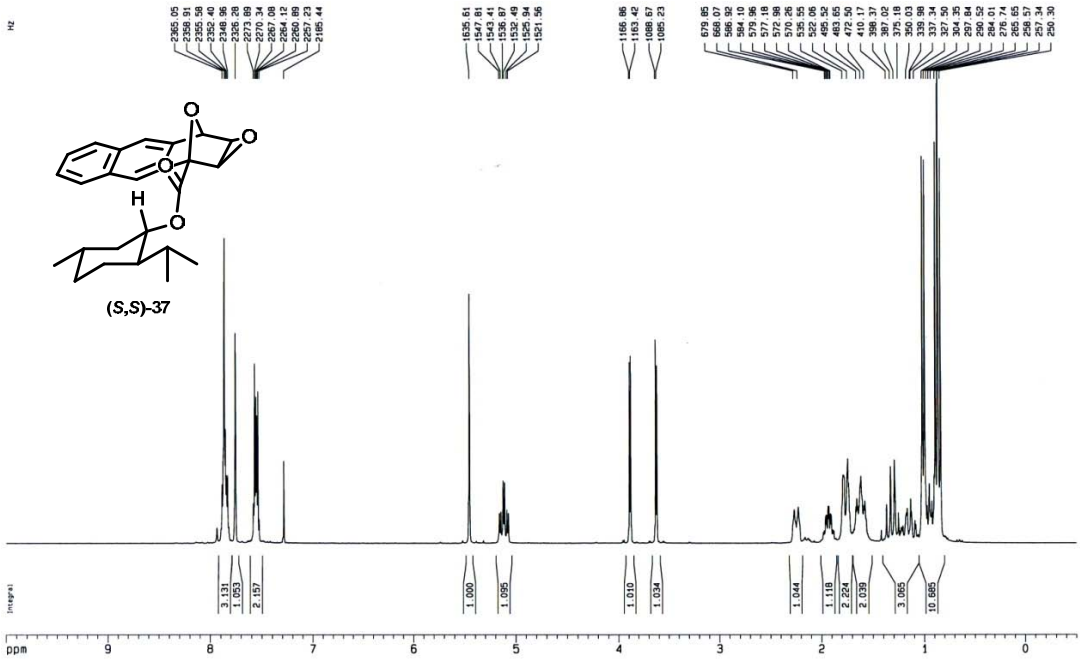


Figure A31. ^{1}H NMR spectrum of compound **(*S*,*S*)-37**.

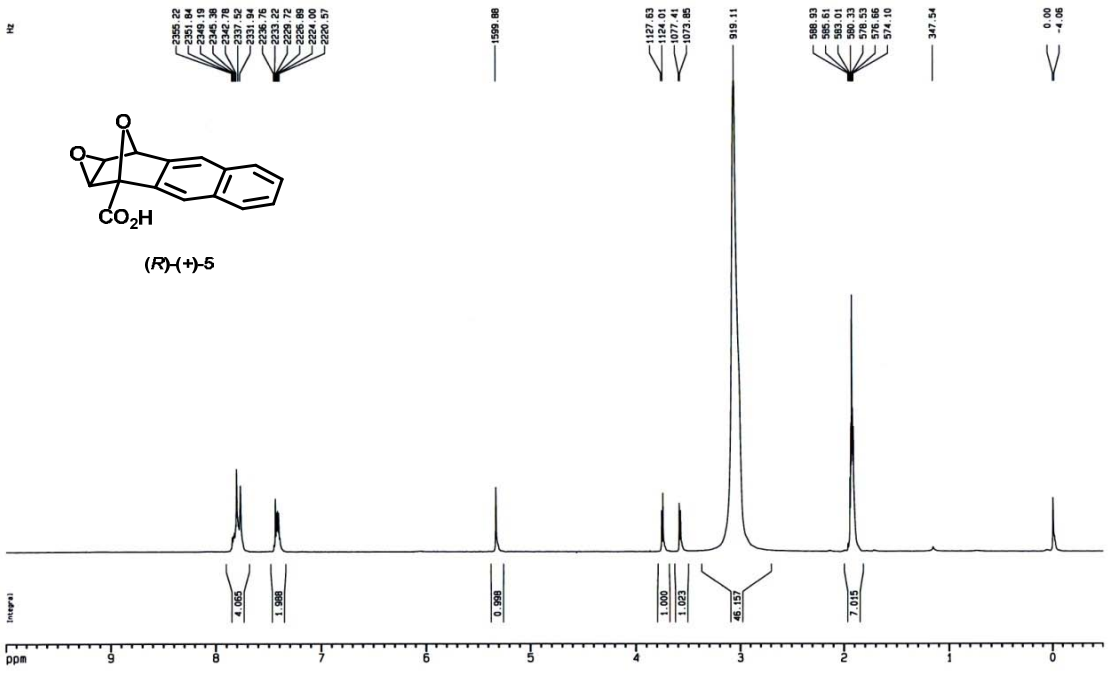


Figure A32. ^{1}H NMR spectrum of compound **(*R*)-(+)-5**.

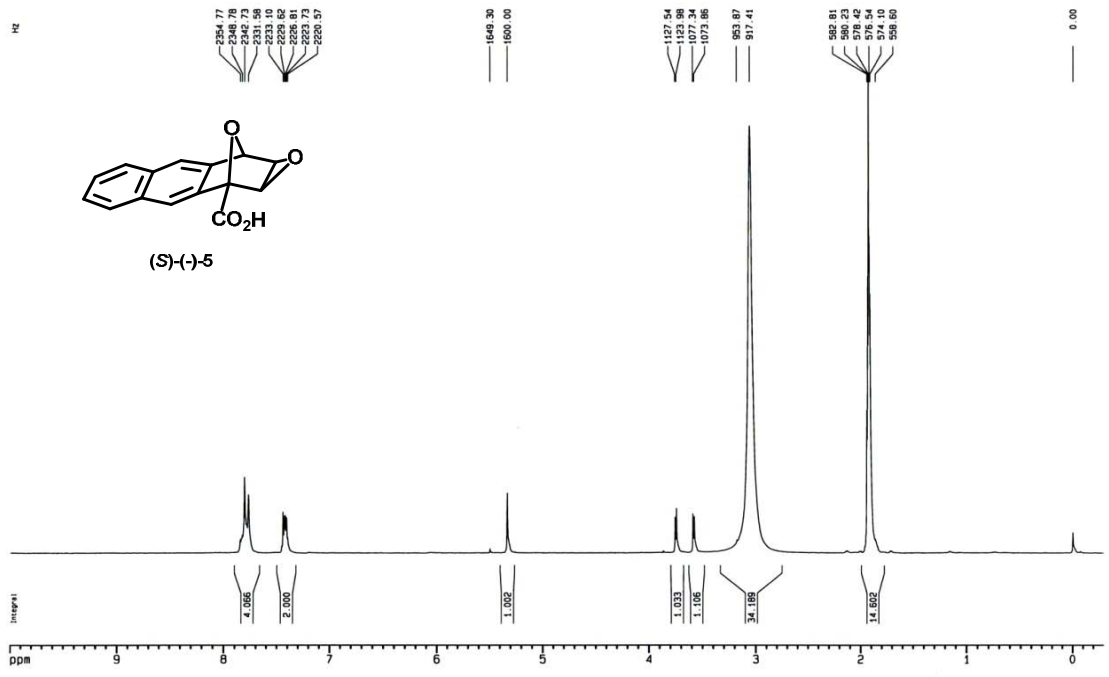


Figure A33. ^{1}H NMR spectrum of compound **(*S*)-(-)-5**.

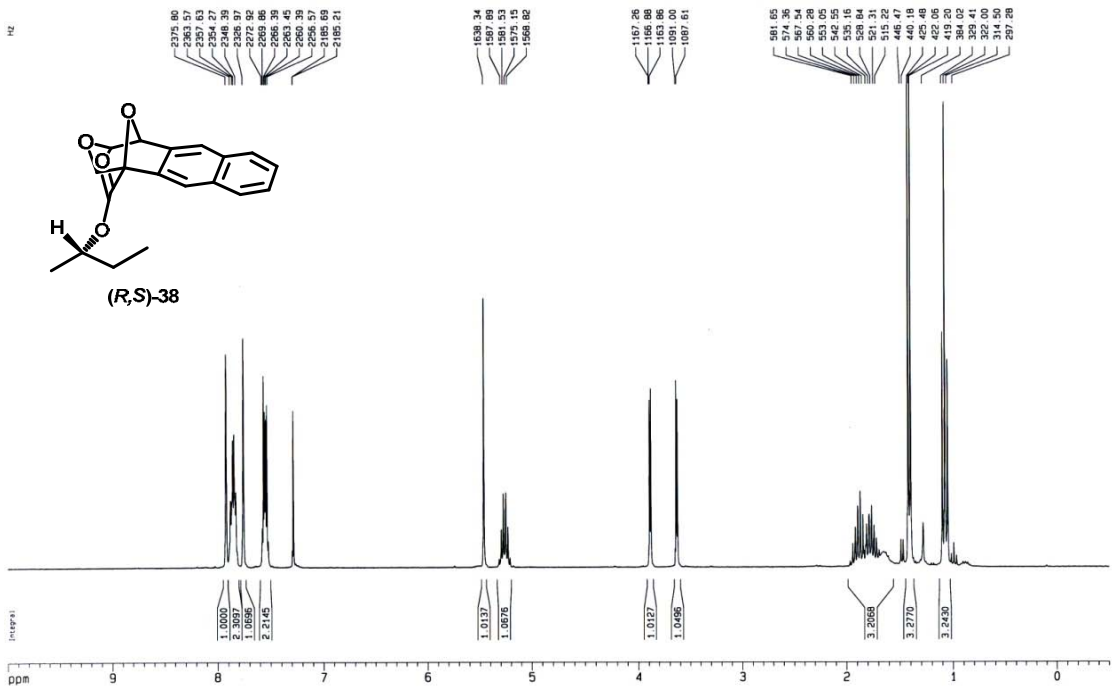


Figure A34. ^{1}H NMR spectrum of compound **(*R*,*S*)-38**.

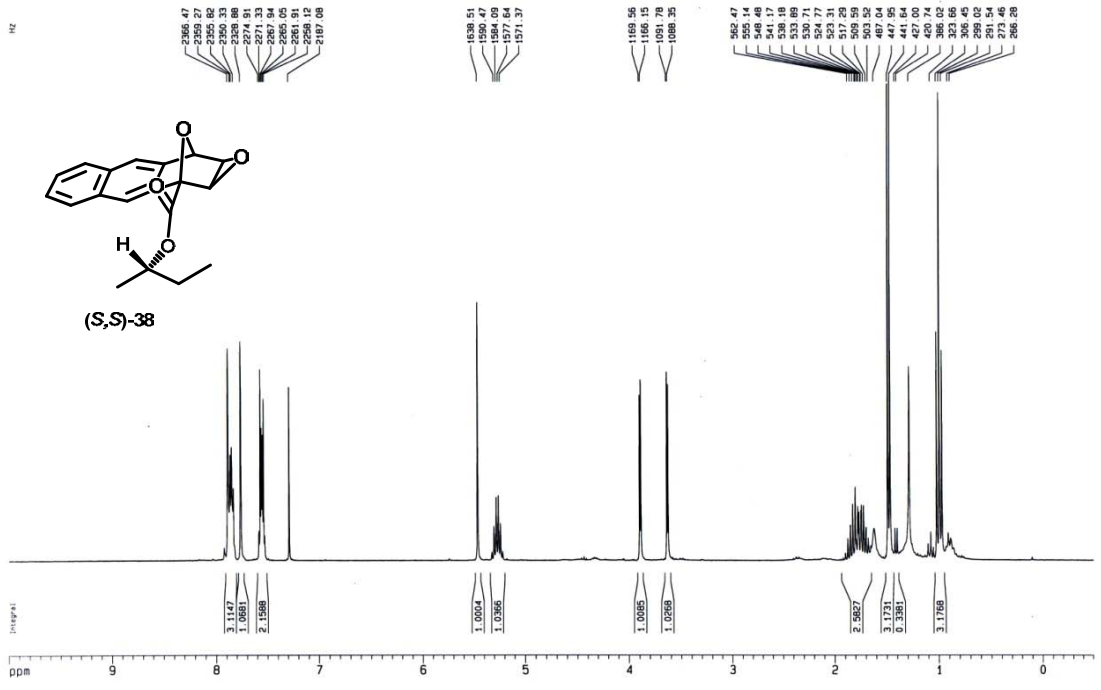


Figure A35. ^{1}H NMR spectrum of compound **(*S*,*S*)-38**.

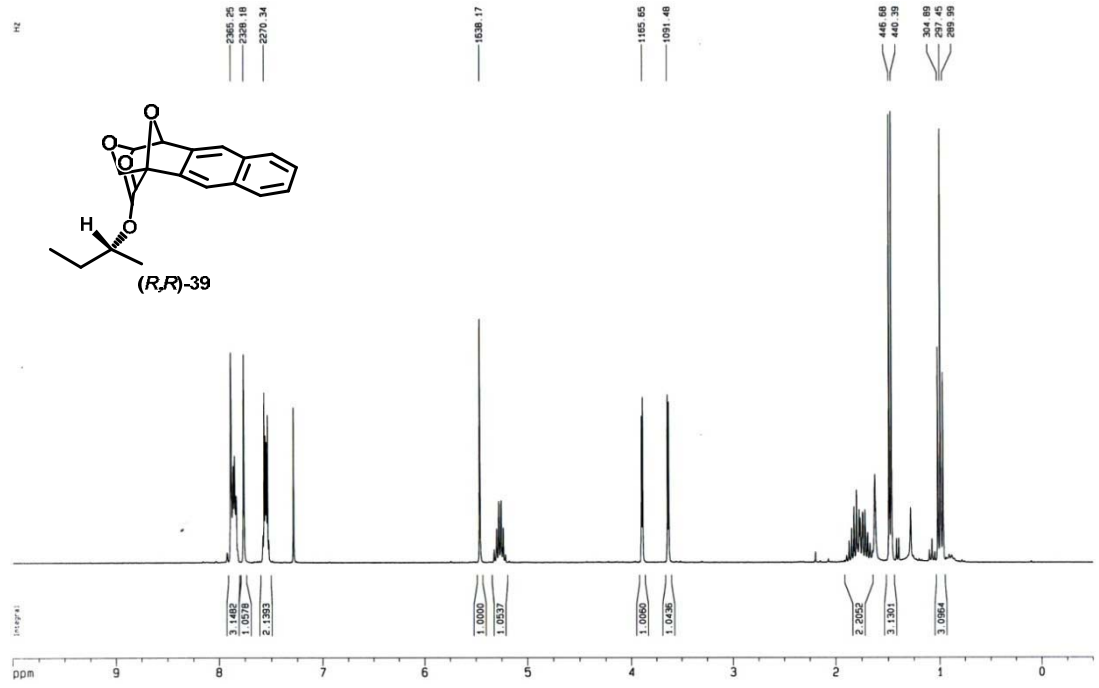


Figure A36. ^{1}H NMR spectrum of compound **(*R*,*R*)-39**.

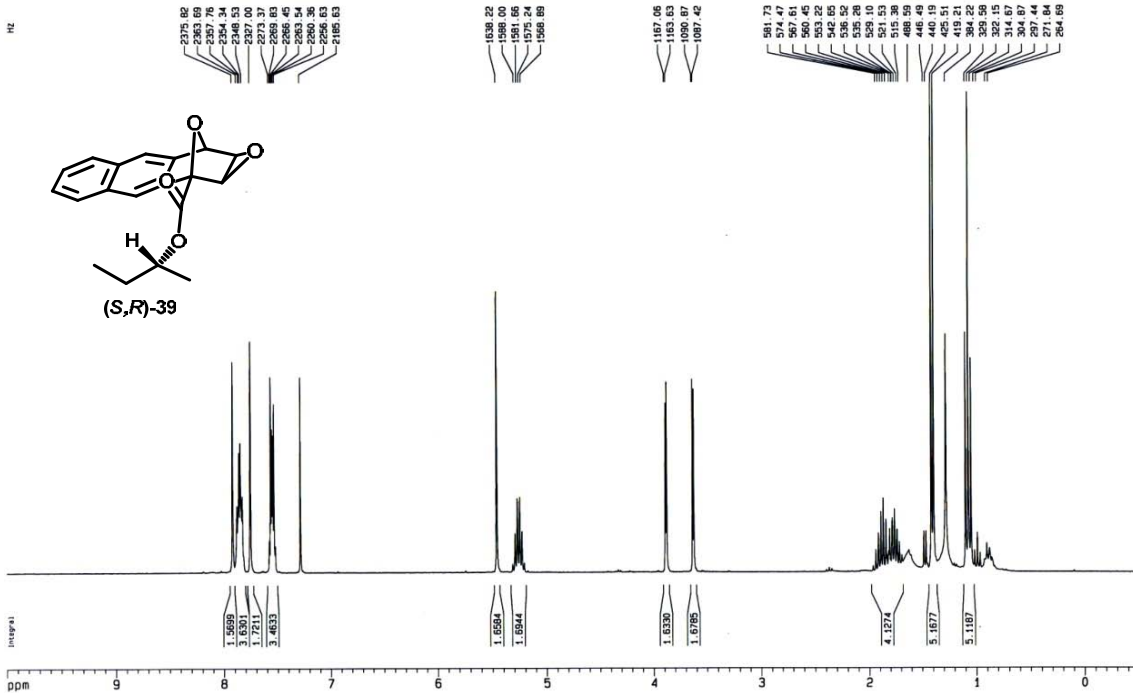


Figure A37. ^{1}H NMR spectrum of compound **(*S*,*R*)-39**.

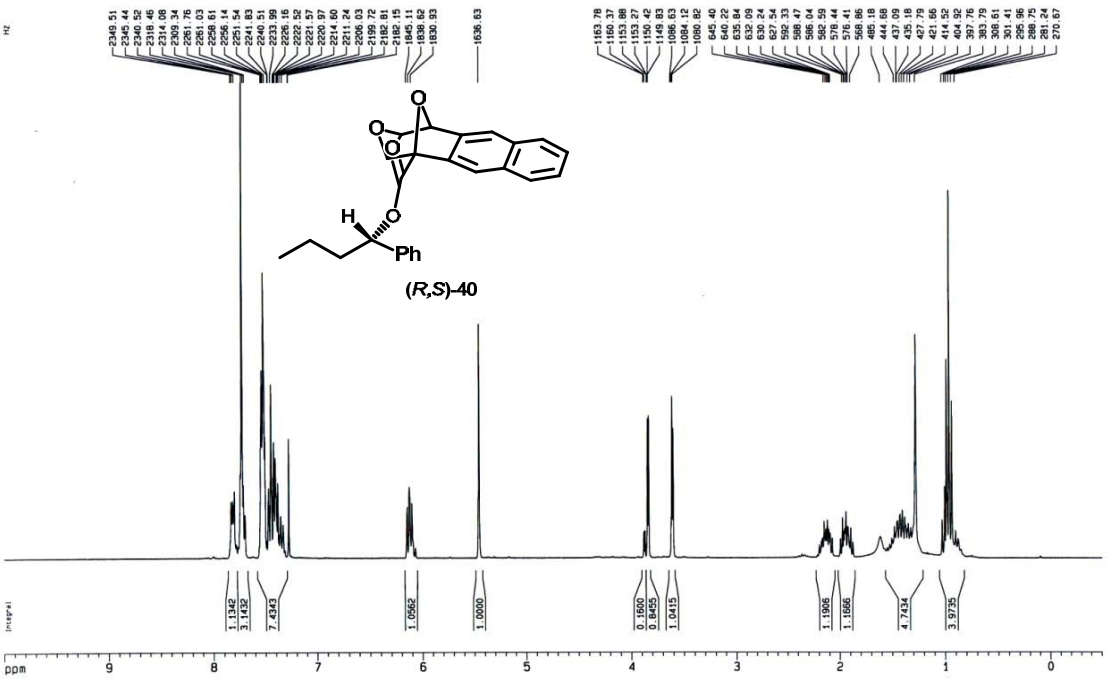


Figure A39. ^{1}H NMR spectrum of compound **(*R*,*S*)-40**.

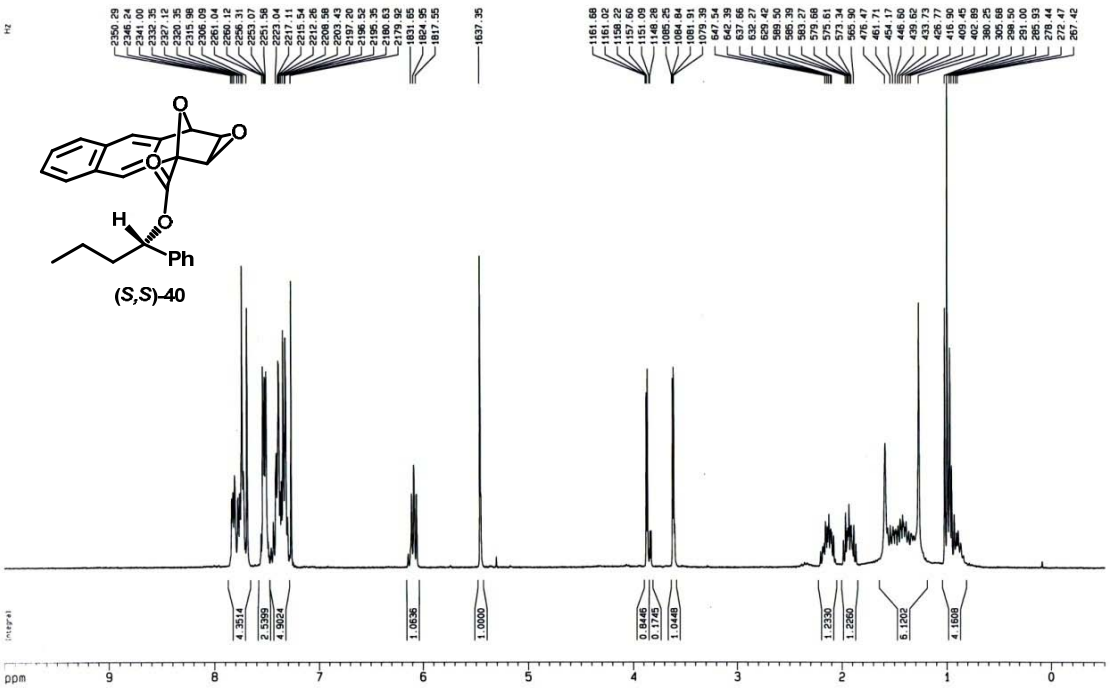


Figure A40. ^{1}H NMR spectrum of compound **(*S*,*S*)-40**.

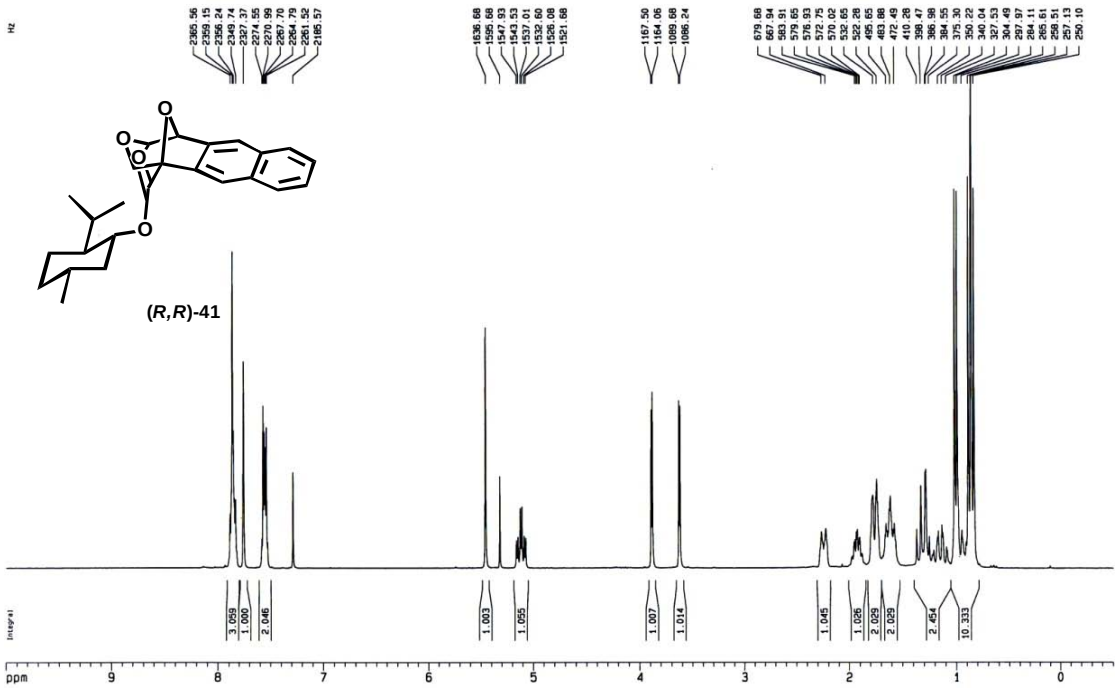


Figure A41. ^{1}H NMR spectrum of compound **(*R*,*R*)-41**.

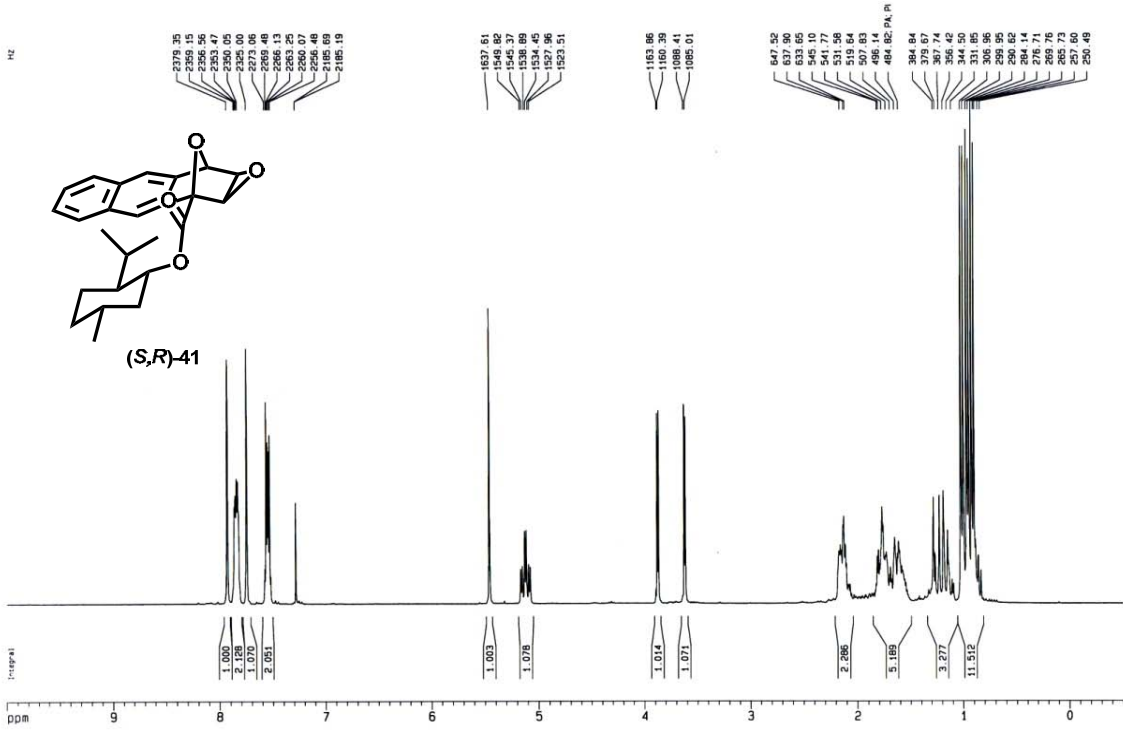


Figure A42. ^{1}H NMR spectrum of compound **(*S*,*R*)-41**.

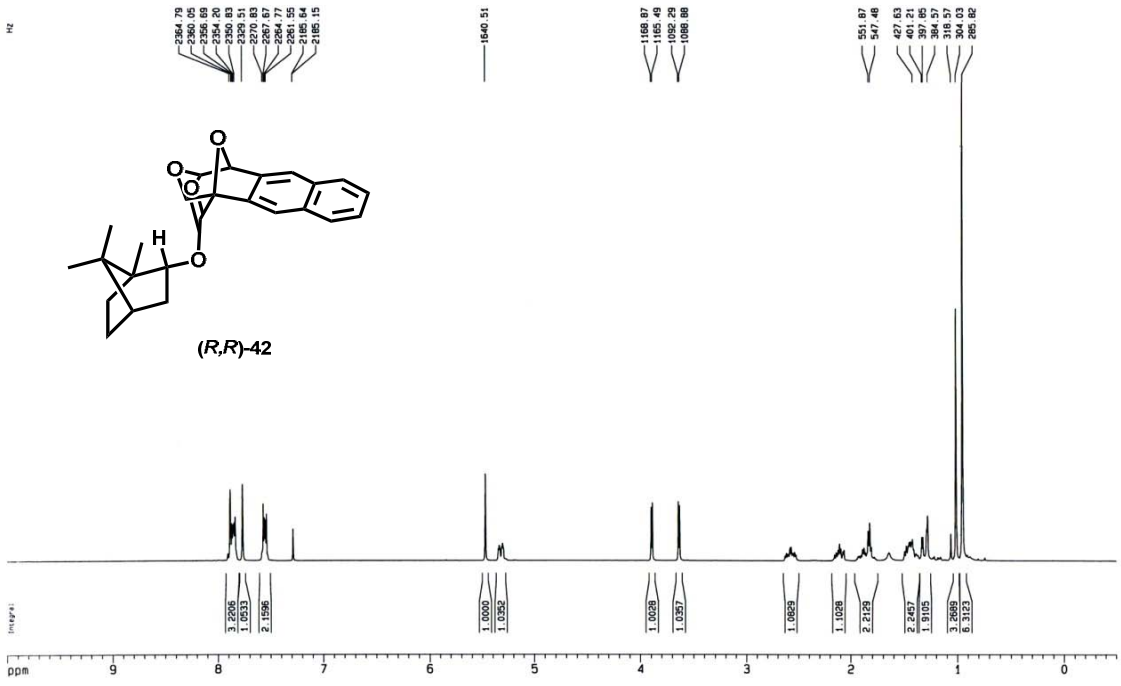


Figure A43. ^{1}H NMR spectrum of compound **(*R*,*R*)-42**.

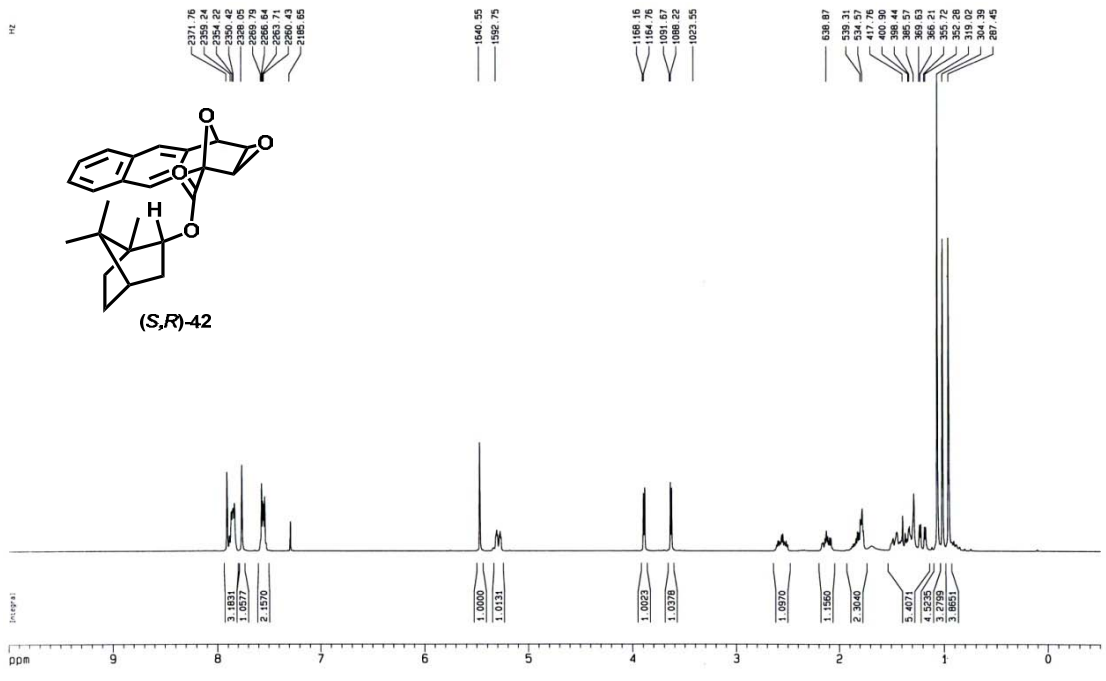


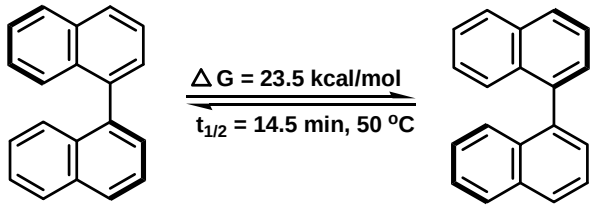
Figure A44. ^{1}H NMR spectrum of compound **(*S*,*R*)-42**.

PART II. Application of THENA for the resolution of binaphthol derivatives

Introduction

Atropisomerism[1,2] is a type of stereoisomerism that arises in systems where free rotation about a single bond is limited so as to allow different optical isomers to be isolated. Typically, atropisomerism appears in *ortho*-substituted biaryls where steric congestion between the substituents restricts free rotation about the sp^2–sp^2 carbon–carbon bond, increasing hindrance to the rotation at the pivotal 1,1'-bond, and thus makes these molecules resolvable into optically pure enantiomers.

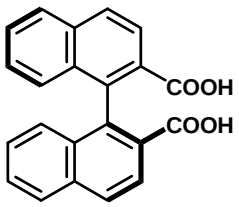
One interesting example of such biaryl systems was 1,1'-binaphthyl **3**, reported by Cooke and Harris in 1963.[3] The molecule was found to be optically active and its racemization half-life was 14.5 min at 50 °C (Scheme 1).



(*S*)-3 (*R*)-3

Scheme 1. Racemization energy of 1,1'-binaphthyl **3**.

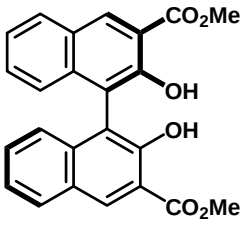
When substituents are introduced at 2,2'-position, the chiral configuration of the 1,1'-binaphthyl compounds becomes very stable. For example, the temperature of racemization of (*S*)-1,1'-binaphthyl-2,2'-dicarboxylic acid **5** is as high as 175 ºC (Figure 1).[4]



(*S*)-5

Figure 1. Optically active (*S*)-1,1'-binaphthyl-2,2'-dicarboxylic acid **5**.

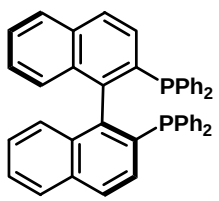
Absolute configuration of chiral binaphthyl compounds was first proposed by Mislow in 1958 on the basis of their optical properties, *i.e.* CD and ORD, stereochemical mechanism, and thermal analysis. This was later confirmed by Yamada and co-workers in 1971 from the X-ray analysis of (*R*)-(+)-2,2'-dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylate ester **6** and its chemical correlation with other binaphthyl molecules (Figure 2).[5]



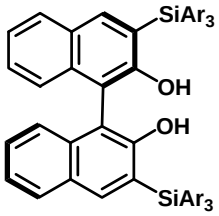
(*R*)-(+)-6

Figure 2. Optically active (*R*)-(+)-2,2'-dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylate ester **6**.

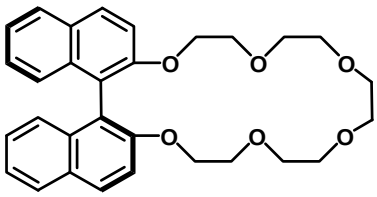
As a result of their highly stable chiral configuration, 2,2'-disubstituted-1,1'-binaphthyls have been used to control many asymmetric processes. Its rigid structure with C_2 symmetry plays an important role in chiral induction. Figure 3 shows examples of binaphthols which have been applied in asymmetric induction and catalysis.[6,7]



(*S*)-7



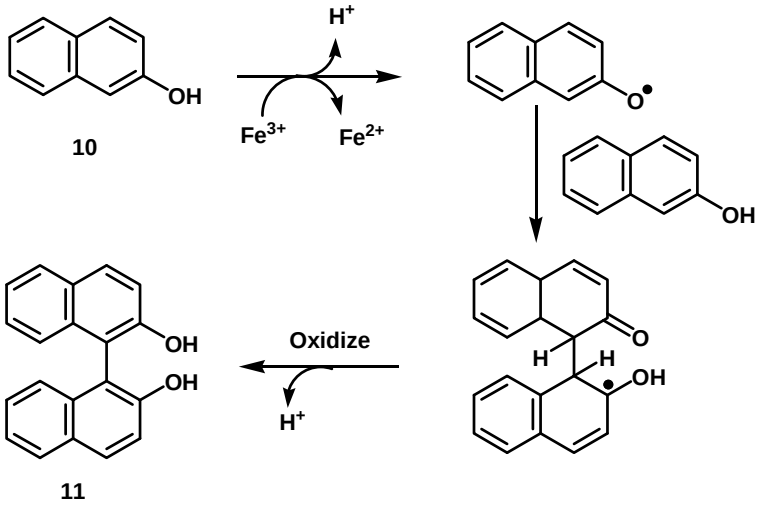
(*R*)-8



(*S*)-9

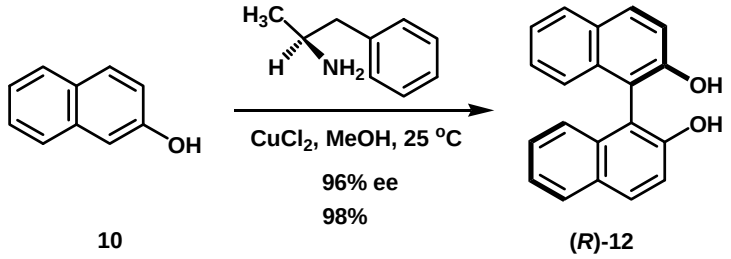
Figure 3. Examples of optically active binaphthol derivatives.

Thus it is essential to establish a simple and convenient method for the preparation of binaphthyl derivatives. Many procedures have been developed for the propose.[1] For example, two molecules of 2-naphthol **10** can be coupled by using iron (III) or copper (II) as the oxidizing agent to produce binaphthol **11** as shown in Scheme 2.[8]



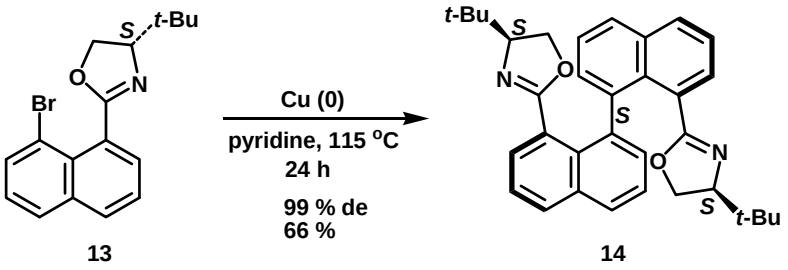
Scheme 2. Oxidative coupling of binaphthol.

Moreover, stereoselective aryl couplings have been reported by employing chiral copper-complex mediated phenolic oxidation. Optically active binaphthol, (*R*)-**12**, could be achieved in good yield with high optical purity (96% ee) (Scheme 3).[9]



Scheme 3. Asymmetric oxidative coupling of *β*-naphthol.

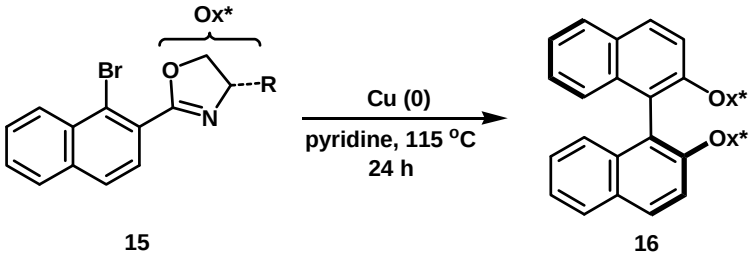
Meyers *et al*. also reported that (*S*)-oxazoline, when subjected to classical Ullmann conditions, could lead to bis-(oxazoline)-(*S*,*S*)-**14** as a single diastereomer (Scheme 4).[10] The difference in stability between the two diastereoisomers appears to be due to the steric interaction of the *tert*-butyl groups. This result implied that the addition of a steric factor, such as substituents at the 2 and 2' positions of the binaphthyl ring system, could raise the rotational barrier of the BINAP-type ligands and could make it usable as a chiral ligand.



13 14

Scheme 4. Enantioselective oxidative coupling by (*S*)-oxazoline.

Thus Meyers *et al.*[11] later applied this method to prepare binaphthyls with oxazoline substituents at the 2 and 2' positions (Scheme 5).



15 16

yields > 90 %

	(*S*):(*R*)
R= Ph	2: 1
R= *i*-Pr	4: 1
R= *t*-Bu	32: 1

Scheme 5. Enantioselective oxidative coupling of binaphthyl by several oxazolines.

The diastereomeric ratio of **16** was found to be sensitive to the size of the substituent (*R*) in the oxazoline ring. Determination of the transition states and copper intermediates revealed that one of the two diastereomeric copper complexes was free of any severe steric interaction caused by the close proximity of the (*R*)-substituents of the two oxazolines.

Besides the asymmetric approach to optically active binaphthyl derivatives, the resolution of racemic binaphthyls is an alternative route which has been proven to be very effective.

For example, an efficient, practical, and inexpensive method was described in 1993 by Brunel *et al.*[12] which involved the application of tricoordinated compound **18**, prepared from phosphorus trichloride and L-menthol (Scheme 6).