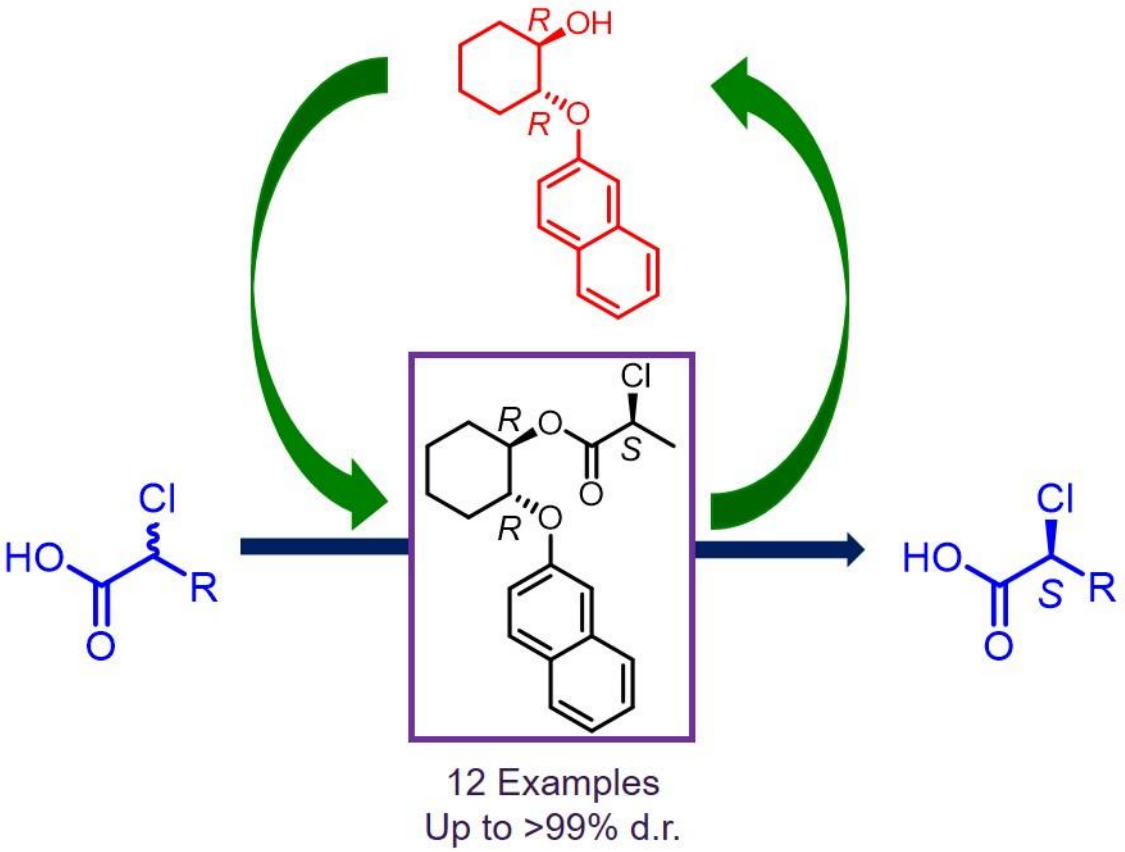
Chapter-3

Synthesis, Resolution and Application of cyclohexanol based chiral Auxiliary



3.1 Introduction:

Synthesis of optically pure organic compounds containing diverse functional groups is an important consideration in modern synthetic endeavours. Optically pure compounds can be obtained by several approaches, either from prochiral substrates by asymmetric synthesis or from racemic samples by various techniques of resolution of enantiomers. Although organo-catalysis and bio-catalysis have emerged as efficient methods to access important chiral molecules, chiral auxiliaries retain a prominent place in the field of asymmetric synthesis.

3.1.1 Chiral Auxiliaries:

In the realm of chiral auxiliaries a prominent position is acquired by chiral auxiliaries based on cyclohexanol framework.[1] The major advantages of cyclohexanol based auxiliaries are threefold in nature. Cyclohexanol derivatives structurally resemble to naturally occurring chiral reagents, thus resulting in wide applications as chiral pool, the rigid framework of cyclohexane ring provides good to high selectivity in stereoselective reactions and are commercial available. As a result some of the most successful chiral auxiliaries have been designed with cyclohexanol framework (Figure 3.1).

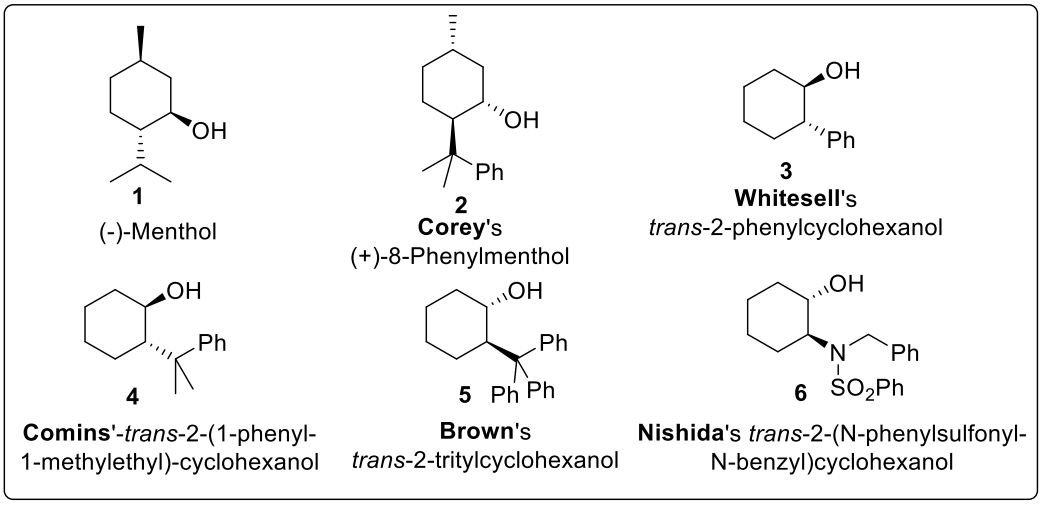
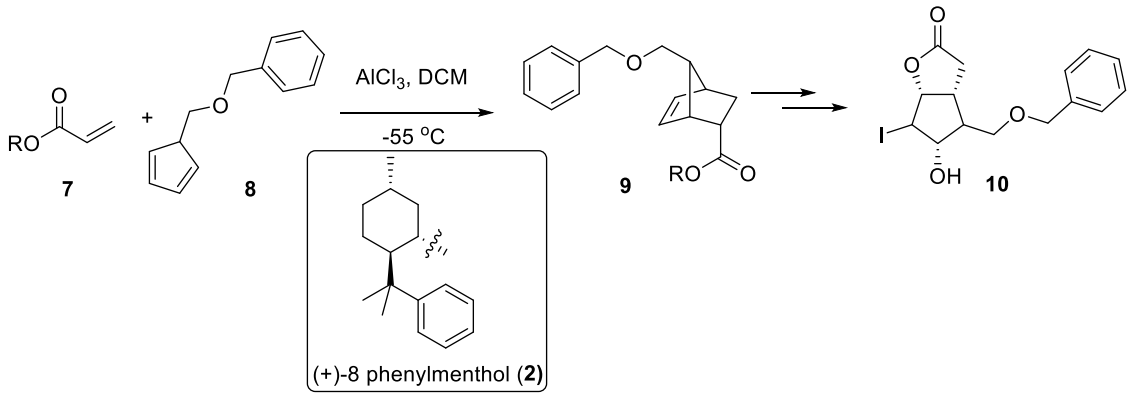


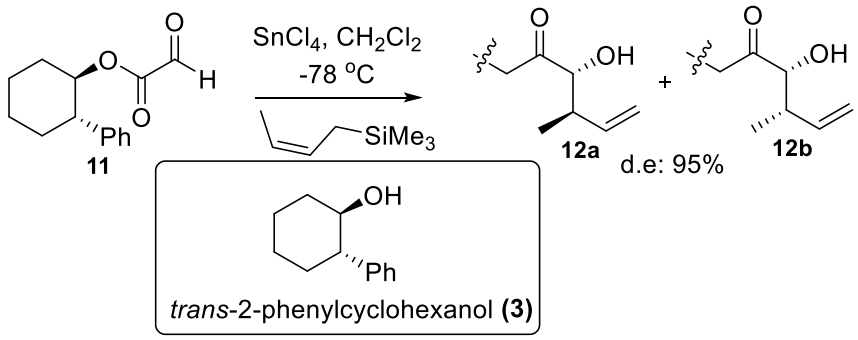
Figure 3.1: Commonly used cyclohexanol based chiral auxiliary.

Naturally occurring cyclohexanol based chiral molecules like (-)-menthol (**1)**, borneol, isoborneol, etc have been conventionally used in asymmetric synthesis as chiral auxiliaries.[2] Despite their natural availability, modifications in the naturally occurring cyclohexanol derivatives are essential to achieve greater levels of stereoinduction. Corey et al utilized menthyl derivative with neighbouring aromatic ring, (+)-8-phenylmenthol (**2)**, as chiral auxiliary in enantioselective synthesis of intermediate useful for the preparation of naturally occurring prostaglandin (Scheme 3.1).[3]



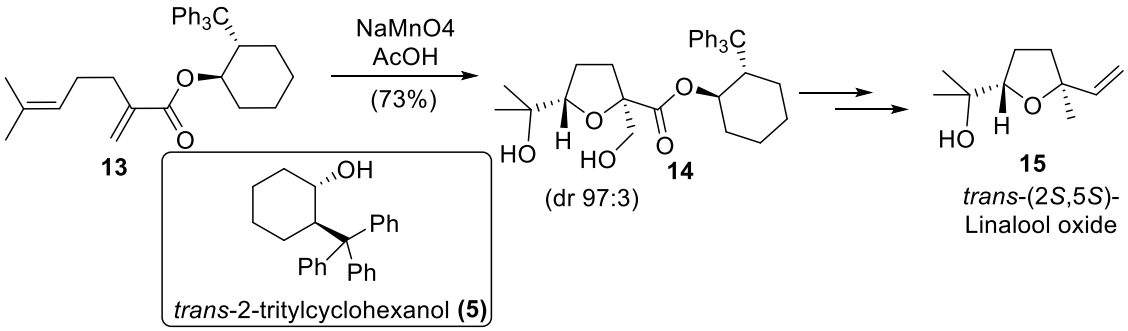
Scheme 3.1: Asymmetric Diels-Alder using (+)-8-phenylmenthol (**2**)

The introduction of the neighboring π-aromatic group on a chiral rigid cyclic structure in (+)-8-phenylmenthol **(2)** as auxiliary demonstrated the improved effectiveness of auxiliary in asymmetric transformations. (+)-8-Phenylmenthol (**2**) has since been successfully employed in many asymmetric processes to attain high level of selectivity. Although 8-phenylmenthol can be efficiently recovered for reuse, the multistep preparation required, is time consuming and thus presents an obstacle on its use. Moreover, access to its other enantiomer is limited due to unavailability of (+)-pulegone in nature. In order to overcome these limitations, Whitesell et al investigated chiral auxiliary *trans*-2-phenylcyclohexanol (**3**) as a substitute for (+)-8-phenylmenthol (**2**) in the ene reactions of the derived glyoxylate ester with similar level of stereoinduction.[4]



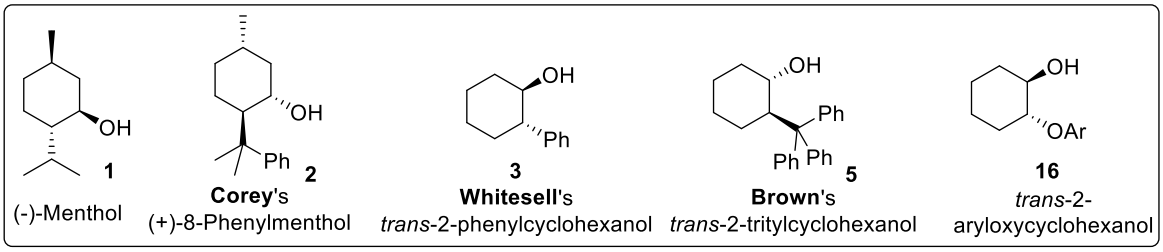
Scheme 3.2: Asymmetric ene-reaction using *trans*-2-phenylcyclohexanol.

The availability of both the enantiomeric forms of *trans*-2-phenylcyclohexanol (**3**) provides an added advantage over (+)-8-phenylmenthol (**2**). However the tedious synthesis of *trans*-2-phenylcyclohexanol (**3**) poses a major limitation on its use. Thus a new class of chiral cyclohexanol derivatives, *trans*-2-tritylcyclohexanol (**5**) has been developed with practical synthesis and resolution by forming menthyl oxalate.[5a] Brown et al have employed *trans*-2-tritylcyclohexanol (**5**) as chiral auxiliary in synthesis of *trans*-(2*S*,5*S*)-linalool oxide (**15**) with high levels of diastereoselectivity which is comparable to conventional cyclohexanol based auxiliaries (Scheme 3.3).[5b]



Scheme 3.3: Synthesis of *trans*-(2*S*,5*S*)-Linalool oxide using *trans*-2-tritylcyclohexanol

Another important class of chiral cyclohexanol derivative used in asymmetric synthesis is *trans*-2-aryloxy cyclohexanol (**16**). The aromatic ring of the ether unit (in **I**) provides an effective shield to control the stereochemistry in the asymmetric reactions using such auxiliaries.[6] The prochiral group attached on R (in **II**) can be attacked from both the faces. However, the aryl unit of the ether should block the back side attack and favour the front attack. This type of auxiliary is effectively employed to introduce chirality by nucleophilic addition reaction of PhZnCl on the prochiral ketone group attached in the form of phenylglyoxylate.[6b] The optically pure *trans*-2-aryloxycyclohexanol derivatives are structurally analogous to more popular auxiliaries like 8-phenylmenthol (**2**)[3] and 2-arylcyclohexanol (**3**),[4] particularly 2-tritylcyclohexanol (**5**).[5b]



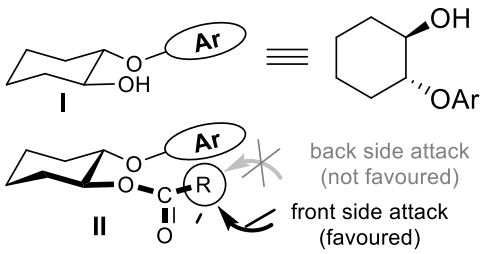


Figure 3.2: *trans*-2-aryloxycyclohexanol as **s**tructural analogue of conventional cyclohexanol based chiral auxiliaries.

However, not many applications of chiral 2-aryloxycyclohexanol in asymmetric synthesis are explored.

3.1.2 Dynamic resolution:

Along with asymmetric synthesis, the separation of enantiomers is an equally important aspect in accessing chiral molecules. This can be achieved by crystallization as salts with

chiral components, by chiral chromatography, crystallization as enantiomorphic solids or spontaneous resolution,[7] subjecting to enantioselective reactions based on difference in their kinetics. Many of these procedures are complex, resulting in the maximum yield of 50%. At the same time there are other strategies involving isomerization of the unwanted isomer in the reaction medium, therefore theoretically increasing the yield to quantitative level. The mechanism of isomerization of the unwanted enantiomer, may differ in such approaches like dynamic kinetic resolution (DKR),[8] dynamic kinetic asymmetric transformations (DYKAT)[9] or dynamic thermodynamic resolution (DTR),[10] where ultimately an optically pure product is formed in an efficient manner (Figure 3.3).

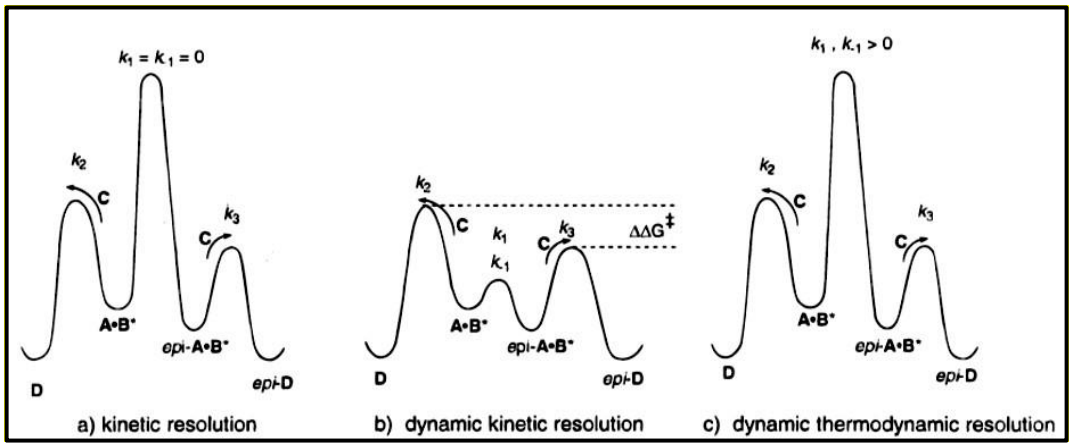


Figure 3.3: Energy diagrams for resolution by a) Kinetic resolution (KR); b) Dynamic Kinetic Resolution (DKR) and c) Dynamic Thermodynamic Resolution (DTR).[10a]

If the diastereomeric complexes **A•B*** and *epi*-**A•B*** do not interconvert and one reacts more rapidly with **C** ($k1 = k\text{-}1 = 0$ and $k2 \neq k3$), then a kinetic resolution may be effected. If the diastereomers **A•B*** and *epi*-**A•B*** equilibrate more rapidly than they react with **C** ($k1$, $k\text{-}1 >> k2$, $k3$), the product ratio is determined by the difference in energies for the two diastereomeric transition states ($\Delta\Delta G^{\ddagger}$). In a third scenario, **A•B*** and *epi*-**A•B*** can interconvert but do not equilibrate in the presence of the reagent **C** ($k1$, $k\text{-}1 > 0$), as represented in figure.[10a]

The developments in the area of DTR have mostly been in the reactions of organolithium reagents leading to generation of chiral products of diverse functionality.[11] The same approach of DTR has also been occasionally employed in deracemization of α-substituted derivatives of carboxylic acids. Few chiral alcohols have been utilised as auxilliaries to anchor the α-substituted acid unit to form esters,[12,13] which were subjected to the suitable conditions of DTR to control stereochemical output.

3.1.3 Importance of α-halo acids:

Optically pure α-halo acids are important class of compounds from synthetic aspect as they are key intermediates in synthesis of α-functional carboxylic acids. The optically pure α-substituted carboxylic acids are either part of the structural motifs of biologically significant compounds or are important intermediates for the synthesis of functional molecules, including amino acids. α–hydroxy acids, mercapto acids, chiral dihydroquinoxalones, chiral morpholinones, etc (Figure 3.4).[14]

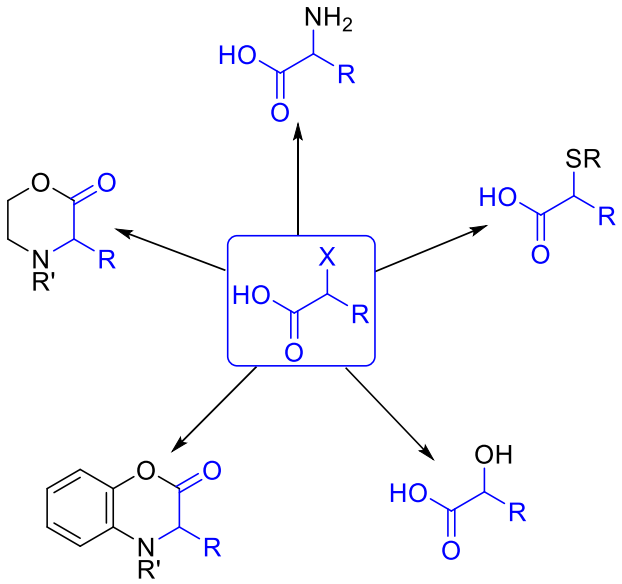


Figure 3.4: Transformations of α-halo acids

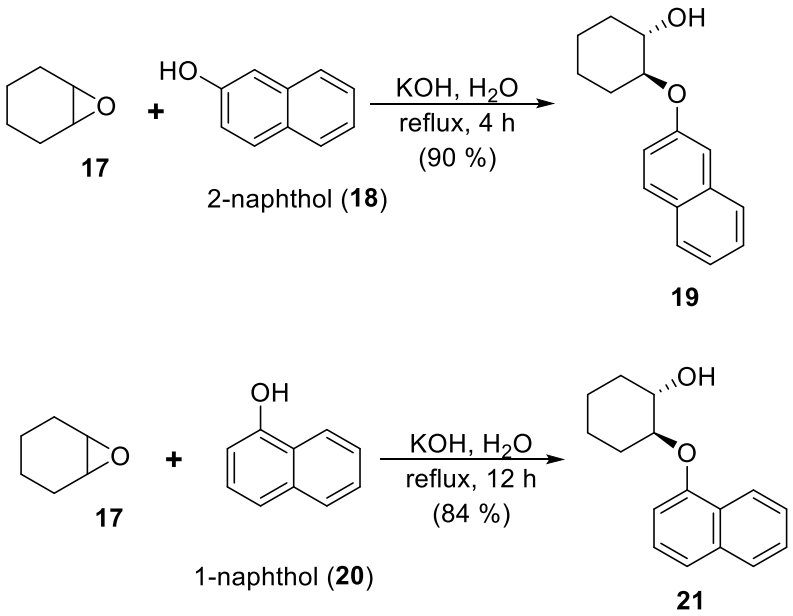
In this chapter, we shall present our studies in the synthesis, resolution and applications of *trans*-2-naphthyloxycyclohexanol as chiral auxiliary in synthesis of optically active α-halo esters by DTR driven deracemization procedure.

3.2 Result and Discussion:

3.2.1 Synthesis of Auxiliary:

The auxiliaries *trans*-2-aryloxycyclohexanol derivatives were synthesized in racemic form by epoxide ring opening of *meso* cyclohexeneoxide (**17**) with corresponding phenoxides formed by treatment with aq. base.[15] The design of our auxiliaries, (**19**) and (**21**) (Scheme 3.4), consists of naphthalene unit as the aryl moiety due to its steric and electronic properties. The naphthalene unit can direct the key step of the process of stereoselection by virtue of C*H*-π and π-π interactions. Accordingly, we obtained *trans*-2-(naphthalene-2-yloxy)cyclohexanol (**19**) and *trans*-2-(naphthalene-1-yloxy) cyclohexanol (**21**) by reaction of cyclohexeneoxide (**17**) with corresponding

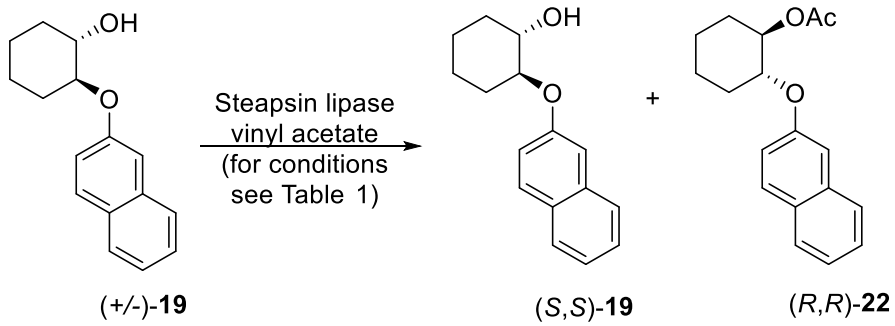
naphthoxides, (**18**) or (**20**), prepared *in situ* with aqueous potassium hydroxide at reflux conditions (Scheme 3.4).[16]



Scheme 3.4: Synthesis of *trans*-2-naphthyloxycyclohexanol (**19**) and (**21**).

3.2.2 Enzymatic Resolution of alcohols:

Having obtained the required racemic samples of alcohols (**19**) and (**21**) in racemic form, we subjected them for resolution by well-established enzyme mediated kinetic resolution protocol.[2] The selective acylation of one enantiomer can be achieved by modulating the reaction conditions using combination of suitable biocatalyst, acyl donor, solvent, duration etc. The optimization procedure was performed on alcohol (±)-(**19**) as a model substrate (Scheme 3.5, Table 3.1). The initial experiment was performed in THF with commercially available Steapsin lipase as immobilized biocatalyst and vinyl acetate as acyl donor, resulting in formation of acetate (**22**) with high optical purity, albeit in low chemical yield. It was further observed that increasing the amount of vinyl acetate resulted in better conversion without loss in selectivity. It was observed that changing the solvent from THF to dioxane resulted in further decrease in chemical yield with no loss of optical purity, however changing the solvent to ethyl acetate resulted in better chemical yield with almost optically pure acetate (**22**). The chemical yield was further improved by increasing the amount to enzyme and reaction time. The reaction showed much improved conversion when it was continued for longer period (9 d) with 3 eq. (w/w) in ethyl acetate. Furthermore it was observed that performing the resolution experiments at high dilution resulted in near perfect conversion and enantioselectivity.



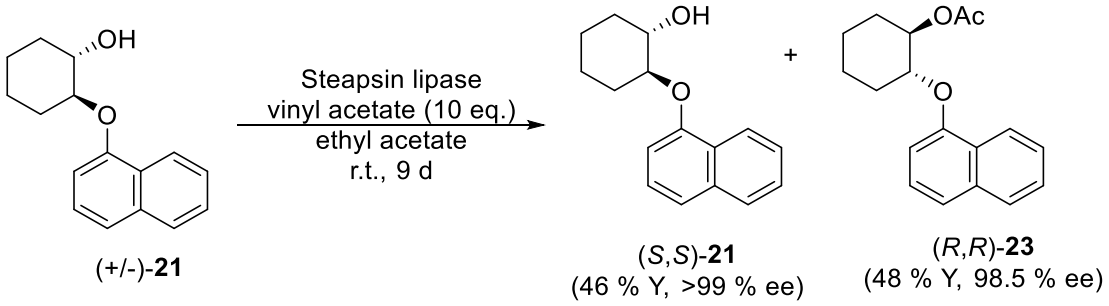
Scheme 3.5: Resolution of (+/-)-(**19**)

Table 3.1: Optimizing conditions for Enzymatic Resolution of (+/-)-(**19**) with Steapsin

Entry	Eq. of VA[a]	Solvent	Lipase w/w eq.	Time (d)	% ee of **22** (%)[b]	% ee of **19** (%)[b]
1	3.0	THF	1.5	3	>99 (17)	13 (57)
2	10.0	THF	1.5	3	>99 (22)	27 (60)
3	10.0	EA	1.5	6	>99 (36)	51 (53)
4	10.0	Dioxane	1.5	6	>99 (22)	13 (46)
5	10.0	EA	3.0	6	>99 (45)	83 (52)
6	10.0	EA	3.0	9	>99 (47)	92 (51)
7	10.0	EA[c]	3.0	9	>99 (48)	>99 (49)

[a]Vinyl acetae; [b]Isolated yield; [c]High dilution; (E >200 in all cases); EA = ethyl acetate;

The above optimized experimental condition was extended for the resolution of other alcohol (+/-)-(**21**) with similar success (Scheme 3.6). The alcohol (**21**) yielded acetate (**23**) in 98.5 % ee while the unreacted alcohol was found to be almost optically pure. The optical purity of all the products of resolution was established by chiral solid phase HPLC analysis without any derivatization.

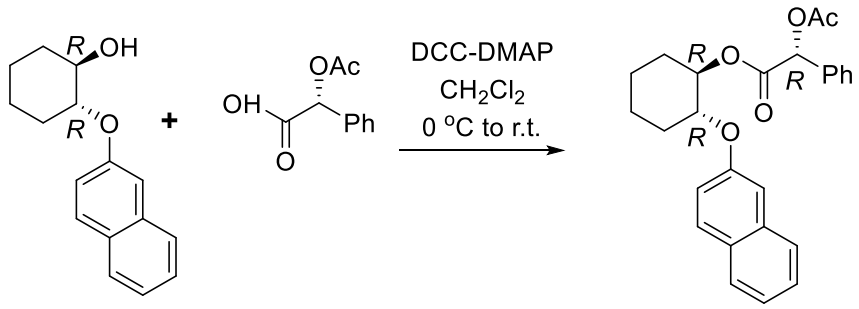


Scheme 3.6: Resolution of (+/-)-(**21**)

An important aspect of asymmetric synthesis involving chiral auxiliary is the accessibility of auxiliary in both the enantiomeric forms. For this purpose the *O*-acetyl derivative (**22**), obtained from enzymatic resolution, was subjected to acid mediated hydrolysis yielding the other enantiomer of alcohol (**19**) without any loss of optical purity thus accessing both the enantiomeric forms of auxiliary (**19**). Similar protocol was followed for the acetate (**23**) in order to access the other enantiomer of alcohol (**21**) in optically pure form thus obtaining both the isomers of auxiliaries (**19**) and (**21**).

3.2.3 Determination of Absolute Configuration:

The correlation of absolute configuration of both the optically pure alcohols (**19**) and (**21**), could not be established due to the lack of literature reference as both the alcohols are being reported in racemic forms. Hence, we converted the alcohols into their ester derivatives with acid of known chiral element. The corresponding diastereomeric esters were purified and their stereochemistry was established by single crystal X-ray analysis. The optically pure alcohols, obtained by careful hydrolysis of *O*-acetyl derivatives (**22**) and (**23**), were treated with (*R*)-*O*-acetyl mandelic acid in the presence of DCC and DMAP under Steglich esterification condition,[17] where the corresponding esters (**24**) and (**25**) were obtained by purification through column chromatography (Scheme 3.7 and 3.8). Their suitable crystals were grown from hexane-dichloromethane and subjected for single crystal X-ray diffraction analysis (Figure 3.5 and 3.6).

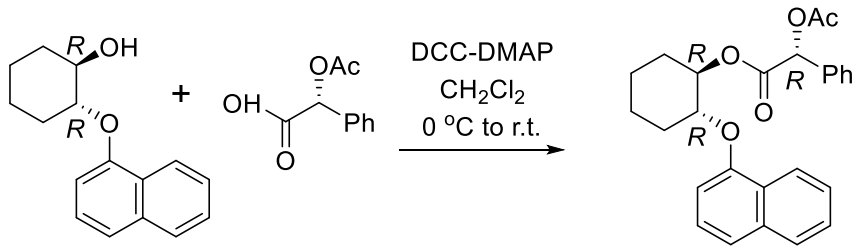


(*R,R*)-**19**

(*R,R,R*)-**24**
(94%)

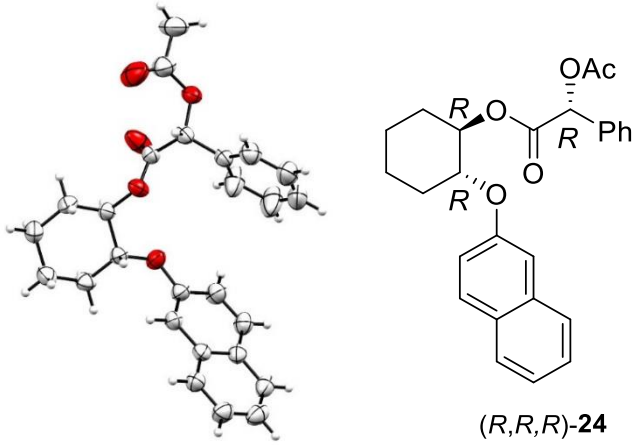
Scheme 3.7: Determination of absolute configuration of optically pure alcohol (*R,R*)-**19**

The single crystal X-ray analysis established the configuration of the unreacted isomer of the alcohols as well the acylated products. The alcohol (**19**) obtained by hydrolysis of *O*-acyl derivative **(22**) exhibited *R,R* configuration while the unreacted alcohol showed *S,S* configuration. Similar trend was observed in case of alcohol (**21**) where the hydrolysed alcohol exhibited *R,R* configuration.



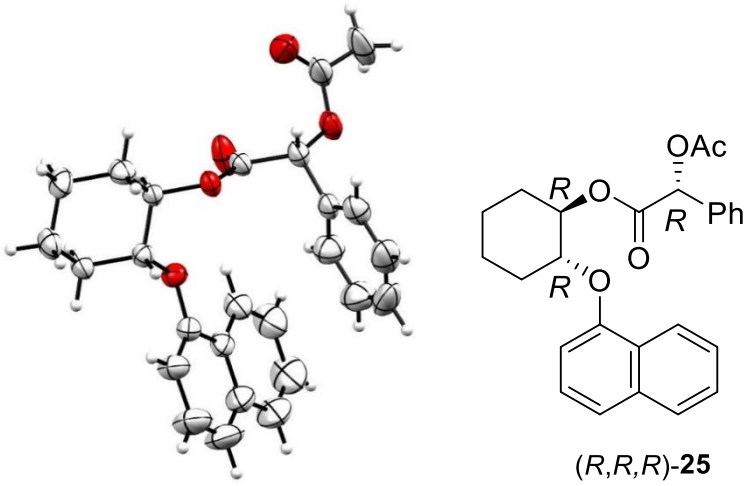
(*R*,*R*)-**21** (*R*,*R*,*R*)-**25** (91 %)

Scheme 3.8: Determination of absolute configuration of optically pure alcohol (*R*,*R*)-(**21**)



(*R*,*R*,*R*)-**24**

Figure 3.5. Determination of absolute configuration of (*R*,*R*,*R*)-(**24**) (ORTEP diagram; CCDC1854344)



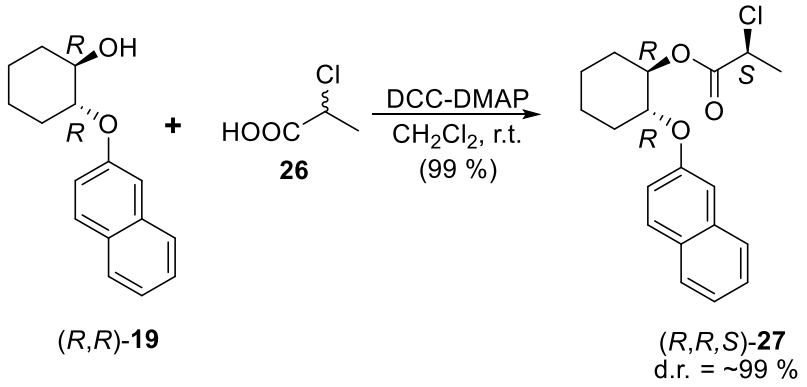
(*R*,*R*,*R*)-**25**

Figure 3.6. Determination of absolute configuration of (*R*,*R*,*R*)-(**25**) (ORTEP diagram; CCDC1854340)

3.2.4 Deracemization of α-halo acids:

The objective of the present study is to establish the scope of these two optically pure derivatives of *trans*-2-naphthyloxycyclohexenols as chiral auxiliary for deracemization of α-halo esters. In this endeavour the optically pure alcohol (*R*,*R*)-(**19**), obtained by

hydrolysis, was treated with racemic 2-chloropropanoic acid (**26**) under the standard coupling conditions in presence of DCC and DMAP as base[17] (Scheme 3.9). The formation of ester was a smooth process, the pure product (**27**) was isolated in near quantitative yield and its NMR analysis indicated the presence of a single diastereomer. The Cα*H* of (**27**) appeared as a q (4.29 – 4.34 δ) in ^{1}H NMR analysis ($CDCl_3$, 400 MHz). To establish the stereochemistry of Cα*H* chiral centre, a suitable crystal of ester (**27**) was subjected to single crystal analysis indicating the configuration as 'S' (Figure 3.7).



Scheme 3.9: Deracemization of α-halo acid

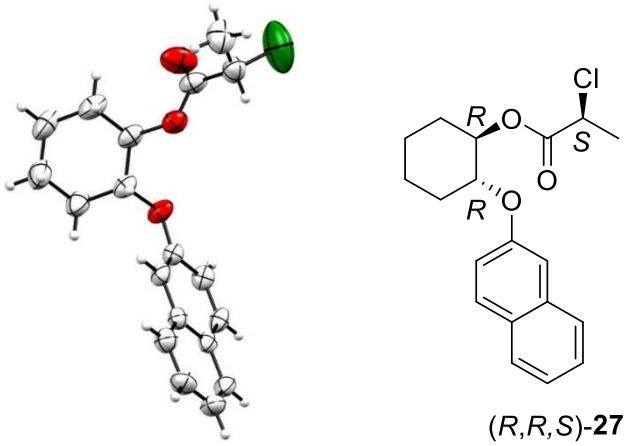


Figure 3.7. Determination of absolute configuration of (*R*,*R*,*S*)-(**27**) (ORTEP diagram; CCDC1854341)

To further establish the stereochemistry of Cα*H* chiral centre, the other diastereomeric ester (*R*,*R*,*R*)-(**27**), with opposite stereochemistry at the newly generated chiral center (Cα*H*), was prepared by coupling (*R*,*R*)-(**19**) with (*R*)-(**26**) and its ^{1}H NMR spectra was recorded. The Cα*H* of (*R*,*R*,*R*)-(**27**) showed a q for Cα*H* at 4.23 – 4.28 δ, which was distinguishable and quantifiable for further optimization study (Figure 3.8).

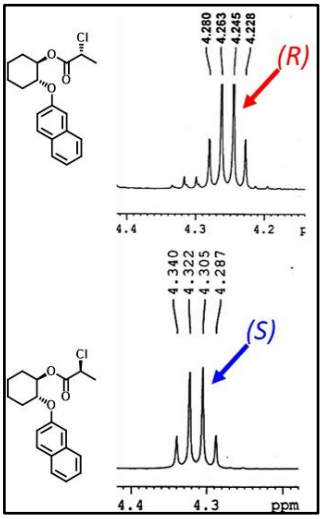
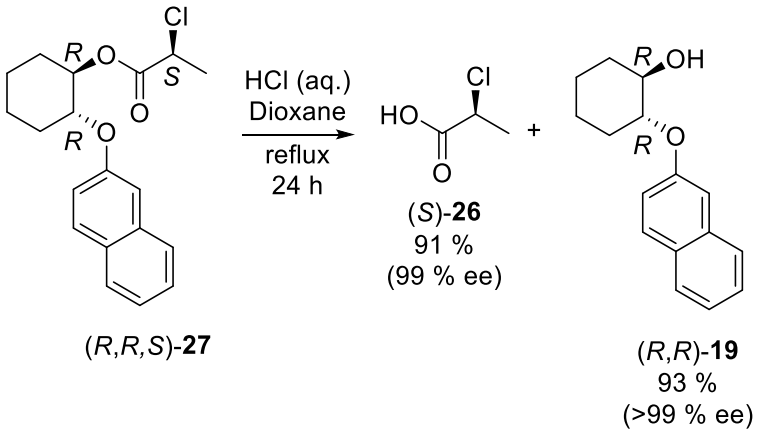


Figure 3.8: Selected region of ^{1}H NMR Spectra of (*R,R,R*)-(**27**) (top) and (*R,R,S*)-(**27**) (bottom)

Furthermore the configuration of C$_{\alpha}$*H* of (*R,R,S*)-(**27**) was also confirmed by performing its acidic hydrolysis and isolating (*S*)-2-chloropropanoic acid, (*S*)-(**26**), without loss of optical purity, by comparing the sign of optical rotation with the literature value (Scheme 3.10). Moreover there was no substantial loss in chemical yield as well as the optical purity of the recovered chiral auxiliary (*R,R*)-(**19**), which is an important and essential criteria for application as chiral auxiliary.



Scheme 3.10: Generation of optically pure (*S*)-**26**

The choice of base in the stereochemical consideration, in the deracemization of similar substrates, plays a crucial role in the final outcome of such reactions.[12d,18] The role of base in this deracemization was also investigated in detail (Table 3.2). It was observed that varying organic bases from DMAP to DABCO showed almost single diastereomeric product while triethyl amine also showed high d.r. of around 98%, while inorganic base like potassium carbonate too showed comparable result.

Table 3.2: Effect of base in deracemization of (**27**)

Entry	Base[a]	% d.r. of **27**[b] (α-*R*:α-*S*)
1	DMAP	0.5:99.5
2	DABCO	0.5:99.5
3	Et_3N	1.0:99.0
4	K_2CO_3	1.5:98.5

[a]20.0 mol % along with DCC (1.0 eq.); [b]Determined by CSP-HPLC (Lux Amylose-2)

The process of deracemization may involve two possible pathways, depending on the kinetic (DKR) or thermodynamic (DTR) aspect. The possible mechanism of deracemization may favour dynamic resolution, since in all the cases, the observed chemical yield being near quantitative. To further explore this possibility, the reaction was performed at three different reaction temperatures to investigate this aspect (Table 3.3). In case of racemic sample of acid (**26**), the reaction showed formation of ester (**27**), as almost a single diastereomer (>99 % d.r.), within the studied temperature range of 0 ^oC to reflux temperature of CH_2Cl_2. The reaction was then performed using scalemic mixture of (*R*)-(**26**), (67:33) under similar temperature range. While in this study, the reaction product (**27**) at ambient and reflux temperature showed d.r. of around 72%, which dropped to 50% at low temperature (0 ^oC). This observation probably suggests the possibility of the mechanism to be dynamic thermodynamic resolution (DTR).[7a]

Table 3.3: Effect of temperature on diastereoselectivity of (**27**) (see Scheme 3.9)[a]

Entry	Initial composition of **26** (*R*:*S*)	Temperature (^oC)	% d.r. of **27**[b] (α-*R*:α-*S*)
1	50:50	reflux	0.5:99.5
2	50:50	r.t.	0.5:99.5
3	50:50	0 ^oC	0.5:99.5
4	67:33	reflux	14.0:86.0
5	67:33	r.t.	14.0:86.0
6	67:33	0 ^oC	25.0:75.0

[a]DMAP (20.0 mol %), DCC (1.0 eq.); [b]Determined by CSP-HPLC (Lux Amylose-2)

The reaction of alcohol (*R*,*R*)-(**19**) with scalemic mixture of (**26**) which initially had the ratio in favour of *R* isomer (*R*:*S* was 67:33), under the standard coupling condition (DCC, DMAP, CH_2Cl_2 or $CHCl_3$), was monitored at different time intervals. The diastereomeric ratio of the product (**27**) was monitored with increase in time. The acid (**10**) which initially had an enantiomer ratio in favour of *R* isomer (33 % e.e.) on coupling with (*R*,*R*)-(**19**) underwent inversion at Cα*H* chiral centre with product ester (**27**) exhibiting *S* configuration at Cα*H* as major product. It was observed that the diastereomeric ratio of ester (*R*,*R*,*S*)-(**27**) improved with the progress of the reaction (Table 4). The d.r. of the product after 3h was 69% which increased to around 72% after 12h. Further continuation of reaction (24 h) leads to increase in d.r. to around 80% while the same reaction when continued for 48h showed increased d.r. of 84%. This gradual increase in the d.r. of product in favour of (*R*,*R*,*S*)-(**27**) suggests that the epimerization process at the chiral centre of Cα*H* of (**27**) proceeds after the ester formation step thereby increasing the d.r. in favour (*R*,*R*,*S*)-(**27**). This study helps us to further establish the mode of deracemization via the epimerization process, which must be controlled by the stereochemistry of the chiral *trans*-2-aryloxycyclohexanol auxiliary.

Table 3.4: Effect of time on diastereoselectivity of (**27**) (see Scheme 3.6)

Entry	Time (h)	d.r. of **27**[b] (α-*R*:α-*S*)	% d.e. of (*R*,*R*,*S*)-**27**[b]
1	0.5	16.0:84.0	68.0
2	1.0	16.0:84.0	68.0
3	3.0	15.5:84.5	69.0
4	6.0	15.0:85.0	70.0
5	12.0	14.0:86.0	72.0
6	18.0	11.0:89.0	78.0
7	24.0	10.0:90.0	80.0
8	48.0	8.0:92.0	84.0

[a]DMAP (20.0 mol %), DCC (1.0 eq.), initial composition of (**26**) (*R*:*S* was 67:33); [b]Determined by CSP-HPLC (Lux Amylose-2)

The effect of initial optical composition of 2-chloropropanoic acid (**26**) on the stereochemical outcome of deracemization product was studied by conducting a series of experiments with varying enantiomer ratio of acid (Table 3.5). As we progress from

higher optical purity of (**26**) in favour of *R*-isomer [80 % e.e. of (*R*)-(**26**)] to its racemic sample, the diastereomeric ratio of the ester product (**27**) gradually increases in favour of (*R,R,S*)-(**27**). The acid (**26**) with an initial composition of (80% e.e. of (*R*)-(**26**) resulted in product (**27**) with d.r. around 5% in favour of (*R,R,S*)-(**27**) thus indicating epimerization at C$_\alpha$*H*. The gradual change in the optical purity of acid (**26**) from 80% e.e. of (*R*)-(**26**) to 10% e.e of (*R*)-(**26**) results in improved d.r of (*R,R,S*)-(**27**) from 5% to 92%. This observation suggests the dependence of initial composition of the coupling partner 2-chloropropanoic acid on the ultimate diastereoselectivity of ester (**27**). Such observation of the relationship of initial composition of acid (**26**) and the final stereochemical output of deracemization is in accordance with the reported example.[10f]

Table 3.5: Effect of initial composition of acid (**26**) on diastereoselectivity of (**27**) (see Scheme 3.6)[a]

Entry	Initial composition of **26** (*R*:*S*)	Product ratio[b] (*R,R,R*)-**27**:(*R,R,S*)-**27**	% d.e.[b] of (*R,R,S*)-**27**
1	90:10	47.5:52.5	5
2	75:25	23.5:76.5	53
3	67:33	14:86	72
4	60:40	10:90	80
5	55:45	4:96	92
6	50:50	0.5:99.5	99

[a]DMAP (20.0 mol %), DCC (1.0 eq.), Reaction time was 12 h; [b]Determined by CSP-HPLC (Lux Amylose-2)

Based on these detailed investigations, we can summarise the plausible reaction pathway in Figure 3.9. The esterification reaction between optically pure alcohol (*R,R*)-(**19)** and racemic acid (**26**) in presence of DCC and DMAP results in the formation of diastereomeric ester (**27**). The base deprotonates the initially coupled diastereomeric ester (**27**) resulting in the formation of enolate intermediate (**28**). This enolate intermediate may undergo re-protonation from the two possible faces / sides leading to formation of two diastereomeric ester products (*R,R,R*)-(**27**) and (*R,R,S*)-(**27**). The re-protonation of enolate (**28**) from Path-A, involves the back side attack on proton, thus furnishing the observed ester diastereomer (*R,R,S*)-(**27**); while the front side attack on proton by Path-B should result in the formation of its epimer (*R,R,R*)-(**27**). Probably due

to the steric crowding offered by the proper orientation of naphthalene ring of naphthyloxy moiety, the former mode of attack in Path-A is more feasible resulting in formation of observed ester (*R*,*R*,*S*)-(**27**) thus supporting the experimental observation.

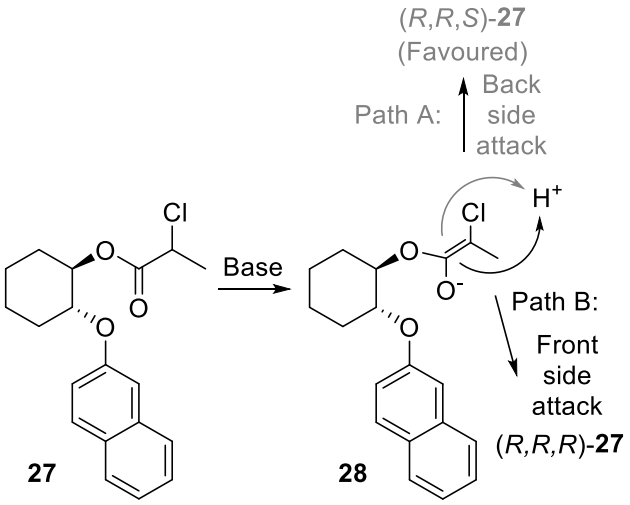


Figure 3.9. Probable mechanism of selective deracemization.

The observation of deracemization in favour of (*R*,*R*,*S*)-(**27**) was further validated by density functional theory (DFT) study of the final diastereomers of ester (**27**) at the B3LYP/6-31+G(d) level.[19] Figure 3.10 depicts the relative energies of both the diastereomers of (**27**). The difference in energy between (*R*,*R*,*S*)-(**27**) and (*R*,*R*,*R*)-(**27**) is about 2.1 kJ/mol which is in agreement with the experimental results and the stereochemical outcome of the deracemization reaction.

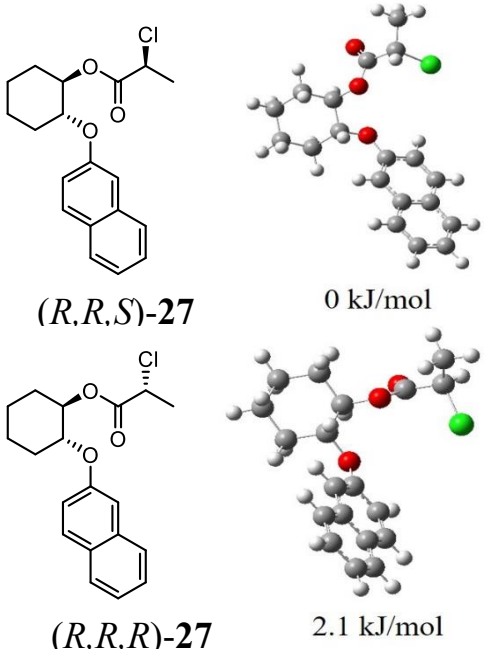


Figure 3.10. Optimized structures of the diastereomers (*R*,*R*,*S*)-(**27**) and (*R*,*R*,*R*)-(**27**) and their relative energies

In the present study we have also synthesized another derivative of naphthyloxycyclohexanol (*S*,*S*)-(**21**), prepared from 1-naphthol (**20**) and cyclohexeneoxide (**17**) (Scheme 3.4). A similar esterification reaction of optically pure alcohol (*S*,*S*)-(**21**) and (+/-)-2-chloropropanoic acid (**26**), under optimized esterification and deracemization condition resulted in the formation of ester (**30a**) with moderate selectivity (68% d.e.; Table 3.6). The ratio of diastereomers of (**30a**) was established by ^{1}H NMR, where the C$_{\alpha}$*H* hydrogen appeared as a distinguishable q signal in the range of 4.1 - 4.3 δ as shown in Figure 3.11.

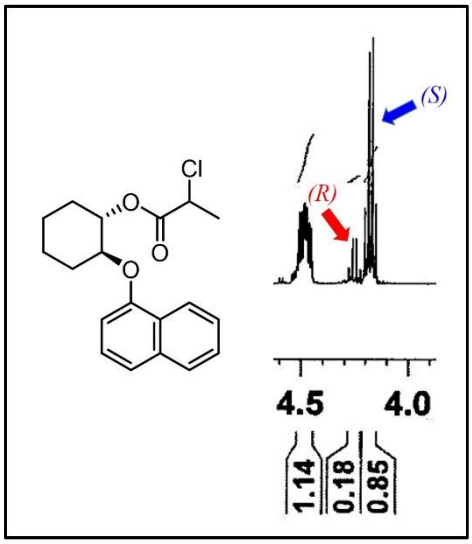


Figure 3.11: Selected region of ^{1}H NMR Spectra of **30a**

In comparison to auxiliary (*R*,*R*)-(**19**), the auxiliary (**21**), showed much lower selectivity with a d.r. value of 68%. This much lower selectivity in this case of deracemization with auxiliary (**21**) could be attributed to two aspects, the steric factors pertaining to the orientation of naphthalene unit of the auxiliary which may not be suitably blocking the face as to provide better stereoselectivity and the lower relative energy difference of the diastereomers of (**30a**) (1.6 kJ/mol) (Figure 3.12) compared to the diastereomers of (**27**) where the relative difference in energy was observed to be higher (2.1 kJ/mol). In both these examples, (**27**) and (**30a**), we have observed the formation of thermodynamically more stable diastereomer as the major product, strengthening the probability of dynamic thermodynamic resolution mechanism in this reaction.

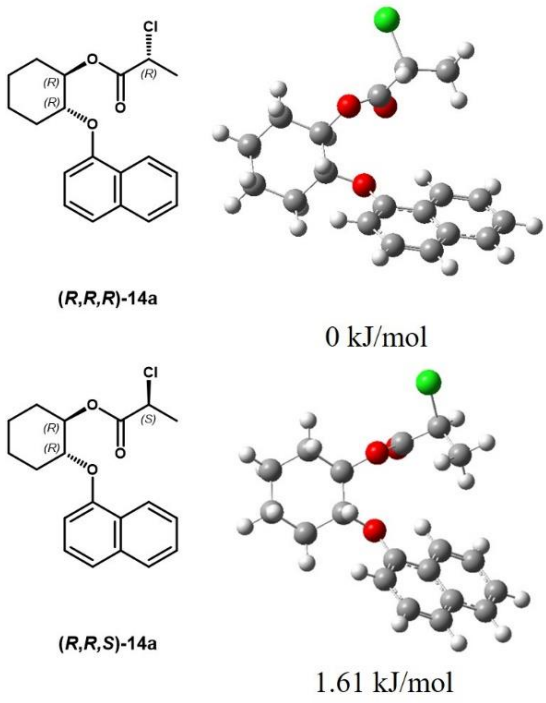
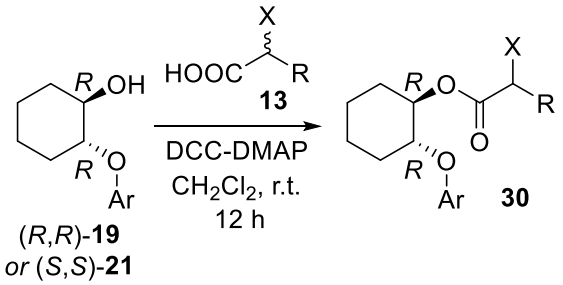


Figure 3.12: Optimized geometries and Relative energies of diastereomeric esters (*R*,*R*,*R*)-(**30a**) and (*R*,*R*,*S*)-(**30a**)

The better selectivity with auxiliary (*R*,*R*)-(**19**) led us to select it for further screening of examples of deracemization (Table 3.6). The reaction of alcohol (*R*,*R*)-(**19**) with 2-bromopropanoic acid resulted in the formation of ester (**30b**) (66% d.e.), which is lower as compared to its chloro analogue, which could be attributed to higher acidity of C$_\alpha$*H*, making its abstraction a more facile process. Replacing methyl with ethyl group in the next example, (**30c**), led to decrease in diastereoselectivity (50% d.e.), which is in agreement with the earlier reports.[10d,10f] Furthermore, introducing bulkier group in (**30e**), resulted in diminished selectivity for chloro analogue (42% d.e.), however marginal reversal was detected for the bromo analogue (**30f**) (46% d.e.). We also examined the case of 2-halo-3-phenylpropanoic acid and 2-halophenylacetic acid as coupling partners in this deracemization study. In the case of 2-chloro-3-phenylpropanoic acid the diastereomer (**30g**) was isolated with moderate selectivity (43%, d.e.), while for its bromo derivative, (**30h**), a small drop in selectivity was seen (38% d.e.). In the case of 2-chlorophenylacetic acid, the selectivity of (**30k**) was observed to be much reduced (34% d.e.), while for its bromo derivative (**30j**), it was much improved (65% d.e.). In the two sets of examples with bulkier substituents, isopropyl and phenyl, the trend was similar. The lower selectivity in the case (*S*,*S*)-(**21**) was also observed in the example with 2-bromophenylacetic acid, as the product (**30i**), was isolated in poor selectivity (8 % d.e.).

In some of the examples (**30a**, **30b** and **30j**) we could observe considerable enrichment of optical purity (98-99 d.e) on a single set of recrystallization, which is an expected phenomenon.[10d] The structures of all the α-halo esters prepared in this study are presented in Chart 3.1.

Table 3.6: Effect of substituents on diastereoselectivity of α-halo esters[a]



Entry	Chiral auxiliary	R in α-halo acid (**26**/**29**)	X in α-halo acid (**26**/**29**)	Yield (%)	% d.e.[b] [**14**]
1	(*S*,*S*)-**21**	Me	Cl	98	68 [(*S*,*S*,*S*)- **30a**] [b,c]
2	(*R*,*R*)-**19**	Me	Cl	99	>99 [(*R*,*R*,*S*)-**27**] [b]
3	(*R*,*R*)- **19**	Me	Br	98	66 [(*R*,*R*,*S*)- **30b**] [b]
4	(*R*,*R*)- **19**	Et	Cl	97	50 [**30c**][b,d]
5	(*R*,*R*)- **19**	Et	Br	98	40 [**30d**][b,d]
6	(*R*,*R*)- **19**	i-Pr	Cl	98	42 [**30e**][b,c,d]
7	(*R*,*R*)- **19**	i-Pr	Br	96	46 [**30f**][c,d]
8	(*R*,*R*)- **19**	Bn	Cl	94	43 [**30g**][b,d]
9	(*R*,*R*)- **19**	Bn	Br	92	38 [**30h**] [b,d]
10	(*S*,*S*)-**21**	Ph	Br	95	8 [**30i**] [b,d]
11	(*R*,*R*)- **19**	Ph	Br	98	65 [(*R*,*R*,*R*)- **30j**][b]
12	(*R*,*R*)- **19**	Ph	Cl	94	34 [**30k**][b,d]

[a]DMAP (20.0 mol %), DCC (1.0 eq.), Reaction time was 12 h; [b]Determined by ^{1}H NMR signal; [c]CSP-HPLC (Lux Amylose-2); [d]Absolute configuration was not established.

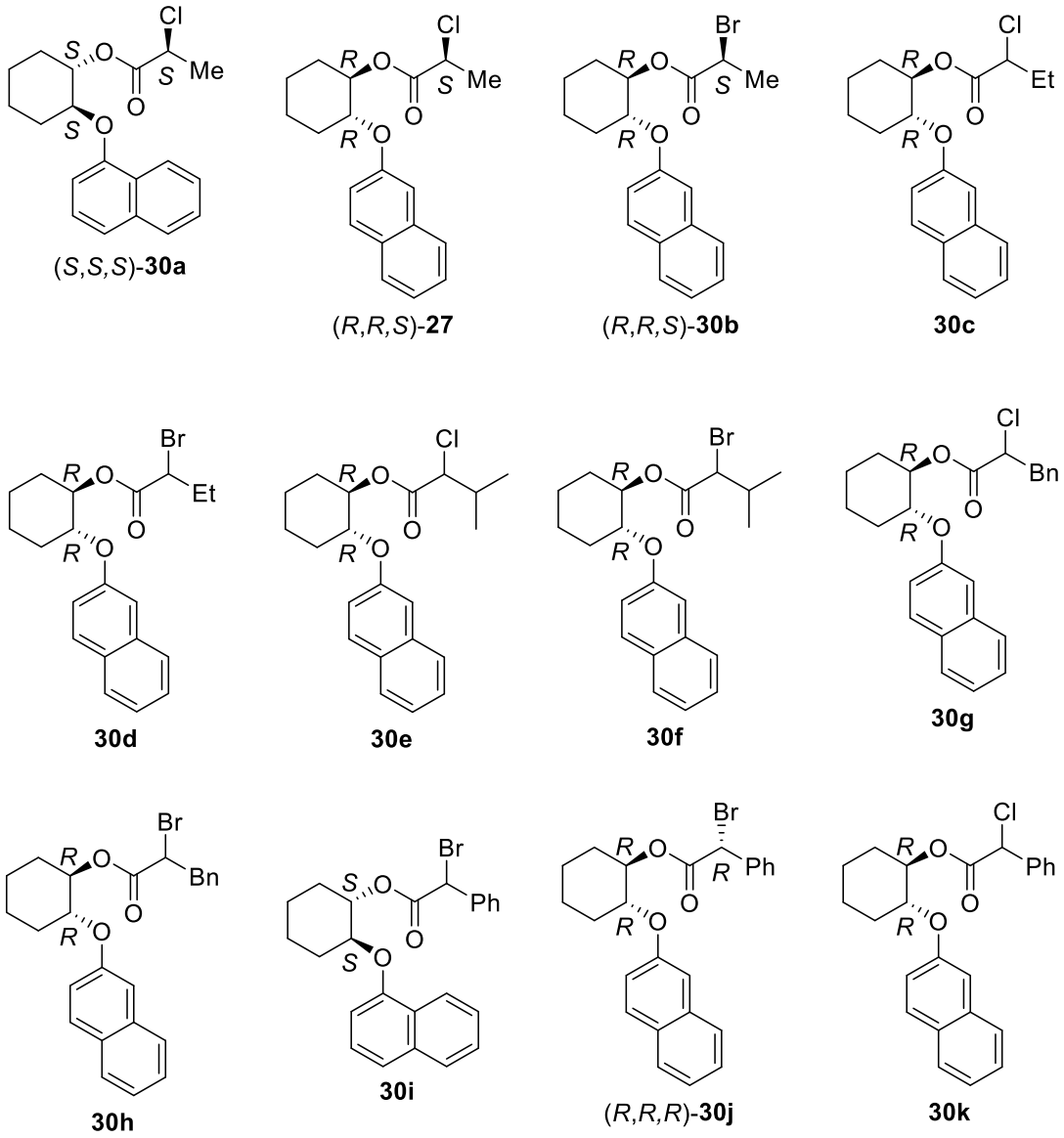


Chart 3.1: Examples of enantiomer enrichment reaction by DTR

Absolute configuration at the enriched chiral carbon of few of the optically pure α-halo esters, (**30a**), (**30b**) and (**30j**), was established by their single crystal diffraction analysis. The ORTEP diagrams of single crystals for (**30a**), (**30b**), and (**30j**) are presented in Figure 3.13.

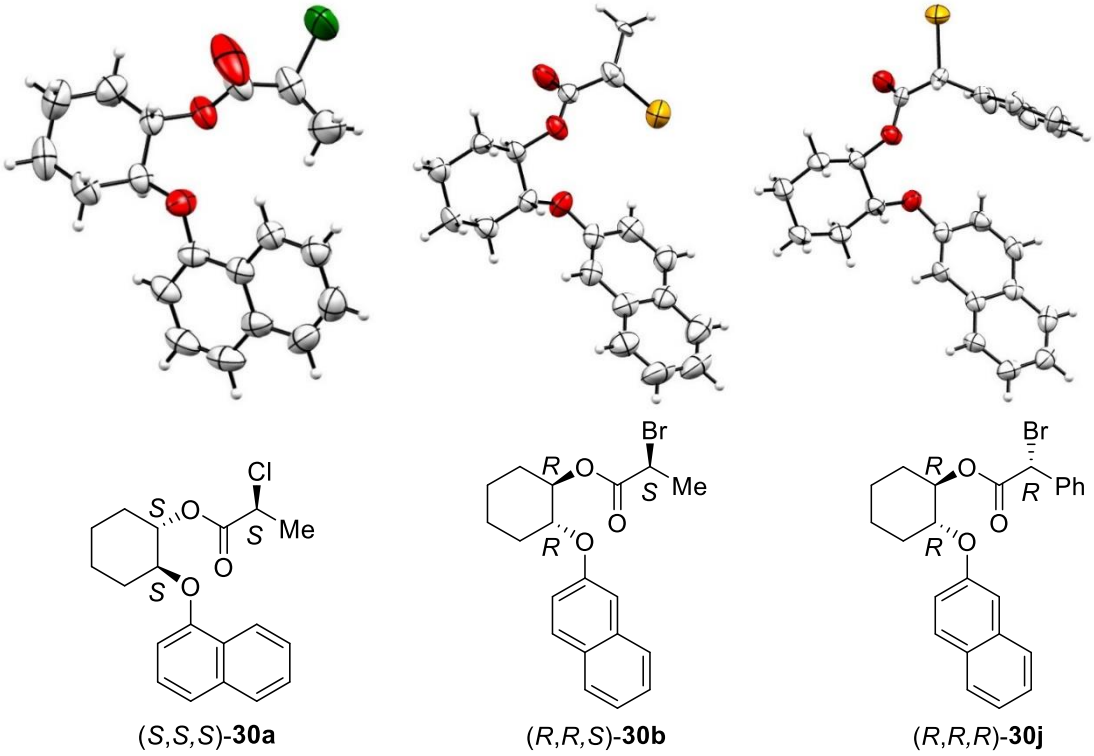


Figure 3.13. ORTEP diagram of (*S*,*S*,*S*)-(**30a**) (CCDC1854339; left), (*R*,*R*,*S*)-(**30b**) (CCDC1854339; centre), (*R*,*R*,*R*)-(**30j**) (CCDC1854339; right)

Thus with these examples we have demonstrated the ability of the present chiral derivative of *trans*-2-naphthyloxycyclohexanol as an efficient auxiliary to introduce chirality in the α-halo acids by a suitable base mediated DTR procedure.

3.3 Conclusion:

We have reported preparation of two derivatives of chiral 2-aryoxycyclohexanol, *trans*-2-(naphthalene-2-yloxy)cyclohexanol (**19**) and *trans*-2-(naphthalene-1-yloxy)-cyclohexanol (**21**), their isomers were separated by enzyme mediated kinetic resolution. The absolute configuration was confirmed by single crystal X-ray diffraction analysis of their esters prepared by coupling with chiral acids of known optical description.

The optically pure alcohols (**19**) and (**21**) were used as chiral auxiliaries for coupling with racemic α-halo acids, where in efficient deracemization resulted in the formation of the product almost as a single diastereomer.

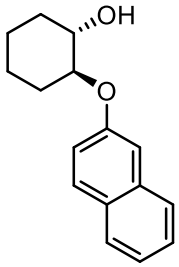
The study of different reaction parameters and the relative energies of the two possible diastereomers, indicate towards the dynamic thermodynamic resolution to be the possible mode of deracemization.

The acid mediated cleavage of the diastereomeric ester product affords both the components in optically pure form, hence this could be useful method to access chiral α-halo acids of considerable importance.

3.4 Experimental Procedure:

NMR spectra of **30a-k** were recorded after passing the mixture through short column of silica gel. For ^{13}C nmr spectra of **30c**-**30i** and **30k** only peaks corresponding to major diastereomer have been picked. The X-ray data collection was carried out on a Xcalibur, Eos, Gemini diffractometer.[20] Specific optical rotations were recorded on Jasco P-2000 polarimeter. Computational studies were performed with Gaussian 16 Revision A.03 using B3LYP/6-31+G(d) basis set.

Synthesis of (±) *trans*-2-(naphthalene-2-yloxy)cyclohexan-1-ol (**19**).



In a solution containing potassium hydroxide (1.68 g, 30 mmol) in water (16 mL) was added β-naphthol (4.32 g, 30 mmol) and heated at 100 ^{o}C. To this solution was added cyclohexene oxide (1.0g, 10 mmol) in 15 min. A heavy precipitation made it necessary to add more water (8 mL) to facilitate stirring. After an additional 40 min, the mixture was allowed to cool to room temperature, filtered and precipitates were washed with 1M KOH solution and water. The dried product (**19**) was further recrystallized from toluene to afford white solid.[16a] (2.21 g, 90%). M.p. 143-145 ^{o}C.

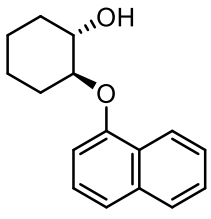
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.73 (m, 3H), 7.48-7.44 (t, J = 7.2 Hz, 1H), 7.38-7.34 (t, J = 7.2 Hz, 1H), 7.25 (m, 1H), 7.21-7.18 (dd, J = 8.8, 2.4 Hz, 1H), 4.19-4.17 (m, 1H), 3.84-3.78 (m, 1H), 2.68 (bs, 1H, -O*H*), 2.29-2.14 (m, 2H), 1.80-1.53 (m, 4H), 1.50-1.38 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6, 134.5, 129.6, 129.2, 127.6, 126.8, 126.4, 123.9, 119.6, 109.3, 82.2, 73.5, 32.1, 29.0, 24.0, 23.9.

IR (KBr) υ: 3454, 3063, 2935, 1626, 1595, 1465, 1260, 1037, 835 cm^{-1}.

Mass (ESI): m/z 242.3 $[M]^+$, 213, 144.1 (100%), 114.

Synthesis of (±) *trans*-2-(naphthalene-1-yloxy)cyclohexan-1-ol (**21**).



In a solution containing of potassium hydroxide (0.56 g, 10 mmol) in water (16 mL) was added α-naphthol (1.44 g, 10 mmol) and heated at 100 ^{o}C. To this solution was added cyclohexene oxide (1.5 g, 15 mmol) in 15 min. The reaction mixture was then allowed to reflux for 12 h and then allowed to cool. The mixture was then extracted with ethyl acetate (3 x 25 mL) and then washed with water (2 x 25 mL). The combined extract was dried over an. Na_2SO_4, concentrated under vacuum and subjected to column

chromatography on silica gel (ethyl acetate/petroleum ether 3:7) resulting in yellowish solid (**21**).[16c] (1.42g, 84%). M.p. 63-65 ºC.

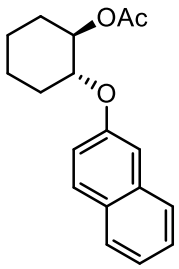
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35-8.33 (m, 1H), 7.86-7.85 (m, 1H), 7.56-7.50 (m, 3H), 7.44-7.41 (m, 1H), 7.00-6.99 (d, *J* = 7.2 Hz, 1H), 4.32-4.28 (m, 1H), 3.98-3.93 (m, 1H), 2.80 (bs, 1H, -O*H*), 2.29-2.19 (m, 2H), 1.81 (m, 2H), 1.57-1.37 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 134.8, 127.7, 126.6, 126.4, 125.9, 125.3, 122.0, 120.7, 107.3, 82.4, 73.4, 32.1, 29.1, 24.0, 23.9.

IR (KBr) υ 3451, 3062, 2945, 1628, 1573, 1457, 1268, 1096, 845 cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{18}KO_2$ $[M+K]^+$ 281.0938 found 281.0944.

General procedure for enzymatic resolution of alcohol.



To a solution of racemic alcohol (**19**) (0.30 g, 1.24 mmol) in ethyl acetate, lipase (0.9 g 3 eq w/w, *Steapsin* lipase) and vinyl acetate (1.14 mL, 12.4 mmol) were added and the reaction mixture was stirred for 9 days at room temperature. The reaction material was filtered through a celite bed and the filtrate was concentrated under vacuum. The crude mixture was then separated by column chromatography over silica gel using ethyl acetate and petroleum ether as eluent. The acetate (**22**) was eluted with 10% ethyl acetate/ petroleum ether (0.17 g, 48%). M.p. 99-101 ºC. *ee* = >99%. $[\alpha]_D^{25}$ = +39.4 (c = 1.0 in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.75 (m, 3H), 7.48-7.45 (m, 1H), 7.38-7.35 (m, 1H), 7.33-7.29 (m, 1H), 7.20-7.18 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.12-5.07 (m, 1H, -C*H*-OAc), 4.45-4.40 (ddd, *J* = 12.4, 8.0, 4.0 Hz, 1H, -C*H*-O-Ar), 2.27-2.24 (m, 1H), 2.15-2.11 (m, 1H), 1.96 (s, 3H, -CO-CH_3), 1.86-1.78 (m, 2H), 1.66-1.61 (m, 1H), 1.58-1.43 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 156.0, 134.5, 129.4, 129.1, 127.6, 126.7, 126.3, 123.7, 119.6, 109.1, 77.6, 74.1, 29.8, 29.6, 23.2, 23.1, 21.2.

IR (KBr) υ: 3052, 2948, 1734, 1626, 1507, 1244, 1035, 836 cm^{-1}.

Mass (ESI): m/z 285.1 $[M+1]^+$, 284.1 $[M]^+$, 225, 144.1, 141.1 (100%), 81.

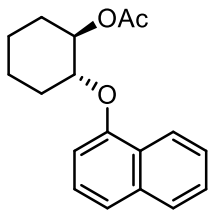
HRMS (ESI): calcd for $C_{18}H_{21}O_3$ $[M+H]^+$ 285.1491 found 285.1496.

HPLC conditions: Chiralcel OD-H column, 10% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 0.5 mL/min. R_t = 8.9 min, major peak (*R*,*R*- isomer), 9.7 min (*S*,*S*-isomer).

Alcohol (*S*,*S*)-**19** was eluted with 20% ethyl acetate/petroleum ether. (0.15g, 49%). *ee* = >99%. $[\alpha]_D^{25}$ = +66.2 (c = 1.0 in $CHCl_3$). HPLC conditions: ChiralCel OD-H column,

10% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 1mL/min. R_t = 10.9 min (*R*,*R*-isomer), 16.7 min, major peak (*S*,*S*- isomer).

Enzymatic resolution of alcohol (**21**).



The title compound was obtained by following the same procedure as for alcohol (**19**) from the racemic alcohol (**21**). The crude mixture was separated by column chromatography over silica gel using ethyl acetate and petroleum ether as eluent. The acetate (**23**) was eluted with 20% ethyl acetate/ petroleum ether as colorless oil. (0.17 g, 48%). *ee* = 98.5%. $[\alpha]_D^{25}$ = -88.3 (c = 1.0 in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ8.26-8.23 (m, 1H), 7.81-7.79 (m, 1H), 7.51-7.47 (m, 2H), 7.46-7.44 (d, *J* = 7.6 Hz, 1H), 7.40-7.36 (m, 1H), 6.97-6.95 (d, *J* = 7.2 Hz, 1H), 5.24-5.19 (m, 1H, -C*H*-OAc), 4.48-4.42 (ddd, *J* = 12.4, 8.4, 4.4 Hz, 1H, -C*H*-OAr), 2.32-2.28 (m, 1H), 2.14-2.11 (m, 1H), 1.92 (s, 3H, -COCH_3), 1.88-1.78 (m, 2H), 1.70-1.62 (m, 1H), 1.57-1.43 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ170.7, 153.9, 134.7, 127.4, 126.4, 126.3, 125.8, 125.3, 122.3, 120.4, 106.7, 78.0, 73.8, 29.8, 29.5, 23.2, 23.1, 21.2.

IR (KBr) υ: 2939, 1735, 1579, 1234, 1097, 738 cm^{-1}.

Mass (ESI): m/z 308.3 $[M+23]^+$, 307.3 $[M+Na]^+$ (100%), 285.3, 225.2, 158.1.

HRMS (ESI): calcd for $C_{18}H_{20}O_3Na$ $[M+H]^+$ 307.1304 found 307.1303.

HPLC conditions: ChiralCel OD-H column, 2.5% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 1.0 mL/min. R_t = 13.0 min (*S*,*S*- isomer), 13.9 min, major peak (*R*,*R*-isomer).

Alcohol (*S*,*S*)-**21** was eluted with 30% ethyl acetate/petroleum ether. (0.14g, 46%). *ee* =~ 99%. $[\alpha]_D^{25}$ = +93.6 (c = 1.0 in $CHCl_3$). HPLC conditions: ChiralCel OD-H column, 25% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 1mL/min. R_t = 8.6 min, major peak (*S*,*S*- isomer), 10.7 min (*R*,*R*- isomer).

General procedure for hydrolysis of acetate:

To a solution of chiral acetate (**22**) (0.1g 0.35 mmol) in methanol, conc. HCl (0.05 mL, 0.53 mmol) was added. The resulting mixture was then refluxed for 3h. The solvent was removed under vacuum and subjected to column chromatography over silica gel using ethyl acetate and petroleum ether to afford chiral alcohol (*R*,*R*)-**19** as white solid. (0.081 g, 95%). *ee* = >99%. $[\alpha]_D^{25}$ = (-66.7) (c = 1.0 in $CHCl_3$).

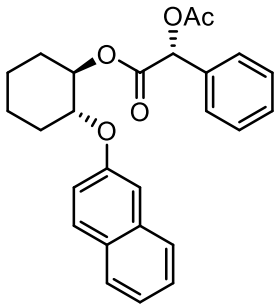
HPLC conditions: ChiralCel OD-H column, 10% Isopropyl alcohol-Hexane, UV = 254 nm, Flow rate = 1mL/min. R_t = 10.9 min, major peak (*R*,*R*- isomer), 16.7 min (*S*,*S*-isomer).

Hydrolysis of acetate (**23**)

The chiral alcohol (**21**) was obtained by following the same procedure as for alcohol (**19**) from the chiral acetate (**23**). The crude mixture was separated by column chromatography over silica gel using ethyl acetate and petroleum ether as eluent resulting in chiral alcohol (*R*,*R*)-(**21**) as low melting yellow solid. (0.078 g, 93%). *ee* = 98.5%. $[\alpha]_D^{25}$ = -93.2 (c = 1.0 in $CHCl_3$).

HPLC conditions: ChiralCel OD-H column, 25% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 1mL/min. R_t = 8.6 min (*S*,*S*- isomer), 10.7 min, major peak (*R*,*R*-isomer).

Determination of Absolute Configuration: Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-(*R*)-2-acetoxy-2-phenylacetate (*R*,*R*,*R*)-(**24**)



Alcohol (*R*,*R*)-(**19**) (0.10 g, 4.1 mmol), DCC (0.084 g, 4.1 mmol) and DMAP (0.010 g 0.8 mmol) were dissolved in CH_2Cl_2 (10 mL) in two-necked flask under nitrogen atmosphere and cooled to 0 ^oC. A solution of (*R*)-*O*-acyl mandelic acid (0.079 g, 4.1 mmol) in dichloromethane (5 mL) was then added drop wise. The reaction mixture was stirred at rt for 4h. The reaction mixture was then filtered through Celite bed, washed with dichloromethane and purified by column chromatography over silica gel (10% ethyl acetate/petroleum ether) affording white solid (*R*,*R*,*R*)-(**24**) (0.16 g, 94%). M.p = 95-97 ^oC. $[\alpha]_D^{25}$ = -73.8 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.77 (d, *J* = 8.0 Hz, 1H), 7.71-7.65 (m, 2H), 7.47-7.43 (m, 1H), 7.38-7.34 (m, 3H), 7.13-7.05 (m, 4H), 6.90-6.87 (dd, *J* = 9.2, 2.4 Hz, 1H), 5.91 (s, 1H, Cα*H*), 5.11-5.10 (m, 1H, -C*H*OCO-), 4.32-4.30 (m, 1H, -C*H*OAr), 2.21-2.18 (m, 1H), 2.14-2.10 (m, 1H, s of –COCH_3 merged), 1.80-1.79 (m, 2H), 1.69-1.40 (m, 4H).

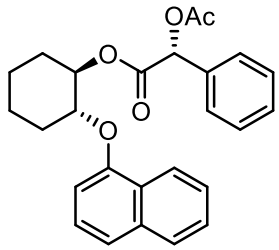
^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 168.1, 155.5, 134.4, 133.4, 129.3, 129.0, 128.9, 128.5, 127.6, 127.4, 126.8, 126.2, 123.6, 119.5, 108.3, 75.3, 74.7, 29.6, 29.3, 23.0, 22.9, 20.7.

IR (KBr) υ: 3061, 2935, 1755, 1736, 1625, 1463, 1278, 1177, 1056, 842 cm^{-1}.

Mass (ESI): m/z 441.2 $[M+Na]^+$ (100%), 359.1, 301.1.

HRMS (ESI): calcd for $C_{26}H_{26}O_5Na$ $[M+Na]^+$ 441.1678 found 441.1659.

Synthesis of (1*R*,2*R*)-2-(naphthalene-1-yloxy)cyclohexyl(*R*)-2-acetoxy-2-phenylacetate (*R*,*R*,*R*)-(**25**)



The title compound was obtained by the same procedure as for ester (*R*,*R*,*R*)-(**25**) from alcohol (*R*,*R*)-(**21**). The mixture was purified by column chromatography on silica gel using 10% ethyl acetate/petroleum ether as white solid (*R*,*R*,*R*)-(**25**) (0.15 g, 91%). M.p = 113-115 ^{o}C. $[\alpha]_D^{25}$ = -135.0 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97-7.94 (d, *J* = 8.4 Hz, 1H), 7.69-7.67 (d, *J* = 8.0 Hz, 1H), 7.40-7.36 (m, 1H), 7.32-7.27 (m, 2H), 7.20-7.16 (m, 1H), 7.14-7.12 (m, 2H), 6.85-6.81 (t, *J* = 7.2 Hz, 1H), 6.72-6.69 (t, *J* = 7.6 Hz, 1H), 6.61-6.59 (d, *J* = 7.6 Hz, 1H), 5.82 (s, 1H, $C_{\alpha}H$), 5.20-5.14 (ddd, *J* = 12.4, 8.0, 4.4 Hz, 1H, -C*H*OCO-), 4.27-4.21 (dt, *J* = 8.8, 4.0 Hz, 1H, -C*H*OAr), 2.12-2.07 (m, 1H), 1.73-1.68 (m, 2H), 1.56-1.52 (m, 1H), 1.46-1.38 (m, 2H), 1.33-1.27 (m, 1H).

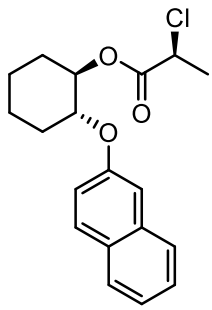
^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 168.4, 152.9, 134.6, 133.2, 128.6, 127.2, 127.1, 126.3, 126.1, 125.6, 125.1, 122.4, 120.0, 105.1, 76.8, 74.6, 74.5, 29.5, 28.8, 23.0, 22.8, 20.7.

IR (KBr) υ: 3055, 2947, 1755, 1739, 1575, 1456, 1368, 1267, 1234, 1054, 764 cm^{-1}.

Mass (ESI): m/z 441.2 $[M+Na]^+$ (100%), 413.3, 359.2.

HRMS (ESI): calcd for $C_{26}H_{26}O_5Na$ $[M+Na]^+$ 441.1678 found 441.1655.

Deracemization of α-halo acid: Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl (*S*)-2-chloropropanoate (*R*,*R*,*S*)-(**27**)



Alcohol (*R*,*R*)-(**19**) (0.1 g, 0.4 mmol), DCC (0.13 g, 0.61 mmol) and DMAP (0.01 g, 0.082 mmol) were placed in a two neck round bottom flask under N_2 atmosphere, dissolved in CH_2Cl_2 (5 mL) and cooled to 0 ^{o}C. A solution of 2-chloropropanoic acid (0.04 mL, 0.4 mmol) in CH_2Cl_2 (2 mL) was added drop wise. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then filtered through celite bed and washed with CH_2Cl_2 and purified by column chromatography over silica gel by eluting with 5% ethyl acetate/petroleum ether. (0.14 g, 99%). M.p = 93-95 ^{o}C $[\alpha]_D^{25}$ = +10.6 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.73 (m, 3H), 7.47-7.44 (m, 1H), 7.37-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.18-7.15 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.16-5.11 (ddd, *J* = 12.4, 8.0, 4.4 Hz, 1H, -C*H*OCO-), 4.49-4.44 (ddd, *J* = 12.4, 8.4, 4.4 Hz, 1H, -C*H*OAr), 4.34-4.29 (q, *J*

= 7.2 Hz, 1H, C$_\alpha$*H*), 2.29-2.25 (m, 1H), 2.16-2.12 (m, 1H), 1.88-1.78 (m, 2H), 1.67-1.57 (m, 5H, d of –C*H*$_3$ merged) 1.56-1.45 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 169.5, 155.8, 134.4, 129.5, 129.1, 127.6, 126.8, 126.3, 123.8, 119.6, 108.9, 75.6, 52.8, 29.4, 29.3, 23.0, 22.8, 21.4.

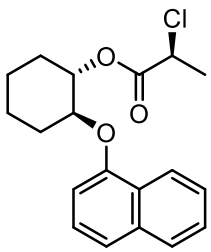
IR (KBr) υ: 2957, 1751, 1739, 1570, 1458, 1371, 1269, 1232, 1059, 794 cm^{-1}.

Mass (ESI): m/z 331.8 [M]$^+$, 188.9, 144.2 (100%), 143.5, 114.9.

HRMS (ESI): calcd for $C_{19}H_{21}ClO_3Na$ [M+Na]$^+$ 355.1071 found 355.1070.

HPLC conditions: Lux amylose column, 5% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 0.5 mL/min. R$_t$ = 14.1 min (*R,R,R*- isomer), 15.8 min, major peak (*R,R,S*-isomer).

Synthesis of (1*S*,2*S*)-2-(naphthalene-1-yloxy)cyclohexyl (*S*)-2-chloropropanoate (*S,S,S*)-(**30a**)



The title compound was obtained by following same procedure as for (*R,R,S)*-(**27**) from alcohol (*S,S*)-(**21**) and 2-chloropropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in formation of white solid. (0.13 g, 98%) M.p = 81-83 ºC. *de* = 68%. $[\alpha]_D^{25}$ = +85.8 (c = 1, CHCl$_3$).

^{1}H NMR (CDCl$_3$, 400 MHz) after crystallization: δ 8.23-8.21 (d, *J* = 6.4 Hz, 1H), 7.81-7.80 (d, *J* = 6.4 Hz, 1H), 7.51-7.45 (m, 3H), 7.41-7.37 (m, 1H), 6.96-6.94 (d, *J* = 6.4 Hz, 1H), 5.31-5.27 (dt, *J* = 7.2, 3.6 Hz, 1H, -C*H*OCO-), 4.53-4.49 (dt, *J* = 7.2, 3.6 Hz, 1H, -C*H*OAr), 4.23-4.19 (q, *J* = 7.2, 1H, C$_\alpha$H), 2.35-2.33 (m, 1H), 2.20-2.18 (m, 1H), 1.90-1.84 (m, 2H), 1.74-1.66 (m, 1H), 1.64-1.59 (m, 2H), 1.57-1.50 (m, 1H), 1.46-1.45 (d, *J* = 6.4 Hz, 3H, -C*H*$_3$).

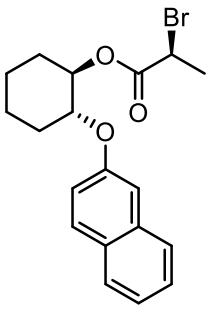
^{13}C NMR (CDCl$_3$, 100 MHz): δ 169.8, 153.6, 134.7, 127.4, 126.4, 126.2, 125.7, 125.3, 122.2, 120.6, 106.4, 75.6, 52.6, 29.6, 29.5, 23.2, 23.0, 21.3.

IR (KBr) υ: 3058, 2942, 1752, 1627, 1458, 1332, 1172, 1085 cm^{-1}.

Mass (ESI): m/z 355.1 [M + Na]$^+$.

HRMS (ESI): calcd for $C_{19}H_{21}ClO_3Na$ [M+Na]$^+$ 355.1071 found 355.1068.

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl (*S*)-2-bromopropanoate (*R*,*R*,*S*)-(**30b**)



The title compound was obtained by following same procedure as for (*R*,*R*,*S)*-(**27**) from alcohol (*R*,*R*)-(**19**) and 2-bromopropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in formation of white solid (0.15 g, 98%). M.p = 92-94 ºC. *de* = 66%. $[\alpha]_D^{25}$ = -12.4 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) after crystallization: δ 7.78-7.73 (m, 3H), 7.47-7.43 (m, 1H), 7.37-7.33 (m, 1H), 7.27-7.25 (m, 1H), 7.18-7.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.15-5.08 (m, 1H, -C*H*OCO), 4.50-4.43 (m, 1H, -CHOAr), 4.33-4.28 (q, *J* = 6.8 Hz, 1H, $C_\alpha H$), 2.29-2.24 (m, 1H), 2.16-2.11 (m, 1H), 1.86-1.80 (m, 2H), 1.72-1.70 (d, *J* = 6.8 Hz, 3H, -CH_3)1.68-1.59 (m, 2H), 1.58-1.54 (m, 2H).

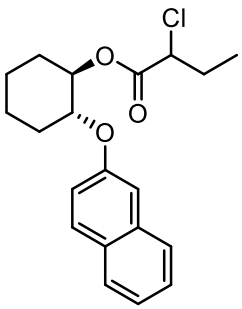
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 155.8, 134.5, 129.5, 129.1, 127.6, 126.8, 126.3, 123.7, 119.6, 108.9, 75.3, 40.5, 29.3, 29.1, 22.9, 22.8, 21.6.

IR (KBr) υ: 3057, 2935, 1737, 1628, 1598, 1446, 1353, 1218, 1160, 1097 cm^{-1}.

Mass (ESI): m/z 377 $[M]^+$, 375, 234, 144 (100%), 114.

HRMS (ESI): calcd for $C_{19}H_{21}BrO_3Na$ $[M+Na]^+$ 399.0566 found 399.0564.

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-2-chlorobutanoate (**30c**)



The title compound was obtained by following same procedure as for (*R*,*R*,*S)*-(**27**) from alcohol (*R*,*R*)-(**19**) and 2-chlorobutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in colorless oil. (0.14 g, 97%) *de* = 50%. $[\alpha]_D^{25}$ = 9.63 (c = 1, $CHCl_3$).

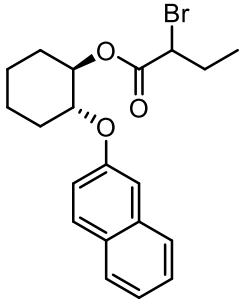
^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ 7.79-7.73 (m, 3H), 7.47-7.43 (m, 1H), 7.37-7.33 (m, 1H), 7.26-7.24 (m, 1H), 7.17-7.12 (m, 1H), 5.16-5.10 (m, 1H, -C*H*OCO-), 4.49-4.44 (m, 1H, -C*H*OAr), 4.14-4.09 (m, 1H, -$C_\alpha H$), 2.29-2.17 (m, 1H), 2.16-2.13 (m, 1H), 1.92-1.79 (m, 4H), 1.68-1.54 (m, 3H), 1.50-1.39 (m, 2H), 0.94-0.91 (t, *J* = 7.2 Hz, 3H, major diastereomer), 0.89-0.85 (t, *J* = 7.2 Hz, 3H, minor diastereomer).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ 169.0, 155.8, 134.5, 129.5, 129.2, 127.6, 126.8, 126.7, 126.4, 126.3, 123.8, 119.6, 119.5, 108.9, 75.7, 59.2, 29.5, 29.4, 28.4, 23.0, 22.9, 10.4.

IR (KBr) υ: 3057, 2939, 1738, 1628, 1464, 1388, 1180, 1081 cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{23}ClO_3Na$ $[M+Na]^+$ 369.1233 found 369.1228.

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-2-bromobutanoate (**30d**)



The title compound was obtained by following same procedure as for (*R,R,S)*-(**27**) from alcohol (*R,R*)-(**19**) and 2-bromobutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in colorless oil. (0.16 g, 98%) *de* = 40%. $[\alpha]_D^{25}$ = +2.13 (c = 1, $CHCl_3$).

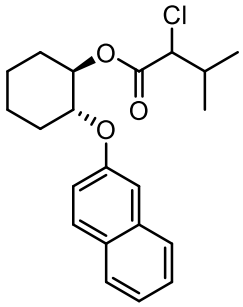
^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ 7.78-7.74 (m, 3H), 7.74-7.43 (m, 1H), 7.37-7.33 (m, 1H), 7.26-7.24 (m, 1H), 7.17-7.13 (m, 1H), 5.15-5.09 (m, 1H, -C*H*OCO-), 4.49-4.45 (m, 1H, -C*H*OAr), 4.12-4.08 (t, J = 7.2 Hz, 1H, -C$_\alpha$*H*, major diastereomer), 4.02-3.99 (t, J = 7.2 Hz, 1H, -C$_\alpha$*H*, minor diastereomer), 2.29-2.25 (m, 1H), 2.17-2.13 (m, 1H), 2.0-1.80 (m, 5H), 1.80-1.71 (m, 1H), 1.66-1.60 (m, 4H), 1.58-1.48 (m, 2H), 1.46-1.27 (m, 2H), 0.92-0.90 (t, *J* = 7.2 Hz, 3H, major diastereomer), 0.87-0.83 (t, *J* = 7.2 Hz, 3H, minor diastereomer).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ 169.1, 155.8, 134.5, 129.5, 127.6, 126.7, 126.4, 123.8, 119.6, 108.9, 75.7, 47.9, 29.6, 29.3, 28.3, 23.1, 23.0, 11.6.

IR (KBr) υ cm^{-1}: 3057, 2936, 1736, 1629, 1465, 1387, 1216, 1156, 1053.

HRMS (ESI): calcd for $C_{20}H_{23}BrO_3Na$ $[M+Na]^+$ 413.0723 found 413.0720.

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-2-chloro-3-methylbutanoate (**30e**)



The title compound was obtained by following same procedure as for (*R,R,S)*-(**27**) from alcohol (*R,R*)-(**19**) and 2-chloro-3-methylbutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in colorless oil. (0.14 g, 98%) *de* = 42%. $[\alpha]_D^{25}$ = +3.63 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ 7.78-7.73 (m, 3H), 7.47-7.43 (m, 1H), 7.37-7.33 (m, 1H), 7.25-7.22 (m, 1H), 7.16-7.10 (m, 1H), 5.15-5.10 (m, 1H, -C*H*OCO-), 4.49-4.36 (m, 1H, -C*H*OAr), 4.07-4.05 (d, *J* = 6.8 Hz, 1H, minor diastereomer), 4.02-4.00 (d, *J* = 6.8 Hz, 1H, major diastereomer), 2.30-2.22 (m, 1H), 2.20-2.13 (m, 2H), 1.85-1.80 (m, 2H), 1.54-1.13 (m, 3H), 0.96-0.95 (d, *J* = 6.8 Hz, 3H), 0.94-0.92 (d, *J* = 6.8 Hz, 3H, major diastereomer), 0.91-0.89 (d, *J* = 6.8 Hz, 3H, minor diastereomer).

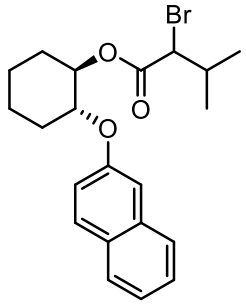
^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ 168.8, 155.7, 134.5, 129.5, 129.1, 127.6, 126.7, 126.3, 123.8, 119.6, 108.9, 75.7, 64.6, 32.6, 29.7, 29.5, 23.1, 22.9, 19.5, 18.1.

IR (KBr) υ: 3058, 2939, 1744, 1629, 1466, 1390, 1217, 1120, 1019 cm^{-1}.

HRMS (ESI): calcd for $C_{21}H_{25}ClO_3Na$ $[M+Na]^+$ 383.1384 found 383.1384.

HPLC conditions: Lux amylose column, 2.5% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 0.5 mL/min. R_t = 15.2 min (minor diastereomer), 17.1 min, (major diastereomer).

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-2-bromo-3-methylbutanoate (**30f**)



The title compound was obtained by following same procedure as for (*R,R,S)*-**30** from alcohol (*R,R*)-**19** and 2-bromo-3-methylbutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in colorless oil. (0.16 g, 96%) *de* = 46%. $[\alpha]_D^{25}$ = -7.13 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ 7.78-7.73 (m, 3H), 7.47-7.43 (m, 1H), 7.39-7.33 (m, 1H), 7.25-7.23 (m, 1H), 7.16-7.12 (m, 1H), 5.14-5.09 (m, 1H, -C*H*OCO-), 4.49-4.44 (ddd, *J* = 12.4, 5.8, 4.4 Hz, 1H, -C*H*OAr), 3.97-3.95 (m, 1H, Cα*H*), 2.30-2.26 (m, 1H), 2.18-2.09 (m, 1H), 1.85-1.80 (m, 2H), 1.63-1.60 (m, 1H), 1.50-1.43 (m, 3H), 1.02-1.00 (d, *J* = 6.4 Hz, 3H, -CH_3) 0.93-0.91 (d, *J* = 6.4 Hz, 3H, -CH_3, major diastereomer), 0.90-0.89 (d, *J* = 6.4 Hz, 3H, minor diastereomer).

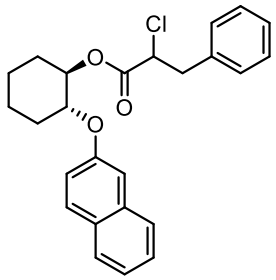
^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ 168.8, 155.7, 134.5, 129.4, 129.1, 127.6, 126.7, 126.3, 123.7, 119.6, 118.8, 75.5, 55.1, 32.3, 29.4, 23.0, 22.9, 19.9, 19.8.

IR (KBr) υ: 3057, 2939, 1737, 1629, 1466, 1389, 1252, 1216, 1152, 1053 cm^{-1}.

HRMS (ESI): calcd for $C_{21}H_{25}BrO_3Na$ $[M+Na]^+$ 427.0879 found 427.0883.

HPLC conditions: Lux amylose column, 2.5% Isopropyl alcohol-Hexane, UV = 254nm, Flow rate = 0.5 mL/min. R_t = 14.4 min (minor diastereomer), 16.0 min, (major diastereomer).

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-2-chloro-3-phenylpropanoate (**30g**)



The title compound was obtained by following same procedure as for (*R,R,S)*-(**27**) from alcohol (*R,R*)-(**19**) and 2-chloro-3-phenylpropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in colorless oil. (0.16 g, 94%) *de* = 43%. $[\alpha]_D^{25}$ = +4.83 (c = 1, $CHCl_3$).

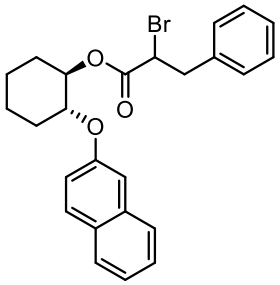
^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ 7.78-7.71 (m, 3H), 7.47-7.43 (m, 1H), 7.37-7.33 (m, 1H), 7.27-7.01 (m, 2H), 7.21-7.14 (m, 1H), 7.13-7.01 (m, 2H), 5.11-5.06 (m, 1H, -C*H*OCO-), 4.47-4.41 (m, 1H, -C*H*OAr), 4.36-4.32 (dd, *J* = 7.2 Hz, 1H, C$_\alpha$*H*, major diastereomer), 4.30-4.27 (dd, *J* = 6.8 Hz, 1H, C$_\alpha$*H*, minor diastereomer), 3.26-3.22 (dd, *J* = 14.0, 6.8 Hz, 1H, major diastereomer), 3.14-3.12 (dd, *J* = 14.0, 6.8 Hz, 1H, minor diastereomer), 3.07-2.96 (m, 1H), 2.25-2.21 (m, 1H), 2.04-2.02 (m, 1H), 1.81-1.80 (m, 1H), 1.75-1.73 (m, 1H), 1.65-1.62 (m, 1H), 1.47-1.42 (m, 3H), 1.30-1.27 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ 168.7, 155.8, 135.9, 134.5, 129.5, 129.3, 128.5, 127.6, 127.2, 126.8, 123.8, 119.6, 109.1, 75.9, 57.7, 41.0, 29.4, 29.2, 22.9, 22.8.

IR (KBr) υ: 3051, 2945, 1734, 1625, 1460, 1258, 1218, 1117, 1034 cm^{-1}.

HRMS (ESI): calcd for $C_{25}H_{25}ClO_3Na$ $[M+Na]^+$ 431.1389 found 431.1386.

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-2-bromo-3-phenylpropanoate (**30h**)



The title compound was obtained by following same procedure as for (*R,R,S)*-(**27**) from alcohol (*R,R*)-(**19**) and 2-bromo-3-phenylpropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in colorless oil. (0.17 g, 92%) *de* = 38%. $[\alpha]_D^{25}$ = -7.0 (c = 1, $CHCl_3$)

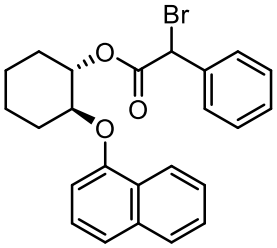
^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ 7.78-7.70 (m, 3H), 7.48-7.43 (m, 1H), 7.38-7.32 (m, 1H), 7.27-7.11 (m, 6H), 7.06-7.01 (m, 1H), 5.13-5.04 (m, 1H, -C*H*OCO-), 4.48-4.47 (m, 1H, -C*H*OAr, major diastereomer), 4.46-4.44 (m, 1H, -C*H*OAr, minor diastereomer), 4.34-4.30 (dd, *J* = 8.4, 7.2 Hz, 1H, Cα*H*, major diastereomer), 4.24-4.20 (dd, *J* = 6.8 Hz, 1H, Cα*H*, minor diastereomer), 3.38-3.33 (dd, *J* = 14.0, 8.4 Hz, 1H, major diastereomer), 3.26-3.20 (dd, *J* = 14.0, 8.4 Hz, 1H, minor diastereomer), 3.16-3.09 (m, 1H), 2.27-2.23 (m, 1H), 2.22-2.13 (m, 1H), 2.03-2.00 (m, 1H), 1.82-1.80 (m, 1H), 1.76-1.72 (m, 1H), 1.46-1.42 (m, 3H), 1.30-1.26 (m, 1H).

^{13}C NMR ($CDCl_3$, 100MHz) major diastereomer: δ 168.9, 155.9, 136.7, 134.5, 129.5, 129.1, 128.6, 127.7, 126.8, 126.4, 123.8, 119.7, 108.9, 75.6, 45.8, 41.1, 29.3, 29.0, 22.9, 22.8.

IR (KBr) υ: 3058, 2939, 1739, 1628, 1462, 1388, 1255, 1174, 1050 cm^{-1}.

HRMS (ESI): calcd for $C_{25}H_{25}BrO_3Na$ $[M+Na]^+$ 475.0885 found 475.0879.

Synthesis of (1*R*,2*R*)-2-(naphthalene-1-yloxy)cyclohexyl-2-bromo-3-phenylacetate (**30i**)



The title compound was obtained by following same procedure as for (*R,R,S)*-(**27**) from alcohol (*S,S*)-(**21**) and 2-bromo-3-phenylacetic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in white solid (0.17 g, 95%). M.p = 110-112 ^{o}C. *de* = 8%. $[\alpha]_D^{25}$ = +61.6 (c = 1, $CHCl_3$).

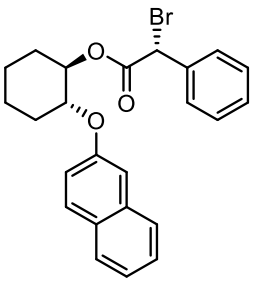
^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ 8.17-8.13 (m, 1H), 7.80-7.78 (m, 1H), 7.49-7.42 (m, 2H), 7.41-7.37 (m, 3H), 7.36-7.30 (m, 1H), 6.90-6.88 (d, *J* = 7.2 Hz, 1H, major diastereomer), 6.84-6.82 (d, *J* = 7.6 Hz, 1H, minor diastereomer) 5.31-5.26 (m, 1H, -C*H*OCO-), 5.27 (s, 1H), 5.25 (s,1H), 4.54-4.49 (m, 1H, -C*H*OAr, major diastereomer), 4.47-4.42 (m, 1H, -C*H*OAr, minor diastereomer), 2.41-2.19 (m, 2H), 1.86-1.68 (m, 2H), 1.66-1.44 (m, 3H), 1.28-1.24 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ 167.9, 153.4, 135.7, 134.7, 128.9, 128.5, 127.3, 126.4, 126.3, 125.7, 125.3, 122.4, 120.5, 106.1, 75.8, 47.3, 29.2, 22.9, 22.8.

IR (KBr) υ: 3063, 2948, 1726, 1576, 1456, 1398, 1274, 1182, 1096 cm^{-1}.

HRMS (ESI): calcd for $C_{24}H_{23}BrO_3$ $[M+Na]^+$ 461.0723 found 461.0717.

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-(*R*)-2-bromo-3-phenylacetate (*R*,*R*,*R*)-**30j**



The title compound was obtained by following same procedure as for (*R*,*R*,*S)*-(**27**) from alcohol (*R*,*R*)-(**19**) and 2-bromo-3-phenylacetic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in white solid. (0.18 g, 98%). M.p = 80-82 ^{o}C. *de* = 65%. $[\alpha]_D^{25}$ = -37.5 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) after crystallization: δ 7.78-7.76, (d, *J* = 8.0 Hz, 1H), 7.71-7.66 (m, 2H), 7.47-7.43 (m, 1H), 7.38-7.34 (m, 3H), 7.20-7.14 (m, 4H), 6.99-6.96 (m, 1H), 5.26 (s, 1H, -C$_\alpha$*H*), 5.16-5.11 (m, 1H, -C*H*OCO-), 4.42-4.36 (m, 1H, -C*H*OAr), 2.20-2.18 (m, 2H), 1.81-1.80 (m, 2H), 1.58-1.51 (m, 2H), 1.49-1.37 (m, 2H).

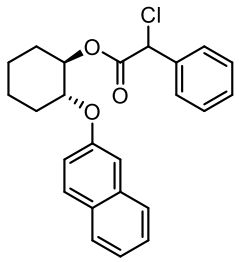
^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 155.7, 134.3, 129.3, 129.1, 129.0, 128.6, 128.5, 127.6, 126.8, 126.3, 123.7, 119.5, 108.9, 47.2, 29.5, 29.3, 23.0, 22.9.

IR (KBr) υ: 3058, 2933, 1746, 1626, 1461, 1352, 1283, 1141, 1057 cm^{-1}.

Mass: 461.1 $[M+Na]^+$, 413.2.

HRMS (ESI): calcd for $C_{24}H_{24}BrO_3$ (M+H) 439.0903 found 439.0901.

Synthesis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl-2-chloro-3-phenylacetate (**30k**)



The title compound was obtained by following same procedure as for (*R*,*R*,*S)*-(**27**) from alcohol (*R*,*R*)-(**19**) and 2-chloro-3-phenylacetic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in colorless oil. (0.16 g, 94%) *de* = 34%. $[\alpha]_D^{25}$ = +4.73 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400MHz) diastereomeric mixture: δ 7.80-7.73, (m, 2H), 7.70-7.66 (m, 1H), 7.49-7.45 (m, 1H), 7.43-7.32 (m, 4H), 7.27-7.22 (m, 2H), 7.16-7.09 (m, 2H), 5.29 (s, 1H, -C$_\alpha$*H*, major diastereomer), 5.23 (s, 1H, C$_\alpha$*H*, minor diastereomer), 5.23-5.09 (m, 1H, -C*H*OCO-), 4.47-4.41 (m, 1H, -C*H*OAr, major diastereomer), 4.38-4.30 (m, 1H, -C*H*OAr, minor diastereomer) 2.26-2.06 (m, 2H), 1.83-1.71 (m, 2H), 1.64-1.50 (m, 1H), 1.48-1.36 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ 167.6, 155.7, 135.8, 134.4, 129.4, 129.1, 129.0, 128.7, 127.8, 127.6, 126.7, 126.3, 123.7, 119.5, 108.9, 76.0, 59.3, 29.4, 29.1, 23.0, 22.9, 22.8.

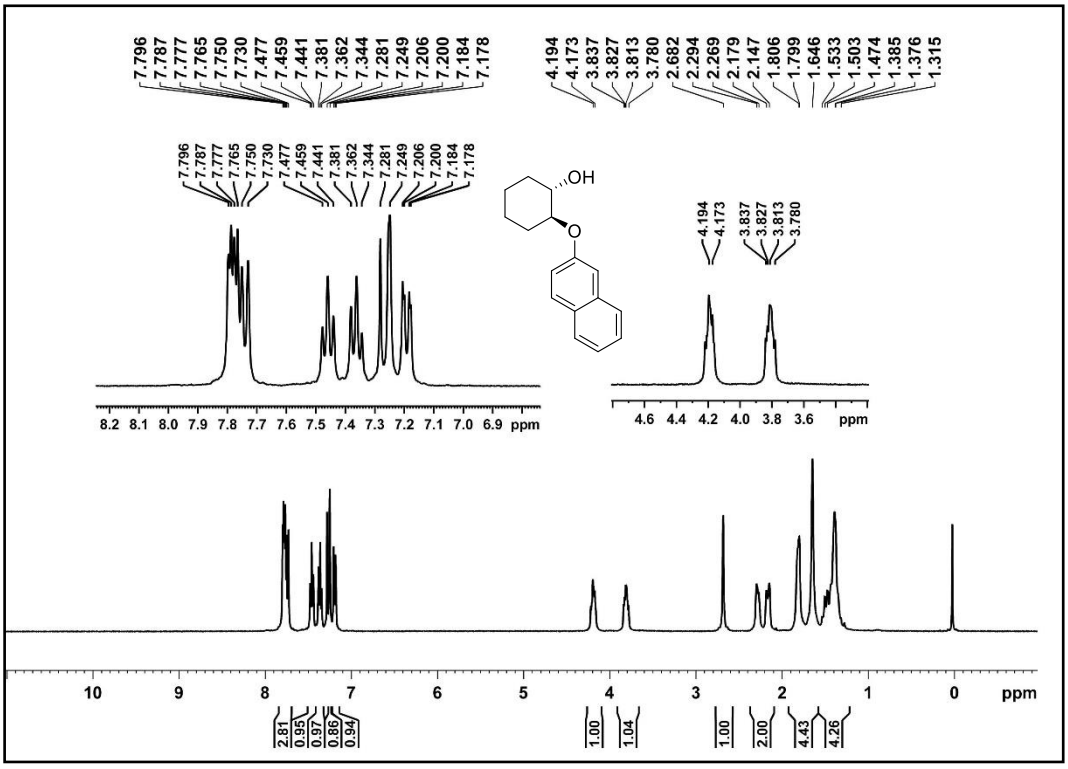
IR (KBr) υ: 3058, 2935, 1752, 1628, 1453, 1351, 1016, 840 cm^{-1}.

HRMS (ESI): calcd for $C_{24}H_{23}ClO_3Na$ $[M+Na]^+$ 417.1233 found 417.1219.

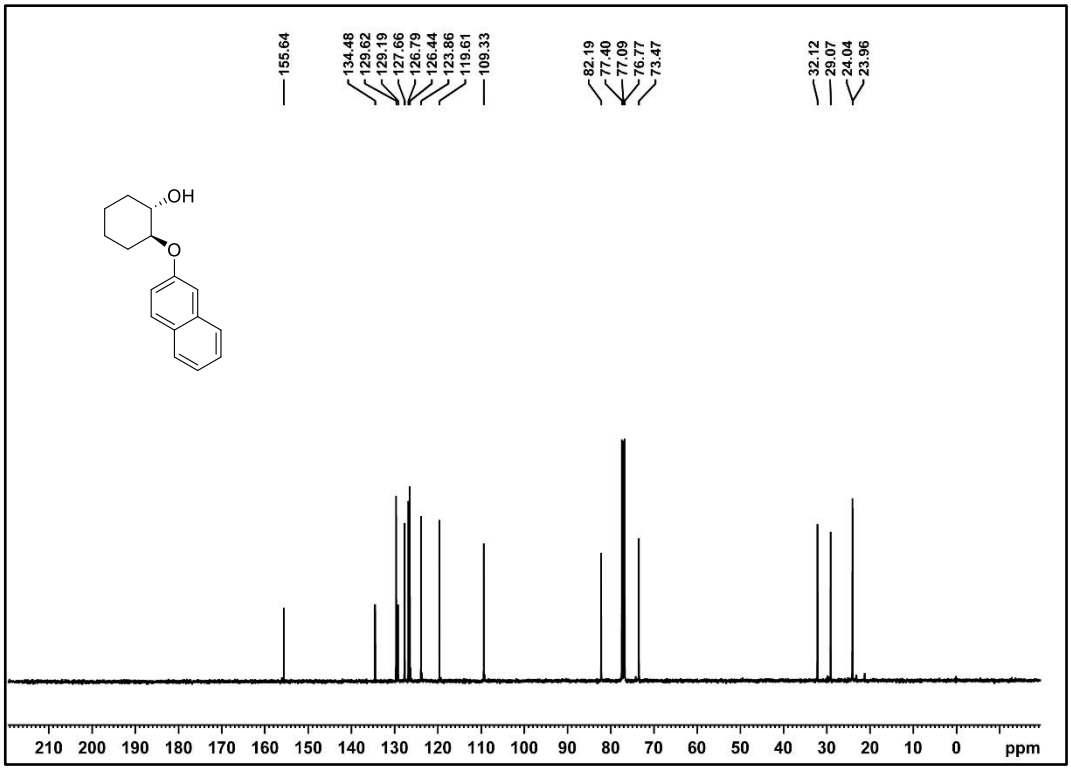
General procedure for hydrolysis of ester: Hydrolysis of (1*R*,2*R*)-2-(naphthalene-2-yloxy)cyclohexyl (*S*)-2-chloropropanoate (*R,R,S)*-(**27**)

In a two neck round bottom flask, fitted with freshly prepared guard tube and condenser, containing chiral ester (*R,R,S)*-(**27**) (0.5 g, 1.5 mmol) in dioxane (8 mL), was added conc. HCl (0.3 mL) and heated at 50 ^oC for 24 h. The reaction mixture was then concentrated under vacuum and subjected to column chromatography on silica gel. The alcohol (*R,R*)-(**19**) was eluted by 10% ethyl acetate/petroleum ether as white solid. (0.33 g, 93%). *ee* >99%. The acid (*S*)-(**26**) was eluted by 30% ethyl acetate/petroleum ether as colorless liquid (0.14 g, 91%). *ee* >99% $[\alpha]_D^{25}$ = 13.9 (neat).[11]

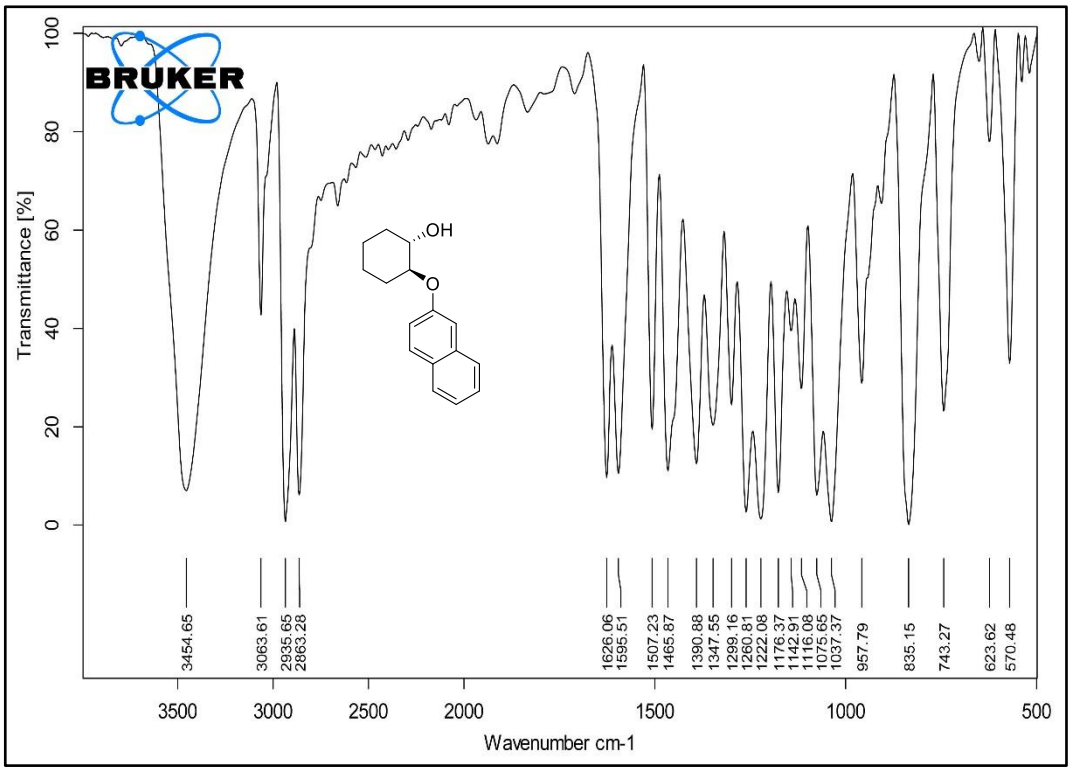
3.5.1 Spectral Data



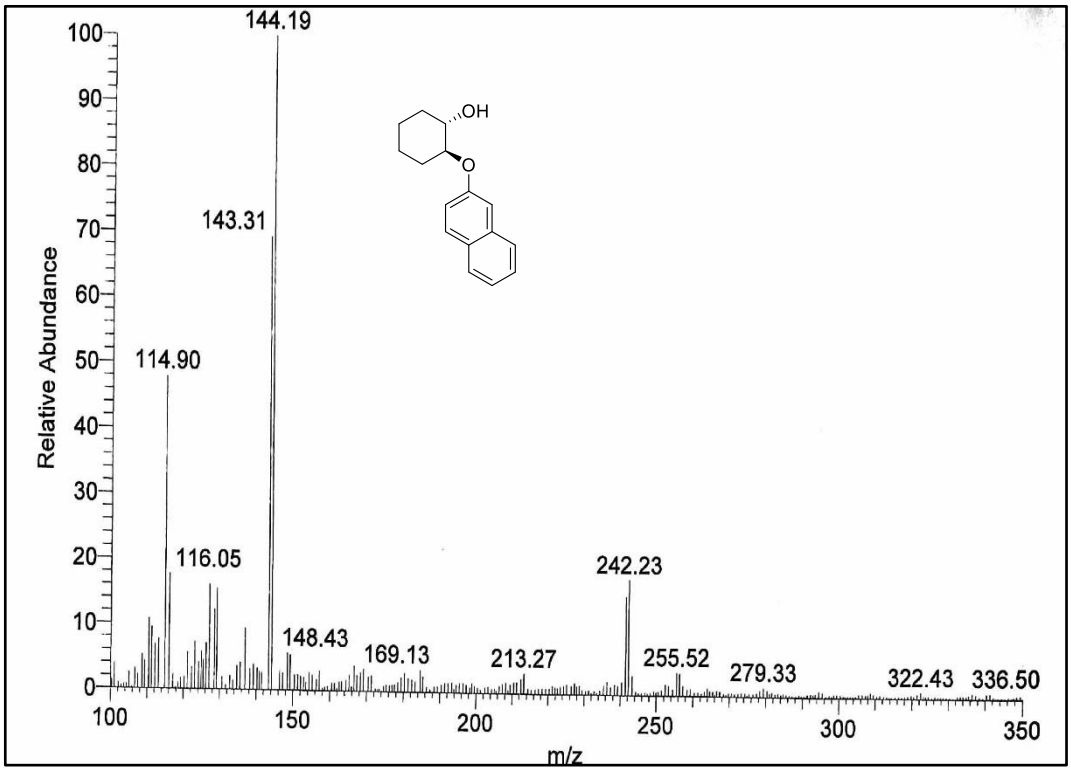
^{1}H NMR Spectra of Compound (**19**)



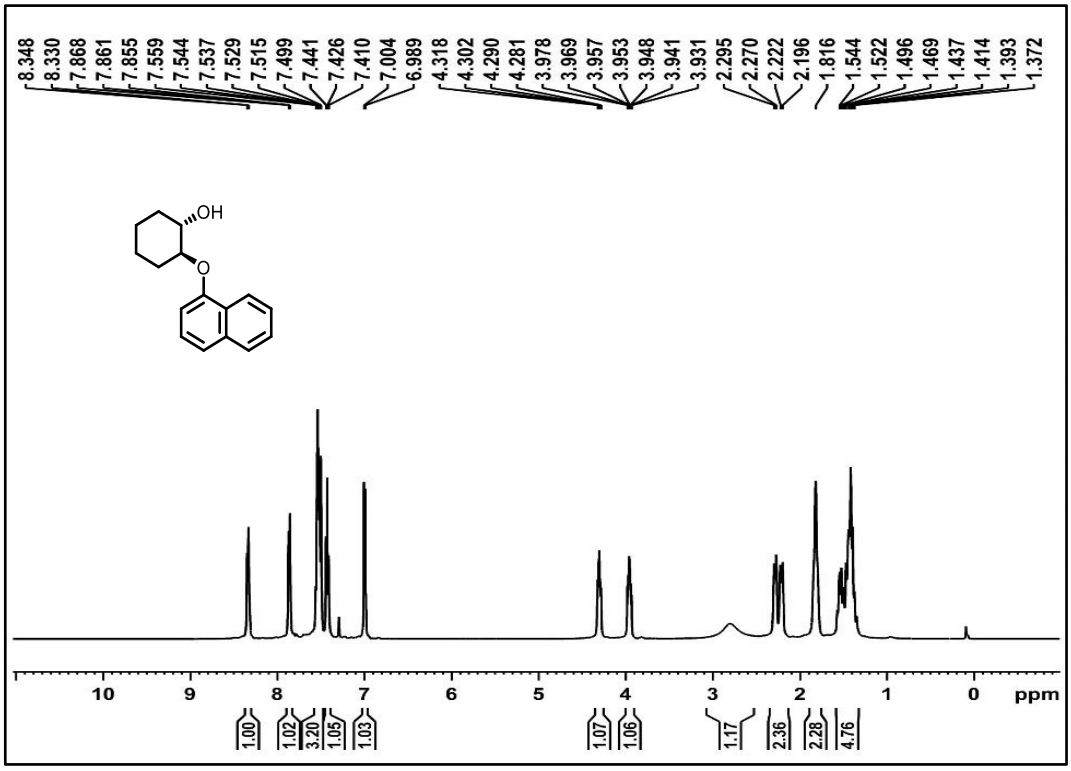
^{13}C NMR Spectra of Compound (**19**)



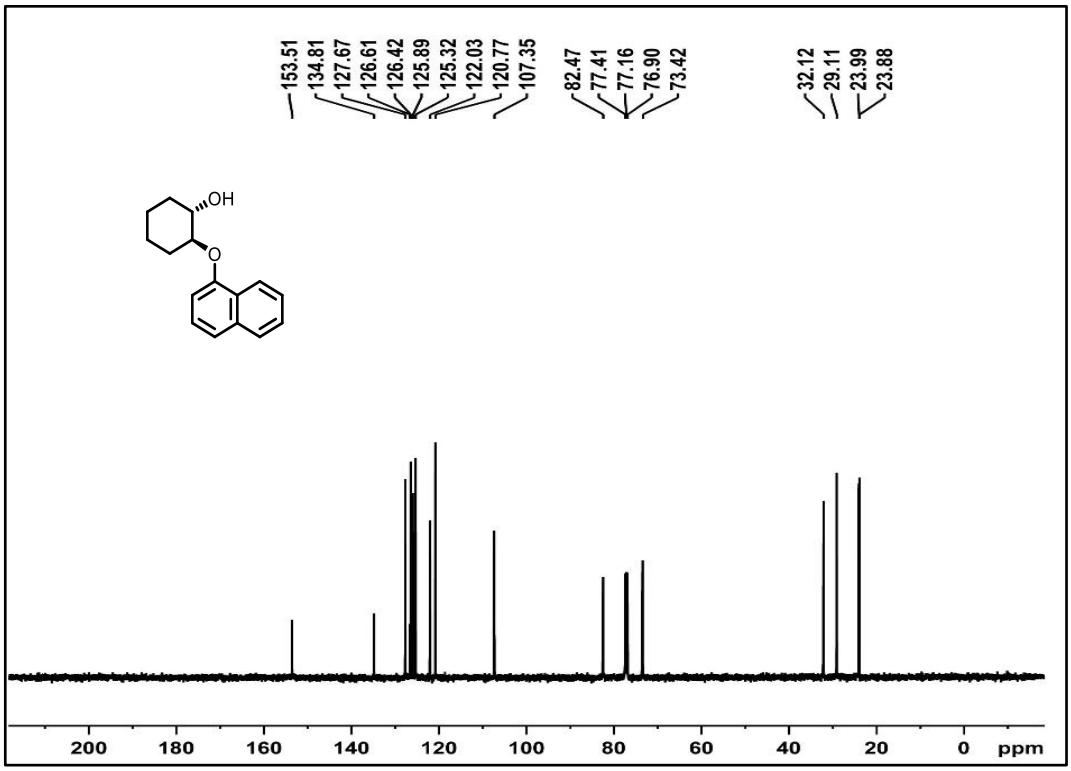
IR Spectra of Compound (**19**)



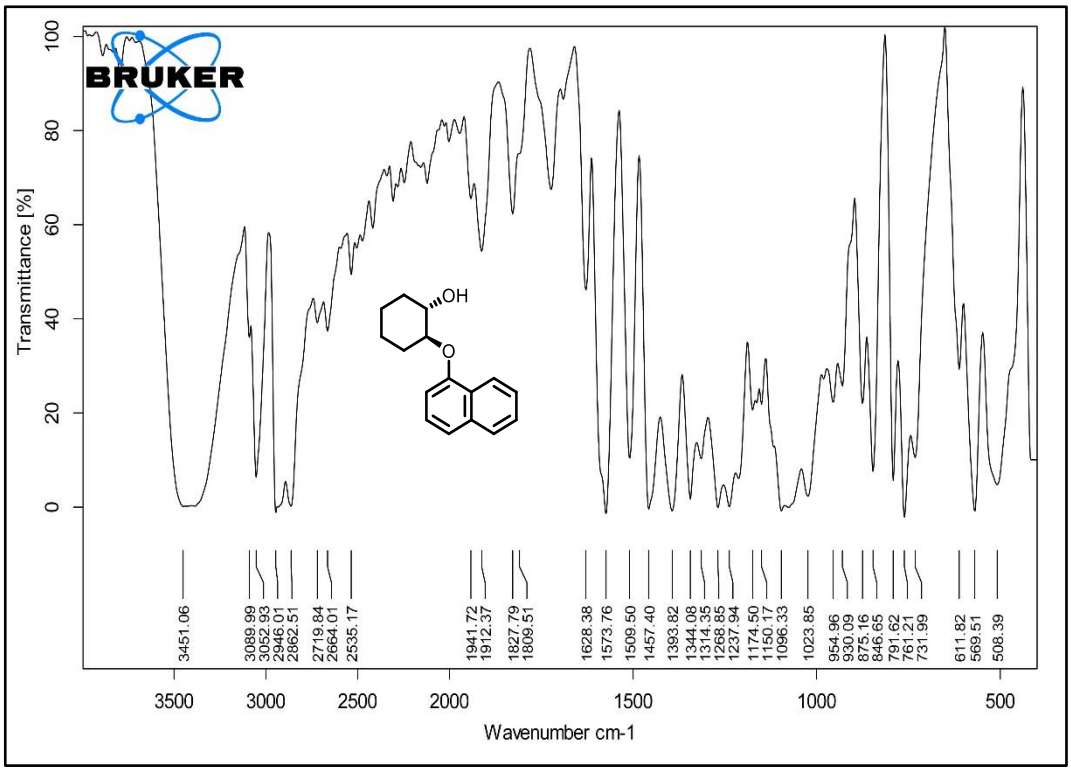
MS Spectra of Compound (**19**)



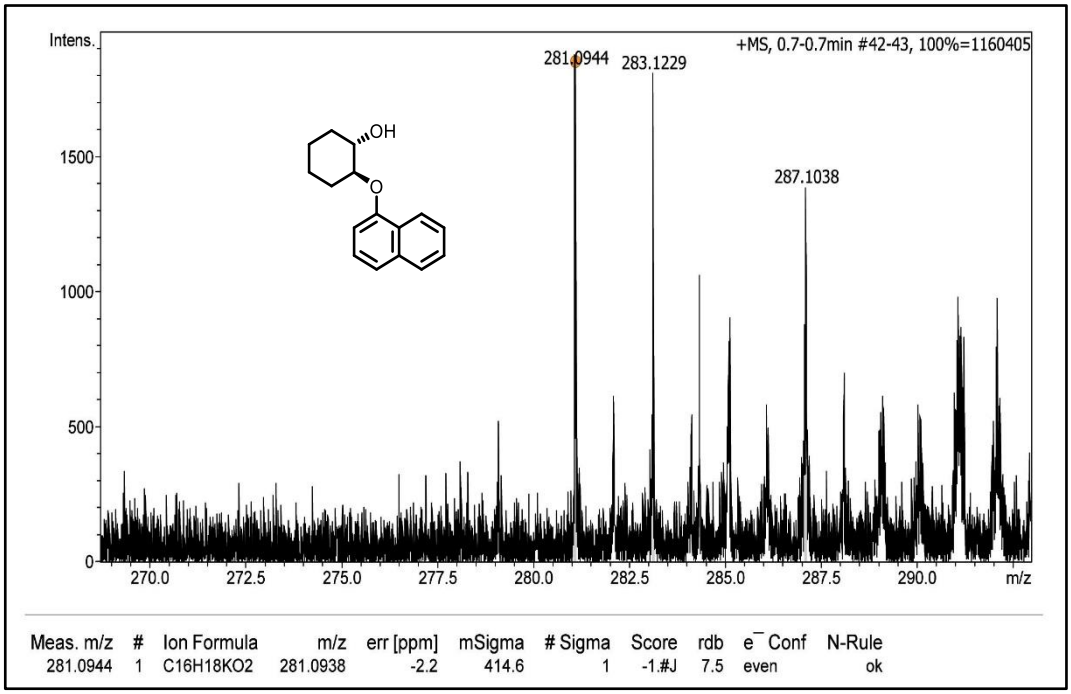
^{1}H NMR Spectra of Compound (**21**)



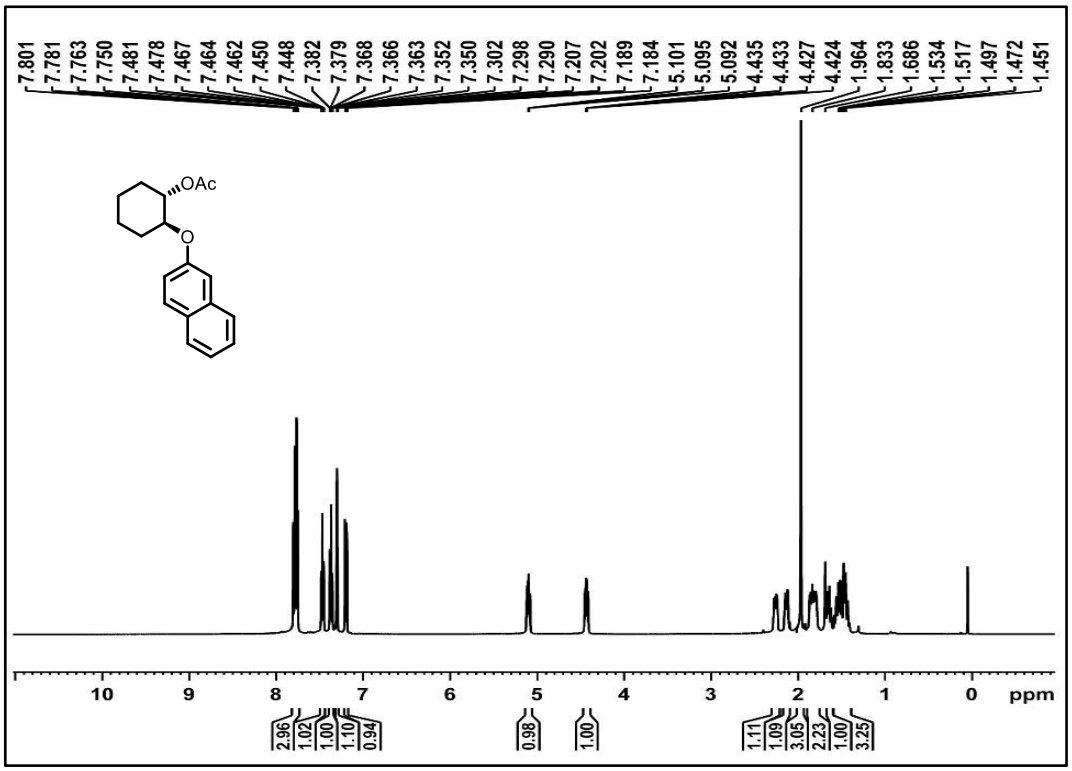
^{13}C NMR Spectra of Compound (**21**)



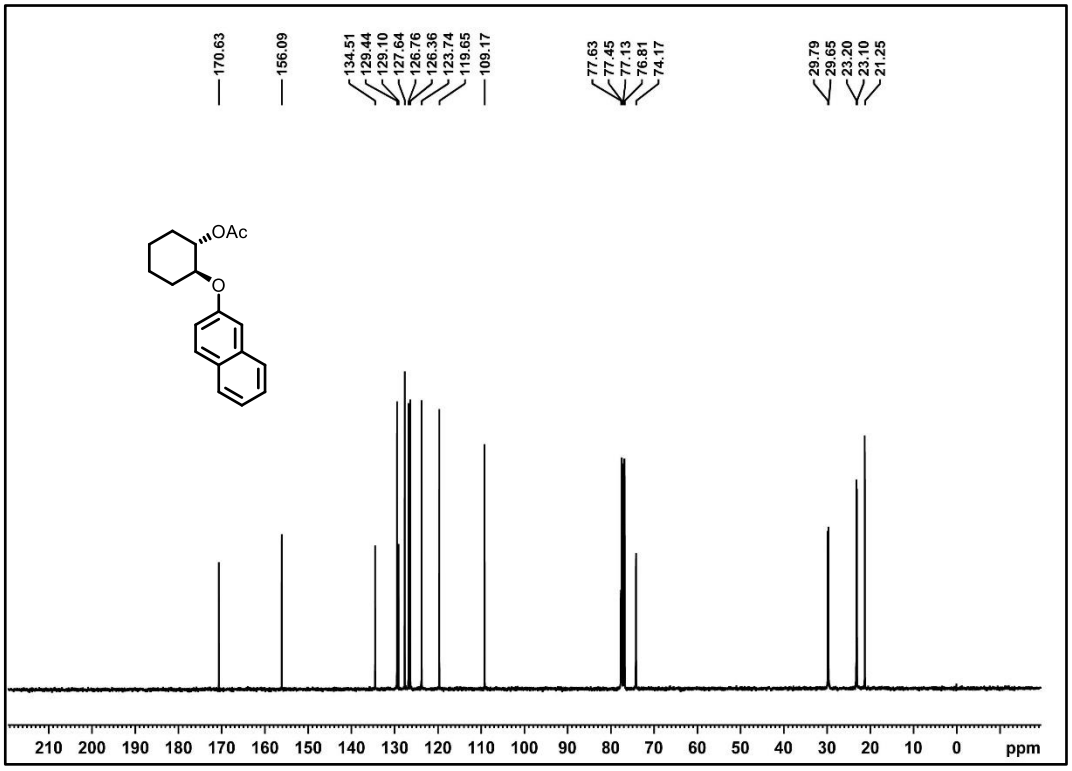
IR Spectra of Compound (**21**)



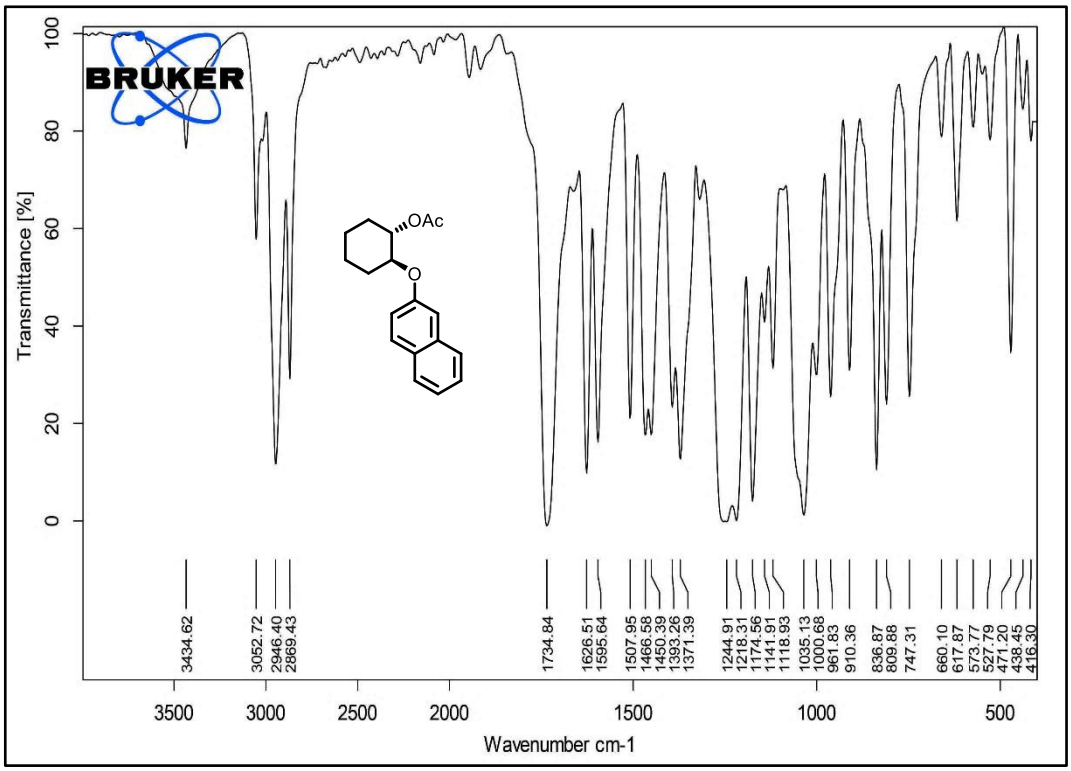
HRMS Spectra of Compound (**21**)



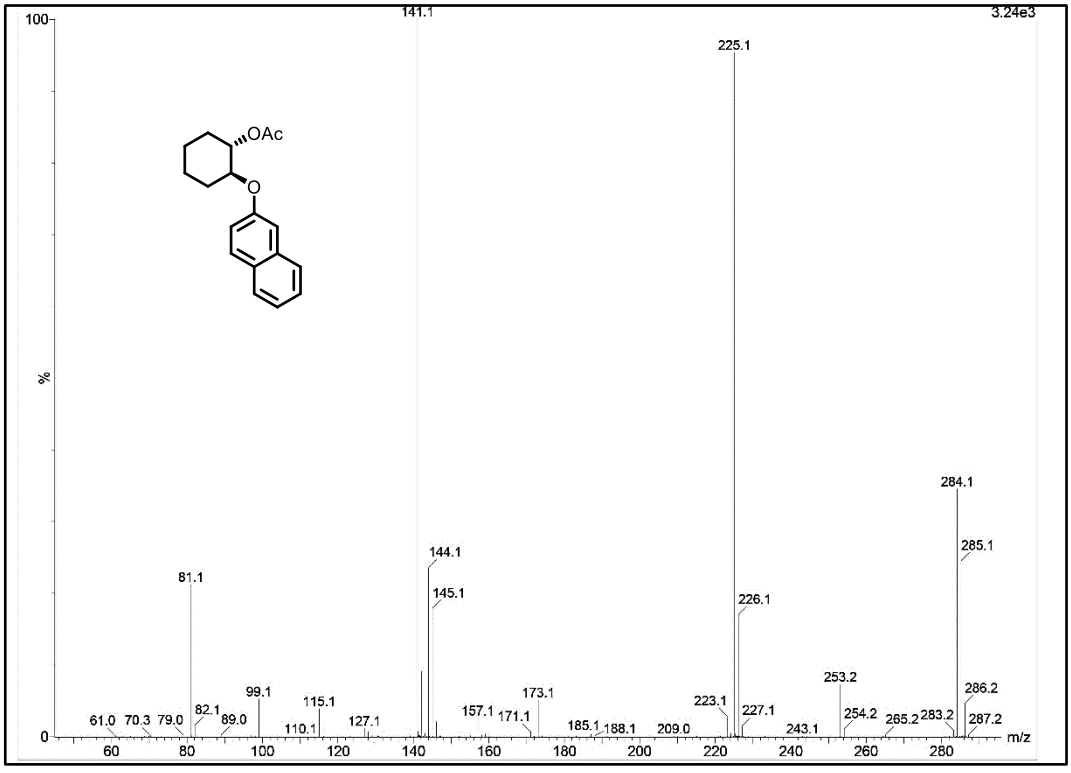
^{1}H NMR Spectra of Compound (**22**)



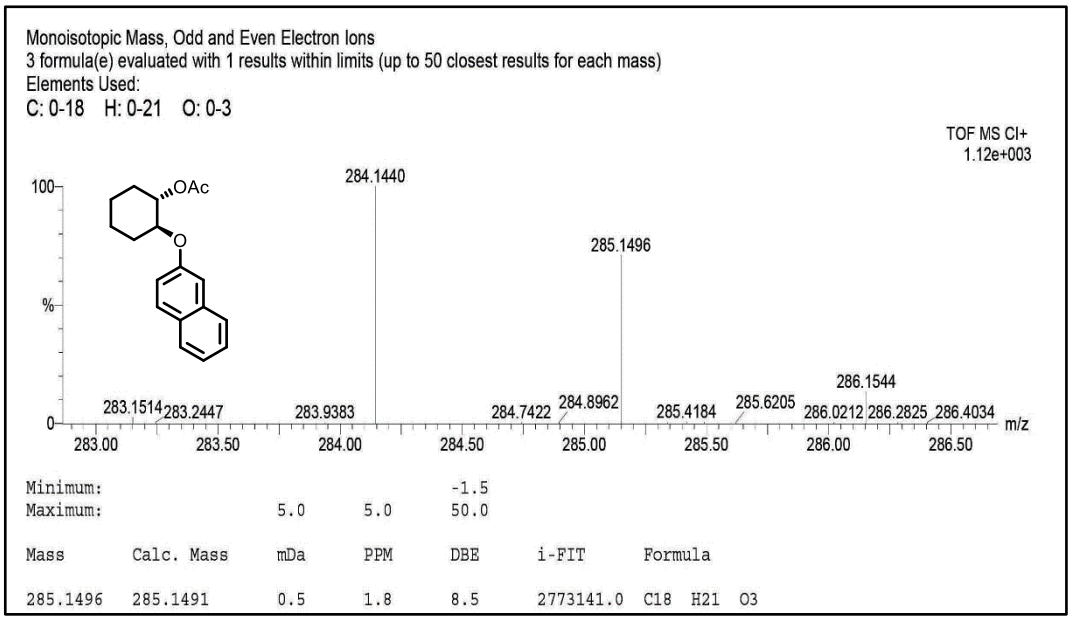
^{13}C NMR Spectra of Compound (**22**)



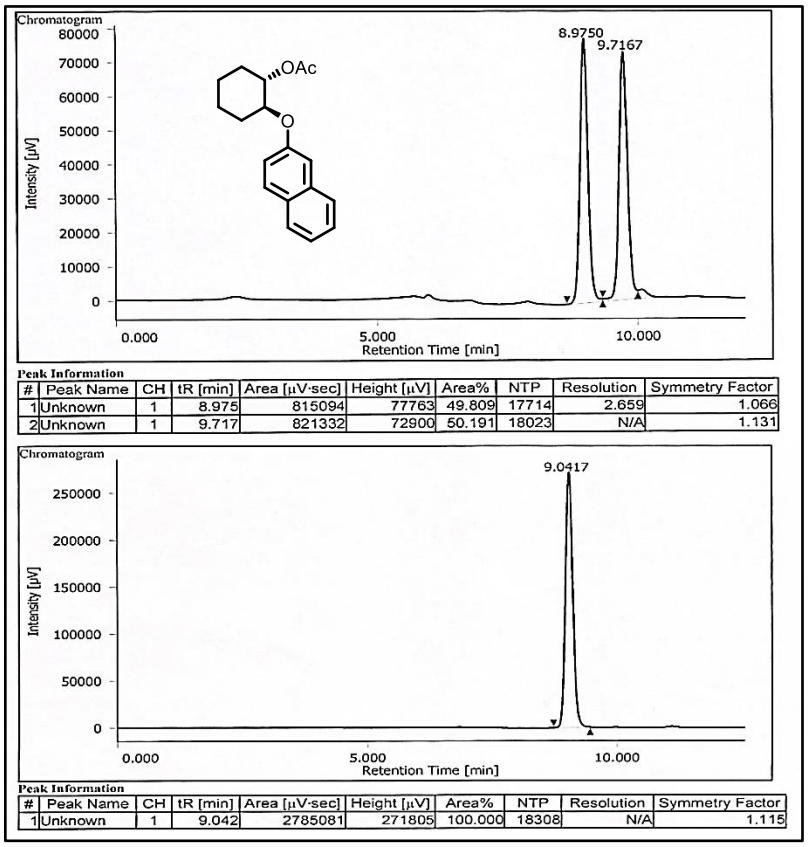
IR Spectra of Compound (**22**)



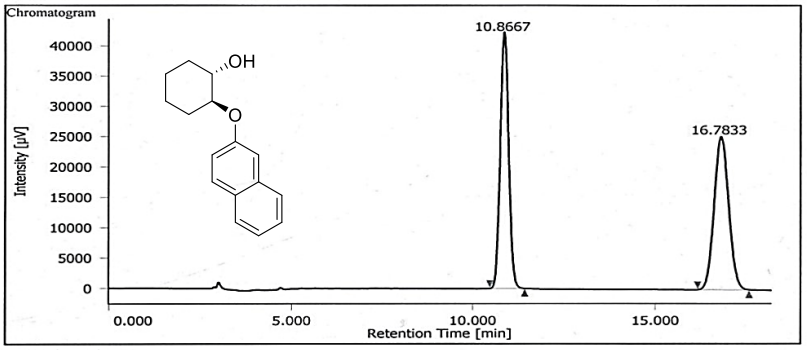
MS Spectra of Compound (**22**)



HRMS Spectra of Compound (**22**)

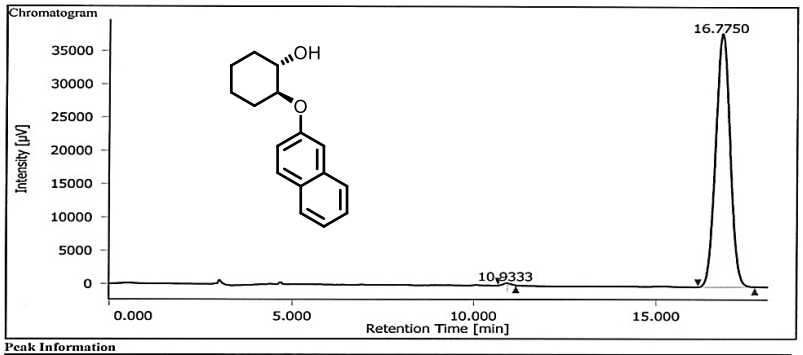


HPLC Chromatogram of rac-**22** (top), (*R*,*R*)- **22** (bottom)
Chiralcel-OD-H column: 10% Isopropyl alcohol-Hexane, UV=254 nm, Flow= 0.5mL/min. R_t = 8.9 min (*R*,*R*)-**22** and R_t= 9.7 min (*S*,*S*)-**22**



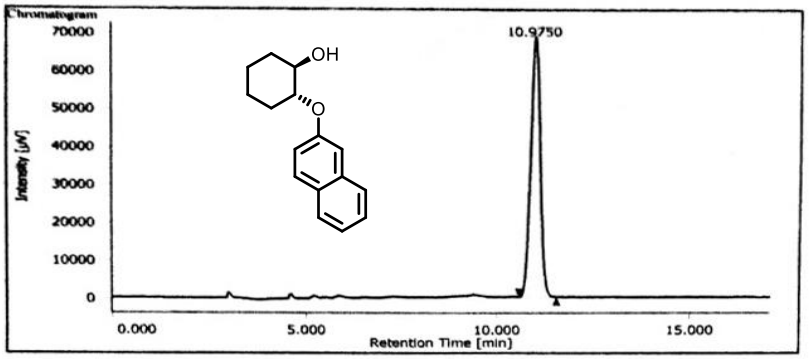
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	10.867	689193	42315	49.637	10195	10.167	1.088
2	Unknown	1	16.783	699285	25210	50.363	8308	N/A	1.073



Peak Information

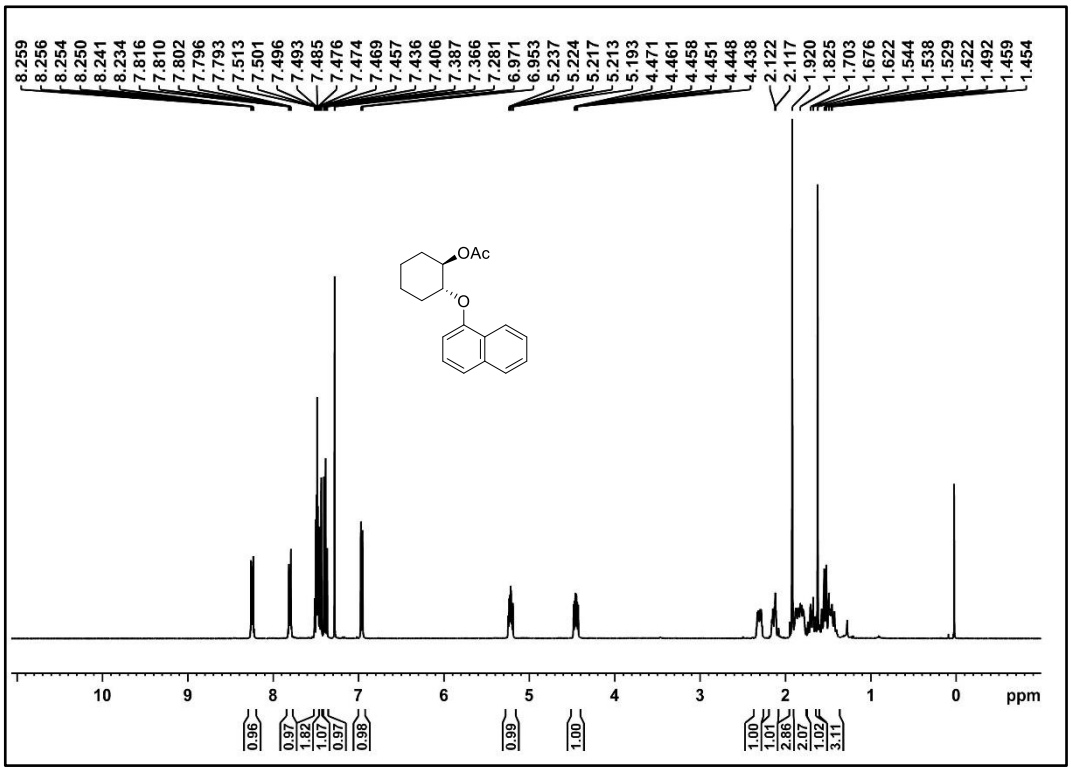
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	10.933	5154	324	0.491	9612	9.998	0.951
2	Unknown	1	16.775	1044826	38155	99.509	8551	N/A	1.084



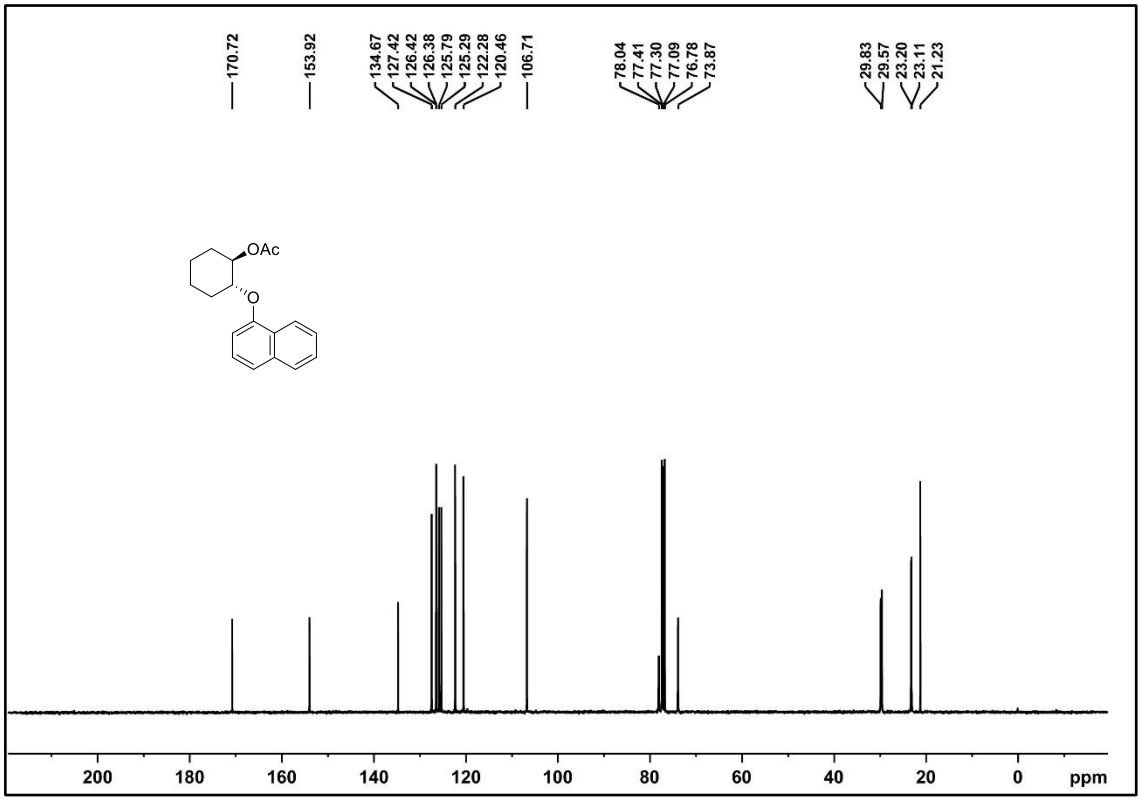
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	10.975	1177374	68626	100.000	9335	N/A	1.090

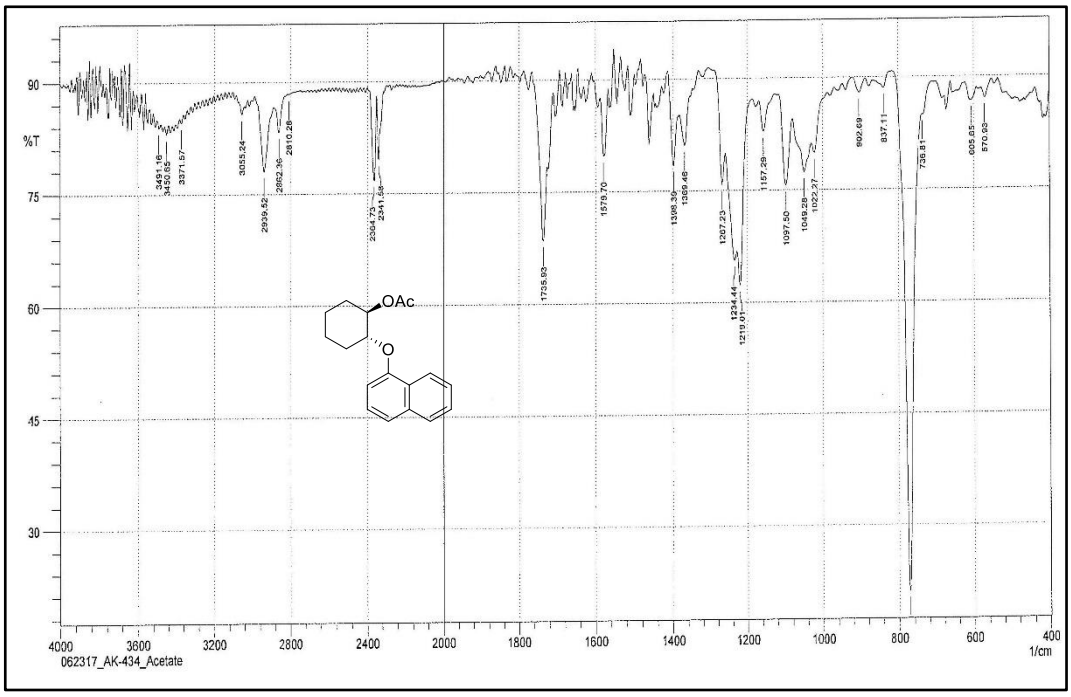
HPLC Chromatogram of rac-**19** (top), (*S,S*)-**19** (middle), (*R,R*)-**19** (bottom) Chiralcel-OD-H column: 10% Isopropyl alcohol-Hexane, UV=254 nm, Flow=1.0mL/min. R_t = 10.8 min (*R,R*)-**19** and R_t= 16.7 min (*S,S*)-**19**



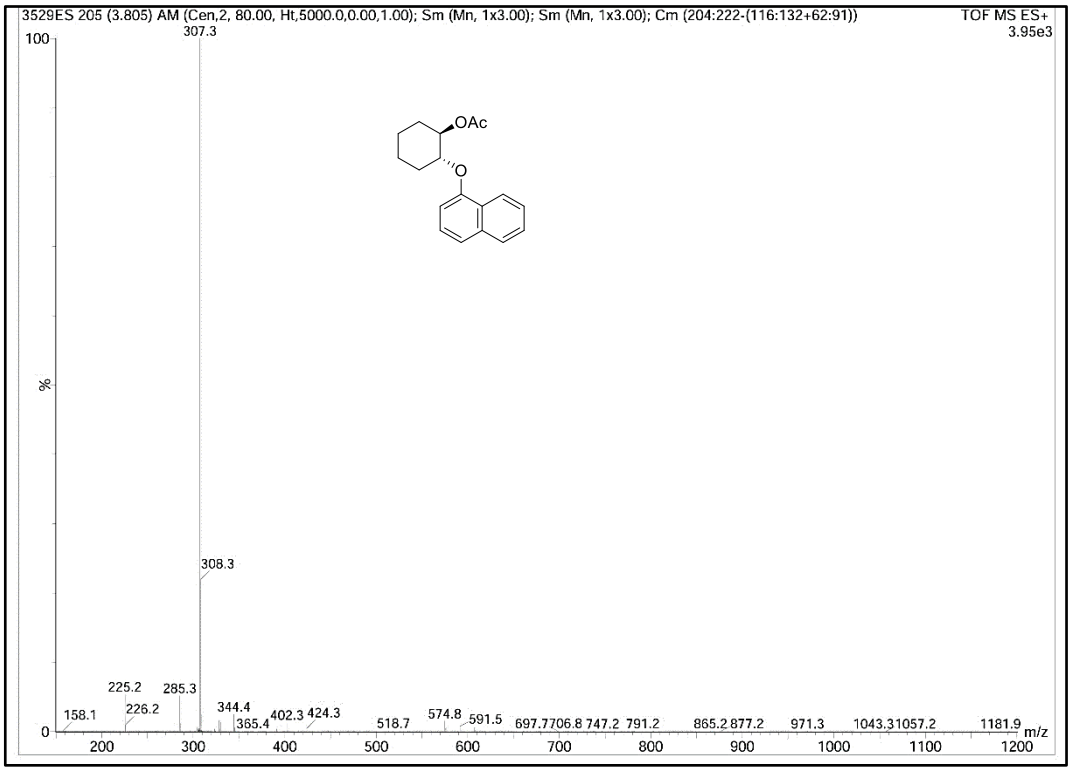
^{1}H NMR Spectra Compound (**23**)



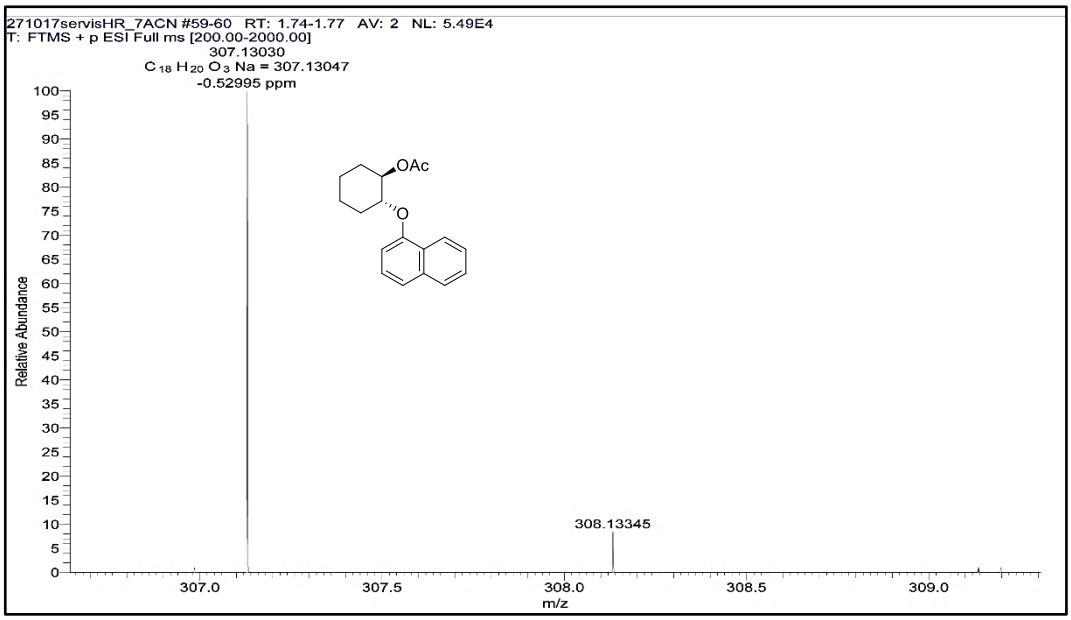
^{13}C NMR Spectra Compound (**23**)



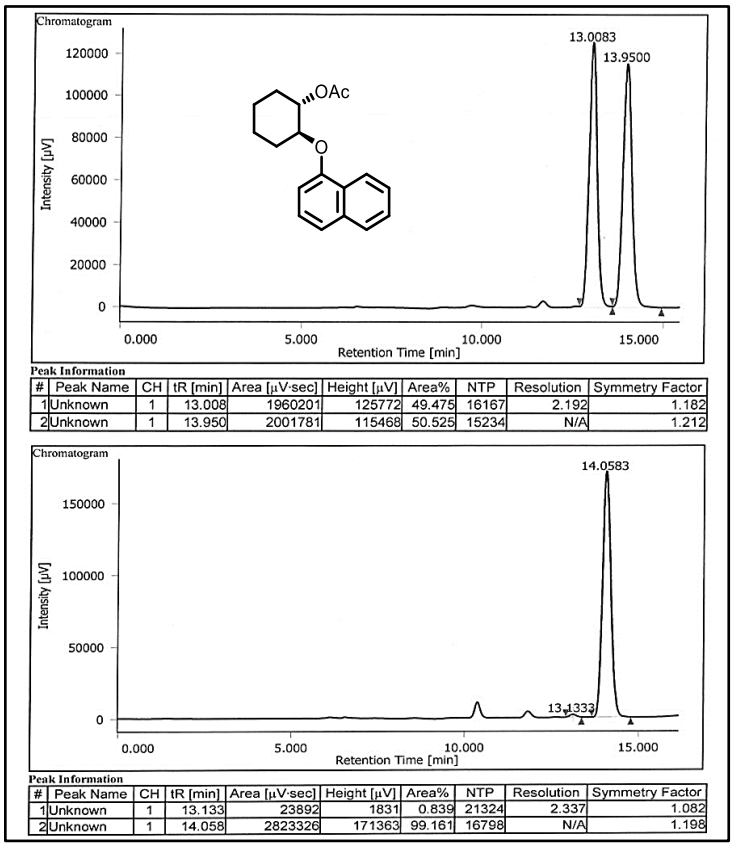
IR Spectra of Compound (**23**)



MS Spectra of Compound (**23**)



HRMS Spectra of Compound (**23**)



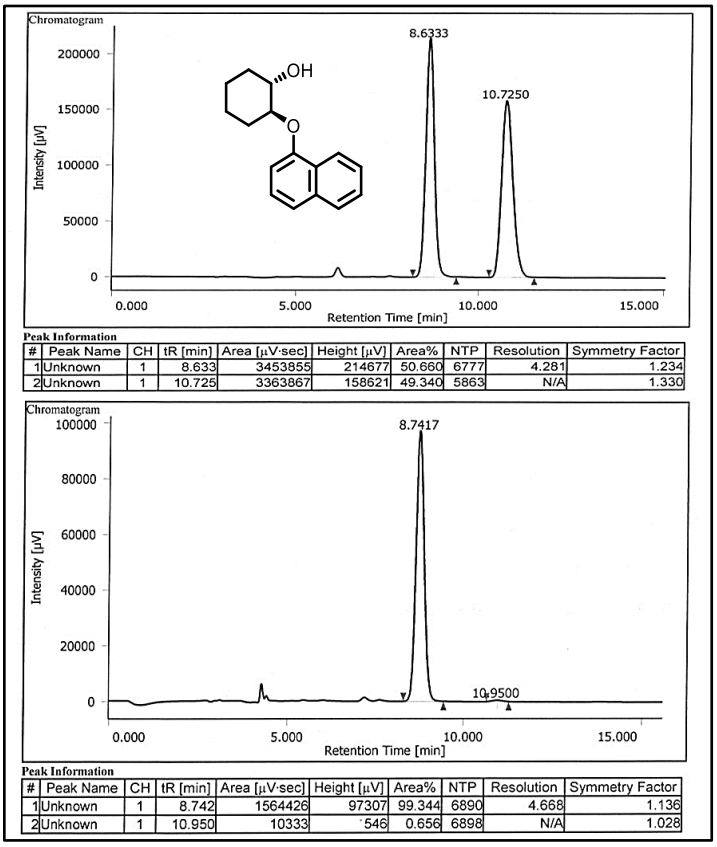
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	13.008	1960201	125772	49.475	16167	2.192	1.182
2	Unknown	1	13.950	2001781	115468	50.525	15234	N/A	1.212

Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	13.133	23892	1831	0.839	21324	2.337	1.082
2	Unknown	1	14.058	2823326	171363	99.161	16798	N/A	1.198

HPLC Chromatogram of rac-**23** (top), (*R*,*R*)-**23** (bottom)
Chiralcel-OD-H column: 1% Isopropyl alcohol-Hexane, UV=254 nm, Flow= 0.5mL/min. R_t = 13.0 min (*S*,*S*)-**23** and R_t= 13.9 min (*R*,*R*)-**23**



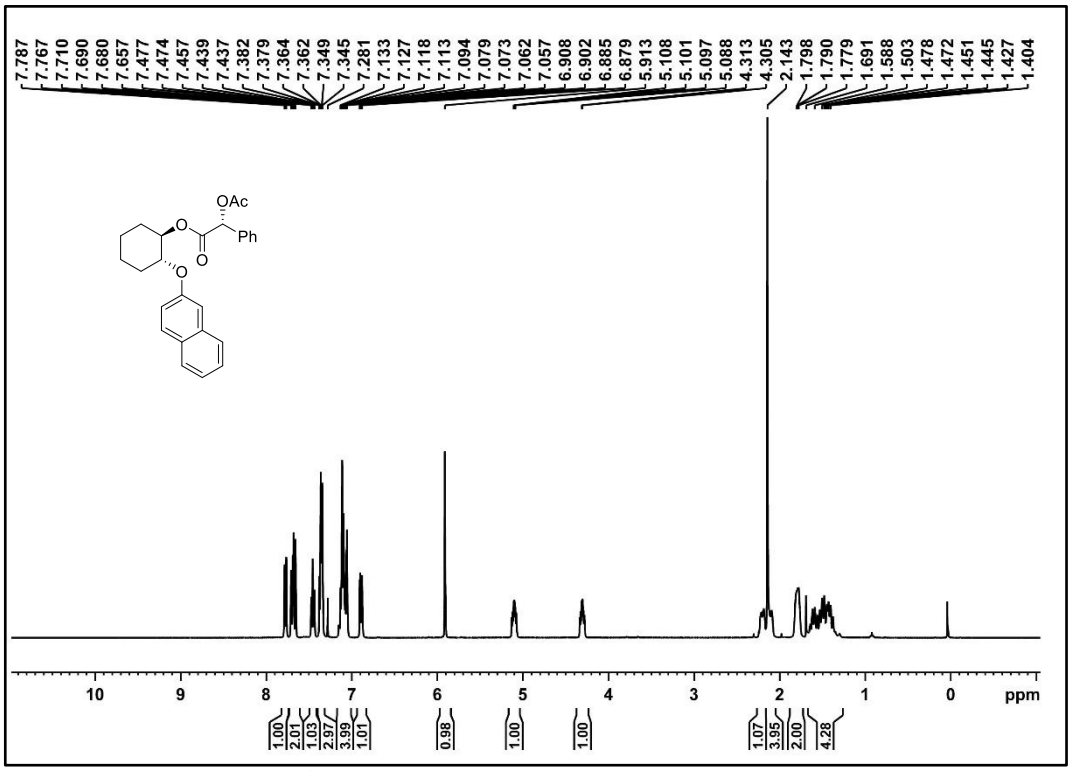
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	8.633	3453855	214677	50.660	6777	4.281	1.234
2	Unknown	1	10.725	3363867	158621	49.340	5863	N/A	1.330

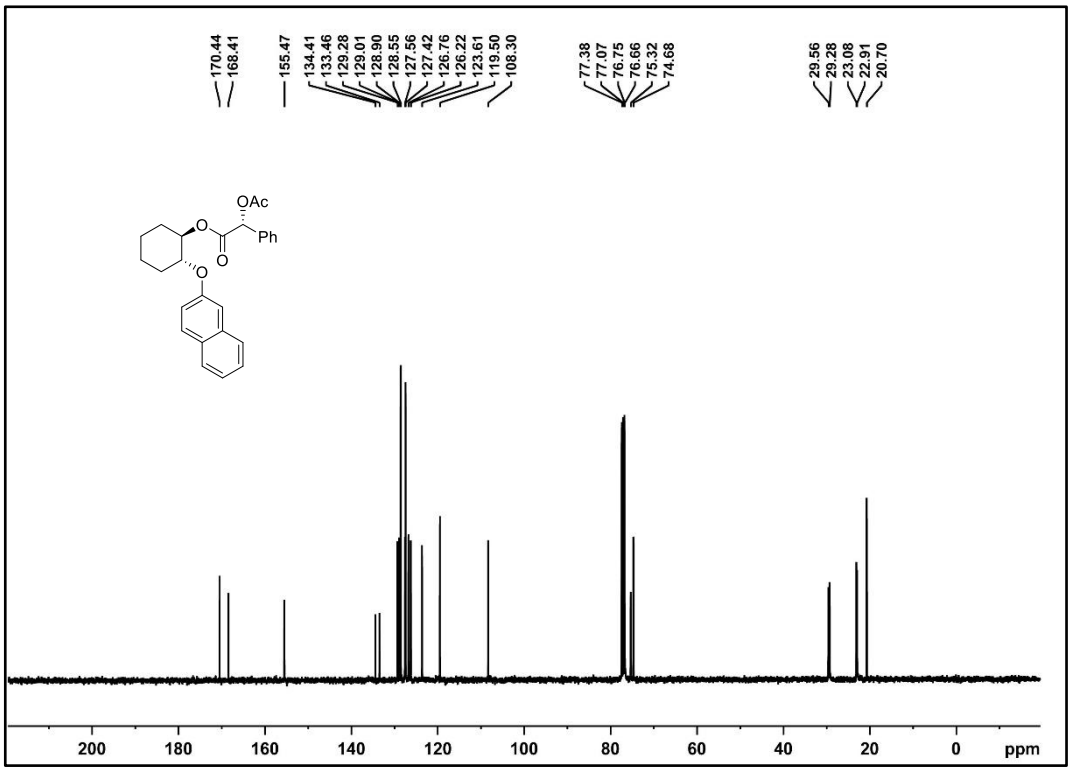
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	8.742	1564426	97307	99.344	6890	4.668	1.136
2	Unknown	1	10.950	10333	546	0.656	6898	N/A	1.028

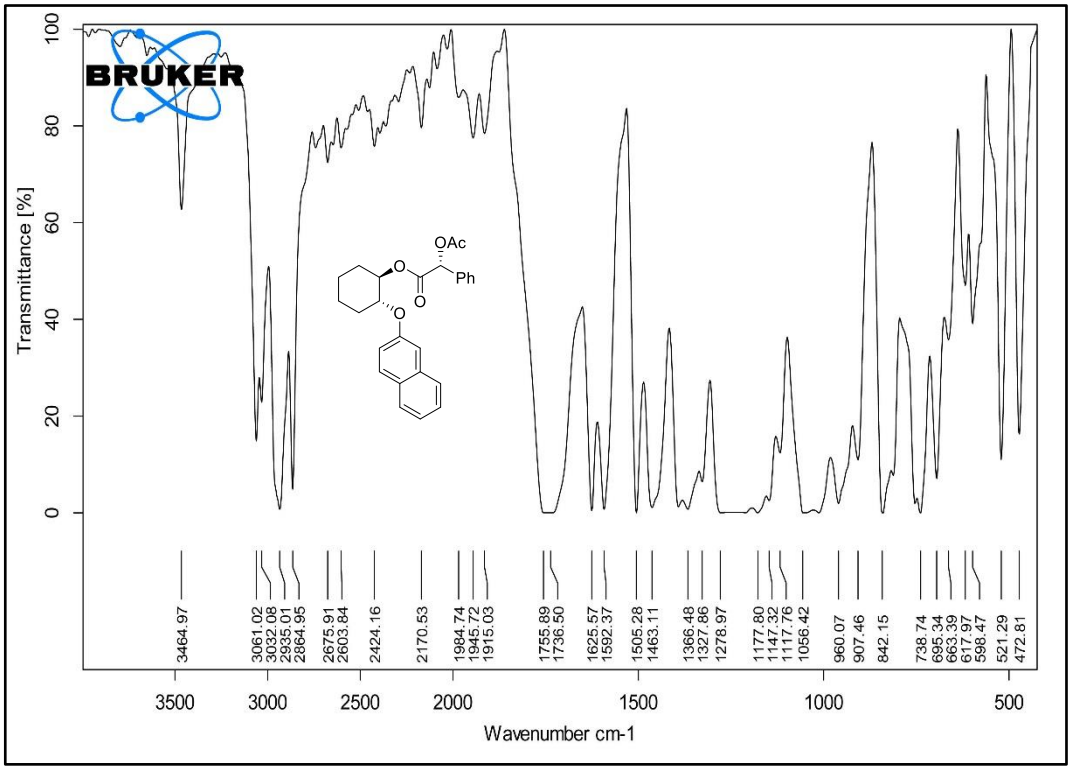
HPLC Chromatogram of rac-**21** (top) and (*S*,*S*)-**21** (bottom).
Chiralcel-OD-H column: 25% Isopropyl alcohol-Hexane, UV=254 nm,
Flow=1.0mL/min. R_t = 8.6 min (*R*,*R*)-**21** and R_t= 10.7 min (*S*,*S*)-**21**



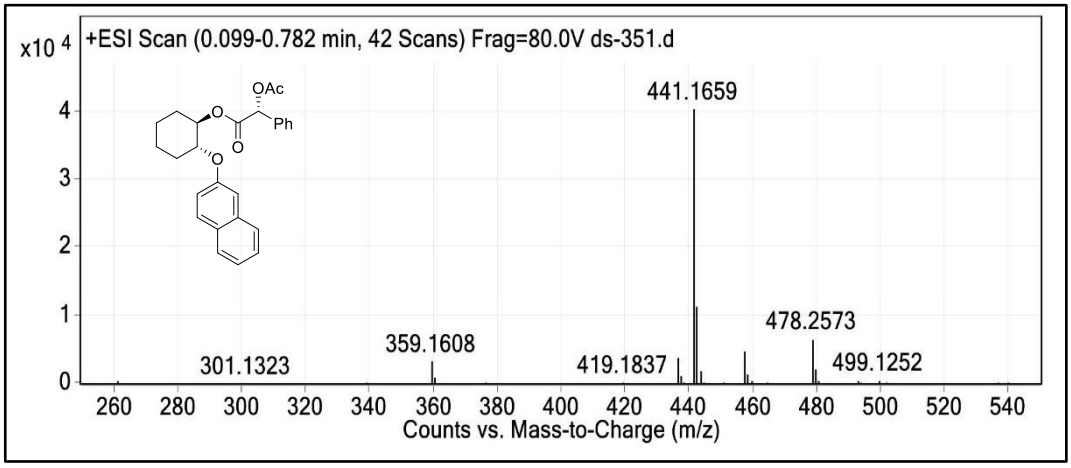
^{1}H NMR Spectra of Compound (**24**)



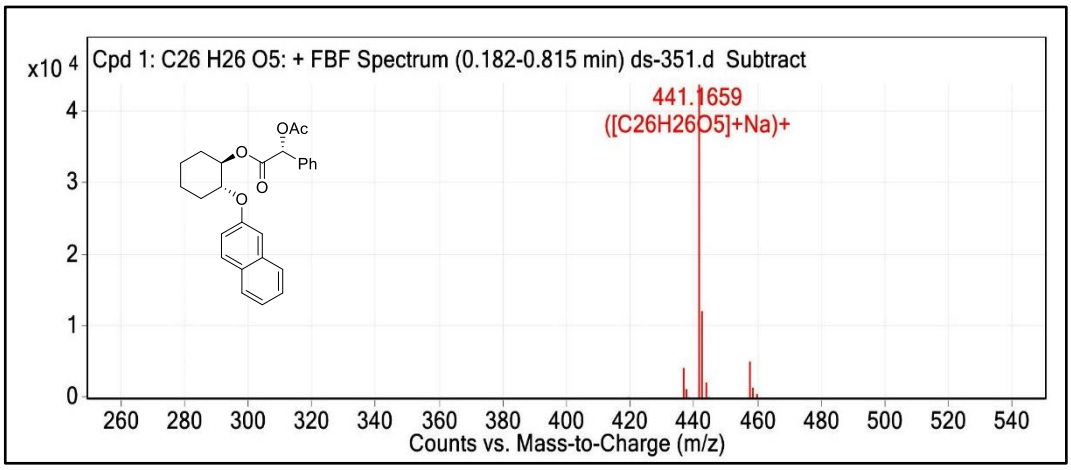
^{13}C NMR Spectra of Compound (**24**)



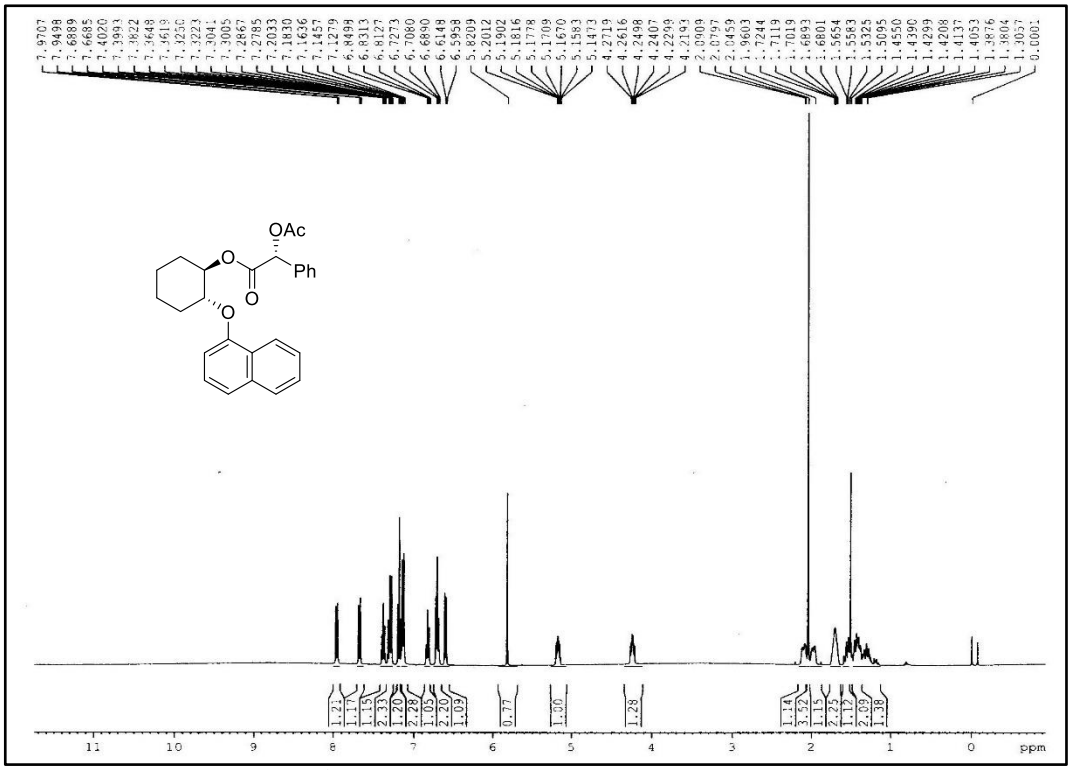
IR Spectra of Compound (**24**)



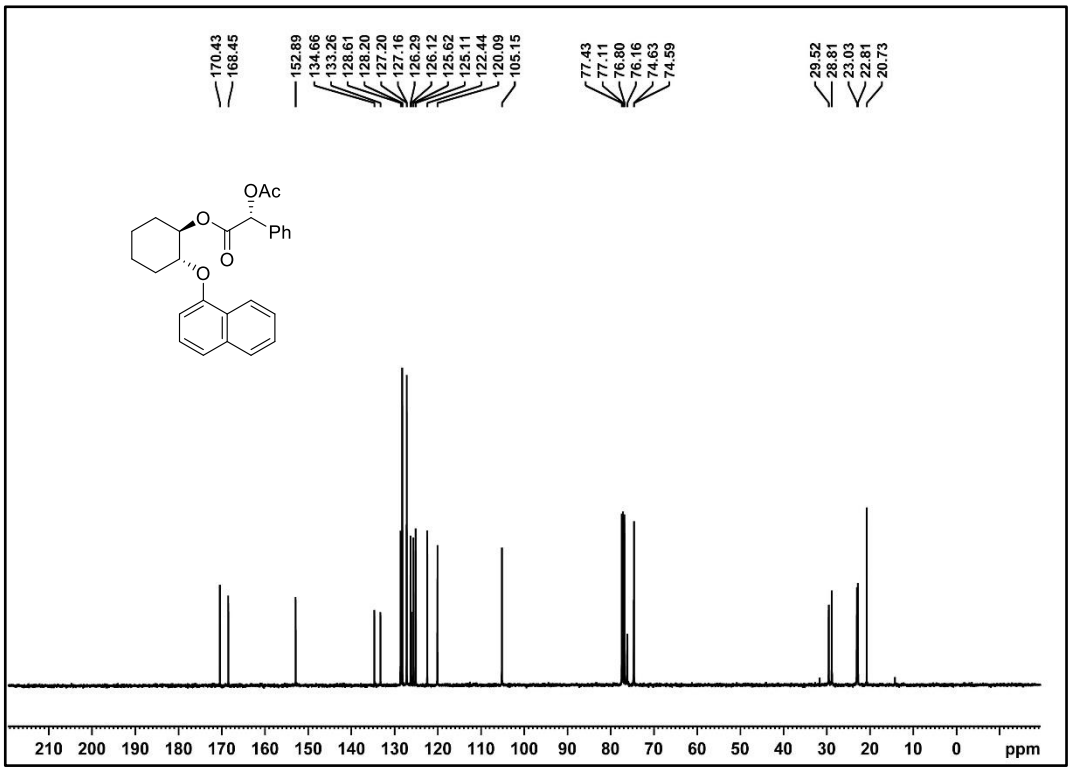
MS Spectra of Compound (**24**)



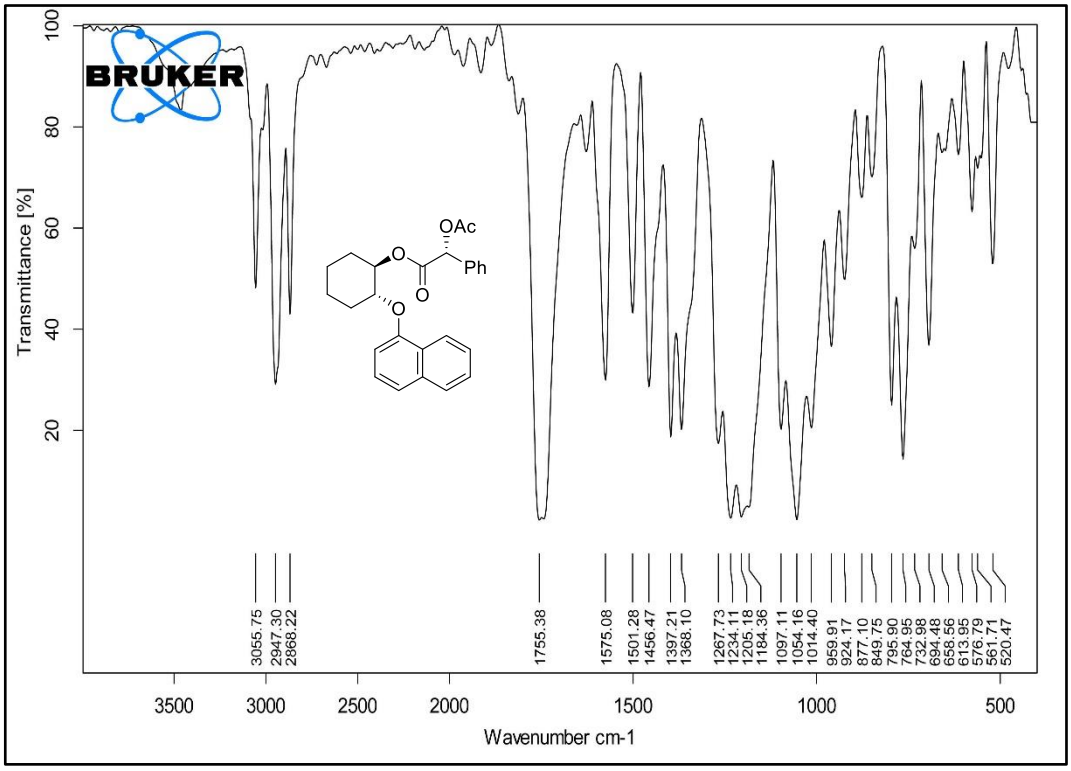
HRMS Spectra of Compound (**24**)



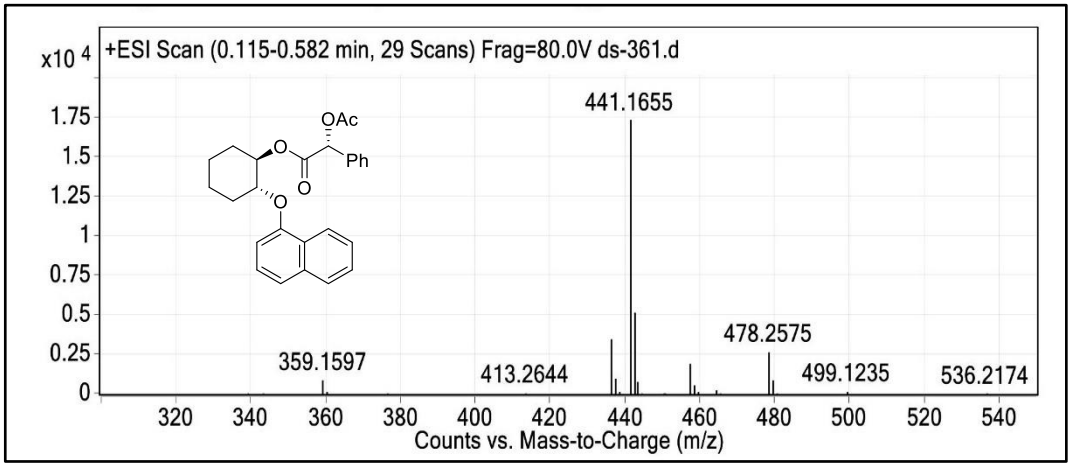
^{1}H NMR Spectra Compound (**25**)



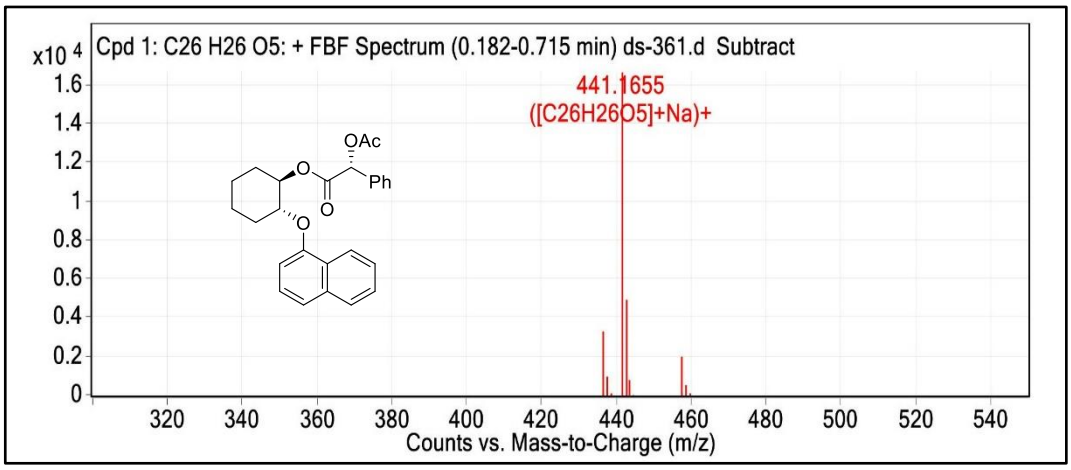
^{13}C NMR Spectra Compound (**25**)



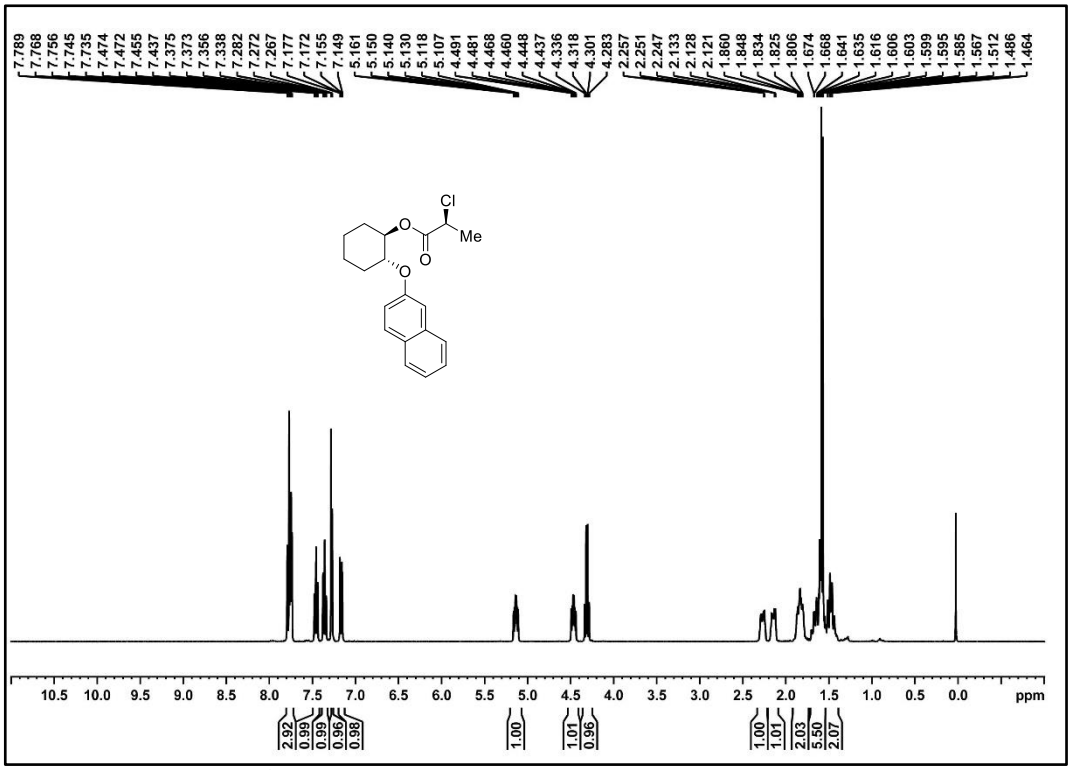
IR Spectra of Compound (**25**)



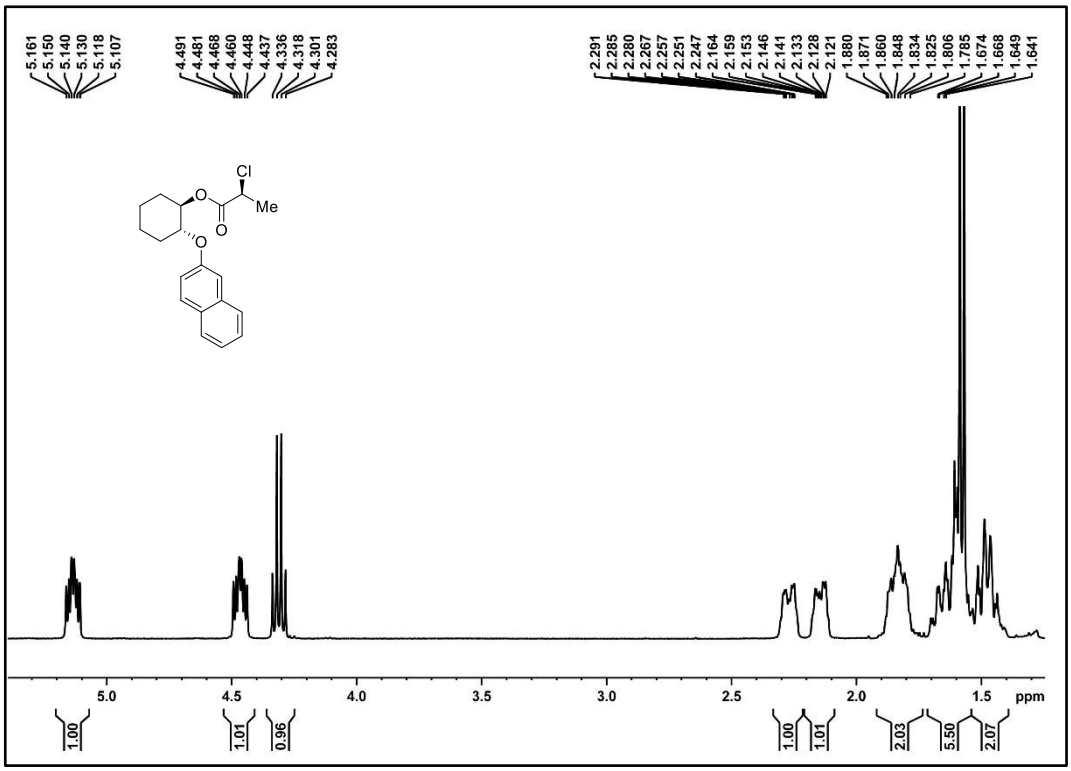
MS Spectra of Compound (**25**)



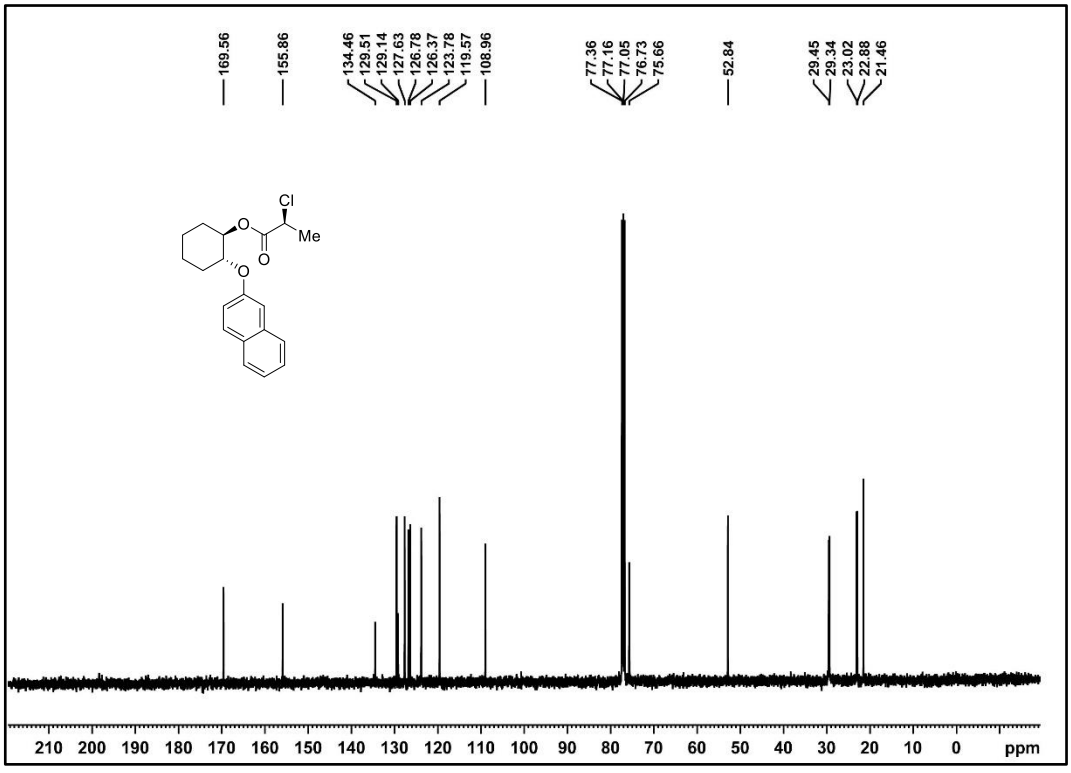
HRMS Spectra of Compound (**25**)



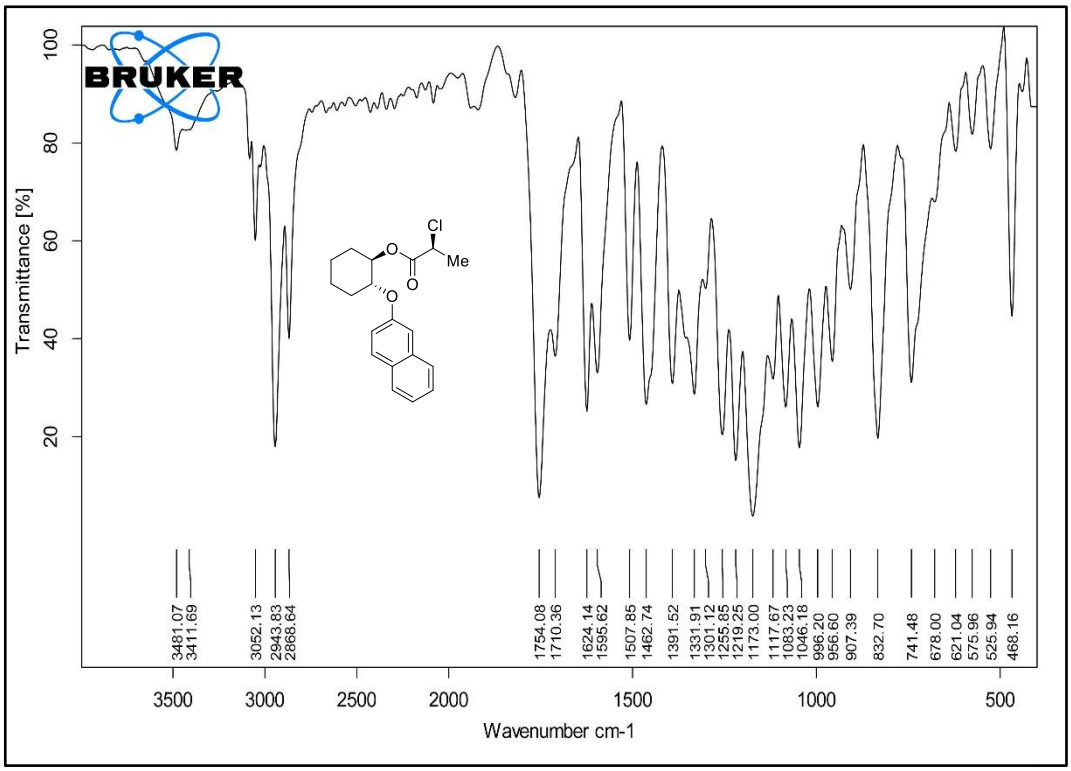
^{1}H NMR Spectra of Compound (*R*,*R*,*S*)-**27**



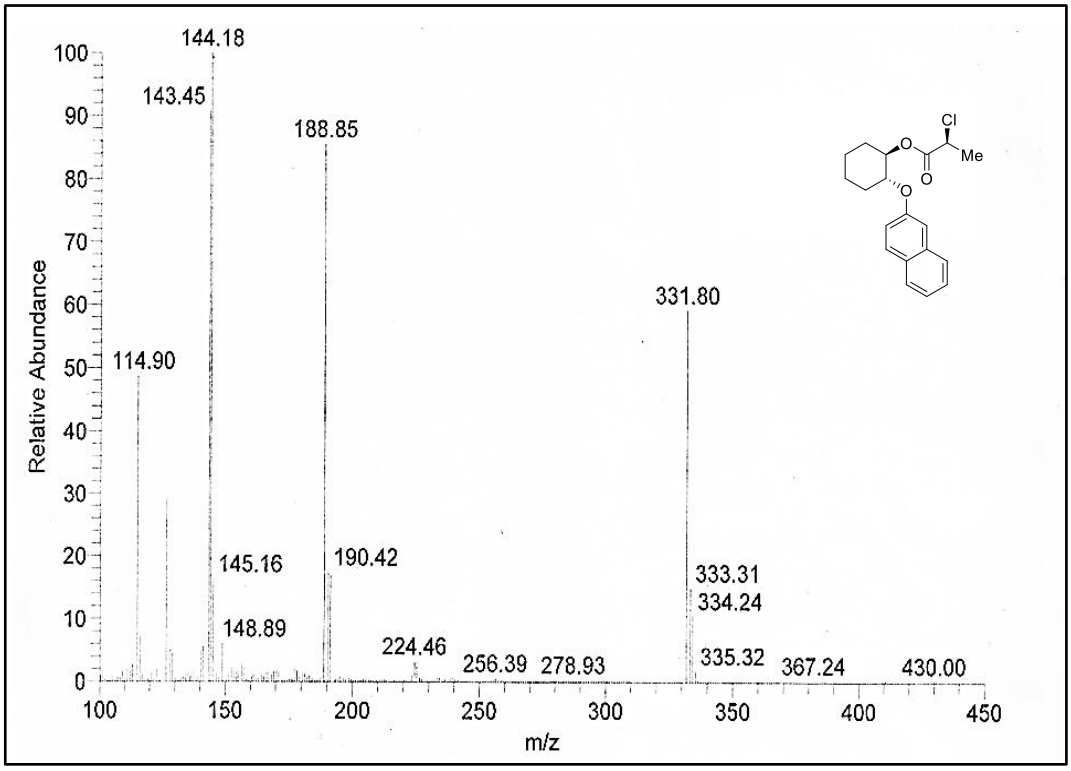
Enlarged ^{1}H NMR Spectra of Compound (*R,R,S*)-**27**



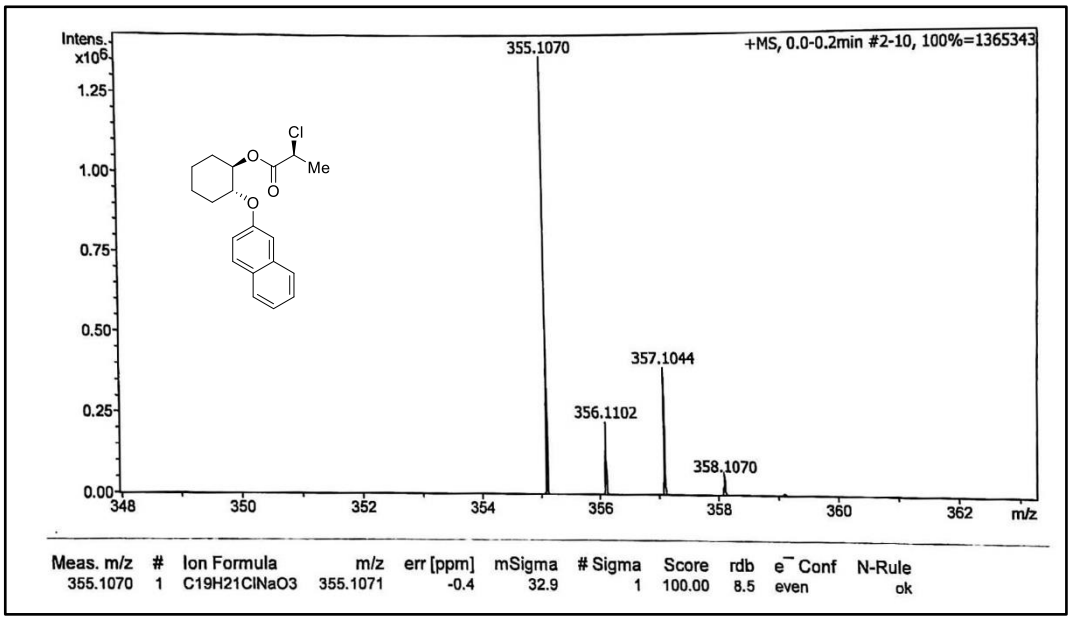
^{13}C NMR Spectra of Compound (*R,R,S*)-**27**



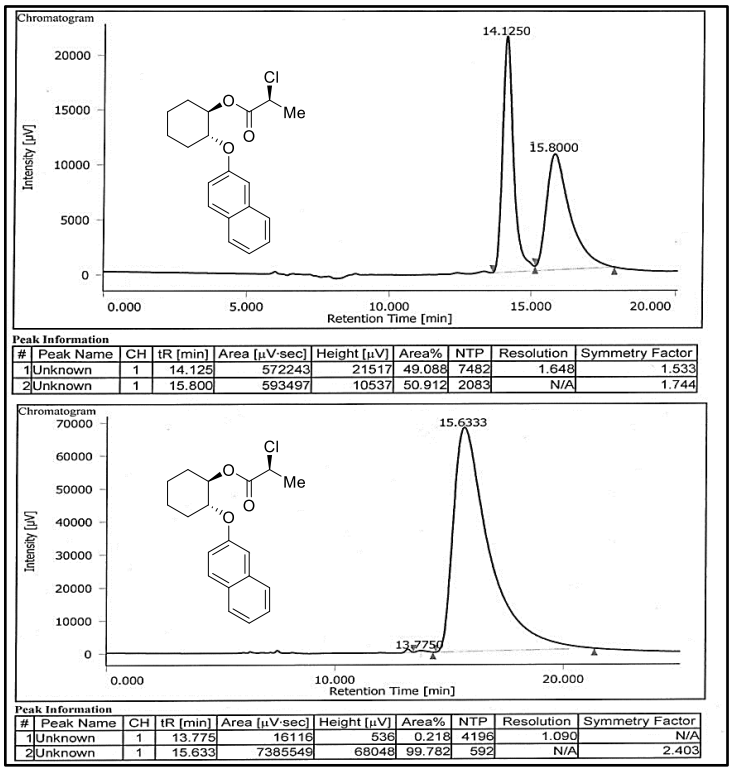
IR Spectra of Compound (*R*,*R*,*S*)-**27**



MS Spectra of Compound (*R*,*R*,*S*)-**27**



HRMS Spectra of Compound (*R*,*R*,*S*)-**27**



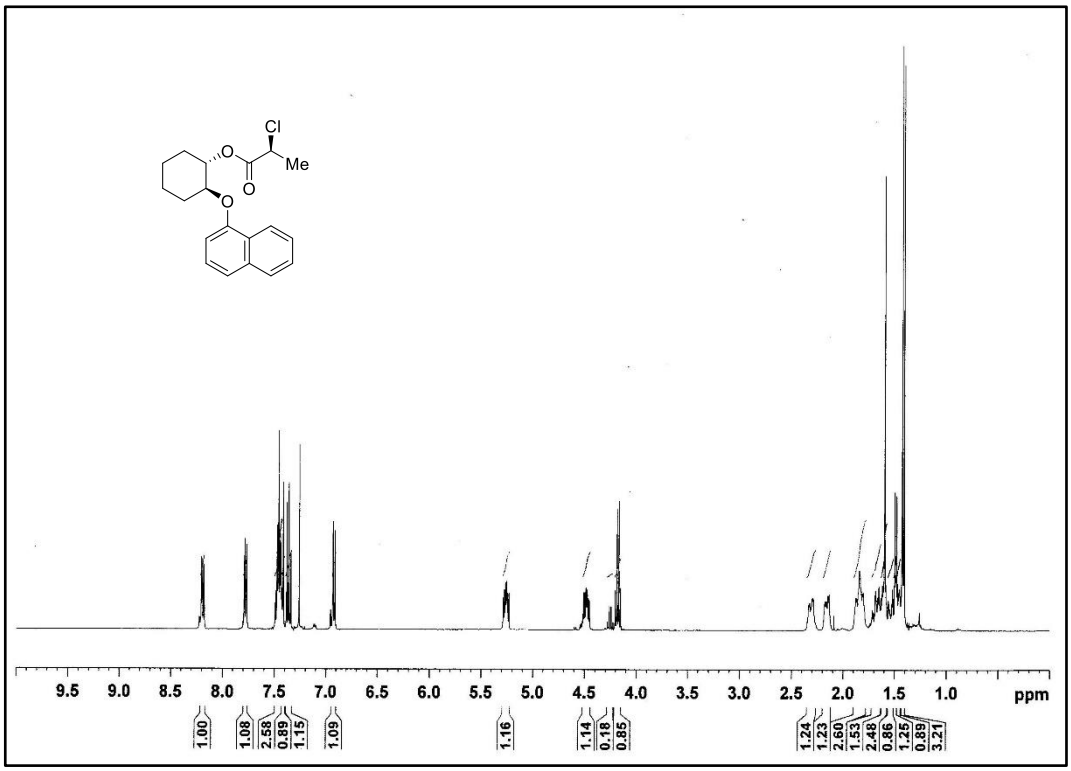
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	14.125	572243	21517	49.088	7482	1.648	1.533
2	Unknown	1	15.800	593497	10537	50.912	2083	N/A	1.744

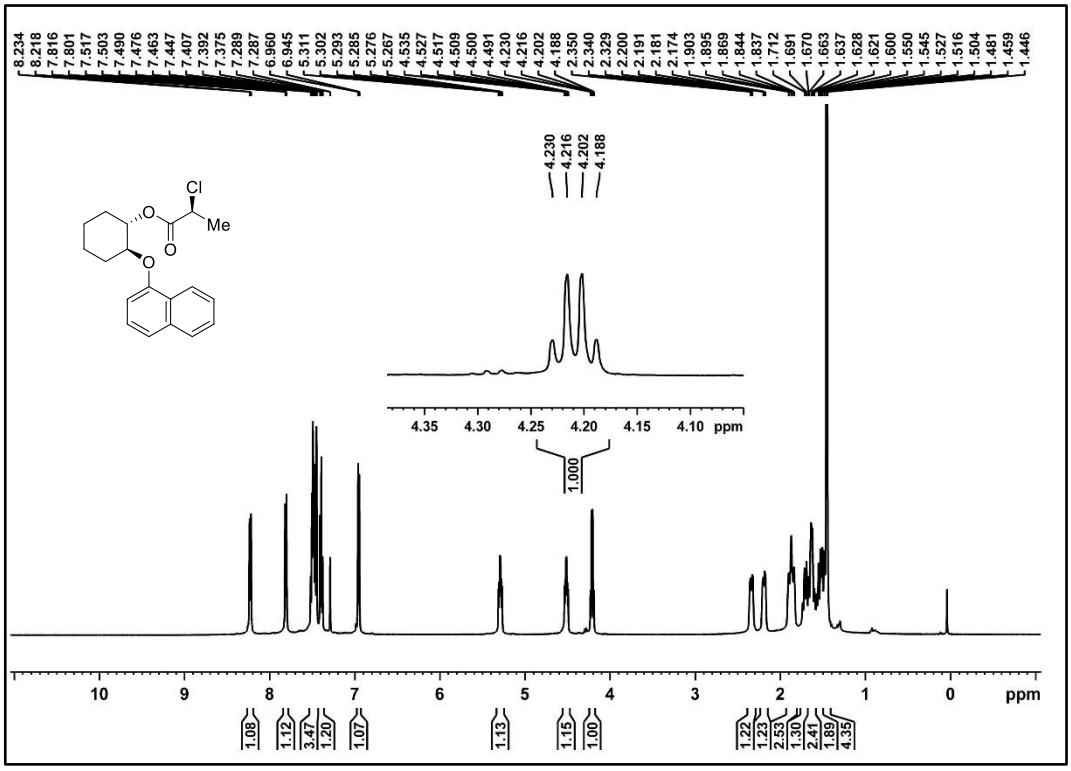
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	13.775	16116	536	0.218	4196	1.090	N/A
2	Unknown	1	15.633	7385549	68048	99.782	592	N/A	2.403

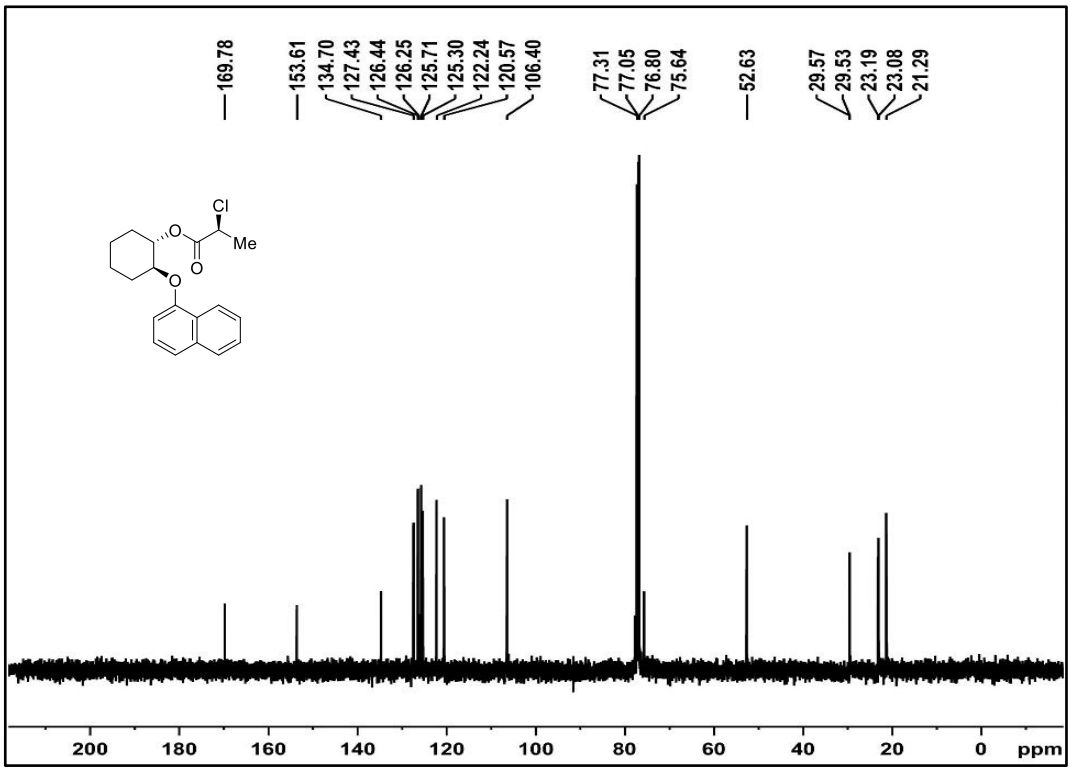
HPLC Chromatogram of diastereomeric-**27** (*R*,*R*,*R*-**27** + *R*,*R*,*S*-**27**) (top), (*R*,*R*,*S*)-**27**(bottom) Lux Amylose column: 5% Isopropyl alcohol-Hexane, UV=254 nm, Flow=0.5mL/min. R_t = 14.1 min (*R*,*R*,*R*)-**27** and R_t= 15.8 min (*R*,*R*,*S*)-**27**



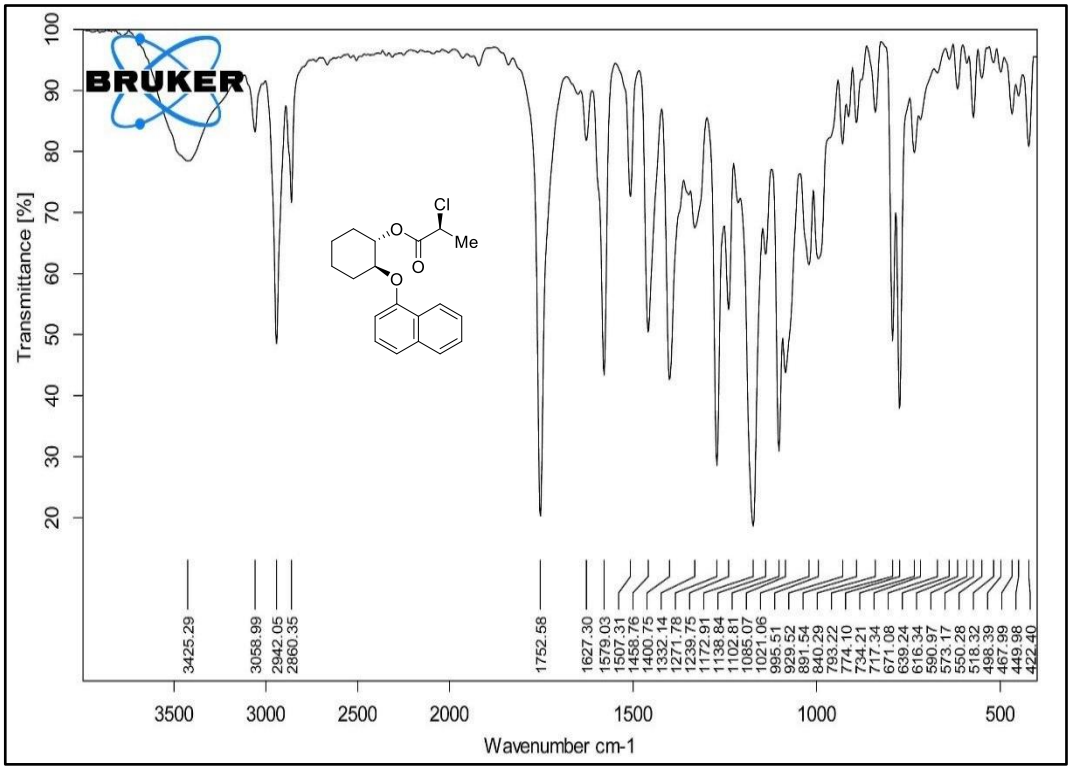
^{1}H NMR Spectra of Compound (*S*,*S*,*S*)-**30a**



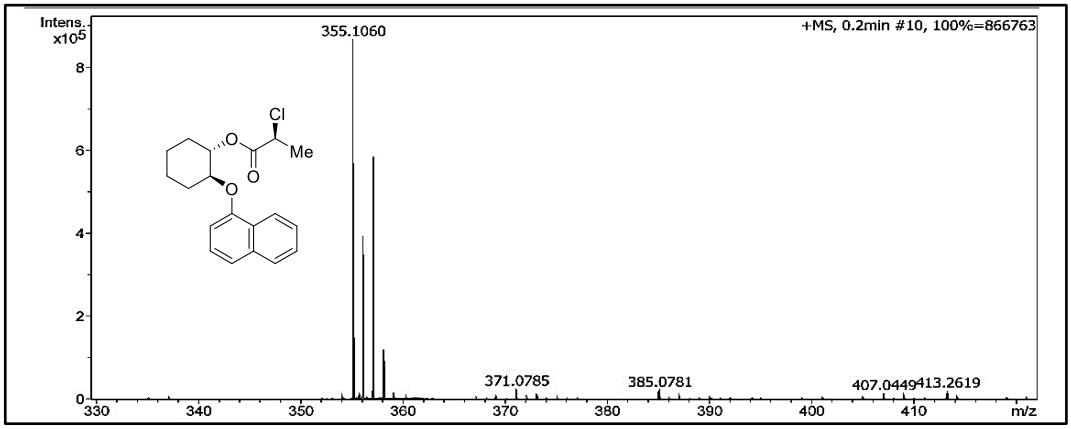
^{1}H NMR Spectra of Compound (*S*,*S*,*S*)-**30a** after recrystallization



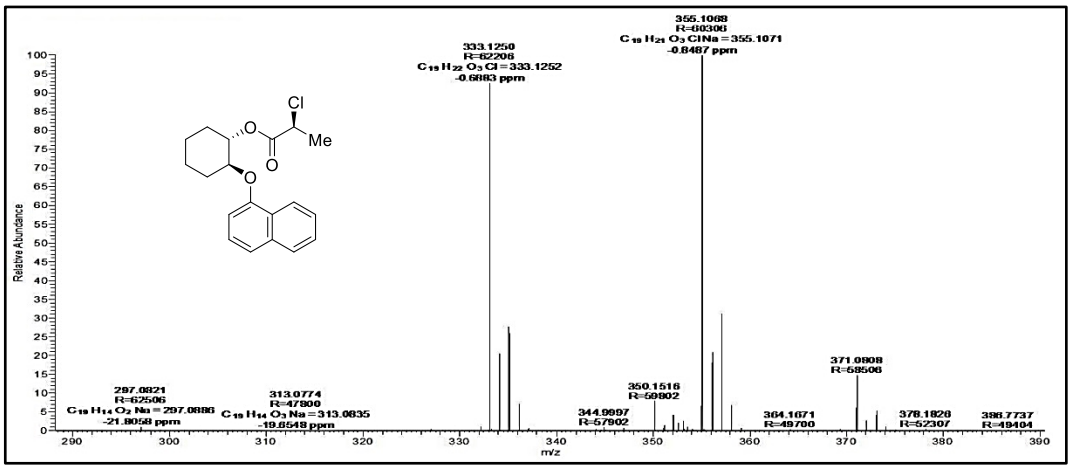
^{13}C NMR Spectra of Compound (*S*,*S*,*S*)-**30a**



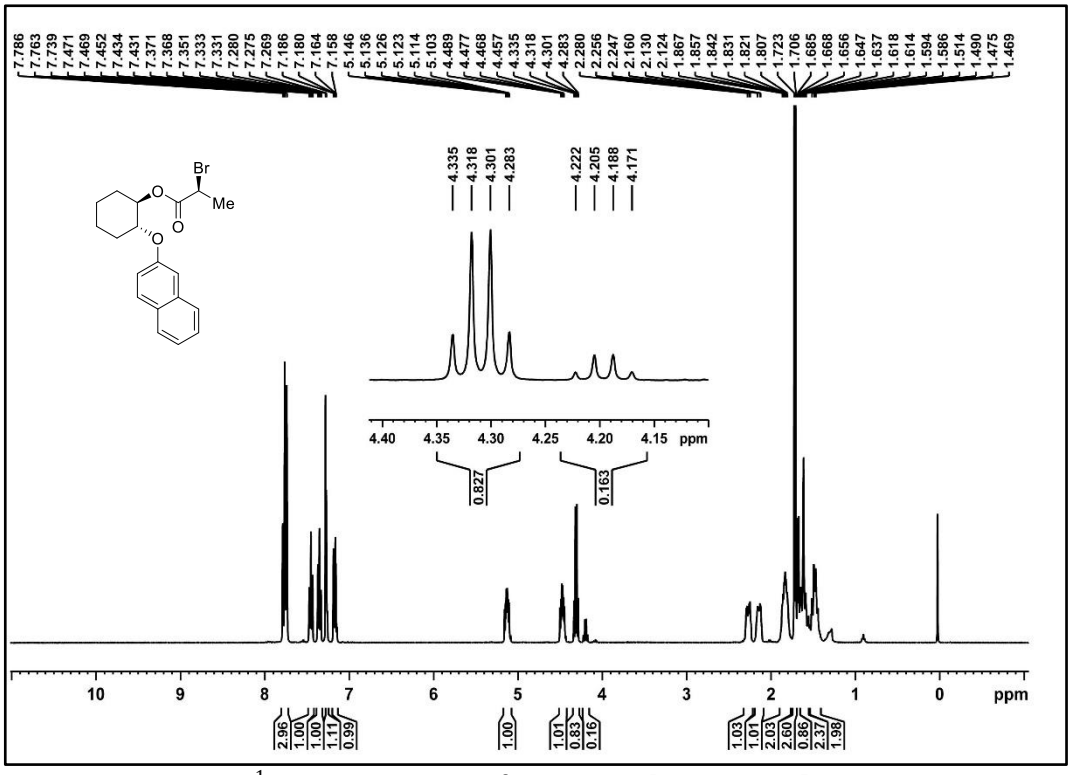
IR Spectra of Compound (*S*,*S*,*S*)-**30a**



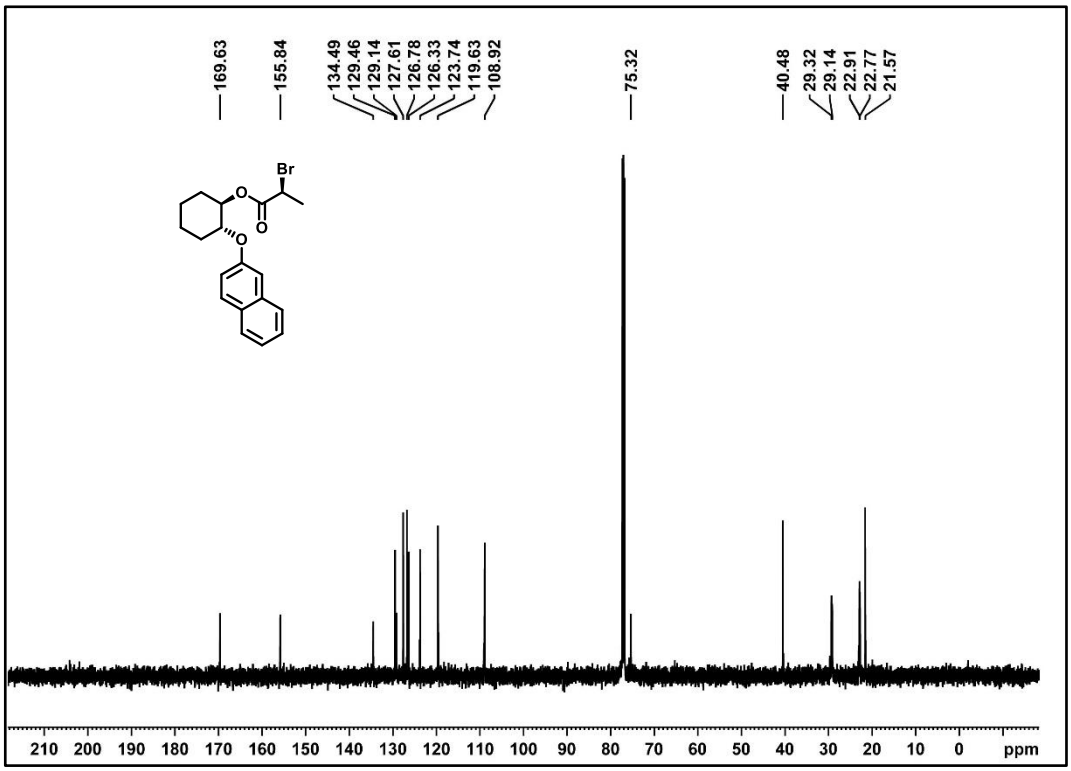
MS Spectra of Compound (*S*,*S*,*S*)-**30a**



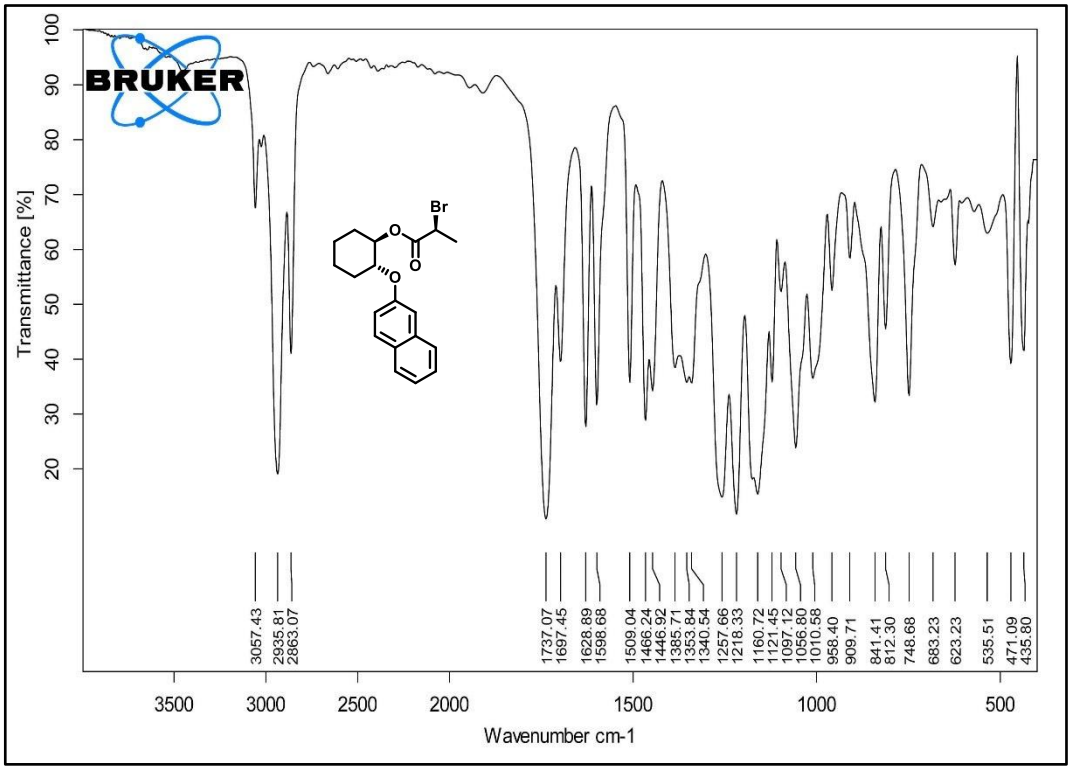
HRMS Spectra of Compound (*S*,*S*,*S*)-**30a**



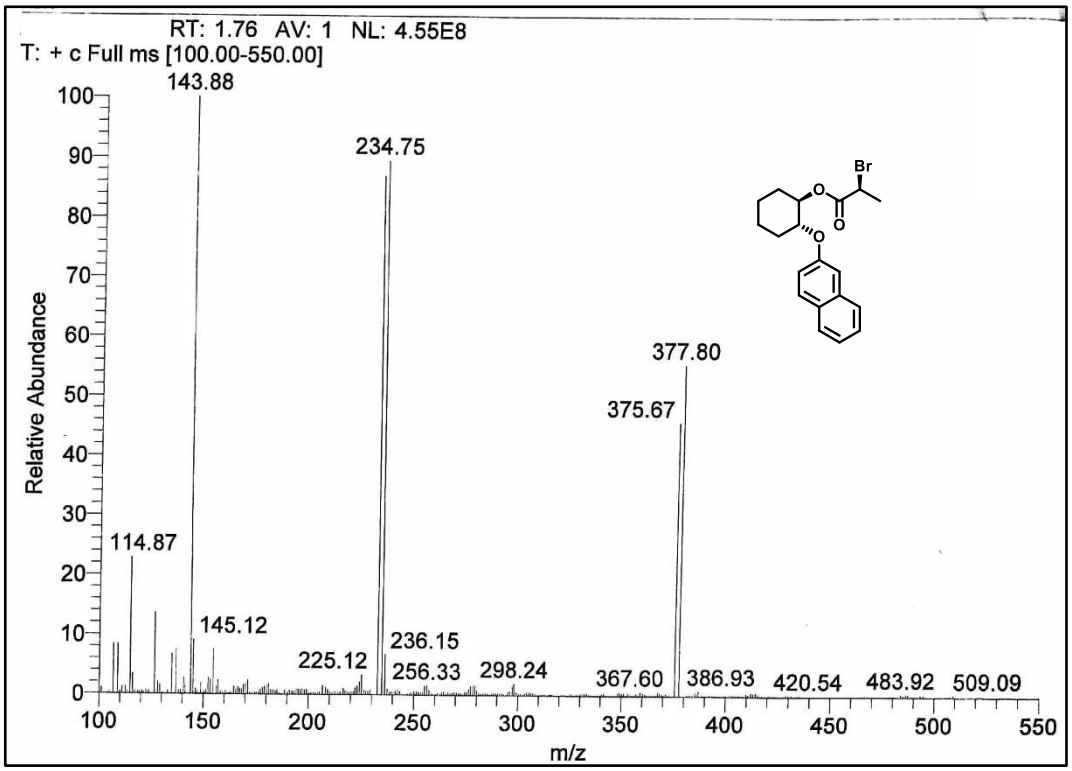
^{1}H NMR Spectra of Compound (*R*,*R*,*S*)-**30b**



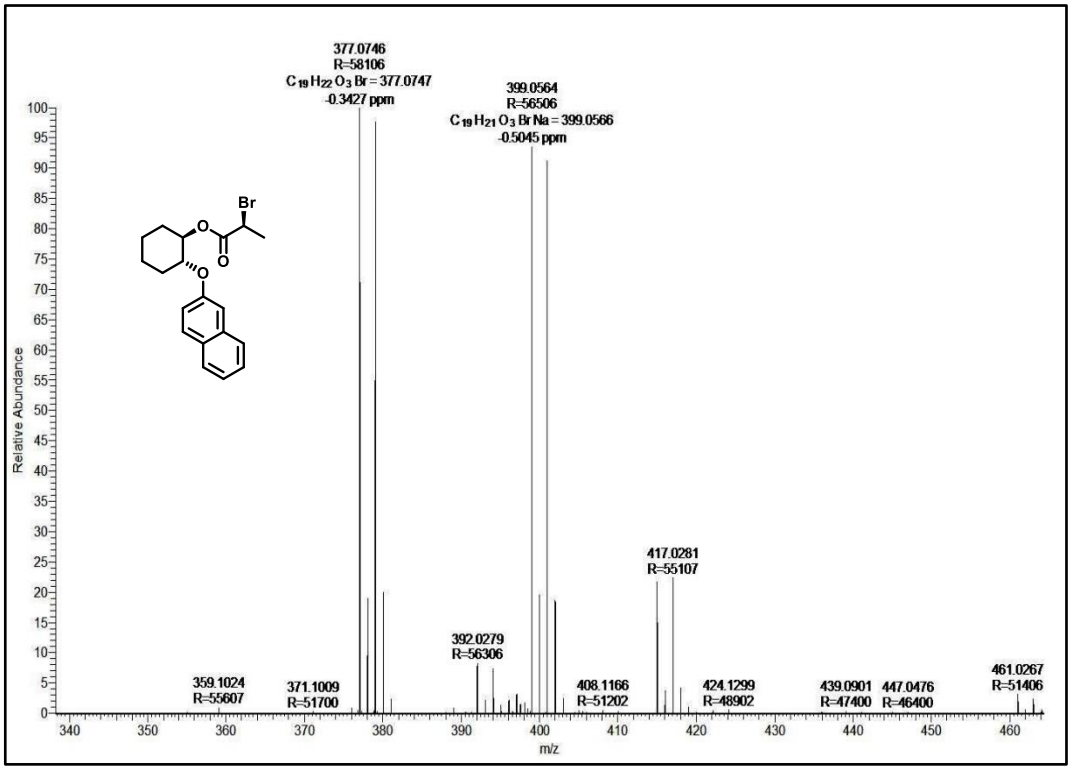
^{13}C NMR Spectra of Compound (*R*,*R*,*S*)-**30b**



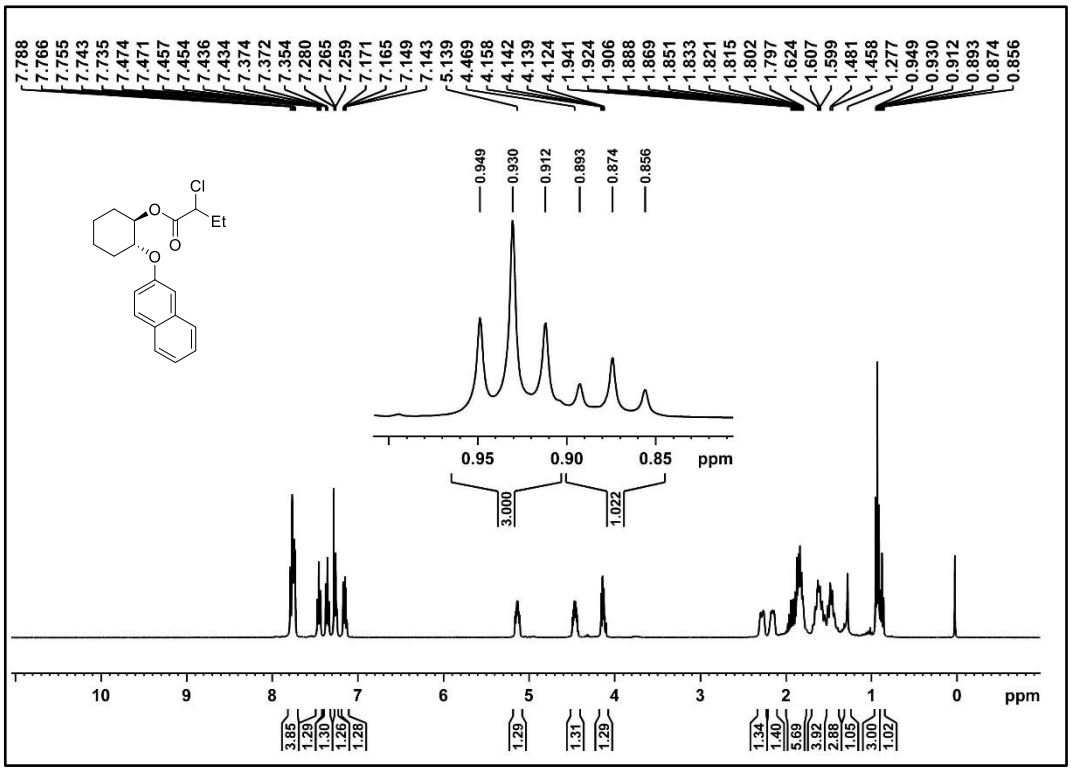
IR Spectra of Compound (*R*,*R*,*S*)-**30b**



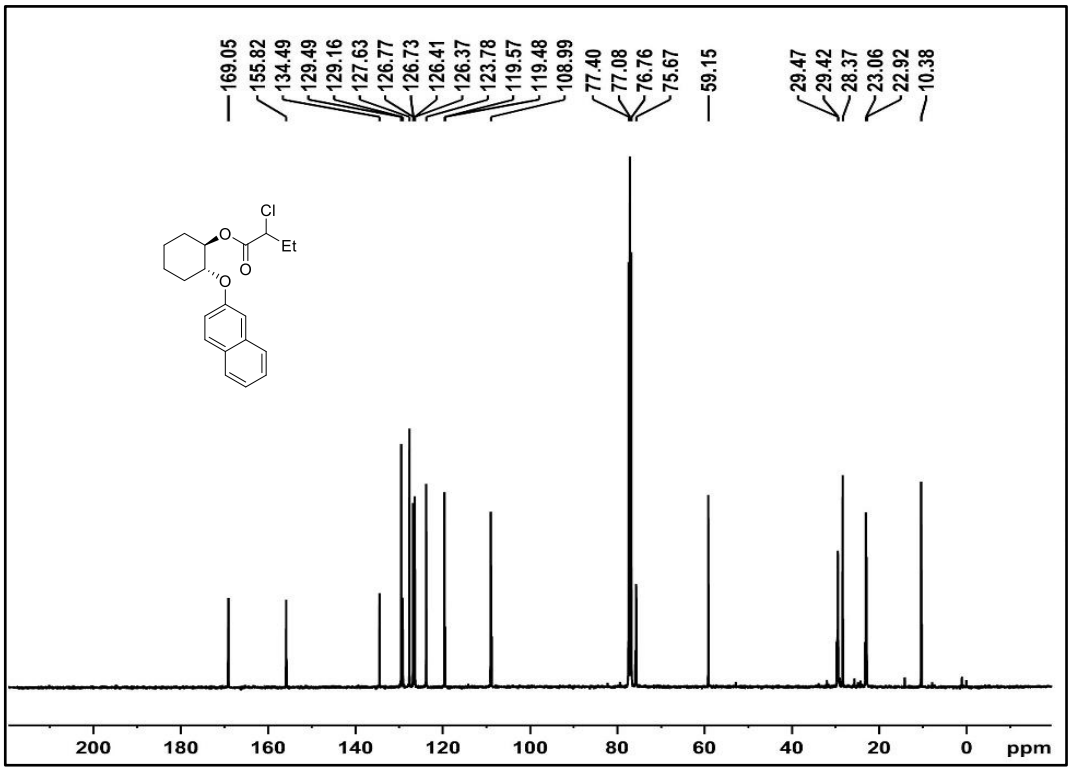
MS Spectra of Compound (*R*,*R*,*S*)-**30b**



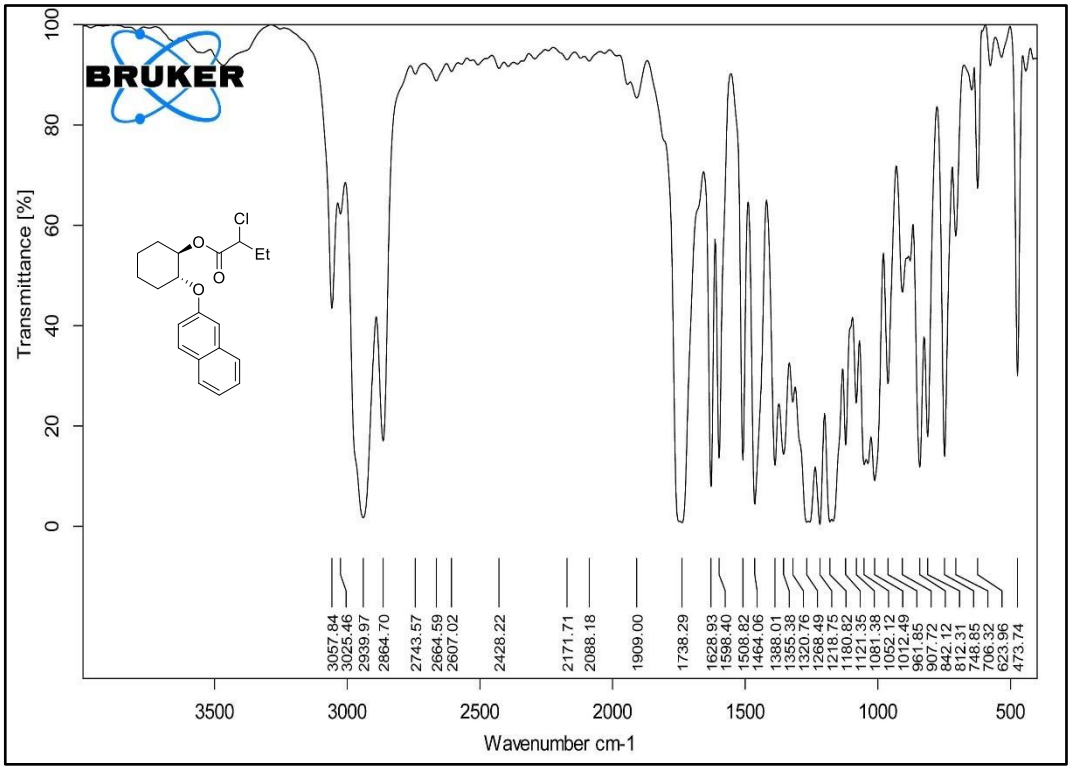
HRMS Spectra of Compound (*R*,*R*,*S*)-**30b**



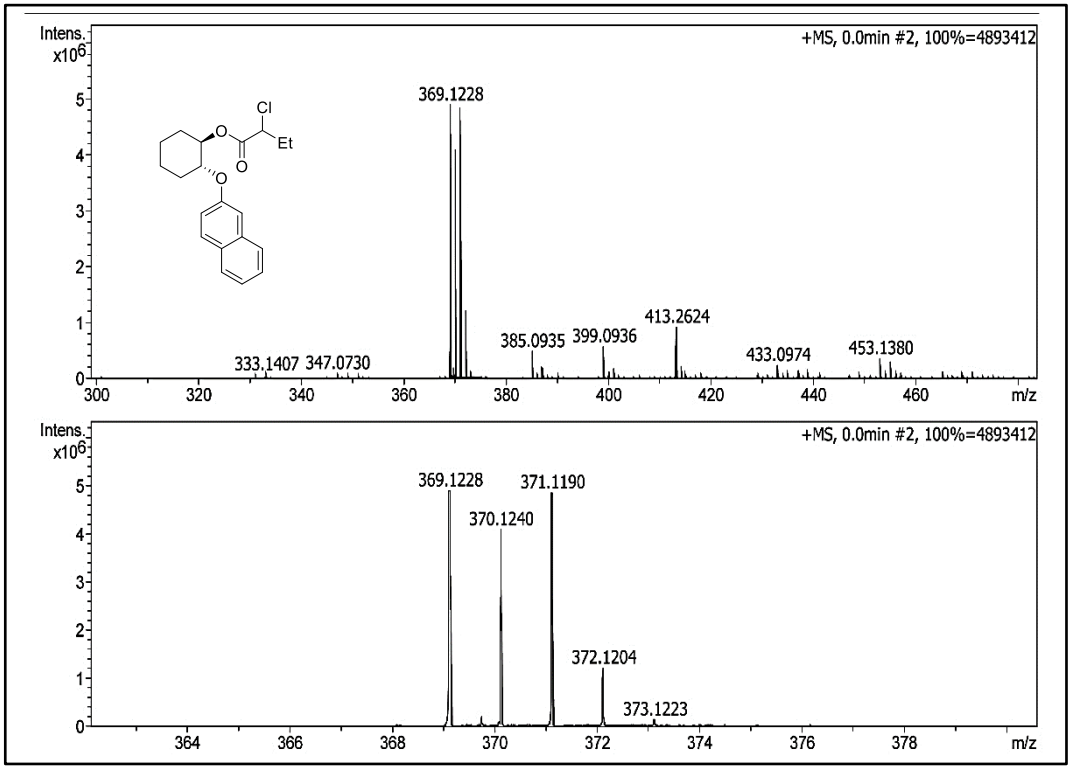
^{1}H NMR Spectra of Compound (**30c**)



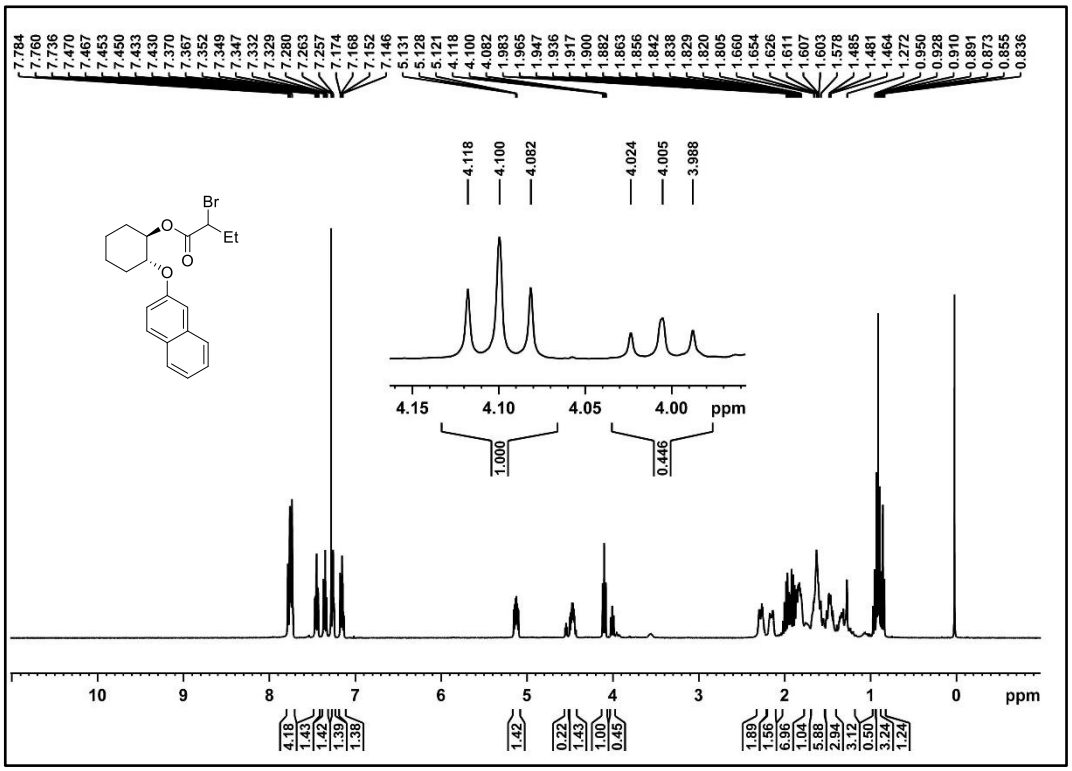
^{13}C NMR Spectra of Compound (**30c**)



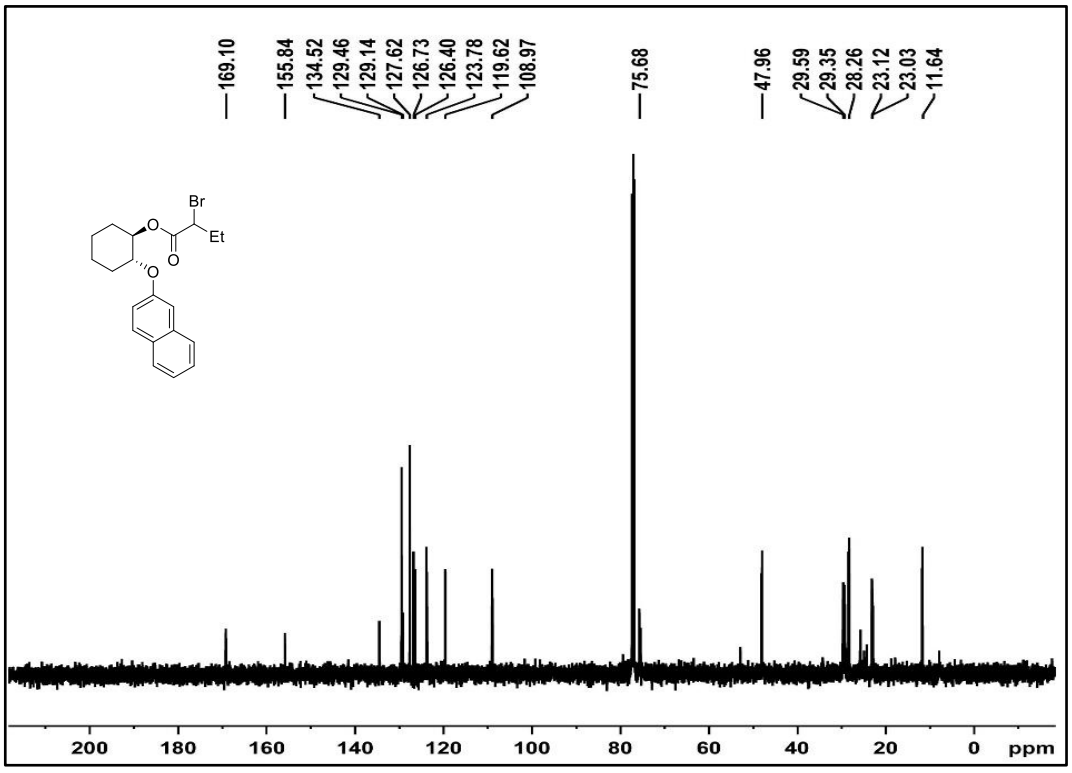
IR Spectra of Compound (**30c**)



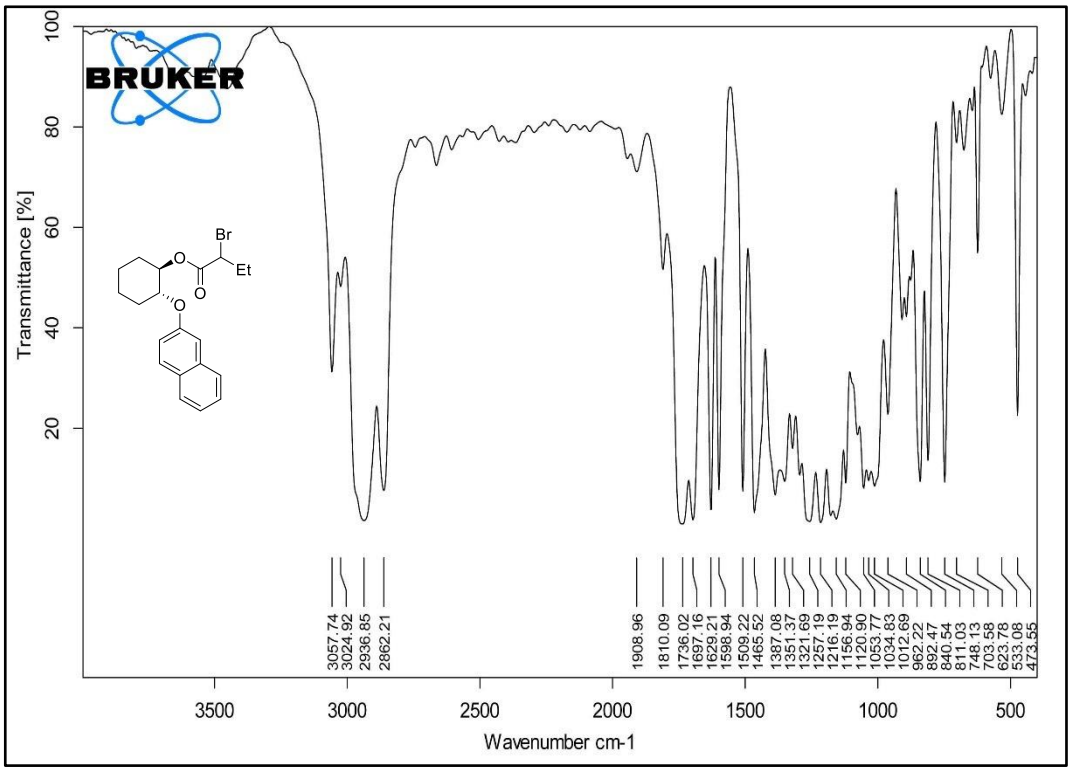
HRMS Spectra of Compound (**30c**)



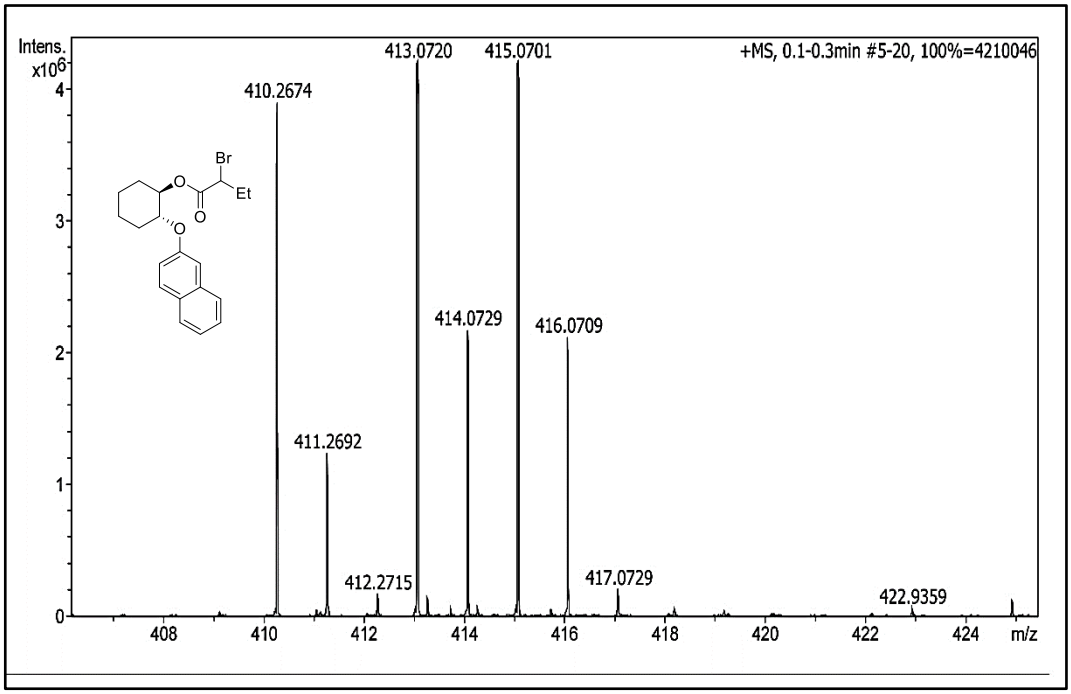
^{1}H NMR Spectra of Compound (**30d**)



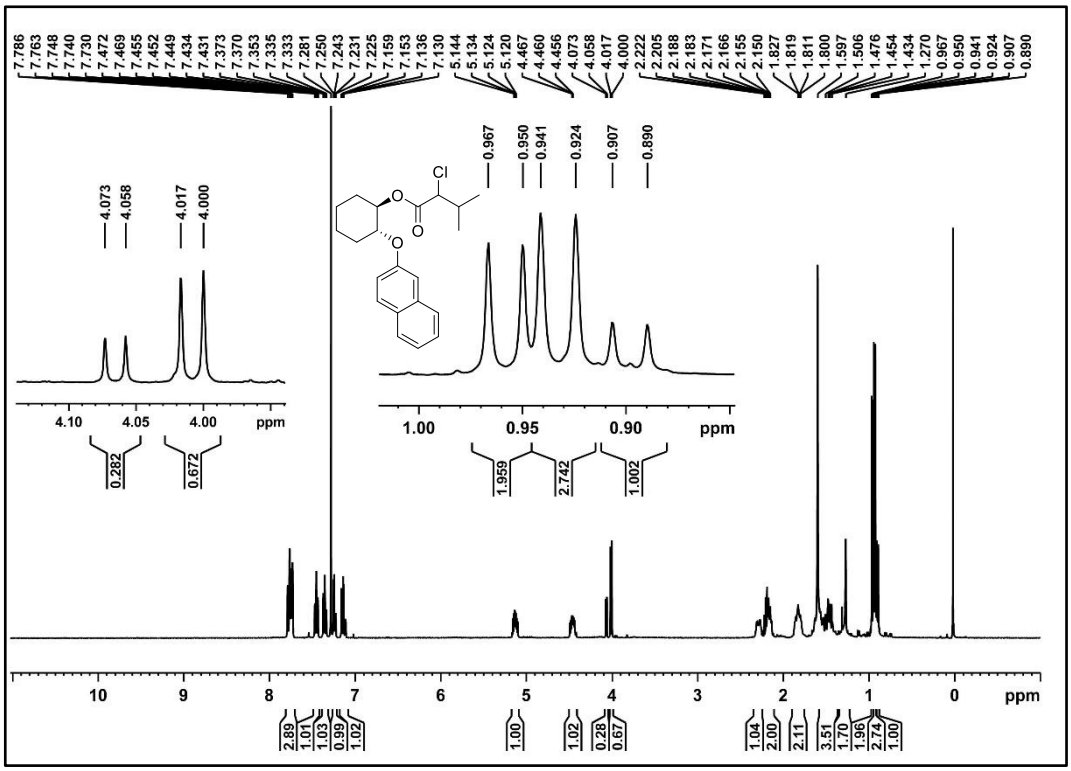
^{13}C NMR Spectra of Compound (**30d**)



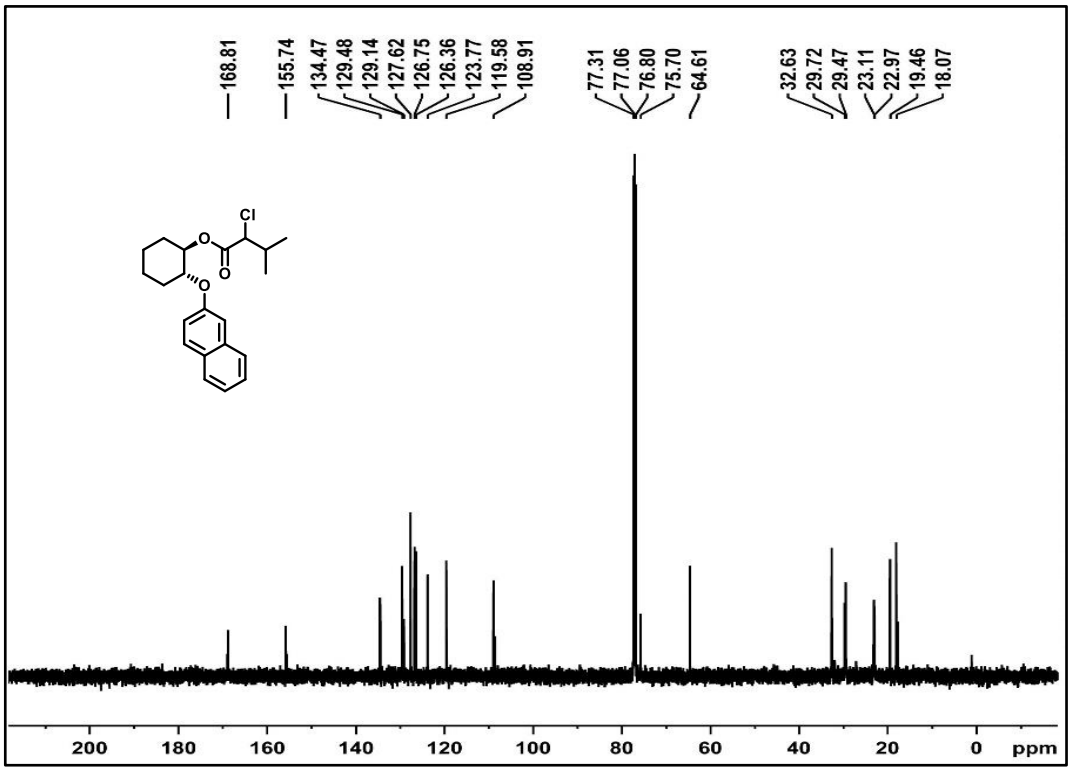
IR Spectra of Compound (**30d**)



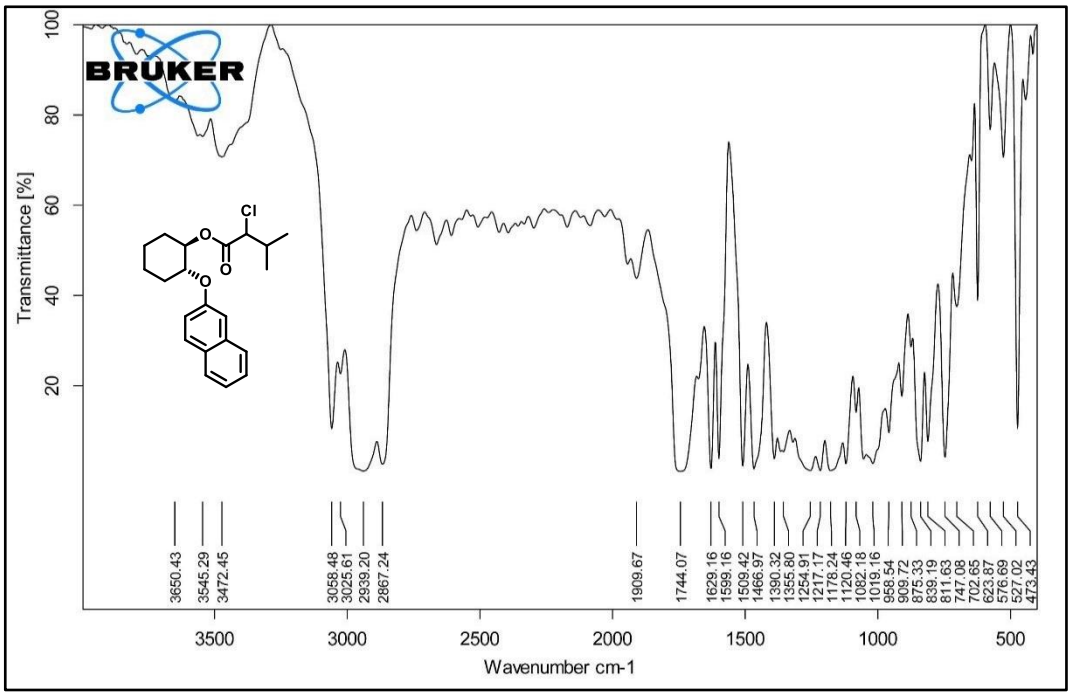
HRMS Spectra of Compound (**30d**)



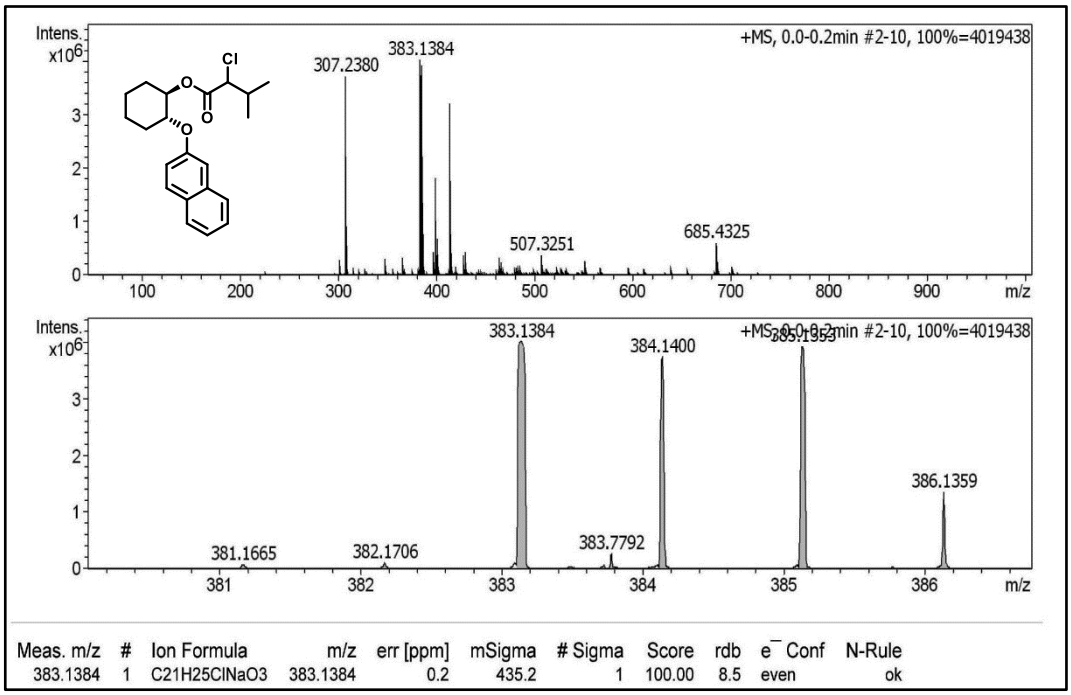
^{1}H NMR Spectra of Compound (**30e**)



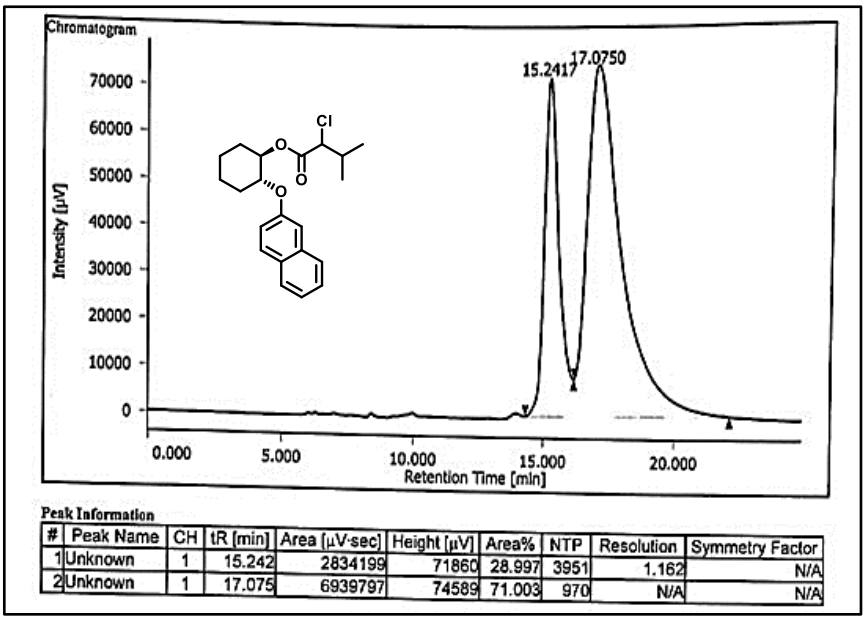
^{13}C NMR Spectra of Compound (**30e**)



IR Spectra of Compound (**30e**)



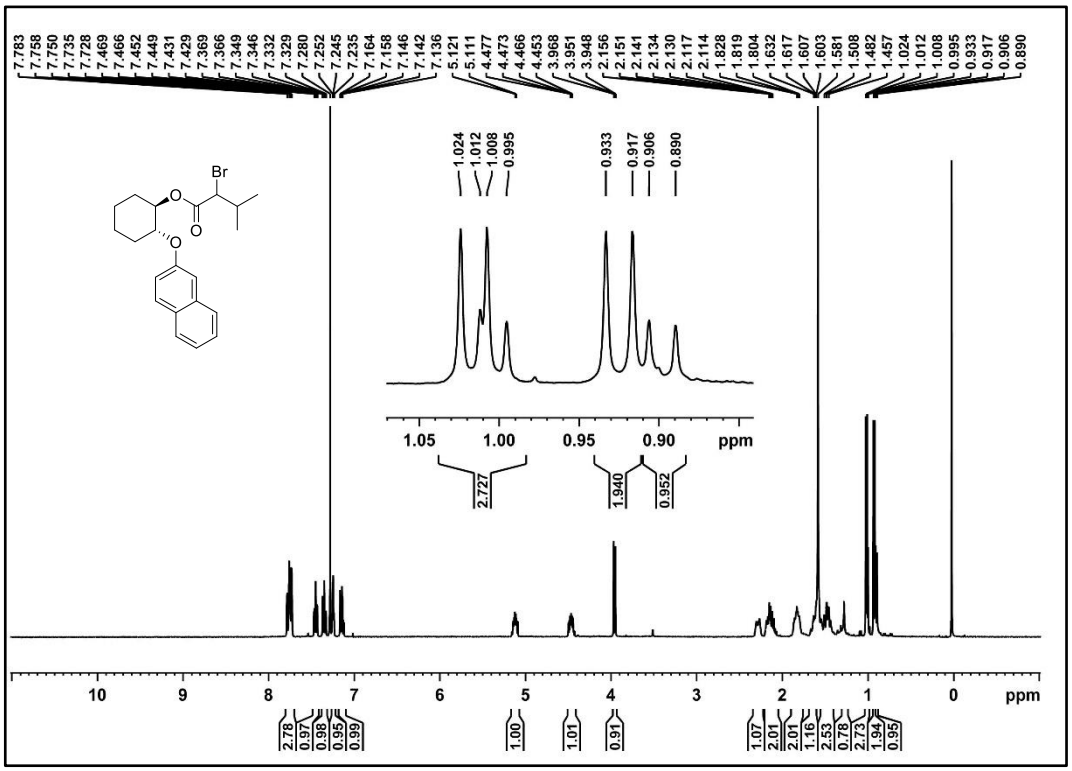
HRMS Spectra of Compound (**30e**)



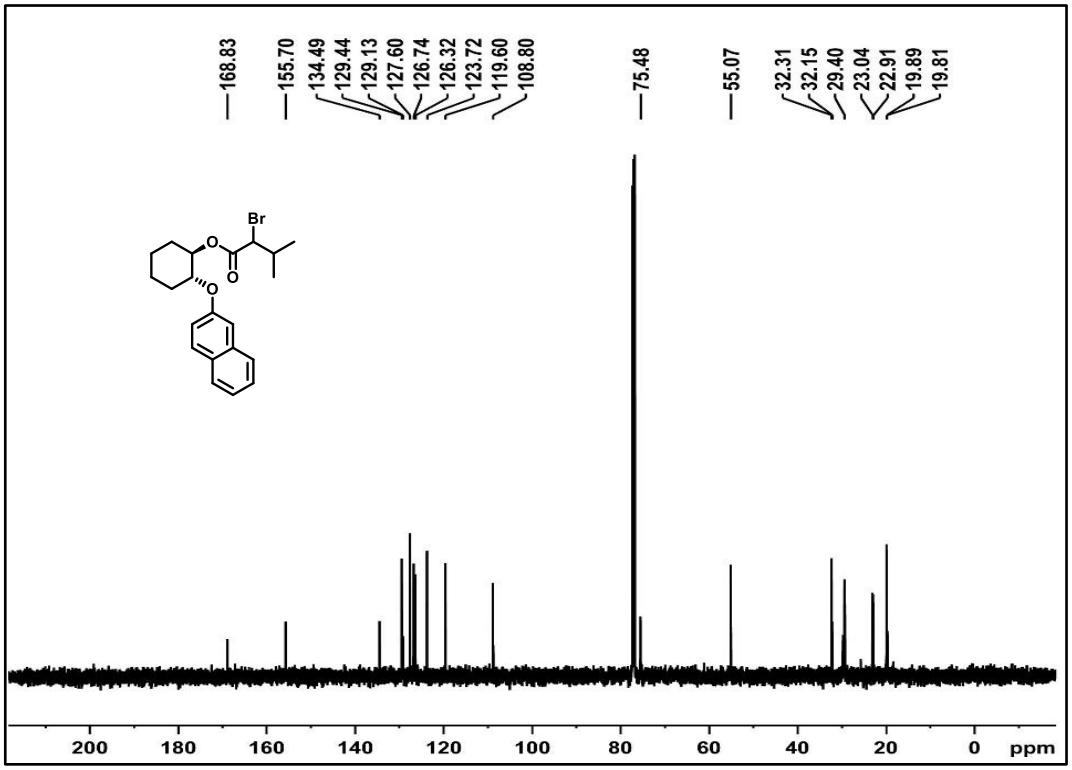
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	15.242	2834199	71860	28.997	3951	1.162	N/A
2	Unknown	1	17.075	6939797	74589	71.003	970	N/A	N/A

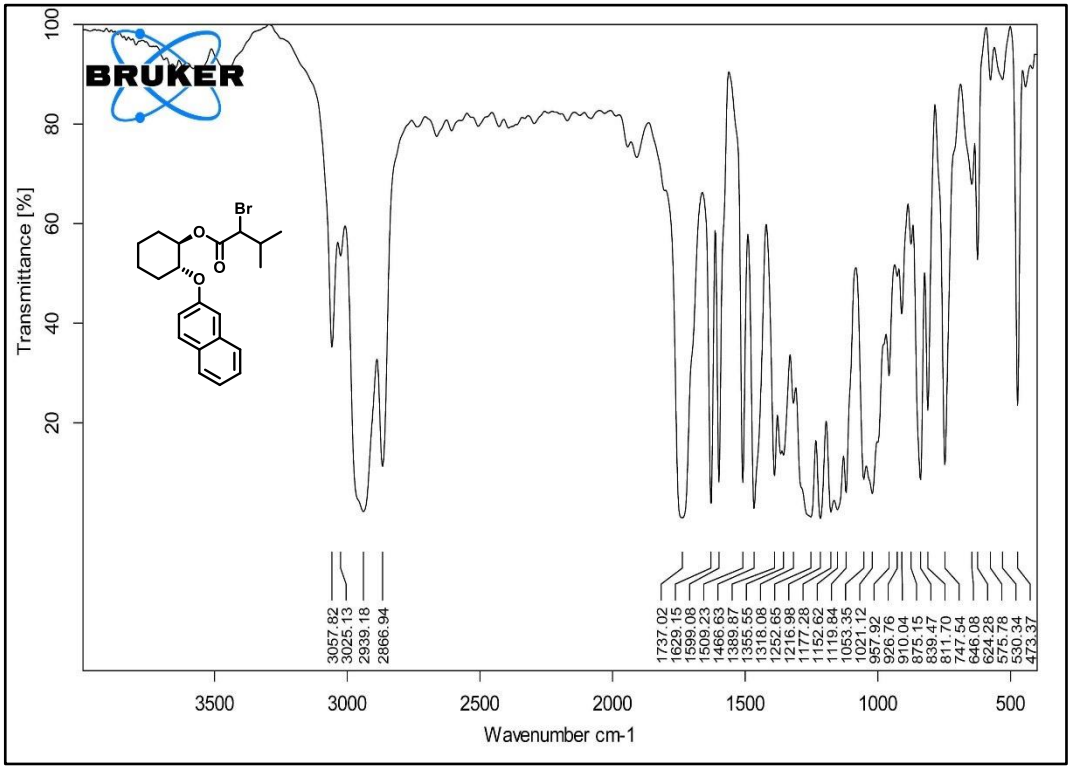
HPLC Chromatogram of (**30e**)
Lux Amylose column: 2.5% Isopropyl alcohol-Hexane, UV=254 nm, Flow=0.5mL/min. R_t = 15.2 min (1st Peak) and R_t= 17.1 min (2nd Peak, major diastereomer)



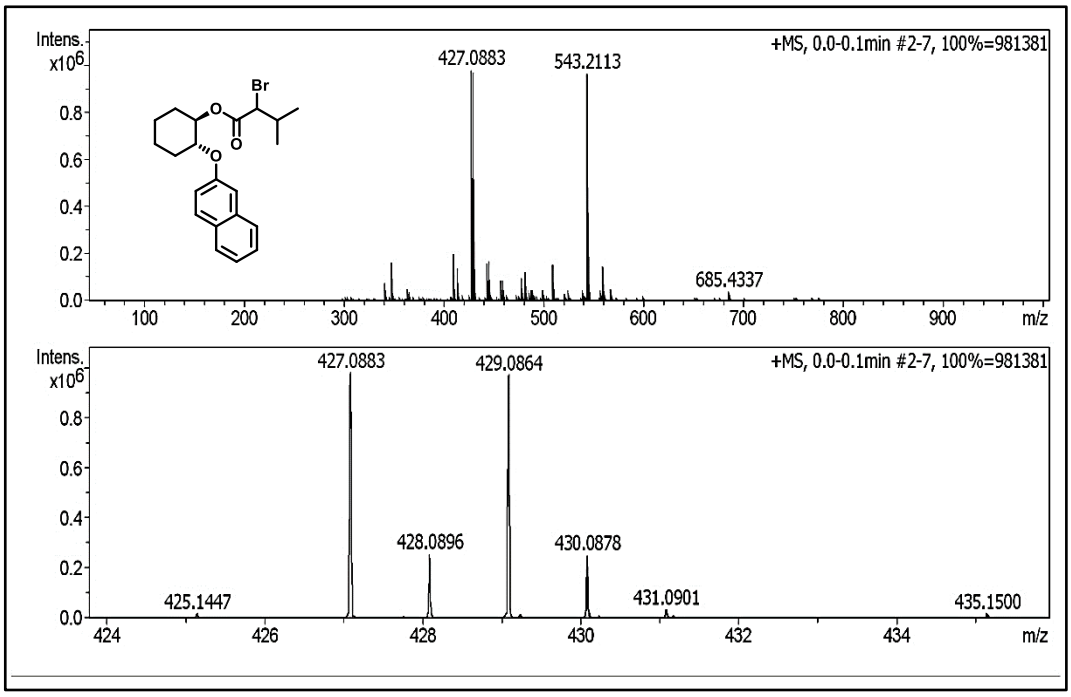
^{1}H NMR Spectra of Compound (**30f**)



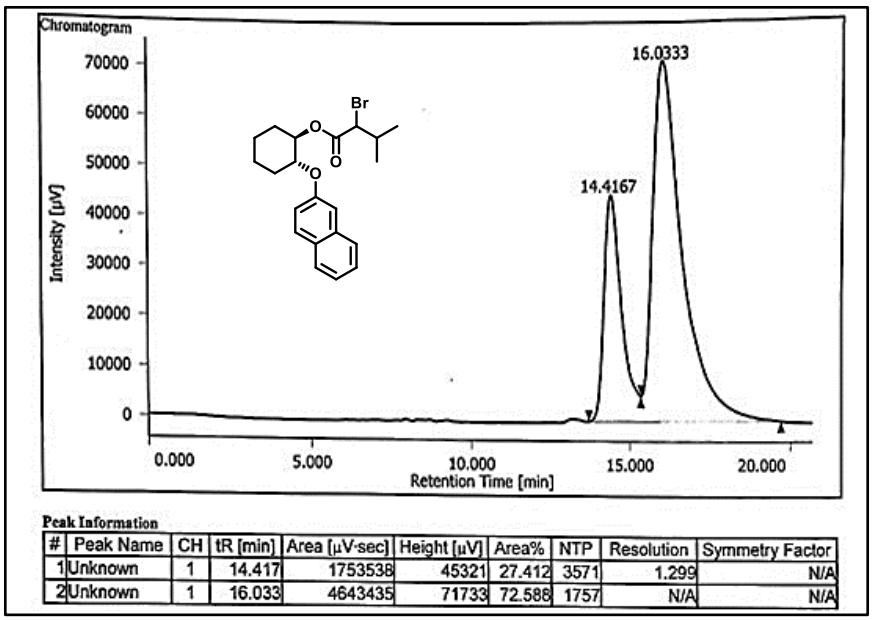
^{13}C NMR Spectra of Compound (**30f**)



IR Spectra of Compound (**30f**)



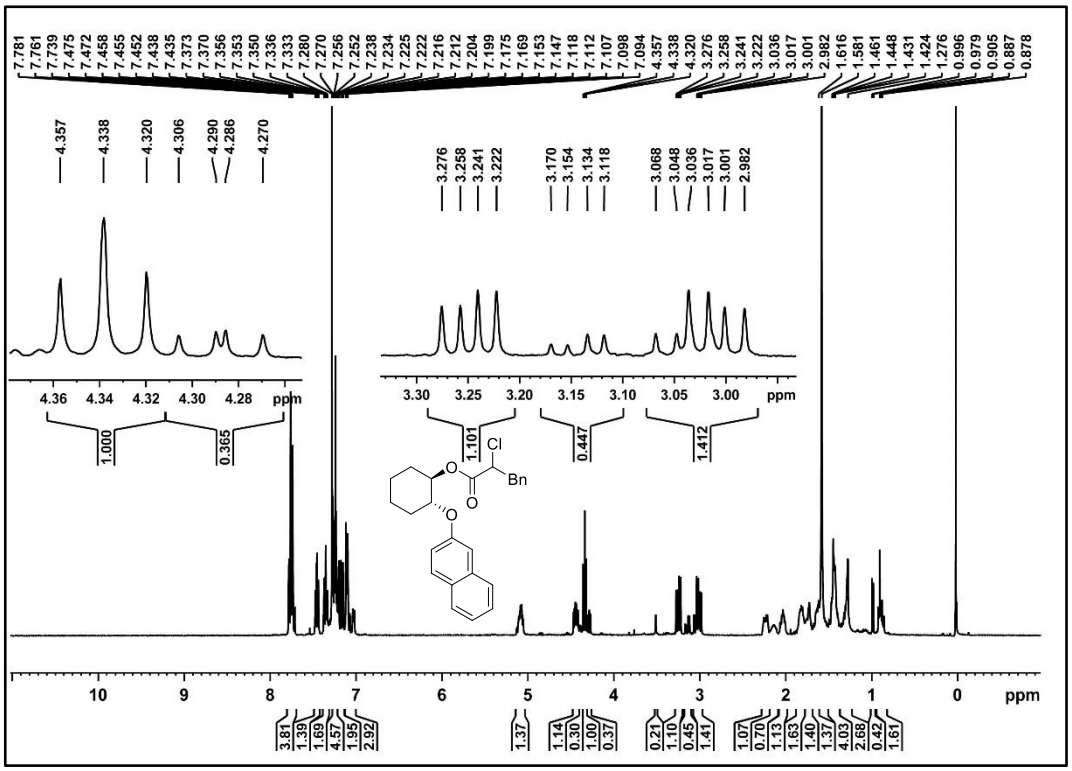
HRMS Spectra of Compound (**30f**)



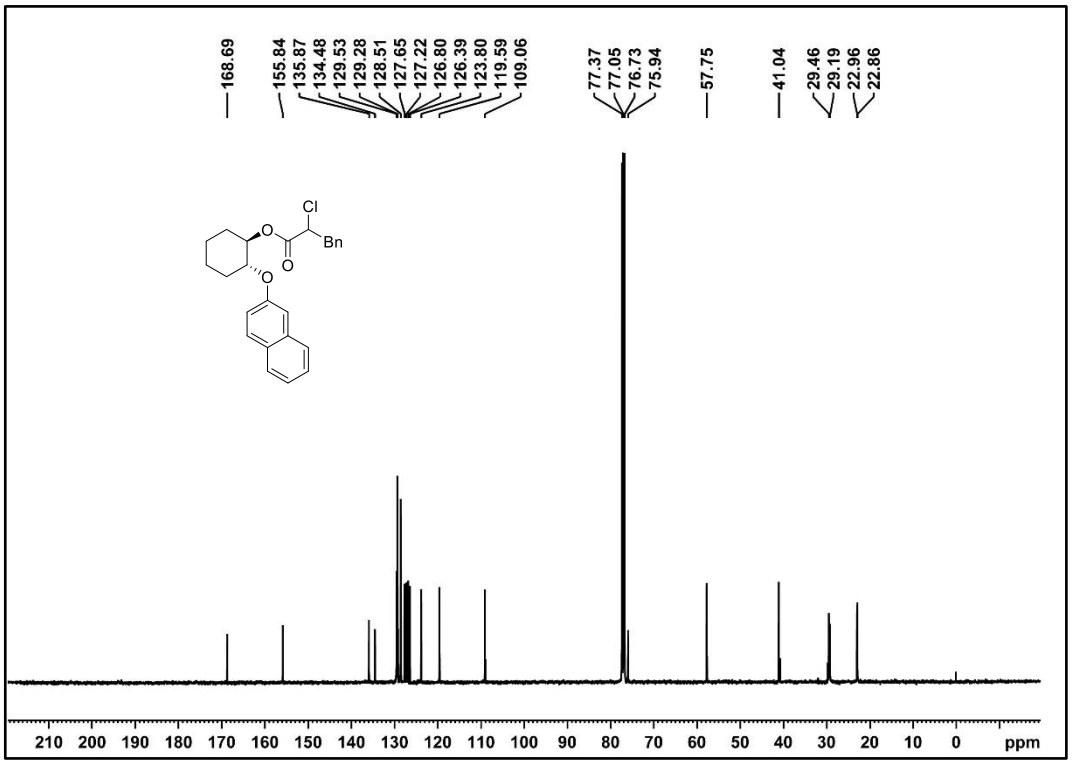
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	14.417	1753538	45321	27.412	3571	1.299	N/A
2	Unknown	1	16.033	4643435	71733	72.588	1757	N/A	N/A

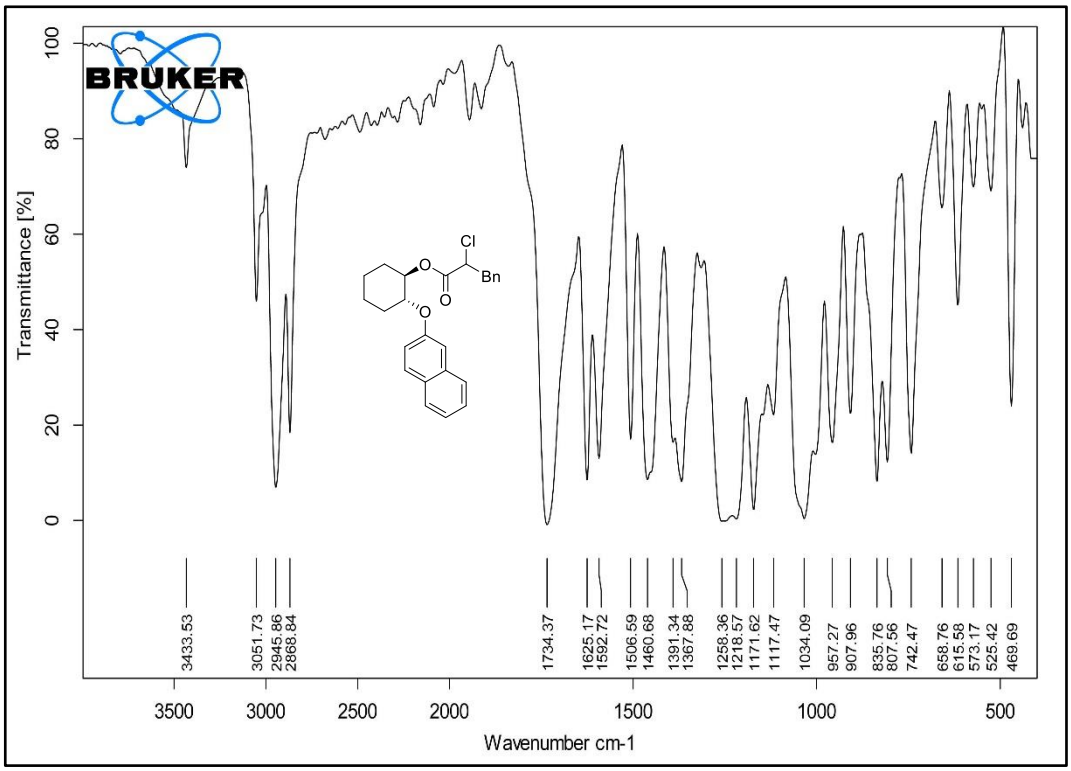
HPLC Chromatogram of (**30f**)
Lux Amylose column: 2.5% Isopropyl alcohol-Hexane, UV=254 nm, Flow=0.5mL/min. R_t = 14.4 min (1st Peak) and R_t= 16.0 min (2nd Peak, major diastereomer)



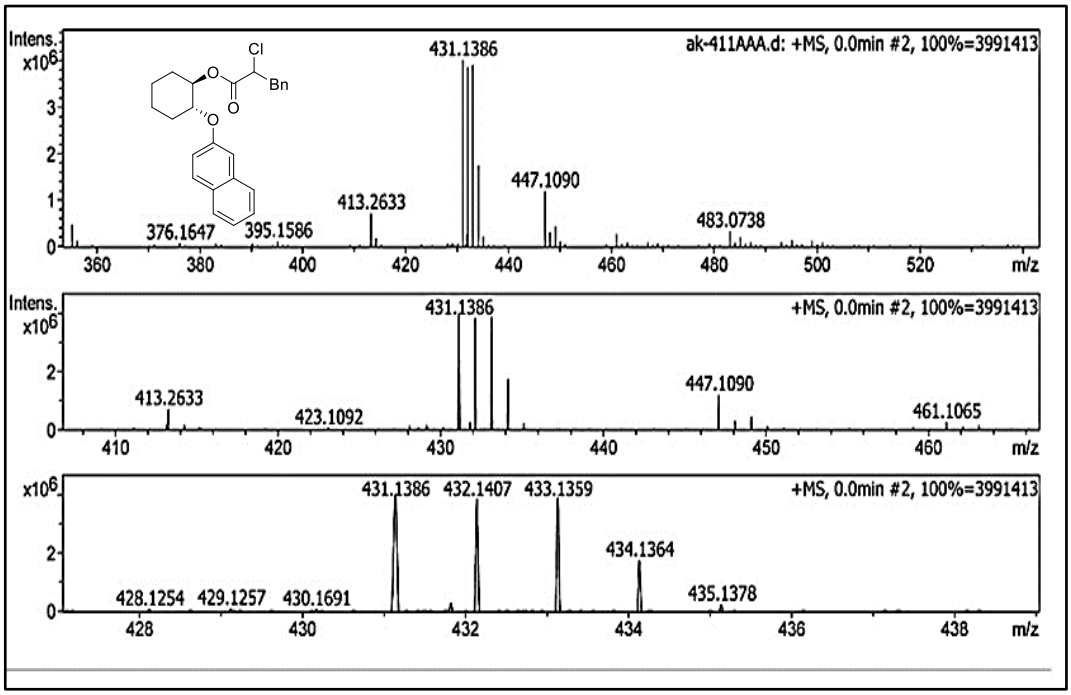
^{1}H NMR Spectra of Compound (**30g**)



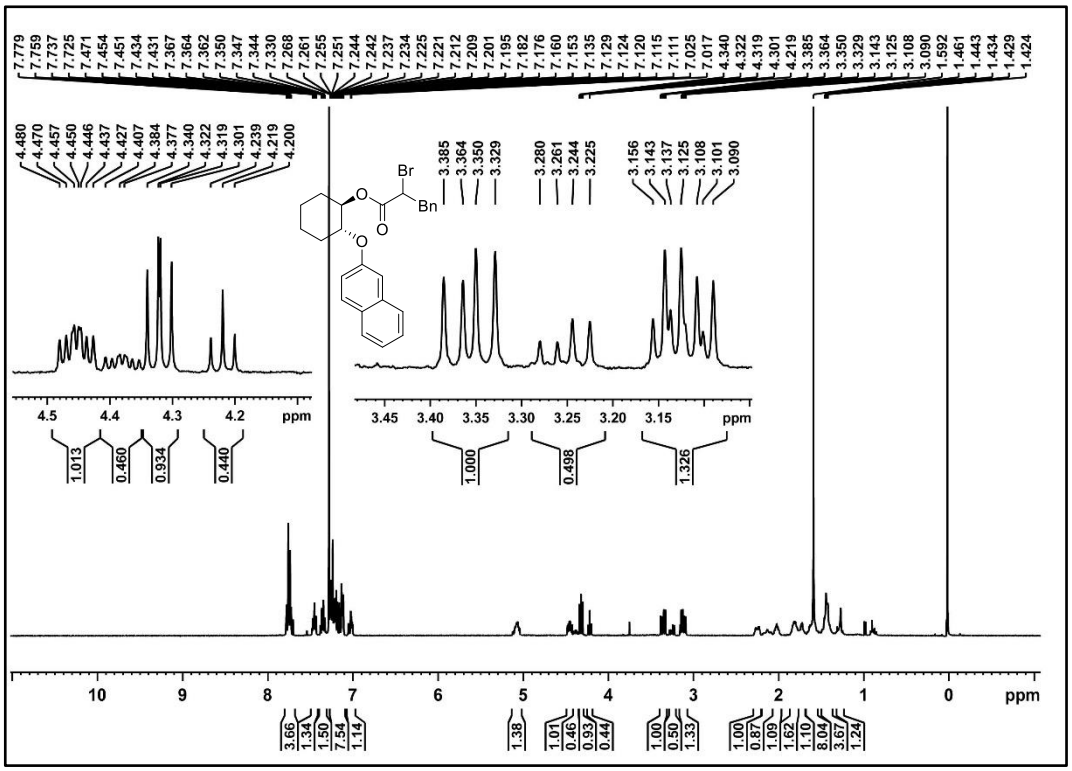
^{13}C NMR Spectra of Compound (**30g**)



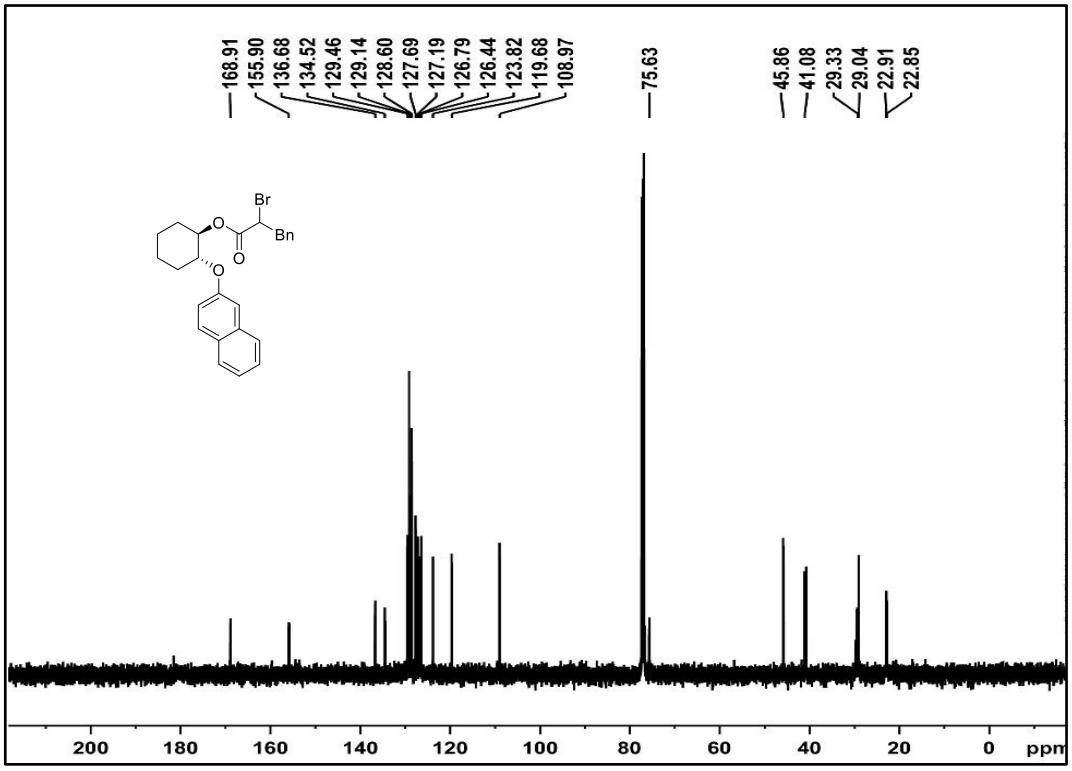
IR Spectra of Compound (**30g**)



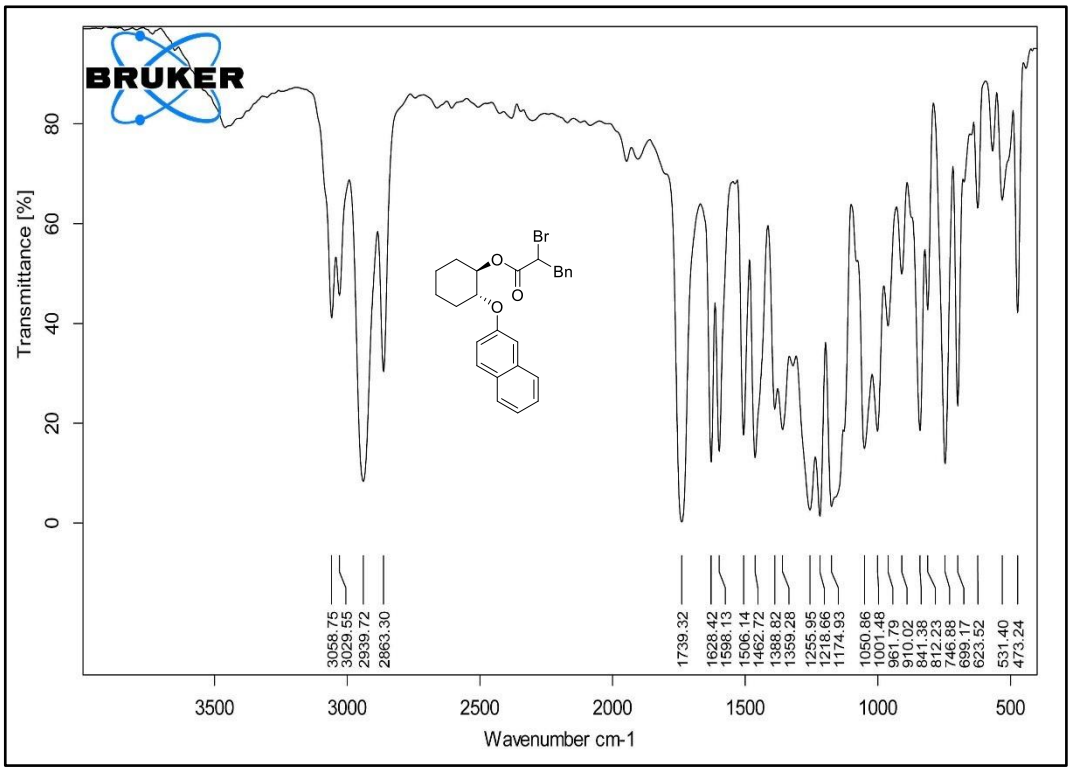
HRMS Spectra of Compound (**30g**)



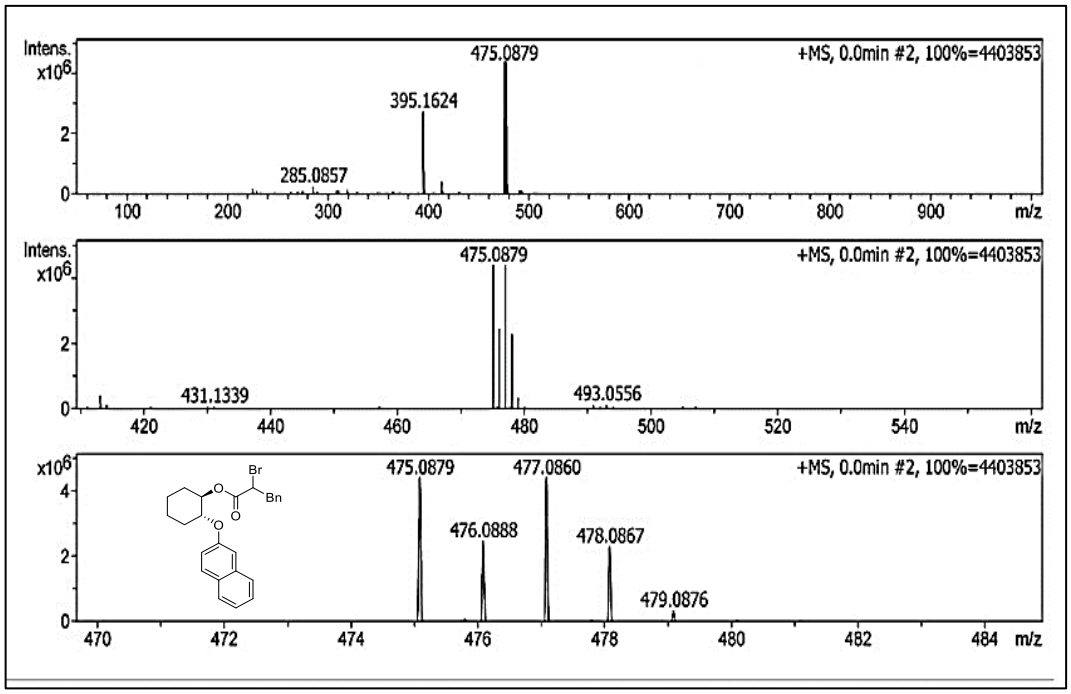
^{1}H NMR Spectra of Compound (**30h**)



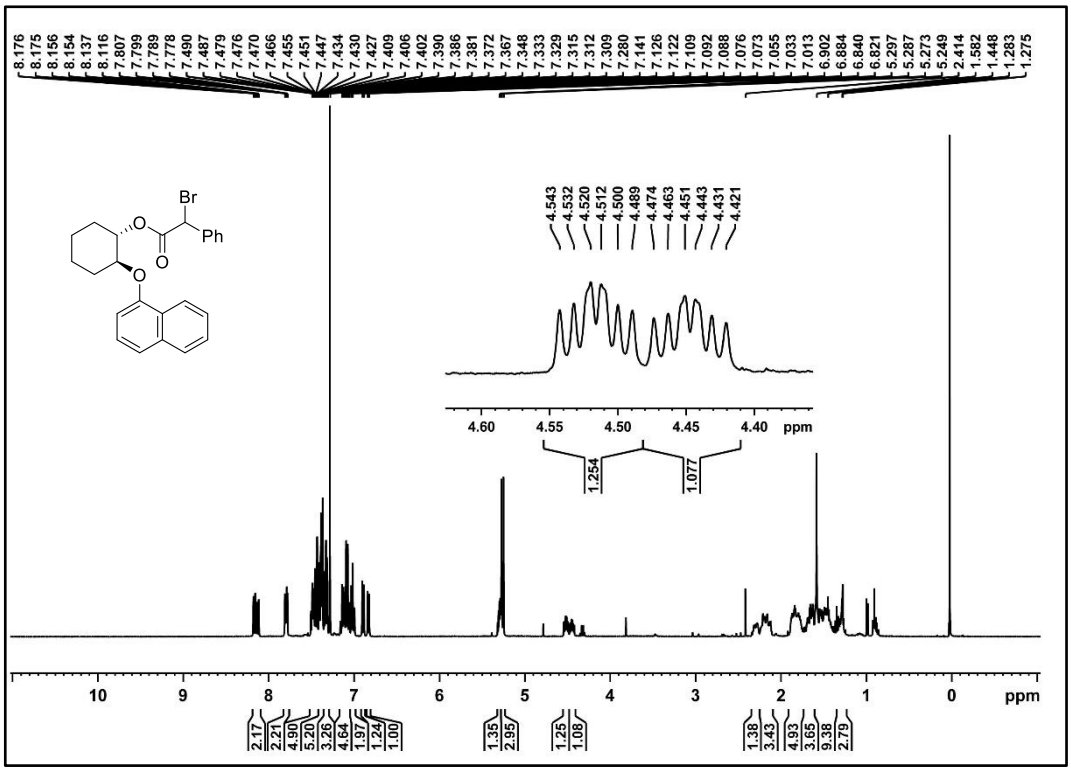
^{13}C NMR Spectra of Compound (**30h**)



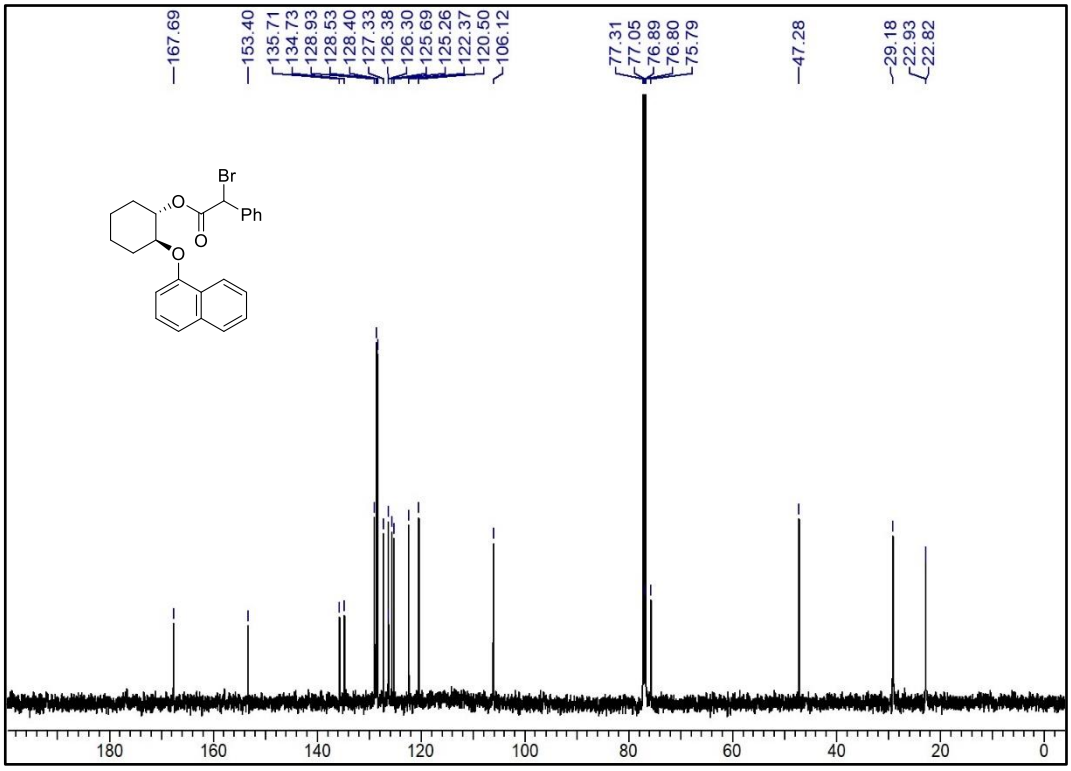
IR Spectra of Compound (**30h**)



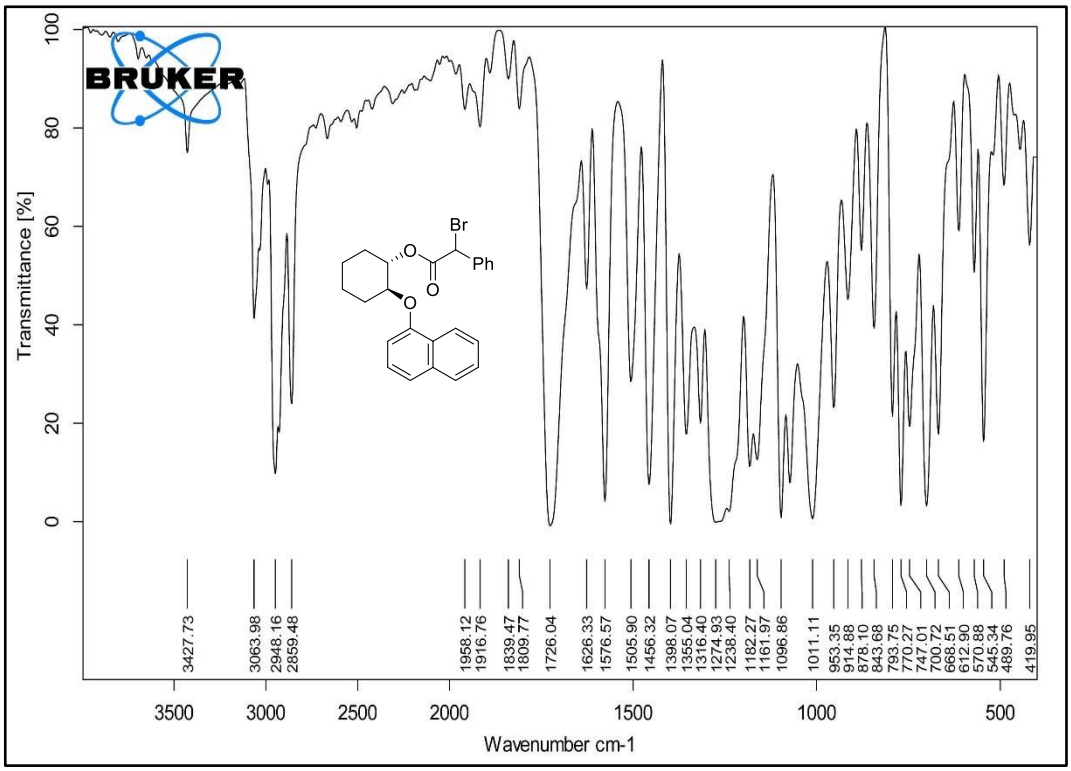
HRMS Spectra of Compound (**30h**)



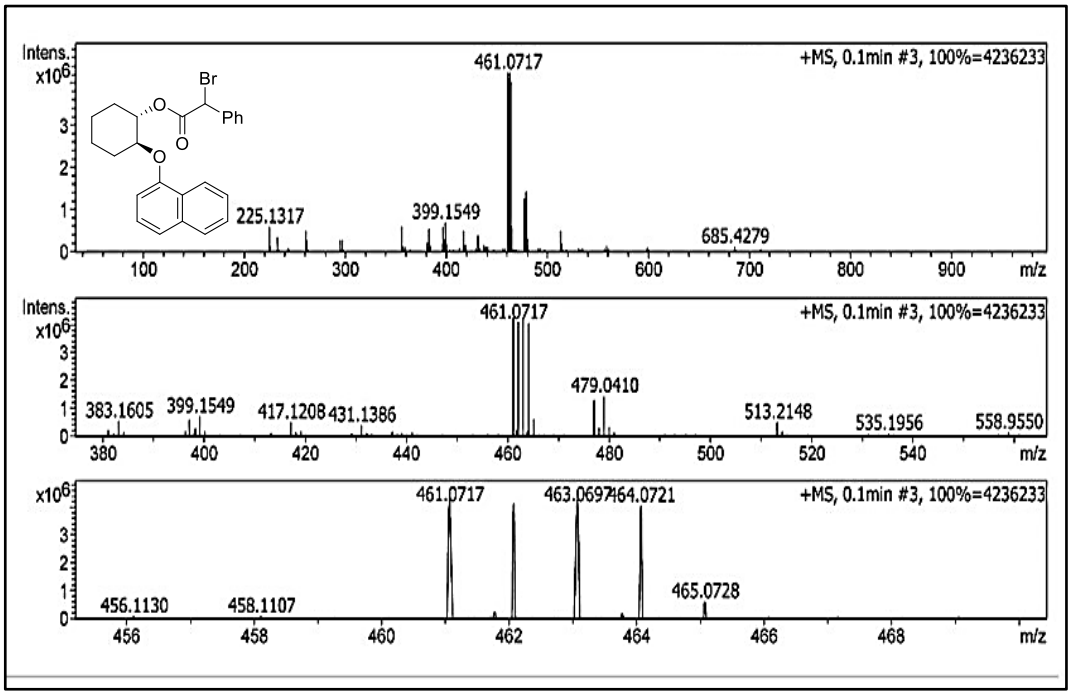
^{1}H NMR Spectra of Compound (**30i**)



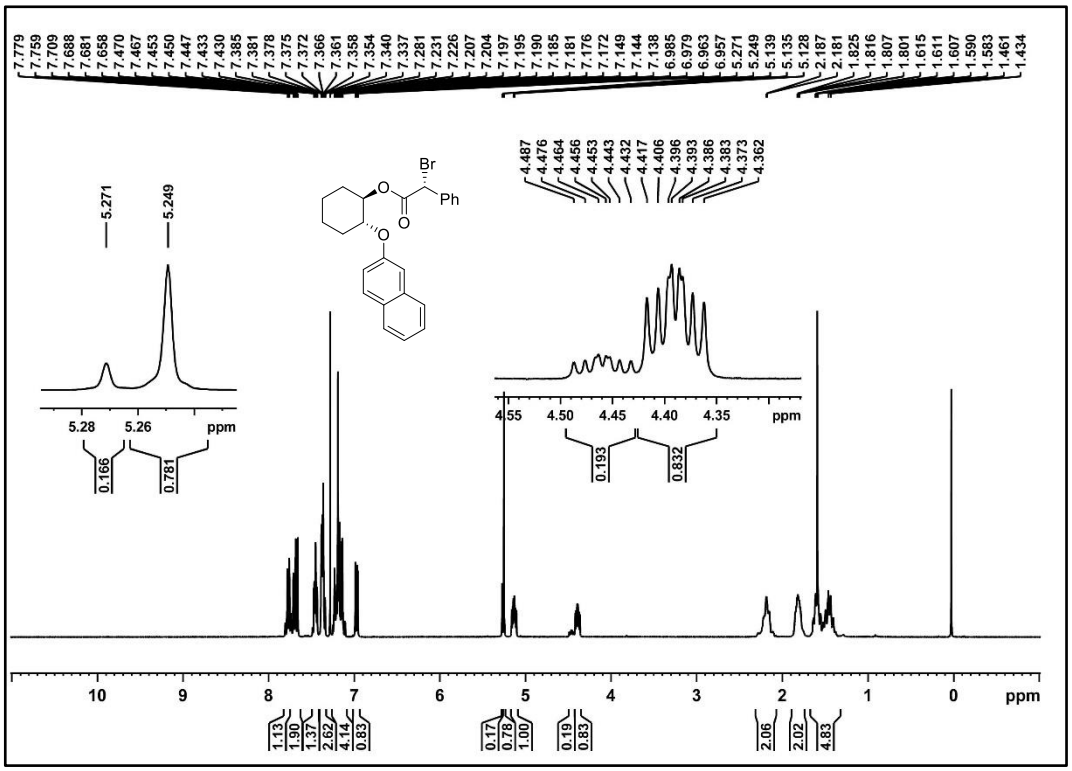
^{13}C NMR Spectra of Compound (**30i**)



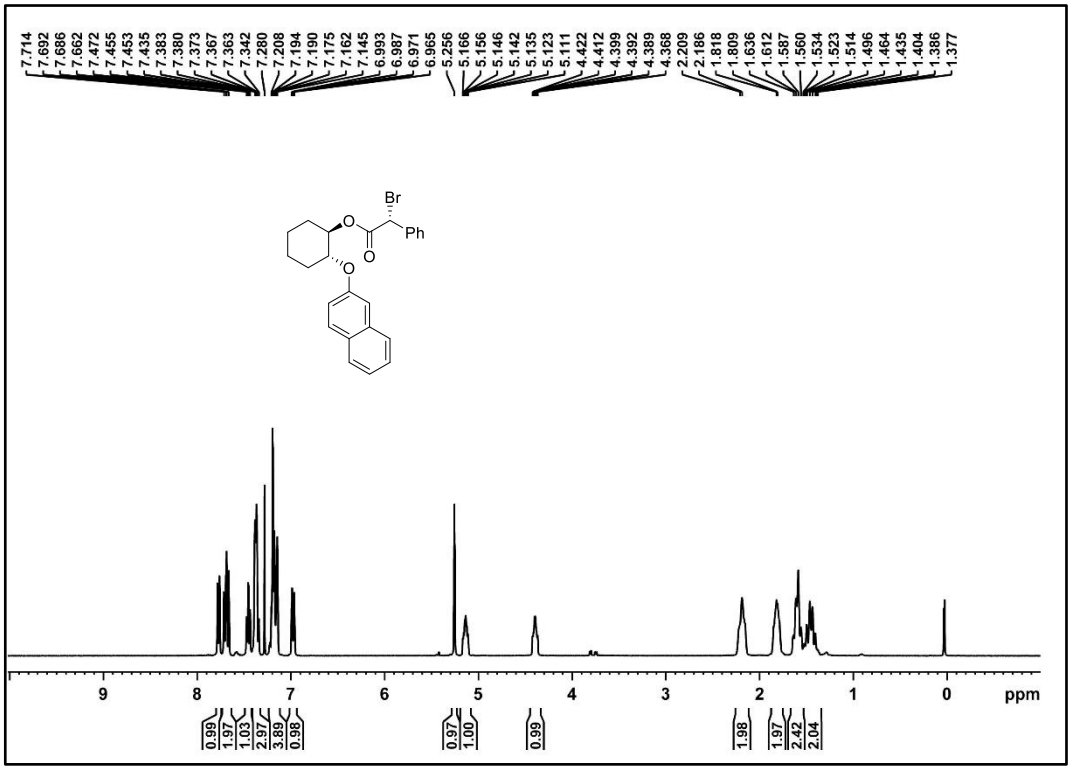
IR Spectra of Compound (**30i**)



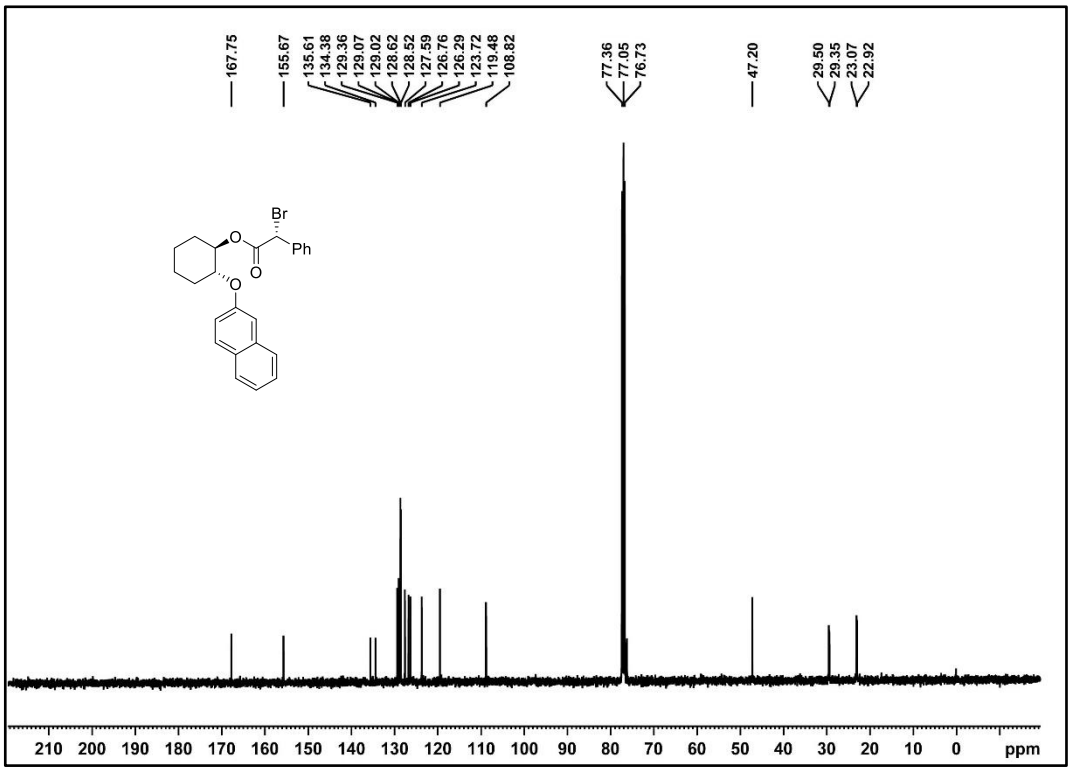
HRMS Spectra of Compound (**30i**)



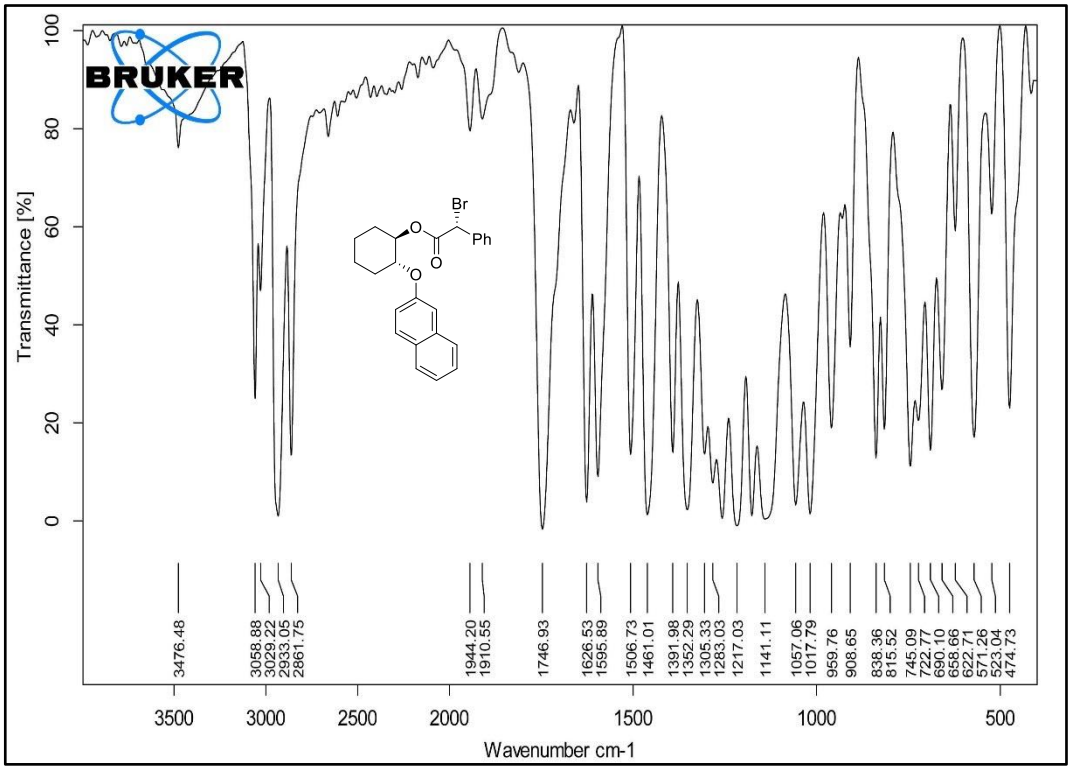
^{1}H NMR Spectra of Compound (**30j**)



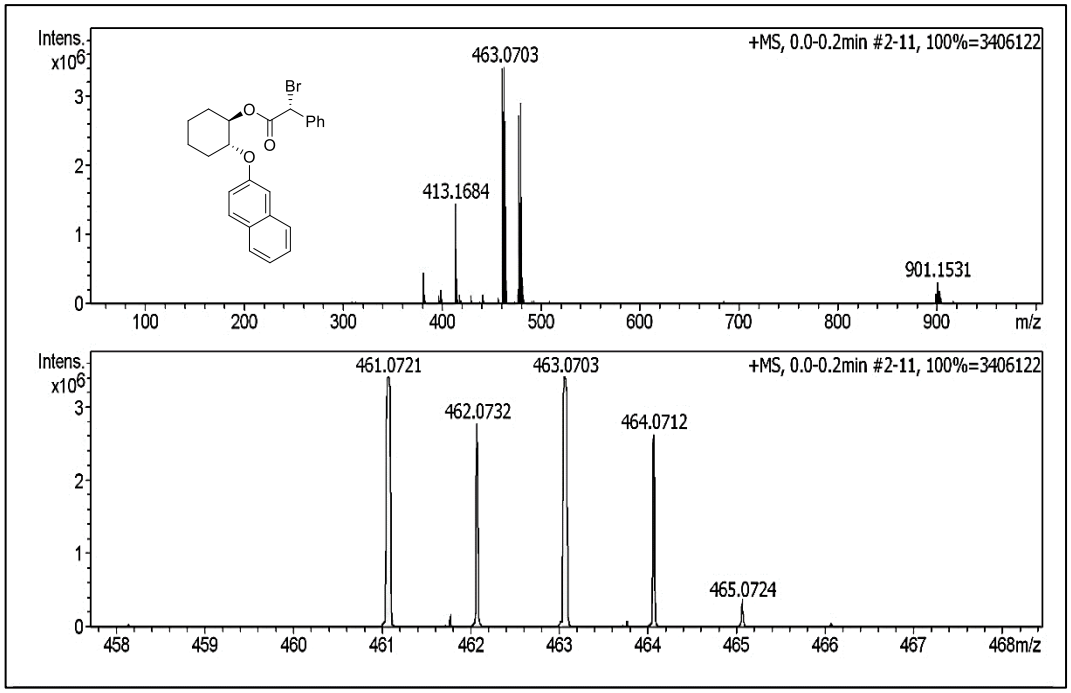
^{1}H NMR Spectra of Compound (*R,R,R*)-**30j** after crystallization



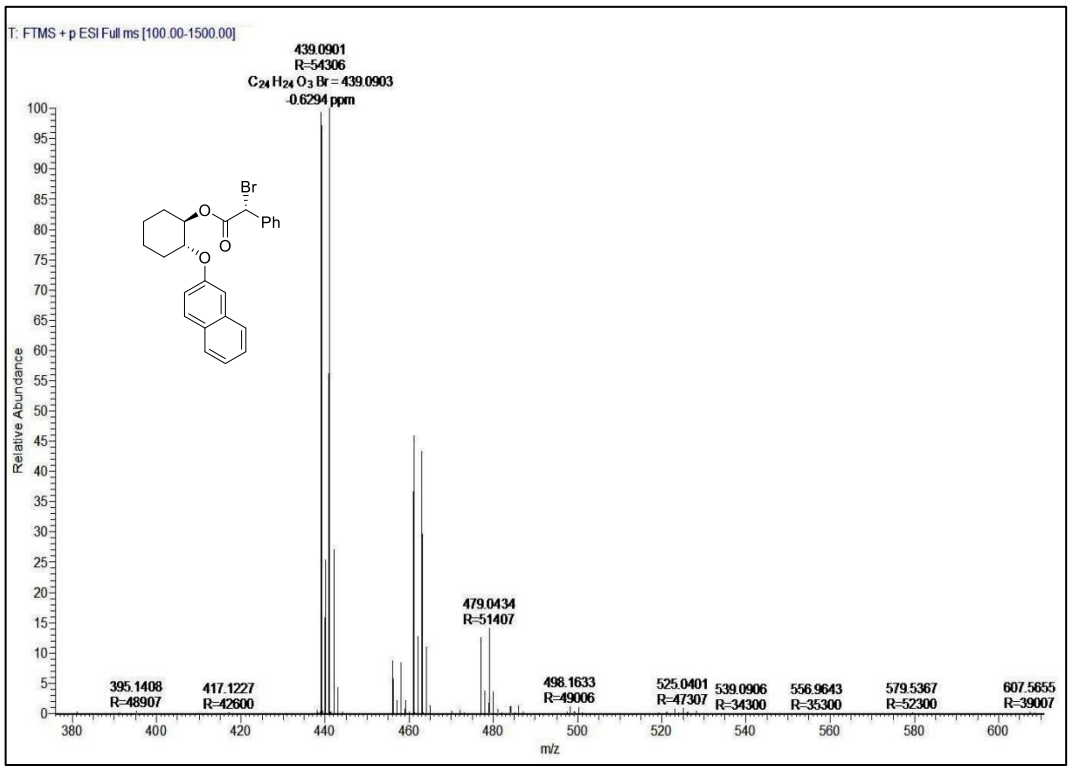
^{13}C NMR Spectra of Compound (*R*,*R*,*R*)-**30j**



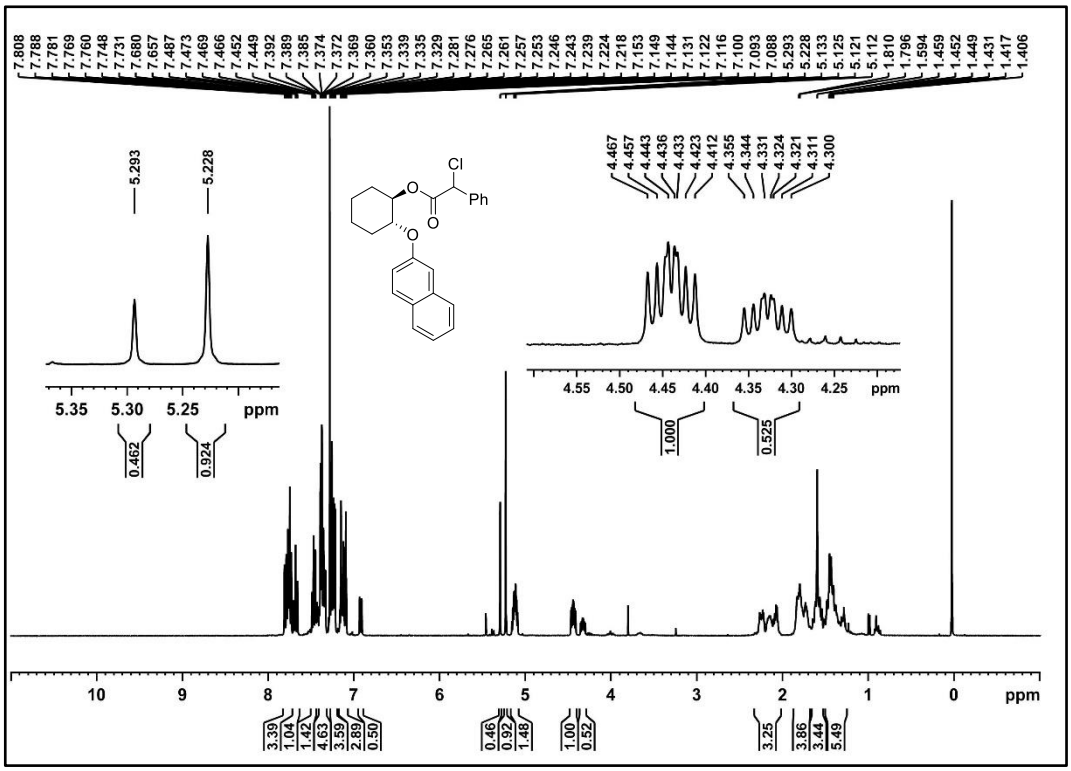
IR Spectra of Compound (*R*,*R*,*R*)-**30j**



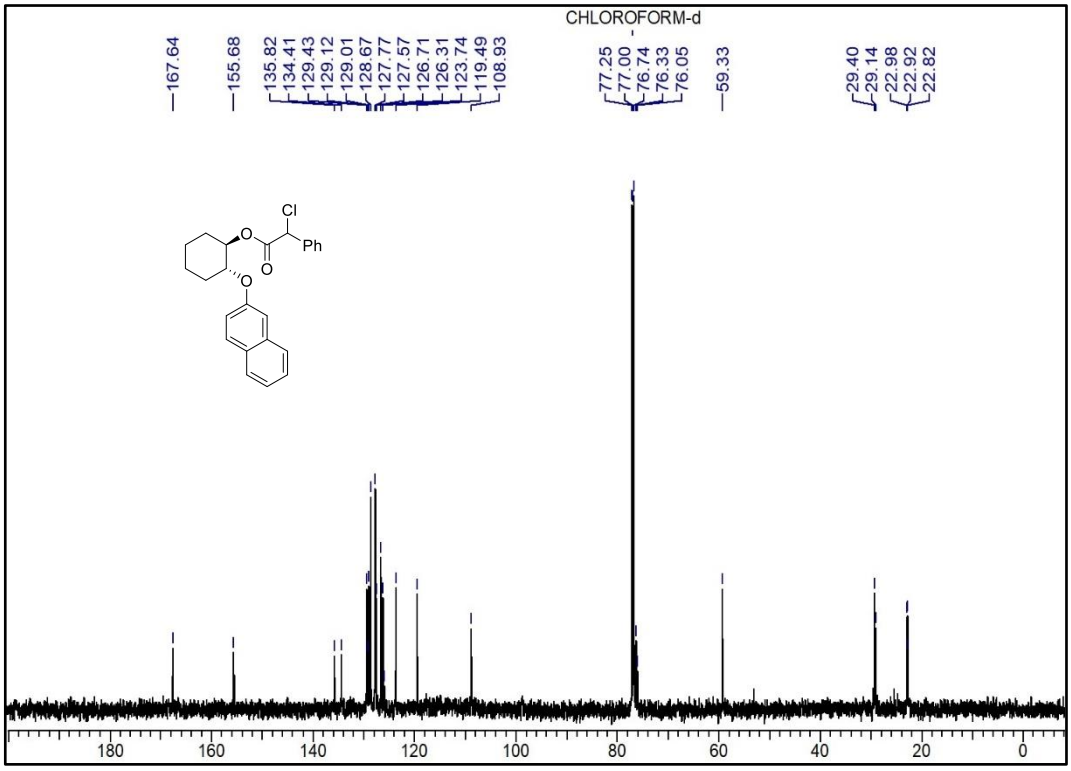
MS Spectra of Compound (*R*,*R*,*R*)-**30j**



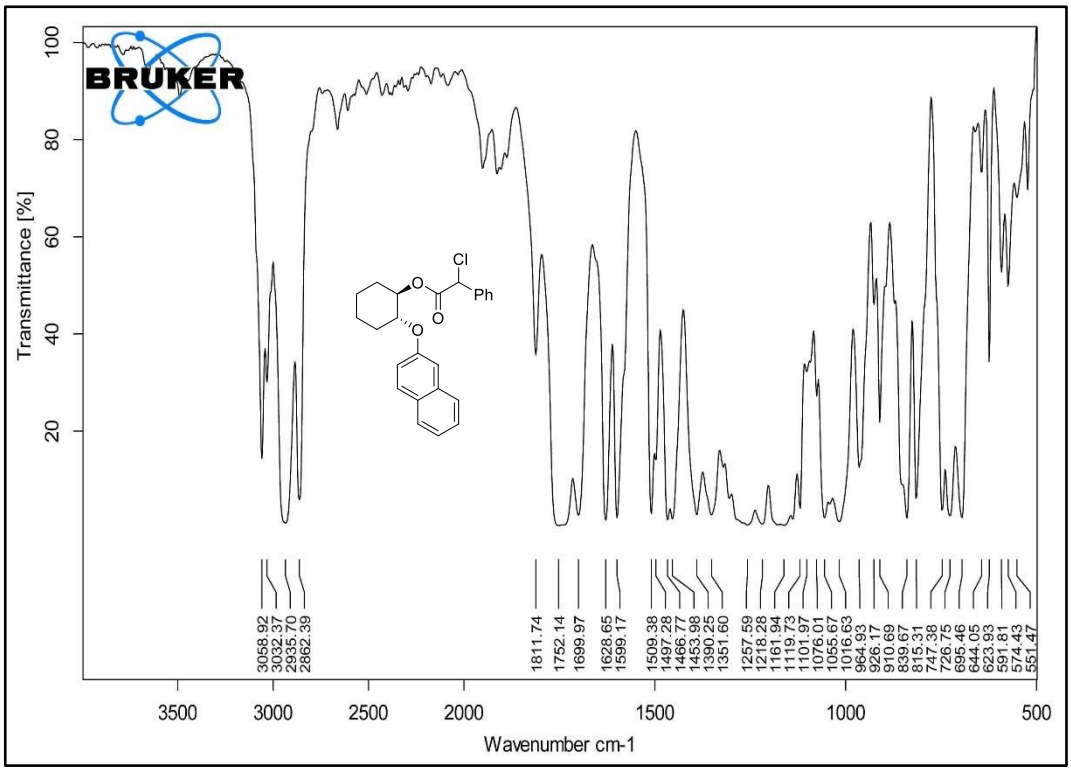
HRMS Spectra of Compound (*R*,*R*,*R*)-**30j**



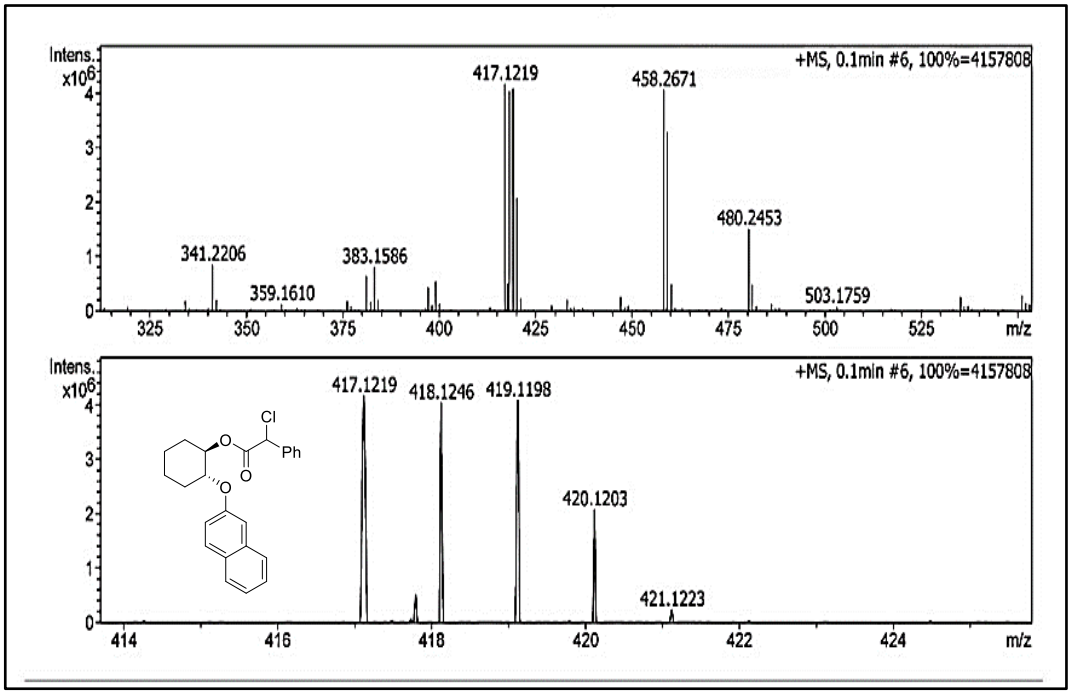
^{1}H NMR Spectra of Compound (**30k**)



^{13}C NMR Spectra of Compound (**30k**)



IR Spectra of Compound (**30k**)



HRMS Spectra of Compound (**30k**)

3.5.2 X-Ray Crystal data:

X-ray crystal data for CCDC No 1854344 (*R*,*R*,*R*)-**24** and CCDC No 1854340 (*R*,*R*,*R*)-**25**

Details	Compound (*R*,*R*,*R*)-**24** CCDC-1854344	Compound (*R*,*R*,*R*)-**25** CCDC-1854340
Empirical Formula	$C_{26}H_{26}O_5$	$C_{26}H_{26}O_5$
Formula Weight	418.49	418.49
Temperature	293(2)	293(2)
Wavelength	0.71073A	0.71073A
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	a = 9.3173(7) Å b = 10.8597(9) Å c = 22.3122(19) Å $\alpha = 90^o$ $\beta = 90^o$ $\gamma = 90^o$	a = 8.2235(6) Å b = 15.8364(13) Å c = 17.2177(13) Å $\alpha = 90^o$ $\beta = 90^o$ $\gamma = 90^o$
Volume	2257.6	2242.3 (3)
Z	4	4
(Density calculated)	1.2311	1.2396
Absorption coefficient(μ)	0.085	0.085
F(000)	888.5	888.5
Crystal size	-	-
2θ range for data collection	6.64 to 57.6^o	7 to 57.92^o
Reflections collected	6917	13939
Independent reflections	5890[R(int) = 0.0198]	5147[R(int) = 0.0330]
Refinement method	Least Squares minimisation	Least Squares minimization
Data / restraints / Parameters	5890/0/280	5147/0/280
Goodness of fit on F2	1.077	1.071
Final R indices [I>2sigma(I)]	R1 =0.0484, wR2 =NA	R1 =0.0551, wR2 = NA
R indices (all data)	R1 = 0.0696, wR2 = 0.0972	R1 = 0.0792, wR2 = 0.1265
Largest difference peak and hole	0.27/-0.23	0.29/-0.23
Flack parameter	-0.8(13)	0.1(11)

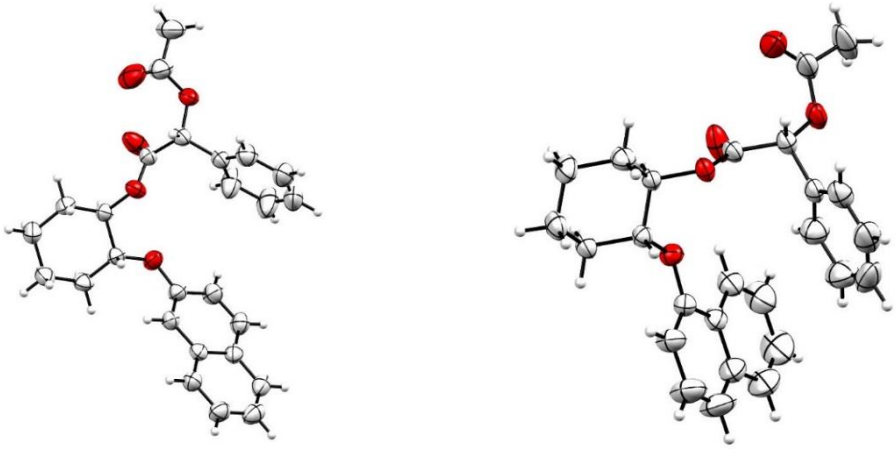


Figure 3.14: ORTEP diagram of the compound (*R*,*R*,*R*)-**24 (**CCDC No 1854344; left) and (*R*,*R*,*R*)-**25 (**CCDC No 1854340; right)
(50% probability factor for thermal ellipsoids)

X-ray crystal data for CCDC No 1854341(*R*,*R*,*S*)-**27** and CCDC No 1854339 (*S*,*S*,*S*)-**30a**

Details	Compound (*R*,*R*,*S*)-**27** CCDC-1854341	Compound (*S*,*S*,*S*)-**30a** CCDC-1854339
Empirical formula	$C_{19}H_{21}ClO_3$	$C_{19}H_{21}ClO_3$
Formula weight	332.83	332.83
Temperature/K	293(2)	293(2)
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a/Å	9.3718(9)	8.8657(9)
b/Å	5.8521(4)	10.5557(9)
c/Å	16.3645(14)	18.970(2)
α/°	90	90
β/°	106.047(9)	90
γ/°	90	90
Volume/Å^3	862.54(13)	1775.3(3)
Z	2	4
ρ_{calc}g/cm^3	1.2814	1.2452
μ/mm^{-1}	0.234	0.227
F(000)	352.5	704.9
Crystal size/mm^3	-	-
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.42 to 58.48	6.38 to 58.18
Reflections collected	10572	11056
Independent reflections	3982 [R_{int} = 0.0335, R_{sigma} = 0.0412]	4101 [R_{int} = 0.0369, R_{sigma} = 0.0506]
Data/restraints/parameters	3982/0/208	4101/0/212
Goodness-of-fit on F^2	1.027	0.958
Final R indexes [I>=2σ (I)]	R_1 = 0.0634, wR_2 = N/A	R_1 = 0.0699, wR_2 = NA

Final R indexes [all data]	R_1 = 0.0846, wR_2 = 0.1482	R_1 = 0.1129, wR_2 = 0.2009
Largest diff. peak/hole / e Å^{-3}	0.42/-0.48	0.57/-0.46
Flack parameter	0.00(14)	-0.16(14)

Figure 3.15: ORTEP diagram of the compound (*R*,*R*,*S*)-**27 (**left**)** and (*S*,*S*,*S*)-**30a (**right) (50% probability factor for thermal ellipsoids)

X-ray crystal data for CCDC No 1854338 (*R*,*R*,*S*)-**30b** and CCDC No 1854342 *(R*,*R*,*R)*-**30j**

Details	Compound (*R*,*R*,*S*)-**30b** CCDC-1854338	Compound (*R*,*R*,*R*)-**30j** CCDC-1854342
Empirical formula	$C_{19}H_{21}BrO_3$	$C_{24}H_{23}BrO_3$
Formula weight	377.28	439.33
Temperature/K	293(2)	293(2)
Crystal system	monoclinic	triclinic
Space group	$P2_1$	P1
a/Å	9.6654(18)	5.8561(5)
b/Å	5.3717(12)	8.9674(8)
c/Å	17.065(3)	10.0618(9)
α/°	90	94.232(7)
β/°	95.420(18)	97.739(7)
γ/°	90	98.721(7)
Volume/Å^3	882.0(3)	515.12(7)
Z	2	1
ρ_{calc}g/cm^3	1.4205	1.416
μ/mm^{-1}	2.342	2.017
F(000)	388.0	226.0
Crystal size/mm^3	-	-
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.2 to 57.88	6.46 to 57.54
Reflections collected	4672	5809
Independent reflections	4672 [R_{int} = 0.0208, R_{sigma} = 0.0640]	5368 [R_{int} = 0.0206, R_{sigma} = 0.0389]

Data/restraints/parameters	4672/0/208	5368/3/253
Goodness-of-fit on F^2	1.059	1.089
Final R indexes [I>=2σ (I)]	R_1 = 0.0709, wR_2 = NA	R_1 = 0.0450, wR_2 = 0.0997
Final R indexes [all data]	R_1 = 0.1239, wR_2 = 0.2044	R_1 = 0.0618, wR_2 = 0.1119
Largest diff. peak/hole / e $Å^{-3}$	0.79/-0.69	0.41/-0.40
Flack parameter	0.07(2)	-0.026(11)

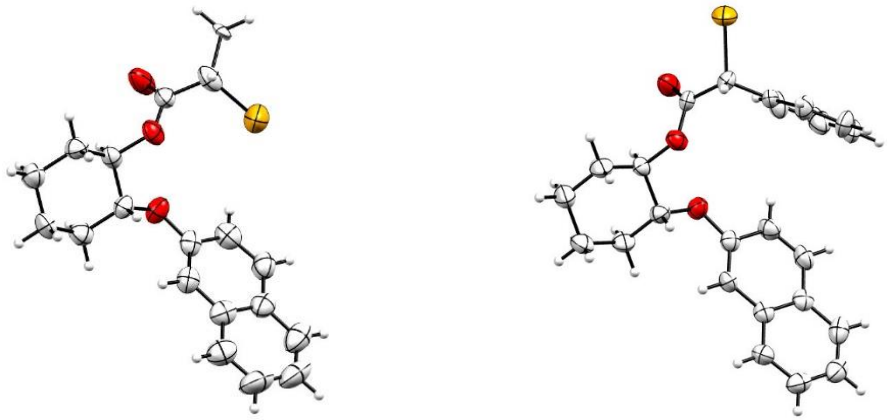


Figure 3.16: ORTEP diagram of the compound (*R*,*R*,*S*)-**30b** (left) and (*R*,*R*,*R*)-**30j** (right) (50% probability factor for thermal ellipsoids)

3.5.3 Computational Studies:

All calculations were performed without symmetry restrictions. Starting coordinates were obtained with Chem3DUltra 10.0 or directly from the crystal structure analysis. Optimization was performed with Gaussian 16 Revision A.03 at the B3LYP/6-31+G(d). Table 3.7 lists the total optimized energies of all compounds; Figure 3.17 and 3.18 depict the optimized structures and relative energies of the diastereomeric 2-chloro propanoate esters (**27**) and **(30a).**

Table 3.7: Optimized energies of Diastereomeric esters (**27**) and (**30a**).

Compound	Method		Optimized Energy [kJ•mol-1]
(*R*,*R*,*R*)-**27**	B3LYP/6-31+G(d)	Minimum	(-3734962.14)
(*R*,*R*,*S*)-**27**	B3LYP/6-31+G(d)	Minimum	(-3734964.20)
(*R*,*R*,*R*)-**30a**	B3LYP/6-31+G(d)	Minimum	(-3734968.66)
(*R*,*R*,*S*)-**30a**	B3LYP/6-31+G(d)	Minimum	(-3734967.04)

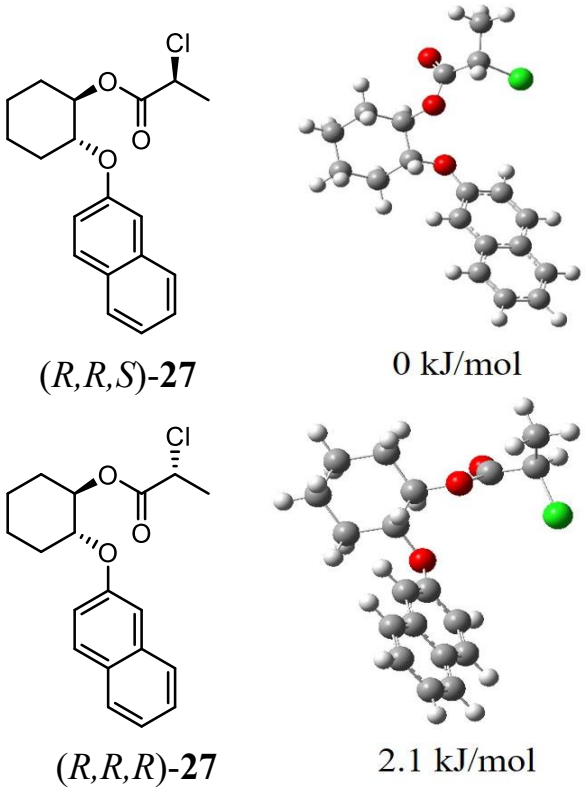


Figure 3.17: Optimized geometries and Relative energies of diastereomeric esters (*R*,*R*,*R*)-**27** and (*R*,*R*,*S*)-**27**

Table 3.8: Standard orientation of (*R*,*R*,*R*)-**27**; [B3LYP/6-31+G(d)].

Standard orientation:

Centre No.	Atomic No.	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	17	0	2.700207	-3.440104	0.096946
2	8	0	2.318656	-0.168030	0.052894
3	8	0	-0.131327	0.536227	-1.060902
4	8	0	4.253098	-0.205075	-1.092270
5	6	0	3.475874	-0.711873	-0.336450
6	6	0	-4.094910	-0.725761	-0.610184
7	6	0	-1.434233	0.189220	-0.821416
8	6	0	-2.048545	-0.504899	-1.891064
9	1	0	-1.547192	-0.672623	-2.704031
10	6	0	-3.469159	-0.026581	0.464475
11	6	0	0.550044	1.413625	-0.144810
12	1	0	0.305604	1.164252	0.800123
13	6	0	-3.333169	-0.936885	-1.785542
14	1	0	-3.738926	-1.401822	-2.534518
15	6	0	-5.424987	-1.187769	-0.462290
16	1	0	-5.852874	-1.658999	-1.193994
17	6	0	-2.136057	0.418815	0.334119
18	1	0	-1.715900	0.891400	1.069224
19	6	0	-4.226057	0.184398	1.648063
20	1	0	-3.826522	0.661931	2.391881
21	6	0	-6.108833	-0.975307	0.698290
22	1	0	-7.013622	-1.310503	0.792442
23	6	0	3.703975	-2.033770	0.386367
24	1	0	4.548955	-2.154884	-0.149126
25	6	0	2.029894	1.202877	-0.348205
26	1	0	2.260586	1.326304	-1.320808
27	6	0	-5.514082	-0.277928	1.751948
28	1	0	-6.016590	-0.118712	2.566326
29	6	0	2.854684	2.161052	0.502918
30	1	0	2.707805	1.958078	1.471495
31	1	0	3.825886	2.033652	0.302010
32	6	0	0.162326	2.859652	-0.400917
33	1	0	0.303313	3.074286	-1.368032
34	1	0	-0.808907	2.983008	-0.196492
35	6	0	2.458326	3.604910	0.218549
36	1	0	2.982747	4.217471	0.810751
37	1	0	2.679078	3.829763	-0.731200
38	6	0	0.985143	3.815399	0.453695
39	1	0	0.741407	4.758896	0.228320
40	1	0	0.776545	3.664892	1.420425
41	6	0	4.536261	-1.886873	1.636150
42	1	0	4.519775	-2.736182	2.147870
43	1	0	5.471664	-1.670438	1.386583
44	1	0	4.171257	-1.156785	2.202725

Rotational constants (GHZ): 0.3311280 0.1260281 0.1027359

Table 3.9: Standard orientation of (*R*,*R*,*S*)-**27**; [B3LYP/6-31+G(d)].

Standard orientation:

Centre No.	Atomic No.	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	17	0	4.152142	-3.169365	-0.267874
2	8	0	2.195965	0.051593	0.382725
3	8	0	-0.198935	0.381026	-0.962320
4	8	0	4.068440	-0.154572	-0.887419
5	6	0	3.321845	-0.566205	-0.032079
6	6	0	-4.067655	-1.146064	-0.488622
7	6	0	-1.477563	-0.041177	-0.739161
8	6	0	-1.919663	-1.059534	-1.628897
9	1	0	-1.229744	-1.396033	-2.398824
10	6	0	-3.620507	-0.120481	0.405021
11	6	0	0.340958	1.448690	-0.182074
12	1	0	0.037417	1.323823	0.868421
13	6	0	-3.175701	-1.592494	-1.503041
14	1	0	-3.505524	-2.373145	-2.187405
15	6	0	-5.373835	-1.677084	-0.334010
16	1	0	-5.704609	-2.457512	-1.018658
17	6	0	-2.312737	0.420024	0.256751
18	1	0	-1.997946	1.199099	0.945832
19	6	0	-4.507705	0.328637	1.419267
20	1	0	-4.171428	1.108284	2.102172
21	6	0	-6.210819	-1.220100	0.659562
22	1	0	-7.211027	-1.635207	0.768098
23	6	0	3.520370	-1.840948	0.790314
24	1	0	2.552921	-2.183179	1.162755
25	6	0	1.860599	1.312101	-0.256999
26	1	0	2.171529	1.252883	-1.305872
27	6	0	-5.770457	-0.207070	1.543765
28	1	0	-6.436618	0.149014	2.327873
29	6	0	2.575527	2.463750	0.452571
30	1	0	2.354281	2.400740	1.528922
31	1	0	3.657341	2.335517	0.332653
32	6	0	-0.109019	2.814887	-0.719900
33	1	0	0.123995	2.842695	-1.794175
34	1	0	-1.198588	2.902750	-0.632253
35	6	0	2.120748	3.824975	-0.092375
36	1	0	2.620784	4.629866	0.462226
37	1	0	2.437040	3.924619	-1.141938
38	6	0	0.596681	3.973402	-0.002104
39	1	0	0.277115	4.928979	-0.438412
40	1	0	0.291779	3.996132	1.056005
41	6	0	4.486075	-1.577125	1.945295
42	1	0	4.593318	-2.471888	2.567361
43	1	0	5.469178	-1.290471	1.557472

44	1	0	4.095768	-0.761230	2.568021

Rotational constants (GHZ): 0.3240605 0.1344641 0.1028433

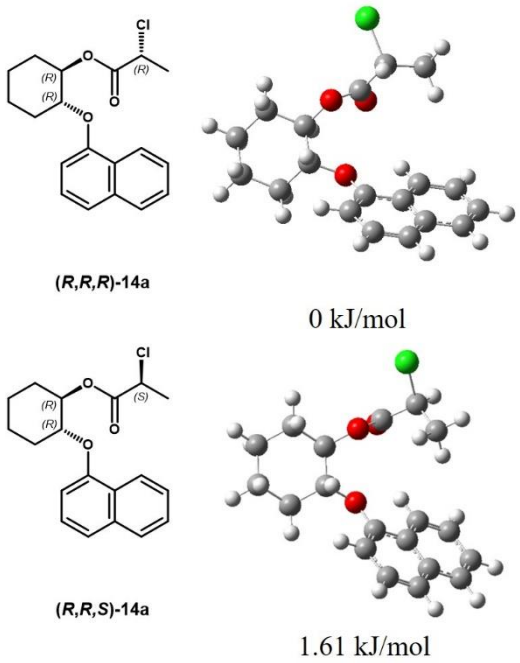


Figure 3.18: Optimized geometries and Relative energies of diastereomeric esters (*R*,*R*,*R*)-**30a** and (*R*,*R*,*S*)-**30a**

Table 3.10: Standard orientation of (*R*,*R*,*R*)-**30a**; [B3LYP/6-31+G(d)].

Standard orientation:

Centre No.	Atomic No.	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	17	0	-3.462623	-3.563960	-0.564225
2	6	0	-2.277612	-1.192663	0.131029
3	8	0	-2.054423	-0.024516	-0.513028
4	8	0	0.385978	0.951184	0.390193
5	8	0	-2.472040	-1.313538	1.315577
6	6	0	2.027504	1.782288	-1.209111
7	6	0	1.614060	0.925593	-0.208386
8	6	0	2.490463	-0.098748	0.281393
9	6	0	2.103089	-0.993148	1.313153
10	1	0	1.113469	-0.895337	1.746784
11	6	0	3.321833	1.647009	-1.767957
12	1	0	3.622135	2.333836	-2.555862
13	6	0	2.970770	-1.966272	1.759279
14	1	0	2.663321	-2.644195	2.551899
15	6	0	-0.631657	1.850473	-0.056172
16	1	0	-0.572912	1.961252	-1.147558
17	6	0	-1.964099	1.184839	0.282798

18	1	0	-1.968596	0.898314	1.338197
19	6	0	4.188216	0.676844	-1.329460
20	1	0	5.180656	0.579312	-1.763137
21	6	0	3.795197	-0.216556	-0.294817
22	6	0	-0.513403	3.214149	0.637843
23	1	0	0.437750	3.684335	0.363677
24	1	0	-0.474986	3.036328	1.721433
25	6	0	4.260975	-2.087629	1.193919
26	1	0	4.937174	-2.859754	1.553621
27	6	0	-3.156479	2.085160	-0.044839
28	1	0	-4.079766	1.575161	0.254195
29	1	0	-3.204361	2.220423	-1.134680
30	6	0	-2.165417	-2.335370	-0.877231
31	1	0	-2.351645	-1.948531	-1.879902
32	6	0	4.660389	-1.232668	0.191553
33	1	0	5.652539	-1.322569	-0.246476
34	6	0	-1.699959	4.127332	0.298472
35	1	0	-1.683261	4.373282	-0.774011
36	1	0	-1.600892	5.078416	0.836033
37	6	0	-3.032349	3.450781	0.646580
38	1	0	-3.100602	3.318073	1.736137
39	1	0	-3.875837	4.089366	0.356843
40	6	0	-0.784401	-2.981533	-0.787458
41	1	0	-0.682477	-3.768718	-1.540202
42	1	0	-0.631891	-3.414746	0.205361
43	1	0	-0.013107	-2.221834	-0.960647
44	1	0	1.379057	2.570569	-1.575332

Rotational constants (GHZ): 0.2645150 0.1808907 0.1214618

Table 3.11: Standard orientation of (*R*,*R*,*S*)-**30a**; [B3LYP/6-31+G(d)].

Standard orientation:

Centre No.	Atomic No.	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	17	0	3.238799	-3.155595	1.442837
2	6	0	2.199757	-1.340489	-0.570021
3	8	0	1.991812	-0.300050	0.189543
4	8	0	- 0.376396	0.940044	-0.452196
5	8	0	2.463956	-1.289651	-1.724133
6	6	0	-1.920371	1.912658	1.146086
7	6	0	-1.582100	1.005726	0.172083
8	6	0	-2.513694	0.017452	-0.250316
9	6	0	-2.181897	-0.969586	-1.200027
10	1	0	-1.340629	-0.959949	-1.596565
11	6	0	-3.187341	1.877081	1.715929
12	1	0	-3.406830	2.490806	2.379103
13	6	0	-3.073210	-1.934792	-1.544916
14	1	0	-2.835647	-2.584894	-2.166647
15	6	0	0.732312	1.724289	0.024787

16	1	0	0.713296	1.759141	1.003810
17	6	0	1.976960	1.022981	-0.429065
18	1	0	1.963387	0.930137	-1.404673
19	6	0	-4.102099	0.972572	1.326344
20	1	0	-4.949975	0.988864	1.707978
21	6	0	-3.801876	-0.006084	0.348566
22	6	0	0.708131	3.131627	-0.534775
23	1	0	-0.084601	3.592289	-0.219039
24	1	0	0.669198	3.093809	-1.503439
25	6	0	-4.343527	-1.955774	-0.971536
26	1	0	-4.951604	-2.614441	-1.219292
27	6	0	3.224298	1.768477	-0.008272
28	1	0	4.007096	1.301541	-0.339321
29	1	0	3.274367	1.793139	0.959541
30	6	0	2.032851	-2.610863	0.256580
31	1	0	2.187293	-3.070816	-0.595453
32	6	0	-4.696748	-1.026088	-0.059286
33	1	0	-5.548595	-1.055364	0.311026
34	6	0	1.951682	3.903746	-0.103615
35	1	0	1.959777	3.995398	0.862292
36	1	0	1.933444	4.792766	-0.491112
37	6	0	3.208118	3.182123	-0.552127
38	1	0	3.240822	3.159034	-1.521519
39	1	0	3.989866	3.661637	-0.235242
40	6	0	0.654907	-3.179485	0.157256
41	1	0	0.570441	-3.917934	0.765616
42	1	0	0.498960	-3.483668	-0.739191
43	1	0	0.013497	-2.501795	0.382476
44	1	0	-1.315054	2.499251	1.483669

Rotational constants (GHZ): 0.2791302 0.1813834 0.1265351

3.6 References:

1. Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.
2. (a) Corey, E. J.; Su, W. -G. *Tetrahedron Lett*. **1988**, *29*, 3423. (b) Ranu, B. C.; Sarkar, A.; Saha, M.; Bhar, S. *Pure and Appl. Chem.* **1996**, *68*, 775.
3. (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380. (c) Whitesell, J.K.; James, D.; Carpenter, J.F. *J. Chem. Soc., Chem. Commun*. **1985**, 1449. (d) Buschmann, H.; Scharf, H.D. *Synthesis*, **1988**, 827.
4. (a) Whitesell, J.K.; Lawrence, R.M.; Chen, H.-H. *J. Org. Chem*. **1986**, *51*, 4779.
5. (a) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. (b) Hazmi, A.M.A.; Sheikh, N.S.; Bataille, C.J.R. Al-Hadedi, A.A.M.; Watkin, S.V.; Luker, T.J.; Camp, N.P.; Brown, R.C.D. *Org. Lett*. **2014**, *16*, 5104.
6. (a) Laumen, K.; Breitgoff, D.; Seemayer, R.; Schneider, M.P. *J. Chem. Soc., Chem. Commun*. **1989**, 148. (b) Basavaiah, D.; Rama Krishna, P.; Bharathi, T.K. *Tetrahedron: Asymmetry* **1995**, *6*, 439. (c) Basavaiah, D.; Rama Krishna, P. *Tetrahedron* **1995**, *51*, 12169. (d) Tőke, E.R.; Kolonits, P.; Novák, L.; Poppe, L. *Tetrahedron: Asymmetry* **2006**, *17*, 2377.
7. Pérez-Garcia, L.; Amabilino, D.B. *Chem. Soc. Rev*. **2007**, *36*, 941.
8. (a) Ward, R.S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475. (b) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5004. (c) Pellissier, H. *Adv. Synth. Catal*. **2011**, *353*, 659.
9. (a) Trost, B.M.; Andersen, N.G. *J. Am. Chem. Soc*. **2002**, *124*, 14320. (b) Steinreiber, J.; Faber, K.; Griengl, H. *Chem. Eur. J.* **2008**, *14*, 8060. (c) Borén, L.; Leijondahl, K.; Bäckwall, J.-E. *Tetrahedron Lett*. **2009**, *50*, 3237.
10. (a) Beak, P.; Anderson, D.R.; Curtis, M.D.; Laumer, J.M.; Pippel, D.J.; Weisenburger, G.A. *Acc. Chem. Res*. **2000**, *33*, 715. (b) Lee, W.K.; Park, Y.S.; Beak, P. *Acc. Chem. Res*. **2009**, *42*, 224.
11. (a) Basu, A.; Gallagher, D.J.; Beak, P. *J. Org. Chem*. **1996**, *61*, 5718. (b) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc*. **2000**, *122*, 11340. (c) Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed*. **2002**, *41*, 716. (d) Clayden, J.; Mitjans, D.; Youssef, L.H. *J. Am. Chem. Soc.* **2002**, *124*, 5266. (e) Coldham, I.; Dufour, S.; Haxell, T.F.N.; Howard, S.; Vennall, G.P. *Angew. Chem. Int. Ed*. **2002**, *41*, 3887. (f) Laumer, J.M.; Kim, D.D.; Beak, P. *J. Org. Chem*. **2002**, *67*, 6797. (g) Wang, L.; Nakamura, S.; Toru, T. *Org. Biomol. Chem*. **2004**, *2*, 2168. (h) Park, Y.S.; Yum, E.K.; Basu, A.; Beak, P. *Org. Lett*.

2006, *8*, 2667. (i) Nakamura, S.; Hirata, N.; Yamada, R.; Kita, T.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 5519. (j) Robinson, S.P.; Sheikh, N.S.; Baxter, C.A.; Coldham, I. *Tetrahedron Lett*. **2010**, *51*, 3642. (k) Carter, N.; Li, X.; Reavey, L.; Meijer, A. J. H. M.; Coldham, I. *Chem. Sci.* **2018**, *9*, 1352.

12. (a) Larsen, R.D.; Corley, E.G.; Davis, P.; Reider, P.J.; Grabowski, E.J.J. *J. Am. Chem. Soc.* **1989**, *111*, 7650. (b) Calmes, M.; Daunis, J.; Jacquier, R.; Natt, F. *Tetrahedron* **1994**, *50*, 6875. (c) Camps, P.; Giménez, S. *Tetrahedron; Asymmetry* **1995**, *6*, 991. (d) Camps, P.; Pérez, F.; Soldevilla, N. *Tetrahedron: Asymmetry* **1998**, *9*, 2065. (e) Nam, J.; Lee, S.-K.; Kim, K.Y.; Park, Y.S. *Tetrahedron Lett*. **2002**, *43*, 8253. (f) Lee, S.-K.; Nam, J.; Park, Y.S. *Synlett* **2002**, 790. (f) Nam, J.; Lee, S.-K.; Park, Y.S. *Tetrahedron* **2003**, *59*, 2397.
13. Jain, N.; Bedekar, A.V. *Tetrahedron Lett.* **2016**, *57*, 692.
14. (a) Corey, E.J.; Link, J.O. *Tetrahedron Lett*. **1992**, *33*, 3431. (b) Koh, K.; Durst, T. *J. Org. Chem*. **1994**, *59*, 4683. (c) Devine, P.N.; Dolling, U.-H.; Heid, R.M.; Tschaen, D.M. *Tetrahedron Lett.* **1996**, *37*, 2683. (d) Akazome, M.; Takahashi, T.; Ogura, K. *J. Org. Chem*. **1999**, *64*, 2293. (e) Diez, E.; Dixon, D.J.; Ley, S.V. *Angew. Chem. Int. Ed.* **2001**, *40*, 2906. (f) Chadha, A.; Bhaskar, B. *Tetrahedron: Asymmetry* **2002**, *13*, 1461. (g) Tang, L.; Deng, L. *J. Am. Chem. Soc*. **2002**, *124*, 2870.
15. (a) Surendra, K.; Shrilakshmi Krishnaveni, N; Nageshwar, Y. V. D.; Rama Rao, K. *J. Org. Chem.* **2003**, *68*, 4994. (b) Das, B.; Krishnaiah, M.; Thirupathi, P.; Laxminarayana, K. *Tetrahedron Lett.* **2007**, *48*, 4263.
16. (a) Guss, C.O.; Rosenthal, R.; Brown, R.F. *J. Org. Chem*. **1955**, *20*, 909. (b) Tamami, B.; Iranpoor, N.; Rezaei, R. *Synth. Commun*. **2004**, *34*, 2789. (c) Lu, H.; Zhou, J.; Cheng, H.; Sun, L.; Yang, F.; Wu, R.; Gao, Y.; Luo, Z. *Tetrahedron*, **2013**, *69*, 11174. (d) Hackbusch, S.; Franz, A.H. *Arkivoc* **2015**, *vii*, 172.
17. Neises, B.; Steglich, W. *Angew. Chem., Int. Ed*. **1978**, *17*, 522.
18. (a) Jähme, J.; Rüchardt, C. *Angew. Chem., Int. Ed*. **1981**, *20*, 885. (b) Calmes, M.; Daunis, J.; Mai, N. *Tetrahedron* **1997**, *53*, 13719.
19. Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F.

Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

20. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre [CCDC No. 1854338, 1854339, 1854340, 1854341, 1854342 and 1854344]. Copies of the data can be obtained from http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CD21EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).